Methylandrostenediol: A Non-Virilizing Derivative of Testosterone in Metastatic Cancer of the Breast.* (17840)

F. HOMBURGER, S. C. KASDON, AND W. H. FISHMAN.†

Cancer Research and Cancer Control Unit, Tufts College Medical School, Boston, Mass., and Clinical Research Laboratory, Jewish Memorial Hospital, Roxbury, Mass.

Methylandrostenediol‡ was chosen for clinical trial in patients with metastatic cancer of the breast because it was the first of a series of compounds tested which on bioassay showed renotropic effects on experimental hydronephrosis in female adult mice resembling those of testosterone propionate. The method and results of these bioassays will be published elsewhere(1). The marked degree of protection afforded the tubular epithelial cells by testosterone propionate and methylandrostenediol in experimental hydronephrosis is illustrated in Fig. 1. This renotropic property of methylandrostenediol is at present under investigation in human renal disorders. Testosterone, vinyl testosterone, cis testosterone, testosterone tocaptate and testosterone carbonate failed to give such renal protection.

Methylandrostenediol was given to 7 women with metastasizing cancer of the breast for periods of 1 to 7 months, and in doses varying from 25 mg in oil given intramuscularly to 100 mg per day intramuscularly in aqueous suspension. The latter dose was found to be clinically the most effective. Pellets of 60 mg implanted every 20 to 30 days were also used. The maximal total dose was 10 g given intramuscularly in aqueous suspension.§

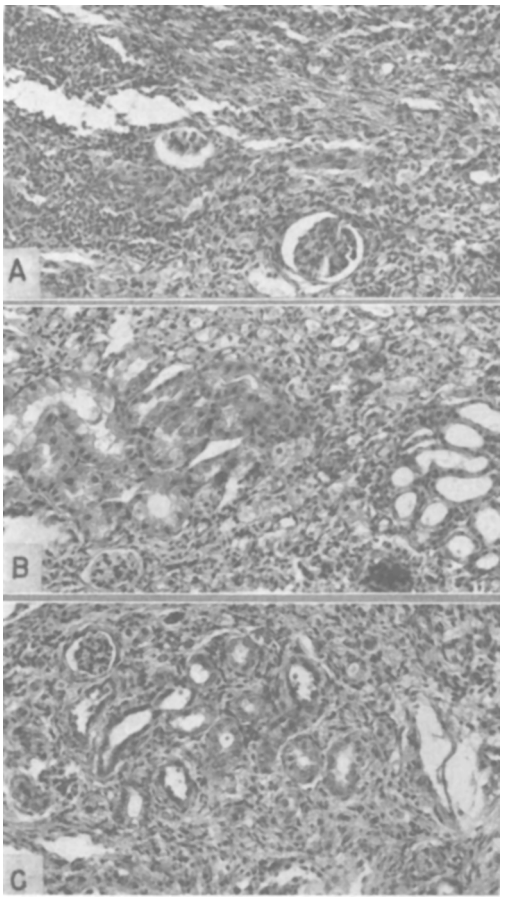

FIG. 1.

A. Fibrosis, round cell infiltration, and glomerular damage caused by unilateral ligation of the ureter lasting 30 days. This control animal received peanut oil. Magnification ×200.

B. Preservation and hypertrophy of tubular epithelium coexisting with destroyed tubules and other evidence of hydronephrosis in an animal treated like the control mouse (A) but receiving testosterone propionate. (Total dose 37.5 mg in 30 days). Magnification × 200.

C. Section from the hydronephrotic kidney of an animal receiving methylandrostenediol showing preservation of tubular epithelium. (Total dose 37.5 mg in 30 days). Magnification × 200.

* This work was supported by grants of the American Cancer Society, Inc., New York, the Massachusetts Division of the American Cancer Society, and the National Cancer Institute, National Institutes of Health, Bethesda, Md.

† The authors express their gratitude to the cooperating institutions: The Boston Dispensary Tumor Clinic, the Jewish Memorial Hospital, Roxbury, and the Holy Ghost Hospital, Cambridge.

‡ Methylandrostenediol is a product of Organon Co., Inc., Nutley, N. J. Other steroids assayed in this work were obtained from the Ciba Co., Summit, N.J., the Merck Co., Rahway, N.J., the Schering Co., Bloomfield, N.J., and from Winthrop-Stearns, Inc., New York City.

1. Homburger, F., Forbes, I., and Desjardins, R., *Endocrinology*, in press.

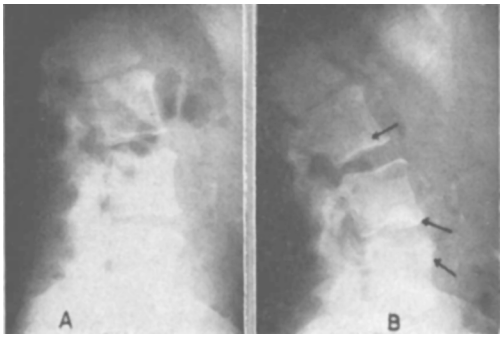

FIG. 2.
A. Patient G. M. X-ray of lumbar spine taken before methylandrostenediol therapy (12/8/48).
B. The same patient, after therapy (4/22/49), showing calcium deposition in lesions identified by arrows.

The patients were women ranging in age from 34 to 64 years, in whom cancer of the breast had been diagnosed as being of from 1 to 8 years duration prior to the initiation of methylandrostenediol therapy. Subjective improvement with varying degrees of euphoria and a sense of well-being occurred in all cases and lasted for from 1 to 7 months under therapy. Objective clear-cut calcification of bone lesions studied by X-ray was found in 2 patients and one is shown in Fig. 2 and 3. Soft tissue lesions regressed in 2 other instances under methylandrostenediol therapy. Studies of blood chemistry (phosphorus, calcium, alkaline phosphatase, NPN and total protein) showed trends comparable to those seen in the course of chemotherapy of breast cancer with testosterone and are illustrated in Fig. 4. There were instances of a drop in blood phosphorus, as well as fluctuations of blood calcium (without, so far, any cases of pathological hypercalcemia). Elevations of blood alkaline phosphatase were observed repeatedly following the administration of methylandrostenediol.

A metabolic study in one woman of 42 without cancer showed that methylandrostenediol has a protein anabolic effect of about 50% of that obtained with a similar dose (25 mg per day for 6 days) of testosterone propionate. These measurements were made by means of nitrogen, phosphorus, calcium and potassium balance studies on the metabolic ward of the Jewish Memorial Hospital. Six-day metabolic periods were alternated with control periods of 12 days. A constant diet was maintained throughout the experiment.

None of the women treated showed any virilizing or toxic signs. One patient who had grown a beard and acquired acne and a deep voice during testosterone therapy lost these symptoms under methylandrostenediol therapy, while she showed subjective as well as objective improvement of her breast cancer. (Fig. 2 and 3).

In summary, methylandrostenediol showed renotropic effects in bioassay resembling those of testosterone propionate. Our preliminary clinical observations seem to indicate that

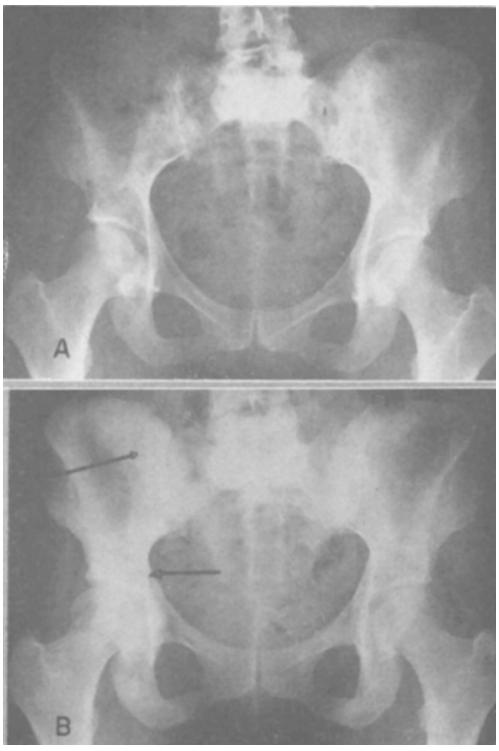

FIG. 3.
A. Patient G. M. X-ray of pelvis before methylandrostenediol therapy (12/8/48).
B. Same patient. X-ray of pelvis, showing calcification of lesions during methylandrostenediol therapy (4/22/49).

§ At the time of correcting galley proofs (June 3, 1950) the maximal total dose given without undesirable effects was 28 g.

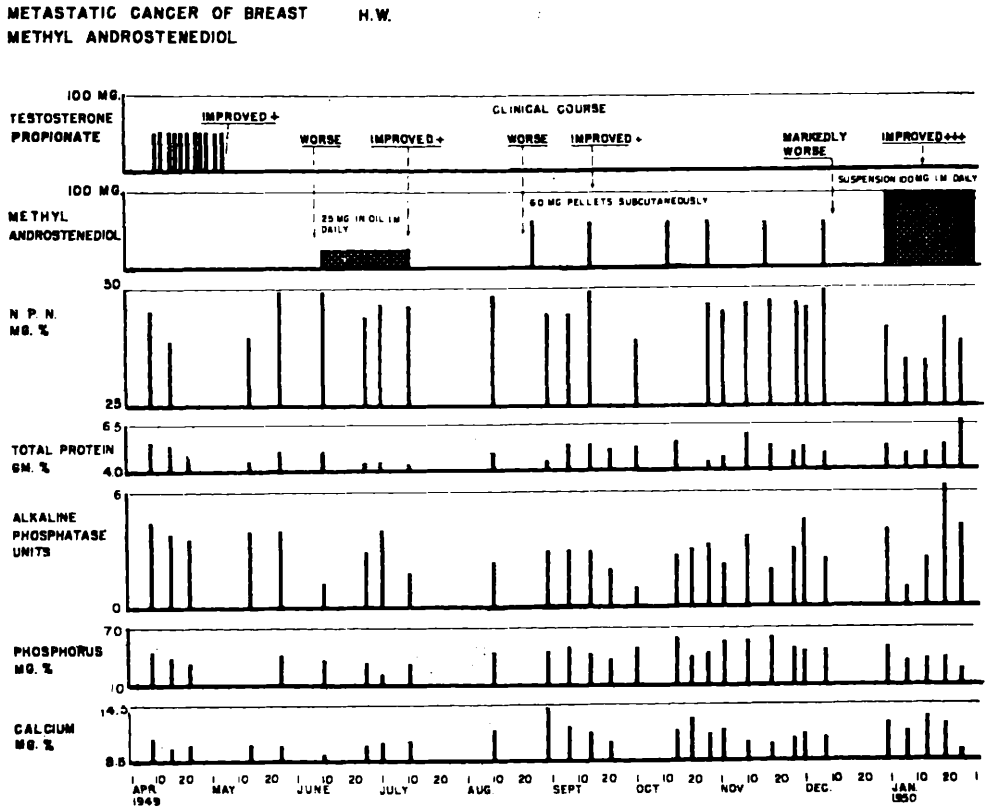

FIG. 4.
Chart of blood chemistry change as related to therapy and clinical changes. Patient H. W.

methylandrostenediol is a non-virilizing steroid hormone with moderate protein anabolic effect, and that it causes subjective well-being in patients with cancer of the breast. It did not bring about in our experience any of the undesirable biochemical phenomena such as water retention or hypercalcemia which often occur with testosterone. In at least 3 out of 7 cases of breast cancer objective regression of soft tissue and bone lesions was observed.

These brief clinical experiences do not justify conclusions as to the exact therapeutic value of this drug. However, they indicate the need for further critical evaluation on a larger scale.

Received March 21, 1950. P.S.E.B.M., 1950, v74.

Alkaline Phosphatase Activity of Human Serum in Cancer.* (17841)

ADOLPH BERNHARD AND LOUIS ROSENBLOOM.
From the Achelis Laboratory of the Lenox Hill Hospital, New York City.

Elevated serum alkaline phosphatase values are generally accepted as indicating either bone disease(1) or liver damage(2-4). The role alkaline phosphatases play in uncontrolled growth has been postulated by Potter (5,6). Potter and Liebel(7) have shown

* Aided by a grant from the Frederick Kolb Fund.