A ny model for the physiology of dystonia must be able to explain how dystonia can be produced in various circumstances. Brain lesions can cause dystonia; responsible sites include the basal ganglia, brainstem, and thalamus, but the most common site is the putamen. Dystonia can be hereditary, and genetic linkage has been found for both generalized and focal dystonia. The only genetic dystonia for which the gene product is known is Segawa disease, a hereditary progressive dystonia with marked diurnal fluctuation. The defect is in guanosine triphosphate cyclohydrolase I, a gene that makes a cofactor for the synthesis of dopamine, which explains why this form of dystonia should be amenable to treatment with levodopa. Another example of dystonia in which a disorder of dopamine pharmacology appears responsible is the dystonia occurring in Parkinson disease, either spontaneously or as a result of treatment. Curiously, the dystonia occurs at both peak and trough dopamine levels.

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Dystonia apparently can also be produced behaviorally. Writer’s cramp and other occupational cramps seem to be caused by excessive repetitive activity. A possible animal model of dystonia was created in nonhuman primates with synchronous, widespread sensory stimulation to the hand during a repetitive motor task. During a period of months, the animals' motor performance deteriorated. After development of the movement disorder, the primary somatosensory cortex was mapped, and receptive fields in area 3b were increased 10- to 20-fold, often extending across the surface of 2 or more digits. The investigators suggested that synchronous sensory input over a large area of the hand can lead to remapping of the receptive fields and subsequently to a movement disorder. However, these tasks also involve repetitive movements, which can lead to remapping of the motor system.

A possible human model of blepharospasm was proposed in a case report of blepharospasm-like symptoms developing contralateral to an eyelid weakened by facial nerve palsy. Hyperexcitability of the normal eyelid might be a maladaptive consequence of the bilateral increase in gain of eyelid movement caused by weakness of the affected lid. This theory is supported by the observation that the eyelid spasms were eliminated by the implantation of a gold weight to assist closure of the paretic eyelid.

If dystonia really can be produced behaviorally, perhaps it would only be possible in persons who are predisposed. The predisposition could be genetic, but the evidence from family studies of focal dystonias indicates that the penetrance is low. Dystonic movements are characterized by an abnormal pattern of activity on the electromyogram with cocontraction of antagonist muscles and overflow into extraneous muscles. Rothwell et al reasoned that the important problem of excessive cocontraction could be caused by deficient reciprocal inhibition, a fundamental process, represented at multiple levels of the central nervous system, that produces inhibition of a muscle when its antagonist is activated. This conjecture led to studies of reciprocal inhibition as rep-
presented in the spinal cord as a reflex. Reciprocal inhibition was found to be deficient. Subsequently, other reflexes, such as the blink reflex in patients with blepharospasm, were investigated, and the general conclusion was that inhibition was deficient at the spinal cord and brainstem levels. Abnormalities of these reflexes may be helpful in supporting a diagnosis of dystonia in patients who are suspected of having the disorder. Even though the reduction of spinal cord and brainstem inhibition is clearly an important mechanism in dystonia, the fundamental disturbance would more likely be an abnormal supraspinal command signal than disordered spinal circuitry.

Several studies indicate that there is some kind of deficiency in patients with various abnormalities of the cortical motor system. Electroencephalographic studies of 2 motor tasks show loss of expected negativity in association with voluntary movement. First, movement-related cortical potentials associated with self-paced finger movements in patients who have hand dystonia show a reduced amplitude of the negative slope component, a negativity occurring just before the onset of movement and thought to be generated in the motor cortex. Second, the contingent negative variation, the negativity between a warning stimulus and a “go” stimulus, shows deficient late negativity with head turning in patients who have torticollis and with hand movement in patients who have writer’s cramp. Like the movement-related cortical potential, the late negativity represents motor function.

Ceballos-Baumann et al used positron emission tomography (PET) and the tracer H15O to measure regional cerebral blood flow in a study of voluntary movement in patients with dystonia. They found abnormal suppression of regional cerebral blood flow in the caudal supplementary motor area and primary sensorimotor cortex bilaterally. (There were also some areas of overactivity, including the contralateral lateral premotor cortex, rostral supplementary motor area, anterior cingulate area, ipsilateral dorsolateral prefrontal cortex, and contralateral lentiform nucleus.) Using the blood flow–PET method, my colleagues and I also have studied several manual tasks in patients with dystonia of the hand and found abnormal suppression of regional cerebral blood flow in the somatomotor cortex contralaterally, premotor cortex bilaterally, cingulate cortex, and supplementary motor area.

In contrast, a study using transcranial magnetic stimulation showed increased excitability of the motor cortex in patients with dystonia. The threshold for the production of motor evoked potentials (MEPs) was unchanged, and the amplitudes of the MEPs showed no increase as the level of background contraction increased. However, there was an abnormal increase in the MEP amplitude with increasing stimulus intensity.

The clue to putting these apparently disparate results together is the observation that inhibition in the motor cortex is deficient in patients with dystonia of the hand. Ridding et al, who used a “double pulse” paradigm in which MEPs are inhibited when conditioned by prior subthreshold transcranial magnetic stimulation of the same scalp position at intervals of 1 to 5 milliseconds, found less inhibition in both cerebral hemispheres of patients with dystonia of the hand than in normal subjects. Chen et al used double pulses at longer intervals, with the muscle either at rest or contracted, to study inhibition in patients with writer’s cramp and found a deficiency only in the symptomatic hand and only with background contraction. This abnormality is particularly interesting because it is restricted to the symptomatic setting, as opposed to many other physiological abnormalities in dystonia that are more generalized. Furthermore, they found that the silent period, a pause in the background electromyographic activity, after an MEP was slightly shorter for the symptomatic hemisphere in patients with dystonia of the hand. This finding also indicates a deficiency of inhibition.

All of these findings can be explained by a lack of inhibition. The deficiencies recognized by the electroencephalogram and PET studies could be deficiencies of inhibition. A reduction of inhibition would lead to a hyperexcitable cortex and excessive movement. Prime studies by Matsumura et al provide strong evidence that the lack of cortical inhibition leads to a disturbance of motor function similar to that found in dystonia. The local application of bicuculline, an antagonist of γ-aminobutyric acid, to the motor cortex led to disordered movement and changed the movement pattern from reciprocal inhibition of antagonist muscles to cocontraction.

Elsewhere, I have summarized the sensory phenomena and abnormalities in dystonia and speculated that sensory dysfunction could drive the motor disorder. Some of the sensory findings are also explicable on the basis of deficient inhibition. Studies using the blood flow–PET method in patients with dystonia show reduced activation to vibration stimuli, possibly as the result of reduced inhibitory neuronal activity. In the median nerve somatosensory evoked response, the N30 component, a frontal negativity occurring at a latency of 30 milliseconds, is enhanced, owing perhaps to increased excitability of the sensory cortex. Sensory receptive fields in the thalamus are enlarged, a finding similar to that of the cortical mapping studies in the primate model. There is no clear explanation of how a sensory trick (geste antagonistique) can alleviate a dystonic posture or how vibration can either induce or ameliorate dystonia other than to suggest that sensory input may have more profound effects if inhibition is lacking.

The acceptance of this hypothesis about inhibition requires recognition that the basal ganglia can influence cortical inhibition. In Parkinson disease, the silent period is shorter than normal and can be improved with dopaminergic treatment, whereas in Huntington disease the silent period is longer than normal. Studies using the double-pulse technique mentioned earlier show that there is a dopaminergic influence on short-interval, intracortical inhibition. Thalamocortical influences on the cortex can be both excitatory and inhibitory, and in some circumstances the inhibitory influence is more profound. Indeed, a major role of the basal ganglia may well be to balance excitation and inhibition. The direct and indirect pathways may act in a “center-surround” manner to help focus the motor command. Loss of surround inhibition might well be the essence of dystonia, as it would lead to an excessive motor command, to over-
flow into inappropriate muscles, be produced by action, and possibly even be task specific.11

This model of dystonia, as a disease caused by a deficiency of cortical inhibition, can explain its genesis from all the known causes. It could result from a lesion of the basal ganglia that would disturb the delicate balance of inhibition and excitation. The lesion might be anywhere in the basal ganglia pathway, including the thalamus. Either a deficit or an excess of dopamine could lead to dystonia, depending on its relative influence on the direct or indirect pathways. Dystonia may also be caused by repetitive use, which in turn leads to larger cortical representation areas, and, at least in some circumstances, this process could be mediated by a reduction in inhibition. Thus, the normal processes of brain plasticity may be pushed too far, with the result being dystonia. A genetic disorder might lead to dystonia by a variety of mechanisms, including the provision of a fertile substrate for a maladaptive plastic change.

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