THE ACTION OF PILOCARPINE ON THE HEART

(Preliminary Communication)

By JAMES M. McQUEEN, M.A., B.Sc., M.B., Ch.B., *Senior Assistant in Physiology, University of Aberdeen.*

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During certain months of the year the vagus nerve has little or no inhibitory power over the amphibian heart. This important functional variation has been noted by several workers, and has been employed as a means of deciding the vexed question of the action of pilocarpine and muscarine on the heart.

If pilocarpine or muscarine has no action on a heart whose vagus is without inhibitory power, and can slow or diminish the force of or stop a heart only when the vagus is active, one would naturally conclude that pilocarpine or muscarine acts on the vagus nerve endings (the cardiac ganglia being for the present left out of account). G. N. Stewart, in his *Manual of Physiology* (Edition 1895, and subsequent editions up to 1906), emphasises this point. 'It is quite in accordance with this' (*i.e.*, the view that muscarine acts on the vagus fibres between the nerve cells and the muscle or the actual nerve endings) 'that muscarine has no effect on a heart whose vagus nerves, as occasionally happens, have no inhibitory power. Pilocarpine has very much the same action as muscarine.'

More recently, this field has been thoroughly developed by MacLean (*Bio-Chemical Journal*, Vol. III, Nos. 1 and 2). He concludes that 'the effect produced on the heart by small doses of muscarine and pilocarpine is in direct proportion to the influence exercised on the heart by the vagus nerve.'

Marshall further pointed out that an immunity to pilocarpine could be induced by repeated dosage (*Journal of Physiol.*, Vol. XXXI, p. 120, 1904). This was true in mammals (Marshall) and in the frog (MacLean).

The writer, working on the amphibian heart (frog, newt and salamander), finds :—

I. In the newt and salamander, the heart may be primarily immune to pilocarpine (*i.e.*, an immunity not due to dosage). Yet the heart can be inhibited on faradisation of the sinus with certain strengths of current.

II. In the frog and salamander, during the immunity to pilocarpine induced by administration of that drug, similar faradisation of the sinus can inhibit the heart.

III. In the frog and salamander, when a heart slowed by early doses of pilocarpine is quickened or enforced by a renewed application of the drug, the revival of cardiac activity does not mean that the heart can no longer be inhibited by faradisation of the sinus.

IV. In the frog, when a heart brought to a standstill by the application of pilocarpine revives naturally or is made to beat again by experimental manipulation, in both instances faradisation of the sinus can lead to a greater or a less degree of inhibition of the now immunised heart.

V. In the salamander, the heart found primarily immune to certain strengths of pilocarpine may be rendered by experimental manipulation susceptible to a dose formerly unable to influence it. Then, later, this dose loses its power over the heart. Throughout, and at the close of the experiment, faradisation of the sinus inhibits the heart.

This cardiac inhibition following on faradisation of the sinus may be due to—

A.—Stimulation of the inhibitory nervous mechanism of the heart. Such an explanation is, no doubt, most in line with current belief. Assuming that it is correct, then the theory that pilocarpine acts on the nerve endings of the vagus must be revised.

One is led in this case to consider the possibility of pilocarpine acting on the heart by virtue of a combination with some substance in the cardiac tissue. A natural immunity to pilocarpine might then be due to the failure of this combination to take place or to the absence of this substance. Immunity produced by repeated doses

of pilocarpine might be explained by supposing that the combination between pilocarpine and this specific substance has been rendered inert.

But inhibition following on faradisation of the sinus may be due to—

B.—The direct action of the induced current on the cardiac tissues independently of inhibitory nerves. If such should prove to be the correct interpretation, then present views as to the reaction of the cardiac tissues to the faradic current require revision.

The writer reserves meanwhile the evidence at his disposal bearing on either view (A or B). It is sufficient to indicate at this stage certain important questions raised by this inquiry.