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## The production of lactic acid in diabetes following the administration of insulin.

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It is evident from recent work on normal animals that following the administration of insulin in large doses marked changes occur in the glucose, lactic acid,[1] and inorganic phosphate[2] content of the blood. Since these constituents seem to be intimately concerned with the metabolism of carbohydrate, it was desirable to extend the study of them to human beings, more especially to diabetics. Also, since the combustion of glucose as well as the formation of lactic acid has a profound influence on the respiratory quotient the metabolism was determined using the respiration calorimeter of the Russell Sage Institute of Pathology.

Four patients with uncomplicated diabetes were studied. They varied from extremely mild to moderately severe. In each case the effect of a single intravenous dose varying from 8 to 33 units of insulin (Iletin, Lilly) was observed. The blood was taken before, and between 1 and 2 hours after, the injection, and analyzed for sugar, lactic acid, and inorganic phosphates. The respiratory metabolism was determined in the calorimeter beginning about 15 to 75 minutes after the injection and continuing for 45 minutes. The patient was then removed from the calorimeter, and a blood sample was drawn for analysis. Immediately after, he was returned to the calorimeter and observed for another three hours. For comparison, a three-hour basal observation of the previous day was used.

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[1] Briggs, A. P., Koechig, I., Doisy, E. A., and Weber, C. J., *J. Biol Chem.*, 1924, lviii, 721.

[2] Wigglesworth, V. B., Woodrow, C. E., Smith, W., Winter, L. B., *J. Physiol.*, 1923, lvii, 447.

TABLE I.

| Name | Time | Glucose | Lactic acid | Inorganic $PO_4$ | R. Q. | Units of insulin | Carbohydrate metabolized | Remarks |
|---|---|---|---|---|---|---|---|---|
| | | mg. per 100 cc. | mg. per 100 cc. | mg. per 100 cc. | | | per hr. gm. | |
| E. V. | Before | 362 | 22.4 | 2.4 | 0.745 | | 0.98 | Severe diabetic. Total G tolerance 40 gm. |
| | 1 hr. 20 m. | | | | | 33 | | |
| | After | 148 | 21.0 | 2.5 | 0.799 | | 3.06 | |
| | Before | 292 | 27.3 | 2.4 | 0.738 | | 0.69 | |
| | 1 hr. 30 m. | | | | | 15 | | |
| | After | 210 | 23.1 | 1.88 | 0.809 | | 3.67 | |
| | Before | 182 | 24.5 | 3.4 | | | | No respiration studies. |
| | 1 hr. | | | | | 20 | | |
| | After | 64.5 | 49.0 | 2.0 | | | | |
| J. D. | Before | 108 | 14.0 | 3.5 | 0.836 | | 5.61 | Mild diabetic. Total G tolerance 208 gm. Profuse perspiration. Tem. dropped .7 deg. in 1st 45 m., pulse rose 60-96. Fell asleep. |
| | 2 hr. 20 m. | | | | | 15 | | |
| | After | 70 | 24.5 | 3.0 | 0.954 | | 9.70 | |
| L. M. | Before | 154 | 15.7 | 3.0 | 0.804 | | 4.14 | Mild diabetic. Total G tolerance over 200 gm. |
| | 1 hr. 15 m. | | | | | 10 | | |
| | After | 94 | 45.7 | 1.7 | 0.920 | | 10.14 | |
| J. M. | Before | 125 | 16.8 | 2.7 | 0.792 | | 5.28 | |
| | 1 hr. 30 m. | | | | | 8 | | |
| | After | 111 | 21.0 | 2.8 | 0.825 | | 7.19 | |

The results in the table clearly demonstrate that the invariable fall of blood glucose following insulin administration is not always accompanied by a rise in lactic acid.

Three separate observations were made on patient E. V. In only one instance was the lactic acid concentration increased after insulin. Although the absolute drop in blood sugar was greater in the other two, 214 mg., and 82 mg. per 100 cc. respectively, no rise in the lactic acid was found.

With the patients J. D. and L. M. the blood glucose fell 38 mg. and 60 mg. per 100 cc., yet the rise in the lactic acid was considerable, while in patient J. M. the fall of the blood glucose noted was small and no change in the lactic acid was observed.

These data justify the conclusion that the production of lactic acid following the administration of insulin depends less upon the absolute fall in the blood sugar than upon the level finally reached.

It is also apparent that insulin may cause a rise of the respiratory quotient without producing any increase in the lactic acid concentration. This rise can, therefore, be ascribed to the stimulating effect on the oxidation of carbohydrate.

If the production of lactic acid were the direct result of the fall in blood sugar it would *not* be expected with a rise. Data were obtained on this point by means of adrenalin.

Four non-diabetic subjects free from any cardiac or hepatic involvement were studied. After lunch 15 to 25 minims of adrenalin were administered subcutaneously. Blood samples were drawn before and exactly 1 hour after the adrenalin injection and analyzed for glucose, inorganic phosphates and lactic acid. The respiratory metabolism was not studied.

From Table II it will be seen that whenever the adrenalin produces a rise of blood sugar there occurred a concomitant lowering of the inorganic phosphates, as well as a rise in the lactic acid.

### *Discussion.*

These results do not favor the theory that insulin acts by converting glucose into lactic acid. Although it causes a rise in the lactic acid the effect is far from constant. Moreover, no quantitative relation is apparent between the blood sugar and the production of lactic acid, such as the theory of Briggs and his associates would demand. With insulin a sharp *fall* in blood *sugar* can be produced *without* an increase in lactic acid. With

TABLE II.

| Case | Time | Glucose | Lactic acid | Inorganic P | Remarks |
|---|---|---|---|---|---|
| | | mg. per 100 cc. | mg. per 100 cc. | mg. per 100 cc. | |
| 1 | Before | 127 | 14. | 2.6 | Adrenalin MXV |
| | 1 hr. After | 235 | 31.5 | 2.0 | |
| | Before | 100 | 16.1 | 2.6 | |
| | 1 hr. After | 170 | 26.6 | 1.76 | Adrenalin MXV |
| 2 | Before | 125 | 19.6 | 2.7 | |
| | 1 hr. After | 250 | 37.1 | 1.9 | Adrenalin MXX same patient |
| 3 | Before | 104 | 15.4 | 3.1 | |
| | 1 hr. After | 230 | 21.0 | 1.5 | Adrenalin MXV |
| 4 | Before | 112 | 19.0 | 2.4 | |
| | 10 m. After | 117 | 26.6 | 2.4 | Adrenalin MXV |

adrenalin a marked *rise* can occur, and instead of a *fall* in lactic acid we observed an *actual rise* amounting often to 100 per cent. The results suggest that there is some factor common to the action both of insulin and adrenalin, which increases the lactic acid in spite of the divergent effects on the blood sugar. Such a common denominator might be a local asphyxia which is a well known cause of the production of lactic acid.

A comparison of the effects of insulin and the adrenalin leads to the following conclusions:

(1) Both extracts lower the inorganic phosphate of the blood.

(2) Extreme drops in blood sugar may occur with no change in the lactic acid concentration. With our patients increases in lactic acid were observed *only* when an insulin hypoglycemia was produced and this may turn out to be the general rule.

(3) Lactic acid increases with an adrenalin hyperglycemia.

(4) Insulin causes an increase in the respiratory quotient over and above that which can be accounted for by the production of lactic acid. This is evidence of the stimulating action exerted by the extract on the oxidation of carbohydrate.