REGULATORY MECHANISMS IN PARKINSONIAN TREMOR

WILLIAM WARD HOFMANN

From the Clinical Neurophysiology Laboratory, Department of Neurology, Veterans Administration Hospital, and the Division of Neurology, Stanford University School of Medicine, Palo Alto, California, U.S.A.

The precise mechanism of the tremor in Parkinson’s disease remains a subject for debate and investigation. The number of conflicting views in the standard clinical and physiological texts and journals attests to the difficulty of the problem. Some investigators suggest that central structures are ‘released’ to periodic discharge (Brain, 1960; Holmes, 1952; Bucy, 1944; Merritt, 1959). Others view the alternating discharge in spinal motoneurones as an uninhibited spinal or bulbo-spinal rhythm (Jung and Hassler, 1960) or disordered function in the reticular formation (French, 1960; Ward, McCulloch, and Magoun, 1948). Peripheral servomechanism function has until lately been somewhat neglected in the analysis of Parkinsonian tremor, although earlier experiments had been interpreted to show that the tremor was not entirely independent of proprioceptive input (Walsh, 1924; Pollock and Davis, 1930).

It is now clear that peripheral length sensors do influence all motor output and that they are not simply passive receptors. Due consideration must be given to indirect alpha cell driving by means of periodic discharges into, as well as out of, the loop circuit. It is the purpose of this paper to show that the amplitude, at least, of Parkinsonian tremor is not independent of peripheral influences and that dysfunction in servo mechanisms may play a distinct role.

MATERIAL AND METHODS

Eight patients with Parkinsonian tremor were studied. Four of these had essentially normal resting muscle tone and the remainder exhibited mixtures of rigidity and tremor. The findings in the group with essentially pure tremor were compared with those in normal subjects, subjects with rigidity as the main finding, and subjects with mixed tremor and rigidity.

The technique employed electromyographic (E.M.G.) and ergographic recording from all subjects. The E.M.G. records were obtained from concentric needle electrodes inserted into the adductor of the right thumb and were displayed on one beam of a dual beam oscilloscope. The ergographic tracings were simultaneously displayed on the second beam and were obtained from a transducer attached to the right thumb against the plane of action of the thumb adductor. The details of the technique are described elsewhere (Merton, 1951; Hofmann, 1962). The patients were asked to develop specified degrees of tension in the thumb adductor and could control the force by simply observing a null indicator. Twitches of the thumb adductor were provided by shocks given to the ulnar nerve at the elbow or at the wrist. Shocks were given at one- to two-second intervals and were superimposed on resting tremor or on sustained, postural contraction of the thumb adductor.

In the first experiments, the ‘silent period’ (Merton, 1951) in the thumb adductor was compared in patients with Parkinsonian tremor, patients with rigidity and tremor, and in tremulous normal subjects. A second group of experiments was carried out after the adductor of the thumb had been heavily infiltrated with local anaesthetic agents. Observations were made on the effect of the drug on the recorded tremor. Lastly, proprioceptive input was modified in the periphery by means of flexion or extension at various joints in all four extremities. The medication for each patient was usually withdrawn on the day of testing. Several of the patients were examined repeatedly.

RESULTS

The patients with resting Parkinsonian tremor presented evidence which suggests that the muscle spindles are alternately responsive and unresponsive to superimposed extrafusal shortening evoked by a twitch (Fig. 1A-D). The peak of sensitivity to twitch seemed to be just at the end of a tremor volley (Fig. 1A), or between volleys (Fig. 1B), while it was always impossible to ‘unload’ the spindles and evoke a silent period while a tremor volley was just developing (Fig. 1C). Twitches given 50 to 75 milliseconds before spontaneous tremor bursts in one subject were capable of damping the next burst to some degree (Fig. 1D). Further, it was observed in all subjects that the output of alpha cells was completely damped after all spontaneous tremor bursts, even while the patient was consciously driving the motor cells to produce a steady degree of tension in the thumb adductor, and when the subject was asked to exert a continuously increasing degree of tension between each twitch each spontaneous tremor burst added to the voluntary output was still followed by motor ‘shutdown’ (Figs. 2A and B).
When spontaneous tremor activity was replaced by steady, voluntary contraction in those patients with normal resting muscle tone, the addition of a twitch was then followed each time by a normal silent period (Fig. 2C) but if a tremor volley supervened, a nerve shock failed to shut off the discharge (Fig. 2D). In patients with severe rigidity and mild tremor, on the other hand, sustained voluntary activity was much less sensitive to withdrawal of spindle input by a twitch. Nevertheless, the slightest superimposed tremor activity in these patients was followed by impressive silence at all degrees of tension (Figs. 3A and B). In a tense, tremulous subject with no evidence of organic neurological disease, twitch responses were normal on sustained voluntary contraction but the superimposed tremorgenic activity was not followed by such alpha quiescence (Fig. 3C).

In two of the subjects, the injection of procaine into the thumb adductor brought about a clear-cut exaggeration of tremor, and it was observed that the grossly heightened activity involved not only the adductor but also all the other muscles visibly participating in the movement of the hand and fingers. At the stage of increased tremor activity these subjects still had normal motor power and normal twitch responses.

Lastly, it was observed that a variety of central
Regulatory mechanisms in Parkinsonian tremor

FIG. 2. A and B, effect of tremor volleys on voluntary motor output in a patient with tremor and normal resting muscle tone. Patient directed to increase adductor tension between twitches. Baseline muscle tension represented by horizontal bar. Spontaneous oscillations in tension (tremor volleys) followed by complete silence of motor activity even while patient was consciously driving motor cells to produce greater tension. C, another patient with tremor and no rigidity. Tremor activity replaced by steady voluntary contraction and twitch evokes normal silent period. D, same patient at rest. Stimulus at arrow (peak of tremor volley) without effect. Calibrations for C and D 2 mV, 1 kg., 1 msec.

and peripheral influences were capable of interfering with Parkinsonian tremor. As shown in Fig. 4, sensory input from local and distant cord segments was quite adequate to abolish the oscillations for varying periods of time. In each example shown the stimulus was brisk; passive movement of a joint and signals from muscle stretch were thought to be responsible for the effects, although exteroceptive (skin) sensation was not blocked. Proprioceptive input from local and distant cord segments was quite adequate to abolish the oscillations for varying periods of time (Fig. 4).
FIG. 3. A and B from two subjects with mixed rigidity and tremor, each attempting to hold steady contraction of thumb adductor. Twitches not followed by normal silent periods, though each tremor oscillation produces significant alpha shutdown. B shows that baseline force of contraction well maintained despite electromyographic silences. C, normal but tremulous subject. Shocks given at arrows. Tremor oscillations not followed by alpha quiescence. D and E, effects of heavy infiltration of local anaesthetic on tremor. D, resting tremor activity. E, five minutes after injection of 5 ml. Xylocaine (R) into adductor. Oscillations in E.M.G. trace (upper) partly due to movement artefact. A and B, 1 mV, 1 kg., 100 msec.
FIG. 4. Effects of proprioceptive input on tremor activity. All records from right hand.

A Passive flexion terminal phalanx, index finger, right hand. Artefact due to contact with examiner. (Amplifier not blocked.) A and B, 1 mV, 1 kg., 100 msec.

B Passive extension left wrist.

C Voluntary clenching left fist. (5 mV, 1 kg., 5 msec.)

D Passive dorsiflexion left foot. Tips of action potentials slightly retouched in all illustrations. Calibration same for all records. (2 mV, 1 kg., 50 msec.)
DISCUSSION

Other studies on subjects afflicted with severe Parkinsonian rigidity (Hassler, 1957; Jung and Hassler, 1960) have suggested that the function of the peripheral length servo is impaired. In subjects with tremor and normal resting tone, however, the damping system is found to be operational except when tremor volleys are in progress, at which point the spindles are not susceptible to 'unloading'. When rigidity and tremor are found in the same subject, the responses to twitches may be defective, but in all subjects studied the silence after even the weakest tremor volley was striking. These lulls after bursts of tremor probably should not be regarded as just lapses in input from suprasegmental levels, since voluntary discharge is silenced too (Figs. 3A and B). A study of the force record (the beam below the E.M.G. record) in Fig. 3A clearly shows that the voluntary contraction was perfectly maintained and that the two tremor bursts following each evoked twitch were simply added to the baseline activity and then the whole was promptly shut off. Figure 3B shows the same type of response more dramatically. Here again, though the evoked twitch was incapable of unloading the peripheral proprioceptors in a patient with mixed rigidity and tremor, each of the several tremor oscillations is followed by complete withdrawal of all alpha cell activity. It seems highly unlikely that lapses in anterior horn cell activity of this type are merely the interval between trains of descending impulses, as the damping is perfectly timed so that the baseline force of contraction is maintained. Furthermore, periodic trains from above should surely be added to the baseline activity, rather than intermittently shutting it off entirely. Although the silent periods following tremor bursts are often a good deal longer than those after twitches, it seems possible that a good portion of the anterior horn cell quiescence reflects regulatory activity in a peripheral servo loop. The oscillations in force output which do occur may be analogous to the oscillations in a mechanical or electrical system when the sensor input or output is too high (Stark and Baker, 1959). Quite different is the tremor of a tense, but otherwise normal, subject as illustrated in Fig. 3C. Here muscle shortening of significant degree is superimposed on a maintained voluntary contraction by irregular tremorgenic activity, and twitches are added at one-second intervals. It can be seen that the twitch is followed by a normal silent period, but none of the tremor oscillations silence the voluntary discharge. It might be inferred that the servo unit is not usually accessible to descending tremor volleys in the normal subject.

Deafferentation, either by drugs or posterior rhizotomy, seems to make Parkinsonian tremor worse, at least in terms of amplitude (Walsh, 1924; Pollock and Davis, 1930), so the oscillation cannot be the result of driving purely through the gamma system. On the other hand, loading the system by externally applied forces reduces the oscillations. These findings strongly suggest that servo mechanisms, such as the muscle spindle apparatus, play an important part in regulating tremor. It is the amplitude of tremor which seems to be under peripheral control, while the frequency may be determined by a central generator. The frequency of typical Parkinsonian tremor is generally too low to be accounted for solely by reverberations in a servo loop (Halliday and Redfearn, 1956, 1958; Marshall and Walsh, 1956).

If the length servo is functionally available in Parkinsonian tremor, the question remains as to why it seems insensitive at one moment and sensitive the next. It has been proposed (Hassler, 1957; Jung and Hassler, 1960) that the servo insensitivity in rigidity may relate to its resting bias. In the case of tremor another explanation is necessary. Failure of the silent period after a twitch given during a tremor volley can hardly be blamed on improper tonic 'setting' of the spindle if it responds normally at all other times. Instead, it seems possible that the temporary unresponsiveness of the length sensor in tremor may stem from heavy gamma efferent driving which proceeds concurrently with the periodic alpha driving. Alpha and gamma firing may be initiated at the same time through a fast channel (Granit, Pompeiano, and Waltman, 1959a and b; Rutledge and Haase, 1961) which is left open to both because of the central lesions of Parkinson's disease. Facilitatory impulses to agonist and inhibitory impulses to antagonist interneurones from the spindle accelerate all through the tremor burst until extrafusal shortening exceeds inafrausal, and, at this point, because of the high spindle bias, a prolonged pause occurs. Twitches added at the very end of a tremor burst may simply hasten the alpha cell damping. If a twitch be given shortly before the onset of a tremor burst, the withdrawal of spindle input may decrease the intensity of the next volley, indicating that the servo is normally responsive in the intervals. Deafferentation could remove the periodic facilitatory influence from the driven spindles but might make the tremor worse because of the blockade of all other damping mechanisms simultaneously.

The central generator of Parkinsonian tremor seems susceptible to a variety of influences. As shown in Fig. 4, desynchronization of anterior horn cell activity could be brought about, not only from
Regulatory mechanisms in Parkinsonian tremor

structures afferent to the same segment of the cord, but from widely removed areas as well. In no case was the passive stretching of a muscle in these manoeuvres thought to be enough to activate the tendon organs, even if the inter-neurones receiving group IB fibres are abnormally sensitive (Hufschmidt, 1960). It can be seen that the inhibitory influence of proprioceptive feedback crossed the midline in some instances. Abolition of rhythmic motor cell discharge in one segment by 'feeding in' proprioceptive impulses at distant segments suggests that this effect is mediated indirectly through central connexions. Desynchronization of the tremor generator, or some blockade of its output, with voluntary motor activity is a well-known example of direct central influence. The sensitivity of tremor activity to a variety of peripheral and central changes sets it quite apart from plastic rigidity, which does not respond similarly, and affirms the venerable clinical impression that impulses responsible for tremor and rigidity in Parkinsonism may utilize anatomically distinct pathways.

CONCLUSIONS

From the evidence presented it is inferred that the tremor of Parkinson's disease is not entirely free of reflex regulation. Removal of the peripheral spindle influence makes the oscillations worse, and the tremor behaves in a manner suggestive of an intermittently overdamped servo system. The failure of the silent period at the peak of a tremor volley is taken to mean that the annulospiral apparatus is being heavily driven at the same time as the alpha cells are activated and that reflex input is, therefore, excessive for a time. This view is supported by the profound silence which develops after each tremor volley, even while the subject is attempting to exert increasing degrees of tension. Thus, the origin of defective spindle pause in tremor is quite different from that in rigidity. The input channels for rigidity and tremor are probably anatomically separate, and both are overactive in some patients. The net clinical result depends upon which factors dominate.

SUMMARY

Eight subjects with Parkinsonian tremor have been examined electromyographically. Factors which can regulate tremor output have been studied, and it has been inferred that the peripheral spindle apparatus plays a significant role. The feedback mechanism in the case of tremor shows defects which are quite the opposite of those found in plastic rigidity.

This work was supported by United States Public Health Service grant no. B-2602.

REFERENCES


---, --- (1959b). Ibid., 147, 399


REGULATORY MECHANISMS IN PARKINSONIAN TREMOR

William Ward Hofmann

*J Neurol Neurosurg Psychiatry* 1962 25: 109-115
doi: 10.1136/jnnp.25.2.109

Updated information and services can be found at:
[http://jnnp.bmj.com/content/25/2/109.citation](http://jnnp.bmj.com/content/25/2/109.citation)

**Email alerting service**

*These include:*

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)