REGULATION OF RESPIRATION. — THE EFFECT UPON SALIVARY SECRETION OF THE INTRAVENOUS ADMINISTRATION OF LACTIC ACID, SODIUM LACTATE, AND HYDROCHLORIC ACID.

By NATHAN B. EDDY. From the Department of Physiology of the University of Michigan, and the Department of Physiology and Pharmacology of the University of Alberta. (With Plates IX. to XIII. and one figure in the text.)

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WHEN the submaxillary gland of the dog was made to secrete at a constant rate by the continuous intravenous injection of pilocarpine, the intravenous administration of sodium bicarbonate, sodium carbonate, and sodium hydroxide always decreased the rate of secretion (EDDY, 1930). Evidence indicated that the decrease in secretion caused by these substances was due primarily to changes in acid base equilibrium of the blood and tissues. The present paper describes the effect upon salivary secretion of lactic and hydrochloric acids. The technique of the experiments has been described in previous papers of this series (EDDY, 1929, 1930).

Lactic acid was administered 21 times to 13 dogs. Its average effect upon secretion, an increase in every instance, has been plotted in fig. 1, and the results in individual experiments are shown in figs. 2, 3, and 4 (Plates IX. to XII.). The increase in secretion was obtained with a dose of 0·3 c.c. per kilogram of M/6 solution. With a dose of 1 c.c. per kilogram of the same solution in all but one case the increase in secretion exceeded 25 per cent. In the one exception the increase amounted to 10 per cent. The maximum increase obtained with the 1 c.c. dose was 147 per cent. In all of the experiments in which this dose was given the effect declined rapidly, and in five out of thirteen trials fell below the original rate within ten minutes. In all of the experiments the chorda tympani had been cut, and in five of them the vago-sympathetic trunk also was divided before the injection of the acid. Grouping these separately in comparison with those done with the vago-sympathetic intact (fig. 1, C), the effect of the lactic acid was more marked and slightly more persistent when the nerve had been cut.

When a dose of 5 c.c. per kilogram of M/6 lactic acid solution was injected the increase in secretion was very much greater. In one

instance it amounted to 570 per cent. However, the duration of the effect was hardly more prolonged than with the smaller dose.

The lactic acid injections always increased the submaxillary blood-volume flow, but to a less extent, comparatively, than secretion—20 per cent. on the average with the 1 c.c. dose and 60 per cent. on the average with the 5 c.c. dose of M/6 solution per kilogram. With both doses, as a rule, the blood-volume flow was still slightly above the original level at the end of ten minutes. Also there was no difference in the effect upon submaxillary blood-volume flow whether the vago-sympathetic was intact or not.

The intravenous administration of lactic acid produced small fluctuations in blood-pressure and some increase in pulmonary ventilation. In both respects the changes were greater with the larger doses of acid, but were more quickly recovered from than the changes in secretion and blood-flow.

The increase in blood-volume flow might be a factor, but did not seem of sufficient magnitude to be the primary cause of the increase in salivary secretion produced by lactic acid. A change in acid base equilibrium is another possible factor, as well as some additional effect of the lactate ion. As checks upon these possibilities we administered another stronger acid, hydrochloric, and a solution of sodium lactate.

Hydrochloric acid in M/6 solution was administered in doses of 0·3 c.c., 1 c.c., and 2 c.c. per kilogram, respectively. With each of these doses salivary secretion was always increased. The increase was about the same on the average as that produced by similar doses of lactic acid (fig. 1). The results were not modified by the previous cutting of the vago-sympathetic. However, they showed some irregularity in duration and magnitude (see fig. 5, Plate XIII.). In two experiments the secretion rate was still above the original level at the end of ten minutes. In all of the others there occurred secondarily a decrease in the rate of secretion below the original level. This was particularly marked in Experiment No. 321 (fig. 5, E). Unfortunately, in this case a record of the blood-volume flow was not obtained. It has been noted previously (Eddy, 1929) that, after the increase in secretion caused by an increase in the carbon dioxide content of the inspired air, there was a similar tendency for the secretion rate to fall below the original level, when the breathing of room air was resumed, especially if the concentration of carbon dioxide had been high or its administration prolonged. With lactic acid too a subsequent decrease in secretion was seen, but in only about a third of the experiments. Perhaps it is to be expected that an increase in glandular activity will be followed by a compensatory decrease. At the same time an acid condition, despite or in addition to its augmenting effect on salivary secretion, may cause some damage to the gland cells which would account for the secondary decrease in secretion. One might expect that the injection of lactic acid would be

less harmful than the injection of hydrochloric acid, and that the recovery process would be better due to the fact that the lactate ion is consumed as food by the body. Its damaging acid effect would be, therefore, more transitory.

Hydrochloric acid increased submaxillary blood-volume flow moderately, to about the same degree as did lactic acid. It produced usually a transient fall in blood-pressure, and it increased pulmonary ventilation, briefly as a rule.

Fourteen experiments were performed in which M/6 solution of sodium lactate was injected intravenously. In a dose of 1 c.c. per kilogram it decreased secretion slightly if the vago-sympathetic was intact. In a dose of 5 c.c. per kilogram a greater decrease in secretion was produced. However, when sodium lactate solution was injected in a dose of 1 c.c. per kilogram with the vago-sympathetic cut, there occurred not a decrease in secretion but an increase (see fig. 1, B).

Sodium lactate produced a moderate increase in submaxillary blood-volume flow of like degree whether the vago-sympathetic was cut or not. It also produced a moderate rise in blood-pressure and a depression of pulmonary ventilation, both transient and both occurring with the vago-sympathetic intact and with it cut (figs. 3 and 4).

These results suggest central as well as peripheral action of sodium lactate on salivary secretion, the former inhibitory and the latter augmentory in character. Although the intravenous injection of sodium lactate may lead to an increased alkalinity of the blood, this need not necessarily bring about a similar change in the secreting cells. For example, if we imagine that the increased concentration of the lactate ions in the blood leads to an equal exchange of lactate and HCO_3 ions between the blood and the cells, the cells would turn more acid because lactic is a stronger acid than carbonic acid. Thus the peripheral augmentory effect of sodium lactate could be interpreted on the basis of hydrogen-ion concentration, and both of its actions could be brought into harmony with the effect of lactic acid injections, following which the augmentation of secretion was greater with the sympathetic supply to the gland cut. This also suggests a central inhibitory action antagonistic to the peripheral action as with sodium lactate.

The act of cutting the vago-sympathetic while the submaxillary gland was secreting at a constant rate under the continuous influence of pilocarpine increased submaxillary blood-volume flow sharply but decreased the rate of secretion (see fig. 6). Cutting the cervical sympathetic by cutting off tonic vasoconstrictor impulses naturally produced vasodilatation in the head region and increased submaxillary blood-volume flow. The blood-flow shortly began to decrease again, but continued, as a rule, for the remainder of an experiment, more rapid than before the nerve was severed. At the end of the tracing shown on p. 324, for example, the blood-flow was 20 per cent. faster than

the original and continued at that rate. Some time after the nerve was cut the secretion slowly increased again, but did not come back to the rate before the nerve was cut. Such recovery as occurred was much slower than the recovery of the blood-flow. Again referring to the tracing in fig. 6, at the end of twenty minutes, when the blood-flow was back to a rate 20 per cent. faster than the original, the secretion rate was but slightly more than half the initial. The results were similar in other experiments.

Increased rate of blood-flow might be expected to increase tissue activity, but very rapid blood-flow through the submaxillary gland after division of the sympathetic might work differently. The increased blood-flow by washing out carbon dioxide would render the cells more alkaline, and it has been shown that the gland cells are very sensitive to changes in acid base equilibrium. Their activity was

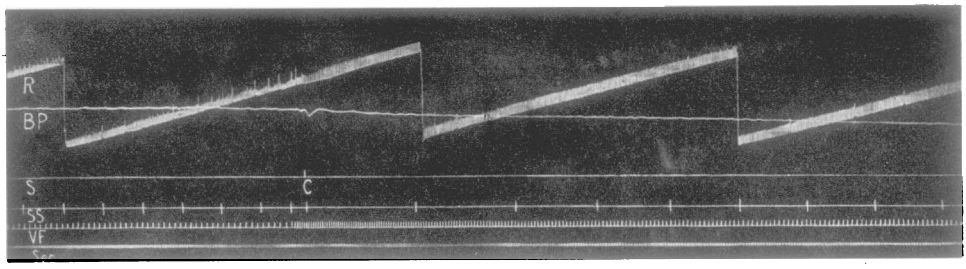

FIG. 6.

decreased by alkaline agents. It is suggested additionally that the results may indicate a central stimulating effect of pilocarpine mediated through the sympathetic, to which we have not been able to find any previous reference.

Sometimes, as in fig. 6, the first drop of saliva after division of the sympathetic fell more quickly. This might be the result of mechanical stimulation of the sympathetic fibres at the time of section.

GESELL (1920) has reported observations supporting a dual mechanism of secretion, elaboration, and liberation, the latter associated with active contraction of certain constituents of the secreting cells themselves. BABKIN and M'LARRIN (1927) and BABKIN and MACKAY (1930) have adduced evidence of motor fibres in the sympathetic whose rôle is to activate the contractile elements of the gland. If the sympathetic supply to the gland was continuously stimulated centrally by the pilocarpine injection, the cutting of the nerve by cutting off the sympathetic motor impulses would allow relaxation of the contractile elements of the gland, just as cutting the vasoconstrictor fibres allows relaxation of the blood-vessels. If the motor effect is upon the gland and not upon the duct (BABKIN and M'LARRIN, *loc. cit.*), its interruption might dam back the secretion ; that is, retard the liberation phase of

secretion, and give the appearance of a slower secretion rate. However, a secretory factor seems to be involved also on account of the incomplete recovery of the secretion rate. For, if the rate of production of saliva was constant, the rate of flow from the cannula should have returned to the original as soon as the relaxed spaces in the gland were filled.

Both lactic acid and sodium lactate increased blood-volume flow to about the same percentage extent with the sympathetic intact or cut. The percentage increase in each case has been calculated upon the rate of blood-flow immediately before an injection. As explained above, this initial blood-flow was greater in those experiments in which the sympathetic had been cut. Therefore, in the same experiments the actual blood-flow through the gland after the injection of the experimental agent was also greater than in others with the nerve intact.

Possibly this more rapid blood-flow would account for the differences in the effects of lactic acid and sodium lactate before and after the cutting of the vago-sympathetic. Against this explanation, however, is the fact that other agents—carbon dioxide and hydrochloric acid, sodium bicarbonate, sodium carbonate, and sodium hydroxide—where conditions in regard to initial blood-flow and increased blood-flow produced by their administration were the same as with lactic acid and sodium lactate, had the same effect upon salivary secretion, qualitatively and quantitatively, both before and after the division of the vago-sympathetic.

Finally, there is another possible factor involved in the action of lactate ions upon secretion. Evidence has been presented (KRAUSE (1927), HIMWICH and ADAMS (1929), and others) that catabolic changes in glandular tissue include the production of lactic acid as a step in the supply of energy to the gland cells. The administration of lactate ions, either as lactic acid or sodium lactate, might increase secretion, therefore, by increasing the energy available to the gland. In other words, the food value of the lactate ions might be a factor in their peripheral augmentory effect upon salivary secretion.

SUMMARY.

In the dog the secretion of the pilocarpinised submaxillary gland is increased by the intravenous administration of lactic and hydrochloric acids. With the latter the increase in secretion varies in duration and magnitude and is followed frequently by a decrease below the original level. Its effect is the same whether the sympathetic supply to the gland is intact or not.

Both agents increase the submaxillary blood-volume flow with the vago-sympathetic intact, but the magnitude of this change seems

insufficient to account for the increase in secretion though it might contribute to it. A similar increase in blood-volume flow is produced after cutting the vago-sympathetic.

The increase in secretion produced by lactic acid is greater if the vago-sympathetic has been cut.

Sodium lactate, intravenously injected, decreases salivary secretion if the vago-sympathetic is intact but increases it if the nerve is cut. It increases submaxillary blood-volume flow in a like degree whether the vago-sympathetic is intact or not.

The differences in the effects of lactic acid and sodium lactate before and after section of the sympathetic supply to the gland suggest a central as well as peripheral control of salivary secretion. The lactate ions appear to be inhibitory to the central and augmentory to the peripheral mechanism of secretion.

All three agents cause transient changes in blood-pressure, and both of the acids always increase pulmonary ventilation, though the change is generally more transitory than the effect upon secretion. Sodium lactate has no effect upon pulmonary ventilation or decreases it. Again the effect is transient.

It is believed that changes in the acid base equilibrium of the tissues and blood are an important factor in the effect upon secretion of lactic acid, of hydrochloric acid, and of sodium lactate. Coincident changes in blood-volume flow probably affected the results, and some additional effect of the lactate ions, such as their use as food material supplying energy for secretion, may be involved.

The act of cutting the vago-sympathetic, while the submaxillary gland was secreting at a constant rate under the continuous injection of pilocarpine, increased submaxillary blood-volume flow sharply but decreased the rate of secretion. Possible mechanisms producing these changes have been discussed.

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For Explanation of Plates see p. 320.

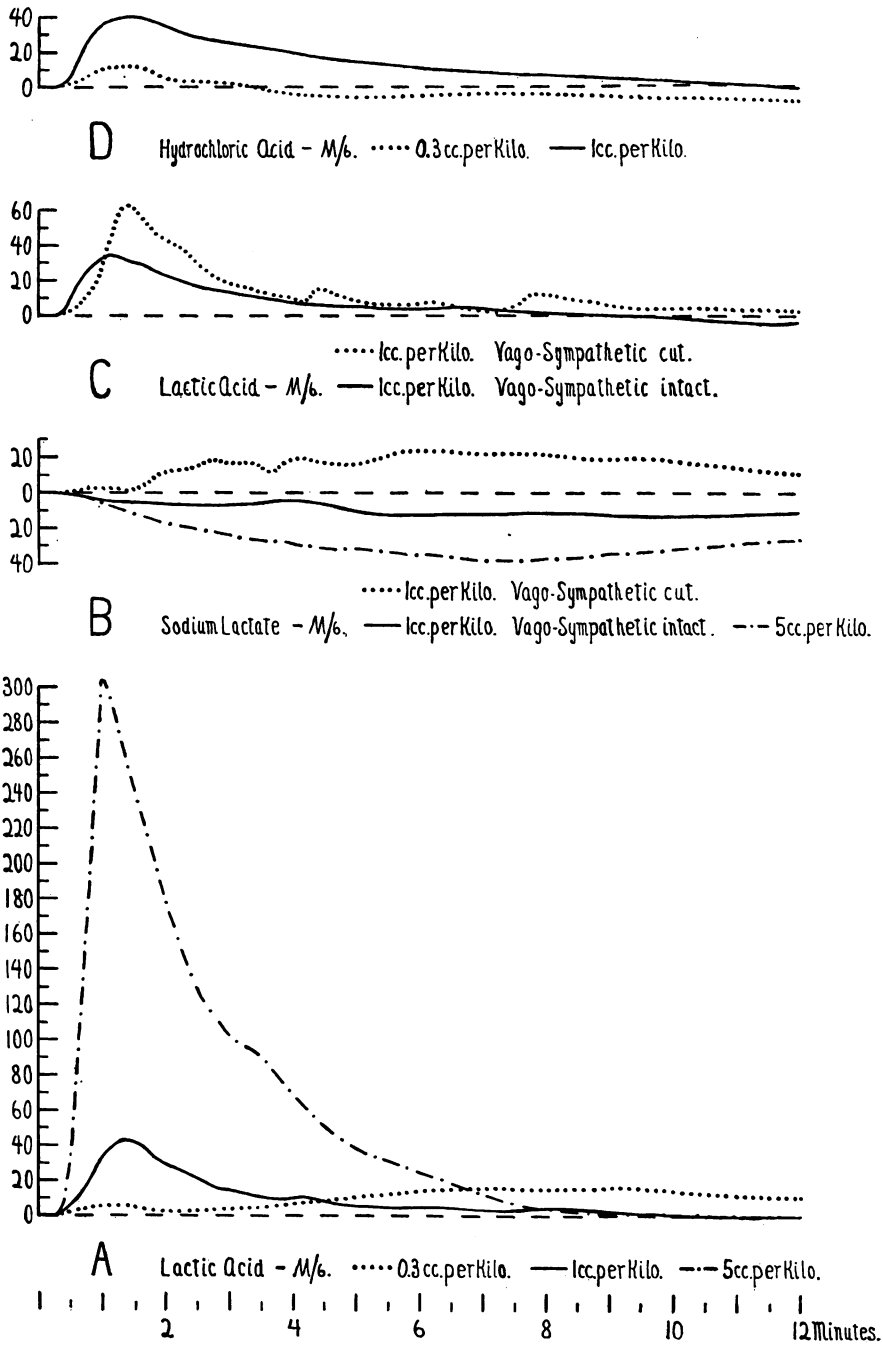

Fig. 1. Salivary Secretion - Average Results.

EDDY, " The Effect upon Salivary Secretion of Lactic Acid," etc.

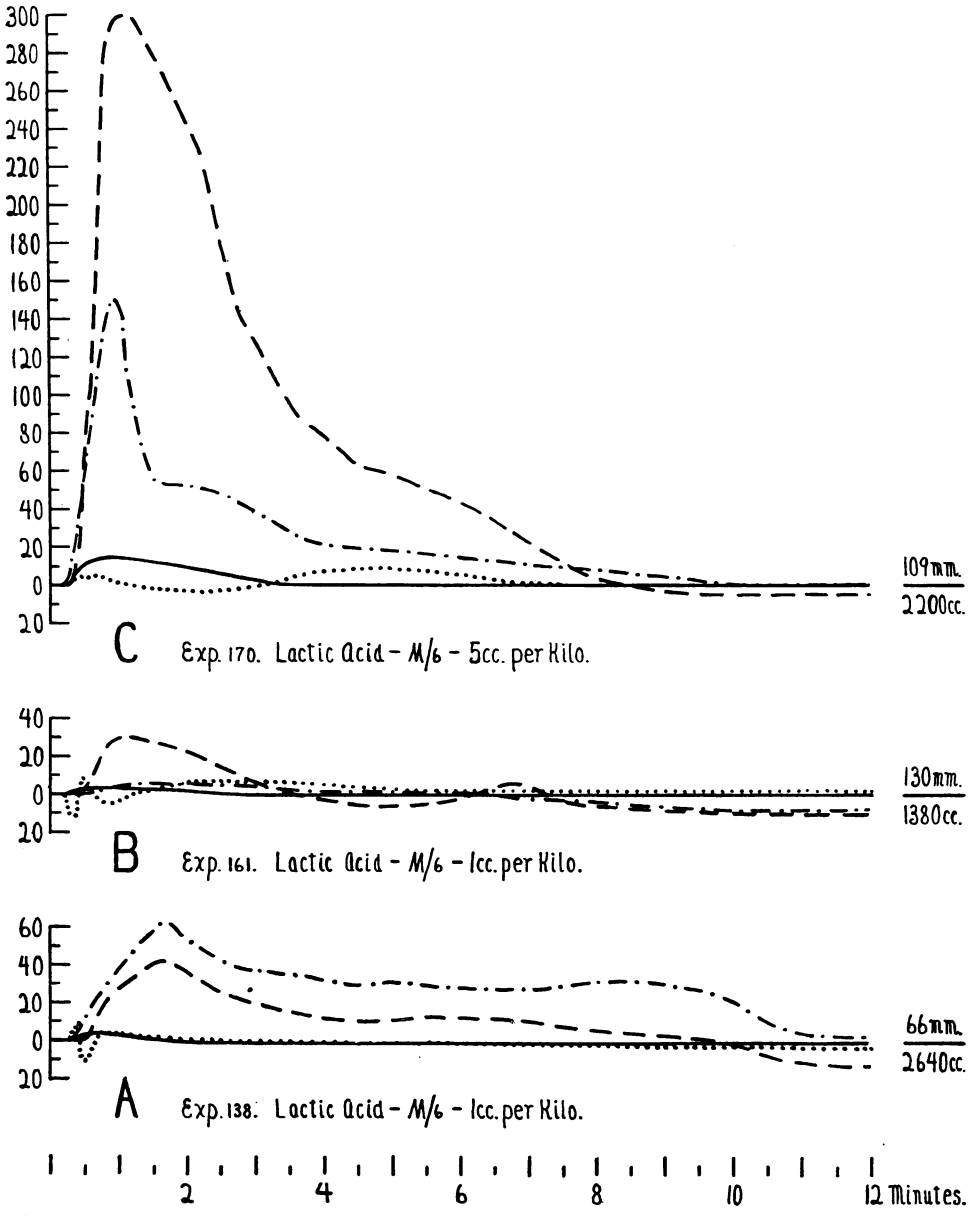

Fig. 2.— Pulmonary Ventilation. ····· Mean Blood Pressure.
– – Salivary Secretion. –·– Submaxillary Blood Volume Flow.

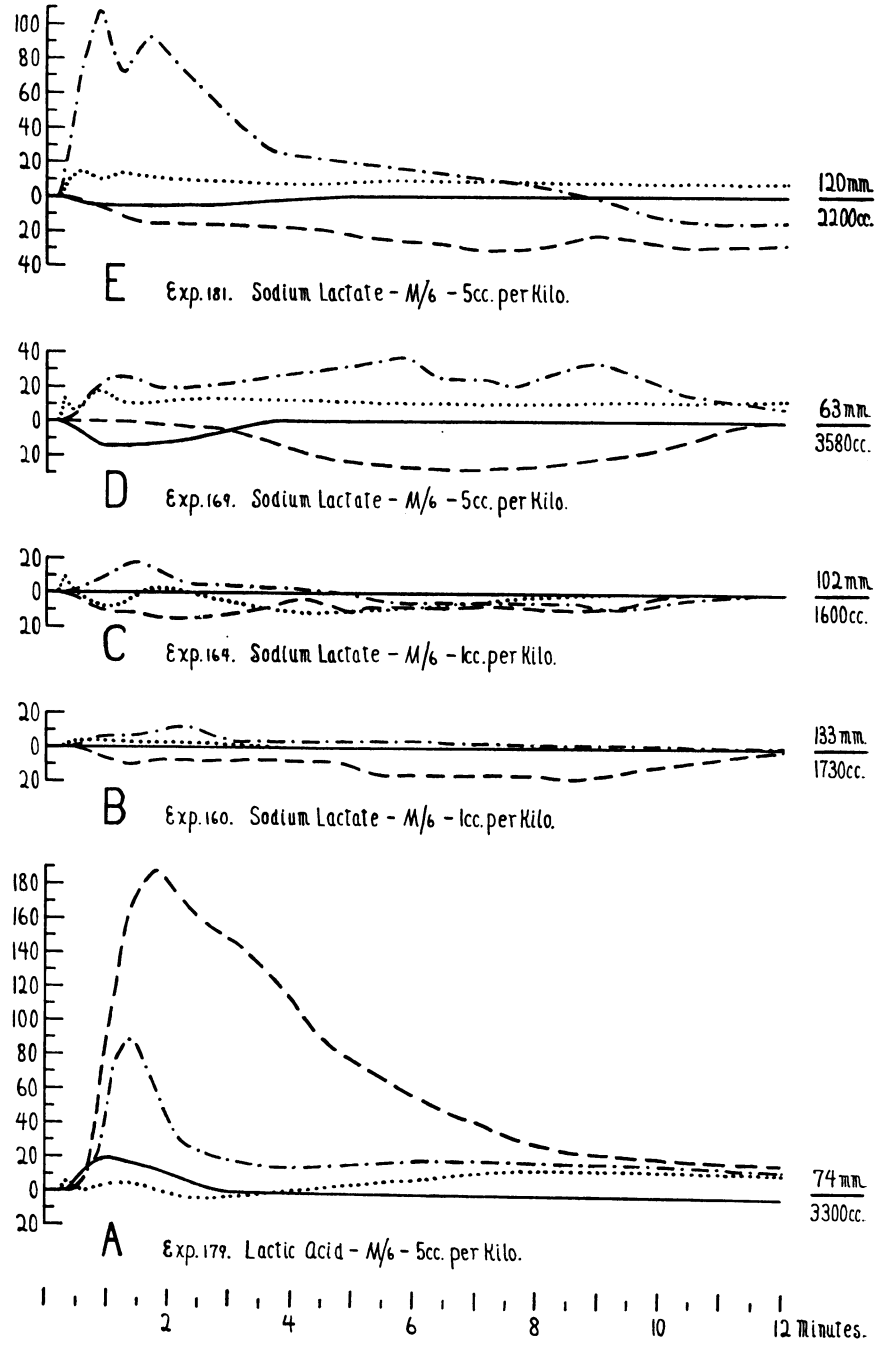

Fig. 3. — Pulmonary Ventilation. ····· Mean Blood Pressure. - - Salivary Secretion. -·- Submaxillary Blood Volume Flow.

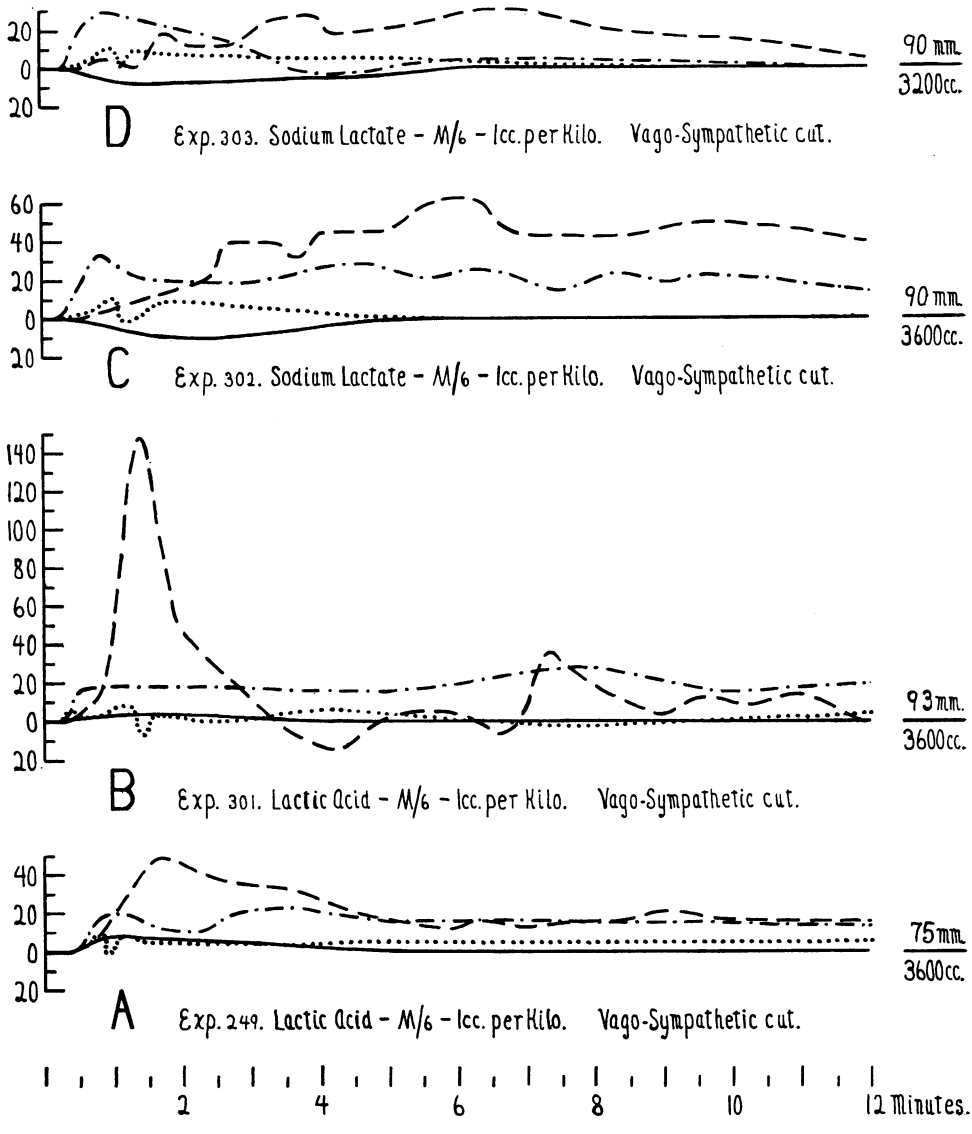

Fig. 4. — Pulmonary Ventilation. ····· Mean Blood Pressure.
– – Salivary Secretion. –·– Submaxillary Blood Volume Flow.

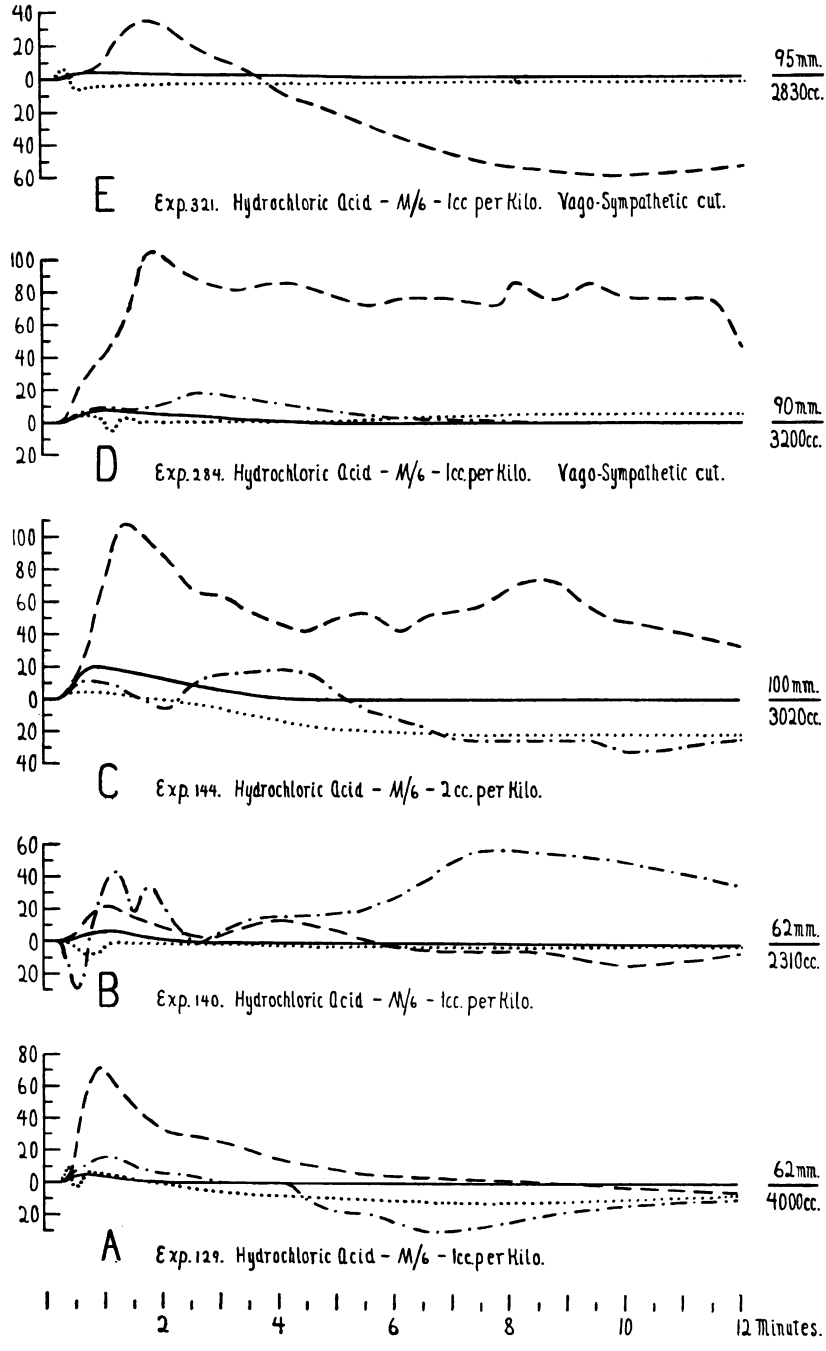

Fig. 5.

EDDY, " The Effect upon Salivary Secretion of Lactic Acid," etc.