tagonized the effect of hyaluronidase. This effect of adrenal steroids was more pronounced when they were released endogenously by the alarm reaction. Estrone also decreased the permeability of synovial membrane.

4. Desoxycorticosterone increased maximally the permeability of synovial membrane to the same extent as hyaluronidase and could not be augmented by hyaluronidase.

5. It is suggested that the normal permeability of the synovial membrane is in part controlled by the balance between adrenal steroids of the DOCA type and of the Compound E type.

6. These findings are consistent with current views of the etiology of rheumatoid arthritis either by hyaluronidases or from exposure to stressing stimuli. They are also consistent with the therapeutic effects of Compound E or of adrenocorticotrophic hormone in the treatment of arthritis.

Addendum: Since completion of this work cortisone acetate and adrenocorticotrophic hormone (ACTH) were made available to us. One mg of cortisone acetate per kg and 0.5 mg of ACTH per kg were almost as effective in decreasing permeability of the synovial membrane as the alarm reaction. With both compounds only 25 to 30% of the dye was excreted in 4½ hours. The remainder was recovered from the synovial cavity. On this basis, the dose of adrenal cortical extract and estrone listed in Table I has cortisone activity of less than 20%, and the normal membrane balance of DOCA:cortisone an activity of 4.5%.

Received Sept. 29, 1949. P.S.E.B.M., 1949, **72**.

Development of Adrenal Cortical Adenomas in Ovariectomized Mice Injected with "Physiologic" Doses of Sex Hormone.* (17407)

MARTHELLA J. FRANTZ† AND ARTHUR KIRSCHBAUM

From the Department of Anatomy, University of Minnesota Medical School, Minneapolis.

Since the development of adrenal cortical adenomas in gonadectomized mice has been inhibited by the implantation of pellets of estrogenic hormone,[1] it might be inferred that withdrawal of gonadal secretion is of primary importance in precipitating the development of the castration-induced adenoma of the mouse adrenal cortex. The objective of the experiments being reported was to determine the effect of the administration of regulated, "physiologic" amounts of estrogenic or androgenic hormone on the induction of adrenal cortical tumors in susceptible ovariectomized mice.

Mice of the NH strain were used in these experiments. NH females develop adrenal cortical tumors spontaneously following ovarian regression, and precociously if gonadectomized.[2] Adrenal cortical adenomas are present in most NH mice of both sexes 5 months after removal of the gonads.

Four NH males and one female which had been gonadectomized at 23 days of age received (by subcutaneous injection beginning 2 weeks after operation) 0.05 microgram of estradiol dipropionate‡ in sesame oil at intervals of from 5 to 9 days. This treatment with estrogenic hormone provided for constant estrus, as determined by vaginal smear. These

* This investigation has been aided by grants from the National Cancer Institute, The Jane Coffin Childs Memorial Fund for Medical Research, and the Cancer Fund of the Graduate School of the University of Minnesota.

† Present address: Department of Anatomy, University of Texas Medical School, Galveston, Texas.

1 Woolley, G., and Little, C. C., *Cancer Research*, 1946, **6**, 491.

2 Kirschbaum, A., Frantz, M. F., and Williams, W. L., *Cancer Research*, 1946, **6**, 707.

‡ The synthetic sex hormones were supplied by Ciba Pharmaceutical Products through the courtesy of F. E. Houghton.

5 animals were autopsied 6 months after the institution of hormone treatment. Administration of hormone was suspended 53 days before autopsy in 2 NH females which received similar treatment.

Two ovariectomized NH females received the same treatment with the estrogen and in addition were injected weekly with 150 μg of progesterone in oil. Two additional ovariectomized females received the estrogen plus progesterone, but treatment was suspended 47 days before autopsy.

Two NH females ovariectomized at 21 days of age were given 17.5 μg of testosterone propionate in oil weekly by subcutaneous injection beginning 2 weeks after operation. This treatment was continued until the animals were autopsied 5½ months after ovariectomy. Three mice were similarly treated except that they received no injections of hormone for the 46 days preceding autopsy.

Histologic serial sections of the adrenal glands were studied following complete autopsy. Representative sections of the reproductive tracts, submaxillary glands and kidneys were observed to assay the hormonal status of the experimental animals.

Cortical adenomas appeared in gonadectomized mice of the NH strain receiving amounts of estrogenic hormone just sufficient to maintain constant estrus. Ovariectomized females receiving masculinizing doses of testosterone propionate (as judged by submaxillary gland histology) also developed cortical adenomas. Similar adenomas were present in the ovariectomized females which received estrogen and progesterone simultaneously, and in ovariectomized females receiving no hormone injections. A group of 4 ovariectomized NH females which received 0.1 μg of estradiol dipropionate weekly for 4 months following operation at 35 days of age had definite adenomas at autopsy.

Seventeen of 20 gonadectomized mice on hormone treatment developed adenomas which were in all respects similar to those observed in controls which had been merely gonadectomized. Weekly injections of 0.05 μg of estradiol dipropionate failed to prevent the development of spontaneous adrenal cortical adenomas in NH females.[3]

Since adrenal cortical adenomas developed in gonadectomized mice receiving maintenance doses of sex hormone, it appears that absence of functional gonadal tissue, rather than withdrawal of sex hormone, is the prime factor in the development of adrenal cortical adenomas in gonadectomized mice. The gonad, as compared to the adrenal, may preferentially utilize trophic hormone of the pituitary gland. When functional gonadal tissue is absent in a strain of mice with an extragonadal sensitive target organ, such as the NH adrenal cortex, adenomas develop.

[3] Frantz, M. F., unpublished data.

Received October 10, 1949. P.S.E.B.M., 1949, **72**.

Search for Antibiotics Active Against *Mycobacterium tuberculosis*. 1. A Streptothricin-like Antibiotic from a *Streptomyces sp.** (17408)

RUSSELL S. WEISER, GRACE M. GARDNER, JORDAN S. LEFLER, AND LEONE ST. VINCENT
(Introduced by Charles A. Evans)

From the Department of Microbiology, University of Washington, School of Medicine, Seattle, Wash.

In a search for antibiotics active against *Mycobacterium tuberculosis* var. *hominis* several hundred antagonists have been encountered and one called *Streptomyces sp.* EI_5 in our records was chosen for intensive study because of its marked activity against the mycobacteria and the low animal toxicity of its crude filtrate.[1] The present report is

* This investigation was supported in part by the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service, and in part by the Alice McDermott Research Foundation of the University of Washington.