of these animals died when an amount equal to 8 test doses of epinephrine was injected intravenously. This same dog had been studied twice before this fatal termination by injecting procaine before epinephrine, employing one test dose of epinephrine the first time and 3 test doses the second time, when the only electrocardiographic abnormality was short runs of ventricular tachycardia.

Epinephrine was given before procaine in 8 experiments with 5 dogs. The same experiment was repeated in 2 of the animals. All the animals survived and the results did not vary; that is, after ventricular tachycardia was established following the intravenous injection of a test dose of epinephrine, the intravenous or intracardiac injection of a test dose of procaine caused a change to auricular tachycardia which then reverted to a sinus rhythm.

Conclusions. The experiments presented support the contention that when procaine is administered to cyclopropanized dogs the incidence of ventricular fibrillation following epinephrine administration is reduced. Sixty percent of the animals developed ventricular fibrillation after injection of one test dose of epinephrine. When procaine was previously administered all animals were protected, and the introduction of 8 test doses of epinephrine were required to produce the fatal complication. The results also indicate that procaine may be efficient in the treatment of ventricular fibrillation induced in the dog by epinephrine during cyclopropane anesthesia. In every instance in which procaine was given intravenously at the time when ventricular tachycardia occurred following the administration of epinephrine, recovery was effected.

11147 P

Estrogenic Therapy by Implantation of Stilbestrol Pellets.

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The new synthetic estrogen, diethylstilbestrol (4:4-dihydroxy-alpha:beta-diethyl stilbene), announced by Dodds and coworkers,[1] has been found capable of producing in animals all the effects previously obtained with naturally occurring estrogens. Early reports

[1] Dodds, E. C., Lawson, W., and Noble, R. L., *Lancet*, 1938, **1**, 1389.

indicated that it would be clinically useful when we began studies upon patients in March, 1939. We found in 41 patients (14 complete castrates, 7 partial castrates, 5 patients with primary eunuchoidism and amenorrhea, and 15 patients with severe symptoms of the spontaneous menopause), that relief of the nervous and vasomotor symptoms, estrous changes in the vaginal smears, proliferative endometrial changes and breast growth could be produced by oral or subcutaneous administration of 1 mg to 5 mg daily of diethylstilbestrol dipropionate. An analysis of these studies is to be published elsewhere.

To determine whether subcutaneous pellet implantation would be effective, hard pellets of diethylstilbestrol dipropionate weighing approximately 100 mg each were implanted in 6 women who had had both ovaries removed. The sterile pellets were inserted through a small subcutaneous incision in the lumbar region and the wound closed with a stitch. Within 2 days the castrate type vaginal smears showed estrous changes and within 7 to 10 days this response was marked. Endometrial biopsies showed active proliferation within 7 days. The menopausal symptoms, both psychic and vasomotor, were greatly relieved. These changes persisted as long as the pellets remained in place. Symptoms recurred within about 2 weeks in 3 cases when pellets were removed and not replaced.

The pellets were extracted and weighed at intervals and the average daily absorption calculated by the weight loss. Pellets have been removed after periods varying from 27 to 53 days. Average daily absorption per pellet has ranged from 0.127 to 0.250 mg, corresponding to a dose of 2,540 to 5,000 international (estrone) units daily. One patient has been maintained on pellet therapy alone for over 4 months, and 3 others for over 2 months each, all with persistent improvement. There is practically no local reaction to the pellets. They become inclosed in a tight fibrous capsule which must usually be removed with the pellet if the pellet is to be obtained intact.

When the dose necessary to produce satisfactory relief of symptoms and active estrous effects upon the vaginal smears and endometrium is compared, it is found that a fraction of the oral or injection dose is sufficient by subcutaneous pellet implantation. Stilbestrol administered by pellet implantation seems to be from 5 to 10 times as effective per unit weight.

The method offers an effective and economical mode of estrogen therapy. One such small "artificial ovary" should furnish sufficient hormone in the average menopausal or oöphorectomized patient to last approximately 400 to 800 days. A larger dose can be furnished

by inserting more than one pellet through a single incision. Smaller doses no doubt would be obtainable by using smaller pellets. No untoward symptoms or toxic effects were noted. Repeated tests of liver function, red blood cell, hemoglobin, white blood cell and blood platelet determination showed no variation from normal.

11148

Peptone-Dextrose Broth for Use in Studies of Antibacterial Activity.*

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A peptone-dextrose broth for use in measurements of the bactericidal activity of sulfanilamide and sulfapyridine has been described.[1, 2] This broth (PD) consisted of 0.7% Neopeptone (Difco), 0.7% Proteose peptone (Difco), and 0.7% Pfanstiehl peptones plus 0.1% dextrose and 0.5% sodium chloride buffered at pH 7.5 ± 0.1. Bactericidal action with the two compounds mentioned above, in concentrations of 10 mg % or less, was demonstrable only at incubation temperatures above 37°C. This bactericidal action was accompanied by abundant control growth in bacteria-broth mixtures containing no drug. The test culture used in these studies was Beta hemolytic streptococcus strain C 203.

Recent attempts to utilize PD broth, made from currently available batches of peptones, in continued studies of antibacterial activity, have been unsuccessful due to failure to obtain growth in broth control tubes at the elevated incubation temperatures which are required for demonstration of bactericidal action with sulfonamide type compounds. Modification of the peptone dextrose test medium thus became necessary for reproduction of previously reported results and for continuance of these studies.

Preliminary tests indicated that a pH of 7.2 ± 0.1 was optimal for growth of strain C 203 in peptone-dextrose broth. However, broth buffered at pH 7.2, and containing peptones as described above,

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1 White, H. J., and Parker, J. M., *J. Bact.*, 1938, **36**, 481.

2 White, H. J., *J. Bact.*, 1939, **38**, 549.