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FATIGUE OF THE SENSE ORGANS IN MUSCLE.

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IN view of modern ideas regarding the mechanism of vital processes it seems inevitable that all living tissue should tend to show a progressive decrease in capacity for response as a result of previous activity. This general property we may describe as fatigue. Although the inclusiveness of the designation must indicate that many of the phenomena which may properly be included thereunder are in many respects dissimilar, they are all alike in that the altered condition is in some way a result of the increased metabolism resulting from previous response to stimulation. Because of this the study of fatigue processes in normal and excised tissue often throws light on the dynamics of the cell or organ and on the functional mechanisms involved. The present investigation is therefore devoted to a study of the action of peripheral sense organs during and after a prolonged response to a continuous stimulus. So far as I am aware there has never been such an objective study of the fatigue of sensory endings, and it is only now made possible by the methods which Adrian (1) has developed for the study of sensory impulses.

Evidence is existent of the fatigue of other portions of the nervous system. The work of Sherrington (2), for instance, has demonstrated that there is a fairly rapid fatigue of that portion of a reflex arc lying within the spinal cord, and the common statement regarding the infatigability of nerve fibres has been discredited by recent work, including that of Gerard, Hill and Zotterman (3) and Gerard (4).

The sensory endings in muscle were chosen as being best suited to an investigation such as this. They are easily stimulated with stimuli of known intensity, reproducible results are readily obtained and one can choose a muscle with few enough end organs to make possible the counting of the individual sensory impulses even at the height of the discharge. The preparation employed was the muscle *flexor superficialis digitorum* with the nerve *tibialis superficialis*. The muscle is large enough to withstand considerable tension and contains a sufficient number of end organs to enable one to observe the way in which fatigue develops within such a group. When it was desired to study the action of a single or a very few endings a majority of the sensory nerve fibres was transected by the method recently described (5). Fig. 1 *A* shows the discharge

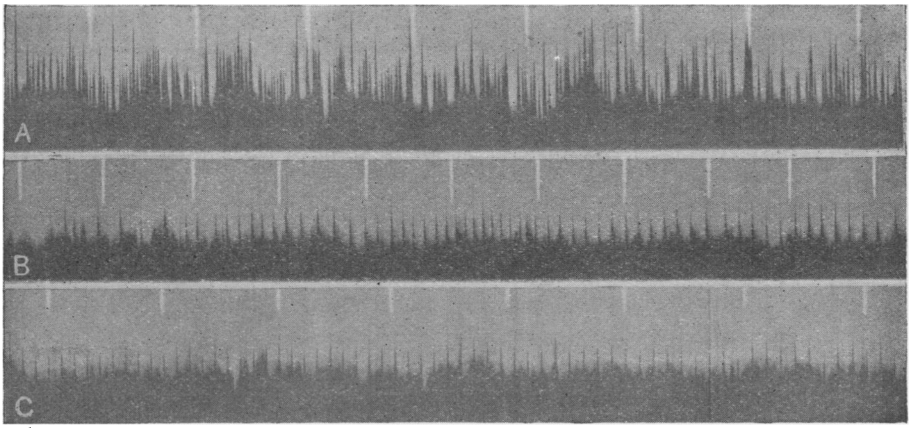

Fig. 1. Discharge of afferent impulses from all of the functioning sense organs in the muscle (*A*) and from single organs (*B* and *C*). In *B* and *C* the nerves had been partially transected so that in each case there was only a single sensory fibre conducting impulses from one end organ. White marks give time in 1/8 sec.

from all of the afferent endings in a muscle; 1 *B* and *C* the discharges from apparently single end organs, all but one of the active sensory fibres having been cut between the muscle and the electrodes.

All of the experiments were made on non-circulated, excised tissue. The muscle was clamped in one compartment of a double moist chamber and a thread from the tendon was attached to a loading lever, this lever being lowered at a definite rate by means of an oil dashpot. The nerve passed into the second compartment where it was slung across two non-polarizable electrodes which in turn connected to a 3-valve amplifier and a capillary electrometer.

Fatigue of response to continuous tension.

When a load is applied to a muscle the frequency of afferent impulses rises rapidly to a maximum and then within a few seconds falls to a frequency from which the decrease is much more gradual. This rapid fall in impulse frequency following the rise to maximum has been ascribed by Adrian and Zotterman (6) to a decline in the effectiveness of the stimulus, *i.e.* to an adaptation of the end organ to the change in its environment. Although the question whether this initial "adaptation" can be properly classed as a fatigue process is largely a matter of terminology, and although it is doubtful whether this initial fall can be clearly distinguished from the true fatigue which occurs with prolonged loading, it is certain that the onset of adaptation is very rapid and the recovery therefrom equally so. Adrian and Zotterman give figures to show that recovery is practically complete within a second. Several experiments made in the course of the present investigation show that if tension is applied to a muscle just long enough to permit the afferent discharge to fall to its adaptation level, then released and applied again within one or two seconds, the stimuli may be repeated several hundred or even thousand times without causing any large decrease in response. This is illustrated in Fig. 2. It constitutes further evidence for rapid

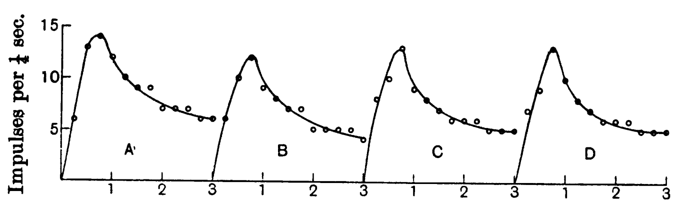

Fig. 2. Effect of repeated stretches on discharge of afferent impulses. 13·6 grm. *A*, 1st stretch; *B*, 102nd stretch; *C*, 163rd stretch; *D*, 250th stretch. About 1-sec. intervals between the end of one loading and the start of the next. Expt. of 10. x. 28.

recovery from the initial fall which Adrian and Zotterman regard as adaptation to the stimulus.

The frequency of afferent impulses throughout the early part of a discharge is higher as the result of a greater stretching force provided this stimulus does not become supra-maximal. Both the maximum impulse frequency and the "adapted frequency" are higher as a result of the greater stimulus. That this increased activity does not continue however under a prolonged tension is shown by Fig. 3 which gives the results of an experiment continued over 24 min. It will be seen that a tension of 45 grm. caused an eventual fall in frequency of afferent impulses to a lower value than that resulting from the smaller stimulus. When the tension was suddenly reduced from 45 grm. to 4 grm. the frequency gradually rose to a new level. The obvious interpretation of the first observation is that the greater rate of activity of the end organs in response to the greater stimulus induces more rapid and more complete fatigue. It brings the action of these sensory endings into line with

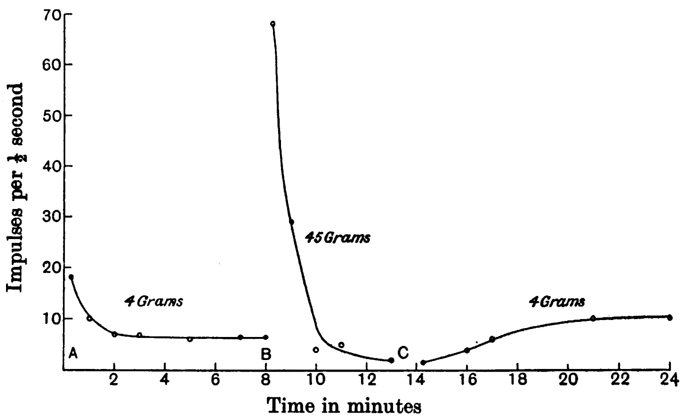

Fig. 3. Effect of varying sustained tension on fatigue. At *A* muscle loaded with 4 grm. At *B*, 41 grm. was added and at *C* the tension was again reduced to 4 grm. Expt. of 28. v. 28.

other excitable tissue in this respect. For instance, a muscle stimulated at a high frequency will soon fatigue, whereas at a lower frequency it may continue contracting indefinitely in a steady state. It is more difficult to find an analogy for the partial recovery from such fatigue during the response to a weaker stimulus. That the increase in frequency under the smaller tension is actually a recovery process, although but partial, is shown by Table I: it will be noted that on again increasing

TABLE I. Fatigue due to sustained tension.

	Impulses per ½ sec.
15 sec. after loading with 45 grm.	160
1 min. ,, ,, ,,	110
2 min. ,, ,, ,,	48
3 min. ,, ,, ,,	3
7 min. ,, ,, ,,	2
15 sec. after reducing tension to 4 grm.	3
5 min. ,, ,, ,, ,,	7
10 min. ,, ,, ,, ,,	12
15 sec. after again increasing tension to 45 grm.	74
1 min. ,, ,, ,, ,, ,,	24
2 min. ,, ,, ,, ,, ,,	3
7 min. ,, ,, ,, ,, ,,	3
15 sec. after tension was again reduced to 4 grm.	1
2 min. ,, ,, ,, ,, ,,	3
6 min. ,, ,, ,, ,, ,,	9

the tension the frequency rises and then falls more quickly than it did when this same load was first applied.

A study of the discharge from preparations containing a number of end organs reveals some facts regarding the onset of fatigue. Fig. 4 *A*

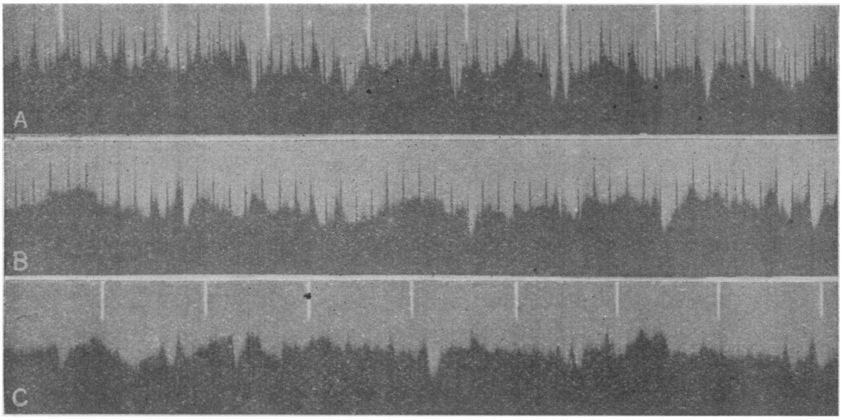

Fig. 4. Electrometer records of the sensory discharge from a muscle under tension of 45 grm. showing the progressive fatigue of end organs. *A*,.30 sec. after the application of the load, discharge from three or more sensory endings. *B*, after 2 min., only one organ active; and *C* after 3 min., no response. White marks give time in 1/8 sec. Expt. of 24. v. 28.

shows the impulse discharge 30 sec. after the initial application of the tension; *B*, 2 min. later. Comparing these two photographs with Fig. 1 *A* and *B* it will be seen that the discharge early in the loading is of the type resulting from the activity of a fair number of end organs, while after a period of sustained tension there is a definitely regular rhythm characteristic of the discharge from a single sensory ending. In Fig. 4 *C* the discharge has entirely disappeared 3 min. after the start of the loading. The natural conclusion to draw from these experiments is that the development of fatigue is marked by more and more end organs dropping out of action due to progressive failure.

This is not to be taken as indicating that the individual sense organ responds at a characteristic frequency until no longer able to do so and then abruptly ceases to function. Adrian and Zotterman have shown that a single end organ is able to discharge over a considerable range of frequencies, and this same point has been established in the present work. In some preparations the decrease in response as the loading continues has been marked by a gradual and progressive fall in the rhythmic impulse frequency. More frequently, and especially after previous fatigue of the end organ, the failure of response is characterized by one or more impulses dropping out of an otherwise fairly regular series, the impulses becoming more and more scattered as the loading continues until finally the discharge ceases. In Table II *A* the

TABLE II. Intervals between successive impulses coming from a stretched muscle.

The series start from the beginning of the stretches. The intervals are expressed in terms of arbitrary time units (1/40 sec.). Series *A* and *B* are both from the same muscle, *B* from a later part of the experiment.

A. 3·7, 2·2, 2·1, 1·9, 1·6, 1·2, 1·1, 1·0, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 0·9, 1·0, 1·0, 1·0, 1·0, 1·0, 1·0, 1·0, 1·2, 1·2, 1·2, 1·2, 1·2, 1·2, 1·2, 1·2, 1·3, 1·3, 1·3, 1·3, 1·3, 1·3, 1·3, 1·3, 1·3, 1·3, 1·3, 1·5, 1·8, 1·7, 1·8, 1·8, 1·8, 1·8, 1·8, 1·8, 1·9, 1·9, 1·8, 1·8, 1·9, 1·9, 1·9, 1·7, 1·9, 1·7, 2·0, 1·8, 1·8, 2·0, 2·0, 2·0, 2·0, 2·2, 2·2, 2·0, 2·2, 2·1, 1·7, 2·2, 1·8, 2·0, 2·0, 2·0, 2·1, 2·3, 2·3, 2·3, 2·3, 2·7, 2·6, 2·9, 2·8, 2·0, 2·8, 2·6, 2·7, 2·6, 2·8, 2·7, 2·7, 2·8, 2·9, 2·8, 2·8, 3·2, 3·2, 3·2, 2·9, 3·0, 3·0, 2·9, 3·0, 3·1, 3·1, 3·0, 3·2, 3·1.

B. 2·0, 1·9, 1·9, 1·3, 1·1, 1·0, 0·8, 0·8, 0·8, 0·7, 0·7, 0·7, 0·6, 0·6, 0·6, 0·6, 0·6, 0·6, 0·6, 0·7, 0·7, 0·6, 0·6, 0·7, 0·6, 0·6, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·5, 0·6, 0·5, 0·6, 0·6, 0·6, 0·6, 0·6, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·7, 0·8, 0·8, 0·8, 0·8, 0·7, 0·8, 0·8, 0·8, 0·9, 0·8, 0·8, 0·8, 0·8, 0·9, 0·9, 0·9, 0·9, 0·8, 0·8, 0·8, 0·8, 0·8, 0·8, 1·3, 0·8, 0·8, 0·8, 0·8, 0·8, 0·8, 0·8, 0·8, 0·8, 0·9, 0·8, 0·7, 1·3, 0·8, 0·8, 0·8, 0·9, 2·8, 4·0, 0·8, 0·8, 0·9, 0·8, 9·0, 0·8, 1·4, 0·9, 0·8, 0·8, 8·0, 0·9, 1·5, 3·1, 5·2, 3·1, 5·2, 1·9, 3·0, 1·2.

decline in frequency is fairly regular, the intervals between successive impulses becoming gradually longer; in *B* there is at first a similar regular increase in interval between impulses, but later whole groups of impulses drop out of the series. It does not seem possible at present to say what factors are responsible for these differences in behaviour.

FATIGUE OF RESPONSE TO STRETCH.

Fig. 2 shows that although the frequency of afferent impulses from a muscle quickly falls during the early part of a short loading, such a stimulus has little effect on the response to a subsequent stretch following at an interval of 1 sec. or less. The experiments described in this section relate to the effects of much longer periods of loading upon the discharge of sensory impulses produced by a subsequent stretch following after a brief interval of rest.

The results of a typical experiment are illustrated in Fig. 5. In order to determine the normal response of the muscle to the given stimulus it was loaded several times at 5-min. intervals. These impulse discharges were all in close agreement: one of them is given in *A*. The last of these preliminary stretches was prolonged for a period of 1 min., the weight was then lifted and again lowered after an interval of 15 sec. The early part of the response is given in *B*. The muscle was similarly stretched after additional periods of sustained tension of 1 min., 3 min., 8 min., and then after "rest" periods of 1, 2, 5, 5, 10 (total of 23) min. respectively interspersed with 30-sec. loadings that produced the afferent

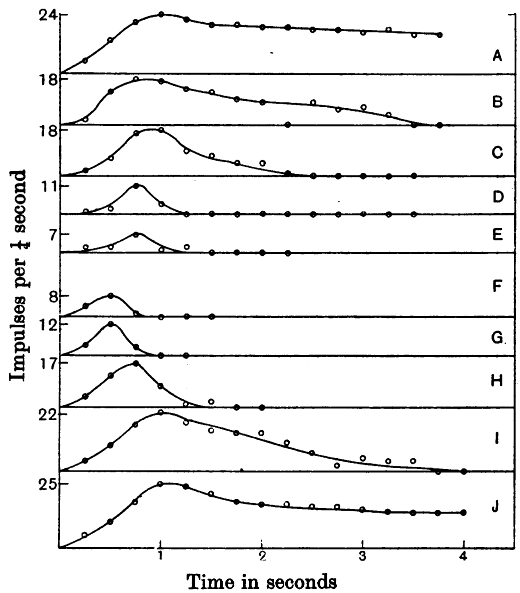

Fig. 5. The discharge of sensory impulses produced by stretching a muscle slowly with a weight of 9·6 grm. *A*, rested muscle; *B*, after a previous continued loading of 1 min.; *C*, 2 min.; *D*, 5 min.; *E*, 13 min. The muscle was loaded another 10 min. and then allowed 1 min. rest before *F*, 3 min. before *G*, 8 min. before *H*, 13 min. before *I* and 23 min. before *J*. The period of tension was interrupted by 15 sec. periods of rest before each of the four loadings; the period of rest by four 30-sec. stretches. Expt. of 9. x. 28.

impulse discharges given in *F*, *G*, etc. The results of this series of observations are presented in a different form in Fig. 6 which gives the degree of the fatigue as a function of the duration of the previous tension. A large number of these experiments have conclusively shown that prolonged tension reduces the capacity of an end organ to respond to a subsequent stretch. The gradual and complete recovery of normal activity makes it seem probable that we are here dealing with a true fatigue phenomenon.

The rate of development of fatigue and recovery is naturally dependent on various conditions such as the state of the muscle, the amount of tension and the like: the values given by the experiments here quoted merely serve to illustrate the general order of magnitudes. The two curves in Fig. 7, for instance, show the effect of varying tension on the rate of fatigue. As would be expected, the end organs fail more rapidly under a higher tension and recover more slowly from the more complete fatigue.

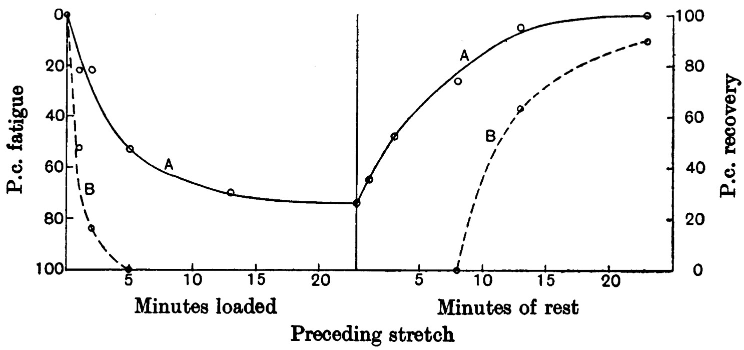

Fig. 6. Rate of fatigue and recovery. *A*. Full line. The maximum impulse frequency in the several stretches is given as per cent. of the maximum frequency in a like stretch of the unfatigued preparation and is plotted against the duration of the previous sustained tension. *B*. Broken line. The impulse frequencies 2 sec. after the start of each stretch are similarly compared during the course of fatigue and recovery. Taken from the series given in Fig. 5.

Following fatigue the discharge frequency during the course of a stretch decreases very much more rapidly than in a normal preparation; the later or sustained discharge may be entirely absent although the

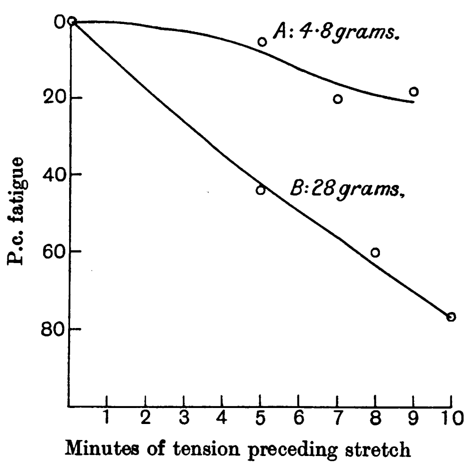

Fig. 7. Rate of fatigue as a function of the load. Maximum impulse frequency during a stretch as per cent. of that from the rested muscle plotted against the duration of a previous tension of (*A*) 4·8 grm., (*B*) 28 grm. Expt. of 25. x. 28.

initial discharge is still of considerable size. This is shown in Fig. 5 *D, E, F, G, H*. Fig. 6 illustrates the same point by showing the much greater rate of fatigue obtained when one considers the impulse frequency 2 sec. after the beginning of the stretch. These variations in the form of the discharge curves following fatigue are markedly similar to the tension-time curves of a muscle produced by tetanic stimulation after previous fatigue. For the purpose of comparison such curves have been reproduced in Fig. 8. Here too the effect of moderate fatigue is most

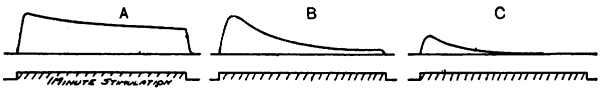

Fig. 8. Fatigue of the mechanical response of a muscle, showing the similarity of this series to the altered response of a sense organ produced by fatigue. *A*, *B* and *C* give the successive responses to 1-min. periods of tetanic stimulation. 1-min. intervals of rest.

evident in the later part of the response, the tension falling more rapidly in the case of the fatigued muscle.

Effects of nitrogen and oxygen.

If the phenomena described above are due to a fatigue of processes similar to those which are characteristic of most living tissues, the rate of fatigue and recovery therefrom should be modified by placing the muscle in an atmosphere of nitrogen or oxygen. This has been done with striking results.

A continuous and fairly rapid stream of either nitrogen or oxygen was bubbled through a series of wash bottles (to prevent drying of the muscle) and then passed through the compartment containing the muscle. This compartment was closed by means of a glass slide sealed on with vaseline. Commercial oxygen and nitrogen were employed: there seemed to be no need in the present investigation for attaining a higher degree of purity.

Fig. 9 is from a typical experiment which shows the fatigue and recovery of these end organs, first when stimulated in nitrogen and later in oxygen. The differences are considerable, clear cut and need little comment. They clearly indicate—as would certainly be expected—that the activity of these sensory endings is in the nature of a chemical process. Their continued functioning is dependent upon an adequate supply of oxygen: lack of oxygen greatly accelerates the fatigue process and retards recovery.

It has been pointed out that the rapid decline in impulse frequency

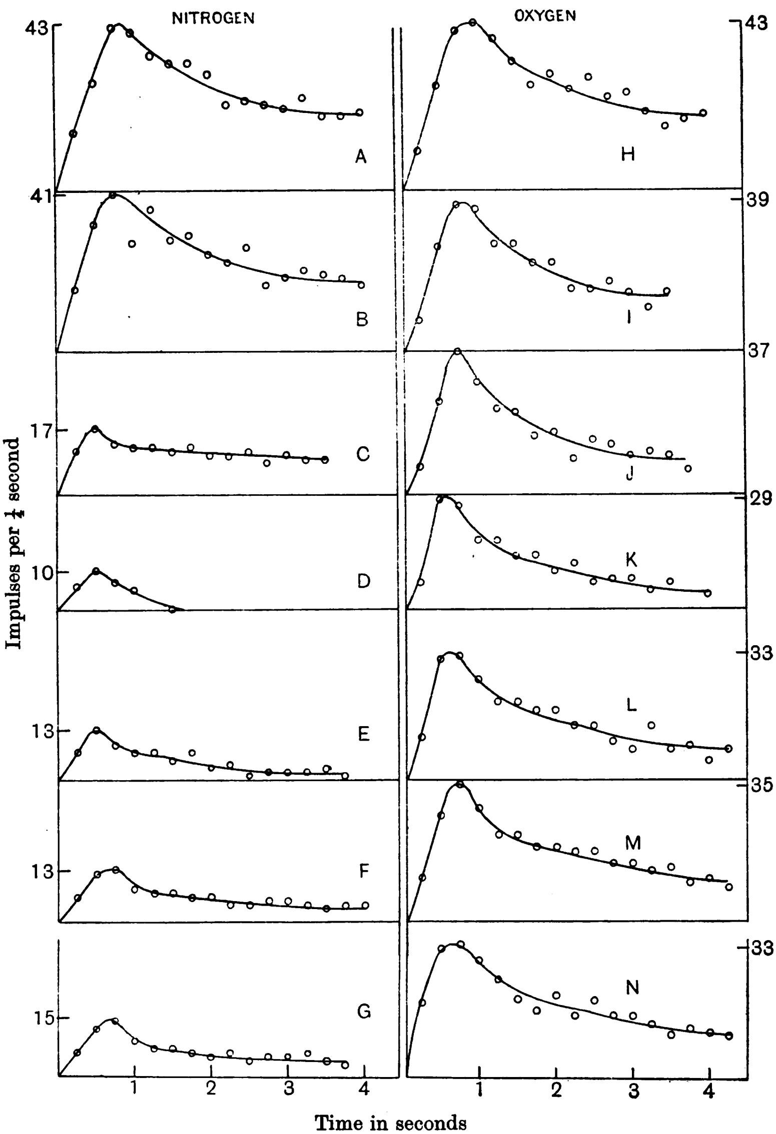

Fig. 9. Effect of nitrogen and oxygen on fatigue and recovery. In *A* to *G* the muscle was loaded with 5·6 grm. in nitrogen; in *H* to *N* the same loads were applied to the muscle in oxygen. *A* and *H* rested preparation; *B* and *I* after 1 min. of a sustained tension of 5·6 grm.; *C* and *J* after 3 min.; *D* and *K* after 7 min. of sustained tension; *E* and *L* after 2 min. rest; *F* and *M* after 6½ min. rest; *G* and *N* after 9½ min. rest. Same muscle employed in both series.

described as adaptation may be due to different causes from those producing the decrease in activity which results from prolonged stimulation. The experiments described in this section show that the latter, or fatigue effect, is greatly increased by lack of oxygen, whereas the former seems to be little modified thereby. This point has not been made a subject of special study, but all of the experiments show that an unfatigued muscle adapts about as rapidly in pure oxygen as in nitrogen. This would seem to indicate that the process is not influenced to any considerable degree by the presence or absence of oxygen and that the cause of adaptation is not therefore a rapid exhaustion of the supply of oxygen. The possibility of course remains that the rapid decline in frequency is due to the inability of the end organs to utilize the available oxygen rapidly enough to meet their needs.

The relative ease with which these sensory organs may be fatigued is perhaps worthy of final comment. It was rather surprising to find that a tension of only 4 or 5 grm. would, when applied for only a few minutes, halve or even quarter the response to a subsequent stimulus. Nor are the great differences in rates of fatigue and recovery in nitrogen and oxygen any less striking. The experiments show therefore that these sense organs stand between peripheral nerve fibres and the tissues of the central nervous system in their ability to resist fatigue and lack of oxygen.

Summary.

The fatigue of sense organs in muscle has been investigated by photographing the afferent nerve impulses during a prolonged loading of the muscle and during stretches following such a sustained tension.

1. The rapid adaptation of the end organs is followed by a more gradual decrease in the frequency of their impulse discharge. This latter decrease is attributed to fatigue. The greater the tension applied to the muscle the greater the decline in frequency, with the result that after some minutes of a sustained tension the frequency of afferent impulses is less under the stronger stimulus. There is partial recovery from this fatigue under a lower tension, the reduction in the stimulus causing an increase in impulse frequency.

2. The decrease in frequency during a prolonged stimulus is due, in part, to the fact that progressively fewer end organs discharge as the stimulus continues. An investigation of single end organs shows that as they fatigue the frequency of their discharge falls. This decrease in discharge frequency in some preparations results from a gradual and

continuous transition from a high to a low value. More often, as the frequency falls, more and more impulses drop out of an otherwise fairly regular series.

3. Muscles have been stretched over a thousand times with only 1-sec. intervals of rest without showing any appreciable fatigue provided the successive stretches were of short duration. If, however, the duration of the tension is prolonged for several minutes the response to a subsequent stretch is greatly reduced. Curves are presented which show typical rates of fatigue and recovery.

4. As fatigue progresses there is less reduction in the maximum impulse frequency than in the frequency at a later stage in the stretch. In other words, the discharge frequency declines more and more rapidly with fatigue.

5. The effect of loading a muscle in an atmosphere of nitrogen is to hasten fatigue of the sense organs and retard recovery. Oxygen has the opposite effect.

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