STUDIES IN DENERVATION

I.—THE CONTRACTILITY AND EXCITABILITY OF DENERVATED MUSCLE

BY

J. DOUPE *

(From the E.M.S. Hospital, Winwick, nr. Warrington)

(RECEIVED 14TH OCTOBER, 1943)

THE electrical reactions of denervated muscles form an integral part of the clinical picture associated with lesions of peripheral nerves. These reactions consist of changes in contractility and changes in excitability, both of which were stressed by Erb (1883*a*). He considered, however, that the former as revealed by the slow contraction was the more important indication of denervation, and this opinion was reaffirmed by Athanassio-Benisty (1918) and by Pollock (1920). In recent years greater stress has come to be placed on the changes in excitability, possibly because technical developments have permitted them to be assessed quantitatively; possibly because it was becoming realized that the shape of the contractions of denervated muscle varied from time to time with the physical state of the limb. Certainly both these considerations lead Adrian (1916) to apply the methods of Lucas to the study of denervated muscle in the human, and he was able to obtain measurements of excitability expressed in strength-duration curves which were diagnostic of denervation. Since then other technical developments have taken place, and it is now possible to make with some facility quantitative studies of both the time relations of the contraction and of excitability. It is the purpose of this paper to report an investigation attempting to correlate these two types of abnormal reaction shown by denervated muscle.

Method

The muscles most commonly employed in this investigation were the extensor carpi radialis and the tibialis anticus. Their contractions were recorded by a modification of the method described by Mendelssohn (1878-9) by placing a tambour firmly on the tendon where this crossed the joint, the joint being in a neutral position. In the case of some muscles such as the abductor digiti quinti the tambour was placed on the belly of the muscle. This tambour was connected by an air-filled system to an optical capsule which reflected a beam on to moving bromide paper. The natural frequency of the recording system was approximately 20 cycles per sec. and the lag in this system amounted to 5 msec. when compared to the stimulus recording system. The limbs were immobilized by moulded plaster casts which were bolted to the table while the tambour was clamped to a rigid iron framework fixed to the same table.

Bipolar stimulation was employed, the current being

applied through electrodes placed near each end of the muscle in positions where it was found by trial that the threshold was lowest and that little stimulation of adjacent muscle was produced. The electrodes were circular pads of saline-soaked cotton wool 1 cm. in diameter backed by a copper or silver chloride disc. These were spring-mounted on rods adjustably attached to the iron framework. The spring-mounting permitted slight movements of the muscle to take place without altering the contact. The stimulating currents were generated by the valve controlled apparatus described by Bauwens (1941*a*) who kindly supplied details of construction. This valuable device supplies rectangular waves of variable duration, frequency, and amperage, and the current output is independent of the resistance of the external circuit so long as this is below 5,000 ohms. In series with the patient was a mirror galvanometer of 60 ohms resistance with a natural frequency of approximately 1,000 cycles per sec. This recorded on the bromide paper the strength and duration of the stimulus.

Action potentials were recorded by use of a Matthews condenser coupled amplifier and oscillograph. A concentric needle electrode of the type described by Adrian and Bronk (1929) was used to pick up the potentials. When recording the action potentials the stimulating circuit was fed by high-tension batteries instead of rectified A.C. and when rectangular currents were used the stimulating electrodes were needles introduced into subcutaneous blebs of procaine as this was found to reduce the stimulus artefact.

The subjects are described in paper A and were chosen because definite information was available concerning the nature of their nerve lesions.

Procedure

After the apparatus was set up the resistance of the circuit was ascertained by the voltage necessary to pass 5 ma. If this was over 5,000 ohms the electrodes were readjusted. The frequency of the stimuli being set between 30 and 60 per min. the contractions were observed visually and if they appeared satisfactory the camera was run for 5-10 secs. The duration or the strength of the stimulus was varied either in the same or in subsequent runs. In the experiments on the effect of temperature the limb was kept immersed in water at 20° C. or 38° C. for 20 minutes just prior to the recording.

Results

The results to be reported are those obtained in experiments which were specially designed in the light of many preliminary observations to demonstrate particular features of the reaction of the muscles. It may be stressed, therefore, that the full weight of the evidence behind each observation will not be fully stated.

It is proposed to present these results to show

* Working on behalf of the Medical Research Council.

first that denervated muscles are prone to develop a repetitive response when stimulated by an electric current and then to illustrate how this property accounts for some of the peculiarities of contraction and excitability.

Repetitive Stimulation

The most satisfactory method of determining the occurrence of this phenomenon would be to record the action potentials of a single muscle fibre. This, however, is nearly impossible in an intact muscle,

for a considerable time after the initiation of the stimulus, and while they are stronger in the early part of the contraction they do not cease until about the peak of the contraction. With stimuli that cease before the peak of the contraction it is possible to show that the action potentials do not persist for longer than 20–40 msec. after the end of the stimulus. Fig. 2 shows the same sort of results recorded from the tibialis anticus of subject R.W. with a lesion of the sciatic nerve. In this instance, a progressive current obtained from another

FIG. 1.—Record ($\times \frac{1}{3}$) of subject A.K. showing the electrical and mechanical responses of the denervated abductor minimi digiti quinti to stimuli of decreasing duration having a moderately abrupt onset and decline. Time on original record is in 20-msec. intervals. For convenience 200-msec. and 1-sec. intervals have been added. The line indicating the stimulus moves in an upward direction when the current is flowing. The record of the muscle contraction was obtained from a tambour on the belly of the muscle. Action potentials were recorded from a needle electrode in the muscle. Calibration showing extent of deflexion and time constant of amplifier was obtained by making and breaking a potential of 10 uv applied to the active lead.

but an approach to this ideal has been made by the use of a concentric needle electrode. The number of fibres affecting such an electrode must be very variable but Brown (1937) has estimated it to be in the region of 100. It is likely, therefore, that in a simple muscle twitch temporal dispersion would cause a short burst of potentials before and with the onset of the mechanical contraction. If, however, the potentials persist throughout the phase of muscle shortening it may be concluded that each fibre is responding more than once and that

stimulator designed by Bauwens (1941a) was used to stimulate the muscle. It is apparent that action potentials persist throughout the whole period of current flow and this is associated with a prolonged shortening of the muscle, both the electrical and mechanical activity persisting until the decline of the current. In Fig. 3 are shown records obtained from subject C.B. also with a sciatic nerve lesion, but using a rectangular stimulating current and with a smaller condenser guarding the amplifier. The size of the condenser has reduced the amplitude of

FIG. 2.—Record ($\times \frac{1}{3}$) of subject R.W. showing electrical and mechanized response of the denervated tibialis anticus to a stimulus of gradual onset and decline. The initial deflection in line recording the action potentials is an artefact caused by closing the circuit which activates the stimulator. Description otherwise is as in Fig. 1

repetitive stimulation is occurring. It is not difficult to show that this is the condition prevailing in denervated muscles.

In Fig. 1 is shown a record obtained from the muscles of the medial border of the hand of subject A.K. who had an old standing lesion of the ulnar nerve. In order to reduce the stimulus artefact the stimulating current was smoothed by putting a 4 uF condenser in parallel with the patient while a 0.05 uF condenser was interposed between the active recording electrode and the amplifier. This record shows that the action potentials do persist

the potentials so that for adequate demonstration they have been reproduced here at double the original size. Three strengths of stimuli 3, 5, and 10 ma. of 2 sec. duration were used. 3 ma. produced neither an electrical nor a mechanical response and has not been figured here. 5 ma. produced a slow type of contraction associated with action potentials during the phase of shortening similar to those shown in Fig. 1. 10 ma. caused a much stronger contraction followed by a period of galvanotonus which persisted until the end of the stimulus. The action potentials also persisted.

A

B

FIG. 3.—Records of subject C.B. showing electrical and mechanical response of the denervated tibialis anticus to two stimuli of different strengths having an abrupt onset and termination. Time is in 20-msec. intervals and vertical lines have been drawn in at 200-msec. intervals. The line recording the action potentials has been enlarged $2\times$ the original size and then cut into sections of 200-msec. length and appended in the appropriate spaces below the reproduction of the original record. The line indicating the tension of the muscle was obtained from a tambour on the tendon.

These results show that repetitive stimulation of the fibres of denervated skeletal muscle is readily caused by a constant current. It may also be inferred that galvanotonus is associated with this phenomenon and has, therefore, the character of a tetanus rather than of a contracture as was suggested by Bremer (1932). Bremer did occasionally observe small fluctuating potentials, but he was instrumentally handicapped and recorded chiefly a large slow potential which he considered, following the work of Bishop and Gilson (1927), to be

associated with the actual contractile process. In the usual absence of such rapid fluctuating potentials as are recorded here he concluded that the muscle was in a state of contracture.

It may be thought that prolonged stimulation by constant currents violates the law of excitation of du Bois Reymond which states that it is the variation in strength of current that produces stimulation. Nevertheless, the phenomenon has long been recognized to occur in nerves, particularly in certain states such as when cool, and Gotch (1900) noted in

1900 that it implied a limitation in the law of excitation. Since then it has been explained by Ebbecke (1924) and by Erlanger and Gasser (1937) as being due to the recovery of the fibre through a stage of hyperexcitability permitting excitation to occur again and Katz (1939) has pointed out that a repetitive response to a persistent stimulus is the natural accompaniment of slow accommodation. However, this picture of a self-resonating system should not be viewed against a static background. The mere fact that an action potential is associated with excitation must indicate that the electrical field of the stimulating current is distorted. Also, the deductions of Bishop (1928) show that when a constant current is applied to a biological preparation the electrical field set up is not constant but fluctuating due to changes in the resistance and capacity of various parts of the tissues. These fluctuations of current plus a hyperexcitable phase during the recovery process provide an alternative or subsidiary explanation for the phenomenon of repetitive stimulation.

The abnormality in the case of denervated muscle is not that the repetitive stimulation occurs but that it is marked at current strengths which are of threshold value. It may be that this abnormality is not due to the denervation but to the way in which the stimulus is applied to the muscle fibre, i.e. direct rather than indirect stimulation. Against this view is the fact that no one has commented on a slowing of the contraction by curare, and it will be seen below that repetitive stimulation appears to cause this. This type of response may be termed with Rosenblueth (1941) a loss of accommodation, but there is no evidence as to whether it is due to an abnormality in the phase of recovery or in the extent of the current fluctuations or to some other factor. In any case the phenomenon is revealed by the degeneration of nerves and may be said to be typical of denervated muscle. It is also desirable to note that what is perhaps an analogous phenomenon has been observed in denervated smooth muscle (paper E).

Contractility

The contraction of denervated muscle is generally described as being slow, and while this is usually true,

it is only true because certain conditions of stimulation and temperature are usually present. The variability in the rapidity of the contraction when the muscle is cold and when it is hot, and when the stimulus is short and when it is long, is shown in Fig. 4. This figure records the results obtained in one of the preliminary experiments on a subject with a lesion of the external popliteal nerve and it indicated the need to amplify the generally accepted statement concerning the contraction of denervated muscle. It will be seen that when the denervated muscle was warm and when the stimulus was short that the contraction was nearly as rapid as that of normal muscle and that a change in either of these factors, that is, temperature or stimulus, influenced the rapidity of the contraction. These two factors will therefore be considered separately.

Temperature.—It is well-known that a fall of temperature slows the rate of contraction of normal muscle and an example of this has been provided in Fig. 4. Tuttle (1941) in a recent investigation on the normal gastrocnemius of man has found that immersion of the leg in crushed ice for 20 minutes caused a prolongation of all phases of contraction so that the peak of the contraction instead of occurring at about 100 msec. after the stimulus fell at 200 msec. while the phase of relaxation underwent a somewhat greater proportionate increase. These observations were repeated here on the denervated tibialis anticus of subject B.R. while recording the temperature of one part of the muscle. After warming of the leg in water at 38° C. for 20 minutes a copper-constantan couple was inserted through a needle to the depth of about 1 cm. into the muscles supplied by the divided external popliteal nerve. The needle was then withdrawn over the wires and a record of a number of contractions of the muscle was obtained when the temperature was 36° C. Crushed ice was then packed around the leg and without moving the electrodes or the recording tambour further sets of records were taken as the muscle temperature fell past each degree C. The duration of the stimulus was maintained at 40 msec. Representative contractions of similar height have been traced and superimposed to form Fig. 5. It will be seen that

FIG. 4.—Records ($\times 1/4$) of subject T.M. showing a comparison of the contractions of the normal in the upper records and those of the denervated tibialis anticus in the lower ones. Time is in 20-msec. and 1-sec. intervals. A downward movement of the stimulus line indicates in this figure the passage of current. Contractions are in response to brief and long stimuli when the muscles were warm and when cool.

FIG. 5.—Reproductions of the records of subject B.R. showing the effect of temperature on the contraction of the denervated tibialis anticus. The vertical co-ordinate which is height of the contraction in cm. has been doubled in respect to the horizontal which is time in order to distinguish clearly between the different contractions. The temperature inscribed below each curve refers to the temperature taken by a thermocouple in the muscle at the time the contraction was recorded. The solid block below the base line indicates the duration of the stimulus.

FIG. 6. Records ($\times 1/8$) and graph of subject L.R. The series of records labelled denervated were obtained from the denervated abductor digiti quinti, while those labelled normal were obtained from the normal muscle of the other hand. In each case records were obtained when the muscle was cool and when it was warm using stimuli of different durations and strengths. The original records have been cut and the sections arranged so that the onset of the stimuli occurs at the first vertical line. The time on the original tracings was in 20-msec. and 1-sec. intervals. The vertical lines have been inserted at 200-msec. intervals. The strength of the stimulus is stated to the left and the duration to the right of the contractions. The line inscribing the stimulus can be seen to move in an upward direction with the onset of the stimulus at the longer, but not with the shorter durations. The graph shows the relationship between the strength-duration curves and the temporal configuration of the contractions of normal and denervated muscles. Abscissae are the duration of the stimulus in logarithmic msec. Ordinates on the left refer to the strength-duration curves and are the strength of the stimulus in logarithmic ma. Ordinates to the right refer to the measurements of the time to the peak of the contraction and are in linear msec. The designation of the various lines of the contraction and of the stimulus so as to conveniently indicate the points at which the duration of the stimulus became less than the time to the peak of the contraction.

A.K. NORMAL
WARM

FIG. 7.—Records ($\times 1/8$) and graph of subject A.K. obtained from the normal and the denervated abductor digiti quinti. Description is given in Fig. 6. The series of contractions labelled A and B were recorded on different occasions.

there is a progressive lengthening of all phases of the contraction with the fall of temperature and at a temperature of 28°C . the time to the peak had increased from about 100 msec. to 200 msec. while the time to full relaxation had also greatly

increased. Thus there is a close similarity to results obtained by Tuttle on normal muscle. The difficulty of making an exact comparison is that it is impossible to estimate the average temperature of the tissues when they are cooled. This difficulty

FIG. 8.—Records ($\times 1/8$) and graph of subject R.W. obtained from the denervated tibialis anticus. Description is as in Fig. 6.

is overcome if the tissues are maintained at approximately blood temperature. This has been attempted in obtaining the results shown in the records in Figs. 6 and 7 in the columns marked warm. It will be seen that when brief stimuli are used that the contraction approximates that of the normal muscle shown in the companion records.

Duration of the Stimulus—In the above section it was seen that when brief stimuli were used to stimulate denervated muscle the contraction resembled that of normal muscle at the same temperature. This resemblance does not obtain, however, when long stimuli are used. This is demonstrated in records reproduced in Figs. 6, 7, and 8 which have been prepared by cutting the original records and arranging the sections so that at the top of each column the effect of a long stimulus is seen, while under this are placed other contractions resulting from successive decreases in the duration of the stimulus. It will be seen that

as the stimulus was shortened so the contraction also became shortened. This effect can be illustrated graphically by using the time from the onset of the stimulus to the peak of the contraction as an index of the rapidity of the contraction and plotting this against the duration of the stimulus. This has been done in the charts in Figs. 6, 7, and 8. From these it is apparent that, when the stimulus was progressively shortened, the time to the peak of the stimulus commenced to shorten soon after the duration of the stimulus became less than the time to the peak. These examples have been prepared by comparing contractions of the same height which have been achieved by varying the strength of the stimulating current. However, the effect can be just as well shown if the strength is kept constant as has been done in obtaining the record shown in Fig. 9, which shows successive contractions to stimuli of decreasing length. It is apparent that as the stimulus became shorter the hinder end of the contraction was abolished.

FIG. 9.—Records ($\times 1/8$) of subject R.W. showing the effect reducing the duration of the stimulus when the strength is kept constant. Time is in 20-msec. and 1-sec. intervals. The duration of the stimulus has been inserted as has also the time to the peak of the contraction and the time to half relaxation.

FIG. 10.—Tracings of the records of subject R.A. showing the effect of the strength of the stimulus on the contraction of the denervated tibialis anticus. The original records were enlarged approximately $2.5\times$ and traced. The scale to the left indicates the strength of current used, to invoke the contraction recorded by the line commencing from the various points on this scale. The time scale is in msec. commencing from the vertical line which represents the onset of the stimulus. The inset scale represents cm. on the original record. The solid lines indicate contractions obtained using stimuli of 500 msec. while the interrupted lines those obtained with stimuli of 40 msec. The onset and the peak of the contraction are shown by short vertical lines.

This phenomenon has been briefly referred to by Bremer (1932) and Rushton (1932). The former attributed it to an electrical contracture, but it has already been shown that this contracture is in reality due to a repetitive stimulation of the muscle

fibres. The latter author believed that it was due to a successive recruitment of muscle fibres basing the explanation on the theory that the weaker the stimulus the longer the utilization period and, therefore, the fibres which were in weak fields of current would respond later than those in the part of the muscle in which the lines of current were concentrated. This theory may be put to experimental test by measuring the latent period and the time to the peak of the contractions which are produced by threshold currents and comparing these times with those resulting from stronger currents. If Rushton's theory were correct the times should become progressively longer as the stimulus is lowered toward threshold strength. This experiment has been performed three times using stimuli of 500-msec. duration and recording the contraction with tambours so sensitive that the recording beam was displaced 1 cm. before any visible or palpable contraction was present in the muscle. The results of these experiments were in agreement and are typified by those shown in Fig. 10. To prepare this figure the records were traced and superimposed on a scale representing the strength of the stimulus. Horizontal alignment was determined by the onset of the stimulus. It is apparent that at near threshold values the latent period became slightly prolonged. This, however, was probably due in part to the fact that the contractions were so weak that the initial stages of them were not recorded, as there was a simultaneous shortening of the time to the peak of the contraction. With stronger currents there was a progressive diminution in the time to the onset of the contraction and this is also shown by a glance at the records in Figs. 6, 7, and 8, in which it will be seen that the stronger currents required at the shorter durations of stimuli produced a more immediate contraction than did weaker currents. These results make it clear that Rushton's explanation accounts for the shortening of the latent period with strong stimuli, but it is also clear that there is a maximum duration of the latent period. In other words, currents which have not caused excitation within this time will fail to do so no matter how long they are continued. That the stimulus response time has a finite value may also be concluded from the measurements of Blair and Erlanger (1936) and of Bogue and Rosenberg (1936) on various nerves. Therefore, if altering the duration of the stimulus beyond the maximal latent period alters the contraction it implies that some other mechanism than progressive recruitment must account for the variation. It will be seen in Fig. 10 that changing the duration of the stimulus from 500 to 40 msec. did alter the shape of the contraction. Also it will be seen in Fig. 9 that when the stimulus was reduced from 660 to 340 msec. there was an alteration in the shape of the contraction, and the maximum latent period even in the coolest muscles has never been found to be longer than 150 msec.

The explanation proposed here ascribes the pheno-

menon to the fact that the stimulus causes repetitive excitation of the fibres and so a shortening of the stimulus results in a shortening of what is virtually a period of tetanic stimulation. It is also probable that the shortening of the time to the peak with very weak stimuli as is shown in Fig. 10 is due to the fact that very weak currents maintain the period of repetitive stimulation for shorter times than do stronger currents. This is indeed a corollary to the observation illustrated in Fig. 3 that strong currents can induce a very prolonged period of repetitive stimulation resulting in the galvanotonic type of contraction.

It has been noted above that a fall of temperature prolongs the contraction resulting from brief stimuli. It is now necessary to consider the influence of this factor on the repetitive element of the response. Evidence on this point may be obtained by comparing the effects of prolonging the stimulus when the muscle is cool and when it is warm. It will be seen from the records reproduced in Figs. 6, 7, and 8, and in the charts plotted from these results that when the muscles were warm an increase in the duration of the stimulus increased the time to the peak of the contraction by 80 msec., while when the muscles were cool the time to the peak was increased by 250 msec. Therefore, it may be concluded that the period during which repetitive stimulation occurs is more prolonged when the muscle is cool than when it is warm.

It is necessary to note that in normal muscle it has been found that lengthening the stimulus also tends to prolong the contraction. That this is very slight at the strength of currents usually employed will be seen in Fig. 7. In Fig. 8 the records are somewhat confused by the occurrence of stimulation at the break of the current but none the less the occurrence of repetitive stimulation in these instances can also be inferred because the prolongation of the time to the peak still persisted after the stimulus was prolonged so as to make the break fall after the peak of the contraction. This effect on normal tissues will be referred to below and it is only required here to conclude that the influence of repetitive stimulation on the shape of the contraction is minimal in normal muscle as compared to denervated muscle, particularly when the latter tissue is cool.

Summary.—The above observations on the contraction of denervated muscles show that with brief stimuli and at similar temperatures the contraction of denervated muscle is similar to that of normal muscle. Bremer (1932) has also stressed this similarity. It may be concluded, therefore, that denervation does not materially affect the contractile processes of muscle. It has also been shown that denervated muscle is abnormally susceptible to repetitive stimulation by constant currents, especially when cool, and that this causes a prolongation of the contraction. These results have been so consistent that they permit the deduction that if a denervated muscle contracts slowly it is cool. In paper H it has been shown that while

denervated muscle has a somewhat greater resting blood flow than does normal muscle it is deficient in the great surges of blood that accompany even slight exercise in normal muscles. Now Grant and Pearson (1937–8) have shown that the temperature of normal resting muscle may fall far below blood temperature, but is immediately elevated by exercise. It may be inferred, therefore, that the temperature of denervated muscles is habitually low and that unless special precautions are taken to warm them routine testing with a galvanic stimulus will ordinarily reveal the slow sluggish contraction described by Erb.

An interesting application of these results is their bearing on an observation reported by Leriche (1939) who noted in a subject with a musculospiral palsy that a sympathetic nerve block caused the limb to become warm and the muscular contractions to become brisk. He attempted to relate the change to the relief of vasospasm in the nerve, but it was clearly a side effect produced by the change in temperature.

Excitability

In the foregoing sections results have been reported indicating that denervated muscle is very prone to show repetitive excitation in response to an electrical current. The effect of this behaviour on the shape of the contraction has been demonstrated and it is now necessary to inquire into its effects on measurements of excitability.

Since the pioneering studies of Lucas the strength-duration curve has been recognized as the most comprehensive statement of the excitability of a tissue. In the construction of these curves one determines the durations that various strengths of current require in order to produce a standard response of the tissue. Usually the minimal recognizable response is chosen as the standard, but as such responses are by definition almost non-recordable it is necessary, if it is desired to correlate the strength-duration curves and the muscular response, to show that supraminimal stimuli do not alter the strength-duration relationship. This has been done by stimulating a muscle with a wide range of current strengths at each duration of stimulus. The height of the responses were measured and the data obtained are shown plotted in Fig. 11. It is apparent that whether a contraction of 2.0 cms. or a threshold response be taken as the standard the same relationship between the strength and the duration of the stimulus is present.

The similarity of these curves indicates that the same excitability factors operate at these different strengths of contraction so it is reasonable to assume that if an explanation can be found for the shape of the strength-duration curves by correlating them with the time relations of contractions of more than minimal strength this explanation will also apply to strength-duration curves obtained from minimal responses. This inference is reinforced by the finding reported above that shape of the contraction does not alter greatly over a wide range of strengths of contraction.

The strength-duration curves reported here were constructed using a minimal response so that the threshold values of the currents might be simultaneously expressed. The presence of minimal responses was ascertained with the aid of the optical magnification of the apparatus.

It is now possible to indicate the significance of the strength-duration curves plotted in Figs. 6, 7, and 8. These curves, examined in conjunction with

which the threshold rises. The most pronounced correlation was found in case L.R. in whom there was the greatest variation in the rapidity of contraction and in whom the most trustworthy strength-duration estimations were obtained. It will be seen that when the muscle was cool the threshold was raised at stimulus durations of less than 500 msec., while when the muscle was warm the threshold did not have to be raised until stimulus duration was less than 160 msec., and these times were approximately 100 msec. less than the time to the peak of the corresponding contractions. In Fig. 12 is shown another way of expressing the same phenomenon. Two series of contractions are shown in this figure which were obtained in the experiment used to plot Fig. 11. It will be seen that when the muscle was cold the contractions were slow and that they diminished in height when the duration of the stimulus was changed from 540 to 300 msec. When the muscle was warm the contractions were rapid and did not fail until the stimulus was reduced to 70 msec.

FIG. 11.—Graphs of subject L.R. showing the effect of the size of the contraction on the strength-duration curve. In the chart to the left are plotted the size of the contraction in cm. against the strength of the stimulus in ma. at the various stimulus durations indicated. Measurements obtained by inter and extrapolation are used in the chart to the right to construct strength-duration curves corresponding to the various heights of contraction indicated. The short vertical lines indicate the chronaxie of these curves.

the measurements of the time to the peak of the contraction, show that soon after the duration of the stimulus becomes shorter than the time to the peak an increased current is required. The pertinent data have been abstracted from these graphs and are set out in Table I. From this it is clear that there is some relationship between the briskness of the contraction and the duration of the stimulus at

TABLE I

Subject		Time to peak	Duration stimulus at which threshold rises	Difference
L.R.	cool	600 msec.	500 msec.	100 msec.
	warm	250	160	90
A.K.	cool	475	300	175
	warm	150	70	80
R.W.	cool	350	160	190
	warm	200	70	130

These observations are interpreted to indicate that strength-duration curves derived from denervated muscle are an expression of the fact that the current in addition to inaugurating the contraction

FIG. 12.—Records ($\times \frac{1}{2}$) of subject L.R. showing the effect of reducing the duration of the stimulus when the denervated abductor digiti quinti was cool and when it was warm. The time is in sec. and being the same in both records was eliminated from the lower in reproduction. The stimulus durations indicated on the upper record apply also to those directly underneath on the lower record.

has a potentiating effect on the contraction. This potentiation is presumably due to the occurrence of repetition and it is thus no mere coincidence that the slow contraction of denervated muscle is associated with a prolonged excitation factor, for both are partly dependent on the same characteristic of the tissue.

It will be noted that the strength-duration curves of denervated muscle are to a certain extent modified by the temperature of the muscle. Thus, in Figs. 6, 7, and 8, it will be seen that the rheobase, i.e. the threshold for long stimuli, is lower when the muscle is cool than when it is warm. This difference in threshold does not obtain with shorter stimuli. Lucas and Mines (1907-8) described a similar effect in nerve and in the nerve-free part of toad muscle. The lower threshold and the greater repetitiveness that are shown by cool denervated muscles when stimulated by long currents appear to be expressions of the same fact. To appreciate this it must be realized that the thresholds with long currents are to a certain extent spurious in that the response even at threshold values is repetitive. This is indicated by the fact that the strength-duration curve, plotted in Fig. 11 for a figurative contraction of 0.0 cm., commences to rise when the stimulus is reduced in duration from 500 to 333 msec. As this time is much longer than any observed stimulus-

response time it must be inferred that threshold is being determined by the tendency of the tissue to respond repetitively.

In Fig. 13 is shown the strength-duration curves obtained from subject F.J. who was known to have a partial denervation of the hypothenar muscles. The kink in this curve would, according to the usual interpretation, indicate that two elements with different excitabilities were present in the tissue and would thus fit into the clinical picture. For comparison, the strength-duration curves of normal muscles have been plotted in Figs. 6 and 7. These of course show time factors which are much smaller than in denervated muscle. However, the point of interest is that the curves show a kink at about 16 msec. which is associated with an increase in the duration of the contraction as shown by the longer time to the peak, and the change in the shape of the contraction is sufficient to be appreciated in the apposite records. The question, therefore, arises whether such kinks in strength-duration curves necessarily indicate, as presumed by Lucas, that two elements of different excitability exist in the tissue or whether they may not arise in some instances from two modes of response in the one element as was suggested to Rushton (1932) by Lapicque. This doubt is of theoretical importance, but from the practical point of view it will be seen

FIG. 13.—Records ($\times 1/8$) and graph of subject F.J. obtained from the partially denervated abductor digiti quinti. Description is as in Fig. 6.

that the difference between the curves obtained from normal and from denervated muscles is more a matter of degree than of kind and indicates that some caution is required in drawing conclusions from such measurements.

Other considerations also indicate that strength-duration curves give less precise information than their appearance suggests. Thus, the contractions resulting from long and short stimuli are not comparable as will be seen from the records of denervated muscles shown in Figs. 6, 7, and 8. They have here been compared on a basis of height, but it is obvious that if area were the basis of comparison different strength-duration curves would be obtained. Another equally crucial objection arises from the concept of the utilization period. The durations plotted in a strength-duration curve are supposed to represent the time required for the current to activate the tissue, i.e. the time during which it is being utilized. It is obvious, however, that in denervated muscle the current is able to affect the tissue even at threshold strengths long after it has first caused stimulation.

The simplest conception of the events occurring in denervated muscle is that following the initial stimulation there is a period in which the current if it is continued re-excites the muscles. If the current flows for only a short time the period during which re-excitation can take place is decreased so that the number of fibres involved in the initial stimulation must be increased if the strength of the contraction is to be kept constant. The number of fibres can only be increased by increasing the strength of the current and in this way one obtains the strength-duration curve of denervated muscle. This reasoning suggests the most serious theoretical objection to these curves as it indicates that the same elements of the muscle are not under observation. Clinical experience supports such a view, for not infrequently if the muscle is being watched while obtaining strength duration measurements it has been seen that the contracting portions of the muscle with long stimuli are not necessarily the same as those with short.

It may thus be concluded that strength-duration curves do not have the same significance in repetitive systems as they do in non-repetitive systems and this is in agreement with conclusions of Arvonitaki *et al.* (1936) on crustacean nerve.

It is pertinent to point out that present conceptions do not attribute to strength-duration curves the same biological significance as was originally claimed for them by Lapicque (1926). The work of Davis (1923), Watts (1924-5), and Grundfest (1932) has shown that the curves are more particularly associated with relation between the size of the fibre and the size of the electrical field impinging upon it. Both Rushton (1932) and Lapicque (1932) have attempted to explain this and it would appear that a sharply localized stimulation as produced by a capillary electrode will rapidly set up a critical degree of depolarization so that a propagated response can be initiated,

whereas if the field of current embraces the whole fibre, the borders of the area of depolarization will be vague and the process of depolarization must continue longer before a sufficient difference exists at any one point to enable it to constitute a focus. The complex nature of the events leading to excitation when large electrodes are used and the fibres are in a relatively even field of current may be realized when it is considered that the current enters one end of the fibre and leaves at the other, thus producing both anodal and cathodal effects over approximately equal areas of the fibres. It is not surprising, therefore, that the time factor should depend on the mode of stimulation. Moreover, it has also been pointed out that the time factor will also vary depending on whether the response under observation is dependent on a single or on a repetitive discharge. It will be seen, therefore, that in denervated muscle, when percutaneous stimulation is used, two factors are present leading to a long time factor of excitation, i.e. the relation of the electrical field to the fibres and the property of responding repetitively.

Clinical Considerations

The phenomena occurring in denervated muscles have been described above from the physiological point of view. It is advisable, therefore, to conclude this paper with some reference to the clinical aspects of electro-diagnosis in peripheral nerve lesions.

In the first place it must be stressed that the information supplied by electrical tests, like that of most other tests, has more value when it is positive than when it is negative. This is well exemplified by the significance of abnormalities of contraction. Thus, the presence of a response indicates that muscle tissue is present. An absence of contraction to all forms of stimuli, while it may indicate complete degeneration of the muscle fibres, is more likely to mean, as explained by Roberts (1916), that due to oedema or some other abnormality in the extracellular constituents of the tissues the current is being blocked or short circuited from the excitable elements. The same restrictions bear on the implications of a slow contraction. If this is present it means that at least some of the muscle fibres are denervated, (other conditions such as myotonia being excluded), but its absence may only mean that the muscle is warm. Similarly, the presence of a response to nerve trunk stimulation is of obvious importance, but its absence is of dubious significance.

Measurements of excitability are subject to the same restrictions of interpretations. If the presence of an excitable element with a short time factor is ascertained it is obvious that nerve fibres are present. The failure to find such an element may, however, be due to various factors, one of which is the relative indifference of regenerating nerve fibres to electrical stimuli as described by Erb (1883b) and more recently by Bauwens (1941b). Similarly, a long time factor would indicate the presence of denervated muscle fibres, but would not

exclude the presence of some fibres with intact innervation.

These assertions suggest only one thing—namely, that every effort should be made to elicit the type of response that is being looked for. Thus, if one desires to determine if a muscle is receiving a nerve supply in the absence of a response to voluntary innervation or nerve trunk stimulation, the cathode should be placed so that it is most propitiously situated in regard to the nerve fibres. As the response to direct stimulation of the muscle fibres may be confusing this should be eliminated so far as is possible without detriment to the immediate object. Therefore, the indifferent electrode should be placed so that the current does not flow through more of the muscle than is necessary, and brief stimuli of 1 to 5 msec. should be used. It is also advisable that these currents should enter the tissues without too much distortion. Therefore, a stimulator such as described by Bauwens (1941) should be employed. This has the added advantage that it will enable two or three points of a strength-duration curve to be ascertained and so give an absolute decision as to whether the response if present is due to the stimulation of nerve fibres or to the direct stimulation of muscle fibres with a low threshold. In the same way, if it is desired to ascertain if denervated fibres are present the maximum opportunity should be given for them to express themselves. The limb should be moderately cool and the electrodes applied to each end of the muscle. A slow contraction with long stimuli or several points on a strength-duration curve will reveal their presence.

A final word may be said with regard to the value of testing with galvanism and faradism. A slow contraction to galvanism or a response when the nerve trunk is stimulated with faradic currents carries obvious implications. Otherwise, the information which can be obtained is of no value and merely supports the clinical findings without adding to them. In some cases the information may be misleading, for faradic currents can, if of sufficient intensity, stimulate denervated muscle.

Summary

An attempt has been made to discover the reasons underlying the slow contraction and prolonged excitation time of denervated muscle.

It was shown in the first place that denervated muscles are prone to develop repetitive excitation when subjected to an electrical current.

This manifestation was found to be responsible, in conjunction with a cool state of the muscle, for the prolonged contraction. The phenomenon of

galvanotonus has also been attributed to repetitive firing of the muscle fibres.

The prolonged excitation time was found to be partially due to repetitive stimulation, and it was also attributed to the relation of the muscle fibres to the field of the current.

Clinical implications have been briefly noted.

Grateful acknowledgment is tendered to Dr. W. Schlapp of the Department of Physiology of the University of Manchester for help in calibrating the stimulator and to Mr. R. W. Taylor of Warrington for advice concerning various electrical problems.

REFERENCES

- Adrian, E. D. (1916). *Brain*, **39**, 1.
 Adrian, E. D., and Bronk, D. W. (1929). *J. Physiol.*, **67**, 119.
 Arvonitaki, A., Auger, D., and Fessard, A. (1936). *C. R. Soc. Biol.*, Paris, **121**, 638.
 Athanassio-Bensity (1918). *The Treatment and Repair of Nerve Lesions*, p. 37, London. University of London Press, Ltd.
 Bauwens, P. (1941a). *Proc. roy. Soc. Med.*, **34**, 715.
 — (1941b). *Ibid.*, **34**, 459.
 Bishop, G. H. (1928). *Amer. J. Physiol.*, **85**, 417.
 Bishop, G. H., and Gilson, A. S. (1927). *Ibid.*, **82**, 478.
 Blair, E. A., and Erlanger, J. (1936). *Ibid.*, **114**, 309.
 Bogue, J. Y., and Rosenberg, H. (1936). *J. Physiol.*, **87**, 67.
 Bremer, F. (1932). *J. Physiol.*, **76**, 65.
 Brown, G. L. (1937). *Ibid.*, **89**, 220.
 Davis, H. (1923). *Ibid.*, **57**, p. lxxxix.
 Ebbecke, U. (1924). *Pflüger's Arch. ges. Physiol.*, **203**, 336.
 Erb, W. (1883a). *Handbook of Electro-therapeutics*, p. 76, New York. William Wood & Co.
 — (1883b). *Ibid.*, p. 75.
 Erlanger, J., and Gasser, H. S. (1937). *Electrical Signs of Nervous Activity*, p. 113, Philadelphia. University of Pennsylvania Press.
 Gotch, F. (1900). *Textbook of Physiology*, Ed. E. A. Schäfer, **2**, 470, Edinburgh and London.
 Grant, R. T., and Pearson, R. S. B. (1937–8). *Clin. Sci.*, **3**, 119.
 Grundfest, H. (1932). *J. Physiol.*, **76**, 95.
 Katz, B. (1939). *Electrical Excitation of Nerve*, p. 44, London, Oxford University Press.
 Lapique, L. (1926). *L'Excitabilité en Fonction du Temps*, p. 220, Paris. Les Presses Universitaires de France.
 — (1932). *J. Physiol.*, **76**, 261. Young J. Pentland.
 Leriche, R. (1939). *The Surgery of Pain*, p. 261, Baillière, Tindall and Cox, London.
 Lucas, K., and Mines, G. R. (1907–8). *J. Physiol.*, **36**, 334.
 Mendelssohn (1878–9). *Physiol. Experimental* (E. J. Marey), No. 2, sect. 4, p. 141.
 Pollock, L. J. (1920). *Surg., Gynec. Obstet.*, **30**, 472.
 Roberts, F. (1916). *Brain*, **39**, 297.
 Rosenblueth, A. (1941). *Amer. J. Physiol.*, **132**, 57.
 Rushton, W. A. H. (1932). *J. Physiol.*, **75**, 445.
 Tuttle, W. W. (1941). *J. Lab. clin. Med.*, **26**, 1913.
 Watts, C. F. (1924–5). *J. Physiol.*, **59**, 143.