II. Post-Tetanic Potentiation and Depression of Generator Potential in a Single Non-Myelinated Nerve Ending

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ABSTRACT   Repetitive activity at the non-myelinated ending of Pacinian corpuscles leaves the following after-effects: (1) With certain parameters of repetitive mechanical stimulation of the ending a depression in generator potential is produced. The effect is fully reversible and has low energy requirements. The effect is a transient decrease in responsiveness of the receptor membrane which is unrelated to changes in resting membrane potential. It appears to reflect an inactivation process of the receptor membrane. Within certain limits, the depression increases as a function of strength, frequency, and train duration of repetitive stimuli. (2) With other, more critical parameters of repetitive stimulation a hyperpolarization of the ending and of the first intracorpuscular Ranvier node may be produced. This leads to respectively post-tetanic potentiation of generator potential and increase in nodal firing threshold. The balance of these after-effects determines the threshold for the production of nerve impulses by adequate (mechanical) stimulation of the sense organ. The after-effects of activity at the node can be elicited by dromic (mechanical) stimulation of the ending, as well as by antidromic (electric) stimulation of the axon; the after-effects at the ending can only be produced by dromic and not by antidromic stimulation.

INTRODUCTION

The production of a nerve impulse by mechanical stimulation of Pacinian corpuscles involves two readily detectable steps of depolarization inside the sense organ: (1) a finely graded generator potential which is produced at the non-myelinated nerve ending inside the corpuscle; and (2) an all-or-nothing potential which is produced at the Ranvier node adjacent to the ending when the generator potential reaches a certain critical amplitude. As in other excitable tissues, an all-or-nothing potential is fired at the node when the

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nodal resting potential is depolarized to a critical level by the generator current from the ending (Loewenstein and Altamirano-Orrego, 1958 a; Loewenstein and Rathkamp, 1958). The mechanical threshold for firing of impulses depends, thus, on the amplitude of the generator potential; and on the nodal threshold, namely on the minimal current required for depolarizing the node to the critical level. In the preceding paper effects of repetitive activity on the mechanical threshold of the sense organ were studied. Repetitive activity was found to have two independent after-effects: depression and facilitation of mechanical threshold for impulse firing. In the present study the mechanisms of these after-effects are investigated in terms of changes in generator potential and nodal threshold. It will be shown that with certain stimulus parameters a post-tetanic hyperpolarization of the non-myelinated ending is
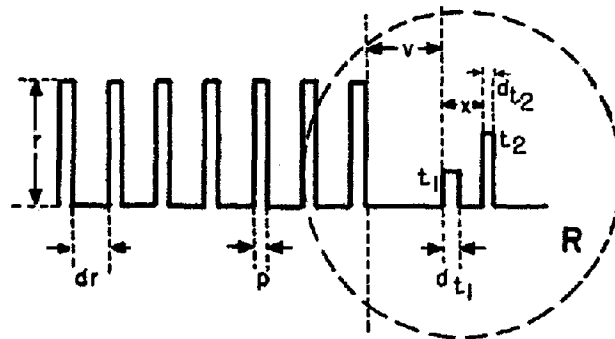

FIGURE 1. Controlled variables of mechanical (dromic) or electrical (antidromic) stimulation. Description in the text.

produced; this causes post-tetanic potentiation of the generator potential. With other parameters, a post-tetanic depression of generator potential ensues; this reflects a decrease in responsiveness of the receptor membrane of the ending which is independent of the resting membrane potential. The balance of these effects determines whether a depression or a facilitation of mechanical threshold results as after-effect of repetitive stimulation.

Methods

The set-up and general procedures have been described in the preceding paper (Loewenstein and Cohen, 1959). Only the following two aspects of the method were modified. The axon of each corpuscle was dissected up to its point of emergence from the corpuscle, and the interface electrode was adjusted to record from this point. Under these conditions, a generator potential produced at the non-myelinated ending inside the corpuscle has to spread over an average distance of 450 μ of intracorpuscular myelinated axon before reaching the interface electrode. Non-polarizable

(Ag–AgCl) electrodes and a high gain D.C. amplifier were employed in the experiments in which after-potentials were recorded.

For some experiments a combination of four square pulse generators, instead of three as described in the preceding paper, was used for driving the piezoelectric crystal. The arrangement allowed delivery of a test pulse at any desired moment after a train of repetitive pulses. The following variables could be controlled independently (Fig. 1): (1) stimulus strength (r) of train; (2) strength of test stimuli (t); (3) duration (p) of each stimulus in the train; (4) duration (d_t) of test stimuli; (5) stimulus frequency of train ($1/dr + p$); and (6) delay (v) of test stimulus with respect to end of train. Either one test pulse alone (t_1) or two successive test pulses (t_1 and t_2) could be delivered. The latter arrangement was used when generator potentials were produced and tested during the refractory period of the node (cf. Loewenstein and Altamirano-Orrego, 1958). The delay (x) between test pulses could be varied independently. The oscilloscope sweep (R) could be synchronized so as to observe any desired portion of the end of train or test stimuli. The arrangement of square pulse generators was built by Mr. J. Fortoul.

RESULTS

Post-Tetanic Depression of Generator Potential

NORMAL GENERATOR POTENTIAL When a Pacinian corpuscle is stimulated with mechanical stimuli of constant strength and at a low repetition rate, generator potentials of fairly constant amplitude are produced. There are spontaneous fluctuations in amplitude of the generator potentials inherent in the nature of the ending's excitation process, but these fluctuations seldom amount to more than ± 12 per cent (Loewenstein and Altamirano-Orrego, 1958 b; Loewenstein and Ishiko, 1959). Within this margin of variability, it is possible to use the mean amplitude of generator potential in response to a given test stimulus strength as a normal reference value (henceforth called *normal generator potential*), if the following two conditions are fulfilled: (1) The receptor must be fully rested; i.e., the frequency of stimulation must be low enough to cause neither depression nor facilitation in the receptor. A stimulus frequency of 1 per sec. was found to satisfy this requirement with a good safety margin in all corpuscles, and was, therefore, used for test stimulation in all the present experiments. (2) The strength and duration of test stimuli must be kept constant. This obvious condition could be satisfied with an accuracy of 0.3 per cent with the aid of the photoelectric monitor system employed in the present work. The normal generator potential as defined above, was used as a reference value in all experiments described in the present paper.

TIME COURSE OF DEPRESSION When a Pacinian corpuscle is submitted to repetitive mechanical stimulation of high frequency, its responsiveness to

produce generator potentials becomes markedly depressed. An example is given in Fig. 2. The corpuscle is stimulated at a low rate with a mechanical test pulse of a given constant strength producing a generator potential of a certain *normal* size (Fig. 2 a). A train of repetitive stimuli of a frequency of 500 per sec. is then applied to the corpuscle for a total train duration of 30 sec. At the end of the repetitive stimulation, the generator potential in response to the previous test stimulus is again recorded. Immediately after the high fre-
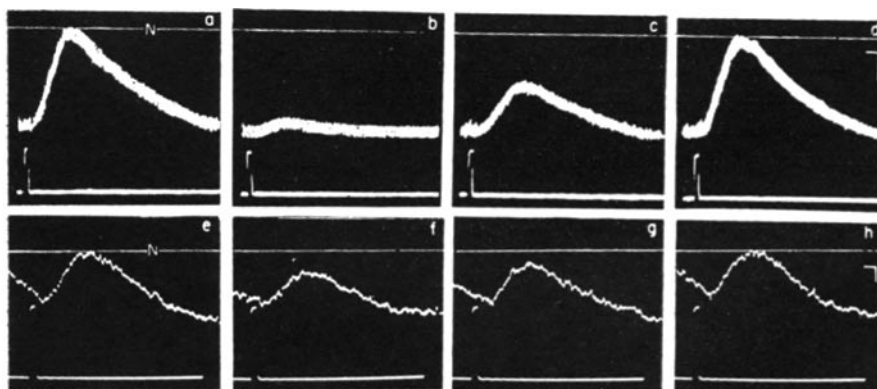

FIGURE 2. Post-tetanic depression of generator potential. The normal responsiveness of the ending was determined with a mechanical test stimulus of subthreshold strength. a, generator potential of the fully rested ending in response to the test stimulus. A train of repetitive mechanical stimuli at 500/sec. was then applied to the corpuscle for a total duration of 30 sec., and the generator potential in response to the test stimulus was recorded b, 0.2 sec.; c, 5 sec.; d, 50 sec. after the end of the train. Lower beam signals mechanical stimulus; upper beam, the electrical activity of the receptor; and N line indicates the mean amplitude of the normal generator potential in this and subsequent figures. Calibration 20 μ v.; 0.5 msec. e–h generator responses from another corpuscle. Generator potentials are here produced by letting the test stimulus fall during the refractory period of a preceding all-or-nothing potential. Only the tail of the preceding all-or-nothing potential is shown on top of which the test generator potential is seen to develop. e, normal generator potential; f, 0.2 sec.; g, 5 sec.; h, 40 sec. after end of a train of mechanical stimuli at 500/sec. applied for 20 sec. Calibration 20 μ v.; 0.5 msec.

quency train, the amplitude of the generator potential is found to be reduced by 85 per cent (b). It is seen to recover thereafter progressively to its normal value over a period of several seconds (c, d). A typical time course of recovery of generator potential from depression is shown in Fig. 3. The time required for the generator potential to recover from its depressed level, as measured immediately after repetitive stimulation to its normal size (henceforth called *full recovery time of generator potential*) is usually of the order of seconds. The full recovery time varies from corpuscle to corpuscle; but in a given corpuscle, and at constant parameters of stimulation, it is rather constant over 30 to 60 minutes of observation. The full recovery time increases as a function of the

reduction in generator potential. The effect of post-tetanic depression of generator potential is fully reversible over many trials, and can in some corpuscles be elicited with strengths of repetitive stimuli as low as one-half threshold strength for normal impulse firing.

The test generator potentials illustrated in Fig. 2 *a–d* were produced with single subthreshold test stimuli. In those cases in which the firing level was too low for obtaining measurable generator potentials by single stimulation, test generator potentials were produced by the method of double stimulation
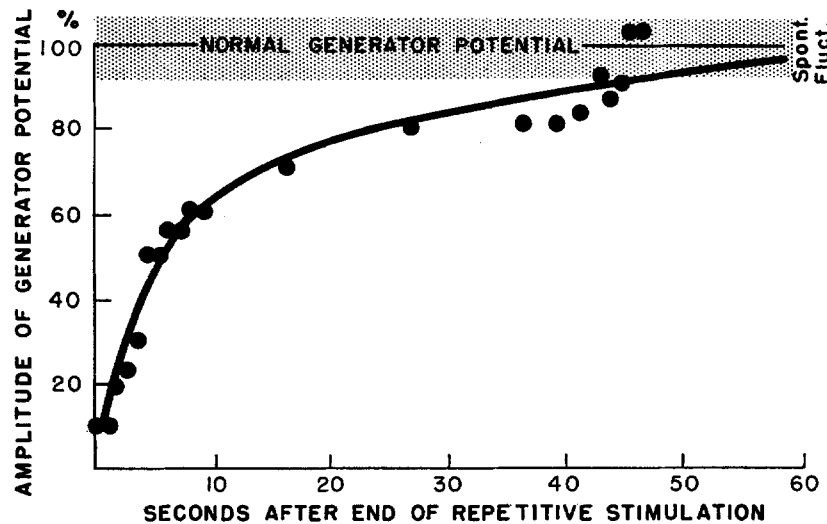

FIGURE 3. Recovery of generator potential after repetitive stimulation. A train of repetitive stimuli at 500/sec. has been delivered to the corpuscle for a total duration of 30 sec. This caused a depression of the generator potential in response to a constant mechanical stimulus. The amplitude of the generator potential (ordinates) was determined at the end of the train (time 0) and is followed thereon until its recovery to fully rested amplitude (normal generator potential). The shaded area delimits the range of spontaneous fluctuation of the normal generator potential in this and subsequent figures.

(Loewenstein and Altamirano-Orrego, 1958 *a*, *b*). By applying a test stimulus after a suprathreshold conditioning stimulus, so that the former falls during the refractory period left by the all-or-nothing potential elicited by the latter, fairly large test generator potentials can be produced without firing of all-or-nothing potentials. Fig. 2 *e–h* gives an example of generator potential depression as tested by this method. The test method of double stimulation gave essentially the same result as that of single subthreshold stimulation.

When generator potentials were produced by the method of double stimulation, it was necessary to make certain that the post-tetanic effect to be tested was not masked or affected otherwise by changes in the "size factor" of refractoriness (Loewenstein and Altamirano-Orrego, 1958 *b*) resulting from depression of the conditioning gen-

erator potential. Satisfactory results were usually obtained when high strengths—well within the saturation range of the (single) generator potential–stimulus strength curve—were used for the conditioning stimulus. As will be seen in the following paper of this series, depression of generator potential decreases progressively to zero in the saturation range.

Besides amplitude, the rate of rise of the generator potential is also diminished during depression. The rate of rise increases progressively towards its original normal value during the recovery phase from depression. The time course of recovery of the rate of rise parallels that of the amplitude of the generator potential.

EFFECTS OF STIMULUS STRENGTH   After the preceding results it was clear that the amplitude of the generator potential increased continuously during its recovery from depression. In order to obtain a reasonably constant measure of depression, the following procedure was used: A test stimulus was selected which would produce a normal generator potential of an easily measurable amplitude. The corpuscle was then stimulated with a train of constant duration containing repetitive stimuli of constant frequency and of a given strength. At the end of this train the previously selected test stimuli were applied at a repetition rate of 1 per sec. Test stimuli and train were synchronized so that the first test stimulus was delivered within 0.25 sec. after the end of the train. Since the first test stimulus fell during the early phase of recovery of the generator potential where there is a rather steep recovery in amplitude, it produces always the generator potential of the smallest amplitude (henceforth called *minimal generator potential*). The *minimal generator potential* is fairly well reproduccable in a given corpuscle, and provides thus a convenient measure of depression.

Fig. 4 illustrates the relationship between the minimal generator potential and stimulus strength of repetitive stimuli. In this experiment the stimulus strength of a train of repetitive stimuli of otherwise constant parameters, was varied within a range of one-third to thirteen times threshold strength. The minimal generator potential is seen to decrease over the entire range of strength. As may be expected, the rate of rise of the generator potential decreases with stimulus strength in a similar manner (Fig. 5).

The requirements of stimulus strength for a given train of repetitive stimuli to produce a detectable generator potential depression, may vary considerably from one corpuscle to another. Thus, for example, in the corpuscle of Fig. 4 a depression could be shown with repetitive stimuli of subthreshold strength (which cause a compression in corpuscle diameter of less than 0.6 μ); while in the corpuscle of Fig. 9 the strength of repetitive stimuli, belonging to a train with parameters otherwise not too different from those of Fig. 4, had to be raised beyond 2.8 times that minimal strength used in the experiment of Fig. 4, in order to produce a detectable depression in generator potential.

However, in a given corpuscle the depression effects are well reproduceable with respect to stimulus strength (as well as with respect to other train parameters, studied below).

EFFECTS OF STIMULUS FREQUENCY   The frequency of repetitive stimuli is another factor which determines the degree of generator potential depression. The curve in Fig. 6 describes a typical frequency–minimal generator poten-
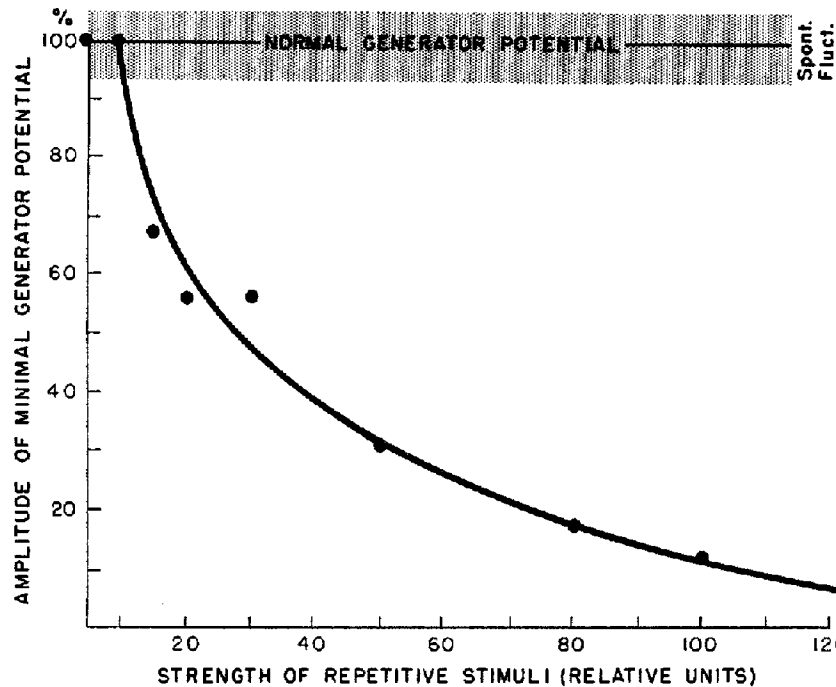

FIGURE 4. Amplitude of depressed generator potential as a function of strength of repetitive stimuli. Trains of repetitive stimuli of constant stimulus frequency (500/sec.) and constant train duration (15 sec.) have been applied to the corpuscle. The resulting depression of generator potential in response to a constant test stimulus was determined for various strengths of repetitive stimuli. The amplitude of generator potential at the end of each train (minimal generator potential) is plotted against stimulus strength of each train.

tial relationship. In this experiment, trains of equal duration containing stimuli of constant strength were delivered to the corpuscle, and the stimulus frequency was varied over a range of 1 to 1000 stimuli/sec. There is a rather steep decrease in minimal generator potential as the frequency is raised from 1 to 200/sec. Between 200 to 900/sec. the reduction is more gradual and tends to reach a maximum around 800/sec. As may be expected, the full recovery time of generator potential increases as function of frequency (Fig. 7).

EFFECTS OF TRAIN DURATION   The minimal amplitude to which the generator potential is driven by a train of repetitive stimuli depends also on

the duration of the train. When a corpuscle is stimulated with a train of repetitive stimuli of constant strength and constant frequency, the minimal generator potential is found to decrease as a function of train duration (Fig. 8). Characteristically, there is a rather sharp decline in amplitude of the minimal generator potential as the duration is prolonged from 1 to about 20 sec.; from there on the amplitude declines gradually, tending to reach a minimum with durations of 1 to 2 minutes.
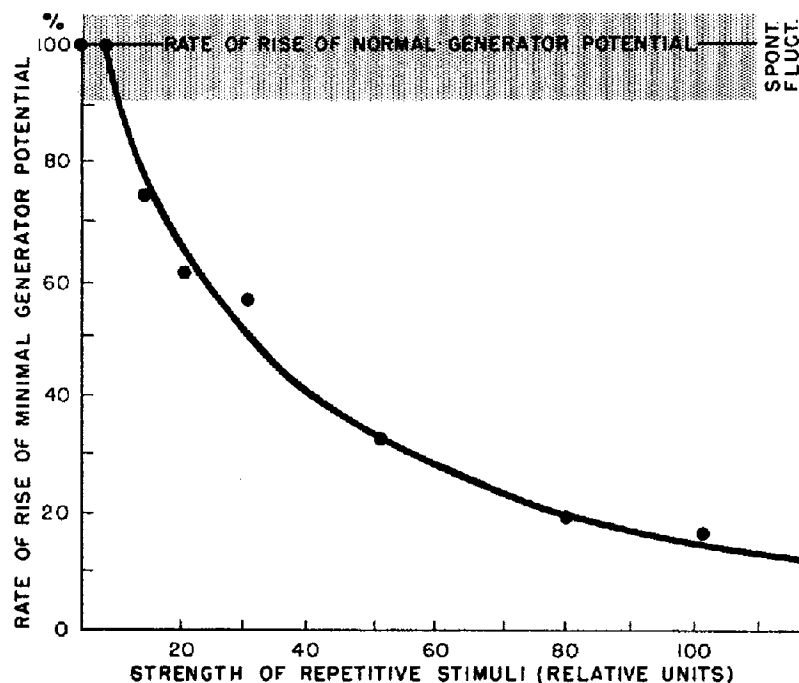

FIGURE 5. Rate of rise of depressed generator potential as a function of strength of repetitive stimuli. The rate of rise of the minimal generator potential of the experiment of Fig. 4 is plotted against stimulus strength of each train.

As was to be expected, the rate of rise of the generator potential was found to decrease as a function of train duration in a manner similar to the amplitude of the minimal generator potential; and the full recovery time of generator potential was found to increase as a function of train duration.

After-Effects on the Firing Threshold of the First Ranvier Node

POST-TETANIC INCREASE IN NODAL THRESHOLD   There are at least two steps in the production of nerve impulses in Pacinian corpuscles: (1) the mechanical stimulus is converted into a graded generator potential; and (2)

the generator potential triggers an all-or-nothing impulse. The two steps occur at distinctly different sites inside the sense organ. The first takes place at the non-myelinated nerve ending, and the second, at the adjacent Ranvier node located at a distance of about 250 μ from the ending (Loewenstein and Rathkamp, 1958). An all-or-nothing potential is set up at the node whenever the generator current flowing between ending and node reaches a certain critical magnitude; *i.e.*, when the nodal membrane potential is reduced to a
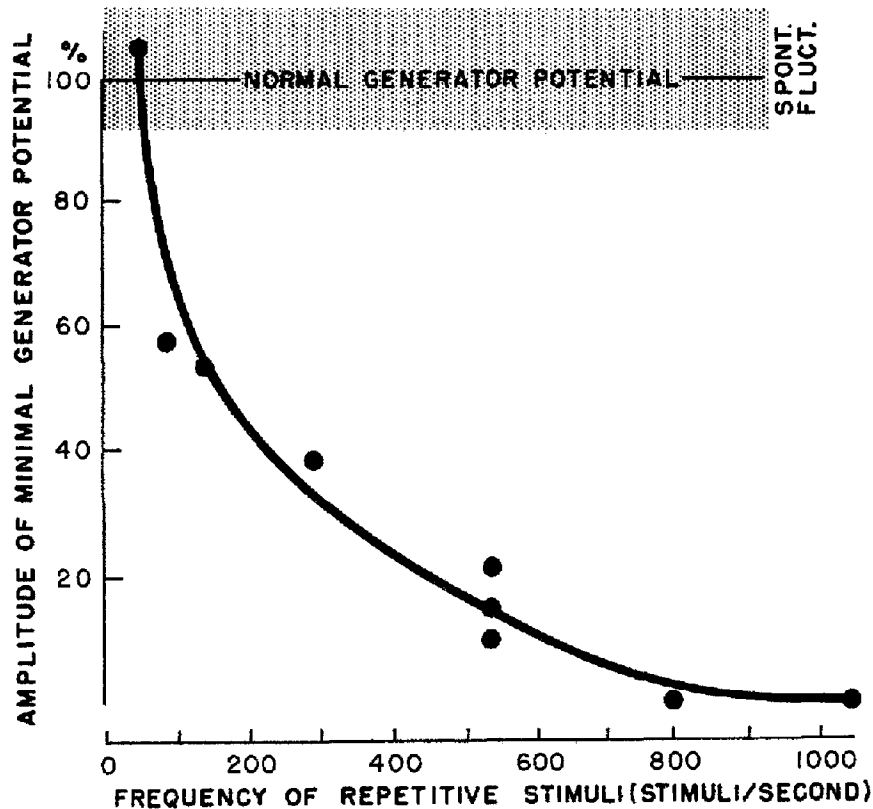

Figure 6. Amplitude of depressed generator potential as a function of frequency of repetitive stimuli. The corpuscle has been stimulated with trains of constant duration (30 sec.) and constant strength. The amplitude of generator potential (ordinates) at the end of each train is plotted against frequency of repetitive stimuli.

critical level by this current (Loewenstein and Altamirano-Orrego, 1958 *b*). The minimal generator potential capable of firing an all-or-nothing potential will henceforth be referred to as *firing height*. Firing of all-or-nothing potentials at the node depends then on two independent factors: (1) on the amplitude of the generator potential, and (2) on the firing height. Increase in mechanical threshold during depression by repetitive stimulation, such as

described in the preceding paper, may thus be caused by either a decrease in amplitude of the generator potential in response to a given mechanical stimulus, or by an increase in firing height, or by both. From what has been learned so far about generator potential depression, it appeared likely that the decrease in generator potential caused by repetitive activity is, at least, one of the factors which determines the rise of mechanical threshold: the time course of threshold recovery from depression parallels that of the generator poten-
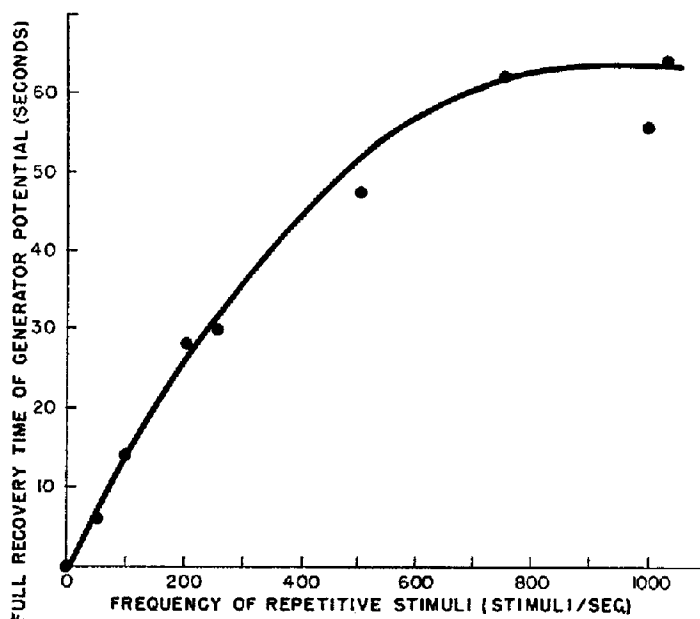

FIGURE 7. Full recovery time of generator potential as a function of frequency of repetitive stimuli. The time required for the generator potential to reach its fully rested amplitude (ordinates) after repetitive stimulation is plotted against frequency of repetitive stimuli. Data from experiment of Fig. 6.

tial; and the relation between full recovery time of threshold and strength is quite similar to that between full recovery time of generator potential and stimulus strength. There are, however, some important differences between the curves describing the dependency of threshold on stimulus frequency and on train duration, on the one hand (Figs. 4 and 5 of preceding paper), and the curves describing the corresponding dependency of generator potential, on the other hand (Figs. 6–8 of the present paper). Although the initial portions of the corresponding curves are of similar shape, a typical generator potential–train duration curve never shows an inflection point like that of a threshold–train duration curve; moreover, there is never a decline in the generator potential–frequency curve, like that in a threshold frequency

curve at high frequencies. This suggested strongly that besides decrease in generator potential, another factor contributed to the threshold depression, and prompted us to seek for changes in the firing height during depression.

The following procedure was used to determine the firing height. The corpuscle was stimulated with stimuli of just critical threshold strength at a repetition rate of 1 or 2 stimuli per sec. known to cause neither depression nor facilitation. Thus out of a number of stimuli, some would produce all-or-nothing potentials while others, falling short of the critical firing height, would produce only generator potentials. 5 to 10 successive responses were
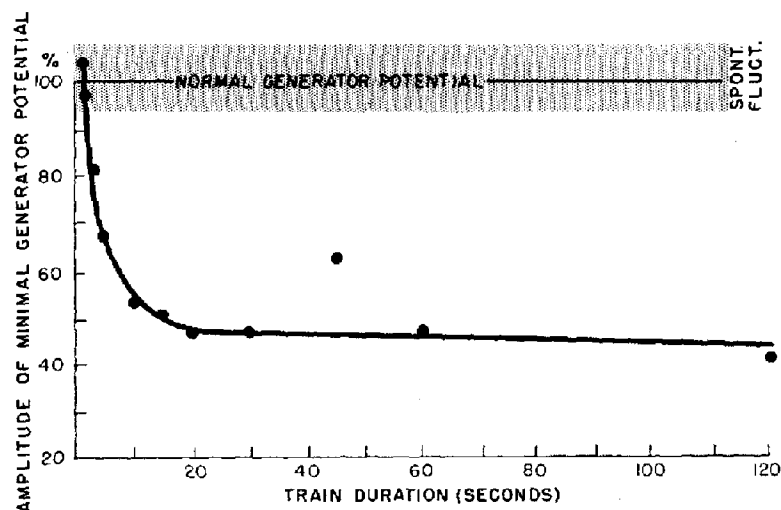

Figure 8.   Amplitude of depressed generator potential as a function of train duration. A depression-inducing train of constant stimulus strength and constant frequency (500/ sec.) has been delivered to the corpuscle. The amplitude of the resulting minimal generator potential is determined for various train durations.

superimposed on successive oscilloscope sweeps; the maximal amplitude of the aborting generator potentials was taken as the firing height. There are spontaneous fluctuations in firing height. But under standard conditions of stimulation, the fluctuations are usually less than ±5 per cent. The super-position of 5 to 10 successive responses produces a reliable measure of firing height; any enduring change in the critical firing height is measurable with a resolution of about 5 per cent of a given firing height value. Changes in firing height were usually determined by the method of double stimulation, as in the example of Fig. 9. The firing height increases exponentially during the refractory period left by a preceding all-or-nothing potential as the stimulus interval is decreased within the refractory period (Loewenstein and Altamirano-Orrego, 1958 *b*); thus by the method of double stimulation the
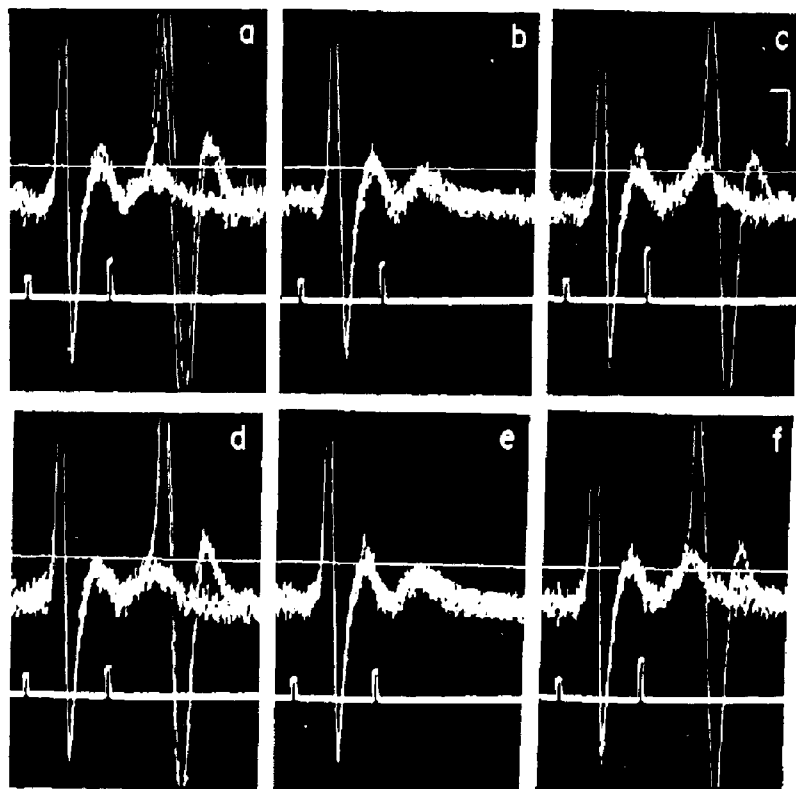
FIGURE 9. Increase in threshold at the first Ranvier node after dromic and antidromic repetitive stimulation. *a*, two successive mechanical stimuli are applied to the corpuscle. The second stimulus (test stimulus) produces a generator potential of just critical threshold amplitude. A train of repetitive mechanical stimuli at 550/sec. is then applied to the corpuscle for 10 sec. *b*, the generator potential in response to the test stimulus of the same strength as in *a* is again recorded at the end of the train. The train caused no change in generator potential in this case, but although the generator potential has the same amplitude and rate of rise as in *a*, it falls now short of the nodal firing threshold. *c*, the strength of the test stimulus has been adjusted so as to satisfy critically the firing threshold at the end of the train. *d–f*, effect of antidromic repetitive stimulation. *d*, normal firing threshold; *e* and *f*, same as in *b* and *c*, respectively, but after a train of repetitive antidromic impulses fired into the corpuscle at the same frequency and train duration as above by electrical excitation of the axon. Calibration: 50 μv.; 1 msec.

normal firing height can be set to an easily measurable magnitude. In a few corpuscles the post-tetanic increase in firing height was measured successively by the method of double and of single stimulation; the increase was found to be the same.

Fig. 9 *a*, shows the normal critical firing height of a corpuscle stimulated with constant test stimuli of just threshold strength at a low rate which causes neither depression nor facilitation. The corpuscle was then stimulated with a train of high frequency stimuli of suprathreshold strength, which in a pre-

ceding trial had been found to cause increase of the mechanical threshold. At the end of the train, the critical firing height was again determined by adjusting the test stimulus strength to the heightened threshold requirement of that instant. The firing height was found to have risen by 40 per cent at the peak of the depression (Fig. 9 c). It decreases then progressively towards its normal value during the recovery period. A typical time course of recovery of critical firing height is given in Fig. 10.
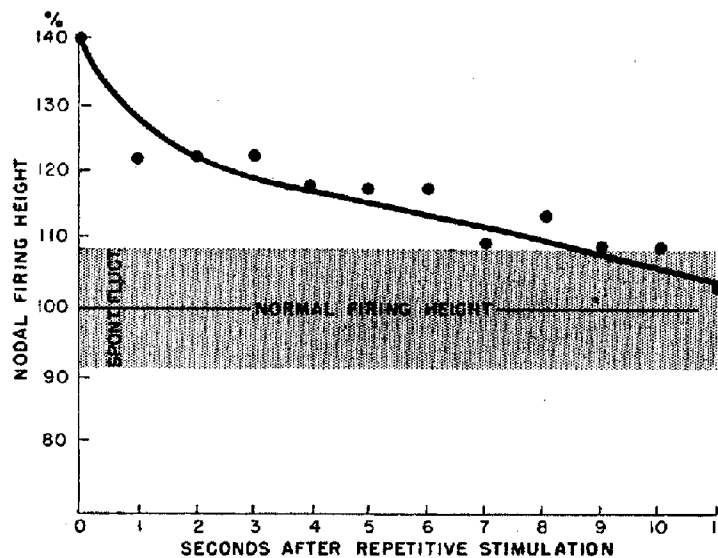

Figure 10. Recovery of firing threshold of intracorpuscular Ranvier node after repetitive dromic stimulation. A train of suprathreshold repetitive mechanical stimuli at 500/ sec. has been delivered to the corpuscle for a total duration of 10 sec. The minimal generator potential required for impulse firing at the first Ranvier node (firing height) inside the corpuscle was measured at the end of the train and followed up to normality with single infrequent test stimuli. (See Fig. 9.)

Post-tetanic increase in firing height was not found in all corpuscles. While depression of generator potential could be shown in practically all corpuscles, after-effects on firing height were found in relatively few cases. However, when present in a given corpuscle, the effect on firing height could be reproduced consistently.

EFFECT OF STIMULUS STRENGTH The post-tetanic increase in firing height reflects a change in excitability of the membrane of the first Ranvier node. The question now arises whether this change is an after-effect of firing of all-or-nothing potentials at the node, or whether it is caused by the activity of local current flowing between node and the mechanically activated non-myelinated ending. It seemed conceivable that the effect might be produced by local subthreshold depolarization of the node under the influence of the generator current from the ending, as well as by actual firing of all-or-

nothing potentials at the node. A comparison between the firing height–stimulus strength relation and the minimal generator potential–stimulus strength relation should help to clarify this point. In the experiment illustrated in Fig. 11 a, a corpuscle is stimulated with a train of constant duration and constant stimulus frequency. The strength of the stimuli contained in each train is varied over a wide range, and the firing height is measured at the end of each train. It will be seen that the firing height increases only at that strength of repetitive stimulation at which firing of repetitive all-or-nothing potentials occurred. At this threshold point the firing height increases abruptly to a new higher level; but from there on the critical firing height does not increase in spite of large increments in stimulus strength. The all-or-nothing behavior of the firing height with regard to strength stands in striking contrast to the dependency on strength of the depression of generator potential which extends even to the subthreshold range of strength (see Fig. 4). This is precisely what one might expect if the rise in firing height were independent of graded subthreshold generator currents from the ending, and were to depend on an all-or-nothing factor alone, namely on firing of all-or-nothing potentials at the node.

The firing of an all-or-nothing potential at the first Ranvier node inside the corpuscle leaves a relative refractory state behind, which lasts about 7 msec. At stimulus frequencies of repetitive stimulation above 140 per sec., each successive stimulus tends to fall then on the refractory trail left by the preceding impulse. During the relative refractory period the critical firing height increases exponentially as the interval between stimuli is progressively reduced (Loewenstein and Altamirano–Orrego, 1958 b). Consequently, the threshold requirements for all-or-nothing firing with mechanical stimuli increase progressively as the frequency of repetitive stimuli is increased (Loewenstein, 1958 a). The threshold for a train of repetitive stimuli of high frequency may thus be considerably higher than the threshold for single stimuli. It is obviously the former of the two thresholds which matters in evaluating the effect of repetitive stimulation on firing height. The simplest results are obtained in corpuscles in which a change in firing height can be produced with frequencies below 140/sec., such as in the experiment of Fig. 11. At higher frequencies discharge patterns of alternating generator and all-or-nothing potentials are produced (Loewenstein 1958 a). Thus, in evaluating the effect of repetitive stimulation at high frequency, another factor, namely the actual firing rate of all-or-nothing potentials during the train of repetitive stimuli must be considered. For example: a train of 200 stimuli per sec. of a given strength produces a discharge pattern in which subthreshold generator potentials alternate with all-or-nothing potentials. The ratio between all-or-nothing potentials and stimuli is 1:2. If now the stimulus strength is increased so as to satisfy the threshold requirements of the corresponding refractory period, the ratio may become 1:1, and the actual firing rate of all-or-nothing potentials may thereby be doubled. Since the after-effect on firing height is frequency-dependent (see below), a further increase in critical firing height is experienced when the firing rate leaps to twice its original value. This may then give the false impression that the increase
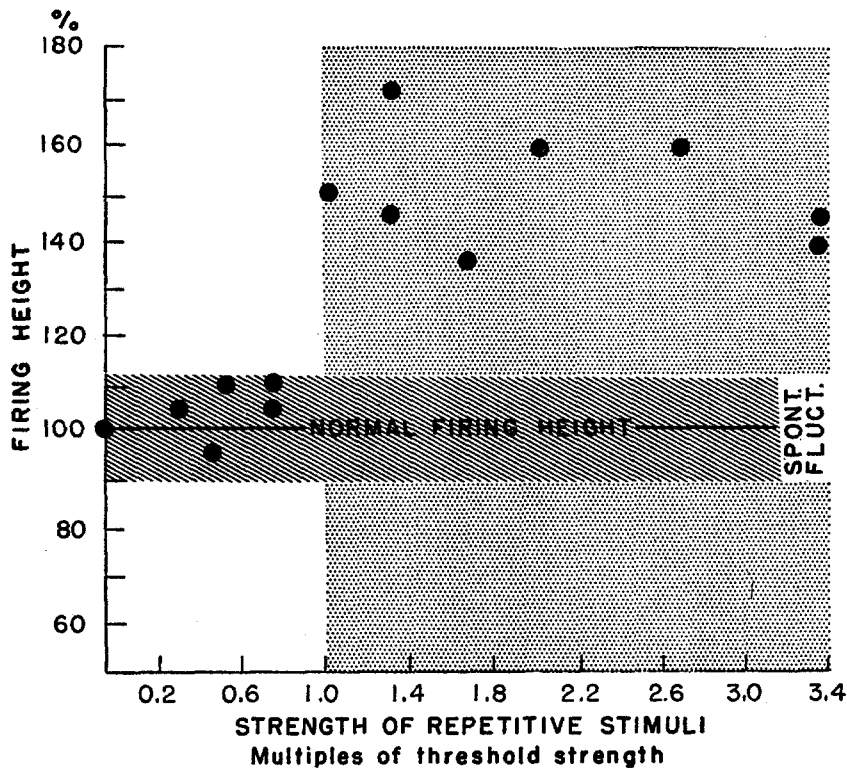
FIGURE 11.   Effect of strength of repetitive dromic stimuli on firing threshold of intra-corpuscular Ranvier node. The corpuscle has been stimulated with the mechanical trains of constant duration (10 sec.) and frequency (130/sec.). The strength of repetitive stimuli was varied over an ample range and the corresponding firing heights (ordinates) of the first Ranvier node were determined at the end of each train with single infrequent test stimuli. Units of abscissae are multiples of that minimal strength (1.0) of repetitive stimuli which causes impulse firing at the node. Note the all-or-nothing behavior of the tested firing height (ordinates) which remains at its normal resting value (100 per cent) throughout the entire subthreshold range of repetitive stimuli (white area) and rises abruptly to a new level when the strength of repetitive stimuli becomes suprathreshold (gray area).

in firing height is graded instead of all-or-none with respect to stimulus strength. However, upon analysis such a graded effect can always be traced to an increase in firing rate.

In summary it may be concluded *that the increase in critical firing height is an all-or-none effect with respect to strength of repetitive stimulation, and is an exclusive after-effect of all-or-nothing activity of the nodal membrane.*

EFFECT OF STIMULUS FREQUENCY   The increase in critical firing height depends on the discharge of all-or-nothing impulses. Because of the conditions imposed by the receptor's refractory state analyzed in the preceding para-

graph, it is not the stimulus rate, but the firing rate of all-or-nothing potentials which determines the level to which the critical firing height is driven by repetitive activity. Within certain limits, the critical firing height was found to increase as a function of the firing rate of all-or-nothing potentials at the node. It will be recalled that the depression of the generator potential is also rate-dependent; it is a function of the rate of generator potentials produced at the ending. Both effects, the decrease in generator potential, and the increase in firing height appear to concur therefore in determining the sharp rise in the threshold when the stimulus frequency is augmented from 1 to 120/sec. (see Fig. 4 of the first paper of this series). At high frequencies of stimulation, when out of a train of repetitive stimuli some may fall during the refractory period of the node, the strength of repetitive stimulation may fall short of the raised threshold requirements for all-or-nothing firing, and the actual firing rate may drop considerably below the rate of stimulation. The critical firing height may thereby fall towards the normal height, and the rise in threshold be carried mainly or completely by the depression of the generator potential at this high stimulus frequency. This explains the decline in the threshold recovery-frequency curve at high frequencies of repetitive stimulation (Fig. 4 of the first paper of this series).

Within certain limits, the increase in critical firing height is also a function of the train duration.

Post-Tetanic Potentiation of Generator Potential

POTENTIATION OF GENERATOR POTENTIAL   In the first of the present series of papers a facilitatory effect was described resulting from repetitive stimulation of the receptor. The effect consists of a lowering of threshold for firing of all-or-nothing potentials to a mechanical test stimulus. Lowering of threshold may be due to an increase in amplitude of the generator potential in response to a given stimulus strength; or to a reduction in firing height; or to both. We have never observed a reduction in firing height, but we have found a potentiation of generator potential in many corpuscles as a consequence of repetitive stimulation.

Fig. 12 illustrates an example of post-tetanic potentiation of generator potential. Test stimuli of constant strength are applied to the corpuscle at a low rate producing generator potentials of approximately equal amplitude (Fig. 12 a) (spontaneous fluctuations in amplitude are less than ±8 per cent). The corpuscle is then stimulated with a train of high frequency stimuli. At the end of the train, the test stimuli are applied again, eliciting now generator potentials of considerably larger amplitude (Fig. 12 b). The amplitude of the generator potential returns then gradually to its original value (Fig. 12 c).

Fig. 13 shows the time course of a typical potentiation. The corpuscle was

stimulated with trains of constant duration and frequency, and the time course of potentiation plotted for four different stimulus strengths of the train. Unlike depression, the potentiation is not at its maximum during, or right after the repetitive stimulation, but is seen to build up to a peak value over several seconds after the train. It decreases then progressively from its
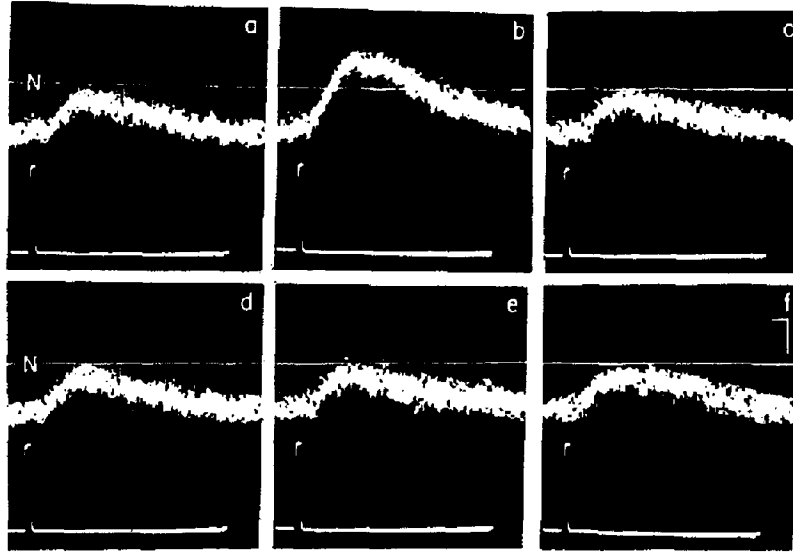

Figure 12. Post-tetanic potentiation of generator potential. *a*, normal generator in response to a mechanical test stimulus. A train of repetitive mechanical (dromic) stimuli is then delivered to the corpuscle at 500/sec. for 5 sec., and the generator potential in response to the test stimulus is recorded *b*, 5 sec.; *c*, 18 sec. after end of the train. *d–f*, absence of potentiation after antidromic repetitive stimulation in the same corpuscle. *d*, normal generator potential in response to mechanical test stimulus. A train of antidromic impulses of same frequency and train duration as above is then sent into the corpuscle by electric excitation of its axon. This fails to produce potentiation of generator potential: *e*, generator potential in response to test stimulus 5 sec.; *f*, 18 sec. after end of the train. Calibration 10 μ v.; 0.5 msec.

peak value to normal over a period which is a function of the degree of potentiation. The degree of potentiation is a function of stimulus strength of the train (Figs. 13 and 14), or more directly, a function of the generator potential produced during repetitive stimulation (Fig. 14).

Potentiation is not found in as many corpuscles as depression; the latter can be shown in almost any corpuscle. It will be noted from Fig. 13 that potentiation as well as depression may be present in the same corpuscle. It may at first sight seem surprising that these opposing effects take place in the same receptor. But as will be analyzed further on, the two effects are caused by entirely different mechanisms; depression and potentiation may not only

occur in the same receptor, but may go on simultaneously as in the experiment illustrated in Fig. 13. If at all present, potentiation is usually best shown after trains of short duration (1 to 10 sec.); with long train duration, depression usually tends to mask the effects of potentiation of generator potential. This limits the range over which train parameters may be varied for studying potentiation. However, in those cases in which a sufficient range of train duration and stimulus frequencies could be explored, the potentiation was found to increase as a function of these two parameters.
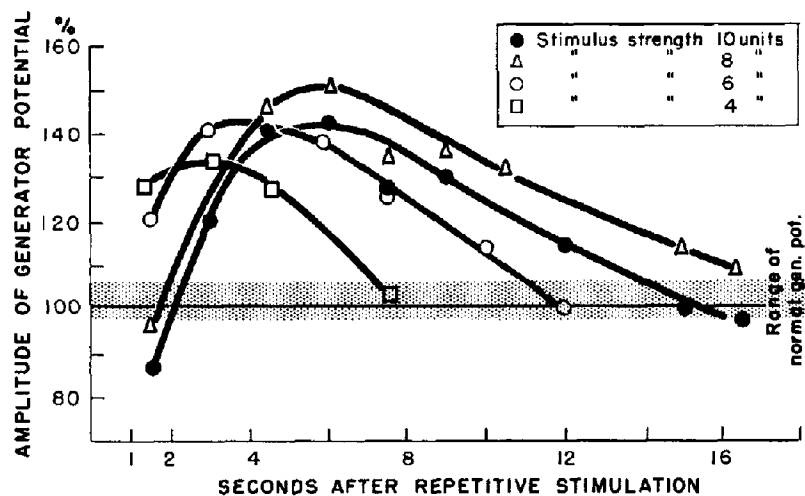

Figure 13. Time course of post-tetanic potentiation of generator potential. The corpuscle has been stimulated with trains of constant frequency (500/sec.) and constant duration (10 sec.). This caused a potentiation of generator potential. The amplitude of the generator potential in response to a constant test stimulus is measured after the end of the train. The time course of potentiation is followed for different strengths of repetitive stimuli. Note that at high stimulus strength potentiation was preceded by depression.

POST-TETANIC AFTER-POTENTIALS   It has been shown that when the ending is hyperpolarized by inward currents, the generator potential in response to a given mechanical stimulus increases (Ishiko and Loewenstein, 1959). It seemed possible, therefore, that post-tetanic potentiation of generator potential is caused by hyperpolarization of the ending. Since the potentiation of generator potential is in some cases fairly large (70 per cent), it seemed reasonable to expect that a possible underlying hyperpolarization be detectable as a D.C. potential difference between ending and inactive axon, the former being positive with respect to the latter. Such a D.C. potential will henceforth be referred to as after-positivity. We had considerable difficulties in obtaining a stable amplification of D.C. potentials of the order of 5 to 20 μv., which was the usual magnitude of the recorded after-positivity in most corpuscles. However, in a few corpuscles, like that of Fig. 15, a relatively large after-potential could be detected with the same electrode placement as

used for the recording of generator potentials (see Methods). The post-tetanic after-positivity followed then the same time course as the post-tetanic potentiation of generator potential (Fig. 15). We can be certain that the after-positivity recorded in the experiment of Fig. 15 was not produced at a Ranvier node, but was exclusively produced at the ending, because the strength em-
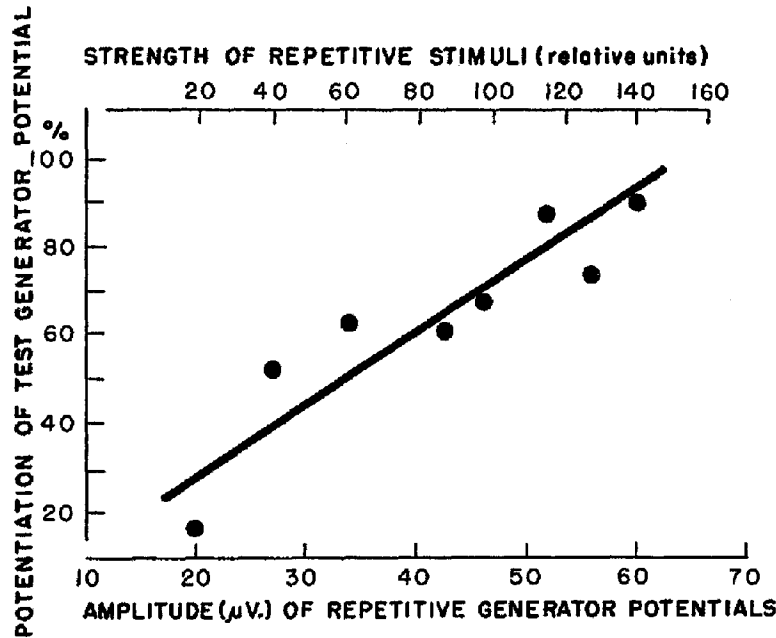

FIGURE 14.   Post-tetanic potentiation of generator potential as a function of strength of repetitive stimuli. The corpuscle has been stimulated with trains of repetitive mechanical stimuli at constant frequency (300/sec.) and constant train duration (10 sec.). Strength of repetitive stimuli was varied within the submaximal range. Potentiation of generator potential in response to a standard mechanical test stimulus (*test generator potential*) is plotted against strength of repetitive stimuli (upper abscissa) and against the amplitude of the first generator potential (*Repetitive generator potential*, lower abscissa) in response to each train of repetitive stimuli. Potentiation of test g.p. = [(potentiated g.p. − normal g.p.) × 100/normal g.p.]

ployed for high frequency stimulation of the receptor was below firing threshold of the node; as appears from preceding experiments (Fig. 11), appreciable changes in nodal resting membrane potential are caused only when the node has discharged all-or-nothing potentials.

Antidromic Repetitive Stimulation

ABSENCE OF ANTIDROMIC POTENTIATION AND DEPRESSION OF GENERATOR POTENTIAL   Direct evidence has recently been given that the membrane of the non-myelinated ending is not excited by the action current from the ad-

jacent node (Loewenstein, 1959). In the experiments on which the evidence is based, the afferent axon outside the corpuscle was stimulated electrically causing an antidromic impulse to travel into the corpuscle. The antidromic impulse could be traced as an all-or-nothing potential as far as the first Ran-
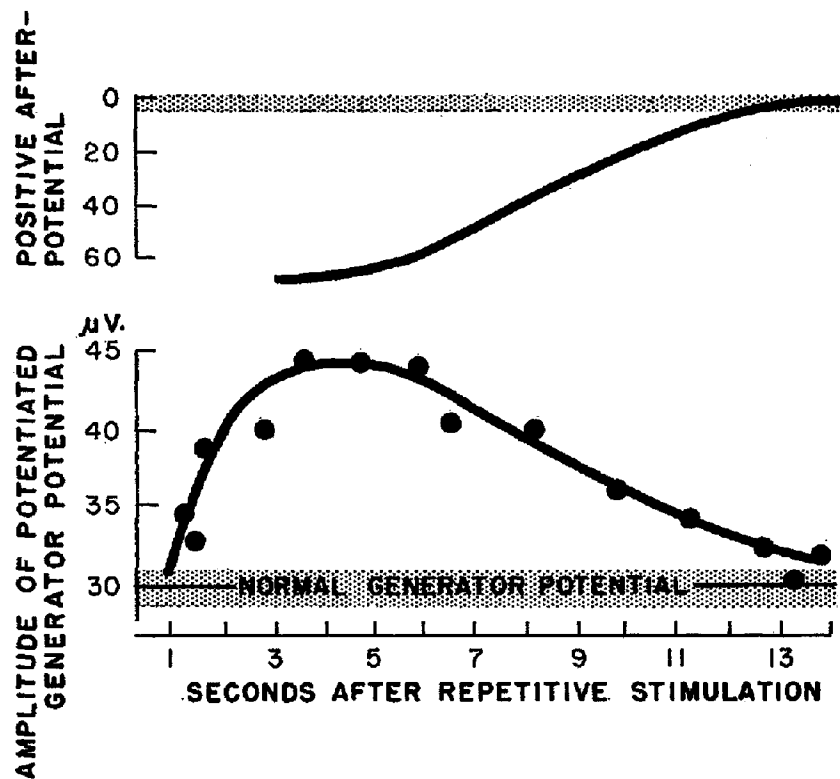

FIGURE 15.   Correlation between post-tetanic potentiation of generator potential and D.C. after-positivity. The corpuscle has been stimulated with a train of repetitive mechanical stimuli at 500/sec. for a total duration of 10 sec. This caused a potentiation of generator potential and a D.C. potential between ending (positive) and inactive axon (negative). The D.C. potential (upper record, scale in arbitrary units) and the potentiated generator potential (lower record, in μv.) were recorded with the same electrodes and with the same electrode placement in two successive runs after the end of the train.

vier node, but no active response could be detected with a microelectrode from any part of the ending's membrane. When an all-or-nothing potential is set up at the node, a current more than five times that minimal current required to excite the node flows outward through the membrane of the ending, yet the ending is not excited by it. The current density is, however, likely to be smaller than that at the node. It could therefore not be decided whether

the failure of single antidromic potentials to produce a detectable response from the ending was due to an insufficient current density, or due to the ending's membrane having a high threshold (if at all) for electrical excitation. The finding of depression and potentiation at the ending, in the present work, allowed a further test of the electrical excitability of the non-myelinated ending. Provided that an antidromic action current from the node were at all to elicit a response at the ending, it seemed reasonable to expect that the cumulative effects caused by repetitive antidromic activation may amplify sufficiently such a response—even if the single response were too small to be detected—so as to reach a detectable value. It will be recalled that both depression as well as potentiation of generator potentials was shown to be brought about as cumulative effects of very small individual (dromic) depolarizations; these effects provided thus a rather sensitive means for detecting and amplifying excitation of the ending.

We have stimulated the afferent axon outside the corpuscle with trains of repetitive electrical stimuli. Trains of repetitive antidromic all-or-nothing potentials were thereby set up at the first Ranvier node, and the train parameters of duration and frequency were varied. It has already been shown that under these conditions all impulses of a train do reach the first node, provided that the frequency is below 700 to 800 per sec. (Loewenstein, 1958 a). Fig. 12 illustrates an experiment in which the effects of repetitive antidromic and dromic stimulation of a corpuscle are compared. The receptor was first stimulated with a train of mechanical stimuli for 5 sec. and at a frequency of 500/sec. This produced a clear potentiation of 60 per cent (peak value) (Fig. 12 b, c). It also caused in this case an increase in critical nodal firing height. An antidromic train of impulses was then sent into the corpuscle which had the same duration and frequency as the preceding dromic train. This produced a similar increase in nodal firing height, but no potentiation whatsoever of generator potential in response to a given mechanical test stimulus was observed (Fig. 12 e, f). We have used a similar procedure in other corpuscles which gave a clear depression or potentiation of generator potentiation upon repetitive dromic stimulation; the invariable result was then that the corresponding antidromic stimulation failed to produce any detectable change in generator potential (Fig. 16). This confirms earlier results (Loewenstein and Altamirano-Orrego, 1958 a; Loewenstein 1958 a; Loewenstein, 1959) in revealing that an antidromic impulse does not excite the non-myelinated ending.

ANTIDROMIC INCREASE IN FIRING HEIGHT   Antidromic stimulation produces, nevertheless, an increase in firing height at the first Ranvier node inside the corpuscle. Fig. 9 illustrates an experiment in which the nodal firing threshold is increased by about the same amount by both dromic and antidromic stimulation. A clear increase in critical firing height, such as shown

in Fig. 9, is not always found after repetitive antidromic stimulation. But, as a rule, whenever a rise in critical firing height is present after dromic stimulation, it can also be produced by antidromic stimulation. The increase in firing height produced by antidromic stimulation determines then, always, an increase in threshold of the sense organ to mechanical stimulation.
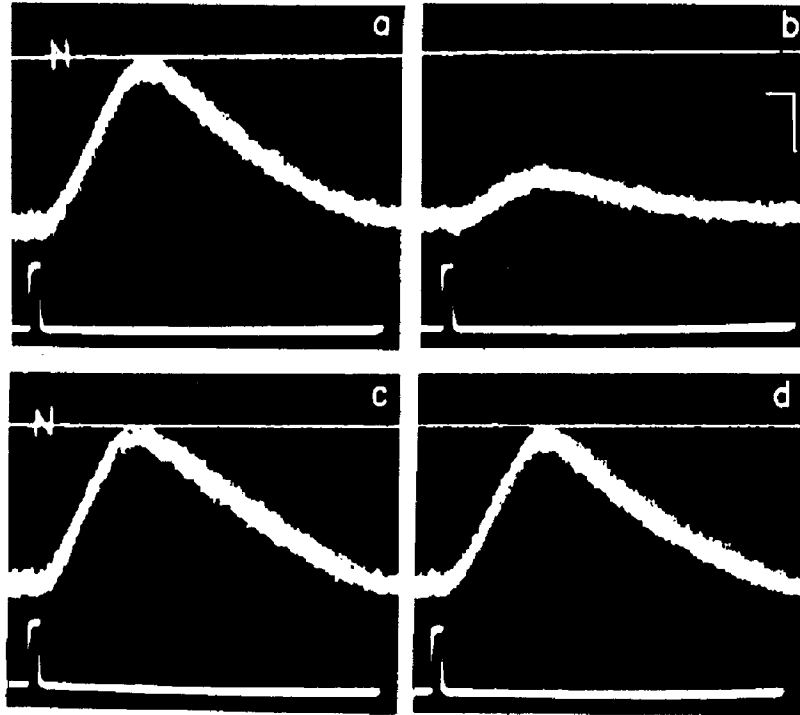

FIGURE 16.   Absence of depression of generator potential after repetitive antidromic stimulation. *a* and *c*, normal generator potential in response to a mechanical test stimulus. *b*, generator potential in response to the test stimulus after application of a train of repetitive mechanical (dromic) stimuli to the corpuscle at 500/sec. for 25 sec. *d*, generator potential after a train of *antidromic* impulses fired into the same corpuscle at the same frequency and train duration as above. Calibration 10 μ v; 0.5 msec.

DISCUSSION

Post-Tetanic Potentiation of Generator Potential

A simple way to explain the post-tetanic potentiation of generator potential is to suppose that the resting membrane potential of the ending increases as a consequence of repetitive activity. There are several reasons for this:

1. The amplitude of the normal generator potential in response to a con-

stant mechanical stimulus increases when the ending is hyperpolarized by an inward flowing current (Ishiko and Loewenstein, 1959).

2. Post-tetanic potentiation of generator potential is found in corpuscles which present after-positivity as the result of repetitive activity of the ending. The after-positivity consists of a D.C. potential difference between ending (positive) and inactive axon (negative). The post-tetanic potentiation of generator potential decays with the same time course as the after-positivity (Fig. 15).
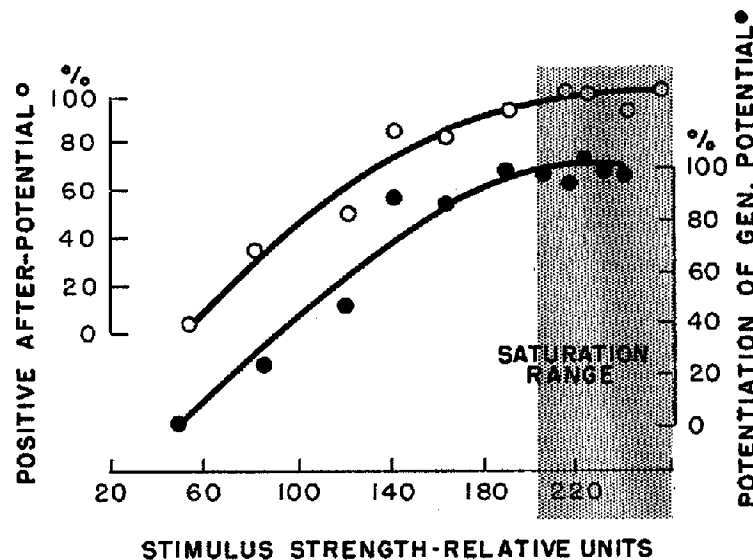

FIGURE 17.   Post-tetanic potentiation and after-positivity as a function of stimulus strength. Trains of constant duration (5 sec.) and stimulus frequency (300/sec.) are applied to the corpuscle. The strength of repetitive stimuli is varied over a wide range. The resulting potentiations of generator potential and positive D.C. after-potentials are measured. Generator potentials and after-potentials are lead off with the same electrode from the same axon parts in successive runs. (See third paper of this series for a definition of saturation range.)

3. Post-tetanic potentiation of generator potential and after-positivity increase parallelly with strength of repetitive stimuli (Fig. 17).

Post-Tetanic Increase in Firing Height

In a variety of excitable tissues the critical level of membrane potential at which firing of all-or-nothing potentials occurs is constant over a wide range of resting membrane potential. If this holds true for the first Ranvier node inside the corpuscle, a larger current will be required to reduce the membrane potential to the critical level when the initial membrane potential has been

increased. This means that in a hyperpolarized node the minimal generator current from the ending required for the triggering of all-or-nothing potentials at the node, namely the firing height, increases above normal. In fact, Ishiko and Loewenstein (unpublished data) have shown that the firing height for the first node increases as a function of the nodal resting membrane potential. A simple way to explain the post-tetanic increase in firing height described in the present paper is, therefore, to assume that the resting membrane potential of the node increases by repetitive all-or-nothing activity. The following observations support this view: (1) The post-tetanic increase in firing height is accompanied by and runs parallel with a post-tetanic increase in amplitude of nodal action potential. (2) The post-tetanic increase in
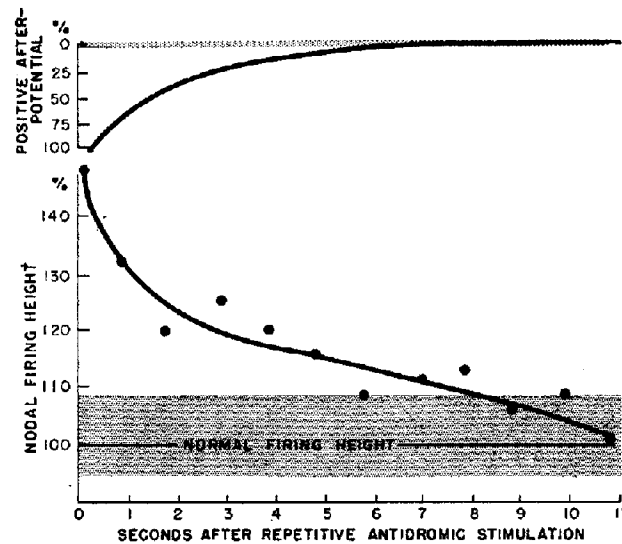

FIGURE 18.   Increase in firing height at the intracorpuscular Ranvier node and after-positivity. A train of antidromic impulses is fired into the corpuscle at a rate of 500 impulses/sec. and for a total duration of 10 sec. This causes an increase in firing height as tested with dromic (mechanical) stimuli, and an after-positivity of nodal origin. Nodal firing height and positive after-potential were recorded in successive runs with the same electrodes from the same sites of axon.

firing height has a time course similar to that of the after-positivity due to nodal activity. This is illustrated in the experiment of Fig. 18 in which repetitive impulses were fired antidromically into the corpuscle by excitation of its axon. Antidromic instead of dromic stimulation was used in order to eliminate the possibility of the ending contributing to the after-potential. As was shown before, antidromic impulses do not excite nor polarize the ending's membrane. (3) The post-tetanic increase in firing height and the magnitude of the post-tetanic after-positivity at the node are both equally related to train duration and stimulus frequency of repetitive (antidromic) stimulation.

It appears, therefore, *that post-tetanic potentiation of generator potential and post-tetanic increase in firing height are caused by post-tetanic hyperpolarization of respectively the non-myelinated ending and the first node of Ranvier inside the corpuscle.*

There is evidence for invertebrate axons (Shanes, 1949, 1951) and for mammalian C fibres (Ritchie and Straub, 1957) that repetitive all-or-nothing activity causes a temporary depletion of extracellular K^+ during the recovery phase and thereby produces an increase in the resting membrane potential. In order to account for the increase in resting membrane potential, it has been assumed that the extracellular K^+ cannot diffuse freely from the excitable membrane, but is restrained by a diffusion barrier between the excitable membrane and the external fluid (*cf*. Frankenhäuser and Hodgkin, 1956; Shanes, 1958). It may be speculated that a similar mechanism of extracellular K^+ depletion may be responsible for the post-tetanic hyperpolarization of the Ranvier node inside Pacinian corpuscles. Besides, such a mechanism would help to explain why an increase in firing height was found only when the ending was subjected to the influence of suprathreshold generator currents (Fig. 11). If the depletion of extracellular K^+ were due to exchanging K^+ for Na^+ from the axon as proposed by Ritchie and Straub (1957), an appreciable depletion of extracellular K^+ may be expected only after all-or-nothing firing at the node; *i.e.*, when an appreciable amount of Na^+ has accumulated inside the axon.

A considerable amount of evidence has been brought forward during the last twenty years to show that high frequency activity facilitates transmission across many kinds of synapses (see Hughes, 1958 for a review). There is evidence suggesting that potentiation of potentials at the presynaptic non-myelinated ending might be involved in the facilitation at certain synapses (Lloyd, 1949, 1952, 1958; del Castillo and Katz, 1954; Wall and Johnson, 1958). Lloyd (1949) long ago postulated that repetitive activity hyperpolarizes presynaptic nerve endings of certain spinal synapses, and thereby causes subsequent impulses to be augmented and their transmitter action to be enhanced. This postulate was based on the close correlation in time course between synaptic facilitation and increase in spike amplitude of the presynaptic nerve. However, actual recording of potential changes in presynaptic non-myelinated endings has not yet been possible. The present preparation offered the opportunity for recording post-tetanic effects directly from a non-myelinated ending. Although generalization in properties from a sensory to a presynaptic ending must, obviously, be taken with caution, it seems of interest that post-tetanic potentiation does occur at a non-myelinated nerve ending.

Post-Tetanic Facilitation of Threshold

The non-myelinated ending and the first Ranvier node inside the corpuscle are separated by a cylinder of myelin of about 250 μ length. Ending and node are both enclosed in lamellar layers which are particularly tightly packed

around the non-myelinated ending (Pease and Quilliam, 1957). A current which flows between ending and node, regardless of the direction, has an internal path of about 22 M Ω resistance through the axoplasm; externally it must span the 250 μ stretch of myelin cylinder, and is probably channeled through the lamellar spaces which represent a resistance of about 60 K Ω (Ishiko and Loewenstein, unpublished data). The resistance is such that one may expect only relatively weak currents to flow between ending and node when the resting membrane potential of the former has been slightly changed. The membrane potential of the node may therefore remain constant in spite of variations in the ending's resting membrane potential. Evidence has been given in the present work that the nodal membrane potential is not appreciably altered when the ending has been hyperpolarized by repetitive stimulation. Potentiation of generator potential due to hyperpolarization can thus occur without change in firing height. A lowering in threshold for the production of all-or-nothing potentials in response to mechanical stimuli is thereby produced. This constitutes the basis of post-tetanic facilitation of threshold described in the preceding paper.

A different situation arises when hyperpolarization is produced simultaneously at the ending and at the node. Then, potentiation of generator potential will occur together with an increase in firing height. If the membrane potential were to increment equally at both sites, the generator potential, notwithstanding its increase by polarization, may then fail to attain the parallelly increasing firing height. This is the situation which arises with repetitive mechanical stimulation of threshold or suprathreshold strength: the ending as well as the node becomes then hyperpolarized. Whether a facilitation of threshold occurs or not will depend on the relative change in polarization at the membranes of node and ending. This explains why potentiation of generator potential was more frequently observed than actual facilitation of threshold. The situation may be compared with that existing at the postsynaptic site of the neuromuscular junction. A more direct coupling appears there to exist between the membranes of the non-regenerative (end-plate) and regenerative (muscle fibre) elements. An increase in membrane potential of the end-plate appears always to bring on a parallel increase in membrane potential of the muscle fibre. Thus an end-plate potential of just subthreshold magnitude may be considerably increased by end-plate hyperpolarization; but it nevertheless fails to reach the critical firing level of the parallelly hyperpolarized muscle fibre (Fatt and Katz, 1951).

A period of supernormal excitability has recently been shown in the Pacinian corpuscle following the discharge of a single impulse (Loewenstein, 1958 b). The facilitation of threshold is brief: it lasts for 1 to 3 msec. and occurs at the first node of Ranvier in the wake of the relative refractory period left by the impulse. This type of facilitation is found only after the firing of an all-or-nothing potential, but not after a generator potential. The site at which

this facilitation is produced (the node) and the underlying mechanisms are quite different from those of the post-tetanic facilitation described in the present series of papers. The post-tetanic facilitation cannot be therefore a cumulative effect of the supernormality, nor is it likely to be related to the latter in any other way.

Post-Tetanic Depression

One of the properties of post-tetanic depression of generator potential is the complete reversibility of the effect. Another property is the low energy requirement of the effect. Depression of generator potential can in some corpuscles, be produced with repetitive stimuli of lower than threshold strength for normal impulse firing. In terms of distortion of the corpuscle, this means a displacement of the capsule of less than 0.6 μ, *i.e.*, of less than 0.16 per cent of its transverse diameter. This amounts to less than 0.3 per cent of the diameter compression which occurs in Pacinian corpuscles of the skin of the foot under normal physiological conditions in the organism. These properties satisfy amply the criteria generally used for excluding "injury" effects.

The amplitude of a generator potential in response to a constant mechanical stimulus increases as a function of the initial resting membrane potential of the ending (Ishiko and Loewenstein, 1959). As a first possibility, this suggests that the post-tetanic depression of generator potential described in the present paper may be due to a reduction in the ending's resting potential after repetitive activity. However, this possibility must be rejected in the light of the following evidence:

1. During post-tetanic depression, the amplitude of the generator potential in response to a given stimulus strength can be reduced by as much as 90 to 100 per cent of its normal value; the decrease in generator potential lasting several seconds after the end of repetitive stimulation. Thus, if the depression were due to a proportional reduction in membrane potential, a fairly large after-negativity should be detectable during the period of depression of generator potential. However, the opposite is observed: post-tetanic depression of generator potential is found in the absence of after-negativity and sometimes even in the presence of after-positivity. As in many other nerves (Gasser and Grundfest, 1936; Grundfest and Gasser, 1938; Lorente de Nó, 1947; Lloyd, 1949; Shanes, 1949; Frankenhäuser and Hodgkin, 1956; Brown and Holmes, 1956), a post-tetanic after-negativity is often seen to build up at the nerve ending of the Pacinian corpuscle, while a train of repetitive stimuli is applied to it; but negativity is superseded by positivity within a fraction of a second at the end of the train. Fig. 19 shows the time correspondence between a typical depression of generator potential and post-tetanic after-potentials. It will be seen that the depression is at its peak and may develop in the presence of a large after-positivity. This rules out the possibility that the depression of

generator potential is determined by or related to the resting membrane potential of the ending. It, furthermore, reveals that when hyperpolarization happens to be present together with depression, as in the present example, the actual depression of generator potential may be more severe than that which is apparent from the amplitude of the test generator potential.

2. When the ending has been hyperpolarized by an inward flowing current, the ratio between normal and depressed generator potential is approximately equal to that at normal resting potential.
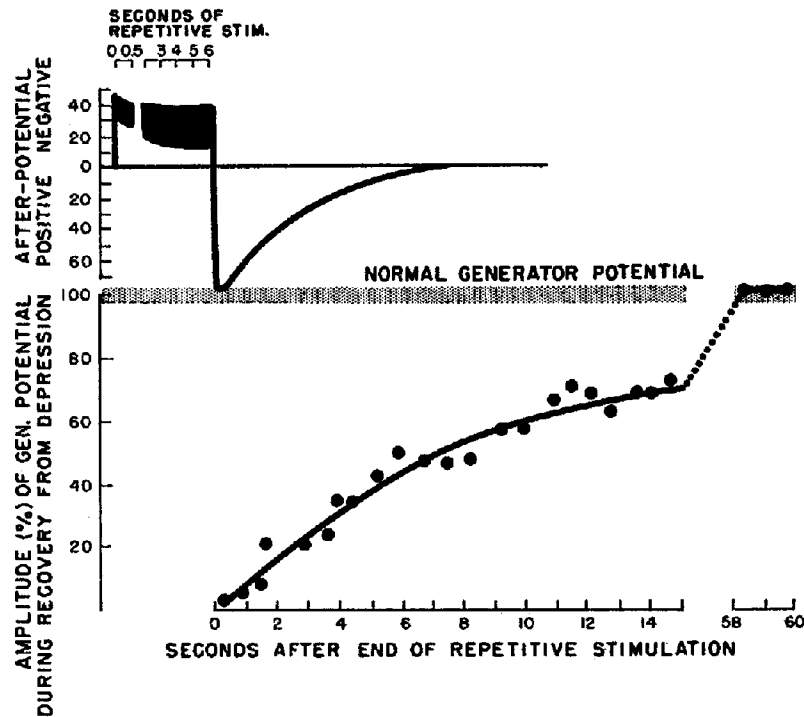

FIGURE 19.   Post-tetanic depression of generator potential unrelated to after-potential. The corpuscle has been stimulated with a train of mechanical stimuli at 500/sec. for 30 sec. The resulting depression of generator potential and negative and positive D.C. after-potentials (arbitrary units) were recorded on two successive runs with the same electrodes and electrode placement.

We may conclude therefore that *post-tetanic depression of generator potential is a transient decrease in responsiveness of the receptor membrane which develops independently of the electrochemical gradients which determine the resting potential across the receptor membrane. Post-tetanic depression, in contrast to potentiation of generator potential, is not caused by changes in the resting membrane potential of the ending.* The depression in generator potential appears therefore to reflect an inactivation process of the receptor membrane.

The question of the nature of the inactivation process is, however, still

open. It seems likely that the mechanical stimulus triggers transfer of charges across the receptor membrane of the ending, and that the generator potential is the overt effect of this transfer. The question of the nature of the depression of generator potential may thus be centered about the following possibilities: (1) is the decrease in responsiveness of the receptor membrane due to a transient inactivation of charge transfer; or (2) is it due to the switching on of a parallel charge transfer mechanism which causes a reduction in total net charge transfer per stimulus; or (3) is it due to a depletion of some material necessary for charge transfer? Depression of generator potential by depletion may, for instance, be caused by a depletion of available charges for transfer. Diamond, Gray, and Inman (1958) have concluded from recent experiments that a large part of the charge transfer may be carried by Na ions moving inward across the ending's membrane. It may be speculated, for example, that if the inward flux of Na ions, as triggered by each mechanical stimulus, were to proceed at a greater rate than the restoring outward flux of these ions, depletion of available charges might eventually occur by repetitive stimulation. If the mechanism were so simple, the resulting accumulation of transferred Na ions on the inner side of the membrane should cause a reduction in resting membrane potential, and should be detectable as a slow cumulative potential of the same polarity as that of the generator potential. However, as stated already, depression is not accompanied by after-negativity. Thus, if depletion of charges were at all responsible for depression of generator potential, there must be in addition an exchange mechanism by which accumulated cations inside the ending might be exchanged temporarily for others which move outside. We have no way, at present, to test this possibility. An alternative depletion mechanism is the depletion of an accessory chemical process intermediate between stimuli and generator potential.

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