FACTORS AFFECTING RECOVERY OF MOTOR FUNCTION AFTER NERVE LESIONS

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IN spite of the very great amount of material available from studies of nerve injuries in man we still have little thoroughly reliable information as to the factors which influence the degree of final recovery. Diagnosis, prognosis, and therapy of nerve lesions would be easier if there was less doubt about the variables which control the speed and degree of recovery. This paper reports the results of an attempt to define more exactly the influence on final recovery of (1) the nature of the lesion, (2) its level, (3) interference with blood supply of the limb, (4) age of the subject, (5) infection, and (6) delay of suture. Study of clinical material has failed in the past to provide answers to these questions mainly because the variables were so numerous. The cases generally have followed war wounds or accidents; the nerve has been injured over varying lengths; the blood supply has been damaged or there has been infection; surgical treatment has varied from case to case and many other factors have been involved which have made comparisons of clinical cases difficult or impossible. Experiments can avoid some of these uncertainties, but they must be arranged so that the criterion of recovery gives a real index that the nerve and muscle have returned to a useful functioning biological unit. Previous estimates of return of motor function in animals following injuries to limb nerves have been mostly restricted to observations of either the return of muscular contraction in response to electrical stimulation of the affected nerve, the so-called " indirect " electrical excitability, or of the restitution of normal use in the affected limb. The reports of the return of indirect excitability may be of two kinds: (*a*) statements that electrical excitability was present after a certain time (Kilvington, 1908), or (*b*) a series of observations made at different times, the earliest positive observation indicating roughly the time of onset of this type of recovery (Holobut and Jalowy (1936), Howell and Huber (1892), Bentley and Hill (1936)). Of these two types of report the second is obviously the more valuable

from a comparative point of view. But reports of the first type are often of considerable value, since they indicate the presence of regenerated fibres, both in the nerve trunk and in the paralysed muscles, and that the muscle endings formed are such that electrical stimulation of fibres in the nerve is adequate to bring the muscle to contraction. But such observations do not imply that a recovery of reflex or voluntary movement has necessarily taken place. Certain processes have to take place in a nerve before it becomes " functionally complete," and these processes may not be over even though many of its fibres have made connections with the periphery, and the muscle responds when the nerve is stimulated electrically (Gutmann *et al.* (1942)). Thus it is possible for a return of indirect electrical excitability to take place without any return of motor function. Clinically, the important entity is the voluntary or reflex movement. Observations alleging " functional recovery " in animals based upon a return of indirect excitability in the absence of evidence of return of voluntary movement have a limited value only. Most observations on the return of voluntary movement take the form of a statement to the effect that the gait of the affected limb eventually became normal. Such observations have been recorded after using nerve grafts (Ingebrigsten (1916), Nageotte (1922)) as a test for the effect of electrotherapy (Friedländer (1896), Chor *et al.* (1939)) and of nerve crossing (Howell and Huber (1892), Osborn and Kilvington (1911), Kennedy (1913), and Barron (1934)). The main defect of observations on gait is that they take no account of the recovery of voluntary movements in individual muscles innervated by the operated nerve, and thus it is not possible to estimate at all accurately the time of onset of recovery in these muscles. At most one may roughly estimate the time of the appearance of a generalized co-ordinated movement. Moreover, a considerable degree of inco-ordination of movement is apparent in the first voluntary movements of reinnervated muscles, as a

result of the heteroinnervation of muscle endings. This is especially noticeable after nerve crossing (Barron (1934), Sperry (1941)), but it may occur to a certain extent following division and suture of a nerve (Watrous and Olmsted (1941)).

Both in man and other mammals it is possible that this inco-ordination may be partly overcome by a process of readjustment in the centres concerned (Watrous and Olmsted (1941)). But this readjustment takes place in the period immediately following the incidence of motor recovery. Therefore observations on gait dating the onset of recovery as the time of commencement of co-ordinated movement will be overestimates, for such times include both the actual time of recovery and the time required for " relearning." In addition, many synergic groups of muscles collaborate in walking movements, and may give an appearance of recovered function in cases where recovery has in fact not taken place. Thus improvement or recovery of function has been recorded at a time when no regenerating fibres could possibly have arrived at the muscle (Friedländer, 1896). Observations on the recovery of gait are therefore not conclusive or exact tests of the recovery of voluntary movement. A more reliable estimate of the time of onset and progress of recovery of voluntary movement following nerve repair in animals may be made by restricting observations to the function of a small group of muscles known to be innervated by the nerve whose recovery is being followed, and whose action cannot be imitated by any other set of muscles (for example Bender and Fulton (1939), after section of the oculomotorius nerve in Macacus). In this way onset of recovery may be accurately dated, and errors due to trick movement avoided. The difficulty is to find a movement which meets these conditions, which may be easily elicited and which may allow frequent examination of the animals essential for the study of onset of recovery.

In order to test factors influencing the recovery of motor function, and to follow the different stages of the process of recovery, it is first necessary to use a standard method of interrupting the nerve. Such methods as cutting the nerve without suturing (Holobut and Jalowy (1936), Friedländer (1896)), injecting the nerve with alcohol (Wolf, 1940), and sutures à distance (Vanlair, 1894) introduce great variations. Even simple stitch sutures cannot all be made alike. Thus Chor et al. (1939) observed onset of recovery after stitching the sciatic nerve at times varying between 55–158 days. Such variations made comparison difficult; for instance, Perroncito (1908), when comparing the constant results obtained from anatomical data with the " immense contraindications and variations of the physiological experiment " stated that " questions of anatomical regeneration of nerves and of functional healing although connected have to be considered separately."

The method of crushing a nerve offers the minimum variation in the time of onset of recovery, and may be thus used with advantage when factors influencing the progress of recovery are being studied. Lee (1929) has maintained that crushing is an uncertain procedure of interrupting a nerve, but if properly done it is followed by complete degeneration of all the fibres. The constancy of the results obtained by crushing permits better assessment than by any other method of trauma.

Methods

Movements which may be elicited reflexly have been chosen as tests indicating onset of recovery of motor function. Postural reflexes have been found to be especially useful. In most of the experiments to be described observations have been made mainly on a small group of muscles innervated by the peroneal nerve of the rabbit, the function of which is to spread three of the toes of the hind limb. These muscles may be caused to contract reflexly as first observed by Langley (1915) in cats, by holding the animal by the loose skin of the back and then suddenly lowering it. The muscles involved in this reflex are the small peroneals (Mm. peronei II, III, IV) innervated by the peroneal nerve, and the M. abductor hallucis innervated by the tibial nerve.* The peroneal muscles spread the second, third, and fourth toes, while abduction of the first toe is a function of the M. abductor hallucis. Reflex spreading of the 2nd, 3rd, and 4th toes thus constitutes an index of peroneal nerve function, while reflex abduction of the first toe characterizes tibial nerve function. Following section of the peroneal nerve there is a loss of ability to spread the 2nd, 3rd, and 4th toes which cannot be simulated by a " trick " movement. During regeneration of the peroneal nerve the first response is a mere flicker of the 4th toe; the spreading increases in amount from day to day, gradually involving the 2nd and 3rd toes. By the use of an arbitrary scale, which may be called the " spreading index," it has been possible to make a rough estimate of the state of recovered function. Degrees of spreading have been indicated as follows: degree 1, just visible spreading of the 4th toe alone, sometimes also of the 2nd and 3rd toes; degree 2, slight spreading of all toes; degree 3, spreading of all three toes, but less than elicitable in the normal animal; degree 4, full spreading of all three toes equal to normal as determined before operation or by comparison with the opposite and control side. By means of daily examinations the progress of recovery in a single case, and the difference in the final degree of recovery attained after different procedures may be estimated. Note has also been made of the progress of recovery of the other muscles innervated by the peroneal nerve, so as to allow comparisons between the recovery of muscles with nerves of different lengths. Other criteria of muscle recovery have been examined, namely (1) the indirect excitability or response to electrical stimulation of the nerve either (a) through the skin, or (b) after exposure of the nerve; (2) the direct excitability of the muscle; (3) the circumference of the limb in the region of the denervated muscles; (4) the weight of the muscles; (5) the disappearance of fibrillation.

The animals used have been rabbits of various ages and races, including some of a month old, which have given evidence about the effect of age on recovery rate. The nerve lesions have been made by aseptic operation under nembutal-ether anæsthesia when the nerve has been interrupted by one of four ways: (1) by repeated crushing at a single point by a fine smooth-tipped watchmaker's forceps; (2) by severance with scissors followed by suture with cockerel plasma (Young and Medawar, 1940); (3) by severance with scissors followed by suture with fine white silk stitches; or (4) by repeated crushing with forceps over a considerable length (4 cm.).

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* The name given to this muscle by Krause (1884) and in other text-books on the anatomy of the rabbit (Bensley (1938)) is M. extensor hallucis. As the main function elicitable reflexly is one of abduction rather than extension, the muscle might be more appropriately named M. abductor hallucis.

The Recovery of Motor Function after Lesions of the Peroneal Nerve

Functions of the peroneal nerve

Most of the following studies depend on knowledge of the sequence of events during recovery of the peroneal nerve. We will therefore first describe the stages of recovery after interruption by crushing at a single point of the continuity of the axons of that nerve. The muscles innervated by the peroneal nerve and their functions (elicited by stimulation of the nerve) are:

M. tibialis anterior: dorsal flexion and some supination of the foot.

M. extensor digitorum: dorsal flexion of the toes.

M. peroneous longus (or primus): pronation and some plantarflexion of the foot.

M. peroneus secundus: abduction of the 4th toe and some abduction of the other toes.

M. peroneus tertius: dorsal flexion of the 3rd toe and some abduction of the 2nd and 3rd toes.

M. peroneus quartus: plantar flexion and some abduction of the 2nd and 3rd toes.

Thus the functions of the muscles innervated by the peroneal nerve are dorsal flexion of the toes and the foot, pronation of the foot and abduction (spreading) of the 2nd, 3rd, and 4th toes.

Recovery after Crushing of the Peroneal Nerve

The palsy after interruption of the peroneal nerve

Fig. 1.—Palsy after interruption of the peroneal nerve, characterized by dropfoot and absence of the spreading reflex.

is characterized by dropfoot and the absence of the spreading reflex (Fig. 1). These features do not produce any marked influence on the stance and gait, which appears normal except for some abduction of the foot when sitting and some dragging of the foot when hopping. In some cases the toes are kept in marked plantar flexion and the animal walks on the dorsum of the toes, where sores may develop. These cases are rare and observations of the gait alone do not allow estimates of the onset of recovery. The dropfoot is marked immediately after interruption of the nerve, but becomes less or disappears, often long before reinnervation of the muscles. This is due to the sitting posture of the animal, which fixes the foot in a bent position. In Man, on the other hand, where the opposite condition obtains, the dropfoot continually increases. On account of this fixation it is not easy to determine the time at which dropfoot recovers in the rabbit. The movement of dorsal flexion of the foot may be elicited reflexly as a nociceptive reaction by pricking the sole. This reflex, however, is not very suitable for a study of recovery because being a general shortening reaction it involves movements of muscles of the hip which may produce actions similar to those of the muscles paralysed by the peroneal nerve lesion. It is easier to produce dorsiflexion of the foot by gentle lowering of the animal in the upside down position.

Of the functions mediated by the peroneal nerve the spreading (abduction) of the 2nd, 3rd, and 4th toes may be most easily studied. Even at rest the effect of interruption of the nerve is clearly seen in the close apposition of the toes, producing a narrow foot (Fig. 1). With the nerve interrupted at the level of the knee by a crush the spreading reflex reappears after 23 to 27 days (12 animals), the earliest sign being a movement of the 4th toe. For the first 2 or 3 days this is a mere flicker, inconstant and sometimes disappearing on repetitions. This is the condition characterized as degree 1. Two or 3 days after the reappearance of the abduction of the 4th toe the spreading of the 3rd and 2nd toes appears (degree 2). During the subsequent days the amplitude of the movement increases (degree 3), finally to return to normal (degree 4) at an average of 8 days (Fig. 2). In some animals the extent of abduction continues to increase, becoming greater than that normally found. This has been observed
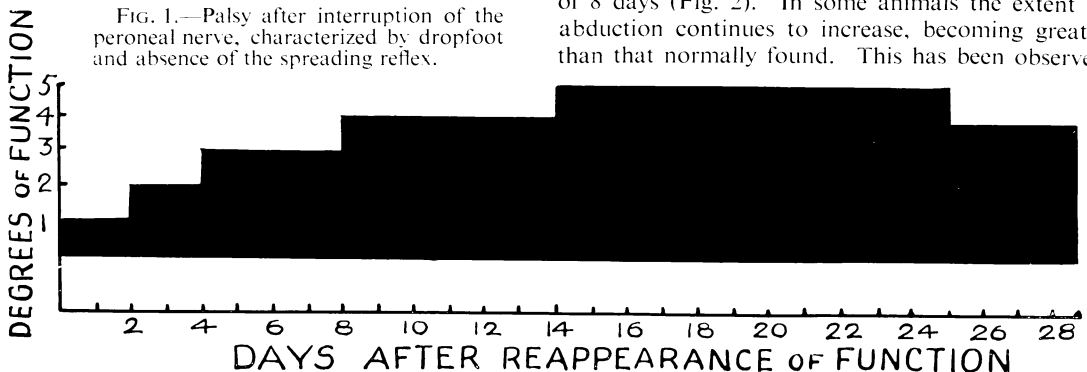

Fig. 2.—Course of recovery of the "spreading reflex" in a typical case after crushing the peroneal nerve at the knee (20 mm. above entry to the M. peroneus longus). The ordinates show degree of spreading observed. For the period from 14 to 25 days after appearance of the spreading it is greater than that normally observed.

in 6 animals, in which a control side had been left for comparison. This over-functioning, which may be expressed as degree 5, is only a temporary phenomenon, and after reaching a maximum about 1 to 3 weeks after the onset of recovery subsequently declines until the movement is of normal extent (see Fig. 2). This over-functioning may be due to the excessive early innervation (Boeke, 1916), and its later correction may indicate that the initial number of fibres is later reduced.

As explained above, it is difficult to determine the exact amount of recovery of the other muscles supplied by the peroneal nerve. Dorsiflexion of the foot usually appears about one week after the first appearance of spreading. It increases in strength in the next few days and becomes normal after about 1 to 2 weeks.

Recovery of Indirect Excitability

For some time before reflex functioning returns the muscles will contract when the nerve is stimu-

successive contractions of the muscles according to their distances from the lesion may be obtained. About 3 weeks later all muscles respond at the same threshold. Contraction of the muscles by stimulation of the skin appears late, about a week after the first appearance of the spreading reflex. The most suitable point for stimulation is just below the knee, where the nerve lies very superficially. The same sequence of recovery as during stimulation of the exposed nerve is obtainable.

Measurements of Circumference

A further method of demonstrating changes during the process of regeneration in the muscles is the measurement of the circumference of the leg. At a point 15 mm. below the crista tibiæ the circumference of the leg has been measured with a thread at weekly intervals after the interruption of the nerve. Each measurement has been repeated three times and the mean taken. Even this somewhat crude method has proved sensitive enough to show

DAYS AFTER OPERATION

	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
RECOVERY OF EXCITABILITY	O	O	O	O ○	OO ○○	O ○○	O	◑ ◒	O ○	◒◒ ◑	◒◒ ●	◒◒ ●	◒ ◒	●● ●● ◒◒		● ◒	●								
OF SPREADING												■■	■■	■■ ■		■									
OF DORSI-FLEXION																		■■	■		■	■■	■■		

FIG. 3.—Onset of excitability and recovery of function after crushing the peroneal nerve about 20 mm. from the M. peroneus longus. Each circle represents an experiment in which the nerve was stimulated at a given interval after crushing. ○ indicates no muscles responding, ◑ response in m. peroneus longus, ◒ in m. peroneus longus and secundus, ● in all muscles innervated by the nerve.
Each black square shows the day on which recovery of spreading (second line) or dorsiflection (bottom line) was observed in one case. Thus the spreading reappeared between 23rd and 27th day.

lated with a faradic current. The time of onset of this indirect excitability has been investigated in a series of animals in which the peroneal nerve has been crushed at the knee. Fig. 3 shows the results from 36 animals in which the peroneal nerve has been crushed at the level of the knee and then exposed for faradic stimulation with bipolar electrodes a number of days before recovery had been expected. In addition the figure shows the times at which recovery of the functions of spreading and dorsal flexion have been seen after such lesions. The muscles begin to respond in the order of their distances from the lesion, the order being the M. peroneus longus, M. peroneus secundus, M. peroneus quartus, M. peroneus tertius, and finally M. tibialis anterior and M. extensor digitorum. The time between first appearance of indirect excitability and reflex function is about 5 days in the case of the M. peroneus secundus; this interval is nearly the same for the other muscles, whose function cannot be so exactly determined. When indirect excitability of a given muscle first reappears the threshold is unduly high, even above the lesion, presumably because of the need for a greater voltage to stimulate the few fibres which have become reconnected. Subsequently the threshold falls. Therefore, after all muscles have just recovered, by slowly moving in the secondary induction coil

FIG. 4.—Differences shown by successive measurements of the circumference of the leg made 15 mm. below the Crista tibiæ in two animals in which the peroneal nerve had been crushed 80 mm. from the M. peron. long. The dotted line indicates the day of onset of the first appearance of reflex functioning.

the onset of the process of recovery. After interruption of the peroneal nerve the circumference decreases, and this decrease stops before either indirect excitability or reflex movements return (Figs. 4 and 5). In some cases it is found by calculation that the cessation of the decrease of circumference coincides roughly with the time at which regenerating fibres arrive at the muscle. The values from individual animals do not always give a smooth curve as that given by the average of the changes of circumference shown in Fig. 5, there being a margin of experimental error of 2 mm. at individual observations. When no regeneration occurs the circumference continues to decrease, though at a slower rate. In a case where a graft had been made (Gutmann and Sanders, 1942) the failure to show a regular increase in circumference had raised the suspicion that no union had been made. Necropsy confirmed that this has been the case.
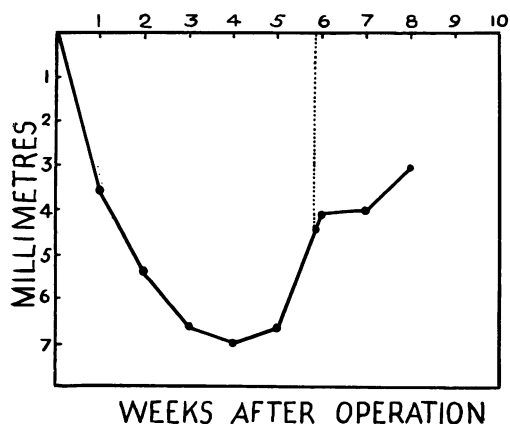
FIG. 5.—Average of the changes in circumference of the leg after crushing the peroneal nerve, calculated from 12 cases. The dotted line indicates the average time of first appearance of reflex functioning in these cases.

Electrical Excitability of the Muscles

Faradic stimulation of the muscle, either directly on the exposed muscle or through the skin, has always produced a response, even 8 months after denervation. Observations have been made on the threshold necessary for eliciting visible function (pronation, abduction of the 4th toe and dorsiflexion of the foot), and for the visible contraction of the muscles. After interruption of the nerve the threshold declines for 2 to 3 days and then increases. During the process of regeneration the thresholds fall again before onset of functional recovery. Some weeks after recovery following crushing of the nerve thresholds lower than that before operation have been observed in a few cases. The changes in threshold, however, are not great, and in view of the considerable strength of stimulus necessary to excite the muscles little reliance is to be placed on this method.

Cessation of Fibrillation

Fibrillations may be readily seen by light reflected from the surface of the muscles. Fibrillation does not cease with the return of indirect excitability or reflex function. About 1 week after return of the spreading reflex, when dorsiflexion is returning, fibrillations may be seen in all muscles, most prominently in M. extensor digitorum and in M. tibialis anterior. Two weeks after the appearance of spreading, fibrillation disappears from the peronei but may persist for 2 weeks in the two more distal muscles. Presumably, therefore, fibrillation only ceases in a given muscle fibre when it becomes innervated, a process which occurs progressively throughout each muscle.

Observations on the Weight of the Muscles

The peroneal nerve has been crushed on one side either, in one series, just before its entry into the M. peroneus longus, or, in another series, high up in the thigh about 110 mm. from the muscle. Necropsy has then been performed either at the moment of recovery of spreading, or, in other animals, at intervals of 1, 2, 3, 4, 6, and 12 weeks after recovery. The M. extensor digitorum and M. tibialis anterior have been excised and weighed. The muscles removed from the living animal have been placed in a Petri-dish on Ringer-soaked gauze and weighed after blotting twice with filter paper. Fig. 6 shows the percentage of the weights of the
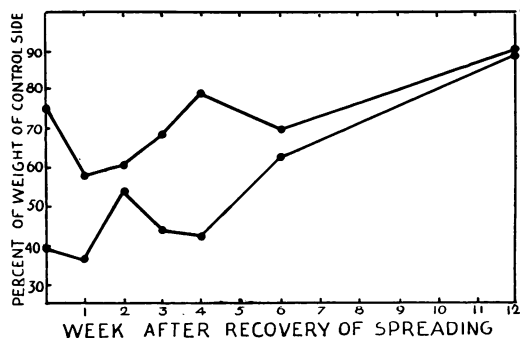

FIG. 6.—Diagram in which the percentage of the weights of the reinnervated M. tibialis ant. compared with the normal muscles of the control side were plotted against time after recovery, upper line after low lesions, lower line after high lesions.

reinnervated muscles compared with those of the muscles of the control side. It may be seen that even after recovery of spreading the atrophy is marked. This is to be expected as at this time the reinnervation of the muscles is not complete. Thereafter the muscles gain in weight slowly, but even 12 weeks after recovery of spreading the initial weight is not completely regained. At this time the initial difference in weight between high and low crushes due to the longer time of denervation ceases to be evident.

Summary of the Process of Recovery

By comparing a number of aspects of recovery after standard lesions at a standard distance a clear picture is obtained of the sequence of events. When the lesion is a crush made 20 mm. from a muscle, say the M. peroneus II, new axons arrive in the muscle 10 days after injury (Gutmann et al., 1942). Soon after this the direct excitability of the muscles ceases to fall, while at the same time the circumference begins to increase, and the first muscle fibres begin to respond on nerve stimulation. The weight of the muscles increases slowly and is nearly normal 12 weeks after recovery. The first sign of reflex functioning appears some 5 days after onset of indirect excitability, and the power of the muscle continues to increase until it reaches normal about a week after the first reflex contractions, though it may become supernormal for a short time. The increasing extent of the movement during the days after its first appearance is presumably a result of increasing numbers of muscle fibres which become innervated.

Factors Influencing the Recovery of Function

Effect of Level of Lesion.—The process of recovery has been watched after crushing the peroneal nerve (*a*) high in the thigh—5 cases, (*b*) at the middle of the thigh—7 cases, and (*c*) just above its entry into the muscles—7 cases. The distances of the lesions from the entry to M. peroneus II are about 105, 40, and 20 mm. The progress of increase in the spreading reflex has been examined carefully in each case. By taking the average of the degree of spreading shown by all the animals of each set at each day after the beginning of recovery a clear picture of the process of recovery may be obtained (Fig. 7). It will be seen that the recovery of spreading is distinctly slower with the lesions more distant from the muscles, the complete recovery (degree 4) being reached at an average of 8 days in Group A, 8·4 days in Group B, and 13·5 days in Group C, after the beginning of recovery. It seems that the time between arrival of fibres at the muscle and onset of indirect excitability and recovery of function is longer after high than low crushes. The first fibres arrive in low lesions (20 mm. from the muscle) after 10 days, in lesions of the middle of the thigh (48 mm. from the muscle) after 16 days, and in high lesions (100 mm. from the muscle) after 27 days (Gutmann et al., 1942). Indirect excitability returns in low lesions in 18 days, in lesions in the middle of the thigh in 30 days and in high lesions in 43 days after operation. Thus the difference between the time of arrival of fibres and the time of onset of indirect excitability is about 8 days after low, 14 days after middle, and 16 days after high thigh lesions.

When interpreting this difference it is to be remembered that after the more distant lesions the muscles have reached a greater degree of atrophy (see Fig. 6), which may be the reason for the later and slower recovery. It is probable, however, that a further reason is the more scattered arrival of fibres on account of the greater distance. Again, a greater degree of maturation may be necessary to achieve function over the greater length of regenerated nerve (Gutmann et al., 1942). The relatively later recovery of longer stretches of nerve can be clearly tested by examining the times of recovery in cases in which the only variable is distance. To do this experimentally it would be
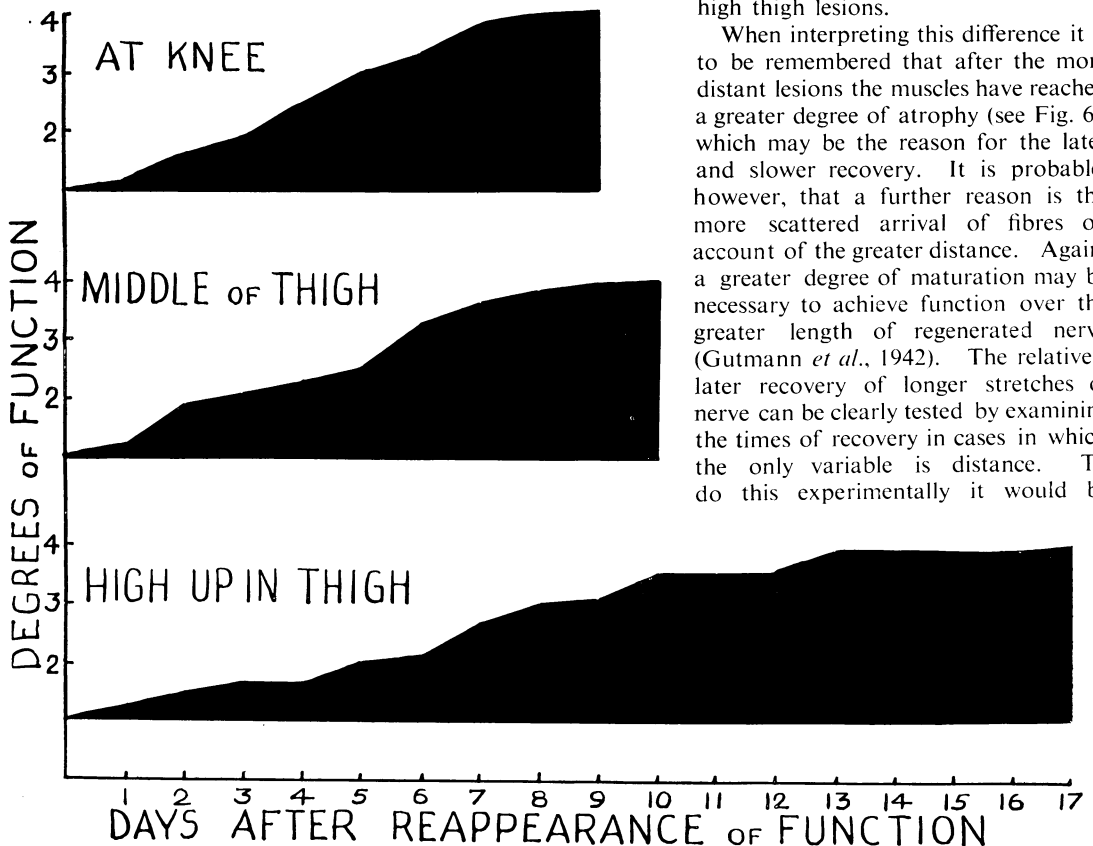

FIG. 7.—Rate of increase in degree of spreading during recovery after crushing the peroneal nerve at the levels shown. The average degree of spreading has been calculated at each day after its beginning by dividing the total " degrees of spreading " at that day by the number of animals.

necessary to compensate for the greater degree of atrophy imposed by the more distant lesions. This has not been attempted in the present series. Fig. 8
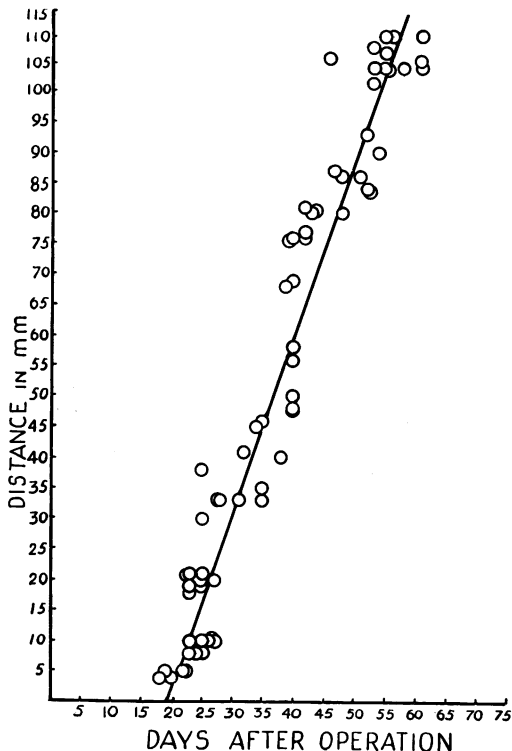

FIG. 8.—Graph showing times of recovery plotted against level of the lesions after crushing the peroneal nerve at varying distances from the M. peroneus longus. The line is the regression line, arithmetically calculated.

is a chart of time of first recovery plotted against the distance of lesion in 69 cases, including those already discussed by Gutmann *et al.* (1942), and 31 others. From these data the rate of advance of regeneration to a level of functional completion sufficient to enable spreading to be performed is given as 2·77±0·09 mm./day. The latent period before functional completion begins to advance beyond the lesion is 18·2 days. These figures, since they include further data, are to be preferred to those already given by Gutmann *et al.* (1942), from which they show no statistically significant differences.

The point to be emphasized is that these points lie remarkably close to a straight line. If recovery of the nerve be relatively more slow in the distant lesions there would be a falling off in the upper part of the curve. The absence of any sign of this shows convincingly that with the distances and functions here considered the rate of recovery of the nerve is nearly constant. We conclude, therefore, that over the distance here considered the level of the lesion has no effect on the rate of nervous regeneration. The improvement after first appearance of recovery is, however, slower with the more distant lesions, probably partly because of greater

atrophy and partly through the greater scatter in time of arrival of functionally complete fibres.

Effect of Type of Injury on Recovery

Recovery after severance and suture.—We may now compare the progress of recovery after severance and suture with that which has been described after crushing the nerve. Fig. 9 shows the times of first recovery observed after lesions at the various levels, including the figures quoted by Gutmann *et al.* (1942) and 8 others. From these results the rate of advance of functionally completed fibres is given as 1·69±0·34 and the latent period before fibres are complete close to the junction as 27·7 days. The times of recovery are more variable than after crushing and the value of the estimate of rate is correspondingly reduced. The figure given is lower (though not significantly) than that given previously (Gutmann *et al.* (1942)) and considerably lower than the 2·6 mm./day obtained by considering paired data of high and low sutures in the same animal. The points shown in Fig. 9 include
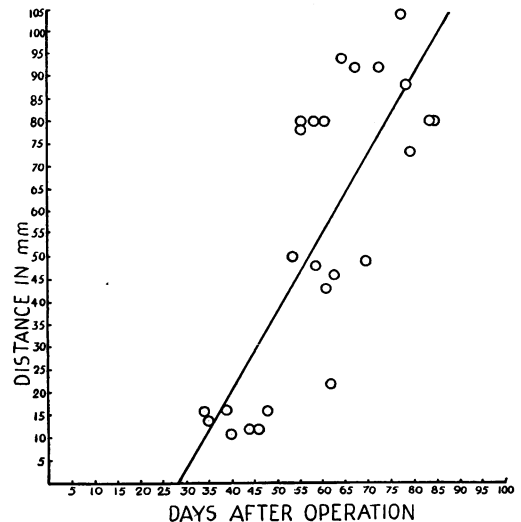

FIG. 9.—Graph showing times of recovery plotted against level of the lesion after suturing the peroneal nerve at varying distances from the M. peroneus longus.

some in which recovery has been much delayed; in these cases histological examination has shown that poor junctions have been made. These points tend to make the estimate appear low, but they are included here to show the full extent of the variability.

The increase in degree of spreading after its first appearance proceeds much more slowly than after crushing the nerve. Although some of the animals have been observed for as long as a year after suture, in no case has full recovery of spreading ever occurred. Fig. 10 shows a typical case of the progress of recovery and should be compared with Fig. 2. Fig. 11 is a photograph of an animal 110 days after operations in which the peroneal nerve has been crushed on the right and sutured on the left sides. The phenomenon of slower improvement

of function during recovery after high lesions is the same in sutured as in crushed nerves, but is less clear on account of individual variations.

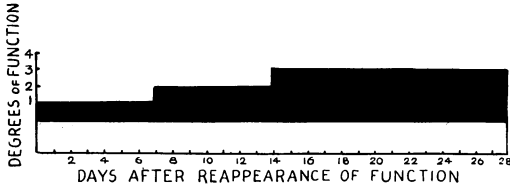The recovery of indirect excitability has also been

FIG. 10.—Course of recovery of the " spreading reflex " in a typical case after suturing the peroneal nerve 80 mm. from the M. peroneus longus.   Compare Fig. 2.

tested in a series of animals by examinations a number of days before expected recovery (Fig. 12). As with crushed nerves, indirect excitability recovers before reflex function, the interval being some

FIG. 11.—Recovery of the spreading reflex 110 days after operation in a case in which the peroneal nerve has been crushed on the right and sutured with plasma on the left side at the same level. Notice the greater extent of spreading of toes on the right side.

10 days. Thus in animal 574 good sutures having been made in both peroneal nerves, 46 days later at a second aseptic operation on the left side there was no response on faradic stimulation of the nerve.

Fifty-one days after suture the right side was examined and contraction obtained in the M. peroneus longus. Recovery of reflex function was seen on the 59th day on the left side and on the 63rd day on the right side.

Data obtained from the onset of indirect excitability suggest that a longer time elapses between arrival of fibres and onset of indirect excitability after suturing than after crushing. Fibres arrive at the muscle 21 days after sutures in the middle of the thigh (48 mm. from the muscle) and the onset of indirect excitability is observed about 47 days after operation. Thus the difference between the time of arrival of fibres and onset of indirect excitability is 26 days after sutures compared with 14 days after crushing at this level.

Measurements of circumference have been taken in the same manner as in crushed cases. These show the same general results, but are more variable. The initial values of circumference are obtained at a later time or not at all. Fig. 13 shows the curve
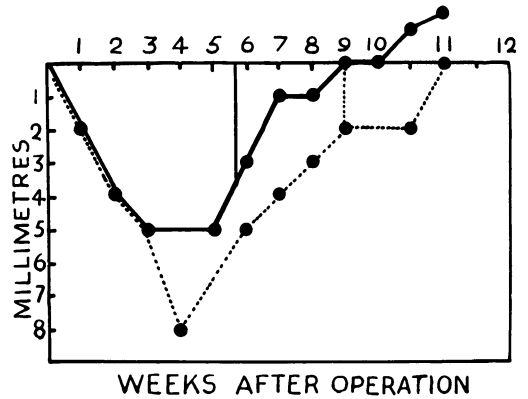
FIG. 13.—Successive measurements of the circumference of the leg made 15 mm. below the Crista tibiæ in a case in which the peroneal nerve has been crushed (continuous line) on the right side and sutured (dotted line) on the left side 48 mm. from the M. peroneus longus. The vertical lines indicate recovery of spreading.

of the values of circumference in an animal in which the peroneal nerve has been crushed on one and sutured on the other side at the level of the middle of the thigh. Fig. 14 shows the changes in threshold on direct stimulation of the M. tibialis anterior through the skin of the same animal.

Examination of the weights of the muscles in a few cases after suture has shown that, as after crushing, there is an initial difference between the

DAYS   AFTER   OPERATION

	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70
RECOVERY OF EXCITABILITY	○	○					○				○	○	●			●																●				
RECOVERY OF FUNCTION																			●	●			●	●		●		●								●

FIG. 12.—Onset of excitability and recovery of spreading after suturing the peroneal nerve 48 mm. from the M. peroneus longus.   Each circle represents an experiment in which the nerve has been stimulated at a given interval after suture.   ○ indicates no muscle responding, ● response in M. peroneus longus (first line) or recovery of spreading (second line).

weights when the nerve is sutured high and low. These differences eventually disappear, but the process after suturing seems to take longer. Thus in 3 animals in which the peroneal nerve has been sutured high on one side and low on the other the weights in grammes are:

	Suture low	Suture high
90 days after operation ..	2·28	1·56
192 ,, ,, ..	1·42	0·98
364 ,, ,, ..	3·20	3·13

After crushing the peroneal nerve the weights 90 days after operation are 1·96 gm. on the side with the low and 1·66 gm. on the side with the high lesions.

After suture, therefore, all processes of recovery are slower than after crushing the nerve. There is a longer delay before functionally complete fibres begin to advance down the nerve and their progress is more slow. There is also a longer delay between
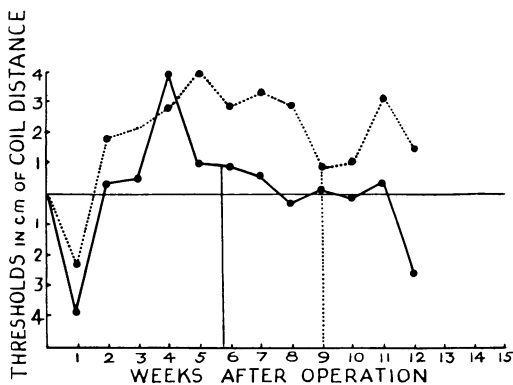
FIG. 14.—Difference in the direct excitability of the M. tibialis ant. stimulated through the skin in a case in which the peroneal nerve has been crushed on the right side (continuous line) and sutured on the left side (dotted line) 48 mm. from the M. peroneus longus.

arrival of fibres and indirect excitability, and a longer delay between appearance of indirect excitability and reflex function; finally the degree of the latter also increases more slowly. Some of these differences may be due actually to a slower advance of the processes of regeneration after sutures than after crushing. In crossing a suture line fibres are supported only by Schwann cells which have grown out with them, or to meet them; the condition of the fibres in this region may affect their advance and increase in diameter in the peripheral stump. However, a considerable part of the differences must be due to the smaller number of fibres reaching each level at a given time. A further factor influencing the final degree of recovery is probably the shunting of fibres into wrong channels, an event more probable after suturing than after crushing. It would be very interesting to be able to estimate separately the influence of these factors, but there are as yet no means of doing this.

No special series of animals has been operated on to estimate recovery after cutting and suturing

with stitches. Suture with fine white silk has been performed in 3 animals and recovery of spreading observed after time intervals similar to those after union with plasma.

Recovery after crossing a nerve gap.—All the above tendencies are still further accentuated in the processes of recovery when this occurs in the presence of a gap between central and peripheral stumps. Gutmann and Sanders (1943) have reported recovery in one case out of 6 animals in which a gap of 2 cm. has been left in the peroneal nerve; it began only after 117 days and had advanced only to degree 2 after 160 days.

Recovery after crushing a length of nerve.—In 3 animals the peroneal nerve in the thigh has been crushed with large flat forceps over a length of 4 cm., a single narrow crush being performed on the other side at the same level to act as a control. The onset of recovery has been recorded at 61, 56, and 54 days on the side with the long crush and
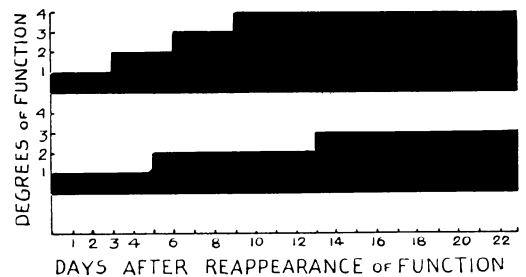

FIG. 15.—Course of recovery of the spreading reflex in a case in which the peroneal nerve was crushed at a single point (upper diagram) on the right side and crushed over a length of 4 cm. (lower diagram) on the left side.

compared with the control side at 51, 48, and 47 days. The degree of spreading has increased at a much slower rate in the nerves with the extensive crushes (Fig. 15), but has varied in the 3 animals. In one animal this difference was still manifest 200 days after operation. At necropsy no difference has been found between the muscle weights of the two sides, these being 3·21 gm. on the side with the narrow crush and 3·28 gm. on the side with the extensive crush. Some differences in the thresholds occur, for the coil distance above the crushes was 92 cm. on the side with the single narrow crush and 56 cm. on the side with the extensive crush. These data suggest that the reason for the differences may be found in an insufficient number of the nerve fibres re-connected with appropriate pathways on the side with the extensive crush. There is, however, a clear indication, even from these few experiments, that the final level of recovery reached after these long crushes is better than that obtained after a suture, for in the former the longitudinal pathways in the nerve are preserved at least to a considerable extent.

Recovery after a second interruption.—In a series of animals the process of recovery has been followed after the nerve has been twice interrupted. In each

rabbit the peroneal nerve has been crushed or cut and sutured on one side near its entry into the muscles. In the animals in which the nerve had been crushed another operation was performed either before (8 and 16 days after the first operation) or after motor recovery (42 days after the first operation). In the animals in which a suture had been performed the second operation was undertaken after motor recovery (61 days after the first operation). The second operation has consisted in all cases in crushing the peroneal nerve on both sides at the same level above the first interruption (about 30 to 40 mm. from the M. peroneus longus). The distances have been controlled with care by measurements made at necropsy. The results show that the onset of recovery has been quicker on the side with the second lesion (see Table I) when the first interruption has been a crush of the nerve. Little difference, however, has been found when the interval between the two operations has been only 8 days. On the other hand a constant difference has been found if the interval between the operations has been 16 or 42 days. On the side with two interruptions the degree of recovery has followed the normal sequence, the only difference being that a normal degree of recovery has been achieved at a later time corresponding to the later onset of recovery. But in two animals in which the second operation has been performed 42 days after the first interruption the degree of spreading became less in, one animal as far as degree 1, about a month after full recovery. No explanation for this strange phenomenon is available.

TABLE I.—TIMES IN DAYS OF RECOVERY AFTER SECOND INTERRUPTION OF THE PERONEAL NERVE

Animal	Kind of first operation	Recovery after first operation	Interval between first and second operation	Motor recovery on	
				Twice operated side	Control side
714	Crush	—	8	24	25
715	Crush	—	8	25	25
578	Crush	—	16	31	34
687	Crush	—	16	27	32
709	Crush	—	16	32	34
579	Crush	24	42	25	28
674	Crush	23	42	30	32
668	Crush	24	42	26	29
584	Suture	50	61	40	35
706	Suture	34	61	40	35
707	Suture	39	61	35	31

In the 3 animals in which the nerve has been cut and sutured at the first operation, recovery of motor function has been delayed after the second interruption. The degree of spreading has been similar to that usually seen after sutures, namely, degrees 2 and 3. However, as in the animals with late second interruption, there has been a regression in the degree of spreading. Originally it

was thought that the difference in the degree of muscle atrophy due to the first denervation would retard the time of onset of functional recovery. That there is such a difference is seen on comparing the weights of the muscles of the two sides. But the greater atrophy does not, apparently, alter the earlier onset of recovery in the animals with the second reinnervation. From these results it is clear that it is easier for motor fibres to bring about a re-establishment of function after a second interruption, if both interruptions are made by crushing. It seems probable that this is due to the fact that after a second interruption more motor fibres arrive at the end organ. After an interruption of a nerve branching of fibres occurs (Watrous (1940), Howe, Tower and Duel (1937)), and more fibres are found in the peripheral stump than in the central stump in the early stages. Presumably after a second interruption these extra fibres degenerate again and there is further multiplication of Schwann cells. As there is an excess of Schwann bands in the peripheral trunk and in the muscle itself the new fibres have a greater chance of finding suitable pathways. At a given time more fibres may thereby arrive at the end organ permitting the earlier initiation of recovery of motor function after the second interruption. The correctness of this explanation is shown by the fact that, when the second interruption after the first crush is performed after an interval of 8 days only, i.e. at a time when few fibres have yet entered the peripheral stump, no clear difference is to be observed in the time of recovery.

Recovery and interruption of blood supply.— In 3 animals the nerve has been crushed high up in the thigh on both sides and on one side the popliteal artery and vein ligatured and cut. Time of onset of recovery has been recorded after 43, 42, and 40 days on the side without ligature and after 45, 42, and 43 days on the side with the ligatured vessels. There has been no marked difference in the spreading index at the time of necropsy, i.e. 3 months after the operation; but in the first week after reappearance of function slight differences could be observed. At necropsy differences in the weight of the muscles have been found, the weight of the M. extensor digitorum being 1·60, 2·50, and 1·78 gm. on the side without ligature of the vessels and 1·22, 2·02, and 1·57 gm. on the side with ligature. Thus the ligature of the popliteal vessels does not seem to have a significant effect on the time and quality of motor recovery although the effect of the ligature is indicated by a greater muscle atrophy. It appears that devascularization of the muscle by ligature of these vessels is incomplete, and that other vessels are sufficient to prevent serious damage to the muscles.

Recovery after cross unions.—In a number of experiments the central stump of the tibial nerve has been sutured to the peripheral stump of the peroneal nerve. Recovery of spreading has been seen in all cases in which the animals have been observed for a sufficiently long time. The time of onset of recovery has been approximately the same

as after primary suture of the peroneal nerve. The variations are smaller than in ordinary sutures. This may be due to the fact that the sutures in cross unions are easy to perform as a long stretch of nerve is available and retraction can be avoided. But the degree of recovery is very poor indeed and spreading can usually be demonstrated only when the animal is held upside down, and then with some difficulty. The degree of spreading has never exceeded degree 2 and in many cases spreading of the 4th toe alone has been observed. In no case has dorsiflexion of the foot been seen with any certainty. This is the more interesting as in all cases stimulation of the tibial nerve produced dorsiflexion. Absence of suitable central connections must therefore be the explanation of the absence of this movement as a reflex function. In other experiments the central stump of the peroneal nerve has been sutured to the peripheral stump of the tibial nerve. No recovery of spreading of the 1st toe has been observed after this procedure, though stimulation of the peroneal nerve has shown clear contraction of the muscles innervated by the tibial nerve.

There is little doubt that some recovery of function follows the crossing of mixed nerves (Rawa (1885), Howell and Huber (1892), Kennedy (1913), Osborne and Kilvington (1911)). Much more controversial is the question of whether normal co-ordinated movements of hetero-innervated structures takes place following cross unions. Earlier authors (Kennedy (1913), Osborne and Kilvington (1911)) have claimed that readjustment may take place, but their views have been strongly criticized by Cunningham (1898) and Sperry (1941)). Watrous and Olmsted (1941), however, have shown that some such readjustment does indeed take place, although it is by no means complete. The experiments described here do not in themselves prove that after cross unions of nerves a central readjustment takes place, since the tibial nerve carries fibres to the M. abductor hallucis which contracts during the spreading reflex of the normal animals, and these fibres, innervating the M. peronei II, III, and IV, would thus be available to produce reflex spreading of the toes following tibial-peroneal cross unions. On the other hand, the absence of any reflexly elicited dorsiflexion of the foot suggests that little readjustment is possible.

Recovery after delayed suture.—The question if and to what degree the time and extent of motor recovery is influenced by a delay in suturing is of great clinical importance. Experimentally the problem is difficult to approach, since, in order to maintain the denervation, a long stretch of nerve must be resected and this fact makes a later suture of the two stumps under standard conditions impossible. In the experiments to be described an attempt has been made to approach the problem by use of cross unions.

At a first operation the peroneal nerve has been cut and resected over a long stretch to make reunion impossible. Even this procedure has not proved satisfactory ; in one case it was found at a

further operation that union had taken place. Therefore in later experiments the central stump has been injected with 20 per cent. formalin to prevent any reunion. After varying intervals of time (1, 2, 4, 6, and 8 months) the tibial nerve has been cut and its stump sutured with plasma to the peripheral stump of the peroneal nerve. At the same time a primary suture of the tibial nerve into the peroneal nerve has been performed on the opposite and control side. This method of bridging a gap has the advantage that a suture may be performed under ideal conditions since a long stretch of nerve is available and retraction can be avoided. But the quality of recovery is poor, for the degree of spreading obtained even on the control side (see above) is only 1 or 2. Nevertheless this technique provides a method for studying effects of delay in suturing. A necropsy has been performed in every case 3 months after the second operation, at times varying from 9 to 35 days after recovery.

The results of the experiments are given in Table II, together with the times of onset of recovery

TABLE II.—RECOVERY AFTER CROSS UNIONS OF TIBIAL INTO PERONEAL NERVE, MADE AFTER THE PERONEAL NERVE HAS BEEN ALLOWED TO DEGENERATE FOR VARYING PERIODS. THE LAST TWO COLUMNS INDICATE THE THRESHOLDS TO FARADIC STIMULATION OF THE NERVE ABOVE THE JUNCTION

Animal	Months before second-ary suture	Onset of recovery in days		Weights of M. tibial. ant. (gm.)		Thresholds coil distance (cm.)	
		Twice oper-ated side	Control side	Twice oper-ated side	Control side	Twice oper-ated side	Control side
642	1	57	55	1·65	1·75	—	—
650	2	74	56	0·79	1·42	42	48
680	4	60	58	1·22	1·74	58	59
595	6	60	53	0·81	1·08	54	62
597	6	55	50	0·84	1·40	38	66
581	8	81	50	0·97	1·42	39	66
606	—	—	66	—	—	—	—
587	—	—	65	—	—	—	—

in two further control cross unions. These experiments show that there is no considerable difference in the time of onset of recovery of motor function after denervation up to 6 months. However, in every case the recovery has been a little later on the twice-operated side, the average time of recovery being 56 days on the control, and 65 days on the twice-operated sides. In the animal with the longest time of denervation (8 months) the difference is more considerable than in the others (1 month). The data suggest that onset of motor recovery begins to be seriously postponed after a period of 6 months. In all cases the side with the primary suture has shown a higher degree of spreading, a difference increasing with the longer time of denervation. As expected, there have been clear differences in the trophic state of the end organs, as indicated

by the weights of the muscles and state of the skin. The thresholds of the nerve have been examined above and below the suture at the time of necropsy, and have been found to be higher on the twice-operated side. However, the differences are considerable only after long periods of degeneration. The fact that the threshold above the junction is higher after secondary suture presumably indicates that fewer fibres have reached the muscle. This, agreeing with the smaller degree of function which returned, indicates one of the possible disadvantages of delay in suturing peripheral nerves (Young, 1942).

Effect of infection on recovery of function.—No special experiments have been undertaken to study the effect of infection on the process of recovery, but some observations on animals accidentally infected allow some conclusions. The infections, found in these rabbits, have been abscesses produced by *Staphylococcus aureus*, and either confined to stitches or going deeper between fascia and muscle. Other cases have shown superficial suppuration of the skin. Abscesses confined to stitches or superficial suppuration of the skin, as observed in 10 animals, had no significant effect on the time or quality of recovery. However, in a case in which there was a large abscess compressing and partly infiltrating one peroneal nerve following interruption by crushing of the nerve on both sides no recovery of motor function was observed on the infected side, whereas on the other uncomplicated side recovery of spreading was recorded after 58 days. This is a later time of recovery than has been observed in any other case with a lesion at this level (distance from point of lesion to M. peroneus longus 78 mm.). Therefore the abscess compressing and infiltrating the one nerve has not only prevented recovery on the infected side but has also delayed the process of recovery on the opposite and uncomplicated side. On the other hand, in another animal in which the peroneal nerve had been crushed on both sides at the same level, a severe lymphangitis developed on the left side, with a bulbous œdema of the skin of the leg and a hydrocele. The animal recovered from this infection. In spite of these conditions recovery of spreading was observed after 38 days on the infected and after 40 days on the uncomplicated side. This is a rather quick recovery on the infected side, and as sensory recovery was also quicker on the side with the previous infection the latter has certainly not delayed the onset of recovery.

Effect of age on recovery.—Gutmann *et al.* (1942) have shown that the rate of advance of functionally completed motor fibres in animals about one month old is markedly higher than in adults, being 5 mm./day after crushing the peroneal nerve, giving a mean latent period of 10·2 days. Results of 5 further experiments in animals of this age can now be added. The peroneal nerve was crushed at different levels and recovery of spreading recorded after 10, 12, 17, 18, 19, 19, 20, 20, and 21 days, the corresponding distances to the M. peroneus longus

being 5, 4, 40, 34, 44, 34, 30, 38, and 31 mm. No exact measurement of the distance is possible in such young and quickly growing animals. Usually the distance has been measured at necropsy at time of recovery, but in a few cases the necropsy was performed several weeks after recovery and then the mean value between the measurement at operation and that at necropsy was taken. Comparing these data with recoveries in adult animals in which the lesion has been made at a corresponding level the clear difference in the speed of recovery may readily be seen.

In a series of young animals the onset of recovery of indirect excitability has been tested. After crushing the peroneal nerve in the middle of the thigh, return of excitability has been found after 13 days. Moreover, the thresholds in the peripheral stump have become lower at a much earlier time than in adult animals. Observations on the quality of recovery indicate that the spreading index degree 4 is achieved at a quicker time than in adult animals, normal spreading being observed about 5 days after first reappearing.

In contrast to this speedy recovery in young animals recovery in old animals has been found to be especially slow. The youngest animal of a series of large animals in which the peroneal nerve was crushed high up in the thigh actually showed an especially quick recovery. Old animals in the series with crush lesions of the peroneal nerve all showed a relatively late recovery. It is more difficult to show the effect of age on recovery in the series where the peroneal nerve has been cut and sutured as this process introduces such great variations. The oldest animal in the series showed macroscopically a good suture. No recovery occurred even after 71 days, therefore a biopsy was performed, but stimulation of the nerve produced contraction of all muscles. Recovery was then recorded 79 days after the operation. The recovery was very late on both sides.

Discussion

Recovery of a muscle is a very complex and prolonged process. It sets in with the reinnervation of the muscle by the first regenerating fibres. This stage is of course a necessary preliminary to recovery, but must not be identified with the recovery of the muscle as a functioning entity. It seems necessary to state this since estimates of the rate of growth of nerve fibres have often been deduced from data on recovery of function. Thus data obtained by Vanlair (1894) from recovery of function have been freely interpreted as estimates of the rate of growth of nerve fibres. But as has been demonstrated elsewhere (Gutmann *et al.*, 1942), the return of function does not provide a test for the estimation of the rate of advance of the regenerating axon tips.

The fact that a muscle is reinnervated before functional recovery appears is demonstrable not only by histological methods, but also by trophic

changes in the muscle. Thus the increase of circumference and the decrease of the thresholds of the muscle to direct stimulation appear before functional recovery. At this stage the muscle does not yet respond to stimulation of the nerve. The gradual increase in the " tone " of the paralysed muscles before any signs of voluntary contraction appear has been clinically observed (Stookey (1922), Tinel (1917)). This observation and others led Hunt (1918) to postulate two sets of motor fibres such as Head, Rivers and Sherren had done for sensory fibres. These two sets of fibres, belonging to the " neo and paleokinetic motor systems," were considered to regenerate at different rates. But the difference in time between arrival of fibres in the end organ and functional recovery suggests that a process of functional completion (Gutmann *et al.*, 1942) must ensue before the regenerated fibres are able to conduct impulses in such a way that contraction of the mass of muscle fibres, visible as a movement, is possible. This process is a very complex one and includes maturation and increase in number of nerve fibres in the end organ, and possibly also central adjustments. A certain number of sufficiently mature fibres must be present before function returns. Apparently the first regenerating axons are able to produce certain trophic changes, but they are either not sufficient in number, have not yet formed proper connections, or they are not yet in a sufficiently mature state to allow return of function.

At a further stage of functional completion the muscle becomes excitable to electrical stimulation of the nerve. Holobut and Jalowy (1936) found return of excitability through the nerve after cutting the sciatic nerve in rats about 28 days after the operation. Howell and Huber (1892), after cutting and suturing the ulnar nerve in dogs, gave the time as 21 days. It is difficult to compare these data with those of the present series as no measurements of the distances from the lesion are given. Onset of indirect excitability will of course vary according to the level of the lesion, and with the method of interruption of the nerve.

Onset of indirect excitability does not imply recovery of function. A further stage of functional completion is necessary before this appears. Thus in cases of unaided union return of excitability is more often observed than actual functional recovery (Gutmann and Sanders (1942)). Excitability of the nerve through the skin appears in these experiments about 1 week after the beginning of recovery, indicating a further stage in the maturation of the nerve. In human cases faradic excitability of the nerve through the skin generally appears a considerable time after the return of voluntary contraction, the longer delay being presumably explained by the greater thickness of the skin.

The process of recovery is not finished with the first return of a movement. The degree of movement, indicated by the spreading index in these experiments described in the preceding pages, increases for some time. Even after the full extent of movement has returned the regeneration is still incomplete, for the muscle continues for some weeks to increase in weight (Fig. 6), the rate of this increase presumably depending on the amount of use of the limb. Moreover, the nerve fibres themselves continue to increase in diameter for many months after functional recovery is apparently complete (Sanders and Gutmann, 1943). The question, therefore, arises—is complete functional recovery in the sense of establishing the same conditions as before the operation ever achieved? After suture the physiological test itself shows that recovery is never complete. Further, Sanders and Gutmann (1943) have shown that even 1 year after suture differences in diameter and number of fibres between central and peripheral stump are still great.

Delay in recovery when a long interval is left between injury and operation has been observed by many authors (Stookey (1922), Spielmeyer (1915), Lewis (1920)). On the other hand, Katzenstein (1913) reported successful recovery after 14 years, and Stopford (1920) stated that if sepsis can be excluded a delay of 12 to 18 months has no effect on the time of onset and on degree of recovery. The question of nervous regeneration after delayed sutures has been studied by Holmes and Young (1942), who have shown that it is not the power of outgrowth which declines after a delay but that changes in the peripheral stump occur which definitely prejudice the maturation of the regenerating nerve fibres. The experiments here described indicate that the degree of recovery is worse after a delay before suturing and that differences in onset of recovery begin to be especially apparent after a delay of 6 months. The reasons are not only the changes in the peripheral stump but also in the end organ. These changes in the muscle are partly irreversible and will by themselves lead to a bad functional result.

Some discussion is necessary of the speed of regeneration and the factors influencing it. The constancy of the time at which recovery has appeared after lesions close to the muscle enables one to estimate that in adult mammals it is not likely that any recovery by outgrowth of new fibres occurs in less than about 15 days, however close the lesion is to the muscle. Recoveries in shorter times than this must be a result of incomplete interruption of the nerve or of trick movements.

The question whether recovery proceeds relatively more slowly with greater distance between lesion and end organ has been much discussed, but very few critical data are available. Stopfordl (1920) concluded that recovery proceeds relatively more slowly in distant lesions. This would of course be expected since latent periods at the suture line and in the muscle occupy a relatively greater time than in the closer lesions. Foerster (1929), however, held that the longer fibres were more vulnerable, being readily damaged in dissociated lesions, and that the same principle applied during recovery. Both of these facts would be explained if a relatively

greater degree of maturation was necessary to reach functional completion after the more distant lesions. However, extensive investigation of times of recovery after lesions at different distances from the muscles have failed to show any relatively greater delay following more distant lesions (see Fig. 8). But it is possible that some effect of the level of the lesion would become apparent when longer distances are considered. In fact, when considering data from recovery of sensation on the foot of the rabbit after crushing the peroneal nerve, the plotting of time of final recovery against the distance of the lesion seems to indicate some relatively greater delay after the more distant lesions (Gutmann and Guttmann, 1943). Longer distances of the nerve have to be reinnervated during recovery of the skin, and therefore there is greater opportunity for the effect of distance on regeneration to be shown.

Some authors (Howell and Huber, 1892, Stookey, 1922) have discussed differences in the speed of recovery of sensory and motor function. Decision on such questions is only possible if the distances from the lesion to the end organs are measured. After interruption of the peroneal nerve in rabbits motor recovery always sets in before sensory recovery, but this is to be expected, since the distance to the skin is longer than to the muscles. But the distance is not the only factor which has to be kept in mind. Although we may consider that the rate of growth of the tips of sensory fibres is the same as that of the motor fibres, this does not imply that the rate of functional completion is the same in both cases. One might expect that functional completion would be achieved more quickly in pain fibres, as these have a smaller diameter. Indeed, after crushing the peroneal nerve the apparent rate of advance of functional completion of motor fibres is 2·77 mm./day, that of pain fibres 3·35 mm./day (Gutmann and Guttmann, 1943).

Differences in speed of recovery after crushing and after suturing might be best explained by the differences in the scar, the result being that less fibres and presumably less matured fibres arrive at the end organ at a certain time. In this connection the fact that a longer time elapses between arrival of fibres and onset of excitability after suturing than after crushing is of interest.

That the rate of functional completion of the nerve is not fixed is shown by the surprising fact that recovery occurs quicker after a second interruption of a nerve. The possible explanation of this is the advantage given by the surplus of Schwann cells produced by the second interruption.

These data all show that other factors besides the rate of growth of the tips of nerve fibres must be considered if estimates of speed of recovery of function and factors influencing it are to be discussed. They indicate again that recovery of motor function is a complex and prolonged process and cannot be adequately discussed in terms of a narrow concept of the process of regeneration merely as an outgrowth of axons.

Summary

1. A good test of the time and degree of functional regeneration of nerve is provided by a study of the recovery of the function of spreading of the toes of the rabbit, following lesions of the peroneal nerve.

2. After crushing the peroneal nerve at the knee fibres return to the muscle after about 10 days, contraction on stimulation of the nerve after about 18 to 20 days, first reflex function after about 25 days. Full reflex function is achieved 8 days later.

3. For a time after recovery from crushing the nerve spreading of the toes may be greater than normal.

4. The circumference of the denervated muscle begins to increase, and its threshold to direct stimulation to decrease, before reflex function, and sometimes before even indirect excitability return.

5. Fibrillations continue in the muscles for about 2 weeks after reappearance of reflex function.

6. The normal weight of the muscles is nearly regained 12 weeks after reappearance of reflex function following crushing of the peroneal nerve.

7. Study of recovery after crushing the peroneal nerve showed that when the lesion is more distant there is a longer delay between arrival of fibres at the muscle and the appearance of excitability through the nerve. The time between the beginning of recovery and its completion is greater after more distant than after near lesions.

8. From a study of recoveries in 69 cases where the nerve was crushed at different levels the rate of advance of regeneration down the nerve is given as 2·77±0·09 mm./day after a latent period of 18·2 days. The rate is not slower with more distant lesions.

9. After severance and suture all the processes of recovery are slower than after crushing the nerve. The rate of advance of regeneration is 1·69±0·34 mm./day after a latent period of 27·7 days. The delay between arrival of fibres at the muscle and return of reflex function is greater than after crushing. After the first appearance of reflex function it increases only gradually in amount and never returns to normal.

10. Recovery after crushing the nerve over a length of 4 cm. is later and less complete than after a local crush, but is more satisfactory than after severance and suture.

11. When the nerve is crushed a second time 16 or 42 days after an initial crush near the muscle the recovery occurs slightly earlier than after a single crush. This difference is not seen when the interval between the crushes is 8 days.

12. Ligature of the popliteal vein and artery does not delay recovery of the muscles following interruption of the peroneal nerve.

13. After union of the central stump of the tibial nerve with the peripheral stump of the peroneal nerve some spreading of the toes returns. This

does not imply central relearning since the tibial nerve contains some fibres which innervate muscles normally producing spreading.

14. Tibial-peroneal cross unions have been used to test the effect on recovery after a delay between injury and suture. In all cases such a delay has been found to retard recovery, but the effect has only been marked when the delay has exceeded 6 months. The degree of recovery has been reduced by delay in suture.

REFERENCES

Barron, D. H. (1934). *J. comp. Neurol.*, **59**, 301.

Bender, M. B., and Fulton, J. F. (1939). *J. Neurol. Psychiat*, **2**, 285.

Bensley, B. A. (1938). *Practical Anatomy of the Rabbit*, Toronto.

Bentley, F. H. and Hill, M. (1936). *Brit. J. Sur.*, **24**, 368.

Boeke, J. (1916). *Verh. Akad. Wet. Amst.*, **18**, No. 6, 1.

Chor, H., Cleveland, D., Davenport, H. A., Dolcart, R. E., and Beard, G. (1939). *J. Amer. med. Ass.*, **113**, 1029.

Cunningham, R. H. (1898). *Amer. J. Physiol.*, **1**, 239.

Foerster, O. (1929). Die Symptomatologie der Schussverletzungen, *Handb. Neurol., Bumke and Foerster*, **2**, Berlin.

Friedlaender, R. (1896). *Dtsch. med. Wschr.*, **22**, 414.

Gutmann, E., Guttmann, L., Medawar, P. B., and Young, J. Z. (1942). *J. exp. Biol.*, **19**, 14.

Gutmann, E., and Guttmann, L. (1943). *J. Neurol. Psychiat*. In press.

Gutmann, E., and Sanders, F. K. (1943). *Brain*. In press.

Holobut, W. S., and Jalowy, B. (1936). *Z. Zellforsch.*, **25**, 541.

Holmes, W., and Young, J. Z. (1942). *J. Anat. Lond.*, **77**, 63.

Howe, H. A., Tower, S. S., and Duel, A. B. (1937). *Arch. Neurol. Psychiat.*, **38**, 1190.

Howell, W. H., and Huber, G. C. (1892). *J. Physiol.*, **13**, 335.

Hunt, J. R. (1918). *Brain*, **41**, 302.

Ingebrigsten, R. (1916). *Lyon chir.*, **13**, 515.

Katzenstein, M. (1913). *Berl. klin. Wschr.*, **50**, 1165.

Kennedy, R. (1913). *Proc. roy. Soc., S. B.*, **87**, 331.

Kilvington, B. (1908). *Brit. med. J.*, **1**, 1414.

Krause, W. (1884). *Die Anatomie des Kaninchens*, Leipzig.

Langley, J. N. (1917). *J. Physiol.*, **51**, 377.

Lee, F. C. (1929). *Physiol. Rev.*, **9**, 575.

Lewis, D. (1920). *J. Amer. med. Ass.*, **75**, 73.

Nageotte, J. (1922). *L'organisation de la matière dans ses rapports avec la vie*, Paris.

Osborne, W. A., and Kilvington, B. (1911). *Brain*, **33**, 288.

Perroncito, A. (1907). *Beitr. path. Anat.*, **42**, 354.

Rawa, A. L. (1885). *Arch. Anat. Physiol.*, **9**, 296.

Sanders, F. K. and Gutmann E. (1943). *J. Physiol.* In press.

Sperry, R. W. (1941). *J. comp. Neurol.*, **75**, 1.

Spielmeyer, W. (1915). *Münch. med. Wschr.*, **52**, 58.

Stookey, B. (1922). *Surgical and mechanical treatment of peripheral nerves*, Philadelphia.

Stopford, J. S. B. (1920). *Brain*, **43**, 1.

Tinel, J. (1917). *Nerve wounds*, London.

Vanlair, C. (1894). *Arch. Physiol.*, **6**, 5e ser., 217.

Watrous, W. G. (1940). *Proc. Soc. exp. Biol.*, **44**, 541.

Watrous, W. G., and Olmsted, J. M. D. (1941). *J. comp. Neurol.*, **75**, 21.

Wolf, A. (1940). *J. nerv. ment. Dis.*, **92**, 614.

Young, J. Z., and Medawar, P. B. (1940). *Lancet*, **2**, 126.

Young, J. Z. (1942). *Physiol. Rev.*, **22**, 318.