Chapter 3

THE CEREBRAL CORTEX: ITS STRUCTURE AND MOTOR FUNCTIONS*

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*Monographs, symposia and reviews: Akert *et al.*, eds., Neural control of motor performance (Zurich symposium), *Brain Res.*, 1972;[1] Brooks and Stoney, *Ann. Rev. Physiol.*, 1971;[23] Brooks *et al.*, *Brain Res.*, 1970;[21a] Brooks *et al.*, *Canad. J. neural Sci.*, 1975;[22] Evarts *et al.*, *Neurosci. Res. Program Bull.*, 1971;[42] Granit, *The basis of motor control*, 1970;[61] Granit and Burke, eds., *Brain Res.*, 1973;[62] Marchiafava, *Ann. Rev. Physiol.*, 1968;[93] Maser, ed., *Efferent organization and the integration of behavior*, 1973;[96] Matthews, *Mammalian muscle receptors and their central connections*, 1972;[98] Paillard, *Handb. Physiol.*, 1960;[103] Paillard and Massion, *Brain Res.*, 1974;[104] Phillips, In: *Brain and conscious experience*, 1966;[111] Phillips, *Proc. roy. Soc.*, 1969;[112] Phillips, *Proc. roy. Soc. Med.*, 1973;[113] Porter, *Progr. Neurobiol.*, 1973;[117] Porter, *Int. Rev. Sci.*, Physiol. ser. 1, 3, 1975;[117a] Porter, *Ann. Rev. Physiol.*, 1976;[118] Stein et al., *Control of posture and locomotion*, 1973;[134] Towe, In: *Efferent organization and the integration of behavior*, 1973;[144] Wiesendanger, *Ergebn. Physiol.*, 1969;[152] Yahr and Purpura, eds., *Neurophysiological basis of normal and abnormal motor activities*, 1967.[154] Since *Annual Reviews* appear each year, only a few especially pertinent reviews have been listed. For detailed discussion of early work see references 24, 52 and 106.

STRUCTURE

INTRODUCTION. This chapter begins by describing some general features of cortical structure and deals specifically with motor areas and pathways. Other cortical and subcortical structures are described in other chapters. In particular, the reader may consult Chapter 6 (Volume I) for a review of the anatomy and function of the thalamus in order to understand the ascending pathways and thalamic nuclei mentioned in this chapter.

In this century improved staining methods have revealed new features of the cortical histology of man and other primates; these structures remain a subject of active investigation, which has taken three main directions: (i) Cytoarchitecture and myeloarchitecture, *i.e.,* the cellular and fiber makeup of cortical areas, was early studied by Campbell, Brodmann, C. and O. Vogt, von Economo, and Koskinas.[see 17, 52] (ii) Dendritic and axonic ramifications were studied with silver impregnation methods by Ramón y Cajal and, more recently, by Lorente de Nó,[see 52] Colonnier,[31] and Scheibel and Scheibel.[129] Further insight into cortical function has been gained by investigating thalamocortical projections to specific regions and efferent projections from them using stains for degenerating myelin sheath (Marchi) and degenerating axon terminals (*e.g.,* Nauta-Gygax and Fink-Heimer Nauta silver stains). Collectively, these anatomical studies provide a structural framework within which functional studies—ablation, stimulation and recording of potentials—can be interpreted. More recently, axoplasmic transport of labeled amino acids (orthograde) and of horseradish peroxidase (retrograde) has aided in tracing the destination and origin of neurons. (iii) The electron microscope has revealed the fine detailed structure of cortical synapses.

The cerebral cortex is divided into two major categories: (i) allocortex (three-layered and rhinencephalic) and (ii) neocortex. Two types of cells, pyramidal and granular, are the main cells of the neocortex. The pyramidal cells (Figs. 3–1 and 3–2), varying greatly in size, have a long apical dendrite directed to the cortical sur-

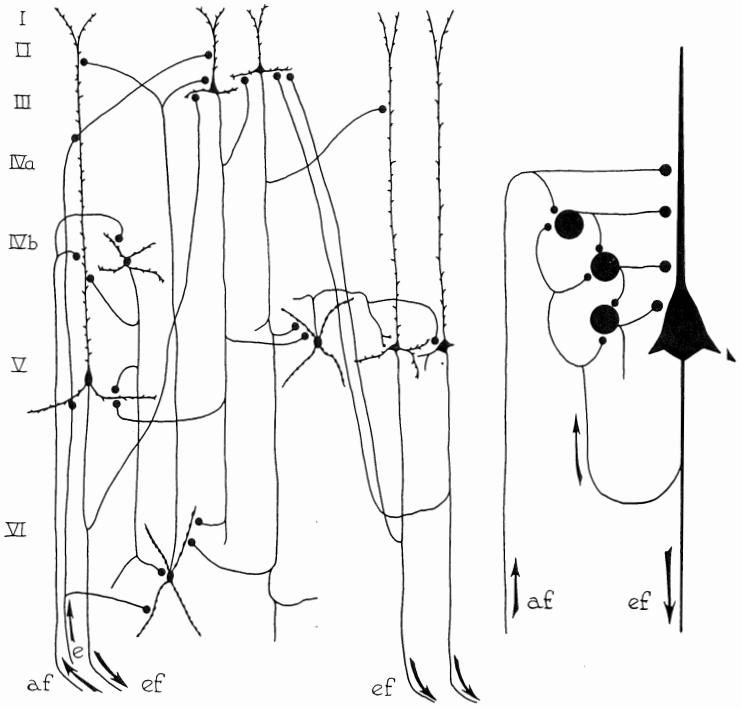


Figure 3–1 Some intracortical neuron chains. Many dendrites and axonal branches have been omitted. Synaptic junctions are indicated by spherical thickening of axon. *af*, axon entering cortex; *ef*, axon leaving cortex; *e*, axon of a cortical association cell originating in layer VI, outside diagram. At right is a simplification of diagram at left. Afferent fiber activates large pyramidal cell and also a system of cortical internuncial cells; recurrent collateral of *ef* delivers impulses again to internuncial system. Roman numerals at left indicate cortical layers. (After Lorente de Nó in Fulton, *Physiology of the nervous system*, 3rd ed. New York, Oxford University Press, 1949.)

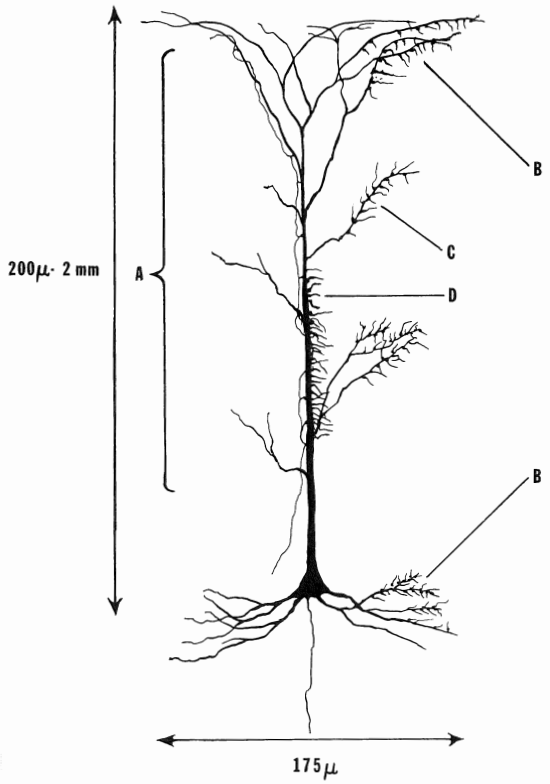


Figure 3–2 A cortical pyramidal cell showing the differential inputs to various terminals. Input to *A* from nonspecific reticular and thalamic afferents; *B*, recurrent collaterals from other pyramidal cells; *C*, callosal fibers; *D*, specific afferents from thalamic sensory nuclei. Note that the dendrites make a roughly cylindrical formation. Dimensions are shown by the arrows. (After Scheibel and Scheibel, from Chow *et al.*, *Neurosci. Res. Prog. Bull.*, 1970, 8, 157–220.)

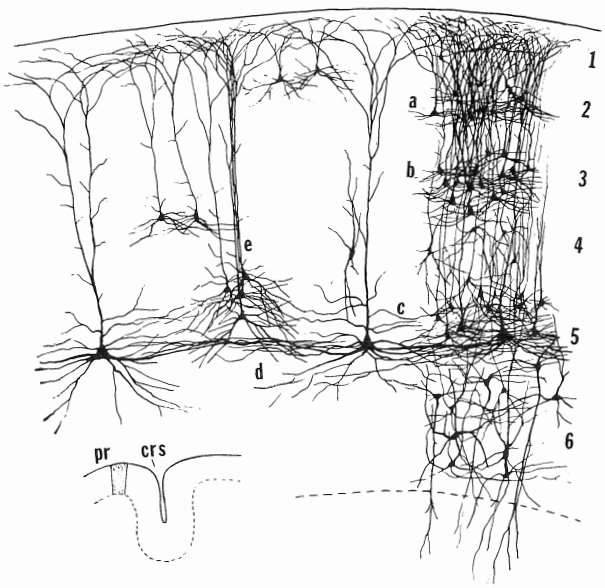


Figure 3–3 Dendritic layers (*a*, *b*, *c*) of precruciate (*pr*) gyrus (adult cat). Numbers at right are cortical layers. Note concentration of horizontally oriented basilar dendrites of pyramidal cells in layers 2, 3 and 5; note the long lateral dendrites of Betz cells (*e*) in layer 5 organized into bundles (*d*) running transversely as do apical dendrites. (From Scheibel *et al., Exp. Neurol.*, 1974, *42*, 307–319.)

face before spreading laterally and short basal dendrites issuing from the cell body. The granule, stellate or Golgi Type II cells have bushy dendrites and axons, and act over short distances.

On the basis of cell and fiber constitution, anatomists distinguish six layers within the neocortex. These may be summarized as follows (see Figs. 3–1 and 3–3):

I. The molecular or superficial plexiform layer. This layer lies immediately beneath the pia-arachnoid and is sparsely populated with nerve cell bodies (horizontal cells of Cajal); its major components are apical dendrites and axons from neurons lying in deeper layers (cells of Martinotti).

II. The external granular layer, or the layer of small pyramidal cells, the latter with apical dendrites terminating in the molecular layer. The axons arising from the basal side of the cell project inward, passing through the white matter of the cerebrum to other cortical areas as association fibers. The other cells in this layer belong to the short axon group called Golgi type II or granule cells.

III. The external pyramidal layer contains larger pyramidal cells, similar to those in layer II.

IV. The internal granular or stellate cell layer, composed of many small multipolar cells. Some have short branching axons, others have long lateral axons but end intracortically. They make up the outer band of Baillarger. All axons terminate intracortically. These cells receive endings of afferents from "specific thalamic" nuclei.

V. The deep layer of large pyramidal cells contains the large (Betz cells) and medium-sized pyramidal-shaped cells. Their long apical dendrites project upward to layer I; their axons pass to subcortical structures; those projecting to the spinal cord contribute to the pyramidal tract.

VI. The layer of fusiform or spindle-shaped cells contains cells more irregular in form than the pyramidal cells and their axons pass into the white matter of the cerebrum and possibly join the pyramidal tract. Their dendrites ascend into the layers of pyramidal cells. This layer also contains some Golgi type II cells.

The relative development of each layer differs from one area of the cerebral cortex to the next. These differences serve to distinguish neocortex as (i) homotypical (having all six layers), (ii) granular (having well developed layer IV) or (iii) agranular (no layer IV). The total number of cells in the human cerebral cortex is estimated to be 2.6 billion.

Physiological Deductions from the Histology of the Cortex. Ramón y Cajal see 119a described some general anatomical features having important physiological implications. First, every area of the cortex receives incoming impulses and gives rise to outgoing impulses; every part of the cortex is, therefore, both the terminal of an afferent path and the beginning of an efferent path. Second, there are provisions for the spread of impulses horizontally. A given area, in addition to discharging caudally over its own efferents, may transmit impulses to another area and discharge over the latter's efferents. Third, as noted, all parts of the neocortex are described as having or departing from a basic structure,

the six-layered cortex. Thus, sensory cortex is usually granular and motor cortex is agranular.

Specific and Nonspecific Afferents. Layer IV of the cortex is a major receptive layer, since the *specific thalamocortical afferents* from relay nuclei mainly end there in a dense compact axon brush without giving off collaterals in the deeper layers. The *nonspecific thalamocortical afferents* arising in nonspecific thalamic nuclei begin to give off horizontal collaterals while still in the white matter; these turn and ascend through the cortex to the outermost layer, ending in terminal branches, which also run horizontally. Because of this dual system of branching, the nonspecific afferents terminate in blocks of cortex. Axons linking cortical areas to each other originate in III, V and VI and terminate in several layers.

The Vth layer is the main "efferent or output layer." For example, Layer V contains all the cells of axons that enter the pyramidal tract as indicated by retrograde transport studies.[33] The apical dendrites of the pyramidal-shaped cells (Fig. 3–2) in these layers ascend, giving off collaterals; a dense tuft of dendrites, issuing from the base of the cell body, may spread laterally or obliquely downward, presenting a far greater area for synaptic contact than the cell body itself. Thus, the pyramidal cell, having a variety of inputs at its various dendritic sites, must integrate them. The pyramidal cells as a class represent the "final common path" for much of the cortical output.

Interneurons. As shown in Figure 3–1, a cortical afferent (af) may directly connect to a cortical efferent (ef); however, through collaterals to cortical cells with short dendrites and axons (cortical interneurons), cortical afferents can effect polysynaptic connections with the same or other efferent neurons. Moreover, the recurrent collaterals of cortical efferents end on other neurons of the same type, forming circular chains capable of re-excitation or "reverberation" (Fig. 3–1, right), a pattern with important physiological implications. *Interneuron* is a generic term including stellate cells and Golgi type II cells. Lorente de Nó[see 52] pointed out that, from mouse to man, cortical cells with short axons increase in number more often than do cells with long ascending or descending axons.

Details of Cortical Neuronal Organization.[20, 28, 31, 129] On the basis of dendritic configuration, Colonnier[31] recognized two basic cortical cell types, (i) pyramidal and (ii) stellate cells. The pyramidal or conically shaped cell bodies give rise to a long apical dendrite, which ascends to and branches in the most superficial cortical layer, and to thick short basal dendrites arising from the ventral end of the cell body. These basal dendrites form a conspicuous lamina in all three pyramidal layers, II, III and V (Fig. 3–3). The basal dendrites of Betz cells may spread over 2 mm, farther than those of other pyramidal cells or of the tangential branches of their own apical dendrite. Both apical and basal dendrites are rich in dendritic spines. The tangential axons in layer I appear to originate mainly in layers V and VI, and some have a spread of several millimeters. The lateral spread of axons in other layers is less than a millimeter.

Pyramidal tract neurons, which happen to be pyramidal in shape, are found in layers V and VI and also give rise to recurrent axon collaterals. Smaller pyramidal cells, which give off descending axons but presumably not long ones, are found in V and VI as well as in layers II and III.

The second class of cells, stellates, has several subvarieties. They are especially concentrated in layer IV of the cerebral cortex and are characterized by dendritic branching with thin processes arising abruptly from the oval or circular shaped cell body. These cells have beaded and often spineless dendritic processes and tend to send axons only a short distance, although some project to the white matter or ascend to layer I. Stellate cells are of particular interest because the axons from cells in specific relay thalamic nuclei end with a lateral terminal spread of only two thirds of a millimeter, predominantly on stellate cells. Specific afferent fibers make very little contact with the small pyramidal cells of layers II and III and not much *direct* or monosynaptic contact in layers IV and V. In contrast, association fibers from other cortical areas end in all layers except I.

Cell bodies of cortical neurons, especially of primates, appear to be arranged in distinct vertical or slightly curved columns of cells separated by ascending and descending axons. Most neuroanatomists agree with this statement,[31] some support it with reservations[18] and a few

challenge it (Ramón-Moliner[see 28]). Colonnier[31] states that "the anatomical columns are not distinct, separate morphological entities" but a physiological phenomenon. It must be kept in mind that columns of cells surrounded by ascending and descending axons may represent mere wiring convenience. That the columns are homogeneous in some functional property (modality of input, topographical locus of receptive fields or both) is widely but not universally accepted by neurophysiologists. Von Bonin and Mehler[18] emphasized that pyramidal cells seemed to have dendrites and terminal axons passing across the 80 μ neuropil space, both making for interaction (and possibly functional heterogeneity) and that columns both fused and split apart. The tangential spread of basal oblique and apical terminal dendrites is estimated at 400 to 600 μ[31] or greater, 2 mm larger than the width of anatomically defined columns, perhaps as large as several columns; the spread of apical dendrites in layer I is put at 1 to 3 mm. Scheibel *et al.*[129] emphasize that basal dendrites group themselves into bundles, which spread to one or more adjacent columns, including dendrites from them, providing a two-way connection. Dendrites interact in some fashion not yet understood. The spread of stellate cells is still larger—several millimeters. Chow and Leiman's[28] figure for the spread of specific thalamocortical afferent terminations (200 to 500 μ diameter) could fall within a column whereas nonspecific afferents could not (1 to 3 mm spread). Scheibel *et al.*[129] suggest, on the basis of average distance between Betz cells, that they form the core of a column and their basal dendrites spreading to neighboring columns may integrate the activity of different columns. Combining figures for column width[18] and basal dendrite spread, a dozen columns could be integrated.

Electron microscopy is providing further details concerning the synaptic structures in the cerebral cortex. The number of synapses is enormous, estimated to average about 60,000 synapses per neuron in the monkey motor area.[31] Two types of central synapses can be distinguished. Type I is characterized by an asymmetrical membrane thickening (increased density of the postsynaptic membrane), a wide synaptic cleft containing a dense extracellular material and synaptic vesicles in the presynaptic neuron termination. This Type I synapse is found especially on dendritic spines and dendritic trunks, with the presynaptic element arising from ascending axons. The second or Type II synapses have less pronounced structural characteristics than Type I, having a thinner cleft free of dense material and lacking postsynaptic membrane thickening. Most type II endings originate in stellate cells of layers III and IV and are found on cell bodies and the base of dendrites; many are the terminals of pericellular baskets investing the pyramidal cells. These endings have been likened to the close pericellular investment of the inhibitory basket cells of the cerebellum. Type I synapses are probably excitatory, while Type II synapses may be inhibitory. Other intracortical cells have a climbing axonic connection making multiple contacts with the apical dendrites of pyramidal-shaped cells. It has been suggested that such multiple contacts underlie a powerful synaptic action. Altogether, the terminal to neuron configuration in the cerebral cortex is simpler than arrangements seen in many other neural structures.

Colonnier[31] summarizes the picture resulting from light and electron microscopy study of the cortical cells somewhat as follows. The axons originating in specific thalamic nuclei end upon the fusiform stellate neurons, with long vertical axon making a climbing fiber contact with the apical dendrites of pyramidal-shaped cells and also activating other stellate cells with vertically coursing axons, thus spreading the excitation throughout the cylinder or column of cortical neurons. The basket cells with their horizontally and more widely coursing axons, if inhibitory as in the cerebellum, would result in a cylinder of excited cells surrounded by a field of inhibited pyramidal cells.

Cortical Sulci, Gyri and Cytoarchitecture. The cerebral cortex of monkeys commonly used in the laboratory differs from one species to another, ranging from the nearly lissencephalic cortex of the squirrel monkey (*Saimiri sciureus*) to the intricately convoluted cortex of the chimpanzee (*Pan*). The most elaborate and extensive cortex is man's. Intermediate in complexity is the fissuration of the commonly used monkeys from the genera, *Macaca, Cercopithecus, Cercocebus* and of the baboon (*Papio*). The brains of these nonhuman primates (Figs. 3–4 and 3–5) possess the basic sulci and gyri of man's cortex but differ in pattern as described in the legend of Fig. 3–5. The sulci and gyri of primates differ markedly from those of the cat but similar cytoarchitectural fields (Fig. 3–6) can be recognized in both. Figure 3–7 is a reference diagram showing the body representation in relation to gyri and sulci. Figures 3–8 and 3–9 will serve as a reference atlas for the cat, to be consulted in connection with the text.

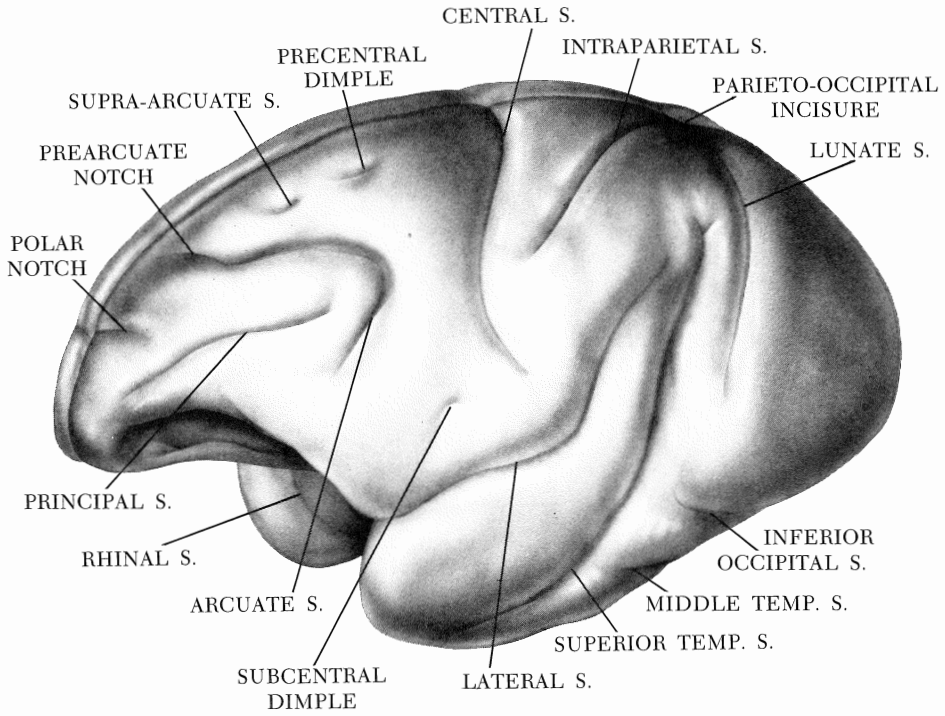


Figure 3–4 Drawing of the monkey brain to aid in visualizing Figures 3–5 and 3–7. (From Talbot *et al., Behavioral science in pediatric medicine.* Philadelphia, W. B. Saunders, 1971.)

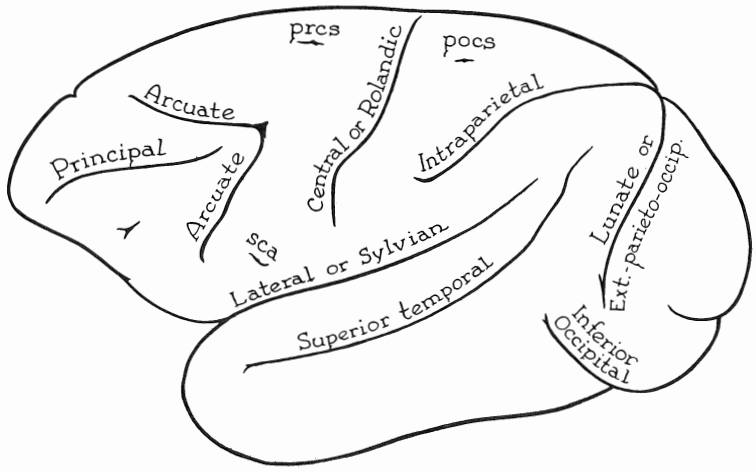


Figure 3–5 Sulci of the left cerebral hemisphere of *Macaca mulatta.* Note following differences from human brain: (i) fewer and less complex sulci, (ii) smaller prefrontal lobule, (iii) ascending course of intraparietal, lateral and superior temporal fissures resulting from (iv) lesser development of posterior parietal region, (v) lesser development of the superior precentral (*prcs*) and postcentral (*posc*) sulci. Sulcus subcentralis anterior (*sca*) may correspond to the human inferior precentral sulcus. (After von Bonin and Bailey, *The neocortex of Macaca mulatta.* Urbana, University of Illinois Press, 1947.)

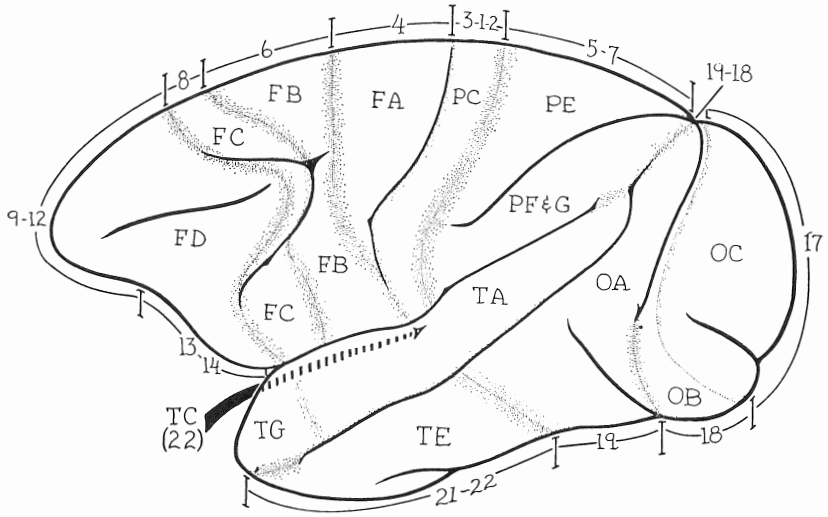


Figure 3–6 Cytoarchitectural map of monkey brain approximately relating terminology of Brodmann (*numbers*) to that of von Bonin and Bailey (*letters*). Broad dotted zones indicate boundaries not defined by fissures and suggest that areas shade into one another. (After von Bonin and Bailey, *The neocortex of Macaca mulatta*. Urbana, University of Illinois Press, 1947.)

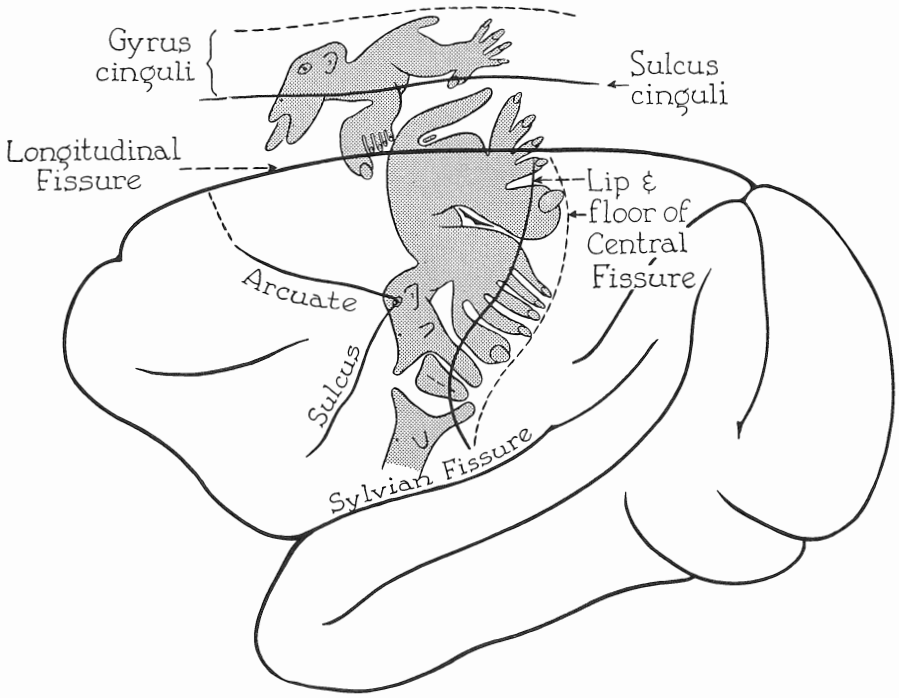


Figure 3–7 Somatotopic organization of primary and supplementary motor areas. Note that central and longitudinal fissures are shown "opened out" with dotted line representing floor of a fissure and solid line lip of fissure on brain surface. At lateral end of precentral gyrus is a second face area MII. In the bay formed by foot, hand and abdomen representation is the precentral dimple, the anterior border of area 4. Much of the primary simunculus and virtually all of supplementary area falls in area 6. (After Woolsey *et al.*, *Res. Publ. Ass. nerv. ment. Dis.*, 1952, *30*, 238–264.)

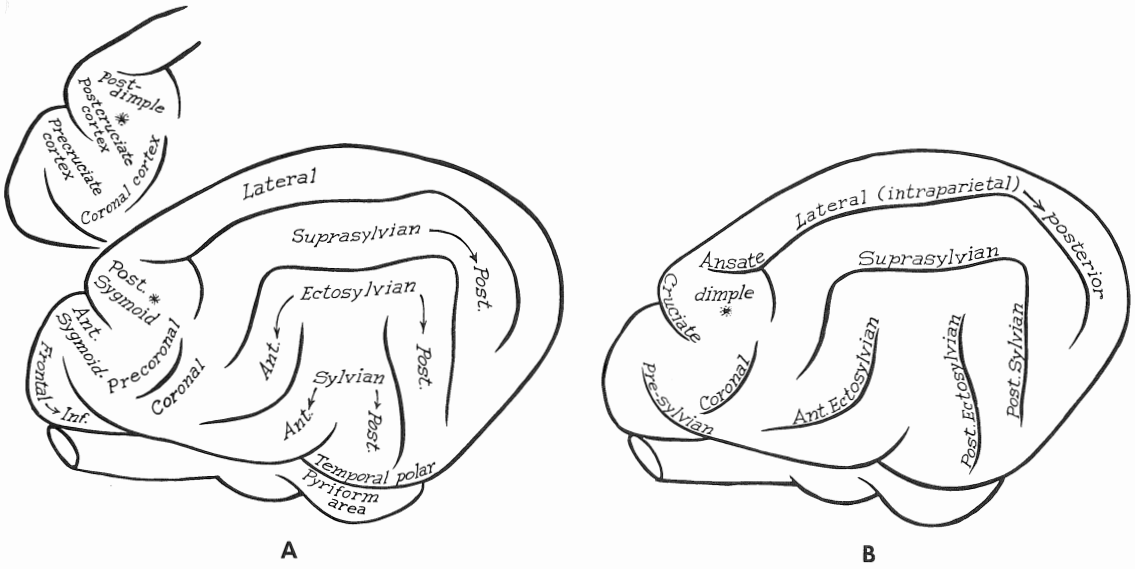


Figure 3–8 *A*, gyri of cat's cerebral cortex. Insert in upper left gives an alternative terminology for frontal pole gyri commonly used in physiological literature. Note that a new term, "precoronal" area, has been introduced in this figure. *B*, sulci of cat's cerebral cortex. Both gyri and sulci vary considerably from cat to cat. (Courtesy of A. Towe.)

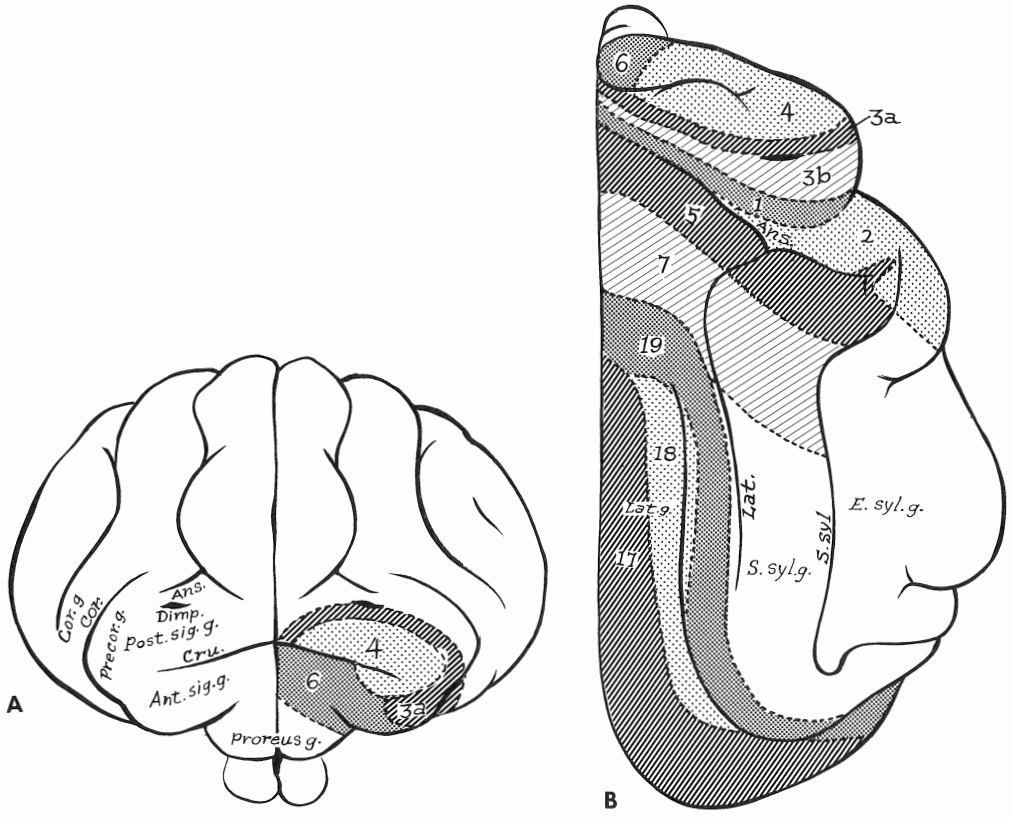


Figure 3–9 Cytoarchitectural fields of cat's cerebral cortex seen from fronto-dorsal view (*A*) and dorsal view (*B*). *Sig. g*, anterior and posterior sigmoid gyrus. (The lateral post sig. g. is renamed precoronal g.) *Cru*, cruciate sulcus, *Dimp*, postcruciate dimple; *Eor* and *Cg*, coronal sulcus and gyrus; *Ans*, ansate sulcus. Numerals are comparable to Brodmann areas. (After Hassler and Muhs-Clement, *J. Hirnforsch.*, 1964, 6, 377–420.)

Although cytoarchitectural makeup offers few clues to function, major differences between cytoarchitectural fields often demarcate functional boundaries established by other means. However, every small cytoarchitectural difference does not imply a functional difference, nor does each function require a unique cytoarchitecture. Some students of cytoarchitecture have overzealously divided the cortical layers into more and more sublayers and the cortical areas into smaller and smaller subareas. Many of these proposed divisions, almost always based on subjective and nonquantitative criteria, could not be verified by a second observer looking at the same sections. Many cytoarchitectural boundaries are not constant from animal to animal, and variations often result from distortions produced mechanically by the cortical folds, which differ notoriously from brain to brain within a species. It is interesting that the revolt against excessive parcellation was initiated by two psychologists[81] rather than by neuroanatomists.

The reverse side of the coin is that some cytoarchitectural areas and even *subareas* have proved to have different physiological properties. This is especially true of the visual, auditory and somatosensory areas. For example, subarea 3a appears to receive specific projections from muscle afferents, while area 3b receives input from cutaneous afferents. However, only in broad outline can function be correlated with cytoarchitecture, *e.g.*, sensory granular (koniocortex) vs. agranular motor cortex.

Experiments on the cerebral cortex are often described in terms of fissures, sulci, gyri, and lobules* and lobes. Cytoarchitectural maps provide an additional language to describe the cortex, a language that is often more compact and detailed than morphological descriptions. It is virtually impossible to follow present and past experimental literature without knowledge of brain maps.

In the interpretation of cytoarchitectural maps it should be realized that the boundaries are usually not sharp; instead, one type of cortex blends into another. Brodmann's numbers[20] can be modified to conform to physiological studies, for example, 3a and 3b. Certain physiological studies indicate that area "1a" may be needed to designate the anterior part of that area abutting on area 3b. Areas may also be combined, *e.g.*, area 3–1–2 for somatosensory cortex. Similarly, use of "areas 9–12" reflects skepticism of the significance of the subareal differences in the prefrontal lobule but describes a region for which there is no other generally accepted term, since some object to the word "prefrontal." In the figures and usages here, the letters signify von Bonin and Bailey's terminology;[18] the initial letter denotes the lobe and the second letter, in alphabetical order, denotes a subarea in that lobe. The numbers are those of Brodmann, which are most frequently used in describing animal experiments. Some of the areas concerned with motor function are discussed in detail in this chapter; others are described in later chapters.

The Brodmann numbers can be remembered more easily by knowing how they were assigned. His monkey brain was cut horizontally beginning at the vertex so the precentral and postcentral regions appeared in the first few sections and received the low numbers (1 to 8), jumping from front to back as different cytoarchitecture was encountered. Thus areas 1 and 2 were encountered on the crown of the postcentral gyrus (Fig. 3–6). Area 3, deepest in the central gyrus, received number 3, giving the puzzling 3–1–2 sequence. The rostral wall of the central fissure and the crown of the precentral gyrus were designated area 4, followed by the parietal association areas 5 and 7, forward against the premotor area 6 and the frontal eye fields 8. The next important numbers, 9 to 12, are frontal; 17 to 19 are occipital; 20 to 22 are in the temporal lobe.

Area 4 (FA) is agranular cortex beginning in the depth of the central fissure and extending up its anterior bank onto the free surface of the precentral gyrus. Here the gray matter is thick (3.5 to 5.0 mm). The giant pyramidal cells of Betz in the fifth layer constitute the major basis for determining the anterior border. Because the size necessary to qualify a cell as a Betz cell is not agreed upon and they do not exist in the inferior part of area 4, the forward boundary is not definitely established.

Brodman's *area 6* corresponds roughly to *FB* and *FA*, although the posterior boundary, as noted, remains unsettled. In this area, the cortex is still thick and agranular, but lacks giant pyramidal (Betz) cells in the fifth layer.

Area 8, corresponding to *FC*, considerably

*There are four lobes: frontal, parietal, occipital and temporal (Fig. 3–5). All smaller divisions are lobules, areas or gyri. Major cortical infoldings are often termed fissures; minor ones, sulci.

modified in shape since Brodmann, is a transitional band with a poorly developed internal granular layer. On the lateral surface, *area 8* is largely buried in the two limbs of the V formed by the arcuate (syn. principal) fissure, but issues from it laterally and medially. The remainder of the frontal lobe (*area 9–12* or *FD*) is uniform in structure, except for an area around the posterior end of the principal sulcus.

Areas 3 and 1 (PB, not designated on map) lie almost entirely buried in the depth of the central fissure and are easily recognized. Like other primary sensory areas, *areas 3b* and *1* are koniocortex ("dusty cortex," referring to their highly granular nature), while *3a* is considered transitional between *areas 3b* and *4. PC,* occupying the free face of the postcentral gyrus, loses the excessive granulation and becomes homotypical, *i.e.,* all six layers are present and none is over- or underdeveloped. Von Bonin and Bailey hold that *area 2* is nonexistent. The posterior boundary of area *PC* lies somewhat anterior to the superior postcentral fissure. The two terminologies can be made congruent by speaking of *Brodmann areas 3–1.*

PYRAMIDAL (PT), EXTRAPYRAMIDAL (EPS) AND PARAPYRAMIDAL (PPS) SYSTEMS*[82, 106, 118, 143, 152]

Views on the functions and anatomy of the pyramidal tract (PT) have been so radically revised in recent decades that we are virtually without a language to discuss the descending motor systems. By definition, *the PT consists of those axons which originate in the cerebral cortex and pass to the spinal cord through the medullary pyramids.* It is only coincidental that the tract originates in pyramid-shaped cells. The term "pyramidal tract" in no way implies axons originating from such cells; in fact, the tract was named before the shape of the cells of origin was known! Axons from the cortex to the cranial motor nerve nuclei are functionally similar to those going to spinal segments. Although such fibers obviously do not pass through the pyramids, they should not be confused with COEPS fibers as defined below.

*The prefix *para,* meaning "beside" or "beyond," among other usages, is adequately vague for this purpose. Usage is generally to speak of the pyramidal *tract,* but the extrapyramidal *systems.* It is equally justifiable to speak of the pyramidal system in view of the extensive "cross overs" to extrapyramidal and efferent pathway nuclei.

The dichotomy implied by the terms "pyramidal tract" and "extrapyramidal system" is much criticized, which is justified if they are regarded as completely distinct anatomically or physiologically. While the PT can be clearly defined as those axons originating in the cerebral cortex and passing through the pyramids, axons of cells comparable to pyramidal tract neurons (PTN's) passing to cranial motor nuclei have no good name. Corticobulbar and corticonuclear, both sometimes used, could mean axons passing to either class of brainstem nuclei (those giving rise to descending pathways and those to motor cranial nerves), and not all cranial motor nuclei are in the bulb (medulla oblongata). PT cells also influence the extrapyramidal system via collaterals to subcortical nuclei, some of which originate descending tracts to spinal neurons, principally the red nucleus and the reticular formation (Fig. 3–10). Corticofugal fibers project directly and by collaterals to the caudate and other basal ganglia nuclei, and to the pontine nuclei. Clearly, the two categories, PT and COEPS (**C**ortically **O**riginating **E**xtra**P**yramidal **S**ystem) defined below leave many descending motor connections that are neither one nor the other, namely, the collaterals of PT axons to subcortical nuclei. As noted, some of these subcortical structures are involved in recurrent pathways to the motor cortex, but others have a direct or multisynaptic pathway to the spinal cord. These collaterals clearly originate from PTN's, but terminate on subcortical neurons; therefore they cannot be called either PT or COEPS. Such collaterals and their descending relays will be termed "parapyramidal system" (PPS) as needed (Fig. 3–11).

The PT cannot even be called exclusively a motor tract since it ends on sensory relays in the dorsal column nuclei and spinal cord (see Chap. 6, Vol. I). Thus, "Even in the decussation, the tract is hopelessly contaminated with other functional systems."[106] The concept of an extrapyramidal system suffers from being a catchall, "all else except the cortically originating axons passing through the pyramids (PTN's)." The extrapyramidal system was long considered an independent subcorti-

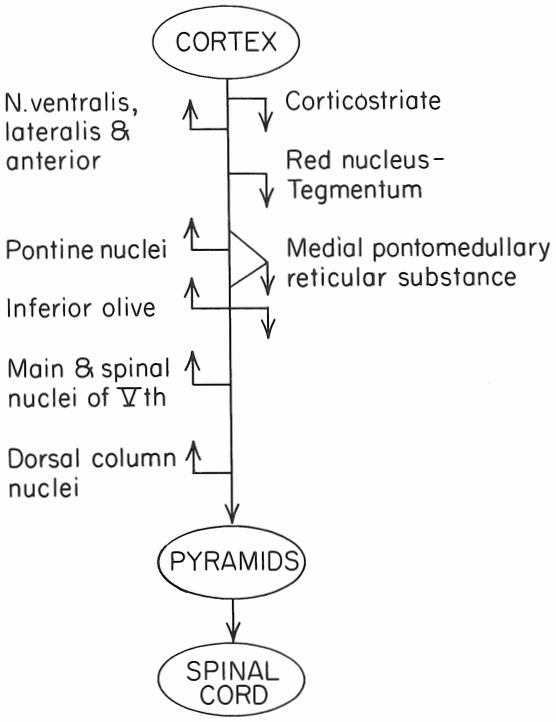


Figure 3–10 Connections of the PT with subcortical nuclei giving rise to descending (*right*) and ascending (*left*) projections. Similar connections are assumed to be made by corticonuclear fibers.

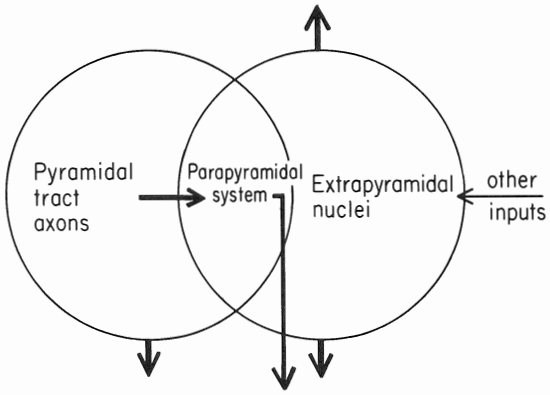


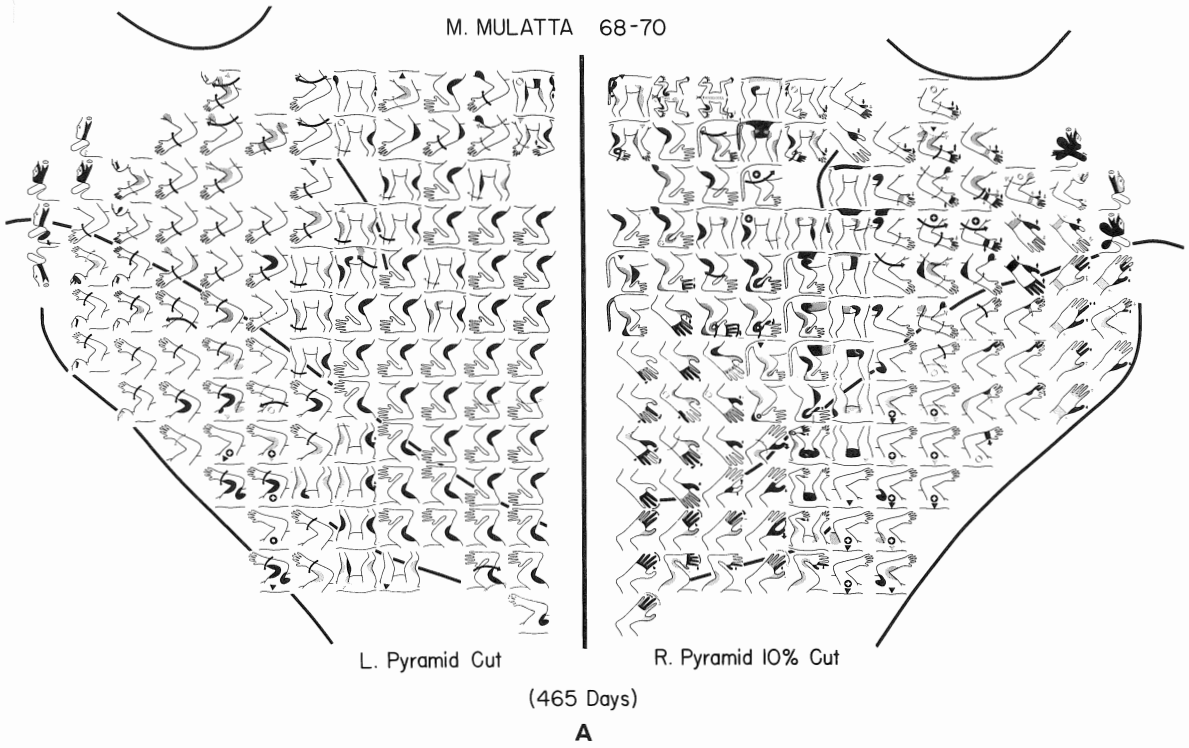
Figure 3–11 Diagram to illustrate terminology for the concept of overlapping pyramidal and extrapyramidal systems via PT collaterals. Downward arrows indicate projections to spinal cord and upward arrows projection to cerebral cortex. It defines a new phrase, "Parapyramidal System" (PPS).

cal system, a thought inherited from the 19th century, but this concept became untenable when the existence of the COEPS became appreciated. Similarly, structures labeled "extrapyramidal" are known to project up to the cerebral cortex, either directly or via the VL-VA nucleus of the thalamus, thus influencing cortical PTN's. With these reservations in mind, the terms may be used (there being no substitutes), if for no other reasons than to identify "extrapyramidal" neurological diseases.

The existence of COEPS is shown by the persistence of a somatotopically organized motor output from motor-sensory cortex after PT section, as demonstrated by Woolsey *et al.*[155] After (465 days) sectioning the PT unilaterally in monkeys, they mapped the movements evoked by stimulating the cortex on both sides (Fig. 3–12*a*). Movements elicited from the normal side, with PT intact (right side, Fig. 3–12), were diverse and many involved distal joints; their cortical distribution is in general agreement with the summary map of Figure 3–7. Movements could also be evoked by stimulating the cortex with the PT sectioned (left side). These movements, mediated by the PPS and COEPS, were more restricted, involving mainly proximal joints and required stimulus intensities two to three times higher than the side with intact PT. These experiments clearly demonstrate an output via PPS and COEPS that also has a rough somatotopic organization in both pre- and postcentral cortex.

To summarize, as seen in Figure 3–12*b*, the descending motor systems of the cerebral cortex can be divided into three classes: (i) the pyramidal tract, (ii) parapyramidal system (PPS)—collaterals from PT to subcortical nuclei that project to the spinal cord—and (iii) the cortically originating extrapyramidal system (COEPS) (see Fig. 3–11). A fourth category is the recurrent extrapyramidal system, which includes the basal ganglia and other subcortical nuclei having inputs besides PPS and the COEPS and projects to the cortex.

PT: Fiber Spectrum.[82, 143] Most of the fibers in the pyramids arise from cerebral cortex cells, since decortication apparently produces complete degeneration in the pyramids. That the pyramidal tract arises solely in the giant Betz cells is a mis-



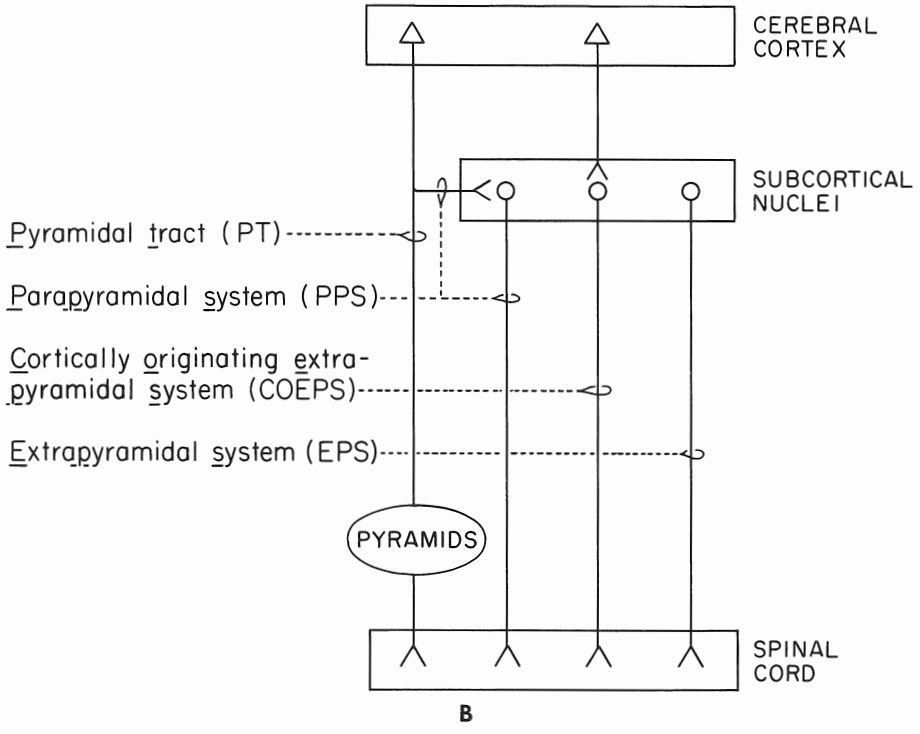


Figure 3–12a. A, Figurine map illustrating movements evoked by electrical stimulation of pre- and postcentral cortex of monkey with a unilateral PT section. Figurines are located at cortical points which evoked the indicated movements. Right hemisphere had most of PT intact; left hemisphere had PT sectioned. Bottom diagonal line is intraparietal sulcus; middle diagonal line is central fissure, and curve at top is arcuate sulcus and heavy line three rows down is the precentral sulcus. From Woolsey et al., *Brain Res*, 1972, *40*, 119–123.

Figure 3–12b. Summary diagram illustrating four categories of descending systems from brain to spinal cord.

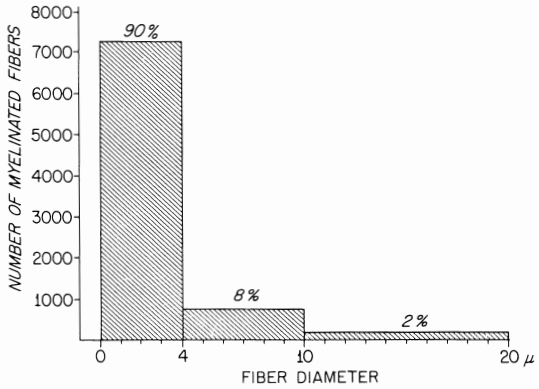


Figure 13–13 Myelinated fiber spectrum of pyramidal tract. (After Lassek, *J. comp. Neurol.*, 1942, *76*, 217–225.)

conception; the tract arises mainly in layer V from small pyramidal cells. In man, the motor area of each hemisphere contains approximately 34,000 Betz cells, enough to account for the 2 per cent of fibers with large diameters ranging from 11 to 20 μ, but not nearly enough to account for the 1.3 million axons in medullary pyramid. Figure 3–13 shows the distribution of the diameters of the myelinated fibers, which constitute the major portion of the PT.[82] The remaining six per cent of the fibers in the tract are unmyelinated and little is known of their origin and function.[34] Towe[143] has summarized the information on the number of axons in the medullary pyramids somewhat as follows. The fiber counts vary widely between studies and even within a given study. The highest counts are in man (1,000,000), chimpanzee (800,000) and the seal, which lacks digits (748,000). The macaque with 400,000 fibers is outranked by the spider monkey (505,000) perhaps because of its prehensile tail. Cats have 186,000 PT fibers. The number of PT fibers is related directly to the square root of body weight. In relation to weight, man has no special superiority in the number of PT fibers, and the discrepancy in favor of the macaque over the cat is reduced.

Although many PT fibers originate in the primate motor cortex (area 4), that the PT originates exclusively there is also a misconception (Figure 3–14). The proportion of fibers originating from the monkey's pre-

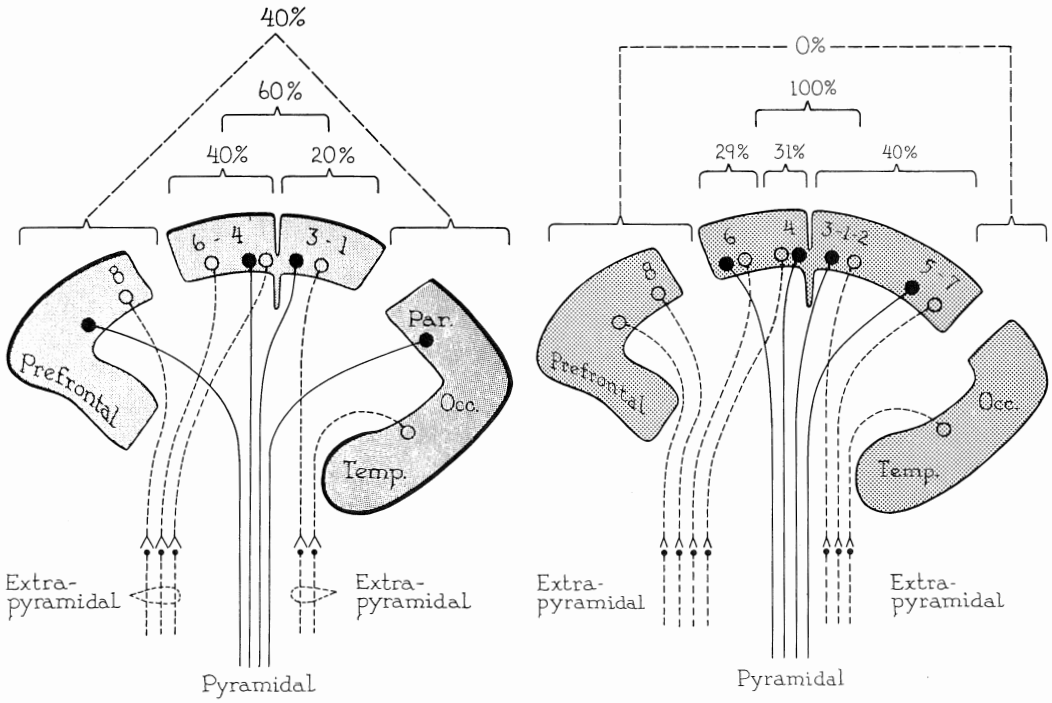


Figure 3–14 Two versions of the origin of the PT and COEPS. Note the overlapping of the two systems even in area 4. The percentages refer to the origin of the PT axons. The differences between the two versions, especially the projection from area 6, depend on a putative longer time for degeneration of fine fibers from area 6. (*Left*, based on data from Lassek, Mettler, and others; *right*, based on Russell and DeMyer, *Neurology*, 1961, *11*, 96–108.)

central gyrus by the most recent estimates[127] is 31 per cent, and that from area 6, contrary to many previous estimates, is put at 29 per cent (Fig. 3–14), undoubtedly too large; retrograde enzyme transport studies show no corticospinal fibers arising in area 6 of the monkey.[33] The 40 per cent of medullary PT axons not originating in areas 4 and 6 arises from the postcentral gyrus and the posterior parietal lobule. The parietal contribution has been confirmed by retrograde axon transport studies[33] and is distributed to the medial portions of the dorsal laminae of the spinal cord.

A recent determination for man based on the results of surgical excision of area 4 was much higher—60 per cent. The prefrontal, occipital and temporal lobes are now not thought to contribute any fibers to the PT. Earlier estimates ascribed a significant share of fibers to these areas because pre- and postcentral gyrus lesions left some 40 per cent of fibers undegenerated. Recent studies indicate that axonal degeneration and disappearance require not a few weeks, but a year. PT axons from the central gyri late to disappear were ascribed to origins other than the motor and sensory areas.

Extrapyramidal Systems (EPS)* from the Cortex. As mentioned briefly above, overlapping with the origin of PT projections are those to a wide range of subcortical structures (COEPS) including the brain stem reticular formation (Chap. 4, Vol. I). The PT axons also give collaterals to some of these same structures so that cortically originating impulses could reach the segmental level directly and indirectly and can both *effect* and *affect* movement. COEPS pathways differ from the pyramidal system in two ways: (i) the chains of neurons are synaptically interrupted in the basal ganglia, in the brain stem nuclei, or reticular formation before reaching the spinal cord, and (ii) by definition, the descending pathways do not pass through the medullary pyramids. These systems of neurons as defined above are termed the "**C**ortically **O**riginating **E**xtra**P**yramidal **S**ystem," abbreviated COEPS. Since the extrapyramidal system also receives subcortical inputs, COEPS is not a synonym for "extrapyramidal system," but refers to that portion of it which originates in the cerebral cortex. The COEPS pathways may be divided into two categories: (i) those terminating or giving collaterals in a nucleus of the brain stem having well-established pathways to the spinal cord and (ii) those connecting with the basal ganglia having multisynaptic connection with the spinal cord. Excluded would be recurrent basal ganglia pathways. The latter will be treated in more detail in the following chapter.

While the relative size of these systems is uncertain, Towe[144] estimated from several studies that only one third of the PT axons that emerge just caudal to the pons actually project into the spinal cord (PT axons to motor cranial nerve nuclei are few at this level). The major COEPS and EPS pathways may be summarized as follows.

Corticorubral System.[97] Unlike the basal ganglia, the red nucleus (RN) has a well-developed descending tract, suggesting its role in corticofugal functions is more direct than that of the basal ganglia. The projection of nonpyramidal and PT axon collateral fibers from the motor cortex to the red nucleus has recently been recognized as one stage in a cortically originating system physiologically similar in many ways to the PT. Its corticofugal projection is somewhat somatotopically organized, having arm, trunk and leg regions of termination; its descending tract pursues the same column (dorsolateral) as the PT and terminates in the dorsal horn in much the same laminae as does the PT (cat). Further, the PT axons give collaterals to the red nuclei (PPS) and the PT and rubrospinal tract are so similar in spinal course and termination that they are lumped together in the "lateral system" of Kuypers (see Chap. 2, Vol. I).

Corticostriatal and Corticopallidal Projections. Glees,[57] using a silver stain, early demonstrated fine connections from cortex to basal ganglia in cat and monkey. Once doubted,

*There are many objections to this term and it was reluctantly used in the abbreviation COEPS. Once considered separate from the PTS, it is now known that the EPS and PTS are intermingled at the cortex, the basal ganglia (itself a defective term) and the spinal cord. The basal ganglia form the largest share of the EPS. Since the major output of the basal ganglia consists of recurrent projections to the cerebral cortex, it is incongruous to label them "extrapyramidal." Perhaps viewed as a *functional* system, the abbreviations rEPS and rCOEPS could be useful to designate recurrent basal ganglion systems and VA-VL of the thalamus. The abbreviation spEPS and spCOEPS, meaning spinal cord-directed systems, could include the red nucleus. It is generally recognized that there is no solution to these terminology problems at this time.

these corticocaudate and corticoputamenal projections have been abundantly demonstrated in recent years in primates.[74] In the chimpanzee they arise in area 4 and none pass to the pallidum, although the pallidum receives second order COEPS input via the corpus striatum.

Corticothalamic Projections.[50] The EPS strictly defined does not include the thalamus but certain of its nuclei have clearly motor functions. In general, a specific cortical area sends fibers to the thalamic nucleus from which it receives fibers. This reciprocal arrangement applies to the motor cortex as well as to the sensory and the association cortex. The cerebral cortex, especially some areas, projects to the thalamic nuclei most concerned with movement, n. ventralis lateralis and anterior, which project heavily to the precentral gyrus and receive input from the cerebellum and the globus pallidus.[76] The precentral gyrus also projects to medial thalamic nuclei (see Chap. 6, Vol. I), the reciprocal connection providing an avenue to ascending reticular system via the center median.

Subthalamic Nucleus and Substantia Nigra. Both receive an indirect input from the cerebral cortex via the corpus striatum. The COEPS and basal ganglia have few efferent pathways to the spinal cord. Many of their connections are rostral, to the cerebral cortex directly or via n. ventralis lateralis and anterioris and hence, presumably, work in conjunction with the motor cortex, affecting its discharge.

Corticopontine Projections. Each of the four major lobes of the brain projects to the pontine nuclei, which relay impulses to the cerebellum, mainly to cerebellar cortex, which, like the pontine nuclei, has developed para passu with the cerebral cortex in the primate series. The connections of the cerebellum are broadly similar to those of the basal ganglia[74] in that the cerebellar output is heavily rostral. The cerebellum has no direct pathway to the spinal cord. The frontopontine tract is the largest corticopontine input arising equally from areas 4 and 6. Besides conveying impulses to the cerebellum, this important tract in primates is thought to give off collaterals to midbrain structures, *e.g.*, the substantia nigra. According to Cajal, some corticopontine fibers are collaterals of corticospinal fibers. The corticopontine system is often invoked in explaining voluntary movement (see below) constituting with the cerebellum an internal feedback loop.

The COEPS and PPS provide not only multisynaptic pathways from cortex to the spinal cord but also recurrent or internal "feedback" circuits via subcortical structures and back to the cortex.

CORTICAL MOTOR FUNCTIONS

HISTORICAL PERSPECTIVE.* Until the early 1930's the concept of cortical control of movement and the explanation for the paralysis resulting from destruction of corticofugal pathways was simplistic, somewhat as follows. The "pyramid"-shaped Betz cells were thought to give rise to the pyramidal tract; interruption of the tract (usually at its origin or in the internal capsule) by cerebrovascular accident caused paralysis, spasticity and the loss or exaggeration of certain reflexes. All three sequelae were ascribed to the disruption of the pyramidal tract. "Upper neuron" disease (spastic paralysis) was contrasted with "lower motor neuron" disease (flaccid paralysis), simplistic terms still used clinically. A related concept was that the pyramidal tract controlled movement while an independent extrapyramidal (subcortical) system was concerned with posture. A subordinate concept was that the cerebral cortex is concerned with control of striate muscles, but not of visceral structures.

In the early 1930's all of these ideas were disproved, principally by a series of interrelated primate experiments at Yale (Fulton, Kennard, Bucy) and at Johns Hopkins (Richter, Tower, Hines), and by careful clinical observations, such as those of Foerster in Germany. The precipitating observation was that ablation of the primary motor area of the monkey (area 4), though causing paralysis, induced not a spastic but a flaccid paralysis. Marked spasticity and forced grasping occurred when area 6 was ablated, and addition of area 4 ablation augmented the spasticity.

The contribution of area 6 to the PT is uncertain, but it is probably not a major contributor to the PT. The definitive experiments by Tower and Hines involved section of the medullary pyramids in cats, monkeys and a chimpanzee. Consistent with the area 4 ablation experiments, pyramidal section produced flaccidity or no change in tone, certainly not spasticity; moreover, "an impressive capacity for vol-

*Bibliographic citations of an extensive literature will not be given in this section; some will be found in other sections or in several sources, *i.e.*, references 24, 52, 106, giving many citations.

untary movement survived pyramid section." Thus developed the concept of a dual output from the precentral motor cortex: pyramidal and extrapyramidal; the latter, as noted, we have termed the Cortically Originating ExtraPyramidal System, or COEPS. Both the PT and COEPS are involved in producing movement but differ in their relation to muscle tonus, as described below. Subsequent work has refined, reinforced and in some cases modified the conclusion from the early work and is discussed throughout this and the next chapters. The guiding theme in what follows is the partition of function and cooperation between the PT and COEPS.

Stimulation and ablation of motor cortical areas were the main resource of neurophysiologists for more than a half century following the stimulation experiments of Hitzig and of Ferrier. These methods have been steadily refined over the past century, the most recent innovation being intracortical microstimulation.

When the recording electrodes were moved up from muscles and nerves to the cerebral cortex, the epoch of *evoked potentials* was inaugurated by Marshall, Woolsey and Bard. Applied to the cerebral cortex, only simultaneously active *populations* of neurons are studied, sufficient for mapping the body representation, but fundamentally the technique mainly produced knowledge of functional anatomy. With the application of single unit recording to the cerebral cortex almost simultaneously by Amassian in this country, Jung in Germany and Li in Canada, commenced a period of brain studies that might be termed the synaptology epoch, further refined when the ultramicroelectrode permitted intracellular recording, revealing membrane excitatory depolarization and inhibitory hyperpolarization.

A continuing controversy concerned the question of effects of anesthesia, barbiturates vs. chloralose,* one suppressing neural events, the other perhaps revealing too much in the way of neuronal connections. An undercurrent of unhappiness still prevailed among many neurophysiologists when it became apparent that the cat was an aberrant mammalian form yielding results inapplicable to man; some turned to the monkey, now extremely expensive, others to the invertebrates.

One of the most recent developments, the chronic unit recording in unanesthetized monkeys in a behavioral situation, appears to have resolved several problems at once: single units vs. mixed populations, the anesthesia controversy and the economics problem simplified.

Pyramidal vs. Extrapyramidal Systems—Ablation. As indicated briefly in the introduction to the section on Motor Functions, studies of the motor systems in the early 1930's[see 52] by regional cortical ablations (principally by Fulton and Kennard) and by section of the medullary pyramids by Tower and Hines profoundly altered the understanding of such common clinical disorders as *hemiplegia* (paralysis) or *hemiparesis* (weakness) and the accompanying *spasticity.* Neurologists and neuropathologists were handicapped in learning the neuroanatomic basis of hemiplegic signs because capsular lesions inevitably damage the PT, the PPS and the COEP systems. In fact, the same is true of all naturally occurring damage to the PT whether in the cortex, internal capsule, brain stem or spinal cord. That all of the signs of hemiplegia should have been ascribed to disruption of the pyramidal tract is understandable, but neurophysiological analysis has now shown that many classic signs of PT damage are in fact caused by damage to the extrapyramidal system, especially to COEPS.

At first sight, the separation of PT and extrapyramidal function (COEPS and PPS) would seem a simple matter, *i.e.*, (i) by sectioning the pyramids and observing the resulting deficits and degree of subsequent recovery of function and (ii) to section the pyramids and stimulate the motor cortex. However, the phenomenon of facilitation exemplified by spinal reflexes demonstrates that in the nervous system the "whole is greater than the sum of its parts," *i.e.*, while each of two individual inputs may yield virtually no response, their simultaneous activation may yield a large response. A notable example of this is an animal preparation that showed little response to stretch of leg muscle or pressure on the pads of the foot but when the two were combined showed a response many times exceeding the sum of the two

*Sometimes called the "barbitchurators" vs. the "chloralosers."

separate responses. Thus, after the PT system is deprived of support of PPS and COEPS the resulting deficit or responses to stimulation indicate what the PT can do *alone,* and only that; their respective roles when functioning together are not learned from such experiments.

The analysis of the neural substrate of hemiplegia provides a convenient outline for summarizing a large volume of new information on the cortical motor system. As illustrated in Table 3–1, hemiplegia or hemiparesis is manifest in three major categories—(i) movement (paralysis or paresis), (ii) postural reflexes (spasticity and exaggerated deep reflexes), and (iii) other reflex signs (*e.g.,* the Babinski sign). Early workers in the 1930's proved that neither the paresis nor the spasticity from cortical lesions could be exclusively ascribed to interference with the PT because the COEPS is also damaged.[see 24, 52] In the subsequent four decades the contribution of the two systems to voluntary movement has been studied extensively by refined observational, electrophysiological and behavioral techniques. The following pages supplement the tabular summary.

MOVEMENT. The pioneering experiment on ablations of cortical motor areas in monkeys was the first indication of the distinctness of PT and COEPS but could not

Table 3–1 *Syndromes Involving Spastic Paralysis*

I. *Movement*	
1. Paralysis	Absence of voluntary movement.
2. Paresis	Weakness and slowness of voluntary movement or deficient motor power.
II. *Postural reflexes*	
1. Spasticity	Resistance to passive movement of a joint, strongest in flexors of arms and extensors of leg, is fundamentally a stetch or myotatic reflex. Felt first is a slight give, a sudden halt to the passive force, followed by a mounting resistance to increased passive movement, terminating in a collapse of the resistance (lengthening or "claspknife" reaction), distinguishes spasticity from *rigidity.* Spasticity is an example of "release of function."
2. Exaggerated deep reflexes Tonic tendon jerk, etc.	Threshold of deep reflexes elicited by a blow on a tendon or muscle is reduced and other muscle groups may participate, e.g., crossed adductor response; presence of myotatic appendage causes "dead beat" rather than pendular termination.
Clonus	A rhythmic series of contractions following the knee or ankle jerks; also elicited by an abruptly applied but sustained passive stretch of extensors is termed clonus.
Rossolimo's reflex (toes) Hoffmann's sign (fingers)	Sudden release of fingers (or toes) after bending them downward causes them to spring backward, stretching the physiologic extensors and causing a brief, smart contraction in all digits. Spasticity and exaggeration of deep reflexes are fundamentally the same phenomenon, differing only in the way the stretch reflex is elicited.
III. *Other reflexes*	
1. Babinski sign present* (Loss of plantar flexion)	Normal adult reflex response to scratching sole is downward or plantar flexion of toes. Babinski sign is an upward or dorsiflexion, especially of great toe, with or without fanning. It is caused by contraction of physiologic flexors and is often combined with flexor contraction at knee and hip.
2. Abdominal and cremasteric reflexes absent	Contraction of abdominal muscles and retraction of testicle to stroking of abdomen and inner side of thigh, respectively, are lost.
IV. *Muscle*	
1. No atrophy of degeneration 2. No electrical reaction of degeneration 3. No fasciculation or fibrillation 4. No contracture	These signs are characteristic of flaccid paralysis. In hemiplegia any atrophy is due to disuse and contracture, to holding the limb in a fixed position.

*A clinical nicety is never to speak of a "positive Babinski sign"—a tautology.

examine these in "pure state." They did, however, demonstrate the greater effect of area 4 lesions upon voluntary movement of the distal than of proximal musculature, greater in higher primates than in lower ones (or in carnivores), and that lesions of area 6 added to an area 4 lesion increased the motor deficits. Somewhat later (1936), the dependence of the motor aspects of contact placing and hopping reactions on the motor areas was demonstrated in monkeys (see Bard[13]). From intensive studies Denny-Brown[35] emphasized defects in exploratory movements and the address of the limbs to objects in space rather than the paralysis of muscles.

Pyramidotomy, and to a lesser degree pedunculotomy, represent the only way the PT can be studied in "pure culture."* Once the PT was proved not to be the sole outlet of the motor cortex to the spinal cord and the sole agent of voluntary movement, the clarification of its actual contributions seemed imperative. The original observations[see 24] of Tower on pyramidotomy in the monkey and of Hines[see 24] in the chimpanzee emphasized the greater deficits in distal movement and the inability of the fingers to perform discrete (independent) and finely graded movements. Subsequent studies[56, 85] are in essential agreement but suggest that Tower may have overestimated the defect from pyramidotomy. Motor activities such as standing, running, climbing and fending off a stick recovered immediately or within a day or two after operation. Use of the hands in grasping was at first possible only as part of a whole arm movement, as in clinging or climbing to the cage wall, but later became independent. In extracting food from a well in a dexterity board, the hand could be brought to the proper position. Independent movements of the fingers, particularly opposition of thumb and forefinger, were permanently lost;[85] fingers were "used in concert" in a "hooking movement." Other movements never fully recovered; they remained slower than normal. Contact placing was absent, but slow hopping responses persisted.

FORCE AND SPEED OF MOVEMENT. One of the three classical clinical signs of hemiplegia is the loss (paralysis) or weakness (paresis) of voluntary movements. This has only recently been examined experimentally and objectively with results that tend to minimize the role of the PT in paresis. In the chronic state, beginning ten months after pyramidotomies of varying completeness, Beck and Chambers[15] measured the strength of a semi-isometric movement at each joint of the monkey's arm. Motor weakness was correlated with amount but not the location of the damage in the pyramid, which is consistent with the lack of topographical organization of the tract fibers at this level.[14] Weakness was not significant until 80 per cent of the pyramids was destroyed. Deficits were least in proximal muscles and greatest in the muscles acting on distal joints, confirming earlier qualitative observations. Thus the deficit in motor force, like that in the execution of independent movements, seems to be correlated with the amount of motor cortex devoted to the control of specific muscle groups.

The maximum isometric force exerted by the opposition of thumb and fingers in partially pyramidotomized (60, 80, 100 per cent) monkeys was measured by Hepp-Reymond and Wiesendanger[64a] by extensive pre- and postoperative training. Within a few days to three weeks, when the manual skill had sufficiently recovered to press the manipulandum, 200 g force was exerted. In two to eight weeks all monkeys could exert the maximum force (700 g), closely approaching the preoperative strength.

In contrast with motor force, speed of reaction in similar experiments was diminished. Preoperative speed criterion was met by unilateral pyramidotomized monkeys only after two months of retraining, and slowness was a permanent deficit in bila-

*Section of the middle third of the cerebral peduncle in monkeys yielded substantially the same result on objective tests as pyramidotomy.[25] Partial pyramidotomy is chosen by some recent investigators to avoid damage to the overlying medial lemniscus and reticular formation. Since the PT axons destined for different levels of the spinal cord are intermixed in the pyramid,[14] partial lesions have no preferential effects on specific limbs.[85] It is remarkable that the axons from the arm and leg area traversing the peduncle, the pyramids and the cervical spinal cord are not segregated but are thoroughly intermixed. The comparison of pyramidotomy and pedunculotomy with the same tests could provide information on the contribution of PPS and COEPS to voluntary movement, pyramidotomy leaving PPS and COEPS intact while the predunculotomy would involve both the PT and variable amounts of PPS and COEPS, depending on the medial-lateral extent of the lesion.

terally operated monkeys. The deficit was not so much in onset of first EMG activity but rather in the slow development of maximal EMG activity. The difference between unilateral and bilateral lesions was unexpected and raises the question whether similar bilaterality exists in man. Clinically, the opportunities to observe bilateral lesions of corticofugal systems are infrequent.

SPASTICITY.[35, 52, 140] A second of the classical signs of hemiplegia, spasticity, was long considered the result of PT damage. This was disproved, however, by demonstrations that lesions of area 4 of the cerebral cortex and of the PT at the level of the pyramids in monkeys and chimpanzee did not produce the hemiplegic type of spasticity. Denny-Brown[35] has described a mild plastic resistance to passive movement of *any joint* appearing after pyramidotomy. The feel of spasticity of hemiplegia is quite different (see Tabular Summary).

An objective means of testing tonic mechanisms is to vibrate a muscle; this stimulates primary more strongly than secondary spindle afferents and yields a sustained though somewhat declining muscle contraction (Fig. 13–15).[12] This tonic vibration reflex (TVR) resembles the myotatic reflex of the decerebrate cat. Being an asynchronous discharge, it is probably a better index of tonus than the H-reflex induced by a more synchronous volley. In the cat, the descending pathway for inhibiting the TVR of ankle extensors originates in the part of the leg area that yields flexion when stimulated, and the postcruciate dimple area; this inhibitory pathway is clearly nonpyramidal; it descends in the medial (frontopontine) segments of the cerebral peduncles and medial and dorsal to it, avoids the red nucleus and dorsal tegmental area but probably reaches the spinal cord from the medial medullary reticular substance, from which TVR is elicitable. This pathway appears to be part of a COEPS rather than of PPS and, if it exists in man, it suggests that COEPS is under voluntary control, since the TVR can be voluntarily inhibited by normal man but not by hemiplegics. Interruption of this pathway could contribute to the spasticity of the leg extensors in capsular hemiplegia. These experiments indicate further that the red nucleus and related tegmental tracts need not be interrupted to release extensor reflexes and produce decerebrate rigidity.

DEEP REFLEXES. Deep reflexes may be elicited by striking a tendon or a muscle with a kneejerk hammer, both producing a very sudden stretch to a muscle or a muscle group. A similar maneuver is to apply a very abrupt passive movement to a joint. Clinically, these maneuvers are said to test "tone."

As described in the Tabular Summary, deep or tendon reflexes, and spasticity, are both stretch reflexes, differing only in the way they are elicited. Like spasticity, they are exaggerated in hemiplegia but not after PT section.

Paradoxically, deep reflexes may appear to be exaggerated in flaccid extremities or diminished in spastic ones, as in the de-

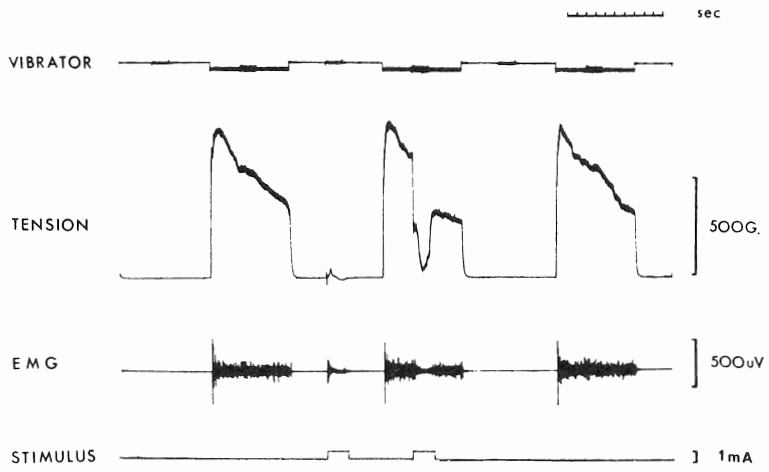


Figure 3–15 Reflex from tonically vibrating tendon of an extensor muscle (TVR). Middle record shows nearly total inhibition of TVR by stimulation of the postcruciate cortex (*lower trace*). (From Ashby *et al.*, *Brain*, 1972, 95, 21–30.)

cerebrate cat. This paradox has stimulated considerable speculation. The simplest and most probable explanation of reduced tendon reflex in spasticity or rigidity is occlusion. The reason for exaggerated tendon reflex in flaccid extremities is the greater effect of a synchronous afferent volley from a tendon tap in exciting motoneurons, than the asynchronous afferent input from tonic muscle stretch. More elaborate explanations in terms of phasic and tonic fusimotor neurons, slow and fast PTN's, have been invoked to explain the apparent opposite behavior of tendon reflexes and spasticity, both involving stretch reflexes. A related phenomenon is the tendency for tapping one tendon to cause jerks in other muscles (*e.g.,* crossed adductor reflex); this seems best explained by mechanical spread of the stretch and over-facilitated myotatic reflex arcs.

CLONUS. This is a rhythmical contraction following a tendon tap or during a suddenly applied but maintained passive movement of a joint. It is clearly an exaggerated deep reflex, and its mechanism is discussed in a previous chapter. Less obvious are the exaggerated deep reflexes of the fingers and toes, the Hoffman sign and the Rossolimo reflex (see Tabular Summary). The next section will show that one form of the grasp reflex is an exaggerated deep reflex. Altogether this makes five categories of exaggerated proprioceptive reflexes: (i) spasticity, (ii) tendon reflexes, (iii) clonus, (iv) Hoffman-Rossolimo and (v) traction reflex grasping. All, with exception of spasticity in the arm, are elicited best or only from antigravity muscles, *i.e.,* physiological extensors.

GRASP REFLEXES. The grasp reflex appears to be of two kinds: (i) the *instinctive grasp reflex* in Denny-Brown's terminology[35] is elicited by superficial stimulation of the palm and is dependent on the PT; (ii) the *traction grasp reflex*[149] has a large component of muscle stretch and is not dependent on the PT. The pathological traction grasp becomes more powerful and spreads to more muscles the stronger the experimenter's effort to break the grasp, to the point that a monkey can be suspended in mid-air by one hand. Fulton[see 52] termed this latter reflex phenomenon, seen after motor cortex lesions, "forced grasping" and considered it to have postural significance because it is influenced by body position; in the operated monkey lying on its side, the upper limb exhibits a strong grasp reflex and spasticity. The grasp reflex resembles spasticity with respect to the effects of cortical lesions, *i.e.,* they are both released by area 6 lesions[122] but are stronger if an area 4 lesion is added to the area 6 lesion. Goldberger[58] has confirmed this observation. Two weeks after area 6 lesions he found it difficult to induce proprioceptive forced grasping but after a prolonged recovery period pyramidotomy reinstated a powerful forced grasping which persisted undiminished for two years. Pyramidotomy as a primary operation did not produce forced grasping; instead, it abolished tactile grasping, fending off a rod and similar movements.

To summarize, the grasp reflex appears to be of two types, one mainly proprioceptive (traction or forced grasping), classifiable with deep reflexes, and the second "instinctive," elicited by light stimulation, perhaps related to contact placing reactions and dependent on the PT.

SUPERFICIAL REFLEXES. Categorized as superficial reflexes are the abdominal and cremasteric reflexes, which disappear in hemiplegia, and the Babinski sign or "extensor reflex of the toes," better termed dorsiflexion of the toes, especially of the big toe. In one sense this reflex represents the disappearance of the normal down-going toe response. The Babinski sign is not found in monkeys, but in the chimpanzee it occurs after area 4 lesions and adding ablation of area 6 adds fanning of the toes.

After pyramidotomy in the chimpanzee, Hines[see 24] observed the Babinski sign and the loss of abdominal reflexes, confirming them as true "pyramidal tract signs." (The status of the cremasteric reflex, elicited by stimulation of the scrotum, could not be tested because the chimpanzee was a Ms.) The plantar reflex, like the grasp reflex, is probably more complicated than is often described, *e.g.,* a return to the infantile status or a mere part of a limb flexion (see Chap. 2, Vol. I).

Figure 3–16 is a summary diagram showing how pyramidal and extrapyramidal signs of hemiplegia, intermixed clinically, have been sorted out experimentally. The diagram would result if the signs of hemiplegia were written on cards and sorted into two piles, one for PT signs and one for those resulting from interruption of

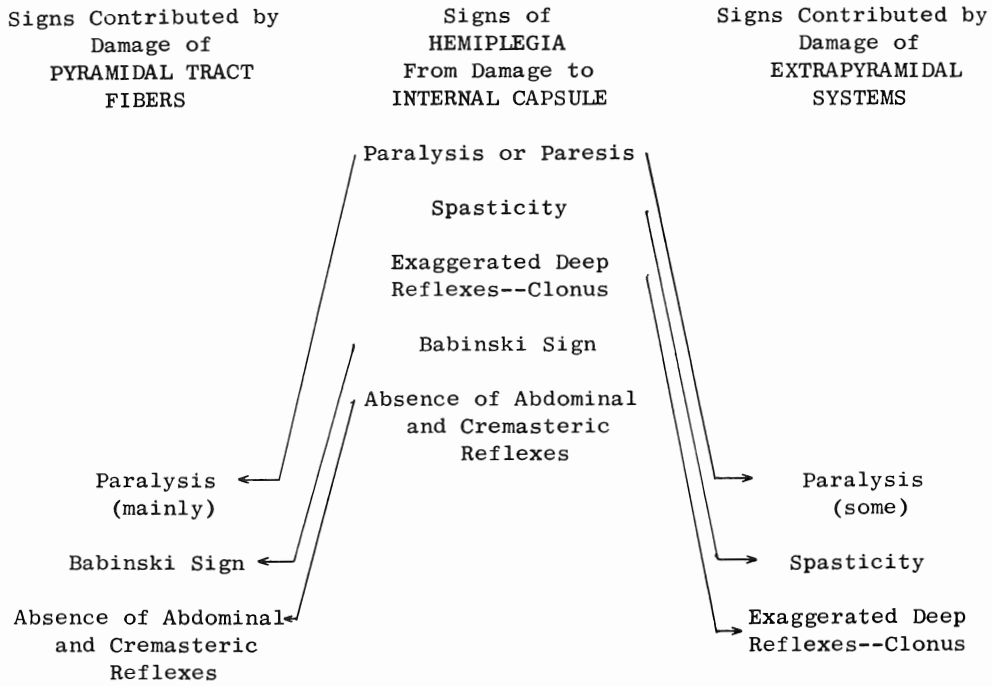


Figure 3–16 Summary diagram showing how pyramidal and COEPS signs of hemiplegia, intermixed clinically, have been sorted out experimentally. The diagram would result if the signs of hemiplegia were written on cards and sorted into two piles, one for PT signs and one for those resulting from interruption of other systems COEPS descending from the cortex.

other descending systems, PPS and COEPS.

In contrast to the division of motor systems into pyramidal and extrapyramidal, Kuypers has suggested an alternate functional division of *brain stem descending systems* into a *lateral* and a *ventromedial* system. These were sectioned separately at the brainstem level in chronically pyramidotomized monkeys.[85] They are distinguished anatomically by their spinal projection and functionally by the behavioral deficits produced by their section. As their name implies, fibers of the ventromedial system descend in the ventral and medial portions of the lower brainstem and spinal cord. They originate mainly in the vestibular nuclei, the medial medullary and pontine reticular formation and the interstitial nucleus of Cajal (see Chap. 2), and terminate mainly in the ventral and medial portions of the intermediate zone, among interneurons and motoneurons thought to be preferentially related to proximal muscles. On the basis of its origins and terminations, one would expect the ventromedial system to be involved in postural control. This is confirmed by consequences of its interruption. Lesions of the medial system in monkeys with PT previously cut produced "striking abnormality . . . of postural changes of the trunk and limbs, a prolonged inability to right and a severe deficit in axial and proximal limb movements." Lesions of the medial system with the pyramids intact resulted in similar though less severe deficits. The use of the hands was relatively little affected. In contrast, the lateral system consists of fibers that descend in the lateral portions of the brainstem and spinal cord and terminate predominately in the dorsal and lateral regions of the intermediate zone, among interneurons and motoneurons related to distal muscles. Most of these axons originate in the pars magnocellularis of the red nucleus. In the spinal cord they join with the corticospinal tract, which occupies a similar posterolateral position and has a similar terminal distribution. Together they constitute the lateral system of the spinal cord and would be expected to control dis-

tal muscles predominately. Lesions of the spinal lateral system in monkeys following pyramidotomy produced additional deficits in finger movements, but little permanent impairment of postural movements (righting, standing, walking, running and climbing).

Lawrence and Kuypers[85] summarize their conclusions concerning the relative contribution of these pathways as follows:

"The ventromedial brain-stem pathways function as the basic system by which the brain exerts control over movement. This control is especially concerned with maintenance of erect posture, integrated movements of body and limbs and with directing the course of progression. The lateral brain-stem pathways, at least in regard to extremities, superimpose upon the above control the capacity for the independent use of the extremity, particularly of the hand. The corticospinal connexions mediate a control similar to that of the brain-stem system but, in addition, provide the capacity for further fractionation of movements as exemplified by individual finger movements."

SOMATOTOPIC ORGANIZATION OF AREA 4 (MI)[155, 156]

That different parts of the body move when different parts of the precentral gyrus are stimulated has been known for more than a century, but the nature and detail of this somatotopic representation remain subjects of experiment and controversy. "Representation of the body," "somatotopic organization" and "topographic organization" are synonymous expressions for the fact that the cortical cells which give rise to the descending fibers activating different muscle groups lie in broadly the same relation to one another as do the muscles in the body. Other authors argue that movements rather than muscles are represented. The two are not mutually exclusive. The motor cortex probably exhibits a spectrum of functions ranging from direct control of specific motoneurons to triggering complex, "wired in" movements programmed at subcortical levels.

Figure 3–7 shows the sequence of motor representation of body structures in the monkey and in man (Fig. 3–17,*A*). The body parts are represented "upside down" in the motor cortex, with the leg area medial, the face area lateral, and the arm area interposed. In man, much of the leg area is buried in the medial longitudinal fissure, and most of the arm and face area lies buried on the anterior wall of the central fissure, barely peeping onto the free surface. In the monkey, more of the motor area lies on the free surface.

The discovery that movement can be elicited by cortical stimulation illustrates how careful observation and astute deductions can interact with more analytical and controlled animal experiments. In 1870, Hughlings Jackson postulated the existence of a somatotopically organized motor area from his observations of the epileptic seizures that now bear his name. In a given patient, a seizure might start in the lips, spread to the face, then to the arm and then to the leg (the "march of epilepsy"). He reasoned that there must exist, somewhere in the brain, structures concerned with the lip, and further, that the remainder of the musculature must be represented there in an orderly fashion, accounting for the successive and orderly involvement during the epileptic discharge. More than a century ago, Fritsch and Hitzig[51] and, independently, Ferrier[44a] discovered the electrical excitability of the motor cortex in dog and monkey, mapped areas for the face, the arm and the leg, and demonstrated the representation of smaller body parts. As we have seen, this subject is active today although the methods have become more sophisticated.

The amount of time available for stimulating the human cerebral cortex in search of an epileptic focus is limited, whereas the nonhuman primate cortex can be explored for hours and days. The most thorough mapping was accomplished by Woolsey and colleagues.[see 156] His results recorded in detailed maps (Fig. 3–12,*A*) are summarized in Figure 3–7. The medial to lateral "motor ladder" is similar in man and monkey, with variations such as the large representation of the prehensile tail in the *Ateles* monkey.[see 52] Notable in Woolsey's mapping (Figs. 3–7 and 3–12,*A*) is the "use" of the anterior-posterior dimension of the motor cortex. The distal musculature of the hands and feet are represented posteriorly, extending into the depth of the central fissure. The muscles acting on the more proximal joints and the axial musculature are activated from progressively more anterior bands of cortex. Certain differences

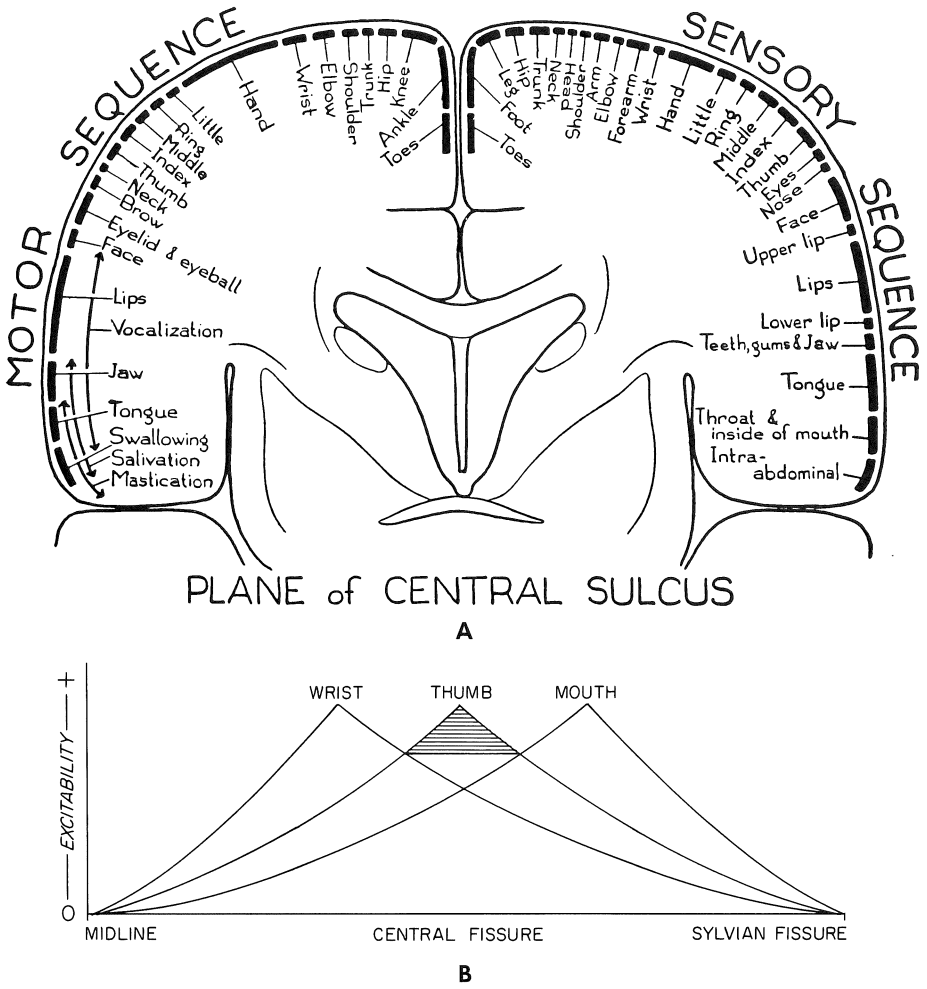


Figure 3–17 *A*, Representation of body parts in the human pre- and postcentral gyrus determined by stimulation. Length of bars indicates approximate extent of cortical area devoted to a given part in a typical patient. The two-headed arrows indicate functions involving more than one structure. (From Rasmussen and Penfield, *Fed. Proc.*, 1947, *6*, 452–460.)

B, Theoretical graphs representing the extreme view of the representation of body parts, showing Hughlings Jackson's concept of somatotopic localization in the precentral gyrus as interpreted by Walslie. Note that the distribution of corticofugal neurons for a given body part is conceived as extending from the midline to the sylvian fissure. What would be called the thumb area (cross-hatched) is only the point where thumb responses outweigh wrist or mouth representation. Excitability is interpreted as the concentration of corticofugal cells. (After Walshe, *Brain*, 1944, *66*, 104–139.)

in the representation of distal and proximal musculature are discussed below.

A functional deduction is commonly made from the amount of cortical space devoted to a given part of the body. The lips, tongue and fingers, which are highly mobile and capable of finely graded movement, have large medial to lateral cortical space devoted to them. The finger and hand areas of the cortex are much greater than the total of those governing the movements of all the other much more massive arm muscles. This arrangement suggests that finely graded movements are obtained by the simplest of all methods—the provision of a larger number of efferent neurons. It is probably not only the number of PTN's but also the number of interspersed intracortical neurons that determines the variety of movement of which the fingers or tongue is capable. In either case, cortical space is required. However, new information indicates a greater representation of proximal musculature than hitherto supposed.

Detailed Somatotopic Organization of Area 4. As mapping techniques have become more refined, the regions of the body as represented in motor cortex have become correspondingly more specific, from general body regions (face, arm, leg) to movements of joints and digits, and finally to single muscles. In contrast to the view that single muscles may be separately represented in specific regions of the motor cortex, Hughlings Jackson and subsequent investigators[150] have long held the opposite view. Impressed by the fact that a patient can recover the use of a limb after destruction of cortical representation of that limb, as previously defined by stimulation, they have defended the idea that a given muscle can be activated throughout the whole precentral gyrus (Fig. 3–17,*B*) and implied multiple representation of muscle groups for different movements. This view, summarized by the statement that "the cerebral cortex thinks in terms of movements, not muscles," has been found persuasive, particularly by British neurologists.

Unquestionably, electrical stimulation at a single cortical locus, especially with prolonged trains of intense pulses, produces activation of many muscles and may result in movement of one or more joints; as a corollary, rather different movements can be obtained from different regions. The basic question is whether this means that the *motor cortex integrates the activities of various muscles into movement.* To do this it would be necessary to have each muscle re-represented many times, *i.e.,* at each locus producing a movement involving that muscle. Obviously, the motor cortex "thinks" in terms of movements in the sense of producing many kinds of movements, but how it does this is the question: by re-representation of muscles, or by activating focal representation of muscles via interneurons.

EVIDENCE FROM SINGLE MUSCLE RECORDING. Responses of individual muscles to systematic stimulation of the motor cortex have been studied in efforts to resolve the question. Whether a single muscle is responding is difficult to discern with the naked eye. Therefore, in monkeys Chang *et al.*[26] isolated the tendons of 13 muscles acting over the ankle and attached them, eight at a time, to myographs. The foot area of motor cortex was divided into millimeter squares (Fig. 3–18, lower right) which were systematically stimulated. The tension produced in each muscle by stimulating each point was recorded on a two-dimensional map of the cortex. Three major results were: (i) Occasionally, only one of eight muscles responded, and the points for such "solitary responses" in a given muscle always fell in a cluster (Fig. 3–18, left). (ii) When the latencies of muscle responses were mapped, the shortest latency responses for a given muscle clustered into contiguous points, and the intermediate- and long-latency responses tended to occur at surrounding points. (iii) Mapping the relative tension responses of any two muscles produced a similar clustering (Fig. 3–18, right).

The latency study has been conducted on monkeys in another way by Bernhard and Bohm,[16] who recorded the latency of impulses in a muscle nerve and correlated it with the point stimulated on the motor cortex (Fig. 3–19). Again, isolatency lines formed concentric rings. Thus, a given muscle can be activated from a fairly wide area of the motor cortex, but a strong short-latency contraction occurs only from a narrow focus.

These studies led to the concept that corticofugal cells activating the motoneuron pool of a given muscle are topographically contiguous in the motor cortex. In fact, as shown in Figure 3–20, for each muscle there appears to be a focus of cortical neurons surrounded by a field for that muscle. The foci for two muscles never overlap, although the field for one muscle may overlap the field and even the focus of another.

The degree of muscle representation is surprising in view of the factors obscuring it. For example, strong, repetitive stimulation recruits additional cortical cells via both direct current spread and excitatory collaterals. Moreover, such stimulation also recruits many subcortical cells via PPS of the activated corticofugal neurons and via COEPS.

MOTONEURONAL RECORDING. The organization of the motor cortex representation of muscles has been studied in more detail by intracellular recordings from single motoneurons. Stimulating the cortical

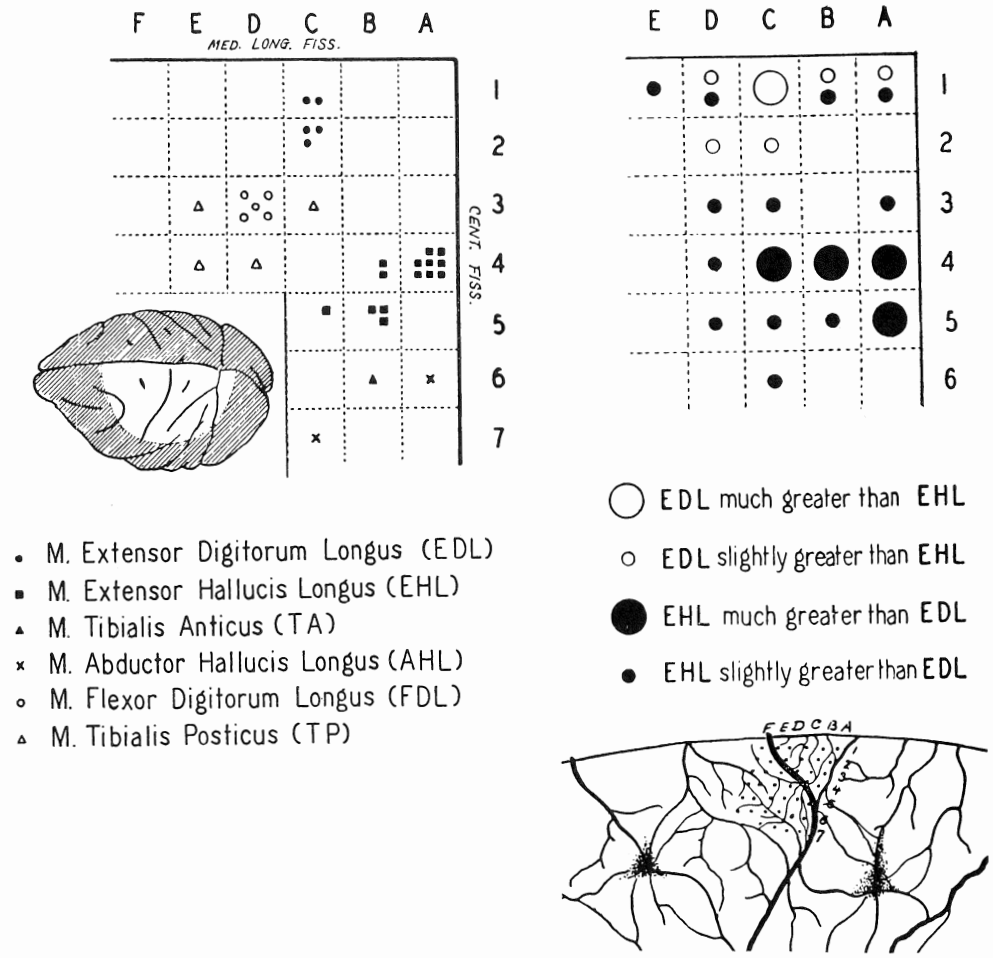


Figure 3–18 Muscle responses evoked by stimulation of different cortical points. *Left*, cortical points where stimulation evoked responses in only one muscle. *Right*, relative strengths of responses in extensor digitorum longus and extensor hallucis longus for given points. *Upper left insert*, the general cortical area investigated (unshaded) and *lower right insert*, pattern of vessels used to locate the grid of stimulated points. Numbers and letters on grid correspond with the charts above. Note that the points for "solitary responses" cluster and the points showing the relative size of response of a muscle pair also form a cluster (focus and field) and approximately correspond in the two diagrams. (After Ruch *et al.*, *Res. Publ. Assoc. nerv. ment. Dis.*, 1946, *26*, 61–83.)

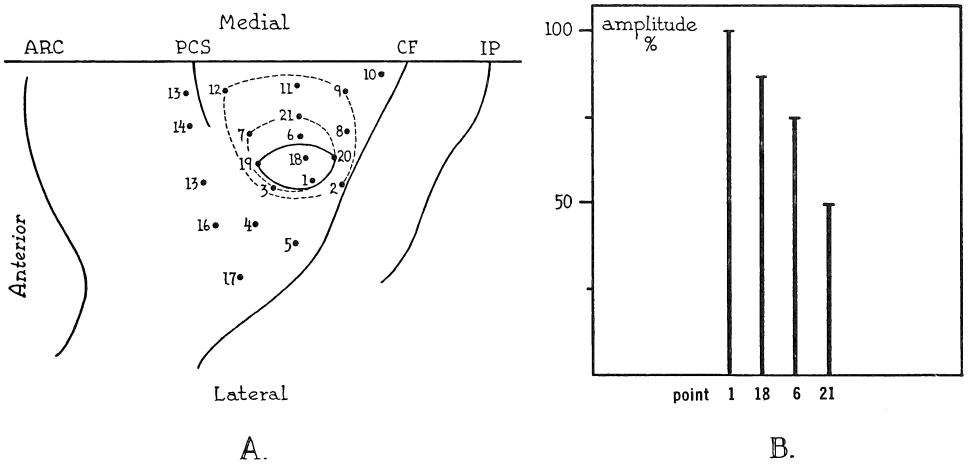


Figure 3–19 *A*, latency (summation time for repetitive stimulation) for monosynaptic activation of triceps motoneurons from different points on left motor cortex of the monkey: 1 sec for inner circle, 3 sec for next (*dashed*) and 7 sec for outer circle. Note closeness of isotime lines inferiorly, suggesting sharp boundary between arm and face areas. (This diagram confirms experiment shown in previous Figure 3–18). *B*, amplitudes of monosynaptic discharge from points in a line running vertically through field for triceps motoneurons at left. (After Bernhard and Bohm, *Arch. Neurol. Psychiat. (Chic.)*, 1954, 72, 473–502.)

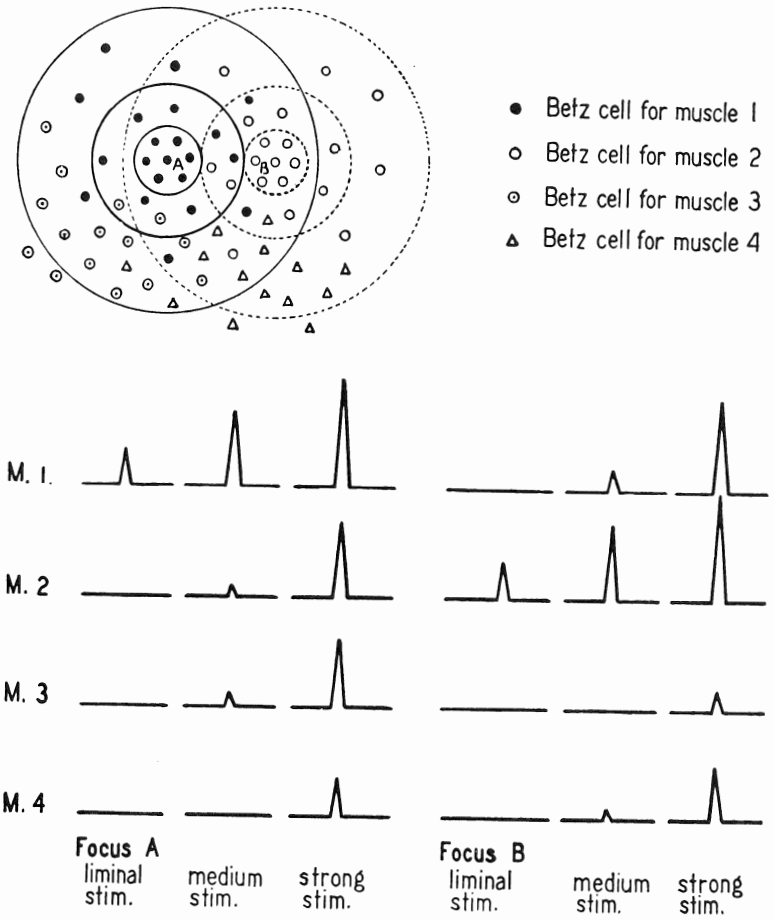


Figure 3–20 Hypothetical distribution of Betz and other corticofugal cells activating individual muscles deduced from experiments shown in Figure 3–18. The cell group for each muscle (*A* and *B*) has a focal concentration and a fringe with lesser concentration overlapping with the fringe and the focus of another muscle. Large concentric circles represent zones of excitation from enclosed cortical neurons judged from the resultant muscle contraction. Myographic records below represent the expected contraction of muscles to cortical stimulation at different strengths proportionate to the concentration of corticofugal neurons in each sphere. Focal zones A and B occupy about 4 to 8 mm^2 of cortical surface. The upper diagram is, of course, deduced from the data represented in the lower diagram. M.1 means muscle 1, etc. (From Ruch *et al.*, *Res. Publ. Ass. nerv. ment. Dis.*, 1946, *26*, 61–83.)

surface by anodal currents to minimize recruitment of cortical interneurons evoked EPSP's in forelimb motoneurons of the baboon.[65, 72, 112] Landgren *et al.*[79] confirmed the existence of a lowest threshold cortical focus for evoking EPSP's in a single motoneuron; surrounding this "best point" was a field of cortical neurons, which also projected to the same motoneuron.

To interpret the results of cortical stimulation it is necessary to know how widely current spread can recruit cells. To determine this for surface stimulation, Landgren *et al.*[79] measured the threshold stimulus intensity required to evoke a response in single PT cells as a function of distance from the lowest threshold point. Typical results are plotted in Figure 3–21,*A*; typically, the threshold stimulus current increased as the square of the distance. From this it is possible to deduce the extent of spread of each stimulus intensity; for example, a 1-ma surface positive shock would recruit cells within a 6-mm-diameter circle. Phillips and Porter[see 114] used these results to estimate the spatial extent of the cortical colony projecting to specific forelimb motoneurons. They plotted the size of the monosynaptic EPSP evoked in a motoneuron by increasing stimulus currents applied at the best cortical point (see Fig. 3–21,*B*). Above a certain stimulus intensity there was no further increase in EPSP size, suggesting that all cells of the colony had been recruited. The spatial spread of this stimulus gives an indication of the spatial extent of the colony. For example, in the motoneuron of a distal muscle illustrated in

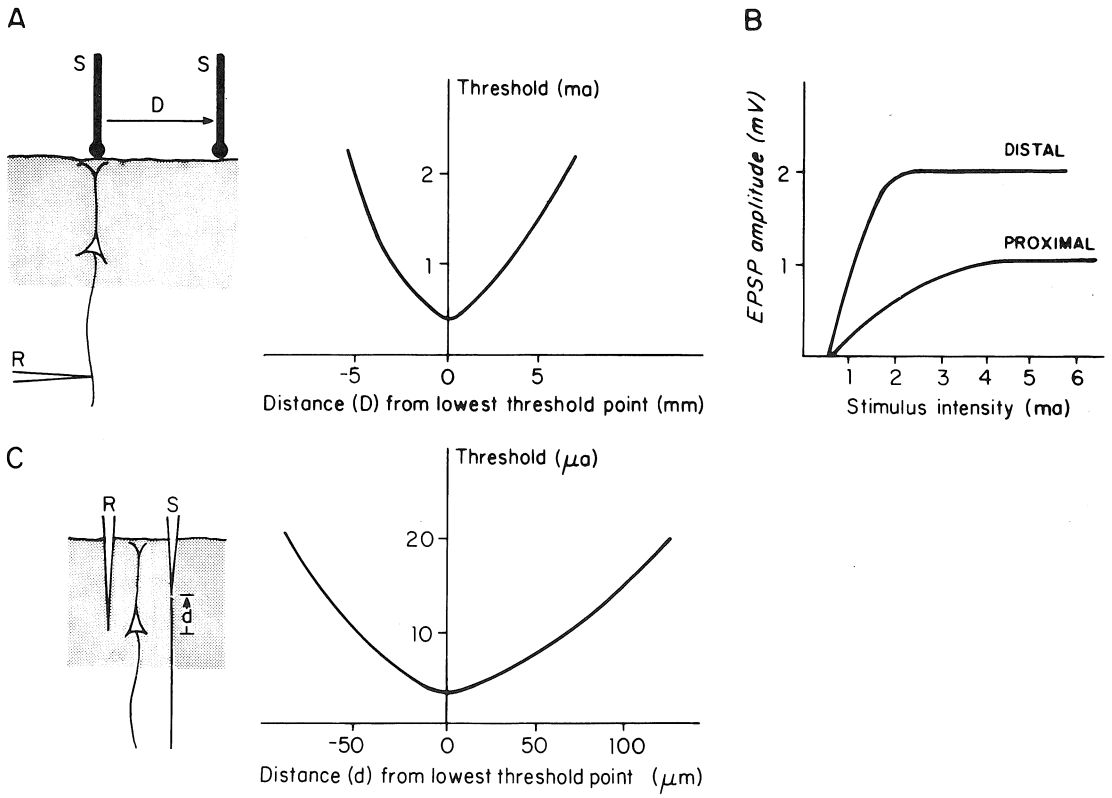


Figure 3–21 *A*, spread of stimulus (S) applied to cortical surface in experiment illustrated at the left. Typical curve of current intensity in milliamperes required to activate a single PT cell as function of distance from best point (0.2 msec surface anodal pulse). *B*, size of monosynaptic EPSP evoked in cervical motoneurons of baboon as function of stimulus intensity for 0.2 mA surface positive stimulus applied at best point; typical curves for motoneurons of proximal muscle (triceps) and distal muscle (ulnar nerve). *C*, spread of microstimulation current applied through intracortical microelectrode; typical curve of current intensity required to activate PT cell (with 0.2 msec intracortical pulse) as function of distance from lowest threshold point. (*A* and *B* after Phillips and Porter, *Progr. Brain Res.*, 1964, *12*, 222–242; *C* after Stoney *et al.*, *J. Neurophysiol.*, 1968, *31*, 659–669.)

Figure 3–31*B*, the maximal EPSP (of 2 mV) was evoked by a stimulus intensity of 2 mA; Figure 3–21*A* indicates that a 2-mA stimulus recruited cells within a 10-mm-diameter area. Phillips and Porter[see 114] found that the colonies for motoneurons to distal muscles tended to occupy smaller cortical areas but evoked larger maximal monosynaptic EPSP's; in contrast, colonies for proximal motoneurons occupied larger areas but produced smaller maximal EPSP's. More recently, Jankowska *et al.*[72] defined the spatial organization of cortical colonies by mapping the cortical points from which monosynaptic EPSP's could be evoked in specific hindlimb motoneurons. These areas, typically between 3 and 7 mm^2, overlapped extensively for motoneurons of different muscles.

INTRACORTICAL MICROSTIMULATION. All of the experiments described to this point employed stimulation of the surface of the motor cortex. Such stimuli must recruit many neurons, blurring topographic relationships. In an attempt to minimize the number of cortical cells recruited, *intracortical microstimulation* (ICMS) was developed by Asanuma and Sakata.[9]

To quantify the effective spread of ICMS currents, Stoney *et al.*[136a] measured the stimulus intensities required to activate a PTN, as a function of distance of the stimulating electrode. At the lowest threshold point, presumably when the electrode was closest to the cell, minimal current intensities were between 1 and 17 μA for 0.2 msec cathodal pulses. As the stimulating electrode moved from this minimal point, threshold intensities increased as the square of the distance. The effective radius of a 10-μA current pulse was calculated to be 80 to 90 microns. Assuming a cell density of 100 cells per 0.001 mm^3 (typical of monkey motor cortex), a 10 μA pulse would directly excite about 285 cells and a 5 μA pulse would activate about 100 cells directly. In addition, other cells would be recruited via fibers passing through the effective sphere of stimulation.[72]

Asanuma and Rosén[7] found that the low threshold points for facilitating the monosynaptic reflex discharge in a given muscle nerve branch were located in a cylindrical volume parallel to the radial fibers and columns of cell bodies (discussed above). The columnar zones were as narrow as 0.5 mm, but some were a few millimeters in diameter.

ICMS opens a third spatial dimension for stimulation, *i.e.*, depth within the cortex. Layer V proves to have the lowest threshold for evoking motor responses, although layers II and III yielded responses to quite low levels of stimulation. Over a larger range of depths and with weak stimuli, the corticofugal neurons could be activated through interneurons (latencies 0.8 to 6.0 msec); this suggests that the interneuron fibers mainly run radially, in agreement with histological findings. The degree to which ICMS activates PTN's directly (D-wave) or synaptically through interneurons has apparently been overestimated. Jankowska *et al.*[72] found the indirect excitation via axons to outweigh direct excitation of the cell bodies. This would explain the radial distribution of low threshold points as being due to the radial orientation of fibers.

Although the preponderance of transynaptic excitation of PTN's would affect calculations of dimensions of columns, numbers of cells recruited, etc., the bearing on the column hypothesis depends greatly on which fibers are stimulated. If they are transverse, the concept of columns is considerably altered. However, the column (if it exists) would seem to be demarcated by a shell of ascending axons presumably shared by adjacent cell columns. This would tend to enlarge and obscure the purity of columns, which is an essential postulate in the columnar hypothesis.[145]

The estimates of the cortical area from which the motoneurons of a specific muscle or a given motoneuron can be affected, subliminally or supraliminally, do not vary greatly from author to author, with the exception of proponents of a strict columnar organization. Fields or colonies for a muscle or motoneuron with foci or "best points" have usually been described. The organizations within such fields have recently been examined[4, 72] and theoretical significance is attached to a lack of a uniform gradient of responsiveness between field and focus. A field is described as "patchy" because a stimulating electrode passing tangentially through the motor cortex passed more than one low threshold point. The theoretical implication was that

such low threshold points indicated a re-representation of the muscles, as demanded by the Jackson-Walshe-Phillips view of the detailed localization in the motor cortex. Before reaching such a conclusion, several reservations are in order: (i) many penetrations reveal one minimum threshold point; others, two; (ii) despite fluctuations in threshold an average gradient to peak excitability was exhibited; (iii) destructive currents[6] as high as 80 μA (500 Hz) were used.

Jankowska *et al.*[72] and Chang *et al.*[26] both found that a large number of leg muscles are represented within a very small cortical area (20 hindlimb muscles in an area less than 30 mm^2); stimulation at the boundaries of this area evoked sharply decreased motoneuronal responses. Unless a strict mosaic or columnar structure exists, extensive overlap is not surprising.

It can be argued that enormous energy is wasted on a controversy that is a "storm in a tea cup," or "much ado about nothing," a problem that is insoluble because (i) unphysiological, even damaging, unselective stimulation is used, (ii) only a small fraction of PTN's are involved and (iii) engineering convenience (economy of "wires" rather than function) may be the primary reason for columns, colonies and fields and foci. Other structural features such as the fineness of sensory and cerebellar input or the length of cortical interneuronal chains may well be of greater functional importance. In fact it seems that this problem of fine localization in the motor cortex directed attention away from the study of cortical interneurons to the point of selecting anodal stimulation to minimize their recruitment.

OTHER CORTICAL MOTOR AREAS

That the mediolateral dimension of the primate precentral gyrus represents the caudocephalad dimension of the body has been known since 1870. By contrast, how the anteroposterior dimension is utilized and what constitutes the forward border of the body representation are still somewhat uncertain. If the mediolateral dimension represents the caudocephalad dimension of the animal, it is logical that the axial-appendicular dimension should be represented in the remaining available (anteroposterior) dimension of the motor area; and, in fact, this is the most recent view. However, by analogy with sensory systems and because of cytoarchitectural differences, it is also logical to think that some portion of the anterior posterior dimension is used for managing movement of different complexity; there is evidence that this is true.

Area 6. In the simunculus based on the experiments of Woolsey *et al.* (Fig. 3–7), the representation of the fingers, toes, lips and tongue is mainly buried in the central fissure, and the successively more proximal musculature is represented more anteriorly in orderly sequence, occupying much of area 6. The threshold for evoking movement is higher for axial than for distal musculature. Note between the two limbs the position of the superior precentral sulcus, which corresponds approximately to the anterior border of the motor area 4 by certain cytoarchitectural and functional studies. If the simunculus in Figure 3–7 is correct, the axial musculature is represented in Brodmann's area 6, which has not previously been considered part of the body representation. Inclusion of area 8 in the angle of the arcuate sulcus is certainly unjustified. It does not receive a projection from VL-VA thalamic nucleus and its *bilateral* removal does not paralyze the eye muscles.

The previous discussion supports the conclusion from early stimulation experiments that area 4 serves the finely graded, independent movements of distal muscles, as exemplified by the digits. Early investigators[see 52] held that stimulation of area 6 near its posterior border with area 4 produced movements similar to those from area 4, which were in fact mediated by connections with area 4. The most anterior portion of area 6 produced adversive movements of eyes and head and may, in fact, blend with the frontal eye fields (see below). Foerster, Fulton and Bucy[see 52] described movements elicited from area 6 itself as being (i) sustained movements involving synergy of the muscles acting on more than one joint and (ii) ipsilateral movement from a restricted point on the superior banks of the superior precentral sulcus.

It is possible that Woolsey's studies place the forward boundary of the topographical representation of the body too far rostral. The arguments are complex. (i) Repetitive unipolar stimulation led to errors through spread of current from area 6 to 4. (ii) The amount of the motor areas devoted to axial-proximal musculature is difficult to understand unless such muscles have a fine motor control equal to that of the digits. There are two possible explanations for the difference between Woolsey's results and those of earlier workers. (i) Stimulation of area 6 by the latter, by involving axial and proximal musculature, gave the appearance of the whole limb moving and adversive movement fields could be confused with motor representation. (ii) The stimulus parameters may have differentially activated the COEPS neurons of area 6 that activate proximal more than distal muscles. This is also indicated by the virtual absence of distal and retention of proximal musculature contraction on stimulating the motor areas contralateral to a unilateral section of a monkey's pyramids (Fig. 3–12,*A*).[155] Not only was the proximal musculature activated from area 6 of Woolsey's map, but *throughout the whole of the free surface of area 4 and that buried in the central fissure.* As indicated in Figure 3–22, the whole of area 4 projects to the red nucleus and both areas 4 and 6 project to the medial reticular system. Furthermore, the corticospinal connection via interneurons to proximal musculature appears in area 4 and widely in area 6. Both findings support the hypothesis that area 6 is predominantly a COEPS area concerned with posture, while area 4 is related to posture and movement. These provocative functional and anatomical studies prompt the speculation that axial and proximal muscles are widely represented to provide a steady postural base for fine digital movements, much as the stance is all important in serving at tennis. If area 6 were merely a part of the body representation, the motor areas differ from sensory areas by lacking a hierarchy of adjacent areas managing successively more complex or "higher levels" of motor function.

Second Motor Area (MII).[137] A small motor area in the lateral extension of the precentral gyrus onto the lip and wall of the sylvian fissure is termed the second motor area MII (Fig. 3–7). The two simunculi are lip to lip and the body representation continues in reverse order to that in the precentral gyrus. Its existence is well established but little is known of its function. The face area of MII is prominent and bilaterally represented, perhaps a contributing factor in relative immunity of the face in hemiplegia.

Supplementary Motor Area (SMA).[108, 156] In both monkey and man, the musculature is represented in a third area of the motor cortex lying on the medial surface of the hemisphere (Fig. 3–7), called the supplementary motor area (SMA) rather than MIII. As described by Woolsey,*see* [153c] it crosses cytoarchitectural boundaries but lies mainly in area 6. The movements elicited from the head region are often "meaningful acts," such as yawning, vocalization and coordi-

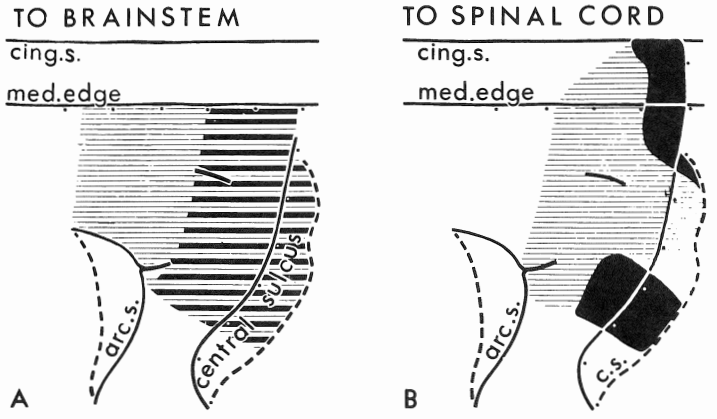


Figure 3–22 Descending projections from motor areas 4 and 6 of monkey brain (central sulcus folded out). *A*, area projecting to medial reticular formation of brainstem shown by thin lines and to the pars magnocellularis of the red nucleus by superimposed heavy lines. *B*, solid black areas show precentral area projecting primarily to dorsolateral intermediate zone of spinal gray horn containing interneurons serving distal arm and leg motoneurons. Thin lines demarcate the parts of area 4 and 6 mainly projecting bilaterally to the ventromedial part of the intermediate zone, containing interneurons connecting with motoneurons of proximal limb and axial musculature. *Cing. s.*, cingulate sulcus; *arc.s.*, arcuate sulcus; embracing area 8, frontal eye fields. The superior precentral sulcus is shown but not labeled. (From Kuypers and Brinkman, *Brain Res.*, 1970, *24*, 29–48.)

nated movements of head and eyes resembling those of area 8 and anterior area 6.

In contrast with those evoked from MI, responses evoked from SMA require strong stimulation, are more affected by anesthesia and consist of the assumption and maintenance of limb postures involving multiple joints rather than quick, phasic movements of single joints; the limb postures are often held many seconds after the stimulus has ceased. The responses are often bilateral, and one stimulation tends to facilitate the next; stimulus trains of several seconds may be required for synchronous EMG bursts. The anterior part of SMA projects to areas 4 and 6 of the same and opposite hemispheres. Stimulation after ablation of precentral cortex indicates that much of the topographic organization is due to these connections and the diffuse responses are to be expected of an area connected with motoneurons through the extrapyramidal system. The latter type of movement is held to be characteristic.[see 134]

Recent anatomical reports indicate that the SMA does contribute fibers to the pyramidal tract; it also has extensive connections with basal ganglia and mid-brain structures, inducing motor effects via the extrapyramidal motor system.[36] Its input being from areas 4, 1, 2, 5 and SII suggests to some that SMA's relationship to MI is hierarchical. That it accounts for effects ascribed to area 6 (e.g., forced grasping) has been affirmed and denied. Wiesendanger *et al.*[see 134] and others discount a postural role for SMA.

Chronic recording of single neurons in SMA of the monkey performing a variety of semicontrolled motor acts yields quite a different picture. As many units were active during distal as during proximal movements. Specific cortical neurons were active in connection with phasic activity of specific muscle groups which, however, were bilaterally activated; this argues against the postural role of SMA.

Sensory and Parasensory Areas. In unanesthetized monkeys nearly the whole free cortical surface yields movements upon electrical stimulation.[see 63] Movements are obtained by stimulating the postcentral gyrus, although thresholds are several times higher than for the precentral cortex. These movements may still be evoked, at higher intensities, after chronic removal of the precentral gyrus, suggesting an independent descending system from postcentral cortex. Although postcentral gyrus contributes to PT (Fig. 3–14), D-waves are rarely recorded from stimulating it. Since thresholds increase after precentral ablation and since pre- and postcentral cortex are interconnected, it seems reasonable to suppose that some effects of postcentral stimulation in normal monkeys may be mediated by precentral cortex.[24]

Area 8—Eye Movements.[see 24] Eye muscles were not represented in the pre-Woolsey maps of body representation, which fits with the idea that there is no biological utility in their separate activation. Stimulation of area 8, the frontal eye fields in both man and animals, causes the extra- and intraocular musculature to contract or relax. The eyes sweep together (conjugate deviation) like the front wheels of an automobile and often "look away from the stimulating electrodes." Stimulation at adjacent points causes the eyes to move obliquely upward and downward, and consensual pupillary constriction and lacrimation also can be evoked. Area 8 is a good example of the overlapping of the cortical representation of visceral and somatic musculature (Fig. 3–23).

Unilateral ablation of area 8 results in lateral deviation of both eyes so that they look toward the side of the lesion. Partial or complete removal of the second area 8 produces a more extensive and longer lasting deviation of the eyes in the contralateral direction;[83] this is reminiscent of Bechterew's nystagmus (Chap. 2, Vol. I) and suggests some kind of antagonistic balance between the fields of the two hemispheres. Woolsey *et al.*[156] devoted part of the frontal eye fields to the primary representation of the body musculature representing eye muscles. This makes area 8 a mixture of a representative and an integrative structure. There is no evidence of this from ablation experiments. Moreover, it is relatively difficult to find single cortical neurons in area 8 whose discharge is related to eye movement. It is probably incorrect to include the cortex anterior to the arcuate fissure in the body schema. Certainly area 8 as a whole serves a higher order function than other areas in his body schema; ablation of it causes a persistent circling towards the side of the lesion and a visual disturbance, but only seeming blindness in the half of

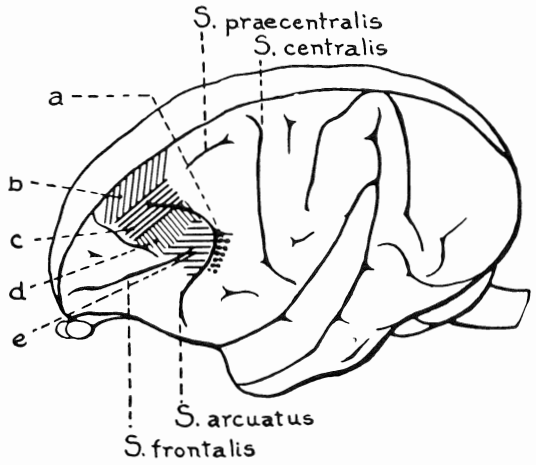


Figure 3–23 Subdivisions of frontal eye field and adjacent area yielding closure of eyelid in monkey (*Macaca mulatta*). *a*, closure of eyelid; *b*, pupillary dilatation; *c*, "awakening"; *d*, conjugate deviation to opposite side; *e*, nystagmus to opposite side. (From Smith, in Bucy, *The precentral motor cortex.* Urbana, University of Illinois Press, 1944.)

the world on the same side as the lesion (hemianopsia or hemiamblyopia). Perhaps this is a form of neglect seen after many cortical lesions, because it disappears if a true hemianopsia is produced in the opposite visual field by removing the visual cortex.

Area 8—Adversive Movements.* In man, a sustained lateral movement of the eyes and twisting of the neck and upper trunk may occur during an epileptic seizure. Such *adversive seizures* are usually caused by a discharging focus in the general region between the motor areas and the prefrontal lobule. The exact relationship of this region to the eye fields, to the forward-lying representation of the axial musculature in area 6, and to the supplementary motor area is not clear.[156] Perhaps a broad area, encompassing all of these areas, constitutes an extrapyramidal adversive field. Penfield and Jasper[107] and others have evoked adversive movements in patients from additional cortical areas such as area 22.

*The prefix "ad," somewhat ambiguous in this usage, literally means "towards" whereas the eye movements from area 8 stimulation are away from the side stimulated, and this is the thing to remember.

The term "adversive movements" does not clearly convey direction or physiological significance. The term "orientational movements" may be substituted. Visual and somatosensory impulses initiated from the right side of the body pass to the left hemisphere. If such impulses are transmitted to ipsilateral area 8, the eyes and the body would turn to the right and thus orient toward the external stimulus. Adversive or orientational movements may therefore be one component of the motor part of attention.

Autonomic Reactions. In addition to the eye fields, autonomic effects may be evoked by stimulation of area 6, the premotor area. These are true cortically induced responses, not nociceptive reflexes activated by stimulation of pain receptors in cerebral blood vessels, nor are they a consequence of somatic muscular contraction. The points yielding autonomic responses in a part of the body coincide closely with the excitable focus for that part. For example, vasomotor reactions in the arm are obtained by stimulating the premotor arm area. These changes may be associated with fluctuations in the systolic blood pressure and the heart rate. Vasopressor points are usually discrete and separable from vasodepressor points, and they are highly susceptible to changes in the type and depth of anesthetic used. This cortical representation of autonomic function has been confirmed by ablation studies, and aids in explaining autonomic changes often observed in clinical cases of hemiplegia.[see 52]

ELECTROPHYSIOLOGIC ANALYSIS OF PYRAMIDAL TRACT FUNCTION

INTRODUCTION. Prior to the 1930's the PT was widely considered to be the sole output pathway for voluntary responses. The discrepant results of experiments in the 1930's showing that the PT was not necessary for movement naturally raised the question—What does it do? Extensive research over the last half century has been devoted to investigating the function of this massive corticospinal system, with many uncertainties still remaining.

Perhaps the two major uncertainties about the role of the PT in movement are

whether the tract is an *executive* or an *executor*, and to what degree it shares cortically initiated movement with COEPS. The cerebral cortex as an executive would imply that it plans, commands or triggers movements without its being involved in controlling the details of the movement, which are executed by subcortical structures. The term "programmer" is preferred to "executive" by some but perhaps should be used for a concept of an intermediate function, *i.e.*, "Do it this way." Thus, in walking, the cerebral cortex may say, "Walk in this direction," but does not say "Left, right, left, right, hup," or "now quadriceps-gastrocnemius, now hamstrings-tibialis anterior." Behavior such as walking, often termed "wired in," is prominent in lower vertebrates but not absent in the higher orders. In the role of an executor, the cerebral motor cortex is conceived of as more directly related to contraction of specific muscles inducing an infinite variety of fine, carefully adjusted muscular contractions involving independent movements of the fingers as exemplified in the delicate manipulations of the watch repairer.

Supporting the hypothesis of an executor role is the greater proportion of cortex devoted to distal musculature in manipulative animals, the number of monosynaptic connections that the PT makes with motoneurons of distal muscles, the severity of ablation effects on distal vs. proximal muscles and the degree to which the motor cortex can separately activate single muscles as opposed to muscle groups or the muscles acting at several joints. Finally, the heavy thalamocortical input to the motor area is scarcely needed unless movements are executed by it, not simply ordered. Also difficult to reconcile with an executive role are three other prominent findings in behavioral and clinical observations on PT interruption, *i.e.*, decrease in force of contraction (clinically termed "power"), the decreased speed of movement and reduction of muscle tonus (flaccidity). In comparison with the control of the digits in skilled movements, these would seem rather low level activities of the kind an executive would delegate. However, one hypothesis derived from Hughlings Jackson[70] says that as the successively higher neural levels developed, they took over or inhibited the activities of the lower level or both. Thus, to execute fine movements, it seems that the cerebral cortex has taken over some of the control of limb posture. Tonic activity of the motor cortex may also control segmental activities by reducing as well as increasing activity at spinal levels.

The second major question is the relative role of the PT and COEPS corticofugal systems. Do they divide responsibility? How effectively does each operate without the other? As discussed in Chapter 4, a third question concerns the role of the PT fibers that act upon the first synapse of sensory systems.

Excitable Properties of the Motor Cortex. Historical Note. Much of the knowledge derived in the late nineteenth and early twentieth centuries from the stimulation of the cerebral motor cortex is now superseded by information obtained with more refined methods both of stimulating and recording. The effects of pyramidal and extrapyramidal activation cannot be separated by cortical stimulation. Briefly summarized, early results of cortical stimulation indicated that: (i) Reciprocal innervation described by Sherrington in 1899 was the rule but exceptions are often seen, *e.g.*, because flexor and extensor points may overlap. (ii) The response latency to repetitive stimulation may be much longer than reaction time, and may in part be traced to the stimulation of overlapping antagonistic flexor and extensor points. (iii) Afterdischarge often follows strong stimulation, being first tonic and then clonic; this is also seen in the Jacksonian type of epilepsy. (iv) Facilitatory and inhibitory effects occur between cortical loci. (v) In the 1930's several phenomena were described, accepted and then discounted, *e.g.*, "suppressor bands" and "spreading depression,"[86] a slowly spreading (2 to 3 mm/sec) decrease in electrical activity and excitability following strong chemical, mechanical or electrical stimulation, especially in the rabbit. Marshall[95] showed that such depression is an important experimental source of error and is caused or greatly increased by dehydration and cooling of the cerebral cortex. It may play a role in postepileptic seizure depression and may account for the so-called "suppressor bands" of the cerebral cortex.

The discussion of voluntary activity cannot be completed in this chapter, which deals mainly with the PT and only partially with the cortically originating extrapyramidal system (COEPS). Complete understanding of the neural basis of voluntary movement must take into account other subcortical structures, especially the cerebellum and basal ganglia. Because serious disturbances of voluntary move-

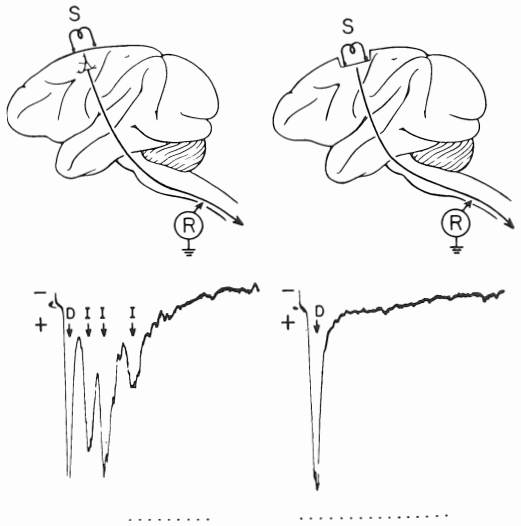


Figure 3–24 Direct (*D*) and indirect (*I*) PT responses to stimulation of motor cortex (*left*) and underlying white matter (*right*) in the monkey. Recording electrode was in the lateral column of spinal cord at C_1. Dots at bottom represent 1-msec intervals. (After Patton and Amassian, *Handb. Physiol.*, 1960, Sec. I, 2, 837–861.)

ment occur after damage to these structures, they probably also play some part, as yet unknown, in cortically induced movement. Thus, voluntary movement, a complex matter, can only be described in piecemeal stages.

Initial Stage of Corticospinal Tract Activity. To investigate the PT activity evoked by a single cortical stimulus, Patton and Amassian[105, 106] recorded the tract response in the monkey's bulbar pyramid or cervical PT. The first deflection is a stable, short-latency (0.7 msec), short-duration, positive wave called the D-wave (Fig. 3–24). Following by 2.0 to 2.5 msec is a series of positive, imperfectly rhythmic waves, which repeat for many milliseconds. Analysis indicated that the first wave represented the response of PTN's directly excited by the stimulus. The later deflections were termed the "I-waves" because they were caused by indirect or interneuronal excitation of PTN's. The longer latencies of the I-waves were attributed to the time consumed in traversing chains of intracortical neurons.

The experiments leading to these conclusions are an excellent example of a neurophysiological analysis. Briefly, relative to the I-waves, the D-wave was more resistant to anesthesia and anoxia, had a shorter recovery cycle, and persisted when the cortex was removed and the underlying white matter was stimulated (Fig. 3–24). The I-waves appeared only when the tip of the stimulating electrode was within the cortex. Further, when the stimulating electrode was moved rostrally in the cerebral cortex, the D-wave disappeared, but the I-wave persisted. The discovery of the I-wave helps to resolve the controversial aspects of localization in the motor cortex. For this reason subsequent studies of D- and I-waves will be discussed in some detail.

Additional evidence that the I-waves depend on cortical interneurons and not on a slower conducting category of PTN's directly stimulated, bypassing the cortical stage, has been provided by Gorman.[60] The maximal conduction velocity in axons of "slow PTN's" is about half that of the axons responsible for the first I-wave discharge, thus eliminating the "slow PTN's" as an explanation. The expected contribution of the slow PTN's to the tract response is apparently not seen because of greater dispersion of the fiber conduction velocities.

As careful as the D- and I-wave analysis was, Kernell and Wu[75] challenged it because anodal surface stimulation, less effective than cathodal in discharging cortical interneurons,[65] may produce only a D-spike. Strong anodal stimulation induced waves similar to I-waves but were held to represent a multiple discharge of the same PTN's rather than their activation by cortical interneurons.[75] Rosenthal *et al.*[125] countered this criticism by recording single PT discharge extra- and intracellularly at the site of stimulation. At certain electrode positions or stimulus strengths, the PTN discharges "jumped" from one latency to another. Latencies for the same PTN fell into two distinct, well-separated narrow latency histograms indicative of a dual mode of activating the PTN. The second and later discharges jump between two nonoverlapping latency bands separated by a time interval equal to D- and I-latency differences (Fig. 3–25). Thus, Patton and Amassian's original interpretations were confirmed. However, stimulation and recording with microelectrodes inserted into the depth of the motor cortex (cat) indicates a very limited horizontal spread of impulses[8] varying with the depth of stimulation. Single synaptic spread was mainly less than 0.4 mm, and polysynaptic spread was about the same except for superficial cortical layers (1.2 mm maximum). However, weak intracortical stimulation does not give the extent of horizontal spread through interneurons because it may excite insufficient neurons to summate and propagate.

Cortical Recurrent Inhibition and Facilitation. In addition to *collaterals* branching from the long descending axons, many PTN's also give rise to *recurrent axons* arising near the cell body. Recurrent axons

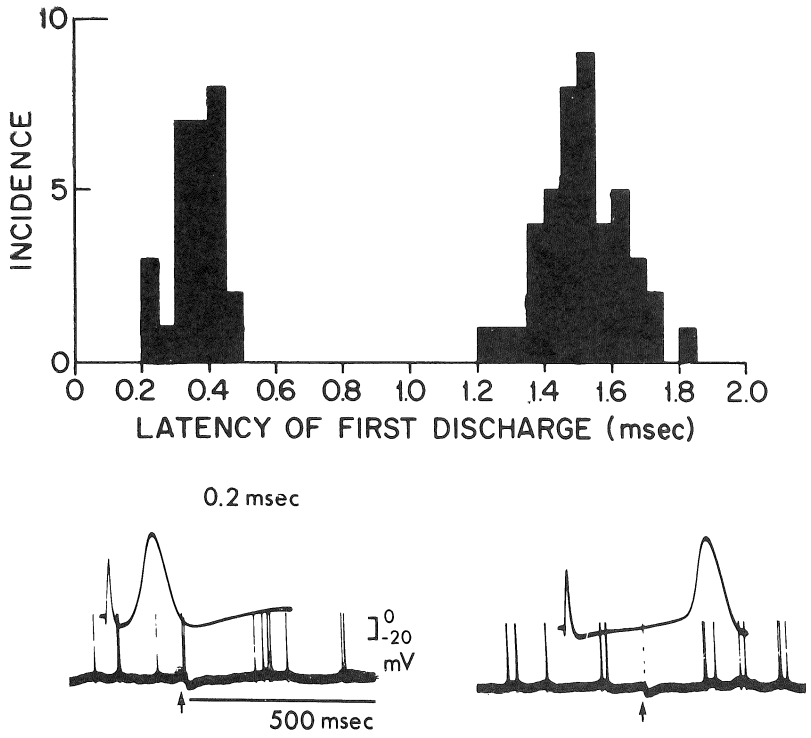


Figure 3–25 Latency distribution of first discharge of a verified PTN stimulated and recorded at the cortex. Note that the initial discharges fall into two groups with no discharges at intervening latencies, confirming D- and I-activation as opposed to repetitive PTN discharge. The mean latencies of the second group of first discharges (*i.e.*, free of any delay from a preceding D-response) suggest that they are disynaptic I-responses. (From Rosenthal *et al.*, *J. Neurophysiol.*, 1967, *30*, 844–858.)

may return to the neuron of origin, or to other cortical neurons, *e.g.*, fast or slow PTN's as described below. They must play a role in the cortical stage of the PT discharge and of movement. Recurrent axons may affect nonPTN's as well as PTN's and may be excitatory as well as inhibitory. Inhibitory connections might serve to channel or constrict the spatial extent of cortical activity and may also limit the firing rates of PTN's. Otherwise focal cortical activity could spread throughout the motor cortex, producing widespread muscular activity as in Jacksonian epilepsy; it also would restrict receptive fields that may be of the wide field variety. Excitatory recurrent axons are the first of potential excitatory feedbacks found at virtually all major levels of the motor systems. Such positive feedbacks could sustain and prolong a corticofugal discharge and are probably important in generating patterns of activity during movements, especially those in which there seems to be little or no time for proprioceptive feedback.

Synaptology of Recurrent Inhibition and Facilitation. Phillips[110] first investigated the synaptology of lateral connection by recording from PTN's intracellularly while stimulating the PT antidromically at the pyramids; single shocks elicited EPSP's at monosynaptic latencies, indicating excitation of adjacent cortical neurons via lateral axons. Higher stimulus intensities induced IPSP's with longer latencies, suggesting an interposed neuron. Stefanis and Jasper[133] established that the PTN membrane changes were not a result of current spreading to the neighboring medial lemniscus, but raised the possibility that many of the phenomena of recurrent excitation may be exaggerated by using antidromic stimulus frequencies much above the physiological range at which PTN's discharge. Others have found that recurrent excitation outweighs inhibition on naturally firing PTN's.

Takahashi *et al.*[139] proved that the EPSP's evoked by antidromic PT stimulation are truly a recurrent excitation, not an antidromic depolarization of the cell. EPSP's were recorded mainly in fast conducting PTN's (>20 m/sec), but were induced by recurrent axons of "slow PTN's." Lateral excitation induced with synaptic delays of 0.3 msec, and frequency fol-

lowing of 200/sec indicated that no interneuron intervened between recurrent collaterals and dendrites. Histological evidence is consistent with slow PTN's being facilitatory to fast PTN's because collaterals from the more superficial small and presumably "slow PTN's" pass to the deeper layers where large, "fast" PTN's are found (cat). However, the functional significance of this recurrent excitatory relation between "slow" and "fast" PTN's remains unknown.

To summarize the speculations about recurrent inhibition and excitation, a positive feedback at the cortical level may reinforce a cortical discharge and constitutes the shortest of the potential "internal feedback loops." One dimension of a program is time, and such positive feedback may contribute to extending PT discharge over time. Recurrent inhibition may "shape" the outflow from the motor cortex by suppressing fringe PTN's discharge which could be advantageous in making discrete movements.

"Fast" and "Slow" PTN's. Population studies of a sufficiently large sample of neurons to permit statistical treatment enabled Towe *et al.*[146] to identify two populations of PTN neurons; one had a peak antidromic latency of 1 to 2 msec after pyramid stimulation and is known as "fast" PTN's; the "slow" PTN's had a comparable latency 3 msec longer. This dichotomy has been verified by intracellular PTN recording and antidromic stimulation and different membrane properties have been established.[139] That the two types originated in deep and superficial layers seems not to hold for the monkey's motor cortex (Humphrey, personal communication). More recent observations on single PT discharge in awake, behaving monkeys show that fast and slow PTN's behave differently. In awake but inactive monkeys, Evarts found that spontaneous activity of "fast" PTN's tended to exhibit lower average firing frequency than "slow" PTN's. However, the reverse held during movement; the fast neurons' discharge accelerated greatly, reaching 80 to 100 imp/sec over brief periods in wrist movement, but fired at much lower rates averaged over longer periods. Many slow PTN neurons (antidromic latencies greater than 1.0 msec) discharge less during movement. Evarts[38] concluded by analogy with spinal motoneurons that slow PTN's may be termed "tonic" (continuously active) and the fast units "phasic" (periodically active).

That the PT is a relatively slow system is consistent with many studies of its fiber size, but inconsistent with the image of the PT as carrying out quick motor responses. Even the small component of large, relatively fast conducting axons is, as we have seen, relatively slow in conduction rate, slower than some bulbospinal systems.* The explanation of this may lie in the extensive collateralization of PT axons and consequent thinning of axons. The preponderance of very slowly conducting axons is difficult to reconcile with the idea that the PT initiates certain types of movements. A calculation for man[144] indicates that two thirds of the PT axons would require 100 msec or more to conduct to the cervical enlargement, *i.e.*, 100/160th of reaction time to an auditory stimulus. Maximal PT conduction velocity within the spinal cord was estimated to be 60 to 70 msec, much slower than conduction in Ia primary afferents. Although the PT is considered the prime mover in the temporal sense, additional knowledge of conduction times in nonpyramidal systems may change this view. As noted, conduction is more rapid in the rubrospinal tract.

Spinal Stage of PT Function. The endings and action at the spinal level of axons of neuronal systems originating in the motor cortex, like those of other descending tracts, are complex and the details are still being worked out. In Chapter 2, Volume I nearly a dozen different possible segmental sites of actions of descending tracts are categorized and discussed in relation to lower brainstem descending pathways. Most of this analytical work by Lundberg and colleagues was performed on cats. In them the action of the motor cortex on reflex arcs, unlike other descending pathways, is facilitatory, but the net result may be inhibitory, due to facilitation of interneurons. For example, stimulation of motor cortex facilitates both the excitatory action on flexor motoneurons of a group of afferents collectively known as FRA (flexor

*Other factors than conduction time are involved in system behavior—starting time, synaptic delays and recruitment time for motoneurons. Recruitment over 50 msec might be more meaningful than latency of first EPSP or motor unit discharge.

reflex afferents) as well as the reciprocal inhibitory action on extensor motoneurons exerted by FRA. Intracellular recording directly demonstrated that these effects are exerted on interneurons. Motor cortex stimulation also causes primary afferent depolarization or PAD, resulting in presynaptic inhibition of subsequent inputs. This is demonstrable for FRA terminals, but not those of Ia afferents. The end result of PAD and effects on interneurons of mass stimulation of the PT or motor cortex would be conflicting, flexion reflex inhibition and facilitation, respectively. Effects of specific cells may be more specific and functionally meaningful.

In the cat the PT ends on interneurons making segmental connections and on neurons giving rise to ascending axons. In the monkey, direct or monosynaptic endings of the PT axons on motoneurons—so-called corticomotoneuronal (CM) fibers—is borne out by histological and physiological study. However, the percentage of PT endings on motoneurons is small; it has been estimated to be 2 per cent for monkeys, 5 per cent for chimpanzee, and 8 per cent for man.[77] The number of monosynaptic endings is greater for motoneurons of distal muscles than for the proximal and axial musculature and can be expected to be greater from the banks of the central fissure than more rostrally. Monosynaptic connections between PT terminals and motoneurons increase abruptly from carnivores to monkeys, and increase continuously throughout the primate series. This, and physiological evidence described above, suggests that the PT becomes progressively more "motor" in primate phylogeny and more an executor than executive (as defined above). For example, working through reflex arcs would be considered an executive action. This may prove to be counterbalanced by increased PT endings on synapses of the posterior column and other sensory systems once their significance is known. Even in primates many PT axons end in the dorsal horn, especially in the lateral part, its base, and in the zona intermedia (see Chap. 6, Vol. I).

The general features of the segmental activity produced by stimulating the pyramids were established by Lloyd[87] in one of the earliest applications of microelectrode recording to the central nervous system. To eliminate all other descending tracts, the medulla was transected sparing only the pyramids; and to eliminate any cortically reflected PT discharge involving ascending pathways, the brainstem was transected (Fig. 3–26) (now termed the Lloyd pyramidal preparation). Single PT shocks were ineffective in evoking spinal cord cell activity; temporal facilitation from a train of stimuli was necessary. Thus, the PT showed a surprising *inertia* for a system supposed to carry out swift voluntary activity. The greater dependence upon facilitation of repetitive stimuli in cat versus monkey was established by Stewart and Preston.[136]

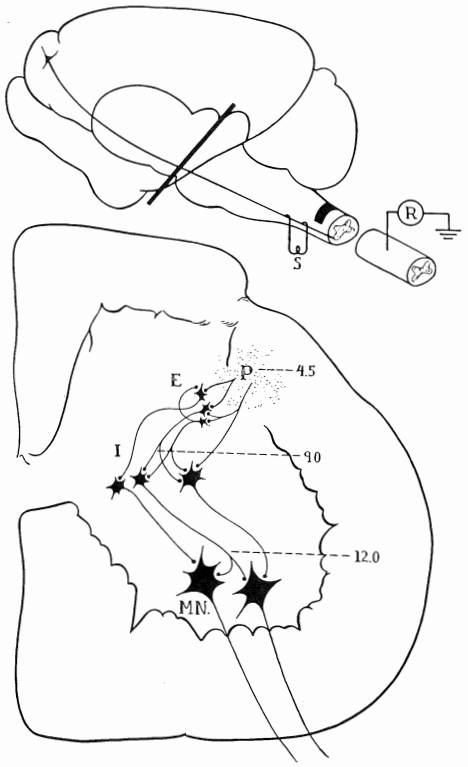


Figure 3–26 Lloyd's experiment on activation of spinal nuclei by pyramidal tract stimulation. Upper drawing shows positions of stimulating and recording electrodes and of brain sections to rule out nonpyramidal conduction and reflected discharge from cortical levels. Time noted at each level is first detectable facilitation of nuclear neurons. Subtraction gives nuclear delay in *previous nucleus*. *P*, pyramidal tract; *E*, external basilar cells; *I*, intermediate nucleus of Cajal; *MN*, motoneuron. (After Lloyd, *J. Neurophysiol.*, 1941, *4*, 525–546.)

It is the fast PTN's that make monosynaptic connections with motoneurons in nonhuman primates. That such PT axons are distributed most heavily to the motoneurons of the distal musculature was confirmed, as the synaptic effects intracellularly recorded were more powerful in such motoneurons.[114] In a further analysis, Clough *et al.*[29] recorded from the motoneurons innervating specific muscles of the baboon's hand. The EPSP's in motoneurons of extensor digitorum longus, (a physiological flexor) and of intrinsic muscles of the hand were larger than in the motoneurons for other forearm muscles. Significantly, virtually *all* the EDL motoneurons received a detectable, monosynaptic CM input. Later, but not much later (<1.5 msec), summating waves of EPSP's occurred, apparently correlated with PT I-waves. Maximal EPSP's averaging over 3 mV in intrinsic hand muscle motoneurons document (and delimit) the net effect of the motoneuron's colony. Thus, in anesthetized monkeys even maximal EPSP's fall short of the required depolarization to fire motoneurons from a resting membrane potential, much less produce strong voluntary contractions.

Whether the monosynaptic PT connections in the primate are sufficiently powerful to qualify for an executor function has been questioned. Landgren *et al.*,[79] by recording EPSP's from baboon motoneurons, demonstrated temporal facilitation consistent with a substantial CM connection. The motoneuron EPSP's produced by successive shocks at high frequencies (200/sec) progressively increased in magnitude; the EPSP at the end of the stimulus was ten times that of the initial EPSP deflection (Fig. 3–27). Since the PT volley remained unchanged in size, the increases could not be due to recruitment of corticospinal cells. This facilitation also explains the efficacy of long duration pulses (500 msec), which set up a high frequency discharge of corticofugal neurons. However, such frequencies are unphysiological, as are the frequently used stimulation rates of 200/sec, well above the 100/sec actually recorded from motor cortex neurons during voluntary movement.[38] Porter[116] found the maximum facilitation between pairs of cortical shocks to occur at 2-msec intervals, corresponding to rates of 500 imp/sec; facilitation decayed to half value in 10 msec, still beyond the usual physiological range.

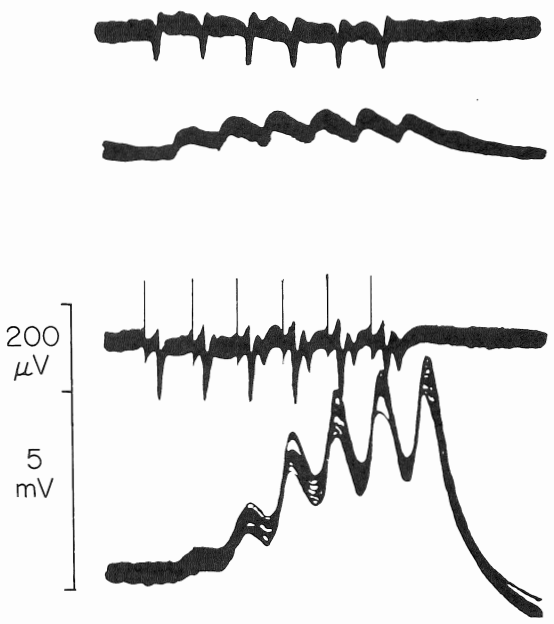


Figure 3–27 Monosynaptic EPSP's evoked in a cervical motoneuron of the baboon by Ia afferent volleys (*above*) and corticomotoneuronal volleys (*below*) at 200/sec. Stimulus intensities were adjusted to give similar magnitudes of initial EPSP's. Note that successive Ia-EPSP's have the same amplitude, in contrast to the increasing amplitudes (facilitation) of successive CM-EPSP's. In both cases the size of the afferent volleys (top traces) remained constant. (From Phillips and Porter, *Progr. Brain Res.*, 1964, *12*, 222–245.)

The effect of PTN→interneuron→motoneuron connections of short latency with repetitive stimulation is not to be excluded from the executor function of PTN (the cat uses its arms skillfully without CM connections). If the PT works by commanding or facilitating segmental reflex arcs, it is acting in an executive fashion, using a "wired in" segmental mechanism. If it has private interneurons or shuts off the segmental afferent input by presynaptic inhibition, then the PT→interneuron→motoneuron system is an executor.

The mode of termination of descending pathways and the degree to which they end monosynaptically on the same part of a motoneuron as segmental afferent fibers would permit deductions as to function. A descending pathway could affect the motoneuron pools either directly or by modulating an afferent input. Unlike the EPSPs from minimal Ia volleys, which increase

greatly with increased strength of nerve stimulation, minimal EPSP's in *lumbar* motoneurons induced by cortical stimulation are mainly augmented by repetitive discharge of corticomotoneurons and then rather weakly at best. However, in forelimb motoneurons EPSP's did increase with intensity of cortical stimulation.

When PT and Ia pathways were simultaneously stimulated, the resulting EPSP's were merely the sum of the two EPSP's, again suggesting termination at different sites on the motoneuron. On the other hand, facilitation of responses to repeated cortical shocks is quite striking (40 to 50 per cent in the majority of cells), while responses to Ia afferents do not appreciably facilitate one another.

If the PT does in fact end on distal segments of motoneuron dendrites, which can extend into the intermediate zone of the dorsal horn, the number of monosynaptic connections with motoneurons may have been underestimated, but distal dendritic synapses are considered not to contribute strongly to motoneuron discharge.

To summarize, we are faced with the apparent paradox that the system credited with contributing the force of muscular movements exhibits very little temporal summation at physiological rates of discharge. Further, these experiments would suggest that the PT does not achieve powerful motoneuron discharge by facilitating one of the strongest segmental afferent inputs, the Ia group of fibers. The two systems both ending monosynaptically show little interaction, at least when evoked by single volleys.

Relation to Different Classes of Motoneurons. Sherrington's finding that cortical stimulation produces reciprocal effects in antagonistic muscles has been confirmed and elaborated. Preston and his collaborators[see 119, 136] have studied monosynaptic reflexes in cats and monkeys with all of the brainstem except the pyramid sectioned.[87] In the cat the effect of PT stimulation on segmental reflexes is a facilitation of flexor motoneurons and inhibition of extensor motoneurons in both fore and hind limbs. In the monkey's arms the relationship is more complicated, as are the movements of the semiliberated forelimbs. PT stimulation commonly evoked a small, brief facilitation, especially in the motoneurons of flexor and fast extensor muscles, presumably via corticomotoneuronal axons. This was followed by a brief and apparently disynaptic inhibition, followed in turn by a prolonged facilitation of motoneurons belonging to fast muscles* (flexors and fast extensors), but a prolonged inhibition in the motoneurons of slow postural muscles. These findings were functionally interpreted as follows: for delicate movements of the digits to occur, the extensor muscles, keeping the forelimbs on the ground in quadrupedal animals, must be inhibited and replaced by a flexed posture at proximal joints, thus enabling the distal muscles to manipulate objects within visual observation.

Some differences between cat and monkey are only apparent ones. In the cat, the physiological extensors of the ankle are clearly antigravity because the ankle is off the ground, and consistently the ankle extensor motoneurons are strongly inhibited by the PT. In the monkey, the ankle joint is on the ground and not tonically extended, and the motoneurons of the ankle extensors are only weakly subject to PT inhibition. Where extensor muscles are clearly antigravity as in knee and hip, both tonic and phasic extensor motoneurons are inhibited (cat and primate). Flexor motoneurons of the elbow are inhibited from the motor cortex in the baboon and facilitated in the cat; in the liberated forelimb of the sitting baboon the elbow flexors oppose gravity.

Extensor digitorum communis, a physiological flexor, receives more corticomotoneuronal excitation than flexor digitorum longus, which is a physiological extensor opposing gravity in quadrupedal standing and locomotion. Understanding the role of the PT in executing fine movement sequences requires making a distinction between manipulation and standing or walking. Palmar flexion of the digits, an antigravity action in standing, is also one of the most common of manipulative maneuvers and presumably would require finer cortical control than dorsiflexion of the fingers.

To summarize, the argument that the motoneurons of the small muscles of the hand receive heavy monosynaptic PT input

*Muscles with a brief time to maximum twitch tensions.

would seem to support the hypothesis that PT is concerned with executing movement. The almost equally heavy monosynaptic PT influence on the motoneurons of extensor digitorum communis can be explained on the grounds that this muscle acts in conjunction with intrinsic finger flexors by stabilizing the wrist.

Granted that reciprocal innervation and cocontraction of antagonists are both functionally useful, the question of how these opposite functions are accomplished remains. The potentiality for both exists at the segmental level: "reciprocal action" through interneurons, and cocontraction through corticomotoneuronal connections. ICMS indicates that both can also be evoked by cortical stimulation. Microstimulation deep in the cortex produced contraction of an agonist and inhibition of the antagonist. In other penetrations, the groups of cortical neurons yielding these opposite effects were spatially distinct though close by or partially overlapping.

PT-gamma Efferent Control. In addition to affecting α-motoneurons (monkey), the PT and COEPS activate fusimotor or γ-motoneurons innervating the intrafusal fibers of the muscle spindle. Fusimotor discharge maintains the sensitivity of the spindle to stretch by contracting its intrafusal fibers, thus preventing it from being slackened or "unloaded" when the surrounding extrafusal muscle fibers shorten. Stimulation applied to reflex afferents and to a wide variety of points in the brain will coexcite or coinhibit both the α- and the γ-motoneurons.[see 61] This is called "alpha-gamma linkage" or, better yet, coactivation.

Thus, in the cat PT inhibition of the α-motoneurons of ankle extensor muscles is matched by inhibition of extensor γ-motoneurons; conversely, both α- and γ-motoneurons to flexor muscles are facilitated. In the monkey[61] the more complex relationship of the PT to motoneurons of ankle flexors and extensors is paralleled by a complex fusimotor activation by PT stimulation.

The alpha-gamma coactivation was documented in fine detail by Mortimer and Akert[101] who showed that the cortical points activating the two types of motoneurons coincided (Fig. 3–28). The γ-motoneurons had discrete areas of cortical representation like those of α-motoneurons (5.0 to 9.5 mm^2), and often the two types of motoneurons in a given filament of the ventral root were activated from the same cortical points (Fig. 3–28). This overlapping representation at the cortex, like the close relation between muscle spindles and motoneurons of adjacent extrafusal fibers (Chap. 8, Vol. I), suggests that a detailed control rather than a global facilitatory action is executed through the fusimotor system.

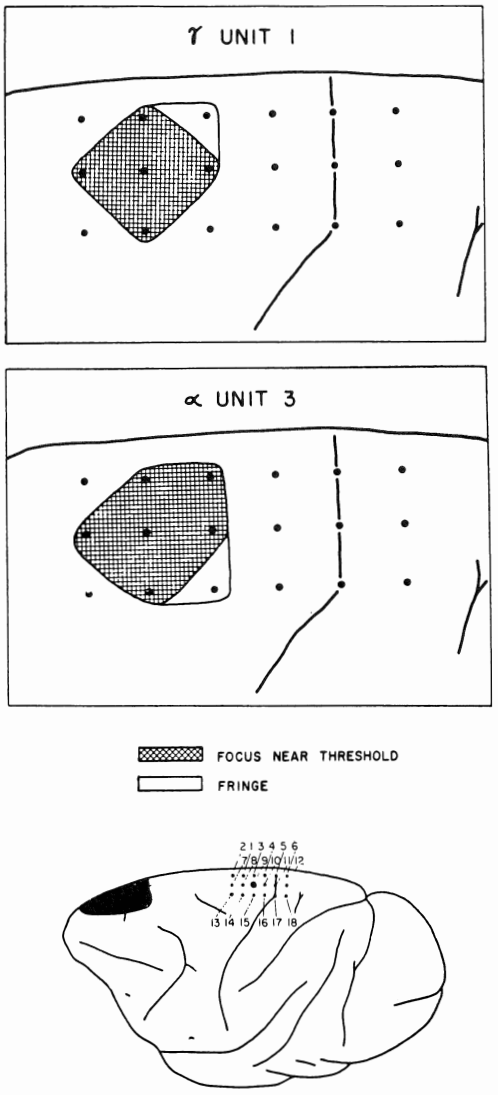


Figure 3–28 Maps showing cortical areas from which gamma (upper) and alpha (middle) motoneurons of a single ventral root filament were caused to discharge by stimulation of monkey's cerebral cortex. Note similarity in size and position of the excitable field (focus and fringe) for α and γ motoneurons and to Figure 3–18. Stimulation points 1 mm apart. (From Mortimer and Akert, *Amer. J. phys. Med.*, 1961, *40*, 228–248.)

Descending control of α and γ motoneurons may be exerted in one or more of several possible ways: (i) PT-COEPS may produce movement by increasing γ-efferent discharge, thereby inducing α-motoneuron discharge via returning spindle discharge; (ii) γ-motoneurons may be coactivated with α-motoneurons, preventing unloading through slackening of the intrafusal fibers by contraction of parallel extrafusal muscle fibers; (iii) spindle activity may be involved in correcting deviations from "intended" movement via either segmental or supraspinal circuits; (iv) γ-efferent activation may be involved only in tonic or postural PT and COEPS activities. The first concept, initially proposed by Merton[see 99] in 1953 and supported by Granit,[61] was later modified to the "follow-up length servo," which states that after an initial direct effect on α-neurons, descending pathways excited them indirectly by activating γ-efferents. The validity of proposition (i) (and also ii and iii) depends on whether γ-firing and spindle afferent discharge are *early* enough and are *strong* enough to explain voluntary contraction.

Any γ-activity in the cortical control of movement has four temporal phases: (i) conduction from motor cortex to γ-motoneuron, (ii) conduction time in the γ-motoneuron, (iii) delay in the intrafusal and extrafusal contraction of muscle sufficient to affect receptor firing and (iv) conduction from spindle afferent impulses to motor cortex directly or through other cortical areas.

The first phase appears to be rapid. Laursen and Wiesendanger[84] used the Lloyd preparation and the Sherrington-Towe strand method by lifting onto electrodes a bundle of pyramid fibers to obtain pure PT stimulation. The γ-motoneurons responded to weaker PT stimulation and with a shorter latency than α-motoneurons, suggesting but *not proving* that larger PTN's activate γ-motoneurons.

In the monkey, some of the γ-motoneurons of the hand receive monosynaptic connections from corticospinal fibers (0.7 to 1.0 msec from the tract wave to the beginning of EPSP, much the same as in α-motoneurons). Although a single monosynaptic EPSP is insufficient to fire γ-motoneurons, temporal summation is even more effective, as with α-motoneurons.

In another study of hand muscles (extensor digitorum communis) of the baboon,[76] γ-motoneurons had higher thresholds to cortical stimulation than did monosynaptically excited α-motoneurons and weak cortical stimuli did not prevent unloading of the spindle.

Although conduction from cortex to γ-motoneuron is rapid, the second and third stages, conduction to the spindle and contraction, are slow. On the whole there seems to be sufficient trade-off between stages *i* and *ii-iii* to permit the gamma-alpha interaction. Vallbo[149a] reached the conclusion from experiments on man that spindle afferent acceleration, though highly variable, occurred *after* the beginning of EMG activity (0.1 to 0.5 sec) and 10 to 15 msec after the beginning of extrafusal muscle contraction. This delay approximates the difference in stage *ii*, α- and γ-efferent conduction time. Whether the γ-α linkage from cortical stimulation is strong enough to be significant relative to α-motoneuron activation is questionable. A subsidiary to the hypothesis is that Ia afferent input to α-motoneurons summates strongly with PT inputs. Phillips[112] and others have questioned the main hypothesis. Whereas the corticomotoneuronal activation of the α-motoneuron group supplying a given muscle of the monkey's hand may be matched by or exceeded by the spindle activation of the motoneuron for the muscle, the reverse is true of some muscles.[29] In man, as in animal experiments, Vallbo[149a] found spindle discharge frequency closely related to the strength of an isometric contraction. From complicated calculations, Vallbo concluded that the fusimotor muscle spindles "do not constitute a very powerful feedback mechanism to hold muscle length constant when load varies." Moreover, the established spreading of spindle discharge from one intrinsic hand muscle to the motoneurons of several related muscles would seem to preclude the motor cortex activating α- through γ-motoneurons in the delicate movements of the fingers.[29] In the monkey, pyramidotomy[56] indicates that the PT exerts a strong tonic facilitatory action on γ-efferents.

TYPES OF SPINDLE AFFERENTS ACTIVATED. In man, axons having the characteristics of primary spindle afferents showed a strong dynamic response during finger movement, but adapted to sustained stretch.[149a] A second type showed greater

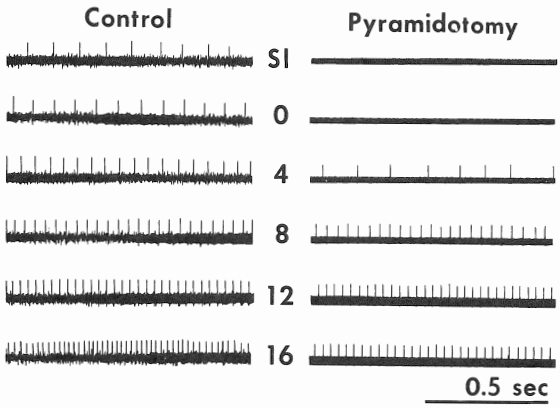


Figure 3–29 Responses from a primary spindle afferent in a normal control monkey and six days after bilateral section of the pyramids. The numbers represent stretch of the gastrocnemius muscle in millimeters during the static phase. (From Gilman *et al.*, *Brain*, 1971, *94*, 515–530.)

static properties and are presumably the secondary spindle afferents. Recording Group Ia discharge during muscular contraction demonstrated that spindle afferent discharge usually *followed* the onset of the EMG activity, *i.e.*, occurred considerably later than α-motoneuron discharge. Significantly, most afferent units (87 per cent) discharged during weak voluntary contractions without detectable muscle shortening (isometric contraction). This suggests that the γ-efferents play a role in weak contractions. As noted above, Vallbo[149a] calculated that γ-spindle discharge could add little to isometric tension induced by α-discharge. Thus, the balance of evidence from animal and human experiments suggests that besides a direct effect on α-motoneurons, PT produces a somewhat delayed coactivation of the γ-efferents, preventing the unloading of the spindle during weak contraction.

INHIBITORY EFFECTS ON γ-EFFERENTS. A further parallel between γ- and α-motoneuron activation is that cortical stimulation may inhibit as well as excite γ-efferents and the effects are generally the same for a given motoneuron pool. γ-motoneurons of soleus, a slow muscle specialized for posture, tended to be inhibited whereas its synergist, gastrocnemius, a fast muscle specialized for movement as well as posture, tended to be facilitated.

Intracellular recording also reveals disynaptic IPSP's in γ-motoneurons from cortical stimulation which could have the same significance as α-motoneuron inhibition in confining a movement to specific muscle group with the added advantage of countering some of the loss of local sign noted in primary spindle activation of cortical neurons (see below).

Presynaptic Inhibition. The fourth way the PT[89] (and COEPS) can play a role in the segmental stage of cortically induced movement is by presynaptic inhibition, *i.e.*, depolarizing and decreasing the synaptic efficacy of primary afferent terminals (PAD). Demonstrable from descending tracts originating in the more caudal brain stem, PAD seems most powerful from cortico- and rubrospinal stimulation.[67] The functional role of PAD may be to reduce segmental influx, switching control of the interneurons and motoneurons to the cortico- and rubrospinal systems. According to this view, the motor cortex would act less as an executive operating through segmental reflex arcs and more as an executor of movement by reducing competing segmental input.

RUBROSPINAL TRACT

Anatomical Considerations. In discussing the anatomy of pyramidal and extrapyramidal systems, COEPS subsystems, which have indirect but relatively uncomplicated descending connections with segmental neurons, were distinguished from subcortical subsystems, which reflect back to the cerebral cortex, potentially constituting intrinsic loops. The red nucleus falls into both classes. It is activated by PT collaterals (PPS) and its descending tract exhibits many parallels to the PT anatomically and functionally and in fact is linked with the PT to form the lateral system of Kuypers. The red nucleus also re-

ceives a heavy input from the cerebellum and projects to the inferior olive, which in turn projects to the cerebellum, forming an intrinsic feedback loop that can affect motor cortex function through the strong connections between cerebellum and motor cortex. This aspect of the red nucleus will be discussed in the next chapter.

The red nucleus has small and large cells, the latter concentrated in the caudal part of the nucleus (pars magnocellularis). Both contribute to the rubrospinal tract. The red nucleus projects much more heavily to the cervical than to the lumbar region, suggesting greater involvement in manipulative than in postural movements. In the cat, the rubrospinal tract, like the pyramidal tract, terminates in the intermediate zone of the gray matter, not among the motoneurons. In the monkey, a topographically organized corticorubral pathway arises in the precentral gyrus and adjoining regions.[78] Whether a significant rubrospinal tract exists in the chimpanzee is questionable, and its status in man is also somewhat uncertain. The number of large cell bodies in the nucleus has decreased in the primate series including man, but this does not mean that the tract is rudimentary since small cells give rise to rubrospinal axons.

The rubrospinal tract is not the only connection between the nucleus and the spinal cord. A projection from the caudal pole to the inferior olivary nucleus influences fusimotor activity by an olivospinal pathway.[5]

It is important to note that mesencephalic tegmental areas adjacent to the red nucleus share many of its properties and may also originate a descending pathway, directly or via bulbar or pontine reticular nuclei. Such a system would need to be taken into account in interpreting the effects of rubral lesions, for example, the early finding that destruction of the red nucleus was not sufficient to produce decerebrate rigidity.

Spinal Stage of Rubrospinal Action. Hongo *et al.*[67] analyzed the segmental termination and action of the rubrospinal tract of the cat. Like the PT, the rubrospinal tract terminates on interneurons, which mediate depolarization of primary afferents and activation of motoneurons. However, in monkeys, Shapovalov *et al.*[132] have reported monosynaptic actions on motoneurons of distal leg muscles in this respect resembling the PT, but the EPSP's are independent, nonocclusive and only arithmetically summative (Fig. 3–30). The *net end effect* on motoneurons in the cat is predominantly the production of EPSP's in flexor motoneurons and IPSP's in extensor

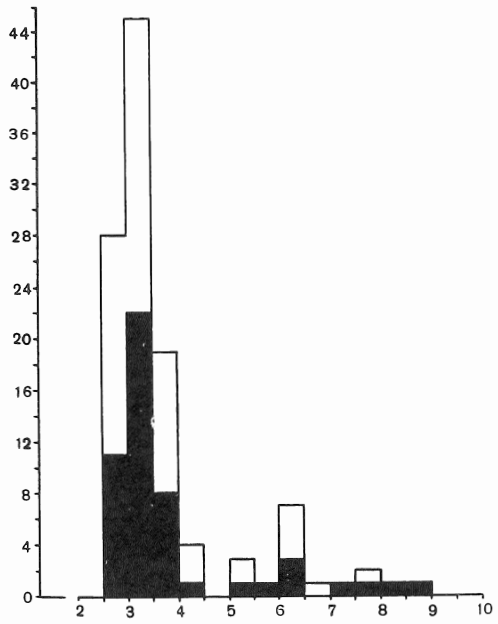


Figure 3–30 Latency distribution of EPSP's in motoneurons evoked by rubrospinal volleys. Black columns represent latencies after acute and chronic damage to the origin or course of pyramidal tract. Ordinates, number of motoneurons; abscissae, latency from magnocellular red nucleus to motoneuron (latency from early peak of cord dorsum potential to onset of EPSP was less than 1.0 msec in 69 motoneurons). (From Shapovalov *et al.*, *Brain Res.*, 1971, 32, 325–348.)

motoneurons. (Facilitation of motoneurons of the toe extensors is only an *apparent* exception since the anatomical toe extensors are physiological flexors, *i.e.*, they do not oppose gravity.) However, Shapovalov found in the monkey the most prominent EPSP to FDL, deep peroneal and plantar nerves which innervate a mixture of flexors and extensors.

The rubrospinal tract also controls conduction over various reflex pathways. The effect on flexor reflexes from FRA (flexor reflex–inducing afferents) is not simply facilitation of the interneurons as the final motoneuron effect of rubrospinal activity might indicate. The rubrospinal tract's action on the powerful Ia interneuronal inhibition of flexor motoneurons would facilitate discharge of flexor motoneurons by disinhibition. Like the PT, the rubrospinal tract may depolarize the terminals of primary afferents (PAD), resulting in presynaptic inhibition. The relationships are quite complex; one complexity difficult to interpret is that the action on afferent terminals of FRA is opposite that on interneurons.

The action on afferent terminals may be to give the right of way to descending as opposed to segmental reflex inputs.

The preponderant flexor facilitation–extensor inhibition in the cat is strongly supported by Orlovsky[102] who recorded from the two classes of muscles while a cat walked on a treadmill. In the forward "swing phase" of the limb the flexors exhibited a strong EMG activity while the extensors were silent. The reverse held for the supporting and propulsive phase of the step. This reciprocal action disappeared when the rubrospinal tract was interrupted.

Rubrospinal-PT Relationship. The role of the red nucleus in voluntary movement viz a viz the PT may be considered in two categories: (i) as an adjunct to the PT in the production of movement, and (ii) as a superimposed mechanism for the control rather than the production of movement (Chap. 4, Vol. I). Some anatomical and functional considerations indicate that the adjunct role of the red nucleus is quantitatively significant. The rapid conduction in the rubrospinal tract, more rapid than in the PT, would indicate some important, primary (at least temporally) role of the rubral component PPS and COEPS. Having two modal velocities, 80 to 90 m/sec and 116 to 120 m/sec (max. 150 m/sec), shown by Eccles *et al.*,[37a] may indicate a dual function of the tract. However, conduction times are not reliable guides to function.

The massiveness of these systems is further indication of importance. Towe[144] estimated that 40 to 60 per cent of the PT axons that issue from the pons disappears into the brainstem before the pyramids are reached. What these fibers can accomplish can be estimated from the recovered motor activity following pyramid section discussed later. Destruction of the red nucleus appears to produce little obvious functional disturbance, this being concentrated in large muscle synergies involved in righting, standing and walking. However, in ablation studies the function of a structure cannot be directly inferred from initial deficits and residual abilities. For example, the participation of the red nucleus in the flexor and extensor phases of walking is clear, yet given time for recovery, the nucleus is not essential to stepping. Involvement in specific motor acts such as contact placing and ballistic arm movements have been documented, but the nature of the involvement remains to be clarified.

Certain data from experiments on monkeys[68a] are difficult to reconcile with the hypothesis that rubrospinal parallels corticospinal function. Insofar as an adjunct function can be identified with PT collateralization to the red nucleus (rather than interaction between PPS and COEPS at the cortex), such adjunct contribution to producing movement seems relatively minor.[68a] Although the PPS constitutes 86 per cent of the rapidly conducting connection between the cortex and red nucleus, slowly conducting direct corticorubral component of COEPS far outweighs PPS connections. Humphrey and Rietz[68a] have disclosed another factor inconsistent with the current view that the corticorubrospinal connections have an executive function. Neither the PPS nor the COEPS discharged the red nucleus cells; their action was facilitatory and that exerted by the COEPS connections far outweighed the facilitation by PT collaterals. While the corticorubral facilitation of the red nucleus neurons was followed by a mild depression of their excitability, none followed PPS facilitation. Therefore, the paradoxical hyperpolarization of rubral cells from pyramid stimulation[148] would appear to be peculiar to the cat.

The magnitude of the corticorubral connection indicates that pyramidectomy even if it induced a retrograde diminished activity of the PPS would leave a substrate for recovery of motor function. (To the contrary, PPS sprouting of terminals appears to occur.) The failure of combined PPS and COEPS action to evoke a strong synchronous discharge of rubral cells such as produced by weak stimulation of n. interpositus of the cerebellum led Humphrey and Rietz[68a] to the conclusion that the role of the corticorubral system is to modulate rubral activity induced by other inputs, and to play a role in feedback control rather than constituting a primary generator of voluntary movement.

The projection of the motor cortex to the red nucleus is described as topographically organized, but so far as is currently known, this is a crude somatotopic organization—leg motor area projecting to the portion of the red nucleus projecting to the lumbar spinal segments, etc. It is a fair assumption that a neural system that is to act

as an adjunct to or substitute for the PT after pyramidotomy should have a highly organized topographical relationship to specific motoneurons. Such a detailed topographical relationship between motor cortex and rubral neurons is yet to be demonstrated anatomically. Only recently has much attention been paid to this problem. However, Ghez[55] has applied the method of microstimulation and microrecording to study the input-output relations of the red nucleus, much as has been done for the motor cortex. In unanesthetized cats, separate rubral loci, weakly stimulated, activated single muscles, but with increased stimulus intensity (10 μA) the loci for flexor and extensor muscles overlapped considerably; the output traversed the contralateral dorsolateral columns, presumably the rubrospinal tract. An obstacle to ascribing a precise control function to the red nucleus is that its neurons have wide field cutaneous receptive fields and respond to deep pressure and joint movements in more than one limb, but a coinciding focus for maximal input and output was usually found.

The red nucleus as a potential feedback loop involving the cerebellum will be discussed in the next chapter.

OVERVIEW OF VOLUNTARY MOVEMENT AND ITS CONTROL IN PRIMATES

INTRODUCTION. This section will present an overview of the issues presented by the control of voluntary movements and some relevant hypotheses and speculations. Recent attempts to put experimental flesh on these speculative bones are discussed in previous and subsequent sections.

Voluntary movement is largely ignored by contemporary psychologists,* mainly because of the mentalistic flavor, if not the religious connotation of free will. Nevertheless, the issues now occupying neurophysiologists were appreciated and attacked by psychologists even in the 19th century. Until the past decade, textbooks of physiology have also avoided the topic of voluntary movement; neurophysiologists deal with the vagaries of the "excitable motor cortex," synaptic events there and at the spinal level, and the damage wrought by experimental lesions at various levels, but little attention is paid to voluntary movement itself. Fortunately, this has changed and symposia on volition have increased from one in three years in the 1960's to two per year in the 1970's.

A distaste for treating "voluntary activity" as fundamentally different from other neural activities is legitimate. The major objection—the concept of a "faculty" of will—is easily disposed of if one accepts an operational definition of voluntary activity, *i.e.*, an act which can be executed upon verbal request (as opposed to a reflex response to an afferent stimulus such as a tap on the patellar tendon). Presumably the individual can make the same request of himself when he wishes or of animals by suitable reinforcement as in operant conditioning. Significantly, operant conditioning is objective and quantitative, and it and other behavioral procedures† are increasingly used to investigate cerebral motor mechanisms of animals in place of the clinical neurological examination.

Sensory (Continuous) Feedback vs. Internal (Intermittent) Feedback Loops. The role of sensory feedback in the control of movement has been the subject of much discussion and experimentation since Charles Bell described the "circle of nerves" in 1826, and Clerk Maxwell quantitatively analyzed feedback control as exemplified by the automatic speed governor of the steam engine. With respect to eye movements, Helmholtz denied feedback from eye muscles. When we voluntarily move our eyes, objects in the external world do not appear to move, whereas they do appear to move if the eyeball is passively displaced by pressing near the lateral canthus. He concluded that we know the position of our eyes "as a result of the effort of will involved in trying to alter the adjustment of our eyes." Today one would not speak of an "effort of will," but the gen-

*A recent comprehensive textbook of experimental psychology has no chapter devoted to the subject and a recent review[73] numbers less than 100 references since 1900.

†The term "behavioral analysis" is becoming obscured by including in it neurological examination or "naked eye" observation of cage behavior. The phrase is best reserved to those observations which are quantitative and objective as seen in formal behavior situations, *e.g.*, operant conditioning; manipulation under standardized conditions as used by Lawrence and Kuypers[85] is semiobjective. Behavioral methodology in sensory neurophysiology is the subject of an essay in the next chapter.

eral idea is embodied in such concepts as "efference" copy or "corollary discharge."

The development of the mathematics and engineering of servosystems and emphasis on radar and sonar during World War II culminated in the publication of Norbert Wierner's *Cybernetics* in 1948; the idea of sensory feedback control of movements gained great impetus. This was furthered by the discovery of gamma efferents and their control of the muscle spindle discharge, which are in turn subject to multiple controls, segmental and supraspinal. Nevertheless, the control of voluntary movement was virtually neglected for nearly two decades. For example, few volumes on physiological control systems discuss the control of movement, or do so in a cursory fashion.

Prior to and concurrent with the application of servosystem concepts to the control of movement,[126] doubts were raised concerning sensory feedback and the reasonableness of Helmholtz's concept was appreciated. On the whole, the present trend is that *some* movements are programmed and executed without benefit of continuous, sensory feedback; others are not.

That a given movement can be controlled by employing the discrepancy between the target and the actual limb position is limited by the slowness of neural events relative to electronic systems. The time for visual correction of movement errors is not pertinent because of retinal delay of about 40 msec.[100] Proprioceptive feedback having only a short sense organ delay could more quickly supply information on the position of the moving part relative to where it was intended to be, assuming the brain holds the goal in mind. The larger question is whether loop time can be derived from reaction time or alternatively deduced from putting together a series of conduction times determined electrophysiologically. The coincidence of correction time in saccadic eye movements and visual reaction time argues for using reaction time in considering ballistic types of movement.

In 1946, the earlier finding of Stetson and Bouman[135] was re-emphasized,[126] that rapid movements present a problem for a feedback system control of movement.* Very rapid movements are sometimes termed ballistic and perhaps best illustrated by saccadic eye movements or the finger movements of a pianist or typist. A ballistic movement in the literal sense means that, as in firing a gun, all the energy is applied *before* the movement begins. However, in most quick movements energy is applied throughout the movement in controlled amounts. The essential idea is that the movements are so quick that correction might not occur except perhaps at the end of the movement.

Skeptical of there being time for correction during the movement, *e.g.*, by proprioceptive information via the cerebellum, the author formulated a theory that the motor cortex and cerebellum formed an intracerebral loop that programmed and controlled movements at least roughly.[126] The argument was that ballistic or rapid movements had to be planned or preprogrammed in advance. The nervous system has few ways of programming or projecting actions into the future, in other words, of "storing impulses" to be discharged after successive delays. One way of storage utilizes conduction time and synaptic delays in circular chains of neurons or reverberating circuits. The reciprocal motor cortex–cerebellar connection was considered to be such a circuit and regarded not only as an error-correcting device,* but as a means by which "an instantaneous order can be extended forward in time" at least "roughing in" a movement by starting quickly and not ending too abruptly with consequent oscillation. This hypothesis is consistent with cerebellar pathophysiology (Chap. 4, Vol. I).

For minimal control in eye-hand coordination the only information needed is that from the motor cortex and the receptors that perceive the goal, *i.e.*, the cortex is the immediate source of input into the system, so the mechanism was termed "input informed† feedback circuits" in contrast to "output informed systems" conventional in engineering—those in which the discrepancy between the goal and the accom-

* Even earlier, Stetson and McDill[see 73] observed that a rapid movement cannot be subject to control after it is once started; alternating movement at a rate of 10 per sec greatly reduced accuracy.

*At this time transcortical conduction in the cerebellum was thought to be needed to transfer information from the areas of somatosensory input (vermis) to the dentate nucleus and thence to the motor cortex.

†Other terms are central efferent monitoring, feedforward control, discontinuous control systems.

plished movement (output) is detected and used as the basis of correction.

These early statements of the problem are still pertinent. The question remains whether the report back from the muscles during voluntary movement occurs with sufficient rapidity to permit effective control throughout the course of the movement (continuous feed back) . . . some of the shorter loops that do not include the muscles constitute internal or intermittent feed back circuits.[77]

It is, of course, possible to add a sensory correction element to the programming when circuit times permit. This has been suggested for the motor cortex-cerebellar circuit, but without rigorous consideration of circuit theory.

Central programming has been emphasized in several recent reviews, but with several modifications: (i) the ambiguous term "input informed" has been replaced by "internal feedback loops," (ii) greater emphasis on them as error correcting rather than programming devices, (iii) this in turn has led some to postulate a pattern or program of the movement as ordered against which the executed movement can be compared, (iv) the number of potential internal feedback circuits in the brain is much greater than the motor cortex–cerebellar loop known at that time. Paillard[103] diagrammed (i) recurrent circuits at the cortical level, (ii) reciprocal connections (circuits between the cortex and thalamic nuclei, especially ventralis lateralis, and (iii) corticofugal input to nuclei of ascending pathways such as those of the dorsal column nuclei and the spinal gray horn.

Experimental Psychology of Voluntary Movement. The necessity for an internal feedback system or other means of programming and correcting rapid movements has been demonstrated by experiments on man. For example, the observation that the rate of an arm movement is increased when large excursions are intended indicates a preprogramming of movement. Whether there is sufficient time for peripheral feedback has been extensively examined in man. As early as 1948, Taylor and Birmingham[141] concluded that corrective movements in a continuous tracking situation (nonballistic), once started, were run off without visual or kinesthetic guidance. Such control is termed intermittent, as opposed to continuous control. The force changed continuously throughout a movement at intervals much shorter than reaction time. In the first 70 msec force increased, and at a slower rate in the next 70 msec, braking force and opposing force each were applied in the subsequent 100 msec, both phases shorter than proprioceptive reaction time. Chernikoff and Taylor[27] found that the time for proprioceptive detection and correction of the drop of an arm when suddenly unsupported was 110 to 120 msec. Higgins and Angel[66] compared visual and proprioceptive error correction in a voluntary tracking of a line randomly and rapidly displaced up or down versus tracking a weight that randomly resisted or increased an intended movement. These authors concluded, "Subjects are able to monitor their own behavior internally comparing the actual motor commands with some reference value." In some manner the program and departures from it (errors) are known to the motor center. Errors from a voluntary movement to a goal are detected better than errors in a passive movement to a target.[see 104] The concept of a programmed movement unmodifiable by either visual or proprioceptive feedback at least in the early stages has been abundantly supported.[45] A subject was asked to target on a light that had suddenly switched to a new position and then turned off (ballistic movement) or to follow a slowly moving one to the new position (tracking). The light was then turned off and its new position was better located under the ballistic condition, indicating that the brain, by ordering a movement, had a prior knowledge of end position (extent of movement) from the program for the movement. (Continuous peripheral feedback did not occur during pursuit because the eye muscles do not have a kinesthetic feedback.)

Follow-up Servo Hypothesis. A proprioceptive feedback that would be fast enough to control ballistic movements was proposed by Merton and colleagues as early as 1953[see 99] and recently reaffirmed. "This theory supposes that the contraction of the main muscle [extrafusal fibers] is driven by the . . . muscle spindles. . . . [They] automatically turn on more contraction via the stretch reflex arc, if the rate of shortening of the main muscle falls behind the shorten-

ing of the spindles . . . follow-up servo action. . . . If an obstruction were met with, the delay in turning on more contraction to overcome it would be only the brief delay associated with the operation of the stretch reflex." However, cutaneous or joint afferents are in some inexplicable way involved because after the anesthetizing of the thumb, which would not affect the receptors in the belly of the muscle, the servo action was lost, the stretch reflex depressed and the "sense of effort" increased.

The basis of the follow-up servo action hypothesis depends on experiments in which a thumb movement was suddenly halted, increasing the muscle tension, or suddenly unopposed, increasing muscle stretch. The EMG response ascribed to the imposed perturbations began in 60 msec, said to be the latency of the stretch reflex in man. In respect to the short latency response to halting a movement, "it is difficult to see how it [increased EMG activity] could arise except by contraction of the spindles stretching the sense ending on them." The response to sudden reduction of an opposing force was a silent period in the EMG. The latency of correction of movements (40 to 60 msec) in this situation (about half that reported for actual corrective movements) was interpreted to mean that a segmental mechanism is involved.

There are several objections to Merton's theory: (i) the spindle correction is operative only on a small fraction (± 5 per cent) of the maximal voluntary contraction force of the muscle (an increase in gain in the servo loop for stronger contractions or when the muscle was fatigued was argued, but the recruitment of large motor units could be responsible); (ii) the latency, though less than that found for the actual correction of errors, is not incompatible by some calculations with a loop to and from the brain; (iii) the possibility that α motoneuron activity is produced by, rather than coactivated with, γ-activity, has found little support; (iv) that halting a contraction is equivalent to stretching is difficult to reconcile with the belief that actual stretching is the stimulus for spindle discharge; (v) the perturbation of a slow finger movement is similar to a correction of a steady position when resistance is suddenly removed. In this case a servosystem is in continuous operation to produce the steady state. Experiments of this type may document spinal servosystems in postural adjustments, but not in voluntary limb movement.

Evidence advanced for a continuously acting peripheral servosystem during a sustained voluntary action against a resistance is the silent period of the EMG when the resistance is suddenly removed or a motor nerve stimulated. In both cases, the muscle shortens and would slacken the intrafusal fibers of the spindles; other possible causes would seem to be acceptable. The short latency (40 msec) of the EMG shut-off may or may not indicate spinal reflex action; the question of quantitative significance arises again since EMG activity begins before the muscle is shortened. The latency of the silent period for the release of intercostal muscles has been set at 22 to 25 msec, clearly a spinal reflex phenomenon.

Ballistic Eye Movements. Saccadic eye movements directed to fixating on a new target result from extraordinarily high frequency discharge in the oculomotor neurons (Chap. 1, Vol. I), but after a relatively long latency of 200 msec. This rate of discharge and speed of movement cannot be voluntarily controlled, *i.e.*, slow saccades cannot be produced. A saccadic eye movement, once launched, cannot be voluntarily or involuntarily altered in its course but only at its end and after incurring another 200-msec delay. The brain apparently can control only two aspects of a saccade: direction and distance, not velocity. These are apparently accomplished by a tightly "wired in" connection so that a restricted group of neurons in the superior colliculus is associated with only one distance and direction of eye movement (see Chap. 1, Vol. I). Saccadic eye movements are striking examples of a "preprogrammed ballistic movement." Behavioral studies confirm the lack of proprioceptive feedback in saccadic eye movement control. Is the behavior of the eye representative of ballistic limb movements? Specifically, does the correction of an error or the meeting of an obstacle involve a proprioceptive reaction time or is there some method for short-circuiting the "turn around time" in the motor cortex?

The concept that internal feedback loops are error-correcting devices carries with it the idea that (i) the target's position in space coming through the distance receptors is in some way recorded and preserved (the target can be removed and the movement be well executed), and (ii) the cortically controlled discharge can be compared and corrected with reference to this

record and without sensory input from the muscles. According to some, for an internal feedback loop to correct deviations of a movement, not only is a program for the movement needed, but also a "copy" of this program (efference copy or corollary discharge) needs to be stored so that it can be compared with the program to correct errors in its execution (or with goal if present and time permits). In simple language, if a peripheral afferent return is not continuously available from receptors detecting the discrepancy between target and the movement, then a central representation of target and the program for cortical discharge must be registered, and some means of detecting discrepancies between them is required. Further, a mechanism for detecting an error in the program is needed. Whether they exist and if so, where such copies originate and are stored, is completely speculative. Eccles[37] has suggested that the correction is accomplished in the cerebellum, which would endow it with a memory that this structure may or may not possess. Further, because the errors of a movement decrease with practice, learning and perception of the program and of the "copy" must be involved; in such learning, peripheral feedback could be operative because initially movements are usually slow enough to permit peripheral feedback. But what learns, and how?

The emphasis on preprogrammed, rapid movements should not discount the role of peripheral feedback in the control of slow movements, which constitute the majority of movement. For nonballistic movements there is sufficient time for the nervous system to employ a continuous feedback signal. In fact, peripheral feedback may arrive just at or just after the end of a rapid movement. Peripheral feedback means that the effect of the motor output is continuously sensed and the information, returned to the brain, is used to correct movement errors. In a conventional feedback circuit, this comparison of goal and movement involves a "comparator," and the cerebellum has been suggested as serving this function. Since the introduction of chronic recording of single cortical units in various structures while a monkey is performing a motor task, the answers to these questions are being sought; such studies are the subject of another section.

Zero Feedback. Deprivation of the afferent return from the periphery by section of posterior roots or pathological destruction of them in man (so-called tabes dorsalis) leads to ataxia, the inability to control movements in direction and force even in semivoluntary acts such as walking (e.g., locomotor ataxia). Vision can in some degree substitute for proprioceptive return (the patient with locomotor ataxia looks at his feet while walking).

As early as 1917, Lashley[80] demonstrated that a patient, apparently totally lacking in sensation from the legs, could move the lower leg any given direction and distance quite accurately. Much of the lower limbs of this patient were anesthetic to touch and deep pressure; he could not detect the position of the leg nor the direction, extent and duration of passive movements of the knee through a 45-degree arc. Even the occurrence of a passive movement was often not appreciated. All tests indicated a lack of significant information from the muscles and their tendons acting on the knee joint and from the joint itself. *However, when asked to move the leg in a given direction, he made no errors.* Moreover, his errors in producing a movement of a given extent were little greater than those of normal subjects. Obviously he retained some intrinsic means of programming and executing movements rather accurately.

The degree to which movement control depends on proprioceptive return has been tested in monkeys after rhizotomy. Descriptions of the consequences range from complete absence of movement to a substantial degree and accuracy of movement. As is recognized in behavioral experiments (see Chap. 6, Vol. I), the lack of contralateral limb movements from unilateral lesions in cage life does not represent any inhibitory effect from the innervated limb, but simply *neglect* seen after many cortical lesions; this can be substantially countered by bandaging the unaffected limb during cage life, by retraining sessions or by making the lesion bilateral.

More broadly, the degree of recovery is related not only to the amount of forced usage and formal training but also to physical therapy and medical care to avoid self-mutilation of the affected limb, pressure ulcers, etc. Another important factor is whether the radicular artery is or is not

spared as demonstrated by Bossom and Ommaya[see 19] in well-performed and verified rhizotomies. Finally, too much has been made of the fact of movement, too little of the gross ataxia.[158] Species differences may exist.

Permanent wild ataxia, even with eyes open, occurs in a cat's rhizotomized limb to the point of wearing off the hair at the side of the head from raising the forelimb too high in a simple reaching movement. Dysmetria almost as great is shown by monkeys, some exhibiting oscillating movements, and is marked in the elbow as well as fingers. Fingers are used simultaneously to grasp food, and only with protracted training were thumb and forefinger used in opposition. Extending an arm and grasping are more difficult than bringing food, once grasped, to the mouth.

On the whole, rhizotomy experiments support the hypothesis that some nonballistic movement, though not perfectly controlled, can be centrally programmed. Possibly the rhizotomized monkeys use mechanisms normally operating only in ballistic movement.

Phylogenetic differences may exist; a cat with unilateral deafferentation of the arm never ceased to show wild ataxia. It is conceivable that voluntary movement is less dependent on peripheral input in monkey and man than in cat.

Explanations for the apparent ability of the deafferented arm of the monkey would seem to be (i) use of vision, (ii) training and (iii) greater call upon internal feedback circuits pre-existing for ballistic or rapid movements.

We are clearly faced with a paradox. Clinically, deafferentation as in tabes dorsalis or interference with ascending pathways, *e.g.*, the dorsal columns, causes great incoordination of movements (ataxia); particularly noticeable is the inability to terminate a movement correctly without using vision. In the monkey, ataxia from dorsal column lesions is greatest when the proprioceptive inflow to the brain is further interrupted by destruction of the external cuneate nucleus. If species differences exist between monkey and cat, the importance of sensory return in the control of movement may differ in monkey and man.

It is clear from the above discussion that the afferent input to the nervous system from peripheral structure is essential for the accurate control of all but ballistic movements. Beyond this statement lies a host of problems such as what deep receptors are involved and in what capacity; when does the velocity of conduction of deep impulses allow them to intervene in the control of movement; and is their arrival in the motor cortex direct or indirect. The answer to all of these questions requires sophisticated electrophysiological analysis, the subject of succeeding sections.

AFFERENT INPUT TO THE MOTOR CORTEX

A decade ago, our knowledge of input to the motor cortex was virtually nil, despite anatomical evidence of its dense thalamocortical projection and the receipt of association fibers. Obviously, a motor cortex without an afferent input, direct or indirect, would be biologically handicapped; it would be "blind." The afferent input to the motor cortex is significant in three ways: (i) providing the goal for a movement (distance receptors), (ii) giving it information for the control of movement and (iii) possibly serving conscious sensation (see Chap. 6, Vol. I).

The afferent input to the motor cortex is abundant, multiple and complex. The major inputs derive from (i) peripheral somatosensory receptors divisible into two subcategories, deep and cutaneous, which may be further subdivided into nerve axon Groups I, II and III from muscle and several categories of afferents from skin; (ii) other cortical areas such as the somatosensory postcentral gyrus; (iii) thalamic nuclei, especially the ventrolateral nucleus of the thalamus, relaying input from cerebellum and basal ganglia; (iv) the main somatosensory nucleus of the thalamus (the ventral posterior nucleus) relaying input from medial lemniscus and the medial group of the thalamic nuclei dominated by the ascending reticular neurons.

Input from Cortical Somatosensory to Motor Areas. The pre- and postcentral gyri interconnections are rich, reciprocal and topographically organized. The receptive fields of interconnected sensory and motor loci neurons are similar. Certain behaviors with a strong directional aspect, such as tactile contact placing reactions, are de-

pendent on the connection between the two gyri.[3, 13] However, cooling of the postcentral gyrus had little effect on the responsiveness of the corresponding points in the motor area to peripheral stimuli, whereas stimulation is well known to do so, indicating that the effect is not tonic. The importance of direct afferent connections to the motor cortical areas is exemplified by the fact that evoked potentials persist in precentral cortex after ablation of the postcentral gyrus.

Cutaneous Afferent Projections. The motor area in the cat and monkey receives a superficial as well as deep afferent input. In the cat the majority of cells respond to cutaneous rather than deep stimulation. In the monkey's motor cortex, the ratio of cells responding to superficial and deep stimulation of the hand is the reverse; 75 per cent of precentral cells respond to joint movement or muscle stretch and only 15 per cent to cutaneous stimuli,[47] while 10 per cent are not driven at all. Thus, there appears to be a marked species difference.

Under chloralose anesthesia, feline motor cortex cells respond to more stimuli than primary sensory cortex cells; precruciate cells have larger receptive fields, often bilateral and embracing more than one limb, that often respond to auditory and visual stimuli. This class of cortical neuron has been termed "wide field," m neurons. This increased responsiveness may be due to chloralose anesthesia (see next chapter). Such wide convergence of input is less prevalent in the unanesthetized monkey than in the cat under chloralose.[144] A second type of precruciate cell has small receptive fields and its afferent input is quite modality specific. Rosén and Asanuma[124] compared responses of cells in specific layers of the monkey and found that both cutaneous and deep stimuli activated cells were in superficial layers, and "undriven" cells, presumably polysynaptically driven, were in the deeper layers.

Proprioceptive Input. MUSCLE VS. JOINT INPUT. The separation of corticopetal proprioceptive input from joints, muscles and fascia is difficult at the receptor level. Proprioceptive sensation will be discussed in Chapter 5 (Volume I), but is briefly mentioned here. In general, joint sensitivity is represented in the posterior parts of the postcentral gyrus and in the parietal association area, which does not exclude representation in classical motor areas. From experiments on man, Gelfan and Carter[54] contended that traction on an exposed tendon was not detected whereas Goodwin *et al.*[59] found that vibration of a tendon, which strongly stimulates Group Ia afferents, is consciously appreciated. In experiments on animals, Swett and Bourassa[138] found that Group I afferent impulses, though reaching the cerebral cortex, did not serve as a conditioned stimulus and concluded that they do not give rise to conscious sensation. Added to the question of whether muscle sense exists is whether it can provide at least some control of voluntary movement, a probability but not a certainty.

As noted earlier, Merton[see 113] performed experiments in which receptors of joints and much of the tendons of the thumb were made ischemic and inexcitable, while those in the belly of the muscle would remain functional. The subject was unaware of passive finger movements, and more important to the control of movement, was unaware that an intended movement had been prevented by the experimenter holding the thumb. The subject believed he had executed the movement.

GROUP I PROPRIOCEPTIVE INPUT (AREAS 3a AND 4). The special usefulness of a feedback to the cerebral cortex from rapidly conducted impulses in the control of movement is obvious. Because the motor cortex is involved in the control of proprioceptive postural reflexes as well as movement, an input from muscle as well as from joint afferents might be necessary to make such control "informed." Such a cortical input was demonstrated early by Amassian and Berlin as well as by Albe-Fessard and colleagues, but was largely ignored (see Chap. 6, Vol. I). That Group I afferents from the muscle spindles do evoke responses in the cerebral cortex was firmly established, originally in cats by Oscarsson and Rosén in 1963, and more recently in monkeys.[88, 115, 153] Although a Group Ia projection to the motor area is still in doubt, it is well established that spindle afferents project to an immediately postadjacent area, *i.e.*, within and anterior to the postcruciate dimple. In the monkey, impulses in Group Ia afferents project strongly to area 3a, a zone of the postcentral gyrus deep in the central fissure and transitional

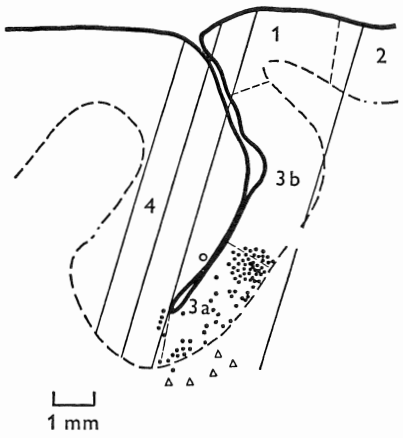


Figure 3–31 Sagittal section through the central fissure arm area; heavy line indicates the surface of the cortex; note the anterior curve in the central fissure. Filled circles, sites of single cortical units which responded to deep radial or deep (palmar) branch of ulnar nerves. Response points from a series of experiments were combined; however, the location of each point and cytoarchitectural boundaries were verified in each experiment. Note concentration at the boundary of 3a and 3b. Oblique lines in areas 2 and 4 are electrode tracts; only one unit response was recorded from area 4 (open circles). Triangles, superficial nerve stimulation. (From Phillips *et al., J. Physiol., Lond.,* 1971, *217,* 419–446.)

cytoarchitecturally between sensory (3b) and motor areas (4). The heaviest Group Ia input is at the border and spreads into area 3b (Fig. 3–31). As in peripheral axon, the conduction in the system to 3a is rapid, in the monkey 3.8 to 5.2 msec from the cervical dorsal root entry zone to area 3a, a pathway involving three synapses. This rapid and secure conduction makes Group I-3a system a strong candidate as one link in a feedback for the control of movement. This projection does not appear to be of sensory significance (see Chap. 6, Vol. I). Area 3a cells are not PTN's, neither do they seem to have potent connections to corticofugal cells of adjacent area 4.[88, 115]

As noted, to assess the role of the proprioceptive input in the cortical control of movement it is necessary to understand the exact source of afferent input to each cortical area. For example, what is the relative density of input to areas 4 and 3a from low threshold stimulation (Group I axons from primary spindle afferent) or slightly higher threshold Group II axons of secondary spindle afferent? Is the input from natural stimulation dynamic, static or dynamic-static (Fig. 3–32)? Are the proprioceptive inputs sufficiently topographically organized to permit control of voluntary movements?

The input to area 4 from muscle spindles and which receptor is responsible have recently been clarified. Hore *et al.*[68] found a concentrated input in area 4 from muscle afferents but only at its junction with 3a, not over the part of area 4 having an output to the muscle group tested. They point out that a slightly different interpretation of the cytoarchitectural boundary would put these neurons into area 3a. In experiments by Lucier *et al.*[88] on cebus monkeys, more prolonged muscle stretch and high frequency vibration suggested a projection (direct or indirect) to area 4 of impulses from primary spindle receptors to non-PTN as well as PTNs.

Hore *et al.* also suggested that the muscle afferent input is different for areas 4 and 3a. As Figure 3–33 shows, the input giving rise to initial burst activity is mainly to 3a, whereas the tonic category was found mainly in area 4, with the dynamic-tonic type of discharge appearing in both areas but predominating in area 4. These dif-

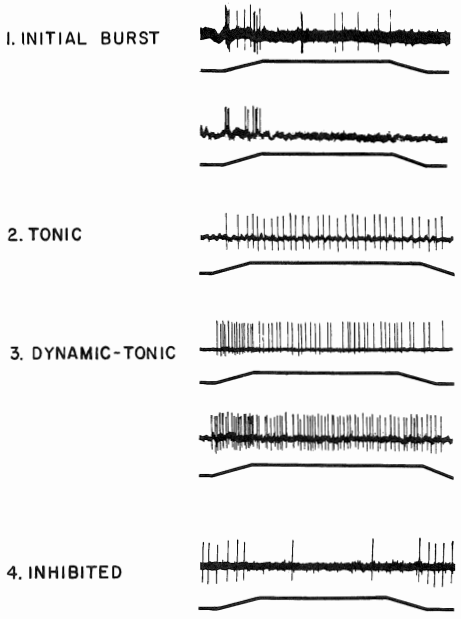


Figure 3–32 Classification of the more common cortical cell responses evoked by muscle stretch. Lower trace of each record is the slow maintained stretch (10 mm at 45 mm/sec); upper trace is the unit response; ankle extensors of the baboon. The proportions of the major types were: initial burst 25 per cent, tonic 12 per cent and dynamic-tonic 42 per cent. (From Hore *et al., J. Neurophysiol.,* 1976, *39,* 484–500.)

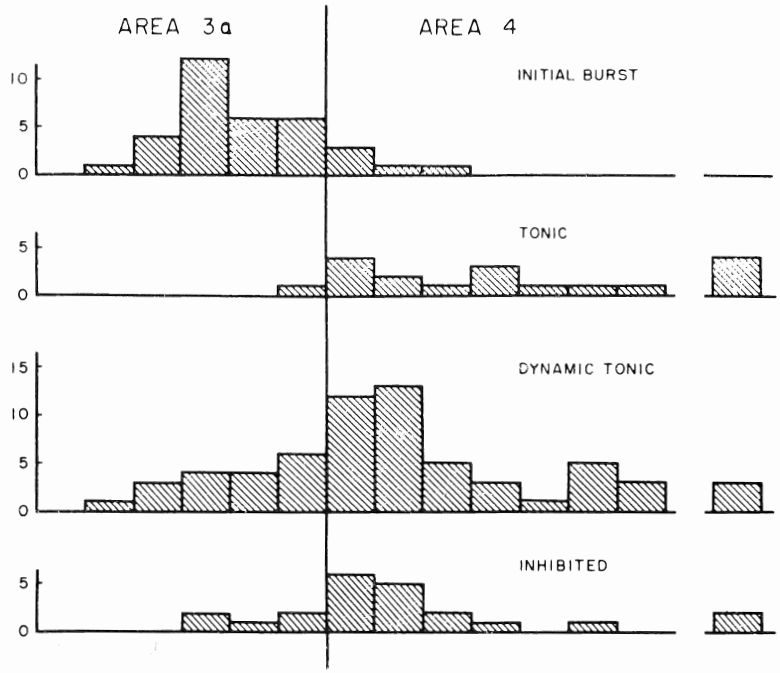


Figure 3–33 Distribution of cortical units in the major categories of response to a slowly applied stretch. Vertical line indicates estimated boundary between areas 3a (*left*) and 4 (*right*); bin size on the abscissae is in 0.55-mm steps. Baboon, ankle extensors. (From Hore *et al., J. Neurophysiol.*, 1976, *39*, 484–500.)

ferences, plus those from muscle nerve stimulation, suggest that area 3a receives no input from group II axons innervating secondary spindle afferents, whereas the same criteria indicate a clear group II input to the motor area, apparently concentrated near the boundary with 3a. This might suggest that area 4 units would be position sensitive, reflecting muscle length, but this is not borne out by chronic unit studies.[47, 49] On the other hand, the units in area 3a encoded the velocity of stretch, and parallel the output of primary afferents, whereas the tonically responding units of area 4 resemble that of secondary spindle afferents. Dynamic sensitivity would seem to be functionally adapted to the monitoring of limb movements and the rapid overcoming of perturbations of an intended movement. This leads to the paradoxical possibility that the motor area must depend on second-hand information in the control of movement but has first-hand information significant to the control of posture.

In the monkey transmission from area 3a to PTNs, if it exists, is apparently not as strong as the activation of PTNs from group II afferents. Succinycholine, a strong activator of intrafusal muscle fibers and consequently the input to 3a neurons, had no appreciable effect on PTN excitability,[153] nor did microstimulation of area 3a. From available electrophysiological evidence the group I-area 3a system does not appear to constitute a simple servoloop (transcortical reflex) in the control of cortically induced movement, as likely as that would seem. Moreover, some of the peripheral topographical specificity, desirable in a servosystem, is lost.[115, 153]

Impulses in group II afferents activate the motor cortex neurons much later than the group I-evoked responses in area 3a, *i.e.*, with a latency from root entry zone to PTN activation of 20 to 25 msec. This reinforces the paradox referred to above, since speed is desirable in the control of movement.

A question germane to the role of muscle afferents in the control of movement is the degree of topographical organization of the input. In one experiment[153] afferents in the group II range exhibited a high degree of convergence, *i.e.*, between as many as six branches of a motor nerve, between branches to antagonistic as well as syn-

ergistic muscles at the thalamus, and between muscle and cutaneous branches of a nerve. Convergence at the cortical level appears greater than at thalamic levels, suggesting that additional specificity is lost between these levels.

POLYSENSORY INPUT. A third type of sensory response in area 4, studied physiologically and anatomically, exhibits wide receptive fields and in varying degrees is polymodal. While such an input is strongest to association areas, it is recorded from motor areas actually more frequently than from somatosensory areas. The thalamic way station in which polymodal somatosensory inputs converge is described in the cat as the centre median, other medial thalamic structures and probably part of the ventrolateral nucleus, all structures projecting to motor cortex or basal ganglia. Such responses are most conspicuous under chloralose anesthesia, virtually abolished by pentobarbital and rare in unanesthetized monkeys.

Columnar Organization and Afferent Input. Mountcastle's columnar hypothesis has been extended to the motor areas. Welt *et al.*[151] concluded that units within a column* of cell bodies have local receptive fields in the same general skin area, although 25 per cent of the units were activated from wide areas, two or even four limbs. Analysis of modality revealed no columns devoted to only one cutaneous modality, *i.e.*, a column that is location-specific is not modality-specific. In the latter respect, the column behaves like polysensory activated PTN's described above. Wide field neurons were not arranged in columns, but could have a focal point within a wider cortical field, yielding the highest discharge frequency. If so, the peripheral location of this focus coincided or overlapped with that of local fields in the same column. Thus, as noted, the column is described as polysensory, but is topographically specific.

With the technique of intracortical microelectrode stimulation (ICMS) introduced by Asanuma and Sakata,[9] the same electrode inserted into the motor cortex is used for stimulation and recording of afferent input. Segregation of PTN columns for cutaneous and deep modalities was strikingly high in the cat, but all cutaneous modalities from a given skin locus converged on the same column. It is therefore not strictly correct to speak of modality-specific columns even in the cat. In both monkeys and cats, Asanuma and his colleagues[10, 125] next compared the skin area providing the input to a local group of cells with the muscle(s) activated by microstimulation of that point. Most cortical cells had relatively restricted receptive fields and their location had a definite relationship to the output from those cells when stimulated. The cutaneous receptive fields for a given cell tended to overlie the muscle activated by stimulation at that point. Thus, cortical neurons originating in a specific locus evoking dorsiflexion of the paw had receptive fields on the dorsal surface of the paw. Cells in which stimulation evoked responses in a palmar flexor of the front paw, m. palmaris longus, received input from the ventral surface of the paw and forearm. In general, stimulation evoked movements *toward* the cutaneous area of sensory input. This was shown dramatically in the monkey's thumb by Rosén and Asanuma.[124] Four directions of movement were related in this fashion to input from four different aspects of the thumb.

The relation between cutaneous input and the specific muscle activated as described by Asanuma *et al.*[10]—a movement *toward* the skin area stimulated—is the opposite to that of a protective movement, which is away from a noxious agent. Asanuma *et al.*[10] suggest that the functional significance of the relationship they have described is that the movement is *cutaneous stimulus seeking, i.e.*, an element in the motor aspect of attention like orientational movements of the eyes. The motor response would act as a positive feedback, directing movement toward the skin area stimulated and perhaps intensifying the stimulus by closer cutaneous contact. This

*Neurophysiological evidence of a columnar organization of the motor cortex is based on the idea that a penetrating electrode will enter successive curved radial columns. The larger the angle of electrode penetration relative to the hypothetical histological columns, the larger the numbers of changes in the position of local receptive fields of the units encountered. Functionally different columns have been described in the somatosensory and visual areas. The neuroanatomical evidence for columns is discussed earlier in this chapter, and the physiological evidence is presented in Chapters 6 and 13, Volume I.

could be termed "exploratory" or "orientational movement," a term applied to lateral movements of the eyes and head from stimulation of the frontal eye fields.

The "towards rule" may not be universal because in awake cats, Sakata and Myamoto[128] elicited *avoidance* movements from cortical zones responding to light cutaneous stimuli. The Asanuma rule is concordant with the grasp reflex of the normal infant, which is toward the lightly stimulated palm, but cannot be expected to explain the pathological grasp reflex, which occurs after ablation of the motor cortex (areas 4 and 6) and therefore is subcortically executed. However, the rule does explain the abdominal and cremasteric reflexes, both dependent on the PT and both withdrawal or defense reflexes. The "towards" relationship cannot explain the first steps of a tactile placing reaction, namely, lifting and then an "away" contraction of the biceps muscle.[3] Nor can it explain the little-known *Berührungs Reflexe* of the cat, a delicate plantar flexion of the cat's foot from light stroking of its dorsum. But as in the grasp reflex, the "towards" reaction is consistent with the down-going toes of the normal plantar reflex which is reversed when the PT is damaged.

A consistent directional rule did not hold for inputs arising from passive joint movements, but the topographical principle did, *i.e.*, the input from a given joint movement was to the cortical locus, which caused movement of that joint. The topographical principle was confirmed by Fetz and Finocchio,[49] recording from precentral cells during active and passive joint movement of unanesthetized monkeys. Cells that were driven by passive movement of a joint were often involved in active movement of that joint; however, there was no general relationship between the effective direction of active and passive movements.[47, 49]

VENTRALIS LATERALIS (VL) AND VENTRALIS ANTERIOR (VA) TO MOTOR CORTEX. The location, input and output of these thalamic nuclei will be described in conjunction with the cerebellum. The cortical projection of VL-VA is unitary, strongly to the area 4, less so to area 6.* The input is triple, *i.e.*, the cerebellum, the globus pallidus and reciprocal connections from the cortical motor areas.

VL-VA AND CONTACT PLACING (CP).[3] Despite the heavy projection of VL-VA to the motor cortex, the contribution of these nuclei to cortical motor functon has been little studied. A cortically managed motor act analyzed in great detail by chronic unit recording is *contact placing*,[3] which will be discussed in the next chapter.

MOTOR CORTEX CELL ACTIVITY DURING MOVEMENT

INTRODUCTION. While the effects of surgical ablation and electrical stimulation clearly demonstrate a functional role for motor cortex in the generation of movement, such techniques cannot specifically define this role. The relationships between activity of precentral cortex cells and specific parameters of movement can only be investigated by observing cortical cell activity in *unanesthetized*, moving animals. Besides revealing cell responses under normal conditions, "chronic" recording in awake animals permits testing the function of these cells during specific behavioral conditions. The animal's behavioral responses can be designed to test a variety of hypotheses concerning the possible functions of the recorded cells. For example, a rapid and repeatable movement in response to a signal—called a reaction-time response—is ideal for investigating the relative timing of central cell activity in the generation of a simple voluntary response. On the other hand, a behavioral task requiring the animal to move different loads through the same displacement is useful for revealing how the cortical cells are related to parameters of position and force. As a third example, response patterns in specific muscles and cortical cells can be directly trained to test the functional relations between them. Each of these behavioral tasks has provided different insights into the function of motor cortex cells, and similar strategies may be used to investigate cells in other regions as well.

Experiments of this type, called chronic unit recording, involve extracellular recording of action potentials of single cortical cells with microelectrodes that can be

*A direct input to the posterior parietal lobe (area 7) has been recently described.

positioned at different depths by a hydraulic micro-drive. The desired behavioral responses are trained through operant conditioning techniques (cf. Chap. 16, Vol. I). The animal's behavior is "shaped" by preferentially rewarding those responses that are closest to the desired final behavior.

Timing of Cell Responses. Basic questions concerning the timing of neural activity during a simple voluntary movement can best be studied in animals performing a reaction-time (RT) response. The subject is operantly trained to detect a brief stimulus and to make a specific motor response as rapidly as possible. The time interval between stimulus and response depends on the stimulus modality and the species. Luschei *et al.*[91] compared minimal reaction times in humans and monkeys to both auditory and visual stimuli. In human subjects releasing a key, agonist muscle (biceps) was activated 80 msec after an auditory stimulus and 125 msec after a visual stimulus; much of this difference is due to conduction delays at the retina. Making comparable responses, monkeys had slightly longer latencies of agonist EMG activation. The release of the key typically occurred about 70 to 100 msec after the biceps activation. Interestingly, the earliest reponse-related change in EMG activity actually occurred in the antagonist muscle (triceps), which was suppressed prior to biceps activation (by 15 msec in man and 55 msec in monkeys). In addition to these response-related changes, Luschei *et al.* discovered an earlier stimulus-related muscle potential in the monkey, occurring 25 to 50 msec after the stimulus. When monkeys were trained to delay the key release, these early EMG responses remained correlated with the stimulus. The functional significance of this unexpected response remains to be determined.

In the first of a series of systematic studies of motor cortex cells during movement, Evarts[39] recorded the responses of single precentral PTN's in monkeys trained to release a bar after a visual stimulus. He found that many precentral cells began to change their activity 10 to 100 msec prior to agonist muscle activity, and that the onset latency of a given cell covaried more closely with onset of muscle activity than with occurrence of the light. The 10 to 100 msec between initiation of activity in motor cortex cells and in muscles is considerably longer than the time required for impulses to travel from cortex to arm muscles (5 to 10 msec via fast PTN's). This suggests that early PTN activity would produce a period of subthreshold facilitation of motoneurons prior to their activation; such facilitation has been confirmed by demonstrating an increase in the H-reflex prior to movement.

In this study, Evarts found that the earliest responses of motor cortex cells began about 100 msec after the visual stimulus. The nature of the intervening neural responses occurring between activation of sensory and motor systems remains an important experimental challenge. To investigate onset times of cells that might precede activation of motor cortex cells, Thach[141a] recorded units in cerebellar nuclei and motor cortex. The recruitment times of most cerebellar units were comparable with those of cortical units. As shown in Figure 3–34, the distribution of recruitment times of cells in both cerebellum and cortex extended over hundreds of milliseconds. This illustrates a fundamental problem encountered in attempts to demonstrate serial activation of different motor centers: within any given region—including motoneuron pools—cells are recruited at diverse times and it is difficult to com-

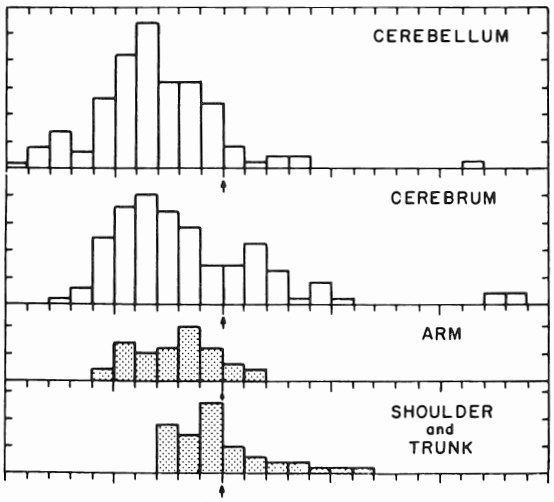


Figure 3–34 Relative onset times of muscle activity and changes in firing rates of dentate nucleus and motor cortex cells in monkey making rapid wrist movements. Histograms plot number of changes observed, in 20-msec intervals relative to first change in force (*arrow*). (From Thach, *Brain Res.*, 1975, *88*, 233–241.)

pare relative onset times of specific cells in different centers. Moreover, although relative onset times have usually been examined as evidence for sequential recruitment, it is clear that each cell exerts its maximal influence when its firing rate is highest, not when the rate first changes. Since the durations of most motor responses are many times the conduction time between centers, recurrent loops could be "traversed" many times during a single response, and the simple concept of serial activation appears to be a gross oversimplification.

The distinction between a pure reflex and a voluntary RT response is particularly well illustrated when the stimulus is proprioceptive—*e.g.*, a perturbation of the responding limb. Hammond[62a] asked human subjects to resist a sudden passive extension of their flexed forearm, and found two distinct components in the biceps EMG response. An early component with a latency of 18 msec was apparently produced via a segmental reflex initiated by the perturbation. A later component beginning at a latency of 50 msec appeared when subjects had been asked to resist the perturbation, but not when they were instructed to "let go." The pathways mediating this late response presumably involve supraspinal structures.

Evidence that motor cortex cells may participate in this late response has been obtained by Evarts and Tanji,[43] and Conrad *et al.*[32] In experiments comparable to Hammond's, monkeys were trained either to push or to pull on a handle after it was perturbed.[43] When the monkey was instructed to pull (a movement requiring contraction of biceps), a perturbation that stretched biceps evoked two EMG responses—a short latency (12 msec) response presumably mediated by the segmental reflex and a longer latency (30 to 40 msec) response possibly mediated by supraspinal pathways. A still later phase of EMG activity appeared to be related to the voluntary pull. Recording from the motor cortex, Evarts and Tanji[43] found many cells responding at 32 to 34 msec, appropriately timed to contribute to the EMG responses of intermediate latency. Moreover, both cortical cell and agonist EMG response were greater when the perturbation was in a direction opposing the required motor response than when the perturbation went in the same direction. These observations are consistent with the concept of a "cortical reflex" designed to resist the perturbation[112]—a reflex that can be enhanced by the animal's "set" to respond. Similarly, Conrad *et al.*[32] observed that when the load opposing an active movement was suddenly increased during the movement, many active motor cortex cells responded with an increased discharge at short latencies after the perturbation.

Relation of Precentral Cells to Force and Position. Whether activity of motor cortex PTN's is more strongly correlated with position or force during an active movement was first investigated by Evarts,[40, 41] who trained monkeys to move a handle through the same displacement but against or with different loads. In these studies, the activity of most motor cortex cells was more consistently related to the force exerted or its rate of change than to wrist position. Similarly, when the monkey held the handle steady, but exerted isometric forces in opposite directions, motor cortex cell activity again covaried with the direction and degree of isometric force that the muscles generated.*

Recording simultaneously from a group of motor cortex cells during alternating wrist movements, Humphrey *et al.*[69] found that a weighted average of their firing rates could be used to predict the subsequent time course of force and position as well as their rates of change. The degree of correlation between predicted and observed trajectories increased with the number of nonredundant, task-related cells included. Correlations were somewhat better for force and velocity trajectories than position or rate of change of force. Humphrey *et al.*[69] stressed the importance of taking into account the firing patterns of a population of cells in optimizing correlations.

The generality of a functional relation-

*Force and position cannot always be distinguished because position is attained and maintained by force and movement involves inertia. Position and force cannot be composed in isotonic contraction (weight over a pulley) since the force exerted by wrist muscles in dorsiflexion position is much stronger than in a palmar flexion position (an effect of muscle length on muscle force).

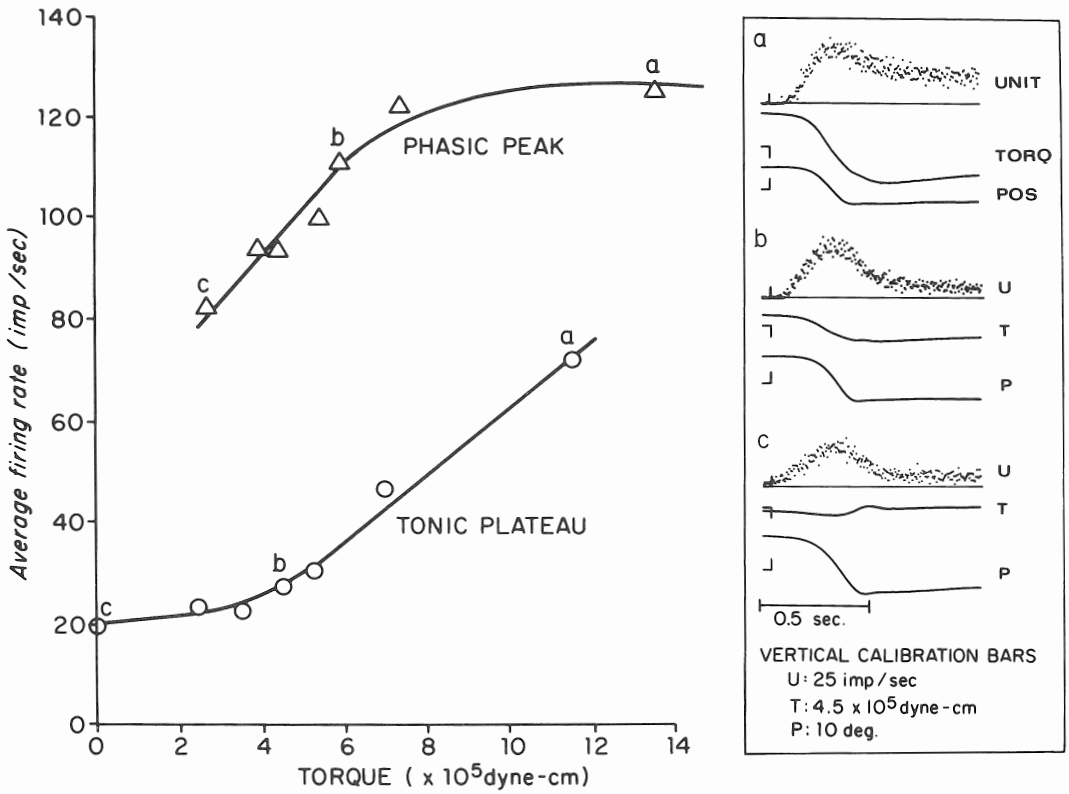


Figure 3–35 Activity of precentral corticomotoneuronal cell during wrist movements against a spring-like load. Average firing rate, torque and wrist position are shown at right for three values of the "spring constant," decreasing from *a* to *c*. Graph plots average firing rate during phasic peak and tonic plateau as a function of active torque. Evidence that this cell was a CM cell is shown in Figure 3–37. (Cheney and Fetz, unpublished observations.)

ship between motor cortex cell activity and force has been challenged by others. Documenting activity of precentral cells during a reaction-time jaw bite, Luschei *et al.*[90] found many cells that fired during the initial bite but were less consistently related to subsequent jaw movements. They questioned whether force output was the only function represented. Schmidt *et al.*[131] documented the activity of precentral cells during wrist movements against a programmed spring-like load. During tonic hold periods, a four-fold difference in load produced, on the average, a 1.5-fold difference in firing rate for all task-related cells. The differences in firing rates were considerably greater when comparing flexion and extension, leading Schmidt *et al.*[131] to conclude that direction, not force, was encoded.

Such discrepant conclusions about functional relationships underscore a basic problem in relating activity of a potentially heterogeneous population of cells to specific behavioral parameters: the selection of appropriate types of cells becomes a critical factor. The motor cortex cells which would be most directly related to generating force are the corticomotoneuronal cells whose activity would directly facilitate motoneuron firing. The activity of these CM cells has recently been found to covary linearly with static force over a considerable range (Cheney and Fetz, unpublished observation). Figure 3–35 illustrates the response pattern of a typical CM cell related to wrist extension. (The basis for identifying this as a CM cell is discussed below and illustrated in Figure 3–38). The firing rate exhibits a phasic peak during the dynamic phase of movement and a tonic plateau during the static hold against the load. If the tonic firing rate is documented at different load levels, a linear

relationship emerges for the upper range of loads. The apparent deviation at the lower range may be related to overcoming internal loads, such as stretching antagonistic muscles.

Relation of Precentral Cells to Muscles. The question of how many different muscles a given motor cortex cell may be functionally related to cannot be resolved by correlating cell activity with movements that involve coactivation of many different muscles. To determine whether individual motor cortex cells are related to one or to several arm muscles, Fetz and Finocchio[49] trained monkeys to contract isometrically each of four representative arm muscle groups—a flexor and extensor of the wrist and of the elbow. The monkey was trained to repeatedly produce bursts of EMG activity in a given muscle with relative silence in the other three. Most motor cortex cells were coactivated with more than one of the four arm muscles. Some cells were coactive with a wrist and an elbow muscle, such as the cell in Figure 3–36. Other cells were coactive with two antagonists of the same joint; still others were coactivated the same way with all four muscles. The fact that many motor cortex cells are activated with several different muscles suggests that in this sense some cortical cells have a "higher-order" relation to muscles than the one-to-one relation of motoneurons. Just as input from many receptors may converge to one sensory cortex cell, the output of a given

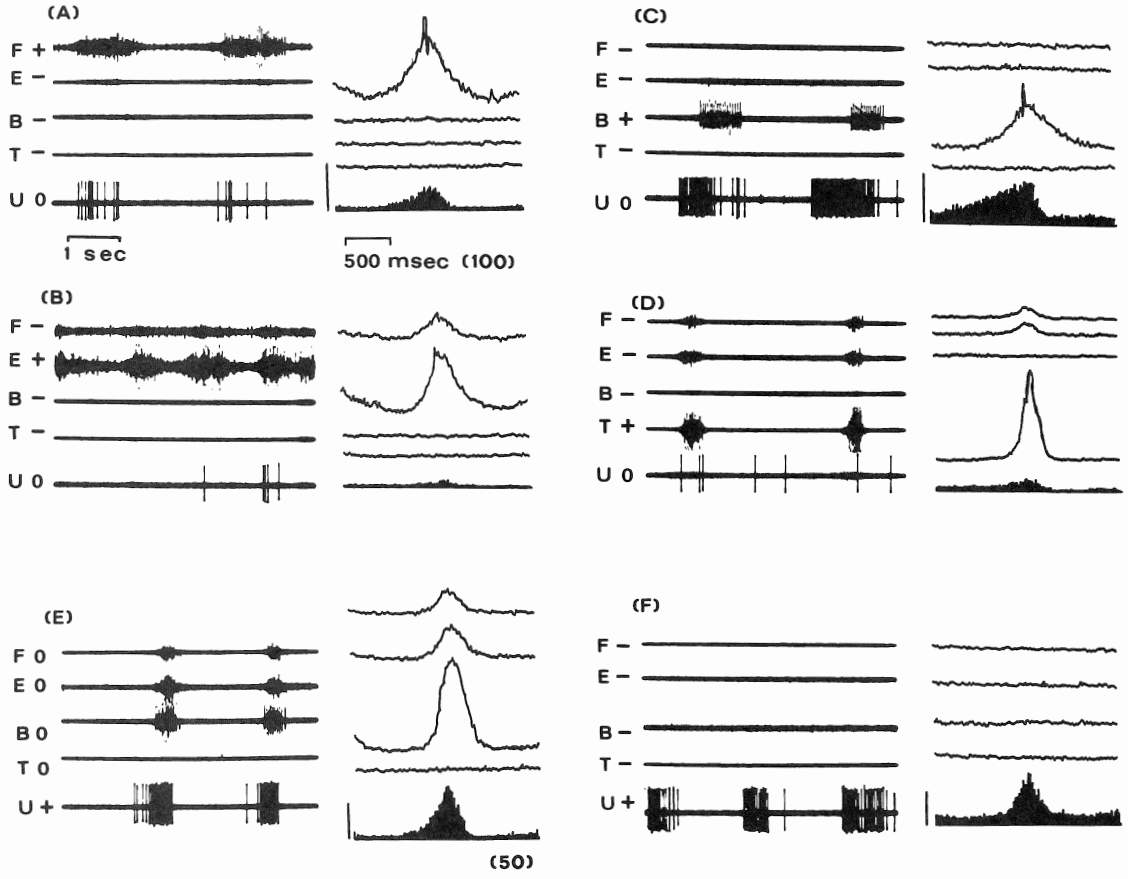


Figure 3–36 Operantly conditioned response patterns of a precentral motor cortex cell (*U*) and four arm muscles—a flexor and extensor of wrist (*F* and *E*) and of elbow (*B* and *T*). Representative trials are shown at left and response averages at right. Symbols after letters indicate whether reward contingency included activation (+) or suppression (−) of that element, or did not include its activity (*o*). *A–D* illustrate responses when monkey was rewarded for isometrically contracting each muscle in isolation. *E*, operantly rewarded bursts of cortical unit activity with associated muscle activity. *F*, response pattern when unit activity and muscle suppression were reinforced. (From Fetz and Finocchio, *Exp. Brain Res.*, 1975, 23, 217–240.)

motor center cell may diverge to affect motoneurons of several different muscles.

Similar conclusions were reached in experiments in which monkeys were trained to activate specific motor cortex cells and the correlated motor responses observed.[46, 47] A monkey rewarded for increases in firing rates of precentral cells quickly learned to activate these cells in "operant bursts," which were often accompanied by movements of the limb. For some cells these movements were relatively specific and repeatable, such as flexion of a distal joint; for other cells the movements were generalized and variable; still other cells were activated with no observable concomitant motor response. Under isometric conditions, the set of muscles coactivated with operant unit bursts—called the cell's "motor field"—was quite repeatable and often included several different arm muscles. For example, operant bursts of the cell in Figure 3–36 (E) were accompanied by activity of biceps and both wrist muscles. Such motor fields were often different for different cells, even in the same region of motor cortex. This suggests that cells related to different muscles of the limb are intermingled.

The stability of a correlation between activity of a motor cortex cell and contralateral muscles may be tested by operantly conditioning its dissociation. The cell in Figure 3–36 was consistently coactivated with the biceps and wrist flexor muscle under several different response conditions: when isometric muscle activity was rewarded (Fig. 3–36A and C), when unit activity was rewarded (Fig. 3–36E) and when the monkey made active elbow movements. However, when the monkey was reinforced for firing the cell without any muscle activity he could readily do so (Fig. 3–36F). Thus, operant conditioning techniques may be used to reveal a considerable degree of plasticity in unit-muscle correlations.

Although consistent covariation between activity of a precentral motor cortex cell and specific contralateral arm muscles may suggest a functional relationship, it can never establish the existence of a direct corticomotoneuronal (CM) connection. Since the cell and muscle could be coac-

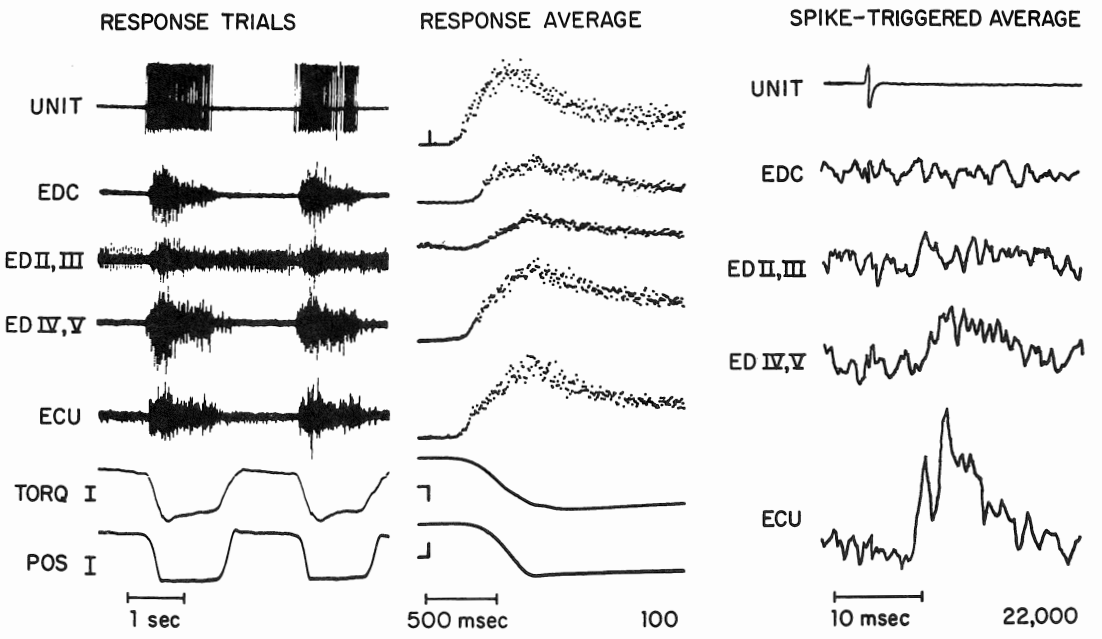


Figure 3–37 Responses of precentral CM unit, four extensor muscles (EDC; ED II, III; ED IV, V; ECU), torque (T) and position (P) during alternating wrist movements. Response averages document relative timing of unit and muscle activity during extension movements. Spike-triggered averages of rectified EMG activity reveal post-spike facilitation of ED IV, V and ECU. (Fetz and Cheney, unpublished observations.)

tivated without being connected, covariation is not sufficient to establish a CM connection. Moreover, since any CM connection is surely subthreshold for activating the motoneurons, a consistent covariation is not even a necessary consequence of a connection. Nevertheless, there remains an intuitive inclination to suppose that activity of connected elements would covary. Whether this is in fact true can be investigated only by employing independent measures of covariation and connections. Although a connection cannot be established by covariations, its presence can be detected by more sensitive cross-correlation techniques. A convenient approximation to a statistical cross-correlation is the spike-triggered average. By summing the EMG following action potentials of individual covarying cortical cells, Fetz *et al.*[48] found that some PTN's produced transient post-spike facilitation of EMG activity in one or more muscles. The cell in Figure 13–37 covaried strongly with wrist extension and its spike-triggered averages reveal a clear post-spike facilitation in two of the six extensor muscles recorded (ECU and ED IV, V, lower right). The latency and time course of these facilitations suggest that they were mediated by monosynaptic EPSP's evoked by this cell in the relevant motoneurons. Other cells produced post-spike facilitation in as many as six muscles. Assuming such facilitations are mediated by monosynaptic CM connections, this suggests that the set of muscles whose motoneurons are contacted by the CM cell—the cell's "muscle field"—may include several synergists of the same joint. More than two-thirds of the CM cells produced facilitation in more than one muscle; activity of such CM cells contributes to the production of a movement through numerous synergists. Other CM cells produced facilitation in only one of the recorded muscles, suggesting that these had more restricted muscle fields. As noted above, those precentral cells that produced post-spike facilitation had firing rates that increased linearly with static force over a considerable range. This establishes a causal relationship between CM cell activity and force output, since these cells directly facilitate the motoneurons producing the force.

MECHANISMS OF RECOVERY

Having reviewed the anatomical and functional characteristics of PT, PPS and COEPS, it should be possible to understand the mechanisms of recovery of motor function after various lesions. Recovery is, of course, the primary interest of the patient and the source of frustration of the neurologist, because too little is known about it and how to maximize it.

Recovery has two aspects that probably involve different structures, different mechanisms or both. These are the recovery (i) from negative symptoms, especially the paralysis or paresis, and (ii) from the positive symptoms, especially spasticity. (The patient is not particularly concerned about an absent cremasteric reflex or an upgoing big toe, or a clonic ankle jerk, except as a companion of spasticity, which restricts his movement.

Factors in Recovery of Voluntary Movement. Explanation of the recovery of voluntary movements following lesions in the cortical arm or leg area has always presented a problem. In fact, the degree of recovery possible when supposedly all of the cortical arm area is destroyed led early clinicians to conclude that the arm is represented throughout the length of the precentral gyrus. Such an assumption is no longer necessary now that it is known that: (i) the PT originating in substantial degree from areas outside the primary motor area may serve movement and (ii) the COEPS supports some voluntary movement. Moreover, the amount and complexity of voluntary activity that can be supported by subcortical motor centers have been *underestimated* in both the monkey and in man, for reasons given below.

Several factors affect the duration and ultimate degree of paralysis.[see 53] (i) *Extent of cortex removed.* In monkeys, removal of area 6 including the supplementary motor area adds to the depth and duration of voluntary paralysis. Consistently, retention of area 6 leaves an animal significant useful movement.* Bilateral removal of areas 4

*Whether this is an argument for the motor capacity of COEPS or of corticospinal fibers is not entirely clear, since the magnitude of the projections from area 6 is uncertain as is the exact border between areas 4 and 6.

and 6 is more paralyzing than a comparable unilateral lesion. If the parietal lobe, which also gives rise to PT axons, is removed, there is a further deficit, only in part attributable to interference with somatic sensation. (ii) *Time between operations.* If bilateral removal of areas 4 and 6—an operation reducing a monkey's immediate motor status virtually to that of a completely decorticate animal—is performed in stages with long periods elapsing between stages, a surprising amount of voluntary ability is recaptured.[147] (iii) *Phylogenetic position.* Clinical signs following isolated ablation of area 4 increase in severity as the primate scale is ascended. Lemurs and New World monkeys exhibit less deficit than do macaques and baboons, and the chimpanzees exhibit a greater deficit. Motor functions are more highly encephalized (actually "corticalized") in the animals with more highly developed brains. (iv). *Age.* If areas 4 and 6 are removed in an infant, the animal is at first little affected. Serious motor deficits begin to appear as the animal matures and as the PT becomes myelinated, but they may never be as severe as in an animal undergoing the ablation as an adult. (v) *Postoperative care.* When cortical areas are removed, passive exercise to prevent muscle atrophy and contractures and nursing care to prevent bedsores, wasting, etc.[147] are important to counteract neglect or nonusage of the affected limbs. (vi) *Retraining.* The amount of forced use* of the paretic extremity in specific movements. (vii) *Time after operation.* Given (v) and (vi) above, recovery continues over a much longer postoperative period than is allowed in many experiments. Other measures designed to promote recovery rest on a clinical, observational basis and are beyond the scope of this book.

Mechanisms of recovery. Even though, as noted, recovery of function is the first concern of the patient, relatively little laboratory research has been devoted to this subject. Definite explanations of the recovery mechanisms from brain injury like that from spinal transection cannot be given. One factor in recovery is the so-called "neighborhood symptom." Whether the cause of the disorder is a vascular accident or a meticulous surgical ablation, some *reversible* damage—trauma, dehydration, ischemia, venous occlusion, edema, free blood, etc.—is inflicted on regions neighboring the areas completely destroyed. As this transient damage abates, the remaining tissue functions at more normal levels, and the paresis shrinks in severity and extent.

Since motor skills can be improved by learning, it is reasonable that use and training can increase the performance of the undamaged neural tissue. This is sometimes termed "compensation." That tracts or cortical areas which have previously not controlled a given muscle do so after a lesion—as implied by the term "vicariation"—is considered doubtful, but we have learned above that cortical neurons can learn. However, performance of the same act with a different unaffected set of muscles is a commonplace phenomenon.

A definite aspect of recovery from cortical lesions established experimentally is that they produce a "cortical shock" (hyporeflexia) resembling spinal shock (Chap. 2, Vol. I). A chronic unilateral lesion of the motor cortex reduces the areflexia in the contralateral limb from a subsequent bilateral spinal transection. Some recovery from the effects of withdrawing the corticofugal component in the spinal transection has occurred. However, the contralateral recovery is not absolute, some renewal of reflex changes occurs from the subsequent spinal transection, confirming the existence of other facilitatory pathways not dependent on corticofugal input.

Release of Function. The sequence of events—areflexia, hyporeflexia, and ultimate hyperreflexia—is typical of both capsular hemiplegia and spinal transection. The hyperreflexia (spasticity) is interpretable as *release of function, i.e.,* release of segmental reflexes from inhibition by a descending pathway. The problem of why this release is not immediately manifest is often overlooked. Release phenomena are

*Forced use may be the kind that a physiotherapist administers for brief periods and patients are encouraged to do on their own. However, the phenomenon of neglect is so marked in laboratory experiments that restraints of the unaffected limb or other methods to promote use should be used. In laboratory experiments,[2] drugs such as amphetamine have increased the performance of animals with neural lesion and perhaps should be used more widely as an adjunct during physiotherapy.

manifest within seconds in certain experimental situations, *e.g.*, decerebrate rigidity or the *increase* in the excitability of the hindlimb flexor and forelimb extensor reflexes following spinal transection in a decerebrate preparation (see Chaps. 1 and 2, Vol. I). In primary transection of the spinal cord or in capsular hemiplegia, descending facilitatory tracts as well as inhibitory ones are removed. According to one interpretation, interruption of facilitatory pathways causes some change in the motoneuron's excitability, thus preventing any manifestation of the withdrawal of inhibition until the motoneuron has recovered excitability. The mechanism of recovery of a neuronal level presents much the same problems in hemiplegia and spinal shock. While hypothetical explanations of recovery from negative signs and symptoms are available, the mechanisms of recovery from release phenomena have virtually not been studied.

What Is Released? Spasticity is a release phenomenon. Two questions must be asked about any release phenomenon. What structures must be damaged to effect the release, and what structures are released? With regard to spasticity and exaggerated reflexes of hemiplegia, the first of these questions has been answered in this chapter. The importance of the second question was first stressed by the philosophically minded neurologist Hughlings Jackson, who pointed out that a negative event (a lesion) cannot cause a positive event (a phenomenon such as spasticity). Except when irritative, a lesion can only be an *antecedent circumstance;* the direct *cause* or underlying mechanism of the overactivity must be the structures remaining functional. Releasing the brake of an automobile does not cause the car to go forward; it is the motor or gravity which does that. Magoun and Rhines[92] have expressed Hughlings Jackson's idea in a homely fashion, likening the motor systems to a Jack-in-the-box. The motor cortex is the lid—but what is the spring that makes Jack jump out of the box?

At first sight, the segmental stretch reflex arc might seem to be the thing that is released in hemiplegia. However, in the higher primates including man, spinal reflexes in themselves are not very strong, or they would not be so depressed after spinal transection. For spasticity to develop, some facilitatory tract from the brain stem must remain functional. Just what tract or tracts are candidates for supporting recovery are described in Chapters 1 and 2 (Volume I).

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