

Effect of Epinephrin: In spite of a cardiac acceleration, produced by the injection of 1-3 c.c. of a 1:50,000 epinephrin solution, a definite decrease in the size of the visible pre-arterioles and arterioles is noted. At times this amounts to a complete cessation of flow in certain vessels. This supplies visible corroborative evidence that epinephrin effects the smaller pulmonary vessels.

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The respiratory exchange and blood sugar curves of normal and diabetic subjects after epinephrin and insulin.

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This communication is based on a series of experiments conducted on 5 normal men and 8 diabetics. The method of determining the respiratory exchange was carried out by the open-circuit Tissot spirometer, with gas analyses by a modified Henderson-Haldane apparatus and calculations of the indirect calorimetry by the method of Zuntz and Schumburg, as recently described by McCann and Hannon.¹ At varying intervals during the experiments samples of blood were taken and blood-sugar determinations were made according to the method of Folin and Wu.² Coincident pulse and blood pressure charts were also kept in most instances.

The 5 normal men showed a similar reaction to 0.5 c.c. adrenalin given subcutaneously. There was a prompt rise of the R. Q., which was most marked about 10 minutes after the adrenalin. The quotient rose to a different extent, varying with the individual. A distinct increase of heat-production occurred with its maximum degree about 30 minutes after injection, remaining above the basal figure for over an hour. There appeared an immediate and marked rise in carbohydrate metabolism

¹ McCann and Hannon, Johns Hopkins Hospital Bull., March, 1923, xxiv, 73.

² Folin and Wu, *Jour. Biol. Chem.*, 1920, xli, 367.

with its maximum about 10 minutes after the adrenalin, as calculated from the non-protein R. Q. Coincident alveolar air analyses in one case indicated that overventilation may play a rôle in the production of the higher respiratory quotients. An elevation of blood-sugar followed the injection of adrenalin reaching a maximum in 40-50 minutes after administration. It was the most constant of any of the observed effects of the drug. The sugar remained above normal limits for over $1\frac{1}{2}$ hours. The pulse rate and blood pressure responded differently in different individuals.

The reaction to adrenalin of the diabetic patients differed in some respects from that in the control cases. Its appearance was the more delayed, the sicker the patient. The R. Q. did not rise nearly as high as in the controls. There was only one diabetic patient whose R. Q. went up as many points as the minimum control. After adrenalin the eight diabetic subjects fell into two groups as regards the total heat production:—four showing an increase from 6 to 18 per cent., the rest ranging from 29 to 43 per cent. above normal. The equivalent figures for the five normal cases lay between 17 and 33 per cent. above the basal heat production. The blood-sugar did not rise as high nor as quickly as in the controls, with one exception. The change was very slow in some cases. The blood-sugar fell in one case, which was repeated with identical result.

The insulin reaction in normal subjects was observed in five experiments in all, only two, however, having complete data. Three and one-half units were usually given intravenously. That dosage brought out a moderate reaction. Two and one-half units caused a very slight reaction and five units required the subsequent administration of sugar to relieve the symptoms of hypoglycemia. The general course was similar in all experiments of this group. There was a marked rise of R. Q., coming to a maximum about 30 minutes after the injection of insulin. An increase of heat production occurred, reaching its highest point later than the maximum R. Q., but returning to about normal by two hours after the injection. There was a rapid fall of blood-sugar which was at its lowest level from 20 to 30 minutes after insulin. By 40 minutes after a dose of $3\frac{1}{2}$ units the blood-sugar was already beginning to rise, and by $2\frac{1}{2}$ hours it had returned to about the normal figure. The diastolic blood pressure usually fell. The systolic pressure rose 10 to 16 mm.

Hg. In one case in which sugar had to be later administered, the b.p. rose from 106/65 to 140/56. There was usually an increase of pulse rate (8 to 12 per min.), reaching its maximum 35 to 40 minutes after injection. This increase was never as marked as when adrenalin was given to the same subject. Respiration was often slightly faster after insulin. The most marked subjective symptoms were twice noted to occur on the initial dose and in a similar repeated experiment the subjective sensations were minimal or absent, although the blood-sugar fell practically as low as on the initial injection. The subjective symptoms were of a different nature from those following the administration of adrenalin:—*i. e.*, after insulin one noted weakness, chills or sweating, dimming of sense perceptions, mental haziness and wandering attention,—presumably due to the hypoglycemia.

In the experiments with diabetics the usual dose of insulin was ten units intravenously. The reaction was similar to that of the controls but the effects were slower to appear and less in extent, considering the dosage. The R. Q. invariably rose sooner or later after insulin. The maximum rise occurred later than in the case of any control at hand and it did not reach as high a figure as was obtained with normal subjects. In a number of cases the R. Q. dropped slightly during the first half hour and then went up. This usually occurred on the initial dose of insulin but after a course of insulin therapy it later disappeared. Two of those subjects reacted but little to either adrenalin or insulin while two others showed marked response to adrenalin and relatively little to insulin. In the case of one normal subject the R. Q. taken ten minutes after insulin on one occasion and twenty minutes after on another showed a similar early drop of quotient. That subject was very sensitive to adrenalin. The extent of heat production varied. As a rule it did not increase markedly and it fell to or below the basal determination within two hours after insulin. The blood-sugar always fell. Its lowest level was reached considerably later than in the case of normal men and persisted at a low level considerably longer. In one patient the lowest level of blood-sugar moved nearer in point of time to the injection of insulin after a period of clinical improvement and the sugar curve also started to rise again sooner than it did on admission.

Intravenous insulin followed from 22 to 53 minutes later by

adrenalin subcutaneously showed a distinctly antagonistic relationship in the control cases. In one case in which adrenalin alone gave a marked rise of R. Q., practically the same reaction to adrenalin resulted when it was preceded by insulin. In another case in which there was relatively little response to adrenalin but more to insulin, the quotients followed the general direction obtained when insulin alone was administered and there was a fall of R. Q. on receiving the adrenalin after insulin. The calorigenetic action of adrenalin following insulin was always less than that of the former when given alone. The curves of heat production after the combined insulin and adrenalin injections lay between the low one produced by insulin alone and the higher one by adrenalin alone, and was closer to the one toward which the subject reacted most when receiving the drugs separately. Adrenalin brought out distinct elevations of blood-sugar but the rise was never as high when given after insulin as when given by itself. The pulse rate and blood pressure curves gave the same general picture with the combination as with adrenaline alone but the extent of circulatory changes was also considerably less.

The effect of adrenalin following insulin in diabetics appeared to depend upon the individual sensitiveness to the drugs and also upon the condition of the patient,—*e. g.*, severity of the sickness, presumable glycogen stores, etc. The R. Q.'s were in agreement with blood-sugar changes. With two patients previously injected with insulin the quotient rose promptly after adrenalin; in two cases it fell. The heat production in this group paralleled the curve of R. Q. In two cases adrenalin after insulin made the blood-sugar rise but in two cases the blood-sugar kept on falling. The two cases in which adrenalin failed to raise the blood-sugar showed relatively little coincident circulatory response to that drug and those patients had also previously proved to be relatively insensitive to adrenalin when given alone.