Full correction of hypercalcemia with treatment occurred in 8 of 13 instances in these patients. Correction of hypercalcuria was observed in 9 of 14 instances. Various possible mechanisms underlying these observed effects are considered.

1. Albright, F., and Reifenstein, E. C., Jr., *The Parathyroid Glands and Metabolic Bone Disease*, Williams and Wilkins, Baltimore, 1948.

2. Pearson, O. H., Li, M. C., Maclean, J. P., Lipsett, M. B., and West, C. D., *Annals N. Y. Acad. Sci.*, 1955, v61, 393.

3. Pearson, O. H., West, C. D., Hollander, M. D., and Treves, N. E., *J.A.M.A.*, 1954, v154, 234.

4. Fiske, C. H., and Logan, M. A., *J. Biol. Chem.*, 1931, v93, 211.

5. Clarke, E. P., and Collip, J. B., *ibid.*, 1925, v63, 461.

Received August 1, 1956. P.S.E.B.M., 1956, v93.

Effect of Sodium Lack on Local Response of the Single Crustacean Motor Axon. (22742)

ERNEST B. WRIGHT* (Introduced by Hermann Rahn)
Department of Physiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Sometime ago it was suggested, as the basic assumption for a theory on excitation of nerve (1), that a local or initial depolarization occurred in the immediate area of nerve to which the stimulus was applied. When this local voltage attained a certain optimum value it released or "triggered" the all or none response. Shortly thereafter this hypothetical local potential was measured directly(2) and examined in some detail(3) in crustacean nerve fibers. However, the actual source of this small potential remained obscure. Recently the all or none response has been studied quantitatively by these same investigators and others(4,5), and it has been established that the action potential is the result of an initial rapid sodium ion current inward through the fiber membrane followed by a slower outward potassium ion flow. The question now remains what is the cause of the small local disturbance always observed in the cathodal region with subthreshold stimulation? Is this also due to ionic currents or is it perhaps the result of the sudden appearance of a hormonal substance? It has been suggested, for example, that the release of ACH might produce the initial or local depolarization(6) as it does an end plate potential at the neuromuscular junction.

* Present address: University of Florida, College of Medicine, Gainesville.

The present work was undertaken to examine the local response of different single crustacean nerve fibers which possessed quite different excitability properties(7). A brief report of this investigation has already been given in abstract. Recently, certain results were obtained which, because of their significance, are described briefly in this paper.

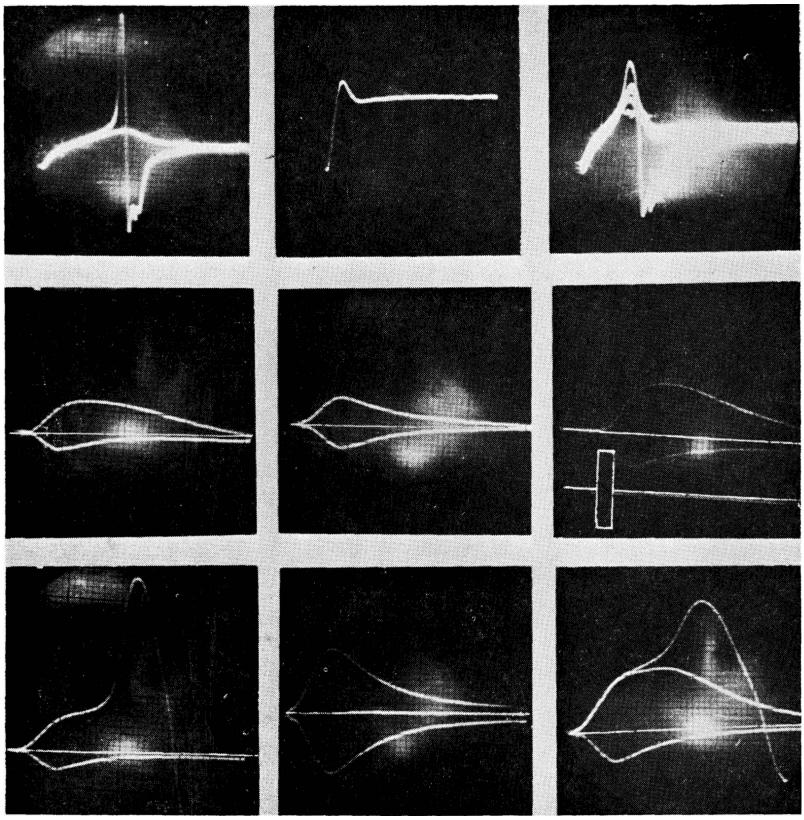
Methods. The lobster single nerve fiber was used throughout. The preparation, mounting and recording technics have been described (8). The local or initial response was clearly observed with subthreshold stimulation when the fiber was entirely raised in oil, the V method, and stimulation and recording occurred in the identical cathodal area. Cole's physiological solution(9) was used with variations for the study of the effect of different ion concentrations.

Preliminary. One day by accident in mixing the physiological solution the buffer was omitted and although the pH was very low, found later to be only 5.8, the nerve fibers functioned well for several hours. Others, too, have noticed the lack of effect of low pH on these fibers (Adelman, personal communication). The importance of this finding however, was that it meant an entirely sodium-free solution could be applied to a nerve fiber, for some slight amount of sodium has always necessarily been included in the form of buf-

A

B

C



NA NA FREE NA

FIG. 1. Electrical response of a single crustacean opener fiber recorded directly at the stimulating cathode. Row A—Response with long duration, 100 ms, stimulation in normal physiological solution, left, sodium free (choline chloride substituted), middle, and normal solution, right. Row B—Recordings with short duration, 0.2 ms, stimuli of negative (upward) or positive (downward) polarity. Note asymmetry, negative deflection much larger in left and right pictures. In sodium free solution, middle picture, deflection is symmetrical. Row C—Same as B with stronger, threshold, stimulus. See text.

fers in so called "sodium free" media.

Results. When a single nerve fiber was dipped into a sodium free solution, containing dextrose or Choline Chloride to maintain the proper tonicity, all nerve electrical activity was extinguished instantly. Not only was the all or none spike immediately abolished, a not unexpected observation, but the subthreshold local response also disappeared at once. The effect was dramatically sudden and complete. With sodium ions added even in small concentrations the local response reappeared as abruptly as it disappeared in the sodium free medium. The recovery of the all or none potential was also extremely rapid but depended somewhat on the amount of sodium placed in the solution. When only a small concentration of sodium was added to the medium the spike appeared, not unlike the spurious response of a fatigued fiber.

A typical experiment is shown in Fig. 1. In the top row, A, the local and spike potentials elicited by "D.C." stimulation of 100 ms. duration are shown in normal, sodium free, and normal solutions, left to right respectively. The sweep speed for these recordings was slow. In the middle row, B, are illustrated the responses to just subthreshold, 0.2 ms. duration shocks. The sweep speed was fast. The bottom row, C, illustrates the recordings with threshold stimulation of 0.2 ms. duration in normal, sodium free and normal solutions, left to right respectively. The short duration shocks applied were both negative, upward deflection, and positive, downward deflection, polarity as shown in the right picture, row B. A just subthreshold negative shock should produce a much larger deflection than a positive shock, due to the local response of the fiber itself in the neighborhood of a cathode(3).

At the start of the experiment with normal solution and D.C. stimulation there was a low voltage long duration subthreshold response and a large diphasic spike with threshold voltage. In the sodium free medium with strong stimulation there was a slight artifact but no real electrical activity. With sodium in the medium again, right hand picture, with varying strengths of stimulation, multiple sweeps, a large amplitude fairly short duration local response is the predominant deflection observed which when large enough produced an all or none response somewhat smaller and longer enduring than the original. Short duration subthreshold pulses normally elicited asymmetrical deflections, that is, the upward or negative deflection was far greater than the downward or positive deflection as expected (Row B, left picture). The negative deflection is augmented by the activity of the fiber, the local response, the positive deflection is not. The local response, catelectrotonus, of the fiber is responsible for the asymmetry of the deflections. These recordings are the same as described years ago(3). This asymmetry was also observed with threshold stimulation. However, with sodium free solution the responses due to positive and negative pulses, weak or strong, became perfectly symmetrical. The local response was gone, and only the shock artifacts of equal magnitude remained. The fiber was electrically totally inactive, or, to all intents and purposes "dead". With the return of sodium to the medium the action potential, slightly smaller and broader, appeared immediately and at the same time a subthreshold response of even greater asymmetry than at the start was recorded. This effect has been seen in all fibers used.

Conclusion. Sodium is necessary for the production of the local response. It has yet to be proven just what the role of the sodium ion is in the development of this local potential. The above findings do not eliminate the possibility of the release of a hormone such as ACH as the "trigger" mechanism, for it has been shown(10) that end plate potentials are all but abolished in the presence of ACH without sodium. However, it seems very likely that the sodium ion is the key to the setting off and development of the action potential. This has been known to be so for whole frog nerve preparations(11). Whether the ion actually moves inward to cause the local potential as it does during the rising phase of the spike remains to be determined. Its presence may simply be required for the initiation of some other reaction. The fact that the results are the same whether dextrose or Choline Chloride is substituted indicates that it is the sodium ion itself that is the essential particle.

Summary. The local or initial response of crustacean single motor axons has been recorded at the stimulating cathode. The deflections caused by a short duration shock of positive and negative polarity are asymmetrical. Normally the deflection caused by the negative pulse is considerably larger. In the absence of sodium, with either dextrose or Choline Chloride substituted, the local potential disappears. The deflections caused by positive and negative pulses become symmetrical. The effect is instantaneous and reversible. It is concluded that the sodium ion is essential for the production of the local or initial response.

1. Hill, A. V., *Proc. Roy. Soc.*, 1936, v119, 305.

2. Katz, B., *ibid.*, 1937, v124, 244.

3. Hodgkin, A. L., *ibid.*, 1938, v126, 87.

4. Hodgkin, A. L., and Katz, B., *J. Physiol.*, 1949, v108, 37.

5. Hodgkin, A. L., and Huxley, A. F., *ibid.*, 1952, v117, 500.

6. Nachmanson, D., and Wilson, I. R., *Electrochemistry in Biology and Medicine*, Wiley and Sons, 1955.

7. Wright, E. B., and Coleman, P. D., *J. Cell. Comp. Physiol.*, 1954, v43, 133.

8. Wright, E. B., Coleman, P. D., and Adelman, W. J., *ibid.*, 1955, v45, 273.

9. Cole, W. H., *J. Gen. Physiol.*, 1941, v25, 1.

10. Nastuk, W., *Am. J. Med.*, 1955, v19, 667.

11. de No, L., *Studies from Rockefeller Inst. for Med. Research*, 1947, v132, part I.

Received August 27, 1956, P.S.E.B.M., 1956, v93.