On the Exodic Excitation and Inhibition.

By

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It is often found that the excited state of a surviving organ, consisting of smooth muscle, caused by the administration of certain drugs, does not disappear on the washing out of the poisons, but becomes more marked. But this phenomenon was considered to be an accident and has not hitherto attracted much attention. Neukirch[1] after applying a large quantity of pilocarpine to the small intestine of a rabbit and keeping up the state of excitement for a certain length of time, washed out the poison and noticed the secondary excitement. When he again applied some pilocarpine the secondary excitement disappeared. So he considered that this secondary excitement was caused by the liberation of the poison from the cells of the organ, into which it had permeated, and called this phenomenon "exodic excitation" (Entgiftungserregung). Afterward Kuyer and Wijsenbeck[2] studied the action of various poisons upon the small intestine and on the uterus both of a cat and of a rabbit, and found that, when pilocarpine, physostigmine or muscarine, which are excitatory drugs, were used, exodic excitation followed, and when adrenaline or tyramine, which are inhibitory drugs, used, exodic inhibition resulted. Ando[3] applied cocaine to the heart and the blood vessel of a frog and found that it caused the exodic excitement. But the investigations of this phenomenon were not very satisfactory and did not attract general attention.

Since the above phenomenon was observed only when a large quantity of the substances was made to act, it seemed to have no direct

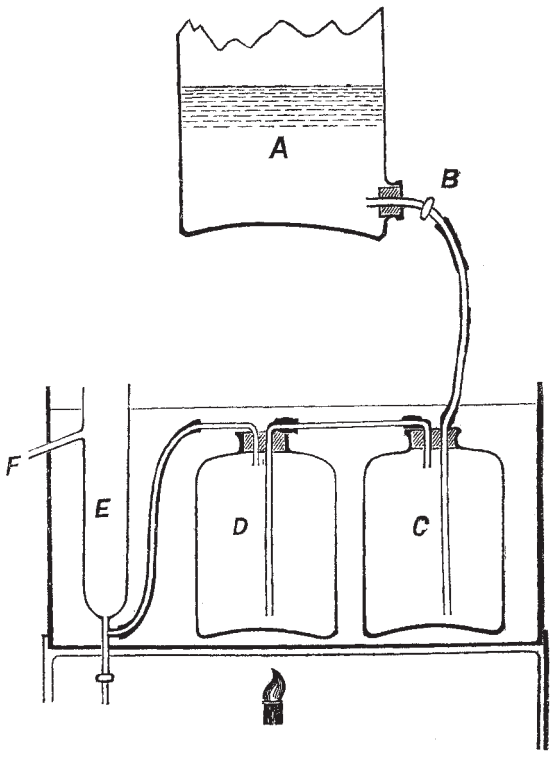
relation to the proper action of the substances. But it is interesting as furnishing us with the materials for studying the mechanism of the action of drugs.

Although this mechanism in many cases is not very clear, we might suppose the following process to occur. Those substances, which can not readily permeate the cells, change the rate of exchange of water and the permeable substances between the cells and the surrounding liquid, while the diffusible substances find their way into the cells, and thus they produce the functional change by causing a physico-chemical change in their structure. The strength of the action of the impermeable substances depends upon the concentration of the substances in the surrounding liquid and that of the permeable substances upon the quantity of the substances permeated into the cells. According to the investigation of Straub[4] it was found that although certain substances permeate the cell, their action resulted not so much from their nature as the permeation itself. Hence the strength of its action does not depend upon the quantity of the permeating substances but upon the difference in concentration between the substances within and that without the cell. He called such substances "potential poisons." Since the exodic excitation and inhibition arise from the difference in concentration in the substances within and without the cell, substances which cause this excitation and inhibition may also be called potential poisons. Neukirch and Kuyer specified only those substances which were mentioned above as having this property. I have repeated the investigation to ascertain whether those substances have really that kind of action, and whether that property is peculiar to those substances, and further have studied the mechanism of this phenomenon.

The organ employed for experiment was the small intestine of a rabbit which had been excised beforehand. The method of maintaining survival was somewhat, though not fundamentally, different from that which is generally used. By the usual method, it is impossible to avoid the exposure of the organ to the air and the mechanical stimulation due to the interchange of the saline solution. The small intestine, in its normal state, but more especially in the excited state, is very sensitive to the stimulation of the air and any other mechanical stimulus and easily subject to spasmodic contraction, thus making discrimination between it and the excitement caused by the interchange of the poison solution very difficult. Therefore I so

arranged my experiment as to avoid atmospheric and any other mechanical stimulus at the time of the interchange of the poison solution.

Fig. 1.



In Fig. 1, A is a reservoir for Ringer's solution. It has a cock B, which is connected by a rubber tube with two heating bottles C and D, and the latter is connected with a vessel E, in which a segment of the small intestine is to be suspended. This vessel has a capacity of 30 c.c. and an outflow tube F on the upper side. Now C, D and E are to be put in a bath of a temperature of 39°C. When cock B is opened Ringer's solution flows through the conducting tube first into C and D, and then into E, and finally issues from F. If the cock of the conducting tube is now shut the solution will fill C and D and stand in E at the height F. Since they are all immersed in it, the temperature of the contents of the bottles will after several minutes become the same as that of the bath. The saline solution in the vessel E is continuously oxygenated, and a segment of the small intestine is suspended in it. The poison is dissolved in Ringer's solution and warmed in the bath, and this solution is discharged into the vessel with a syringe. When the poison solution is to be washed out, cock B is opened so that the liquid flows out of the issue tube. When the quantity of the liquid flowing out attains 150 c.c. the cock is shut. By this manner, without giving any noticeable stimulus to the small intestine, the poison solution in the

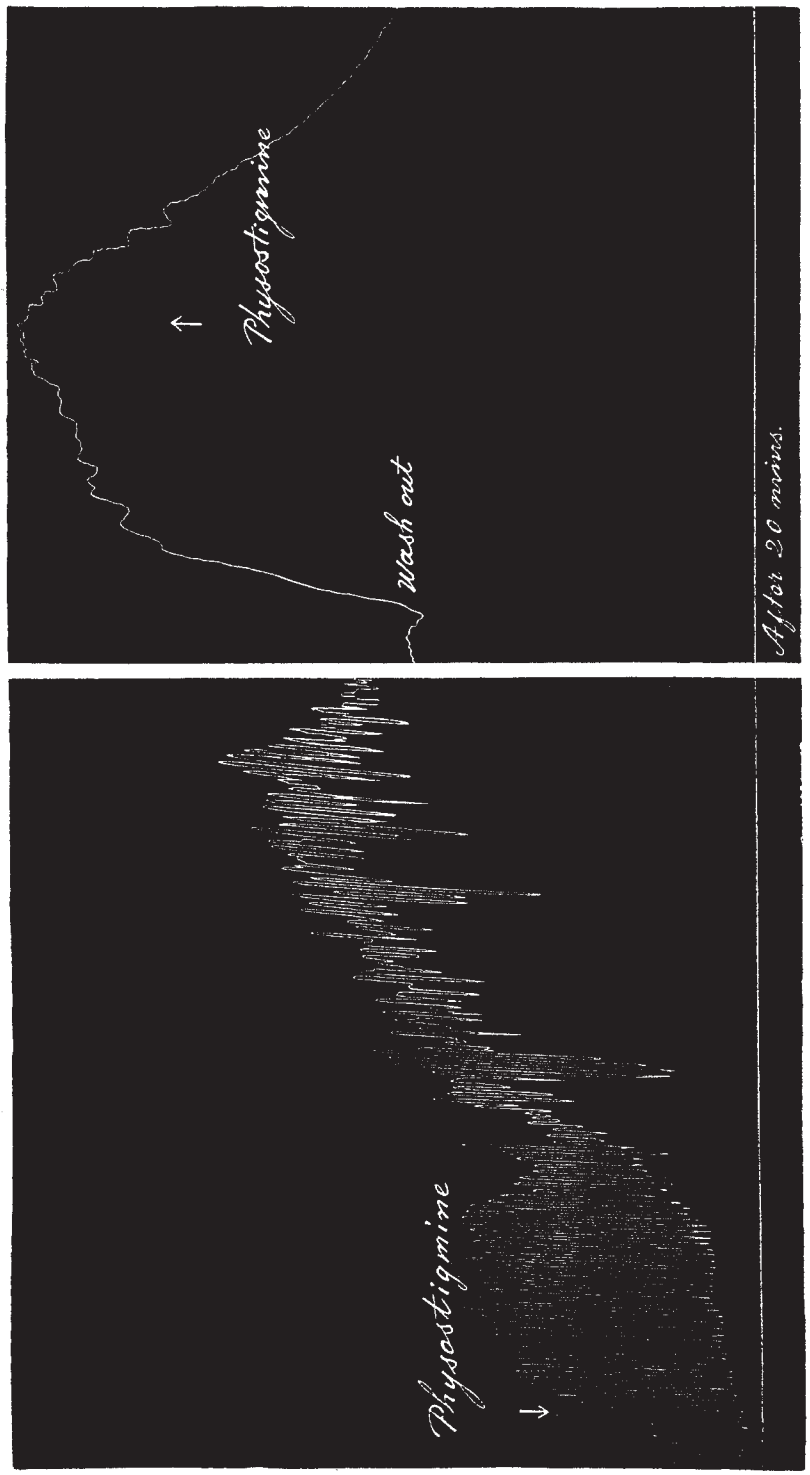


Fig. 2.

vessel can be washed away to such degree as to make it impossible to detect it physiologically.

The substances which have been reported as having exodic excita-

tive action are such alkaloids as pilocarpine, muscarine and physostigmine. In order to ascertain whether this action is peculiar to the above mentioned substances or is a general property of all alkaloids, I made experiments with several other alkaloids: atropine, cocaine, nicotine, strychnine, morphine, quinine and veratrine, which in a small or large quantity give rise to the excitement of the intestine. When a large quantity of one of them was made to act upon the intestine for a certain length of time, and then washed out, the excitement increased, and when it is reapplied, the excitement disappeared. For instance, a small quantity, say 1–2 mgrms. of physostigmine was added to the saline solution, the tonus of the intestine increased and its movement augmented. When this quantity of the poison solution was interchanged with Ringer's solution, the intestine was always restored to the normal state. When the poison was increased, however, to 10–20 mgrms. the same phenomenon was observable only at the beginning. But in proportion as the tonus increased, the movement became weaker. After about 15 minutes, when the poison solution was interchanged with Ringer's solution the tonus much increased and sometimes the movement became intense too. If the intestine is left in this condition, it will gradually return to the state previous to washing, if it is left for still longer it will approach to the normal state. If at the time of the excitement caused by the interchange of the poison, the same quantity of poison solution be added, the secondary increase of tonus disappears (Fig. 2).

Thus we see that a certain concentration of poison is needed to produce the exodic excitement. The quantity needed is not the same for all the various substances. The following table shows the approximate concentration.

Pilocarpine	0·01 %	Morphine	0·01 %
Muscarine	0·01 %	Quinine	0·01 %
Atropine	0·01 %	Physostigmine	0·005 %
Nicotine	0·01 %	Cocaine	0·005 %
Strychnine	0·01 %	Veratrine	0·001 %

When the small intestine is in a state of excitement it is sensitive even to a slight stimulus and an increase of tonus and an augmentation of movement often results. Therefore in order to avoid the stimuli of the air, the difference of temperature and other mechanical stimulations accompanying the interchange, I made the above arrangement in my experiment. Although in the experiment arranged in

this way, the strong mechanical stimulations accompanying the ordinary method may be avoided, yet we can hardly eliminate the stimulation of the flow of the liquid caused by the interchange. In order to examine, whether or not the above described secondary excitement was due to the flow of the liquid, I dissolved physostigmine in the whole quantity of Ringer's solution in a concentration of 0·005 per cent and suspended the small intestine in it for a certain length of time, and made the interchange of the liquid. But in this case no secondary excitement followed. Hence it is evident that the secondary excitement was caused by the interchange of the poison solution with the normal Ringer's solution, and not by the mechanical stimulation of the flowing liquid. And this conclusion is corroborated by the fact that the secondary excitement disappeared on the reapplication of the poison.

From the above experiment it is clear beyond doubt that the phenomenon of the secondary excitement is caused by the escaping of the poison from the cells into which it had previously entered. When the cells of the smooth muscle of the small intestine are immersed, for a time, in the poison solution, they absorb a certain quantity of the poison, and excitement is observable. At this stage, a certain equilibrium of the concentrations of the poison within and without the cells is maintained. But when the concentration of the poison of the surrounding liquid suddenly decreases, there arises a sudden difference in the concentration, the equilibrium is lost, and consequently the secondary excitement follows.

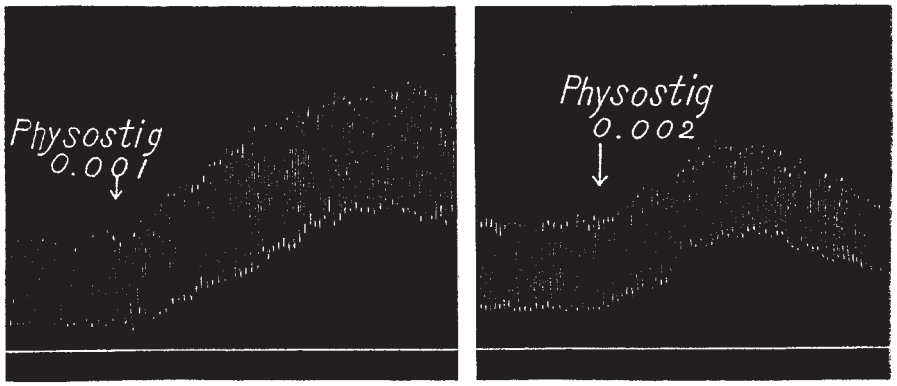
According to Trendelenburg[5] the smooth muscle is excited by the hypotonic solution. Apparently, the secondary excitement is caused by the difference in the osmotic pressure, for it arises when the concentration of the poison outside the cells suddenly decreases, and the equilibrium which is obtained by the absorption of poison by the cells of the small intestine is disturbed. In order to examine whether the secondary excitement was caused by the osmotic action, I substituted for the poison a salt contained in Ringer's solution, and a similar excitement was observed. But the excitement in this case was different from that which was caused by alkaloids and showed a sign of the return of the inhibited movement caused by the hypertonia to the ordinary state as the result of washing. And in order to produce such a phenomenon, a large quantity of salt was needed. In the case of sodium chloride, the quantity was indeed 0·05–0·5 per cent and

there is no comparison between the pressure of this substance and that of alkaloids. Therefore we can not ascribe the secondary excitement in the case of alkaloids to the change in osmosis.

According to Straub, when the heart of an aplysia is poisoned with muscarine, it will stop pulsation for a time and then begin to beat again. At this time, an addition of muscarine to the liquid will stop the beat again, but after a certain length of time the heart will resume pulsation. At this moment the quantity of muscarine contained in the structure of the heart is quite enough to stop the beat of any other heart. The action of alkaloids in the cells is not very clear, but it seems that it makes physico-chemical combinations with the constituents of the cells. From the action of muscarine on the heart it may be inferred that the physico-chemical combination itself produces a certain stimulation.

This kind of phenomenon is not peculiar only to the action of muscarine, but may be seen in the action of many other alkaloids. For instance, when a small quantity of physostigmine is applied to an excised small intestine, there arises a temporary increase of tonus together with an augmentation of movements, and after a time, the ordinary state is resumed. But an addition of a small quantity of the poison will bring forth the same phenomenon again (Fig. 3). After

Fig. 3.



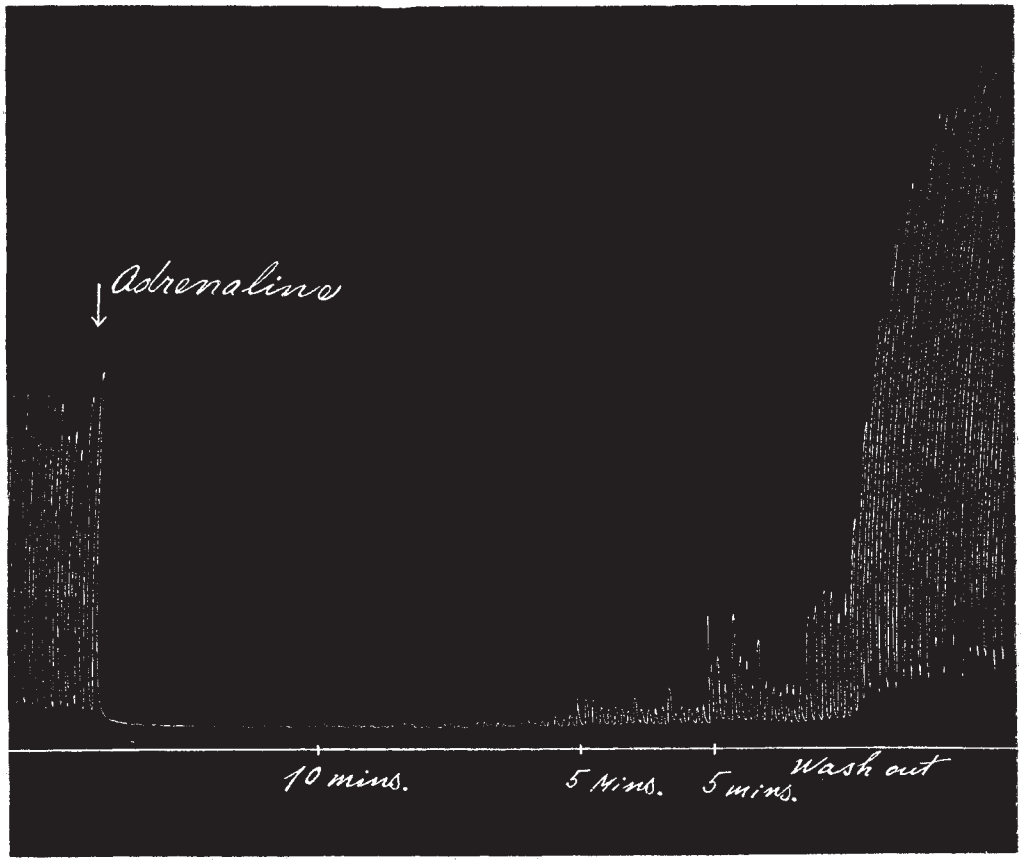
repeating this procedure several times, the quantity of physostigmine contained in the bath is found to be sufficient to produce a typical change in the other segments of the intestine. This phenomenon

must, therefore, be due to the stimulation produced at the moment of the combination of the alkaloid with the constituents of the cells. And the reason why this phenomenon does not appear when a large quantity of physostigmine is applied is that the quantity is excessive and recovery is very slow so that we cannot observe it during a short experiment. If this is so, we can easily suppose that a certain stimulation will be produced when an alkaloid which was previously combined with the cells is now liberated from them. In short, the exodic excitement is originated when the equilibrium between the concentration of the poison within and that without the cells is disturbed and the poison is liberated from the cells.

According to the investigation of Kuyer and others, certain substances such as adrenaline which have an inhibitory action on the small intestine would give rise to exodic inhibition. But when I made various quantities of adrenaline act on the small intestine of a rabbit for ten to thirty minutes and then washed out the poison, first a return to the ordinary state and then an excitement were the invariable results. In other words, the increase of tonus and the acceleration of movements, but never the secondary inhibition followed. As in their experiments they employed the small intestine of a cat, the question might arise whether a different result might have been followed if a different animal had been experimented on. So I used a cat instead of a rabbit, and repeated the experiments, but could never demonstrate the exodic inhibition. The small intestine of cat, compared with that of a rabbit, is much more irregular in its movements, and often a succession of contractions with intervals of rest of indefinite and unequal length is seen, so that in the case of such a preparation it is impossible to get the correct result. Perhaps this phenomenon was confused with the exodic inhibition, or there might have been errors owing to the imperfection either of method or procedure.

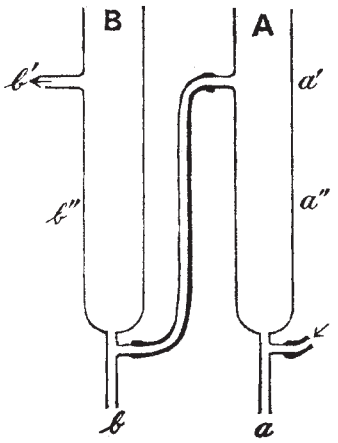
As I have just stated, on washing away adrenaline instead of the inhibitory phenomenon, the increase of tonus and the augmentation of movements follow. Compared to the pretoxic state, the amplitude of movements and the degree of tonus are considerably greater (Fig. 4). How is this phenomenon to be explained? When adrenaline is applied to the intestine, it relaxes, its movement comes to a standstill, and it is in a state of rest. Now when the poison which has been inhibiting the motion of energy thus economized disappears, the

Fig. 4.



intestine would begin its movements at once with reserved energy. I have isolated a segment of the small intestine of a rabbit together with the sympathetic nerve and immersed it in Ringer's solution kept in body temperature. The sympathetic nerve was stimulated with induction current for more than ten minutes and after it was at rest, the stimulus was removed. But the state was not different from that observed before the stimulus was applied. Hence this phenomenon is not due to the fact that the intestine has been in a state of temporary rest. Again, since a small quantity of adrenaline increases the tonus and causes augmentation of the movements of the intestine (Hoskin[6] and Tashiro[7]), may it not be that the concentration of the poison decreases by the interchange of the poison solution and this small quantity of the poison brings about excitement? In order to solve this problem, I made an experiment in the following way.

Fig. 5.



As is seen in Fig. 5, two vessels A and B were immersed in a bath and filled with Ringer's solution to the height of a'' and b'', and in each of them, one preparation of the intestine was suspended. 0·1 mgrm. of adrenaline was introduced into the A vessel, and after about twenty minutes, when the movements of the intestine reappeared, the liquid in the A vessel was removed from the outflow tube a and then the fresh Ringer's solution was introduced to the height a''. When the movements of the intestine considerably augmented, Ringer's solution was permitted to flow into vessel A, so that the content of the vessel flowed into vessel B, and when the liquid in the latter came up to the height b', the flow was stopped. Then the segment of the intestine in vessel B was often inhibited. Hence we may conclude that the quantity of adrenaline in vessel B was enough to inhibit the movements of the intestine, and consequently the quantity of adrenaline eliminated into the liquid after washing was also enough to cause the inhibitory action. And the augmentation of the movements of the intestine is not due to the action of a small quantity of adrenaline, but to the excitement caused by the exit of the poison.

To sum up the result of the above experiments. Many alkaloids have the property of causing exodic excitement. This action arises when the substance once combined with the cells is separated from them, and has nothing to do with osmosis. Adrenaline also acts in the same way, but without any sign of exodic inhibition.

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