

THE USE OF TESTOSTERONE PROPIONATE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE BREAST

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NUMEROUS INVESTIGATORS, stimulated by the researches of Lacassagne and of Loeb, have demonstrated that the administration of the estrogenic hormones produces mammary carcinoma in mice. An attempt to counteract this carcinogenic effect of estrogens by means of androgens was a logical consequence. That this result could be achieved in animals was early established by several investigators (Raynaud, Lacassagne, Murlin, and his collaborators).

This principle of inhibiting the activity of the gonadal hormones of one sex by the administration of the gonadal hormones of the opposite sex has been employed in recent years in the treatment of human cancer. Encouraging results have been obtained in the treatment of prostatic cancer by the estrogens.

There are, however, surprisingly few reports of the use of androgens in the treatment of human carcinoma. In 1939, publications by Ulrich, and by Loeser, described favorable changes in patients with advanced carcinoma of the breast coincident with the administration of testosterone propionate. The latter author, in 1941, reported additional cases which appeared to be favorably influenced by this therapy. In a recent publication, Fels obtained gratifying results in one of three patients treated with testosterone propionate.

Farrow and Woodard (1942), on the other hand, using small doses of testosterone propionate concluded that in certain instances osseous metastases from breast carcinoma were stimulated by this agent.

We have investigated the effects of large doses of testosterone propionate on advanced carcinoma of the female breast. Eleven patients received this treatment, four of whom have to date exhibited a favorable response. The abstracts of these four case histories follow:

CASE REPORTS

Case 1.—S. K., a 63-year-old married white woman, 13 years postmenopause, was admitted to the Clinic on January 30, 1945. She had noticed a mass in the right breast near the nipple in August, 1939. She was a Christian Scientist and, therefore, paid no attention to the mass until about four years later, at which time it had become very large. This, however, gave her no great concern but a mass in the right side of her neck, which had been increasing in size for four months, alarmed her. She feared it might strangle her, and for that reason she sought medical attention.

The physical findings on February 1, 1945, were as follows (Fig. 1). The right breast was elevated, nipple retracted and stuck flush with the areola margin. The breast was completely replaced by a hard, nodular mass but was still somewhat movable on the chest wall. The skin overlying the mass was pinkish in color and there was pigskin appearance most marked on the medial and lower aspects of the breast extend-

ing over to the sternum. There was an area of redness and impending ulceration just medial to the areola border and there was a similar area on the inferior aspect of the breast. The left breast was negative. There were numerous skin nodules, some 0.5 cm. in diameter, extending on to the abdominal wall. There were several similar nodules

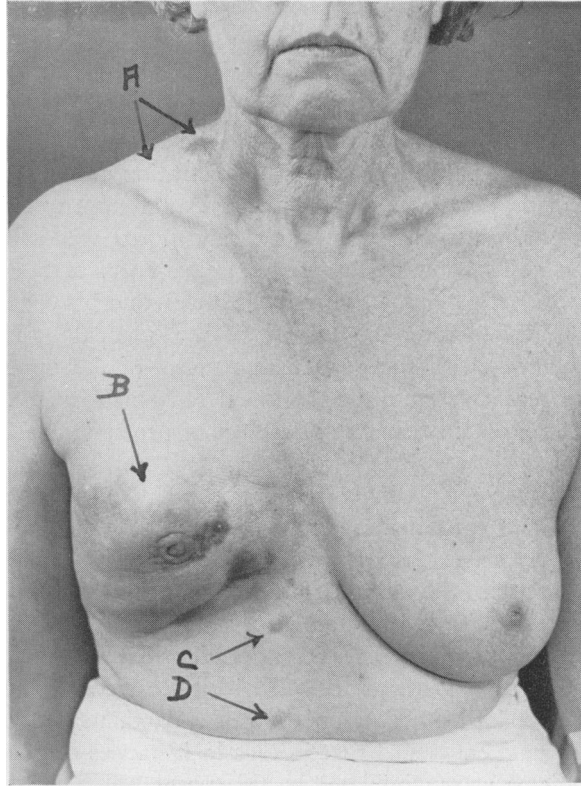


FIG. 1.—Case 1: Photograph shows the lesions before instituting testosterone propionate therapy. A group of enlarged nodes may be seen in the right supraclavicular area (A). The right breast is completely filled with a large mass whose nodules are discernible; one large protruding mass is seen just above the areola (B). Below the areola there is an extensive area with pigskin appearance and dimpling. Medial to the areola is an area of impending ulceration. Below this is a similar larger area in which ulceration is imminent. Medial to these areas and extending almost to the opposite breast is another area of *peau d'orange* appearance. Two nodules, one higher than the other, may be seen in the skin of the right upper abdomen near the midline (C and D).

in the skin overlying the right scapula. The right supraclavicular space was filled with a hard, fixed, nodular mass with several hard nodules in the right postcervical chain extending to the level of the mastoid process. There were numerous nodules in the skin of the right neck. There were several hard, shotty nodules in the left supraclavicular space. Numerous large hard nodes were palpable in the right axilla.

Biopsy of the breast was reported as infiltrating duct carcinoma and an excised

skin nodule revealed mammary carcinoma involving the lymphatics. Roentgenograms of the chest, lumbar spine and pelvis were negative for metastases.

Therapy.—On March 2, 1945, 300 milligrams of testosterone propionate in pellets were implanted subcutaneously. From March 5 to March 24, 1945, 2,600 milligrams of testosterone propionate were administered intramuscularly in 200 milligram doses.

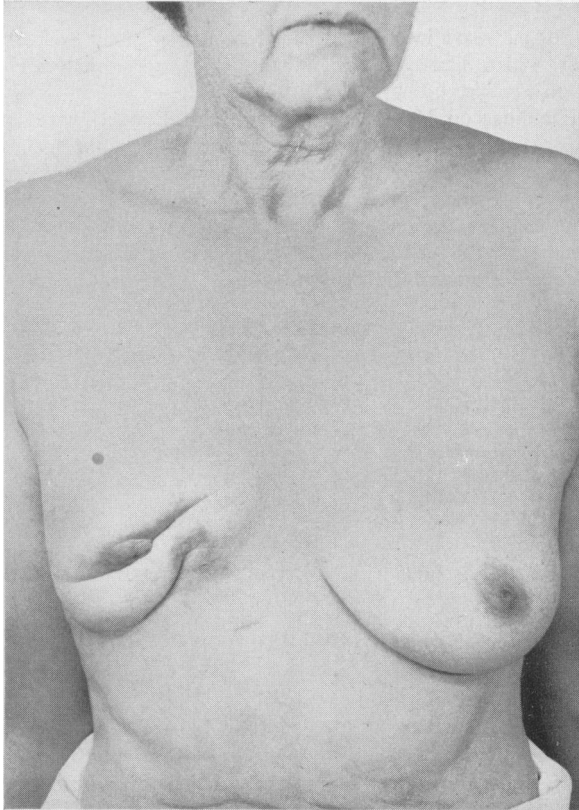


FIG. 2.—Case 1: This photograph was taken about 3.5 months after the preceding one. Within this period the patient had received 3,975 milligrams of testosterone propionate. The right supraclavicular nodes are no longer present. No nodules can be seen in the breast. The protuberant mass above the areola is no longer present. Likewise, the areas of impending ulceration and of pigskin appearance have entirely disappeared leaving the skin of the breast smooth. The upper skin nodule in the abdominal wall was removed for examination. The scar of the excision may be seen. The lower nodule has completely disappeared.

Over an interval extending from March 24 to June 6, 1945, 25 milligrams of testosterone propionate were injected intramuscularly three times a week. The total dose administered up to June 6, 1945 was 3,975 milligrams.

Progress.—Examination on April 17, 1945, about one month after instituting the therapy, revealed the right supraclavicular mass to be very much smaller. Nodes were no longer palpable in the right postcervical chain. The skin nodules in the neck and

in the scapula region were no longer present. Only one minute, soft node was palpable in the right axilla.

Examination on April 14, 1945, revealed the right breast to be soft and freely movable on the chest wall. The areas of redness on the medial and inferior aspects of the breast were markedly diminished in extent and the masses underlying these areas were much smaller and softer. No supraclavicular or axillary nodes were palpable.

On May 12, 1945, some increase in facial hair was noted and, on May 19, 1945, two skin nodules which had persisted in the right upper anterior abdominal wall were no longer discernible.

The physical findings on May 26, 1945, were as follows: There was a slight pink coloration of the medial aspect of the right breast with slight induration underlying it. No masses were palpable in the breasts. The areas of impending ulceration in the right breast were no longer present. No lymph nodes were palpable in the cervical, supraclavicular or axillary regions. No skin nodules were present (Fig. 2).

Roentgenograms of the chest, lumbar spine and pelvis made at this time were negative for evidence of metastatic disease.

| LABORATORY DATA | | | | | | | |
|---------------------------|--------|---------|---------|--------|---------|---------|--------|
| | 2/1/45 | 2/13/45 | 2/15/45 | 3/9/45 | 3/31/45 | 4/21/45 | 6/2/45 |
| Blood: | | | | | | | |
| Hb..... | 84 | | 70 | | 79 | 82 | 78 |
| R. B. C..... | 4 | 3.5 | 3.5 | | 3.9 | 3.9 | 3.8 |
| W. B. C..... | 6.5 | | | | 6.7 | 5 | 8 |
| Polys..... | 77 | | | | 84 | 77 | 88 |
| Lymphs..... | 22 | | | | 15 | 23 | |
| Monos..... | 1 | | | | 1 | | 12 |
| Hematocrit..... | | 34% | 32% | | | 32% | |
| Alkaline phosphatase..... | 1.6 | | | 2.1 | | | 2.4 |
| Serum phosphorus..... | 3.5 | | | 2.7 | | | 3.78 |
| Serum calcium..... | 11.1 | | | 10 | | | 10.6 |
| Urine: | | | | | | | |
| Sp. gr..... | | 1.005 | | | | | 1.010 |
| Albumin..... | | 0 | | | | | 0 |
| Sugar..... | | 0 | | | | | 0 |
| Micro..... | | 0 | | | | | 0 |
| Body weight (lbs.)..... | 126 | | | 130 | | 135.5 | 131.5 |

The gain in weight of 9.5 lbs. in 11 weeks coincided with the disappearance of the lesions. The subsequent weight loss was due to a throat infection which interfered with swallowing.

Case 2.—A. S., a married white woman, age 47, underwent a radical mastectomy for a Grade 3 infiltrating duct carcinoma of the left breast in 1935. The lymph nodes were not involved. In 1937, she underwent roentgen castration as a prophylactic measure. The patient was asymptomatic, and apparently free of disease until January, 1945. At that time she complained of pain in the lower back radiating down both thighs to the legs. Roentgenologic studies of the lumbar spine and pelvis failed to reveal metastases. The pain continued to increase. Roentgenograms taken 2.5 months later (April 9, 1945) revealed extensive metastases to the lumbar spine and pelvis. The chest was negative for metastases. Physical examination revealed no other evidence of disease.

Therapy.—From April 14, to June 28, 1945, she received a weekly intramuscular injection of 200 milligrams of testosterone propionate, for a total dose of 2,400 milligrams.

Progress.—When she began treatment she was unable to walk without aid and could not sleep because of pain in the lumbar spine and hips. Some relief was obtained from large doses of codeine. The pain gradually subsided and, on May 19, 1945, she was asymptomatic.

• On June 1, 1945, roentgenograms were again taken of the lumbar spine and pelvis. Compared with those taken in April, 1945, a slight increase in density in the areas of metastases was noted.

Roentgenologic studies made on June 21, 1945, revealed a further increase in the density in the bones involved by the metastases, indicating still further osteoblastic change since the earlier films were made. These changes may be seen by a comparison of Figures 3 and 4. The patient has remained asymptomatic to date. Aside from the regressing process in the lumbar spine and pelvis there is no evidence of disease.

LABORATORY DATA

| | 4/9/45 | 4/28/45 | 5/10/45 | 6/7/45 |
|---------------------------|--------|---------|---------|--------|
| Blood: | | | | |
| Hb..... | | 56 | | 60 |
| R. B. C..... | | 2.7 | | 2.9 |
| W. B. C..... | | 9.3 | | 5 |
| Polys..... | | 58 | | 60 |
| M eos..... | | 5 | | |
| Lymphs..... | | 37 | | 40 |
| Serum calcium..... | 11 | | 10 | 10 |
| Alkaline phosphatase..... | 5.5 | | 21.5 | 25.2 |
| Serum phosphorus..... | 4.07 | | 2.52 | 2.86 |
| Body weight (lbs.)..... | 122.5 | | 131.5 | 137 |

The gain in weight of almost 15 lbs., and the great increase in the serum alkaline phosphatase are noteworthy.

Case 3.—S. K., a 42-year-old single white woman, menstruating regularly, consulted the Clinic December 6, 1944. She became aware of a painless mass in the left breast one year previously but failed to seek medical advice. About two months prior to admission the breast began to pain, and she noticed that the skin over it was dimpled, the nipple retracted and that it was now smaller than the opposite breast. One month later she began to experience pain in the left lumbar region which extended to the buttock and radiated down the posterior aspect of the left thigh. Because of this pain it was difficult for her to walk or change position when sitting or lying, and for this reason she came to the Clinic.

Examination revealed an elevation and deformity of the left breast with retraction of the nipple and areola. There was pronounced dimpling involving most of the breast integument. In the subareola region, extending outward on the 5 o'clock radius was a poorly-outlined mass measuring 2 x 3 cm. There were several small firm nodes palpable in the left axilla. There was no supraclavicular adenopathy.

Aspiration biopsy of the breast mass was reported as carcinoma. Roentgenograms of the lungs were negative but those of the lumbar spine and pelvis revealed numerous areas of bone destruction which were interpreted as carcinoma metastases. The patient failed to return to the Clinic after this preliminary investigation, and it was subsequently learned that she suffered a psychic disturbance which necessitated her being hospitalized.

Three months later, March 1945, she returned. During her stay in the mental institution she received 1,300 r to the left breast. There was no other therapy to the primary site and none to the metastatic lesions. Physical findings were essentially the same as at the previous examination. However, in addition to the pain in the lumbar region which made walking difficult, she now complained of pain in the cervical spine and in the left shoulder.

Roentgenograms, made March 20, 1945, revealed metastases to the bodies of the cervical vertebrae, to the outer third of the left clavicle, to the neck and glenoid of the left scapula and to the head of the left humerus. There were widespread metastases to the lumbar spine and pelvis (Figs. 5 and 6).

Therapy.—On March 10, 1945, 300 milligrams of testosterone propionate in pellets were implanted subcutaneously. From March 12 to March 31, 1945, she received 2,400 milligrams of testosterone propionate intramuscularly in doses of 200 milligrams. From March 31 to June 21, 1945, she received 1,400 milligrams of testosterone propionate intramuscularly in 25 milligram doses. The total dose administered was 4,100 milligrams.

Course.—On April 7, 1945, the pain in the right hip was diminished. Examination of the left breast on April 28, revealed it to be less deformed and the mass smaller and softer. On May 19, 1945, she complained of pain in the upper right ribs in the axillary region, and roentgenologic studies disclosed evidence of extensive metastases to the right ribs. On May 26, 1945, she reported amenorrhea for the preceding two

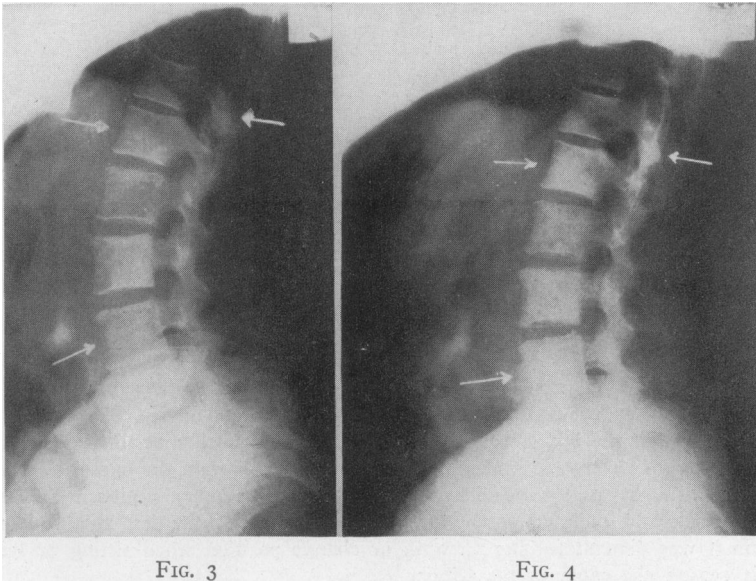


FIG. 3.—Case 2: All of the lumbar vertebrae are involved by metastases. Note the lack of density in the bodies and transverse processes.

FIG. 4.—Case 2: The increased density of the bodies and transverse processes of the vertebrae due to a deposition of calcium is readily appreciated by comparison with the preceding figure. There was an interval of three months between this and the preceding roentgenogram during which time the patient received 2,400 milligrams of testosterone propionate.

months. There was marked facial hirsutism. June 9, 1945, she stated that she had had no pain in the cervical spine for the past month. Pain in lumbar spine and hips was less. Roentgenologic studies were reported as follows: "A comparison of the films of the cervical spine made June 5, 1945, with those made on March 20, 1945, shows a marked change in the appearance of the metastases. There is now a diffuse increase in density in the bodies of the lower cervical vertebrae and in some areas of the remaining vertebrae. This change is also present in the laminae and transverse processes as well as in the upper ribs visualized" (Fig. 7).

"A comparison of films of the lumbar spine, pelvis and left shoulder girdle made June 12, 1945, with those made March 20, 1945, reveals a striking change in the appearance of the metastases in all areas. There is the same diffuse increase in density as was noted in the cervical spine" (Fig. 8).

June 21, 1945: The patient feels well and has no pain. The mass in the left breast and the left axillary nodes are still palpable.

TESTOSTERONE PROPIONATE IN CANCER

| | LABORATORY DATA | | | | | | |
|---------------------------|-----------------|--------|---------|---------|---------|---------|--------|
| | 12/6/44 | 3/8/45 | 3/23/45 | 3/31/45 | 4/20/45 | 5/29/45 | 6/5/45 |
| Blood: | | | | | | | |
| Hb..... | 87 | 62 | | 65 | | | 73 |
| R. B. C..... | 4.6 | 3 | | 3.2 | | | 3.4 |
| W. B. C..... | 12.2 | | | 8.4 | | | 9.2 |
| Polys..... | 58 | | | 46 | | | 42 |
| Monos..... | 3 | | | 2 | | | 4 |
| Lymphs..... | 38 | | | 49 | | | 48 |
| Hematocrit..... | | 21% | | | 18% | | |
| Serum calcium..... | 11.7 | | 12.5 | | 11.4 | 10.7 | |
| Alkaline phosphatase..... | 3.9 | | 4.9 | | 9.3 | 9.4 | |
| Serum phosphorus..... | 3.10 | | 3.79 | | 2.92 | 3.02 | |
| Urine: | | | | | | | |
| Sp. gr..... | | 1.013 | | | | | 1.008 |
| Albumin..... | 0 | 0 | | | | | 0 |
| Sugar..... | 0 | 0 | | | | | 0 |
| Micro..... | 0 | 0 | | | | | 0 |
| Body weight (lbs.)..... | | 120 | | 124 | 126.5 | 128 | 130 |

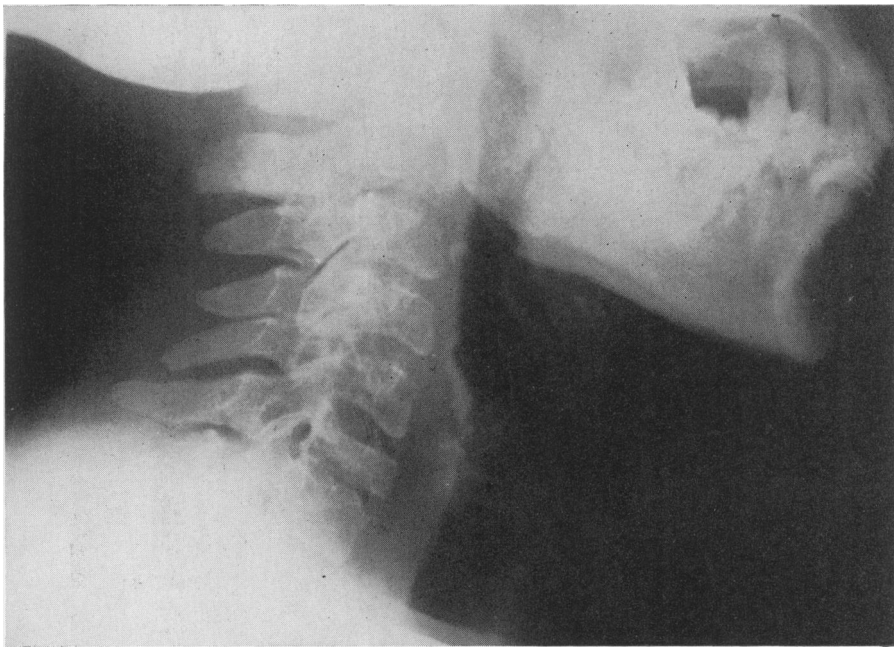


FIG. 5.—Case 3: Shows metastatic disease involving all of the cervical vertebrae with collapse of the 6th.

The gain in weight (10 lbs.) and the increase in serum alkaline phosphatase are the significant changes.

Case 4.—D. F., a 44-year-old white woman, menstruating regularly, consulted the Clinic in October, 1944, because of a mass in the right breast of one year's duration. A diagnosis of carcinoma was made and a radical mastectomy performed. Pathologic examination revealed an infiltrating duct carcinoma Grade 3; axillary lymph nodes clear. She received a cycle of postoperative roentgenotherapy to the right axilla through three ports. She was asymptomatic and apparently free of disease until March, 1945. At this time, she complained of pain in the lower part of her back radiating down the left thigh posteriorly. The pain was so severe that she could not sleep. Large doses

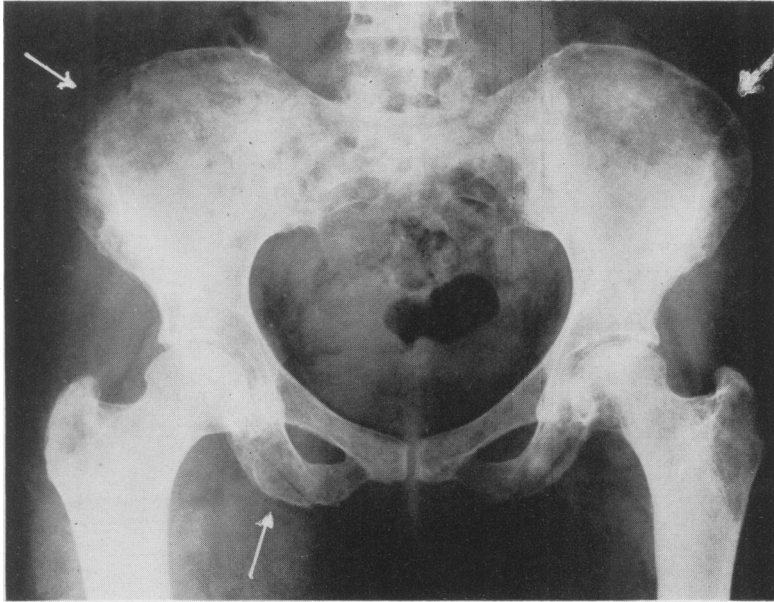


FIG. 6.—Case 3: There is extensive metastatic involvement of the lumbar spine, pelvis and femora.

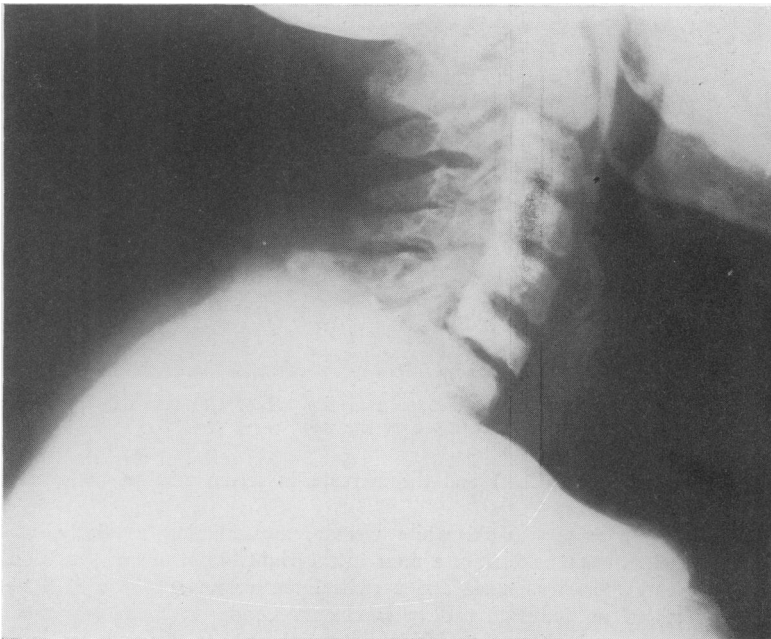


FIG. 7.—Case 3: This is a roentgenogram taken about 3.5 months later. The increased density of the vertebral bodies due to the deposition of calcium is striking. During the interval between the first and second roentgenograms the patient received 4,100 milligrams of testosterone propionate.

of codeine did not control it. Roentgenograms revealed evidence of a large area of destruction in the left ala of the sacrum (Fig. 9). She was given testosterone propionate, 200 milligrams daily, for one week, and 25 milligrams three times a week for ten weeks. The total dose administered was 2,150 milligrams.

Course.—At the end of the first week of treatment the pain was less and she was able to sleep, something she had been unable to do for three weeks preceding the treatment. The pain gradually subsided until at the end of the eighth week she was entirely free of pain. Roentgenologic studies during this period disclosed a progressive regenera-

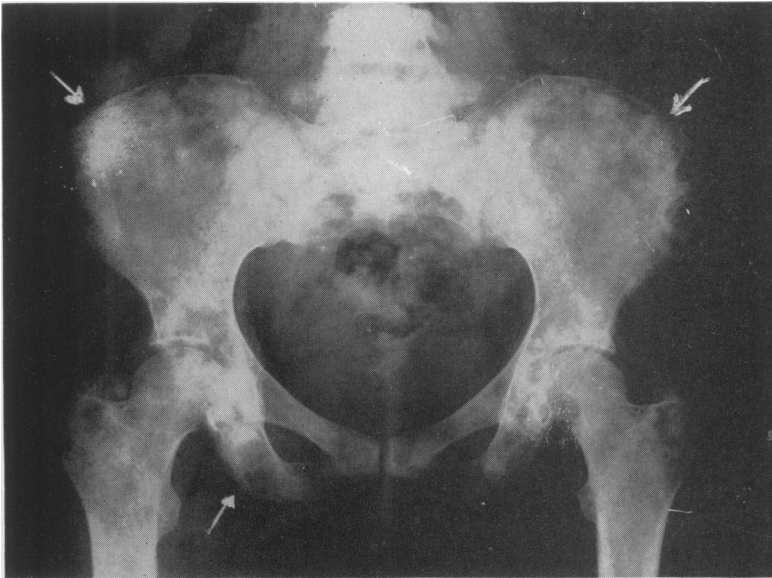


FIG. 8.—Case 3: An increase in calcification after testosterone similar to that revealed in the cervical spine is seen by comparing this roentgenogram with the preceding one. Arrows call attention to a few of the more prominent metastatic areas which have decreased in size or disappeared altogether. There is pronounced calcification of the lumbar vertebrae and alae of the sacrum.

tion of bone in the area of destruction in the left ala of the sacrum (Fig. 10). At the end of June, three months after the initiation of testosterone therapy the patient resumed her work as a comptometer operator. She was asymptomatic at this time and, aside from the calcifying lesion in the ala of the sacrum, there was no evidence of disease. The therapy produced an amenorrhea and some facial hirsutism.

There was some gain in weight but no significant change in serum alkaline phosphatase.

COMMENT.—In a number of the patients under investigation the expected masculinizing effects of testosterone; namely, hirsutism and deepening of the voice, were encountered. Amenorrhea was produced in those women in whom menstruation had been present before instituting the therapy. An increase in libido, as noted by Shorr and coworkers and Abel, was found in some instances.

Large doses of testosterone produced no discernible effect on the blood picture or renal function as judged by routine examination of the urine. All of the patients who improved under testosterone therapy exhibited an increase

in weight. This may have resulted from the nitrogen retention which is produced by the testosterone. On the other hand, the relief from pain and the consequent ability to sleep may have been contributory factors in the weight gain.

Changes in the serum content of alkaline phosphatase were manifest in two of the three patients described above with bone metastases (Cases 2 and 3). Alkaline phosphatase is produced by bones which are attempting to repair damage from metastases or other causes, and its serum level may, therefore, be used as an index of bone regeneration. It is not clear why the third case, despite marked osteoblastic changes, failed to reveal the expected serum phos-

| LABORATORY DATA | | | | |
|---------------------------|----------|---------|---------|---------|
| | 10/11/44 | 3/22/45 | 4/19/45 | 5/29/45 |
| Blood: | | | | |
| Hb..... | 82 | | 80 | 71 |
| R. B. C..... | 3.9 | | 4 | 4 |
| W. B. C..... | 7.2 | | 9.2 | 10.6 |
| Polys..... | 58 | | 71 | 80 |
| Monos..... | 1 | | 2 | |
| Lymphs..... | 41 | | 27 | 20 |
| Serum calcium..... | | 11.7 | 11.4 | 12 |
| Serum phosphorus..... | | 3.6 | 3.78 | 3.64 |
| Alkaline phosphatase..... | | 2.5 | 2.9 | 3.1 |
| Urine: | | | | |
| Sp. gr..... | 1.018 | | | 1.020 |
| Albumin..... | 0 | | | 0 |
| Sugar..... | 0 | | | 0 |
| Micro..... | 0 | | | 0 |
| Body weight (lbs.)..... | 159 | 163 | 161.5 | 163 1/8 |

phatase increase. The serum calcium and phosphorus remained within normal limits in all cases. A rise might have indicated an increase in the osteolytic process.

Of the seven patients who failed to show improvement with testosterone therapy two are dead. One had pulmonary and the other liver metastases. Another, who was in a very advanced stage when testosterone therapy was instituted has been unable to continue because she lives in a distant city. A fourth patient had generalized osseous metastases and a serum calcium of 15.5 milligrams per cent when first seen. She received 1,000 milligrams of testosterone propionate within a period of five days. This produced a further increase in the serum calcium associated with nausea, vomiting and depression. The clinical picture was similar to that described by Farrow and Woodard in patients with osseous metastases who had received small amounts of testosterone propionate. Cessation of testosterone therapy produced a drop in the serum calcium and a disappearance of the toxic manifestations. After a lapse of time, during which the serum calcium remained stabilized at about 14 milligrams per cent, testosterone propionate was again cautiously administered. The calcium level once more began to rise and the patient again became nauseated, therefore, this therapy was discontinued. Roentgenologic studies revealed progressive changes in the bone lesions. It would appear that testosterone is contraindicated in patients with hypercalcemia associated with osseous

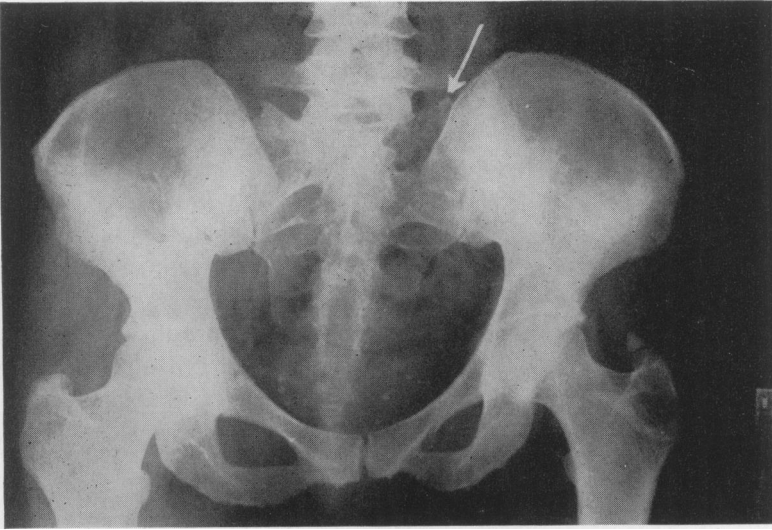


FIG. 9.—Case 4: A large area of metastatic disease involving the left ala of the sacrum is seen.



FIG. 10.—Case 4: This roentgenogram was taken three months after the one shown in the preceding figure. In the interim the patient had received 2,150 milligrams of testosterone propionate. The increased density in the involved ala is well-defined.

metastases. The importance of routine blood chemical studies in patients receiving testosterone therapy is obvious.

The three remaining patients are still under treatment. All have widespread soft-part metastases but no osseous involvement. Although these patients have not as yet exhibited clinical regression it is too soon to predict the ultimate outcome. It is of interest that biopsies of skin nodules in two of these cases have shown cellular changes. These cellular alterations are described by Dr. Fred Stewart as follows: Of the nodule in one case he says: "Mammary carcinoma. Rather marked focal hydropic degeneration. Mitoses still present." His description of the nodule from the other case is: "Mammary carcinoma. Cells definitely hydropic and nuclei pycnotic. Rare mitoses still seen. The tumor does show distinct differences from the expected."

It is of interest that similar hydropic changes in the cells of prostatic carcinoma have been observed after the administration of estrogens (Shenken, Burns and Kahle).

SUMMARY AND CONCLUSIONS

1. Eleven cases of advanced breast cancer, treated with large amounts of testosterone propionate, are reported.

2. No toxic effects were noted in individuals with normal serum calcium levels, each of whom received several thousand milligrams of testosterone propionate over a period of three months.

3. Four patients, one with soft-part and three with osseous metastases manifested remarkable improvement.

4. The evidence of improvement was the regression of the primary lesion and soft part metastases in one case and an increase in calcification in areas of osseous metastasis in three cases.

5. Disappearance of pain coincided with the osteoblastic changes.

6. In two of the cases that exhibited deposition of calcium in the bone metastases there was a coincident elevation of the serum alkaline phosphatase.

7. Four patients did not respond to the therapy and three others are still under treatment, without clinical evidence of improvement. Metastatic nodules from two of the latter group, on microscopic study, revealed hydropic changes.

8. One patient with an initial hypercalcemia associated with osseous metastases manifested a further rise in serum calcium associated with toxic manifestations in consequence of testosterone therapy. This emphasizes the importance of blood chemical studies in patients receiving this treatment.

9. We believe that testosterone propionate in large doses may, in certain instances, exert a favorable influence on advanced carcinoma of the female breast.

10. The number of cases studied is too small to gauge the frequency of this favorable reaction. From our limited experience the beneficial effects are unpredictable and uncertain. Likewise, the duration of the favorable response and the amount of testosterone propionate necessary to maintain this improved status is as yet unknown.

The authors wish to thank Dr. Helen Q. Woodard of the Department of Chemistry, Memorial Hospital, for making the blood chemical studies embodied in this report. We also are indebted to the Schering Corporation of Bloomfield, N. J., for furnishing us with the testosterone propionate (Oreton) used in this investigation.

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