be a factor in cardiac compensation during the induction stage of artificial hyperpyrexia.

Conclusions. Analysis of the polygrams recorded during artificial fever suggest that the distressing symptoms one observes and the subjective discomfort experienced by patients during the induction of artificial hyperpyrexia are caused by an inadequate filling of the heart. The inadequate filling of the heart may be accounted for, in part at least, by an insufficient duration of the filling time. These observations further support the belief that the undesirable symptoms which occur during artificial fever therapy are caused by a temporary cardiac decompensation resulting from inadequate filling. Reduced cardiac filling probably results from (1) a reduced venous return resulting from uncompensated peripheral vasodilatation, (2) a shortening of the filling time, and (3) reduced blood volume.

Compensation may be accounted for not only by an increase in the efficiency of the emptying of the ventricles but also by a more adequate filling brought about by an increase in the venous return, an increase in the duration of the filling time and possibly by increased atrial activity.

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A Histological Problem Concerning the Conditions at the Nerve Endings in Skeletal Muscle.

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Until the recent appearance of the chemical transmission hypothesis[1] it was generally assumed that the excitation of skeletal muscle was effected electrically by the action current of the nerve ending. At present neither the chemical nor the electrical hypothesis can be considered to be well established. It seems likely from the nature of the problem that much of the decisive evidence must come from a demonstration that the structures and arrangements at the neuromuscular junction are more suited to the one type of transmission than to the other. In any case, the point of view must be consistent with respect to the structure of the junction and its function. It is our purpose to discuss a serious inconsistency which exists at present

1 Dale, H. H., Feldberg, W., and Vogt, M., *J. Physiol.*, 1936, **86**, 353.

in regard to the electrical polarization of the membrane of nerve ending.

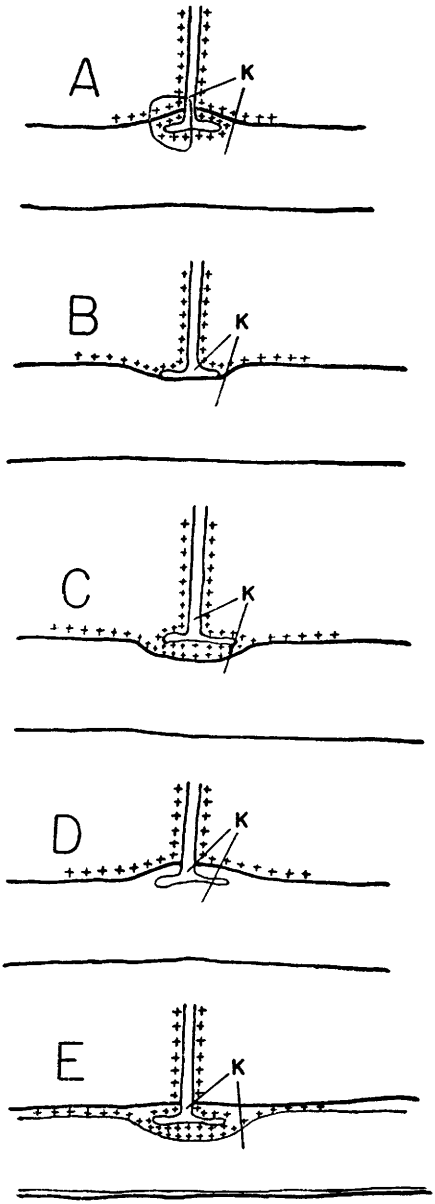
The polarization of the membranes* of both nerve and muscle is believed to be a consequence of semi-permeabilities. The membranes are impermeable to anions while permeable to certain cations, notably to K which is the principal cation within the cell but which exists in relatively low concentration in the extracellular fluid. The K ions are retained within the cell for the most part in association with the impermeable negative ions thus providing a concentration difference from inside to outside which accounts satisfactorily for the observed membrane potential.[2, 3] It is believed that in the case of muscle the polarized membrane is associated with the sarcolemma or a plasma membrane immediately underlying it. The nerve according to the most generally accepted histological description penetrates the muscle membrane after losing its sheaths and lies embedded in the specialized sarcoplasm of the end plate. Thus Fig. A probably is in best accord with current histological and physiological opinion. Here the nerve membrane is represented as being polarized after it penetrates the polarized muscle membrane. This representation is, however, quite impossible according to the K hypothesis for if both sarcoplasm and neuroplasm are of similar high K content there can be no appreciable difference of K concentration across the membrane of the nerve ending and consequently this membrane cannot be polarized. But if the nerve ending is not polarized after it enters the sarcolemma it cannot, according to current views, convey a nerve impulse electrically, neither can it act as a secretory organ in accord with the chemical hypothesis, because organs known to secrete in response to stimulation do so on account of or accompanied by membrane depolarization.

This difficulty can, conceivably, be avoided in a number of ways. According to Fig, B, for example, it may be supposed that the polarizable membranes of the nerve and muscle are actually in contact. But in the contiguous regions the K gradients across the membranes and consequently the polarizations will be suppressed. However, the polarized regions of the nerve and the muscle will be essentially continuous over the boundary of the contiguous region permitting easy electrical conduction. It might be expected, however, that this arrangement would permit as much diffusion into the muscle of a

* Although there is no exact indication from electrical measurements of the location of the polarization it must from physico-chemical considerations, almost certainly be across the cell membrane and not across connective tissue sheaths.

2 Fenn, W. O., Cobb, D. M., Hegnauer, A. H., and Marsh, B. S., *Am. J. Physiol.*, 1934, **110**, 74.

3 Fenn, W. O., *Physiol. Rev.*, 1936, **16**, 450.



FIGS.

In Fig. A is represented schematically the current concept of the positions of the polarized membranes of the muscle and nerve as indicated by the plus signs. The other figures depict alternative arrangements. In Fig. E the inner lines represent the boundaries of the myofibrils. In all cases the lines from the letter K point to regions rich in potassium. The figures are discussed in the text.

chemical formed in the nerve at one time as at another so it would not be well adapted to chemical transmission.

Another possibility is depicted in Fig. C, in which it is supposed that the polarized membrane of the muscle fiber is not penetrated by the nerve, but folds in around the ending, leaving access for free circulation of extra-cellular low K fluid. The space between muscle and nerve substance would probably need to be of the same order as that separating nerve fibres in a nerve bundle. This arrangement would permit the nerve endings to be polarized throughout and would probably be more favorable for chemical than electrical transmission for reasons which need not be discussed here.

Still another possibility is indicated in Fig. D. In this case which is essentially a correction of the current concept in Fig. A, to allow for high K around the ending it is assumed that the membrane of the nerve ending is not polarized after entering the sarcoplasm and that the polarizable membranes of the nerve and the muscle come into contact at the point of entry permitting a continuous polarization over the junction. This arrangement which is in best accord with histological opinion, presumably would be admirably suited to electrical, but not to chemical transmission for the reasons given in connection with Fig. B. In this case, the nerve ending could be assigned only trophic functions since it would not be necessary for transmission.

A fifth possibility is represented in Fig. E. Here it is assumed that the high K region of the muscle is within the myofibrils and not in the sarcoplasm. In this case the polarized membrane of the muscle would be around the fibrils only and the nerve endings being surrounded by low K would be polarized and capable, therefore, of conveying impulses to their termini and effecting electrical or more probably, chemical transmission. The existence of this possibility is supported by the evidence for a periterminal network connecting the myofibrils and the endplate but opposed by studies on embryos[4, 5] which suggest that nervous stimulation of a muscle fiber is possible as soon as a motor nerve makes contact with its outer membrane. Also, as mentioned above, high K is thought to occur in the sarcoplasm on the basis of chemical work.

It cannot be denied, of course, that there is a possibility that the membrane polarization of the nerve ending is maintained by other means in an arrangement like Fig. A, even within a sarcoplasm of high K content. This is perhaps rather unlikely, however, and in addition this arrangement would give rise to a continuous current flow if the membrane potentials of the nerve and the muscle were

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[4] East, E. W., *Anat. Rec.*, 1931, **50**, 201.

[5] Tello, J. F., *Z. f. Anat. u. Entwicklunges*, 1922, **64**, 348.

similar in magnitude. For a line of possible current flow, as indicated by the loop on the left in Fig. A, starting within the nerve ending and crossing first the sarcoplasm, then the muscle membrane and then the nerve membrane again outside the muscle would encounter 2 polarizations in one direction and only one in the other. Consequently, the potential would not be balanced and current would flow continuously.

A discontinuity between the polarized membrane of the muscle and that of the nerve in the Fig. D arrangement would also allow local currents to flow from each membrane through the discontinuity. The smaller the discontinuity, however, the less the current and there would seem to be no reason why the discontinuity and, therefore, the current might not be thought to be vanishingly small even if the way were not clear for assuming a strict continuity of the nerve and muscle membranes.

The arrangements in Fig. B and D would probably permit electrical conduction both from nerve to muscle and from muscle to nerve. This would not raise any physiological difficulty however, because, since the nerve is refractory longer than the muscle, it is improbable that an impulse would be reflected, as it were, to return up the nerve again.

It appears from the literature that while the structure of most of the components of the motor nerve endings have been studied intensively, the relations between the physiologically important membranes have received little or no attention. This problem is presented, therefore, in the hope that some histological or embryological inquiry with the physiological questions in mind may yield more conclusive evidence than is afforded by the existing physiological data as to whether the neuro-muscular transmission is more probably chemical or electrical. Also any light which may be thrown on the relations of the polarized membranes at these or other synapses will be, for reasons similar to those discussed here, of the greatest assistance in developing ideas as to the nature of synaptic transmission in general.