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THE RELATION OF THE NORMAL HEART RHYTHM TO THE ARTIFICIAL RHYTHM PRODUCED BY SODIUM CHLORIDE.

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[FROM THE HULL PHYSIOLOGICAL LABORATORY OF THE UNIVERSITY OF CHICAGO.]

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I.

THE experiments here recorded were undertaken primarily with the view of determining what part, if any, the intrinsic nervous tissue in the heart takes in the production of rhythm in parts of the heart not normally automatic when immersed in an isotonic sodium chloride solution. The fact that curarized skeletal muscle twitches more or less rhythmically in a pure sodium chloride solution suggests that the rhythm produced by this same chemical in non-automatic parts of the heart is idio-muscular.. But it is also possible that the local nervous plexus in the heart strips is involved in the artificial rhythm, and this may account for the fact that the rhythm of isolated heart strips in sodium chloride approaches in regularity more closely to the normal heart rhythm than does the sodium chloride rhythm of skeletal muscle. This question cannot be attacked directly in the vertebrate heart, because the nervous and the muscular tissues cannot be separated for the necessary experiments, let alone the fact that the function of the intrinsic nervous tissue in the vertebrate heart is still, at least according to some physiologists, an unsettled question.

None of these difficulties confronts us in the Limulus heart. The function of ganglion and the nervous plexus in this heart is no longer a matter of controversy. The two tissues can be isolated so that the action of a chemical on either tissue may be accurately studied apart from that on the other. And finally, a pure sodium chloride solution (isotonic) produces, to all appearance, the same type of transient rhythm in the non-rhythmical part of the Limulus heart as in the classical strips from the apex of the vertebrate heart.

For these experiments the Limulus heart is prepared as shown in diagram *B* (Fig. 1). The median dorsal nerve cord or ganglion is extirpated for the whole length of the heart. The heart is transsected in the middle of the second and the third segments, and the intervening part removed, thus leaving the anterior and posterior ends of the heart connected by the lateral nerves or rather nerve plexus only. Both ends of the heart can now be suspended in separate chambers for graphic registration, and either end immersed in sodium chloride while the other end is bathed in plasma or sea water. It has been shown in a previous paper in this journal that most of the fibres of the lateral nerve plexus in the middle region of the heart are motor fibres to the muscle of the anterior segments. Hence, if the posterior end of the preparation (*B*, Fig. 1) is placed in sodium chloride, the anterior end remaining in plasma, the anterior end would begin to beat in synchrony with the artificial rhythm of the posterior end, provided the solution produced a rhythm in the lateral nerve plexus directly or in case the idio-muscular rhythm was in some way communicated to the nerve plexus.

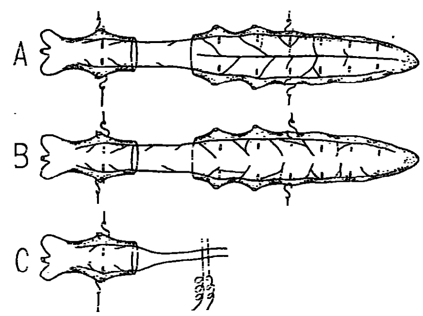

FIGURE 1. — Diagrams to illustrate the preparation of the Limulus heart for studying the relation of the sodium chloride rhythm to the normal rhythm. Dorsal view of the heart. Diagram *A*, ganglion extirpated in the first three segments, and part of the second and third segments removed, leaving the two ends of the heart connected by the lateral nerves. Anterior end is immersed in the sodium chloride, while the posterior end is kept in plasma or sea water. Diagram *B*, heart prepared as in *A*, with the exception that the ganglion is extirpated throughout its whole length. Preparation used for studying the relation of the nerve plexus to the sodium chloride rhythm. Diagram *C*, preparation of the first two heart segments and the lateral nerves for studying the changes in the response of the muscle to stimulation of the nerves during the sodium chloride rhythm.

Some experiments were also made with a preparation similar to that shown in diagram *C* (Fig. 1) the lateral nerve plexus on both sides being isolated from the middle of the second to the fourth or fifth segment and placed in the sodium chloride solution. If the sodium chloride produces rhythmic activity in the nerve plexus, the anterior end of the heart would begin to contract rhythmically in the plasma or sea water bath.

I desired, in the second place, to study the changes in the response of the heart muscle to the normal stimulus produced by the sodium chloride in developing the rhythm in the ganglion free part of the heart. So far as I know, this has not yet been done, despite the numerous researches on artificial rhythm in the vertebrate heart, but the question is now being investigated on the vertebrate heart in this laboratory by Professor Lingle. The Limulus heart lends itself admirably to an accurate study of this question. The heart preparations made use of for these experiments are illustrated in diagrams *A* and *C* (Fig. 1). The preparation *A* is arranged for simultaneous tracings from the two ends of the heart, and the plasma or sea water in the chamber containing the anterior end replaced by $\frac{6}{10}n$ sodium chloride. In such a preparation the anterior end beats in synchrony with the posterior end, while the sodium chloride rhythm is being developed in the former. In the tracing from the posterior end we have a check on the rhythm of the ganglion so that the changes in the amplitude or rate of the contractions of the anterior end can be traced directly to the action of the sodium chloride.

The preparation in diagram *C* was used as follows. The muscle was immersed in the isotonic sodium chloride solution, and the isolated lateral nerves placed in a watch glass filled with plasma. From time to time the nerves were lifted out of the solution and stimulated by induction shocks, and the variation in the muscular response during the different phases of the sodium chloride rhythm recorded.

II.

When the dorso-median nerve cord or ganglion has been removed from the heart, the intrinsic nerve plexus takes no part in the rhythm produced by immersing the heart in isotonic sodium chloride. This is shown by the following experiments. 1. By placing the lateral nerves of preparation *C* (Fig. 1) in the sodium chloride, and leaving the muscle part in plasma or sea water, no rhythm is produced in the anterior end. 2. When the posterior end of preparation *B* (Fig. 1) is placed in sodium chloride and the anterior end in plasma or sea water, the rhythm developed in the posterior end never affects the anterior end, despite the fact that the lateral nerves connecting the two ends of the heart remain intact and capable of functioning. It is therefore evident that the rhythm produced by sodium chloride in the ganglia free heart is idio-muscular, and that this idio-muscular activity does not affect the superficial nerve plexus after the ganglion has been removed. Furthermore, the sodium chloride is not able to produce a rhythm in the dorsal nerve plexus in the absence of the ganglion.

In a previous paper in this journal I have shown that an isotonic solution of sodium chloride may inaugurate a transitory rhythm in a quiescent heart ganglion of Limulus. The latent period of the ganglionic rhythm in sodium chloride is much shorter than that of the heart muscle. In fact in some preparations the ganglionic activity in sodium chloride has run its course before the idio-muscular rhythm appears, so that there is a definite pause between the neurogenic and the myogenic rhythm. In other preparations the ganglionic and the idio-muscular rhythm may overlap. The ganglion continues in activity for a while after the idio-muscular contractions have begun, but the latter invariably persist much longer than the former.

III.

As shown by the response of the heart muscle to electrical stimulation of the lateral nerves, *there is a gradual increase in excitability of the heart muscle immersed in an isotonic sodium chloride solution up to the time when the idio-muscular contractions appear.* The heart muscle not only responds to the same stimulus with contractions of increasing amplitude, but shortly before the idio-muscular rhythm begins, the heart muscle may respond with two or three contractions to the same stimulation of the lateral nerves that called forth only one contraction at the beginning. In several experiments the electrical stimulation of the lateral nerves after a bath of the muscle in sodium chloride for 35 to 45 minutes actually started the idio-muscular rhythm. The heart muscle continues to respond to the stimulation of the lateral nerves for some time (20 to 40 minutes) after the inauguration of the rhythm, but towards the end of the rhythm the stimulation of the lateral nerves has no effect, although the heart muscle is affected by direct stimulation.

The changes in the heart muscle leading up to the sodium chloride rhythm are therefore in the direction of increased sensitiveness to the normal stimulus, but the heart muscle can also contract rhythmically in sodium chloride when in such condition that it can no longer respond to the normal stimulus. The same will probably be found to be true for skeletal muscle in the vertebrates. For the vertebrate heart it must be left undecided till we have succeeded in separating the two tissues for experimental purposes.

IV.

The heart muscle immersed in an isotonic sodium chloride solution continues to respond to the normal impulse or stimulus to the rhythm reaching it from the ganglion through the lateral nerves for some time after the idio-muscular contractions have developed, but

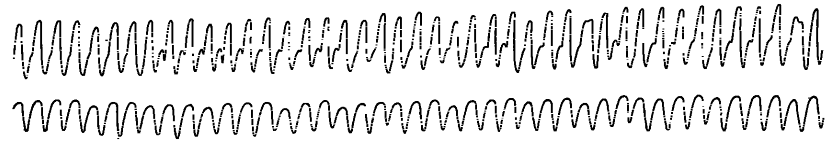

FIGURE 2. — One-half the original size. Simultaneous record from the two ends of the Limulus heart, prepared as shown in diagram *A*, Fig. 1. Upper tracing from anterior end, forty minutes after immersion of the anterior end in $\frac{5}{10}n$ NaCl. Showing development of the sodium chloride rhythm while the muscle still responds to the nervous impulses from the ganglion through the lateral nerves.

towards the end of the sodium chloride rhythm the heart muscle no longer responds to the normal stimulus just as it fails to respond to the artificial stimulation of the lateral nerves. The preparation used in these experiments is that represented in diagram *A* (Fig. 1), the anterior end being immersed in the sodium chloride solution. Under these conditions the normal rhythm is superimposed on the artificial rhythm for a while. The appearance of the tracings of this composite rhythm is very variable, depending on the regularity, or rather irregularity of the idio-muscular contractions. In rare instances the idio-muscular contractions were strong and fairly regular from the beginning, in which case the rate of the rhythm of the anterior and the posterior end of the heart usually presented the ratio of two or three to one. A typical record of this type is reproduced in Fig. 2. The upper record is from the anterior end. The neurogenic or stronger contractions are superimposed on the idio-muscular or weaker contraction. The rate of the latter rhythm is nearly the same as that of the former at the stage of the experiment represented on the tracings, but such a regularity is not long maintained, as the idio-muscular contractions become more rapid and irregular before the final cessation of the rhythm. In Fig. 3 is reproduced the most common form of this compound rhythm. By close inspection of the upper record it will be seen that the sodium chloride contractions start as a rapid series of more or less rhythmical twitches or beats, on which the normal or neurogenic rhythm is superimposed. The former increases in strength and then tends to obscure the normal rhythm, but the latter can be plainly made out by artificially accelerating the ganglionic rhythm as well as by abolishing the former. This is rapidly ac-

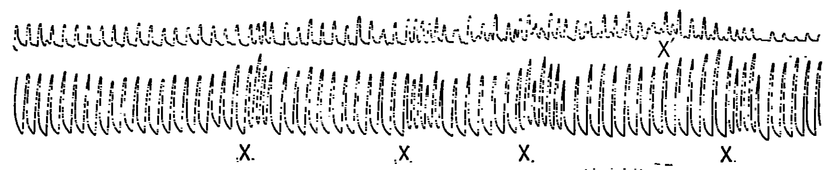

FIGURE 3. — About one-third the original size. Simultaneous tracings from the two ends of the Limulus heart, prepared as in diagram *A*, Fig. 1. Upper tracing from anterior end, immersed in $\frac{6}{10}$ *n* NaCl. Showing the normal rhythm superimposed on the idio-muscular sodium chloride rhythm. *X* = acceleration of the normal rhythm by mechanical stimulation of the ganglion on the posterior end. *X'* = the $\frac{6}{10}$ *n* NaCl surrounding the anterior end replaced by plasma, showing the quick cessation of the sodium chloride contractions as well as depression of the neurogenic contractions.

complished by replacing the sodium chloride by plasma or sea water, as shown on the right-hand side of Fig. 3 at *X'*.

When after development of the idio-muscular rhythm, the sodium chloride is replaced by plasma or sea water, not only are the idio-muscu-

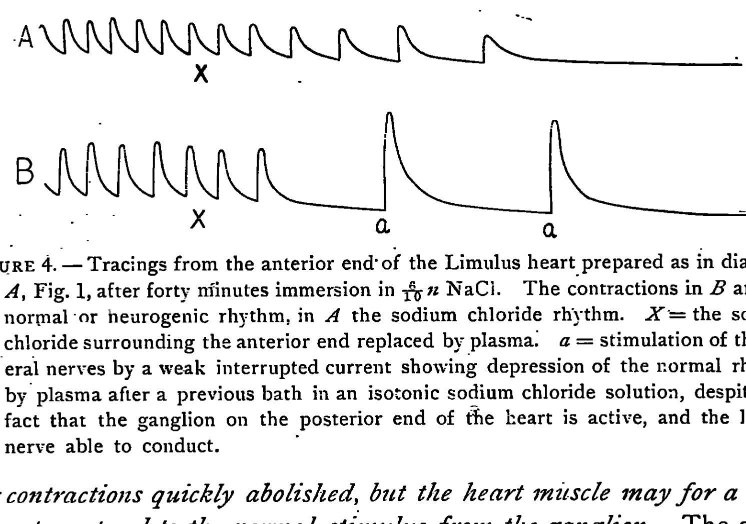

FIGURE 4. — Tracings from the anterior end of the Limulus heart prepared as in diagram *A*, Fig. 1, after forty minutes immersion in $\frac{6}{10}$ *n* NaCl. The contractions in *B* are the normal or neurogenic rhythm, in *A* the sodium chloride rhythm. *X* = the sodium chloride surrounding the anterior end replaced by plasma. *a* = stimulation of the lateral nerves by a weak interrupted current showing depression of the normal rhythm by plasma after a previous bath in an isotonic sodium chloride solution, despite the fact that the ganglion on the posterior end of the heart is active, and the lateral nerve able to conduct.

lar contractions quickly abolished, but the heart muscle may for a time cease to respond to the normal stimulus from the ganglion. The anterior end of the preparation (diagram *A*, Fig. 1) thus comes to a complete standstill for a longer or shorter period until the normal rhythm is resumed. The striking thing about this cessation of the response to the normal stimulus is this, that on electrical stimulation of the lateral nerves the heart muscle can still be made to contract although it does not respond to the nervous impulses from the ganglion. Escape of the current directly to the muscle was guarded against. The fact that the muscle contracts on stimulation of the lateral nerves shows that the nerves and nerve endings remain functional. The heart muscle contracts also on direct stimulation. The failure of the normal stimulus to produce contractions is therefore difficult to explain, except on the assumption that the electrical stimulation of the nerves gives rise to nervous impulses of so much greater intensity than those coming from the ganglion that in this state of reduced excitability the muscle responds to the former but not to the latter.

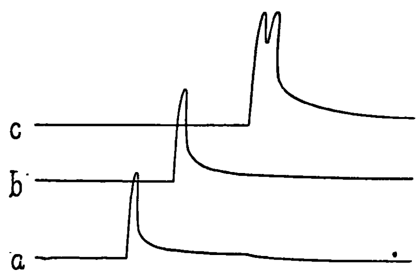

FIGURE 5. — Tracings from the anterior end of the Limulus heart, prepared as in diagram *C*, Fig. 1. The muscle part immersed in an isotonic solution of sodium chloride. *a, b, c*, stimulation of the lateral nerves by the same strength and duration of the interrupted current at fifteen-minute intervals. Showing increased response of the heart muscle to stimulation of the lateral nerves with the length of time of immersion in the sodium chloride solution.

V.

The Limulus heart muscle immersed in an isotonic sodium chloride solution exhibits the following changes in tonus. When the heart muscle is completely isolated from the ganglion, there is a gradual lengthening of the muscle in the sodium chloride up to the time when the idio-muscular contractions appear. It is not clear to me whether this lengthening is an actual tonus relaxation or merely a passive response to the pull of the light recording lever. As the contraction begins there is a gradual increase of the tonus till the end of the rhythm. During the latter part of the rhythm tonus waves usually appear on the records simultaneously with the fundamental contractions, and the former usually persist for some time after the latter have ceased. With the cessation of the more rapid or fundamental rhythm, the heart muscle begins to lengthen again. The tonus rhythm may persist for a while during this relaxation process. When the preparation is transferred from sodium chloride to plasma or sea water, the tonus is rapidly diminished as the idio-muscular rhythm disappears.

VI.

It has been shown in a previous paper in this journal that in the Limulus heart the conduction takes place in the nerve plexus and not from muscle cell to muscle cell. The proof of this is conclusive. We have now, furthermore, seen that the sodium chloride rhythm is idio-muscular and that the nerve plexus (minus the ganglion) takes

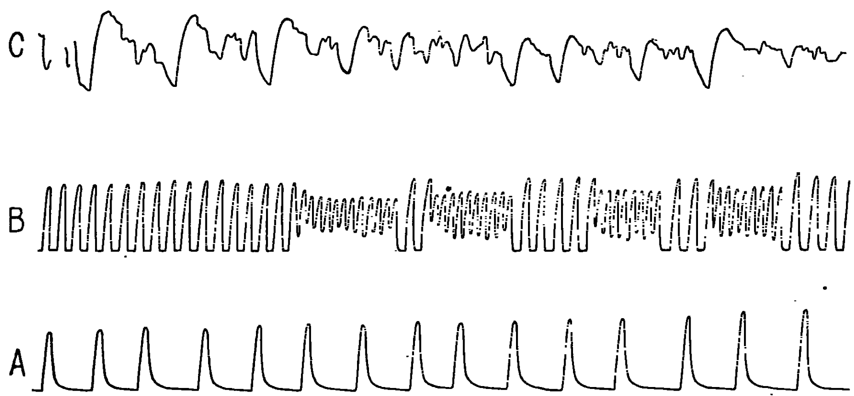

FIGURE 6. — Tracings from ganglion free segments of the Limulus heart immersed in $\frac{8}{10}$ *n* NaCl, showing some types of the idio-muscular sodium chloride rhythm.

no part in it. In view of these facts it is significant that the *sodium chloride rhythm may closely approach the regularity of the normal rhythm*, because such a regularity involves practically the simultaneous contraction of all the muscle cells in the preparation. How is such a co-ordination effected in the Limulus heart in the absence of conduction from muscle cell to muscle cell when the tissue that normally serves to correlate the activity is not involved?

It is in a very few preparations, however, that such a regular sodium chloride rhythm is obtained. In the majority of the preparations the rhythmical twitchings are quite as irregular as the corresponding contractions of skeletal muscle, and in the preparations exhibiting the greatest regularity of the contractions it is invariably superseded by inco-ordination and irregularity before cessation of the activity. The sodium chloride rhythm may begin with a perfectly regular and gradually augmented series of beats which finally pass into a state of inco-ordination. It may begin by irregular and incoordinated twitchings and change for a brief period to a regular coordinated rhythm involving simultaneous contraction of all parts of the preparations to again be superseded by inco-ordination. Or, thirdly, the sodium chloride rhythm of a preparation may be irregular throughout its whole course. Typical tracings of these different forms of the sodium chloride rhythm are represented in Fig. 6.

The irregular rhythm requires no special explanation, as that type of activity is what is to be expected under the circumstances, but the presence of an to all appearance perfectly regular rhythm under these conditions is more difficult to account for. There appear to be only two alternatives. Either the sodium chloride alters the muscular tissue so that a wave of contraction can be conducted from muscle cell to muscle cell, a process which does not occur normally in this heart; or the co-ordination is effected by means of an intercellular nerve plexus so related to the dorsal or superficial plexus connecting the ganglion with the heart walls that the impulses do not pass from the former to the latter. These suggestions are, of course, only working hypotheses. My observations so far rather tend to discredit the second alternative, but it must at the same time be admitted that we have no direct evidence of the truth of the first, either for the Limulus or the vertebrate heart. We do not yet know whether the contraction wave is normally conducted from muscle cell to muscle cell in the vertebrate heart, but according to Guenther[1] the sodium chloride rhythm in strips from the tortoise ventricle is at first confined to the part of the strip immersed in the solution. The same author states that this is also true for curarized skeletal muscle. In other words, the sodium chloride rhythm of skeletal muscle is of such a nature that one end of the muscle cell may be in rhythmic activity while the other end is at rest, despite the fact that the whole fibre retains its normal conductivity and contractility. The interpretation of the fact for the tortoise ventricle may be the same as suggested above for the Limulus heart. The main difficulty in testing the hypothesis in the vertebrate heart is the unsettled question of the normal mechanism of conduction.

[1] GUENTHER: This journal, 1905, xiv, p. 73.

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