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REGENERATION IN THE RAT

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The ability of regenerating axons to branch is common knowledge. However, not all of the branches thus produced are destined to make functional connections or even to survive, and superabundant nerve sprouting does not imply correspondingly abundant peripheral innervation.

Dogliotti (1935) has based practical recommendations for improving the innervation of limbs with partial neurogenic paralysis upon the recognized ability of nerves to regenerate a larger number of branches peripherally than they had originally possessed. More recently, Aird and Naffziger (1939) have extended these experiments and critically discussed the earlier literature bearing on the problem. While substantiating the possibility of amplifying the peripheral fiber volume of a nerve, their results yet indicate that the increased nerve fiber count does not necessarily signify a commensurate functional improvement.

In none of the past nerve fiber counts has the proportion of actually reinnervated muscle fibers been determined. In order to do this, we started several years ago a systematic investigation of the problem in the rat. However, circumstances have forced several interruptions and, eventually, termination of the project in a somewhat fragmentary state.² Since facts bearing on nerve repair have gained increased practical significance, we present the results of our experiments as they stand, even though a number of points remain to be settled.

We first produced an over-all reduction of the nerve fiber complement of the sciatic nerve trunk by partial radicotomy.³ In a second operation, the sciatic nerve was cut and the two ends were reunited. The animals were examined after periods varying from seventy-four to one-hundred and eight-one days. The gastrocnemius muscles of the normal and operated sides were prepared, and tension after "maximal" stimulation of either the muscle or the sciatic nerve was recorded isometrically. A comparison of the results of direct and indirect stimulation was to furnish an estimate of the proportion of muscle fibers that had become reinnervated. Comparison with the corresponding values of the unoperated control side revealed deficits of muscle power and muscle

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² The experiments had been started in 1941 with the assistance of Dr. Donald Ross. When he left for service in the armed forces, the work was resumed in co-operation with the junior author, Dr. C. J. Campbell, who, too, had to abandon it for military duty.

³ Hines, in a recent brief report (1942), refers to his use of a similar procedure.

innervation due to the operation. After the physiological tests, some of the nerves were fixed and sectioned and fiber counts were made, as specified below.

MATERIAL AND METHODS. All operations were done on albino rats of between 200 and 300 grams body weight. The preliminary operation aimed at destroying part of the sciatic roots, L4, L5 and L6. To facilitate identification of the roots in the operation, the segmental location of a needle inserted in the sacral region of the unoperated animal was determined by x-rays and served as a landmark. In most cases, ventral roots L4 and L5 were destroyed, mostly by extradural resection. From two to seven days later, the sciatic nerve was cut in the proximal third of the thigh. The severed nerve ends were reunited by sutureless arterial tubulation, as described by Weiss (1941a, 1943).

Three types of operations were performed.

Operation A. Radicotomy on the right side with no further nerve section. Left side intact. This operation was to reveal the nerve fiber loss due to radicotomy.

Operation B. Ventral roots L4 and L5 destroyed on the right side. Sciatic nerve sectioned and reunited. Left side intact for control. This was the prevailing type of operation.

Operation C. Right side treated as in operation B. In addition, radicotomy on the left side. This operation was intended to show any superiority of terminal innervation after nerve section over the innervation from a reduced nerve not allowed to regenerate.

The kymographic records were taken in light ether anesthesia. The sciatic nerve was exposed in its full length and cut at its emergence from the lumbar plexus. All branches except the tibial were cut. The gastrocnemius muscle was connected with an isometric lever whose excursions were sufficiently linear within the range of tensions tested. All stimulations were done with the muscle under an initial resting tension of between 40 and 80 grams. The nerve was placed over platinum electrodes, supplied from the secondary coil of a Du Bois-Reymond inductorium with two dry cells in the primary circuit. The preparation was kept irrigated with Ringer's solution and the electrical tests were not started until after the effects of the ether anesthesia in the peripheral nerve had subsided. Single break shocks, as well as tetanic stimulation, were applied. For direct stimulation, the electrodes were placed on opposite ends and opposite sides of the muscle belly. All tension values referred to in this paper were obtained by slightly supramaximal stimuli.

Following the physiological tests, the nerves were fixed under stretch in Bouin's solution, sectioned, and impregnated according to Bodian's silver method. Fiber counts were made on cross sections with the aid of a camera lucida.⁴ This method was found to be correct for silver stains within about 6 per cent (Litwiller, 1938a), but in the case of young regenerated nerves containing large numbers of fine fibers, the error may well be assumed to be nearer to 10 per cent.

⁴Counts were made with the assistance of Dr. Raymond Litwiller.

Of one hundred and twenty operated animals, only sixteen have come through to the terminal tests.

Fiber counts. The purpose of the radicotomy was largely defeated by the prompt regeneration of the severed roots. Sections through proximal levels of the sciatic nerve show numerous regenerating fibers, frequently in strands, interspersed with the old fibers of the nerve. In eight cases subjected to operations A or B, listed in table 1, the total of nerve fibers counted in the proximal sciatic on the partially radicotomized side, is 43,802, while the corresponding total for the unoperated side is 43,167. One must bear in mind, however, that the transected root fibers had to regenerate for a distance of approximately 30 mm. before arriving at the level of the distal nerve section. Assuming conservatively a rate of advance of between 2 and 3 mm. per day (Gutmann et al., 1942), it would have required some two to three weeks for the fibers to span this

TABLE 1
Nerve fiber counts at standard sampling levels of experimental and control sciatic nerves

CASE	OPERATION	LEFT (CONTROL) SIDE		RIGHT (EXPERIMENTAL) SIDE			
		Proximal n_{cp}	Distal n_{cd}	Proximal n_{op}	"Gap" region n_{oi}	Distal n_{od}	Regeneration index $r = \frac{100n_{od}}{n_{op}}$
D4	A	5605	5495	4799		5400	
D5	B	5850		5860	2576	2595	44
D10	B	5350	4935	7505*		5655	76
D12	B	5895		5235	4245	3218	61
D15	B	5385		5590	5545	4695	84
D18	B	4572		5460		3245	62
D37	B	5165		4613	4770	3425	71
D38	B	5345		4435	4855	4075	92
E1	C	4655	5525	5415	5240	5210	96

* Apparent overcount due to overstained preparation.

distance. Thus those sciatic fibers belonging to the undamaged roots should have had ample time to occupy all available peripheral pathways prior to the arrival of the second growth of root fibers.

Table 1 lists sample nerve fiber counts. On the right side, which, except for case D4, is the one on which the sciatic nerve had been transected and allowed to regenerate, counts are reproduced at three levels: normal level far proximal to the nerve union; a level well inside the old peripheral stump, with the counts of all branches of the tibial and peroneal nerves combined in a single figure; and through the so-called "gap" region, which is the level of transition from the proximal to the distal stump.

In none of the cases pertinent to the problem, i.e., series B and C, has there been an increase in the number of fibers distal to the nerve union over the number found in the proximal stump, such as described, for instance, by Greenman (1913). The last column of table 1 gives the ratio of number of nerve fibers

counted distally to the nerve union over that counted proximally in per cent values. The distal deficit ranges from 4 to 56 per cent. In half of the cases, the peripheral nerve has been filled up to more than 75 per cent. In case D5, the deficit is already present in the gap; in case D37, it appears beyond the gap; in case D12, the gap yields a count intermediate between the proximal and peripheral stumps; and in case D38, there is even a slight increase in the gap region, preceding the peripheral decline. The peripheral fiber deficit is not due to insufficient time allowed to the regeneration. If percentage regeneration is plotted against time elapsed after transection, provided the latter is more than two months, the points scatter at random (fig. 1). For example, case E1 shows a deficit of only 4 per cent at seventy-four days, while case D18 shows a 38 per cent deficit as late as one-hundred and sixty-six days after the operation. It is

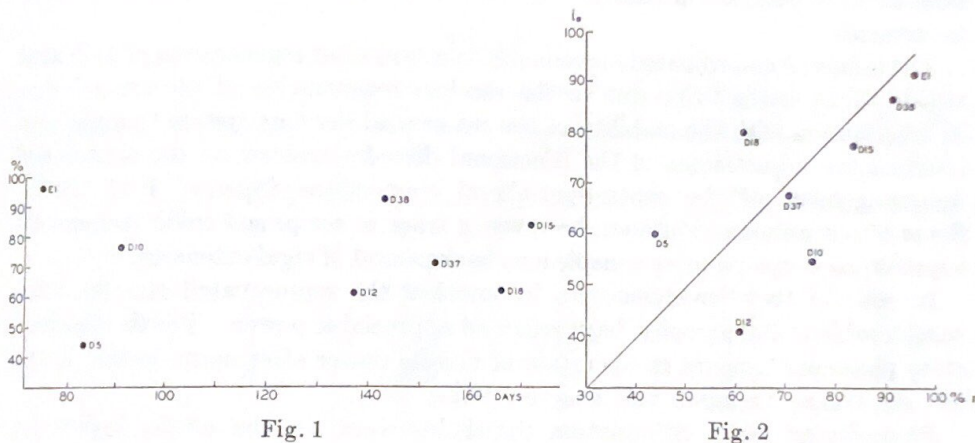


Fig. 1. Nerve fiber count in the regenerated distal portion of the nerve, expressed in per cent of the fiber count in the old proximal portion, at various periods after nerve section.

Fig. 2. Relation between volume of nerve fiber regeneration and proportion of reinnervated muscle fibers. Abscissae: Regeneration index (r , table 1). Ordinates: Innervation index (i_0 , table 2).

safe, therefore, to conclude that the observed distal deficit is permanent, particularly in cases D12, D37 and D18, with more than four months' regeneration time.

Some clue as to the cause of the peripheral fiber deficit has been found in the histological examinations. Details of the course of regeneration in nerves united by arterial sleeves have been presented elsewhere (Weiss, 1943). It was described there that this method precludes the profuse branching commonly found in the scar region at the suture line. Under ideal conditions, therefore, the number of fibers in the gap may be expected to equal the number of fibers in the proximal stump, and to continue without essential change into the peripheral stump. Fibers deflected or arrested in their advance constitute a permanent loss to the peripheral nerve, and statistically, there has been more loss than was compensated by sporadic ramifications. Actually, in all three cases with a major peripheral nerve deficit, i.e., D5, D12 and D18, the fiber loss could

be traced to faultiness of the arterial link. As described previously (Weiss, 1943), any leak in the arterial wall may cause appreciable fiber escape. In cases D5 and D12, a stream of nerve fibers has escaped through a leak in the arterial sleeve. In case D18, the peripheral deficit can be traced to excessive width of the arterial sleeve around the peripheral stump, which has permitted part of the nerve fibers to escape through the open space. The important fact about these cases is the consistent lack of spontaneous compensatory amplification of the regenerating fiber volume by peripheral branching.

All our observations on the return of motility conform with the description given in an earlier paper (Weiss, 1943). Briefly, as motility returns, it involves essentially co-contraction of the dorsi-flexors and plantar flexors of the foot, with the latter prevailing owing to their greater bulk. The result was mostly rigid extension of the foot with flexion of the toes. There were indications of gradual ankylosis of the ankle, attributable to the lack of antagonistic joint movements.

The failure of co-ordinated movements to return after regeneration of a divided sciatic nerve seems to be due to the random regeneration of the nerve fibers, in conjunction with the inability of the rat central nervous system to make any re-educative adjustments of the functional disorder created by the anatomical disarrangement of the central-peripheral connections (Sperry, 1941, 1943). Some of our animals exhibited, however, a trace of reciprocal ankle movements superimposed upon a more conspicuous background of rigid extension.

In spite of their irrelevance for locomotion, the reinnervated muscles, after considerable initial atrophy, have regained appreciable power. For the degenerative phase and general recuperation of muscle power after nerve section in the rat, see Hines, Thomson and Lazere (1942).

Physiological tests. Stimulation thresholds were, on the whole, higher for the regenerated than for the control nerves, which may be ascribed to the heavier connective tissue sheath around the former. A comparison between the isometric tensions obtained from gastrocnemius muscles after "direct" and after "indirect" sciatic nerve stimulation, as well as between these and the ones obtained from the opposite (control) side, is presented in percentage values in table 2.

The ratio of maximal tensions recorded after indirect and direct stimulation expresses the degree of functional reinnervation of the muscle. A maximal stimulus to the muscle directly sets all contractile elements in operation. A maximal stimulus to the nerve activates all innervated muscle fibers. Accordingly, any excess of tension obtained on direct stimulation over that obtainable by indirect stimulation can be ascribed to muscle fibers which have failed to receive innervation. This would be strictly valid only if the average sizes of innervated and uninnervated muscle units are statistically the same. If the innervated units should prove to be, on the average, larger and, therefore, stronger, an empirical correction factor would have to be introduced.

With this qualification in mind, the ratio of "indirect" over "direct" tension may be used as index of the proportion of innervated to total number of muscle

fibers. This ratio, expressed in per cent values, will be referred to as the innervation index (i). The third column of table 2 reveals that the innervation index of normal control muscles (i_c) is mostly well under 100 per cent. This means that even in a normal muscle a varying fraction of fibers cannot be stimulated through the nerve. The average innervation deficit for the normal control muscles in the thirteen cases of series A and B is 7.5 per cent. This compares well with a deficit of 8.3 per cent computed from values given for seven control gastrocnemius muscles by Hines, Thomson and Lazere (1942, table 1). The most plausible explanation of this deficit would lie in injury suffered by some nerve fibers during the manipulation; another few fibers may be in the process of degeneration, constantly proceeding in nerves (less than 1 per cent according to Duncan, 1930). Some others may have undergone

TABLE 2

SPECIMEN	OPERATION	INNERVATION INDEX (i)		MUSCLE POWER ON OPERATED SIDE IN PER CENT OF CONTROL SIDE	INNERVATION QUOTA ON OPERATED SIDE IN PER CENT OF CONTROL SIDE
		Left (control) side	Right (experimental) side		
		i_c	i_o	m	n
D4	A	84.5	78.5	79.0	73.5
D6	A	84.2	50.0	46.5	27.5
D8	A	100.0	73.5	143.5	105.7
D2	B	92.5	31.1	31.2	10.5
D5	B	89.5	60.0	41.5	27.6
D7	B	92.5	60.3	89.2	58.2
D10	B	95.0	54.7	53.2	30.6
D12	B	93.1	40.9	21.8	9.5
D15	B	100.0	77.7	85.0	66.0
D18	B	92.0	80.5	108.0	94.5
D25	B	92.5	78.0	68.8	58.2
D37	B	92.5	67.8	93.5	68.5
D38	B	95.2	87.0	120.5	110.0
E1	C	90.6	91.5	92.1	93.1
E2	C	45.0			100.0

degeneration as a result of the lesion of the symmetrical nerve of the opposite side. Contralateral effects of this kind have been described (Greenman, 1913; Tamaki, 1933), but seem to subside with increasing age after the operation (Tamaki, 1936).

In contrast to a deficit on the control side of 7.5 per cent, the deficit on the experimental side is much greater, the average of thirteen cases being 36 per cent. This means that, on an average, fewer than two-thirds of the fibers of the gastrocnemius have received reinnervation.

Besides being less completely innervated, the experimental gastrocnemius is also weaker than its control. The power ratio between the experimental gastrocnemius and its opposite control is given in the fifth column (m) of table 2. The figures represent maximum tension of the experimental muscle expressed in percentage of the maximum tension obtainable from the normal opposite

muscles. While in three cases (D8, D18, D38) the reinnervated muscle has obviously overshoot its normal partner, all other cases show reduced power in the reinnervated muscle. How the loss is to be apportioned between atrophy and degeneration, cannot be determined from these figures.

A comparison between the trend of the innervation index and the muscular power index points toward a continued increase in muscle power beyond the attainment of the final innervation ratio. While in none of four cases examined less than one-hundred forty days after the operation, the muscle index exceeds the innervation index, it surpasses it appreciably in all but one of six cases examined later than one-hundred forty days. This would indicate that the non-innervated fibers of a partially reinnervated muscle continue to gain, possibly benefitting from the passive exercise to which they are subjected by their innervated partners.

The general result of these tests is that in most cases a certain fraction of the denervated muscle fibers have remained without reinnervation.

Nerve fiber counts through regenerated nerves could furnish an accurate measure of the degree of peripheral reinnervation only if the average size of the motor units should prove to be the same before and after regeneration, since the effectiveness of muscle reinnervation is determined both by the number of regenerated motor neurons and the extent of their intra-muscular branching. Little attention has been given to this point in the past. In this connection the following data deserve mention.

In figure 2, the innervation indices (i_o) of the experimental muscles (table 2) have been plotted against the fiber regeneration indices (r), as listed in table 1. The graph thus correlates the proportion of reinnervated muscle fibers of a given muscle with the proportion of regenerated nerve fibers counted in the peripheral nerve stump. There is, on the whole, correspondence among the two values, as is expressed in their scattering about a straight line inclined under a 45° angle. Four cases, D15, D37, D38 and E1, conform very closely, indicating that the size of the motor units was nearly the same before and after regeneration. In contrast, cases D5 and D18 show an unexpectedly high, and cases D10 and D12 an unexpectedly low, innervation index for the number of fibers actually counted in the nerve trunk. In this connection, misregeneration of sensory fibers into muscles must be taken into account. Functional tests of such fibers have shown them to be much inferior to motor fibers in establishing transmissive connections (Weiss, 1934, 1935). Consequently, even if the fiber mass of the nerve is distributed proportionally over the periphery, the number of functionally effective efferent fibers in any one muscle might be smaller than extrapolation from the total fiber count would indicate.

The lesson of these results is that the number of nerve fibers counted in the peripheral nerve provides no reliable index of the degree of reinnervation attained in the muscle, although statistically the two factors are correlated. This conclusion agrees with the view expressed by Aird and Naffziger (1939). Consideration of the manner in which terminal reinnervation occurs can readily account for the observed variability. If a nerve fiber arrives in the muscle

inside of an old degenerated Schwann tube, it is likely to reoccupy all the terminal ramifications of this tube. Thus the original pattern of innervation will be retraced and that motor unit will be restored to its original size. If some of the old branches have become obliterated or obstructed, these would be missed by the regenerating fiber tips, and a corresponding reduction of the size of the motor units would ensue, as, for instance, in cases D10 and D12. Excessive terminal ramifications, on the other hand, may be expected in nerve fibers which have taken extratubal courses and arrived in the muscle without the benefit of an old branching pattern as guide. Such fibers may stray about and innervate any number of not yet innervated muscle fibers. Earlier studies in amphibians have shown that when nerves are made to enter a muscle by paths other than the original portals of the motor points, their branches tend to pervade the muscle profusely (Fort, 1940). If this should hold for mammals, too, a fairly complete reinnervation of all muscle fibers, even from a small number of reinnervating extratubal nerve fibers, might be expected. The fact that this has not occurred in the majority of our cases seems to prove that most of the regenerating fibers have come by intratubal courses. Being thus trapped in the old innervation beds, they had no opportunity for a compensatory expansion within the muscle.

DISCUSSION. The facts reported in this paper underscore the complexity of the quantitative aspects of nerve regeneration. Factors bearing on the volume of peripheral innervation are, in proximo-distal, as well as chronological, progression: 1, number of fibers in the proximal nerve stump; 2, incidence of branching among the regenerating sprouts; 3, number of fiber branches entering or by-passing the peripheral nerve stump; 4, proportion of fibers surviving subsequent resorption; 5, number of fibers establishing effective transmissive peripheral connections; 6, number of intramuscular terminal ramifications (size of the "motor unit"); 7, degree of muscular atrophy and degeneration during the denervated period, and of muscular recovery after reinnervation.

1. Proximal fiber source. The number of neurons assigned to any one given peripheral area is fairly constant among members of the same species. Embryonic factors affecting this nerve quota have been extensively studied (review: Detwiler, 1936). Once established, it fails to respond to demands for additional peripheral innervation. Adult spinal centers do not send out new nerve fibers into districts experimentally overloaded with tissues requiring innervation. Consequently, saturation with nerve fibers of an enlarged periphery could be effected only by increased peripheral branching of the existing neurons (Weiss, 1937). Conversely, a tissue mass of subnormal size, when confronted with a normal nerve source, fails to absorb the total available nerve supply, and accepts nerve fibers only in proportion to its actual mass (Weiss and Walker, 1934; Litwiller, 1938b). Saturation density reached, the supernumerary nerve fibers remain unconnected. The final fate of such fibers is not known.

These facts have led to the realization that the volume of peripheral innervation is not primarily determined by the size of the nerve fiber source (Weiss, 1941b). The peripheral tissues themselves exert a decisive control over the

density of their innervation by regulating the admission quota, though not the production quota. Unless branching is enhanced by special means, an undersized nerve source is bound to remain undersized even in the face of greater peripheral demand.

2. *Degree of branching.* Brief discussions of the mechanism of nerve branching have been presented on earlier occasions (Weiss, 1934b, 1941b). The facts do not support the notion that regenerating nerve fibers branch from intrinsic causes as do trees. Nerve fibers branch only in response to inhomogeneities in their environment. The intensity of branching is, therefore, a function of the incidence of both gross mechanical obstacles and submicroscopical disorientations of the contact substrata along which the nerve fiber proceeds. The growth energy of the regenerating fiber must also be considered in that branches which would have remained abortive in weakly growing fibers might assert themselves in a more vigorously growing fiber. In conclusion, the number of branches formed is determined by the local factors of the course, rather than the distal factors of the destination, of the nerve fiber.

In this fact lies the explanation of the failure of undersized nerve sources in our experiments to provide full peripheral reinnervation. A loss of fibers through leaks in the splicing sleeve was never compensated by increased branching prior to, or after, entry into the peripheral stump. The reason for this lies in the mechanics of the tubular splice, which precludes the formation of a disoriented scar (Weiss, 1943). We might have obtained a better filling of the peripheral stump if the condition at the suture line had been less orderly. The same argument applies to the observation of Hines (1942) that regeneration following the crushing of the tibial nerve does not make up for a reduction of the fiber complement of this nerve produced by partial radicotomy. Unlike nerve section, mere crushing often fails to rupture the neurilemmal tubes, hence fails to provoke the extensive branching characteristic of a messy scar. Consequently, neither our own nor Hines' negative results are necessarily at variance with the claim of the earlier authors that an effective peripheral amplification of nerve volume by branching in the scar is feasible. For practical purposes, it should be remembered, however, that any merit the scar may have in causing branching, is nullified by the increased resistance it offers to the further advance of the multitudinous branches.

3. *Neurotization of peripheral nerve stump.* What proportion of the nerve fibers present in the gap will actually enter the distal nerve stump, seems to be entirely a matter of chance. The hypothesis of a chemotropic direction of nerve fibers towards the distal stump (Cajal, 1893; Forssman, 1900), occasionally disputed in the past (Dustin, 1910), has been found untenable in view of experimental evidence (Weiss, 1934b, 1941b). Nerve orientation is determined wholly by the pathway structure of the scar. Moreover, strands of sheath cells, growing proximad into the scar, may serve as traps for nerve fiber sprouts (Young, 1942). Similar traps are constituted by the degenerated Schwann tubes of the peripheral stump. However, since, as a rule, more than one regenerating nerve fiber may enter into a tube (Boeke, 1921), the number of tubes actually invaded is no measure of the density of reinnervation of the peripheral stump. While some of

the old tubes become overpopulated, others remain abandoned. Nevertheless, the total number of fibers in the distal nerve stump approximates its normal capacity, regardless of the size of the proximal supply (Weiss and Cummings, 1943).

4. *Maturation of peripheral stump.* Of the fiber branches entering the peripheral nerve stump, not all are destined to survive and mature. But neither the criteria nor the mechanism of secondary fiber branch elimination are known (cf. Young, 1942). Spatial crowding within undistensible tubes, metabolic competition among the several branches supplied from a common nerve cell, and presumably effects extending into the nerve fiber from its terminal organ are factors which will have to be considered in this connection. Their operation may remove much of the initial overproduction caused by the branching in the scar (cf. Boeke, 1921).

5. *Neuro-muscular connections.* The terminal branching pattern of the regenerated motor neuron depends on the channels through which the nerve fibers arrive, as well as on the condition of the muscle fibers. Nerve fibers regenerating inside of an old Schwann tube find a preformed pattern of arborization. Extratubal fibers will follow irregular courses. As stated above, there are indications that this latter category is not prevalent.

Innervation of a single muscle fiber by several nerve fibers may occur on occasions, but is functionally irrelevant. Its regular occurrence is prevented by a protective reaction which renders the innervated muscle fiber immune to impregnation by further nerve branches (cf. Fort, 1940). Attempts at so-called "hyperneurotization" by forcing more than one nerve ending upon a muscle fiber (Erlacher, 1914) are based on questionable physiological premises and have no practical significance.

This brief survey, incomplete as it is, may yet give an idea of the intricacies of the problem of quantitative recovery in nerve regeneration. It makes it obvious that the mere fact of an increased fiber count below the suture line of a peripheral nerve is no sufficient guarantee of functional enhancement. This is not to say that under certain conditions practical benefits may not come from inducing peripheral nerve fibers to divide by making them regenerate. Our data merely caution against accepting such peripheral amplification as either the sole, or even a pertinent, gauge of terminal improvement.

SUMMARY

In an attempt to determine whether the volume of fiber regeneration after nerve transection is indicative of the degree of recovery of power in the reinnervated muscles, nerve fiber counts of regenerated sciatic nerves were compared with measurements of isometric tension produced by the gastrocnemius muscle after "direct" and "indirect" stimulation with "maximal" shocks. The following conclusions have been reached.

There is no constant relation between the number of fibers growing from the proximal stump of the nerve and the number found in the peripheral stump (table 1). Spontaneous regulatory axon branching to compensate for fiber deficits does not occur. Profuse branching may, however, be evoked by scar

tissue at the suture line. Yet, even this does not of itself insure that the volume of nerve fibers reaching the muscles will be correspondingly amplified.

From 9 to 69 per cent of the muscle fibers of the reinnervated muscles have failed to receive functional reinnervation (table 2). These deficits can be correlated with fiber deficits in the peripheral nerve trunk only very grossly (fig. 2). In the individual case, the discrepancy may be great. For instance, a quota of only 62 per cent regenerated fibers in the nerve may reinnervate as many as 80 per cent of the muscle fibers (D18), while, conversely, nerve regeneration of as much as 76 per cent may provide only 55 per cent reinnervation (D10).

Factors affecting the density and functional effectiveness of regenerative muscle reinnervation are 1, number of fibers in the proximal nerve stump; 2, axon branching in the scar; 3, fiber admission into the peripheral stump; 4, secondary resorption of fiber branches; 5, proportion of fibers effecting myoneural junctions; 6, extent of intramuscular axon branching; 7, condition of the muscle fibers. This variety explains why regenerative success is not solely predicated on the intensity of fiber proliferation at the suture line.

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