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## Dehydration and Basal Insulin Requirement.

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It is a matter of common clinical experience in treating diabetic patients, that the amount of insulin required to produce a given effect may be quite different under different circumstances. It is often found that the insulin requirement for a patient on admittance to a hospital becomes much less as his condition becomes well controlled. This lack of effectiveness of insulin in diabetics not in good control, becomes very marked in coma when very large doses of insulin must be given to produce the effect that can be brought about by a small dose in the same patient when under good control.

In searching for a cause of this change in the effectiveness of insulin one thinks of the various accompaniments of uncontrolled diabetes such as glycosuria and ketosis. The most apparent result of glycosuria which tends to change the "internal environment" of the organism is dehydration. This factor was, therefore, the first variable chosen by us for investigation of its effect on insulin action and the particular insulin function we selected was the basal insulin requirement.* This latter may be defined as the rate at which insulin must be given to the fasting diabetic animal in order to maintain his blood sugar at a normal constant level. This requirement has been shown by Greeley[1] to be remarkably constant for an individual diabetic dog under standard conditions so that it would be easy to determine whether any desired factor could alter this requirement.

Dehydration can be readily produced in the diabetic by giving an excess of sugar or meat along with restricted water. We tried to do this without causing any other complication to supervene. This can be done by giving a dog a large amount of sugar or meat the day before the test and at the same time giving the usual insulin. The extent of dehydration was determined by changes in the water content of the plasma. For this, oxalated blood was collected and centrifuged in a well corked tube for 2 minutes. A weighed sample of the plasma was then dried at 105° to constant weight. For control figure we ran a series of plasma water content determinations on our diabetic dogs in good condition. We made 21 such determinations

* The insulin used in this work was contributed by the Eli Lilly Company.

1 Greeley, P. O., *Am. J. Physiol.*, 1937, **120**, 345.

which gave an average water content of 93.0%—range 92.40 to 93.44%.

The determinations of the basal insulin requirement were carried out by the method described by Greeley.[1] This consists of first bringing the blood sugar to normal by a dose of 2 or 3 units of insulin and then determining the rate at which insulin must be injected to maintain the blood sugar at this normal level.

We determined first whether glycosuria without dehydration would affect the basal insulin requirement. For this we fed on the day before the run, a large excess of sugar with water *ad lib.* and the usual insulin. This was done on 3 dogs as follows:

Dog $B_2$ was given 300 g extra sucrose the day before the test with water *ad lib.* and usual insulin. Her urine volume for that day was 3304 cc with 87 g glucose, in contrast to a normal average of 600 cc and only a trace of sugar. The normal basal insulin rate had been previously established to be between 0.14 to 0.17 units per hour. The rate found during this run was 0.16 units per hour. That the dog was not dehydrated was apparent from the plasma water determination of 93.8 taken during the run.

Dog $T_1$, female, received 300 g of extra sucrose the preceding day with water *ad lib.* and insulin. This animal excreted 29.8 g of glucose and 2280 cc of urine in contrast to a normal of 500 cc and a trace of sugar. The normal basal insulin rate for this dog had been established at 0.08 to 0.11 units per hour. The rate found during this experiment was 0.09 units per hour with the plasma water 93.3%.

Dog $C_1$ received 475 g of glucose the preceding day with water *ad lib.* and usual insulin. This resulted in a urine volume of 1425 cc and 10.5 g of glucose. The rate found was 0.20 units per hour.

No basal rate was run on this last animal but the rate found can be compared directly with the rate required when the animal was dehydrated one week later. This was done by feeding extra glucose for 2 days prior to the experiment with the usual insulin. The animal lost 2 kg weight in these 2 days and the plasma water fell to 89.5%. The basal insulin rate was found to be 0.54 units per hour which is an increase of 170% over the rate found without dehydration.

Severe dehydrations were also produced in 2 other dogs. Dog $B_1$ was given 500 g extra sugar with 1000 cc water and the usual insulin the day before the test. It excreted 1650 cc urine with 41 g glucose. The basal insulin requirement was found to be .55 units per hour, which contrasted with the rate on this animal under standard conditions of .35 units per hour.

Dog $H_1$ was given 200 g extra sugar, restricted water, and 10 units insulin instead of the usual 18 units the day before the test. It lost 1 kg in weight, urine sugar and volume not recorded. The basal insulin requirement was found to be .60 units per hour which contrasts with the normal for this dog of .28 units per hour.

The foregoing are the most severe conditions of dehydration which we produced. Besides these we brought about moderate degrees of dehydration in our experimental dogs in order to see whether the less serious conditions, such as one might meet in ambulatory patients, would affect the basal insulin requirement. The dehydration was produced as in those cases already cited but the amount of the extra glucose or protein given was less; the amount of insulin given was not changed from the routine dosage administered on ordinary days to keep the animal in a "steady state". In other words, the dogs received the same dosage of insulin throughout the "dehydrating period" as they received every day, the only change being an increase in the "superfluous glucose". The results are given chronologically for each dog in Table I.

In these dogs there is seen to be a definite tendency of the basal insulin rate to increase with a reduction of the water content of the plasma.

TABLE I.

| Date | Rate | Plasma Water | |
|---|---|---|---|
| Dog $B_1$, Female | | | |
| 12-4-36 | .41 | 91.90 | Given extra sugar day before |
| 12-23-36 | .22 | 92.55 | ,, ,, ,, ,, ,, |
| 1-14-37 | .45 | 91.18 | ,, ,, ,, ,, ,, |
| 1-20-37 | .21 | 92.94 | Normal |
| 1-27-37 | .15 | 92.23 | ,, |
| 2-4-37 | .22 | 92.73 | ,, |
| 2-11-37 | .16 | 93.80 | ,, |
| 2-16-37 | .14 | 92.93 | ,, |
| 2-18-37 | .20 | 90.66 | Given extra sugar day before |
| 2-23-37 | .12 | 92.64 | Normal |
| 2-25-37 | .24 | 91.70 | Given extra meat day before |
| 3-5-37 | .42 | 91.49 | ,, ,, sugar ,, ,, |
| 3-9-37 | .17 | 92.40 | Normal |
| 3-18-37 | .15 | 92.33 | ,, |
| Dog $T_1$, Female | | | |
| 1-27-37 | .11 | 93.20 | Normal |
| 2-4-37 | .12 | 92.66 | ,, |
| 2-11-37 | .08 | 93.34 | Given extra sucrose day before (no dehydration) |
| 2-16-37 | .08 | 93.24 | Normal |
| 2-17-37 | .12 | 92.10 | Slight dehydration |
| 2-23-37 | .12 | 93.05 | Normal |
| 2-25-37 | .20 | 92.16 | Given extra meat day before |
| 3-5-37 | .16 | 92.64 | Extra sugar—no dehydration |
| 3-11-37 | .30 | 91.99 | Given extra meat and sugar day before |
| 3-18-37 | .09 | 92.77 | Normal |

Our results do not necessarily conflict with those of authors who report that dehydrated animals show a prolonged action of insulin.[2] We measured only the effect of dehydration on the basal insulin requirement, the insulin given intravenously. All these authors cited gave the insulin subcutaneously; it is not improbable that dehydration slows up the absorption rate of insulin from the tissues. Others have shown that dehydration slows up the return of the blood sugar to normal after administration of glucose by stomach or intravenously.[3] Drabkin and Shilkret[4] report that spastic convulsions were not observed in desiccated animals after insulin although they appeared in those given fluids.

*Summary.* Depancreatized dogs maintained on a standard regime were dehydrated by producing glycosuria along with restricted water intake. It was found that the basal insulin requirement of the animals in this state was increased above that which they had normally without dehydration, but with other conditions the same.

If the dogs be given enough water so that no dehydration results from the glycosuria no increase in the basal insulin requirement results.

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## Choline Esterase and Esters of Thiamine.

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The possible relationship between the physiological rôles of thiamine and choline esterase led the authors, in a previous study,[1] to investigate the inhibition of the enzyme by thiamine. Since thiamine occurs in the animal body largely as the pyrophosphate ester, cocarboxylase, a study of the effect of this compound upon choline esterase was undertaken, and it was found that, in contrast to the pronounced inhibitory action of thiamine, the pyrophosphate ester produced very little inhibition.

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[2] Andrews, E., *Arch. Int. Med.*, 1926, **38**, 136; 1927, **40**, 637.

[3] Tisdale, F. F., Drake, T. H., and Brown, A., *Am. J. Dis. Child.*, 1925, **30**, 837; *ibid.*, 1926, **32**, 854.

[4] Drabkin and Shilkret, *Am. J. Physiol.*, 1927, **83**, 141.

[1] Glick, D., and Antopol, W., *J. Pharm. and Exp. Therap.*, 1939, **65**, 389.