**Chemistry.** — *The Sugar Excretion of Rats with Severe Diabetes, induced by Alloxan under the Combined Influence of Insulin and Growth Hormone.* By G. VAN WIERINGEN and S. E. DE JONGH. (Pharmacological laboratory, University Leyden.) (Communicated by Prof. P. J. GAILLARD.)

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*Introduction.*

The growth hormone, administered in large quantities, is now generally considered to possess diabetogenic potency. This is also the case in animal species, e.g. the rat, with a pancreas capable of great resistance, as shown in previous work in this laboratory [1]). It was shown that sugar excretion of rats with slight alloxan diabetes increased when the growth hormone was administered. Rats which had been injected with alloxan but had not become diabetic, did not develop diabetes with growth hormone, probably because the pancreas was too resistant to *both* substances. Severe alloxan diabetes did not become worse through growth hormone. Was this because sugar excretion had reached its maximum? We shall try to answer this question.

*Method.*

Four adult rats which, after one alloxan injection of 75 mg/kg, excreted 3 or more g. glucose per day, were regularly observed during four days. In two the sequence was as follows: (*a*) control period, (*b*) insulin period, (*c*) control period, (*d*) growth hormone + insulin period, (*e*) control period. In two others the periods (*b*) and (*d*) were interchanged. $2 \times 5$ IU of insulin, $2 \times 10$ rat tail units of growth hormone, (1 U in 350 $\gamma$) were administered daily. It was ascertained whether sugar excretion was diminished more by insulin alone than by insulin plus a (diabetogenic) dose of growth hormone.

*Results.*

The results are given in tables which show that the growth hormone did not have a diabetogenic action. The average fall caused by insulin is

$$\frac{(3.9 - 1.3) + (4.6 - 1.0) + (5.1 - 1.1) + (5.3 - 0.8)}{4} \text{ g.} = 3.7 \text{ g.}$$

with insulin + growth hormone the average fall was

$$\frac{(4.8 - 1.4) + (5.3 - 1.2) + (4.3 - 1.05) + (4.7 - 1.25)}{4} \text{ g.} = 3.5 \text{ g.}$$

DAILY SUGAREXCRETION IN GRAMS; ALLOXAN TREATED RATS.

| Rat I | | Rat II | | Rat III | | Rat IV | |
|---|---|---|---|---|---|---|---|
| 3.8 | Contr. | 4.3 | Contr. | 4.5 | Contr. | 5.4 | Contr. |
| 4.4 | | 5.4 | | 5.2 | | 5.9 | |
| 3.4 | | 4.3 | | 4.7 | | 5.9 | |
| 3.5 | | 4.4 | | 4.3 | | 4.7 | |
| 4.2 | | 4.6 | | 5.4 | | 4.6 | |
| Av.: 3.9 | | Av.: 4.6 | | Av.: 4.8 | | Av.: 5.3 | |
| 1.6 | Insul. | 2.1 | Insul. | 2.8 | Insul. + Growthh. | 2.0 | Insul. + Growthh. |
| 1.2 | | 1.2 | | 1.6 | | 1.4 | |
| 2.0 | | 0.5 | | 0.9 | | 1.0 | |
| 0.4 | | 0.2 | | 02 | | 0.5 | |
| Av.: 1.3 | | Av.: 1.0 | | Av.: 1.4 | | Av.: 1.2 | |
| 2.7 | Contr. | 3.5 | Contr. | 4.1 | Contr. | 3.9 | Contr. |
| 3.6 | | 4.6 | | 4.7 | | 5.0 | |
| 5.2 | | 5.2 | | 5.7 | | 6.5 | |
| 5.7 | | 5.6 | | 5.8 | | 5.7 | |
| Av.: 4.3 | | Av.: 4.7 | | Av.: 5.1 | | Av.: 5.3 | |
| 1.3 | Insul. + Growthh. | 2.5 | Insul. + Growthh. | 1.8 | Insul. | 1.4 | Insul. |
| 1.4 | | 1.0 | | 2.0 | | 1.2 | |
| 0.6 | | 0.4 | | 0.5 | | 0.3 | |
| 0.9 | | 1.1 | | 0.0 | | 0.4 | |
| Av.: 1.05 | | Av.: 1.25 | | Av.: 1.1 | | Av.: 0.8 | |
| 1.3 | Contr. | 3.8 | Contr. | 2.6 | Contr. | 4.2 | Contr. |
| 3.3 | | 4.5 | | 3.9 | | 5.5 | |
| 4.1 | | 5.7 | | 6.0 | | 6.7 | |
| 3.8 | | 5.0 | | 5.9 | | 4.6 | |
| Av.: 3.1 | | Av.: 4.75 | | Av.: 4.6 | | Av.: 5.25 | |

The increase on suspension of insulin was

$$\frac{(4.3 - 1.3) + (4.7 - 1.0) + (4.6 - 1.1) + (5.25 - 0.8)}{4} \text{ g.} = 3.5 \text{ g.}$$

Suspension of insulin + growth hormone:

$$\frac{(5.1 - 1.4) + (5.3 - 1.2) + (3.1 - 1.05) + (4.75 - 1.25)}{4} \text{ g.} = 3.3 \text{ g.}$$

The total average sugar excretion per day was:

for all normal periods: 4.6 g.
for all insulin periods: 1.05 g.
for all insulin + growth hormone periods: 1.2 g.

Growth hormone did have no more influence on animals with severe diabetes, whose sugar excretion was greatly suppressed by insulin administration, than on rats with severe alloxan diabetes not treated with insulin. The negative results previously obtained were not due solely to a possible maximum sugar excretion.

*Discussion.*

The simplest interpretation of our data would be, without doubt, a denial of the supposed diabetogenic effect of growth hormone in the rat. Our previous investigations do not favour this view, nor does the earlier work of MARX and others [2], who worked on partially depancreatized rats.

Taking this into consideration we must assume that the growth hormone can do no more than give the results previously obtained with alloxan. On good grounds YOUNG [3] presumed that the growth hormone, impedes carbohydrate utilization through a decrease of sensitivity to insulin. It follows that alloxan should also do this and to such a degree that there is nothing left for the growth hormone. Few objections can be raised against this assumption. It is generally known (it appears also from our data) that very large amounts of insulin are required to make an alloxan-diabetic animal sugar-free. An alloxan animal requires much more insulin than an animal without a pancreas [4]; this is ascribed to some factor in the pancreas. The idea that alloxan does more than merely restricting insulin production [5] is gaining ground. We conclude that our negative results are due to a sugar utilization which has already been impeded to the highest degree by alloxan.

*Summary.*

Even when the sugar excretion in rats with severe alloxan diabetes is kept low by insulin, the growth hormone is not capable of increasing this (in contradistinction to the sugar excretion in rats with slight diabetes).

REFERENCES.

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