THE RELATION OF ADRENALIN HYPERGLYCEMIA TO DECREASED ALKALI RESERVE OF THE BLOOD.

BY JOHN P. PETERS, JR., AND H. RAWLE GEYELIN.

(From the Medical Clinic, Presbyterian Hospital, and the Coolidge Fellowship and the Blumenthal Fellowship, Columbia University, New York.)

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During the course of some attempts by one of us to increase the food tolerance of diabetic patients by subcutaneous injections of adrenalin, it was observed that one of the patients showed more or less pronounced hyperpnea immediately after the administration of adrenalin. This observation, taken in connection with the fact that lowering of the alkaline reserve of the blood is often accompanied by some degree of hyperpnea, led to the investigation of the effect of adrenalin upon the CO₂ combining capacity of the blood. The fact that adrenalin also causes hyperglycemia, that the administration of acid increases this hyperglycemia (1), and as pointed out by Elias (2), that the intravenous injection of acid alone causes hyperglycemia, led to the suspicion that adrenalin causes hyperglycemia by lowering the alkaline reserve of the blood. Therefore to investigate this hypothesis parallel estimations of blood sugar and blood CO₂ combining capacity have been made after administration of adrenalin in cases of diabetes and in normal individuals.

To complete the study, observations on alveolar CO₂ tension, blood pressure, pulse rate, and glycosuria are added.

Three cases of diabetes were chosen because of the ease in which rapid and extreme changes in blood sugar can be produced. Later two normal men were also studied in the same way, showing that the changes observed were not peculiar to diabetics.

The procedure was as follows: All the cases were studied fasting, the periods of fasting before the administration of adrenalin ranging from 11 to 41 hours. From 15 to 30 minutes before the administration of adrenalin and at varying intervals thereafter, blood was obtained for estimation of the plasma CO₂ combining
capacity and for sugar analysis. Samples of alveolar air were taken for estimation of the CO₂ tension. Blood pressure and pulse rate were also determined.

Adrenalin 1:1,000 (Parke, Davis and Company) was given subcutaneously in doses of 10 to 21 ml. Patients were carefully watched for appearance of symptoms, and the fast was continued to the end of the period of observation.

The blood sugar was determined by the method of Lewis and Benedict and the blood CO₂ by the Van Slyke method, the results being expressed in terms of alveolar air. Alveolar CO₂ tension was determined by the Fridericia method. The sugar in the urine was determined quantitatively and qualitatively by the Benedict methods. Charts and protocols follow at the end of the paper.

From a study of the charts it will be noted that in all the experiments the subcutaneous administration of adrenalin in doses ranging from 10 to 21 ml of the 1:1,000 solution produced a diminution in the blood CO₂ combining capacity synchronous with a rise in the blood sugar concentration. These changes occurred in all cases in varying degrees within the first half hour and reached their maximum intensity within 3 hours. They were followed within 6 to 8 hours by a drop in the blood sugar to its original level or to a level lower than that previously observed. The blood CO₂ combining capacity returned to its original level or above except in Cases 3 and 4, where within the experimental period the former level was not quite attained. We have not been able to explain this observation. In Case 5 the blood CO₂ returned to approximately its original level within the 1st hour but 4 hours later it was even higher than it had been in the first observation after adrenalin. In this case it will be observed that a relatively small dose of adrenalin was given, the reaction in every respect was comparatively slight, and as in Case 1, there was no sugar in the urine.

Alveolar CO₂—The incompleteness of the observations as regards the alveolar CO₂ is due to the difficulty encountered in getting good samples of air in Cases 1 and 2, while in Case 3 the same difficulty obtained half an hour after adrenalin was given.
DISCUSSION.

It might be argued that the hyperpnea produced by adrenalin was not due to a change in the reaction of the blood and that the low values obtained for the plasma carbonates were due merely to a diminution of the CO₂ tension of the blood caused by over ventilation. This would reduce the whole effect to an expression of the Zuntz reaction, a shifting of the carbonates from the plasma to the cells in response to a lowering of the carbon dioxide concentration of the blood. If this were the case the alveolar air determination should reveal the effects of the "Auspumpung." The alveolar values, however, are higher than those obtained from the plasma, an indication that the respiratory mechanism has not been able to remove the increased CO₂ offered to it (3, 4). On the other hand, if we were dealing with a simple carbon dioxide acidosis the plasma carbonates should rise instead of fall. The dyspnea and the fall in plasma carbonates must, therefore, represent a real diminution of the fixed alkali of the blood.

The mechanism of epinephrin hyperglycemia and glycosuria, although not yet clear in all its details, can be ascribed most probably to an increase in glycogenolysis. The evidence has been thoroughly discussed in a recent paper by Mackenzie (5) and need be considered here only as it has a bearing on our special problem. The effects of epinephrin, especially as regards carbohydrate metabolism, are strikingly like those of acid though very little attention has been paid hitherto to this aspect of its behavior.

Elias (2) was the first to point out that the administration of acid produced a hyperglycemia and glycosuria and that this was due to an increased glycogenolysis. This action was independent of the adrenals and could be demonstrated even in the perfused liver washed free from blood. Alkali produced an opposite effect. He used hydrochloric acid and sodium carbonate. Macleod (6) found that the hyperglycemia and glycosuria of asphyxia were dependent on a carbon dioxide acidosis. Both the hyperglycemia and glycosuria failed to appear when the liver was excluded from the circulation, but were not prevented when the hepatic nerve plexus was cut. The parallelism between the action of acid and the action of adrenalin fails only inasmuch as the investigation on the effect of acid is not so complete as the investigation on the effect of adrenalin.
Underhill (1) was able to increase epinephrin hyperglycemia and glycosuria by the administration of hydrochloric acid, and, what is more significant, he was able to diminish hyperglycemia and glycosuria and even, in one case, to prevent it by the administration of sodium carbonate. The inhibitory effect of carbonate in preventing hyperglycemia and glycosuria was obtained only when it was injected at least half an hour before the epinephrin. This suggests that carbonate acts by establishing conditions unfavorable to the production of the regular adrenalin effect.

In view of this experimental evidence and the time relations of the CO₂ and hyperglycemia curves, it seems more than probable that at least a part of the hyperglycemia and glycosuria following the injection of adrenalin was caused by a diminution of the alkalinity of the blood.

Diminished blood alkalinity as the probable cause of hyperglycemia is particularly suggested by a study of the time relation of the curves in the three diabetic cases (1, 2, and 3). In the charts of these cases it will be noticed that the apex of the blood CO₂ curve is attained from 1 hour to 1 hour and 40 minutes before the apex of the blood sugar curve is reached. This did not occur in the two normal individuals whose blood sugar and blood CO₂ curves reached their peak simultaneously. A possible explanation of this discrepancy lies in the fact that in the diabetic the whole reaction extends over a longer period than in the normal cases. In this connection it is possible that determinations made sooner after the administration of adrenalin and at more frequent intervals in the normal cases would have shown a similar relationship.

We have recognized that the change in blood reaction and change in sugar content have occurred in all cases at the time of the first observation, that is, within 20 minutes. Whether it could be found that the changes occurred simultaneously and immediately after adrenalin was given or whether one precedes the other has not been shown.

Determinations at 2 to 5 minute intervals after adrenalin might possibly show that the blood CO₂ change preceded the blood sugar change, and if that were the case the evidence would be even more convincing that diminished alkalinity played the lead-
ing rôle in the production of hyperglycemia. It was difficult, however, to find patients willing to submit to such frequent venepuncture as this plan would necessitate and such estimations were not made.

The degree of acidemia which was produced by the injection of adrenalin was probably sufficient to bring about the increase in the blood sugar, for Elias by the injection of acids was able to induce glycosuria in dogs even when the acidemia was not sufficient to cause air hunger. In two of our cases the acidemia following adrenalin was accompanied by severe hyperpnea. That this hyperpnea was not out of proportion to the change of blood reaction was evident from the fact that it was not sufficient to lower the alveolar CO₂ tension to the level required by the concentration of carbonates in the plasma.

Ritzmann (7), who administered adrenalin intravenously, studied its parallel effect upon glycosuria and hypertension. He concluded that adrenalin affected carbohydrate metabolism only when it caused vasoconstriction. He did not make observations on the blood sugar.

Lusk (8) found that adrenalin was without influence upon the oxidation of sugar and agreed with Ritzmann that adrenalin acted upon carbohydrate metabolism by vasoconstrictor effect, the vasoconstriction causing asphyxia of the tissues. Pollak (9) showed that both hyperglycemia and glycosuria were more readily produced by subcutaneous than by intravenous administration of adrenalin. It is well known that vasoconstrictor effects are uncertain after subcutaneous administration. In two of our cases after the subcutaneous administration of adrenalin the rise in the blood sugar was accompanied by hypertension. In two others there was an increase in the blood sugar but no rise in the blood pressure. This does not rule out vasoconstriction of the liver vessels but a vasoconstriction sufficient to cause asphyxia of the tissues is at least improbable. Tissue asphyxia, however, in itself increases the acidity of the blood and tissues.

Epinephrin and acid also have other physiological properties in common. According to Trendelenburg (10) they both cause relaxation of the bronchial muscle and vasoconstriction. How far the parallelism can be carried and to what extent the action of adrenalin is dependent upon the associated acidosis it is impossible to say.
The discovery of an acid intoxication from adrenalin is strangely at variance with Crile's theory of shock, but the experimental evidence of an alkalinizing action on the part of the adrenals brought forward by Menten and Crile (11) is entirely unsatisfactory. Bedford (12) has recently shown that, contrary to Crile's statement, there is an increase in the adrenalin content of the blood flowing from the adrenals, during prolonged shock in dogs.

CONCLUSIONS.

1. The hyperglycemia produced by subcutaneous injection of adrenalin in three cases of diabetes and two normal individuals was accompanied by simultaneous diminution of the alkalinity of the blood. This taken in conjunction with other experimental evidence strongly suggests that decreased alkalinity of the blood plays a very important rôle in the production of hyperglycemia of this type.

2. Vasoconstriction as demonstrated by peripheral hypertension is not of prime importance in producing the changes noted.

BIBLIOGRAPHY.

2. Elias, H., Biochem. Z., 1913, xlvi, 120.
Case 1.—M. M. Female. Age 46 years. Diabetes mellitus of 2 to 3 years' duration.

Oct. 18, 1916, after a fast of 39 hours, adrenalin \( m \)12 injected subcutaneously at 9.30 a.m. Within a few minutes of its administration the patient complained of throbbing in head and throughout body; slight headache. Fibrillary twitching in muscles of arms and trunk; slight hyperpnea. Within 15 minutes after the administration of the drug all subjective symptoms had disappeared.

Pulse increased from 88 to 122, 7 minutes after adrenalin, and then dropped to 90.

_Urine._—Before adrenalin: sugar 0. After adrenalin: sugar 0.
Case 2.—S. K. Male. Age 52 years. Diabetes mellitus of 10 years' duration, and pulmonary tuberculosis of at least 2 years' duration.

Oct. 25, 1916, after a fast of 41 hours, adrenalin \( \text{mg} 20 \) given subcutaneously at 11.30 a.m. There were no subjective or objective symptoms observed. No increase in pulse rate.

Urine.—Before adrenalin: sugar 0. After adrenalin: taken hourly for 4 hours, contained 2.35 gm. of sugar. After this became sugar-free.
Case 3.—S. D. Male. Age 44 years. Diabetes mellitus of 5 years' duration.

Nov. 2, 1916, after a fast of 23 hours, adrenalin \( \text{mg} \) injected subcutaneously at 9 a.m. Almost immediately (within 5 minutes) the patient complained of throbbing throughout body, and felt as though "blood was all in legs and stomach." Hyperpnea quite marked. Complete subsidence of subjective symptoms within 10 minutes.

Pulse increased from 78 to 110, 5 minutes after adrenalin was given, and then dropped to 80 15 minutes after the adrenalin had been given.

Urine.—Before adrenalin: sugar 0. After adrenalin: 1st hour, sugar 0; 2nd hour, sugar faint trace; for remainder of the day, sugar 0.

Nov. 8, 1916, after a fast of 14 hours, adrenalin \( \text{m} \) 30 injected subcutaneously at 9.40 a.m. Within 3 minutes the patient became very pale and hyperpneic, with palpitation sensations and alternate numbness and tingling in hands and feet. Face showed anxiety and distress although he insisted that he enjoyed the sensations. 15 minutes later all symptoms had disappeared.

Pulse increased from 80 to 115, 5 minutes after adrenalin was given, then dropped to 90.

Urine.—Before adrenalin: sugar 0. After adrenalin: 1st hour, sugar trace; for subsequent 12 hours, sugar 0.
Nov. 16, 1916, after fasting for 11 hours, adrenalin $1:10$ given subcutaneously at 9.20 a.m. Within 5 minutes mild sensations of constriction of the head, which passed almost immediately. No hyperpnea.
Pulse rate not increased.
Urine.—Contained no sugar at any time.
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