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# THE AFTER EFFECTS OF SUDDEN CHANGES IN STIMULATION RATE UNDER DIFFERENT CONDITIONS OF ANÆSTHESIA.

BY GRACE BRISCOE.

(*From the Physiological Laboratory of the London School of Medicine for Women.*)

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RECENT work has made it clear that executant nerve-muscle units receive trains of impulses from the spinal cord, the only variable being the spacing between the impulses [Adrian, 1930]. It is of interest to enquire if the result of a given train of impulses has any effect on the response to an aftercoming train of different frequency when these trains follow each other without pause. It will be shown that the nature of the response to a given strength and rate of stimulation is dependent on the previous activity or degree of recovery from activity in the test muscle.

Two types of stimulation rates have been used, slow rates (20–35 per sec.) and fast rates (130–160 per sec.). The effects due to sudden change in stimulation rate have been studied in peripheral preparations of mammalian muscle with intact circulation. These effects fall under two heads, the muscle either lengthens or shortens. Since the terms "lengthening" and "shortening" reactions, "inhibition" and "facilitation" have all acquired special meanings, the non-committal terms of "depression" of contraction and "accretion" of contraction will be used to indicate greater or less length. The effects are conditioned, and can even be reversed, by the state of anæsthesia existing at the moment of trial.

## METHODS.

The quadriceps muscle of the cat has been used mainly, tibialis and soleus muscles occasionally. After denervation of the limb by section of the main nerve trunks, the thigh is held vertically by a drill through the lower end of the femur, and the movement of the leg recorded by a thread attached to the patellar tendon. There is no disturbance or exposure of the muscle and care is taken not to interfere with the blood supply. The nerve is excited by the discharges of a neon lamp flashing circuit [Briscoe and Leyshon, 1929], and sudden changes of rate are secured by plugging a resistance in and out of the charging circuit. Removal of the resistance only increases the rate of flashing, it makes no appreciable difference even with the fastest rate used to the quantity and shape of each individual discharge of the condenser, as tested by the cathode ray oscillograph [Leyshon, 1930]. The rates used are inscribed simultaneously with the muscle tracing by means of a telephone frequency recorder devised by Leyshon [1931]. For a double preparation the discharges are led through the primary coil of an induction apparatus and two secondary coils are used, one on either side of the primary coil. For stimulation, the cut nerve is threaded under and over silver wire electrodes and the attached thread is secured to the electrode holder by plasticine, so that the nerve does not slip and is maintained at a slight constant stretch. The nerve is shielded and kept warm by a flap of skin. The stimulating currents all flow through the nerve in the same direction, the cathode being next the muscle.

## THE ANÆSTHESIA.

It has been found that in cats a combined anæsthesia of dial and ether produces a comparatively steady state in which the changes ensuing on sudden alterations of stimulation rate can be repeated not only in the same preparation, but in different preparations. A dose of dial (0·5 c.c. per kg.) is given intraperitoneally and during induction ether is also given. After a short period (10–20 min.) it is usually possible to discontinue the ether and the preparation remains anæsthetized for several hours. The corneal reflexes and knee jerks remain active, there is, usually, no exaggeration of muscle tone in the intact limbs and peripheral nerve muscle thresholds for recordable movements are very constant, unless modified by prolonged stimulation. The reactions can be shown under ether alone if the anæsthesia be kept light (corneal reflex lively), but this requires continual attention, and peripheral thresholds rise and fall according to the depth of the anæsthesia. A coarse tremor in the contraction of the muscle sometimes develops under ether, occasionally under dial-ether, and the depressions with slow rates are then not well shown as a steady contraction cannot be obtained with submaximal stimulation. Under dial only the onset of contraction in response to a slow rate is less precipitate, and the muscle in response to a fast rate shows "fatigue" more slowly than under ether (Figs. 3 and 4). Depressant effects on change of rate are less readily obtained than under the combined anæsthesia of dial and ether. In the intact limbs accentuation of extensor tone may be found.

Under deep dial the corneal reflex may be slow, or even absent, yet prolonged contractions can be maintained in the quadriceps. Similar absence of the corneal reflex under deep ether would be accompanied by inability to maintain any contraction for more than a few seconds.

## Results.

The depressions and accretions of contraction resulting from change of stimulation rate are conditioned not only by the state of anæsthesia, but by the strength and frequency of the slow and fast rates and also by the length of time each rate is allowed to act.

In order that the effect of different anæsthetic conditions might be studied, and comparisons made more profitably between different preparations, a standardized method of testing the muscle has been adopted. For the slow rate the lowest frequency compatible with fusion has been used, and for the fast stimulation the rate has been increased approximately fivefold. These rates are alternated in 5-sec. spells at three different strengths: I, sufficient to produce partial extension of the leg; II, sufficient for full extension; III, double or treble strength II. All the shocks are quite mild, as strength III may be trebled without being perceptible to the tongue.

The fusion rate itself is a variable depending on: (*a*) The muscle used. Soleus can be maintained in a steady contraction by rates well below 20 per sec., while tibialis usually requires rates from 35 to 45 per sec. (*b*) The strength of stimulation used. In a previous investigation on maintained contractions in the quadriceps [Briscoe, 1931] the majority of fusion rates lay between 20 and 25 per sec. In the present investigation the majority of fusion rates (using the same technique for stimulation and recording) lie between 25 and 30 per sec. This difference is probably due partly to the fact that only stimuli of strength II, just sufficient for full extension, were used in the first study. It has been found in the present work that strength III (double or treble II) sometimes disclosed the stimulus rhythm and an increase in rate was needed to obtain fusion. (*c*) The duration of the stimulation. Mere continuance of a maintained contraction tends to lower the fusion rate; to quote an extreme example, it was found that the rate to quadriceps nerve could be reduced from 23 to 14 per sec. after the leg had been held in full steady extension for 1 hour. In the present experiments prolonged contractions have not been aimed at, probably another factor accounting for the higher average fusion rates in this work. (*d*) The anæsthetic. In 1931 the anæsthetic mainly used was dial, and it was noted that the addition of ether to the anæsthesia might cause a disclosure of the stimulus rhythm. In the later work a combination of dial and ether has been used in most of the experiments. In five consecutive dial only preparations the average fusion rate was 27·2 per sec., in five consecutive ether only preparations the

**average was 29 per sec. The fusion rate in one quadriceps under dial only was 28 per sec., when the quadriceps of the other leg was tested after ether had been given its fusion rate was 32 per sec. Under ether only a stimulus rhythm at 30 per sec. could just be read in the muscle trace, after a nearly full dose of dial had been given the rhythm could just be read at 27·5 per sec.**

*Depressions of contraction following change of stimulation rate.*

Two types of depression will be described: (*a*) with stimuli of strength I depression occurs when the rate is suddenly reduced; (*b*) with stimuli of strength III depression occurs when the rate is suddenly raised.

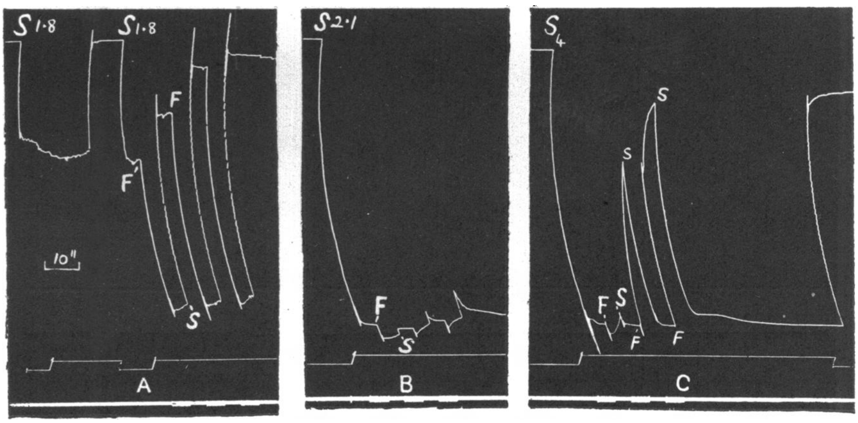


**Fig. 1. Cat. Quadriceps. Dial and ether anæsthesia. In all tracings contraction is downwards and negative pole next the muscle. Upper signal, electrode curcuit. Line rises when circuit made. Lower, frequency recorder, enlargement in line indicates when fast rate used. Slow rate 30 per sec. Fast rate 165 per sec., same strength. A, strength I. Potential divider 1·8. Control curve of uninterrupted slow stimulation given first, then with same strength, slow and fast rates are alternated in 5-sec. spells. B, strength II. Potential divider 2·1. Little change on alternation of rates. C, strength III. Potential divider 4. Marked depression with second and third fast spells and recovery with slow rate.**

(*a*) When the quadriceps holds the leg in partial extension due to weak slow stimuli, a sudden change to a fast rate of equal strength causes an increase of contraction. On return to the slow rate the leg falls back to a position less than its original extension. Repetition of fast spells accentuates this depressant effect for slow rates (Fig. 1 A). Neither rate tested alone in resting muscle produces such swift relaxation, but alternation of rates has that effect. Alternation of rates at strength II produces little change (Fig. 1 B).

(*b*) When the quadriceps is holding the leg in as full extension as is possible with slow stimuli of strength III, a sudden raising of the rate causes an increase of contraction, if the stimulation has only lasted a few seconds. If the stimulation has lasted 20–30 sec. the abrupt raising of the rate causes a sudden depression of contraction, which is restored as soon as the slow rate is resumed (Fig. 1C). Repetition of the change of rate

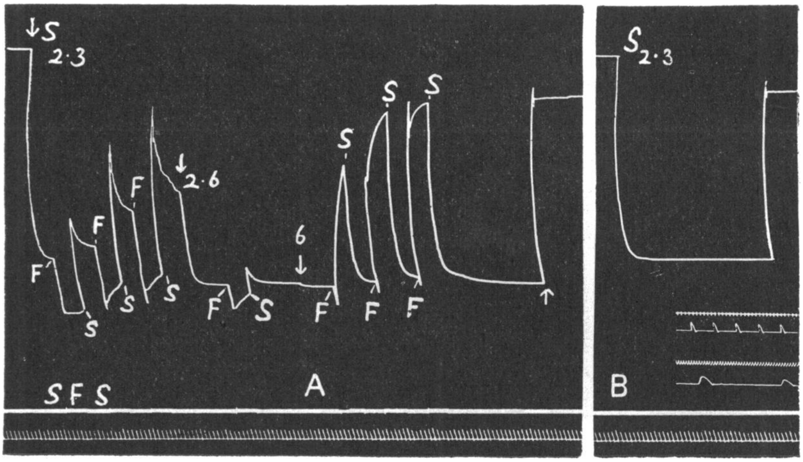


Fig. 2. Quadriceps. Dial and ether. Upper signal, frequency recorder. Lower, time in seconds. A, reversal of type of depression with continuous stimulation. At the first arrow stimulation starts with submaximal slow rate, potential divider at 2·3. Slow and fast rates alternated, sudden depression on reverting to the slow rate. Recovery begins quickly, as strength is only just below that required for full extension. At the second arrow the potential reading is increased to 2·6, extension becomes full and little depression after fast spell. At the third arrow potential increased to 6. Rapid depressions with fast rate, preceded by brief excitatory effect. Contraction recovers and is maintained on reverting to slow rate. At the fourth arrow, stimulation off. B, control curve of submaximal slow stimulation, taken 37 sec. after close of tracing A. Inset slow rate (30 per sec.) and fast rate (150 per sec.) on faster rates of drum. Time, 0·2 sec.

gives more pronounced effects and the curve of relaxation (shown with fast records) due to increase of rate may be as speedy as that due to cessation of all stimuli.

Depressions of both types can be shown in flexor muscles, but the frequency of both slow and fast rates has to be increased. A rate of 40–45 per sec. is suitable for maintaining a smooth contraction in tibialis anticus. If the nerve to quadriceps and the nerve to tibialis are excited simultaneously from the same source so as to receive the same alternations of rates, opposite effects can be shown in the two muscles. For example, extensor receives stimuli of strength III, flexor, stimuli of strength I. When the rate is raised, extensor relaxes while flexor shortens further; when the rate is slowed, extensor shortens and flexor relaxes [Briscoe, 1932].

The reversal of depression depending on intensity of stimulation can be shown simultaneously in similar muscles if both quadriceps are prepared. To give an example, one secondary coil was placed 17 cm. and the other 25 cm. from the primary coil to obtain reciprocal effects on alternations of rates in the two legs, one quadriceps (secondary 25 cm.) relaxing with the slow rate while the other (secondary 17 cm.) shortened, and *vice versa* with the fast rate. This observation is important as it excludes changes due to internal environment, such as variable depth of anæsthesia, or to difference in type of muscle used.

Reversal of the type of depression can be shown in a continuous tracing by increasing the potential supplied while stimulation is in progress (Fig. 2). In this tracing depression with fast spells during stimulation at strength III is well marked, but the preliminary excitatory effect of the fast rate is seen to be more persistent than in Fig. 1.

### *The recovery from depressant after-effects.*

The depressions caused by fast stimuli following low frequency stimuli of strength III are progressive. The depressions of contraction seen when slow rates of strength I follow fast spells are transient and disappear slowly or quickly according to the condition of anæsthesia. In Fig. 3 A it will be noticed that the emergence of contraction after such depression takes longer than the establishment of contraction from a resting condition. At any moment during the recovery process the muscle can be brought into full contraction by reverting to the fast rate, or it can be restored to its original amount of contraction by a slight strengthening of the slow rate (Fig. 2). The block is relative and easily surmounted. After a pause for complete recovery the nerve is stimulated by short spells of the slow rate by opening and closing the electrode circuit every second or so (Fig. 3 B). A number of short tetani of even depth result. A spell of the same stimuli at a faster rate is now applied to the nerve for three to five seconds. Immediately this tetanus is over, the same short spells of slow frequency stimuli are applied. The first spell may not elicit any answer, or a very small one, the second will produce a larger one, the third still better, till eventually tetani of the same depth as in the controls are obtained.

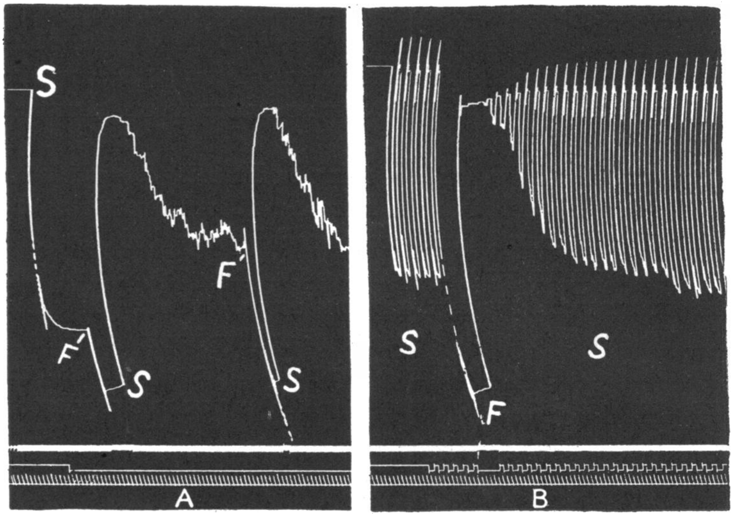


Fig. 3. Quadriceps. Ether only. Slow rate 30 per sec., fast rate 155 per sec. Upper signal, frequency; middle, line falls when circuit made. Lower, time in seconds. A, continuous submaximal stimulation. Depression due to change of rate after 5-sec. spell of fast stimulation. Recovery curve is tremulous, temporary setback after 1-sec. fast spell. B, same strength of stimuli. Short tetani of slow stimuli before and after 5-sec. spell of fast rate.

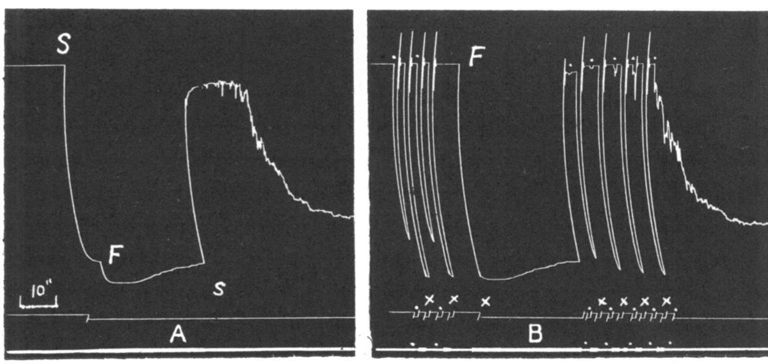


Fig. 4. Quadriceps. Dial only. Extensor tone in intact limbs, with occasional extensor spasm and outspreading of claws. Slow rate to cut nerve, 32 per sec.; fast rate 145 per sec. Fusion rate in this muscle was unusually high. Upper signal, line falls when circuit made. Lower signal, frequency, enlargement with fast rate. A, continuous submaximal stimulation. Depression due to change of rate after 30-sec. spell of fast rate. Recovery curve is tremulous. B, 1 min. later. Tremor has disappeared, recovery is complete. Same strength of stimuli. Short tetani of slow and fast rates alternated. White dots show when slow rate is used, crosses for fast rate. After 30-sec. spell of fast rate, practically no reply to slow rate, good contraction with fast rate. Gradual recovery under continuous slow stimulation.

No general rule can be given as to the time which should elapse before the muscle can be considered to be "resting." Each preparation must be tested to find out the necessary period for recovery under given conditions of stimulation and anæsthesia. In Fig. 3 the anæsthetic is ether and marked depression is shown after a 5-sec. spell of the high rate. In Fig. 4 the anæsthetic is dial only, and a 30-sec. spell of fast stimuli is necessary to produce a similar depression (in this preparation a 5-sec. fast spell had no depressant after effect). The tremulous character of the recovery curve

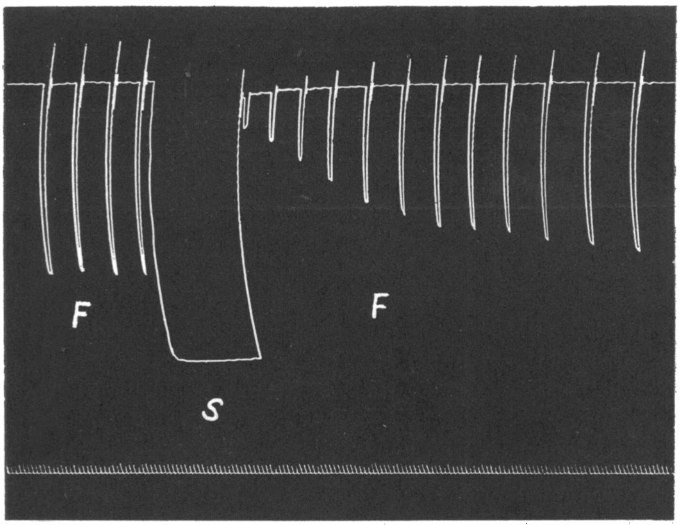


Fig. 5. Quadriceps. Dial and ether. Four submaximal tetani on fast stimulation rate from neon lamp, followed by maximal contraction producing full extension for 21 sec. on slow rate from induction apparatus. Immediately after slow spell same fast stimuli as before produce smaller contractions. Time in seconds.

will be noted, this feature disappears as soon as recovery is complete. In Fig. 4 B short tetani of slow and fast rates are tested in turn as controls. After a half-minute spell of fast stimuli, there is practically no response to a short spell of the slow rate, while the response to the fast rate is but slightly impaired. The block is selective, stimuli of a certain (submaximal) strength are ineffective at slow rates, effective at fast rates. There is, temporarily, an apparent rise of threshold for weak slow stimuli.

Are the swift relaxations seen with fast stimulation of strength III also due to depressant after effects of previous activity? It is well known that continuous stimulation of a nerve with fast stimuli leads eventually to relaxation of its muscle. But this familiar "fatigue" relaxation is very different from that shown here. By a sudden increase of rate as much relaxation may take place in one-tenth of a second as would take several seconds if the same fast rate had been supplied to the nerve of resting muscle. Attempts to duplicate the events shown in Fig. 3 B by inserting a spell of slow stimuli of strength III between short tetani caused by fast stimuli showed that fast spells have a depressant effect on further fast spells if spaced too closely. Resting periods sufficiently long to allow for recovery must be given between each fast spell to secure a control series of curves of even depth. A definite depressant after effect can be shown by making the slow stimuli stronger and the fast stimuli weaker (Fig. 5). This can be done by delivering one set of shocks from an induction apparatus and the other from the neon lamp, or by using two sets of induction apparatuses, interrupted at different rates.

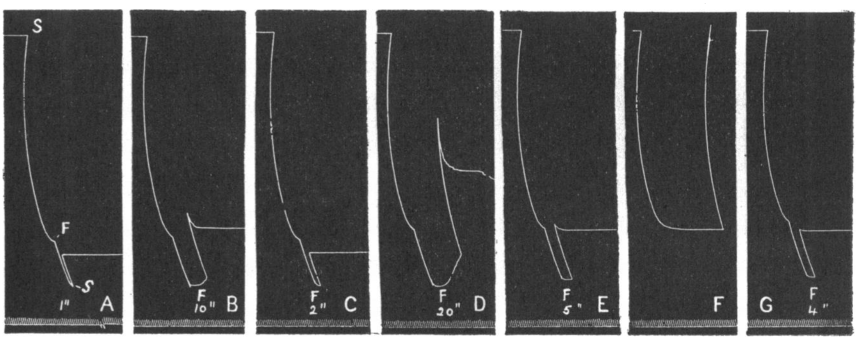


Fig. 6. Transition from accretion to depression. Quadriceps. Dial anæsthesia. Extensor tone present in intact limbs. Five seconds of slow rate (28 per sec.) followed by different lengths of fast rate (160 per sec.). Pauses of 1 min. before each trial. Curves taken in random order shown. A, 1-sec. spell fast rate—after effect, accretion of contraction. B, 10-sec. spell fast rate—after effect, depression of contraction. C, 2-sec. spell fast rate—after effect, accretion of contraction. D, 20-sec. spell fast rate—after effect, marked depression, beginning of recovery shown. E, 5-sec. spell fast rate—after effect, depression very slight and transient. F, Control curve before final trial. G, 4-sec. spell fast rate, no after effect.

*Accretion of contraction following fast rates.*

Under certain conditions a temporary increase in the amount of contraction produced by a weak slow rate can be shown following a spell of fast stimulation.

(*a*) The fast stimulation must be brief, Fig. 6 shows the transition from accretion to temporary depression of contraction as a result of prolonging the fast spell. Control curves of uninterrupted slow stimulation were taken before each trial.

(*b*) The fast stimuli must be applied in the early stages of a maintained contraction. If tried later the same period of fast stimulation will produce a depressant after effect.

(*c*) Dial anæsthesia is favourable for showing this excitatory after effect. A condition of enhanced extensor tone is found fairly frequently in dial anæsthesia and may be seen as a passing event in light ether or dial-ether anæsthesia. A definite sensation of resistance and subsequent yielding is felt when the knee on the intact side or the forelimbs are passively flexed. While this general extensor tone is present weak slow stimuli are less easily depressed by the after effects of fast stimulation. The spells of fast rate have to be repeated or prolonged to obtain marked depression (Fig. 4). If the anæsthesia be deepened sufficiently with ether to diminish extensor tone in the intact limbs results similar to those shown in Figs. 1 and 2 are obtained in the experimental muscle. With deep dial anæsthesia accretion after very short fast spells may still be obtained though the intact limbs are toneless (Fig. 8 A).

*Decerebrate preparations.*

The depressions caused by alternation of rates are first demonstrated under ether, or combined dial and ether anæsthesia, using the standardized slow and fast rates in the three different strengths.

The decerebration is carried out by the trephine method with as little disturbance as possible, the electrodes are left in position, and within a few minutes of decerebration the test rates are tried again. It has been found that when marked or moderate extensor rigidity develops in the intact limbs, the effects of weak slow stimuli applied to the cut nerve are not depressed but strengthened by the after effects of short fast spells, so that accretion of contraction occurs, even though depressant effects have been shown with the same stimuli just before decerebration (Fig. 7). This alteration in response is seen best when the onset of rigidity is progressive and occurs within a few minutes of decerebration. Sudden violence or marked delay in onset are not so favourable. Control curves of uninterrupted slow stimulation should be taken. If it is found that a partial extension is not steadily maintained, then depression rather than accretion will be seen on alternation of rates. If for any reason, *e.g.* administration of more ether, the decerebrate tone temporarily wanes, or if the rigidity be lessened by exposure of the brain stem to cold, depression may be shown again in the denervated limb. If rigidity is slight or fails to develop the curves show much the same picture as before decerebration. Accretion is not seen but there may be a lessening of the depressant effect. These results have been seen whether ether alone or combined ether and dial were the preliminary anæsthetic.

In acute spinal preparations the results resemble those obtained under deep anæsthesia. Stimuli which just before transection have produced excitatory after effects (decerebrate rigidity being present in the intact limbs) will after transection produce depressant effects.

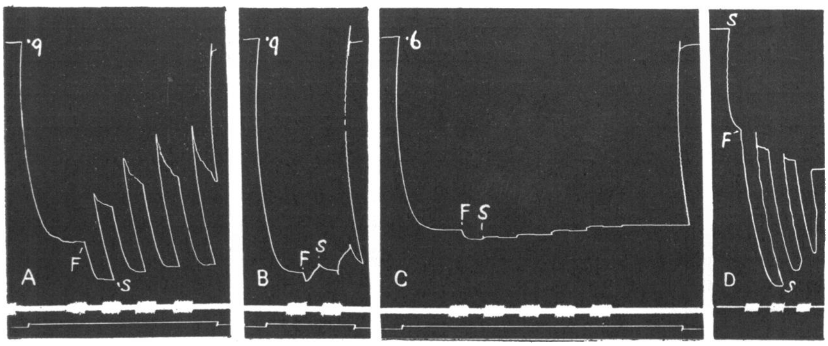


Fig. 7. Quadriceps. Dial and ether. Slow rate 26 per sec., fast rate 155 per sec. A, submaximal curves (potential divider 0·9) taken just before decerebration at 2.50 p.m. The muscle had been in use since 11.40 a.m. B, 2.56 p.m. Rigidity appearing, 0·9 now gives curves of strength II type. C, 3.2 p.m. 0·6 gives submaximal contraction. Before decerebration 0·6 gave no response. No depression on alternation of slow and fast rates. D, another preparation. Preliminary ether, no dial. Decerebrate rigidity present. Contraction improves after 5-sec. fast spells.

*Reversal of after effects with ether.*

If a well-marked excitatory effect is present, showing accretion of contraction after a brief fast spell, a small quantity of ether added to the anæsthetic can reverse this result and produce a depression with the same conditions of stimulation (Fig. 8). In the first few seconds of ether administration tone in the intact limb may be heightened and accretion of contraction may be well marked in the experimental limb. This stage passes on quickly to one of general relaxation of tone and of depressant effects after fast spells. Events on the two sides do not always run parallel, as depression may appear in the denervated limb while the intact limb is still passing through the stage of increased tone. Changes in tone as shown by extensor resistance to flexion can be recorded by a simple graphic method recently described [Briscoe, 1934].

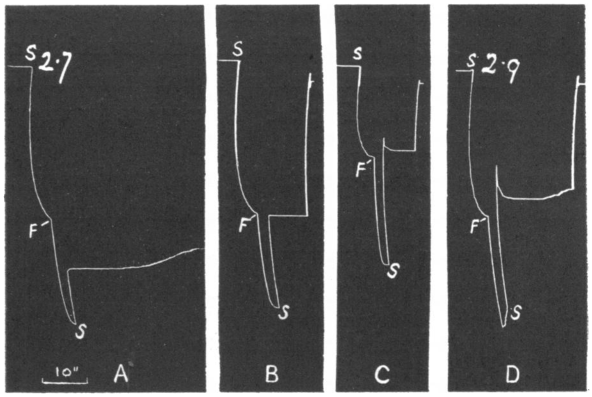


Fig. 8. Dial anæsthesia, rather deep, no extensor tone. Fusion rate 27 per sec. In each case 5 sec. of slow rate followed by 2 sec. of fast rate, then slow rate resumed. A, before giving ether. Accretion after short fast spell. B, 30 sec. after starting ether. No accretion. Same stimuli. C, 10 sec. later. Depression after fast spell. After this responses to slow and fast stimuli rapidly diminished. D, 4 min. after ether started. Strength of stimulus raised from 2·7 to 2·9 to obtain same size contraction as in control. Depressant effect after fast spell.

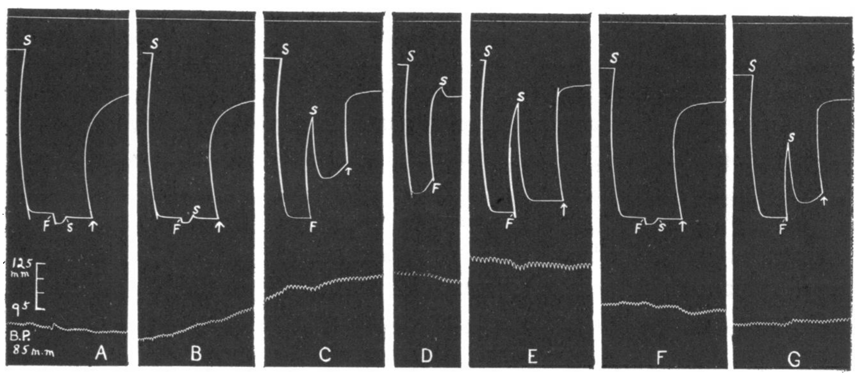


Fig. 9. Dial anæsthesia. Fusion rate 28 per sec. All stimuli of same strength, double that necessary to produce full extension, slow rate interrupted after 10 sec. by 5-sec. spell of fast rate. Arrow denotes cessation of stimulation. Lower trace, blood-pressure. A, before ether. Excitatory effect with fast spell. B, 40 sec. after ether started. Blood-pressure rising. C, 90 sec. after ether started. Rapid depression with fast spell. D, 3·5 min. after ether started. Contraction not maintained with slow or fast stimulation. Ether stopped at end of fourth minute. E, 2 min. after ether stopped. Partial recovery, especially for slow stimuli. Relaxation curve ↑ more sudden than in A and B. F, 6 min. after ether stopped. Recovery for slow and fast rates. Relaxation curve more gradual. G, 2 min. after more ether added. Brief excitatory effect with fast spell, then rapid depression.

With stimuli of strength III reversal can also be shown (Fig. 9). Control curves of the fast rate applied to resting muscle show that contraction gives way far more rapidly after ether than under dial only. The depression on change of rate (Fig. 9C) is only partly due to the after effect of preceding slow stimulation.

These reversals do not appear to be dependent on blood-pressure changes, as rapid depressions consequent on ether administration can be shown with a rising blood-pressure, and after recovery the results can be repeated without much alteration in the pressure (Fig. 9F, G). This observation has been repeated in decerebrate preparations. After transection of the cord peripheral depressions are seen accompanied by low blood-pressures.

*Controls.*

Are the depressant effects described due (*a*) to neon lamp stimulation, (*b*) to local stimulation fatigue in the nerve trunk?

(*a*) As the results have been repeated with ordinary induction shocks, using two primaries interrupted at different rates, they do not appear to be dependent on neon lamp discharge. The two induction apparatuses have been placed at right angles some yards from each other, as an additional safeguard. The two methods of stimulation can be combined, using the neon lamp for slow rates and an induction coil for fast rates and *vice versa*. If the transfer by commutator from one system to another be done quickly no loss of tension need ensue from the change over.

(*b*) Local fatigue in the nerve trunk under the electrodes is unlikely, as the results have been repeated using two sets of electrodes 15 mm. apart on the nerve. The change of rate and transfer from one pair of electrodes to the other is done simultaneously. As each frequency is applied to a fresh portion of nerve the possibility of local stimulation fatigue appears to be excluded. Again, weak slow stimulation from the neon lamp has been maintained uninterruptedly through the electrodes next the muscle and fast weak induction shocks have been applied in short spells from the second pair of electrodes 15 mm. distant. Temporary depression of contraction is seen when each fast spell ceases. Depressant effects have been obtained with non-polarizable electrodes.

The above points indicate that these depressions are produced not in the peripheral nerve trunk at the site of stimulation, but either in the nerve terminals or the neuromuscular junctions or in the muscle fibre itself.

*Curarized preparations.*

It is usually held that failure in "Wedensky inhibition" takes place at the neuromuscular junctions. Repetition of the present experiments in curarized preparations leads to the same conclusion, although the results are not very satisfactory, largely owing to the difficulty of stimulating directly large muscles such as quadriceps *in situ*. Soleus and tibialis are muscles more suitable for direct stimulation; in neither have swift relaxations been obtained by abruptly changing the rate of stimulation.

## Discussion.

The slow rates of stimulation used in this investigation were chosen because it had been shown experimentally that rates of this order applied to the cut nerve could maintain the leg in postures of full extension. This observation that slow rates can maintain prolonged contractions has been confirmed by Hallowell Davis and Davis [1932]. The experimental production of fast rhythmic movements, by varying the amplitude of stimulus applied to the cut nerve, showed that a ratio of at least 1 to 15 had to be maintained between the rate of movement and the basic rate of stimulation [Briscoe, 1931]. A fast rate of 160 per sec. would be sufficient to carry fast movements of 10 or 11 per sec. Both slow and fast rates are higher than the firing rates found in individual muscle fibres during postural reflexes [Denny-Brown, 1928] and during voluntary movement [Adrian, 1929]. Probably these natural rhythms can maintain steady postures and smooth movements because of their asynchronous character.

The relaxation of muscle contraction caused by fast strong rates following slow rates has long been known under the general term of "Wedensky inhibition." The depressions with stronger fast rates described here may be regarded as examples of this phenomenon, but the depressions and accretions of contraction shown with slow weak stimulation following fast rates cannot be included under this description.

The various theories to account for "Wedensky inhibition" have been fully discussed by Fulton [1926] and need not be recapitulated.

The main points which emerge from this investigation are as follows. Under combined dial and ether anæsthesia strong slow rates of stimulation are effective in establishing and maintaining contraction even after a profound depression has been caused by a fast rate of stimulation. Nevertheless, the preceding depression has some effect, as there may be a disclosure of stimulus rhythm and contraction is not established as rapidly as in resting muscle. Further strengthening of the stimulation tends to mask this latter effect, but increases the rapidity and depth of depression seen with fast spells. On the other hand weak slow stimuli are very susceptible to the after effects of contractions caused by fast stimuli of the same strength.

Since the stages can be shown by which (*a*) accretion passes over to depression (Fig. 6), (*b*) depression with slow stimuli passes over to depression with fast stimuli (Figs. 1 and 2), it is possible that these results may all be examples of the same underlying process. Reversal of effect, consequent on smaller or greater concentration, is familiar in the action of many drugs. It is suggested therefore that when sustained contraction is enhanced after brief spells of fast stimulation, small accumulations of after effects (whatever their nature) exercise a favourable influence, so that temporarily contraction is more effective, and that larger accumulations, resulting from longer fast spells, have a reverse effect, so that temporarily contraction is less effective. It has been pointed out that the stimulation (strength II) required to keep the leg in a position of full extension is very mild. When strength III stimulation is used the number of elements replying to the slow rate may be so great that the unfavourable after effect of fast stimulation may be disguised and the leg maintained in full extension.

In the sudden lengthening due to a fast strong rate following a slow one, "Wedensky effect," the duration of preceding activity is clearly important as the character of the response to a given fast stimulus may be excitatory or depressant according as to whether the duration is short or long. The depth of the depression obtained is increased as the spells of fast stimuli are repeated, especially if closely spaced. It would appear that the after effects of the fast spells are added to the after effects of slow stimulation to produce these results.

The reactions recorded in different conditions of anæsthesia and in decerebrate preparations, with and without the presence of extensor activity, indicate that observation of the general tonic condition of the preparation is helpful in the interpretation of results obtained in the denervated limb. Since connection with the central nervous system is severed on the experimental side, changes occurring in the rest of the body could only be communicated through the circulation. The dependence of all these reactions on the blood stream is shown by the observation that a leg can be held in full extension for hours with a stimulation rate of 20–25 per sec. to quadriceps but will give way in a few seconds if the circulation to the limb be occluded.

It is usually stated [Starling, 1933] that drugs such as ether depress the functions of the spinal cord, and that this central effect is obtained with much smaller concentrations than those required to abolish conductivity in peripheral nerve. A concentration of ether sufficient to reduce decerebrate rigidity in the intact limbs will also produce the depressant effects already described in the denervated limb. Since skeletal muscle is used as an indicator of events in the spinal cord, it may be permissible to suggest that the depression of reflex activity, caused by deepened anæsthesia, may have a peripheral as well as a central factor as the indicator is itself subject to change.

The depressions seen with submaximal stimulation are not due to overwork of the muscle, as marked depressions may be obtained at the first trial after only a few seconds' stimulation, yet may be unobtainable after prolonged use if rigidity has set in following decerebration (Fig. 7 C). The records obtained in atonic decerebrate and spinal preparations in the absence of dial show that the reactions are not confined to special conditions of anæsthesia.

## Summary.

Under combined dial and ether anæsthesia sudden relaxations of contraction have been obtained in peripheral preparations of mammalian muscle, extensor and flexor, by abruptly changing the frequency of stimulation applied to the motor nerves.

If the stimuli applied to the quadriceps nerve are too weak to produce full extension of the leg, raising of the rate causes further contraction, but return to the slow rate produces a temporary depression of contraction which recovers completely if the slow rate be continued.

If the stimuli are of a strength more than sufficient to produce full extension, sudden raising of the rate produces a depression which becomes more marked if the fast rate be continued.

Temporary increase of the contraction caused by a slow submaximal rate is seen after short spells of fast stimulation under certain conditions of anæsthesia. This result can be reversed, and depression shown instead of accretion, by deepening the anæsthesia with ether.

When decerebrate rigidity is present in the intact limbs it is difficult to show in the denervated limb the type of depression seen when a stimulus of submaximal strength is suddenly reduced in rate.

The depressions which follow sudden raising of the rate may be regarded as examples of "Wedensky inhibition," but not the temporary depressions or accretions of contraction which follow sudden reductions of rate.

It is suggested that these reactions are due to the after effects of preceding stimulation, small concentrations of "after effect" exercising a favourable influence leading to increase of contraction, and large concentrations an unfavourable influence, leading to depression of contraction.

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