5. Kalliomaki, J. L., Saarimaa, H. A., and Toivanen, P., Ann. Rheumatic Diseases **23**, 78 (1964).

6. Graeme, M. L., Fabry, E., and Sigg, E. B., J. Pharmacol. Exptl. Therap. **153**, 373 (1966).

7. Glenn, E. M., Am. J. Vet. Res. **27**, 339 (1966).

8. Evans, J. S., Proc. Soc. Exptl. Biol. Med. **106**, 350 (1966).

9. Chu, M. Y. and Fischer, G. A., Biochem. Pharmacol **11**, 423 (1962).

10. Talley, R. W. and Vaitkevicius, V. K., Blood **21**, 352 (1963).

11. Bloch, J. B., Am. Assoc. Cancer Res. **6**, 21 (1965).

12. Newbould, B. B., Brit. J. Pharmacol. **21**, 127 (1963).

13. Pearson, C. M. and Wood, F., Arthritis Rheumat. **2**, 440 (1959).

14. Waksman, B. H., Pearson, C. M., and Sharp, J. T., J. Immunol. **85**, 403 (1965).

15. Currey, H. L. and Ziff, M., Lancet **2**, 889 (1966).

16. Flax, M. H. and Waksman, B. H., Intern. Arch. Allergy Appl. Immunol. **23**, 331 (1963).

17. Pearson, C. M., J. Chron. Diseases **16**, 863 (1963).

18. Burstein, N. A. and Waksman, B. H., Yale J. Biol. Med. **37**, 177 (1964).

19. Glenn, E. M., Bowman, B. J., and Koslowske, T. C., Biochem. Pharmacol. March Suppl. **1968**, 27.

20. Glenn, E. M., Bowman, B. J., Kooyers, W. M., Koslowske, T. C., and Myers, M. L., J. Pharmacol. Exptl. Therap. **155**, 157 (1967).

21. Glenn, E. M. and Kooyers, W. M., Life Sci. **5**, 619 (1966).

Received July 16, 1968. P.S.E.B.M., 1968, Vol. 129.

Estradiol Antagonism of Chlorpromazine Hyperglycemia* (33444)

TOM S. MIYA AND TAGHI GHAFGHAZI[1]

Department of Pharmacology and Toxicology, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Indiana 47907

Several investigators have reported the antidiabetic effect of the female sex hormone. Nelson and Overholser (1) have shown that estrone reduces hyperglycemia and glycosuria in monkeys administered pituitary extract. Estradiol propionate in rabbits (2) and in women (3) have been shown to decrease hyperglycemia, and Rodriguez (4) has shown that about 50% of alloxan-diabetic rats treated with estradiol maintain normal blood sugar levels.

In a previous publication (5) we reported the interaction of estradiol and chlorpromazine with respect to the metabolism of the latter. This report on the antagonism of chlorpromazine hyperglycemia by estradiol is submitted as a portion of our continuing studies on the interaction of hormones with drugs.

Materials and Methods. Male albino Holtzman rats weighing approximately 200 g were employed. Estradiol valerate in sesame oil 25 μg/rat, s.c., were administered on day 0 and day 5. Three days after the second injection the animals were fasted 16–20 hr with water *ad libitum* prior to chlorpromazine administration. Groups of 5 treated and control rats were administered chlorpromazine 10 mg/kg, i.p. or glucose 2 gm/kg, i.p. and blood glucose was determined by the glucose oxidase method [2] on blood obtained by the orbital sinus technique (6).

In the second experiment, rats were treated with estradiol as previously described. The diaphragms were removed and incubated in 10 ml of Krebs-Hensleit solution containing 2 g/liter glucose in a shaker incubator at 37° using oxygen. Disappearance of glucose from the media was followed at various time intervals and is reported as milligrams of glucose disappearance per gram of tissue. Determinations were made with 5 mg chlorpromazine added as well as with untreated rat diaphragms.

Results and Discussion. As shown in Fig.

* Supported in part by USPHS Grant MH-08803 and GM-15005.

[1] Iranian Government Fellow.

[2] Glucostat, Worthington Biochemical Co.

1, pretreatment of the animals with estradiol lowered the hyperglycemic effects of chlorpromazine as well as that of glucose administration.

Figure 2 shows the *in vitro* glucose uptake by the rat diaphragm. The assumption is made that glucose uptake is occurring concomitantly with glucose disappearance from the media. After 30 min the curve for glucose disappearance from the media in the estradiol-treated and control preparations are parallel until the end of the sampling period (140 min.). The initial rate of disappearance was greater, however, in the estradiol-treated preparation and remained at a higher level. The addition of 5 mg of chlorpromazine to the media markedly decreased the disappearance of glucose from the media.

In studies to be published, we have shown in our laboratories that chlorpromazine decreases the peripheral utilization of glucose (7). The mechanism of this effect is not clear. Roskoski and Steiner (8) have studied the characteristics of sugar transport in the isolated rat uterus. They have shown that the transport of a glucose analogue, 3-o methyl-D-glucose is increased by estrogen pretreatment and that this estrogen effect is inhibited by actinomycin D or cychoheximide. It is unlikely that chlorpromazine exerts its activity by a similar mechanism. Studies are in progress to elucidate the mechanism of this antagonism.

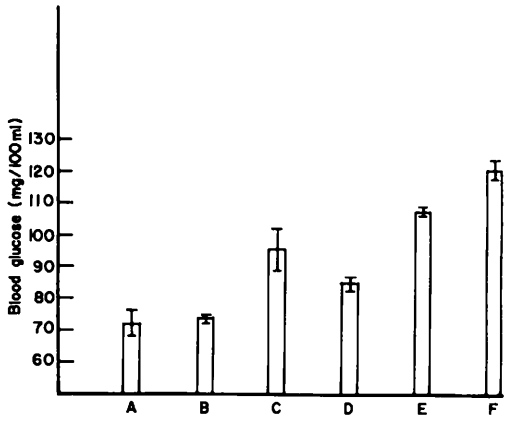

FIG. 1. Effect of estradiol valerate on chlorpromazine and glucose-induced hyperglycemia in the rat. Blood glucose determined 90 min post chlorpromazine or glucose injection. A = saline; B = estradiol; C = chlorpromazine; D = estradiol plus chlorpromazine (C vs. D $p > .05 < .1$); E = estradiol plus glucose; F = saline plus glucose (E vs. F $p < .005$).

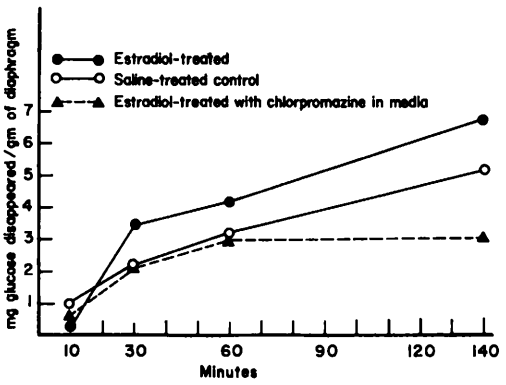

FIG. 2. Glucose disappearance from media containing estradiol-treated rat diaphragm.

Summary. Estradiol administration antagonized the hyperglycemic effects of chlorpromazine in rats. Studies using isolate rat diaphragms indicate that this antagonism is brought about by a mechanism probably involving glucose transport.

1. Nelson and Overholser. Endocrinology **20**, 473 (1963).

2. Talaat, M. and Habib, Y. A., Arch. Intern. Pharmacodyn. **153**, 290 (1965).

3. Gynaecologia **143**, 400 (1957).

4. Rodriguez, R. R., Endocrinology **55**, 1 (1954).

5. Fletcher, H. P., Miya, T. S., and Bousquet, W. F., J. Pharm. Sci. **54**, 1007 (1965).

6. Stone, S. H., Science **119**, 100 (1954).

7. Ghafghazi, T., Miya, T. S., Mennear, J. H., and Chalmers, R. K., J. Pharm. Sci **57**, 1690 (1968).

8. Roskoski, J. R. and Steiner, D. F., Biochim. Biophys. Acta **135**, 347 (1967).

Received July 17, 1968. P.S.E.B.M., 1968, Vol. 129.