STUDIES OF PHYSIOLOGICAL TREMOR IN NORMAL SUBJECTS AND PSYCHIATRIC PATIENTS

by

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CONTENTS

PART ONE

REVIEW AND DISCUSSION OF THE LITERATURE RELATING TO THE GENERAL CHARACTERISTICS OF PHYSIOLOGICAL TREMOR

Introduction

The tremor that can be observed in a normal subject when an attempt is made to maintain a part in a stationary position against the force of gravity or an applied load has been variously called 'physiological', 'postural', or 'static' tremor. In this thesis it will be referred to henceforth as 'physiological' tremor.

In the earlier studies of physiological tremor, the movements of the trembling part were recorded graphically or photographically, and the records thus obtained subjected to visual inspection and analysis. While such studies were of value in defining the general characteristics of the tremor, they threw little light on the nature of the physiological mechanisms responsible for its production.

In Part 1A below, some of these earlier studies are reviewed. Certain general criticisms apply to these investigations, and are included in the discussion in Part 1B.

Part 1A. Review of Earlier Studies of Physiological Tremor

Techniques for the graphic recording of limb tremor were developed and widely used by French clinicians from about 1870 onwards. This led to a more or less unanimous description of the rate and amplitude of the tremor in certain pathological conditions. Some of the conclusions arising from these observations were summarised by Charcot (1897) and Marie (1895). In the early French literature a heated controversy is recorded regarding the question of whether limb tremor should be regarded as a purely pathological phenomenon, or whether it could be observed in normal subjects who were not suffering from any nervous or mental disease. This argument is now largely of academic interest, in view of the crudity of the recording techniques which were then used, and the results of subsequent investigations. However, the discussion figured prominently in French neurological literature until the end of the 19th century. While these investigations were under way in continental Europe, important contributions were made by workers in England and America.

Schafer and Horsley (1886) studied myographs obtained from the limbs of dogs, cats, rabbits and monkeys during electrical stimulation of various parts of the nervous system at rates of 10,20,30,40 and 50 c/s (the abbreviation 'c/s' will be used to indicate 'cycles per second'). Movements were detected by means of a tambour which either made direct contact with the limb or was attached via an elastic band to a tendon: the oscillations were recorded on a smoked drum. When the stimuli were applied to the exposed cerebral cortex, it was observed that the undulations of the myograph lever did not vary with the rate of excitation but maintained a nearly uniform rate of about 10 c/s. The variation between different individuals of the same species was often observed to be as great as inter-species variation. When the stimulating electrodes were applied to the corona radiata, tracings practically identical with those produced by cortical stimulation were obtained. They differed from the latter mainly in respect of the absence of 'epileptoid' after-discharges occurring after the cessation of the stimulus; these discharges often included a prominent 2-4 c/s clonus. Similar myograph recordings were obtained during stimulation of the peripheral cut end of the spinal cord. When, however, the stimuli were applied to a motor nerve, the muscle contraction followed the rate of excitation up to a frequency of about 20 c/s. Above this frequency, individual contractions became progressively less complete, and above 30/sec a completely fused tetanus was observed. Schafer and Horsley concluded from these results that every prolonged contraction of the skeletal muscles which is provoked by natural or artificial excitation is a tetanic contraction produced by a series of impulses generated in the 'nerve-centres' and passing along the nerve fibres at about 10/sec. From their observations, they concluded that the point of origin of the rhythm was the spinal motoneurones.

Schafer, Canney and Tunstall (1886), carried out similar observations in twenty human subjects. The muscle chosen for study was brought into contact with a receiving tambour, and the mechanical movements produced by swelling of the contracting muscle were transmitted so as to cause a corresponding deflection of the lever of a recording tambour. The opponens pollicis was usually studied. Occasionally the movement of the part, instead of the muscle, was recorded. No significant qualitative differences in the tracings were observed. The record of muscular contraction thus obtained showed "a series of undulations which succeeded one another with almost exact regularity, and could be interpreted as indicating the rhythm of the muscular response to the voluntary stimuli which provoked the contraction. The undulations maintained their rate over the whole duration of contraction. There was a slight relative degree of irregularity in height, with occasional slow waves". The frequency of the wave-form lay between 8 c/s and 13 c/s, with a mean for 20 subjects of 9.795 c/s. From these findings Schafer and his colleagues concluded that voluntary contraction in man is produced by an incomplete tetanus associated with from 8-13 impulses/sec in the motor nerve. This was in the same range as that observed by Horsley and Schafer in other mammals. The rate of the tremor observed during a voluntary contraction in man was similar to that due to the activity of the spinal cord alone in the experimental animals studied by Horsley and Schafer.

Wolfenden and Williams (1888) studied the tremor occurring in patients suffering from paralysis agitans and disseminated sclerosis. They found slower tremor rates, with movements of relatively large amplitude occurring at about 5 c/s. Inspection of their tracings suggested that a "fusion of vibrations at the usual rate" might be occurring, producing a tremor of half the normal frequency.

In 1897, Eshner carried out an investigation, the objects of which were to determine; (1) whether or not a demonstrable tremor exists in healthy individuals; (2) whether or not any relation or gradation exists between various kinds of tremor; and (3) whether or not various forms of disease present, as to their tremor, distinguishing characteristics. He detected the movement of the trembling part by means of an elastic membrane stretched over a ring. On the underside of the membrane was attached a vertical rod which was joined by a sliding band to an aluminium horizontal lever or registering needle. The lever was fixed a short distance from this junction by a pivot allowing it to move freely in a vertical plane. Any movement of the membrane was transmitted to the registering needle, being magnified in proportion to the length of the latter. Eshner calibrated the sensitivity of his apparatus by placing weights on the membrane (1-4 ozs.) and noting the height of the registering needle against a prepared scale. This scale consisted of lines radiating from a centre which corresponded to the fulcrum of the aluminium lever. Thus a given individual could be required to produce the same amount of finger pressure on the membrane in different experimental sittings. By means of a plate fastened beneath the membrane to one of the legs of the supporting tripod, it was possible for the subject to approximate the finger above with the thumb below in a prehensile attitude, without bringing them into contact, and with a measured amount of pressure. The index, middle and ring fingers were studied in over 100 healthy and diseased subjects.

Eshner's findings constituted a major contribution to the knowledge of the characteristics of physiological tremor; in addition, some of his conclusions might be profitably reinvestigated with the more satisfactory techniques that are now available. His main results in normal subjects were as follows; (1) tremor was observed in all the healthy subjects; (2) a mean rate of about 10 c/s was found; (3) the frequency of the tremor bore an inverse relation to its amplitude and (4) most of the movements were rather irregular in character. These findings have been consistently confirmed by other workers. In addition, it was noted that those acts were performed with least tremulousness which the subject was in the habit of executing. For example, watchmakers and eye-surgeons showed less tremor in exercising slight pressure, while those unaccustomed to delicate manipulation displayed more movement under the same conditions, and less under the reverse. The amplitude of the movement was smaller when the thumb and fingers were in an attitude of prehension than when the fingers were applied directly to the contact button of the membrane. Eshner suggested that this may have been due to the sense of support and the inhibiting influence of a well-defined act. Furthermore, the mental attitude of the subject seemed to have an appreciable influence on the tremor record; the more intelligent and careful subjects displayed greater amplitude of movement under the same conditions as compared with those who were unintelligent or indifferent. A practice effect was observed; familiarity with the necessary manipulation on the part of the subject was associated with a reduction in tremor amplitude.

In the first two decades of this century, no significant advances were made in the techniques of tremor detection and recording, and little was added to the findings described above. Some measurements were made of the effects of experimental variables on the tremor, but as the results of these studies have all been reinvestigated and expanded under more satisfactory technical conditions by other workers at a later date, they will not be considered here.

The optical system devised by Mehrtens and Pouppirt (1928) was a considerable improvement on the mechanical techniques previously employed. They recorded, on moving film, the shadow cast by a needle attached to a thimble on the end of the trembling finger. The needle interrupted the rays of light cast by a slit lamp. Unfortunately, Mehrtens and Pouppirt did not carry out a displacement calibration, they reported their observations in a somewhat anecdotal manner, and the shadow cast by the needle was rather too thick to allow clear observation of tremor movements of small amplitude. Normal subjects, and patients suffering from a variety of disorders - Parkinsonism, hyperthyroidism, alcoholism and hysteria - were studied. The effects of the administration of thyroid extract and adrenaline to normal subjects were also examined. As already mentioned, no measurements of the relative amplitude of tremor in different subjects, and in the same subject under varying conditions, were made. Furthermore, no indication of the numbers of subjects studied in the different groups was given. In the group of normal subjects the "observed rate of oscillation" varied between 9 c/s and 15 c/s. The range of amplitude observed was "considerable". It was noted that the tremor observed in individuals exhibiting little clinical evidence of emotional "strain" or "tension" was of small amplitude, or indeed, barely perceptible with the technique employed. In those showing clinical evidence of emotional "lability" the tremor was of larger amplitude.

Young (1933) carried out an investigation of tremor in normal subjects which was of special interest because of the care taken to standardise the mechanical conditions under which movement occurred. Firstly, fixation of the joints whose movements was not required was achieved by means of suitable rests, plasticine casts, and specially shaped cylinders. Secondly, a visual fixation point was provided. A light-weight, rigid pointer was attached to the trembling part, and the subject was required to hold it opposite the centre of a "bull's-eye" target. The movements of the finger were detected by means of an altimeter diaphragm which was connected through high-pressure tubing to the diaphragm of a "phonelscope" - an optical lever - which was used for photographic recording. Five normal subjects were studied.

Recording separately the movements at the tip of the index with the metacarpo-phalangeal joint only, the metacarpo-phalangeal joint and wrist, or metacarpo-phalangeal joint, wrist and arm, free to move, did not produce records showing very different tremor rates. The range observed lay between 10 c/s and 12 c/s. When, however, the altimeter diaphragm was attached to the distal end of the forearm so that only movements occurring at the elbow and shoulder joints were recorded, the oscillations were of much larger amplitude, and at about 6 c/s. In another experiment the limb was free to move at the wrist and the metacarpo-phalangeal joint, and the subjects were asked to "tense the muscles of the hand and arm, and, keeping them tense, centre the pointer on the target as well as the tense conditions permit". This resulted in a considerable increase in the amplitude of the tremor, and a very slight increase in frequency. The effect of the production of an "anticipatory" state of mind was also studied. The subjects were told that they would hear two clicks, and that on hearing the second click they should perform a movement of extension (or flexion). Examination of the tremor in the interval between the two auditory signals showed that during this period there was, in most subjects, a change in rate (either an increase or a decrease), and, with some subjects, in the first one or two records (when the conditions were still unfamiliar), an increase in amplitude. Young also investigated the effect on the tremor of withdrawing the feedback of information to the subject regarding the position of the trembling part. His observations arising out of this procedure are highly relevant of the results of the experiment described in Part 4 of this thesis. The subjects were asked to centre the pointer on the target and then close their eyes while the record was being taken; movements were permitted at the metacarpo-phalangeal and wrist joints. In all five subjects the tremor rate was reduced following eye-closure, and in three of the subjects it dropped by over 1 c/s.

In discussing the results of withdrawal of visual feedback, Young suggested that the decrease with respect to amplitude and rate may have been due to the fact that the subjects were less on the "qui vive" when their eyes were closed. One of the subjects reported himself as being "less on a tension", another more "relaxed" when the eyes were closed. "Postural stability" with respect to tremor for both amplitude and rate appeared to be decreased as the introspective "strain" or effort increased; it seemed that a visual check on performance operated in such a way as to produce "conflict" or an "emotional factor" which caused an increase in the amplitude of tremor. The results of a detailed reinvestigation of the effect on the characteristics of the visual presentation of positional error will be given in Part 4, together with a more extensive discussion of its physiological basis.

Sollenberger (1937) obtained records of physiological tremor by photographing the movements of a fine wire attached to a thimble placed on the tip of the subjects' forefingers. The movements were amplified 20 times by an optical system. Calibration was achieved by means of an ocular micrometer. Tremor rates were assessed by counting the number of "complete" oscillations occurring in one and two-thirds seconds. In the two subjects studied rates of 15.1 c/s and 11.1 c/s were found. Voluntary tensing of the muscles controlling the finger appeared to increase the average amplitude and decrease the average frequency. The performance of mental arithmetic by the subjects had a similar effect.

Part 1B. Critical Discussion of Earlier Studies

Some of the more satisfactory investigations of the general characteristics of physiological tremor reported in the earlier literature have been reviewed. They provide a considerable body of evidence that a mechanical ripple can be detected in a part when an attempt is made to maintain it in a stationary position against the force of gravity or an applied load. These earlier studies must, however, be criticised in several respects.

In all the studies except those of Mehrtens and Pouppirt, and that of Sollenberger, a mechanical system was used for detecting the tremor. A receiving or a recording tambour, or both, were usually employed. In others, e.g. that of Eshner, a pivoted lever was also utilised.

When either of these types of system is used to detect tremor movements, the elastic resistance of the tambour membrane, or the mass of the moving lever, consititute mechanical factors which tend to reduce the sensitivity of the system with respect to tremor of large amplitude, or damp movements of small amplitude.

The resonant properties of the moving parts of the recording system must also be expected to modify the amplitude of the response to tremor at any particular frequency. Where a tambour was used to detect the tremor it was clearly necessary to permit a degree of flexibility in the membrane that would avoid excessive damping of the mechanical vibrations. This probably resulted in the use of a diaphragm having a low resonant frequency. Thus the natural period of oscillation of the system may in some investigations have been in the range of frequencies within which the harmonic components of physiological tremor are located. This was especially likely in certain studies e.g. that of Eshner, where the membrane was attached to a pivoted lever. In those studies where the elastic resistance of the detecting system constituted the load against which the moving part operated, the resonant properties of the detecting and recording equipment may well have played a considerable part in determining the character of the myograph record obtained.

Inaccuracies arising from the use of a mechanical system for detecting and recording tremor were avoided in those investigations where an optical system was used e.g. Mehrtens and Pouppirt (1928) and Sollenberger (1937). However, in all these earlier studies, the records of the tremor were subjected to visual inspection and assessed quantitatively in terms of arbitrary and necessarily rather subjective criteria. For example, Sollenberger defined a "tremor" as "a change from an upward direction on the record through zero to a downward direction". His measurements were then expressed as "tremors per second".

The development of more satisfactory methods of detecting mechanical movement, or its derivatives with respect to time e.g. velocity or acceleration, and the use of frequency analysis techniques, have shown that physiological tremor cannot validly be described as consisting of oscillations at only one frequency. In a myograph record a relatively rhythmic component at 8-10 c/s can often be seen to be superimposed on irregular movement at a mixture of frequencies in which no clearly rhythmic features can be discerned. If the velocity or acceleration of the part is recorded this appearance is accentuated. The shape of a plot of amplitude per unit band width against frequency depends on whether one records displacement or one of its derivatives, but the rhythmic elements produce a "hump" in the spectrum, usually at

8-10 c/s. The fact that the more rhythmic components in a complex wave-form are relatively prominent on visual inspection has probably led to the frequent description of a "dominant" tremor frequency at 8-10 c/s.

It should also be noted that the appearance of a myograph record depends in part on the speed at which it has been recorded. If the surface on which the record has been made, - paper, film etc. - has been slow-moving, the lower frequencies are relatively prominent; as the surface speed is increased, the higher frequency components become progressively more obvious. This effect may have sometimes given rise to misinterpretation of data.

Thus the earlier investigations were all unsatisfactory in some respects. Some of the results of more recent studies will be discussed later.

PART TWO

DISCUSSION OF EVIDENCE RELATING TO MECHANISMS WHICH MAY UNDERLIE PHYSIOLOGICAL TREMOR

Introduction

The nature of the mechanisms responsible for physiological tremor have not been defined in terms that give a satisfactory account of all the observed phenomena. Several studies, some of quite recent date, have been specifically concerned with the problem. Rather different accounts of the origin of the tremor have been developed. In the following pages, these studies, and others that may indirectly provide evidence as to the nature of the processes involved, will be discussed.

It has already been noted in Part 1 that a relatively rhythmic component at 8-10 c/s can often be discerned in the myograph record of physiological tremor, superimposed on irregular movement at a mixture of frequencies in which no obviously rhythmic features are evident.

If a signal proportional to the movement of the trembling part is subjected to harmonic analysis, and the amplitudes of movement per unit band width are plotted as ordinates against frequency, it is observed that the curve so obtained falls off in a fairly regular manner with increasing frequency. This is the kind of pattern expected if the part under study is an inertial system on which forces are acting in a random manner (Halliday and Redfearn, 1956). Deviations from this random "base-line" curve may be taken to indicate either that there are external forces acting on the system at the frequencies concerned, or that there are resonances at those frequencies.

Thus in discussing the mechanisms that underlie physiological tremor, processes that might give rise to the random, irregular element, and those that could produce non-random activity superimposed on this background, will be considered.

Classification of Mechanisms

The evidence relating to the mechanisms that may underlie physiological tremor can be conveniently classified into two main divisions.

Firstly, there is that evidence which deals with certain aspects of the neural control of skeletal muscle, (Section 1 below).

Secondly, there is data concerned with mechanical and other factors that may be of importance, (Section 2 below).

Within these two main divisions, various functional and anatomical subdivisions can be described.

Section 1. Features of the Neural Control of Skeletal Muscle which may be concerned in the Production of Physiological Tremor

A. Characteristics of Motor Unit Activity

In all but the most powerful contractions, a voluntary muscle effort is thought to be associated with the repetitive discharge of a population of muscle units firing at rates below their twitch fusion frequencies. However, as we have seen, a mechanical ripple, representing a relatively small proportion of the forces involved, can always be seen to be superimposed on the main effort. There is evidence that this tremor represents, under given conditions, a fairly constant proportion of the total force exerted (Hammond, Merton and Sutton, 1956).

As has already been noted, inspection of a myograph record, and frequency analysis of physiological tremor, suggest that a considerable proportion of the movement is random in character. The mechanisms which underlie and vary the amplitude of this arrhythmic element in the tremor are obscure, and any discussion of their possible nature is necessarily rather speculative.

In the discussion which follows, part (i) will be concerned with the consideration of processes which, theoretically, might underlie the random component of physiological tremor, and part (ii) will constitute a review of some of the relevant evidence.

(i) Theoretical

One effect that might contribute to the observed tremor might be the mechanical impulse imparted to the limb by the arrival in the muscle of each action potential travelling along the axons of the motoneurones. Explanations of physiological tremor in these terms have been proposed by various workers, e.g. Schafer and Horsley (1886). In spite of the observation of Marshall and Walsh (1956) that discharge of a single muscle unit (which was probably hypertrophied) can produce a detectable movement in a limb, there are certain objections that can be raised in regard to this view. Firstly, the movement produced by a single muscle unit is probably rather small. Secondly, there is evidence that motor units start firing at 7 c/s (Adrian and Bronk, 1929) or even higher frequencies (Bigland and Lippold, 1954). Thus, if this was the only mechanism operating in producing the tremor, little or no activity would be observed at the lower end of the frequency scale, though some movements would be seen at the lowest frequencies in association with errors related to the direct visual and proprioceptive control of the part. Since tremor is observed at each frequency, including those in the lower range, other mechanisms must also be involved.

While the mechanical effect of each individual discharge of a motor unit may not be important in the production of tremor, variation in the discharge rate, and hence in the tension developed by each unit, might result in a detectable mechanical ripple. If these variations in firing rate occurred randomly with respect to time in each unit, the force developed by a population of motor units behaving in this way might be expected to show superimposed irregular fluctuation at a mixture of frequencies.

It might also be expected that forces producing movement of the part might arise as a result of the chance synchronization of firing in simultaneous trains of motor unit discharges. For example, two units firing at closely related frequencies would tend to "get into step" for a greater or lesser length of time depending on the proximity of their discharge frequencies. During the time that they were nearly "in step" their firing would impart a relatively large force to the limb at a frequency close to that of the units concerned. The forces due to this process would, furthermore, tend to wax and wane at a frequency equal to the difference in the rates of discharge of the two units, i.e. their beat frequency. The "beating" between motor units firing at rates below their twitch fusion rates could, therefore, result in synchronization of unit discharge over a range of frequencies. For example, a group consisting of three units discharging at 8,10 and 12 c/s respectively would tend to produce a relatively small beat frequency at 4 c/s and one of larger amplitude at 2 c/s. Similarly, a pair of units discharging at 6 c/s and 9 c/s would tend to beat at 3 c/s. True beating effects are perhaps unlikely to be responsible for the higher frequency components in the frequency spectrum. In order to obtain high beat frequencies a wide separation of oscillator, i.e. motor unit, frequencies is required. However, as the rate of discharge of motor units increases they approach their twitch fusion frequencies; evidence presented by Marshall and Walsh (1956) suggests that the responses of the human forearm muscles become smoothed at quite low frequencies. Thus the high frequency mechanical oscillations required to cause high beat frequencies between motor units probably cannot be produced.

It has already been noted that the frequency spectrum of physiological tremor is such as might be expected in an inertial system on which forces are acting in an approximately random manner. In terms of the above theory, this would imply that the numbers of units displaying synchronous firing, due to beating and/or random fluctuations in discharge rate, appear to be distributed in approximately equal numbers at each point on the frequency scale if observations are carried out over a long enough time interval. However, rotation of function among the muscle units, and random fluctuations in their individual discharge rates must tend to make the force at any particular frequency vary irregularly with respect to time.

Deviation from the theoretical curve expected in terms of a random input of energy can usually be observed between about 5 and 15 c/s (Halliday and Redfearn, 1956, and personal observations). Certain aspects of the 8-10 c/s frequency range will be discussed later.

It has already been noted that muscle units firing at closely related frequencies will tend to "get into step" and discharge relatively synchronously for longer or shorter intervals. If there was some "favoured" frequency of motoneurone discharge, the resultant intermittent synchronous firing would produce an excess of mechanical activity at and near this modal frequency. In fact, available evidence suggests that during light or moderate contractions, motor units do indeed usually tend to fire at or near ten times per second.

As was noted at the beginning of this section, the mechanisms which underlie and vary the amplitude of physiological tremor are obscure. The effects that might be evident as a result of the operation of some of the mechanisms considered in the foregoing discussion can be summarised as follows.

Firstly, maximum smoothness would be observed in a number of units firing at rates below their twitch fusion frequencies if there was regular spacing of the firing of all the units i.e. if the different units fired in regular rotation. On the other hand, the randomly asynchronous recruitment of units would be expected to lead to greater mechanical tremor as a result of interaction between simultaneous trains of impulses in the way suggested above.

Secondly, an increase in tremor amplitude might be expected if there was a recruitment of an increased number of muscle units firing over a given range of frequencies.

Thirdly, an increase in the irregular mechanical component would be expected if there was any overall tendency to synchronous rather than asynchronous discharge of motoneurones.

(ii) Review of Relevant Literature

In regard to the first suggestion made above, there is evidence for rotation of function in muscle unit activity during a continuous contraction, (Adrian and Bronk, 1929; Hoefer and Putnam, 1939; Bigland and Lippold, 1954). Inspection of the records obtained by these workers would seem to indicate, however, that the timing of the firing of individual motor units usually shows a considerable degree of irregularity.

In regard to the second point, there is evidence that increased force of contraction, over a considerable range of contraction strengths, is related mainly to recruitment of more motor units (Bigland and Lippold, 1954). A plot of firing rate of an individual unit against force of muscular contraction is often found to follow an "S"-shaped curve, with an increase in discharge frequency with increase in tension at low levels of contraction strength, after which the firing rate remains approximately constant over a considerable range of increasing tension while other units are being recruited; a further increase in discharge frequency then occurs when the tension developed in the muscle nears its maximum. As was noted previously, tremor amplitude tends to vary approximately proportionately with contraction strength (Hammond, Merton and Sutton, 1956).

In regard to the third suggestion made above regarding mechanisms that may vary tremor amplitude, a number of studies have been concerned with the investigation of the extent to which synchronization of motor unit activity can be observed in normal and pathological conditions.

There is a considerable amount of evidence suggesting that in some pathological conditions there is an increased tendency for synchronization of motor unit activity to occur. In patients presenting spastic conditions Hoefer and Putnam (1940) found that where voluntary effort was possible at all, it was relatively weak, both by ordinary observation and in terms of the amplitude and frequency of the spikes produced. Furthermore, simultaneous motor unit leads showed a high degree of synchronization in all the muscles examined.

Denny-Brown (1949) found an increased tendency for different motor units to discharge together in muscles affected by poliomyelitis.

Marx, Isch and Rohmer (1950) reported some interesting observations made on a 26 year-old male subject who had suffered an acute attack of polio 6 years previously. They studied motor unit activity in the vastus muscle using implanted electrodes. A region was found in which the record showed the discharges from two fairly clearly identifiable units. The spikes often synchronized with one another; a method of quantifying the overall degree of synchronization involving measurement of the time intervals between the discharges of the two units was developed. The measurements were displayed graphically, and the spikes were seen to be manifesting a high degree of synchronization. Arvanitaki (1942) showed that a nerve impulse can be transferred from one giant axon to another without the intervention of a synapse if the two fibres are rendered sufficiently hyperexcitable by reduction of the calcium content of the ambient solution. With this observation in mind, Marx and his coworkers administered 0.1G. of calcium gluconate intravenously to the patient. This produced desynchronization in terms of the quantitative criteria which they had developed. They suggested that this evidence was consistent with the view that the poliomyelitis had altered the characteristics of the spinal neurones in such a way that "ephaptic" transmission (as described by Arvanitaki) could occur within the central nervous system. The same authors studied a patient who had been subjected to the inhalation of mercury vapour for several weeks. He had developed a tremor of the left upper limb. Electromyographic records of the biceps and the forearm flexors on that side revealed a tendency for synchronized motor unit discharges to occur. They suggested that the mercury poisoning had produced a synchronization of motoneurone discharge similar to that thought to occur in pathological processes associated with damage to the anterior horn, especially poliomyelitis. Clinical cure was associated with progressive normalisation of the myograph record.

Criticisms have been expressed of some of the studies purporting to demonstrate synchronization of motor unit activity in pathological conditions. Denny-Brown (1949) suggested that some of the synchronous discharges observed in subjects with anterior horn cell disease may have resulted from leading from one and the same large unit which had been uncovered by the disappearance of smaller units. Kugelberg and Taverner (1950) studied the effect of stimulation of peripheral nerve with a slowly rising current in subjects with various kinds of anterior horn cell disease. The stimulus produced iterative discharge of motor units; often the action potentials obtained simultaneously in two different leads were of identical size, form and polarity. However, the fact that peripheral stimulation can in certain subjects give rise to synchronous activity does not necessarily prove that the latter is never of central origin. Furthermore, it would seem that the patients studied by Kugelberg and Taverner showed a very advanced degree of atrophy.

Hoefer and Putnam (1939) studied the records obtained simultaneously from coaxial needle electrodes implanted in three spatially separated parts of each muscle investigated. They concluded that during gentle contraction in normal skeletal muscle different motor units show independence in respect of frequency and pattern of discharges, and in the variation and size of spikes. There appeared to be some "rotation" in the temporal pattern of unit activity; as one became relatively quiescent, another would start discharging more rapidly.

It has been known for some time that during intense muscular effort muscle unit discharges tend to synchronize at a rate of about 50 per second, (Adrian, 1947).

Some investigators have attempted a more systematically quantitative approach to the study of motor unit synchronization.

Buchthal and Madsen (1950) carried out an experiment in which they attempted to determine the degree of synchronization that could be observed in action potentials led off simultaneously from different parts of normal and atrophic muscles. From bipolar electrodes situated in two parts of the muscle under investigation the action potentials were led to two independent differential amplifiers, observed on an oscilloscope, and recorded. Since the spikes varied in shape, direction and duration, they were rectified and shaped into rectangular pulses. The two trains of rectangular pulses were counted by two mechanical counters and simultaneously led to an instrument reacting only to coincident input pulses. The duration of the rectangular pulses was adjusted to the mean duration of the action potentials observed (5 m.sec. with the electrodes used), corresponding to a "coincidence interval" of 10 m.sec. (Two impulses were considered to be coincident if they were discharged within a limited, defined time interval - the coincidence interval). The biceps brachii muscle was studied during slight voluntary effort over periods of 120 secs. The results obtained by Buchthal and Madsen were as follows. (1) The number of coincident impulses that would be statistically expected in terms of the observed discharge frequencies was calculated, and compared with the number of synchronous spikes measured by the coincidence counter. The difference between the two showed a normal distribution, with the majority of readings clustered round zero in healthy subjects; (2) 70%-100% synchronization was observed with less than 20% of the electrode positions investigated in healthy muscle, (excluding some of the small muscles of the hand, where a greater degree of synchronization was observed); (3) synchronization of a similar degree was observed in muscles with atrophies of peripheral origin; (4) with atrophies of central origin, 70%-100% synchronization of action potentials occurred at more than 60% of the electrode positions investigated; (5) it was noted that after a fatiguing contraction, at a time when muscular power was no longer significantly reduced, the number of points at which 70%-100% synchronization of action potentials could be observed rose from less than 20% to 38%.

In discussing these results, Buchthal and Madsen considered the possibility that the synchronization of activity in the two signal trains might be due to their having led off from fibres of the same muscle unit. In the light of available knowledge of the anatomy of muscle units, the authors concluded that this explanation of their findings was unlikely, and that the effects observed were more likely to be due to the fact that synchronization of motor unit activity was occurring.

Taylor (1962) made observations on human subjects without anaesthesia and on cats and rabbits which were either anaesthetized or decerebrated. Electromyograms were recorded via implanted electrodes during voluntary contractions in the human subjects, and in stretch reflex contractions in decerebrate or anaesthetized cats. In all cases an appearance of grouping of action potentials was seen. The frequency of the bursts of activity was usually about 10 per second in human muscles, and up to about 15 per second in cats and rabbits. A further characteristic of the grouping was that each unit fired only once in each group. When the strength of contraction was increased, both the rate of discharge of the units and the frequency of the grouping increased, but each unit still fired only once in each group. The effect of interrupting possible reflex loops was examined in two ways. First, the posterior nerve roots were cut and the spinal cord was severed immediately below the phrenic nerve outflow. In all cases, occasional grouping of action potentials in the diaphragm persisted, indistinguishable from that previously noted. Secondly, the motor side of any possible reflex arcs was interrupted in two decerebrate cats by paralysis with curare. Action potentials were recorded from a small number of motor fibres in the upper root of the right phrenic nerve. Action potential frequency distribution histograms were constructed. A comparison of distributions before and after curare revealed no significant change in the motor discharge pattern. Thus reflex feedback did not appear to be important in producing this apparent synchronization of motor unit activity.

Taylor investigated the possibility that the grouping of action potentials might be a purely chance appearance without biological significance. This possibility was tested by observing the behaviour of an electronic model, and by a statistical analysis of electromyographic records. The results obtained indicated no true tendency to synchronization or desynchronization of motor neurone activity in excess of that which might be expected if one assumes that the motoneurones discharge fairly regularly, repetitively, and are independent of one another.

These findings, therefore, failed to confirm those of Buchthal and Madsen and other workers in regard to the occurrence of synchronization of motor unit activity. However, Taylor's study was made on only a small number of units over rather short periods of observation. Furthermore, the test contractions were of small magnitude. Taylor suggested that the grouping of motoneurone discharge of the type he described might contribute to the rhythmic component of physiological tremor often seen at 8-10 c/s. However, it was shown by Halliday and Redfearn (1956) that increasing the force of contraction by loading the trembling part does not alter the frequency of the rhythmic component to any marked extent. (This has been confirmed in personal observations several times). However, as already noted, increasing the strength of contraction increased both the rate of discharge of the units and the frequency of the grouping in Taylor's observations. Thus while chance synchronization of the type which he described may play a part in the production of physiological tremor, other mechanisms almost certainly operate as well.

It might reasonably be expected that spatially related muscle units would tend to "get into step" as a result of mechanical interaction.

Furthermore, Merton (1954), has argued that electrical interaction between muscle fibres seems to be the only plausible explanation of the increase in tension and time course of contraction seen in muscle twitches induced by synchronous as opposed to slightly asynchronous volleys in the motor nerve. One doubts whether the latter kind of interaction is important in producing the kind of synchronization of motor unit discharge which might be associated with an increase in the amplitude of the tremor components.

Some degree of synchronization of motoneurone activity might occur in association with the "coupling" of reflex arcs within the spinal cord. Cohen (1953) investigated the localisation of the stretch reflex in decerebrate cats. Strips of quadriceps femoris mucle, about 2-3 mm. in diameter, were stretched, and the resulting reflex tensions were measured. The associated reflex tension in the remainder of the muscle was measured separately in the patella tendon. A comparison of the strip and patella tension of a given preparation showed the localization of stretch in that preparation. When a 3 mm. stretch was applied to the muscle strip, the rest of the muscle showed no response. The effect of various procedures, e.g. turning the head towards the recorded limb, evocation of the crossed extension reflex in the limb under study, and higher rates of strip stretch, was studied. These procedures have in common the characteristic of increasing the number of impulses bombarding the quadriceps motoneurone pool per unit time. When a 3 mm. stretch was now applied to the strip of muscle, a response was seen in the patella tendon, indicating a reduction in the degree of localization of the reflex response. When patellar responses did occur, only a sharp, twitch-like contraction resulted. This occurred immediately after the stretch had been applied, when the afferent inflow decreased and no patellar response was usually recorded. Cohen suggested that at highest rates of strip afferent firing (produced by more rapid stretch), and during bombardment from other sources, the motoneurones which would otherwise have been in the subliminal fringe were raised to a level of excitability at which they discharged, and the firing of these extra-strip cells reduced the degree of localization of the reflex.

Special cell systems may be concerned in keeping the degree of synchronization at a minimum. Renshaw (1941) studied some of the effects of antidromic volleys produced by stimulation of the ventral roots of the spinal nerves. Such a volley was found to be followed by a small centrifugal volley in the motor axon carrying the antidromic discharge. He presented evidence suggesting that the centrifugal volley arose as a result of repetitive discharges in some of the antidromically activated motoneurones, rather than reflex discharges synaptically excited through recurrent collaterals. Antidromic volleys were also found to condition the synaptically activated discharges of other motor cells. Inhibition typically occurred if the "tested" and the "conditioning" motor nerves were branches to the same muscle, or muscle group. The very early onset of this inhibition was consistent with the view that it might be transmitted via recurrent collaterals of the motor axons. It would seem that the firing of a group of motoneurones may produce a decrease in the excitability of motoneurones innervating synergistically acting muscle units. Our detailed knowledge of the mechanics of the "Renshaw cell system" have been expanded by Eccles, Fatt and Koketsu (1954), utilising a microelectrode suitable for recording from within the cell body of motoneurones.

As has already been noted, in certain conditions associated with spinal cord damage, there is a tendency for increased synchronization of muscle unit discharge. The cellular damage associated with these disorders might result in interference with the Renshaw inhibitory system, or increase the extent to which interaction can occur between spinal reflexes or motoneurones innervating the same muscles or muscle groups. It is not necessary to suppose that such effects will only be evident when structural changes have occurred at the spinal level. Alterations in the biochemical milieu, or abnormal patterns of nervous impulses reaching the spinal segments from sources elsewhere in the nervous system might result in an alteration in the degree of synchronization of motoneurone discharge. The former condition might be evident in thyrotoxicosis, shown by Lippold et al. (1959) to be associated with an increase in tremor amplitude over a considerable range of frequencies. The latter situation i.e. a change in the pattern of bombardment of the motoneurone pool, might be the cause of the increased tremor amplitude observed in "anxiety states", (Redfearn, 1957; Graham, 1945; and personal observations).

Observations have been reported that have indicated that muscular fatigue is associated with an increased tremor amplitude (Sutton and Sykes, 1956; Lippold, Redfearn and Vuco, 1957). An abnormally high degree of synchronization has also been reported in fatigued as compared with normal muscle, (Buchthal and Madsen, 1950). One interpretation of these results would be that the increased tremor amplitude observed in conditions of fatigue, is caused by the associated increase in the degree of synchronization of motor unit activity.

No studies have yet been reported which have attempted to correlate an acceptable measurement of motor unit synchronization with a quantitative assessment of tremor amplitude.

B. Reflex Oscillation

As has already been observed in Part 1, a relatively rhythmic component can often be identified in a myograph record of muscular contraction. This feature is associated with the appearance of a "hump" in the frequency spectrum. Several studies have been concerned with studying the possibility that at least some of the tremor in this frequency range may be caused by oscillation in the stretch reflex system. The receptor components of this system consist of muscle spindles which lie in parallel with the main muscle fibres and share their attachments; they are, therefore, extended when the muscle lengthens, and relaxed when it shortens. The reflex connexions are such that impulses set up by stretching a given muscle cause excitation of the motoneurones supplying that particular muscle. The lengthening of the muscle results in an increased contraction which tends to resist the extension. Thus during the attempt to maintain a part in a static position, (the situation studied in Parts 3-5), the stretch reflex system has the properties of a "length servo", i.e. an error actuated closed-loop mechanism using negative feedback from the spindles to maintain a constant muscle length. There is evidence that the stretch reflex may also operate as a "follow-up" length servo, producing movement of the part (Eldred, Granit and Merton, 1953).

In engineering practice the assessment of the stability of a control system is a problem that is frequently encountered. Where the system is linear, and the derivatives of the differential equation relating input to output are not of a higher order than second, a complete mathematical description of the system response is obtainable. The stability of the system is determined by the magnitude of one of the terms in the transient solution.

With more complicated linear servomechanisms, a complete description of the performance of the system cannot be obtained. However, methods have been developed for determining stability; these involve the observation of the response of the system to sinusoidal inputs at various frequencies. From such measurements, the "transfer function" of the mechanism, containing information about the phase and amplitude relationships of output to input, can be developed. This can be expressed in various ways, e.g. algebraically, using the operator "j", or displayed graphically as a plot in polar coordinates of the output as a function of frequency, (a "Nyquist" Plot). The input in such a diagram is represented by a vector of unit length and zero phase angle. In practice, the loop transfer function, (relating output signal to error signal), is studied in preference to the overall transfer function. One reason for this is that if the device is unstable, a closed loop response from which the overall transfer function could be developed is unobtainable since the system will oscillate freely, possibly causing damage.

If there is a frequency at which the loop transfer function, expressed algebraically or geometrically, indicates a 180° phase change, then the possibility of instability exists because the error measuring device will introduce a further 180° phase change so that the total phase change round the loop is 360° or 0°. Hence an initial disturbance at the servoamplifier input gives rise to a signal fed back in phase. If the gain of the loop is greater than unity, the output runs away to an extreme position displaying a train of oscillations whose amplitude increases as a geometrical progression until the system saturates. With loop gains of less than unity, oscillations showing a greater or lesser degree of damping are observed. These considerations only apply with precision to linear systems, and in spite of rather doubtful evidence to the contrary (e.g. Stark, 1961), the mechanisms associated with neuromuscular control probably usually display a considerable degree of non-linearity.

In the stretch reflex system, instability might arise from the phase shift resulting from the necessary delay between the application of a stretch stimulus and the development of the resulting corrective muscular forces. The delay includes the time for conduction in the fibres of the reflex arc, which are among the largest in the body, and the time taken for the mechanical response of the muscle to get under way. Not only will there be a tendency for rhythmic activity to develop in response to a static stretch; if energy is fed into the system in the frequency range where the period of oscillation of the muscle is twice as long as the delay round the loop, negative feedback energy derived from stretching of the muscle will become positive because its phase is reversed by the delay round the loop, and oscillation may build up and tend to be self-maintained.

Some workers have reported observations that were considered to be consistent with the hypothesis that the tremor rhythm with a frequency at 8-10 c/s is associated with oscillation in the stretch reflex. Other investigators have rejected the theory on the grounds that it does not explain all their findings.

The two sets of evidence will be considered separately.

(i) Evidence supporting the Hypothesis that Stretch Reflex Oscillation is concerned in the Production of the 8-10 c/s Tremor Components

(a) Effect of Cooling of the Muscles acting on the Trembling Part.

Lippold, Redfearn and Vuco (1957) found rhythmical grouping of electrical activity in most of the muscles that they studied in normal individuals. The presence of small mechanical oscillations at the same frequency as the groups of muscle action potentials, and bearing a constant phase relation to them, could often be demonstrated. The tremor, and the action potential grouping, were relatively prominent in certain circumstances, e.g. during postural activity. It was also clearly evident after fatigue had been induced by a 4-minute contraction at 75% maximal strength; an increased degree of grouping, and augmentation of the associated tremor, could be seen for up to 30 minutes after such an effort.

In their main experiment, Lippold et al. recorded action potentials from the human calf-muscle. The leg was placed in a bin which could be filled with water to above knee level at any desired temperature. The frequency of the action potential bursts was determined by visual selection of the central point in each group and measurement of the time-interval between such points. Comparison of the degree of synchronization was sometimes made by means of histograms depicting the distribution of intervals between successive motor unit spikes.

Mechanical movement was recorded with an RCA 5734 transducer triode attached to a bending bar connected to a hinged foot platform, or strapped to the calf and connected to a needle inserted through the skin, with its tip in the gastrocnemius muscle. During 15-20 minutes immersion of the limb at 9 degrees Centigrade there was a progressive reduction in amplitude and frequency of the mechanical tremor from about 9 c/s to about 6 c/s, on average. In addition, the rhythmical bursts in the myograph record became progressively less sharply defined and less frequent. During the period of cooling, the duration of muscle twitches, induced reflexly or by direct stimulation, increased by a factor of 2-3.

Lippold et al. concluded from these observations that "... there can be little doubt on these and other grounds that this electrical rhythmicity is the basis of physiological tremor ...". It might be suggested, however, that some of their own observations do not altogether support this statement. One of their illustrations displays electromyograms which indicate that separate rhythms of similar frequency must have been present simultaneously in different groups of units in the biceps brachii. Since these groups of units were only 1 cm. apart, the mechanical processes in which they were involved, or the effects of their contraction, should have been very closely related. Yet it is obvious that both sets of rhythmic discharges could not be in phase with the tremor rhythm. Unfortunately, tension records were not provided in association with these particular electromyograms.

These workers argued that the demonstration of the fact that the frequency and amplitude of the mechanical ripple changes in association with an alteration in the contraction time of the muscles concerned constitutes evidence supporting the hypothesis that the 8-10 c/s rhythm is caused by oscillation in the stretch reflex servo-loop, rather than by purely intraspinal factors. While this may be true, these observations can also be regarded as being consistent with other hypotheses, e.g. that of Marshall and Walsh (1956), who suggested that the 8-10 c/s tremor frequency is the result of the muscles acting as "low-pass" filters with respect to mechanical movements in response to impulses arriving via the motor nerve. (This latter hypothesis will be discussed in greater detail later).

Sutton and Sykes (1956) also observed a marked reduction in the 9 c/s tremor component as a result of cooling the active muscles in water at 15 degrees Centigrade for 15 minutes. Their conclusions regarding the origin of the tremor were similar to those of Lippold et al.

Marshall and Walsh (1956) studied the effect on tremor at the wrist of cooling the forearm in a bath of crushed ice. A record of the acceleration of the trembling part showed a striking reduction in the amplitude of the "tremor waves", and also an apparent reduction in frequency. As noted above, however, they arrived at an explanation of the origin of tremor that differed from that of Lippold et al.

(b) Effect of Deafferentation.

Halliday and Redfearn (1958), detected photo-electrically, and automatically analysed the frequency of tremor in eight tabetic patients showing varying degrees of deafferentation. In the most severely deafferented patients there was no sign of the "hump" usually observable in the tremor spectrum. In other patients, who showed less severe sensory loss, the tremor rhythm was present, and of greater amplitude than normal, and the frequency of the peak was abnormally lowered by loading. The authors argued that this feature can be compared with the behaviour of a failing servo with insufficient energy at its disposal to cope with the increased load. It was observed, also, that increasing the load on the trembling part from 50G to 100G in the two most tremulous patients caused a diminution in amplitude. These findings were regarded as suggesting that as a result of the destruction of many of the stretch reflex arcs, the remaining loops may have reached saturation and displayed oscillation at the full extent of their power. This failure to increase amplitude by loading at these relatively low tensions was not seen in any other subjects.

Lippold, Redfearn and Vuco (1959) carried out a harmonic analysis of the fluctuations in muscular tension that occurred during shivering in anaesthetized cats. They found that a rhythmic element in the myograph record associated with a distinct "hump" in the frequency spectrum at about 13 c/s was abolished by deafferentation. They suggested that this dependence of the rhythmic component of the tremor on the integrity of the reflex arcs provided support for the view that the tremor in this range is due to oscillation in the stretch reflex.

(c) Effect of Sinusoidal Stretching of Muscle Receptors.

Lippold, Redfearn and Vuco (1958) studied the reflex responses of the tibialis anterior muscle of anaesthetized cats to sinusoidal stretching at various frequencies. The magnitude of the motor response was measured roughly by adding together the amplitudes of the action potential spikes. This value varied with the frequency of stretching. Between 9 and 14 c/s there was a peak in the size of the integrated action potential, with a maximum at 12-13 c/s. If these workers were correct in their suggestion that this observation indicated that a certain degree of self-oscillation was taking place in the stretch reflex servo loop, it must be assumed that a plot of tension against frequency would have shown a similar peak, since the internal shortening of the muscle must have been greater where the integrated action potential was relatively large. (The external length of the muscle was controlled by the mechanical system which applied the sinusoidal stretch). Unfortunately, although arrangements were made for recording the tension changes in the tendon during stretching of the muscle, this was apparently not carried out in this particular experiment.

Furthermore, while the increase in the motor response in this range is consistent with the occurrence of stretch reflex oscillation, it does not exclude the possibility of frequency-dependent central augmentation.

(ii) Observations that are not consistent with the "Stretch Reflex Oscillation" Theory

(a) Frequency of Tremor in Muscle Groups with Short Reflex Pathways.

Marshall and Walsh (1956) studied the tremor that could be detected (using an accelerometer) at the wrist, elbow, shoulder, ankle and hip. They reported that the frequency of the recorded oscillation was "much the same" at these different sites.

Lippold, Redfearn and Vuco (1959) carried out a frequency analysis of forearm tremor detected under virtually isometric conditions. They found that the frequency at which the "hump" appears in the spectrum varied according to the muscle groups that were active. In six subjects, the "hump" in the spectrum when the tension recorded was due mainly to the contraction of the triceps muscle was lower by several cycles per second as compared with that observed when the effort was exerted by the wrist flexors. While this evidence would appear to negate the "servo-oscillation" theory, it must be pointed out that the length of the reflex arcs is not the only factor that would determine the frequency of resonance. Differences in the contraction times of the muscle groups concerned might vary this frequency, a relatively long contraction time being associated with a low frequency of oscillation.

(b) Tremor in Children.

Marshall (1959) studied the tremor that could be observed in 287 children, using the technique developed by Marshall and Walsh (1956). A tremor with a frequency of about 6 c/s was observed in young children. At the age of about 9 years, a fairly rapid transition to the adult 8-10 c/s type of rhythm was seen. The diameter of the peripheral nerves increases up to the age of about 6 years and then remains approximately constant. The H-reflex latency approximately doubles between the age of 6 years and adult life, presumably in association with the lengthening of the reflex arcs (Wagman, 1954). This might be expected to be associated with a progressive reduction in the frequency of the tremor if the reflex oscillation theory was valid. In fact, the opposite was observed in the children studied by Marshall.

However, as noted above, the delay in the neural components of the reflex system is not the only factor that would determine the frequency of the oscillation. Also, as Marshall suggested, the tremor in children may not be a slower version of that seen in adults, but rather a separate phenomenon with its own neural mechanism which is suppressed and replaced by the adult tremor. Whether the 8-10 c/s components which are prominent in adult tremor are absent, or merely of relatively low amplitude, in children, would only be revealed by a more satisfactory method of detecting and analysing tremor than that employed by Marshall.

(c) Effect of Interruption of Reflex Arcs.

Taylor (1962) observed grouping of action potentials in the motor nerves of anaesthetized animal preparations following deafferentation and curarisation.

Van Buskirk and Fink (1962) reported the persistence of tremor following deafferentation in experimental animals. Their evidence will be discussed in greater length in Section 2.

(d) Cardio-vascular Effects.

Evidence reported as supporting the hypothesis that physiological tremor is "ballistocardiographic" in origin will be considered in Section 2.

Summary re: the "Stretch Reflex Oscillation" Theory.

A selection of the evidence relating to the hypothesis that some of the components in physiological tremor are due to oscillation in the stretch reflex has been given above.

While it seems likely that such oscillation does, indeed, occur, other mechanisms probably also contribute to the tremor, some within the frequency range at which the stretch reflex loop might be expected to resonate.

C. Occurrence of Oscillation with every Voluntary Movement

During an attempt to hold a part in a stationary position, involuntary drift occurs. Small corrective movements are made in order to bring the member back into the desired position. The occurrence of even a small damped oscillation in association with these movements could result in a peak in the frequency spectrum of the kind that is usually observed. If, for example, some resonance existed within the motor system, but outside any servo loop, then small jerky movements made at lower frequencies might produce "ringing" at a higher frequency.

Sutton and Sykes (1956) examined this possibility in an experiment in which normal subjects were required to exert a specific force on a loaded joystick while monitoring their performance on an oscilloscope screen. A record of the responses of the subjects when they were required to follow abrupt changes in the demanded force was obtained using a pen oscillograph. These workers concluded that although the sensitivity of the apparatus was sufficient to show up the 8-10 c/s elements in the tremor, this frequency was obvious before, after, and even, in a few subjects, during the change in the muscular force applied, with no particularly marked oscillation occurring immediately after the response.

D. Inherent Spinal Rhythmicity

Synchronized muscle unit discharge resulting in mechanical tremor might result from an inherent rhythmical tendency or property of the spinal system of motoneurones and interneurones, or of the neurones themselves.

There seems little doubt that there are electrically excitable cells outside the nervous system which are capable of spontaneous activity. Bullock and Terzuolo (1957) used intracellular electrodes in order to study in detail the characteristics of the spontaneous discharges of cells in the cardiac ganglion of the California spiny lobster.

The question of whether spontaneous rhythmic activity can be observed in central neurones has been discussed at length by Burns (1958). He concluded that such activity has not been clearly demonstrated.

Rhythmic bursts of impulses might arise as a result of the way in which the spinal interneurones and motoneurones are interconnected.

A type of neuronal organisation that might result in a rhythmic output was proposed by Graham Brown (1914). He studied the phenomenon of "narcosis progression", the walking or running movements which sometimes occur in cats under the influence of a general anaesthetic. These movements were observed, after division of the cord in the thoracic region, at a depth of anaesthesia at which the spinal reflexes were abolished. On one occasion they were observed to occur bilaterally after unilateral deafferentation.

From these and other observations Brown concluded that a patterned discharge could be elaborated in the spinal centres without the operation of the afferent side of the reflex arcs. He proposed the view that rhythmic phenomena of this type are due to balance of "equal and opposite activities" in antagonistic centres (or "half-centres"). This balance, he suggested, arises as a result of the characteristics of the interconnexions between the "half-centres", which determine the time-course of the alternate excitation and inhibition of the latter.

Forbes (1922), in discussing the nature of rhythmic reflexes and after-discharges, put forward the "delay-path" theory. According to this hypothesis, afferent impulses have at their disposal many different paths, all converging on the motoneurones. Some paths are simple, and others, involving a relatively larger number of interneurones, are complicated. The impulses travelling through the short paths take a short time, while those travelling through longer paths reach the motoneurones later. A continuous series of impulses arrives at the motoneurones through progressively more complicated pathways in response to a given afferent volley.

No evidence indicating the existence of "delay-paths" operating in this way has been forthcoming. Furthermore, it would be expected that the "delay-paths" proposed by Forbes would establish connexions with a progressively increasing number of interneurones and other reflex arcs. Thus some degree of irradiation of the initiating reflex would be expected. In fact, rhythmic reflexes and after-discharges remain, under normal circumstances, limited to a given muscle group or groups.

Lorente de No (1933) defined, by means of ablation experiments, the structures necessary for the production of the motor discharges responsible for the eye movements occurring in response to vestibular stimulation. All the experiments were carried out on anaesthetized rabbits. Vestibular stimulation was effected by rotation, or by means of small, heated needles; the eye movements were recorded isotonically.

It was found that the maintenance of the pattern of eye movements characteristic of nystagmus was dependent on the integrity of certain neural elements. These included neurones with a long axis cylinder in Deiter's nucleus and in the descending root of the trigeminal nerve; the neurones with a short axis cylinder in the same nuclei; the neurones in the angular and ventromedial nuclei; the neurones of the reticular substance; and the motoneurones innervating the muscles concerned. Even though the vestibular nuclei were kept intact, the muscle reactions were often absent if the reticular substance was damaged. The duration of the after-discharge following stimulation appeared to be dependent on the state of the reticular relays.

Lorente de No suggested that these observations were consistent with the view that the neurones concerned in the elaboration of the pattern of motoneurone discharge associated with nystagmus are arranged in closed circuits which he called "self re-exciting chains". The input end of such a chain receives the afferent vestibular impulses, which set the whole machinery into activity.

While the concept of such "reverberating circuits" has figured prominently in the literature, such systems have never been identified anatomically; nor has the circulation of impulses in closed chains of neurones been demonstrated by recording techniques. As Lorente de No himself remarked, " .... it must not be forgotten that this is a tentative explanation which, to be sure, new experiments will prove to be at least incomplete".

E. Suprasegmental "Pacemakers"

A rhythm might be imposed on the motoneurones by bursts of impulses arising from a source or sources higher in the nervous system. Such evidence as is available would seem to suggest that the occurrence of normal physiological tremor is not dependent on the operation of such a mechanism.

As was noted in Part 1, Schafer and Horsley (1886) observed the effect of stimulation of the cerebral cortex, the internal capsule, and the cut end of the spinal cord in experimental animals. Though the stimuli were applied at different frequencies, the associated muscular contractions always showed a superimposed mechanical oscillation at about 10 c/s.

Lippold, Redfearn and Vuco (1959) applied a continuous stimulus to the motor cortex of anaesthetized cats. The resultant muscular contraction showed a superimposed tremor with a frequency spectrum qualitatively similar to that seen during voluntary contraction in human subjects, though the rhythmic component occurred at a higher frequency in the cats.

The cerebral alpha rhythm and the rhythmic component of physiological tremor are of similar frequency, and at one time it was thought that they might derive from a common source. This is a difficult problem to investigate because of the phase alterations likely to occur in the pathways concerned. However, Lindquist (1941) showed that while hyperventilation markedly slows the alpha rhythm, it does not produce similar changes in muscle tremor.

Marshall and Walsh (1956) studied two subjects who had suffered complete transection of the spinal cord. The flexor withdrawal reflex was evoked by stimulation of the sole of the foot. In both patients, a 10 c/s tremor could be observed, superimposed on the reflex contractions.

Section 2. Mechanical and other Factors which may operate in the Causation of Physiological Tremor

A. Resonant Properties of the Trembling Part

The purely mechanical properties of the moving parts of the limb under observation - the bones, tendons, and muscles - might contribute a "natural frequency" of oscillation to the tremor, similar to the resonant frequency of a vibrating reed or tuning fork. The resonant properties of the system must indeed play some part in modifying the amplitude of movement resulting from rhythmical muscular forces of any particular frequency. The question is, in fact, to what extent these rhythmic properties are important.

Halliday and Redfearn (1956) studied the frequency spectrum of finger tremor using a photo-electric device for detecting the movements of the part. They found that loading the finger with 50 or 100G, while increasing the amplitude of the tremor, did not alter its harmonic composition.

However, the loading with the 100G weight profoundly affected the mechanical properties of the finger. In a series of 46 subjects, the mean frequency of the die-away oscillations following a sharp tap on the finger fell from 27.4 to 7.6 c/s. They concluded that the frequency composition of the tremor is virtually independent of the resonant properties of the limb.

Marshall and Walsh (1956) studied tremor frequencies during relatively slowly executed movements in which the tension of the muscles concerned could be kept fairly uniform over significant periods of time. If the resonant properties of the limb had been important in determining tremor frequency, it would have been expected that the superimposed mechanical ripple would have been more rapid when the movements were performed quickly. The muscles acting on the part would then have been relatively tense and would have produced a higher natural frequency in the limb than during slow movements when the muscles were lax. The frequency of the tremor was not found to vary with the velocity of the movement. They also argued that the natural frequency of the limb would vary throughout the course of a rapidly executed movement because the tension in the muscles acting on the part would be continuously changing. Hence, if physiological tremor resulted mainly from frequency-selective amplification, due to the resonant properties of the part, of energy fed into the limb, it would be expected that the tremor frequency would vary throughout the course of such a movement. This was not, in fact, observed; the number of oscillations occurring in a given time did not change significantly with the phase of the movement.

Thus at low or moderate contraction strengths, the resonant properties of the part do not appear to be important in modifying the frequency characteristics of the tremor.

At high contraction strengths, under certain conditions, the situation may change. Halliday and Redfearn (1956) noted " .... a considerable increase in tremor frequency when the subjects were asked to hold the finger as rigidly as possible". In unpublished observations of my own, I have noted that the powerful simultaneous contraction of the prime movers and antagonists acting on a part was associated with the appearance of well-defined peaks in the frequency spectrum. It would seem, for the following reasons, that these tremor components may have been related to selective amplification of energy fed into the part as a result of the resonant properties of the limb. (1) The frequencies of the peaks in the spectrum were reduced by loading the part; (2) their frequency rose with increased force of muscular contraction; (3) the number of peaks in the spectrum was related to the number of joints at which movement was permitted during the time when the measurements were made; and (4) no grouping of action potentials could be observed in a record of the electrical activity of the active muscles carried out simultaneously with the harmonic analysis of the tremor.

B. Mechanical Smoothing of Muscular Contractions

Marshall and Walsh (1956) found that if the forearm muscles were caused to contract by stimuli of uniform intensity, stimulation of the muscles more frequently than about 15 times per second did not result in corresponding shocks of significant amplitude being imparted to the limb. Indeed, the amplitude dropped off sharply above about 10 c/s. As was noted in Section 1A, it has been reported that motor units when first recruited discharge at a frequency of 7 c/s or more.

Marshall and Walsh suggested that a physiological tremor at or about 10 c/s was a consequence of an input of neural energy extending from this frequency range (i.e. about 7 c/s) upwards. Only the energy with a frequency below about 15 c/s would be effective in evoking mechanical oscillation, higher frequency activity being smoothed by the mechanical properties of the muscles.

This hypothesis does not, it would seem, account for all the characteristics of physiological tremor. If, for example, muscle units do indeed start firing at 7 c/s, as suggested by Adrian and Bronk, this theory does not account for the large amplitude oscillations at lower frequencies seen in a harmonic analysis of physiological tremor. Furthermore, it is difficult to see how the effects of tabetic deafferentation described by Halliday and Redfearn (1958) could be accounted for purely in terms of this hypothesis.

Thus while fusion of individual muscle twitches with increasing frequency may play a part in determining the relative amplitudes of the harmonic components of physiological tremor, it is probably not the only process involved.

C. Cardiovascular Factors

Evidence has been put forward (Brumlik, 1962; Van Buskirk and Fink, 1962), which has been considered by these authors to support the hypothesis that physiological tremor is mainly or entirely due to body oscillations occurring in response to the impact of blood ejected into the arterial system at cardiac systole. This line of enquiry was suggested by the fact that the wave-form in a "ballistocardiogram" has prominent elements at about 10 c/s.

Brumlik detected tremor by means of accelerometers attached to various parts of the body, usually the upper limbs. The amplitude of the tremor was then stated in terms of the displacement of the part studied. This must have been a very approximate estimate, since the amplitude calibration varied with frequency. Although an automatic frequency analyser was used in some of the experiments, it would seem that in those studies where an amplitude calibration was applied, tremor frequency was ".... read directly from the record". Since this constituted a record of a continuously changing acceleration, one would expect that calculations of amplitude, made, presumably, by measurements of acceleration maxima, would not give correct estimates of displacement magnitude.

In the first experiment, an accelerometer was taped over the dorsum of the second phalanx of the third digit. The limb was supported by a sling two inches wide attached to the ceiling. Records were taken from the upper limb with the sling providing support at a point 2" proximal to the radial styloid, at the mid-forearm, and at the elbow. Each subject was studied in three postures: (a) lying supine, (b) sitting, and (c) standing. The average amplitude and frequency were measured (how these measurements were made, and over how long a period, was not defined). It was found that the amplitude and frequency increased with the transition from the standing, through the sitting, to the supine position. In addition, these parameters showed an increase in magnitude as the support of the limb was moved proximally. This observation may be compared with the findings of Lippold, Redfearn and Vuco (1959), who, as has already been mentioned, also reported that forearm tremor measured under virtually isometric conditions was of larger amplitude than that recorded at the wrist; however, these workers noted that the characteristic "hump" in the spectrum was several cycles slower when the support was provided at the elbow. Brumlik also reported that with the subjects in the supine position, waves of relatively large amplitude which showed the same frequency as the heart-beat, and a constant phase relationship with it, could be seen in the record. This feature was especially noticeable when the sling provided support at the elbow. All subsequent recordings were made with the subjects in this posture, i.e. in the supine position with the elbow supported.

In "some" subjects, (and only when the limb was supported at the elbow), the amplitude of tremor of the left upper limb was of greater magnitude than the right. In others, tremor amplitudes were symmetrical. Tremor frequencies were, however, "consistently" higher on the left. The number of subjects studied, and the proportion falling into each category, was not stated. It was also noted that the tremor amplitude increased as the accelerometer was moved distally along the limb on each side (the support being provided at the elbows).

Tremor was recorded during natural sleep, and during hypnosis, in two subjects. The relevant illustration of the published records has been badly labelled, and one recording channel appears to have been omitted in the "sleep" study.

During sleep, however, the tremor seems to have diminished in amplitude, and rhythmic increases in amplitude temporally related to cardiac systole could be seen; they were also evident in the "waking" record. During hypnosis, the tremor amplitude is reported as having shown large oscillations related to cardiac systole, and to have waxed and waned with the respiratory cycle; none of these features are clearly evident in the published records.

In another experiment, two subjects were studied, one showing a marked degree of sinus arrhythmia, another suffering from atrial fibrillation. Brumlik's report that ".... the pattern of finger tremor again .... corresponded with events in the cardiac and respiratory cycles" is not clearly illustrated in the published records relating to the observations on the first subject. The record of tremor obtained from the second subject is too short to permit satisfactory assessment.

The effect of neuromuscular blockade was studied by the intravenous administration of 50 mg. succinylcholine to a conscious human subject. During the resultant apneic period, oxygen was administered by bag-breathing. The tremor persisted during the period of blockade.

In another procedure, it was observed that application of a sphygmomanometer cuff did not result in any change in tremor amplitude or frequency after 3 minutes of arterial occlusion.

During the voluntary elevation of the unsupported arm, and during ".... maximal contraction of all the limb muscles", a considerable increase in tremor amplitude was seen. A pattern consisting of amplitude peaks in the tremor record related to events in the cardiac cycle was no longer evident. Frequency analysis showed that at these higher contraction strengths, sub-peaks in the low and high frequency range (3.5 - 4.0 c/s, and 14-18 c/s) appeared in addition to the maximal activity at 8-10 c/s. (The frequency analysis was apparently carried out on the signal proportional to the acceleration of the part, without conversion to displacement amplitude).

Brumlik argued that these observations support the hypothesis that physiological tremor is due to the fact that ".... the cardiac impulse so jars the entire body that the completely relaxed limb is thrown into a series of oscillations by a shock wave travelling up and down the extremity".

While the way in which the investigation was carried out, and the mode of presentation of the results, makes detailed assessment difficult, the observations do not appear to entirely support the view that ".... the ballistocardiographic nature of normal tremor at rest has been demonstrated, whereas a neuromuscular component has been excluded". The findings, one might suggest, are consistent with the view that under certain special conditions (i.e. especially when the subject is supine, with the upper limb supported at the elbow by a non-rigid sling), vibrations may be detected in the extremity that are due to the ballistic effects of cardiac activity; a neuromuscular component has not been excluded by these experiments. To further clarify the situation, the effect of neuromuscular blockade on tremor around one joint (e.g. the metacarpo-phalangeal joint) should be studied. The findings of Brumlik relating to the effect of arterial occlusion differ from those of other workers, who have reported a considerable diminution in tremor amplitude in association with ischaemia, (Halliday and Redfearn, 1954; Sutton and Sykes, 1956, and Van Buskirk and Fink, 1962). Brumlik had some difficulty in accounting for the absence of oscillation related to the timing of the cardiac cycle during voluntary movement of the limb, or during powerful muscular contraction. He suggested that during these stronger efforts a "neuro-muscular component" may make its appearance. The increased amplitude under these conditions was, he suggested, ".... due to the removal of the limb support, coupled with muscle tension (which) may mechanically multiply the amplitude". The additional peaks seen in the frequency spectrum at higher contraction strengths may have been due, he proposed, to amplification of harmonic components of the ballistocardiogram, and to neuro-muscular effects. It is a little difficult to see why the mechanical conditions produced by increased strength of muscular contraction should amplify some of the vibrations due to cardiac action, and yet completely eliminate the "primary" vibration due to cardiac systole. Furthermore, it has already been noted that there is some evidence (Section 2A above) that additional peaks of activity, probably related to the effect of mechanical resonances in the limb, may become apparent at high contraction strengths. There is no special reason to suppose that these features represent responses to cardiac activity.

Van Buskirk and Fink (1962) carried out a study of tremor in normal subjects, certain groups of patients, and anaesthetized dogs which had been subjected to various surgical procedures.

In the studies carried out on human subjects, a photocell was activated by means of a light bulb attached to the tip of the index finger; the palm of the hand was supported. The signal from the photocell was presumably inversely proportional to the square of the distance of the light source from it; thus it must be assumed that the records showed a relatively greater degree of attenuation of the larger movements of the finger. The tracings of the amplified signal were assessed by visual inspection.

In six normal subjects, application of a brachial cuff resulted in "complete obliteration" of the tremor within three to eight minutes.

When the cuff was released, the oscillations returned to their normal amplitude within three to six minutes.

In none of the subjects were large amplitude oscillations related to the cardiac cycle evident.

In those patients who had suffered proprioceptive loss, the tremor amplitude was "often" reduced, though the apparent frequency was unchanged.

In the animal experiments the recording instrument was a ceramic phonograph cartridge with the activating needle placed in contact with the skin over the muscles of the hind limb. The limb was clamped at two points which were not defined in the description given; nor was the position of the detecting cartridge with reference to these clamps indicated.

Tremor appeared to persist, though with reduced amplitude, after dorsal root section or even after removal of the spinal cord below the eleventh thoracic segment. Injection of intra-arterial adrenaline to animals subjected to the latter procedure resulted in an increase in the tremor amplitude. When the limb and the recording apparatus were supported on a table other than that supporting the animal, the tremor disappeared in "most" experiments.

Van Buskirk and Fink interpreted their data as supporting the view that physiological tremor is a "ballistocardiographic" phenomenon. However, the theory does not provide an explanation for certain observation, e.g. the increase in tremor amplitude noted by Halliday and Redfearn (1958) in patients who had suffered partial tabetic deafferentation, and their failure to show a further augmentation in amplitude with moderate loading. Furthermore, the effects of arterial occlusion on tremor observed by Van Buskirk and Fink were exactly opposite to those reported by Brumlik; yet both argued that their findings were consistent with a "ballistocardiographic" causation of physiological tremor.

While these studies must be regarded as unsatisfactory, they do establish a case for a more detailed examination of the possible role of cardiovascular factors in the causation of physiological tremor. A starting point might be an investigation of the precise effect of ischaemia on tremor, which has never been fully and satisfactorily documented. Furthermore, as will be noted in Part 4, withdrawal of visual information regarding neuromuscular performance often produces a change in the amplitude and frequency of the rhythmic component of physiological tremor. It would be interesting to see whether there are corresponding changes in heart-rate, or in the oscillations of the conventional ballistocardiogram. In addition, the studies of Van Buskirk and Fink on experimental animals should be repeated and extended under much more precisely defined conditions.

PART THREE

METHODS USED IN THESE INVESTIGATIONS FOR DETECTION AND MEASUREMENT OF TREMOR

Introduction

In any investigation of physiological tremor the character of the data obtained depends on whether the equipment used detects and records the amplitude of movement of the part under study, or some other time-dependent variable, e.g. its velocity or acceleration.

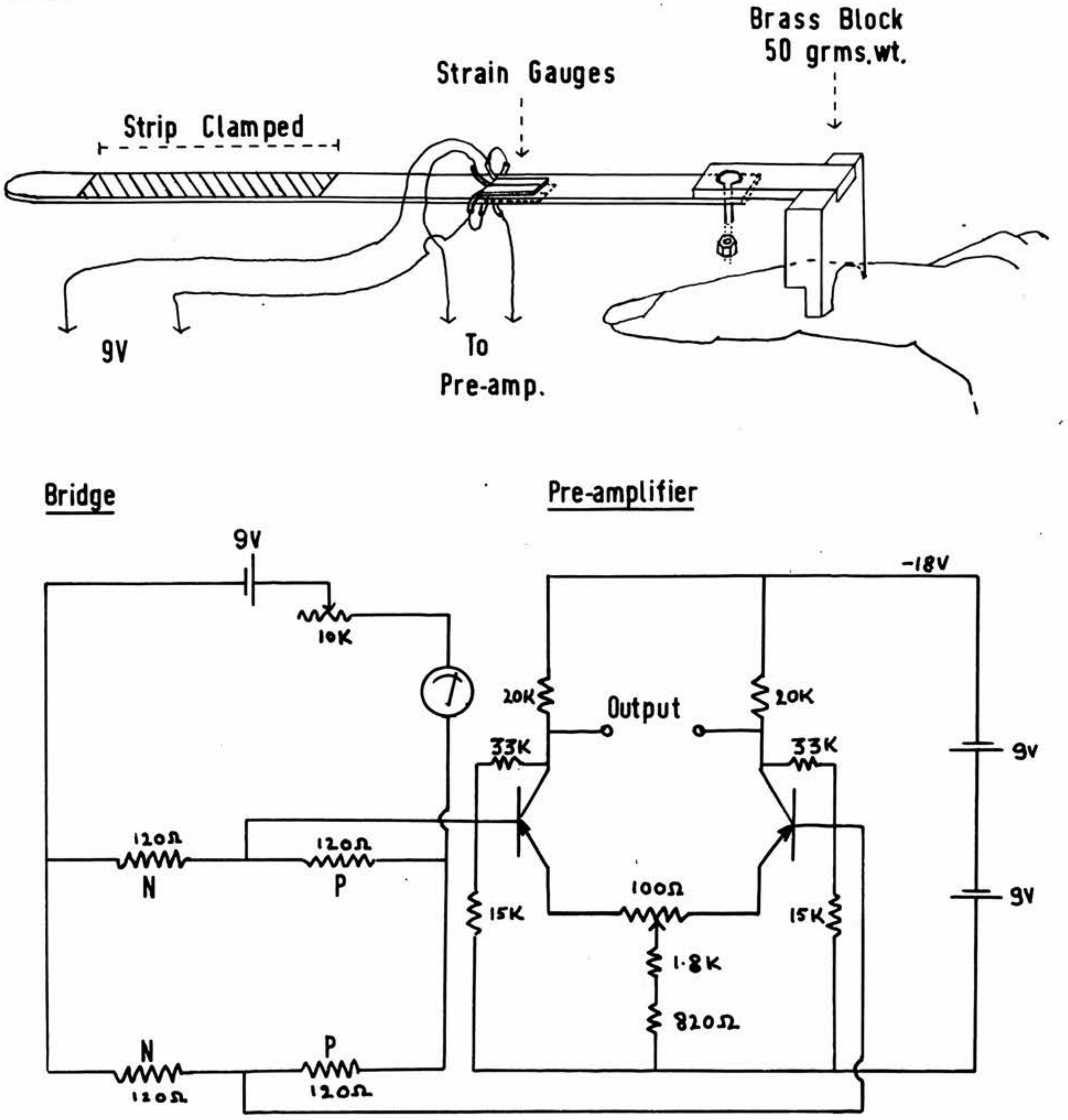
In the investigations described in this thesis the technique employed measured the vertical movement of the index at the metacarpo-phalangeal joint under virtually isotonic conditions. The subjects attempted to hold the part in a stationary position by extension of the finger against a load applied to the dorsum of the proximal phalanx. The tremor superimposed on this effort resulted in an error of positioning which varied in a complicated way with respect to time.

In most of the studies the performance of the subjects was displayed to them on an oscilloscope screen, so that they could make corrective movements under visual control. During other recordings, they were asked to close their eyes before the commencement of the period of measurement; on such occasions they were mainly dependent on information from their proprioceptive receptors.

Section 1. Mechanical Support of the Limb

The subjects were seated in a chair during the test procedure. One forearm and wrist were comfortably supported on a firm rubber arm rest. In all subjects the dominant side was studied. The palm of the hand rested on a crossbar; the thumb and three fingers were supported on a platform

FIG.1


Strip Clamped
Strain Gauges
Brass Block
50 grms.wt.
9V
To
Pre-amp.
Bridge
9V
10K
120Ω
N
120Ω
P
N
P
120Ω
120Ω
Pre-amplifier
-18V
20K
20K
Output
33K
33K
100Ω
15K
15K
1·8K
820Ω
9V
9V

extending anteriorly below this bar. The index finger was extended. The interphalangeal joints of this digit were splinted with a light metal strip and cellulose tape so that the turning moment due to the weight of the part did not change significantly as a result of variation in the degree of flexion of the finger.

The vertical and horizontal positions of the arm-rest, crossbar and platform could be adjusted by means of screw-clamps and measured by means of a centimetre scale. This allowed the comfortable positioning of the limb in subjects of different size. It also permitted standardisation of the supporting system in any given subject, so that the experimental conditions could be accurately reproduced for retest purposes.

Section 2. <u>Transducer System</u>

General Description.

A method of detecting tremor was required which was cheap, robust, and easily constructed, and which gave a reliable and accurate indication of the variation in the position of the trembling part with respect to time.

In the method used, the lower end of a 50G brass weight, rounded to fit the finger, made contact with the dorsum of the proximal phalanx of the index. The distance of the point of contact from the base of the finger-nail was measured in each subject. Prior to each testing session an ink mark was placed at this point. During each recording the weight rested on this mark, and hence the mechanical disadvantage at which the index extensor muscles were required to operate was standardised for each subject.

A short horizontal extension from the weight was bolted to a strip of spring steel. The latter was clamped in a heavy cast-iron adjustable myograph stand made from standard components supplied by C.F. Palmer (London) Ltd. Silicon filament semi-conductor strain gauges were fixed to each surface of the strip of spring steel about the mid-point of the long axis of the flexible section.

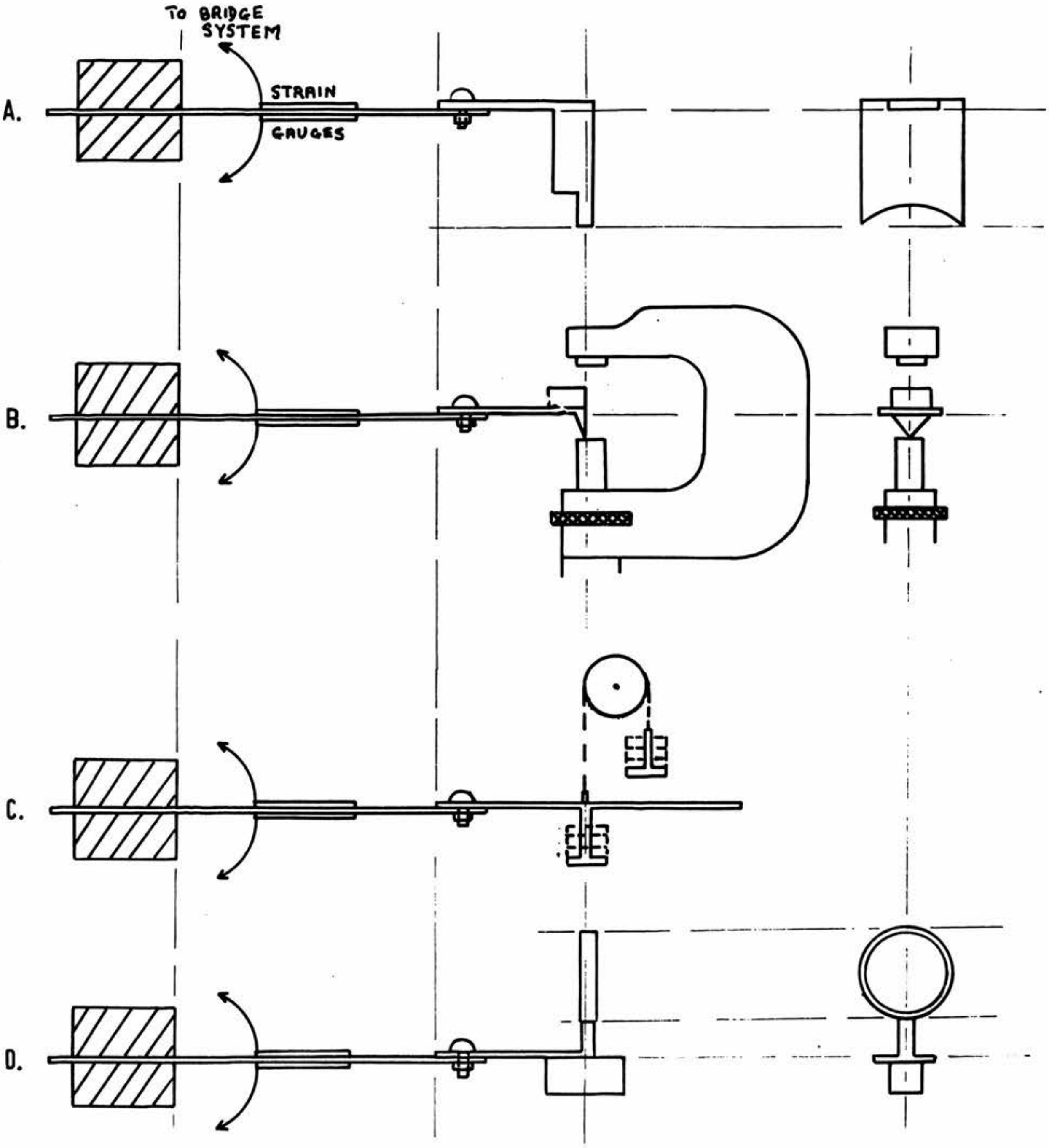
This type of strain gauge was used in preference to the resistance wire type for the following reasons. (1) They are smaller, and offer less resistance to stressing forces; (2) they give a higher output per microstrain than the wire type; and (3) they are of relatively low impedance (120 ohms each), and so cause no problems due to pick-up of stray interference. This type of gauge is supplied by the manufacturers, (Messrs. J. Langham Thompson, Park Avenue, Bushey, Herts), in two forms. The 'P' type gauge displays a uniform increase in resistance per unit tensile strain, and a reduction in resistance when it is compressed. The 'N' shows reverse effects on extension and compression. In the present arrangement, a pair consisting of a 'P' and an 'N' type gauge were mounted on the upper surface of the metal strip, and a matched pair on the lower surface. The maker's type numbers of the gauges used in these studies were 3A-1A-120P, and 3A-1A-120N.

The gauges constituted the arms of a bridge. Movement of the finger, and hence of the weight, in a vertical direction, resulted in the bridge becoming unbalanced. When recording was not actually in progress a horizontal bar, providing support for the strip and the attached weight, could be brought into position by a screw adjustment.

The apparatus described above is illustrated in the diagrams in Fig. 1, and Fig. 2A. The arm-rest, the clamps holding the crossbar and platform, and the bar supporting the weight in the intervals between recordings, have all been omitted for the sake of clarity. The flexible

FIG.2

For explanation, see text.



steel strip was 0.04 mm. thick, and 12.75 mm. wide. The length of the flexible portion from the point of clamping was 70 mm. The length of the horizontal extension from the 50G weight was 38 mm. The overall length of the steel strip and the horizontal extension when they were bolted together was 90 mm. The meter in the battery circuit provided a means of checking the current through the bridge. The magnitude of this current determined the sensitivity of the system, for which the 10K variable resistance provided a 'fine-adjustment' control.

Possible sources of error arising from the mechanical characteristics of the system were investigated, and are discussed in the Appendix at the end of this part. It was considered that such inaccuracies in measurement as may have occurred were not likely to have given rise to misleading interpretations of the observations.

Linearity of Transducer Response.

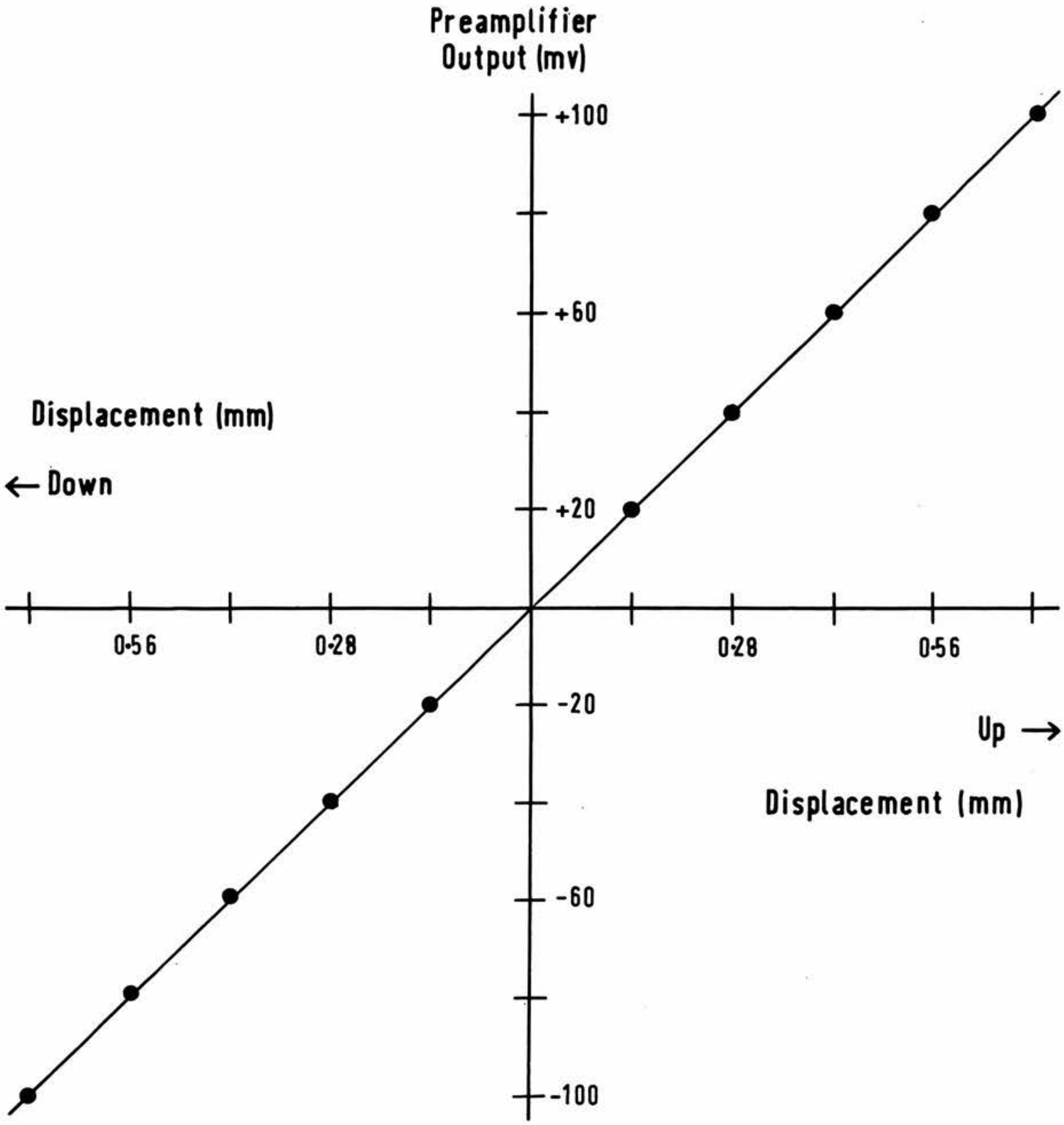
The relationship between the magnitude of vertical displacement of the weight and the size of the resultant signal voltage from the system has been investigated as follows.

A light, rigid extension, equal in length to the horizontal arm of the 50G weight, was bolted to the end of the steel strip to which the gauges were attached. A micrometer was mounted on a stand in such a way that movement of known magnitude of the mobile element of the micrometer could produce a vertical deflection of the end of the strip extension either upwards or downwards away from the position it occupied with no weight attached. This arrangement is illustrated in Fig. 2B. The resultant out-of-balance voltages for different amounts of displacement were amplified in a DC amplifier and measured with a suitably calibrated oscilloscope.

Fig. 3 shows a series of measurements obtained in this way. It is

FIG.3

DEFLECTION LINEARITY TEST



seen that a linear relationship was observed between vertical movement of the extension attached to the end of the steel strip and the resultant signal voltage. It has been found that the range of displacement shown in Fig. 3 includes the largest deflections observed during actual tremor recording.

Section 3. Amplification of Signal Voltage

The signal voltage from the transducer system was amplified using a differential preamplifier employing transistors, and one of the 'Y' amplifiers of a Tektronix TK 502 oscilloscope. DC amplification was used throughout. This resulted in a 'flat' response down to zero cycles per second; this was necessary since it was required that the signal voltage should give an accurate indication of the vertical position of the part over quite long intervals of time, i.e. up to 60 seconds in some experiments. Push-pull amplifiers were used in order to minimise effects due to in-phase interference and power-supply output fluctuations.

Drift in the pre-amplifier, the circuit diagram of which is shown in Fig. 1, was minimised by the use of a 'heat-sink', i.e. by embedding the transistors in a brass block measuring 2.0 X 1.2 X 6.5 cms. The transistors were Mullard Type OC200. The dry batteries used for operating the pre-amplifier (and for polarising the bridge) were Vidor Type VT4. The introductioh of a balancing potentiometer into one of the arms of the bridge would have reduced its sensitivity; the system was therefore balanced by adjustment of the 100 ohm potentiometer common to the emitter leads of the transistors.

Maximum drift occurring in the amplifiers, plus that due to thermal instability of the strain gauges, showed a mean value equivalent to an input signal to the preamplifier of 1.88 microvolts when measured over ten ten-second intervals (ten seconds was the recording time used in these experiments). A 1.88 microvolt signal produced a spot deflection on the oscilloscope of 0.006 cm. at the gain used during display to the subject. A signal of this magnitude was equivalent to a 0.00085 mm. vertical movement of the index at the point of contact with the 50G weight. This may be regarded as negligible.

The zero adjustment of the system consisting of transducer, balanced bridge and amplifiers was checked at 12-minute intervals during the testing of each subject. Maximum drift voltages (measured at the pre-amp output) occurring in each of ten twelve-minute intervals showed a mean of 6 millivolts. This was equivalent to a spot deflection of 1.5 mm. at the gain used during display to the subjects. A signal of this magnitude was equivalent to a vertical movement of the index of 0.042 mm. at the point of contact with the 50G weight, which would result in a change in the loading of the finger due to bending of the strip of (4×10^{-2})%. This can also be regarded as negligible.

The drift voltages never occurred at a velocity which resulted in their being detected by the filter circuits described below in Section 5B.

From the practical point of view, it was important that the batteries operating the transistor pre-amplifier and driving the current through the bridge should be in good condition. As they deteriorated, the slow reduction in volts between their terminals during operation could cause a noticeable drift in the DC setting of the system.

Section 4. Visual Monitoring of Performance by the Subjects

The subjects were provided with visual information concerning the position of the trembling part. The output of the amplifier was used to deflect a spot on an oscilloscope displayed to them. The screen was coated with blue phosphor of short persistence. Vertical displacement of the 50G weight on the end of the steel strip produced a proportional deflection of the spot. The subjects were required to superimpose this moving spot, which tended to move downwards in response to the action of the load, on a stationary one which represented the 'equilibrium' or 'target' position. This represented an alignment of the finger such that the steel strip and strain gauges occupied the position that they took up without the 50G load attached. 0.14 mm. movement of the index at the point of contact with the weight produced a 1.0 cm. deflection of the spot on the screen.

The subject was positioned in relation to the oscilloscope display at a distance such that a spot displacement of 1.0 cm. on the screen subtended an angle of approximately 0.66 degrees at the eye.

There were several reasons for permitting the subjects to monitor their performance visually. They can be enumerated as follows:-

(1) Part of this investigation was specifically concerned with studying certain aspects of the effect of visual monitoring of performance on the characteristics of physiological tremor.

(2) It was necessary to minimise effects due to the elastic resistance of the steel strip and strain gauges. Using this display technique, the voluntary effort exerted by the subjects was directed towards making the amount of bending that occurred as small as possible.

(3) The findings relating to the mechanical characteristics of the transducer assembly, detailed above and in the Appendix at the end of

this Part, only applied if the movements occurred about a mean position represented by the alignment of the steel strip and strain-gauges without the weight attached. Detailed measurements of the mean position of the transducer assembly during tremor recording in relation to its equilibrium position were not made, but inspection of the twelve DC myograph records used to determine the maximum amplitude of movement (as described in the Appendix), suggested that the mean position of the part during tremor recording was at or near the 'target' alignment.

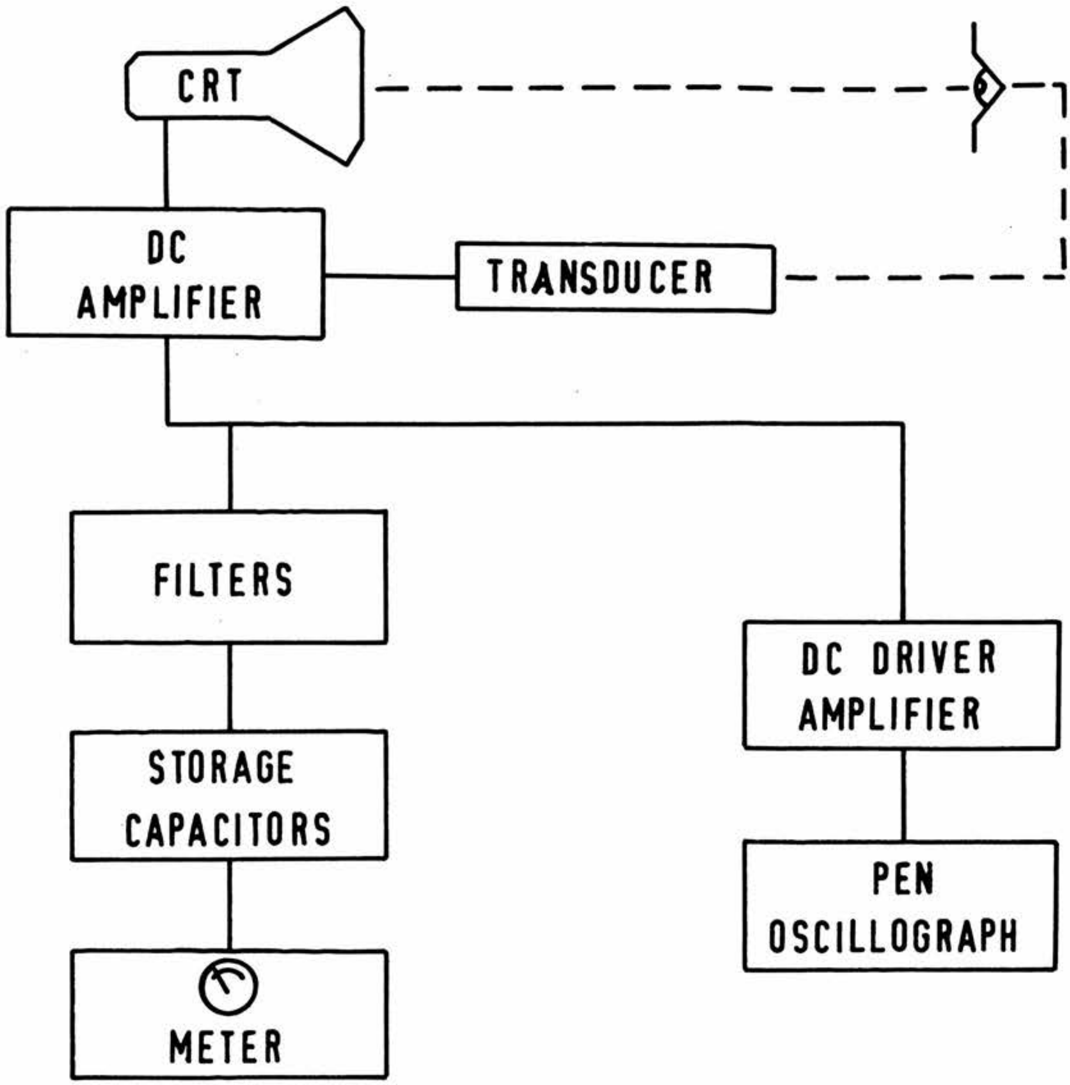
(4) It was desirable that the mechanical conditions under which the muscular effort took place should be reliably reproducible in a given subject. In the studies reported here, the testing procedures each consisted of several consecutive measurements, with rest intervals intervening. It was important that the subject should take up the same position for each test run. In certain studies, intervals of several weeks separated the occasions of testing. As already noted, the frame giving support to the limb could be adjusted to any required positioning of the non-moving parts. Since the subject was required to align his index in a manner that was predetermined, the position of the trembling part with reference to the static supporting frame could be reliably reproduced.

Section 5. Recording and Measurement of the Signal

The signal from the output stage of the Tektronix 502 amplifier was used to operate various pieces of apparatus. By observing the display on the oscilloscope produced by standard sine- and square-wave inputs before and after switching in this ancillary equipment, it was verified that connection of this ancillary apparatus did not interfere with the

FIG. 4

LAYOUT DIAGRAM



functioning of the amplifier.

The types of measurement carried out are now described. A layout diagram of the equipment is shown in Fig.4.

A. Myograph Record.

A standing voltage of +225 volts was superimposed on the signal output obtained from each side of the Tektronix balanced amplifier. It was desirable that this fixed voltage should be reduced to near earth potential before being used to drive a pen. This was achieved by connecting the Y-plates through two resistor chains to a -180 volt stabilised negative rail. The wipers of the potentiometers placed in these resistor chains were connected to the grids of a push-pull cathode follower stage. The potentiometers could then be adjusted so that the grids were at earth potential when there was no signal output from the amplifier.

The balanced output from the cathode-follower stage was led to a two-stage DC amplifier. The first stage produced a small amount of amplification, the second provided the power needed to drive the pen of an Ediswan oscillograph.

This system could be used to give a record of displacement in which all the frequency components down to zero cycles per second were accurately represented.

B. Frequency Analysis.

The movement occurring when the subjects attempted to hold the index finger in a stationary position in a vertical plane resulted in a positional error which constituted a complex function of time. Arrangements were therefore made to obtain information regarding the mean amplitude of this error per unit bandwidth over a range of frequencies.

Various techniques were considered for obtaining this data.

Probably the most satisfactory method would involve carrying out a mathematical analysis of the signal over a given time using Fourier's theorem. This would necessitate obtaining an appropriate number of 'Y-ordinate' measurements (as determined by Shannon's 'folding' theorem). Both the process of measurement of the wave-form and the mathematical analysis would be extremely laborious, especially the latter, if carried out manually. In order to expedite matters, a device that automatically obtained a measure of the instantaneous amplitude of the signal waveform at suitably frequent intervals would be needed. This 'digitiser' would be required to operate a high-speed punch which would produce a perforated tape suitable for feeding to a digital computer programmed to carry out the mathematical analysis. While this arrangement would give a high degree of precision, it was rejected for the purposes of the present experiment on the grounds of (a) expense, and (b) the inevitable delay between the collection of the data and receiving the results of its analysis, since it would not have been possible to have a computer 'on-line'.

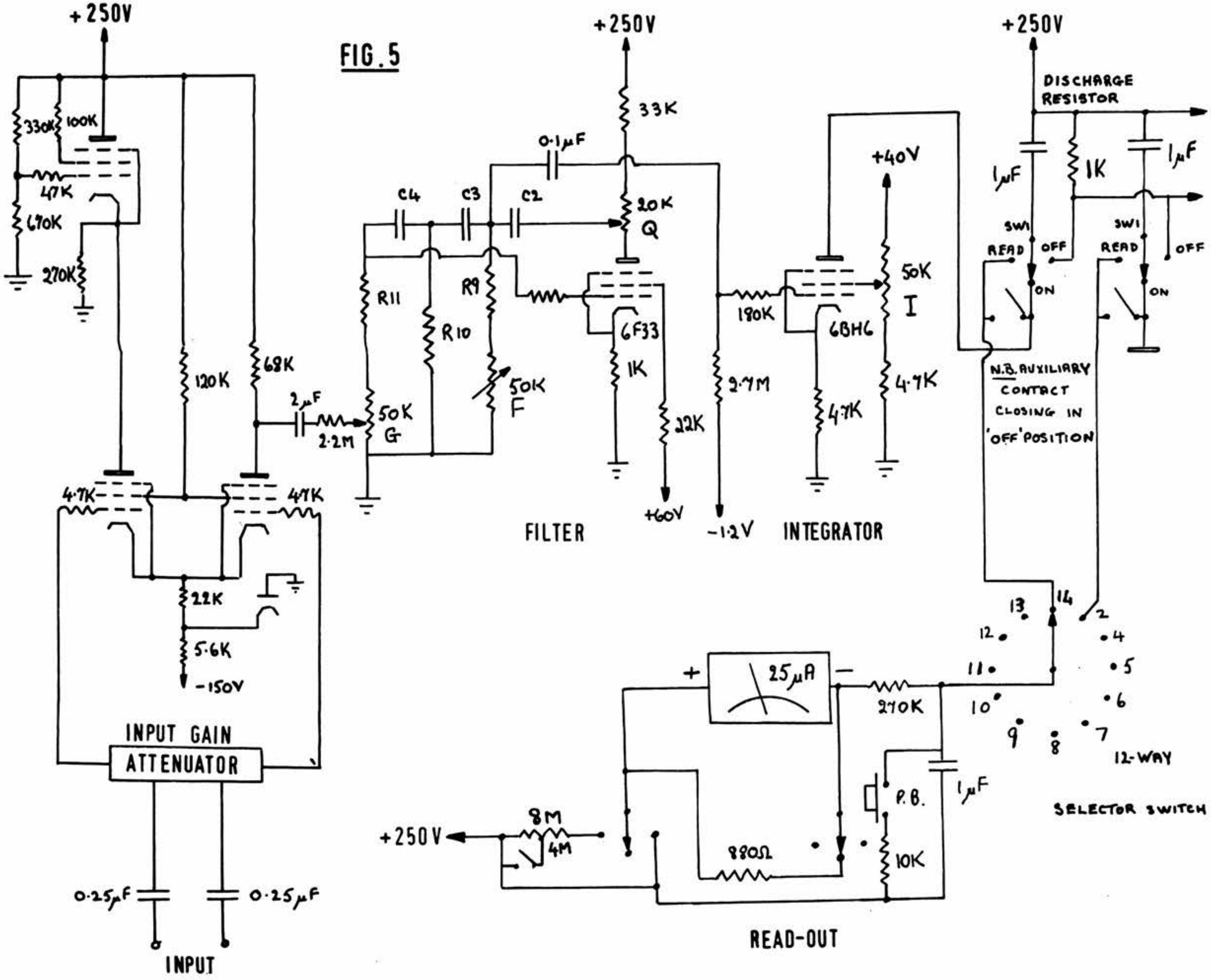
Another technique of harmonic analysis would involve recording the signal on film or tape and then passing the latter at various speeds through the input end of a filter of known resonant frequency and bandwidth. The frequency of the signals in the original record accepted by a filter used in this way depends on the ratio of the 'playback' velocity to the 'recording' velocity; so also does the effective bandwidth with respect to signals at the 'accepted' frequency. One therefore gets a measurement of the amplitude of the signal per log bandwidth, and an adjustment must be made if an estimate of amplitude per unit bandwidth is required. If one makes such an adjustment, as one ascends the frequency scale, contributions will be made to the 'accepted' signal by components in the original wave-form further and further removed from the required frequency. In spite of these drawbacks, this technique can give a high degree of 'resolution', i.e. a large number of measurements can be obtained and plotted as a curve of amplitude against frequency. This method of analysis was not, however, used in this investigation as it was considered to be rather laborious.

In the technique actually employed, the differential output from the final stage of amplification was passed through a compressor stage to make it single-ended. The output from this stage was then applied simultaneously to the inputs of a set of tuned frequency-selective circuits.

The circuits used were based on the filters described by Baldock and Grey Walter (1946) and are illustrated digrammatically in Fig.5. Each consisted essentially of a phase-shift oscillator which served as a resonator, and which selectively amplified those fractions of the input signal which matched the preset frequency of each oscillator. The frequency selected by each filter was determined by the values of C2, C3 and C4, and R9, R10 and R11. The constants of the circuits were chosen so that when there was no input signal the feedback was just too small to maintain oscillation. The frequency range of particular interest was the band including the 8-10 c/s components. The filters were therefore tuned to give peak responses at intervals of one cycle per second between 4 and 14 c/s inclusive.

A circuit tuned to give a maximum response at 2 c/s was also included to give a measure of the relative amplitude of the lower frequency components. The power supply used to operate the filter circuits was highly stabilised.

FIG. 5



+250V
330K
100K
47K
470K
270K
120K
68K
4·7K
47K
22K
5·6K
-150V
INPUT GAIN
ATTENUATOR
0·25μF
0·25μF
INPUT
2μF
2·2M
50K
G
C4
C3
C2
R11
R10
R9
50K
F
0·1μF
33K
20K
Q
6F33
1K
22K
+60V
FILTER
180K
9·7M
-1·2V
6BH6
4·7K
50K
I
4·7K
+40V
INTEGRATOR
DISCHARGE
RESISTOR
1μF
1K
1μF
SW1
READ
OFF
ON
N.B. AUXILIARY
CONTACT
CLOSING IN
'OFF' POSITION
25μA
270K
1μF
P.B.
10K
880Ω
8M
4M
READ-OUT
12-WAY
SELECTOR SWITCH

The output from each filter was fed to the integrator section. The output voltage from the tuned resonator was proportionally converted to current in the anode circuit of the integrator pentode (6BH6). This current was used to charge a storage capacitor. In practice the capacitors were connected to the anodes of the integrator pentodes for a period of ten seconds by moving the manually operated 12-way 3-position switch (SW-1) from the 'read' to the 'on' position. The interval was timed with a stop-watch. When the switch had been returned to the 'read' position the charge on each capacitor was read on the 0-25 microammeter, used as a voltmeter when either 8 Megohms or 4 Megohms was in series with it. After the reading had been taken the capacitor was discharged through the 10K resistor by operating the press-button. When allowance had been made for the standing current through the integrator valve, the individual voltages were proportional to the mean amplitude of movement of the part (in arbitrary units) at the relevant frequency during the period of observation.

Calibration was carried out at regular intervals using standard sine-wave inputs from an oscillator. With SW-1 in the 'off' position the auxiliary contact closed, passing the current from the integrator circuit selected by the 12-way switch through the meter. A linear relation obtained between input voltage and output current in the overall system, so that the microammeter, (with the series resistor suitably shunted), could be used to monitor the performance of the resonator circuits. Adjustment of the 'F' potentiometer was made so as to peak the integrator anode current at the relevant input frequency. Adjustment of the 'G' control set the gain of the individual resonator. The width of the resonance curve was set by the 'Q' potentiometer and was adjusted so that each filter gave 6db attenuation at 0.5 c/s from the required 'central' frequency.

In displaying the results graphically, the mean amplitude of displacement away from the 'target' position has been plotted against frequency on a log-log scale for the following reasons.

(1) The logarithmic ordinate scale effectively displays the amplitude relationship (in terms of ratios) observed under different conditions.

(2) The logarithmic frequency scale conveniently accentuates peaks observed at the upper end of the range studied. The usefulness of this feature will be evident in the reports of specific investigations given later.

(3) A logarithmic plot is useful in considering the amplitude/frequency characteristics in terms of electrical circuit analogy.

Section 6. Testing Procedure

It was necessary to define with some accuracy the timing of the events in each test run in order that effects due to fatigue, practice, etc., should be standardised. Timing of the various events was achieved by reference to two stop-watches.

At the commencement of each test run the pen oscillograph was switched on. The subject was required to bring the index finger into contact with the under-surface of the 50G load. He had previously been warned that after a five-second count-down the support holding the weight would be removed, and he would be required to bring the weight into the 'target' position by means of an extension effort of the index, (with the aid of the oscilloscope display of his performance). Ten seconds after the support was removed, the storage capacitors were switched into circuit for ten seconds. The supporting bar was then brought back into position. The pen oscillograph was switched off. A rest period was then allowed before the next test run. A three-minute interval separated the beginning of each test run from the commencement of the next.

On each alternate test run the subject was required to close his eyes in response to a verbal command 7-8 seconds after the support was removed, and to keep them closed until asked to open them at the end of the ten-second recording period. The experimenter observed the subject in order to ensure that this request was carried out.

Section 7. <u>Composition of Test Groups</u>

Details regarding the sources, and age and sex distributions of the groups of subjects studied, will be given later where appropriate.

Section 8. <u>Control of Ambient Temperature</u>

In view of the effects of limb temperature on physiological tremor that have been reported (Sutton, 1954; Marshall and Walsh, 1956; Lippold, Redfearn and Vuco, 1957), the temperature of the room in which the observations were made was thermostatically controlled at 65 degrees F.

PART 3. - APPENDIX

In this appendix, some of the characteristics of the transducer assembly used for the detection of the tremor movements will be discussed.

A description will be given of the methods used in assessing the magnitude of such errors of measurement as may have occurred.

A. Effects due to Temperature Sensitivity of the Strain Gauges

The resistance of a strain gauge is altered by a rise or fall in its temperature. Thermal effects were minimised in these experiments by the method of mounting. As they were attached in close proximity on the same steel strip, any alteration in conditions producing a change in the temperature of one gauge was likely to have a similar effect on the other. Alterations in resistance due to temperature changes therefore tended to cancel one another. As the gauges constituted the arms of a bridge, the production of spurious signals as a result of temperature changes was minimised.

Mounting the strain gauges on either side of a metal strip in the manner described minimised non-linearities that might have arisen as a result of twisting strains. For the most part, only movements occurring in a vertical direction were recorded and measured.

B. Effects due to the Elastic Resistance of the Metal Strip and Strain Gauges

The muscular forces acting on the index worked against (i) the weight of the finger, and (ii) the 50G weight applied to the dorsum. Another factor determining the loading of the part was the elasticity of the metal strip and the strain gauges. When bent away from their 'equilibrium' position in either direction, their resistance to further deflection increased. When upward movement occurred, the bent strip exerted a force in the same direction as that due to the weight of the load. When downward deflection occurred, the strip acted as a spring opposing the downward movement of the load. The extent to which the elastic resistance of the strip may have interfered with movement has therefore been assessed as follows.

A light, rigid extension of known weight was bolted to the metal strip instead of the usual 50G load. Its length was such that its centre of gravity acted downwards at the same distance from the end of the strip as did that of the weight when the latter was in position. Different weights were attached to the extension at its centre of gravity so that they deflected the strip in a downward direction. By means of a single pulley with negligible frictional resistance the weights could be arranged so as to produce an upward deflection. These arrangements are illustrated in Fig.2C. The signal arising from the strain gauges was amplified as described in Section 3 and displayed on an oscilloscope.

The bridge was balanced so that the output from the strain gauges with the strip in its equilibrium position was zero. It was observed that the signal increased in a linear manner with respect to increases in the magnitude of the weight attached to the extension. The signal arising when a given load produced an upward deflection of the strip via the pulley was equal to that occurring when it acted in a downward direction.

For any given applied weight, the strip took up a deflected position in which the elastic resistance of the metal strip and strain gauges equalled the force due to the effect of the weight. Thus measurement of the deflection of the strip, or of the equivalent vertical deviation of the spot on an oscilloscope (as indicated by the results shown in Fig.3), as a result of the action of a given weight, gave a measure of the elastic resistance of the strip and the attached strain gauges as a result of that amount of vertical deflection.

The range of vertical movement encountered during recording of physiological tremor was assessed by using the DC amplified signal from the transducer to drive an oscillograph pen as described in Section 5A. The deflections of this pen were calibrated in terms of the vertical movements of the test weight using a micrometer as described in Section 2 above. Thus the range of movement occurring during tremor recording could be determined.

As already noted, the muscular forces acting on the index worked against the weight of the finger and the 50G load, the other factor affecting the loading being the elastic resistance of the strip and strain gauges. The latter acted in such a way as to increase the loading during deflection upwards, and decrease it during movement downwards, away from the zero position. Since the range of movement occurring during tremor recording, and the elastic resistance of the strip resulting from that movement, had now been determined in the manner described above, the magnitude of the variation in the mechanical resistance of the flexible transducer assembly could be calculated.

It was estimated that the force due to the elastic resistance of the strip was never greater than 1.0G weight, over the range of movement encountered. Thus the loading of the part, (excluding the weight of the finger, which was, of course, constant), varied by 2.0%, as a result of the elasticity of the metal and the silicon filaments. Thus the tremor was detected and measured under virtually isotonic conditions.

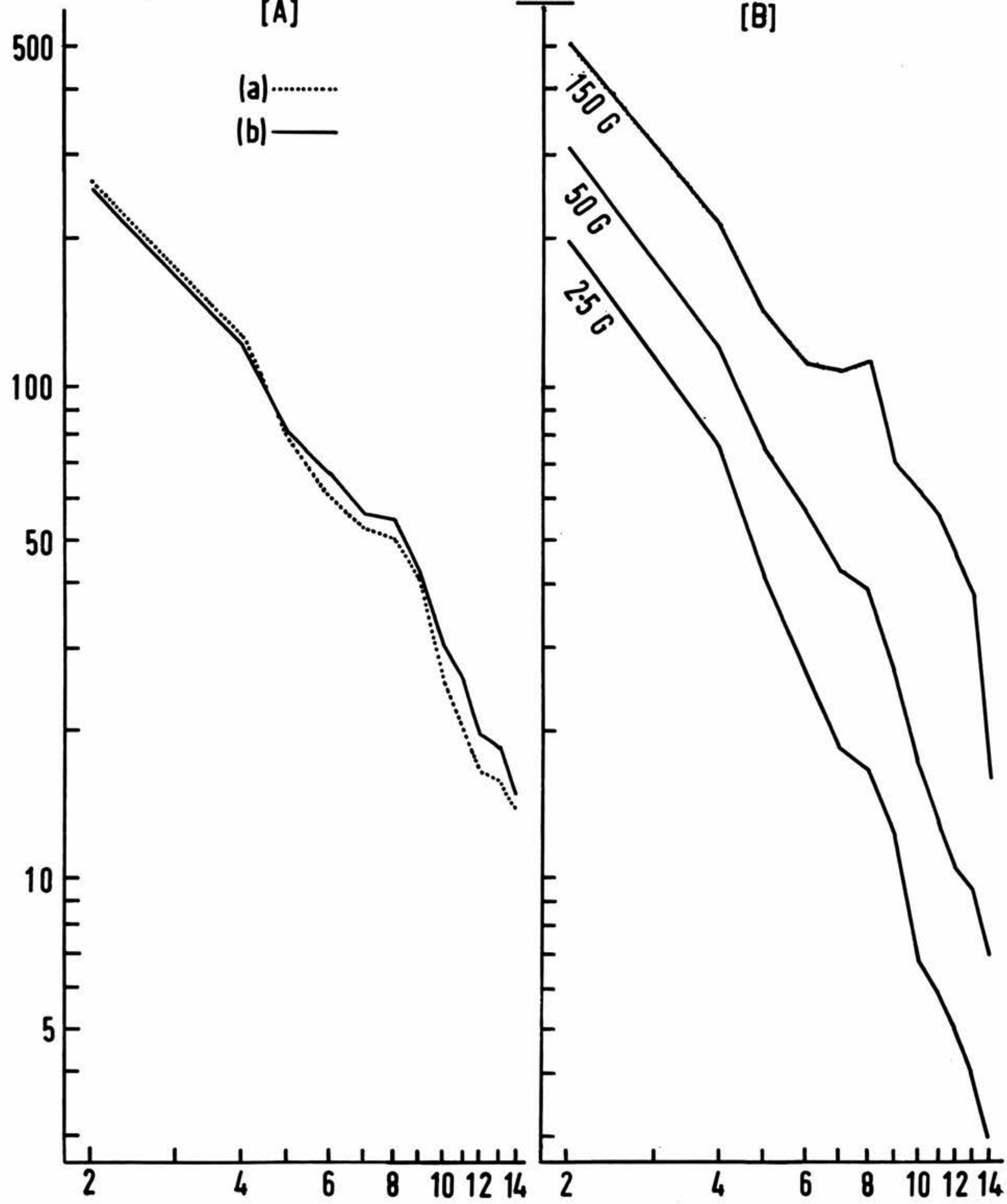
C. Natural Frequency of the Transducer Assembly

As noted above, the force due to the elastic properties of the strip with the strain gauges mounted on it was small in comparison with that due to the mass of the right-angled weight. Nevertheless, the resonant properties of the system must have played some part in modifying the amplitude of movement at any particular frequency. It was therefore necessary to make an assessment of the extent to which these resonant properties were significant.

The resonant frequency of the strip plus the attached strain gauges (without the weight attached) was estimated by deflecting the strip and strain gauges away from their resting position to give a signal voltage, and then observing on an oscilloscope the die-away oscillations that followed their release. As measured by this method, the natural frequency of these components was 62.5 c/s. This is well above the frequency range of importance in studies of physiological tremor. In the experiments to be described, and those of Halliday and Redfearn (1956), the amplitude of components above 14 c/s was relatively very small indeed.

It was considered to be undesirable that the natural frequency of the strip and strain gauges, with the 50G weight attached, should be assessed by producing a displacement and then allowing the system to oscillate freely. The resultant stresses might have caused irreversible damage to the strain gauge filaments. Therefore, instead of obtaining a measurement of the natural frequency of the system, the extent to which the resonant properties of the system may have been important in determining the relative amplitude of the various frequency components of the tremor has been assessed as follows.

FIG.6



Variation in the magnitude of the weight bolted to the end of the strip must have been effective in causing changes in the natural frequency of the movement-detecting system. Thus, if the resonant properties of the transducer assembly had significantly influenced the movement of the trembling part, variation in the weight attached to the end of the strip might have been expected to produce obvious changes in the composition of signal observed during tremor recording under standard conditions. The extent to which this effect might have been important was investigated in two ways.

(i) Index tremor was observed in the manner described in the main text of Part 3. However, the distribution of the load was reversed on alternate ten-second intervals. In a series of 18 observations on one subject, the 50G weight was bolted to the strip and made contact with the dorsum of the proximal phalanx of the index as described in Section 2. In a series of 18 readings made alternately with these, a 2.5G made contact with the dorsum, and a 50G weight was attached to the palmar surface of the proximal phalanx. Thus the load on the part remained virtually constant, while the mass attached to the end of the metal strip changed in magnitude by a factor of 100. A harmonic analysis of the signal from the transducer was carried out during 10-second periods of tremor observation. Since 18 pairs of readings were taken, the total time during which measurements were made under each condition of loading was 180 seconds.

The frequency spectra derived by averaging the two sets of observations are shown in Fig.6(A). The dotted line (a) shows the results obtained with the 50G weight attached below the finger and the 2.5G weight in contact with the dorsum; the full line (b) shows the average of the readings obtained with the 50G weight in contact with the dorsum of the phalanx.

No obvious differences can be seen between the two spectra. Both fall off in amplitude as the frequency increases, with similar negative slopes. A hump can be seen between 6 c/s and 10 c/s, with a small peak at 8 c/s.

(ii) Harmonic analysis of the tremor was carried out with three different loads, i.e. 2.5G, 50G, and 150G, bolted to the end of the strip and applied to the dorsum of the proximal phalanx of the index. Six ten-second intervals were averaged with each loading. The different loadings were studied in random order, so that errors that might have arisen from any changes in performance that may have occurred in the course of repeated testing would be avoided. The resultant frequency spectra have been plotted in Fig.6B. It is seen that the amplitude of the tremor at each frequency increased as the load increased. The harmonic composition of the movements occurring over the range of frequencies studied did not, however, show any obvious changes, even though the resonant frequency of the transducer system must have altered appreciably. A small peak in the spectrum became more prominent as the load increased, but its frequency did not alter. There appears to have been a relatively large amount of damping of the tremor components at the extreme high-frequency end of the range during studies with the 150G load.

From these results it would seem to be safe to discount the possibility that resonances produced by a combination of mass and compliance in the metal strip, strain gauges, and the attached weight, had significant effects on the frequency characteristics of the movements of the trembling part.

If the movements had been of an amplitude such that a considerably greater degree of bending of the metal strip had been produced, 'local' resonant effects might have become apparent. Thus this technique would probably not be suitable for the precise measurement of tremor of relatively larger magnitude than that encountered in these investigations.

D. Contact of the 50G Weight with the Trembling Part

Since the movements of the part were transmitted to the transducer through the contact made by the 50G weight resting on the dorsum of the proximal phalanx, the possibility that the weight might have been making intermittent contact with the dorsum was considered. This would have resulted in the weight failing to accurately follow the movements of the part.

A special attachment, illustrated in Fig.2D, was made. It consisted of the usual horizontal arm and 50G weight. In addition, rigidly attached to it, was a metal ring that accurately fitted the proximal phalanx of the index in two normal subjects. The ring was of the same thickness as the edge of the weight which usually made contact with the dorsum of the finger. This type of attachment ensured that the movement of the part was fully transmitted to the strain gauges.

The tremor measurements observed with the two types of attachment i.e. with the finger fitted through the ring, and while supporting the usual 50G weight on the dorsum, were compared with regard to amplitude and frequency content. No differences were observed in the two subjects studied.

Although only two subjects were studied in this respect, it was considered that serious inaccuracies were not arising as a result of the weight losing contact with the finger.

It would have been inconvenient to use the ring-type contact throughout these experiments. Firstly, fairly large numbers of subjects were studied, and a considerable number of loaded extensions with a selection of ring sizes would have been required to fit fingers with different diameters. Secondly, it was found that in fitting the digits through the rings and getting the assembly set up, untrained subjects tended to cause excessive wear and tear in the strain gauges.

E. Considerations Relating to the use of a 50G Load

These considerations can be enumerated as follows:-

(1) This degree of loading was sufficiently large to evoke a fairly clear 8-10 c/s 'hump' in the frequency spectrum of most subjects. Halliday and Redfearn (1956) showed that this feature was accentuated by loading of the trembling part, and this was also observed in the experiment described above in section 'C'. Some of the characteristics of tremor occurring in this frequency range have been investigated in the studies reported in the following pages.

(2) The load was sufficiently large to make the force due to the elastic resistance of the metal strip and strain gauges negligible (see section 'B' above).

(3) The load was not so large that the subjects found difficulty in supporting it, or experienced fatigue of the part during the testing procedure.

(4) The load was not so large that it was unwieldy. Too heavy a load would have resulted in excessive twisting strains in the transducer, and other complications.

PART FOUR

PHYSIOLOGICAL TREMOR: COMPARISON OF CHARACTERISTICS WITH AND WITHOUT VISUAL MONITORING OF POSITIONAL ERROR

Introduction

The experiments of Young (1933) were referred to in Part 1. He studied the tremor of the extended finger when movement was permitted at the metacarpo-phalangeal and wrist joints. A light-weight, rigid pointer was attached to the trembling part. The myographs obtained when normal subjects were required to hold the free end of the pointer, under visual control, opposite a small target, were compared with those produced when the subjects were asked to close their eyes while the record was being taken. From visual inspection of the records Young concluded that eye closure was associated with a drop in tremor amplitude. Furthermore, there appeared to be a reduction of one or more cycles per second in the frequency of the most obvious component.

Sutton and Sykes (1956) studied hand tremor. They used equipment that had originally been designed for work on manual tracking, (Sutton, 1955, 1957). The operator was required to press on a joystick, using his wrist muscles, with a fixed force of 2.3 Kg. A voltage proportional to this force was generated and used to deflect the spot on an oscilloscope facing the subject, whose task it was to hold the spot at the 2.3 Kg mark. The associated tremor was recorded on film and subjected to harmonic analysis. The most striking feature observed in the force spectrum was a marked reduction in the amplitude of the tremor at 8-9 c/s on eye closure.

In the experiment described below, certain characteristics of physiological tremor occurring with, and without, visual monitoring of a display of positional error, have been measured and compared in twenty normal subjects. The specific questions to which answers have been sought are:-

(1) Is eye closure, with consequent removal of visual information regarding performance, associated with changes in the characteristics of physiological tremor, detected and recorded under the conditions described in Part 3?

(2) If detectable changes do occur, in what proportion of normal subjects are they found?

(3) What range of variation in response to eye-closure is compatible with normal neuro-muscular function?

Methods

The equipment and testing procedure were as detailed in Part 3. The 'eyes open' and 'eyes closed' recording runs alternated, with an intervening rest period of three minutes. Thus physiological processes with a time-course relatively shorter than the duration of the experiment that might have affected the tremor characteristics (e.g. fatigue, practice effects, or fluctuation in emotional state), were likely to have been of similar average intensity under the two conditions.

Twenty normal subjects were studied, ten male and ten female. They were mainly drawn from the academic, technical, and secretarial staff of a research institute. At the time they were studied, none of the subjects had had previous practice in the test situation.

Results

The outputs of the filter circuits were integrated during the ten-second test runs. The numerical values thus obtained during the six runs with each subject monitoring the screen, and the similar series with eyes closed, were separately averaged. In this way, a measure, in arbitrary units, of the amplitude of twelve components of the tremor was obtained. These averages referred to a total analysis time of sixty seconds with, and a similar time without, visual monitoring of the error display by each subject.

Section 1. Characteristics of Tremor with Visual Monitoring of Positional Error

The averages of the measurements obtained from each subject are shown in Table 1.

The data obtained from the whole group was pooled to give the mean tremor amplitude per unit bandwidth at each frequency. The results are shown in the 'open-circle' amplitude/frequency plot in Fig.7. (N.B. In Figs.7-10, the open and closed circles show measurements obtained when the eyes were open and closed respectively.) Logarithmic axes have been used for the reasons already noted in Part 3, Section 5B.

The amplitude of movement is seen to diminish with increasing frequency, except between 6 and 11 c/s. In this region there is an upward deflection of the curve away from its downward trend at lower frequencies, with a maximum at 8 c/s. The average amplitude at 9 c/s is seen to be only slightly less than that at 8 c/s. The ordinate at 2 c/s is a little below the height that might be expected from the slope between 4 and 6 c/s.

Inspection of the data in Table 1 shows that the general shape of the curve is similar for all the subjects, with an upward deflection of the curve between 6 and 11 c/s. In eighteen of the subjects there are maxima at either 8 or 9 c/s, producing a clear peak in the spectrum. Subject No.8 shows a maximum at 6 c/s; subject No.16 shows no definite peak, but a maximum upward deviation from the downward trend with increasing frequency is seen at 8 c/s. For purposes of description, a curve will be said to show a peak between 6 and 11 c/s where:-

a) a definite maximum (in the strict sense of the term) is seen in the upward deviation of the curve in this range, or b) where no definite maximum exists, but a point of maximum upward deflection can be seen on inspection of the curve.

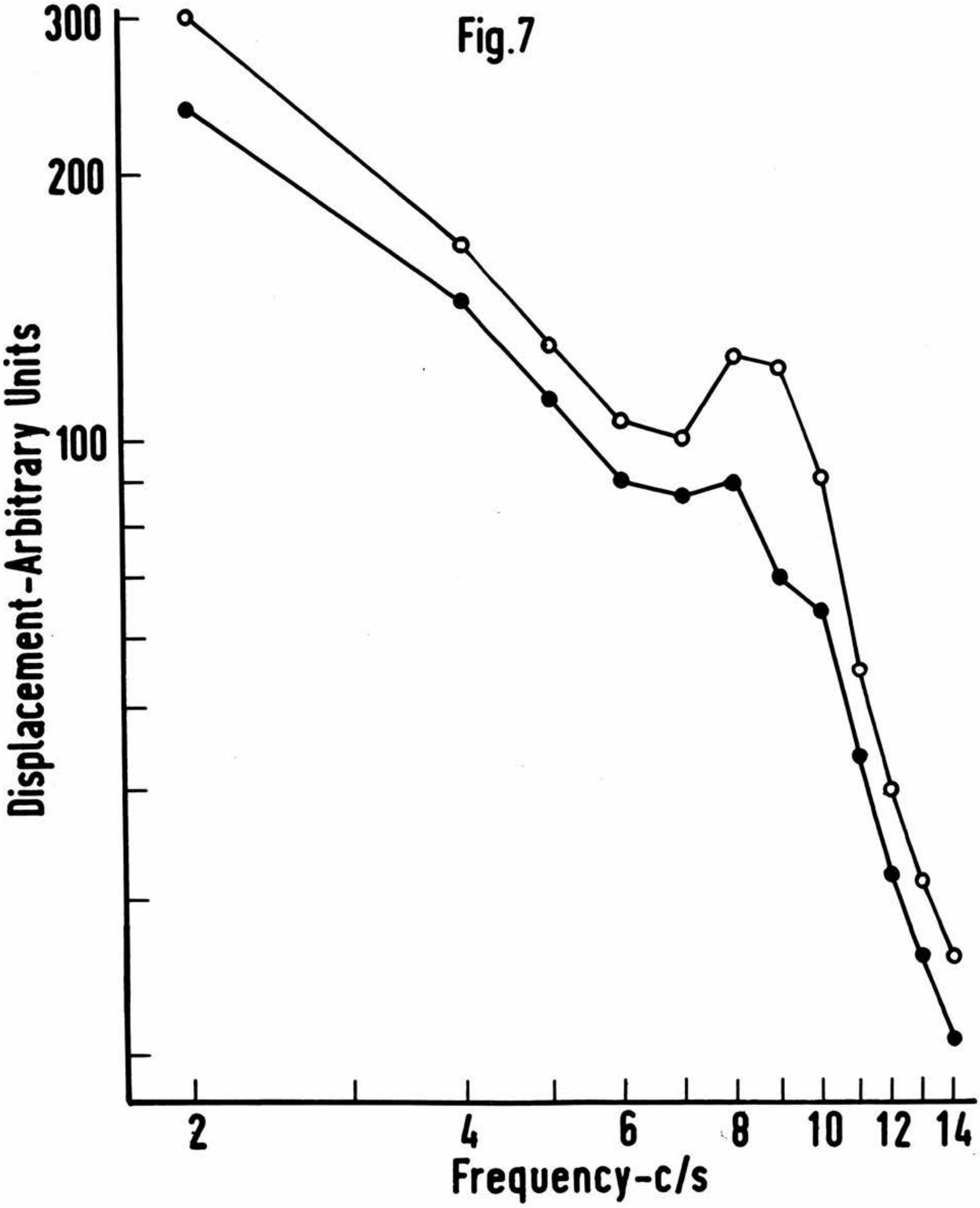


Fig.7
300
200
100
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s

TABLE I. Normal Subjects-Eyes Open

Each figure shows the mean amplitude per unit bandwidth during six ten-second periods of observation.

Subject No.	Frequency c/s											
	2	4	5	6	7	8	9	10	11	12	13	14
1	420.0	192.0	134.0	110.0	110.0	158.0	94.0	56.0	36.0	20.0	18.0	16.0
2	408.0	202.0	150.0	146.0	152.0	184.0	202.0	190.0	78.0	42.0	40.0	24.0
3	354.0	184.0	156.0	118.0	84.0	102.0	104.0	78.0	50.0	30.0	26.0	20.0
4	146.5	64.5	45.0	25.5	28.0	35.5	23.0	16.0	9.5	7.0	6.0	6.0
5	203.0	123.0	101.0	82.0	75.0	86.0	79.0	59.0	35.0	19.0	17.0	17.0
6	502.0	248.0	184.0	172.0	168.0	200.0	122.0	84.0	64.0	42.0	42.0	36.0
7	332.0	214.0	142.0	113.0	91.0	102.0	112.0	106.0	113.0	90.0	74.0	43.0
8	90.5	56.5	45.0	53.0	38.0	36.0	28.0	19.5	17.5	16.5	16.0	7.0
9	372.0	224.0	158.0	124.0	126.0	164.0	226.0	154.0	78.0	52.0	42.0	38.0
0	291.0	201.0	175.0	145.0	157.0	159.0	125.0	90.0	59.0	47.0	42.0	10.0
1	318.0	170.0	128.0	108.0	110.0	130.0	150.0	120.0	68.0	44.0	38.0	30.0
2	433.0	242.0	211.0	167.0	169.0	211.0	230.0	116.0	61.0	44.0	35.0	30.0
3	286.0	176.0	156.0	118.0	110.0	162.0	180.0	146.0	76.0	48.0	38.0	32.0
4	414.0	198.0	134.0	106.0	114.0	164.0	146.0	102.0	60.0	52.0	40.0	36.0
5	262.0	166.0	142.0	115.0	115.0	158.0	167.0	112.0	84.0	59.0	58.0	42.0
6	178.5	72.5	52.5	43.0	43.0	41.0	29.5	22.5	16.0	10.5	10.5	9.0
[illegible]	179.5	114.0	89.5	70.5	75.5	97.5	73.0	63.0	41.0	32.0	28.0	28.0
[illegible]	258.0	173.0	138.0	92.0	70.0	71.0	78.0	83.0	62.0	40.0	31.0	24.0
[illegible]	244.0	136.0	104.0	87.0	85.0	116.0	128.0	86.0	52.0	36.0	32.0	32.0
[illegible]	303.0	172.0	133.0	101.0	94.0	111.0	117.0	108.0	77.0	50.0	46.0	38.0

TABLE 2. Normal Subjects-Eyes Closed

Each figure shows the mean amplitude per unit bandwidth during six ten-second periods of observation.

ject .	Frequency c/s											
	2	4	5	6	7	8	9	10	11	12	13	14
	354.0	174.0	130.0	120.0	128.0	102.0	68.0	42.0	24.0	18.0	16.0	16.0
	226.0	96.0	90.0	108.0	100.0	114.0	80.0	86.0	48.0	28.0	24.0	20.0
	228.0	122.0	118.0	104.0	80.0	66.0	50.0	40.0	22.0	18.0	14.0	12.0
	134.0	69.0	51.0	39.5	26.5	26.5	21.5	15.5	11.0	7.0	7.0	7.0
	181.0	99.0	99.0	81.0	66.0	70.0	62.0	40.0	26.0	26.0	15.0	13.0
	354.0	220.0	178.0	132.0	120.0	110.0	92.0	74.0	46.0	38.0	34.0	26.0
	298.0	206.0	170.0	133.0	103.0	126.0	116.0	139.0	121.0	89.0	74.0	48.0
	81.0	46.0	45.0	56.5	36.5	31.5	24.0	21.0	14.5	12.5	11.0	9.5
	338.0	152.0	118.0	104.0	136.0	130.0	90.0	80.0	52.0	40.0	32.0	20.0
	217.0	137.0	120.0	128.0	101.0	100.0	80.0	56.0	43.0	32.0	27.0	8.0
	254.0	162.0	136.0	100.0	106.0	118.0	132.0	104.0	72.0	46.0	34.0	28.0
	258.0	108.0	78.0	76.0	68.0	70.0	64.0	34.0	25.0	19.0	17.0	15.0
	319.0	218.0	174.0	152.0	146.0	178.0	170.0	136.0	84.0	50.0	40.0	30.0
	336.0	92.0	62.0	56.0	40.0	50.0	46.0	34.0	20.0	16.0	16.0	14.0
	256.0	161.0	137.0	126.0	131.0	148.0	126.0	104.0	69.0	47.0	43.0	36.0
	177.0	72.0	57.0	49.0	38.0	28.5	23.0	18.0	12.5	9.0	6.5	6.5
	146.5	88.0	79.5	75.5	77.0	74.0	53.0	44.0	38.5	27.5	25.0	25.0
	174.0	122.0	97.0	71.0	52.0	43.0	45.0	54.0	38.0	27.0	22.0	20.0
	195.0	102.0	98.0	101.0	82.0	89.0	80.0	61.0	38.0	30.0	26.0	25.0
	235.0	120.0	129.0	97.0	101.0	107.0	91.0	88.0	74.0	50.0	40.0	29.0

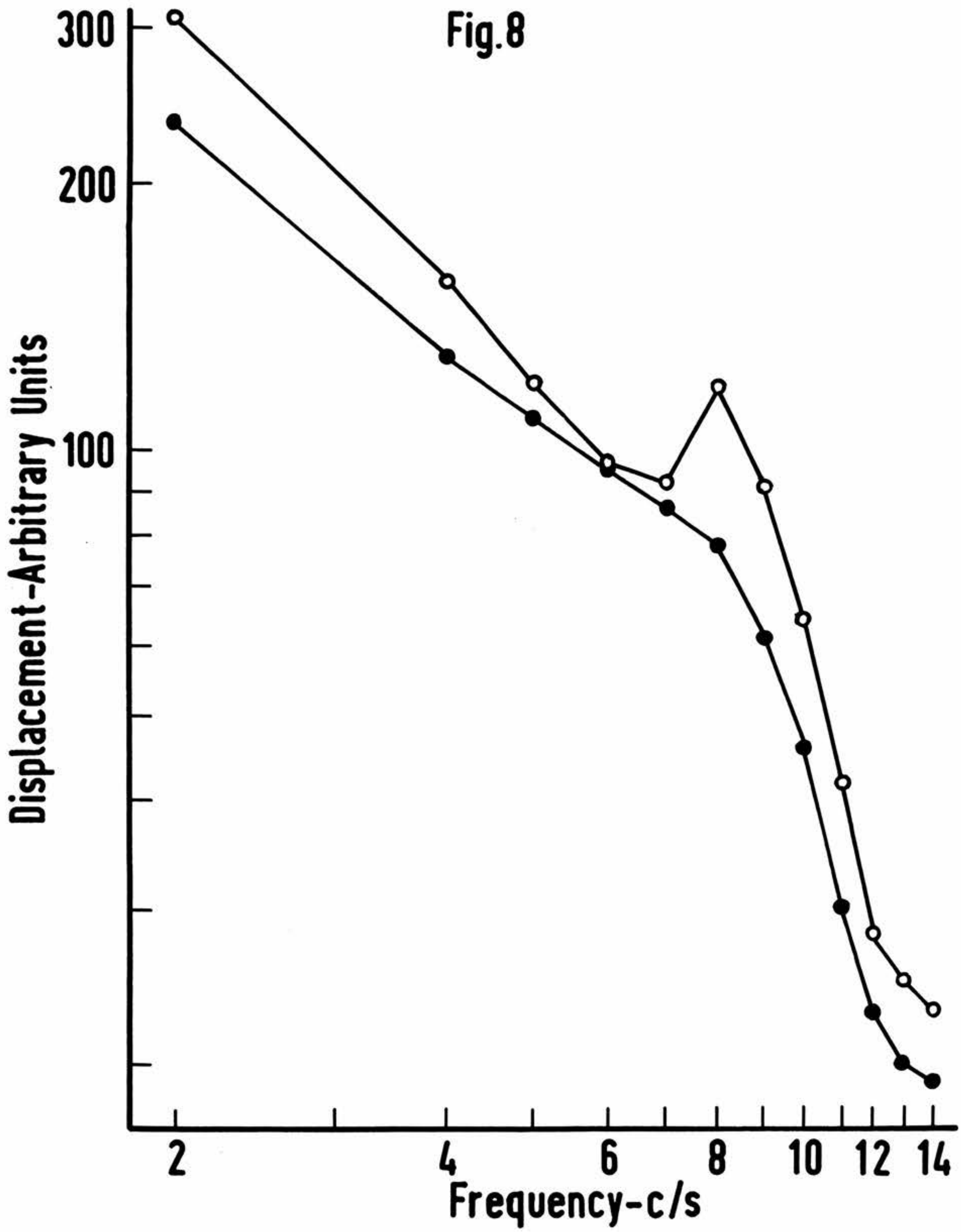


Fig.8
300
200
100
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s

Section 2. Effects of Eye Closure on Tremor Characteristics

A. General Features

The pooled data from the whole group following eye closure is shown by the 'closed-circle' amplitude/frequency plot in Fig. 7. The figures from which this curve is derived are given in detail in Table 2.

Comparison of the two curves in Fig.7 shows that eye-closure was associated with a marked reduction in tremor amplitude between 7 and 11 c/s. There is a smaller, and approximately ~~unfirom,~~ uniform, fall in amplitude at frequencies outside this range. (N.B. Equal ratios are represented by equal lengths on a logarithmic scale). In the 'eyes closed' curve, the 2 c/s amplitude measurement falls at the point produced by extrapolating the curve between 4 and 6 c/s to the lower frequency end of the scale.

Inspection of the data given in Tables 1 and 2 reveals effects of eye closure on the tremor characteristics that are obscured by pooling the measurements from the whole group. The detailed distribution of different types of response to eye closure will now be considered.

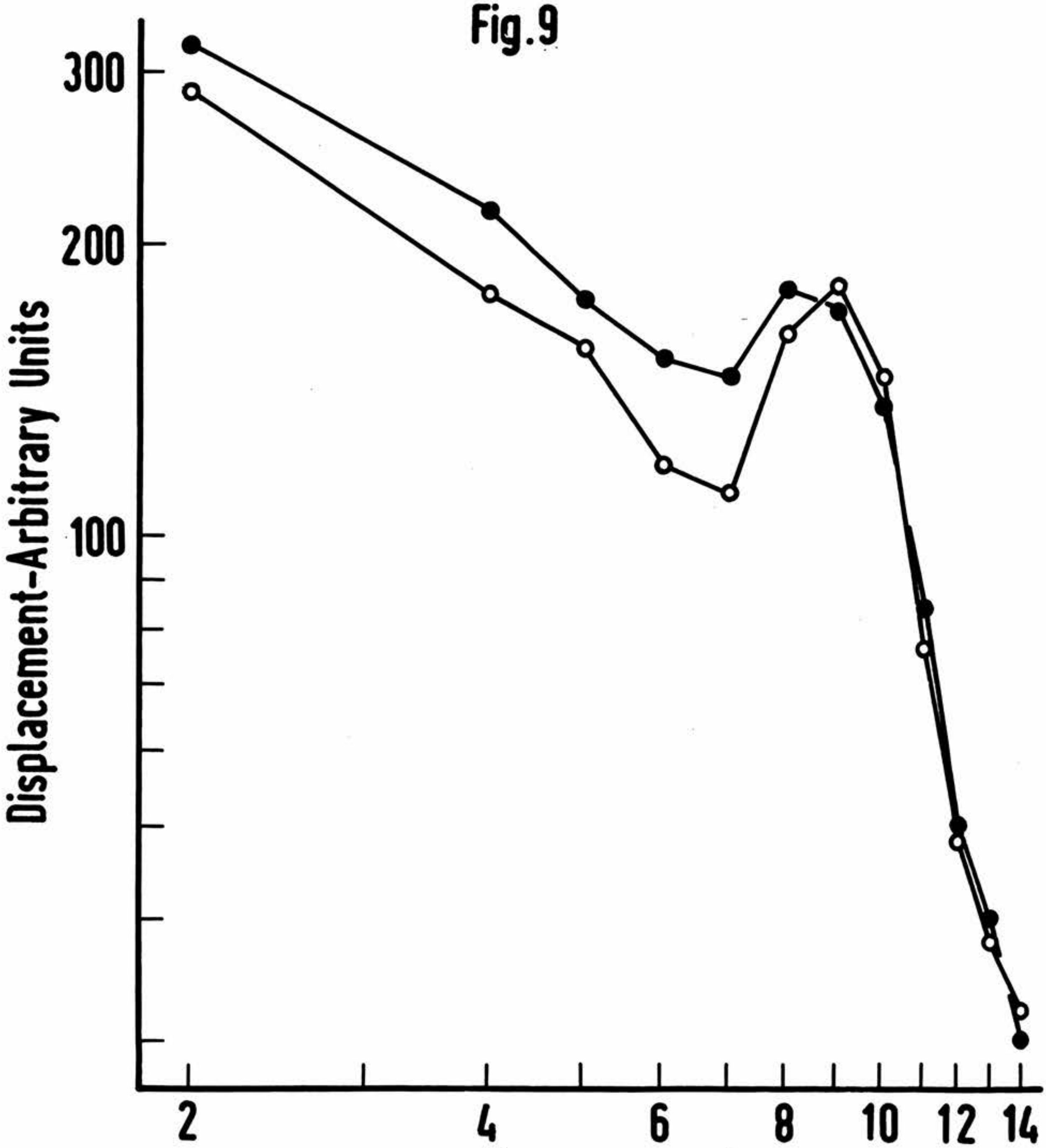
B. Changes in Amplitude at each Frequency

The data from six subjects (nos.1,3,4,6,10 and 19), showing reduction in the amplitude of the 8-10 c/s components after eye closure particularly markedly, has been pooled, and the resulting averages plotted in Fig.8.

In all the subjects an upward deviation of the curve away from the main downward trend is evident in the 6-11 c/s range after eye closure. In the data from two subjects, (Nos.3 and 6), peaks are obvious in the 'eyes open' spectra, but no definite points of maximum upward deviation of the 'eyes-closed' curves can be identified.

In the results from the remaining eighteen subjects a peak is

Fig.9



300
200
100
Displacement-Arbitrary Units
2
4
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12
14
Frequency-c/s

identifiable in the 'eyes-closed' spectrum between 6 and 9 c/s. In fourteen sets of data, (nos.1,2,4,5,9,11,12,13,14,15,16,17,19 and 20) this peak is relatively less prominent than in the 'eyes-open' curve. In two sets (nos.10 and 18), it is of similar size. In one (no.8) it is relatively slightly more prominent. Subject no.7 shows two peaks in each curve; they are of similar relative amplitude.

Seventeen of the subjects showed a reduction in tremor amplitude following eye closure at nine or more of the twelve frequencies studied. However, three subjects, (nos.4,7 and 13), differed from the others in manifesting an increased amplitude, when the eyes were closed, at six, eight and nine separate frequencies reppectively.

The data from the subject showing the most markedly anomalous response to eye closure (no.13) has been plotted in Fig.9. Although the activity was of greater amplitude at most frequencies when the eyes were closed, the peak at 8-10 c/s in the 'eyes closed' spectrum is seen to be relatively smaller, as in the majority of the group. A similar pattern was observed when this subject was studied again under identical conditions six weeks after the first test.

The data relating to the effect of eye closure on the amplitude at each frequency has been summarised in the first column of the 'control' series in Table 5, (see Part 5).

C. Changes in Frequency Distribution of Activity

As already noted above, eighteen subjects show a peak in the spectrum, usually of relatively small magnitude, between 6 and 9 c/s, in the 'eyes-closed' curves. The data in Tables 1 and 2 shows that in twelve subjects the peak maximum is at a lower frequency in the 'eyes-closed' series. In ten of these subjects (nos.1,2,7,12,13,15,16,17,19 and 20) the component of largest amplitude in the upward deflection of the curve is located 1 c/s below the

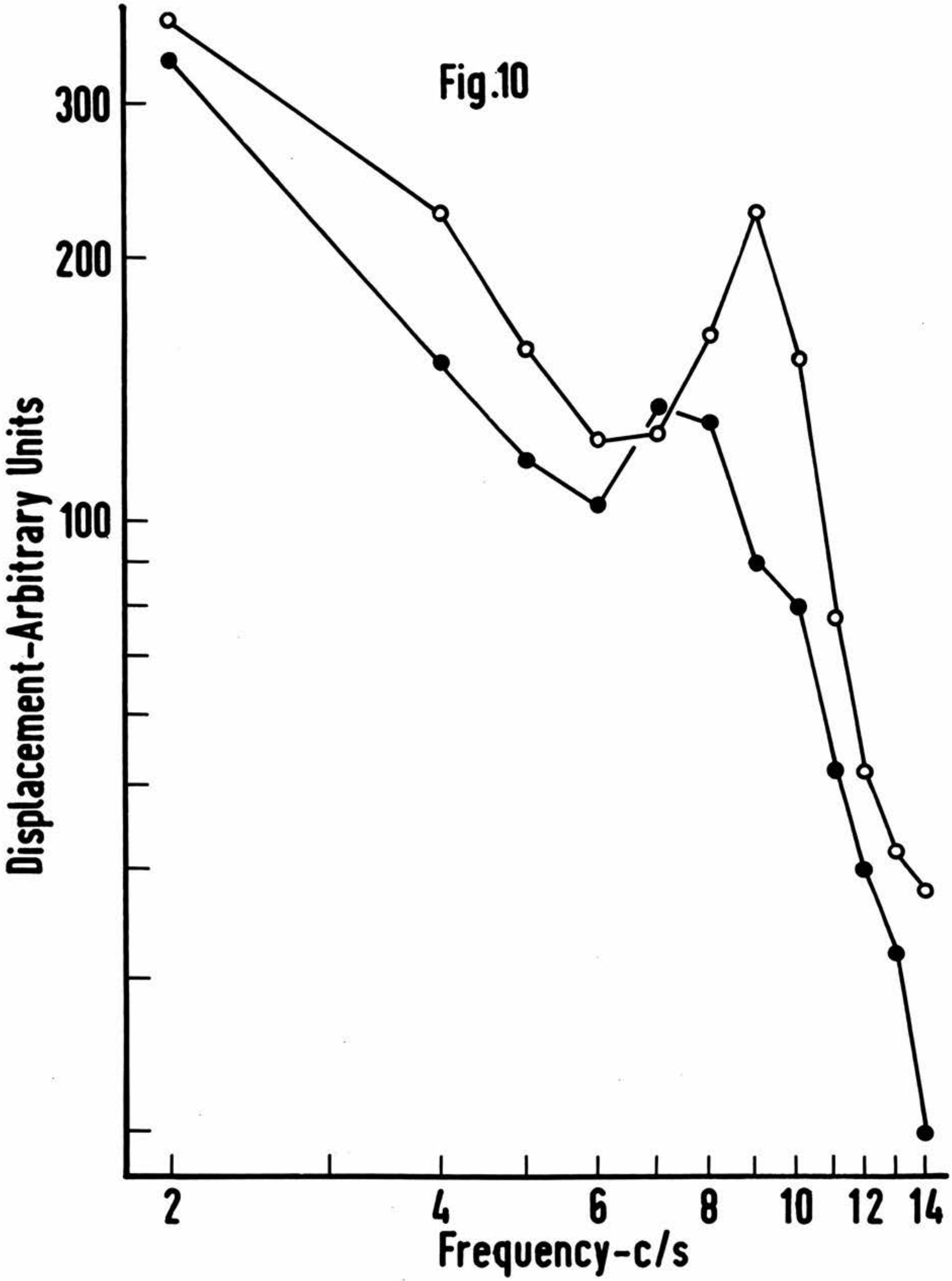
Fig.10
300
200
100
Displacement-Arbitrary Units
2
4
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8
10
12
14
Frequency-c/s

frequency at which it occurred with the eyes open. In the results from two subjects (nos. 9 and 10), a drop of 2 c/s is seen. In the remaining six subjects showing a peak following eye closure (nos.4,5,8,11,14 and 18), no drop in its frequency is evident. Changes in frequency distribution may have occurred in the other two subjects, but definite statements can only be made where a peak was evident in both curves.

The frequency of the peak did not increase with eye closure in any of the subjects.

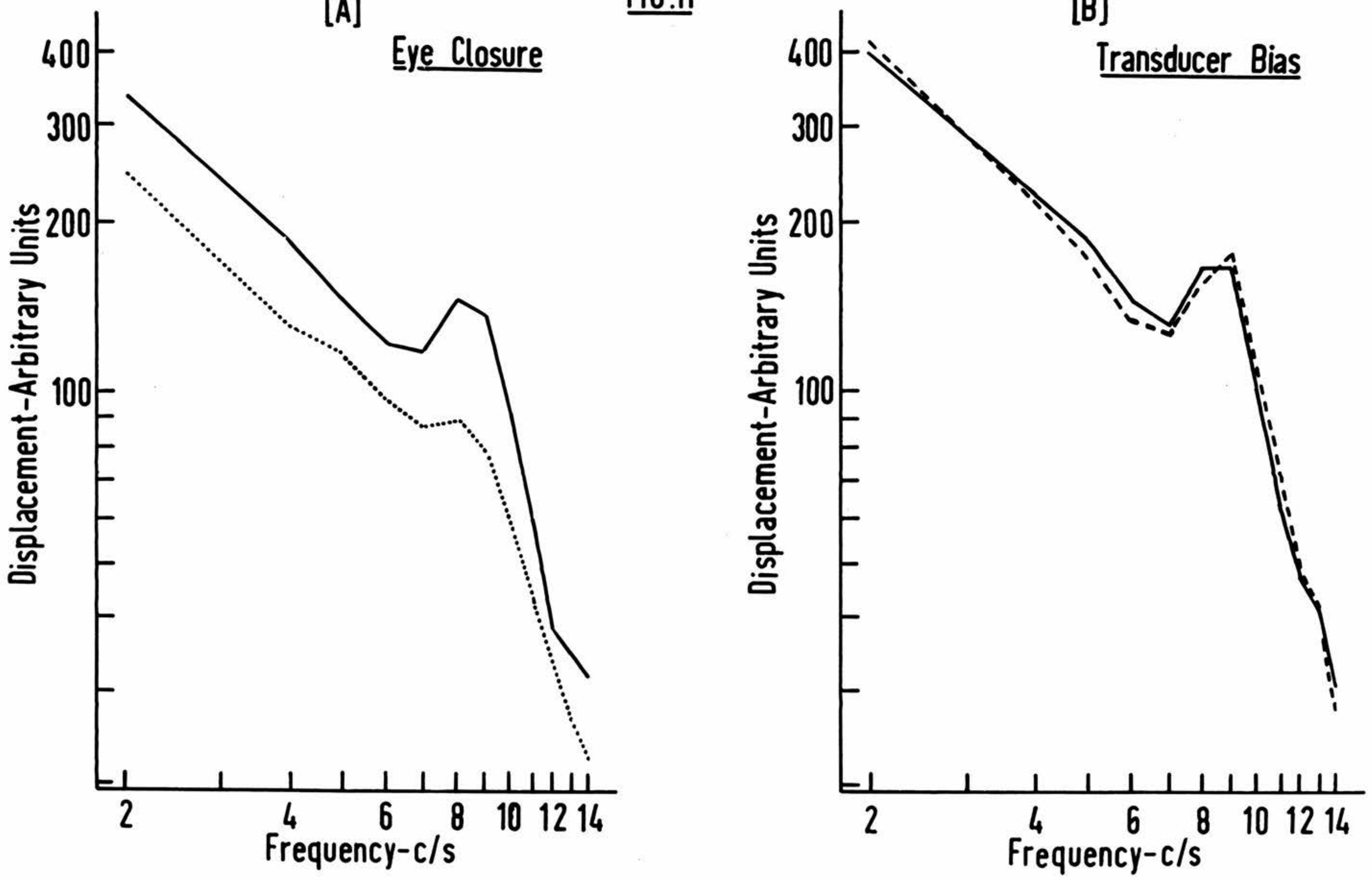
The results from subject no.18 are shown in Fig.10. The large amplitude upward deviation of the curve with a maximum at 9 c/s associated with visual monitoring of the error display is replaced by one of smaller amplitude, with a peak at 7 c/s in the 'eyes-closed' spectrum. The shift of the peak towards the lower end of the spectrum with eye closure results in the curves overlapping at 7 c/s. This alteration in the frequency distribution of the tremor activity in each subject also accounts for the approximation of the curves between 5 and 7 c/s in Fig.8.

The data relating to changes in frequency distribution is summarised in the second and third columns of the 'Control' section of Table 5, (see Part 5).

Section 3. Assessment of Effects due to Deflection of the Transducer Assembly with the Eyes Closed.

When the subjects monitored the position of the finger by means of the display on the oscilloscope screen, the tremor movements were centred on the target spot. When the eyes were closed, however, the mean position of the part tended to drift either up or down away from the required level. This meant that the tremor was detected with the transducer assembly, consisting of the metal strip and strain gauges, deflected away from its 'equilibrium position', i.e. the position it occupied with no weight attached. Errors that might have arisen from any resultant changes in the mechanical characteristics of the assembly were therefore assessed as follows.

FIG.11


[A]
Eye Closure
400
300
200
100
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s
[B]
Transducer Bias
400
300
200
100
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s

The myographs, recorded with the direct-coupled amplifier, obtained simultaneously with the performance of the frequency analysis when the eyes were closed, were studied in five subjects, (nos.5,8,9,19 and 20). The deflection of the trace away from the target position was measured at one-second intervals on the stretch of myograph record obtained during the harmonic analysis. In each of these five subjects the part drifted either upwards or downwards following eye closure, and did not move first in one direction and then in the other during the period studied. The sixty measurements obtained from the myographs of each subject were averaged. The magnitude and direction of the oscilloscope spot deflection equivalent to this amount of pen movement was calculated from suitable calibration figures.

These subjects were then studied again under identical conditions to those observed on the first occasion of testing. The subjects did not shut their eyes, however. Prior to each alternate test run the spot on the oscilloscope was deflected away from the level representing the equilibrium position by an amount equivalent to the average, for that subject, of the pen deflections measured at one second intervals on the records obtained during the test runs with the eyes closed. Thus, on each alternate test run, when the subjects brought the spot on to the target position under visual control, they were in fact bending the transducer assembly by an amount equivalent to the average deflection that occurred during the period of frequency analysis when the eyes were closed during the first test.

In Fig.11 changes in the characteristics of the tremor seen in these five subjects in association with the withdrawal of visual information regarding performance (A), are compared with those observed when the transducer was 'biased' in the manner described above (B). The tremor observed when the eyes were closed (A, dotted line), was of considerably smaller amplitude at each frequency than that which was observed during visual monitoring (A, full line), and the movement in the 8-10 c/s was markedly reduced. The calculated bending of the transducer had, however, no clear-cut effect either on amplitude at each frequency or on the relative prominence of the 8-10 c/s components, (transducer normal-11B, full line: transducer biased-11B, dashed line).

During the testing of some subjects an immediate reduction in tremor amplitude with eye closure was evident in the oscilloscope display before obvious 'drift' had occurred.

Discussion

Comparison with Results of Previous Studies.

In previous investigations of the effect of eye closure on the characteristics of physiological tremor, small numbers of subjects have been studied. Young (1933), and Sutton and Sykes (1956), investigated five and four subjects respectively. In this experiment, twenty individuals have been investigated so as to obtain information regarding the normal range of variation of response.

In Young's experiments, the mechanical conditions under which the tremor was observed were not very clearly defined; the extent to which the recording system interfered with the movements, or may have contributed a resonant frequency, was not considered in detail. Furthermore, the records were assessed by visual inspection.

In the present experiments, tremor has been examined under virtually isotonic conditions, with a loading of 50G on the moving part. In the investigation of Sutton and Sykes, the situation was rather different. The tremor was recorded under isometric conditions, and the voluntary muscular effort involved was forty-six times greater than in this experiment. They carried out a frequency analysis of the forces exerted during the task, and presented their data in the form of power spectra. Their curves, (which show a greater negative slope with increasing frequency), can be compared with the displacement spectra calculated from the results of this investigation.

In the results of the present experiment, eye closure was found to be associated, in the majority of subjects, with a marked reduction in the peak usually seen in the spectrum between 6 and 11 c/s; a smaller reduction in amplitude outside this range was clearly evident in most of the subjects studied. One 'anomalous' subject showed an increase in amplitude at nine of the twelve frequencies studied. Attenuation of activity between 7 and 11 c/s was evident in all the subjects studied by Sutton and Sykes; it was especially obvious where the tremor peak was large in the 'eyes open' curve. In two of their subjects there was also a clear reduction in amplitude at frequencies outside this range. In none of the four subjects was there a generalised increase in amplitude at frequencies above 2 c/s on eye closure.

In the present investigation, one consistent feature occurring with eye closure was an increase in the relative amplitude of tremor at frequencies immediately below that at which the peak occurred in the 'eyes-open' curve; where a clear peak persisted with the eyes closed, it was usually at a lower frequency than that observed when the subject concerned monitored the oscilloscope display of positional error. Inspection of the data of Sutton and Sykes shows that a peak was evident following eye closure in only one of their subjects; it was located at a frequency 2 c/s below that at which a maximum was evident in the 'eyes-open' curve. Young reported a decrease in the frequency of the most obvious tremor component with eye closure.

Thus it may be stated that the occurrence of certain changes in tremor characteristics with eye closure reported by other investigators have been found under the experimental conditions detailed in Part 3. The frequency with which these changes occurred in a series of twenty normal subjects has been defined. The occurrence of some anomalous results suggests that a considerable variation in the pattern of response is compatible with normal neuro-muscular functioning.

Temporal Stability of Effects of Eye Closure.

All the data reported in detail was obtained from subjects who were unpractised in the test situation. It has already been noted that the subject showing the anomalous response to eye closure gave similar results on retesting after six weeks. Several other subjects showed persistence of their original pattern of response after various test-retest intervals.

However, the possibility that changes may occur in the pattern of response with serial testing over a prolonged period is not ruled out by these results.

Possibility that Reduction in Tremor Amplitude was due to the Physiological Effect of having the Eyes Closed rather than to Removal of the Visual Stimulus.

Sutton and Sykes studied this possibility in two subjects. They found that if the subject kept his eyes open, but the oscilloscope spot was extinguished, the reduction in tremor was still observed. Thus the effect on the tremor characteristics appeared to be related to removal of visual information rather than the process of eye closure.

This matter has not been systematically reinvestigated in the present series of studies.

Characteristics of Tremor with Visual Monitoring of Error Display.

The general shape of the curve is found to be the same for all the subjects, with amplitude falling off in a regular manner with increasing frequency. A possible explanation of this finding has been discussed by

Halliday and Redfearn (1956). They compared the plot of the observed data with a theoretical curve calculated on the assumption that there was a random input of force over the range of frequencies studied. There was a close relationship between the two curves, though the curve derived by experiment departed from the calculated one between 5 and 15 c/s, with a maximum deviation at 8 or 9 c/s. They therefore suggested that in their experiments the trembling part was behaving as would an inertial system on which forces were acting in a random manner. The peak at 8-9 c/s was, they suggested, due either to resonances, or to an input of force superimposed on the random element, at those frequencies.

The visual reaction time is usually said to be about 0.25 - 0.50 seconds, (Walsh, 1957), so that at and below 2-4 c/s it can be expected that movements carried out under direct visual control will be encountered. It was noted that in several plots of the data from groups and single subjects there was a slight reduction in the amplitude at 2 c/s with the eyes open as compared with that which would have been predicted by extrapolating the curve between 4 and 6 c/s to the lower frequency end of the spectrum. This feature was not usually seen in the data obtained when the eyes were closed. This effect may have arisen because some of the activity at 2 c/s may have been composed of corrective movements carried out under direct visual control when the eyes were open.

Mechanisms which may Underlie the Changes in Tremor Characteristics on Eye Closure.

In view of the delays involved in the pathway from the retina to the peripheral musculature, it would seem to be unlikely that alterations in the characteristics of tremor on eye closure, especially in the 8-10 c/s range, would arise as a result of changes in a feedback system involving the external error detecting system, the visual pathway, the descending pathways, and the neuromuscular effector mechanisms. It would seem more probable that the changes in tremor characteristics might originate in an alteration in conditions at the spinal level of motor organisation.

The nature of the mechanisms that might be associated with these effects at the spinal level of motor organization must be a matter of conjecture. However, they may be in some way linked to the brain-stem and diencephalic 'arousal' systems. Subjects 'aroused' by being subjected to stress situations often show an increase in tremor amplitude (see 'Introduction' to Part 5). Furthermore, it was noted, in the course of developing the procedure for these experiments, that extraneous, unexpected stimuli e.g. sudden loud noises, were usually associated with a transient augmentation of tremor amplitude, and sometimes, with a brief increase in the prominence of the 8-9 c/s peak. During the course of the main investigation the subjects were interrogated about their subjective sensations, and several said that they felt more 'relaxed' during the test runs when their eyes were closed.

While the mechanisms determining the relative amplitude of the peak at 8-9 c/s may be linked to, or identical with, those regulating the amplitude of the random component, they may be in some degree independent. Evidence consistent with the latter possibility is provided by, (a) the marked supression of the tremor peak in some subjects, without a comparable drop in the vertical position of the spectrum, on closing the eyes, and (b) the increase in the amplitude of the 'random' component, with a decrease in the relative prominence of the peak (and an absolute reduction in two of its component frequencies), in the single subject showing a highly anomalous response.

Eye closure was associated with a reduction in tremor amplitude at most of the twelve frequencies studied in the majority of subjects. While considerable interest has centred on the activity at 7 to 11 c/s, the nature of the mechanism responsible for the 'random component' present in the whole frequency range studied in the present experiment remains obscure. The possibility that its amplitude may be related to the degree of synchronization of motor unit activity, and the level of the excitatory state in the motoneurone pool, was discussed at length in Part 2, Section 1A.

A considerable reduction in the prominence of the tremor components at 7-11 c/s was related to eye closure in the majority of subjects. In Part 2, Section 1B, the evidence regarding the theory that the peak often seen in the tremor spectrum might be due to a small amount of oscillation in the stretch reflex system was discussed. The way in which such a mechanism might operate in determining the amplitude and frequency of the peak will now be considered.

In terms of this theory, the amplitude of oscillation at the frequency where the phase shift in the loop is 180 degrees is determined by the overall gain of the system. This is related to (a) the size of the error signal evoked by a given displacement or velocity input, which is in turn determined by the spindle sensitivity, and (b) the loop gain, dependent on the intensity of the central excitatory state. For a given overall gain, the output of energy in the frequency range where oscillation is likely to occur will be proportional to the amplitude of the input. Thus in a logarithmic plot, the relative size of the peak should remain unchanged while the curve of the tremor spectrum varies its vertical position. A reduction in the relative amplitude of the peak would reflect a drop in system gain, and vice versa.

The frequency at which oscillation is likely to occur will be determined by a number of factors.

The signal may be sent through pathways with different numbers of synapses in the spinal cord, causing variation in the central delay. However, the greater part of the loop delay is probably peripheral.

The rate of conduction in the nerve fibres of the neural arc is an important factor affecting the duration of this delay. However, there is no evidence that rapid changes in nerve conduction velocity can occur under normal physiological conditions.

Another factor determining both the amplitude and frequency at which oscillation will occur in the stretch reflex system is the muscle contraction time. This is dependent on the physical properties of the muscle. As already noted in Part 2, several workers have observed that cooling of a part causes profound changes in the amplitude and frequency of the manifest tremor. It would seem unlikely that a change in the physical properties of the muscle occurred between the moment of eye closure and the commencement of frequency analysis in this series of experiments.

If it is assumed that the delays in the feedback pathways are constant, the frequency at which oscillation is likely to occur will be determined by the point in time in each cycle of events at which the spindle discharge reaches a level at which it results in a detectable positive feedback response. For a given amplitude of oscillation, the point at which this level is reached will be dependent on both the spindle sensitivity, and the intensity of the central excitatory state. Thus an increase in either of these parameters would be expected to result in an increase in the frequency of oscillation, and vice versa. On the other hand, if the gain were to remain constant while the amplitude of the random input to the system increased, the displacement, and the velocity, attained at a given point in a cycle of events at a given frequency would be relatively larger. Thus a spindle discharge evoking a positive feedback response would occur earlier in the cycle, and reinforcement of reflex muscular responses would occur at a higher frequency. Thus ~~when~~ if a generalised increase in tremor amplitude ~~occurs~~ occurred, the frequency of the peak might also be expected to rise, provided that its relative amplitude ~~remains~~ remained constant. Conversely, a drop in the amplitude of the random component might be expected to be associated with a reduction in the frequency of the peak.

In this experiment, eye closure was consistently associated with a reduction in the relative prominence of the peak at 8-9 c/s and where it persisted in attenuated form, with a lowering of its frequency. In terms of the above argument, this would be consistant with a reduction in gain in the stretch reflex system, due either to a drop in spindle sensitivity, or a diminution in the intensity of the central excitatory state. The reduction in amplitude at each frequency which also usually occurs with eye closure would not be expected to produce a reduction in the relative amplitude of the peak, though it might contribute, in part, to its drop in frequency. In the one subject showing a considerable increase in tremor amplitude outside the 8-10 c/s range with eye closure, the peak was suppressed in the usual manner; the associated tendency for the frequency to drop may have been compensated by the increased input of energy at each frequency, including the 8-10 c/s range.

It is very difficult to make measurements of stretch reflex excitability in the intact human subject. Cooper, Halliday and Redfearn (1957), developed a precise method for measuring tendon jerk responses. However, as has been pointed out by Hammond, Merton and Sutton (1956), the brief synchronous volley of the tendon tap probably produces an accidental overload condition of the reflex mechanism, and is not a truly physiological response. Techniques based on Merton's (1951) method for measurement of the silent period of the spindles during an evoked twitch have been used in investigating Parkinsonian tremor, (Hofmann, 1962). Hammond (1956), found that the mechanical response of the elbow flexors to sudden stretch at constant velocity could be modified by prior instruction to the subject to 'let go' or 'resist' when pulled. The modified responses involved shorter latencies than the reaction time to a sensory stimulus. Hammond concluded that a stretch reflex mechanism was at work which could be preset by nervous activity from the brain.

It must be emphasised that the whole preceding discussion of the tremor mechanisms that may be involved in the observed effects of eye closure is to a considerable extent rather speculative. Interpretations of the observed data can be developed in terms of some of the other theoretical possibilities discussed in Part 2. Some workers, e.g. the American protagonists of the 'ballistocardiographic' theory of physiological tremor, would regard the above discussion as being entirely misguided.

Problems for Further Study.

The present investigation was concerned with exploring the nature of the changes in tremor characteristics that might be associated with eye closure. Certain general patterns of response have been observed, though considerable variation is apparently compatible with normal neuromuscular functioning.

In following up the results that have been obtained, one could carry out experiments designed to give a more detailed quantitative description of the response patterns. One could determine, for example, whether the mean amplitude of movement at each frequency with the eyes closed differs significantly from that observed during visual monitoring of the error display. The inter-subject variability observed in this study was, however, considerable, and data suitable for statistical analysis would be more satisfactorily obtained by carrying out long series of pairs 'eyes open' and 'eyes closed' tests on individual subjects showing typical responses. This point can be illustrated by considering the amplitude of tremor observed at 8 c/s. An analysis of variance carried out using the figures in the relevant columns in Tables 1 and 2 shows that for the group of subjects as a whole, the amplitude of tremor at 8 c/s dropped significantly on eye closure, the value for p being less than 0.05 but greater than 0.01. When, however, twenty trials were carried out using one subject (No.3), a similar calculation using the measurements of tremor amplitude at 8 c/s showed a very highly significant drop on eye closure, the value of p being much less than 0.001.

In view of the marked effect of eye closure on tremor amplitude at all the frequencies studied - not only the 8-10 c/s range - investigations might be undertaken which would be directed towards clearing up the obscurity surrounding the mechanisms underlying the activity that constitutes the greater part of the tremor at each frequency. The theory that tremor amplitude may be related to the prevailing degree of synchronization of motoneurone discharge was discussed in Part 2. Thus, as a starting point, one might set up the hypothesis that measurements of tremor amplitude would correlate with quantitative assessments of motor unit synchronization. The latter could be carried out, for example, using the coincidence counting technique developed by Buchthal and Madsen (1950).

If stretch reflex oscillation does contribute to the peak in the spectrum at 6-11 c/s, factors which might be expected to affect its relative prominence might include (a) the delay in the reflex arc, (b) the threshold and sensitivity of the muscle spindles, and (c) the twitch time of the muscles involved. Factor (a) is probably fairly constant in a given subject under controlled conditions, but may vary slightly. Factor (b) - muscle spindle sensitivity - is very difficult to measure in the intact human subject; the techniques used by Hammond (1956) and Hofmann (1962) have been mentioned above. Factor (c) - the twitch time - also presents problems in regard to measurement; it might be possible to measure it with moderate accuracy, using, for example, the capacitance manometer method developed by Buller, Dornhorst, Edwards, Kerr and Whelan (1959). However, it is clear that attempts to correlate changes in the characteristics of individual functional components of the stretch reflex with variations in the features of physiological tremor are likely to encounter many difficulties.

The American work on the 'ballistocardiographic' theory of the causation of physiological tremor should be repeated and expanded under satisfactory experimental conditions.

While all the observations in this investigation were carried out using a fixed error display gain, the apparatus gives sufficient DC stability to allow a considerable increase in the amplitude of the oscilloscope deflection for a given positional error. It would be of some interest to study the effect of increasing the feedback gain; this would indicate whether the changes associated with the removal of the visual display is purely an 'on-off' effect, or whether there is a graded response to changes in the amplification of the 'external' error detecting system.

It was observed that when some subjects closed their eyes, the DC myograph record consistently showed a steady drift away from the target position. Others, equally consistently, made corrective movements which resulted in their staying close to the required position. Although none of the subjects could subsequently give an account of the way in which they had performed during the time that they had their eyes closed, some of them appeared to have a more definite 'proprioceptive memory pattern', against which they were able to compare the current position of the part, and were able to make appropriate corrective movements. If sufficient normative data was available regarding this 'proprioceptive drift', it might provide the basis for a method of detecting sub-clinical deficits in proprioceptive function.

Summary

(1) The physiological tremor detectable in the proximal phalanx of the index finger during an extension effort of 50G has been detected and measured under virtually isotonic conditions. The characteristics during visual monitoring of a display of positional error, and following eye closure, have been compared in twenty normal subjects.

(2) The general shape of the curve relating amplitude of displacement to frequency was the same for all the subjects. Amplitude diminished with increasing frequency, except between 6 and 11 c/s, where an upward deviation of the curve away from the trend at lower frequencies was evident. In nineteen subjects a clear peak was evident at either 8 or 9 c/s, and at 6 c/s in one subject.

(3) In sixteen subjects eye closure was associated with a reduction, often very marked, in the prominence of the peak between 6 and 9 c/s. One subject showed a very slight increase in its relative amplitude when the eyes were closed.

(4) Most subjects showed a reduction in tremor amplitude on eye closure at frequencies other than those in the 6-9 c/s range. Seventeen of the subjects showed a reduction in amplitude at nine or more of the twelve frequencies studied. Three showed an increase in amplitude at six or more frequencies.

(5) Eighteen subjects showed an identifiable peak in the spectrum between 6 and 9 c/s when the eyes were closed. In twelve subjects it was located at a lower frequency than that seen when the eyes were open. In six subjects the frequency of the peak was the same under the two conditions.

(6) The occurrence of a small proportion of anomalous results suggests that a considerable variation in the pattern of tremor response to eye closure is compatible with normal gross neuro-muscular function.

PART FIVE

AN INVESTIGATION OF PHYSIOLOGICAL TREMOR IN EMOTIONALLY DISTURBED PATIENTS

Introduction

It is common knowledge that normal people who have been made anxious, or patients who are suffering from morbid anxiety, often display a more obvious tremor than normal unstressed subjects.

Various studies have shown a variable transitory increase in tremor amplitude in subjects subjected to different kinds of 'stresses'. This was observed, for example, in an experimental 'frustrating situation' (Sherman and Jost, 1942), and during mental arithmetic, reaction time tests, and in response to sudden noises (French, 1944). The most satisfactory study of 'situational' anxiety was that carried out by Lippold, Redfearn and Vuco (1959). They studied tremor of the index finger under isometric conditions during an extension effort of 50G, while the subjects maintained the demanded force by monitoring their performance on an oscilloscope. A frequency analysis of the tremor was carried out. They compared the data from a group of normal unstressed subjects with that observed in medical students awaiting an important interview. In the latter group, the tremor amplitude at each frequency was relatively large, and a discrete peak at 10-12 c/s was apparent which was absent in the data from the controls.

Several studies of 'morbid' anxiety using optical (Mehrtens and Pouppirt, 1928), electromyographic (Brazier, 1945) and electromagnetic (Friedlander, 1956) methods for detecting tremor, and visual inspection and various techniques for measurement of the records, have given consistent results. These workers concluded that morbid anxiety was associated with tremor of abnormally large amplitude, while no significant change occurred in what was usually described as the 'predominant frequency', i.e. the frequency of the most obvious component on visual inspection of the records. The most satisfactory investigation of this type was that of Graham (1945). He used a photographic method for detecting and recording tremor, and examined the records in respect of amplitude and frequency. A group of 100 patients diagnosed as 'anxiety states' showed a mean tremor amplitude 100% greater than that of a control series of 52 normal subjects. The mean amplitudes of the two groups differed significantly when compared statistically. No significant difference was seen in respect of the frequencies of the most obvious components discerned by visual inspection.

Redfearn (1957) studied the finger tremor of 29 normal subjects and 32 neurotic patients, using a photoelectric method for detecting and recording the movement of the part. Records of the tremor during 4½ second periods were subjected to frequency analysis, and an estimate of mean tremor amplitude was obtained by planimetric measurement. The tremor amplitude was found to be 100% greater in the neurotic group, and differed significantly from that found in the controls. A composite spectrum obtained by pooling the frequency analysis data from all the subjects was found to be similar in form to that obtained from the normal subjects, with no well-marked differences in frequency content. In the neurotic subjects, the tremor was usually of larger amplitude than that of the controls, and tended to show a slight peak at 8-9 c/s.

In Part 4 it was suggested that the effects of eye closure on the characteristics of physiological tremor might be linked to the operation of the arousal system. The increased amplitude observed in anxious patients (or anxious normal people), might also be related to aspects of the functioning of these mechanisms. On the basis of this suggestion it is not possible to predict what differences, if any, there might be in response to eye closure in anxious patients as compared with normal subjects. If it is assumed, for example, that tremor amplitude is directly related to the level of 'arousal', then eye closure might be expected to be associated with increased apprehensiveness regarding the accuracy of performance of the demanded task in anxious patients, with a resultant increase in tremor amplitude on withdrawal of visual information. On the other hand, assuming that the initial level of arousal in the anxious subjects is relatively high, eye closure might have a relatively greater 'sedative' effect than in normal subjects, producing a correspondingly larger reduction in tremor amplitude.

In the experiment described below, the characteristics of the tremor displayed with and without visual monitoring of a display of positional error have been studied in twenty-two emotionally disturbed psychiatric patients. The data has been compared with that obtained from the normal subjects studied in the investigation described in Part 4.

Methods

The equipment and testing procedure were as detailed in Part 3.

The control data was that obtained from the normal subjects studied in Part 4.

The patients were all considered on clinical grounds to be suffering from anxiety of abnormal intensity. This was their most prominent symptom; patients with marked depressive symptoms, thought disorder, hallucinations or delusions, were excluded from the series. In the majority of patients who were found to be manifesting 'pure' morbid anxiety, the illness was relatively chronic in character, and often seemed to be continuous with the previous personality. Acute emotional disorders which had developed suddenly in people of normal personality were usually complicated by ideas of reference, delusions, guilt, etc.

None of the patients had received drugs (other than short-acting night sedation), or any other form of physical treatment, at the time that they were studied.

The mean age of the patients was 38.1 years (S.D.:8.8).

Brief details of the clinical features exhibited by each member of the group are given below. Subjects nos.1-12 were male, nos.13-22 were female.

Clinical Data.

(1) Always quiet, timid, shy. Attacks of pallor, sweating, 'tenseness', breathlessness, since age of 18, (now 38). Intermittent; increasing in severity and frequency; recently related mainly to travelling or the anticipation of it.

(2) Always tense, has never been at ease in meeting strangers. Particularly unhappy in last year; has been drinking heavily intermittently, but not for some weeks. Some disturbance of sleep and appetite.

(3) Lifelong anxiety and tension in everyday situations. Discharged from Army 15 years ago with diagnosis of 'anxiety neurosis'. Difficult marital situation has increased worries recently; drinking heavily in last six months until three weeks ago.

(4) Always lacking in friends and interests. Moodiness, headaches, mild hypochondriacal preoccupation, increasing in severity over a period of eight years.

(5) Lifelong history of anxiety, nervousness, poor sleep after very mild stress. Numerous admissions to neurosis units. Has recently felt quite unable to cope with life.

(6) History of recurrent episodes of insomnia, anorexia, tremulousness, since early teens. Illnesses usually precipitated by mild stress in the course of normal employment, but for two years until the present breakdown, had remained well in the protected environment of a rehabilitation unit.

(7) Always rather tense, nervous, but well able to cope with everyday life. In last six months, increasing anxiety, insomnia, fear and apprehension, especially in relation to travelling. So severe in last three weeks that he has been unable to go to work.

(8) Always shy, withdrawn, awkward in company. Gradual onset over one year of agitation, insomnia, mild depression.

(9) Student who has always been tense, anxious under stress. No major exams in the offing, but onset in the last six to eight weeks of insomnia, mild anorexia, tremulousness, inability to concentrate, irritability.

(10) Mild depression of two years duration in a solitary, immature young man. In last three months has been tearful, agitated, nervous, shaky; has slept badly and lost weight. Has been unable to continue his studies as a trainee radio operator.

(11) Always quiet, shy. Life-long lack of self-confidence; gradual onset during the last three years of insomnia, self-reproach, mild depression, lethargy.

(12) Long-standing feelings of sexual inferiority. Lethargy, listlessness, irritability, excessive worry about 'everything', during last eighteen months. Various somatic symptoms - 'layered headaches, legs feel like ice' etc.

(13) Previously fairly normal personality, though rather quick-tempered. In last six months to one year, tendency to be tearful, sweats, feels excessively embarrassed in situations which would not formerly have worried her.

(14) Borderline intelligence. Always dependent, argumentative, anxious, self-conscious, with transient moods of depression. Very unhappy marriage. Moderate but labile depression since still-birth of son eight months ago; insomnia; inability to concentrate to the extent of doing housework.

(15) Always very quiet and shy. Five years ago, a friend died in the

street. Patient developed feelings of anxiety and tension when passing place in a bus two months afterwards. Then 'panic' attacks, with fear of death, whenever she left the house. Has not worked for three years because of inability to leave home.

(16) Second illness characterised by mild depression and anxiety in an immature and dependent woman.

(17) Previously of normal personality except for mild obsessional tendencies, (houseproud etc.). Onset over a period of five months of depression, anxiety, mild self-reproach.

(18) Previously of fairly normal personality, though tendency to irritability. Anxious, tense, labile depression, following road accident one year ago in which she was not seriously injured.

(19) Tendency to anxiety before present illness. Anxiety and derealisation when left alone at home, building up over 6-7 years. Sudden increase in severity in last five months.

(20) Anxiety and mild depression in a woman of tense, nervous disposition.

(21) Has always been shy, anxious, gauche, afraid of meeting people. During three months before admission, anxiety and depression, repeated washing of the hands. Latter related to feelings of guilt about her contaminating people and things with which she comes into contact. These ideas not held, however, with delusional intensity.

(22) Always tense, subject to depressive moods in which she has drunk alcohol in excess. Present illness, characterised by dejection, tension, anxiety, various somatic manifestations of anxiety, has been building up over the last nine years, and is really continuous with the previous personality.

Results

The normal subjects whose tremor characteristics have been described and discussed in Part 4, have been used as controls in considering the data from the group of psychiatric patients. Details of the measurements made on each patient are shown in Tables 3 and 4.

Section 1. Characteristics of Tremor with Visual Monitoring of Positional Error; Comparison of Patients with Normal Subjects.

In Fig.12 the pooled data from the patients (B) is compared with that from the controls (A). In Figs.12 and 13, the full-line curves show measurements obtained with visual monitoring of the error display, the dotted lines those made after eye closure.

The general shape of the full-line ('eyes open') curves in Figs.12A and 12B are similar; there are, however, certain differences.

The curve obtained from the measurements on the patients lies at a relatively higher amplitude. Thus this group showed a higher average tremor amplitude at each frequency than the controls.

The negative slope of the curve with increasing frequency is relatively less in the plot of the data from the patients.

The upward deviation of the curve between 6 and 11 c/s is relatively slightly more prominent in the patient group, with a maximum at 9 c/s, as compared with that at 8 c/s in the 'control' curve.

Section 2. Effect of Eye Closure on Amplitude at each Frequency - Comparison of Patients with Normal Subjects.

The data from all the patients has been pooled, and in Fig.12B the full-line and dotted curves show the averaged results with visual monitoring of the error display, and with the eyes closed, respectively. These plots can be compared with the normative data in Fig.12A.

FIG.12

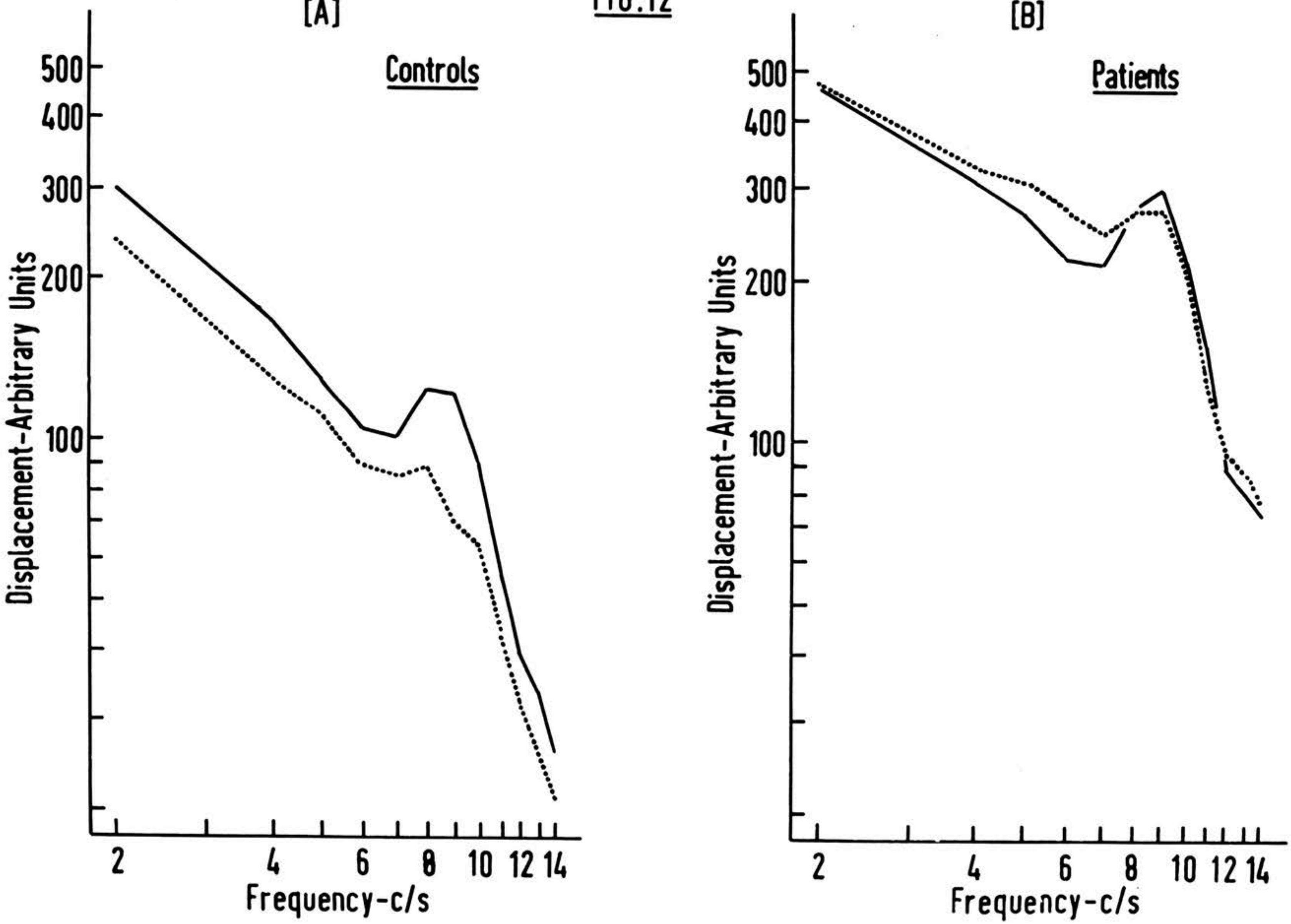

[A]
Controls
500
400
300
200
100
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s
[B]
Patients
500
400
300
200
100
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s

TABLE 3. Patients - Eyes Open

Each figure shows the mean amplitude per unit bandwidth during six ten-second periods of observation.

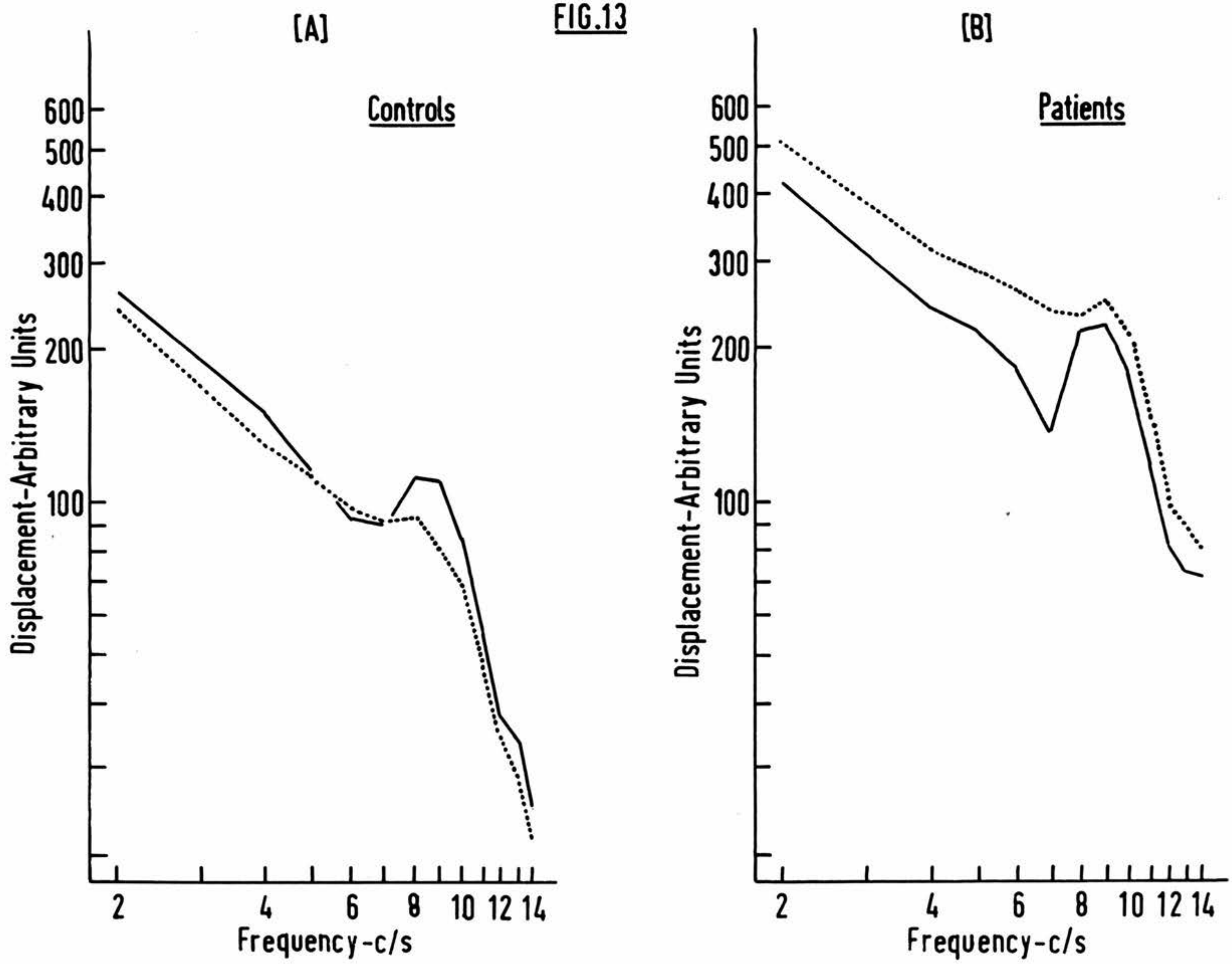
Subject No.	Frequency c/s											
	2	4	5	6	7	8	9	10	11	12	13	14
1	544.0	224.0	210.0	202.0	240.0	318.0	506.0	307.0	196.0	136.0	118.0	103.0
2	520.0	208.0	126.0	142.0	186.0	276.0	396.0	332.0	172.0	110.0	88.0	75.0
3	450.0	254.0	244.0	224.0	274.0	484.0	370.0	180.0	128.0	98.0	84.0	72.0
4	422.0	254.0	206.0	156.0	142.0	142.0	92.0	54.0	34.0	30.0	28.0	24.0
5	548.0	366.0	244.0	202.0	224.0	342.0	548.0	408.0	182.0	100.0	80.0	70.0
6	444.0	304.0	284.0	252.0	312.0	436.0	596.0	564.0	236.0	148.0	124.0	240.0
7	518.0	320.0	304.0	322.0	318.0	412.0	366.0	230.0	190.0	146.0	154.0	136.0
8	360.0	260.0	228.0	174.0	212.0	318.0	296.0	194.0	126.0	80.0	82.0	71.0
9	217.0	137.0	146.0	106.0	89.0	104.0	111.0	91.0	66.0	47.0	39.0	33.0
10	592.0	792.0	788.0	584.0	592.0	678.0	766.0	494.0	292.0	200.0	166.0	134.0
11	182.0	98.0	98.0	84.0	106.0	193.0	231.0	125.0	78.0	52.0	45.0	27.0
12	414.0	284.0	238.0	196.0	156.0	124.0	96.0	88.0	74.0	60.0	58.0	58.0
13	440.0	186.0	144.0	102.0	92.0	94.0	82.0	72.0	84.0	68.0	60.0	55.0
14	396.0	164.0	130.0	106.0	108.0	138.0	212.0	136.0	82.0	56.0	48.0	41.0
15	333.0	196.0	201.0	171.0	150.0	185.0	207.0	121.0	86.0	71.0	66.0	57.0
16	688.0	302.0	214.0	154.0	138.0	106.0	72.0	50.0	34.0	32.0	30.0	24.0
17	306.0	156.0	154.0	150.0	166.0	224.0	272.0	230.0	158.0	110.0	88.0	68.0
18	532.0	336.0	396.0	332.0	244.0	240.0	228.0	168.0	152.0	108.0	88.0	76.0
19	242.0	113.0	103.0	78.0	63.0	46.0	35.0	28.0	19.0	19.0	18.0	20.0
20	518.0	270.0	242.0	206.0	160.0	164.0	132.0	94.0	72.0	56.0	58.0	50.0
21	1344.0	1352.0	944.0	696.0	594.0	594.0	576.0	320.0	208.0	184.0	160.0	152.0
22	416.0	258.0	220.0	198.0	210.0	330.0	322.0	308.0	218.0	130.0	102.0	68.0

TABLE 4. Patients - Eyes Closed

Each figure shows the mean amplitude per unit bandwidth during six ten-second periods of observation.

Subject No.	Frequency c/s											
	2	4	5	6	7	8	9	10	11	12	13	14
1	306.0	128.0	154.0	144.0	154.0	252.0	406.0	274.0	126.0	84.0	80.0	75.0
2	378.0	212.0	248.0	212.0	214.0	278.0	396.0	298.0	162.0	100.0	94.0	81.0
3	362.0	238.0	266.0	266.0	240.0	398.0	304.0	168.0	110.0	80.0	78.0	65.0
4	506.0	290.0	250.0	244.0	200.0	136.0	72.0	52.0	44.0	30.0	28.0	24.0
5	270.0	162.0	144.0	130.0	136.0	194.0	250.0	190.0	80.0	46.0	40.0	34.0
6	546.0	424.0	516.0	508.0	524.0	548.0	556.0	408.0	240.0	148.0	132.0	240.0
7	442.0	324.0	318.0	352.0	372.0	394.0	296.0	252.0	196.0	140.0	158.0	148.0
8	564.0	372.0	324.0	300.0	312.0	408.0	528.0	332.0	158.0	108.0	92.0	80.0
9	211.0	145.0	127.0	116.0	130.0	129.0	141.0	106.0	73.0	48.0	39.0	28.0
10	608.0	704.0	788.0	640.0	720.0	860.0	648.0	440.0	256.0	164.0	136.0	124.0
11	140.0	83.0	98.0	73.0	68.0	101.0	137.0	102.0	58.0	37.0	32.0	24.0
12	568.0	458.0	332.0	282.0	224.0	154.0	134.0	130.0	102.0	100.0	94.0	86.0
13	372.0	208.0	156.0	112.0	96.0	80.0	80.0	92.0	108.0	72.0	58.0	53.0
14	382.0	178.0	129.0	112.0	106.0	142.0	116.0	74.0	54.0	38.0	38.0	33.0
15	261.0	173.0	170.0	142.0	142.0	156.0	169.0	115.0	76.0	49.0	50.0	41.0
16	876.0	416.0	292.0	224.0	148.0	124.0	92.0	80.0	52.0	48.0	40.0	28.0
17	520.0	356.0	328.0	320.0	308.0	340.0	496.0	432.0	304.0	212.0	176.0	136.0
18	568.0	360.0	416.0	356.0	272.0	256.0	228.0	228.0	184.0	128.0	104.0	80.0
19	175.0	117.0	109.0	107.0	71.0	49.0	39.0	27.0	24.0	19.0	19.0	17.0
20	524.0	300.0	300.0	238.0	176.0	152.0	138.0	102.0	74.0	74.0	76.0	62.0
21	1368.0	1184.0	1064.0	808.0	616.0	576.0	448.0	272.0	168.0	144.0	128.0	120.0
22	506.0	346.0	262.0	242.0	198.0	208.0	280.0	422.0	280.0	142.0	100.0	50.0

FIG.13


[A]
Controls
Displacement-Arbitrary Units
600
500
400
300
200
100
2
4
6
8
10
12
14
Frequency-c/s
[B]
Patients
Displacement-Arbitrary Units
600
500
400
300
200
100
2
4
6
8
10
12
14
Frequency-c/s

The relationship of the two curves in Fig.12B is seen to differ considerably from that observed in Fig.12A. The eyes closed curve shows tremor of larger amplitude between 2 and 7 c/s in the patient group. However, the upward deviation of the curve away from the main trend is relatively smaller for the 'eyes closed' plot, so that at 9 c/s the 'eyes open' lies above the 'eyes closed' curve. Above 9 c/s the curves indicate that there was little difference in the amplitudes of the activity under the two conditions at the upper end of the frequency range studied.

The reversal of the normal effect of eye closure on the amplitude of tremor at each frequency was evident in particularly marked degree in fourteen subjects, (nos. 2,4,6,7,8,9,12,13,16,17,18,19,20 and 22). The data from these subjects has been pooled and plotted in Fig.13B. The curves from these patients can be compared with those shown in Fig.13A; these were derived from the fourteen normal subjects who showed this type of response to eye closure to the most marked extent, (nos. 1,4,5,7,8,9,10,11,13,15,16,17,19 and 20). Examination of the detailed results shows that all fourteen of the patients displayed an increase in amplitude with eye closure at six or more of the twelve frequencies studied. In the series of fourteen controls, nos.13,7 and 4 showed an increase in amplitude on eye closure at nine, eight, and six frequencies respectively; the remaining controls in this sub-group displayed an increase in amplitude on withdrawal of visual information at three frequencies or less.

The results illustrated in Fig.13B show that in this sub-group of fourteen patients eye closure was associated with an increase in amplitude at most frequencies; however, there was a considerable reduction in the prominence of the clearly defined peak seen at 9 c/s in the 'eyes open' curve. This is a similar pattern of response to that seen in the results of the single subject in the control group who gave a clearly different result from the other members of the group (no.13).

In the control curves in Fig.13A, it is seen that eye closure caused a reduction in amplitude at most frequencies, with suppression of the 8 c/s peak. The over-lapping of the curves at 5-7 c/s is due to the shift to a lower frequency on eye closure, of the component of largest amplitude in the upward deviation of the curve (described and illustrated in Part 4).

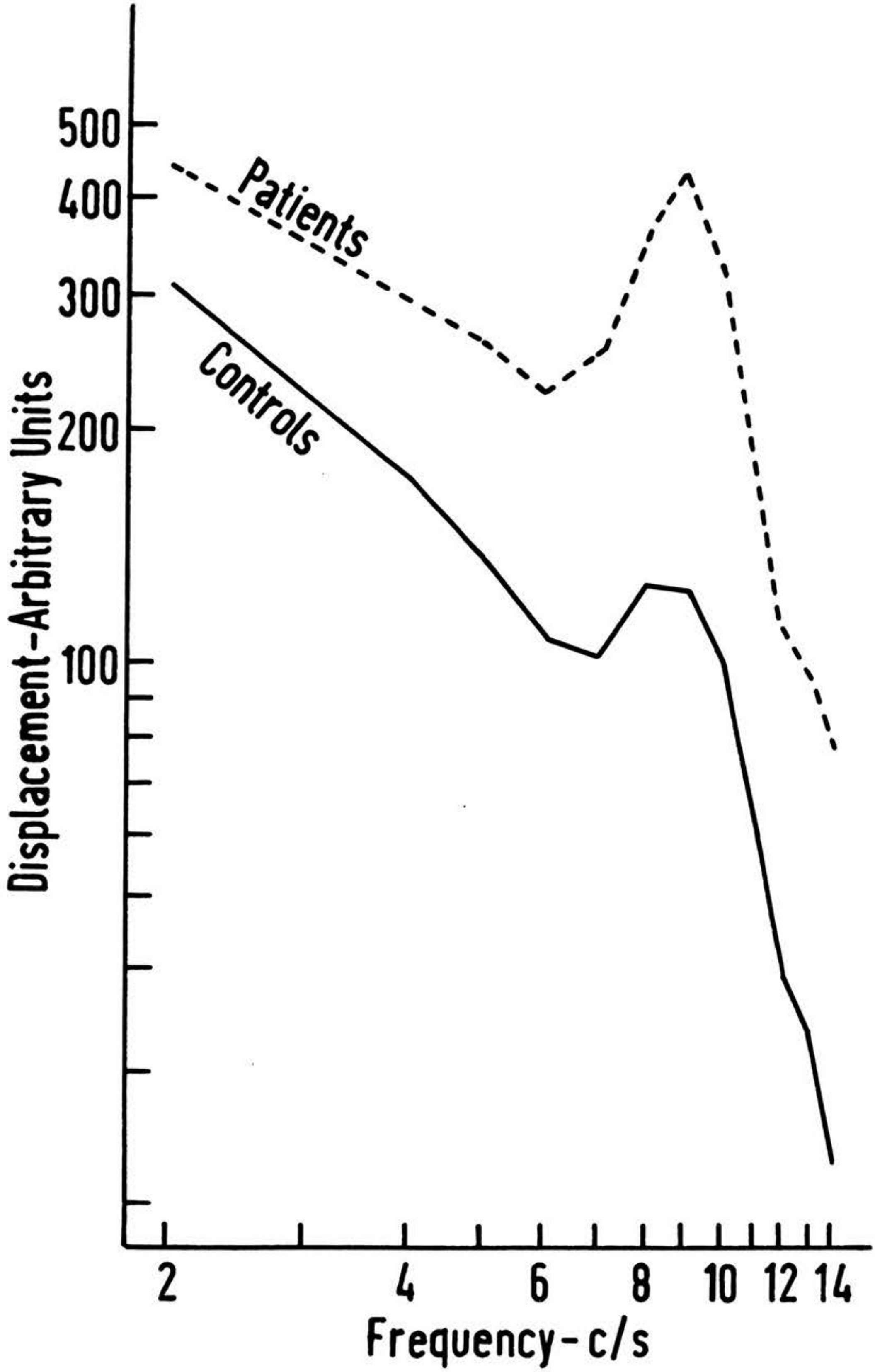
Section 3. Changes in Frequency Distribution of Activity with Eye Closure - Comparison of Patients with Normal Subjects.

In the results from sixteen of the twenty-two patients, peaks occur in both the 'eyes open' and 'eyes closed' amplitude/frequency spectra. No change in the frequency of the peak is seen to have occurred with eye closure in twelve of these subjects; the relevant numbers in Tables 3 & 4 are 1,2,3,5,6,7, 9,11,12,13,15 and 17). In one subject the frequency of the peak is located 1 c/s higher on the frequency scale in the data obtained after eye closure (no.8); in another (no.22), the frequency of the peak is 2 c/s above that at which it is found in the results produced when the subject was monitoring the oscilloscope display. In two subjects (nos.10 and 14), the peak occurred at a frequency 1 c/s lower than when the eyes were open.

This contrasts with the results in the control group, where a clear reduction in frequency of the peak occurred in 60% of the subjects, and none showed an increase.

Inspection of the curves obtained from the data of two of the subjects (nos.8 and 22), shows that increase in the frequency of the peak from 8 to 9 c/s with eye closure was associated with an increase in its relative prominence.

FIG.14


500
400
300
200
100
Patients
Controls
Displacement-Arbitrary Units
2
4
6
8
10
12
14
Frequency-c/s

Section 4. Frequency Distribution of Tremor Activity with Visual Monitoring of Positional Error-Comparison of Patients with Normal Subjects.

It has already been noted that the upward deviation of the curve between 6 and 11 c/s with the eyes open is relatively more prominent in the patient group as a whole; this effect is even more marked in the sub-group whose data is plotted in the 'full-line' curve in Fig. 13B.

Inspection of the figures in Table 3 shows that nine of the patients showed this feature particularly markedly, (nos.1,2,3,5,6,8,10,11, and 17). In Fig.14, the data from these patients, (dashed curve), is compared with that of the nine controls showing the most prominent spectrum peaks, (nos.1,2,3,4,5, 7,9,10 and 13).

The amplitude at each frequency is clearly considerably greater in this patient sub-group. The curve of the data from the patients shows a very large peak, with a maximum at 9 c/s, which contrasts with the smaller peak in the control data, with a maximum at 8 c/s.

Section 5. Tabular Comparison of Results from Patients and Controls.

Some of the results from the two groups have been summarised for purposes of comparison in Table 5. An explanatory key is provided.

Section 6. Statistical Analysis of the Results from Patients and Controls.

Inspection of Figs.12 and 13 suggests that in the control group the tremor amplitude at each of the frequencies studied was usually less when the eyes were closed than when the position of the trembling part was displayed to the subjects. In fourteen of the patients, however, the relative positions of the amplitude/frequency plots are seen to be reversed.

In order to carry out a statistical analysis of the measurements from the two groups, it was necessary to derive a quantity expressing the relative amplitudes of the two measurements of tremor amplitude obtained from each pair

TABLE 5. Distribution of Response Patterns

No.	Controls			
1		B		
2		B		
3		-	-	
4	A		C	
5			C	
6		-	-	
7	A	B		
8			C	
9		B		
10		B		Nil
11			C	
12		B		
13	A	B		
14			C	
15		B		
16		B		
17		B		
18			C	
19		B		
20		B		

No.	Patients			
1			C	D
2	A		C	D
3			C	D
4	A	-	-	
5			C	D
6	A		C	C
7	A		C	
8	A		C^x	D
9	A		C	
10		B		D
11			C	D
12	A		C	
13	A		C	
14		B		
15			C	
16	A	-	-	
17	A		C	D
18	A	-	-	
19	A	-	-	
20	A	-	-	
21		-	-	
22	A		C^x	

Key to Table 5.

A:- Increase in amplitude on eye closure at six or more frequencies.

B:- Reduction in frequency of peak in spectrum on eye closure.

C:- No change in frequency of peak in spectrum on eye closure.

C^x:-Increase in frequency of peak in spectrum on eye closure.

D:- Very prominent peak at 8-9 c/s.

- - : No peak in one or both curves.

of test runs. Several such criteria can be developed.

In this analysis, the ratio of the amplitude during visual monitoring to that seen following eye closure has been calculated for each pair of readings. Thus a ratio of unity indicated that in a given pair of test runs, the amplitudes observed under the two conditions were identical. Where the ratio is greater than unity, the amplitude during visual monitoring was relatively the larger, and vice versa.

Six pairs of readings were obtained from each subject, and so 120 ratios were calculated for the controls, and 84 ratios for the fourteen patients, at each frequency.

An analysis of variance was then carried out to determine whether the mean of the ratios derived from the sub-group of fourteen patients differed significantly from that obtained from the controls, at each of the frequencies studied.

In carrying out this analysis, it was necessary to take account of the fact that, at each frequency, the data was not only subdivided into two groups, but that within the two groups it was again split up into units comprising six pairs of test runs from each subject. It was therefore necessary to establish that the process of splitting the data into six components from each subject did not give rise to a source of variation associated with a variance estimate so much greater than the variance estimate based on the residual (i.e. experimental) error that the ratio of the former to the latter estimate was unlikely to have arisen by chance. Furthermore, a computation had to be carried out to determine whether interaction of the effects due to the subdivision of the data into two groups of subjects, with six measurements from each subject, introduced variation significantly greater than might have been expected if it was assumed that it constituted merely a component of the variation due to the overall experimental error. The variance estimates associated with these two sources of variation can be termed the 'between pairs' and the 'groups by pairs interaction' variance estimates respectively. Finally, in calculating a variance estimate based on the variation of the readings from individual subjects within the two groups, the arithmetic process had to take account of the fact that six pairs of measurements were obtained from each subject. The latter can be termed the 'within groups' variance estimate

F-ratio tests showed that at none of the frequencies studied were the 'between pairs' or 'groups by pairs interaction' variance estimates greater than would have been expected on the assumption that they were independent estimates of the variation due to the experimental error.

When the 'between groups' and 'within groups' variance estimates were compared, the values of 'F' and 'p' obtained at each of the frequencies studied are shown in Table 6.

The mean of the ratios of the relative magnitudes of the tremor obtained from each group gives a quantitative measurement of the nature of the response to eye closure found in the relevant series of subjects. It can be seen that, in respect of this response, fourteen patients, considered as a group, differed significantly from the controls at one frequency, highly significantly at seven frequencies, and very highly significantly at four of the frequencies studied.

TABLE 6. Results of Analysis of Variance

Frequency	F	p
2	14.7035	<0.001
4	16.5658	<0.001
5	10.8121	<0.01
6	10.2979	<0.01
7	7.3775	<0.05
8	11.2044	<0.01
9	15.9570	<0.001
10	16.1023	<0.001
11	12.3127	<0.01
12	7.5499	<0.01
13	12.6810	<0.01
14	10.3323	<0.01

Note. There is one degree of freedom for the greater variance estimate, and ~~three~~ thirty-two degrees of freedom for the lesser variance estimate, throughout.

Discussion

Comparison with Results of Previous Investigations

A comparison of the curves obtained from the patients and controls in this investigation might suggest at first sight that the difference in average amplitude between the two groups was rather less than that reported by other workers. Redfearn (1957), and Graham (1945), both found the tremor to be greater by 100% or more in the patients with symptoms of anxiety. However, two points should be noted. Firstly, the subjects studied by these workers controlled the trembling part with the aid of proprioceptive information only; thus in relating the present results to those of previous investigations, the 'eyes closed' curves should be compared. The difference in amplitude between the two groups is greater than that in regard to the 'eyes open' curves. Secondly, the relatively greater negative slope with increasing frequency seen in the control series results in a greater difference in amplitude between the two groups at the high frequency end of the spectrum. In carrying out his measurements, Graham concentrated on tremor in this range. Redfearn's planimetric assessment of mean tremor amplitude was carried out on the record of a signal proportional to the velocity of the part studied; in such a record the components of higher frequency are relatively more accentuated than those at the lower end of the spectrum, in comparison with a record of displacement. Thus, if one considers only the higher frequencies, i.e. above about 5 c/s, the amplitude differences found in this experiment are similar to those described by Graham and by Redfearn.

In the frequency spectra published by Redfearn (1957), none of the anxious subjects showed a really accentuated peak in the spectrum at 8-10 c/s. As already noted, Lippold, Redfearn and Vuco (1959) found a relative accentuation of tremor in this range in normal subjects in a stress situation. In this series of studies, nine patients were found who, as a group, showed a very well developed peak at 9 c/s when the eyes were open. Furthermore, the anxious group as a whole, and the fourteen subjects from within that group showing a significantly anomalous response to eye closure, displayed, during visual monitoring of the error display, relatively prominent peaks with maxima at 9 c/s. A feature common to this investigation and that of Lippold et al. was the subjects' monitoring of a visual display of performance, and this may have been the factor responsible for evoking this feature in the frequency distribution of activity. Indeed, when the nine relevant subjects closed their eyes, the relative prominence of the 9 c/s peak was reduced.

Mechanisms which may underlie the Differences between the Patient and Control Groups.

If stretch reflex oscillation occurs, one of the factors likely to play a part in determining both its frequency and amplitude is the muscle contraction time. This is dependent on the physical properties of the muscle, i.e. the viscosity of the muscle fibres, the compliance of the series - elastic component, etc. Lippold et al. (1957) showed that cooling the muscles lengthens the contraction time, and greatly reduces the amplitude and frequency of the tremor manifest in the part on which they act.

Bowman and Zaimis (1958) found that adrenaline, in physiological concentrations, shortens the contraction time in the soleus of the cat. In states of anxiety, which are associated with increased adreno-medullary activity, there may be a reduction in the 'viscosity' of some or all of the skeletal muscles, producing an increase in the amplitude of the movements in response to reflex oscillation. This change in the physical properties of the muscle would also be expected to be associated with some degree of increased amplitude of response, at each frequency, to a given input of motor energy; this would tend to produce a spectrum curve located at a relatively high level in a plot of data obtained by frequency analysis of tremor.

In the discussion in Part 4 regarding the nature of the factors determining the amplitude and frequency of the peak in the spectrum, it was argued that for a given level of spindle bias, a vertical movement of the curve, reflecting a generalised proportional change in energy input at each frequency, would be associated with a peak in the spectrum of similar relative amplitude, but with a maximum at a higher frequency. The 'eyes open' curve from the normal subjects shown in Fig.12A can be compared with that derived from the data of the patients shown in Fig.12B; the peaks are of similar relative amplitude, but that obtained from the patients, and showing a larger tremor amplitude at each frequency, has a peak at 9 c/s as compared with that at 8 c/s in the data from the normal group.

It was further argued that an increase in system gain would cause an augmented relative peak amplitude, and an increased frequency of oscillation. This could provide an explanation of the characteristics of the data from the patients illustrated in Fig.14, where a peak of relatively large amplitude is associated with a clear displacement of activity away from 8 c/s towards 9 c/s, when compared with subjects with less prominent peaks.

In the patient group, two general patterns of response to eye closure emerge which differ from that seen in the normal group.

Firstly, in the pooled results from fourteen patients, there was a general increase in amplitude over the range studied when the eyes were closed. The relative size of the peak, however, fell. This latter feature, according to the above theory, would be expected to reflect a drop in system gain. As with the single control subject showing a distinctly anomalous response on eye closure, the expected tendency for the frequency of the peak to fall with the drop in the system gain may have been compensated by the increased random input of energy at each frequency. In the two patients who showed a definite increase in the frequency of the peak on eye closure, a generalised increase in amplitude over the whole range of frequencies was associated with maintenance of the prominence of the peak in the spectrum. This is consistent with the nature of the mechanisms, discussed in Part 4, that might be concerned in the determination of the amplitude and frequency of the peak in the spectrum.

Secondly, six of the patients showed a generalised reduction in amplitude at most of the twelve frequencies studied on eye closure. The attenuation of the peak was, however, much less marked than in the normal subjects, and in the averaged results from this group of patients, eye closure was associated with a slight increase in the amplitude of the 8 c/s components as compared with those at 9 c/s, but the maximum remained at the latter frequency. In terms of the above theory, it would be said that in this sub-group of patients eye closure was associated with only a slight reduction in system gain, if any.

In the remaining two patients, eye closure was associated with a generalised reduction in amplitude at each frequency, and attenuation of the peak in the spectrum. This is the normal response found in the majority of the controls, and discussed in Part 4.

The mechanisms that may be concerned in determining the amplitude of the 'random' tremor component evident at each frequency in the range studied is still obscure. However, in Part 2 it was suggested that it may be in part determined by the prevailing overall tendency for synchronization of motoneurone discharge, and the intensity of the activity in the motoneurone pool. It was also suggested above that the physical properties of the muscle, determined, for example, by humoral factors, may play a part in determining the mean level of tremor amplitude, though the short-latency response to eye closure is likely to be due to the operation of neural mechanisms.

As with the normal subject showing an anomalous response to eye closure in Part 4, the results from the patients showing a generalised increase in amplitude at most frequencies, but a marked reduction at 8-9 c/sec, might be interpreted as indicating some degree of independence of the mechanisms determining the amplitude of the 'random' tremor component on the one hand, and those regulating the size of the peak usually evident in the spectrum, on the other. Inspection of Fig.13 shows that both the sub-group of fourteen patients, and the controls, showed a marked reduction in the prominence of the peak at 8-9 c/s on eye closure. However, the statistical analysis shows that, in spite of this similarity, the overall difference in response between the two groups at the relevant frequencies was significant beyond the 1.0% level.

General Considerations.

In this group of patients, a high proportion displayed abnormality in their tremor characteristics, especially in relation to the response to eye closure, when they were studied using the techniques of measurement and assessment described. It should be noted that these subjects were rather carefully selected in terms of the clinical disorder that they displayed. The primary symptom in all subjects was anxiety - a tendency to respond to everyday situations with excessive apprehension, 'nerviness', and 'jumpiness' - sufficiently prolonged and severe as to cause them to seek specialist psychiatric advice, and in many instances, to enter hospital for treatment. Patients with severe obsessional symptoms, or whose anxiety was related to fairly 'well-encapsulated' situations or patterns of thought, were not included in the series. This was true also of patients whose illness was primarily depressive, i.e. those who experienced a mood of profound despondency, or whose mental content was composed of a 'ceaseless roundabout of painful thought'. In many subjects, the current illness appeared to be an acute phase in a long-standing emotional disorder. Sometimes this chronic disturbance dated from an early age, and seemed to be rooted in the personality. Whether patients showing less intense anxiety, or those with emotional disorders of a more complicated kind in terms of the clinical pattern, display similar abnormalities of the kind described, has not been determined.

These patients were studied on only one occasion, when they had had no previous practice in the test situation. The temporal stability of these abnormal tremor patterns, and responses to eye closure, has not been investigated. This is clearly a matter of some importance, as one would like to know whether one is dealing with an aspect of individual physiology with stable characteristics, or whether the mechanisms concerned show responses to changes in the mental state of the individual, to growing familiarity with the test situation, to medication etc.

These studies were carried out partly on the basis of the hypothesis that the changes in tremor characteristics seen in normal individuals as a result of eye closure might be related to the operation of the brain-stem and diencephalic 'arousal'mechanisms. According to some workers, (Shagass, 1954; Shagass and Naiman, 1954; Shagass, 1956), anxious subjects show a greater degree of 'arousal' - measured in terms of the amount of sodium amytal per Kg. of body weight that is required to produce characteristic EEG changes and speech slurring - than normal subjects. It might therefore be of some interest to study the effects of eye closure in normal subjects subjected to considerable stress, in order to see whether they display the features seen in the anxious patients. A suitable stress might be provided, for example, by a reward/punishment situation in which the subjects might be told that the accuracy of their muscular control would be measured, and that if their performance fell below a certain level, they would receive a painful electric shock.

Another reason for carrying out studies of this kind in normal individuals lies in the occurrence of a qualitative and not simply a quantitative difference in the nature of the response to eye closure observed in a high percentage of emotionally disturbed subjects as compared with controls, (i.e. a tendency to show an increase rather than a decrease in tremor amplitude). This leads one to speculate on the possibility that there may be a physiological difference between normal, transient anxiety in a 'stress' situation, and pathological anxiety. Malmo (1957), discussed various aspects of this idea. He suggested that a neural change may occur, related to excessively severe and prolonged 'arousal', giving rise to abnormalities of neurophysiological response. Studies of 'stressed' normal subjects of the type suggested above would give information relating to this possibility.

Clinical Application of Studies of Tremor Characteristics.

From the results obtained in these experiments it would seem that in studies of the characteristics of tremor in emotionally disturbed subjects, the arrangements for frequency analysis do not need to be as elaborate as those used in this investigation. The range of frequencies in which the greatest difference in amplitude between normal and emotionally disturbed subjects is found is located towards the upper end of the frequency range, between 7 and 10 c/s. This range also gives a clear-cut indication of abnormal response to eye closure, i.e. a marked reduction in amplitude in most normal subjects, and an increase or relatively slight attenuation in a high proportion of emotionally disturbed subjects. Thus much of the information derived from the above experiments could be obtained by using a single filter with a central frequency between 8 and 9 c/s, and a fairly wide bandwidth - say ± 1-2 c/s. If several narrow-bandwidth filters were used, no more than four would be required, centred at 7,8,9 and 10 c/s. Alternatively, the 'playback' technique, using a single tuned filter of known bandwidth, would seem to be suitable for this application. For example, a single filter tuned to a central frequency of 8.5 c/s, and with a bandwidth of ± 1.5 c/s, would be used to cover the region of the spectrum in which the peak is usually observed. It could then be used to obtain a measure of the amplitude of activity towards the low frequency end of the spectrum by doubling the playback speed; the filter would then selectively amplify signals with a frequency of 4.25 c/s, with a bandwidth of ± 3.0 c/s.

The results of these experiments, summarised in Table 5, show that, under the conditions described, no single type of frequency distribution of activity, or response to eye closure, is typical of the emotionally disturbed patients. However, certain patterns show a numerical preponderance in the patient group; these have been designated as types A,C and D in Table 5. Only five of the twenty controls, but twenty of the twenty-two patients, show one or more of these patterns. Of the remaining two patients, one shows a tremor of very large amplitude, and the other would be classed under D were it not for a very marked slope of the curve between 2 and 6 c/s.

This technique therefore reveals a preponderance of abnormal responses among the emotionally disturbed patients. However, its practical usefulness is limited by the high incidence of false positives, especially on assessments made in terms of response 'C'. Of the normal group, 35% showed characteristics more frequently evident (95%) in the emotionally disturbed patients. Thus, if one was presented with the data obtained from a particular individual without any knowledge of the history, and was asked to make a clinical diagnosis on the basis of the objective findings, one would give the wrong answer on a rather high proportion of occasions. One would be helped to some extent by supplementary evidence in the data other than that of the presence or absence of one of the features predominating in the patient group. In the latter series, for example, the occurrence of more than one type of abnormality was more common than in the controls; again, when an increase in amplitude occurred on eye closure in the anxious subjects, it was usually of greater magnitude than such abnormal responses as occurred in the normal individuals.

It would seem desirable, however, that the techniques of tremor measurement described in these experiments should not be used as a diagnostic tool in isolation. They might, however, constitute a useful component of a battery of physiological measurements from which emotional disturbance and its severity could be inferred in terms of some complex factor relating several variables.

Summary

(1) The physiological tremor displayed by 22 emotionally disturbed patients has been compared with that which was found in a group of 20 normal subjects. The characteristics during visual monitoring of a display of positional error, and following eye closure, have been studied.

(2) The average amplitude of the tremor at each of the twelve frequencies studied was relatively large in the patient group under both recording conditions.

(3) The pooled data from the patients showed a relatively smaller negative slope with increasing frequency, in the curve relating amplitude to frequency.

(4) Fourteen (63.5%) of the patients showed an increase in tremor amplitude following eye closure at six or more of the frequencies studied when compared with the amplitudes observed when they were monitoring the visual display of performance. This pattern was seen in three subjects (15%) in the control series. A statistical analysis showed that these patients differed significantly from the controls at all, and highly significantly at most, of the frequencies studied, in respect of the amplitude response to eye closure. These subjects could not be separated from the other members of the group of patients by virtue of their sharing certain characteristic clinical features.

(5) The patients, when compared with the controls, tended to show a relatively large peak at 8-9 c/s when they were monitoring the visual display of positional error. This feature was particularly prominent in a sub-group of nine patients (41%).

(6) In the results from 12 members (60%) of the control group, a relatively small peak was seen in the spectrum following eye closure, at a

lower frequency than that observed during visual monitoring of the error display; this feature was seen in two (9%) of the patients.

(7) Following eye closure, six (30%) of the controls showed a peak with a maximum at the same frequency as that observed during visual monitoring. This feature was seen in twelve patients (55%), and in a further two patients (9%) eye closure was associated with an increase in the frequency at which the peak was located.

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ACKNOWLEDGEMENTS

Acknowledgements

I should like to express my gratitude to Professor Sir Aubrey Lewis for his advice and encouragement during this research.

Thanks are also due to Dr. C. Rashbass for helpful discussions; to Dr. A.E. Maxwell for advice regarding the statistical analysis of the data; to Mr. G.H. Cox for help with the electronics; and to Mrs. C. Sutton for secretarial assistance.

This work was carried out with the aid of grants from the Ford Foundation and the Bethlem Royal and Maudsley Hospitals Research Fund.