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Effect of Local Ischemia upon Human Nerve Fibers *in vivo*.*

I. MACLAREN THOMPSON AND H. STEWART KIMBALL.† (Introduced by David M. Greenberg.)

From the Division of Anatomy, University of California Medical School, Berkeley.

In each experiment ischemia was induced in the forearm and hand by inflating to a pressure of about 160 mm. Hg. a Riva-Rocci sphygmomanometer applied above the elbow. The median, ulnar or radial nerve was stimulated at the wrist by an alternating current of 160 cycles per second, using the generator and electrode described by Thompson *et al.*[1]; the minimal current (expressed as ma × v) evoking sensation was recorded as an indicator of the threshold for stimulation of sensory fibers. A threshold reading was taken every 2 minutes after inflation of the sphygmomanometer, for about 16 minutes.

Thirteen such experiments were performed, involving 4 subjects. The results are exemplified in the following experiment, wherein the right radial nerve was stimulated; the first figure of each pair denotes the number of minutes after the induction of ischemia, the second figure is the threshold at that time: 0, 5.5; 2, 7.2; 4, 5.2; 6, 2.8; 8, 2.4; 10, 1.1; 12, 0.8; 14, 1.6; 16, 11.5. In every experiment there was, on the whole, a rapid and progressive lowering of the threshold for about the first 12 minutes. The average fall in threshold per unit of time significantly exceeded the corresponding value in each of 4 groups of control experiments; the most important group consisted of 14 experiments wherein nerves were similarly stimulated *proximal* to a sphygmomanometer arresting the circulation. In 5 of the 13 instances the threshold drop progressed throughout the duration of the experiment; but on 8 occasions (though in no control experiment) there was a terminal rise (exemplified above) to values equalling or exceeding the initial figure. We infer that the ischemia of the nerve first increased and later diminished the irritability of those fibers first stimulated by a current increasing from zero.

These results confirm the opinion of Lewis, Pickering and Roths-

* Aided by a grant from the Board of Research of the University of California.

† Mr. Kimball's share in this work was incorporated into his M.A. thesis, deposited in the Library of the University of California.

1 Thompson, I. M., *et al.*, *Univ. Calif. Publ. Anat.*, 1934, **1**, 167.

2 Lewis, T., Pickering, G. W., and Rothschild, P., *Heart*, 1931, **16**, 1.

child[2] that such ischemia affects the nerve fibers, not merely the nerve endings. But Bishop, Heinbecker and O'Leary[3] attribute the effect to the pressure whereby the ischemia is produced. In view of the work of Erlanger, Gasser, and others, it seems clear that we studied the thresholds of large, easily-stimulated fibers. The initial drop in threshold, followed by a rise above the normal, so closely parallels the observations of Heinbecker[4] on threshold changes in anoxemic excised frog nerves that we consider our results to confirm Heinbecker's work and extend it to human nerves *in vivo*.‡ But asphyxia attacks the small fibers first,[4] whereas pressure affects first the large fibers (Gasser and Erlanger[5]); in our experiments the large fibers, though more susceptible to pressure, manifested behavior characteristic of asphyxia. Our work thus presents another aspect of a difficulty that has confronted previous investigators, and attempts to explain which have been offered by Zotterman,[6] by Bishop, Heinbecker and O'Leary[3] and by Gasser.[7] Both pressure and anoxemia seem to contribute to the result. (Terms like anoxemia and asphyxia are here used to designate the total chemical environment of the nerve fibers determined by circulatory arrest; a more particular discussion is offered by Gerard.[8]) It may be that pressure increases the susceptibility of the fibers to ischemia; this would explain the early onset of anoxemic phenomena in the large fibers. But how could pressure applied in the arm affect susceptibility to asphyxia throughout the forearm and hand? Possibly by blocking the passage along the nerve fibers of those "trophic" influences from the nerve cells whose existence is suggested by Wallerian degeneration, and has recently been upheld on other grounds by Parker.[9] §

Alternatively, and perhaps preferably, accepting the view that pressure does not contribute toward the phenomenon,[2, 7] our results may be regarded as confirming, from a study of irritability, Gasser's[7]

[3] Bishop, G. H., Heinbecker, P., and O'Leary, J., *Am. J. Physiol.*, 1933, **106**, 647.

[4] Heinbecker, P., *Am. J. Physiol.*, 1929, **89**, 58.

‡ Comparison of our data with the time-relationships recorded by Heinbecker[4] leads us to believe that had the 5 experiments wherein the threshold did not rise been prolonged, that phenomenon would have occurred.

[5] Gasser, H. S., and Erlanger, J., *Am. J. Physiol.*, 1929, **88**, 581.

[6] Zotterman, Y., *Acta Med. Scand.*, 1933, **80**, 185.

[7] Gasser, H. S., *Proc. Assn. Res. Nerv. and Ment. Dis.*, 1935, **15**, 35.

[8] Gerard, R. W., *Am. J. Physiol.*, 1930, **92**, 498.

[9] Parker, G. H., *Am. Nat.*, 1932, **66**, 147.

§ It must be assumed that "trophic" impulses are more easily blocked by pressure than are ordinary nerve impulses.

conclusion from experiments on conductivity, that in mammalian nerves *in vivo* asphyxia affects the large fibers first.

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Effect of Lactogenic Hormone on Embryonic Tissues Cultivated *in vitro*.

A. J. SALLE AND I. L. SHECHMEISTER.

From the Department of Bacteriology, University of California, Berkeley.

Since lactogenic hormone* is known to produce a specific effect on epithelial cells of the pigeon crop[1] *in vivo,* experiments were designed to determine whether it would stimulate the growth of embryonic pigeon crop epithelium cultivated *in vitro.* If stimulation could be observed in this manner such a test might be more delicate and superior to the present methods employed for determining hormonal potency.

Preliminary to testing the hormone on the specific crop epithelium, which reacts to it *in vivo,* experiments were carried out on the following non-specific tissues cultivated *in vitro:* (1) Embryonic chick connective tissue, (2) embryonic chick epidermis, (3) embryonic pigeon oesophageal epithelium. Finally the hormone was tested on cultures of embryonic epithelium taken from the crop sac areas known to be reactive *in vivo* in the hatched pigeons.

In all cases the dilutions were performed in triplicate. Also, every experiment was repeated 3 times before the results were reported. Each flask contained about 12 fragments of tissue.

(1) *Embryonic Chick Connective Tissue.* Chick heart tissue from 10- to 14-day-old embryos was used as the source of fibroblasts. The tissues were finely cut into fragments of about 1 mm. in diameter and immersed in Tyrode solution until ready for use.

The embryonic fluid was prepared by mincing 14-day-old chick embryos in a tissue grinder and suspending the pulp in 4 parts of

* Anterior pituitary mammotropic principle, prolactin, galactin, mammotropin. The preparations used in these experiments were kindly supplied by Dr. W. R. Lyons of the Division of Anatomy. The hormone caused crop sac epithelial growth in 24-48 hours when given in doses as low as 0.1 microgram intradermally over the crop sac area.

1 Riddle, O., Bates, R. W., and Dykeshorn, S. W., *Am. J. Physiol.,* 1933, **105**, 191.