REGULATION OF RESPIRATION. — THE EFFECT UPON SALIVARY SECRETION OF THE INTRAVENOUS ADMINISTRATION OF SODIUM BICARBONATE, SODIUM CARBONATE, SODIUM HYDROXIDE, SODIUM CHLORIDE, AND SODIUM SULPHATE.

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IN a previous report (EDDY, 1929) it has been shown that the submaxillary gland of the dog, continuously stimulated by the intravenous administration of pilocarpine, is sensitive to small changes in the carbon dioxide and oxygen contents of the inspired air. To an increase in carbon dioxide the gland responded by increased secretion ; to lowered oxygen the gland responded by decreased secretion. Though both responses are not in the same direction, the sensitivity of glandular activity is like that of the respiratory mechanism to similar changes in the inspired air. GESELL and his co-workers (1929) in their studies in respiration, in addition to studying the effects of changes in the inspired gases, have investigated the effect of the intravenous administration of a variety of substances; in the main, agents which affect oxidations and the acid base equilibrium of the body. We have continued our study of the responsiveness of the submaxillary gland by determining the effect upon it of the same agents.

The technique of the experiments has been described in the previous report (EDDY, 1929). Blood-pressure, salivary secretion, and submaxillary blood-volume flow were recorded simultaneously. For the last the bloodless method of GESELL (1924) was employed. Respiration and rate of oxygen consumption were recorded also through a rebreathing tank, in connection with which precautions were taken to keep the oxygen content of the air reaching the animal constant to within 1 per cent. In all the experiments the chorda tympani was cut in the preparation of the submaxillary duct for cannulisation. Pilocarpine, 1 : 100,000, was injected intravenously at a rate to

maintain a steady flow of saliva. The dogs were under morphine-urethane anæsthesia. Experimental agents were injected into the femoral vein.

The first substance used was sodium bicarbonate. To avoid its rapid change in solution to carbonate, it was weighed and dissolved in distilled water at room temperature immediately before an injection was to be given. Then the injection was made rapidly at room temperature. Solutions of other substances with which sodium bicarbonate is compared in this paper were prepared and injected in a similar manner. The average results upon secretion which sodium bicarbonate produced are shown in fig. 1, and the results in individual experiments are illustrated in figs. 2 and 5. The numbers on the scale at the left of each figure represent percentage variations in salivary secretion and submaxillary blood-volume flow, millimetres of fluctuation in mean blood-pressure from the level at the beginning of the procedure, and fluctuations in pulmonary ventilation (20 on the scale equals a difference of 2 litres of air breathed per minute). The figures on the zero line at the right give the initial mean blood-pressure in millimetres of mercury and the initial pulmonary ventilation in cubic centimetres per minute. The time in minutes from the beginning of an injection is shown at the bottom of the figure.

The invariable effect of the intravenous administration of sodium bicarbonate was a decrease in the rate of salivary secretion (fig. 1, A). Using molecular solution, 0·2 c.c. per kilogram of body-weight decreased the secretion 20 per cent. on the average. As a rule the rate of secretion was back to that at the time of injection in about ten minutes. One cubic centimetre per kilogram of molecular solution decreased secretion 36 per cent. on the average, and at the end of ten minutes the rate of secretion was still 24 per cent. below that at the time of injection. Following the injection of 5 c.c. per kilogram of molecular solution of sodium bicarbonate, the salivary secretion was decreased 73 per cent., and there was only slight recovery in the rate of secretion at the end of ten minutes. With these larger doses of sodium bicarbonate recovery would occur in time, but it might require more than forty-five minutes.

The submaxillary blood-volume flow was decreased rarely (fig. 2, A) following the intravenous administration of molecular sodium bicarbonate solution, 1 c.c. per kilogram. It was usually increased by this dose (fig. 2, B ; fig. 5, A and B). With a dose of 5 c.c. per kilogram of molecular sodium bicarbonate solution, submaxillary blood-volume flow was always increased markedly (fig. 2, C and D). Using a different method, GESELL and BRONK (1927) have demonstrated an increase in both carotid and femoral flow of blood following intravenous administration of sodium bicarbonate.

As a rule we found that the injection of sodium bicarbonate caused an increase in mean blood-pressure, which was more marked and more persistent with the larger doses. Pulmonary ventilation was unchanged

or increased initially. Not infrequently there was a secondary decrease in pulmonary ventilation with gradual recovery.

GESELL (1920) in his studies on the submaxillary gland of the dog showed a close parallelism between tissue activity and volume flow of blood under certain conditions. Here, however, we have an agent, sodium bicarbonate, which increased markedly the volume flow of blood and at the same time decreased markedly the secretion of the submaxillary gland. Some other factor, obviously, was at work which more than offset the effect of increased blood-flow. Two possible factors are change in the acid base equilibrium of tissues and blood, and the withdrawal of water from the tissues on account of the hypertonicity of the solution injected.

Sodium carbonate, which is more strongly alkaline, was injected in half-molecular solution 12 times in 8 dogs. Its average effect upon secretion is shown in fig. 1, B. The doses used were 0·2 c.c. and 0·5 c.c. per kilogram of body-weight, respectively. It will be noted that the effect upon secretion of these doses of half-molecular sodium carbonate solution were very like the effects of similar doses of molecular sodium bicarbonate solution. In other words, sodium carbonate had approximately twice as great a depressant effect upon salivary secretion as sodium bicarbonate.

The results in typical individual experiments with sodium carbonate are shown in fig. 3, A and B. Transient depression of blood-pressure and of pulmonary ventilation was produced by sodium carbonate. Submaxillary blood-volume flow was increased sharply at first, simultaneously with the fall in blood-pressure. The return of the blood-volume flow to the normal level was more gradual than the recovery of the blood-pressure. The two experiments shown were performed upon the same dog—the one before and the other after the vago-sympathetic trunk was cut. The fluctuations in blood-pressure and in blood-volume flow were greater after the vago-sympathetic was cut. The effects upon salivary secretion and pulmonary ventilation were practically identical in the two cases. Similarly, in other experiments with sodium carbonate and in the experiments with sodium bicarbonate the effect upon submaxillary secretion was the same whether the vago-sympathetic was cut or not.

As a further test of the effect of alkalinity upon salivary secretion we injected 1 c.c. per kilogram of sodium hydroxide in M/6 solution 5 times in 4 dogs. Typical results are shown in fig. 3, C, D, and E. Secretion was decreased on the average 18 per cent. The effect upon secretion was the same whether the vago-sympathetic was cut or not. In three of the five experiments submaxillary blood-volume flow was recorded, and in each case the flow was increased. Pulmonary ventilation and blood-pressure were depressed transiently, as a rule, by the intravenous injection of sodium hydroxide in the dose employed.

It is conceivable that salt solutions of different molecular concentration might affect the rate of salivary secretion by affecting the water content of the blood or the water available to the gland cells. For example, in our previous experiments (EDDY, 1929) we observed that isotonic sodium chloride solution, injected intravenously after blood loss occasioned by the open-drop method of recording blood-volume flow, increased slightly submaxillary secretion and increased submaxillary blood-volume flow. In the present series of experiments both sodium bicarbonate and sodium carbonate were injected in hypertonic solution. Possibly the hypertonicity of the solution, by withdrawing water from the tissues, including the gland cells, might contribute to the depression of secretion observed. We approached this question in three ways: first, the comparison of the effect of the injection of neutral salts, sodium chloride and sodium sulphate, in equal bulks of isotonic and hypertonic solutions, and in equal dose of the salt (sodium chloride only) in isotonic and hypertonic solution ; second, the comparison in the same animal of the injection of the same bulk and same molecular concentration, both isotonic and hypertonic solutions, of a neutral salt, sodium chloride, and of sodium bicarbonate ; third, the comparison in the same animal of the administration of the same amount of sodium bicarbonate in isotonic and in hypertonic solution. The average results of these experiments are shown in fig. 1, C, D, and E, and individual results are illustrated in figs. 4, 5, 6, and 7.

As was seen before, sodium chloride in isotonic solution, 6 c.c. per kilogram of body-weight, increased salivary secretion. The same amount of sodium chloride in hypertonic solution, 1 c.c. per kilogram, decreased salivary secretion (fig. 1, C and D). Again, a similar bulk of sodium chloride solution injected in hypertonic form, 5 c.c. per kilogram of molecular solution, depressed secretion (fig. 1, D). The injection of the same bulk of hypertonic sodium bicarbonate solution, 5 c.c. per kilogram of molecular solution, depressed secretion very much more (fig. 1, D). Equal amounts of sodium bicarbonate had practically identical effects whether the substance was injected in isotonic or hypertonic solution (fig. 1, C).

Sodium sulphate affected salivary secretion in the main like sodium chloride ; in isotonic solution it increased salivary secretion ; in hypertonic solution it decreased it (fig. 1, E). In the latter case there occurred a transient initial increase in secretion in three of the four experiments.

All of the injections of neutral salt solutions increased submaxillary blood-volume flow. The increase was greater with the hypertonic solutions. The effect of the neutral salt solutions was the same whether the vago-sympathetic was cut or not. These injections produced minor changes in blood-pressure and pulmonary ventilation, which are illustrated in the figures.

Sometimes following the depression of the secretion upon the

injection of hypertonic solution of sodium chloride, there occurred an increase in the secretion rate to or above the original level, and a fairly prompt decrease again below the original level. This was especially marked in Experiments 134 and 309 (fig. 4, D, and fig. 5, D). In these and other experiments in which the same tendency was shown, submaxillary blood-volume flow was very greatly increased. We suggest that the result was due to the conflicting effects upon the glandular activity of increased blood-flow and of withdrawal of water on account of the hypertonicity of the solution injected. The same explanation could be applied to the initial increase in secretion which usually occurred when hypertonic sodium sulphate solution was injected. A similar conflict might occur when sodium bicarbonate was injected. In other words, one could imagine that the depression produced by bicarbonate would be greater if the increase in blood-flow were prevented. As a matter of fact, the decrease in secretion following the administration of the same dose of sodium bicarbonate was usually greater in those experiments in which the increase in blood-flow was less.

From the results described we feel justified in concluding that the effect upon salivary secretion of the intravenous injection of sodium bicarbonate, or of sodium carbonate, or of sodium hydroxide was due mainly to a change in acid base equilibrium, though the effect may have been contributed to by water withdrawal from the tissues by the hypertonicity of the solution injected, and may have been modified by coincident changes in submaxillary blood-volume flow.

In connection with this conclusion it might be advisable to compare effects of carbon dioxide, of sodium bicarbonate, and of sodium carbonate on pulmonary ventilation, mean blood-pressure, and salivary secretion. Pulmonary ventilation and mean blood-pressure are augmented by administration of carbon dioxide and by administration of sodium bicarbonate, and depressed by sodium carbonate. On the other hand, salivary secretion is augmented only by carbon dioxide and depressed by both sodium carbonate and sodium bicarbonate. GESELL (1923), GESELL and HERTZMAN (1926), and GESELL and M'GINTY (1927) have offered a possible explanation for the difference in the effects of bicarbonate and carbonate on pulmonary ventilation and mean blood-pressure on the basis of the relative rate of migration of acid and of base between the blood and tissues. Whereas intravenous injection of sodium carbonate leads to a lowering of carbon dioxide pressure in the blood and a consequent withdrawal of carbon dioxide from the tissues, injection of sodium bicarbonate leads to an increased carbon dioxide pressure in the blood, with a consequent flow of carbon dioxide into the tissues or a retardation of the movement of carbon dioxide from the tissues to the blood.

In the light of this suggestion the difference between the effects of bicarbonate and carbonate on pulmonary ventilation, mean blood-

pressure, and salivary secretion may not be as great as they appear to be. In the first place, the effects of bicarbonate on pulmonary ventilation are never very great ; they may not occur at all, and they are dependent on relatively rapid injection and a healthy condition of the tissues (GESELL, 1927). This agrees with our results that sodium carbonate and sodium hydroxide, which produce a movement of carbon dioxide from the tissues to the blood, produce the greater depression of salivary secretion. The effects of bicarbonate and of carbonate on pulmonary ventilation, mean blood-pressure, and salivary secretion then appear to have at least a relative, if not an absolute, resemblance.

An additional series of experiments with sodium bicarbonate, we believe, deserve a descriptive word. If an animal of 18 to 20 kilograms was made to re-breathe from a tank containing a limited supply of air (15 litres) without carbon dioxide removal, as carbon dioxide accumulated and oxygen was used up salivary secretion increased early and progressively to a marked degree, and submaxillary blood-volume flow increased much more slowly and not very greatly, while pulmonary ventilation increased progressively and little or no change in blood-pressure occurred. At the end of ten minutes of such re-breathing, secretion had increased on the average (3 experiments) 100 per cent. and blood-volume flow only 20 per cent. Analysis showed that in the same length of time in the re-breathing tank carbon dioxide had increased to 4·75 per cent. (average figure). The increase in secretion was due to the accumulation of carbon dioxide, or rather, we believe, to increased hydrogen-ion concentration which the accumulating carbon dioxide produced.

Intravenous administration of sodium bicarbonate increases the carbon dioxide content of the blood and of the expired air, and increases oxidations (GESELL *et al.*, 1929), yet it decreased salivary secretion. If the effect of sodium bicarbonate and of carbon dioxide upon salivary secretion was due, as we have indicated, to changes in acid base equilibrium, then one should offset the other ; that is, the administration of sodium bicarbonate should prevent or delay the increase in secretion which re-breathing would produce ; or, re-breathing after the administration of sodium bicarbonate should cause the secretion rate to recover more promptly. We tried this in three experiments upon the same dogs as were used for the re-breathing experiments already described.

To each of the dogs molecular sodium bicarbonate solution, 5 c.c. per kilogram, was administered intravenously. Later, when conditions were again normal, the animal was made to re-breathe for ten minutes, with the effects described. When the animal had recovered completely, the same dose of sodium bicarbonate was administered. Two minutes later the animal again began to re-breathe, and the re-breathing was continued for ten minutes as before. The average results are shown in fig. 8. The increase in secretion shown in fig. 8, B, as produced by

re-breathing after injection of sodium bicarbonate, is obtained from the difference in the effects of the sodium bicarbonate, shown in fig. 8, A. At the end of ten minutes of re-breathing after sodium bicarbonate administration, carbon dioxide had accumulated in the tank to 4·74 per cent. (average figure).

The results in these re-breathing experiments indicate distinct antagonism between the quickening effect upon secretion of increasing carbon dioxide in the inspired air and intravenously administered sodium bicarbonate. This further supports, we believe, the idea suggested that the effect in each of these cases was due primarily to a change in acid base equilibrium.

Summary.

In the dog salivary secretion, elicited by continuous administration of pilocarpine, is decreased by intravenous injection of sodium bicarbonate, of sodium carbonate, or of sodium hydroxide. The decrease in secretion produced by sodium bicarbonate is greater the larger the dose, and is obtained in like degree whether the bicarbonate is injected in isotonic or in hypertonic solution. The effect of sodium carbonate upon secretion is greater than that of sodium bicarbonate, and the effect of sodium hydroxide greater than that of either of the other two substances.

Intravenously administered sodium bicarbonate prevents almost completely the augmenting effect upon salivary secretion of a ten-minute period of re-breathing, though carbon dioxide accumulated in the re-breathing tank to the same extent as in a similar period of re-breathing without sodium bicarbonate administration.

Each of the three alkaline agents increases submaxillary blood-volume flow as a rule.

Sodium chloride or sodium sulphate intravenously administered in isotonic solution increases submaxillary secretion and blood-volume flow. Both agents administered in hypertonic solution decrease salivary secretion but increase more markedly submaxillary blood-volume flow. The effect upon secretion of isotonic and hypertonic solutions of sodium chloride and sodium sulphate appears to be due to the increase in blood-flow and to their influence upon the fluid available to the gland cells by withdrawal of water from the tissues.

The described effects of the alkaline substances and neutral salts were obtained with the chorda tympani cut, and were not affected by cutting also the vago-sympathetic.

It is suggested that the effects upon salivary secretion of intravenous injection of sodium bicarbonate, sodium carbonate, and sodium hydroxide are due mainly to changes in acid base equilibrium, in which the hydrogen-ion concentration of the interior of the cell may be a major factor.

A comparison of the effects of carbon dioxide, of sodium bicarbonate, and of sodium carbonate on pulmonary ventilation, mean blood-pressure, and salivary secretion is made.

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EXPLANATION OF PLATES I. TO XVIII.

The numerals on the scales at the left of the curves represent percentage variations in salivary secretion and submaxillary blood-volume flow, millimetres of fluctuation in mean blood-pressure from the level at the beginning of the procedure, and fluctuations in pulmonary ventilation (20 on the scale equals a difference of 2 litres of air breathed per minute). The figures on the zero line at the right of Plates II. to VIII., X. to XIII., and XV. to XVIII. give the initial mean blood-pressure in millimetres of mercury and the initial pulmonary ventilation in cubic centimetres per minute. The time in minutes from the beginning of an injection is shown at the bottom of each plate. Other explanations are given in the text.

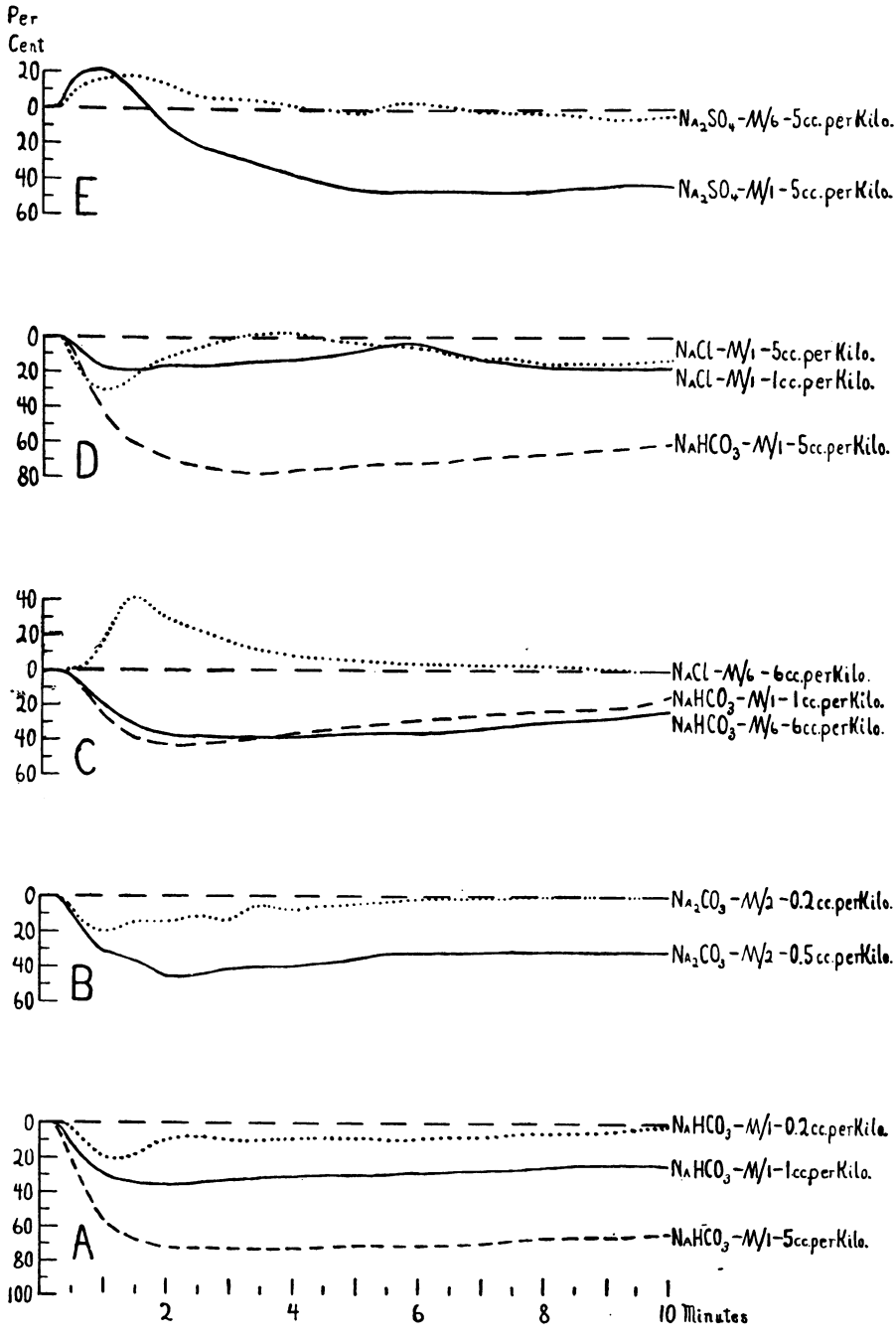

Fig. 1. Salivary Secretion—Average Results.

EDDY, " The Effect upon Salivary Secretion of Sodium Bicarbonate," etc.

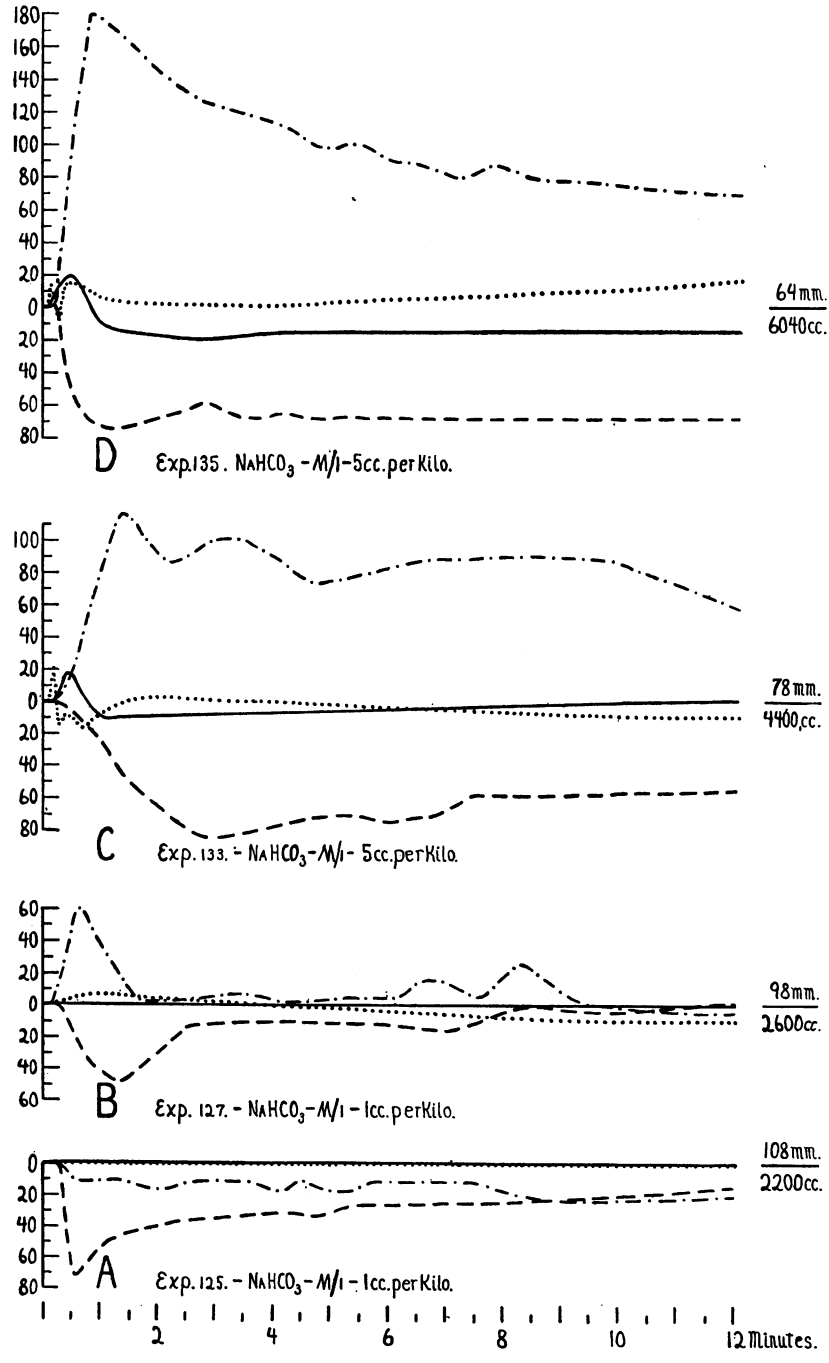

Fig. 2. — Pulmonary Ventilation. ····· Mean Blood Pressure. - - Salivary Secretion. -·- Submaxillary Blood Volume Flow.

EDDY, " The Effect upon Salivary Secretion of Sodium Bicarbonate," etc.

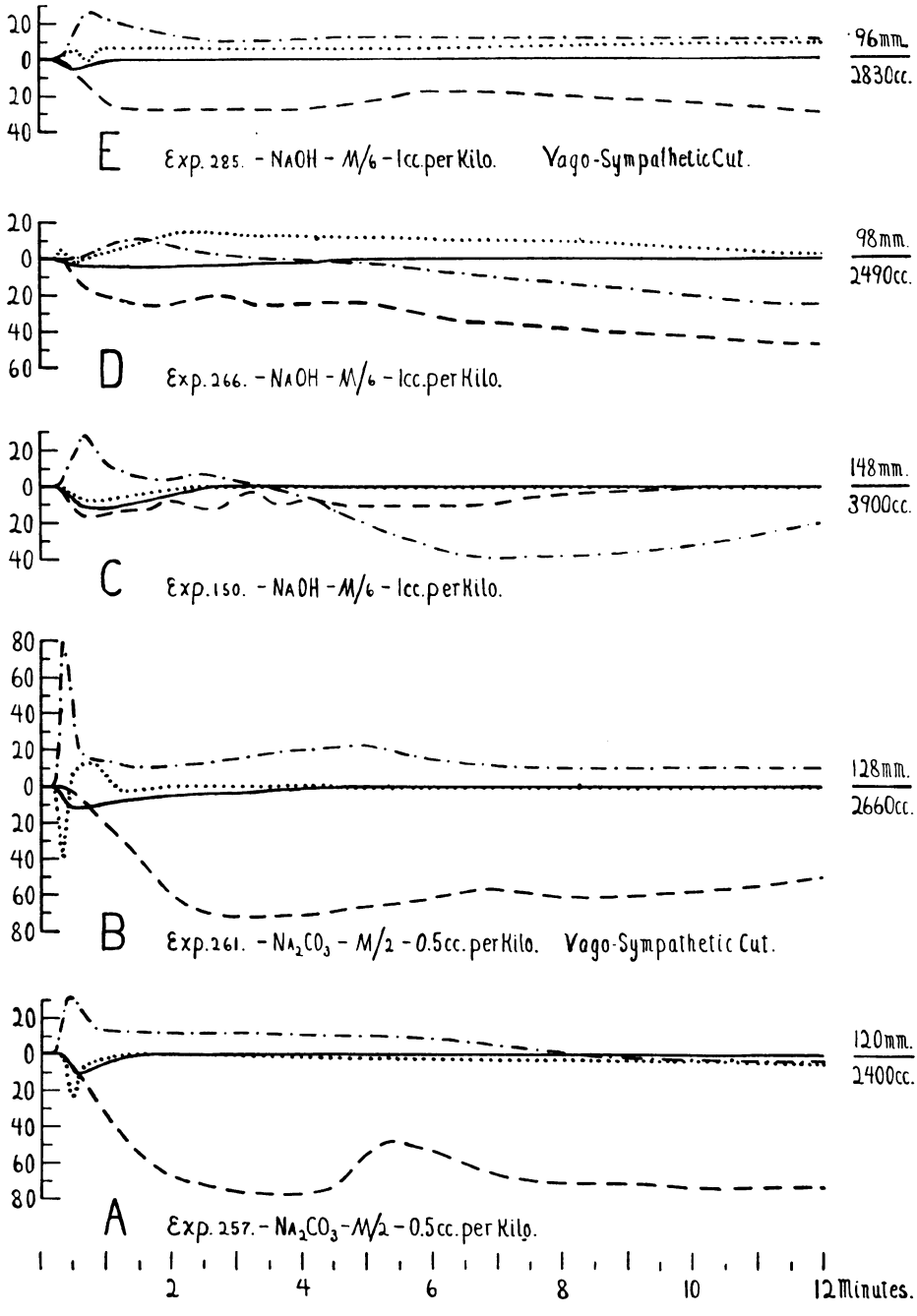

Fig. 3. — Pulmonary Ventilation. ····· Mean Blood Pressure. – – Salivary Secretion. –·– Submaxillary Blood Volume Flow.

EDDY, " The Effect upon Salivary Secretion of Sodium Bicarbonate," etc.

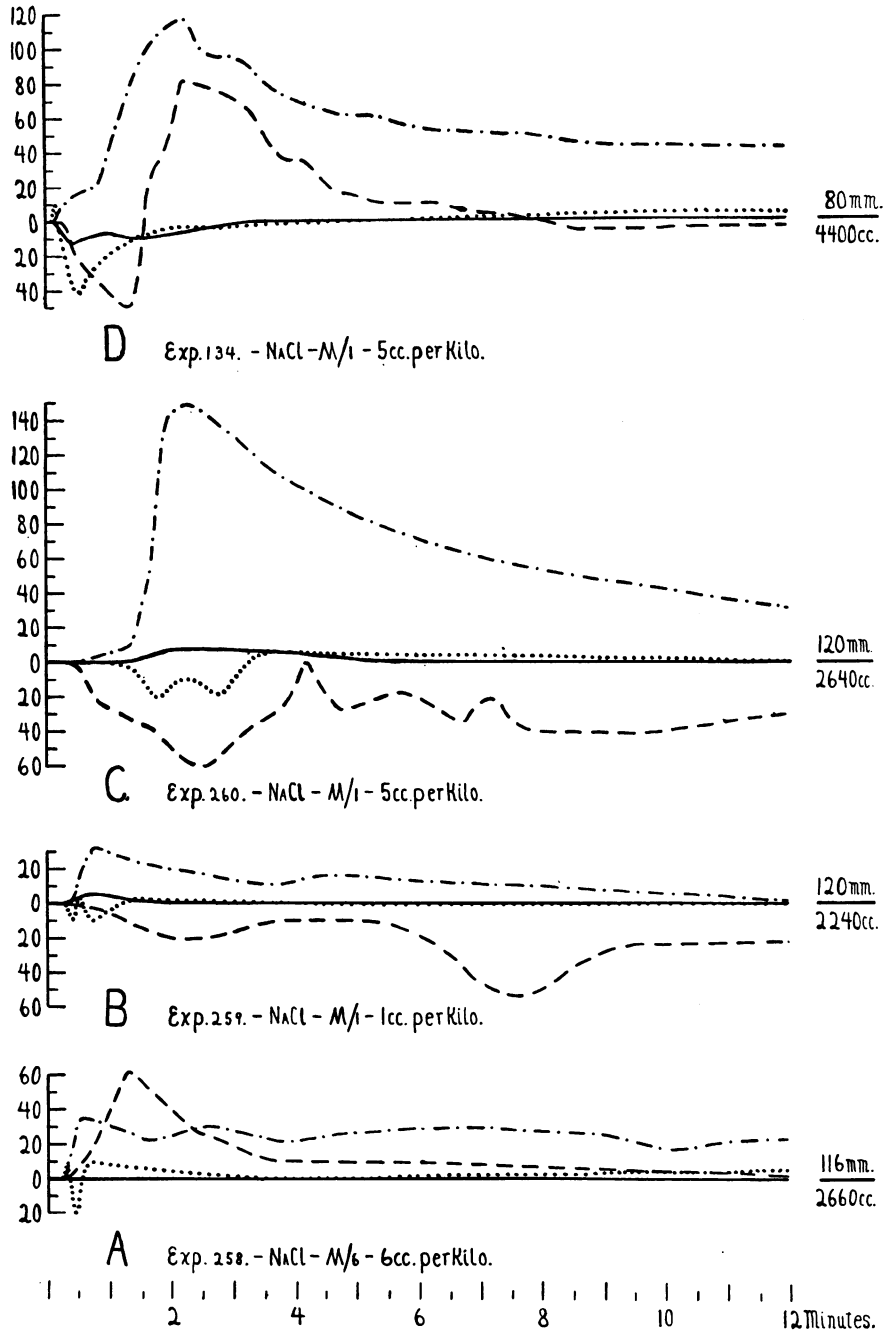

Fig. 4. — Pulmonary Ventilation. ····· Mean Blood Pressure. – – Salivary Secretion. –·– Submaxillary Blood Volume Flow.

EDDY, " The Effect upon Salivary Secretion of Sodium Bicarbonate," etc.

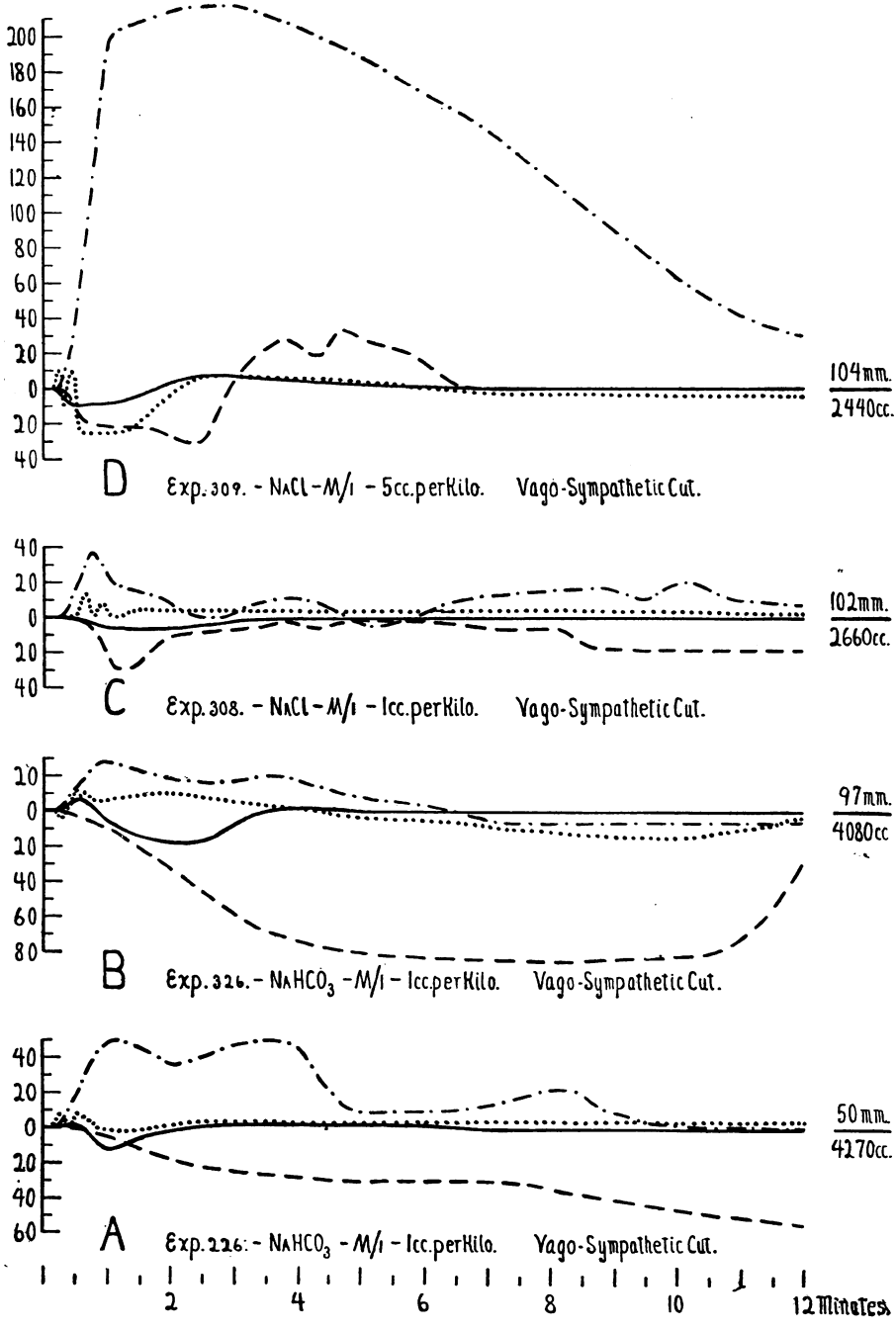

Fig. 5. — Pulmonary Ventilation. ····· Mean Blood Pressure. - - Salivary Secretion. -·- Submaxillary Blood Volume Flow.

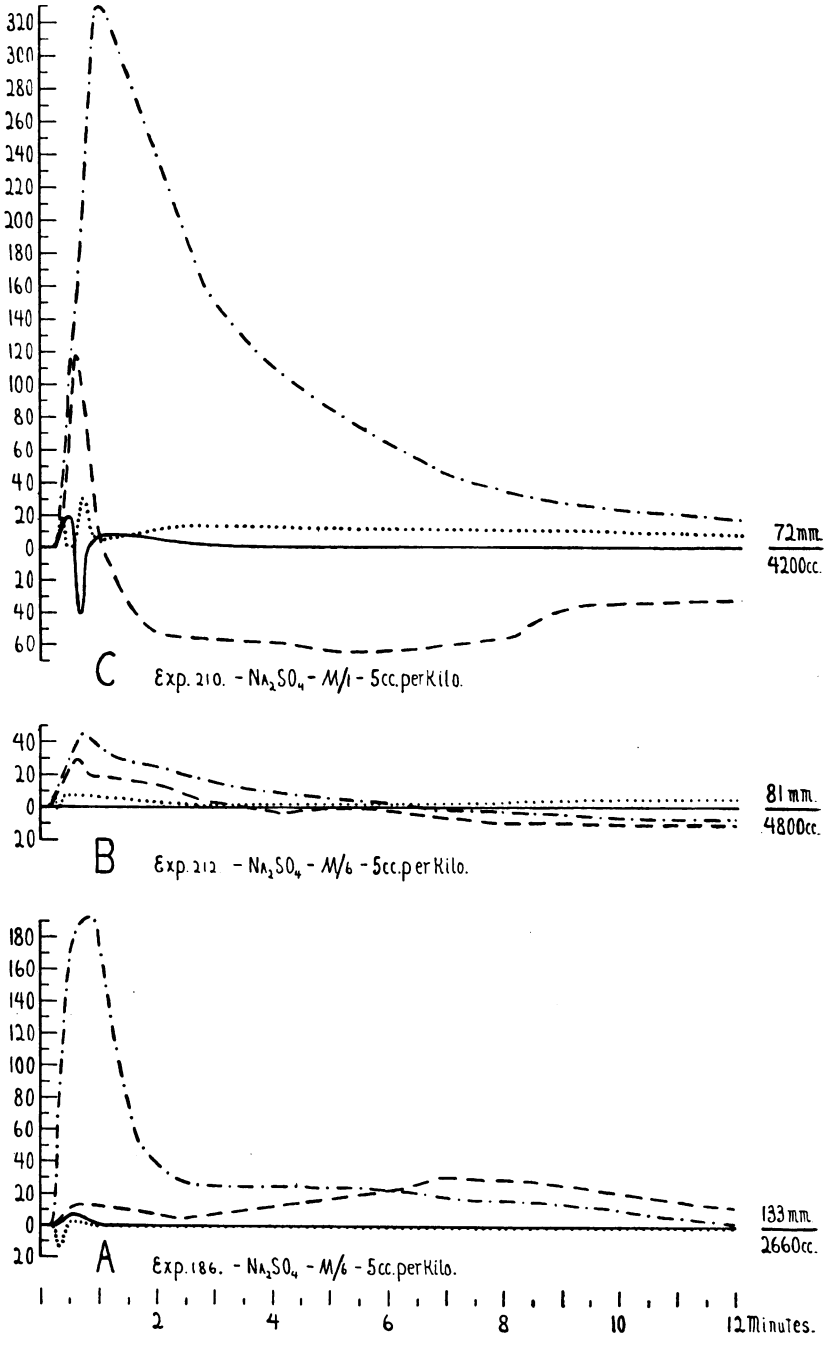

Fig. 6. — Pulmonary Ventilation. ····· Mean Blood Pressure. - - Salivary Secretion. -·- Submaxillary Blood Volume Flow.

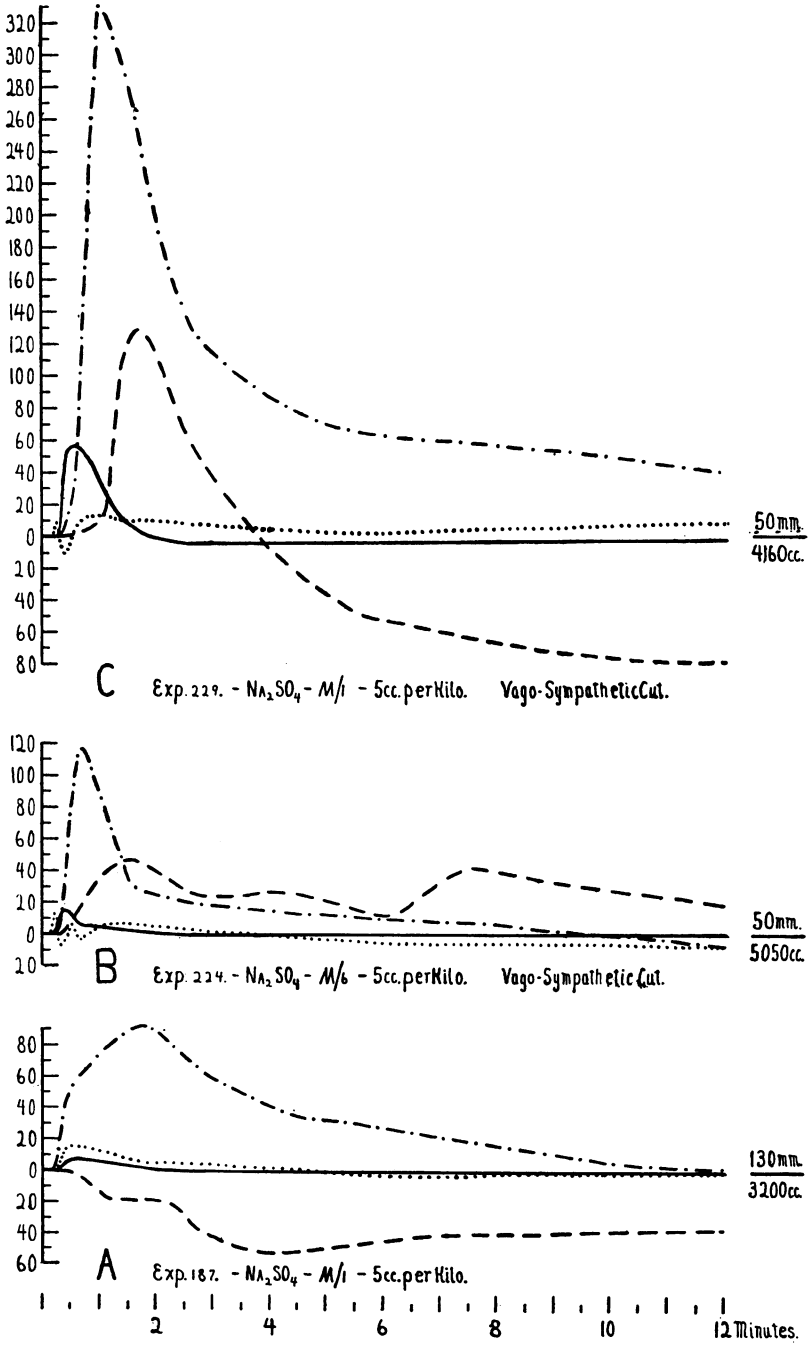

Fig. 7. — Pulmonary Ventilation. ····· Mean Blood Pressure. – – Salivary Secretion. –·– Submaxillary Blood Volume Flow.

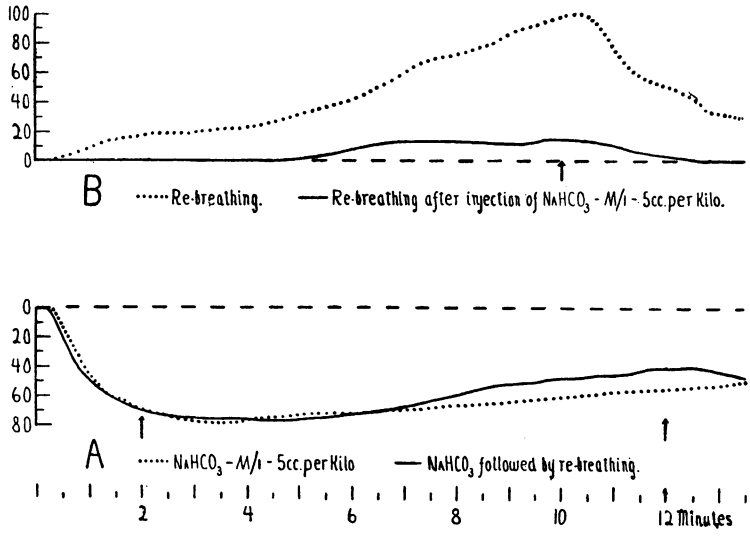

Fig. 8. Salivary Secretion – Average Results

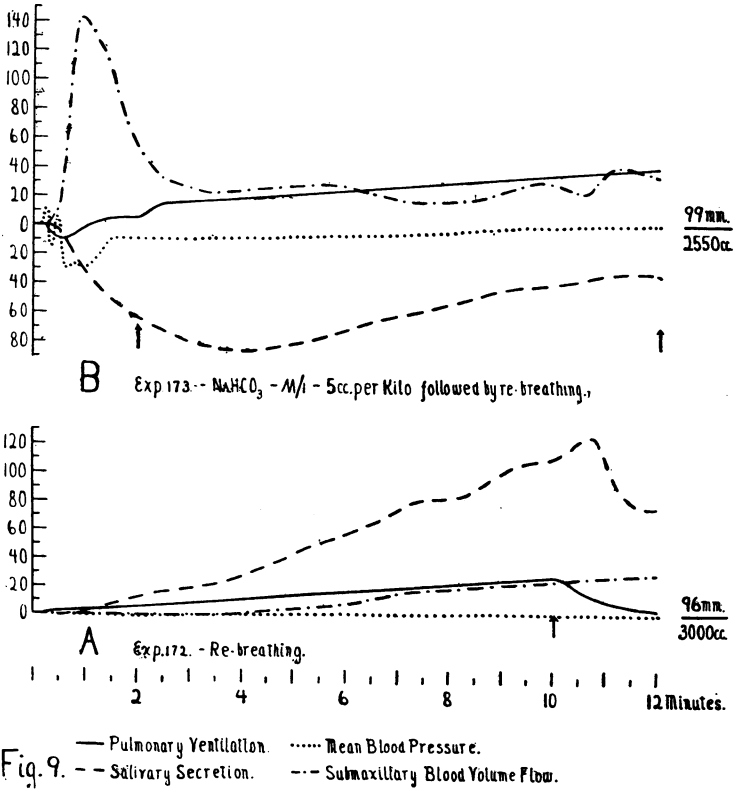

Fig. 9.