GENERATOR PROCESSES OF REPETITIVE ACTIVITY IN A PACINIAN CORPUSCLE

By WERNER R. LOEWENSTEIN*

(From the Institute of Physiology, University of Chile, Santiago)

ABSTRACT

Response patterns resulting from repetitive mechanical stimulation of the corpuscle depend on (1) the time course of recovery of the generator potential, on (2) the recovery of critical firing height, and on (3) the stimulus strength/generator potential function. By either augmenting stimulus frequency at constant strength, or by reducing strength at constant frequency, a sequence of propagated potentials is turned into a pattern of alternating regenerative and generator responses. In such a pattern an extra impulse can be set up whenever an extra stimulus produces a generator potential of enough amplitude to reach the firing height of the corresponding period. The new requirements of firing height introduced by the refractory trail of the extra impulse determine resetting of periodicity and appearance of a "compensatory pause." The decay time of the single generator potential is independent of stimulus duration. This is interpreted as a factor determining receptor adaptation. Upon repetitive stimulation at intervals above $\frac{1}{2}$ decay time of the single generator potential, a compound generator potential is built up which shows no spontaneous decline. However, in spite of being considerably greater than the firing height for single impulses, the constant level of depolarization of the compound generator potential is unable to produce propagated potentials. A hypothesis is brought forward which considers the generator potential to arise from membrane units with fluctuating excitability scattered over the non-myelinated nerve ending.

INTRODUCTION

In the preceding study factors were analysed which govern refractoriness of generator and propagated events in Pacinian corpuscles. Correlations between stimulus interval, magnitude and minimal height of generator potential for firing of impulses were found which determine the threshold requirements for propagated firing at any instant. The present experiments were done to test the validity of aforementioned relations in the rhythmically active corpuscle.

The experimental set-up has been described in the preceding paper.

RESULTS

Repetitive Activity by Mechanical Stimulation

Response Patterns.—By suitable selection of stimulus strength and frequency, a train of equal mechanical stimuli may produce a response pattern in which

* Present address: Department of Physiology, Columbia University, College of Physicians and Surgeons, New York.
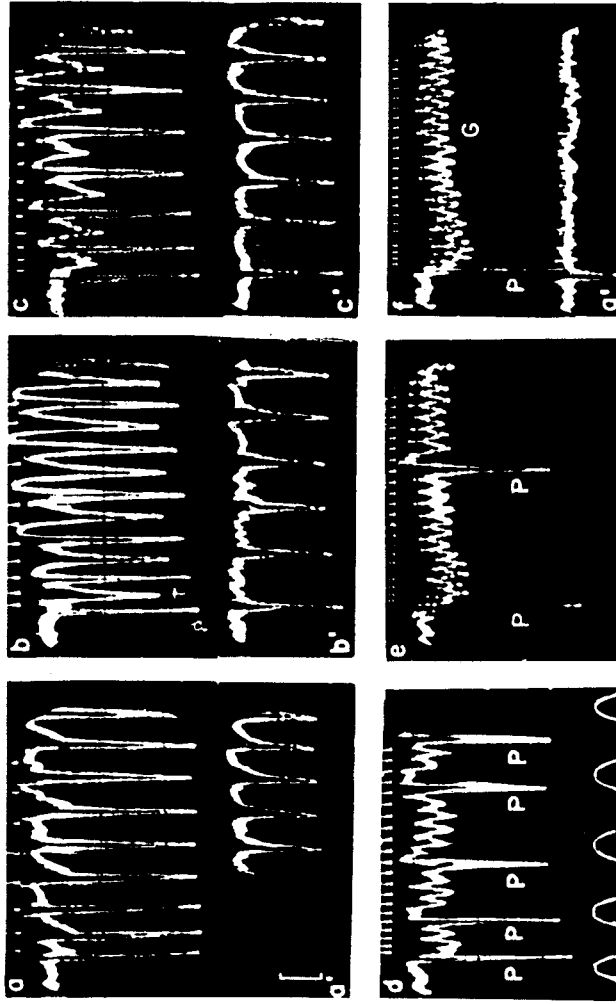
FIG. 1. Differences in refractoriness of generator and propagated events revealed by repetitive stimulation. Mechanical stimulation at constant strength. Stimulus frequencies (see vertical bars on top of each frame): a, 250; b, 280; c, 370; d, 600; e, 625; f, 650/sec. a, b, c, d, e, f, recording leads at axon's emergence from corpuscle for recording of local events. a', b', c', f', same stimulus frequencies and strengths as respectively a, b, c, f, but with recording leads placed at some distance from corpuscle for the exclusive recording of propagated responses. P, propagated potentials. T, local all-or-none responses blocked before emerging from corpuscle. G, generator potentials. Downward deflections mean "corpuscle negative." Calibration: 100 cycles/sec.; 50 μV.

each stimulus sets up a propagated potential (Fig. 1 *a*). If the frequency is now increased, while the stimulation continues at same strength as before, failure of propagated responses may occur (*b*). The former 1:1 relationship between propagated potentials and stimuli, as recorded with leads placed on the axon
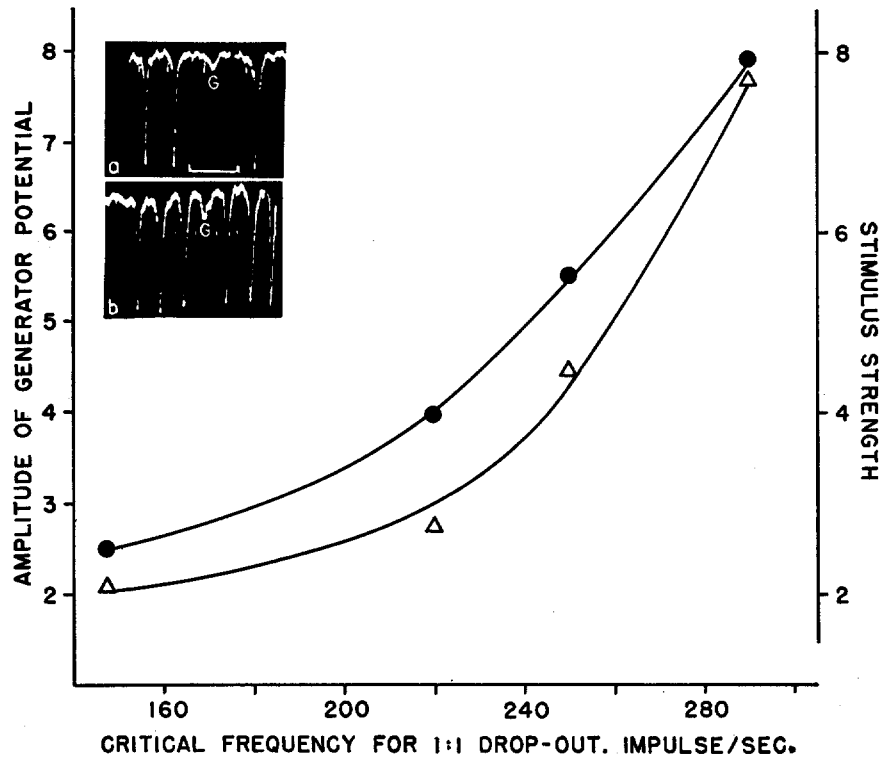

FIG. 2. Relation between magnitude of generator potential and critical stimulus frequency at which failure of propagated responses occurs. The corpuscle is stimulated with trains of equal mechanical stimuli. Each train has a total duration of 35 msec. Stimulus strength is adjusted so as to cause failure of one propagated response at each given frequency. The values of the generator potential (*G*) of the failing propagated response (left ordinates, circles) and of the stimulus strength (right ordinates, triangles) are plotted against the corresponding frequencies. Time of inset: 10 msec.

at some distance from the corpuscle, is turned into a 1:2 relation. With leads arranged for the recording of the corpuscle's local activity, patterns of alternating propagated and local potentials are detected. The latter are, at first, mainly all-or-none potentials blocked within the corpuscles. They correspond to the *abortive T spikes* described in the foregoing paper. With a further progressive increase in frequency, the *T* potentials are reduced and finally abolished. At that stage, another type of sequences, namely of alternating propagated (*P*)

and generator potentials (G) may be observed (Fig. 1, d to e). With a further rise in stimulus frequency, the propagated response/stimuli-ratio may shrink to 1:3, 1:4, ..., and finally only one single spike response is left (d to f).

Besides the two aforementioned patterns, a third type of alternation is observed in a number of corpuscles. An example is illustrated in Fig. 4 a. Here only the first out of a series of successive stimuli produces a propagated response (P). Thereupon follows a sequence of generator (G) and non-propagated all-or-nothing events.

The simplest situation for analysis was the type of sequence in which propagated potentials recurred with generator potentials. This could usually be obtained by appropriate setting of stimulus parameters. Occasionally, corpuscles were found which under no circumstances gave aborted T responses. The only kind of pattern then seen was that of alternating propagated and generator potentials (Fig. 3 a).

Firing Height/Frequency Relation.—Production of a 1:1 relation between propagated responses and stimuli requires a direct relationship between stimulus frequency and stimulus strength. In the experiment of Fig. 2, the period between mechanical stimuli was varied between values ranging from 1 to approximately ½ relative refractory period. The minimal stimulus strength which just critically satisfied requirements for a 1:1 ratio was measured and plotted against the corresponding period.

A similar direct relationship exists between stimulus frequency and amplitude of the generator potential. Strength was adjusted so as to be critically at threshold for each given frequency. In a number of response patterns, a propagated potential would drop out (Fig. 2, inset). The amplitude of the corresponding generator potential was used as index of the "firing height" (see preceding paper for a definition), and plotted against the corresponding stimulus frequency (Fig. 2). As was expected, the curves describing the frequency/strength —and frequency/firing height functions are roughly parallel.

Extra Impulses during Repetitive Activity.—If an extra impulse is intercalated between a regular sequence of alternating all-or-none and generator events, a shift in response pattern may be observed. In the example of Fig. 3, an extra stimulus is interpolated in the regular order of stimuli shortly after the second stimulus belonging to a series of equal periodic stimuli. The extra stimulus is of sufficient strength and close enough to the preceding stimulus to cause summation of the corresponding generator responses. The threshold condition at that moment may thus be satisfied and a propagated extra potential (P_e) be produced instead of solely a generator potential of the regular pattern. The extra impulse causes then a phase shift of half a cycle in the sequence. Records of propagated potentials led off the axon at some distant region from the corpuscle, show then a "compensatory pause" as an afterpart of the extra impulse (Fig. 3 b').

In the hope of obtaining more information on the nature of the abortive T spike, patterns of alternating all-or-none (T) and generator events were disrupted at various delays. In the experiment illustrated in Fig. 4 b, the extra stimulus is placed so as to sum up with the second stimulus of the regular sequence. It has now become strong enough to fire a T event, instead of merely
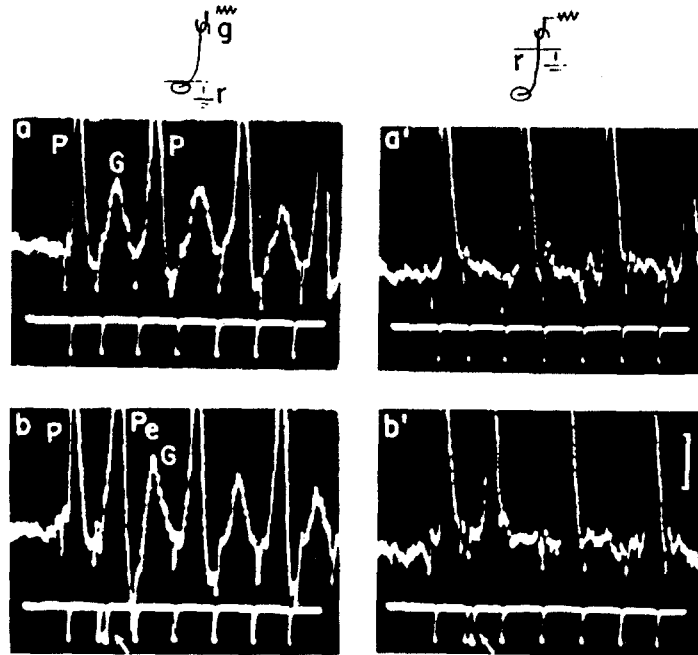

FIG. 3. Phase shift due to an extra stimulus in the sequence of propagated (P) and generator (G) potentials produced by repetitive stimulation. a, a', the crystal delivers stimuli to the corpuscle at a regular rate of 250/sec. Lower beam signals the electric pulses applied to the crystal. b, b', at arrow mark an extra stimulus is added to the regular sequence of stimulation. a and b, recording earth electrode placed at the emergence of axon for recording of local potentials. a' and b', the same at some distance from corpuscle. Note the "compensatory pause" in b' following the extra impulse (P_e). In this and the following figures "corpuscle negativity" is shown upward.

a generator potential. The next generator potential in response to the third regular stimulus becomes greatly reduced and the following response is converted into a fully propagated potential (P). The original pattern is thereafter recovered. When the extra stimulus falls somewhat more delayed than before, but still close enough to the second regular stimulus to allow for summation of generator potentials, the corresponding generator response is therewith augmented. This causes the third response to be converted into a generator potential. The original periodicity is thereupon resumed with a $\frac{1}{2}$ cycle phase shift
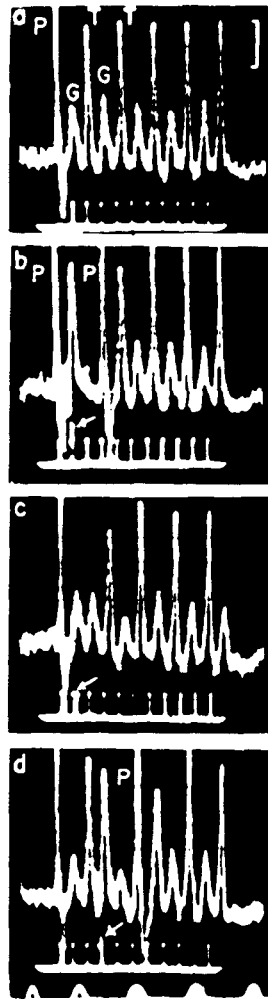
Fig. 4. Changes in pattern of alternating all-or-none and generator events caused by an extra stimulus. The corpuscle is stimulated mechanically at a regular frequency of 370/sec. (Lower beam signals stimuli). This causes a pattern (a) in which one propagated impulse (biphasic potential P) is followed by an alternating sequence of generator (G) and abortive T potentials. The latter are non-propagated all-or-none potentials blocked within the corpuscle. In b, c, d an extra stimulus is interposed at arrow mark at various instants within the stimulus sequence. Note the phase shift in c of the sequence of the original pattern and the appearance in b and d of a propagated impulse (P) when the preceding generator potential is made low by the extra response. Calibration: 100 cycles/sec.; 50 μV.

(Fig. 4 c). In Fig. 4 d, a similar situation as in b is produced. Only that in d the effective size of the extra stimulus is slightly smaller. The subsequent generator potential is expectedly reduced and the event thereafter is transformed into a fully propagated potential (P). It seems noteworthy that whenever a generator potential belonging to a series of alternating T and G events is made to decrease sufficiently, the succeeding T event is turned into a propagated impulse.
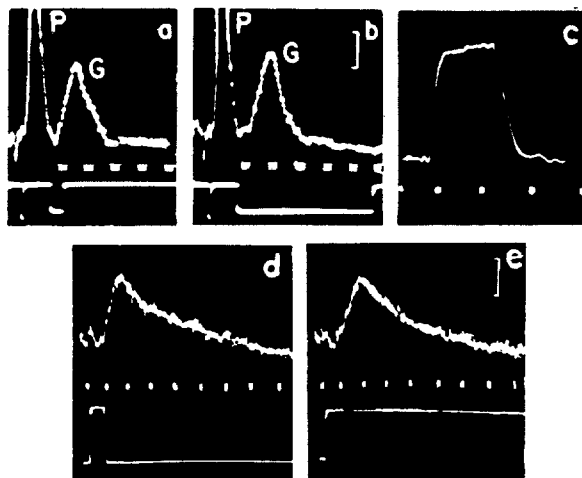

FIG. 5. Adaptation of the receptor as revealed by unrelatedness between stimulus duration and duration of generator potential: a, b, two successive mechanical stimuli are applied at 1 msec. interval producing respectively a propagated potential (P) and a generator potential (G). Downward deflections of lower beam (slightly dephased with respect to upper) signal the electric pulses applied to the crystal. Duration of mechanical stimuli determined photoelectrically a, 1.5 msec.; b, 10 msec.; c, photoelectric record showing a typical time course of a deflection of stimulating stylus of 1.8 msec. duration; d, e, another corpuscle, anesthetized with procaine; generator potential in response to mechanical stimuli of d, 1 msec.; e, 1 sec. duration. Upward deflections of lower beam (retouched) signal electric pulses applied to the crystal. Vertical calibration of a, b, d, e, 25 μV. Time: a, b, 2 msec.; c, d, e, 1 msec.

Adaptation of the Generator Process.—The generator potential set up in response to a single mechanical stimulus decays to zero in 4 to 8 msec. This agrees with Gray and Sato's (1953) values obtained in anesthetized corpuscles. Time courses of generator potentials were studied at varying duration of mechanical stimuli ranging from 1 msec. to 1 sec., while the stimulus strength was held constant. For example, the duration of the generator potential (G) of Fig. 5 remained the same whether produced by a mechanical stimulus of 1.5 msec. (a) or of 10 msec. duration (b). G could not be prolonged however long the stimulus was made. The generator response of the foregoing example was

obtained during refractoriness of the propagated event. Essentially the same results were obtained with generator potentials of corpuscles in which propagated potentials were abolished by bathing the preparation in Krebs' solution
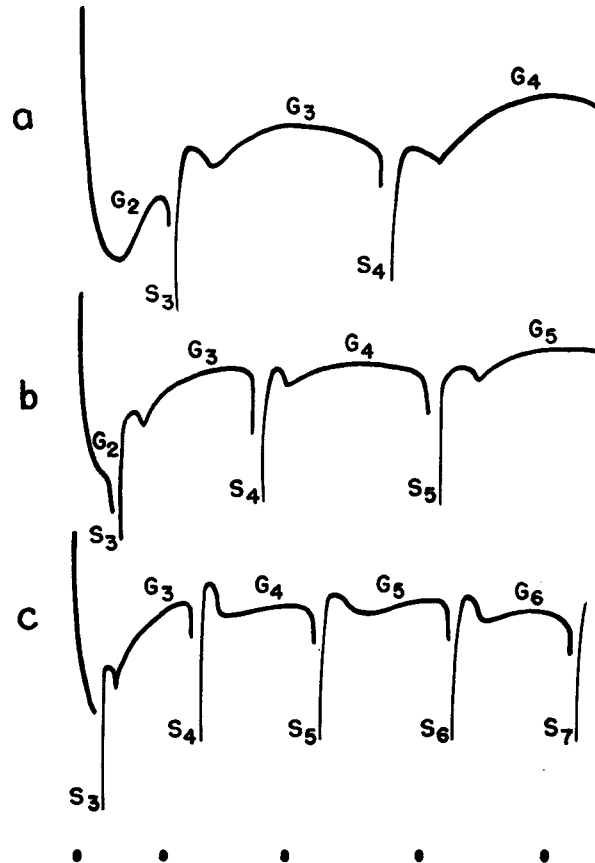

Fig. 6. Building up of successive generator potentials at high frequency stimulation. Tracings of generator potentials (G) produced by frequencies of a, 560; b, 770; c, 1000 mechanical stimuli/sec. Initial vertical deflection of each record corresponds to the end of propagated potential which is the first response. S, stimulus artefacts. The numbers give the chronological order of stimuli and corresponding responses. Relative height of depolarization level cannot be estimated from these records due to stimulus artefacts. Time: 1 msec. between dots.

containing 0.2 per cent of procaine (Fig. 5 d, e). At any given stimulus strength, the decay time of the generator potential, whether obtained by subthreshold stimulation, during refractoriness of the propagated potential, or after abolishing the latter by procaine, was found to be constant for a given receptor. It

cannot be said whether this also holds true for stimulus durations of less than 1 msec. Because of physical properties of the damped stimulator system, durations of mechanical stimuli could not be diminished below 1 msec. without reducing their strength at the same time.

However the "spontaneous" decay of the generator potential is not due to incapacity of the receptor for maintaining a generator potential. The receptor can sustain well a composite generator potential provided it is restimulated at high enough frequency. Beyond a certain frequency of repetitive stimulation, only the first out of a series of stimuli sets up a propagated response. Each successive stimulus occurring before the preceding generator potential has sufficiently declined, is seen to produce a new generator response; the potential thus composed settles finally at an average value of depolarization (Fig. 6). At first, with periods of say, $\frac{1}{2}$ decay time of the corresponding single generator potential, the outlines of the individual generator potentials may still be partially recognized in the compound generator potential. But as the stimulus frequency is increased, the composite potential becomes rather smooth, and besides, the final level of depolarization is reached earlier. With repetitive mechanical stimulation a generator potential can thus be built up which shows no appreciable decline over 50 msec. of observation (Fig. 7). The decrement of potential in these illustrations is apparent. The dotted line in each record represents the real time course of generator potentials after correcting for the time constant of the condenser coupled amplifier.)

An analogous non-adaptive behaviour of the composite generator potential could be shown in corpuscles in which all-or-nothing activity was blocked by procaine (Fig. 8).

The amplitude of the composite generator potential can be graded with stimulus intensity (Figs. 7 and 9). Within certain limits of strength, the final level of depolarization obtained with repetitive stimulation at constant frequency is roughly a linear function of stimulus strength. In experiments in which the stimulus could be made strong enough, a maximal strength was found above which the final level of depolarization started to decline (Fig. 9).

Spontaneous Repetitive Activity

In general, Pacinian corpuscles do not show "spontaneous" activity. However, occasionally "spontaneously" discharging corpuscles were found. It seemed reasonable that repetitive activity of "spontaneous" origin and that produced by mechanical stimulation of the corpuscle are ruled by the same principles of refractoriness. The latter has, however, the advantage that variables are more easily controlled. In the hope of extending the analysis discussed in the next section to the "spontaneously" active corpuscle, the following experiment was done.

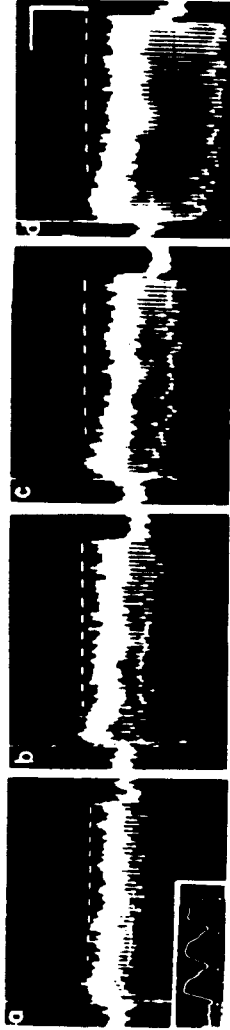Propagated impulses from a spontaneously discharging corpuscle were re-

FIG. 7. Non-adaptive behaviour of the generator potential built up by high frequency stimulation at various degrees of strength. The corpuscle is stimulated mechanically at constant frequency of 900/sec. Stimulus strength in relative units: a, 6; b, 8; c, 10; d, 15. The decay in generator potential is apparent; the dotted lines on each record represent the real time course of the generator potential after correction is made for the time constant of the condenser coupled amplifiers. Calibration of abscissa, 10 msec.; ordinates, 50 μV. Inset, photoelectric record of deflections of the crystal's stylus applied to the corpuscle. Time between dots, 1.1 msec.
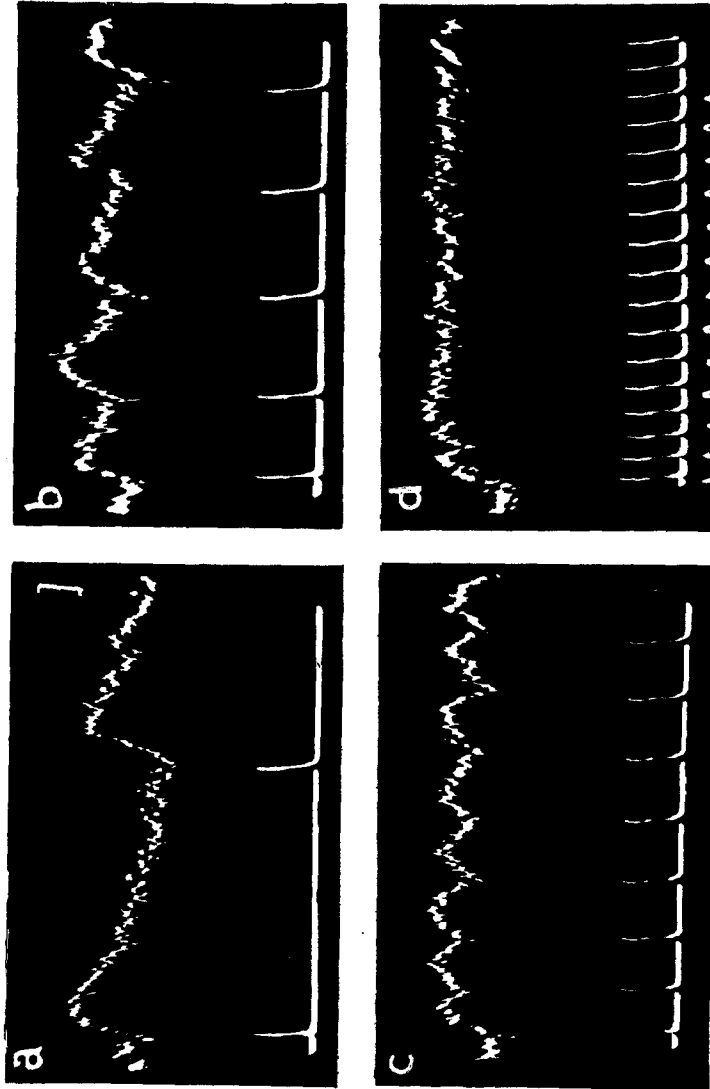
FIG. 8. Generator potentials at various stimulus frequencies. The corpuscle has been anesthetized with procaine for blocking of all-or-none activity. Stimulation with constant mechanical stimuli at stepwise increasing frequencies from *a* to *d*. Lower beam signals stimuli. Note that the built-up potential of *d* shows no appreciable decay. Time, 1 msec.; 25 μV.

corded over a given period on successive oscilloscope sweeps, and their tracings superimposed in Fig. 10 *a*. The impulses occurred at random at intervals shorter than one relative refractory period of the receptor. The corpuscle was then stimulated with a mechanical stimulus of suprathreshold strength, which at the same time triggered each sweep. Again, the tracings of the resulting frames, collected over a similar period of observation as before, were superimposed.
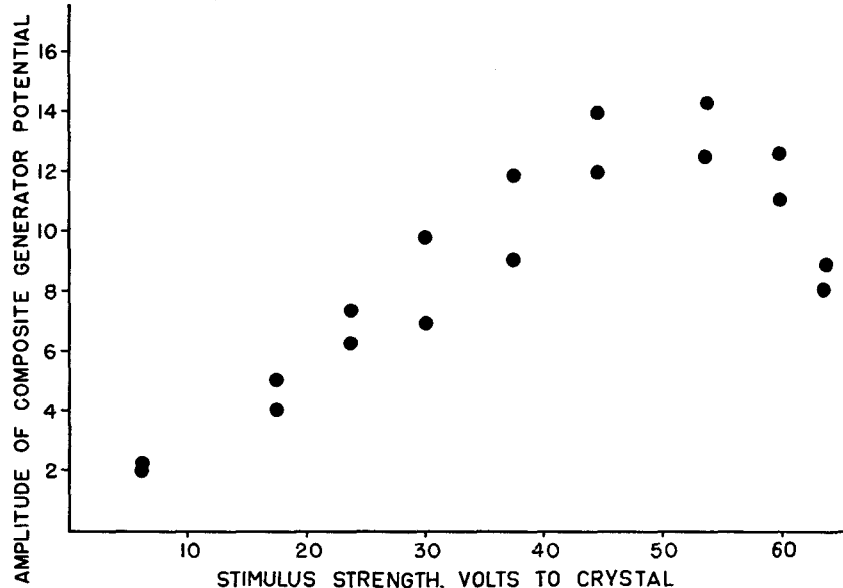

Fig. 9. Amplitude of composite generator potential as a function of stimulus strength. Final level of depolarization built up by stimulating a non-anesthetized corpuscle with mechanical stimuli at a constant frequency of 900/sec., is plotted against stimulus strength.

Fig. 10 *b* shows that all spontaneous spikes (*S*) are cleared away for a certain time after the mechanically evoked response (*M*). The relative refractory period of the corpuscle was previously measured with mechanical stimulation. It was found that the period of silence in spontaneous firing subsequent to *M* was equal to one relative refractory period.

Some of the *S* potentials discharged at random may have occurred just before an *M* potential. Some of the mechanical stimuli which produced the *M* response might therefore have fallen eventually within the absolute refractory trail of an *S* potential. To reduce the probability for this happening, another potential (not shown in Fig. 10) was set up by suprathreshold mechanical stimulation ½ relative refractory period before the *M* potential, which explains the absence of *S* potentials at the beginning of the trace.

ANALYSIS

It has been described in the preceding paper that when two mechanical stimuli are successively given at an interval below 7 msec., the second stimulus
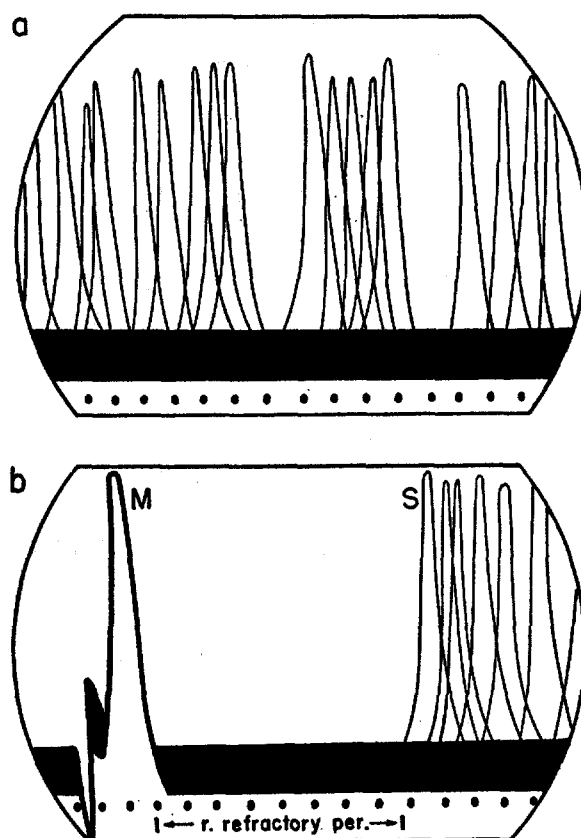

FIG. 10. Clearing away of spontaneous propagated activity by a mechanically driven impulse. The corpuscle presents spontaneous propagated discharges. *a*, tracing of 31 superimposed successive frames showing spontaneous impulses discharged at random by the undisturbed corpuscle. *b*, result of 34 superimposed successive frames, the corpuscle now being mechanically stimulated. Note disappearance of spontaneous activity (S) throughout the relative refractory period left behind by the mechanically driven impulses (M). Time: 10 msec. between dots.

finds the receptor in a refractory state so that (1) the magnitude of the second generator response becomes smaller than the first, and (2) the generator's firing height is increased. The time course of recovery of the generator event (N) and that of the firing height (L) have been schematically represented in
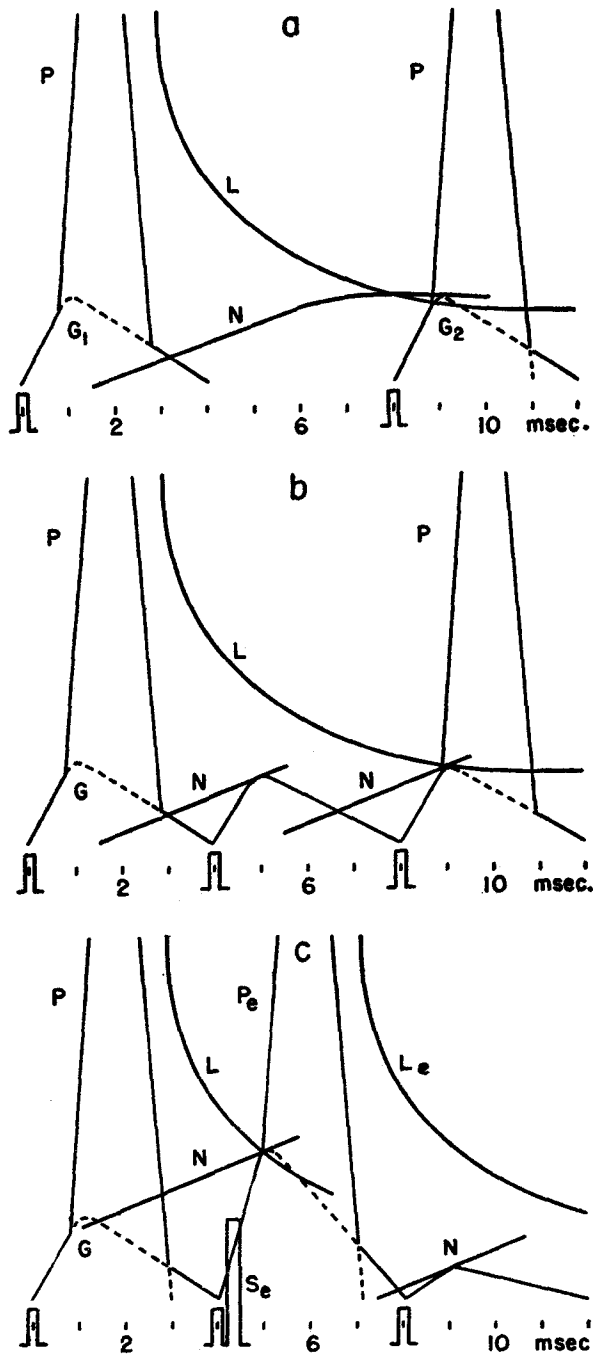
Fig. 11. Analysis of effect of frequency (*a*, *b*) and of an extra impulse (*c*, P_e). *L*, recovery of firing height. *N*, recovery of responsiveness of generator event; size factor of refractoriness has been represented by height of *N* at the instant, arbitrarily chosen, at which the preceding generator potential reaches peak value. Open rectangles denote stimuli. See text for description.

Fig. 11. The curves have been drawn with data from typical experiments of the preceding paper. In general, propagated impulses (P) will be discharged whenever the generator potential (G) reaches the firing height (L) of the corresponding period. A generator potential produced in response to a stimulus of just threshold strength reaches the firing level only after at least one relative refractory period. With a period of less than 1 relative refractory period, as given in the example of Fig. 11 b, the corpuscle fires a propagated impulse with every second threshold stimulus. Patterns of alternating propagated and generator potentials are expectedly produced by repetitive stimulation. By increasing the stimulus strength, G_2 may satisfy the firing level at an earlier moment of its recovery course, and eventually a one-to-one relationship between stimuli and propagated responses ensues (Fig. 12 b).

L represents the recovery of the minimal firing height of generator potential on top of an unknown base of membrane potential. If the propagated potential has a negative tail, as is suggested by the existence of a supernormal phase (Loewenstein, 1958), the corresponding recovery curve of the critical firing level of membrane potential would be expected to develop somewhat more steeply than that of L.

The amplitude of a generator potential falling on the refractory trail of a preceding generator potential, is inversely related to the latter's amplitude. This would seem therefore to determine a periodical alternation in size of generator potential. With the parameters of Figs. 11 b and 12, the recurrent changes in size may actually be expected to be very small. They have been somewhat exaggerated in the drawing for the purpose of a better schematic representation of the size factor of the refractoriness of the generator process. At periods below one-half decay time of the generator potential, a composite generator potential can be built up which holds itself at a certain level. The size factor appears then to be mainly represented by this constant level and alternations in size are no longer seen (c.f. Fig. 8).

If the stimulus strength is constant, and the period is reduced, a 1:1 ratio between propagated responses and stimuli may turn into a 1:2, 1:3, ···1: ∞ relationship (Fig. 1). At first, with a slight reduction below the critical period for a 1:1 ratio, while the conditions for full propagation are no longer fulfilled, G may still be high enough to attain firing level of the first node of Ranvier (see next section for a discussion on the origin of the T spike). But as each successive generator potential falls on the refractory trail of the preceding one, the action current of the first node may be insufficient to satisfy firing requirements of the still refractory second node, and impulses may thus become blocked. Whether the resulting response pattern is of the type of alternating propagated and T events (Fig. 1 b) or of alternating T and G events (Fig. 4 a) would depend on the magnitude of action current of the first node and, hence, indirectly on the size of generator potential (see next section), and on the period of the stimulating sequence.

A less complicated situation turns up when the period is made short enough to eliminate T activity, or when this is naturally absent. A pattern of propagated potentials in response to every stimulus may be converted into a sequence of propagated and generator potentials, by reducing the stimulus frequency so
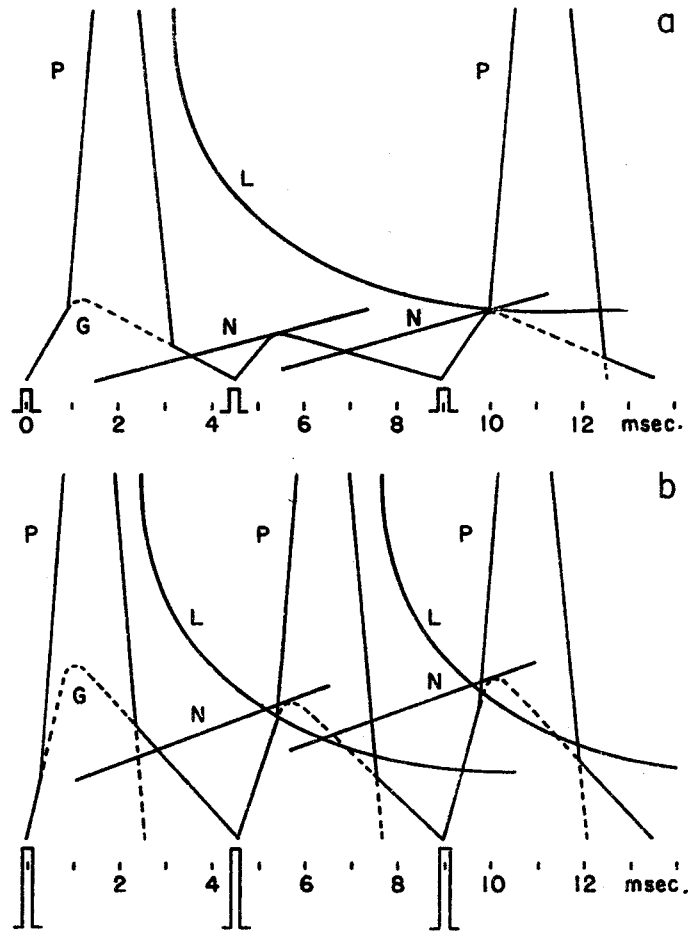

FIG. 12. Representation of effect of stimulus strength. Denotation as in Fig. 11.

that only each second, third, etc., generator event reaches the level for propagated firing (Figs. 1 and 11). The direct relation found between critical frequency and stimulus strength, or critical frequency and firing height fits in well with the present interpretation.

In a regular sequence of recurrent propagated and generator potentials, an extra impulse can be set up whenever an extra stimulus (S_e) produces a generator potential of enough amplitude to reach the firing level at the corresponding

period. The new requirements for propagated firing (L_e) introduced by the refractory trail of the extra impulse (P_e), determine resetting of periodicity and appearance of a "compensatory pause" (Figs. 11 c and 3). The "compensatory pause" resembles that caused by an extra systole of the heart. It seems probable that generation of systolic and extra systolic potentials underly mechanisms similar to that of the corpuscle and that the present relations may be extended to other structures at which impulses are generated.

Repetitive activity of spontaneous origin may be treated similarly. The demonstration of a minimal interval between propagated potentials equivalent to 1 relative refractory period, of the example of Fig. 10, would seem to indicate that the non-aborting generator potentials just attained the firing height of the fully recovered receptor. Thus, without direct measurement, the amplitude of the spontaneous generator potential may be calculated from the silent period in spontaneous discharge subsequent to a mechanically driven response. By this method, and by direct measurement of the aborting generator potential in spontaneously active corpuscles, it was found that the frequency of spontaneous discharge is directly related to the amplitude of generator potential. In two corpuscles in which the function of generator potential/frequency of discharge was established for spontaneous activity, also the function generator potential/minimal frequency at which failure of propagated response occurs with mechanical stimulation was studied. They were found to be practically equal.

DISCUSSION

The rate with which a mechano-receptor adapts to a stimulus appears to be linked to the rate of decay of its generator potential (Loewenstein, 1956 a, b). A slowly adapting receptor maintains a generator potential when a mechanical stimulus is applied and continuously sustained. If by anesthetics or by other means the generator potential is prevented from reaching firing level, it attains then a certain degree of depolarization (static level) proportional to stimulus strength, and maintains this level fairly well over prolonged periods of observation. This is well illustrated by the muscle spindle (Katz, 1950) and the slow stretch receptor cell of Crustacea (Eyzaguirre and Kuffler, 1955).

On the other hand, in rapidly adapting receptors, the generator potential decays rapidly below threshold value, although the mechanical stimulus prevails. The fast stretch receptor nerve cell of Crustacea and the Pacinian corpuscle provide good examples. Two mechanisms may be evoked to explain the "spontaneous" decay in generator potential of fast adapting mechano-receptors: (1) The generator potential decays because the nerve ending is unable to sustain a continuous depolarization. This implies that the membranes of rapidly adapting sensory endings possess properties different from those of slowly adapting endings. However, in the present work, the Pacinian corpuscle was shown to be capable of sustaining well a generator potential over a prolonged period of

observation, provided it is restimulated at high enough frequency. (2) The fall in the single generator potential is determined by events prior to the generator potential. This again raises the question whether adaptation in mechano-receptors may have a mechanical basis. A mechanical component in adaptation has been postulated for the frog's tactile receptor (Loewenstein, 1956 *b*). This rapidly adapting receptor may be turned into a slowly adapting one by stretching its nerve terminal. In recent experiments, which will be described later, Pacinian corpuscles could be rendered slowly adaptive by similar means. It would seem, therefore, that adaptation in Pacinian corpuscles, *i.e.*, the decay of the single generator potential is, at least in part, determined by mechanical factors.

A direct relationship between the amount of depolarization of the static generator level and the frequency of discharged potentials has been shown for the muscle spindle of the frog (Katz, 1950) and for the slow stretch receptor of crustacean (Eyzaguirre and Kuffler, 1955). This is a widespread property among excitable tissues. It was therefore somewhat surprising that the constant level of depolarization which can be built up at the nerve ending of Pacinian corpuscles by repetitive stimulation was found unable to produce repetitive firing of propagated potentials, in spite of being considerably greater than the minimal firing height of the single generator potential. It was all the more unexpected in view of the fact that the Pacinian corpuscles, which gave "spontaneous" activity, were found able to discharge repetitively on top of a certain level of depolarization after the fashion of the aforementioned slowly adapting receptors. The situation recalls the behaviour of sympathetic nerve cells (Eccles, 1954) which are also unable to set up repetitive discharges with high frequency stimulation, although a high level of generator potential can be built up. The phenomena may be related to "Na inactivation" (Hodgkin and Huxley, 1952) occurring at the first node of Ranvier of the Pacinian corpuscle due to a constant current flowing outward across the node to the steadily depolarized non-myelinated nerve terminal.

Important evidence for locating the origin of electric activity at the unmyelinated portion of the nerve ending has already been given by Gray and Sato (1953) and Diamond, Gray, and Sato, (1956). Several observations, namely the fluctuations, gradation, maximal value, size factor (of refractoriness) of generator potential, and the building up of composite generator potentials, point toward the existence of functionally independent units at the nerve terminal. In line with what is known at another generator structure, *i.e.* the motor end-plate (Fatt and Katz, 1952; Castillo and Katz, 1956), it seems attractive to postulate a patch-like make-up of the nerve ending membrane which seems incapable of producing regenerative potentials. The diagram of Fig. 13 represents hypothetical generator patches (*G*) acting somewhere at the end of the chain which transduces mechanical into electrical events. Each patch constitutes a unit of generation of minimal current. Graduation of the generator
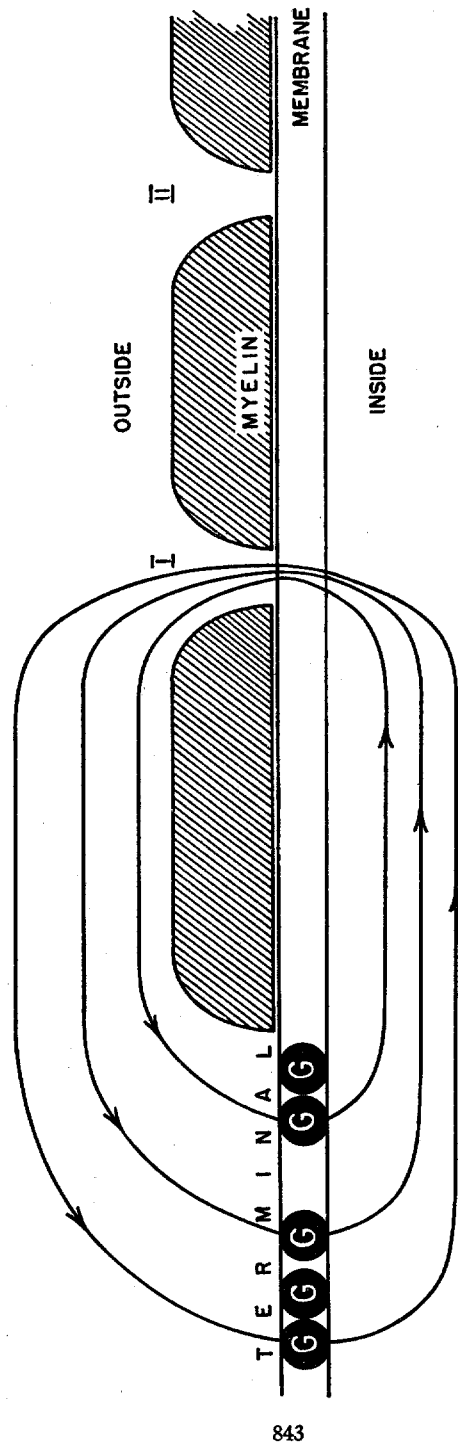
Fig. 13. Representation of current flow between "generator units" (G) of unmyelinated membrane portions of nerve ending and first node of Ranvier (I).

843

potential with increasing strength of mechanical stimuli may be accomplished by spatial summation of G patches. An upper limit in generator current should be expected when all available patches are activated. This may account for the ceiling in the single generator potential which is found starting from a certain maximal stimulus. It also explains the size factor of refractoriness of the generator potential, if the additional assumption of spontaneous fluctuations in excitability of individual G units is made. This seems reasonable, in view of the observed spontaneous fluctuations in threshold and in generator potential. They recall the fluctuations in end-plate potentials of skeletal musculature, which Fatt and Katz (1952) have shown to be caused by fluctuations of their miniature units, arising from active spots scattered all over the myoneural junction (Castillo and Katz, 1956). When a given stimulus activates a certain amount of available G units out of a number of fluctuating G units, the number of non-refractory G patches still available for a second stimulus, may be expected to be inversely related to the strength of the first stimulus (size factor of refractoriness). When a maximal mechanical stimulus activates all available G units, an analogous situation to absolute refractoriness of the all-or-none event of a node, namely a period of complete irresponsiveness of the generator potential may be expected, and is in fact found. The hypothesis also provides an explanation for summation of generator potentials with iterative stimulation of the corpuscle. Alternations of occupied and free membrane patches with a spontaneously fluctuating excitability, may enable the receptor to sustain a certain level of depolarization when repetitively stimulated. As a corollary, and determined by the size factor of refractoriness, there should be a decline in the composite generator potential, when the stimulus is increased beyond a certain maximal strength. A decline in depolarization was, in fact, found in preparations in which the strength of the iterative stimulation could be made high enough. In recent experiments further and more direct evidence has been given for the existence of generator units distributed all over the non-myelinated nerve ending of Pacinian corpuscles (Loewenstein and Rathkamp, 1958).

It seems likely that the regenerative potential arises at the first intracorpuscular node of Ranvier (Diamond, Gray, and Sato, 1956). The responsiveness of a node is known to decrease during refractoriness (Tasaki, 1953). Since the safety factor for propagation of impulses between nodes also diminishes during the refractory state (Tasaki, 1953), it is conceivable that an "all-or-nothing" current of the first node, diminished during the refractory period, may become insufficient for starting a potential at the second still refractory node. Hence, provided the current flowing between the active generator units of the terminal and the first node is strong enough, a potential may be set up at the first node, and then abort. This may account for the T spike. It seems of interest that during the refractory period, regenerative potentials showed a certain graded behaviour related not only to the interval between potentials, but also to the

size of the corresponding generator potential. Although the T potential behaved in all-or-none manner with regard to a certain range of mechanical stimuli, it could be graded in small all-or-nothing steps when the entire range of available generator potential was displayed. Moreover on raising sufficiently the stimulus strength, a previously abortive T spike, eventually became propagated. This may explain also why in a sequence of alternating T and generator events, such as shown in Fig. 4, an abortive T spike, became invariably propagated, whenever the corresponding generator potential was increased as result of a reduction of the preceding one. The fact that the refractory regenerative potential can be graded in steps suggests that it may be of composite nature and that the responsible membrane structure at the node may have a unit arrangement.

REFERENCES

Castillo, J. del, and Katz, B., 1956, Localization of active spots within the neuromuscular junction of the frog, *J. Physiol.*, **132**, 630.

Diamond, J., Gray, J. A. B., and Sato, M., 1956, The sites of initiation of impulses in Pacinian corpuscles, *J. Physiol.*, **133**, 54.

Eccles, R. M., 1954, Intracellular potentials recorded from a mammalian sympathetic ganglion, *J. Physiol.*, **130**, 572.

Eyzaguirre, C., and Kuffler, S. W., 1955, Processes of excitation in the dendrites and in the soma of single isolated sensory nerve cells of the lobster and the crayfish, *J. Gen. Physiol.*, **39**, 87.

Fatt, P., and Katz, B., 1952, Spontaneous subthreshold activity at motor nerve endings, *J. Physiol.*, **117**, 109.

Gray, J. A. B., and Sato, M., 1953, Properties of the receptor potential in Pacinian corpuscles, *J. Physiol.*, **122**, 610.

Hodgkin, A. L., and Huxley, A. F., 1952, The dual effect of membrane potential on sodium conductance in the giant axon of Loligo, *J. Physiol.*, **116**, 497.

Katz, B., 1950, Depolarization of sensory terminals and the initiation of impulses in the muscle spindle, *J. Physiol.*, **111**, 261.

Loewenstein, W. R., 1956 *a*, Modulation of cutaneous mechanoreceptors by sympathetic stimulation, *J. Physiol.*, **132**, 40.

Loewenstein, W. R., 1956 *b*, Excitation and changes in adaptation by stretch of mechanoreceptors, *J. Physiol.*, **133**, 588.

Loewenstein, W. R., 1958, Facilitation by previous activity in a Pacinian corpuscle, *J. Gen. Physiol.*, **41**, 847.

Loewenstein, W. R., and Rathkamp, R., 1958, Localization of generator structures of electric activity in a Pacinian corpuscle, *Science*, **127**, 341.

Tasaki, I., 1953, Nervous Transmission, Springfield, Illinois, Charles C. Thomas.