THE NATURE OF DYSTONIA*

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KINNIER WILSON's striking demonstration of damage to the putamen in hepatolenticular degeneration in 1912 established for the first time that severe motor disability could be related to an "extrapyramidal" structure. The disputed changes in the globus pallidus in parkinsonism and in the caudate nucleus in Huntington's chorea, described earlier by Gerbrandus Jelgersma and by Alois Alzheimer, became of greater significance from that time onwards. Though many since Constantin Trétiakoff (1919) have attributed the parkinsonism of lethargic encephalitis to degeneration of the substantia nigra, others, including myself, have disputed the importance of nigral changes in this connection.

The chief characteristics of extrapyramidal disorder are rigidity of muscles and involuntary movements. There have been many attempts to relate these symptoms to disorder of one or another of the basal nuclei. A fundamental difficulty has been the absence of any knowledge of the function of these regions of the brain in normal health. Stimulation of these nuclei in animals failed to produce any regular disturbance of motor function. Experimental lesions of them either failed to have any remarkable effect, or were so large that any resulting motor disorder could be attributed to damage to neighboring pyramidal structures. Study of the degeneration of their connections by the Marchi method showed only short pathways interconnecting the ganglia, without any tract descending to centers lower than the subthalamic region. Damage to that region produced degeneration descending only a little lower. There was the authority of Cajal for the absence of any direct pathway from the cortex to the basal ganglia, and more recent anato-

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mists have denied pathways from the basal ganglia to the major motor centers of the pons. Some anatomists[1] throw doubt on the existence of any motor system that could be characterized as "extrapyramidal." These difficulties in defining the supposed motor centers were increased further by the finding of neurosurgeons that destruction of the globus pallidus could relieve extrapyramidal symptoms of the kind that are commonly attributed by neurologists to damage of this structure.

Finally, to complete the confusion of ideas, certain physiologists and anatomists brought forward evidence that what the neurologists had defined as the classical signs of disorder of the pyramidal tract were in fact not produced by experimental damage to that tract.[2] Bucy, Keplinger, and Sigueira[3] have recently described a patient who recovered ability to move the fingers and toes, with moderately good use of the hand, after a lesion in the cerebral peduncle that destroyed an estimated 83 per cent of pyramidal fibers.

Diseases of the Basal Ganglia

It is clearly necessary to bring some order in this state of chaos of all our concepts of the elements of control of movement by the brain. My own approach to these questions is incorporated in two monographs, one on the basal ganglia[4] published in 1962, and another in press,[5] which should appear in 1965. In the first I outlined the general nature of the disturbance in diseases of the various basal ganglia, in relation to their neuropathology. I found that the fundamental disorder was a disturbance of attitude. This began with instability of posture, with a tendency to patterned attitudes that at first were labile and gradually became more fixed. Any passive movement of the limb away from the prevailing attitude met a resistance that was in the beginning plastic and yielding, but gradually became more springy in quality as the abnormal attitude became more fixed. This phenomenon was defined as dystonia. It is of the same nature in all diseases of the basal ganglia, differing only in its pattern and speed of development. It is not associated with any remarkable degree of change in tendon reflexes. Two fundamental patterns could be distinguished, one with flexed arms and extended lower limbs, and usually extended spine, which I called hemiplegic dystonia. This is most commonly produced by lesions of the putamen. The other is one of general flexion, which is related to damage to the globus pallidus. Transition forms are com-

mon. As destruction of the globus pallidus affects its most medial segment the flexion posture is less intense, though still present.

Involuntary Movements

Involuntary movements are considered by us to result from instability in the factors operating to produce dystonia, varying from the more labile fluctuations of chorea, through the gross alternations of athetosis, to the more violent conflict of tremor as the pathways converged on the globus pallidus. In some diseases that affect more and more of the basal ganglia the type of involuntary movement was observed to change in the order mentioned. As destruction at any one level became complete the conflict lessened and eventually disappeared, leaving a fixed dystonia. In the experimental animal the characteristic movements have therefore not been produced by gross lesions, which could not imitate the diffuse effects of disease. If the lesion was large enough the characteristic flexion dystonia was produced by severe pallidal lesion in monkey, and hemiplegic dystonia by damage to the putamen or outer segment of pallidum. In man anoxic necrosis of these ganglia had the same effects.

I also noted that in the early stages of human diseases, the involuntary movements were modifiable by cutaneous and other stimulation and represented perversions of the contact and other avoiding and exploratory reactions that result from damage to various extra-Rolandic areas of the cortex. In diseases such as postencephalitic parkinsonism and familial parkinsonism the loss of corticostriate fibers and corticopallidal fibers were found to be more prominent than damage to striatum or pallidum. We noted also that large bundles of poorly medullated and nonmedullated fibers normally run from the cortex to these ganglia in the external and internal capsules. Their pattern has more recently been described for the rabbit by Carman, Cowan, and Powell.[6] The characteristic disorders of function could therefore be produced without direct damage to the basal nuclei, thus explaining earlier difficulties in relating symptoms to lesions in the various nuclei.

Torticollis and Torsion Dystonia

The series of dystonic disorders we have mentioned relate to the conditions on Huntington's chorea, athetosis, dystonia musculorum deformans, and parkinsonism. Associated with unilateral forms of these

there is commonly distortion of the attitude of the head and neck in combination with dystonia in the limbs. These must be clearly distinguished from another series of dystonic disorders that comprise either isolated postural deviation of the neck (pure torticollis) or a rotary distortion of the neck and limbs on their longitudinal axes (subthalamic, or torsion dystonia). Torticollis of the isolated type arises from damage to the pretectal region, and is then due to distortion of optokinetic reflexes.[5] Torsion dystonia arises from lesions of the ventral mesencephalic tegmentum and is associated with disorders of tonic labyrinthine reflexes.[7] There is not space to discuss these special types of dystonia further here, and the remainder of my remarks deals with disorders of the extrapyramidal system of the basal ganglia (hemiplegic and flexion dystonia).

The Extrapyramidal Component of Spastic Hemiplegia

Since the work of Fulton and Kennard in 1938 and of Sarah Tower in 1940, it has been realized that removal of the centers for arm and leg adjacent to the central sulcus in the hemisphere, or section of the pyramid in the medulla, in monkeys did not result in the classical spastic hemiplegia of capsular lesions.[2] Fulton and Kennard thought that additional damage to area 6 was necessary to convert the hypotonic paralysis into a spastic one. Marion Hines claimed that the critical area was a strip (4S) on the anteromedial part of area 4; Denny-Brown and Botterell[8] concluded that the cortex around the superior precentral sulcus (Figure 1, SPS) was the essential area; and more recently Travis, and also Travis and Woolsey[12] decided that the "supplementary area" overlapping both area 6 and area 4 was critical (Figure 1). I have recently again set forth elsewhere[9] my evidence that the region of the superior precentral sulcus within area 4 is the origin of an extrapyramidal pathway, removal of which in addition to removal of the posterior strip of area 4, induces the typical hemiplegic attitude of spasticity. Both this and the supplementary area remain excitable after section of the medullary pyramid. Section of the medullary pyramid alone induces increased and often repetitive tendon reflexes, with a mild stretch reflex in all muscle groups in the limbs.[9] The condition is not flaccidity, nor is it classical spasticity. The limbs, as Tower noted, are held slightly flexed and offer a soft resistance to full extension or flexion, a mild stretch reflex. What is missing is the hemiplegic posture

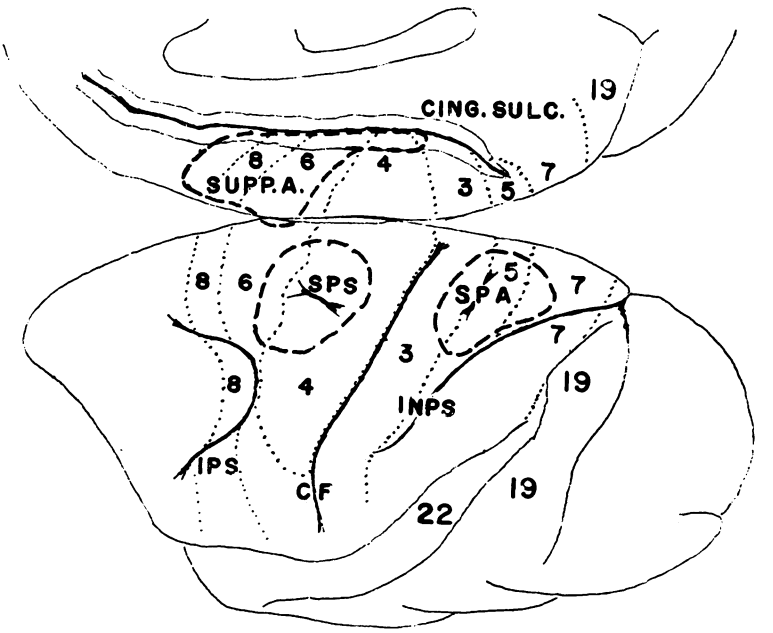

Fig. 1. Diagram of lateral view of left hemisphere of a macaque monkey, with contiguous area of medial aspect shown above. In front of the central sulcus (*CF*) there lie areas 4, 6, and 8 of Brodmann. Surrounding the superior precentral sulcus (*SPS*) is an area of cortex still excitable after section of the pyramid in the medulla. On the medial surface the supplementary area (*SUPP. A*) similarly remains excitable. The cortex surrounding the superior parietal sulcus (*SPA*) at times yields a movement synergy of the limbs. The second sensory cortex, buried in the sylvian fissures, is not shown. Adversive movement of the head and eyes can be obtained by electrical stimulation of areas 8, 7, 22, and 19.

of flexed upper limb and extended lower limb, the greater heightening of tendon reflexes with clonus, and the greater intensity of stretch reflex that is called the clasp-knife phenomenon. All these are added by additional ablation of the extrapyramidal cortex in the region of the superior precentral sulcus.[9] The pathway for these effects must travel outside the cerebral peduncle, for in their excellent study of peduncle lesion in the monkey, Cannon, Magoun, and Windle in 1944[10] found that the resulting hemiplegia was not spastic, and that subsequent ablation of cortex led to further loss of movement and converted the condition to spasticity. The only remaining descending pathway must be that through Forel's field to the midbrain and medullary reticulum, via the central tegmental tract, by short neuronal links.

The epiphenomena that characterize capsular hemiplegia in man are dynamic additions to the fundamental release of stretch reflexes by

pyramid lesion. The hemiplegic posture of flexed upper extremity, extended lower, with its related bias of reflex exaggeration in flexors of arm and extensors of leg, and of traction reaction in the arm and positive supporting reaction in the leg, are completely reversed by holding the monkey (or human) upside down in space. It is then the leg that becomes flexed, the arm extended, with corresponding change of distribution of altered reflexes. The extrapyramidal effect is a reflex bias of attitude, taking origin in the labyrinth, transmitted via the neck reflexes, and abolished by section of the 8th nerves.[9]

Increased stretch reflexes result from heightened sensitivity of muscle spindles, which results from innervation of the small gamma motor neurones. Pontine reticular centers can drive these neurones, as in classical decerebrate rigidity, and provide tonic neck and labyrinthine reflexes and positive supporting reactions. Section of the dorsal roots to a limb abolishes these effects by breaking the "gamma loop" by which the muscle spindles activate the ordinary (alpha) motor neurones. The labyrinthine effects that provide the hemiplegic postural changes resulting from cortical lesions are different. They are transmitted directly to alpha neurones, for if the dorsal roots of the hemiplegic limb are sectioned the hemiplegic attitudes, reversed by labyrinthine effects, remain. The limbs still offer some soft springy resistance to passive movement away from their prevailing posture, but less than before. The tendon reflexes, clonus, and the stretch reflex are then, of course, abolished. Hemiplegic spasticity resulting from capsular and cortical lesions has therefore two components: an increased stretch reflex (increased gamma innervation) and an attitudinal dystonia (a direct alpha innervation).

The hemiplegic spasticity resulting from ablation of area 4 is not as severe as that resulting from capsular lesion or from decortication. The decorticate monkey is spastic, but in the first days can still walk stiffly and right himself. He exhibits all the phenomena of bilateral spastic hemiplegia of severe degree. But by the fifth to seventh day he is becoming stiffer still, and after the first week presents a statuesque fixity of attitude of the type we see in the grotesque postures of dystonia musculorum deformans. This is no longer changed quickly by labyrinthine stimulation. This spastic dystonia represents a maximal degree of combination of extrapyramidal and pyramidal disorder, with both gamma and alpha facilitation. Since the dystonia is greater than

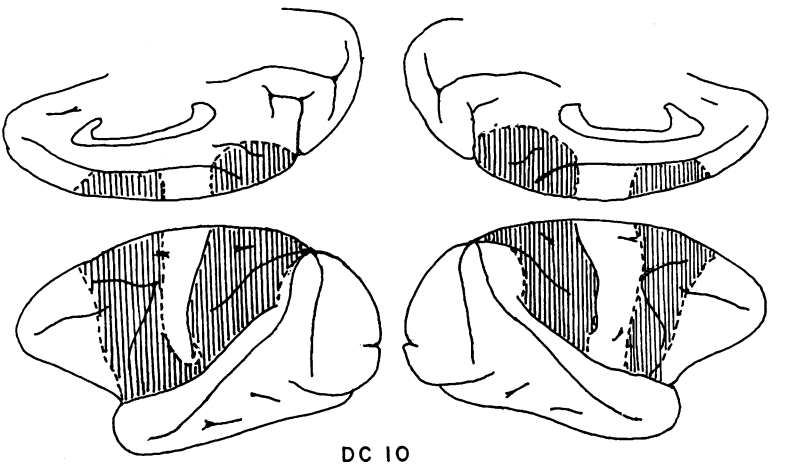

Fig. 2. Diagram of the brain of monkey DC10 showing the areas of cortex removed, one hemisphere at a time, by suction, leaving pial bridges intact, carrying pial vessels to the precentral cortex, which remained histologically intact and electrically excitable.

from ablation of area 4 there must be additional extrapyramidal projections in other areas of cortex.

Paralysis and Loss of Ability for Movement

The clinician uses the term "paralysis" in a variety of connotations. The most frequent use is to describe the loss of power of muscular contraction in response to a request to make a given movement. As a result of lesions of cortex or corticospinal pathways the defect is not a failure to innervate any discrete group of muscles, but various degrees of difficulty in making delicate and precise movements. With increasing difficulty the patient has to innervate progressively more muscles in order to use any one of them. Eventually he can activate only the limb as a whole, and then by contraction of only proximal muscles.

In the experimental animal this is also the defect from cerebral lesions, but it is more obvious that the remaining responses are reflex in nature. As each reflex recovers from the initial shock of lesion the monkey learns to use it to attain his desired ends. After bilateral area 4 lesion the monkey can pick up small objects, using the thumb in opposition to the fingers, but only as a reaching grasping or plucking movement of his limb as a whole. After bilateral combined area 4 and parietal lesions the animal can no longer carry objects to the mouth, but can still pluck and hook objects toward him by a sweeping pawing

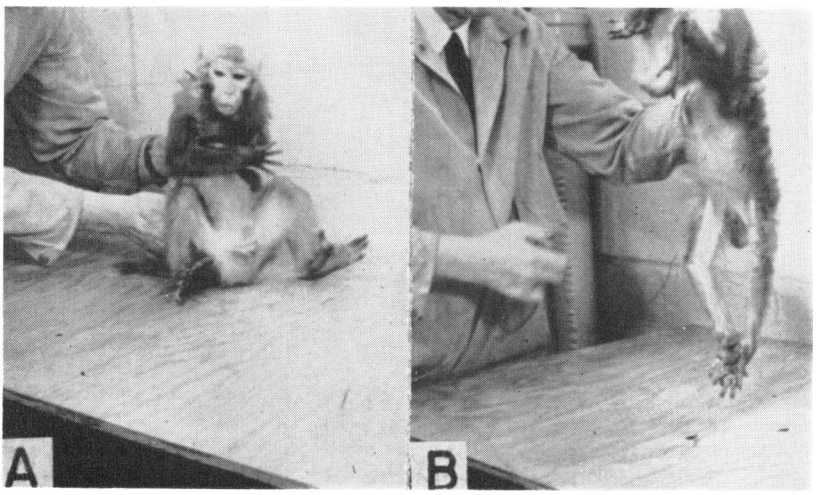

Fig. 3. The monkey DC10 propped up in sitting posture (*A*) and suspended head downwards (*B*) to show the lability of posture. These postures were present for over 4 weeks. (After Denny-Brown, D. *Sherrington Lectures, 1963*. University of Liverpool Press.[5])

or progressive movement. The tilting and hopping reactions likewise deteriorate from precise adjustments of posture to a turning progression movement of all four limbs that nevertheless serves to maintain postural stability. These are also the residual movements after pyramid lesion, which blocks both by pre- and postcentral corticospinal transmission. These less precise stepping or pawing movements are also present in the recently decorticate animal, before increasing dystonia results in too great fixity of posture. The results of hemispherectomy indicate that this class of movement in any limb can be initiated by either hemisphere in man as well as monkey. There is reason to believe therefore that if the release effects of extrapyramidal lesion could be avoided completely the hemiplegic limb would have a wide range of effective use, though it would lack precision and specialization in movement.

Cortical Dystonia

The greater dystonia of the decorticate monkey, and the several areas from which movement could still be elicited by stimulation after pyramid section, made it probable that some areas of cortex in addition to that of the area of the superior precentral sulcus must give rise to extrapyramidal projections. In the past two years, with the assistance of Sid Gilman, I have carried out a long series of ablation experiments in

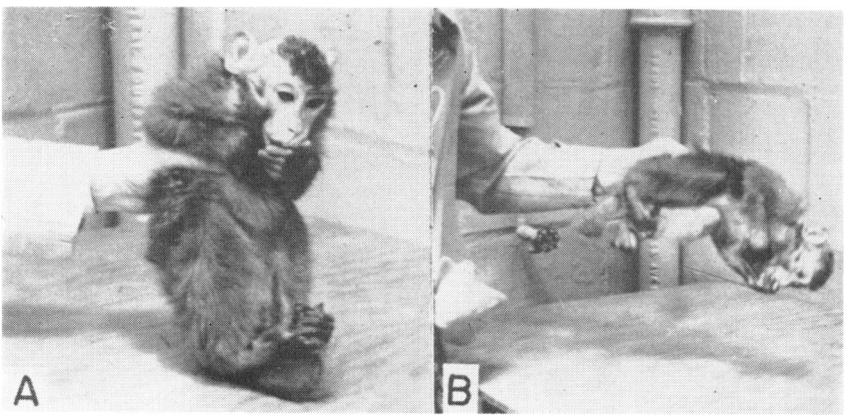

Fig. 4. The monkey DC10 showing the change in posture resulting from section of the 8th nerves bilaterally. This posture continued until sacrifice of the animal 3 days later.

monkeys in a search of these additional extrapyramidal areas. We began by ablating all areas 6 and 8, and all parietal lobe, bilaterally (Figure 2), leaving area 4 histologically intact and electrically excitable. The result was a dystonic animal without increase in tendon reflexes.[9] In sitting posture the arms were flexed, the lower limbs semiextended (Figure 3). If leaned backwards the arms flexed further, the legs extended further. If he was held head downwards the lower limbs flexed tightly, the upper limbs extended. Intermediate postures resulted in instability of the position of the fingers, which opened and closed irregularly. In all these postures the limbs offered a springy resistance to any attempt to displace them, flying back to the original posture when released. Section of the dorsal roots to both arms made no difference to these postures, so that the gamma system was not involved.

The dystonia from cortical ablation was identical with that resulting from lesion of the outer globus pallidus. In both cases section of the 8th nerves converted the postures to flexion dystonia (Figure 4). Some degree of flexion then persisted under all circumstances, but broad contact with the lateral aspects of the limb girdles, chest, abdomen, or rump then greatly intensified the flexor resistance.

Ablation of area 6 alone, 8 alone, or parietal lobe alone results only in some very mild plastic resistance to passive movement. The minimal cortex to be removed in order to produce unmistakable dystonia is a combination of either 6 or 8, with either 2 or 7. Combined ablation of areas 6 and 7 produced more dystonia than any other two areas. Addi-

tional ablation of areas 8, 2, 5, or 22 produced only additive effects.

It became apparent therefore that full release of extrapyramidal dystonia resulted from loss of a wide area of cerebral cortex surrounding the pre- and postcentral gyrus on all sides. The pathway concerned converges on the basal ganglia, to proceed to the midbrain reticulum via the efferents of the globus pallidus. The labyrinthine component of this mechanism, which provides its most intense tonic effects, joins the system at the level of the internal medullary lamina of the globus pallidus. Lesion here abolished the attitudinal change induced by position in space.[4] The effects of body contact that determine the posture of flexion dystonia appear to be mediated at midbrain level in the midbrain reticulum, the body contact righting reflex of Magnus. The system then continues to the lateral medullary reticular nuclei by the central tegmental tract, and thence to the lateral column of the spinal cord as the lateral reticulospinal tract, to reach the alpha neurones. It is completely independent of the tonic labyrinthine reflex, which influences the gamma neurones via medial medullary mechanisms and the ventral reticular and vestibulospinal tracts. The two systems are interrelated at various levels, notably by parapyramidal tracts such as the frontopontine tract, but these have nothing to do with the phenomena we have been discussing.

The powerful reflex mechanism that results in the most troublesome types of dystonia and conflict in movement is chiefly related to the labyrinthine component. This enters the system in the medullary laminas of the globus pallidus, and anatomical considerations indicate that it is derived from the centrum medianum of the thalamus. It appears to us that surgical palliation of dystonia has effect by altering this reflex factor.

The areas of cerebral cortex that give rise to extrapyramidal projections each yield, when stimulated, a monotonous response of adversion of head and eyes and progression movement. In two fields there is some specialization. In the supplementary area there is a predominance of flexion movements related to avoiding behavior, with its vocalization. In the second sensory cortex there are extension movements essential to delicate exploratory behavior. In the auditory cortex, area 22, stimulation pricks the ears, as well as producing the stereotyped movement. Without any of these areas the animal appears to be unable to perform

any of the delicate refinement of movement that depend on the integrity of area 4, though this cortex is still electrically excitable. The animal cannot explore space with the limbs. Similarly, after severe pallidal lesion interrupting all extrapyramidal facilitation at a lower level, the movements that otherwise require integrity of area 4 are not possible.[11] We conclude that the pyramidal system is useless to the organism without a substrate of extrapyramidal activity. The extrapyramidal system enables the "set" of the motor act, the pyramidal system provides the more delicate adjustments.

Some estimate of the part played by each of the extrapyramidal cortical areas in determining projected motor reactions can be made by planning cortical ablations so as to allow activity of only one such area. Thus if all the extrapyramidal cortical areas were excised on both sides, except for residual intact frontal fields 6 and 8 on one side, the effect of that field was found to be visual direction of exploration that had been initiated by contact (e.g. palpation). Area 22 on one side enabled a more purely visually directed task, its tactile aspects still remaining defective. The postcentral area is essential for motor performance that has purely tactile guidance. In each case the full development of such performance is in the limbs of the opposite side, though some degree of improved function is seen in the ipsilateral limbs. The extrapyramidal mechanism can therefore activate the limbs of both sides, and each area can compensate in some degree for the others.

The diffuse origin of the small-celled cortical extrapyramidal system has importance in the understanding of dystonia resulting from some types of diffuse encephalitis. The problem is complicated by a remarkable degree of compensation. The production of dystonia by cortical ablation is maximal when a large extent of the cortical areas is removed in a short interval of time. If the different areas are ablated one by one a remarkable degree of compensation for loss of projected types of movement takes place. Only mild dystonia then occurs, worsened slightly following removal of each additional area. When the last significant area (e.g. postcentral gyrus, or supplementary area) is then removed, all four extremities, trunk, and head suddenly develop a fixed dystonic posture. This is, I believe, the reason for the remarkable degree of recovery of ability for movement noted by Travis and Woolsey[12] following repeated cortical ablations. I am inclined to maintain however that the most disabling factor is dystonia. The remarkable ability for

movement that remains following peduncle lesion or after extensive hemispherectomy in man is due to the absence of the dystonic mechanism of the basal ganglia.

I conclude that the uniformity of the nature of dystonia resulting from release of extrapyramidal mechanisms in cerebral cortex is interpreted to mean that a variety of areas of cortex related to specialized environmental stimuli must each use the same fundamental motor mechanism, the labyrinthine and body contact phasic righting reflexes. Though these basal ganglionic reflexes are intimately concerned in the facilitation of movement, loss of their cortical control results in fixed attitudes, providing the conflicts of innervation we have called dystonia.

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