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Neurologic Mechanism of Symptoms of Irritation in Tetany

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THE SYMPTOMS of irritation in an attack of tetany in adult man consist of tingling, which begins in the face and hands, and, somewhat later, a feeling of tension and spasm in the face and the small muscles of the hand. If the attack is aggravated, the tingling and spasm spread from the hand proximally along the arm. Immediately afterward the same symptoms begin to manifest themselves peripherally in the legs, spreading proximally and finally reaching the trunk. In addition, fascicular twitches in muscles, bordering on spasm, irregularly occur. It was previously shown[1] that these symptoms of irritation studied in the arm were caused by spontaneous discharges first and foremost in the proximal part of the longest nerve fibers. The activity starts in the tactile fibers, from which the typical sensation of tingling originates, and, somewhat later, is set up in other afferent fibers, producing a feeling of tension. At about the same time it reaches the motor fibers, giving rise to fasciculation. The question whether the spasm is caused by direct excitation of motor fibers or reflexly, by the afferent discharge, was left open.[1b]

In the present work, the mechanism of excitation of nerve during hyperventilation and hypocalcemic tetany is analyzed electromyographically and compared with direct electrical excitation and ischemic activation of the same nerve. It is further shown that the motor discharge in tetany is caused by direct excitation of the motor nerve fibers.

MATERIAL AND TECHNIC

This investigation deals mainly with experimental tetany elicited by forced respiration for five to fifteen minutes in 14 subjects, most of whom were examined

This study was aided by a grant from Stiftelsen Thérèse och Johan Anderssons Minne.

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1. Kugelberg, E.: (*a*) Accommodation in Human Nerves and Its Significance for the Symptoms in Circulatory Disturbances and Tetany, Acta. physiol. Scandinav., 1944, supp. 24, p. 8; (*b*) Neurologic Mechanism for Certain Phenomena in Tetany, Arch. Neurol. & Psychiat. 56:507 (Nov.) 1946.

from two to four times. A patient with parathyroprival tetany, with blood calcium values about 6 mg. per hundred cubic centimeters, was also studied.

Electromyographic registration was carried out with concentric needle electrodes connected to one or two condenser-coupled amplifiers operating on a cathode ray tube. The ulnar nerve was stimulated with slowly rising currents, mainly by monopolar excitation. The cathode was then placed over the "nerve point" at the wrist, a few centimeters proximal to the elbow or at the axilla. Unless otherwise indicated, the action potentials were recorded from the first dorsal interosseous muscle. Further technical details have been given by Kugelberg and Skoglund.[2]

The ischemia was produced by a pneumatic cuff distended well over the area of determination of the systolic pressure. In some experiments the ulnar nerve was blocked directly at the elbow with 5 cc. of a 2 per cent solution of procaine hydrochloride containing epinephrine hydrochloride in a strength of 1:50,000.

RESULTS

General Characteristics of Motor Discharge.—The activity evoked by hyperventilation nearly always started with spikes of a regular rhythm, continuous from the outset, or in long runs, interrupted by shorter or longer intervals of inactivity. At the start the frequency was usually between 5 and 15 per second, oftenest about 10 to 12 per second; occasionally, however, slow, regular frequencies, down to 3 or 4 per second, were observed (figure, record *1b*).

Sometimes the activity consisted of single spikes (record *1a*), more rarely of triple spikes (record *1b*), but most commonly of double spikes, separated by an interval of five to fifteen milliseconds (most records). The first spike usually had a small amplitude. With increasing intensity of the tonic contraction in the muscle, new units, usually with a progressively larger amplitude, were "recruited" (figure, *2* and *6*).

In record *2a*, the activity starts with a double spike, having an amplitude of 80 microvolts and a frequency of 10 per second. The next unit to come in is a double spike, with an amplitude of 450 microvolts and the same frequency. The mechanism that caused the duplication shows a tendency to fatigue, for after some tens of seconds the action potential often becomes single, without any change of rhythm (record *2b*). The next unit brought into operation had an amplitude of 600 microvolts and a frequency of 9 per second and was a single spike (record *2c*). With increasing intensity of contraction, another small, distinct spike might arrive, and the base line then became more irregular, owing to the picking up of activity from distant units. At the same time, the frequency increased somewhat, and in record *2d*, in the units "recruited" as *2* and *3*, it was 14 per second.

2. Kugelberg, E., and Skoglund, C. R.: Natural and Artificial Activation of Motor Units: A Comparison, J. Neurophysiol. 9:399, 1946.

At this point the experimental subject lost consciousness; hence the hyperventilation could not be carried further. The same general conditions are shown in *6*, during the recording of which the activity could be intensified.

As in voluntary contraction,[2] in stimulation with a slowly rising current[3] and in ischemic excitation,[4] the different units in tetany are activated according to the size of their spikes. The small motor units thus have a lower threshold for excitation by hypocalcemia or hyperventilation than the larger ones. The differentiation of units with different thresholds is distinct and striking during hyperventilation because the excitation sets in so slowly.

Double Spikes.—The double spikes observed during tetany in man were first described by Turpin, Lefebvre and Lerique,[5] who asserted that they were produced by repetitive response in the end plate. These spikes are identical in appearance with those elicited by activation of the motor nerve by ischemia,[4] in which they are caused by an iterative response to excitation in one and the same nerve fiber. The same is true during hyperventilation.

If the arm of the experimental subject was compressed at the elbow before forced respiration began, the peripheral structures were excluded from the effect of the changes in the blood due to the hyperventilation. Double spikes, nevertheless, appeared in connection with the spasm (record *3a*). If the subject made a slight voluntary contraction and the record was made from the muscle after the cessation of the spontaneous activity, but while the pneumatic cuff was still on, double spikes were likewise obtained (record *3b*). The result was the same when the nerve was stimulated with a slowly rising current proximal to the cuff (record *3c*). Nor was the central nervous system necessary for production of the double spikes, as they were elicited even if the nerve had been blocked with procaine proximal to the place of excitation (record *3d*). The hyperventilation or hypocalcemia evidently changes the authorhythmic properties of the nerve fibers in such a way that duplication is produced on excitation.

It is interesting to note that the electromyographic picture of the voluntary contraction was likewise changed in the same direction, to double spikes and the machine-like regularity of the rhythm which was

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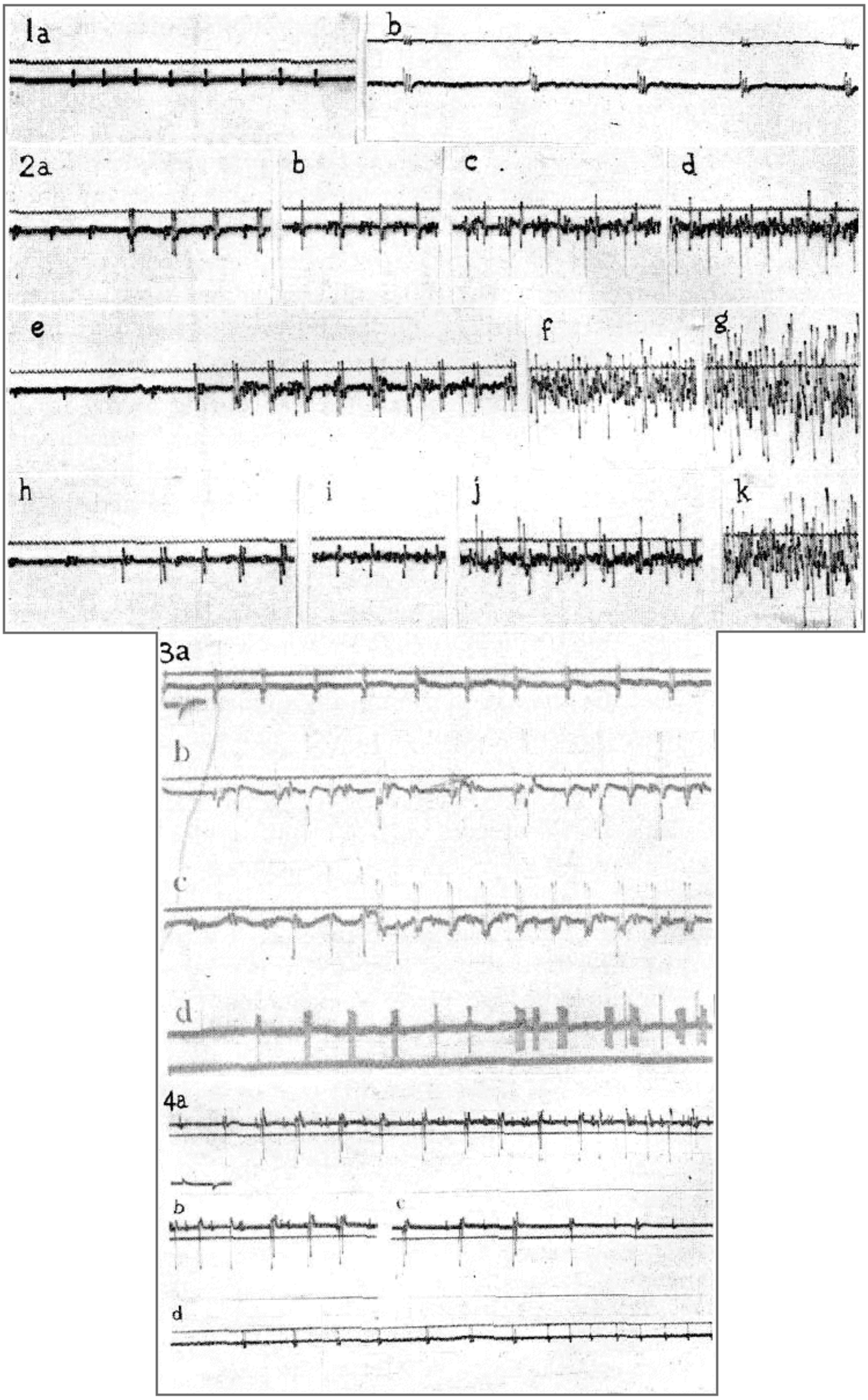
3. Kugelberg and Skoglund.[2] Skoglund, C. R.: The Response to Linearly Increasing Currents in Mammalian Motor and Sensory Nerves, Acta physiol. Scandinav. (supp. 12) **4**:6, 1942.

4. Kugelberg, E.: Activation of Human Nerves by Ischemia: Trousseau's Phenomenon in Tetany, Arch. Neurol. & Psychiat, this issue, p. 140.

5. Turpin, R.; Lefebvre, J., and Lerique, J.: Modifications de l'électromyogramme élémentaire et troubles de la transmission neuromusculaire dans tétanie, Compt. rend. Acad. d. sc. **216**:579, 1943.



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characteristic of the response of the nerve fiber activated during tetany (record 3*b* and records 4*a* and *b*). The change thus produced in the nerve seems also to determine the voluntary response in the motor neuron. It is true that the double spikes have been described by Gilson and Mills[6] under normal conditions, but they occurred then much more rarely, and less constantly, than in latent tetany.

As shown by records *2* and *6*, the spikes in the spontaneous spasm of tetany were not double throughout. First, the mechanism of duplication showed a tendency to fatigue, and, second, the doubling was much less prominent in spikes with a large amplitude, as was true in ischemic excitation.[4] Thus, the nerve fibers with a high threshold have less tendency to this kind of rhythmicity.

Furthermore, the duplication of spikes is suppressed when the frequency increases. This is strikingly evident in voluntary contraction (records *4a, b* and *c*). The parathyroprival patient made a light voluntary contraction, with slowly increasing strength. A large, easily distinguishable unit was selected for observation. Single at the start, it was almost immediately doubled, with a frequency of 8 to 9 per second (record *4a*). Slowly the contraction increased in strength, as indicated by the livelier background activity. When the frequency then suddenly rose to 13 or 14 per second, the duplication ceased, but returned when the intensity of the contraction diminished and the frequency was reduced (records *4b* and *c*). Similar general conditions are shown in record *4d,* taken from another subject who made a slight voluntary movement ten minutes after hyperventilation.

In this way, the double spikes behave like those described by Hoff and Grant,[7] elicited in a crossed extensor reflex (cat) at low temperatures and in conditions of acidity or veratrine poisoning. The same applies to the long trains of iterative impulses evoked in human nerves during the recovery from prolonged ischemia, when the rheobase and the accommodation in the nerve fibers are very low.[8] Evidently, the double spikes

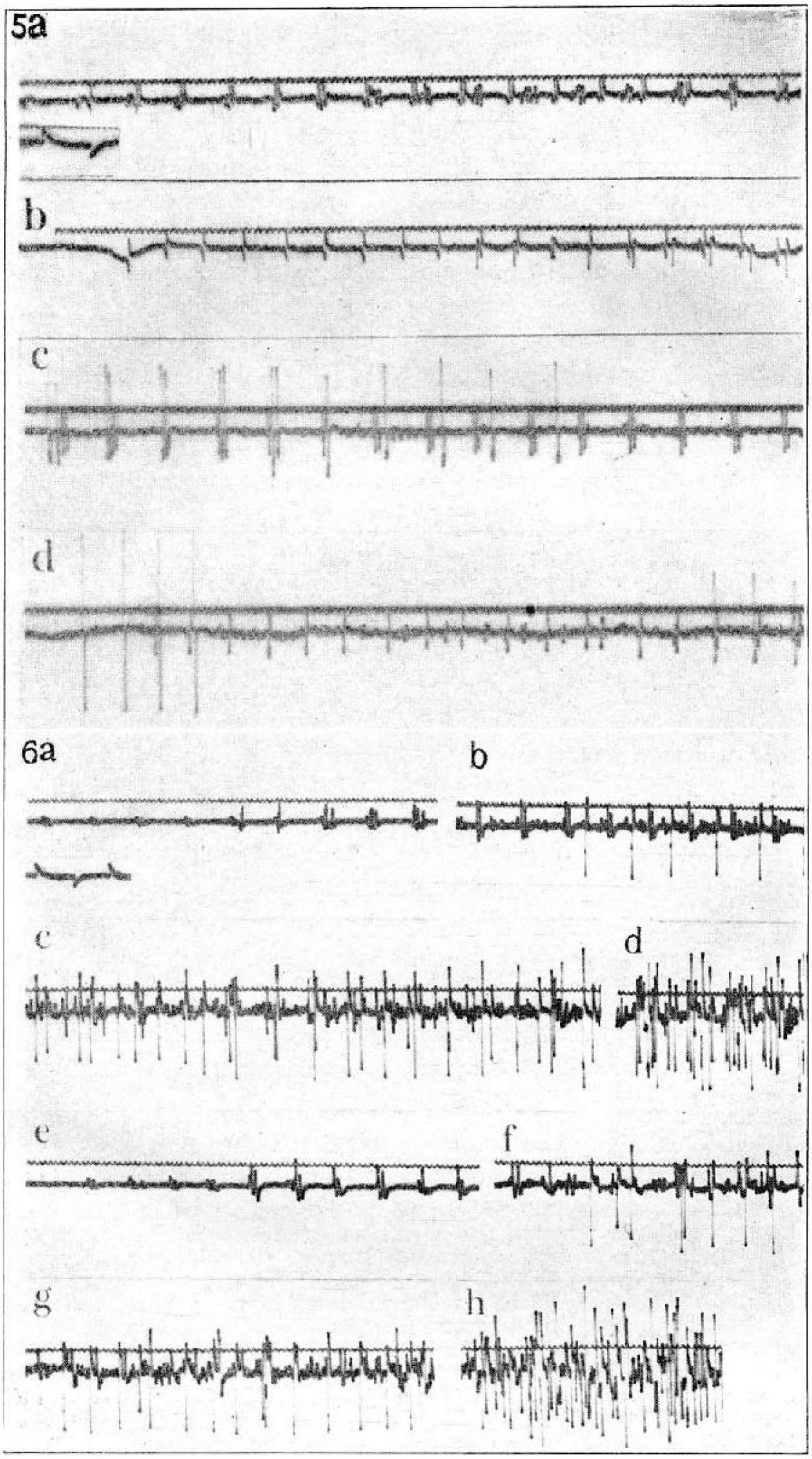
6. Gilson, A. S., and Mills, W. B.: Activities of Single Motor Units in Man During Slight Voluntary Efforts, Am. J. Physiol. **133**:658, 1941.

1: (*a*) Single spikes, and (*b*) triple spikes, at the start of discharge in a case of hyperventilation. In this, and in the accompanying records, tracings were taken from the first interosseous muscle; calibration, 100 microvolts; time, 1/100 second.

2: (*a, b, c* and *d*) Spontaneous tetany spasm, (*e, f* and *g*) electrical stimulation and (*h, i. j* and *k*) discharge on compression by pneumatic cuff in a case of hyperventilation. A full description is given in the text.

3: (*a, b,* and *c*) Double spikes, present though the circulation to the peripheral part of the arm had been shut off by compression before hyperventilation began. (*a*) spontaneous tetany; (*b*) voluntary contraction, in another case; (*c*) electrical stimulation; (*d*) parathyroprival tetany. The ulnar nerve was blocked at the ~~wrist~~ elbow. Electrical stimulation was made at the wrist. A full description appears in the text.

4: (*a, b* and *c*) Voluntary contraction, with cessation of double spikes as the frequency rises in a case of parathryoprival tetany; (*d*) a similar record in a case of hyperventilation.



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are abortive forms of such grouped discharges, which also show a rhythmic cycle in about 7 milliseconds. Earlier work on grouped discharges was done by Adrian,[9] Erlanger and Blair[10] and Fessard.[11]

The occurrence of double spikes can be correlated with the accommodation in the nerve. If the ulnar nerve is stimulated alternately at the axilla, where the changes in excitability are most marked, and at the wrist, where the changes are much less pronounced,[1a] differences are brought out in the electromyogram.

In a hyperventilation experiment (figure, *5*), the rheobase at the axilla before forced respiration was 3.1 milliamperes, and the threshold for prolonged iterative response was about 2.5 times that value. Distally, at the wrist, the corresponding figures were 2.25 milliamperes and three times the rheobase. After five minutes' forced respiration, the rheobase fell proximally to 1.0 milliampere, with a tetanic response at the very threshold; thus, the accommodation was nil. Distally, the values were then 1.5 milliamperes and twice the rheobase. Excitation proximally now produced the typical double spikes (record *5a*), whereas distally (record *5b*) the units were single ones. In size and form, the units were very similar in the two cases, the one unit being directed upward, the other downward. Presumably, therefore, the same nerve fibers were tested proximally and distally.

Records *5c* and *d* show the same conditions in a case of parathyroprival tetany: double spikes on excitation proximally (*c*) but not on excitation distally (*d*).

Comparison of Electrical Stimulation and Activation of Nerve by Hyperventilation.—In the ulnar nerve, tetany first activates the fibers mediating light touch, which have a lower threshold than the motor fibers for an iterative response to a constant or slowly rising current.[1a] Moreover, it activates the longest motor fibers of the small muscles of the

7. Hoff, H. E., and Grant, R. S.: The Supernormal Period in the Recovery Cycle of Motoneurons, J. Neurophysiol. **7**:305, 1944.

8. Kugelberg, E.: "Injury Activity" and "Trigger Zones" in Human Nerves, Brain **69**:310, 1946.

9. Adrian, E. D.: The Effects of Injury on Mammalian Nerve Fibers, Proc. Roy. Soc., London. s.B **106**:596, 1930.

10. Erlanger, J., and Blair, E. A.: Observations on Repetitive Responses in Axons, Am. J. Physiol. **114**:328, 1936.

11. Fessard, A.: Propriétés rythmiques de la matière vivante: II. Nerfs isolés, Paris, Librarie scientifique Hermann & Cie, 1936.

5: (*a*) Electrical stimulation at the axilla, and (*b*) stimulation at the wrist, in a case of hyperventilation; (*c*) stimulation at the elbow, and (*d*) stimulation at the wrist, in a case of parathyroprival tentany. A full description appears in the text.

6: (*a, b, c* and *d*) Spontaneous spasm of tetany, and (*e, f, g* and *h*) electrical stimulation, in a case of hyperventilation. A full description appears in the text.

hand before the shorter ones to the flexor carpi ulnaris, which have a higher threshold for iterative response than those to the hand.[1a] Furthermore, tetany affects the proximal part, where the threshold for iterative response is lower,[12] rather than the distal portion; hence, it is reasonable to assume that the nerve fibers are discharged according to their electrical thresholds, as was found to be true in ischemic excitation. It should be noted further that the tactile paresthesia produced by electrical stimulation is exactly like that in tetany.[1a] The appearance of the tonic spasm in the muscles of the hand during tetany can be as faithfully reproduced by stimulation with a constant current. This is shown also in the electromyographic picture of the spasm (records *2* and *6*).

The experimental subject was first instructed to hyperventilate until spasm was elicited and could be recorded (records *2* and *6, a, b, c* and *d*). The spasm was then allowed to subside. Five minutes later the ulnar nerve at the axilla was stimulated with a slowly rising current (records *2 e, f* and *g* and *6 e, f, g* and *h*). Comparison of the records shows that the spikes are substantially identical and that the frequency and the type of "recruitment" are also similar. The cathodal polarization of the nerve thus reactivates in identically the same way the discharge produced by hyperventilation.

If the electromyographic picture of electrical stimulation before hyperventilation is compared with that of the spontaneous spasm, it will be seen that they are, broadly speaking, alike. Whether the units mobilized in the two conditions are identical is difficult to determine, as the needle changes its position during the course of the test. Aside from the double spikes and the machine-like regularity of the rhythm, the patterns of the impulses correspond fairly well, showing the same type of "recruitment."

Comparison of Activation of Nerves in Tetany and Activation and Paralysis Produced by Ischemia.—It has previously been pointed out that the symptoms of irritation caused by ischemia in latent tetany exactly reproduce those in the spontaneous attack of tetany.[1b] The order in which the symptoms of ischemic paralysis spread will now be compared with the corresponding phenomena of irritation associated with hyperventilation.

The accompanying table, data of which are from a case of hyperventilation, shows the sequence in which the paresthesia and the spasm in the small muscles of the hand and the extensors and flexors of the forearm spread upward in the spontaneous attack of tetany and in ischemic excitation. The table also shows the spread of the anesthesia and motor paralysis associated with prolonged ischemia. The ischemic paralysis was first tested on the one arm. The experimental subject was

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12. Kugelberg, E., and Skoglund, C. R.: Responses of Single Human Motor Units to Electrical Stimulation, J. Neurophysiol. 9:391, 1946.

then instructed to hyperventilate. The manifestations of the symptoms of irritation on the other arm were then recorded. When the symptoms of irritation had subsided, on the termination of forced respiration, a pneumatic cuff was distended as high as possible on the same arm, and records of the new symptoms were taken.

As shown in the table, there is good correspondence between the way in which the symptoms spread and the sequence of tactile and motor excitation in tetany, as well as between the tactile and the motor paralysis in ischemia. The electromyographic picture of motor activation in tetany is also faithfully reproduced in the corresponding picture for ischemic excitation (figure, 2), records *a, b, c* and *d* showing activation by tetany and records *h, i, j* and *k* activation by ischemia. The frequency of spikes and type of "recruitment" are the same, and the spikes first appearing seem identical in the two cases.

Activation of Nerves in Hyperventilation (Tetany) and in Excitation and Paralysis Caused by Ischemia

	Hyperventilation Excitation	Ischemia	
		Excitation	Paralysis
Small hand muscles	4 min.	20 sec.	16 min.
Upper limit of disturbances in tactile sensation	About wrist	About wrist	About wrist
Extensors of fingers and wrist	5 min.	30 sec.	18-19 min.
Upper limit of disturbances in tactile sensation	4 cm. above wrist	10 cm. above wrist	4 cm. above wrist
Flexors of fingers and wrist	....	....	20-21 min.
Upper limit of disturbances in tactile sensation	....	....	13 cm. above wrist

Place of Origin of Motor Activity Induced in Tetany.—The experiments previously reported[1] show that the symptoms of irritation observed in tetany in the human arm are due to spontaneous discharges first and foremost in the proximal part of the nerves in the arm. As both afferent and efferent fibers discharge, the question whether the spasm was a reflex or was precipitated by direct excitation of motor fibers[1b] was left open. Now, since identically the same symptoms of irritation are produced by ischemia and since, as has been shown here, the spasm is due to direct excitation of motor fibers,[4] it is clear that direct excitation also is the mechanism of the spontaneous spasm of tetany.

More direct evidence in favor of this view might be obtained by blocking the brachial plexus with procaine and then inducing hyperventilation. As it is difficult, however, to obtain an effective block even if the procaine is injected into the nerve, it was considered advisable to refrain from an experiment involving such risks. In a case of inveterate hypocalcemic tetany bordering on spasm, with spontaneous double spikes in the first and fourth interosseous muscles, the ulnar nerve was blocked at the elbow. Despite the apparently perfect blocking, the impulses continued in the fourth interosseous muscle. They came with a regular frequency of 7 to 8 per second. It may be presumed that they had been generated peripheral to the block.

COMMENT

In this study, the investigation was confined to the arm, and chiefly to its distal part, especially the ulnar nerve and the muscles innervated by it. This restriction is due to the difficulty of carrying the symptoms of irritation associated with hyperventilation farther proximally on the arm or down to the legs. The investigation deals only with tactile and motor fibers. It is likely that afferent fibers other than those for touch sensation may be excited and may be responsible for the feeling of tension in the affected parts of the body. This sensation, however, is vague and is not suited to quantitative analysis.

The basis of this investigation consisted mainly in cases of acute tetany produced by forced respiration—an advantageous factor. In cases of chronic hypocalcemia, as is well known clinically, the patient becomes inured to the condition, so that after a time he can stand far lower values for the blood calcium without phenomena of irritation than if the change had set in suddenly. The habituation seems to take place in different ways for different kinds of fibers. Thus, in a chronic case, I have, for example, seen fascicular twitches and slight spasm without paresthesia. It is evident, therefore, that in chronic cases the spread of the various symptoms of irritation and the order in which the different types of fibers are activated cannot be regarded as tests of the reaction of the normal nerve to the stimulus of a value equal to that in acute cases. This may account for the atypical distribution of the spasms which is sometimes reported. A difference in circulation of the blood and in temperature in different parts of the body may have similar consequences, thus accounting for the rare cases of hemitetany that have been described, chiefly after extensive lesions in the central nervous system, such as those in hemiplegia (Spiegel[13]).

Experiments on animals and in vitro show that in cases of low calcium concentration or ~~hyperventilation~~ alkalosis, various nerve structures, such as the motor end plates (Kuffler[14]), the nerves (Lehmann[15] and others) and the ganglion cells (Bronk and associates[16]), discharge spontaneously.

13. Spiegel, E.: Hemitetanie bei Grosshirnläsionen, Deutsche. Ztschr. f. Nervenh. **65**:310, 1920.

14. Kuffler, S. W.: The Effect of Calcium on the Neuro-Muscular Junction, J. Neurophysiol. **7**:17, 1944.

15. Lehmann, J. E.: The Effect of Changes in the Potassium-Calcium Balance on the Action of Mammalian A Nerve Fibers, Am. J. Physiol. **118**:613, 1937.

16. Bronk, D. W.; Larrabee, M. G.; Gaylor, J. B., and Brink, F.: The Influence of Altered Chemical Environment on the Activity of Ganglionic Cells, Am. J. Physiol. **123**:24, 1938.

Inasmuch as extremely low values are exceptional in man, the chief problem is to ascertain what structures have the lowest threshold for activation. My previous experiments show that in man there are particular nerves and nerve fibers in which spontaneous discharges are primarily responsible for symptoms of irritation during attacks of tetany elicited by forced respiration.

It may be questioned whether the mechanism for the symptoms of excitation in tetany produced by hyperventilation is exactly the same as that in hypocalcemia. In hyperventilation compensatory changes in the circulation, as described, for example, by Gibbs, Maxwell and Gibbs,[17] may modify the locus for the first manifestation of spontaneous activity.

However, the symptoms of irritation are exactly the same in the two kinds of tetany. Moreover, in 1 case it was shown that the typical double spike discharge occurred in the nerve in connection with hypocalcemia; hence, it may be inferred that the peripheral nerves also play a large part in the generation of the symptoms of irritation. It is evident, however, that if the ionized calcium content falls sufficiently the nerve fibers and ganglion cells at the center will also begin to discharge.

The principal result of this study is the observation that hyperventilation causes the different nerve fibers to discharge according to their thresholds for an iterative response to a constant or a slowly rising current, and that the spread of ischemic excitation and paralysis is the same as that for tetanic activation. The anatomic basis for this observation may be the size of the fiber.[1b] It may also be asked whether the common factor is not simply the state of calcium in the nerve fiber.

If these conditions are generally valid, it should be possible, by observing the spread of the symptoms in tetany, to obtain a rough, but simple, test of the iterativity of the peripheral nerves in man. The tendency to repetition is so organized that the nerves to the face and those to the hands are the first to discharge spontaneously; in the arm, the longest fibers, and then the shorter ones, discharge, the motor fibers to extensor muscles being more inclined to repetition than those to the flexors. The hands and the face are the parts best represented in the cerebral cortex, and their nerve supply is phylogenetically best developed, another aspect of their unique position.

Moreover, there are many indications that the relative differences between long and short fibers, between fibers to flexor and fibers to extensor muscles, and between fibers to the hands and to the face on the one side, and to other parts of the body on the other, which ischemia and tetany have shown to exist in the peripheral nerves, are found also in the central paths right up to the cortex, and there play an important part under pathologic conditions. The great majority of the cerebral

17. Gibbs, F. A.; Maxwell, H., and Gibbs, E. L.: Volume Flow of Blood Through the Human Brain, Arch. Neurol. & Psychiat. 57:137 (Feb.) 1947.

symptoms of irritation, such as paresthesia accompanying migraine and other vascular disturbances and sensory and motor jacksonian seizures, have a predilection for the hands and the face. It must be left to further investigations to shed fuller light on this subject.

SUMMARY

The symptoms of irritation associated with tetany, chiefly elicited by forced respiration, have been studied in the human arm and hand. The electromyogram of the spasm is described.

The following conclusions are drawn:

1. The spasm is caused by spontaneous discharges arising first and foremost in the proximal part of the longest motor nerve fibers. The double spikes previously observed are due to an iterative response in nerve fibers of low accommodation. They are commonest in units of small amplitude and become single spikes with a rise in frequency.

2. Hyperventilation or hypocalcemia produces discharges in the A fibers of the ulnar nerve according to their threshold for an iterative response to a slowly rising or constant current.

3. Stimulation of a nerve in latent tetany with a slowly rising current reactivates, in certain respects, the spontaneous motor discharge of tetany. In both electrical and tetany activation the activity starts with a unit of small amplitude and is followed by units of progressively larger spikes. In most experiments, the units "recruited" are the same. There is little or no difference in the frequency of discharge.

4. The changed autorhythmic properties of the motor nerve fibers in tetany are also impressed on the pattern of impulses evoked by voluntary contraction.

5. The order of activation of the various nerve fibers in the arm in tetany is similar to that in ischemic activation and paralysis. The effect of ischemia on the motor nerve is exactly the same as that of hyperventilation or hypocalcemia with respect to the order of activation of spikes of various sizes and the frequency of discharge.

In tetany activation and in ischemic activation and paralysis, the common factor involved ~~in the iterative response to a constant current~~ is briefly discussed. It is suggested that the relative differences between nerve fibers in the periphery revealed by ischemia and tetany may be maintained right up to the cortex.

NOTE.—The fundamental work of Lorente de Nó[18] has appeared since these papers were sent in for publication, on March 3, 1947, and cannot be discussed here, though it evidently affords explanations of observations made.

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18. Lorente de Nó, R.: A Study in Nerve Physiology, Studies from the Rockefeller Institute of Medical Research, New York, 1947, vols. 1 and 2.

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