Pathophysiology of spasticity

Spasticity is a frequent and often disabling feature of neurological disease. It may result in loss of mobility and pain from spasms. The core feature of the spastic state is the exaggeration of stretch reflexes, manifest as hypertonus. The stretch reflex threshold is reduced, and its gain may be increased. The result is the velocity-dependent increase in resistance of a passively stretched muscle or muscle group detected clinically. Often, this is associated with a sudden melting of resistance during stretch, the clasp-knife phenomenon. In addition, there may be other related signs, such as weakness, impairment of fine movements of the digits, hyperreflexia, loss of cutaneous reflexes, Babinski's sign, clonus, spasms and changes in posture. Spasticity is traditionally ascribed to damage to the pyramidal tract. Work, however, particularly in animals, clearly implicates additional motor tracts in the pathophysiology of the spastic syndrome. The present editorial draws together old and new observations to provide a working hypothesis explaining the pathophysiology of spastic hypertonus, and some of the related elements of the human spastic syndrome. Possible changes in spinal neuronal circuitry have been the focus of several recent reviews and will not be discussed.

Inhibitory supraspinal influences

Some instances of lesions of the pyramidal system causing hypertonus and hyperreflexia have been reported in animals, but these signs were not striking and may have resulted from coincidental damage to non-pyramidal motor pathways. More remarkable is the fact that pyramidal tract lesions have not led to spasticity in the hands of experimenters. Destruction of the primary motor cortex in area 4, section of the medullary pyramids, or lateral corticospinal tract have lead to weakness (particularly involving fine movements of the digits), hypotonia and hyperreflexia in monkeys and apes observed for up to several months following lesioning.

The findings in humans have been rather more difficult to interpret. Attention must be paid to the exact extent of pathologic or iatrogenic lesions, and sufficient time must be allowed for spasticity to develop. Flaccid weakness may be present for up to six weeks before spasticity develops after cerebral and spinal lesions.

It is often argued that the lesions of the pyramidal tract in man can cause spasticity on the basis that hypertonia may follow surgical excision of the precentral gyrus and therefore of the primary motor cortex in area 4. Such operations, however, may entail damage to areas other than area 4, and to the cortical origins of motor systems separate from the pyramidal tract. Excision of the ventral precentral gyrus (arm area) involves removal of part of area 4 and, in addition, the ventral portion of area 6 (the premotor area), which occupies the anterior border of the precentral gyrus. Removal of the superior part of the precentral gyrus (leg area) risks damage to the supplementary motor area, and fibres leaving it. More important therefore may be those cases in whom hemiparesis of cortical origin is not accompanied by spasticity. One such case was recently reported in whom MRI demonstrated a lesion confined to the precentral gyrus.

Spasticity does not follow the unilateral section of the corticospinal tract in the human cerebral peduncle. Flaccid hemiparesis has been reported after infarcts involving the basis pontis and medullary pyramids but tone was examined just days after the stroke. Other cases have been reported in whom spasticity has supervened, but infarction extended beyond the pyramids. Brown and Fang describe a case of sharply localised infarction of the corticospinal tract at the pontomedullary junction in which an initially flaccid hemiparesis may have become spastic, but clinical details are scanty. Hypotonia is conspicuously absent in limited cordotomies involving the lateral pyramidal tracts.

In summary, it is unlikely that damage to the pyramidal tract alone plays a major role in the production of spasticity. This is in contrast to weakness and loss of superficial reflexes, such as the abdominal reflexes, which are common accompaniments of isolated lesions of the pyramidal tract. The association between corticospinal tract damage, and tendon hyperreflexia and the Babinski response is less clear cut.

This does not mean, however, that the motor cortex cannot influence tone. Perhaps the most tangible proof of this is the common clinical observation that capsular lesions often lead to more striking spasticity than cortical lesions. The implication must be that such lesions interrupt fibres originating in cortical areas other than the primary motor cortex (area 4), and that these fibres form part of a motor system influencing tone separate from the corticospinal tract. Extensive cortical lesions, involving premotor and supplementary motor areas, add spasticity to the paralysis seen with focal lesions of area 4 in monkeys. Forester reported an epileptic patient with a mild hemiparesis due to traumatic injury of the precentral gyrus who developed a spastic hemiplegia following...
excision of the premotor cortex. In animal experiments, spasticity is more marked if such lesions are bilateral, suggesting that these non-pyramidal projections can have bilateral effects. The fibres influencing spasticity run with the corticospinal tract as far as the cerebral peduncles. In the cat they lie in the medial portion of the peduncle and in the area just dorsal to this, before ending in the bulboreticular formation dorsal to the medullary pyramids. Within the internal capsule there may be some separation of the pathways, with axons from the primary motor cortex, premotor cortex, and supplementary area passing through the posterior limb, genu, and anterior limb of the internal capsule respectively. This may explain why small capsular lesions in the anterior limb tend to be associated with spastic hypertonus, whereas those involving the posterior limb are not. Large infarctions in the middle cerebral artery territory and subcortical infarcts undercutting most of the descending fibres in the corona radiata lead, in time, to a spastic hemiplegia as they involve both corticospinal and corticoreticular projections.

Although the available evidence suggests that isolated lesions of the pyramidal tract do not cause spasticity, this, of course, need not mean that the pyramidal tract has no influence over tone under normal circumstances. This point is admirably illustrated by Bucy's analogy that removal of one kidney has little effect on homeostasis. This does not mean that the excited kidney was without effect, only that the remaining kidney has assumed the entire load. Similarly, ipsilateral supplementary motor and premotor areas, or contralateral motor cortex may assume some of the functions of the destroyed corticospinal fibres from the precentral gyrus. This has been increasingly recognised as underlying the return of power following pyramidal lesions; but its role in tone has not been addressed.

The influence of cortical motor areas over tone is principally mediated by a powerful inhibitory mechanism in the bulboreticular formation. Electrical stimulation of the ventromedial reticular formation dorsal to the pyramids inhibits the patellar reflex and gastrocnemius-soleus tonic vibration reflex in intact cats, and abolishes extensor tone in decerebrate preparations and in cats rendered spastic by chronic cerebral lesions. The inhibitory effects in intact animals are potentiated by simultaneous stimulation of the premotor cortex or internal capsule. The anterior and paramedian cerebellar cortex and fastigial nucleus may also modulate the inhibitory actions of the reticular formation, at least in the cat.

Inhibitory influences survive section of the pyramidal tract in the medulla and are conducted in the cord by the dorsal reticulospinal tract in the dorsal half of the lateral funiculus. The available evidence suggests that the tract occupies a similar position in humans in close relationship with the lateral corticospinal tract. It is the loss of the cortical drive to the bulbary inhibitory centre which is principally responsible for the spastic hypertonus following lesions of the frontal cortex or internal capsule. In contrast, spasticity is not often a striking feature of human bulbar lesions, perhaps because lesions in the region of the inhibitory centre also involve respiratory and vasomotor centres and are usually incompatible with life.

The inhibitory centre in the caudal brainstem and the dorsal reticulospinal pathway tonically inhibit flexor reflex afferents as well as spinal stretch reflexes. Thus damage to this system in the lateral funiculus releases flexor reflexes in animals. Shahani and Young have pointed out that flexor spasms are qualitatively no different to the flexor reflexes recorded in patients with spinal transections and normal subjects, raising the possibility that flexor spasms are a release phenomenon consequent to damage to the dorsal reticulospinal pathway. In addition, it is now believed that the clasp-knife phenomenon is caused by the inhibitory effects of flexor reflex afferents, and lesions involving different levels of the dorsal reticulospinal system release the clasp-knife phenomenon in cats.

Excitatory supraspinal influences

Vestibulospinal activity is important in maintaining decerebrate rigidity, but may have a lesser role in supporting tone in spasticity. Injury to the vestibular nuclei alone has little effect on spasticity in the spastic cat. In contrast, transection of the bulbopontine tegmentum leads to a marked reduction in spasticity. Electrical stimulation of the reticular formation of the dorsal brainstem facilitates the patellar reflex in the intact animal, and increases hyperreflexia, hypertonus, and clonus in the cat made chronically spastic by previous extirpation of the motor cortex. The facilitatory effects, unlike the inhibitory effects of the reticular formation, are not affected by stimulation of the motor cortex or internal capsule. Thus the reticular formation gives rise to both inhibitory and excitatory systems influencing spasticity. The latter originates in a diffuse area extending from the basal diencephalon, central grey and tegmentum of the midbrain, the pontine tegmentum, and the lateral bulbar reticular formation, outside of the inhibitory field. The spinal projections of this system involve the ventral half of the cord. This facilitatory reticulospinal system is central to the state of spasticity, although vestibulospinal influences may make some contribution as lesions of the vestibular nuclei and bulbopontine tegmentum have a greater effect on spasticity in the cat than tegmental lesions alone. Damage to vestibulospinal and facilitatory reticulospinal pathways in the anterior funiculus of the cord may also contribute to the release of flexor reflexes and spasms.

Descending spinal pathways

The lesions of the spinal cord affecting tone have been carefully documented in the monkey. Lesions of the ventral funiculus lead to hyperreflexia in the setting of essentially normal tone, while those confined to the lateral corticospinal tract in the lateral funiculus lead to hypotonia, hyperreflexia and loss of cutaneous reflexes. In contrast, extensive lesions of the lateral funiculus (that include the dorsal reticulospinal tract) are followed by spasticity and hyperreflexia, as is severing of the lateral funiculus in animals with a previously disrupted corticospinal tract. Spasticity is less marked if the vestibulospinal tracts are also cut. The distribution of hypotonia following the disruption of the dorsal reticulospinal fibres in the lateral funiculus is identical to that following frontal lobe lesions.

Information about the distribution of pathways influencing stretch reflexes and tone in humans comes from cordotomies. Putnam performing this operation for parkinsonism, observed that unilateral section of the dorsal half of the lateral funiculus was followed by a severe initially flaccid paralysis. As power returned spasticity, hyperreflexia, and clonus appeared. Hyndman, treating intractable pain, cut the intermediate portion of the lateral funiculus bilaterally at the thoracic level, and found...
that hyperactive knee and ankle jerks, ankle clonus and Babinski’s sign appeared immediately, but spastic hypertonus only developed in one out of six patients, and then was only mild. Histological confirmation of the extent of the lesions, however, was absent in these cases. Spasticity did not develop after bilateral anterolateral cordotomies, in some cases extending posteriorly to involve the lateral corticospinal tracts.23 55 54

Cordotomies have also been used in the treatment of spasticity. Bucy observed that unilateral or bilateral section of the vestibulospinal tract in the anterior funiculus of patients with congenital spastic paraplegia or quadriplegia only caused a transient reduction in extensor tone in the lower limbs.55 He concluded that the vestibulospinal tract contributes to the maintenance of human spasticity, but other descending pathways are capable of maintaining spasticity at its full intensity in the absence of vestibulospinal influences. The cordotomies performed by Bucy were said to spare the deeper sulcal regions of the anterior funiculi, but there was no histological confirmation of this. In contrast, extensive unilateral or bilateral anterior cordotomy (which included the deeper sulcal areas) was followed, after a transient period of flaccidity, by the loss or considerable reduction of extensor tone in the legs, despite the reappearance of hyperreflexia, adductor spasm, and clonus.56

On the strength of these findings it seems that lesions must involve the dorsal half of the lateral funiculus to produce spastic hypertonus in man. Presumably lesions here interrupt the inhibitory dorsal reticulospinal tract to cause spasticity.45 In patients already spastic, extensive anterior cordotomy, but not partial anterior cordotomy, abolishes extensor tone. This, like the results of animal experiments,50 suggests that the medial reticulospinal tract originating in the excitatory areas of the brainstem reticular formation51 is more important than the vestibulospinal tract in maintaining spastic extensor tone. The human medial reticulospinal tract runs in the subcommissural territory, in association with the median longitudinal bundles,39 and is likely to have been spared by Bucy’s limited incisions.50

In summary, two major balancing descending systems exist controlling tone in humans: on the one hand, the inhibitory dorsal reticulospinal tract; and, on the other, the facilitatory medial reticulospinal and vestibulospinal tracts.

Peripheral effects
Recent studies have challenged the classical view that exaggerated stretch reflexes are the major cause of established spasticity. In the swing phase of gait, the tibialis anterior shows abnormally high levels of activity, despite the lack of any EMG activity in its antagonist, the triceps surae muscle.61 This suggests that mechanical changes in the extensor apparatus of the ankle, rather than muscle activity in the triceps surae itself, lead to increased resistance to dorsiflexion movements. Direct measurement of the resistance of the relaxed ankle to slow displacement in hemiparetic subjects has confirmed the importance of mechanical factors.2 Factors that might contribute to the increased mechanical resistance to movement are alterations in tendon compliance1 and physiological, morphometric, and histochemical changes in muscle fibres.7

Given the velocity dependence of the stretch reflex,42 these mechanical factors may be particularly important during functional movements of the leg, which occur at low angular velocities.61

How the influence of central and mechanical factors on tone and function change with time is, as yet, unclear. There is limited evidence to suggest that stretch reflex gain reduces over the months to years following the initial lesion.2 Conversely, if we are to assume that contracures represent the extreme end of the mechanical factors resisting limb movement, then there is reason to believe that their development is delayed. The issue of the natural history of central and mechanical factors is an important one, as early treatment of hypertonia may avert mechanical changes. This has been the finding in an animal model of spasticity, and has prompted an investigation of the disease modifying effects of botulinum toxin in spastic cerebral palsy.63

Conclusion
Normal tone consists of a balance between inhibitory effects on stretch reflexes mediated by the dorsal reticulospinal tract and facilitatory effects on extensor tone, mediated by the medial reticulospinal tract, and, to a lesser extent in humans, by the vestibulospinal tract. In cortical and capsular lesions some of the drive on the inhibitory centre in the caudal brainstem is lost resulting in a spastic hemiplegia, in which antigravity posture predominates, but flexor spasms are unusual. In practice partial spinal lesions usually involve the lateral corticospinal and dorsal reticulospinal tract, as most commonly seen in multiple sclerosis where demyelinating lesions have a predilection for the lateral funiculi.44 Damage to the corticospinal tract leads to paressis, while loss of inhibitory influences from the dorsal reticulospinal tract, leaves the effects of the medial reticulospinal and vestibulospinal tracts unopposed. In this situation there is often severe spasticity with tone being greatest in the antigravity muscles, so that paraplegia in extension may be seen. Extensor and flexor spasms are common, although the former tend to predominate.59 This is the clinical picture of multiple sclerosis relatively early in its course.

The present hypothesis may also explain the marked spasticity in the legs in the presence of spasms, but little or no weakness in many patients with hereditary spastic paraparesis. Here, there is involvement of the dorsal reticulospinal tract in the thoracolumbar cord with a degree of sparing of the corticospinal tracts. Support for this comes from pathological reports46 and from the relative normality of electromyographic responses in leg
muscules to electrical stimulation of the motor cortex in patients with this condition.  

In severe or complete cord lesions there is loss of all supraspinal influence on the cord. Hyperreflexia is not as marked as in some cases of incomplete cord lesions, as the descending excitatory systems are no longer acting unopposed. Flexion spasms are very prominent, however, as flexor reflexes are released from the inhibitory influences of the dorsal reticulospinal, vestibulospinal and medial reticulospinal tracts. Paraplegia in flexion may then supervene. This is often the case in advanced multiple sclerosis, when lesions have also interrupted function in the descending tracts of the anterior funiculus.

Of course the pattern of spasticity is not fixed and solely determined by the degree of damage to different descending pathways. Stimulation of flexor reflex afferents—for example, by pressure sore, can transform paraplegia in extension into paraplegia in flexion. Conversely, standing reduces flexor tone and favours extensor tone, a phenomenon that is readily used to advantage in physiotherapy. An additional factor in complete transection is the delayed reorganisation within the isolated cord, which may underlie the change in balance from flexor to extensor spasms sometimes seen a year or more after division of the cord.  

I have expanded on old hypotheses to provide a schema explaining the pathophysiology of human spastic hypertonus. The hypothesis is largely based on animal work, as relevant human observations are few and imperfect. Opportunities to study spasticity in patients are common and it is hoped that this editorial will encourage careful clinical observation, supervised, where necessary, by lesion localisation with MRI, to refute or develop this schema in the future. Acquired pathology rarely respects anatomical boundaries and it may be that further investigation in humans requires the technique of lesion superimposition that has proven so useful in other contexts.

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NEUROLOGICAL STAMP

Jan Evangelista Purkinje (1787–1869)

Purkinje was born in Libochovice, Bohemia (now Czechoslovakia) and educated by Piarist monks. He studied philosophy at the University of Prague, was ordained a priest and became Father Salverius. In 1819, aged 32, he graduated in medicine. Purkinje, who had already made significant contributions to physiology, applied unsuccessfully for several University appointments within the Austro-Hungarian Empire. Through friendship with Goethe he was appointed Professor of Physiology at Breslau University in 1823 against the opposition of the Faculty. In 1850 he was invited to the Chair of Physiology in Prague which he held until his death.

His early work included the influence of the head position on the directional component of vertigo, and the maintenance of posture and equilibrium, culminating in Purkinje's Law of Vertigo. Purkinje explored aspects of vision and discovered in 1825 a phenomenon known as the Purkinje effect (as light intensity decreases, red objects are perceived to fade faster than blue objects).

While examining birds' eggs he discovered the germinal follicle, sometimes called the Purkinje vesicle. In 1837 he located the Purkinje cells in the cerebellar cortex, and two years later the Purkinje fibres lying beneath the endocardium.

Purkinje also introduced the term protoplasm to describe the living embryonic material of the egg. He made original contributions to the histology of sweat glands, skin, bone, dental structures and was the first to discover the uniqueness of the human fingerprint. He noted that pancreatic extracts digested protein and he made comparative studies of cellular structures of plants and animals. Purkinje was among the first to use a microtome and one of the first to teach microscopy as part of a university course. He also studied digitalis toxicity (on himself) and the effects of belladonna and opium. Purkinje translated poetry from German, Russian, and Polish and wrote some of his own. At age 80, he learned Hungarian so that he could translate a libretto.

He was honoured by Czechoslovakia in 1937 (Stanley Gibbons 371 and 372, Scott 232 and 233) on the 150th anniversary of his birth.

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