THE RELATIONS OF THE THYROID GLANDS TO GLYCOSURIA.*

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Eppinger, Falta and Rudinger[1] have found that adrenalin injections no longer produce a glycosuria after extirpation of the thyroid glands. According to their investigations the diet has but little influence upon the results, for the same data are obtained regardless of whether the dogs are in a fasting condition or are kept on a generous diet, even of sugar. This relation of thyroid gland to sugar excretion they explain as follows: The pancreas produces a substance which regulates the oxidation of sugar in the body. The secretion of the thyroid glands exercises a control over the internal secretion of the pancreas, holding it in check; likewise the internal secretion of the adrenals holds in check this internal pancreatic secretion. Consequently a glycemia results when adrenalin is injected. This in turn produces a glycosuria. Now, if the check on the pancreas exercised by the thyroids be removed, an increased function of the pancreas follows, and the adrenalin is not able to depress it sufficiently to cause glycosuria. In favor of this view is the fact that glycosuria results in normal dogs from intravenous injections of thyroid extract.

Zuelzer,[2] instead of removing this check on the pancreas, added pancreatic extract itself, thereby neutralizing the inhibition exerted by the injected adrenalin. As a result no glycosuria appeared.

Experiments by Pick and Pineles[3] on young goats with the thyroid glands removed show that no glycosuria results upon the administration of adrenalin. On the other hand, in thyroidless

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[1] H. Eppinger, W. Falta and C. Rudinger, *Zeit. f. klin. Med.*, 1908, lxi, 1.

[2] Zuelzer, *Verhand. des Kong. f. inn. Med.*, 23 Kong., 1906.

[3] E. P. Pick and F. Pineles, *Biochem. Zeit.*, 1908, xii, 473.

rabbits Eppinger, Falta and Rudinger have demonstrated that adrenalin produces a strong glycosuria. This is likewise the case in guinea-pigs, thyroidectomy having no influence on the power of adrenalin to produce glycosuria.

At the suggestion of Dr. MacCallum we took up the problem of the relation of the thyroid glands to the pancreas. For this investigation dogs were used, and both adrenalin and ether were employed in producing a glycosuria. Reference has already been made to the views of Eppinger, Falta and Rudinger concerning the relation of adrenalin injections to glycemia and glycosuria. Seelig[4] has shown that dogs fed on an exclusive meat diet constantly show a more or less high degree of glycosuria from ether inhalation. This glycosuria is accompanied by a hyperglycemia, and after the anesthesia the glycogen content of the liver is found to be much reduced. Sugar appears in the urine during the course of the experiment and appears to increase with the duration of the ether anesthesia. The sugar excretion, however, disappears very rapidly after the removal of the ether.

We proceeded as follows: Female dogs were operated upon to facilitate catheterization. After complete recovery from the operation the dogs were placed upon a diet consisting of a definite amount of lean meat per diem. Kept on this exclusive diet for a definite number of days the animals were at length subjected to ether anesthesia. On the day preceding the ether treatment the dogs each received 300 c.c. of water through the stomach tube in the morning and 300 c.c. more in the afternoon. Care was taken that the dogs received no other water.

One hour and a half preceding the administration of the ether the dogs again received 300 c.c. of water. No food was given on the day of narcosis. Immediately prior to the ether treatment the bladder of each dog was thoroughly emptied with a catheter and then the animals were anesthetized and kept as nearly as possible in the same stage of narcosis for exactly three hours. The urine was collected at this time and again three hours later, the bladders being completely emptied upon this occasion. This gave a six-hour excretion of urine to work with.

[4] A. Seelig, *Arch. f. exper. Path. u. Phar.*, 1905, lii, 490.

Several days later both thyroid glands were removed, care being taken to preserve the parathyroids. The dogs, while recovering from the effects of the operations, received a mixed diet. Then the exclusive meat feeding was started again. Ether anesthesia followed the requisite number of days later. After a mixed diet again for some days powdered thyroid glands were fed daily together with the usual allotment of meat. The dogs were then ready for further anesthesia.

These details are mentioned to emphasize the fact that unless the animals are kept upon an absolutely definite diet and the same conditions minutely observed throughout the experiments the results are meaningless. This is clearly shown by reference to the last column of Table I. Dog 5,009 here shows that by excessive meat feeding the quantity of excreted sugar is greatly increased. We have had to discard the data from several dogs for this very reason.

The adrenalin experiments were similarly conducted. Adrenalin chloride solution, 1 to 1,000, was injected intraperitoneally in approximately the same part of the abdomen each time. Here the twenty-four-hour urine was collected; and, from data covering several weeks of the earlier part of our work, it became evident that the animals would have to be catheterized every few hours throughout the period of the collection. Working with comparatively small quantities of dextrose, such as appeared in these experiments, the results could be easily vitiated by fecal matter and vomitus; for adrenalin, injected in sufficient quantity to produce a satisfactory glycosuria, is usually followed by some of the characteristic symptoms.

Like Eppinger, Falta and Rudinger, we found that the dogs displayed a very great variation in the comparative amounts of dextrose excreted. This also proved to be the case with ether. Furthermore, from a number of dogs not recorded in the tables, we found that dogs in apparently the same physical conditions evinced very remarkable differences in their susceptibilities to adrenalin poisoning.

The sugar determinations were made by Benedict's modification of Fehling's method.

Tabes I and II give the results from four dogs.

TABLE I.

Table Showing Results of Ether Experiments.

	Dog 5,809. Normal.	Dog 5,809. After thyroidectomy.	Dog 5,809. Thyroidless; fed 14.254 gm. dried thyroid.	Dog 5,009. Normal.	Dog 5,009. Normal.	Dog 5,009. After thyroidectomy.	Dog 5,009. Thyroidless; fed 6 gm. thyroid.	Dog 5,009. Thyroidless; fed 14.254 gm. dried thyroid.	Dog 5,009. Thyroidless.
Diet.	One pound ground beef per day for 4 days.	Ditto	Ditto.	One pound ground beef per day for 5 days.	Ditto	Ditto.	Ditto	Ditto.	Four pounds meat per day for 5 days.
Grams of dextrose in urine before etherization.	0	0	0	0	0	0	0	0	0
Ether.	3 hours.	3 hrs.	3 hrs.	3 hours.	3 hrs.	3 hrs.	3 hrs.	3 hrs.	3 hours.
Cubic centimeters of of urine per 6 hours.	84	40	47.5	68	270	100.5	152	93	132
Grams of dextrose in urine per 6 hours after etherization.	1.752	0.174	1.014	0.264	0.242	less than 0.073	0.168	0.534	0.9

Table I, Dog 5,809.—Before thyroidectomy an ether anesthesia resulted in an excretion of 1.752 gm. of dextrose in the urine. After thyroidectomy the sugar content of the urine from ether inhalaation dropped to 0.174 gm., *i. e.,* it fell to 10 per cent. of the original amount. When this dog was fed with powdered thyroid gland, however, the narcosis resulted in an increased excretion of sugar—1.014 gm. This represents 57 per cent. of the original quantity of sugar.

Table I, Dog 5,009.—Ether narcosis before thyroidectomy caused an excretion of 0.264 gm. dextrose in the urine. This was repeated two weeks later under the same conditions and practically the same amount of sugar was found in the urine—0.242 gm. The volumes of urine in these two cases, however, were very different as shown by the table. Following thyroidectomy ether narcosis resulted in a very decided fall in the dextrose content—less than 0.073 gm. This is less than 27.5 per cent. of the original amount. With moderate thyroid feeding the ether anesthesia showed an increase in the dextrose of the urine to 0.168 gm., *i. e.,* over 63 per cent. of the original quantity. When the thyroid dosage was greatly increased a remarkably larger quantity of dextrose resulted from the narcosis—0.534 gm., or 202 per cent. of the original amount. Here evidently the amount of powdered thyroid absorbed far exceeded the normal output of the intact thyroid glands.

TABLE II.

Table Showing Results of Adrenalin Experiments.

	Dog 8,308 Normal.	Dog 8,308 after thyroidectomy.	Dog 8,308 6 weeks after thyroidectomy.	Dog 1,609 Normal.	Dog 1,609 after thyroidectomy.
Weight of dog in kilos.	9.6	9.6	12	8.6	8.6
Grams of dextrose in urine before adrenalin injection.	0	0	0	0	0
Cubic centimeters of adrenalin solution 1–1000 injected.	7	7	9	6	6
Cubic centimeters of urine secreted per 24 hours.	694	250	135	190	115
Grams of dextrose in 24 hour urine after adrenalin injection.	2.63	0.71	1.458	5.9	3.47

Table II, Dog 8,308.—An injection of 7 c.c. of adrenalin chloride solution 1 to 1,000 into a dog weighing 9.6 kilos resulted in 2.63 gm. of dextrose in the twenty-four-hour urine. Following thyroidectomy a similar injection demonstrated a fall to 0.71 gm. of dextrose in the urine, or 27 per cent. of the original amount in the normal animal. When the thyroids were allowed to regenerate for six weeks an injection of the same sort resulted in a rise in the sugar content of the urine to 1.458 gm., or 55 per cent. of the original amount.

Table II, Dog 1,609.—Weight of the animal was 8.6 kilos. An injection intraperitoneally of 6 c.c. adrenalin showed 5.9 gm. of dextrose in the twenty-four-hour urine. On removal of the thyroids, and repeating this injection, the amount of excreted sugar fell to 3.47 gm. or 57 per cent. of the original amount. Unfortunately this dog was accidentally killed before further experiments could be carried out.

RÉSUMÉ.

1. After thyroidectomy the glycosuria, produced by ether or adrenalin in the normal animal, is greatly reduced.

2. Thyroidless dogs fed on powdered thyroid glands show a return of glycosuria more or less proportional to the amount ingested when treated with adrenalin or ether.

3. As the thyroids regenerate the ether or adrenalin glycosuria increases similarly.

The results of these experiments leave no doubt in our minds that the secretion of the thyroid glands is connected in some obscure way with the metabolism of sugar in the body or exerts some control over organs whose duty it is to participate in the sugar metabolism.

In conclusion we wish to express our great indebtedness to Dr. MacCallum for his advice throughout the course of this work, and also for performing the thyroidectomy operations