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Effect of Stilboestrol on Certain Phases of Carbohydrate Metabolism.*

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Carbohydrate levels in intact animals are affected not only by insulin, anterior pituitary extracts, and adrenal-cortical-hormone, but apparently also by certain sex hormones. Zunz and LaBarre¹ found an increase in blood sugar after the administration of estradiol. Gilder and Phillips² showed that rats treated with this hormone had higher levels of liver glycogen when glucose-fed than did normal animals. Engelhart and Riml³ found that the injection of corpus luteal extracts in guinea pigs increased liver glycogen. More recently, Gaunt, Remington, and Edelmann⁴ administered progesterone to intact ferrets in acute experiments and found that the carbohydrate levels were elevated. However, progesterone, testosterone, or stilboestrol were without effect. Because of the potency of stilboestrol as an estrogen, we have studied its effect on carbohydrate levels after longer periods of administration.

Rats weighing from 150 to 200 g, when treatment began, received 0.05 mg of stilboestrol† subcutaneously twice daily for periods of 5, 10, and 20 days. Determinations were made for blood sugar, liver- and muscle-glycogen, and urinary nitrogen, and the gonads, adrenals, and pituitaries were weighed and studied histologically.

The blood sugar level was found to be raised somewhat after only 5 days of treatment, and considerably more after 20 days. The liver glycogen was increased markedly even after 5 days of injections, and the muscle glycogen showed a slight drop after 20 days of treatment. The latter is of doubtful significance. The urinary nitrogen, determined for the last 24 hours of a 36-hour fast, was quite variable. Since it was not markedly altered in animals that were treated for

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¹ Zunz, E., and LaBarre, J., *Arch. Int. de Physiol. (Liege)*, 1939, **48**, 287.

² Gilder, H., and Phillips, R. A., *Proc. Am. Physiol. Soc.*, 1939, 86.

³ Engelhart, E., and Riml, O., *Klin. Wchnschr.*, 1934, **13**, 101.

⁴ Gaunt, R., Remington, J. W., and Edelmann, A., *PROC. SOC. EXP. BIOL. AND MED.*, 1939, **41**, 429.

† Stilboestrol was generously supplied by Dr. J. A. Morrell of E. R. Squibb and Sons.

TABLE I.
Chemical and Organic Changes in Rats Receiving 0.1 mg Stilboestrol Daily (averages).

Days treated	No. of animals	Wt at end of 36-hr fast g	Blood sugar, mg %	Glycogen		Urinary N last 24 hr, mg/g	Wt adrenals, (2) g	Wt ovaries, (2) g	Wt testes, (2) g	Wt pituitary, g
				Liver, mg %	Muscle, mg %					
Control	9	170	68 ± 4†	75	310	.802	.0414	.0655	2.257	.0077
	6	169	73 ± 12†	231	354	.774	.0626	.0820	2.330	.0116
10	10	149	74 ± 8†	331	311	.774	.0520	(3)*	(2)*	.0124
	8	131	84 ± 6†	409	260	1.042	.0720	(6)*	(4)*	.0144

* Numbers in parentheses are number of animals.

† Standard deviation.

5 or 10 days, it is possible that gluconeogenesis from fat produced the increased carbohydrate levels. However, gluconeogenesis from protein might account for the heightened levels of carbohydrate in animals treated with stilboestrol for 20 days since the urinary nitrogens were increased significantly.

The effect of stilboestrol on the endocrine glands is significant. The estrogen apparently stimulates the release of hypophyseal luteinizing hormone and inhibits the production of follicle-stimulating hormone, since the ovaries showed large corpora lutea and small follicles. The adrenals were increased in size, particularly in the females, and the entire male reproductive system was damaged. In these respects stilboestrol duplicates the response obtained with natural estrogens.

The question arises, of course, as to the mechanism whereby these effects on carbohydrate metabolism are produced. The stilboestrol action may be through the adrenals, the gonads, or both. Adrenal cortical hormone will raise the carbohydrate levels in intact animals⁵ in a manner similar to that described here for stilboestrol. Consequently, one might suspect that the effect obtained is through the adrenals. This is substantiated by the work of Zunz and LaBarre, who found that blood sugar levels were not raised in dogs under estradiol treatment after the adrenals were tied off. On the other hand, Gaunt, *et al.*,⁴ found that progesterone was effective in producing the elevation of carbohydrates in the adrenalectomized ferret. It seems likely that increased production of progesterone is not the primary factor in causing the changes described here since stilboestrol is effective in males as well as in females. Until further studies are completed no conclusions can be drawn concerning the exact manner in which stilboestrol effects these changes in the carbohydrate levels.

⁵ Katzin, B., and Long, C. N. H., *Proc. Am. Physiol. Soc.*, 1939, 135.