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On the Working Mechanism of Atropin.

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On the Working Mechanism of Atropin.

By

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Introduction.

Concerning the problem as to the action of atropin upon the vagus nerve, *Cushny*[1] considered, from the researches of *Rossbach*[2] and others, that this drug perhaps affects the nerve-endings of vagus. But it is uncertain whether atropin affects junctional tissue or non-medullated postganglionic stretch. Quite recently, by the experiments of *Cowan* and *Ing*[3], *Fromherz*[4], and *Sudo*[5], it was made clear that curare and quatanary ammonium which have hitherto been believed to act upon the nerve-endings, paralyse non-medullated nerve fibres. This fact leads us naturally to suppose that this drug acts upon the non-medullated part of nerve fibres themselves.

The present investigation was undertaken to decide on the subject whether atropin acts upon the non-medullated postganglionic nerve fibres, or upon the nerve-endings of vagus.

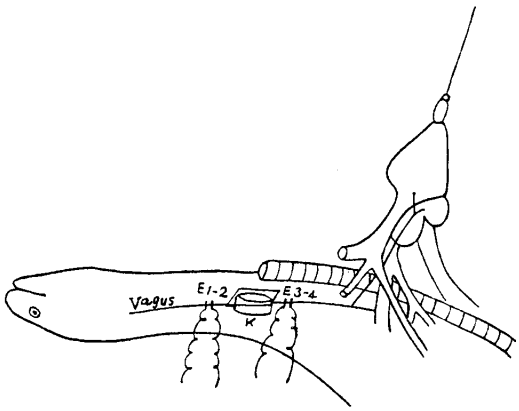
Experimental.

As the experimental material, the tortoises of medium size were used. After preparing the heart and the vagus nerve, the apex of ventricle was attached to a recording lever which registers the contractions on a rotating kymographion.

As shown in Fig. 1, the vagus nerve was prepared and one part of it was enclosed in a vessel (K), made of bamboo, of which the diameter was about 1.5 cm. In the vessel (K), various solutions were introduced as much as required and afterwards it was closed tightly by a cover glass. On each side of the vessel, the vagus nerve was mounted on stimulating electrodes E_{1-2} and E_{3-4} respectively, which were connected to the secondary coil of *Du-Bois Reymond*'s in-

ductorium, of which the primary coil being connected to a 2 volt accumlator. The liminal strength of the stimulation of vagus just to arrest the heart beats by faradic stimulation with the electrodes E_{1-2} was determined beforehand. The stimulation current used never exceeded over that of the coil distance of 4 - 8 cm, because any stronger current may spoil the nerve fibre and cause any troublesome uncertainity on the experimental results through electrical spreading.

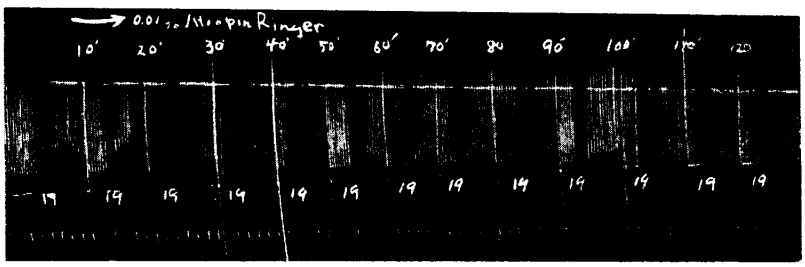
Fig. 1.



(A). Action of atropin in its various concentration on medullated nerve fibres under the normal condition.

As shown in Fig. 1, after atropinised *Ringer*'s fluid had been filled in the vessel (K), the change of liminal strength of vagus stimulation just to arrest the heart beats was investigated.

Fig. 2.



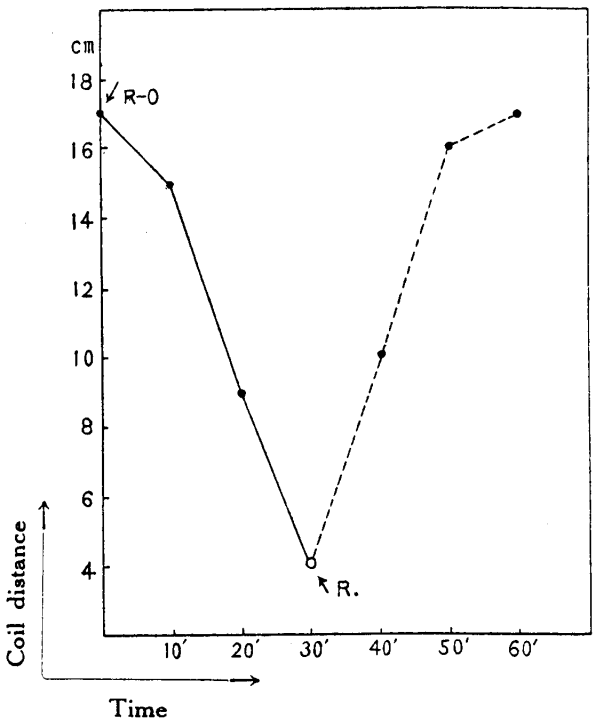
Several experiments made in this way showed that atropin at high concentration narcotises and finally kills the nerve fibres of vagus, while at low concentration such as 0.01 %, it has no influence

at all on the nerve fibres even after 2 hours application. When applied directly to the heart muscle, atropin naturally paralyses it and the effect of vagus stimulation on the heart beats is extinguished.

(B). Action of atropin on the medullated nerve fibres under asphyxiated condition.

a). Preliminary experiment. A *Ringer*'s fluid with little oxygen content was prepared from spring water which contained 1.7 – 3.6 cc. oxygen per liter after *Winkler*'s method, and the vessel (K) was filled with the fluid. The nerve was seen to be entirely paralysed in 20 – 60 minutes, judging from the disappearance of the effect of vagus stimulation with the electrodes E_{1-2}. After replacing the above-said *Ringer*'s fluid with normal one, recovery occurs perfectly in 30 minutes. The results are represented in Fig. 3.

Fig. 3.



——— paralysis } the threshold-strength of stimulation with the electrodes
····· recovery } E_{1-2}.

o . . . indicates where the vagus stimulation was ineffective.

R – O . indicates application of *Ringer*'s fluid with little oxygen content.

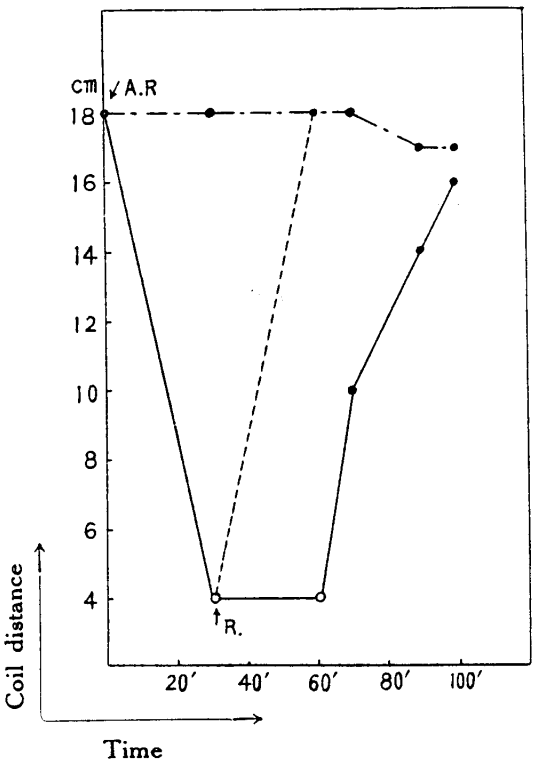
R. . . . indicates application of aerated *Ringer*'s fluid.

b). Proper experiment. After the preliminary experiments, the following tests were made :

Exp. 1. Vagus nerve immersed in 0.01 % atropinised *Ringer*'s fluid with little oxygen content, then it was replaced with aerated *Ringer*'s fluid.

Exp. 2, 3, 4. Vagus nerve immersed in 0.01 % atropinised *Ringer*'s fluid with little oxygen content, then it was replaced with 0.01 % atropinised aerated *Ringer*'s fluid and left for some time in that fluid.

Exp. 1.



——— the threshold-strength of stimulation with the electrodes E1—2.

– – – – the threshold-strength of stimulation with the electrodes E3—4.

..... the supposed recovery curve refered to the preliminary experiments.

o. . . . indicates where the vagus stimulation was ineffective.

A.R. . indicates the application of 0.01 % atropinised *Ringer*'s fluid with little oxygen content.

A.N.R. indicates the application of 0.01 % atropinised aerated *Ringer*'s fluid.

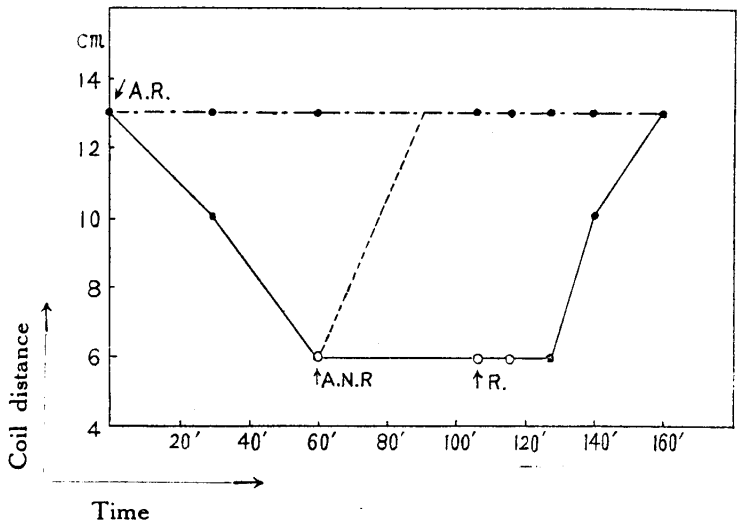
R. . . . indicates the application of aerated *Ringer*'s fluid.

In this test, the changes of time course as to the liminal strength of vagus stimulation to arrest heart beats was determined by the

stimulation at the electrodes E_{1-2}, and at the sometime, the excitability of nerve through the electrodes E_{3-4} was checked as the control. The results are represented in the following figures.

Experimental results. Comparing these results with those of the preliminary observations, the following summary may be made:

Exp. 2.



——— the threshold-strength of stimulation with the electrodes E_{1-2}.
– – – – the threshold-strength of stimulation with the electrodes E_{3-4}.
····· the supposed recovery curve refered to the preliminary experiments.
o . . . indicates where the vagus stimulation was ineffective.
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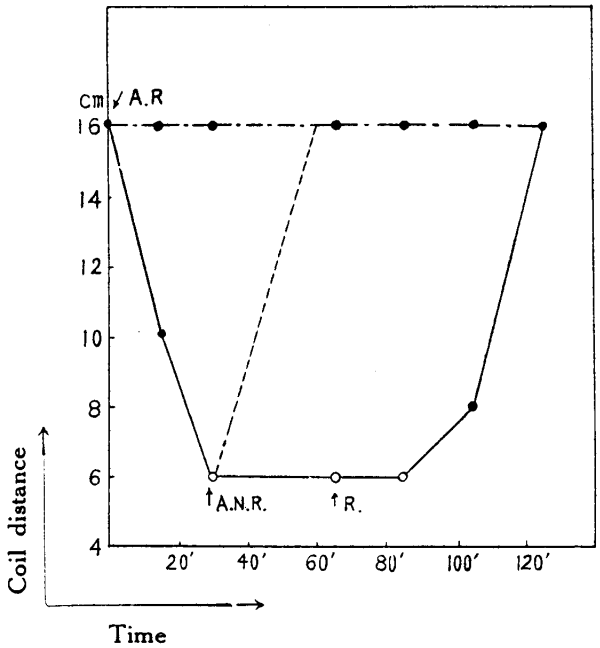
A.N.R. indicates the application of 0.01 % atropinised aerated *Ringer*'s fluid.
R. . . indicates the application of aerated *Ringer*'s fluid.

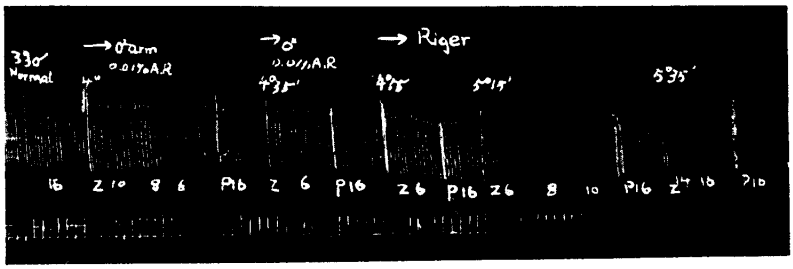
Atropin does not affect the medullated nerve fibres, though in high concentration it kills them. It is assumed that the medullary sheath prevents the penetration of atropin into the axiscylinder. But as shown in the above diagram, the vagus comes to be paralized by the drug when the nerve fibres are asphyxiated, so that it can now penetrate the medullary sheath. It must be added, however, that this paralized one will regain its normal condition, if it is washed in *Ringer*'s fluid.

c). Action of atropin on the non-medullated nerve fibres. After the median nerve cord and the lateral nerve trunks of the limulus

heart were exposed, a mass of cotton, immersed in 0.01 % atropinised *Ringer*'s fluid, was placed on the center of the nerve. After 5 - 10

Exp. 3.





——— the threshold-strength of stimulation with the electrodes E1—2.
- - - - the threshold-strength of stimulation with the electrades E3—4.
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o . . . indicates where the vagus stimulation was ineffective.
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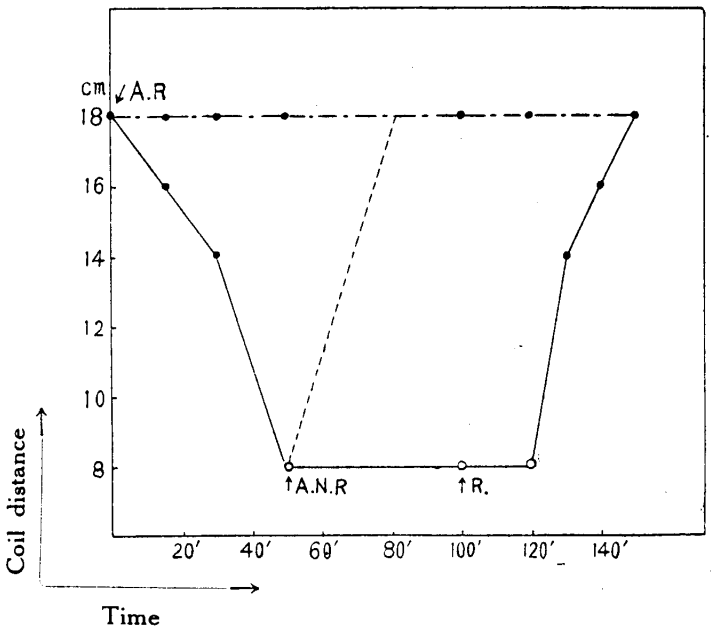
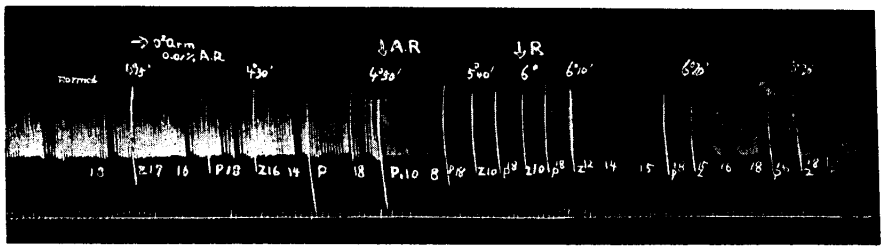
R. . . indicates the application of aerated *Ringer*'s fluid.

minutes were allowed to elapse, the first sign of heart block appeared and the blocked part of the heart, as the impulses from ganglion died away, ceased to beat after 15 - 25 minutes. At this

time, the faradic stimulation applied beyond the atropinised part had no effects, but the stimulation given to this side of the atropinised

Exp. 4.





——— the threshold-strength of stimulation with the electrodes E1—2.
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part caused vigorous contractions. By washing the narcotised part with *Ringer*'s fluid, the recovery from narcotised condition occured within 30 – 40 minutes.

Discussions.

It is generally assumed that atropin affects the nerve ending especially the ending of vagus nerve. In this investigation the author endeavored to find where and how atropin affects the nerve. The efferent fibres of vagus nerve belong to autonomic, also their post-ganglionic fibres are non-medullated. It may be supposed that atropin affects the latter. If so, the medullated preganglionic fibre in asphyxiated condition will be affected also, as many investigators such as *Cowan* and *Ing, Fromherz,* and *Sudo,* experimentally proved that the asphyxiated medullated nerve is paralysed by many drugs, e.g. curare which do not affect non-asphyxiated medullated nerve. For this reason it is supposed that the asphyxiated medullary sheath increase their permeability of the drug. For instance, under the normal conditions, as a result of medullary sheath resisting the entrance, atropin cannot affect medullated nerve fibres, whereas under the asphyxiated conditions, as *Simon*[7], *Winterstein* and *Hirschberger*[8] said, owing to the increased permeability of medullary sheath, the drug easily passes and affects axiscylinder and paralyses it, as in the non-medullated nerve fibres.

From the results obtained in this investigation, the former conception which hither-to have been generally accepted, on the action of atropin, that this drug affects the nerve endings of vagus, is considered unsatisfactory and the latter view must be qualified to the effect that this drug affects the non-medullated postganglionic fibres.

Conclusion.

In conclusion, concerning the action of atropin on the nerve fibres may be stated as follows :

1. Atropin affects and paralyses the non-medullated nerve fibres of limulus heart.
2. Atropin affects and paralyses the medullated preganglionic fibres of vagus of the tortoise under asphyxiated conditions.

My sincere thanks are due to Prof. Dr. *S. Oinuma* for suggesting this investigation and also for his constant advice.

Literature.

[1] *Cushny,* Heffter's Handbuch d. exp. Pharm. Bd. 2, H. 2, 608, 1924. — [2] *Rossbach,* Pflüger's Archiv. Bd. 10, 383, 1884. — [3] *Cowan* and *Ing,* J. of Physiol. Vol. 79, 75, 1933. — [4] *Fromherz,* J. of Physiol. Vol. 79, 67, 1933. — [5] *Sudo,* Okayama I. Z. Jg. 47, Nr. 3, 797, 1935. — [6] *Winkler,* Abderhalden's Handbuch d. Bioch. Meth. Bd. 3, H. 2, 1910. — [7] *Simon,* Hoppe-Seyler's Z. 118, 96, 1922. — [8] *Winterstein* and *Hirschberger,* Pflüger's Archiv. Bd. 217, 216, 1927.