8. Carter, C. E., *Ibid.*, 1950, v72, 1466.
9. Loring, H. S., and Pierce, J. G., *J. Biol. Chem.*, 1948, v176, 1131.
10. Heinrich, M. R., Wilson, D. W., and Gurin, S., *Fed. Proc.*, 1949, v8, 205.
11. Potter, V. R., and Heidelberger, C., *Physiol. Rev.*, 1950, v30, 487.
12. Brown, G. B., *Fed. Proc.*, 1950, v9, 517.
13. Arvidson, H., Elliasson, N. A., Hammarsten, E., Reichard, P., and Ubisch, H. V., *J. Biol. Chem.*, 1949, v179, 169.
14. Hammarsten, E., and Reichard, P., *Ibid.*, 1950, v183, 105.
15. Mitchell, H. K., and Houlahan, M. B., *Fed. Proc.*, 1947, v6, 506.
16. Mitchell, H. K., Houlahan, M. B., and Nyc, J. F., *J. Biol. Chem.*, 1948, v172, 525.
17. Paege, L. M., and Schlenk, F., *Arch. Biochem.*, 1950, v28, 348.
18. Michelson, M. A., Drell, W., and Mitchell, H. K., *Proc. Nat. Acad. Sc.*, 1951, v37, 396.

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Lack of Effect of Cortisone on Inhibitory Action of Antigonadotropic Sera. (19200)

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Numerous clinical and laboratory reports have indicated that cortisone and pituitary adrenocorticotropin (ACTH) may affect normal immune responses by altering the normal interaction between antigen and antibody(1-4).

The formation of an antigonadotropic substance in the serum of patients and laboratory animals after prolonged injection of pituitary gonadotropic extracts has been extensively studied(5). The exact relationship between this antigonadotropic substance and other types of antibodies is as yet obscure(6). In view of the recent observations suggesting an alteration in antigen-antibody reaction by cortisone, we have tested the effect of this compound upon the inhibitory properties of potent antigonadotropic sera.

Several batches of a concentrate of hog pituitary gonadotropin, prepared according to the method of Meyer and McShan(7), were employed as antigen. Young female sheep were injected subcutaneously daily with 200 mg of this powdered antigen in saline suspension for 700 days. Serum was prepared in the usual manner and stored in the frozen state until used.†

The same pituitary preparations used as antigen were also employed in testing the inhibitory potency of the sheep serum. For this purpose, weanling female rats of the Holtzman strain were given subcutaneously 3.3 or 5 mg of the antigen in 0.5 cc water daily for 3 days. A saline suspension of cortisone acetate (0.25 cc) was administered subcutaneously daily for 5 to 11 days beginning 2 to 8 days before the administration of the antigen or antiserum. The antisera were administered subcutaneously daily at a dosage of 0.5 cc or 1 cc as indicated in Table I. All animals were autopsied 24 hours after the last injection.

The data in Table I show that both sheep sera employed were highly effective in suppressing the gonadotropic response in the test rats. The addition of cortisone, even when administered for as much as 8 days prior to the antisera did not reduce the inhibitory effect of the antigonadotropic sera. Thus, there appeared no interference with expected interaction between antigen and antiserum as suggested by other studies.

Summary. Cortisone administration did not interfere with the antigonadotropic effectiveness in the rat of inhibitory sheep sera

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TABLE I. Effect of Cortisone on Inhibitory Action of Antigonadotropic Sera.

Series	Total dose of pituitary antigen* (mg)	Daily dose of antigonadotropic sera (cc)	Daily dose of cortisone acetate† (mg)	Ovarian wt (mg)
A	0	0	0	14 ± 3
	10	0	0	38 ± 6
	10	1	0	12 ± 2
	10	1	.5	13 ± 3
B	0	0	0	17 ± 3
	10	0	0	54 ± 11
	10	1‡	0	18 ± 3
	10	1‡	1	26 ± 7
	10	1§	0	21 ± 2
	10	1§	1	30 ± 5
C	0	0	0	15 ± 3
	15	0	0	28 ± 4
	15	1‡	0	14 ± 4
	15	1‡	.75	13 ± 3
	15	.5‡	0	12 ± 2
	15	.5‡	.75	13 ± 2

* The antigen preparation used in Series C was less potent than that used in Series A or B.
† Cortisone given for 11 days beginning 8 days before antigen in Series A and for 5 days beginning 2 days before antigen in Series B and C. All animals were 23-29 days of age at autopsy. ‡ Sheep serum #5. § Sheep serum #13.
Series A includes 15 animals per group and Series B and C include 6 animals per group.

prepared by the prolonged administration of hog pituitary gonadotropin.

1. Rich, A. R., Berthrong, M., and Bennett, I. L., Jr., *Bull. Johns Hopkins Hosp.*, 1950, v87, 549.
2. Fischel, E. E., *Bull. N. Y. Acad. Med.*, 1950, v26, 255.
3. Bjorneboe, M., Fischel, E. E., and Stoerk, H. C., *J. Exp. Med.*, 1951, v93, 37.
4. Chase, J. H., White, A., and Dougherty, T. F., *J. Immunol.*, 1946, v52, 101.
5. Zondek, B. and Sulman, F., *The Antigonadotropic Factor*, Wms. & Wilkins Co., Baltimore, 1942.
6. Meyer, R. K., and Wolfe, H. R., *J. Immunol.*, 1939, v37, 91.
7. Meyer, R. K. and McShan, W. H., *J. Biol. Chem.*, 1943, v151, 259.

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Antibiotic Synergism Requires Simultaneous Presence of Both Members of a Synergistic Drug Pair.* (19201)

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Much information is available on the effect of synergistic pairs of antibiotics *in vitro* and *in vivo*, but the mechanism of synergistic action is not known. An understanding of this mechanism might permit more rational and efficient use of drug combinations. A number of theories, not necessarily mutually exclusive, may be proposed to explain synergism, among them the following: (a) The two drugs of a synergistic pair combine chemically to form a compound more effective than either drug alone; (b) one drug kills those organisms that are resistant to the other agent; (c) one drug acts principally on multiplying bacteria, the other on resting organisms; (d) one drug may potentiate the action of another, *e.g.*, by increasing the permeability of the cell wall; (e) potentiation may occur through the simultaneous blocking of alternate enzymatic pathways, *i.e.*, if a given anabolic process essential for growth may proceed by two different

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