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Evidence that the primary change in stimulation is an increase in the permeability of the limiting membranes of the irritable elements.

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Various facts and theoretical considerations indicate clearly that the process of stimulation in muscle or nerve has its seat at the semi-permeable boundary layers or plasma membranes of the irritable elements, and consists in a sudden and reversible increase in the permeability of these membranes. After a brief review of this general evidence the following experiments were described.

I. *Experiments with the Larvæ of Arenicola cristata.*—These are the free-swimming ciliated larvæ of a marine annelid; they are small worm-like organisms about 0.3 mm. in length, readily obtained in large quantity by rearing. The larvæ have a well-developed muscular system; the special peculiarity which fits them for the purpose of the following experiments is the presence throughout the whole body of a water-soluble yellow pigment; this substance is contained *within the cells*, and does not visibly leave the latter except under conditions of markedly increased permeability—as on death or after treatment with cytolytic substances (*e. g.*, saponin); it then diffuses into the medium and, if sufficient larvæ are present, colors the latter a bright straw yellow. Its exit thus serves as a convenient index of increased permeability. It was found that during strong chemical stimulation a rapid loss of pigment always occurs: the rate and degree of this loss run closely parallel with the intensity of the stimulating action, as indicated by the extent and duration of the muscular shortening. Pure isotonic ($m/2$) solutions of neutral sodium salts ($NaCOOCH_3$, NaCl, NaBr, $NaNO_3$, $NaClO_3$, NaI, NaCNS) all cause strong and persistent muscular contraction accompanied by rapid loss of pigment; the addition of a little calcium chloride to the solution (1 c.c. $m/2$ $CaCl_2$ to 25 c.c. $m/2$ sodium salt) prevents both the

stimulating action and the loss of pigment. Potassium salts show a similar stimulating and permeability-increasing action, neither of which, however, is checked by the addition of calcium. Isotonic LiCl solution shows moderate stimulation with moderate loss of pigment; both are checked—as in the case of NaCl—by calcium. On the other hand while pure *m*/2 CsCl produces well-marked stimulation and loss of pigment, the addition of calcium does not check, but on the contrary markedly accentuates both effects. Mixtures of potassium and magnesium chlorides show varying action according to the relative proportions of the salts; in pure isotonic $MgCl_2$ solution there is neither stimulation nor loss of pigment, but complete reversible muscular anæsthesia; the same is true of mixtures containing a decided excess of $MgCl_2$ (*e. g.*, 1 volume *m*/2 KCl+4 volumes *m*/2 $MgCl_2$); when the proportion of KCl is increased to one half or more, stimulation and with it loss of pigment appear; in mixtures of equal parts both effects are slight; in mixtures of 2 vols. *m*/2 KCl to 1 vol. *m*/2 $MgCl_2$ both are somewhat increased; in a mixture of 4 vols. *m*/2 KCl to 1 vol. *m*/2 $MgCl_2$ there is moderate stimulation with moderate loss of pigment, though both effects are decidedly less marked than in pure *m*/2 KCl. Saturated solutions of chloroform or ether in sea-water produce strong contraction with rapid loss of pigment; weak solutions anæsthetize without stimulating or visibly increasing permeability.

II. *Experiments with Frog's Muscle.*—It was pointed out that many cytolytic substances produce slow and usually irreversible contraction in vertebrate skeletal muscle; this is the case with soaps, bile-salts, various hæmolytic alkaloids or glucosides (*e. g.*, saponin, digitalin, solanin, agaricin), strong solutions of lipoid solvents (chloroform, ether, benzol, toluol, etc.), certain foreign blood sera and certain bacterial toxins (*e. g.*, tetanus). The contraction is typically slow and steady, unaccompanied by twitching, and passes over into permanent rigor. It was found that after treatment of the muscle for some minutes with pure isotonic solutions of various neutral sodium salts the response to many of the above substances is so altered that rapid and vigorous contractions with twitching may result. This sensitizing action increases in the order: NaCl, NaBr, $NaNO_3$, $NaClO_3$, NaCNS and NaI, being usually slight

with the first two salts, and well marked with the others, particularly with iodide and sulphocyanate. Frog's gastrocnemii immersed for five minutes in *m*/8 NaI or *m*/8 NaCNS show rapid contraction and twitching when immersed in isotonic solutions of the following substances in Ringer's solution or physiological salt-solution: saponin, digitalin and solanin (marked action); agaricin and aconitine (relatively slight action); chloroform (marked action); Na-oleate (marked action); bile-salts (marked action); horse and dog serum (marked action with vigorous twitching); tetanus toxine (vigorous twitching); rattlesnake venom (moderate action). The intensity of the stimulating action shows a general parallelism with that of the hæmolytic action.

Muscles may be similarly sensitized to osmotic stimuli (distilled water and hypertonic sodium chloride solution). This fact, as well as the fact that colloidal substances (serum, etc.) may show marked stimulating action, furnishes additional proof that stimulation depends essentially on an alteration of the plasma membrane.

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Nature of the muscular contraction.

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The comparison of histological preparations of uncontracted and contracted smooth muscle indicates that during the contraction of this tissue fluid passes from the fibers to the interstitial spaces. It seems possible, therefore, that the contraction of smooth muscle may be brought about by an interchange of fluid between its cells and their surroundings in the same way that the movements of *Mimosa* are caused by changes in the turgor of its cells. This hypothesis may be tested by investigating the effect of swelling reagents and their opposites on the length of smooth muscle. The hypothesis would be supported if it could be shown that smooth muscle lengthened when immersed in solutions which cause it to gain in weight and shortened in the opposite class of solutions.

The changes of weight and the changes of length of frog's smooth muscle have been followed in Ringer's solution, in various