# The Physiology of Idiopathic Dystonia

C.D. Marsden and John C. Rothwell

**ABSTRACT:** Dystonia is mysterious and its pathophysiology is uncertain. The fundamental motor abnormality is an abnormality of muscle command signals, such that the wrong agonists may be activated for too long, there is abnormal co-contraction of agonist and antagonists, and there is excessive and misdirected action of synergists and postural fixators. The result is action dystonia. In addition, muscle spasms may occur spontaneously. The peripheral motor apparatus, the corticomotoneurone pathway, and (as far as is known) the proprioceptive feedback machinery, are all intact in primary dystonia. However, a defect of interneuronal machinery has been identified in both the brainstem and spinal cord. In blepharospasm there is hyperexcitability of the lower brainstem interneurones responsible for the R2 component of the blink reflex. In the dystonic arm there is loss of the later phases of Ia reciprocal inhibition from extensors to flexors. Both deficits may be due to loss of normal basal ganglia inputs onto interneurones. The known sites of focal lesions that may cause symptomatic dystonia all impair basal ganglia output. However, whether such abnormal interneuronal function is sufficient to explain dystonia is not known. Among many unanswered questions are 1) are the cortical instructions for movement specified correctly, and 2) what is responsible for the spontaneous dystonic spasms?

**RÉSUMÉ: Physiologie de la dystonie.** La dystonie est une affection mystérieuse et sa pathophysiologie est incertaine. L'anomalie motrice fondamentale est une anomalie de la signalisation qui commande les muscles, de telle sorte que les mauvais agonistes peuvent être activés pendant trop longtemps, qu'il y a une cocontraction des agonistes et des antagonistes, et qu'il y a une activité excessive et mal dirigée des ambocepteurs synergiques et posturaux. Le résultat est la dystonie d'action. De plus, des spasmes musculaires surviennent spontanément. L'appareil moteur périphérique, la voie corticomotrice, et (en autant que nous sachions) le mécanisme de rétroaction proprioceptive, sont tous intacts dans la dystonie primaire. Cependant, un défaut dans le mécanisme interneuronal a été identifié dans le tronc cérébral et dans la moëlle épinière. Dans le blépharospasme, il y a hyperexcitabilité des interneurones de la région inférieure du tronc cérébral responsables de la composante R2 du réflexe de clignotement. Dans la dystonie du bras, les phases tardives de l'inhibition réciproque de type Ia des extenseurs aux fléchisseurs sont perdues. Ces deux défauts sont peut-être dûs à la perte des influx venant normalement des noyaux gris centraux vers les interneurones. Les sites des lésions focales connues comme causant une dystonie symptomatique entravent tous l'influx efférent des noyaux gris centraux. Cependant, nous ne savons pas si une fonction neuronale ainsi altérée est suffisante pour expliquer la dystonie. Parmi toutes les questions dont nous ne connaissons pas la réponse, nous pouvons nous demander si 1) les instructions corticales pour commander le mouvement sont spécifiées correctement? et 2) qu'est-ce qui est responsable des spasmes dystoniques spontanés?

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Torsion dystonia is characterised by sustained and forceful muscle contractions which twist the body and/or limbs into characteristic postures. Attempted voluntary movement exacerbates the dystonia, producing an "overflow" of activity to distant muscles during action.[1,2] Tendon jerks are normal and in spite of abnormal muscle activity most patients with dystonia are capable of carrying out a wide variety of voluntary movements with reasonable accuracy.[3]

Conventional electrophysiological investigations have revealed no abnormalities in patients with idiopathic torsion dystonia. EMG, nerve conduction, EEG, and evoked potential studies all are normal. Using the new technique of high voltage stimulation of the human brain through the intact scalp[4] we have also been able to extend this to examine corticospinal tract function in dystonia. Central conduction times for biceps and thenar muscle activation were assessed by subtracting the latency of muscle activation produced by segmental stimulation over the spinal cord from that seen following stimulation of the scalp over motor cortex. Table 1 shows that conduction times in patients with dystonia are the same as those in normal individuals. This suggests that large diameter corticospinal tract axons are functioning normally. In addition to these conventional techniques, there are several more specialised physiological techniques now available which shed some light on the possible pathophysiological mechanisms involved in dystonia.

## EMG Patterns in Dystonia

***Rest*** Polymyographic analysis has been performed in patients with torsion dystonia of the limbs, trunk, neck (torticollis) and cranial muscles, particularly blepharospasm.[3,5-7] It confirms

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**Table 1: Corticospinal Tract Latencies in Dystonia**

| | Normals (n = 10) | Dystonics (n = 5) |
|---|---|---|
| Cortex-Biceps | 10.0±0.8 | 10.0±0.8 |
| Cortex-Thenar | 19.6±1.0 | 19.0±1.2 |

Values are mean ± 1 S.D. ms

and extends the clinical impression of the muscle contractions referred to above. In mildly affected patients there is no involuntary muscle activity when at complete rest. In this state, the patients appear indistinguishable from normal. Moderately and severely affected individuals have continuous, involuntary muscle activity even during attempted complete relaxation, which disappears only during deep sleep. Characteristically this involuntary EMG activity does not follow the normal pattern of reciprocal innervation. Antagonist muscle groups at a joint are active simultaneously and the EMG is described as co-contracting.

Involuntary EMG activity in dystonia can be classified into three types, depending on the length of the EMG bursts.

1) Almost continuous spasms of muscle activity lasting many seconds and terminated by relatively short periods of silence (Figure 1 (top)).

2) Shorter (up to 2 s) EMG bursts, sometimes repetitive and rhythmical, separated by similar periods of silence (Figure 1 (middle)). This pattern of EMG bursting was termed "myorhythmia" by Herz.[5]

3) Brief (less than 500 ms) bursts of activity resembling those seen in myoclonus. The combination of relatively long spasms of EMG activity in some muscles, with brief myoclonic-like bursts in other muscles sometimes is termed "myoclonic dystonia"[8] (Figure 1 (bottom)).

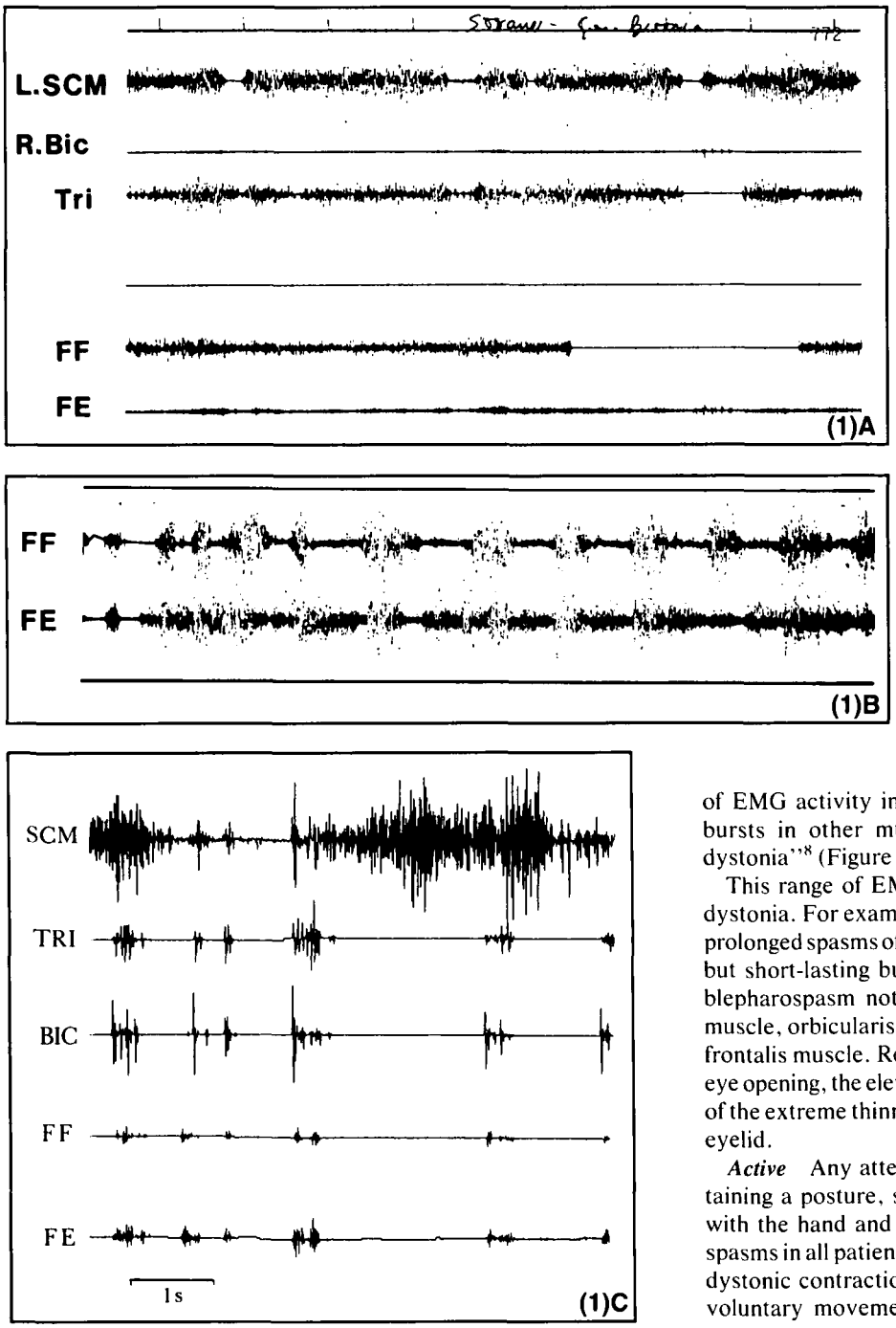


*Figure 1 — Three types of involuntary muscle activity in different individuals with generalised dystonia. **A)** continuous periods of muscle activity lasting from 2 to 30 s. **B)** repetitive, rhythmical, and co-contracting spasms lasting only 1 to 2 s each ("myorhythmia"). **C)** rapid, irregular and brief jerks lasting only some 100 ms. Muscles are left sternocleidomastoid (L.SCM), right biceps (R.Bic), triceps (Tri), wrist and finger flexors (FF) and wrist and finger extensors (FE). (From Rothwell et al 1983, with permission.)*

This range of EMG patterns is seen in all forms of torsion dystonia. For example, patients with blepharospasm may have prolonged spasms of eye closure, or relatively regular, repetitive, but short-lasting bursts of closure.[7] Similarly, eye closure in blepharospasm not only involves contraction of the agonist muscle, orbicularis oculi, but also of one of its antagonists, the frontalis muscle. Recordings from the main muscle involved in eye opening, the elevator palpebrae is extremely difficult because of the extreme thinness of the muscle and its location within the eyelid.

***Active*** Any attempt at voluntary movement, either in sustaining a posture, such as standing, or performing some task with the hand and arms, exacerbates the involuntary muscle spasms in all patients with dystonia. In mildly affected patients, dystonic contractions can be seen only when certain types of voluntary movement are made (action dystonia). The most


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striking examples of this are the occupational cramps, a form of focal dystonia.[9] A person with writer's cramp may be able to use his affected hand to feed and drink normally. Excessive involuntary muscle activity only becomes noticeable in the performance of the most delicate manual tasks such as writing or typing or playing a musical instrument.

The excessive involuntary contractions (which are co-contracting in antagonist muscles like those seen at rest), appear in muscles that normally are not involved in the task. The activity is sometimes described as "overflow", suggesting that voluntary effort cannot be directed effectively to the appropriate muscle groups. However, despite excessive activity in some muscle groups, activity in the prime moving muscles sometimes may be relatively spared. For example, in all the patients whom we have examined, even with gross generalised dystonia, there has been alternating activity in flexor and extensor muscles during rapid waving of the wrist or elbow (Figure 2). Slower, or more delicate movements, however, show relative degrees of inappropriate activity in antagonist muscles depending upon the severity of the patient's clinical symptoms.

Dystonia therefore is mainly characterised by excessive ill-directed muscle activity. Yet, in spite of this, patients with dystonia usually can carry out a great variety of motor tasks. These clinical observations indicate that patients with dystonia are capable of generating and conceiving the idea and motor plan to move, but either 1) the selection and/or quality of the motor programmes is abnormal, or 2) the physiological mechanism(s) responsible for executing motor programmes are altered. In the following section we have examined these possibilities in the light of newer physiological techniques.

**Specialized Physiological Investigations**

In view of the constant existence of co-contraction and frequent observation of abnormal postures in patients with dystonia, abnormalities of the stretch reflex and reciprocal inhibition have been first considered as the possible pathophysiological basis of dystonia.

***Stretch Reflexes*** Stretch reflexes have been examined in the flexor muscles of the thumb, wrist and elbow by two groups of workers.[3,10] The technique involves the subject exerting a constant background contraction of the appropriate flexor muscle against a small force offered by a low inertia electric motor. At irregular and random intervals, the force supplied by the motor suddenly is increased so as to extend the joint and stretch the flexor muscle. A reflex EMG response to the stretch can be recorded in averaged records beginning with a latency of some 20 ms or so following the disturbance. The response consists of two main components: the first is a short latency (or M1) response of about 20 ms duration which probably reflects activity in the same neuronal pathways as are responsible for the tendon jerk. The second part of the response, which has a latency of about 50 ms and a duration of 30-40 ms is known as the long latency (or M2) component. It may represent activity traversing a transcortical (or long loop) reflex pathway.

Both Rothwell et al[3] and Tatton et al[10] found that the sizes of both short and long latency components of the stretch reflex EMG response were within the normal range in patients with dystonia. Rothwell et al[3] used relatively rapid muscle stretches and concluded that there was no change in the duration of either component of the reflex. Tatton et al[10] who used a much wider range of stretch velocities, found this to be true only at high

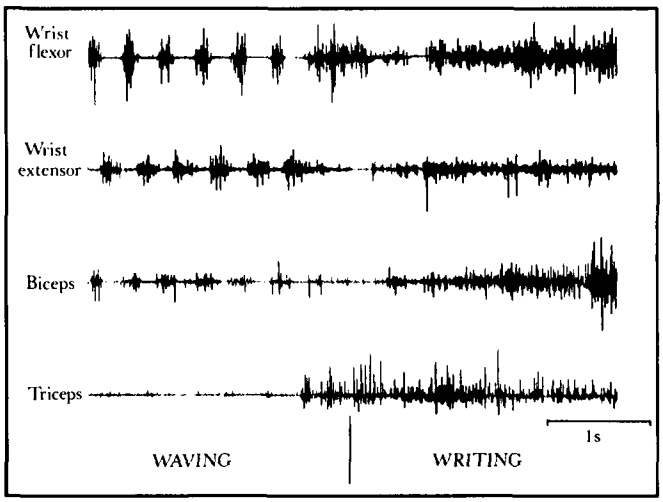


*Figure 2 — Normal reciprocal activation of wrist flexors and extensors during waving (left), and resumption of typical co-contraction when the subject stops to pick up a pen and write his name (right). (From Rothwell et al, 1983, with permission.)*

velocities. At lower rates of stretch, the duration of the long latency component of the EMG was prolonged in dystonic patients, even though its size remained within the normal range.

There is a further abnormality in the stretch reflex which is reminiscent of the EMG activity seen in attempted voluntary movements. In normal subjects, the stretch reflex activity is fairly well localised to the agonist and synergist muscles involved in the stretch. However, in dystonia, there is a conspicuous "overflow" of reflex activity to muscles distant from the joint being studied.[3]

Finally, stretch of one muscle will always be accompanied by passive shortening of the antagonist muscle. In normal individuals, this produces a reflex reduction in activity of the shortened muscle, at about the same latency as the agonist stretch reflex. However, in patients with dystonia, there is sometimes a paradoxical activation of the shortened antagonist muscle. This is particularly clear in the tibialis anterior muscle in the leg during passive dorsiflexion of the ankle. It is not so readily obtainable in muscles of the arm. This response is presumably the same as the shortening reaction (or Westphal's phenomenon) seen in the same muscle in patients with Parkinson's disease. In tibialis anterior, a small shortening reaction sometimes is seen even in normal individuals. The mechanism of the shortening reaction has been investigated in some detail.[11] Anaesthetic block of afferents in the stretched (triceps surae) muscle does not change the size of the reflex, so that afferents from the joint and/or the shortened muscle are thought to be involved. One possibility is the removal of some tonic Ib inhibitory influence from Golgi tendon organs when the muscle is shortened.

**H-reflex Studies**

Although the tendon jerks and the M1 component of the stretch reflex are normal in dystonia, an abnormality has been described in the H-reflex recovery curve by Matsuoka et al.[12] Using paired H-reflex testing with a stimulus intensity of 1.1 times H-reflex threshold, there was a facilitation of the recovery curve from 100 ms onwards (phases IV and V) which was similar to that seen in Parkinson's disease and which is also seen in spastic patients. Such changes are not easy to interpret. The H-reflex recovery curve is believed to reflect activity in

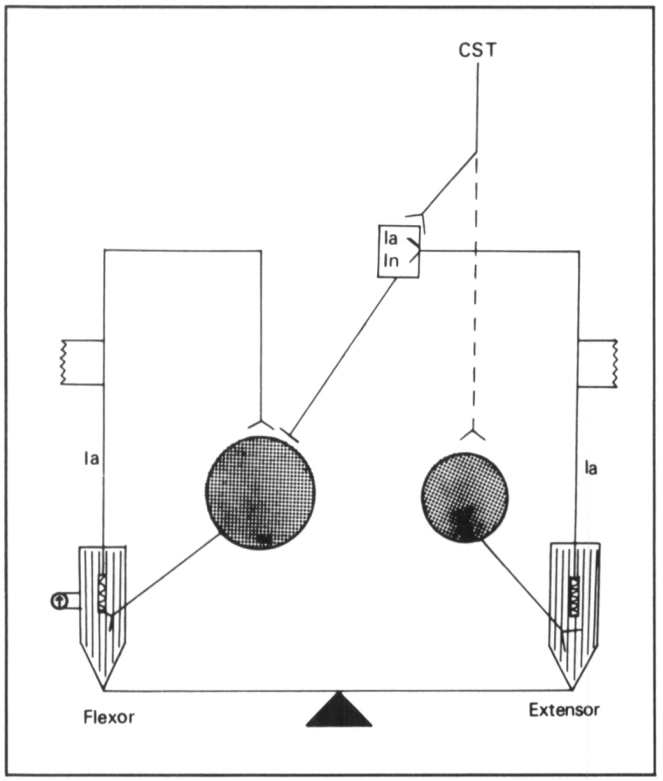


*Figure 3 — Diagrammatic summary of the central and peripheral components of reciprocal inhibition. Both the direct corticospinal tract (CST) projection to the extensor muscles of the wrist (central inhibition) and the Ia afferent fibres from extensor muscle spindles (peripheral inhibition) send branches to the Ia inhibitory interneurones (IaIN) of the spinal cord. These then project monosynaptically to inhibit the flexor motoneurone pool. The excitability of the alphamotoneurones can then be tested by eliciting H-reflexes in flexor muscles at different times after a conditioning shock has been applied to the extensor afferents in the radial nerve. (From Rothwell et al, 1983, with permission.)*

both spinal and supraspinal neuronal pathways. At present such "changes in excitability curves signify only that the reactivity of inter-neuronal circuits is altered".[13]

**Reciprocal Inhibition**

Some of the mechanisms responsible for reflex inhibition of antagonist muscles can be examined at rest in the flexor and extensor muscles of the forearm.[14] Animal studies have suggested that two mechanisms operate to produce the normal reciprocal inhibition of antagonist muscles during voluntary activation of the agonist. These are shown in Figure 3. The descending command activates the agonist motoneurones and at the same time excites the group of Ia inhibitory interneurones within the grey matter of the spinal cord. These interneurones inhibit the motoneurones of the antagonist muscle. In addition to this, when movement begins, contraction of the agonist muscle, particularly during slow movements, may be accompanied by an increase in discharge from agonist muscle spindle afferents, due to alpha-gamma linkage. Activity in the primary afferent Ia fibres also feeds onto the spinal Ia inhibitory interneurone to produce further inhibition of the antagonist motoneurones. We can refer to this latter action of the agonist spindle afferents as peripheral antagonist inhibition, whilst the initial action of the descending command is known as central antagonist inhibition. Since the principal EMG deficit in dystonia is a lack of reciprocal inhibition, it is of some interest to investigate any possible abnormalities in the system.

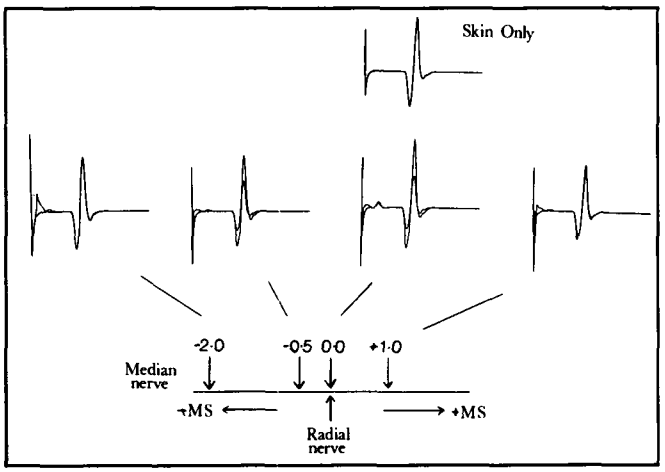


*Figure 4 — Summary of the timing convention used in testing reciprocal inhibition between the extensor and flexor muscles in the forearm. The occurrence of the median nerve test shock was expressed relative to that of the radial nerve conditioning shock (time line at bottom of the figure). Above the time line are some representative average (of 10) control and test H-reflexes from the forearm flexors of a normal subject, superimposed at four different time intervals. Maximum inhibition is seen at −0.5 and 0.0 ms. If the conditioning radial nerve test shock is applied to the surrounding skin alone, then no effect is seen on the flexor H-reflex (top traces). (From Rothwell et al, 1983, with permission.)*

In the relaxed arm, a single electrical stimulus given to the radial nerve at sub-motor threshold intensity will excite only the largest afferent fibres in the nerve. These are predominantly muscle afferents from the extensor muscles together with a proportion of large diameter cutaneous afferents from the back of the forearm. Any inhibition directed towards the flexor muscles can be detected with monosynaptic testing, using H-reflexes in the forearm flexor muscles. The experimental arrangement therefore is to give a single sub-motor threshold conditioning stimulus to the radial nerve in the spiral groove. At different times before and after this conditioning volley, a single sub-motor threshold stimulus is given to the median nerve in the cubital fossa to elicit monosynaptic H-reflexes in the flexor muscles in the forearm. By comparing the size of a series of conditioned flexor H-reflexes with the size of control H-reflexes obtained without a radial nerve shock, the depth of flexor inhibition can be calculated. Figure 4 illustrates the technique and timing convention used.

If the radial and median nerve stimuli are given at about the same time, the radial nerve volley evokes a strong (>50%) inhibition of the flexor H-reflex. Previous studies have indicated[14] that this inhibition is produced via the classical disynaptic Ia reciprocal inhibitory pathway in the spinal cord. This period of inhibition lasts only some 2-4 ms, but is followed by 2 equally deep but much longer lasting phases of inhibition from about 10-40 ms and 60-500 (or more) ms. The mechanisms responsible for these later phases of inhibition are unclear at present. However, they can be evoked in the forearm muscles by sub-motor threshold stimuli of the radial nerve, suggesting that the same large diameter afferents are responsible as for the disynaptic phase of inhibition. We have suggested[15] that in the arm, the later phases of inhibition in the H-reflex testing curve are produced by presynaptic influences on the terminals of the flexor Ia afferents. The reason for this is that only the early and short-lasting



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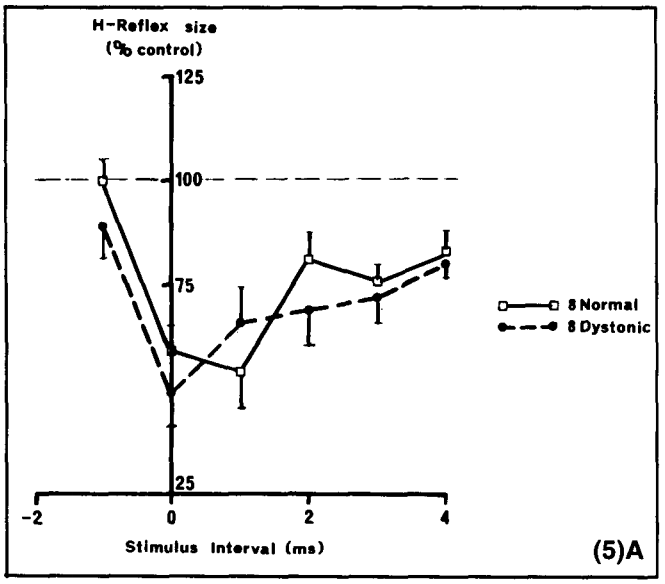


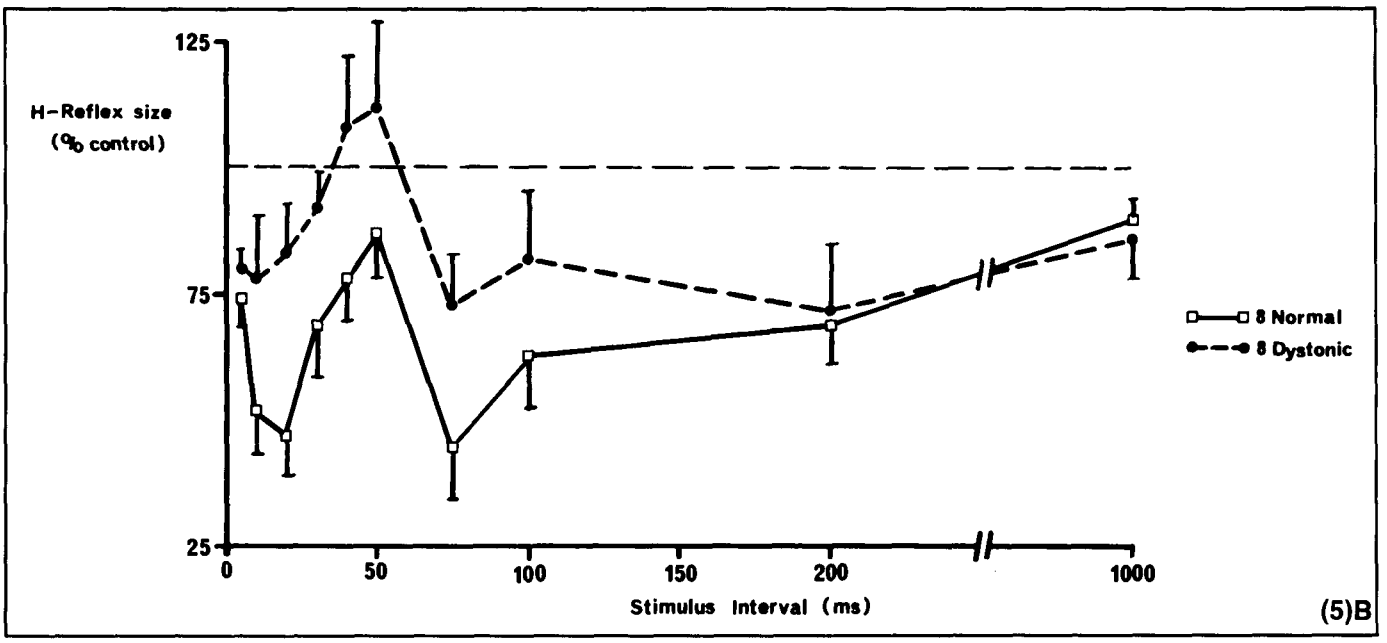

*Figure 5 — Time course of first (A) and later (B) phases of reciprocal inhibition in eight normal (continuous line) and eight dystonic (dotted line) subjects. Average values are plotted ± 1 SE. There is no difference between normal and dystonic subjects in the first (disynaptic) phase of reciprocal inhibition. However, the second phase of inhibition (from 10-50 ms) is much reduced in the patients.*

able to confirm that the reciprocal inhibition curve shows similar abnormalities in a patient with symptomatic hemidystonia secondary to an arterio-venous malformation in the basal ganglia.

Unfortunately we are uncertain of the mechanism underlying this change in peripheral reciprocal inhibition. It is tempting to suggest that it represents a decrease in the effectiveness of presynaptic inhibitory mechanisms in the spinal cord. However, it is equally possible that in dystonia, the radial nerve stimulation produces some excess of excitation from some other source which obscures the normal reciprocal inhibitory curve at 50 ms or so.

### "Ballistic" Movements at a Single Joint

Abnormalities of movement control in dystonia are described clinically in terms of difficulties with complex movements such as writing, eating or walking. Such movements are made up of many sub-units, the timing and scaling of which must be carefully controlled to produce an accurate outcome. From the physiological viewpoint errors might therefore arise from defects in 1) the production of the simple sub-units of each complex task, 2) the relative timing of the sub-units or 3) the relative amplitudes of the units. The study of ballistic single joint movements provides a method of analysing the simple sub-units which might be involved in more complex tasks.




disynaptic inhibition can be seen in the EMG if the flexor muscles are activated by a descending voluntary command rather than by H-reflex testing. The same is true if high voltage cortical stimulation is used to activate corticospinal inputs to the motoneurone: radial nerve stimulation fails to evoke late periods of inhibition of cortically-evoked flexor activity.[15] Presynaptic inhibition might therefore be directed preferentially to the Ia terminals from peripheral receptors and not to the terminals of descending tracts from the brain.

Testing reciprocal inhibition between forearm muscles with this technique reveals no abnormality of the early disynaptic inhibition in idiopathic torsion dystonia. However, the later phases of inhibition are greatly reduced, and there is a period of frank excitation at 50 ms or so (Figure 5). We have also been

Rapid limb movements from one position to another are characterised in man by a bi- or tri-phasic pattern of EMG activity in antagonist muscles acting about the joint. There is an initial burst of activity in the agonist muscle, which provides the propulsive force for the movement. This is followed by a burst of activity in the antagonist muscle, which serves to halt the movement at the appropriate position. The relative size, duration and timing of these bursts of EMG activity is remarkably precise and adjusted carefully to the speed and amplitude of the required movement. The EMG pattern can even be observed in deafferented patients,[16,17] indicating its independence of afferent feedback. Thus study of this type of movement can provide insights into how the brain executes internally-planned movements.



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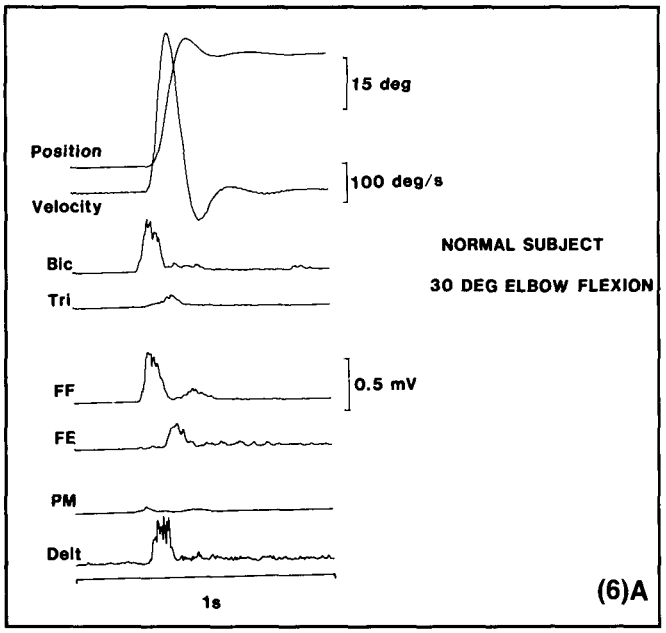
In our own experiments we have asked patients with dystonia affecting the arm to make rapid elbow extension or flexion movements through an angle of 10-60° as rapidly as possible in their own time. One of the surprising findings of this study was that despite their clinical difficulties, almost all the patients were able to perform the task. Most patients could perform movements of different amplitudes when required, although their accuracy was more variable than usual. However, the EMG pattern responsible for the movement often showed differences from normal. There was a wide range of variation in the pattern of muscle activity, ranging from normal to unrecognisable. In the most severely affected patients, the EMG bursts tended to be longer than normal and there was often inappropriate co-contraction of the antagonist, rather than the precisely-timed burst seen in normals. In addition, recording from other muscles of the arm, usually used as fixators or synergists reveals that in many patients with dystonia, there is an "overflow" of EMG activity. Whereas in normal subjects postural and fixator muscles are activated briefly at the same time as the prime movers, in dystonia there is a tendency for there to be excessive and prolonged activity in the same muscles (Figure 6). Such observations suggest that even in the simplest of movements about a single joint, errors in size and timing of muscle activity are present, as seen when more complex movements are performed.



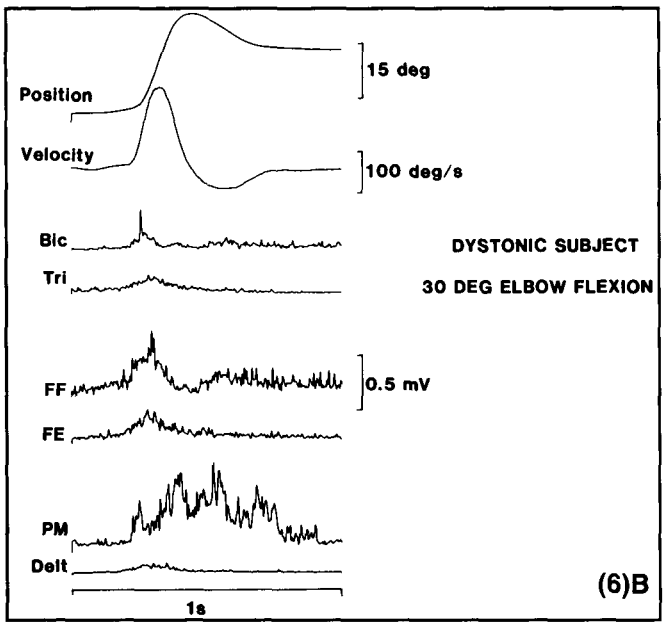




*Figure 6 — Average (of 8) position, velocity and rectified EMG traces recorded during a rapid, self-paced elbow flexion through 30 degrees. Data are from a patient with segmental dystonia affecting the neck and right arm (A) and a normal subject (B). Muscles are biceps (Bic), triceps (Tri), wrist and finger flexor (FF) and extensor (FE) muscles, pectoralis major (PM) and anterior deltoid (Delt). Note the co-contracting pattern of EMG activity in the prime moving muscles, biceps and triceps, and the massive "overflow" to the postural fixators, pectoralis and deltoid in the patient.*

## Conclusions

A general feature of all the physiological tests described above is a lack of inhibition (or excess excitation) in both reflex and voluntary movement. There is an increase in duration of both the long latency stretch reflex, and the first burst of agonist EMG activity in ballistic arm movements. There is excessive co-contraction of antagonist muscles during voluntary movement, and abnormalities in the time course of reciprocal inhibition between wrist flexors and extensors. There is overflow of activity to non-prime moving muscles in both voluntary and reflex movements and the shortening reaction is enhanced.

Even though the physiological deficits seen in these tests are very similar, it is unlikely that they result from abnormalities at a low level of the motor system. This conclusion rests on clinical observation. In many patients with dystonia there are muscles usually involved in dystonic spasms which can, on occasion, be activated almost normally. The extreme example is dystonic writer's cramp where the muscles of the forearm and hand may be well controlled in many tasks, but produce a dystonic posture when the patient attempts to write. At the other extreme are patients with generalised dystonia who may be unable to walk forwards, but can run, climb stairs or walk backwards relatively easily. If the deficit in dystonia lay at a low level in the CNS, then one would expect it to be evident in all types of movement. Since this is not the case, we must assume that dystonia represents a high-level disorder of movement control.

This conclusion is consistent with the concept that dystonia is due to abnormal function of the basal ganglia. The available data indicate that symptomatic dystonia may be produced by isolated lesions in the putamen, caudate, globus pallidus (rarely), and thalamus, or their connecting pathways.[18-21] This conclusion confirms previous suggestions that lesions of the striatum with sparing of the globus pallidus are the primary cause of symptomatic dystonia.[22] The major output of the strio-pallidal complex ends, via the thalamus, in the supplementary motor area. This suggests that the erroneous selection and modulation of motor programmes which occurs in dystonia, may arise as a consequence of inappropriate information being delivered to the supplementary motor cortex. Why the same apparent lesion of the basal ganglia may produce different types of dystonia or even no motor disturbance at all, is still unresolved. Equally obscure is the frequently observed time-delay between the cerebral insult responsible for a basal ganglia lesion and the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final appearance of dystonia. Prospective studies, with detailed clinical and physiological analysis of motor function, are needed to correlate different types of dystonia with the topography and evolution of lesions recognised by CT, MRI and PET scans.

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