POST-TETANIC POTENTIATION OF RESPONSE IN MONOSYNAPTIC REFLEX PATHWAYS OF THE SPINAL CORD*

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Some processes in nervous tissue are essentially discontinuous in nature, others, like heat and carbon dioxide production, and positive after-potential, are cumulative; they tend to develop in some relation to the number of impulses carried, not infrequently to appear in measurable form only after a number of actions have been compressed into a limited time. In such conditions of activity not only are cumulative processes demonstrable in nerve, but indications of their influence may be found in the altered responsiveness of simple synaptic relays and of neuromuscular junctions. The usual sequel to a period of tetanic stimulation in junctional tissues is a more or less prolonged increase in the transmitted response to standard, iterative, but infrequently elicited pre-junctional nerve volleys into which train of volleys the tetanus has been interpolated (2, 7, 10, 11, 23, 35, etc.). The observed phenomena have been called post-tetanic facilitation, or post-tetanic potentiation; the latter designation is to be preferred.

A number of mechanisms with varying degree of experimental justification have been proposed to account for the phenomena that have been described. However it is not strictly a matter for rivalry between hypothetical alternative mechanisms (*cf.* in particular reference 10), for the descriptions of post-tetanic increases in response or responsiveness of various tissues preclude the possibility of fitting the phenomena to a common mold.

Post-tetanic increments of response have been encountered too in the study of spinal reflex mechanisms (5, 14, 36, 38). However, it is widely recognized that analysis of mechanism in the central nervous system at once is confronted with a new factor, the activity of internuncial chains. The potentialities for explaining prolonged effects in the central nervous system with the aid of a flexible internuncial system are enormous. On the other hand, it is logical that cumulative processes, as elementary properties of nerve tissue, should influence action there as elsewhere. Again, the aim is not to support a rivalry of hypothesis, but rather to extricate the cumulative process from supposed domination by the internuncial system, so to assess the respective rôles of discontinuous (*i.e.* internuncial barrage) and cumulative processes in the mechanisms for enduring alteration of transmission in the central nervous system. The description of experiments that follows relates an attempt to account for the striking post-tetanic potenti-

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* Presented before the American Physiological Society, Detroit, April 20, 1949.
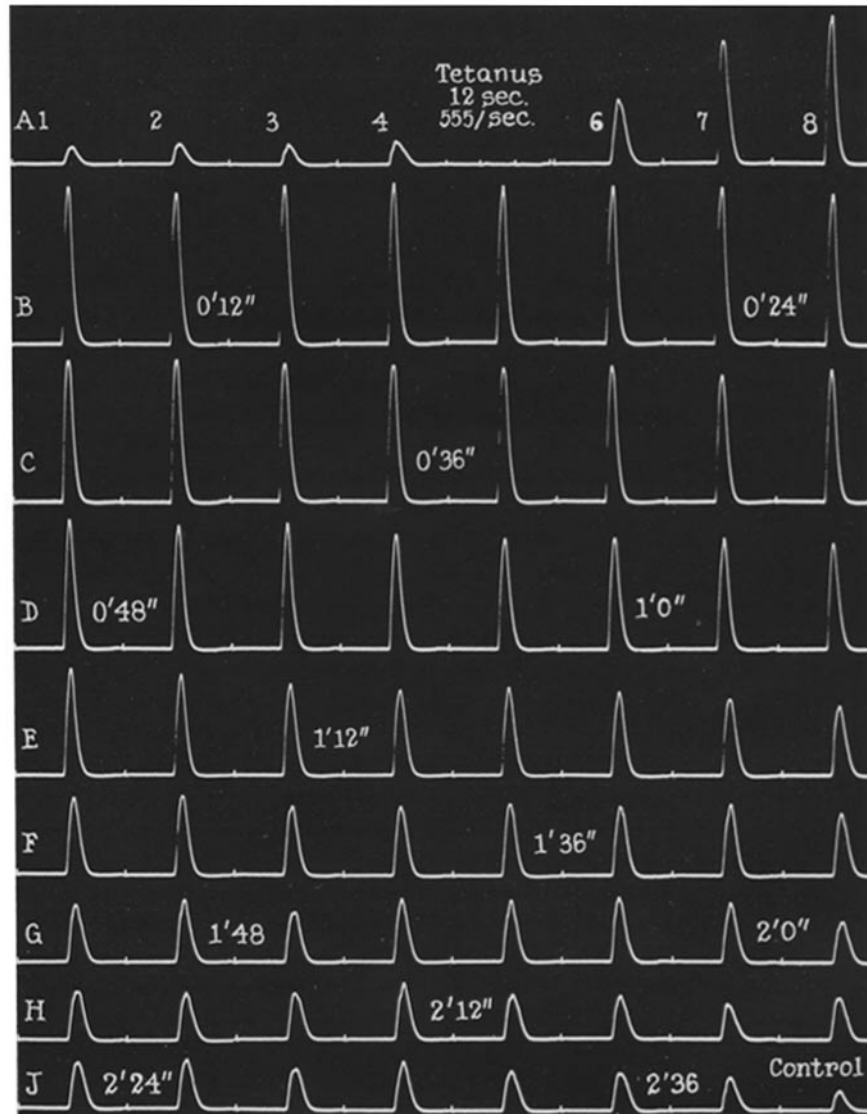
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FIG. 1. Monosynaptic reflexes of gastrocnemius muscle recorded at regular intervals before and following an intercurrent tetanus to illustrate the phenomenon of post-tetanic potentiation.

ation of response that has been encountered in the monosynaptic reflex pathways of the cat spinal cord. It will be evident how closely a number of the present experiments, experimental results, and conclusions resemble those of Larrabee

and Bronk (23), whose observations concerned the activity of sympathetic ganglia.

Potentiation of Monosynaptic Reflex Transmission in the Spinal Cord.—In the experiment illustrated by Fig. 1 single shock stimuli were delivered in regular succession once each 2.4 seconds to the nerve of gastrocnemius muscle, the monosynaptic reflex discharges evoked by those stimuli being recorded from the first sacral ventral root severed distally and placed upon appropriate leads. Such reflex responses, of fairly uniform magnitude in the absence of other stimulation, are seen in A 1, 2, 3, 4, and J 8 of Fig. 1. Between the recording of responses
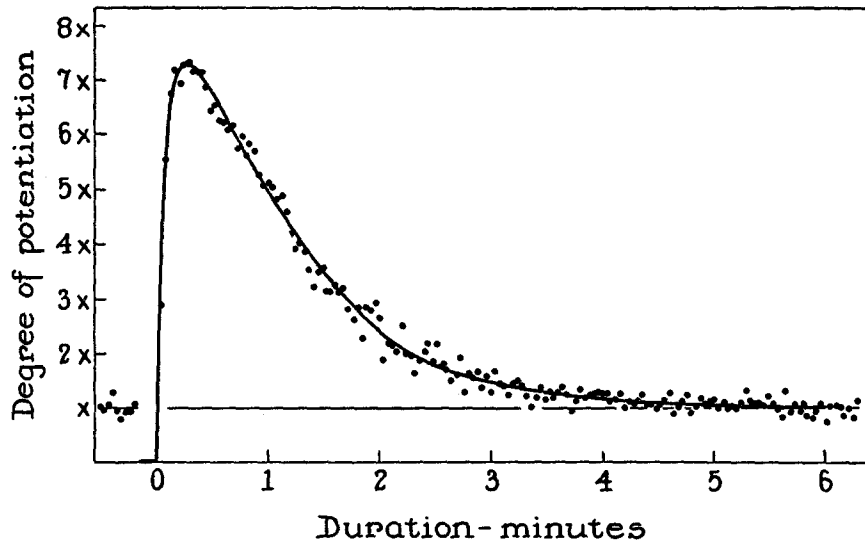

FIG. 2. Time course of post-tetanic potentiation following tetanic stimulation. Amplitude of monosynaptic reflex response expressed in multiples of the average pre-tetanic value is plotted against time in minutes after the end of tetanic stimulation.

A 4 and A 6 the gastrocnemius nerve was tetanized for 12 seconds at a stimulation frequency of 555 per second, following which the monosynaptic responses increased progressively (A 6, 7, 8) to a maximum (row B), thereafter slowly waning in magnitude to be still about twice the normal after more than 2 minutes (row J). By plotting amplitude of each response on a suitable time scale, a "curve of potentiation" such as that illustrated in Fig. 2 is obtained. The phenomenon of post-tetanic potentiation in monosynaptic reflex pathways is quite general, all of a number of pathways pertaining to various muscles, flexor and extensor, having behaved in similar fashion in similar circumstances of stimulation.

A cumulative process underlying post-tetanic potentiation of response might reside in the presynaptic elements or the postsynaptic elements of the monosynaptic reflex arc, or it might be assumed that extracellular agents, excitor

substances or appropriate ionic species, liberated into the synaptic environs to persist there for due time, by their action could augment transmission. Finally, as earlier stated, when junctions within the central nervous system come under
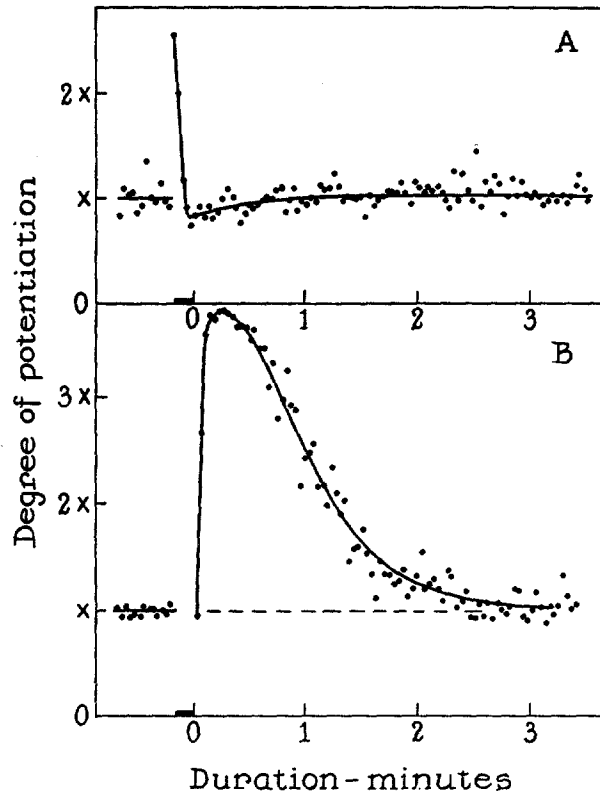

Fig. 3. Absence of post-tetanic potentiation when tetanus and test stimulations are applied to different nerves. A, Monosynaptic reflexes of knee flexor muscles before, during, and after tetanization of the sural nerve. Typical flexor reflex facilitation of the test response occurred during the tetanus, to be followed by a period of depression. In contrast, B shows the typical potentiation following tetanization of the knee flexor muscle nerves employed for test stimulation.

observation, even though they constitute a monosynaptic pathway, the possible play, through convergent chains, of internuncial barrage, must be considered.

The need for experimental elimination of internuncial barrage as a factor for post-tetanic potentiation in monosynaptic reflex paths stems from the fact that tetani induce threshold changes in the stimulated fibers, the effects of which must be obviated by the use of shocks supramaximal for the group I afferent fibers of the monosynaptic reflex pathway. As a consequence of this necessity,

higher threshold afferent fibers, possessing extensive ramification to the inter-
nuncial pools, unavoidably are stimulated. Interneurons thrown into activity
by stimulation of muscle nerves in general are excitatory to flexors and inhibitory
to extensors. That post-tetanic potentiation of flexor (Fig. 3 B) and extensor
(Fig. 2) monosynaptic reflexes is similar, therefore, provides the initial clue to
the effect that internuncial activity is not responsible for potentiation.

Unfortunately it is neither possible to tetanize monosynaptic paths in proven
isolation, nor to tetanize the internuncially relayed pathways of a given muscle
nerve leaving its monosynaptic paths at rest. Hence the obvious and most direct
controls for the participation of interneurons cannot be applied. However one
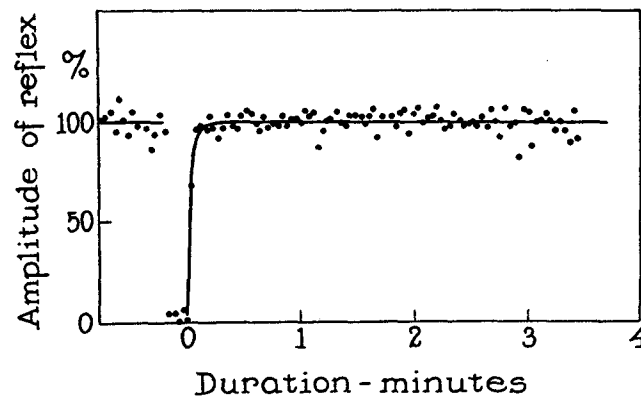can tetanize a variety of afferent nerves known to relay through internuncial

Fig. 4. The monosynaptic reflex response of an extensor muscle was inhibited dur-
ing tetanic stimulation of the ipsilateral peroneal nerve. At the close of the tetanic
period the monosynaptic reflexes returned to normal amplitude without displaying
potentiation.

pathways to the motoneurons that form part of any given monosynaptic test
system. For instance, Fig. 3 A plots the amplitude of regularly evoked mono-
synaptic reflex responses of semitendinosus motoneurons before, during, and
following tetanic stimulation of the sural nerve. As would be expected the mono-
synaptic responses were facilitated during the tetanus, but the only effect in
the post-tetanic period was a slight depression that passed off during the
first minute. Figure 3 B, practically a continuation of Fig. 3 A, shows the
potentiation of semitendinosus monosynaptic reflex responses that followed
tetanization of the semitendinosus nerve itself. Another experiment for which
an extensor monosynaptic system was tested is shown in Fig. 4. Monosynaptic
reflex responses to stimulation of the gastrocnemius nerve were elicited at regu-
larly recurring intervals, the interpolated tetanic stimulation being applied to
the peroneal nerve. During that tetanus the gastrocnemius test reflex was in-

hibited and, at the close of the tetanus, it required several seconds for the gastrocnemius reflexes to regain normal amplitude, but once this was accomplished no further change ensued.

The foregoing experiments demonstrate that tetanic and monosynaptic test stimulations must be applied to the same nerve for the characteristic post-tetanic potentiation of reflex discharge to ensue. This fact makes participation of internuncial activity an unlikely cause of post-tetanic potentiation of monosynaptic reflex discharge. However it is not disproved uniquely thereby.

Post-Tetanic Responses through Plurisynaptic and Monosynaptic Pathways Contrasted.—Fig. 5 presents the result of an experiment in which reflex discharge through internuncially relayed pathways was observed before, during, and subsequent to a tetanic stimulation of those same pathways. The sural nerve was afferent for all stimulations, the reflex discharges being recorded from the first sacral ventral root. Because of variability in the response to single shocks a number of control observations (A 1 to C 2 in Fig. 5) preceded the tetanus. Between the recording of C 2 and C 4 the sural nerve was tetanized for 12 seconds at a frequency of 575 per second. From the records that follow it is seen that the effect of tetanization on subsequent transmission was slight and evanescent. Thus, while it is clear from Bernhard's experiments (1) that interneuron chains act to produce the characteristically dispersed flexor reflex discharges of single shock excitations, there is no evidence for prolonged self-perpetuating activity of the sort that would have to be postulated to account for post-tetanic potentiation. This is not to deny that interneurons may act for the perpetuation of states of activity in other circumstances, it merely indicates that the conditions for post-tetanic potentiation are not of necessity those in which neuron chains can maintain a barrage of the motoneurons.

It is of some interest to inquire into the failure of plurisynaptic chains to reveal in a convincing manner evidences of the potentiating action. In explanation of the failure one might suppose the underlying action not to occur, or that having occurred some part of the system cannot respond in a revealing manner. The former supposition is tantamount to postulating drastically different fundamental properties for the nerve elements entering into monosynaptic and plurisynaptic reflex systems. Such a postulate seems unlikely when one recalls that sympathetic ganglia exhibit post-tetanic potentiation (7, 23) remarkably like that in spinal monosynaptic systems despite the fact that fibers of quite different properties are concerned in transmission through ganglia and spinal cord. The latter supposition has more merit. It is a logical necessity for potentiation to occur that a subliminal fringe exist in the test system at the junctions where the post-tetanically reinforced action is exerted. Since tests by the use of flexor monosynaptic reflexes reveal at the final common path an adequate subliminal fringe "surrounding" the discharge zone when the tested action is provoked by a sural nerve volley (26) or even a peroneal nerve volley (1), it follows that the defect underlying the failure of plurisynaptic systems clearly to exhibit post-tetanic
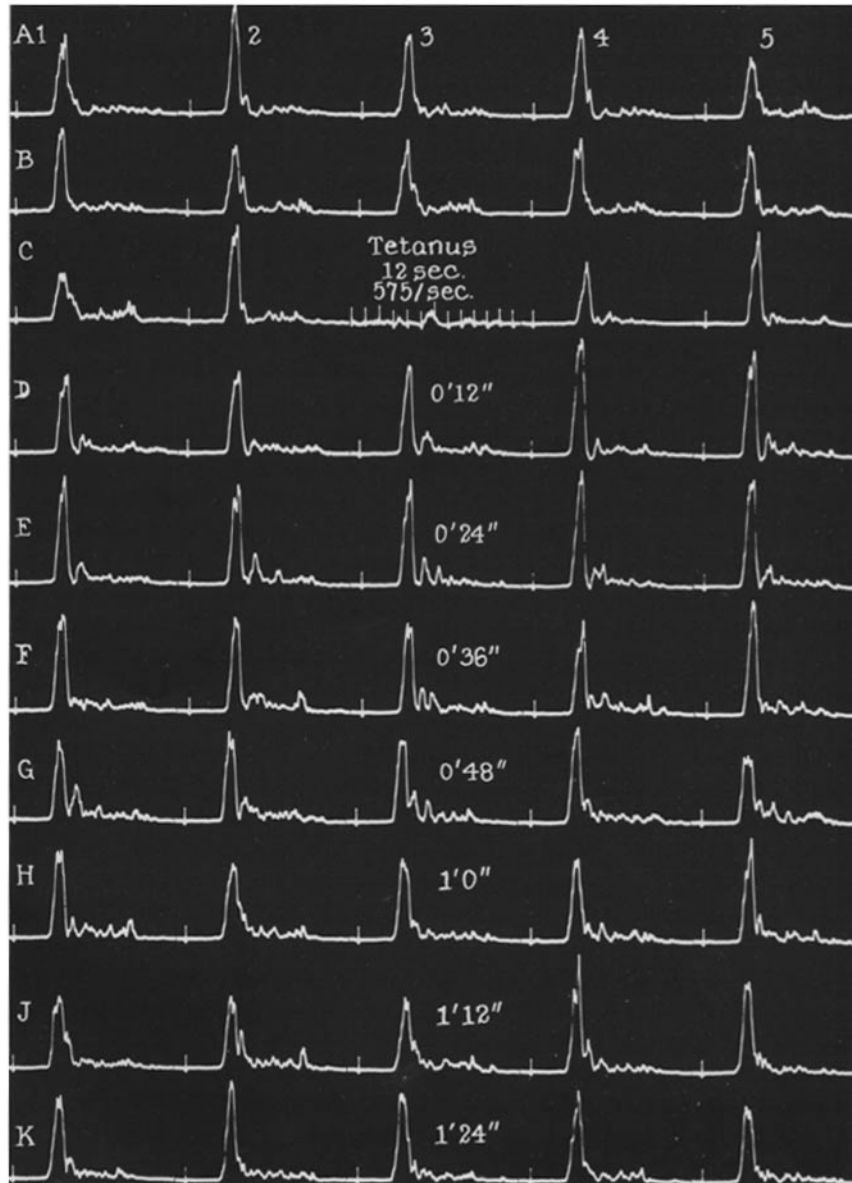
FIG. 5. An example of the relatively insignificant change in plurisynaptic reflex discharges following an intercurrent tetanization of the afferent nerve (sural).

potentiation lies not at the synaptic junctions with motoneurons, but upstream. It is of interest in this connection that Huges and Gasser (21) could find no

facilitation of negative intermediary potential in the presence of marked facilitation of the flexor reflex. It is not unlikely that the failure of negative intermediary potentials to exhibit facilitation, and the failure of the plurisynaptic reflex paths to display undoubted post-tetanic potentiation, share a common basis among the properties of the initial internuncial relays.

Post-Tetanic Effects Tested by Antidromic Volleys.—A number of possible mechanisms for post-tetanic potentiation may be put to test by means of direct observation of the responses of motoneuron somata. In a certain number of motoneurons antidromic impulses fail to penetrate the soma, with the result that the somatic action potential evoked by a maximal antidromic volley, in an otherwise "resting" spinal cord, is less than full size. The block to antidromic conduction is labile and easily relieved by maneuvers that facilitate even mildly the monosynaptic reflex response of the motoneurons. For instance the relatively mild internuncial bombardment of lumbosacral motoneurons during the course of a long spinal reflex (24, 30) is effective in relieving block (25), and it can be shown in this system that the degree of relief is proportional to the intensity of the internuncial barrage as measured by facilitation of a monosynaptic reflex test (29). Brooks and Eccles (9) have shown the relief of block by group I afferent volleys closely to resemble in time course the residual facilitation of motoneurons by similar volleys (27). In short, the degree of penetration into motoneurons of antidromic volleys is a delicate test for the working of excitatory influences upon those motoneurons.

Several hypothetical post-tetanic excitatory events should be uncovered by the use of antidromic test volleys. Among these would be any enduring intrinsic rise in excitability of the motoneurons themselves, a possibility raised by the observations of Kleyntjens on frog spinal cord (22). Such an effect might be the result of the motoneurons having fired a number of impulses as seems to be the case in Kleyntjens' experiments (although the usual sequel to discharge in the cat is depression) or the result of some change, not associated with firing but developed under the influence of repetitive impingement of presynaptic impulses. Another hypothetical event that should influence response to antidromic volley tests would be the release by presynaptic action into the environment of the motoneuron somata of an extracellular agent that might modify for several minutes the excitability of the motoneurons. Additionally the antidromic volley test forms another means of controlling the possibility of action by self-perpetuating internuncial activity.

Admittedly if the somatic responses to antidromic volleys were to be augmented in the period following a presynaptic tetanus, it would not be possible without other evidence to differentiate between the mechanisms mentioned. However, absence of a post-tetanic augmentation would speak against them all and weigh heavily in favor of the remaining possibility: that an enduring change in the properties of the presynaptic fibers following intense activity alters some essential character of subsequent impulses conducted by them.

Fig. 6 illustrates an experiment performed in examination by means of anti-dromic volleys of the after-effects of a presynaptic tetanus. A segmental reflex pathway was employed, the test stimulations being delivered to a ventral root whereas the tetanic stimulation, of 12 seconds duration at a frequency of 575 per second, was directed to the ipsilateral dorsal root of the same segment. Re-
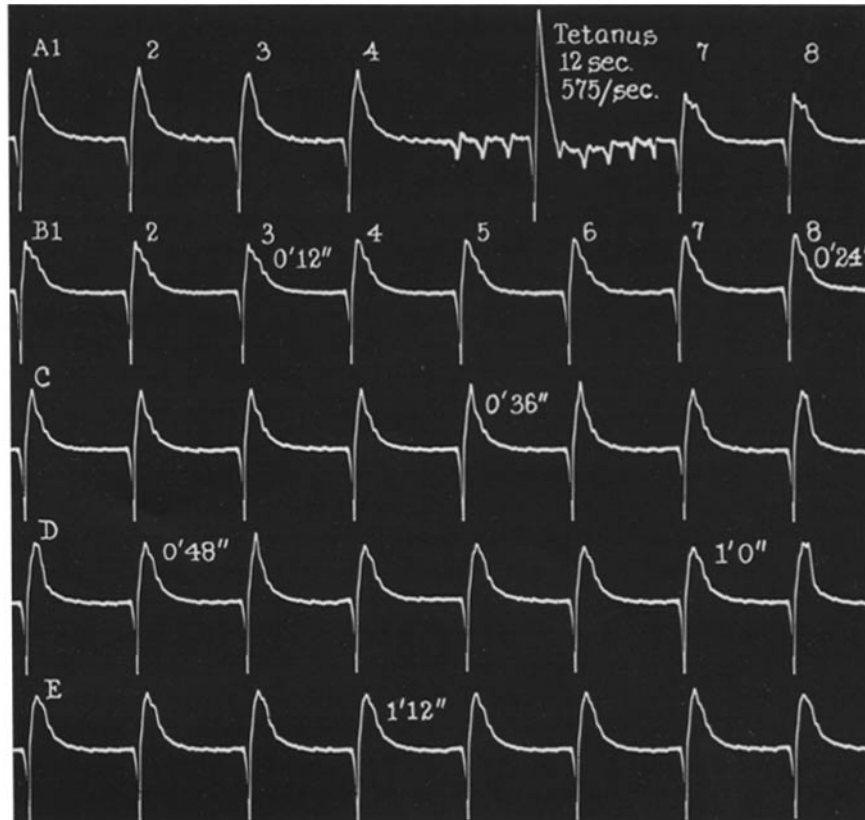

FIG. 6. Increase, during a presynaptic tetanus, of the soma response to antidromic volleys followed by depression during the early post-tetanic period.

cordings were obtained through the use of a microelectrode inserted to the ventral horn. In parallel experiment the segmental monsynaptic reflexes elicited by stim-uli to the tetanized dorsal root were seen to be potentiated for several minutes following comparable tetanic stimulation.

Responses A 1, 2, 3, and 4 of Fig. 6 anteceded the period of tetanic stimula-tion, and serve to establish the course of somatic responses elicited at regular intervals of 2.4 seconds. Between responses A 4 and A 7 is a record, obtained during the presynaptic tetanus, in which may be seen the regularly recurring

action potentials of the presynaptic impulses, and a single interpolated antidromically evoked somatic response of the motoneurons. This latter reveals the characteristic increment in response that resulted from the impingement of presynaptic impulses. Following the tetanus (A 7, 8 et seq.) the somatic responses were depressed rather than enhanced. These results not only lend support exclusively to the hypothesis of change in the presynaptic fibers, they further show that the potentiation of monosynaptic reflex discharge develops in the face of a post-tetanic depression in the postsynaptic elements (cf. also reference 23). Depression of the sort illustrated by Fig. 6 undoubtedly resembles that seen in Fig. 3 A, and, as will be seen later, accounts in part for the character of the rising phase of potentiation.

Potentiation of Facilitation and Inhibition.—Impulses that arise in the group I afferent fibers of a given muscle not only initiate monosynaptic reflex discharge of the motoneurons supplying that muscle, but, by direct impingement, they facilitate action in the monosynaptic paths of synergist muscles, and inhibit action in the monosynaptic paths of antagonist muscles (28). If, as the preceding evidence suggests, the mechanism underlying potentiation may be traced to some altered property of the presynaptic afferent fibers then the facilitator and inhibitor actions of those fibers presumably should be potentiated in the post-tetanic period along with their transmitter action. Tests of this expectation have been fashioned according to the following argument. Changes in the magnitude of a reflex discharge reveal themselves directly to the recording system applied to the motor axons, not so changes in facilitation and inhibition for the examination of which a standard test reflex is required. Furthermore, it is now clear that the only reflex actions potentiated following an afferent tetanus are those instigated by subsequent stimulation of the tetanized afferent fibers. Thus it follows on two counts that demonstration of a potentiation of facilitation or inhibition requires the establishment of two systems of test shocks, the first of these, applied to the tetanized nerve, to explore the after-effects of the tetanus, the other, applied to the nerve of a synergist or antagonist muscle, to reveal, by changes in the monosynaptic reflexes of those muscles, the degree of facilitation or inhibition derived from test stimulation of the tetanized nerve. Since the intensity of facilitation or inhibition of a reflex in a two-shock system (the response to the second testing the action of the first) is a function of the time interval between the shocks, then for the combined shocks to be a valid test for the influence of prior tetanization it is obvious that the individual shocks of the pair, throughout any given experiment, must bear a constant temporal relation to each other.

In the experiment illustrated by Fig. 7 the nerves of the two heads of gastrocnemius muscle were arranged for independent afferent stimulation. One nerve was stimulated by single shocks, once each 2.4 seconds, to evoke a regular succession of monosynaptic reflex discharges. For alternate applications shocks to that nerve were delivered in isolation, magnitude of the monosynaptic responses

so elicited being represented in Fig. 7 by dots, and in combination with an ante-
cedent shock to the other gastrocnemius nerve, the magnitude of the facilitated
monosynaptic responses that resulted being represented in Fig. 7 by circles.
Thus, when the one shock was given, the size of the resulting monosynaptic
reflexes tested for direct effect imposed by tetanization of the other nerve,
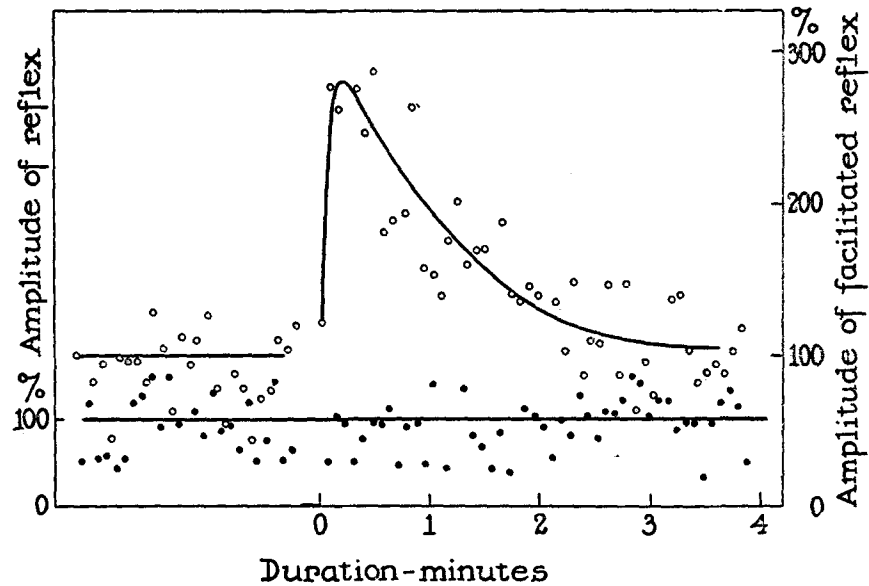whereas when the two shocks were given in sequence the size of the facilitated

Fig. 7. Following tetanization of the nerve to one head of a muscle (gastroc-
nemius) the facilitating action of a volley in that nerve upon the monosynaptic reflex
responses of the other head is potentiated in characteristic time course (circles).
However there is no direct effect of tetanizing the nerve to one head upon the mono-
synaptic reflex response of the other (dots).

monosynaptic reflexes tested the after-effect of tetanization upon the facilitatory
action of subsequent volleys stimulated in the recently tetanized nerve.

The observations recorded in Fig. 7 show that tetanization of the nerve to one
head of gastrocnemius is without direct potentiating effect upon transmission
of monosynaptic reflexes arising in the nerve to the other head of gastrocnemius.
But the facilitating action that a volley in the nerve to one head exerts upon
transmission through the monosynaptic pathway of the other head, subsequent
to tetanic activation of the "facilitator" nerve, is potentiated in a manner and
degree that reproduces the course of post-tetanic potentiation of monosynaptic
reflex discharges. Comparable result has been obtained in experiment with the
pathways of semitendinosus and biceps femoris posterior.

Potentiation of inhibitory action has been studied in the same manner as potentiation of facilitation, the only and necessary difference in procedure being the selection for stimulation of nerves to an antagonist rather than a synergist muscle pair within the myotatic unit. Illustrated by Fig. 8 is an experiment that utilized the nerve supply to the pretibial muscles, tibialis anterior and extensor longus digitorum, as afferent for the measured monosynaptic test reflexes, and
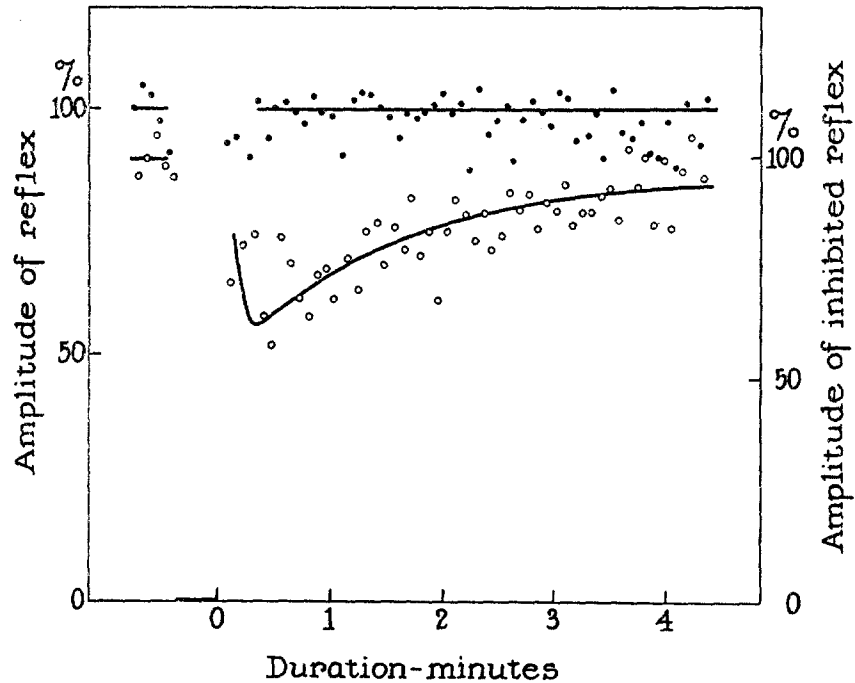

Duration-minutes

FIG. 8. A tetanus of the nerve to one muscle (gastrocnemius) potentiates the inhibitory action of subsequent volleys in that nerve upon the monosynaptic reflex responses of antagonists (ankle flexors) within the myotatic unit (circles). Tetanization of the one nerve again is without direct effect upon the monosynaptic reflex evoked by stimulation of the other nerve (dots).

the nerve to gastrocnemius as a source of inhibitory volleys. With the two shocks in close temporal approximation the intensity of inhibition was not great. Once the amplitude of control (dots) and inhibited (circles) monosynaptic responses was established, the gastrocnemius nerve was tetanized, following which the inhibitory action of subsequent gastrocnemius nerve volleys was potentiated for several minutes, although transmission through the monosynaptic pathways of the pretibial muscles was not influenced directly.

The experiments of Figs. 7 and 8 not only support the notion that the tetanic

aftermath is localized to the afferent fibers tetanized, they demonstrate also that any of the tangible synaptic actions, regardless of direction, of impulses in those afferent fibers are potentiated following a tetanus. This being so, the simplest conclusion would be that the change underlying post-tetanic potentiation influences the afferent fiber generally, rather than merely the terminals (23), probably in such a way that the impulses engendered in it subsequent to tetanization are greater than normal. Apparently Boyd (2), studying post-tetanic decurarization of the cat's tongue, was the first to suggest the possibility that
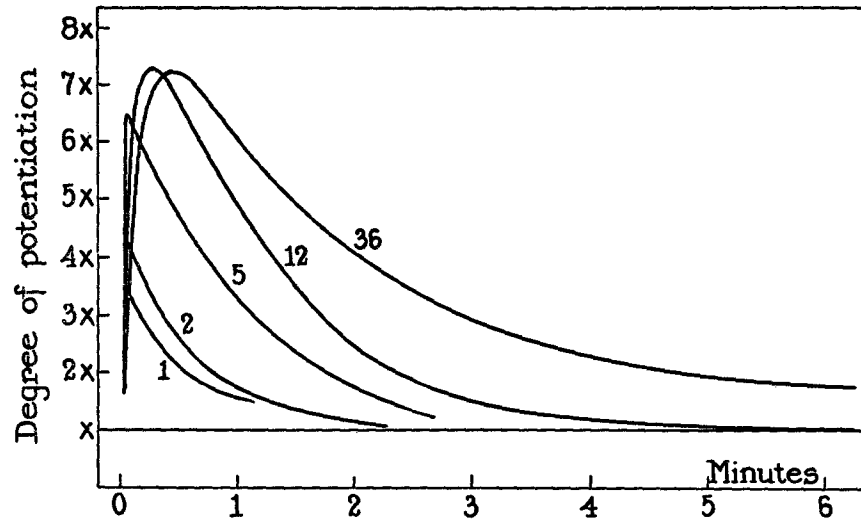

FIG. 9. Time course of post-tetanic potentiation after various durations of repetitive stimulation (1, 2, 5, 12, and 36 seconds) at a constant frequency (ca. 500 per second).

post-tetanic change in the nerve impulses was responsible. His suggestion, often dismissed, according to the present indications should be reinstated.

Influence of Changed Duration and Frequency of Stimulation upon the Course of Post-Tetanic Potentiation.—Considerable information as to the properties of a cumulative process such as underlies post-tetanic potentiation may be obtained by varying either the duration or frequency of stimulation. Fig. 9 plots the course of potentiation following tetani of varying durations, but of constant frequency. With the shorter tetani (1 or 2 seconds) the first post-tetanic response revealed the maximum enhancement. Following the 5 second tetanus maximum was attained on the second and third post-tetanic responses. As the tetanus was further lengthened (12 and 36 seconds) the rising phase of potentiation was progressively slowed. The earlier experiments (Figs. 3 A and 5) suggest, in explanation, that post-tetanic potentiation develops in the face of an opposing depression

that in turn bears its own peculiar relation to the duration of stimulation. If that opposing depression is due to the summation of subnormality in postsynaptic structures, then of course the ability of those structures to follow the tetanus frequency becomes an added factor modifying the relation between depression and severity of tetanization. By the nature of the experiments of Figs. 3 and 9 it is not possible to locate the depressed structures, but in the experiment of Fig. 5, in which antidromic volleys were employed to test the effects of a presynaptic tetanus, the early post-tetanic depression of somatic responses proved the motoneurons at least to be in a depressed state. Comparable depressions and slowing of the rising phase of post-tetanic potentiation in sympathetic ganglia have been described by Larrabee and Bronk (23).
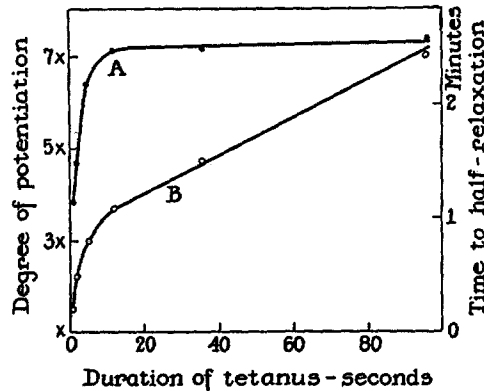

FIG. 10. Intensity (A) and duration (B) of post-tetanic potentiation of a mono synaptic reflex as a function of duration, in seconds, of a tetanus at constant fre quency.

Another feature of post-tetanic potentiation is the fact that a ceiling is reached with tetanic stimuli of about 10 seconds duration or greater. Once the ceiling is reached, further prolongation of a tetanus results in more prolonged potentiation. This effect can be seen in the plots of Fig. 9 and to better advantage possibly in Fig. 10. Curve A of Fig. 10 expresses as a function of tetanus duration the degree of potentiation of the largest single response recorded during the post-tetanic period. Curve B similarly relates duration of potentiation, measured by the time to half-relaxation, to the duration of tetanic stimulation. It is seen that the magnitude and duration of post-tetanic potentiation were increased in parallel fashion with lengthening of the tetanus until the ceiling was reached. Thereafter, continuing increase in the duration of potentiation fell into an approximately linear relation with the duration of the applied tetanus.

Figs. 11 and 12 present the results of two experiments in which was investi-
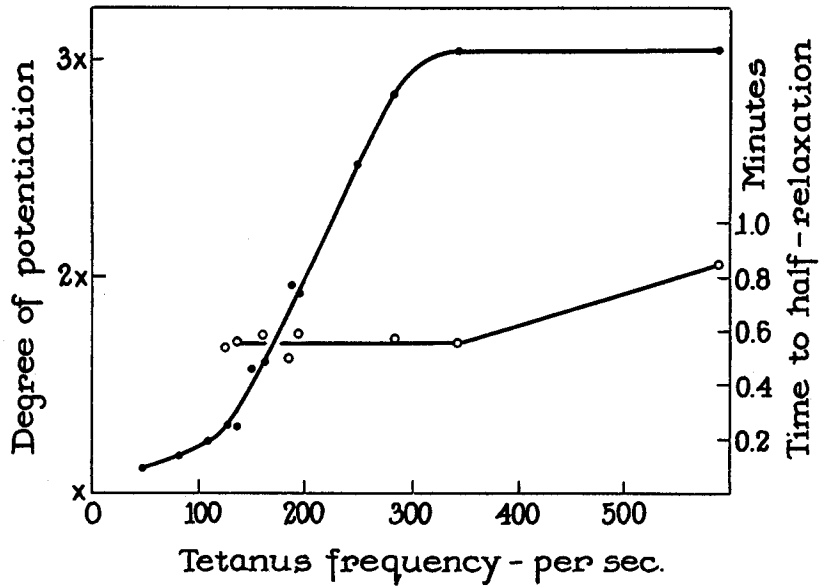
FIG. 11. Intensity (dots) and duration (circles) of post-tetanic potentiation of a monosynaptic reflex as a function of tetanus frequency, duration of stimulation being held constant at 12 seconds.
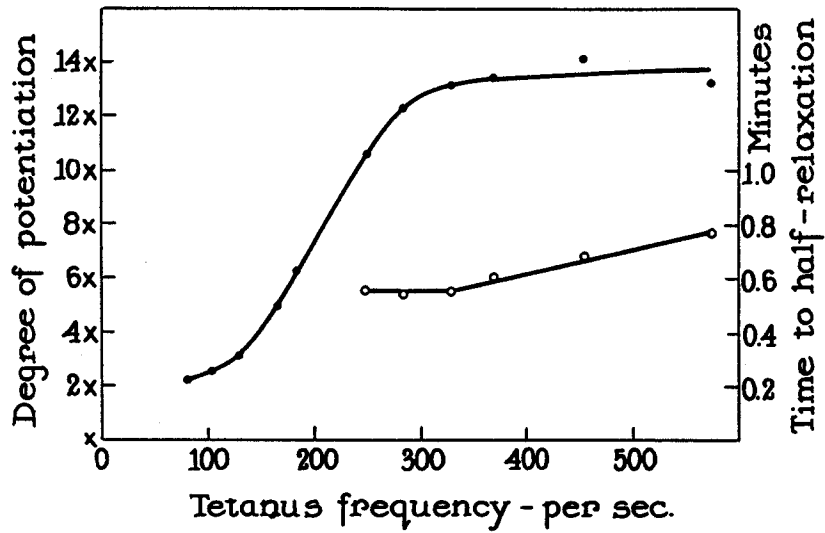

FIG. 12. As in Fig. 11, but from another experiment, a comparison of the two experiments illustrating an inverse relation between degree of potentiation and initial size of the reflex discharge

gated the influence upon post-tetanic potentiation of change in frequency of the applied tetanus. It is of interest to compare the two experiments, for in one (Fig. 11) a fairly large monosynaptic reflex resulted from the test stimulation applied in isolation, and the maximal degree of potentiation was correspondingly low (3 X), whereas in the other (Fig. 12) the relatively small test reflex response at the peak of potentiation was multiplied 14-fold..

At the lower frequencies of tetanic stimulation measurement of the degree and duration of post-tetanic potentiation is difficult, for the normal variability of reflex response can obscure small effects, particularly when there is no opportunity to overcome the effect of variability by the use of repeated measurement. In one experiment definite potentiation of monosynaptic reflex response was recorded following stimulation at a frequency of 15.5 per second. There seems to be no readily available explanation for the initial upward concavity in the curves relating degree of potentiation to tetanic frequency. In one experiment the concavity was not obvious. Presumably other interfering, but unresolved, phenomena influence the post-tetanic response.

Following tetani in the frequency range between about 100 and 300 per second the degree of potentiation was found to vary linearly with the tetanic frequency, but with further increase in frequency the degree of potentiation approached a maximum. There was no significant change in duration of the post-tetanic potentiation with increasing frequency of stimulation until the ceiling in degree of potentiation was reached, but further increase in the tetanization frequency prolonged the after-effect.

The observations of Figs. 10 to 12 are of interest because they point unmistakably toward certain resemblances between the phenomenon of post-tetanic potentiation and the positive after-potential developed by tetanized nerves (15, 17, 19). Discussion of the similarities between these events is the more pertinent because of the fact that some process in and restricted to the tetanized presynaptic fibers themselves has been shown to underlie post-tetanic potentiation.

That the after-potentials of nerve may last for several minutes is well known. Gerard (19) and Gasser (15) found them to persist in frog nerve for 10 to 15 minutes. Unfortunately for the present purpose there has been little study of the prolonged positive after-potential as it appears in mammalian nerve. However, Gasser and Grundfest (17) have shown that the degree of after-positivity in mammalian nerve (as in frog nerve) increases to a ceiling with increasing severity of tetanization, after which a prolongation of the after-positivity reflects the further increase in tetanization. Furthermore, as concerns duration they gave the following figures as representative: a 10 second tetanus resulted in after-positivity that regressed to half-value in 15 to 30 seconds; after a 30 second tetanus half-relaxation required more than 1 minute. Comparison of these properties of after-positivity in mammalian nerve tissue with those re-

quired of the hypothetical process responsible for the occurrence of post-tetanic potentiation confirms the notion of close correspondence. In the circumstances, and considering that the number of unrelated coexistent and parallel events in a nerve fiber must be limited, it seems not unlikely that the cause of post-tetanic potentiation is tied to the positive after-potential process.

Observations on Presynaptic Fibers in Relation to Post-Tetanic Potentiation.— The observations and correlations that have been described lead to the following specific hypothesis as to the mechanism of post-tetanic potentiation in monosynaptic reflex systems of the spinal cord. (I) Following tetanic stimulation the stimulated afferent fibers enter a period of prolonged positive after-potential. (II) During the after-potential the intramedullary collaterals must be reasonably uniformly hyperpolarized, otherwise an external field would be established which might be expected to influence the excitability of nearby or synaptically related postsynaptic units. (III) The spike potential per fiber during the phase of post-tetanic hyperpolarization is increased over the resting, or pretetanic, value. (IV) Post-tetanically exalted afferent impulses upon reaching the afferent termini, or such other places from which they may act for transmission, and for facilitation or inhibition of transmission, do so with intensity enhanced roughly in proportion to the amount by which they are exalted. (V) The stimulation frequency requirements are such that one might conclude not unreasonably that positive after-potential could operate for increased responsiveness in the normal functioning of the nervous system.

The several steps of the foregoing hypothesis for the most part either have been tested, or are amenable to test. They may be considered seriatim.

(I and II) Most pertinent for present purposes are the observations of Woolsey and Larrabee (38) on positive after-potential in dorsal roots. Unfortunately these have never appeared *in extenso*. However, those authors observed[1] positive after-potentials lasting, in a dorsal root, for "more than a minute" following tetanic stimulation. The potentials so recorded were undoubtedly those of the extramedullary dorsal roots themselves, and not electrotonic extensions from the intramedullary projections. Recording within the spinal cord of a "P 2" positive after-potential seems impossible *a priori* for the available evidence indicates the absence of any significant external field accompanying the hyperpolarization. However, the fact that Woolsey and Larrabee (38) recorded augmented D.R.V. dorsal root potentials (31) in a recently tetanized root may be taken as evidence that the intramedullary projections of those roots were hyperpolarized in the post-tetanic period.

(III) The postulate of relative increase in the spike potential when written upon positive after-potential has developed out of an interesting history. Increase in nerve activity following a tetanus apparently was noted first by Wal-

[1] Records of their observations were presented at the 1940 meeting, in New Orleans, of the American Physiological Society.

ler (37). Richards and Gasser (34, *cf.* also reference 18) found an increased spike potential when frog C fibers were stimulated during the after-positivity of an antecedent response. Later, increase in mammalian C fiber spikes during the after-positivity created by a tetanus was described by Grundfest and Gasser (20). Subsequently a number of investigators confirmed the effect in mammalian C fibers and in sympathetic ganglia. At the same time increase in C fiber negative after-potential intercurrent upon positive after-potential was
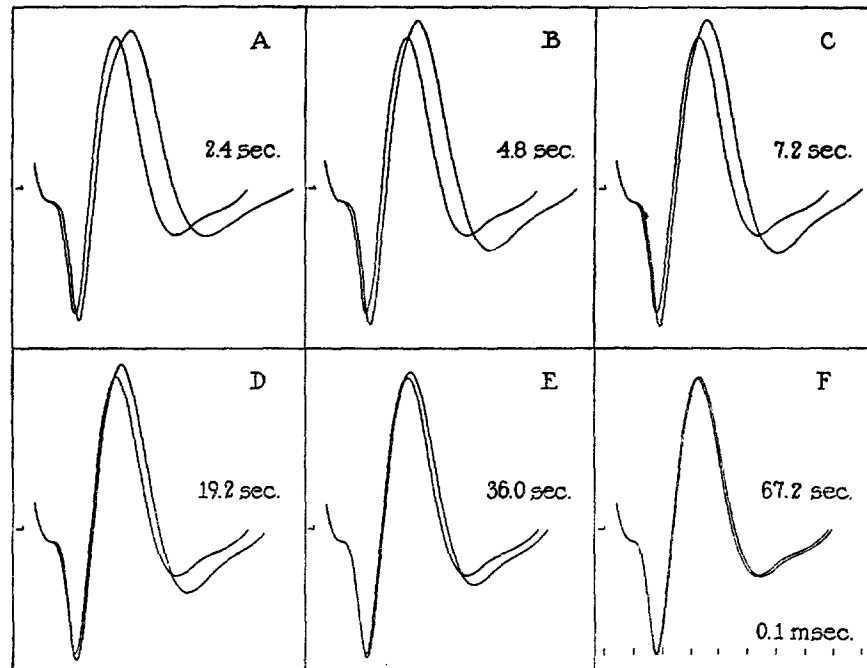

FIG. 13. Change in the recorded action potentials of afferent volleys at the stated times following the end of tetanic stimulation. Each observation, A to F, includes a control record and a post-tetanically altered record superimposed by tracing.

documented. Likewise Gasser has shown (16) an increase in mammalian A fiber negative after-potential on stimulation during the prolonged after-positivity following a tetanus. But as far as the present author is aware increase in the mammalian A fiber spike in the post-tetanic period has not been described. Obviously then, proposition III of the foregoing hypothesis must be put to test.

Fig. 13 presents the results of an experiment in which the intramedullary spike potentials of afferent volleys were recorded before and after a dorsal root tetanus. In order clearly to indicate the changes consequent to tetaniza-

tion, each observation (A to F of Fig. 13) of a post-tetanic spike is superimposed upon a spike potential recorded prior to tetanization. It is seen from the records that conduction velocity following the tetanus was subnormal in progressively diminishing degree, and that the spikes, in fulfillment of expectation, were increased over the pretetanic size. True, one cannot confirm by direct experiment the parallel existence of hyperpolarization in the intramedullary afferent fibers, and so prove the parallelism between positive after-potential and increase in spike size. Still the body of circumstantial evidence for the association is reasonably complete. Even in the unlikely event that positive after-potential ultimately should prove not to be the mechanism of increase in the spike potentials of the intramedullary afferent projections, the fact of the post-tetanically increased spikes remains to satisfy the requirement for increase of presynaptic action in support of potentiation in the reflex pathways.

It should be noted that increase in afferent spikes following a tetanus has been seen with any location of a microelectrode along the collateral projections in the spinal segment under observation, and in the extramedullary segment of a tetanized dorsal root. Potentiation of the "focal synaptic potential" of Brooks and Eccles (8) also has been noted.

(IV) This proposition requires some comment. It is important to emphasis, in accordance with the observations above, that the altered property involves the extramedullary and intramedullary course of the fibers, not merely the synaptic terminations. This being so, it follows that any action at or near fiber terminations that is tied to the nerve impulse, and this presumably includes all excitatory and inhibitory synaptic phenomena, should be enhanced. The experiments illustrated by Figs. 7 and 8 stand in support of this notion. As far as the present experiments go there has been no suggestion of reversal of action, as for instance has been seen when activity is intensified by strychnine (33) rather than prior tetanization.

From another point of view it is probable that concentration of attention upon the presynaptic terminations rather than the fibers as a whole has delayed recognition of the rôle played by exalted impulses in the causation of post-tetanic potentiation. However, it should be noted that Eccles (12) has made the pertinent suggestion recently that positive after-potential of the preganglionic fibers might provide an explanation of the phenomenon in sympathetic ganglia as described by Larrabee and Bronk (23).

Proposition IV includes the postulate of approximate parallelism between the alteration in presynaptic fibers and the potentiation of reflex response to action in those presynaptic fibers. This can be tested by comparing the temporal course of increase in spike size with that of potentiation. It is important for such a test that the two events be measured simultaneously, for small variations occur from experiment to experiment. The requirement is satisfied by use of the double-beam oscillograph with leads arranged to record simul-

taneously the afferent spike potential and the monosynaptic reflex response. Fig. 14 presents the results of an experiment performed in the manner indicated. The upper plot charts the course of reflex potentiation, the lower that of increase in afferent spike potential. It is clear that the two responses, presynaptic and postsynaptic, varied in parallel during the post-tetanic period.

Proposition V deals not with the mechanism of post-tetanic potentiation, but rather with the question of its potential significance as a means for increased
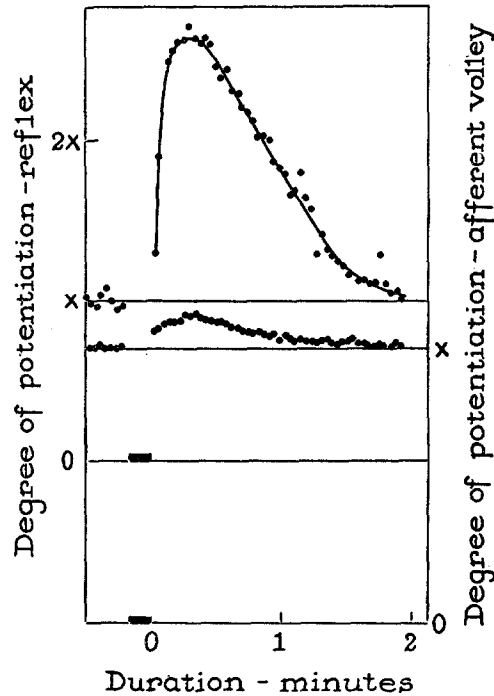

Fig. 14. Changes in amplitude of presynaptic (below) and postsynaptic (above) volleys of a monosynaptic reflex pathway simultaneously recorded, following a presynaptic tetanus.

response in the naturally activated nervous system of the intact organism. The decision between physiologically significant mechanism and laboratory curiosity depends primarily on the relation between the frequencies normally encountered and those requisite for potentiation.

Definite potentiation has been encountered following a train of 176 volleys at 15.5 per second, or, in another instance, a train of 372 volleys at 31 per second. At no time when frequencies as low as 50 per second were employed did post-tetanic potentiation, in degree sufficient to rise well above the random variation, fail to occur. Since there now appears to be little doubt that the mus-

cle spindle is the afferent end-organ to the monosynaptic reflex paths, and, since it is these same paths that exhibit the phenomenon of potentiation, the observations of Matthews on afferent discharge frequencies of end-organs in muscle (32) are the most pertinent for the purpose of comparison. In making that comparison responses from the A type of ending should be chosen, and the frequencies during static rather than phasic stretch considered. Even with this last restriction imposed the frequencies reported by Matthews as resulting from quite modest loadings are in excess of those required for potentiation. Hence it is possible that impulse potentiation by means of positive after-potential could represent a normal mechanism for increased response in the spinal cord.

Potentiation and After-Discharge.—These functions are unrelated. Whatever may be the mechanisms of after-discharge, its occurrence demands a continued action of, or upon, the postsynaptic neurons such as has been shown not to exist in the circumstances that support post-tetanic potentiation of the type herein described.

Some Prior Observations on Post-Tetanic Increase of Response in the Spinal Cord.—There exist a number of instances in which enhanced responses have been obtained following tetanic reflex stimulation. Experimental conditions have differed widely as have the results. A study of the individual manifestations of increased response leaves no doubt that the phenomenon presently under consideration does not present the only mechanism available to the spinal cord for achieving a superficially similar end-result. However self-evident this statement may seem, nevertheless consideration of a few examples is in order, particularly with respect to those studies in which test stimulation followed tetanic stimulation of the same afferent fibers.

The use of single shock test reflexes for gauging the responsiveness of the reflex arc was introduced by Sherrington and Sowton (36), who described an augmentation of such reflexes lasting on a declining scale for 16 seconds following the close of a 5 second tetanus. From the nature of the reflex test and the relative brevity of the effect, one might conclude that some factor other than increased afferent impulses determined the experimental finding. Also, similar effects were noted when tetanic and test reflexes were elicited by stimulation of separate nerves.

There is every indication that Woolsey and Larrabee (38) must have observed post-tetanic potentiation, but their mention of facilitation in response to test shocks stimulating roots adjacent to that tetanized suggests the participation of additional mechanisms that apparently have not operated in the circumstances of the present experiments. Prolonged positivity, the basis for increase in afferent spike size, in their experience was confined to the root tetanized.

Striking post-tetanic effects were obtained by Bremer and Kleyntjens in

their study of the spinal cord of batrachians (5). Strongly suggested by their records is the conclusion that the post-tetanic facilitation of which they speak is related primarily not to a potentiating mechanism, but to after-discharge. It may be noted that after-discharge is a prominent feature in the spinal control of certain batrachian muscles (3–6), including iliofibularis, the contractions of which provided the usual indicator in the experiments of Bremer and Kleyntjens. Although future experiment may prove otherwise, present indications are that the phenomenon of Bremer and Kleyntjens differs fundamentally from post-tetanic potentiation as manifested by the monosynaptic reflex paths of the cat spinal cord.

Potentiation at Other Junctions.—More than perfunctory mention of potentiation at other junctions cannot be justified in the absence of experimental observation. It does seem possible, however, that the operation of positive after-potential in the motor nerve fibers might account for post-tetanic decurarization (2) and potentiation of end-plate potential (13), but not, for instance, for potentiation in normal muscle, which Brown and von Euler (10) clearly distinguished from decurarization.

<div align="center">SUMMARY</div>

Following tetanic afferent stimulation of a monosynaptic reflex pathway> the transmission through that pathway of isolated reflex volleys is enhanced for some minutes. Post-tetanic potentiation is comparable in the monosynaptic reflex arcs of flexor and extensor muscles. The facilitator and inhibitor actions of monosynaptic reflex afferent fibers, as well as the transmitter action, are potentiated following tetanization. Little post-tetanic change attends reflex transmission through plurisynaptic reflex arcs.

Various tests for excitability change made independently of the tetanized afferent fibers reveal none or a slight depression. Hence the potentiating influence of a tetanus is limited to subsequent action on the part of the recently tetanized fibers themselves. Increase in the size of the individual impulses comprising an afferent volley such as might occur during positive after-potential, would accommodate the requirement for a limited process and provide for increased synaptic action. The proposed association between post-tetanic potentiation and positive after-potential (*i.e.* hyperpolarization) is supported by the following lines of evidence:—

1. Changes in intensity and duration of potentiation with change in frequency and duration of tetanic stimulation are characteristic of, and parallel to, the changes of positive after-potential in similar circumstances.

2. Afferent impulses are increased following a tetanus, and in a fashion that parallels the course of monosynaptic reflex potentiation.

Post-tetanic potentiation, as here described, and after-discharge, whatever may be its mechanism, are unrelated phenomena.

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