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THE RESPONSE OF A SINGLE END ORGAN.

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INTRODUCTION.

THIS paper describes a series of experiments that have been made to investigate the general properties of the sensory end organ which is stimulated by the stretching of a muscle, and is especially concerned with the phenomena of adaptation, *i.e.* the gradual fall in the frequency of the discharge under a constant stimulus.

The muscle receptors were used by Adrian and Zotterman [1926 *a*] in their original study of the response of the end organ, and by Bronk [1929] in the study of fatigue, but in the present work a much more detailed survey has been made possible by the use of a preparation which can be relied upon to contain one and only one end organ. This preparation has given such constant results that the effect of a number of factors which influence the response has been analysed in a quantitative way, and with the aid of these data it has been possible to formulate a working hypothesis as to the nature of adaptation.

PART I.

METHOD OF INVESTIGATION AND GENERAL FEATURES OF THE RESPONSE.

Adrian and Zotterman [1926 *b*] have shown that all the types of end organ which they examined reacted qualitatively in much the same way, giving a rhythmic discharge, so that a study of any one type will give results which probably have a general application. The end organs chosen for the present investigation were muscle proprioceptors, as their responses could be evoked repeatedly without difficulty, and their stimulus, stretching, could be easily measured, controlled and graded. The oscillograph described in a previous paper [Matthews, 1929 *a*] was used to record the action currents from the nerves, and with this instrument frequencies as high as 2000 per sec. can be detected and measured.

In the early experiments the muscle part of the double preparation described in a previous paper [Matthews, 1929 *b*] was used. This muscle contained a small number of end organs, and sometimes rhythmic discharges could be picked out from the records. But it soon became clear that little could be learnt without studying the response of a single end organ.

Adrian and Zotterman investigated the response of a single end organ in the sterno-cutaneous muscle by cutting the muscle down until only one end organ was left, and Bronk [1929] has succeeded in recording action currents from a single end organ by the method devised by Adrian and Bronk [1929] to lead off the response of a single motor neurone, viz. transecting the nerve distal to the electrodes until only one active fibre remains. Either of these methods might have been used. However, the experiments on the skin-nerve-muscle preparation suggested that a suitable preparation might be found intact in one of the tiny muscles in the frog's toe, and after some search a preparation was found which yielded responses showing a single rhythm (see Fig. 1). This preparation avoided the uncertainty of cutting nerve or muscle

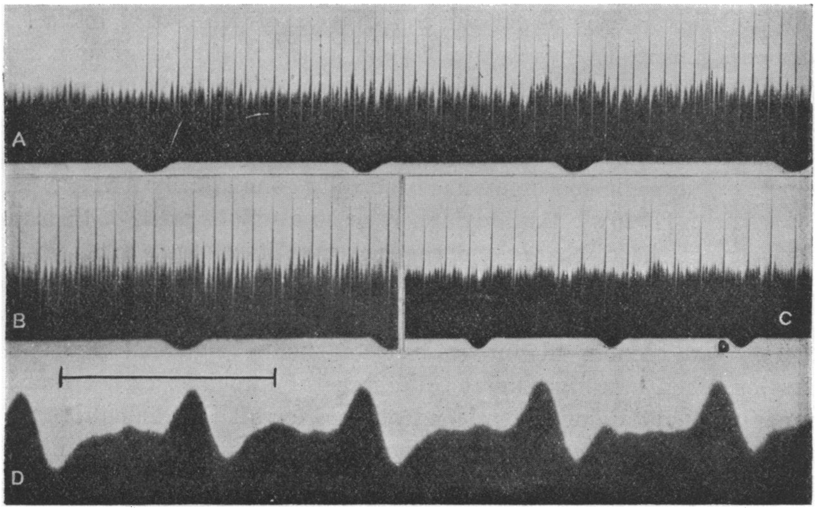


Fig. 1. Rhythmic response in nerve evoked by stretching preparation from the frog's toe. Temperature 17° C. [90·11.] A. On loading with 5 g. B. 2 sec. later. C. 5 sec. later. D. Similar response recorded at high speed to show extreme regularity of the discharge. Time marker 1/5 sec. in A, B and C. Line in D represents 0·01 sec. All figures read left to right. The numbers in brackets are the reference numbers of the experiment from which the figures are taken.

and when set up on the electrodes would remain in good condition for some hours.

The preparation.

The preparation consists of the small muscle on the upper outer side of the middle toe of the frog (M. ext. br. prof. dig. III): the contraction of this muscle causes extension of the toe with some flexion to the side. The nerve which supplies it is the peroneal, of which the lateral branch only is required for this preparation. The dissection presents no special difficulties, and some 500 preparations have been made. It was found that about two out of three preparations gave a single rhythmic response; of the others, sometimes more than one rhythm appeared, and sometimes no response was obtained. In the earlier experiments the tendon of the muscle was cut and a silk thread attached to it, but in the later experiments the whole muscle was freed from its neighbours and only the top end was left attached to the bone; as the nerve entered high up in the muscle this could be done without damage to it.

The evidence that a regular rhythm from a muscle receptor is the response of a single end organ has been fully gone into by Adrian and Zotterman [1926 *a*]. Although there is no absolute proof of this, the regularity of the discharge and the fact that it can be evoked many times successively from the same muscle preparation, leave little doubt that it is produced by a physiological unit of some sort.

There are obvious advantages in using such a single end organ preparation when investigating the discharge of impulses, rather than a preparation containing several end organs, for all the difficulties that arise in analysing a composite discharge are avoided and the smallest changes in rhythm can be followed with great accuracy. The preparation employed gives results which are exactly repeatable, for the records obtained from two similar loadings with an interval of rest between have the same rhythm at any instant after loading.

Nature of the end organ responding to stretch.

The muscles from the preparations were usually stained and examined under the microscope at the conclusion of an experiment. Various stains were used, methylene blue, gold chloride, gold chloride and osmic acid. It was usually possible to find one end organ of the type described by Cajal [1904] and classed as muscle spindles; once two were found, but never more. They have a much simpler structure in the frog than the mammal, and were never found to be supplied by more than one nerve fibre.

As it has been suggested [Denny Brown, 1928] that the mammalian muscle spindle is an organ responding to active contraction of the muscle but not to passive stretch, tests were made in two experiments to see if the end organ responding to stretch was indeed the muscle spindle. Fine threads of silk were placed round the muscle at intervals of 1–2 mm. and drawn tight successively, starting at the tendon end; the response to stretch was investigated with a pair of telephones connected to the amplifier. Tightening the first three or four threads had no effect on the response, but, as the next was drawn tight, a burst of impulses was set up and the preparation ceased to yield any response to stretch. The muscles were then stained with methylene blue and examined under the microscope. In one a muscle spindle was seen between the last thread which did not abolish the response and the one which did, and in the other a muscle spindle was found under the thread which abolished the response. No other end organs could be found in either muscle. There seems little doubt that the structure which responds to stretch and tension is the muscle spindle. In all the preparations examined it was found about the middle of the muscle.

Method.

The preparation was set up with the nerve passing into a moist chamber and over electrodes of thread dipping into U-tubes of Ringer's fluid (see Fig. 2); from these leads were taken to the amplifier by silver wires coated with silver chloride. The muscle itself was supported through the bone by a pin which stuck into the floor of a small ebonite chamber, containing about 5 c.c. of Ringer so that the muscle was completely immersed, and the thread from the tendon was led out through a slot. This thread was led over a pulley and arranged so that it could be loaded with weights or springs; for gradual loading these could be controlled by a dashpot or loading machine (see p. 96). In some experiments the preparation was enclosed in a double-walled brass box. The thread to the tendon was led out through a slot, and water could be circulated between the double walls, so that the preparation could be brought to any desired temperature. The temperature was measured by a small copper-constantan couple coated with celluloid, placed in the fluid close to the muscle, and connected to a mirror galvanometer; this enabled the temperature to be read to 0·05° C. The cold junction was immersed in water in a thermos flask.

A slow-speed camera driving Ciné Bromide paper (Kodak) at 9 or 18 cm. per sec. was used to record the oscillograph deflections, with a clock time marker showing 1/5 second. In the later experiments (115 onwards) a double camera was used, which had the advantage of being able to give simultaneous records at 4 metres and at 18 cm. per sec.

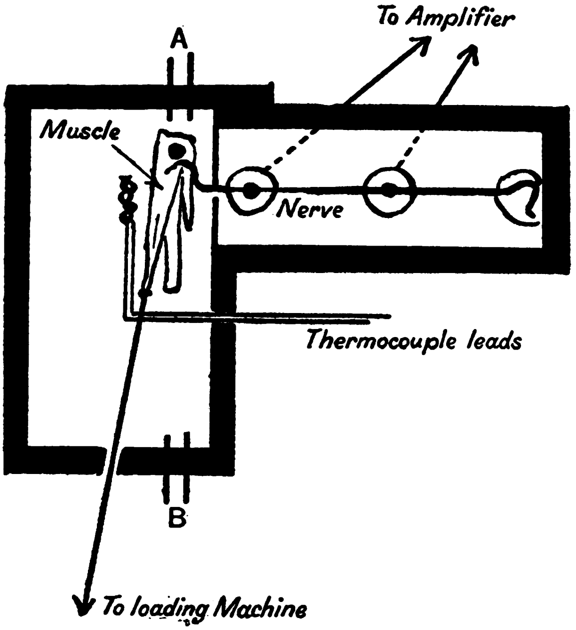


Fig. 2. Diagram to show arrangement of preparation electrodes, etc., in the moist chambers.

In this camera part of the beam of light from the oscillograph falls on a moving mirror camera such as has been described in a previous paper [Matthews, 1929 *b*], and part is diverted by prisms into a slow-speed moving paper camera. The two parts of the camera are driven by one motor through magnetic clutches and can be engaged independently.

In the earlier experiments the apparatus was not effectively shielded from a 93 cycle A.C. power main which induced currents in the leads, etc., causing regular waves at 93 per sec. to appear in some of the records. Fortunately the action currents stand out clearly from this artefact, especially when they are recorded diphasically. Further shielding has now eliminated it.

Results.

In the initial experiments a weight of 2 g. was used and the load was put on in about 1/5 sec. When the muscle is tetanized the maximum tension it develops is of the order of 10 g., so that a tension of 2 g. is such as might be expected to occur during life. The discharge reaches a maximum rate of about 120 per sec. as the load reaches its full value, and declines in the way shown in Fig. 3. Examples of typical records are shown in Fig. 1.

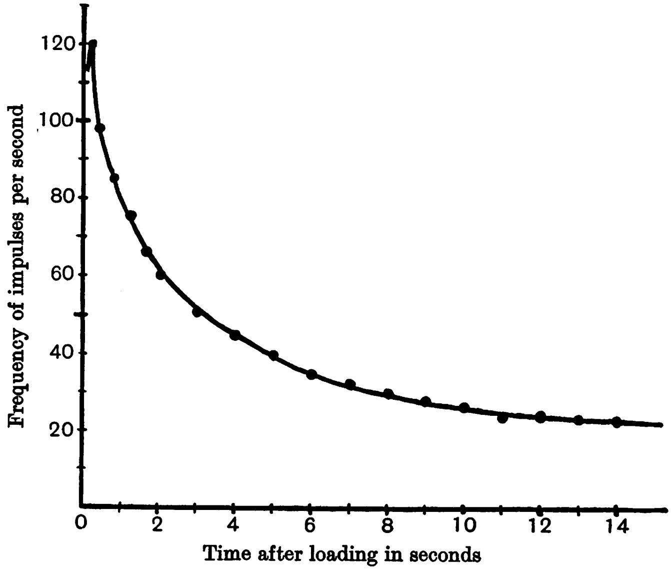


Fig. 3. Graph to show the decline in frequency of the response after a load of 2 g. is hung on the thread from the tendon. Temperature 15° C. [81·3.]

Regularity.

The regularity of the discharge is very striking. If each successive interval is measured and plotted against the number of impulses set up, and a smooth curve drawn among the points, the mean fluctuations of the points on either side of the curve are never more than 3 p.c. when the mean rate is 70 per sec. (see Fig. 4); the irregularity increases at lower frequencies and the series becomes quite irregular when the frequency has fallen below about 20 per sec.

It will be seen from Fig. 3 that the frequency reaches a maximum rate at about the same time as the stimulus and then declines steadily, the fall becoming slower towards the right, and tending to reach a steady value. Often the frequency here becomes steady for 20–30 sec., and when the frequency falls further the discharge loses its regularity and becomes a random series of impulses, though occasionally there is a tendency for impulses to drop out of an otherwise regular series, as has been noticed by Bronk [1929]. With small loads the slow random discharge goes on for some minutes, but with heavier loads the discharge stops entirely much earlier, and with very heavy loads the discharge is often completely over in a few seconds, but the latter seem to inflict permanent damage on the end organ and, after a few such loadings, there is no response. With heavy loads the irregularity sets in at a much higher frequency. A rate of about 20 per sec. seems to be the lowest at which these end organs can set up impulses in a regular series (at 15° C.). When rates of less than 20 per sec. occur the impulses are irregularly spaced, but often groups of four or five impulses appear at a spacing corresponding to 20 per sec. when the mean rate has fallen to 12–14 impulses in the second.

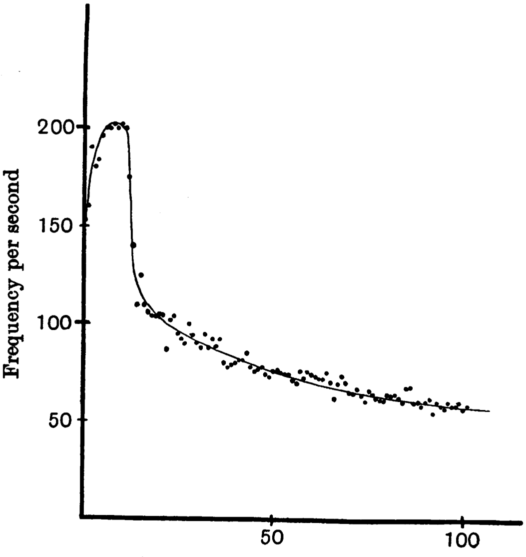


Fig. 4. Graph showing the regularity of the discharge. Each point is determined by measuring the interval between one impulse and its successor. Temperature 15° C. Sudden loading 10 g. [113·42.]

Constancy of results.

The close agreement of successive discharges is very remarkable. If the muscle is loaded at 5-minute intervals, the discharges of impulses are so closely alike that the number of impulses set up in any fixed period, *e.g.* 5 sec., rarely varies from the mean by 1 p.c. The 5-minute interval between the loadings is necessary, for, as Bronk [1929] has shown, if a muscle is loaded repeatedly at very short intervals, the discharge is much reduced, which reduction he ascribed to fatigue. Loadings are, therefore, always carried out at an interval of 5 minutes or more, and after each the fluid in the muscle chamber is changed. Under these conditions records can always be repeated on any given preparation with discrepancies of only 1 or 2 p.c. For the first hour after the preparation is set up the rhythms tend to rise slightly: this may be due to the removal of harmful substances set free in the dissection, or recovery from minor injuries. After this the rhythms remain steady for a period of 3–4 hours, and then begin to vary again. Occasionally the end organ ceases to set up impulses abruptly without any previous signs of failure, but whether this is due to cessation of conduction by the fibre concerned or to some sudden change in the end organ or its neighbourhood is uncertain. In these cases the muscle still responds to electrical stimulation of the nerve through the recording electrodes.

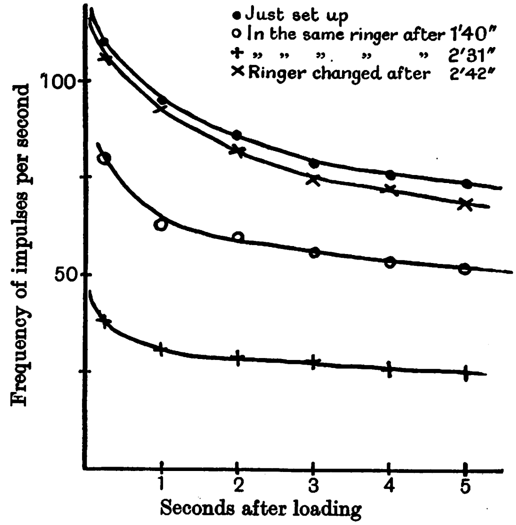


Fig. 5. Graphs showing the effect on the end organ response of keeping the preparation in the same 5 c.c. of Ringer. Temperature 15° C. [138.]

It is found that if the preparation is not irrigated frequently but kept in the same 5 c.c. of Ringer the frequency of impulses set up by a given load rises slightly in the first hour, but falls steadily throughout the next, the preparation giving no response after about 2½ hours. If the inexcitable preparation is then washed with fresh Ringer the response returns in a few minutes to its initial value. This is illustrated in Fig. 5. Bubbling air through the Ringer does not delay this onset of inexcitability; so that it seems probable that the inexcitability is the result of some product of the tissues themselves. It is interesting to compare this loss of excitability in the end organ and recovery in fresh Ringer with the reversible inexcitability of muscle studied by Dulière and Horton [1929]. Here, too, there is a rapid recovery in fresh Ringer, and the explanation suggested by them, namely, a raised potassium content in the interspace of the tissue, may account equally for the failure of the sensory end organ.

The composition of the Ringer used throughout these experiments was as follows: NaCl 0·65 p.c., $NaHCO_3$ 0·015 p.c., KCl 0·02 p.c., $CaCl_2$ 0·025 p.c.

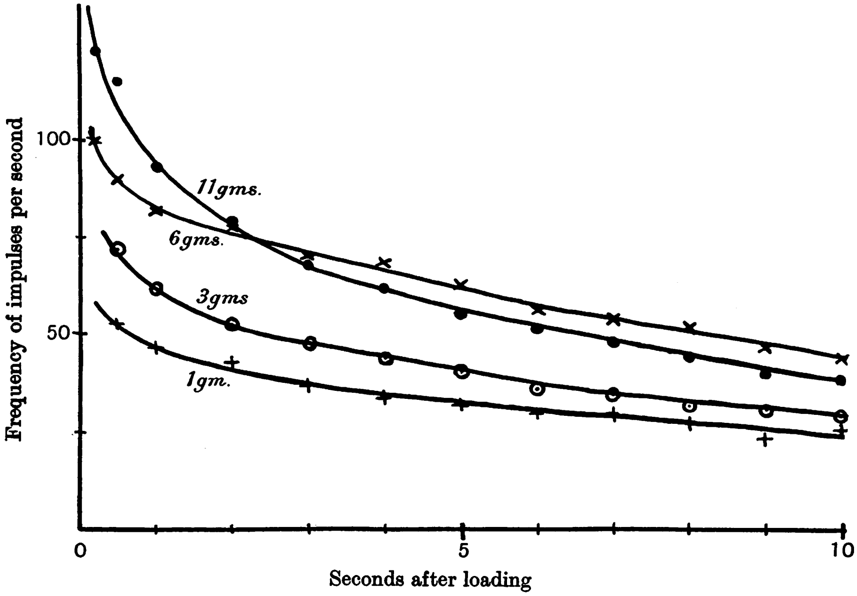


Fig. 6. Graphs showing the response evoked by various loads. Temperature 16·5° C. [135.]

Relation of load to discharge.

Adrian and Zotterman [1926 *b*] have shown that, for all end organs so far investigated, the frequency of impulses set up increases with the stimulus. With this single end organ preparation it has been possible to investigate this relationship with considerable accuracy.

The discharges obtained with different loads are shown graphically in Fig. 6, and it will be seen that the curves are of the same general shape, but with the heaviest load the fall in frequency is more rapid.

If the frequency at any instant in the first 2 seconds after loading be plotted against the logarithm of the load, the points lie very nearly on a straight line; this is illustrated from two experiments in Fig. 7. It has long been held that, as a stimulus increases in geometric progression, the sensation increases in arithmetic progression (Fechner's Law). These experiments suggest that this is due in part, at least, to properties of the end organs rather than to the central interpretation of the sensory message by the brain. For a group of end organs the relation of the stimulus to the total frequency will be somewhat modified, because the stronger stimuli will affect end organs which do not respond to weak stimuli. This can be seen in a muscle containing several end organs; only one end organ may respond to the small load, but as the load is increased the response of other organs appear severally. Such end organs would thus appear to have a definite threshold, and this is confirmed by the response of some single end organ preparations to small loads. A load of ½ g. may produce a considerable response starting at 25–30 per sec. and soon becoming irregular; but a load of ¼ g. often produces no response at all, although controls show that the tension reaches the tendon. But this is only found to occur in preparations from which there is no resting discharge; when a resting discharge is present it is increased by the slightest stimulus.

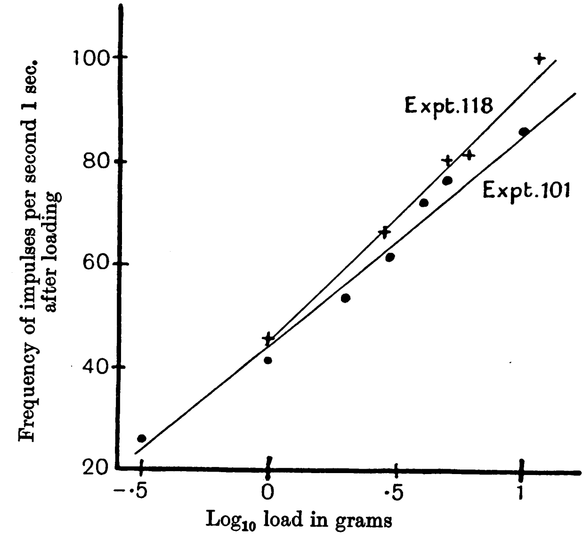


Fig. 7. Graphs showing the relationship of the frequency 1 sec. after loading to the logarithm of the load. Temperature 15° C.

Resting discharge.

Adrian and Zotterman [1926 *a*] found that the end organs in frog's muscles set up a slight discharge of impulses (3–5 per sec.) in the absence of any external tension. In the single end organs studied in this work the rate of discharge was much less, rarely above 2 per sec., and often completely absent. When present it was quite irregular. It was found to cease for 10–30 sec. after the preparation had been stimulated, thus confirming Adrian's findings. In some preparations the end organ appears to be in a no-threshold state (evidenced by the response in absence of stimulation), and in others cited above to have a definite threshold. This might be due to the way in which the end organ is situated in the muscle, rather than to some property of the organ; in some cases it being under slight deformation when there is no tension on the tendon, in others the tension not reaching it until the muscle

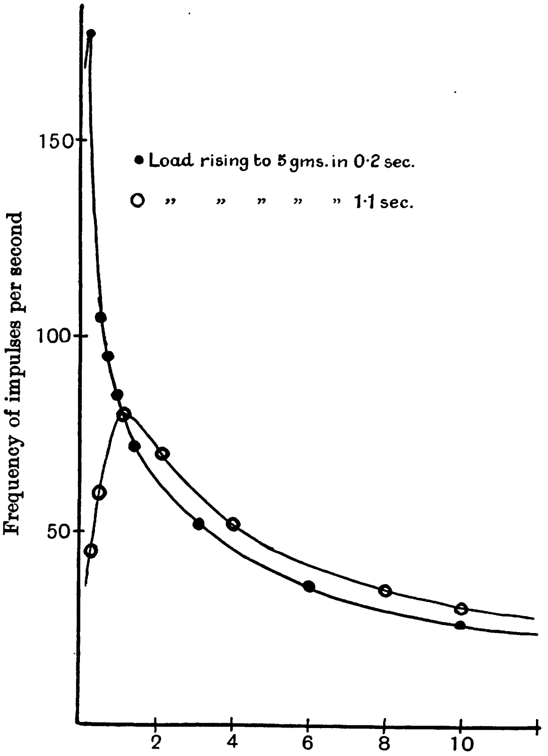


Fig. 8 A. Response evoked by loading the muscle with 5 g. in 0·2 and 1·1 sec. Temperature 19° C. [98, 12, 13, 14.]

has been slightly deformed. There is little doubt that the resting discharge originates in the same nerve fibre as the response to tension, as it never appears superimposed on this, as might be expected were it in an independent fibre, and moreover its absence after stimulation makes it highly probable that it arises in the same physiological unit.

Rate of loading.

In Fig. 8 A are shown the responses recorded when a single end organ is loaded at various rates. As might be expected, with slower loading the frequency falls less rapidly than when the load has reached its full value in a very short time. The degree of adaptation at any moment after the start is therefore less with the slower loading. These results are replotted in Fig. 8 B. Here abscissæ represent the number

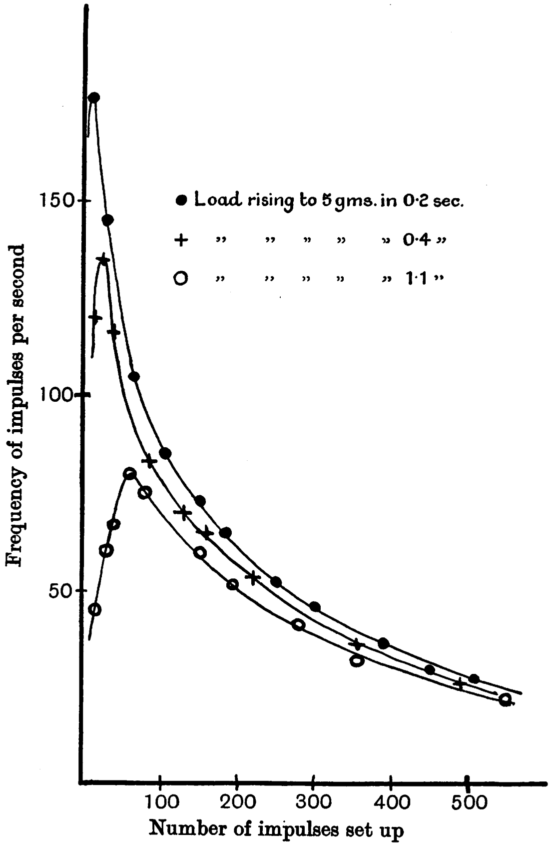


Fig. 8 B. Same results replotted against number of impulses set up, also for loading in 0·4 sec.

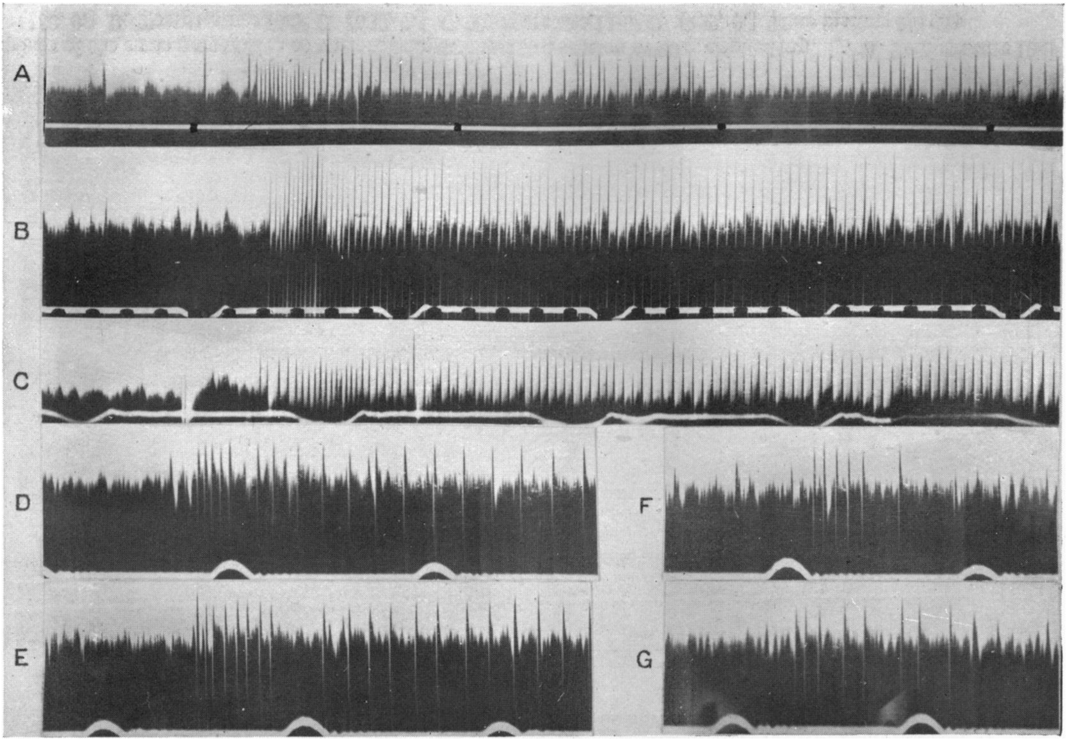
of impulses set up, and it is clear that the fall in frequency of the response is not conditioned only by the number of impulses which have been discharged; after *e.g.* 200 impulses have been set up the frequency after rapid loading is greater than that with slow loading. In the first case the load is at its full value throughout the discharge, but in the second it is smaller at the beginning. It appears, therefore, that in setting up a given number of impulses the larger load produces less change in state of the end organ, and less adaptation per impulse set up. More direct evidence on this point will be presented in Part III of this paper.

It is clear from the curve of the rapid loading (Fig. 8 A) that, at the beginning of the discharge, the adaptation to the stimulus takes place very fast, so that considerable adaptation will already have taken place when the load reached its full value. Now, however great the stimulus, there must be some limit to the frequency of impulses which can be set up even before any adaptation has occurred, and in order to determine this absolute maximum frequency the loading would have to be instantaneous and very excessive, so as to constitute an invariable and maximal stimulus. If this were done the end organ should discharge at its maximum rate, and this rate should depend on its internal conditions rather than on the stimulus.

Rapid loading.

An attempt was made to load the muscle in this way by dropping a weight through about 1 cm. before letting the thread to the tendon take the load. A record of the results is shown in Pl. I, A. The decline in frequency during the first second after loading is shown graphically in Fig. 9. The initial frequency is about 240 per sec., and the fall is very rapid during the first 0·2 sec. and then slows up and becomes more and more gradual.

In these experiments the loading still took a finite time, probably about 0·01 sec., and owing to the momentum of the falling load the initial tension must have been much more than the weight of the load. This raised a doubt as to whether the initial rapid fall in frequency was caused by internal factors of the end organ, or was merely due to the fall in the stimulus after the momentum had been absorbed. For these reasons a spring-loading device was made. It consisted of a light spiral spring, which could be set to any desired tension by moving the anchorage at one end, the other being attached to a light wire hook to which the thread from the tendon was tied. The hook was held by a trigger so



Records of responses evoked by sudden loading. A. 20 g. wt. Temperature 15° C. [82.] B. 20 g. spring. Temperature 15·4° C. [113.] C. 20 g. spring. Temperature 14·5° C. [136.] D, E. 2 g. Temperature 16° C. [105.] F, G. Response to stretch only, 2 g. 15·5° C. [190.] (D, F, rapid loading. E, G, less rapid loading.)

Fig. 1.

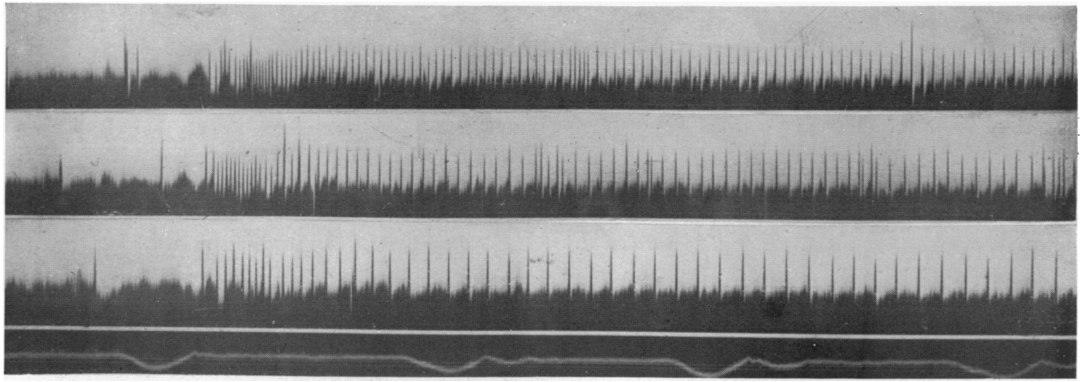


Fig. 2.

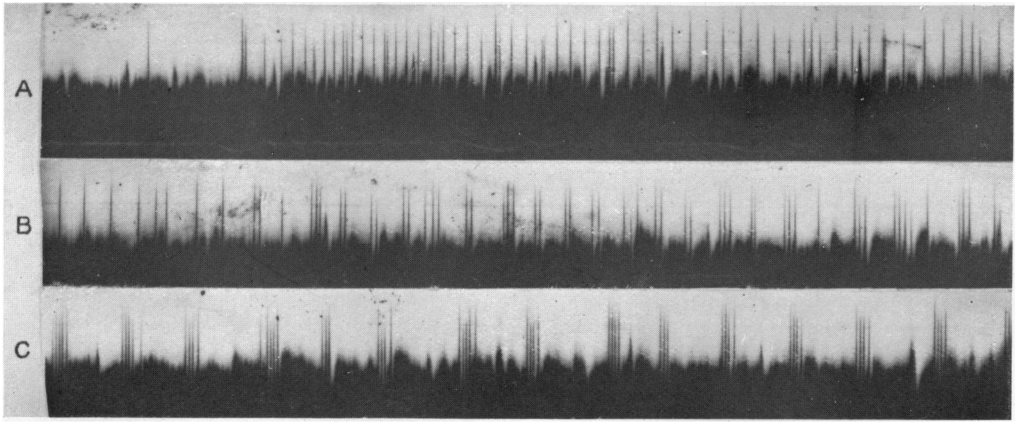


Fig. 1. Response of the same preparation at various temperatures to a tension of 20 g. applied rapidly. A. Temperature 19·8° C. [132, 6.] B. Temperature 15·0° C. [132, 7.] C. Temperature 11·0° C. [132, 8.] Time marker 1/5 sec.

Fig. 2. Response of preparation that has been kept at 24° C. in sodium chloride alone for 30 minutes. Temperature 20° C. [143.] A. On loading. B. 2 sec. later. C. 5 sec. later. Time marker 1/5 sec.

that the thread was just taut, and on releasing the trigger the spring tension was communicated to the thread almost instantaneously. The moving parts of this apparatus weighed about 0·2 g., and tests with a tension of 20 g. showed no detectable overloading.

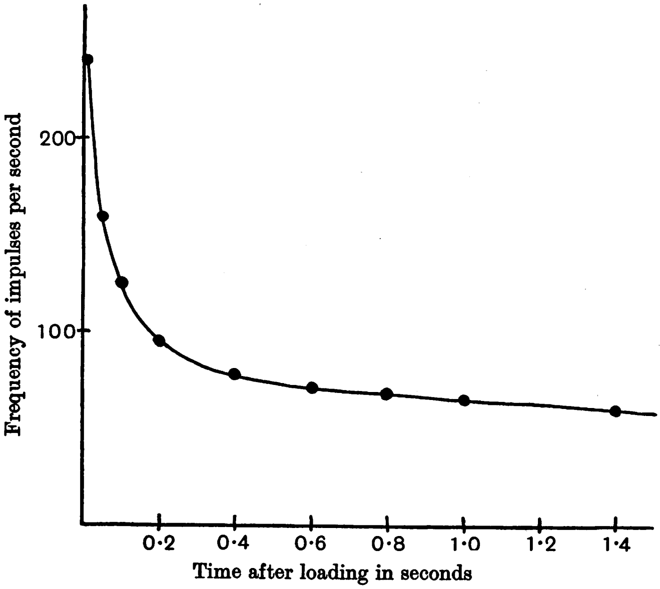


Fig. 9. Graph of response during first second after sudden loading with a large load. 100 g. Temperature 14° C. [82·2.]

With this method of loading the time-frequency curves were much the same as those previously recorded. The maximum frequency often reached 260 per sec. (at 14° C.). We must, therefore, conclude that the rapid initial fall of frequency is due to the properties of the end organ, and not to a fall in the external stimulus.

Extension and tension.

Close examination of records such as those of Pl. I, A, B and C, reveals that, with large loads, the frequency falls throughout the discharge and there is no sharp discontinuity, so that there is little doubt that the rapid initial discharge is produced by the same physiological unit as the later part of the discharge. But with small loads applied rapidly the frequency falls very abruptly after about 0·05 sec., and there is often even a slight pause in the discharge (see Pl. I, D, E). This still occurred when all possible precautions were taken to avoid initial overloading; the pulley was eliminated, and the thread made to slide over a smooth brass ring, a thread loop was substituted for the wire hook so that the moving parts of the system were reduced to a mass of 70 mg. In four preparations a brief response appeared during extension, and there was no response to continued tension (see Pl. I, F, G). The brief response in Pl. I, F, G is not unlike the initial part of the response in Pl. I, D, E, and suggests that the initial rapid response is connected with extension. Another possibility is that, owing to differences in viscosity, the initial elongation of the various elements in the muscle differs from the equilibrium attained later. Thus, if the terminal parts of the structure upon which the nerve endings are distributed were more viscous than the middle region, there would be an initial over extension of this region followed by a certain amount of contraction as the more viscous portions elongate. Or if the end organ were relatively more viscous than the surrounding muscle fibres, just after rapid loading, it would support more than its share of the load, and as it yielded the muscle fibres would take up more of the tension.

When the stimulus is large, small variations in it do not appreciably affect the frequency of impulses set up (see paragraph on load-frequency relationship), and so any effect of viscosity in causing initial overloading will be much less apparent. The fall in frequency must then depend on the internal state of the end organ, the stimulus being in effect very great throughout. It seems possible that the abrupt initial fall with small loads and the smooth fall with large loads may be accounted for in this way. In the former case the initial stimulus to the nerve ending is large, and would fall as viscous yielding occurred, leading to an abrupt fall in the frequency of response; in the latter the stimulus is very great all the time, and the smooth fall of frequency results from changes in the state of the end organ occurring progressively.

Refractory period.

Adrian [1921] gives the duration of the absolute and relative refractory periods for frog's motor nerve as 0·0025 and 0·01 sec. respectively at 16° C., and it has been shown in a previous paper [Matthews, 1929 *b*] that, in the frog, the fibres carrying motor impulses have similar characteristics to those carrying proprioceptor impulses, so that these values will apply to the fibre supplying the end organ. The highest frequency recorded at 16° C. is 290 per sec. In this case each impulse is set up 0·0035 sec. after its predecessor, so it is evident that, before much adaptation has occurred, a second impulse is set up in the nerve fibre very soon after the end of the absolute refractory period, and throughout the early part of the discharge with sudden loading the impulses will be travelling in incompletely recovered nerve. **Gotch** [1910] and **Gasser** and **Erlanger** [1925], working with electrical stimulation, have shown that impulses travelling in incompletely recovered nerve are conducted more slowly than in rested nerve, and that the absolute magnitude of the second action potential from the whole trunk is smaller than the first. These effects should be detectable in the early part of discharge from the end organ, although conditions are not entirely comparable, for these effects were found for the second of two impulses set up by electrical stimulation, and here a series of more than two impulses is being considered and, as **Brücke** [1926], **Forbes** [1929] and others have shown, when a nerve trunk is stimulated repeatedly there are signs of a progressive change in time relations.

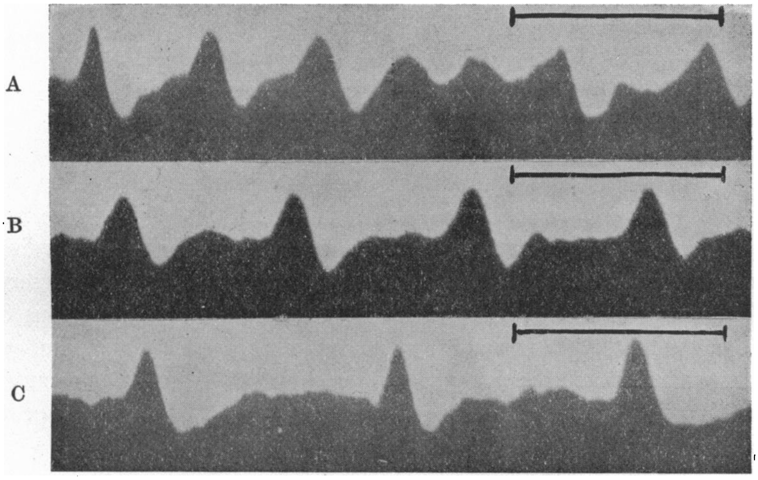


Fig. 10. High-speed records of the discharge produced by sudden application of a 20 g. spring load. A, B and C are records of the response to the same load. Temperature 14·5° C. [136.] A was taken coincident with loading; the left-hand deflection being that of the first impulse of the series. B. 2 sec. later. C. 5 sec. later. The line in each represents 0·01 sec.

High-speed records of the response to sudden application of large loads were taken (see Fig. 10). With diphasic recording there is clear evidence that the early impulses of the series are conducted more slowly than the later impulses which are not following each other at so short an interval, and all seem to be conducted more slowly than the first impulse which is travelling in fresh nerve. The rising potential gradient also appears to be less steep.

Monophasic records have also been taken after the nerve was damaged at the distal electrode by application of a drop of boiling Ringer. This always led to a reduction in the absolute magnitude of the potentials necessitating the use of more amplification, which caused a rather unsteady base line. The reduction in the potential when the impulses are travelling in close succession is not great but, from a large number of measurements, amounts to as much as 15–20 p.c. when the interval between the responses is 4σ. There is also some slowing of the rising potential gradient, but it is difficult to assess its magnitude accurately. This result is in general agreement with that obtained recently by Adrian [1930] in mammalian sensory fibres.

That the impulses are modified when travelling close behind each other shows that they are all carried by one and the same nerve fibre. And it is interesting that the diphasic records show that the impulse is conducted more slowly, and differs markedly from the first of the series, even when it occurs at an interval of 0·012 sec. after the previous one (see Fig. 10 A, C). This supports the view that recovery from each impulse of a long series may be rather different from that occurring when only two isolated impulses are considered, as in most of the published data on recovery.

Recovery curve of the nerve ending.

Adrian and Zotterman [1926 *a*] have fully discussed the rhythmic activity of nerve endings, and have pointed out that a regular discharge is to be expected from the general properties of excitable tissues, which after activity are at first completely inexcitable and then recover their excitability gradually. Thus, as the nerve ending recovers from the first impulse, at a certain stage in its recovery it becomes sufficiently excitable for the stimulus to re-excite it, and this leads to a rhythmic discharge of impulses. The greater the stimulus the earlier in its recovery will the nerve be excited, and so the frequency will increase with the stimulus. These authors have shown that adaptation might be the result of a fall of the excitability of the end organ leading to a decline in the effectiveness of the stimulus or to a slowing of the recovery or to both. By plotting the interval between responses against the load, they obtained a representation of the recovery curve of the end organ at a certain time after loading and, on the assumption that adaptation occurred at the same rate throughout the discharge, they deduced the recovery curve for the unadapted ending and found it very much slower than that of a nerve fibre. But they were not able to record the discharge during the first second after rapid loading owing to their base line being upset by a large deflection at the moment of loading, which they attributed to a mechanical movement of the nerve on the electrodes. In the present research this disturbance was eliminated by passing the nerve through a slot into a chamber separate from that containing the muscle (see Fig. 2), and by having the electrode nearest to the muscle connected to earth. Under these conditions it has always been possible to see every impulse right from the start without any serious disturbance (see Pl. I).

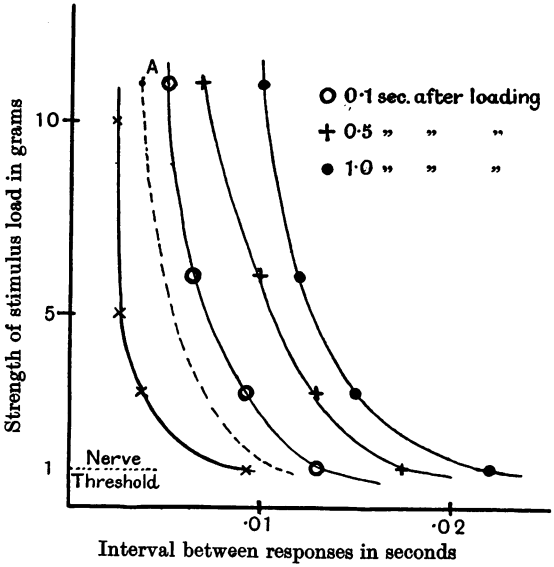


Fig. 11. Recovery curves of end organ at various intervals after loading (15° C.). The left-hand curve is the recovery curve of a nerve fibre at 15° C. plotted to the same time scale determined by the method of muscular summation.

The experimental findings failed to confirm Adrian and Zotterman's assumption, for, as has been shown in a previous section, just after loading adaptation occurs very rapidly and, before it has occurred to any extent, the interval between the impulses is only slightly longer than the absolute refractory period of the nerve fibre.

In Fig. 11 are plotted the strength of stimulus and interval between response for a single end organ 1·0, 0·5 and 0·1 sec. after loading; one point is also given for the interval 0·05 sec. after loading. It has been pointed out above that, with small loads, it is possible that viscous overloading occurs, so that the points for the small loads just after loading are uncertain, as the end organ may be sustaining a greater fraction of the load at the start. With the large loads, however, this has little effect on the response, and so the values are reliable and the recovery curve 0·05 sec. after loading must pass through the point *A*. If the curve obtained 1 sec. after loading is reconstructed through this point, we shall probably obtain a tolerably accurate representation of the recovery curve of the end organ that has been loaded for 0·05 sec. The recovery curve of the motor fibres of the frog's sciatic is shown on the same time scale. This suggests that the nerve fibre and ending have very similar characteristics, and that before adaptation occurs the recovery of the two may even have identical time relations.

DISCUSSION.

The most surprising of the above observations is that the end organ is able to respond at such a high rate initially. The rhythmic responses that have been recorded range from 260 down to about 20 per sec. (at 15° C.). If these rhythms are due to the return of excitability in one and the same structure in the way discussed above, we must conclude that the return of full excitability takes at least thirteen times as long as the first return of excitability. In the nerve fibre it takes about 10 times as long; but there is another possibility that must be considered in this connection. It will be seen from Fig. 9 that, with rapid loading, the response starts at such a rate that the impulses are separated by little more than the refractory period of the nerve fibre, and that the frequency falls rapidly until the impulses are separated by about the interval necessary for complete recovery of the nerve fibre, and thereafter falls slowly. These facts suggest that, with very intense stimuli applied suddenly, a continuous instead of a rhythmic state of excitation may be produced in the end organ, and that this sets up an impulse in the proximal part of the nerve fibre whenever the latter has recovered sufficiently and that, at a later stage, the response of the end organ becomes rhythmic and gives the lower frequencies which appear.

If the higher initial rates are, in fact, produced by continuous instead of intermittent activity in the end organ, it is clear that this can have no absolute refractory period at all. The chief argument against this view is the absence of any discontinuity in the curve with large stimuli, but an injured region in a sensory nerve fibre can certainly act as a continuous stimulus to the neighbouring intact fibre [Adrian, 1930], and the initial disorganization produced by the rapid extension of the end organ may cause it to behave temporarily as a region of continuous activity. This disorganization caused by rapid stretch might be comparable to that which Gasser and Hill [1924] found to occur in muscle fibres if they were rapidly stretched while contracting.

That some sort of continuous activity can occur in the end organs will be shown in Part II of this paper, where experiments are cited in which an end organ under abnormal conditions is found to set up groups of impulses following each other at a high frequency, the groups occurring at rates of 20–50 per sec. and strongly suggesting the presence of two rhythmic structures having different time relations, one presumably being the nerve fibre and the other some modified part of it in the end organ.

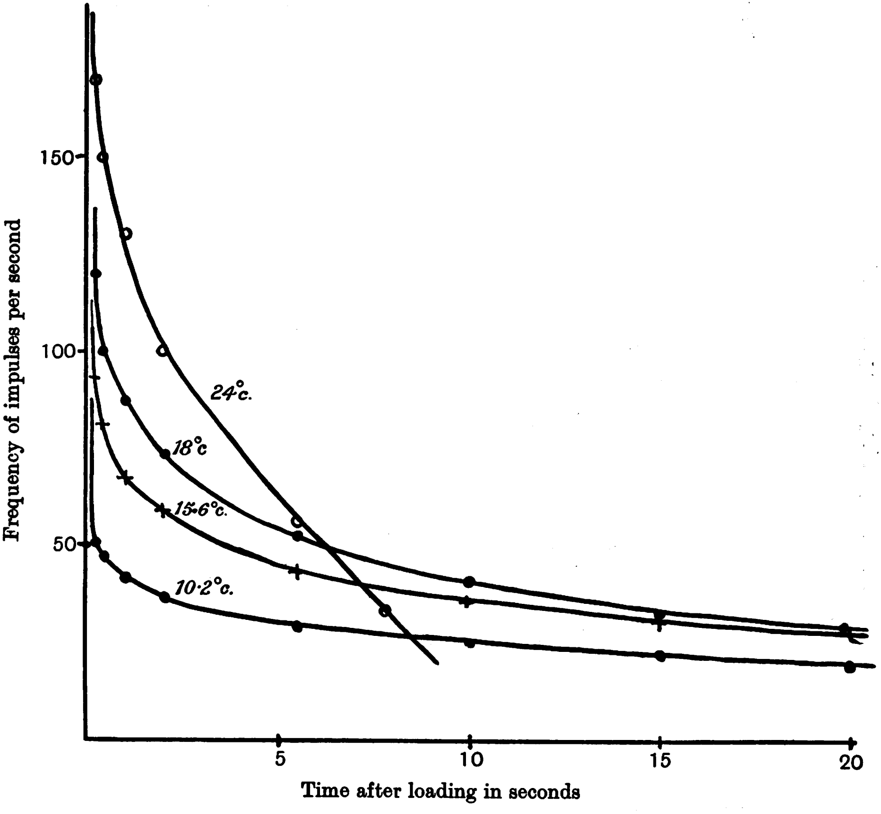


Fig. 12 A. Graphs of response at various temperatures to a load of 2 g.

PART II.

FACTORS AFFECTING THE RESPONSE TO STIMULATION.

Temperature.

When the temperature of the preparation was altered the response changed very markedly; records from a typical experiment are shown in Pl. II, fig. 1, and discharges are shown graphically in Fig. 12 A.

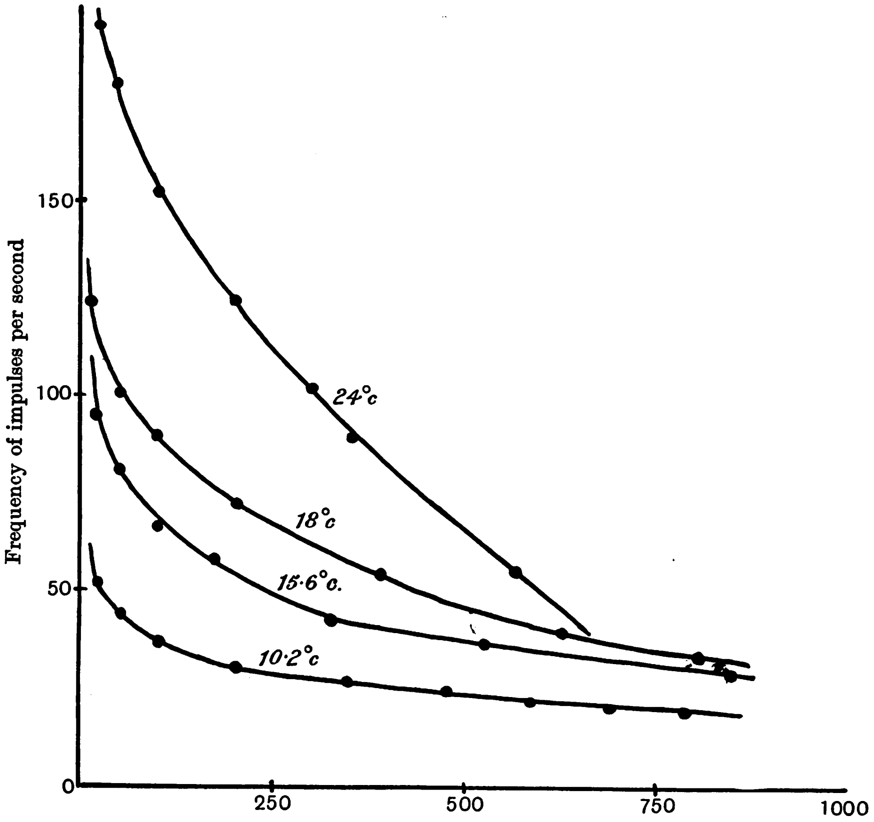


Fig. 12 B. The same replotted against number of impulses set up. [131.]

A rise in temperature caused a large increase in the initial frequency of impulses set up for a given stimulus, but the response declines much more rapidly, and at the higher temperatures became more and more brief, but for the same stimulus the number of impulses set up since the start at any instant is much greater than at lower temperatures, and the whole change in the response might be due to a more rapid recovery after each impulse, and not to any change in the process which constitutes adaptation, for if this was partly the result of the setting up of impulses the more rapidly they were set up the faster would adaptation occur. The results shown in Fig. 12 A are therefore replotted in Fig. 12 B with the number of impulses set up, as ordinates. The fall of frequency is still greatest at the higher temperatures, and so evidently adaptation is accelerated by the rise of temperature; but clearly by these methods it is impossible to dissociate the effect of temperature on the recovery after each impulse, and on the process of adaptation, and so no numerical measure of the effect of temperature on adaptation can be obtained.

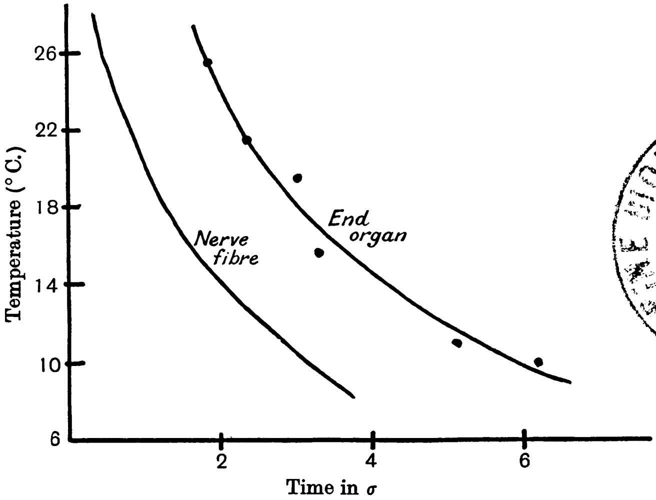


Fig. 13. Graph showing the effect of temperature on the least interval between impulses recorded from the end organ and also on the absolute refractory period of a nerve trunk.

Temperature and refractory period.

Experiments were made to see if the maximum frequency of impulses which the ending set up varied with temperature in the same way as does the refractory period of a nerve fibre. The results of such an experiment are shown in Fig. 13, in which the temperature is plotted against the interval between the responses 0·05 sec., after sudden application of a large spring load. The left-hand curve shows the effect of temperature on the absolute refractory period of a frog's sciatic nerve. The data are those of Amberson [1930] which he has shown are in general agreement with the results of other researches on this point. His method, that of measuring the least separation between two stimuli that gives rise to a greater total action current than the first alone, will give the refractory period of the fibres which recover most rapidly, but Erlanger, Gasser and Bishop [1927] have shown that the fibres of a mixed nerve trunk differ little in their absolute refractory periods, so that for the fibres with which we are concerned here the temperature-refractory period curve will be approximately that shown.

From these considerations it is evident that, throughout this range of temperature, tension on the muscle can re-excite the nerve fibre soon after its absolute refractory period is over. It was suggested in Part I that the initial rapid part of the discharge might result from the end organ being in a continuous state of excitation, and the rhythm then depending on the recovery of the nerve fibre. The similarity of the effect of temperature on the refractory period of the nerve and the least interval between the responses to tension certainly fits in with this view; if continuous excitation can take place, the highest frequencies will always be determined by the fibre rather than the end organ. On the other hand, if continuous excitation does not occur, we must conclude that the absolute refractory period of the end organ is of the same order as that of the nerve fibre, and is affected by temperature in much the same way. Owing to the probable change in adaptation rate with the temperature it is impossible to say whether the temperature coefficient of recovery remains the same for low as for high frequencies of discharge.

The effects of ions.

It was found that the nerve ending was very sensitive to changes in the ions present in the Ringer in which it was immersed. Experiments were made to investigate the effects of the common ions separately, and together.

The following solutions were used:

			p.c.		p.c.
(1)	Ringer	NaCl	0·65	$NaHCO_3$	0·015
		KCl	0·02	$CaCl_2$	0·025
(2)	Na ion	NaCl	0·75	—	—
(3)	Na and K ions	NaCl	0·75	KCl	0·037
(4)	Na and Ca ions	NaCl	0·75	$CaCl_2$	0·025

There is no great difference in the anion content of these solutions, so that differences in their effects must be attributed to the metallic ions. It was found that slight variations occurred, using solutions more or less concentrated, but these were quite insignificant in comparison with the differences that occurred when any of the cations was present or absent. The effect of changes in the latter are very striking, and begin to appear 2 or 3 minutes after the change has been made in the fluid bathing the muscle.

In all the experiments records were first taken from the preparation in Ringer, then the irrigating fluid was changed and records were taken every 5 minutes to follow any change that occurred in the response. After each record the preparation was irrigated with the solution which was being examined. At the conclusion the preparation was again irrigated with Ringer, and records were taken for a further half-hour to see if the response would return to its original value or whether irreversible changes had taken place.

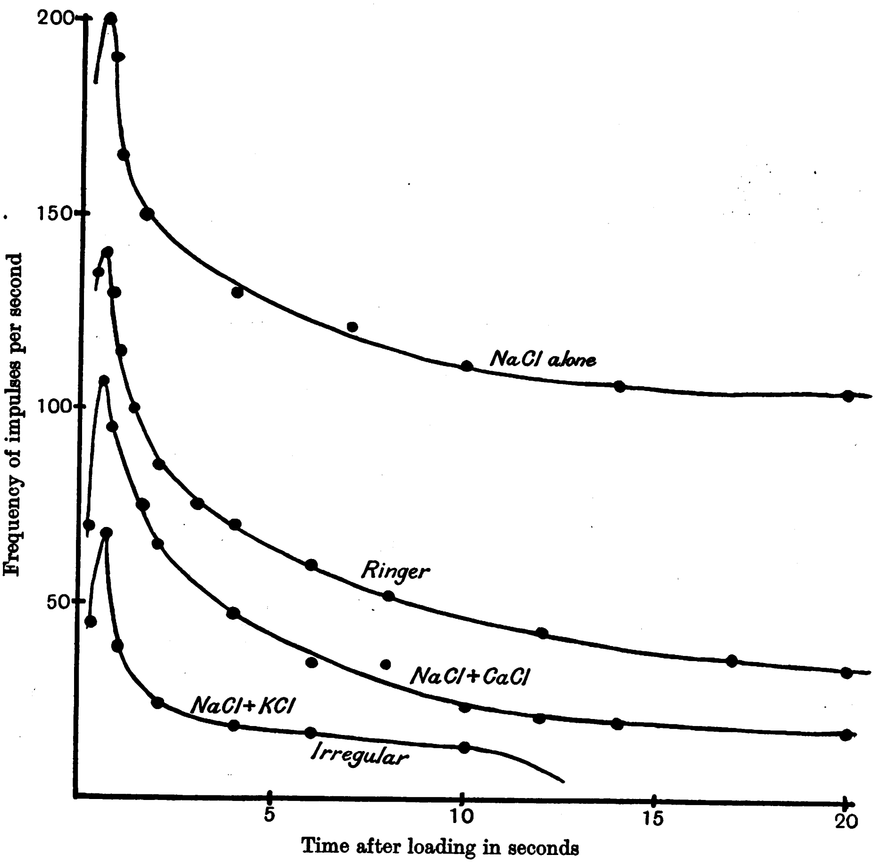


Fig. 14. Graphs showing the response of an end organ when the muscle is loaded with 5 g. in fluids of various ionic compositions. Temperature 17° C. [92.]

The results of a typical experiment are shown graphically in Fig. 14. The results of experiments on nine preparations were in complete agreement with each other and may be summarized as follows:

1. When Ringer is replaced by a solution containing only sodium chloride and potassium chloride.

(*a*) The discharge soon becomes small.

(*b*) A considerable resting discharge appears (15–16 per sec.).

(*c*) The discharge becomes irregular at a higher frequency than usual.

(*d*) The depression rapidly proceeds to extinction of the discharge, after about 40 minutes the preparation becomes inexcitable and unless transferred to Ringer at once fails to recover at all; in any case recovery is never complete.

2. When Ringer is replaced by a solution containing only sodium chloride and calcium chloride.

(*a*) The discharge is slowly depressed.

(*b*) A considerable resting discharge is present (4–12 per sec.).

(*c*) The discharge is very regular even at low frequencies (10 per sec.).

(*d*) Complete inexcitability is not reached in 2 hours, and preparation has never failed to recover in Ringer.

3. When Ringer is replaced with a solution containing sodium chloride only.

(*a*) The discharge increases rapidly, and reaches a steady state in about 1½ hours.

(*b*) A resting discharge of 2–6 per sec. appears.

(*c*) After loading the discharge falls in about 10 sec. to a steady very rapid discharge which continues for some minutes. It only falls very slowly and becomes irregular when the frequency has fallen to about 85 per sec. This irregular discharge continues at a rate of about 60 per sec. for 10–30 minutes, the frequency falling very slightly.

(*d*) The preparation returns to normal in a few minutes when replaced in Ringer.

It will be seen that potassium and calcium are apparently antagonistic, for if either is absent from the Ringer the discharge is much depressed, but if both are absent the discharge is enormously increased. Thus, if we start with the end organ in sodium alone and add either sodium or potassium the response is rapidly suppressed, but if both are added the resulting depression is very much less and the preparation soon comes to a steady state. We must, therefore, conclude that potassium and calcium each partially neutralize the depression caused by the other. This is further supported by the observation that the resting discharge which is small in sodium alone becomes large if either potassium or calcium are added, but disappears if both are added.

Calcium unopposed by potassium merely has a depressing action, but potassium unopposed by calcium has a further toxic effect; for if the preparation is left without calcium for some time, it fails to recover when calcium is replaced, but after potassium has been absent for some time recovery occurs when it is replaced. So that it seems that the action of calcium is depressant only, while potassium has in addition a toxic action. The increased resting discharge in NaCl + CaCl or NaCl + KCl suggests that the excitability is above normal, and if this is so the depression of the response to loading by calcium or potassium, when added to sodium chloride, cannot be attributed to lowered excitability, but must rather be due to alterations in the adaptation and rhythmicity.

It will be seen in Fig. 14 that when only sodium is present the discharge maintains a very high rate. This cannot be due to increased excitability alone, for however great the stimulus given to an end organ in Ringer, a discharge of this type does not occur. It is possible to produce a high initial frequency with large loads, but the frequency falls in a few seconds to far less than that which is maintained for minutes by the same end organ in sodium alone. There must, therefore, be in addition a large change in the course of adaptation. Further information on this can be obtained from the records of the response of the same end organ to various loads in Ringer and in sodium alone (see Fig. 15 A, B). It will be seen that the earlier parts of the discharges evoked by a load of 1 g. do not differ materially, but that the frequency is maintained at a higher level in sodium alone. There does not here appear to be much alteration in excitability. But with heavier loads applied slowly the whole response is of higher frequency when the end organ is in sodium alone, but if the load is applied rapidly the differences in the early part of the discharge are not very great. It seems that in sodium alone the course of adaptation is delayed, and this delay is most marked when the end organ is being "worked hard." In Part III more direct evidence will be brought forward that the increased response in sodium is due partly, if not entirely, to an increase in the rate of a process which antagonizes adaptation.

In a preceding section it has been noted that a strong stimulus is able to re-excite the nerve fibre soon after its absolute refractory period is over. The great increase in the discharge in sodium suggested that the maximum rate of discharge might also be greater, and experiments were made to investigate this point. It was found that the maximum frequencies produced by sudden loading with large spring loads were only slightly greater in sodium alone than in Ringer throughout the range of temperature investigated. That the greatest initial frequency is little higher in sodium makes it very probable that the limit is set by a structure, the absolute refractory period of which is little affected by the absence of potassium and sodium.

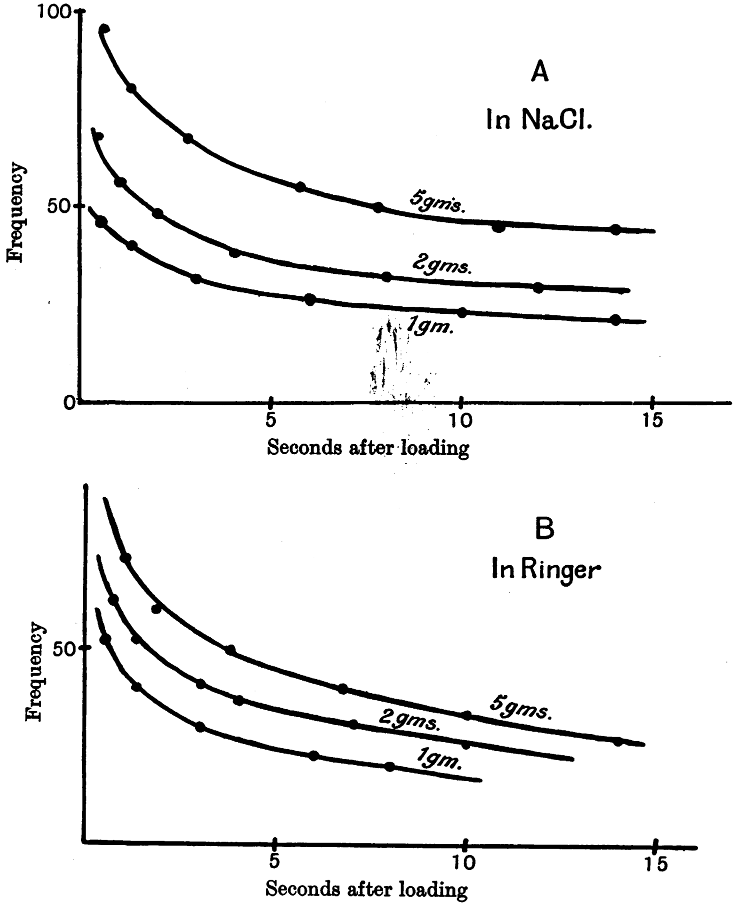


Fig. 15. Response of an end organ to various loads. Temperature 15·7° C. [101.]
A. In sodium chloride alone. B. In Ringer.

Grouped impulses.

It is found that if the end organ preparation is kept at about 25° C. in sodium chloride alone for some time a discharge of a most striking type develops, and once it has developed remains until the temperature is lowered below 18° C. This is illustrated in Pl. II, fig. 2. When the preparation is loaded the discharge starts rhythmically in the normal manner, but when the frequency has fallen to 50 per sec. the impulses begin to occur in pairs instead of singly, and as the rhythm slows further the impulses appear in groups of three, four and five, separated from one another by time intervals of 2–5σ. This discharge continues for about a minute, the rhythm becomes slower, and the groups a little longer. The regular evolution of this type of discharge and the high rate at which the groups appear rule out the possibility of their being due to twitching of the muscle fibres. This muscle only gave occasional twitches in NaCl.

These grouped discharges show a remarkable resemblance to those Adrian [1930] has found to occur in mammalian sensory nerves, and suggest that the two have a common origin in fundamental properties of end organs and nerve fibres.

This type of discharge has only been met with under somewhat abnormal conditions, and probably never occurs in the living frog; but nevertheless it is extremely interesting in the light it throws on the end organ. The rhythm of the groups' response is quite normal, and is presumably determined by the recovery of the end organ. To what then are the groups due? The short interval between the impulses in the groups suggests that this rapid rate is connected with the return of excitability in the nerve fibre. It is suggested that, under the conditions existing here, the end organ is rhythmically producing a state of excitation, but that this state of excitation lasts abnormally long so that the nerve responds again to the state of excitation as soon as it has recovered sufficient excitability. At the beginning of the discharge only one impulse is set up at each excitation, so we must conclude that, as adaptation takes place, the duration of the excitatory state increases as the discharge of the end organ becomes slower. It has been suggested in Part I of this paper that the rapid rate of the first part of the response to rapid loading may be due to the rhythmic properties of the nerve fibre rather than the nerve ending, and these dual discharges increase the probability of this being the true explanation. Spontaneous rhythmic discharges of groups of impulses have also been observed at temperatures of 22° C. and over in Ringer, but it has not been possible to obtain them with certainty; for the present their discussion has been omitted.

Effects of an electric current.

Since the end organ is very sensitive to the ionic composition of the fluid round it, it seemed worth while to see how it would be affected by the passage of an electric current through it. We know so little of the site of the structures where the rhythm of the end organ originates that it is impossible to orientate a flow of current with respect to their arrangement, but it is possible to send a current through the muscle and see whether the response is affected by it and depends on its direction. The non-polarizable electrodes *A*, *B* (Fig. 2) were connected through a reversing switch in series with a battery, rheostat and milliameter, so that currents could be sent through the tissue in either direction. The currents used were only a few milliamps and, as the cross-section of the chamber was some ten times that of the muscle, the currents in the muscle itself were very small, and were not sufficient to make the muscle twitch when they were started or stopped. There was some current escape into the recording electrodes but only at the moment of make or break, and this did not seriously interfere with the record of the sensory impulses.

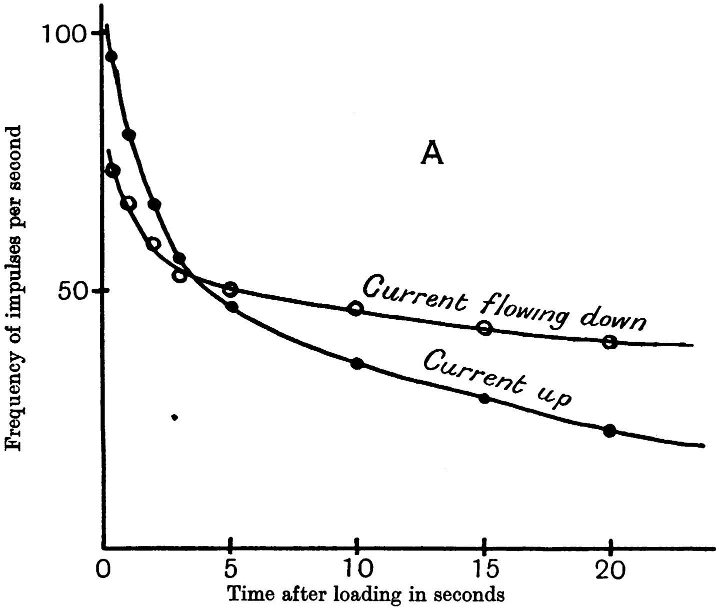


Fig. 16 A, B, C. Effect of current flow through the muscle on the response of the end organ to a load of 5 g. Current 7 m.a. Temperature 15·4° C. [140.] A. The current was turned on 5 sec. before loading.

The effect of a current flowing up or down the muscle is shown in Fig. 16 A; the current was switched on 5 sec. before loading and left on throughout the discharge. The flow is said to be up when the tendon end of the muscle is connected to the positive pole of the battery, and down when it is connected to the negative pole. The first part of the discharge is affected very little by a flow of current, but afterwards,

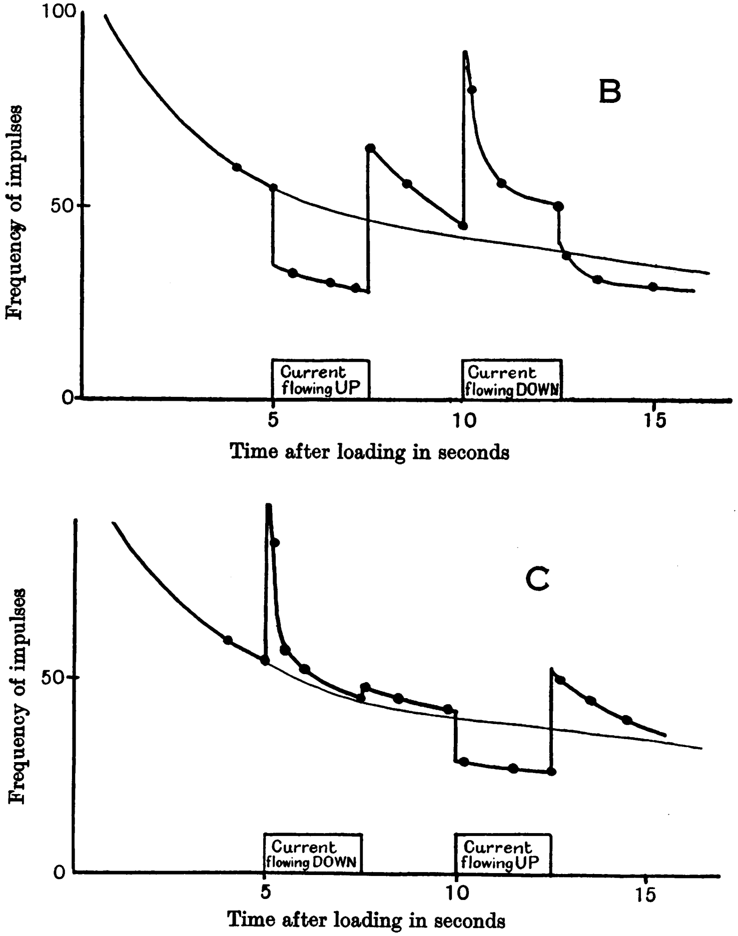


Fig. 16 B, C. Muscle was first loaded and the current turned on at the points indicated. Temperature 16·5° C. [139.]

when the current is flowing up, the frequency falls more rapidly than when it is flowing down. This occurred in all of five preparations on which it was tried. With the current flowing down the muscle the response continued regularly for 3 minutes, but with the current reversed the discharge fell much more rapidly and became irregular after 30 sec., and ceased entirely about 1 minute after loading. With the current flowing up adaptation is more rapid than with no current, when flowing down it is less rapid.

The effects of current flow through the muscle are more striking if the current is turned on after the muscle has been loaded. The results of experiments in which this was done are shown in Fig. 16 B, C. Again, it will be seen that an upward flowing current reduced the response whilst it is increased when the current flows down.

Hydrogen-ion concentration.

Experiments made to discover if the end organ response was influenced by the *p*H of the Ringer bathing it. Buffered solutions were made up in the way described by Mines [1913], using borate and acetate mixtures, and their approximate *p*H determined with indicators. The discharges from the end organ were recorded when it was irrigated with Ringer of *p*H 8·7, 7·3 and 6·0, but it was found that any of the solutions produced a gradual reduction of the response, which seemed to occur at about the same rate with all these H-ion concentrations. This depressing action of the buffer solutions made it impossible to determine the effect of the *p*H with certainty. There did not seem to be any great difference in the action of the solutions of different *p*H, but clearly further experiments are required to determine this, using buffers that do not themselves influence the response. These have not yet been undertaken.

Hydrocyanic acid.

The effect of irrigating the single end organ preparation with 0·05 p.c. hydrocyanic acid was to cause a slight increase in the discharge, which was rapidly followed by depression of the response and complete extinction in about 30 minutes. The results of a typical experiment are shown in Fig. 17. It will be seen that the discharge becomes more and more brief. The response never returned even if the preparation was irrigated with Ringer alone before the response had completely disappeared, but under these circumstances it continued to respond to loading with a very brief discharge of moderate frequency for an hour or more. It is interesting to compare these results with those of Bronk [1929], who found that if a muscle was placed in nitrogen the response from its receptors to tension was depressed in much the same way; the discharge became more and more brief, but complete recovery took place when the oxygen was readmitted to the muscle. The general action of hydrocyanic acid on living cells is to destroy some link in the oxygen utilizing mechanism, and so these results confirm those of Bronk in showing that the continued action of the end organ is dependent on some oxidative process.

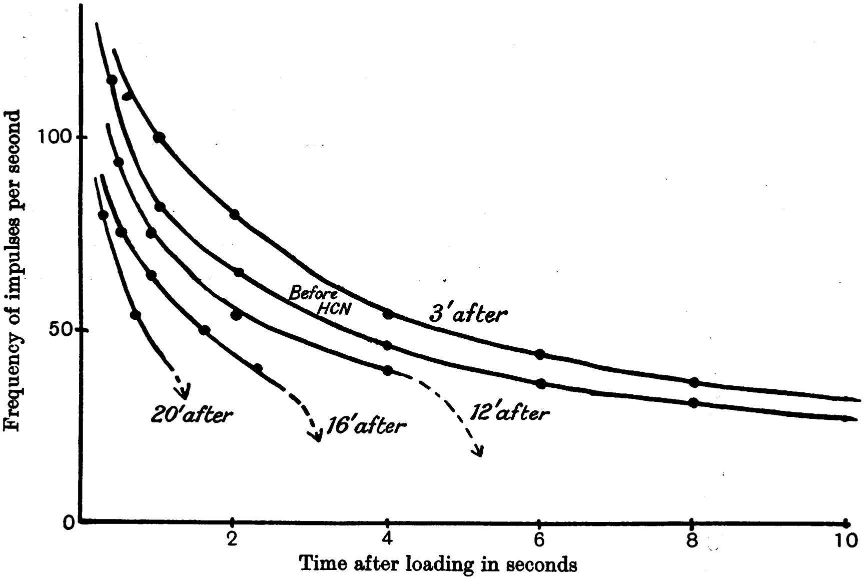


Fig. 17. Effect on response to 2 g. of irrigating muscle with Ringer containing 0·05 p.c. hydrocyanic acid. Temperature 19° C. [98.]

Part III.

The mechanism of adaptation.

The records obtained by Adrian and Zotterman [1926 *b*] on the cat's pressure receptors and by Bronk [1929] on the tension receptors of the frog's muscle seem to indicate that the adapted state passes off very rapidly when the stimulus is withdrawn, for after a rest of 1 sec. a renewal of the stimulus gives nearly the same maximum frequency as in the fresh preparation, and the frequency after 5 sec. stimulation is also not greatly reduced. But an analysis of the response of the single ending to repeated loading shows that there is a considerable after effect which appears after a few seconds of loading and disappears in a few seconds after unloading, and is therefore quite distinct from the fatigue process studied by Bronk, which took a minute or more to appear and many minutes to disappear completely. This transient depression of the response after loading is thus an adaptation remainder rather than a true fatigue. The evidence of this adaptation remainder is that, when the preparation is reloaded after a few seconds' rest, the initial high frequency falls off much more rapidly, reaching the low value (which Bronk speaks of as the plateau) in a shorter time (see Fig. 18). So although the capacity to respond initially at a high rate returns very rapidly on cessation of the stimulus, the capacity to maintain the discharge at a high rate does not return so rapidly. The total number of impulses set up by a given period of stimulation will be smaller than in the fresh preparation, and in this sense the adaptation passes off relatively slowly.

So clearly in investigating the state of the end organ, we must consider not only the frequency of impulses set up at the beginning but also the maintenance of this frequency. If we judge the state of the end organ by the number of impulses it sets up in a given time of fairly long duration, we obtain a measure of adaptation which takes into account not only frequency at any instant, but also its maintenance and the "adaptation remainder" referred to above. It has been possible in this way to map out the course of the development of the adapted state, and of the recovery from it.

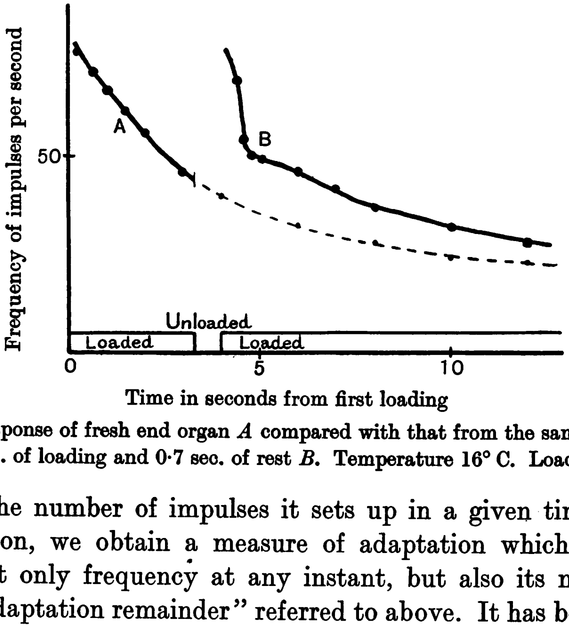


Fig. 18. Response of fresh end organ *A* compared with that from the same end organ after 3·3 sec. of loading and 0·7 sec. of rest *B*. Temperature 16° C. Load 2 g. [104.]

Disappearance of adaptation.

The preparation was loaded with a small weight (2–5 g.), and after 5 sec. the weight was raised and then lowered again after varying intervals. These were determined to 0·02 sec. by an automatic loading machine.

The thread from the tendon was led over a small pulley and tied to one end of a light aluminium lever to which the loading weight was also attached. As long as the other end of the lever was depressed the weight was supported by the lever, but when this was released the thread supported the load. This end of the lever was depressed by a cam, and when the latter was rotated half a turn the lever was free to rise, and the other end fell until the thread from the tendon supported the load. Thus rotation of the cam caused loading and unloading to occur alternately every half revolution. The cam was driven from a gramophone motor through a magnetic clutch, and the current to the latter was controlled by a timing plate, consisting of a large metal disc rotated by the gramophone motor every 5 sec. In the rim were sixty equidistant holes in which pins could be inserted to make contact with a brush which closed the circuit of the magnetic clutch for just long enough for the cam to make one half revolution. Thus if the cam was placed to depress the lever and lift the load, and three pins were inserted in the timing disc, the first caused the cam to make half a revolution, thus loading the muscle, the second caused unloading, and the third reloading. By varying the positions of the pins these operations could be carried out at any predetermined instants.

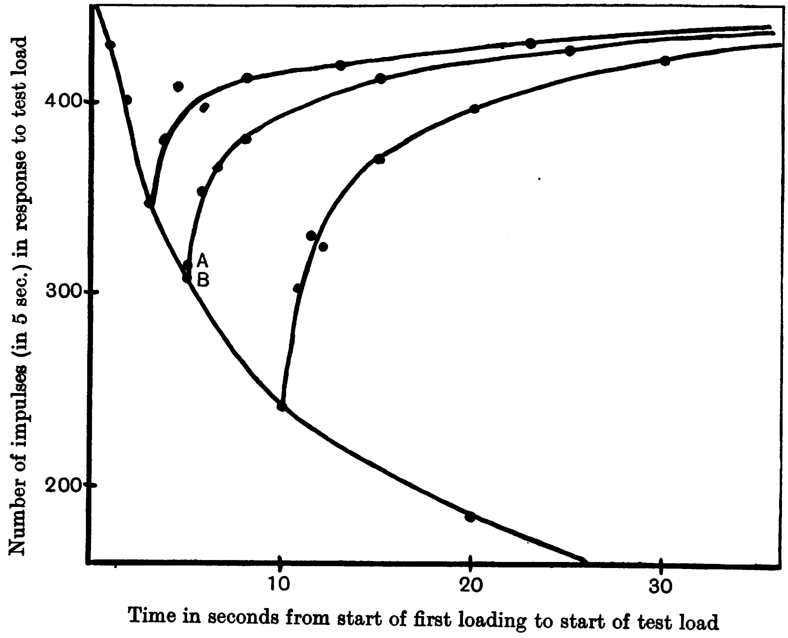


Fig. 19. Number of impulses set up in 5 sec. when a test load is applied after various periods of loading and rest. Temperature 15·2. Load 5 g. throughout. [141.]

The falling curve shows the fall in response to the test load when it is applied immediately on unloading after various durations of initial load.

The rising curves show how this response rises again when the muscle is unloaded for varying rest intervals after 2·9, 5, and 10 seconds' loading.

The number of impulses set up in the first 5 sec. after reloading was counted in the photographic record of the discharge, and compared with the number set up when the same load is applied to the resting end organ. By this method the comparison is between the effect of extension and 5 sec. tension on resting end organ and adapted end organ, differences in the responses can only be due to differences in the state of the end organ when the second (test) loading was carried out. By measuring the response to a test load it is possible to obtain a quantity which represents the end organ's capacity to set up and maintain a discharge of impulses in response to a fixed load, and it is assumed that the smaller the response to the test load the greater the adaptation of the end organ, and that the response to the test load and the adaptation are related quantitatively.

In Fig. 19 the falling curve shows the number of impulses set up by the end organ in response to the test load when it is applied later and later after the first loading (the first load is raised just before the test load is applied). The capacity of the end organ to respond becomes progressively less as the first loading is prolonged, but the fall is most rapid at first and becomes slower as the fall progresses.

If now the end organ is given longer periods of rest before the test load is applied, the return of the end organ to the resting state can be mapped out in the same way. An illustrative protocol of a typical experiment is given in Table I: the results are those shown graphically in

TABLE I. Exp. 141. Temp. 16·5° C. Load 5 g. throughout.

Number	Time	Interval in sec. between first loading and unloading	Interval in sec. between first loading and reloading	No. of impulses set up by first loading in 5 sec. Mean 450	No. of impulses set up by test (2nd) loading in 5 sec.
1	3.11	10·0	10·8	457	302
2	3.16	2·9	3·7	—	380
4	3.26	5·0	5·8	448	352
5	3.31	10·0	15·0	453	370
7	3.40	2·9	7·9	—	413
9	3.55	10·0	20·0	453	396
10	4.3	2·9	12·9	—	420
12	4.13	5·0	15·0	455	414
13	4.19	10·0	10·2	452	242
14	4.24	2·9	3·1	—	346
15	4.32	5·0	5·2	454	307
16	4.37	10·0	12·1	451	325
17	4.43	2·9	5·9	—	396
18	4.54	5·0	7·9	448	380
19	5.0	10·0	30·0	447	422
20	5.6	2·9	22·9	—	430
21	5.12	5·0	25·0	448	428
22	5.20	10·0	11·65	446	330
23	5.25	2·9	4·5	—	408
24	5.32	5·0	6·65	445	365
25	5.39	0·9	1·1	—	429
26	5.46	20·0	20·2	447	184
28	5.56	5·0	5·2	446	311
29	6.2	1·75	1·95	—	400

Fig. 19, the falling curve shows the fall in the response to the test load; the rising curves show how the response returns towards normal when the preparation is left unloaded after three durations of first load (complete recovery after 5 sec. loading takes about 1 minute). The general reliability of the determinations shown in Fig. 19 is well illustrated by the points *A* and *B*, which are readings of the same point taken near the beginning and end of the experiment. Between them some 1½ hours and fourteen loadings intervened.

Thus activity on the part of the end organ leads to a state of depressed rhythmicity, which gradually passes off during rest. The organ is, however, still able to set up impulses at nearly as high a rate as the resting organ if the stimulus is increased or renewed.

It was mentioned in a previous section that when a muscle was loaded, unloaded, and immediately reloaded, the frequency rose to almost its initial value. In some preparations the rise on reloading was much less marked than in others, and in these when reloading was carried out immediately after unloading the frequency did not rise at all except for one or two irregular impulses at the start. If reloading was carried out very rapidly there was a much more definite rise. The results of a typical experiment in which little rise occurred on immediate reloading are shown graphically in Fig. 20. The left-hand curve represents the response to the initial loading, the other curves represent the discharges produced by reloading later and later after unloading. The first is a smooth curve, but the later curves are obviously not smooth. A large number of points were taken from the records to construct these curves, so that the irregularities of the records might be fully represented. It is clear that the irregularities in the curves are due to physiological variations and are far outside the experimental error, moreover the trough in the curve shows a certain regularity in the different records if the curves are placed below each other with the instants of reloading superimposed as in Fig. 20 B. The trough in the curve shows that about 1 sec. after reloading there is a pause in the adaptation of the end organ; its possible significance will be discussed later. This phenomenon was found in many (sixteen) preparations, though seldom as clearly marked as in the experiment cited. The slight inflexion in Fig. 18, curve *B*, is typical of a number of experiments.

In the experiment illustrated in Fig. 20 there was very little rise in frequency just after reloading if this was effected soon after unloading; this was not always the case. The discharges shown in Fig. 18 are typical of a larger number of experiments. In most preparations the capacity to respond initially at a high rate returned on unloading much more rapidly than the capacity to maintain the discharge at a high rate.

In Part II it was pointed out what an enormous change occurs in the discharge of an end organ when it is irrigated with sodium chloride alone.

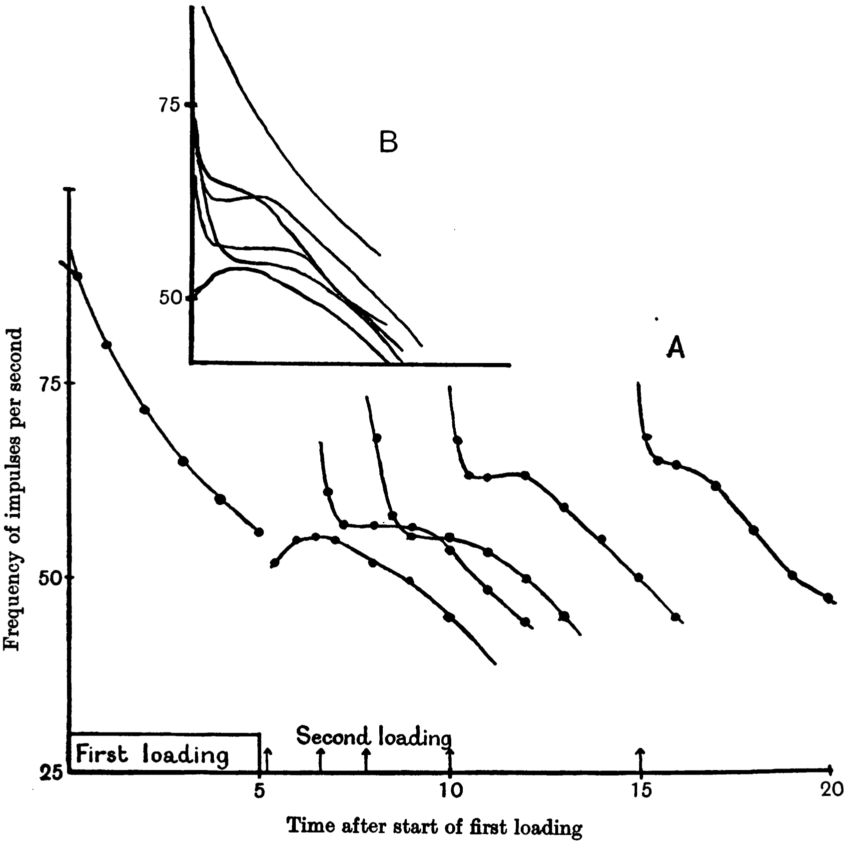


Fig. 20. Response of end organ to test load when applied later and later after the end of 5 sec. loading. Inset: same curves with the moment of loading superimposed. Load 5 g. Temperature 15° C. [135.]

The recovery of an end organ from the adapted state in Ringer and sodium chloride has been mapped out on several preparations, and it is found that the end organ returns to the resting state very much more rapidly in sodium chloride. The results of a typical experiment are shown in Fig. 21: ordinates represent the number of impulses set up in response to the test load in the 5 sec. following reloading. It will be seen that in sodium chloride the end organ has returned nearly to the resting condition after 4 sec., whereas in Ringer about 10 sec. is necessary for a comparable recovery.

The great increase of the response in sodium chloride, and the cessation of the fall of frequency after about 10 sec., is therefore due in part if not wholly to an acceleration of the process which causes the organ to recover from adaptation. The response of the same organ to different loads in Ringer and sodium chloride is illustrated in Fig. 15. It will be seen that the response to the small loads is not very different in the two fluids, but that with the heavier loads the discharge is maintained at a much higher level in sodium chloride. Thus the recovery from the adapted state is nearly as fast in Ringer when the adaptation and recovery are small, but when they are large (with the heavier loads) the recovery from adaptation is less rapid in Ringer than in sodium chloride.

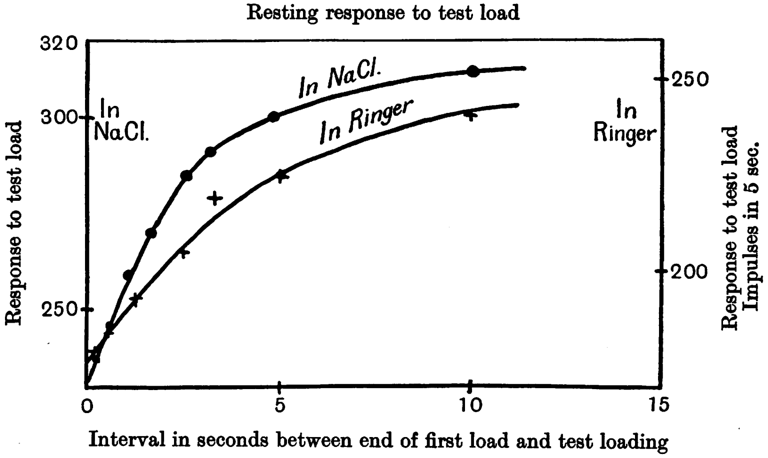


Fig. 21. Disappearance of adaptation in Ringer and sodium chloride solutions. Load 2 g. Temperature 16° C. [111.]

Rate of recovery.

It has been shown above that, as adaptation progresses, the rate of recovery from the adapted state increases (see Fig. 19). Experiments were made to determine the course of the change in the recovery rate. This can be done by finding the difference between the responses to reloading immediately after unloading and also after a rest of 1 sec. The difference gives a measure of the recovery that has occurred in the 1 sec. rest, and by placing the unloading and reloading later and later after the initial loading, a series of values can be obtained representing the recovery rate when more and more adaptation has occurred. The results from such an experiment are shown in Fig. 22. It will be seen that after about 10 sec. loading the recovery in Ringer tends to reach a steady maximum rate. It has already been shown that, after irrigation with sodium chloride alone, recovery takes place more rapidly. It was found that after the preparation had been irrigated with sodium chloride for 1½ hours the initial recovery rate throughout the discharge was much increased (see Fig. 22), and this supports the view expressed above that the increased discharge in sodium chloride is largely a result of an increased recovery rate preventing the nerve ending from becoming as much adapted as it does in Ringer.

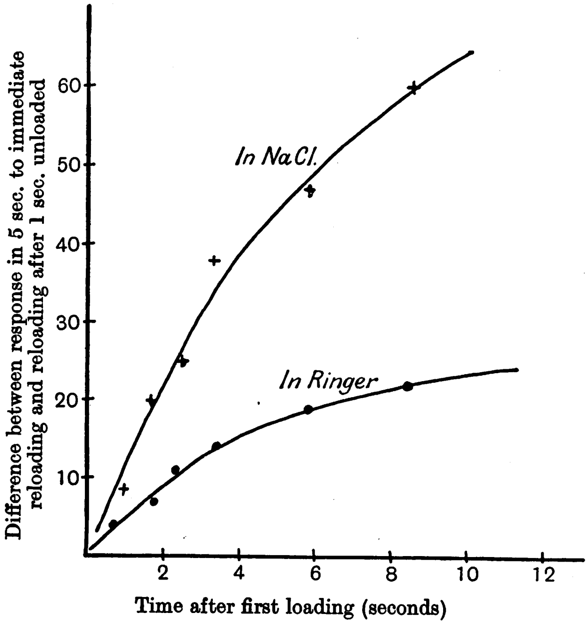


Fig. 22. Rate of recovery in Ringer and sodium chloride. Abscissæ difference between the number of impulses set up in 5 sec. if preparation is reloaded immediately or after 1 sec. of rest. Ordinates time after start of the first load when the test is made. Load 4 g. Temperature 16° C. [112, 113.]

Adaptation and load.

By these methods it is possible to map out the course of adaptation when varying loads are applied to the muscle. A weight is applied to the thread from the tendon, and after an interval is lifted and immediately

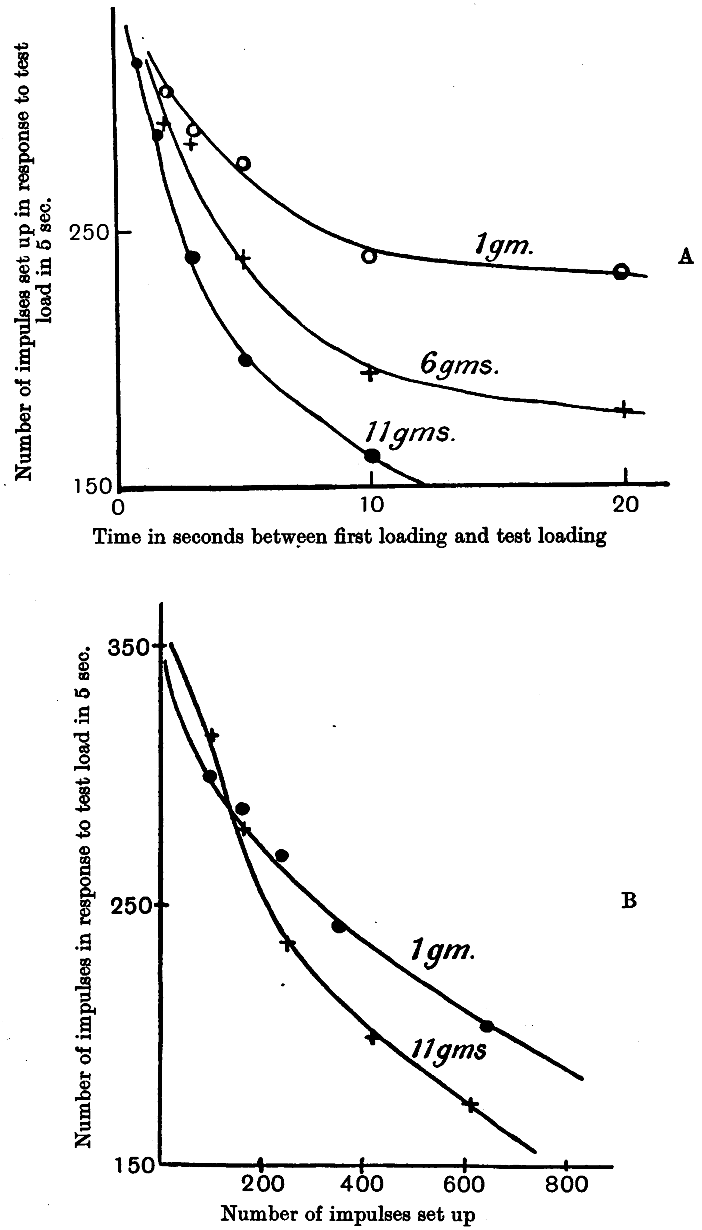


Fig. 23. Adaptation to various loads measured by the response to a test load of 11 g. A. Response to test load plotted against duration of first loading. B. Ditto against number of impulses set up during first loading. Temperature 16·5° C. [135.]

replaced by the test load; the resulting response will depend on the state of the end organ at the instant of reloading. In this way a measure of the adaptation is obtained; by altering the first load, and the time when it is replaced by the test load, the course of adaptation to various loads is determined. The results of such determinations are shown in Fig. 23 A. As might be expected, adaptation occurs much more rapidly with large loads; the larger load sets up a much greater number of impulses in a given instant of time. For this reason the figures are replotted in Fig. 23 B against the number of impulses that have been set up by the first load. It will be seen that at first the curves for small loads fall most rapidly, but are later overtaken by those of the larger loads. Thus, at the beginning, the large loads set up more impulses for the same change in state of the end organ than do the small loads, so that there is less adaptation per impulse, and this has always been found to occur in a number of experiments in which this point has been investigated.

Test load.

In all the above experiments the test load was equal to or greater than the largest initial load used. The reason for this was that if a small test load was applied after a large initial load the small load produced very little or no response in the first 5 sec. after its application, and only later did impulses appear, so the method cannot be used in these cases.

It is evident from this that a definite threshold which is absent from the resting end organ (evidenced by the resting discharge in the absence of any stimulus) appears and increases with adaptation, so that loads which produce a discharge from the resting end organ are sub-threshold when applied to the adapted end organ. Thus with adaptation the excitability of the end organ falls.

DISCUSSION.

It has been shown that the end organ has a maximum power of setting up impulses when resting and that, during stimulation, in proportion to the stimulus and time it has been acting, this power is reduced and returns when the stimulus ceases or is reduced. Bronk [1929] has shown that these end organs undergo fatigue which is greatly increased in the absence of oxygen, and we must here consider why the processes which are investigated in this paper are classed as adaptation rather than fatigue. The fall of response which Bronk investigated, and which was affected by the presence or absence of oxygen, only appeared after some minutes of activity, and took many minutes to disappear, whereas the process considered in this paper began to appear in the first second of activity and the end organ returned to very nearly its resting state in a few seconds. From his experiments on the response in oxygen and nitrogen Bronk concluded that the initial fall of frequency must be ascribed to causes other than fatigue. He says: "It has been pointed out that the rapid decline in impulse frequency described as adaptation may be due to different causes from those producing the decease in activity which results from prolonged stimulation. The experiments described show that the later, or fatigue effect, is greatly increased by lack of oxygen, whereas the former seems to be little modified thereby—all of the experiments show that an unfatigued muscle adapts about as rapidly in pure oxygen as in nitrogen." So that it is probable that the initial fall of frequency and development of the adaptation remainder is not influenced by the presence or absence of oxygen, and is quite distinct from fatigue. It has been shown that the development and disappearance of the adaptation remainder are greatly influenced by the ionic composition of the fluid in which the preparation is immersed. It is difficult to see why this should occur if the adaptation remainder was the result of fatigue.

The end organ has a potential store of impulses which is used up during stimulation and replaced during rest, and it is probable that this restoration is not immediately dependent on oxygen, though Bronk's [1929] work and the observations on hydrocyanic acid quoted above show that the whole process is ultimately dependent on changes of an oxidative character. What then are the changes underlying adaptation which are responsible for the fall in the end organ's power to respond? It is generally supposed that the occurrence of an impulse in a nerve (or muscle) fibre is due to the breakdown of a polarized surface, and the resulting passage of ions from the interior of the fibre. During the period immediately following the impulse the surface reverts to the polarized, impermeable state. An electric stimulus acts because it can depolarize the fibre, and a mechanical stimulus presumably has the same effect because it causes a momentary (or permanent) disintegration of the surface layers. Since there is no reason to suppose that the end organ differs essentially from any other excitable structure, we may assume that tension on the end organ stimulates it by deforming the surface membrane sufficiently to produce complete instability. The breakdown is followed by a refractory phase and a gradual return of the membrane to its normal polarized condition, but the continued action of the stimulus causes a renewed breakdown as soon as recovery has advanced far enough for the stimulus to become effective. Various explanations of the refractory phase and its gradual disappearance have been put forward, but it is probably safe to assume that the recovery depends on the gradual restoration of some component, *e.g.* a replenishing of the store of ions which maintain the surface polarization. It seems possible to account for most, if not all, of the facts on the assumption that the rate of recovery depends on the concentration of this substance in the immediate neighbourhood of the surface membrane, that the concentration is reduced by the stimulus and whenever an impulse is set up, and that it is restored from two sources: (*a*) by diffusion from neighbouring regions, (*b*) by a process of replacement, probably involving a chemical breakdown.

The depletion of the store would be caused in the first instance by the stimulus, and an inadequate stimulus might cause some loss without ever setting up an impulse. Whether the loss would be greater when an impulse is set up is an open question. Up to the present it has been impossible to stimulate these end organs in such a way that they become adapted without setting up any impulses, but Adrian's experiments with gradually increasing stimuli show that it is the stimulus rather than the setting up of impulses that is the important factor in producing adaptation, though the stimulus always results in the setting up of impulses the two factors causing adaptation cannot be completely dissociated.

The above hypothesis agrees with all the existing data on end organs, but several points need amplification. It is assumed that the substance which is removed during adaptation is replaced rapidly at the membrane (by the (*b*) process) and that it is also drawn from a "reservoir" by diffusion ((*a*) process) and similarly replaced during rest. It is necessary to assume this diffusion from a reservoir to explain the observation that, on cessation of the stimulus, there is a rapid return of the power to respond initially at a high rate but a slower return of the power to maintain a high rate of response. Most of the data on adaptation might perhaps have agreed with a simpler hypothesis, *e.g.* one involving restoration by coupled chemical reactions, but one set of observations, namely, the inflexion in the curves of Fig. 20, can only be accounted for if it is assumed that diffusion from neighbouring regions is an important factor in the restoration of the substance removed during adaptation, and it is very difficult to account for these observations in any other way. The hypothesis offers an elegant explanation of this which is most easily shown with the aid of diagrams.

In Fig. 24 A is shown the resting concentration of the substance up to the membrane; on stimulation the concentration near the membrane will fall as in B and will be restored by the (*b*) process occurring at the membrane, and also by diffusion. Consequently as the stimulus is prolonged the concentration gradient up to the membrane will change as in B, C and D. If now the stimulus is removed the concentration close to the membrane rises rapidly (Fig. 20 E) owing to process (*b*), and the concentration farther from the membrane will rise slowly owing to diffusion as in F; so on reloading the conditions at the membrane are nearly the same as in the resting end organ, and at first it will respond at nearly the same initial rate, but the concentration at the membrane and therefore the rate of response will fall much more rapidly than on first loading (see Fig. 20 G). Moreover, a hump will occur in the concentration gradient, and until this has smoothed out there will be a pause in the fall in concentration at the membrane. It seems possible that this might account for the pause in the fall of frequency of response of the end organ which occurs soon after reloading.

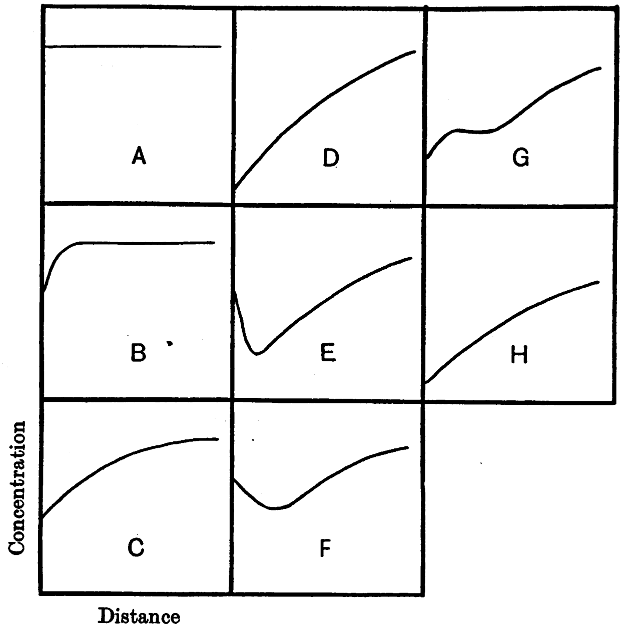


Fig. 24. Diagrams to show concentration of a substance diffusing from a region of fixed concentration up to a point where it is being utilized. The different figures show the concentration gradient at different times.

The mechanism which has been ascribed to the nerve ending differs very little from that of the nerve fibre, and if adaptation is due to removal of the ions along a polarized membrane we should expect it to occur to some extent in the nerve fibre. Brücke [1926] has shown that, during the prolonged activity of a nerve fibre, the refractory period lengthens. This slowing of recovery might be due to the causes that have been suggested to produce adaptation of the nerve ending, but it is very slight compared to that of the ending, and so it is suggested that in the fibre the removal of ions is much less owing to the permeability never being increased by deformation, and so the fibre is not much affected by the slight loss of ions.

It is clear from the profound effect an electric current has on the decline of the end organ response, that adaptation is closely bound up with membrane polarization. The mechanism suggested for the end organ might certainly be influenced by an electric current in the way observed, a current flow in one direction tending to delay the diffusion (*a*) process and cause an earlier fall of the concentration of the substance at the membrane, reversed current flow aiding diffusion and maintaining the concentration at the membrane, and thus the response, at a higher level.

Cylindrical diffusion from the centre to the membrane surface of the fibre would be too rapid to account for the behaviour of the end organ in the way suggested, so that it must be assumed either that diffusion occurs from some reservoir, *e.g.* from the myelinated part of the fibre to the adjacent non-myelinated part at the termination of the medullary sheath, or else that adaptation is due to substances which escape from the membrane into the surrounding regions "clogging" the action of the membrane. The above hypothesis holds equally in the latter case.

SUMMARY.

1. A method is described of making a muscle preparation containing a single nerve ending responding to stretch.

2. This nerve ending is found to lie in the centre of the muscle, where histological preparations reveal a single muscle spindle.

3. The response in the nerve when the muscle is stretched is recorded with a moving iron oscillograph. It is found to be extremely constant for any given tension.

4. If the muscle is kept in a small quantity of Ringer for some time the response in the nerve is first depressed and then disappears, but returns to its initial magnitude when the Ringer is changed.

5. The frequency of response is found to be roughly proportional to the logarithm of the load.

6. When the muscle is loaded rapidly the interval between the impulses set up is only a little greater than the absolute refractory period of the nerve fibres concerned, and also the time relations of the action currents of these impulses are modified, showing that they are travelling in an incompletely recovered nerve fibre. It seems possible that these rapid discharges may be due to continuous rather than intermittent excitation of the nerve fibre.

7. The viscosity of the end organ may account for the discontinuities in the response when small loads are applied rapidly.

8. The interval between the impulses at the highest frequency recorded varies with temperature in much the same way as does the absolute refractory period of a nerve trunk.

9. The behaviour of the end organ is greatly modified by the ionic composition of the surrounding fluid. In sodium chloride the frequency of discharge remains high for some minutes; addition of either calcium or potassium alone reduces the response below that obtained in Ringer. Moreover, calcium and potassium appear to have an antagonistic action.

10. Rhythmic discharge of grouped impulses occurs when the preparation is kept at 25° in sodium chloride; the significance of these is discussed.

11. The response can be modified by passing a steady current through the muscle. The change in the response depends on the direction of current flow.

12. Hydrocyanic acid is found to cause a transient increase in the response later followed by extinction of the discharge.

13. Adaptation is examined, and it is found that there is an after effect lasting several seconds after the stimulus is removed.

14. This adaptation remainder has been measured quantitatively and is found to develop as stimulation is prolonged and vanish in a few seconds after the stimulus is removed.

15. The adaptation remainder is found to be a function of the total stimulation, *i.e.* the magnitude of the load and the time it has been acting.

16. A hypothesis is suggested to account for the observed behaviour of these end organs.

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REFERENCES.

Adrian (1921). *J. Physiol.* **55**, 193.
Adrian (1930). *Proc. Roy. Soc.* B, **106**, 596.
Adrian and Bronk (1929). *J. Physiol.* **67**, 181.
Adrian and Zotterman (1926 *a*). *J. Physiol.* **61**, 151.
Adrian and Zotterman (1926 *b*). *J. Physiol.* **61**, 465.
Amberson (1930). *J. Physiol.* **69**, **60**.
Bronk (1929). *J. Physiol.* **67**, 270.
Field and Brücke (1926). *Pfluegers Arch.* **214**, 103.
Cajal (1904). *Textura del sistema nervioso*, **1**, 404..
Denny Brown (1928). *Proc. Roy. Soc.* B, **103**, 321.
Dulière and Horton (1929). *J. Physiol.* **67**, 152.
Erlanger, Gasser and Bishop (1927). *Amer. J. Physiol.* **81**, 473.
Forbes and Rice (1929). *Amer. J. Physiol.* **90**, 119.
Gasser and Erlanger (1925). *Amer. J. Physiol.* **73**, 613.
Gasser and Hill (1924). *Proc. Roy. Soc.* B, **96**, 398.
Gotch (1910). *J. Physiol.* **40**, 250.
Matthews (1929 *a*). *J. Sci. Inst.* **6**, 220.
Matthews (1929 *b*). *J. Physiol.* **67**, 169.
Mines (1913). *J. Physiol.* **46**, 217.