Hypercalcemia, a Complication of Hormone Therapy of Advanced Breast Cancer*††

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Steroid hormones and castration have been successfully employed in the palliative treatment of advanced mammary cancer (3, 8, 9, 12, 16, 17, 24, 29–31, 35). Complications may arise during this therapy, however, which necessitate special consideration; one of the more serious of these is hypercalcemia. The progressive advanced stages of the syndrome are manifested by anorexia, nausea, vomiting, apathy, weakness, drowsiness sometimes merging into disorientation, stupor or coma, vascular collapse, and in some instances, death (1, 2, 9, 15, 18–22, 32, 34). Associated with these symptoms are an elevation of the serum and urinary calcium, frequently electrolyte changes, and sometimes renal insufficiency.

The present report records the changes observed in nine patients with obvious hypercalcemia culled from a series of 361 women with advanced cancer of the breast who were treated with sex steroid hormones. The complication in this series occurred only in patients with osseous involvement. Eighty-four of 253 patients treated with estrogens and 97 of 108 treated with androgenic hormones demonstrated osseous metastases. Of these, seven patients treated with androgens and two patients treated with estrogens developed profound manifestations of the hypercalcemia syndrome. Two patients with hypercalcemia, not included in the above consecutive series, were studied recently and have been incorporated in this report. In addition, a number of patients developed clinical manifestations compatible with a slight and transient hypercalcemia. Since these were usually of short duration, laboratory evidence of hypercalcemia was unavailable or inconclusive.

The following are case reports of eleven patients with osseous metastases secondary to breast cancer who developed hypercalcemia confirmed by laboratory examination during the course of steroid therapy.

CASE I

L. B., age 63. M.G.H. #404392 (Charts 1 and 2). This woman was admitted to the Metabolic Ward of the Massachusetts General Hospital on January 8, 1948, for study and treatment of recently obvious manifest metastases from a breast cancer treated 5 years previously by radical mastectomy. She complained of weakness and loss of weight. Examination revealed a 5.5 X 4.5 cm. raised, fixed mass above the left eye invading the orbit and displacing the globe downward, partially impairing vision; a moderate degree of ptosis of the upper lid and limitation of upward gaze; a 3 X 2.5 cm. raised hard mass in the right parietal area near the midline and two firm 0.5 cm. lymph nodes in the left supraclavicular area. There was no evidence of recurrence in the operative field. The remaining physical examination was non-contributory. Her weight was 58 kg.

Pertinent blood studies were: hemoglobin, 13.0 gm.; serum calcium, 10.5 mg. per cent; serum phosphorus, 3.8 mg. per cent; NPN (nonprotein nitrogen), 26 mg. per cent; and total protein, 5.9 gm. per cent. Liver function studies, phenol sulfoln.

*Normal blood chemistry values at the Massachusetts General Hospital and Pondville Hospital:

<table>
<thead>
<tr>
<th>Component</th>
<th>Normal Range</th>
</tr>
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<tbody>
<tr>
<td>Serum calcium</td>
<td>9–10.8 mg. per cent</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>2.5–3.8 mg. per cent</td>
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<tr>
<td>NPN</td>
<td>15–35 mg. per cent</td>
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<tr>
<td>Total protein</td>
<td>6–8 gm. per cent</td>
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*This work was aided in part by an Institutional Grant from the American Cancer Society and in part by the Damon Runyon Memorial Fund to the Massachusetts General Hospital for Tumor Studies.
† The testosterone propionate was generously supplied by the Ciba Pharmaceutical Products, Inc. (Perandren) and the Schering Corporation (Oreton).
‡ This is publication No. 784 of the Cancer Commission of Harvard University and No. 169 of the Pondville Hospital.
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1 I. T. Nathanson and B. J. Kennedy, unpublished data.
Chart 1.—Case 1: Hypercalcemia due to stilbestrol, showing serum chemistries and balance data for calcium, phosphorus and nitrogen. The daily intake is charted from the 0 line downward, and the average daily excretion from the bottom line upward. A negative balance is therefore indicated by extension of the column above the line; and a positive balance by a clear area below the 0 line.
phthalein (PSP) excretion test, and urinalysis were within normal limits. Radiographs revealed a 5 × 4 cm. osteolytic lesion in the right parietal bone and a 4 × 3 cm. defect in the left frontal bone. There were dense, lobular, metastatic infiltrations in the lungs below the right hilus and overlying the arch of the aorta. A biopsy of the mass of the left forehead was consistent with metastatic carcinoma of the breast.

The patient was placed on a constant, neutral ash, low calcium (135 mg.) diet. Metabolic studies were commenced after an interval of 6 days to insure stabilization of the patient on the diet. Urines and stools were collected in 3-day pools throughout the study, except as indicated. The essential components were calculated in order to determine the metabolic balance. Pretreatment control studies were carried out for 18 days, divided into six periods of 3 days each. The patient was ambulatory. During the control period, the studies indicated a nitrogen equilibrium, negative calcium and phosphorus balances, and essentially constant blood levels (Chart 1).

Estrogenic therapy, diethylstilbestrol, 15 mg. daily, was instituted at the conclusion of the control period on February 11, 1948. That evening, the patient was unusually drowsy, nauseated, and vomited several times. Since this persisted for the ensuing 3 days, the patient remained in bed. There was no change in the serum calcium the first morning after medication, but the serum phosphorus value was reduced from 4.1 to 3.0 mg. per cent. The serum protein had risen from 5.9 to 7.3 gm. per cent, but the NPN had decreased to 19 mg. per cent. On the fourth day the serum calcium was 18.4 mg. per cent; serum phosphorus, 2.7 mg. per cent; and an indirect bilirubin was 2.8 mg. per cent. By the 6th day vomiting ceased, but pain in the back developed. The mass invading the left orbit appeared to further displace the left eye downward, and diplopia occurred. The serum calcium had risen to 16.7 mg. per cent. The condition of the patient became precarious. The diet had to be discontinued, and adequate stool collections for metabolic studies were not possible. In spite of little or no intake of food, the urinary excretion of both calcium and phosphorus was considerably increased, and the pretreatment level of urinary nitrogen excretion was maintained. The highest urinary excretion of calcium, 670 mg. in 24 hours, was obtained on the 7th day of medication (Chart 1). Disorientation developed at this time. Intravenous glucose and saline administration, because of dehydration, was followed by improvement in orientation and appetite. Estrogen therapy was continued because of this suggested improvement. For the next 5 days the urinary and serum calcium remained high, with a serum calcium level of 15.1 mg. per cent and a total protein of 5.9 gm. per cent. During this time the phosphorus excretion in the urine diminished to the control level, and the serum phosphorus reached its lowest value of 1.6 mg. per cent. There was also a slight but definite rise in the serum calcium balance several months later. The rise of serum calcium between balance studies was due to a high calcium intake while the patient was at home.
alkaline phosphatase. On the 16th day, the serum and urinary calcium had decreased, and the serum indirect bilirubin was 0.87 mg. per cent. The PSP excretion test, serum total protein, and NPN remained normal.

Twenty-five days after the onset of estrogen therapy, the drowsiness had disappeared, and the serum calcium had descended to 11.4 mg. per cent on continued stilbestrol therapy. In the succeeding 2 weeks the back pain diminished. Definite regression of the metastatic lesions was obvious by the 40th day of treatment. The mass over the left eye was flat, and a considerable decrease in size of the pulmonary lesions was observed. A biopsy of the mass at the vertex of the skull on the 50th day revealed scattered islands of cancer cells within edematous-looking fibrous tissue. These findings were consistent with those frequently observed in lesions of other patients following successful estrogen therapy (18). The patient was discharged on the 60th day of therapy because of marked improvement. The therapy was continued.

Four months after commencing therapy, the masses over the left eye and right parietal area were not discernible, vision and motion of the eye were normal, and the left supraclavicular nodes were impalpable. The pulmonary lesions had apparently disappeared, and there was evidence of calcium deposition at the site of the previously destructive areas of the calvarium. Further metabolic studies demonstrated that the patient was in positive calcium, phosphorus, and nitrogen balance. Following this study the patient remained well and free of symptoms during the ensuing 5 months.

The patient was admitted for a third metabolic study, 9 months after the onset of therapy. Examination revealed still further regression of the metastatic deposits. The lesions in the calvarium were depressed, hard, and appeared to be partially calcified. The patient remained in positive calcium balance and in nitrogen and phosphorus equilibrium. A biopsy of the paretal lesion of the skull at this time demonstrated new bone formation near the dura with residual islets of cancer cells. Tumor cells had apparently disappeared from the outer table of the skull.

During the ensuing several months, a weight of 74.5 kg. was attained (a gain of 31.5 kg. since the initial episode of hypercalcemia). There was no further apparent change in the disease until 1 year after the onset of continuous estrogen therapy. The original lesion in the left frontal region became reactivated and continued to increase during the succeeding 2 months. X-rays revealed new destruction of the frontal bone surrounding the calcified area in the original left orbital lesion and of the floor of the anterior cranial fossa. Another osteolytic lesion involved the crest of the left ilium. There was recurrence of back pain. Finally, a fourth metabolic study 14 months after the onset of therapy demonstrated a slight negative calcium balance. During the 60th week of stilbestrol therapy, testosterone propionate, 100 mg. intramuscularly, 3 times weekly, was added. During 2 months of this combined therapy, the disease continued to progress. Stilbestrol was discontinued, and testosterone was omitted 1 month later. The patient progressively failed and died 21 months after the date stilbestrol therapy was commenced.

Comment.—Symptoms of hypercalcemia began almost immediately after estrogenic hormone therapy was instituted. First, there was an increase of urinary phosphorus and a decrease of serum phosphorus. Shortly thereafter, a rapid and profound rise in serum and urinary calcium occurred within a short period. Continued nitrogen loss with a significant decrease in intake was accompanied by a decrease in weight. There was no evidence of renal insufficiency, despite the high excretion of calcium in the urine. The metabolic effects closely resembled those produced by the administration of parathyroid extract, even to the sequence in which they occurred: (a) increased urinary phosphorus, (b) fall of serum phosphorus, (c) rise of serum calcium, and (d) increased urinary calcium. Though parathormone lowers the phosphorus level of blood of normal patients, if the serum calcium rises above a critical level of 14–15 mg., then the urinary phosphorus decreases and the serum phosphorus rises. Furthermore, the effect of parathormone in some cases gradually wears off, and the first evidence of this is a decreased phosphorus elimination (4). Similar alterations in metabolism were observed in this patient. The situation in this patient is of especial interest in that hypercalcemia and strongly negative calcium, phosphorus, and nitrogen balances, apparently initiated by stilbestrol, eventually were reversed with accompanying clinical improvement during continuation of the hormone. The rise in alkaline phosphatase preceding the reversal may be of significance in predicting the response of other patients.

CASE II

M. T., age 56. P.H. #27446 (Chart 3). This patient was admitted to the Pondville Hospital 1 year after a right radical mastectomy for carcinoma, because of pain from an osteolytic lesion in the sixth thoracic vertebral body. She was ambulatory. The serum calcium was 11.8 mg. per
cent. On March 27, 1949, intramuscular injections of 100 mg. of testosterone propionate were given 3 times a week. The hormone was omitted 6 days later after the third injection because of vomiting. The serum calcium was 12.8 mg. per cent. On April 7, stilbestrol, 15 mg. daily, was started, but was discontinued after 4 days because of nausea. By April 14, the serum calcium was 18.0 mg. per cent, but fell to a normal level 2 days later. Estrogen therapy was then resumed. There was no change in the calcium values in the ensuing 2 months, and the patient continued to receive therapy for partial relief of pain. After 5 months of estrogen therapy, the patient omitted the medication because of nausea. During the subsequent 15 months there was a gradual progression of the disease until her death on December 16, 1950.

Comment.—This case demonstrated that transient hypercalcemia may occur at the onset of hormone therapy. The frequent nausea and vomiting and occasional drowsiness observed during the early courses of estrogen therapy may be a manifestation of this syndrome in some patients. There is some evidence that similar states, although more transient and less profound than those observed in these first two cases, may occur undetected in other women with comparable disease receiving steroid hormones. This demonstrates the necessity of close observation of these patients and of frequent serum calcium determinations.

CASE III

J. W., age 65. M.G.H. #622418 (Chart 4). This woman was admitted to the Metabolic Ward of the Massachusetts General Hospital in June, 1948, because of an inoperable, primary carcinoma of the right breast with probable extensive osseous metastases. There were anorexia, weakness, weight loss, and back pain. The patient was placed on a constant low calcium (135 mg.) diet. Metabolic studies similar to those in Case I revealed positive nitrogen and phosphorus balances and calcium equilibrium. The initial serum calcium was 8.9 mg. per cent; serum phosphorus, 3.9 mg. per cent; NPN, 21 mg. per cent; and total protein, 6.1 gm. per cent. X-rays suggested diffuse osteoporosis, but an aspiration of the bone marrow demonstrated neoplastic cells. Testosterone propionate, 100 mg. 3 times weekly intramuscularly, was commenced in July, 1948. In the ensuing 60 days, there were an increase in appetite, slight weight gain, and partial relief of pain without obvious change in the demonstrable lesions. This temporary respite was followed by an increase of back pain, increase in size of the primary breast lesion, and an extension of osteolytic metastases. Because of this progression, androgen therapy was discontinued on the 87th day, and 15 mg. of stilbestrol daily was commenced the same day. At this time, the serum calcium was 16.0 mg. per cent; serum phosphorus, 3.2 mg. per cent; total protein, 6.7 gm. per cent; and the NPN, 21 mg. per cent (Chart 4). The patient was semi-ambulatory. Ten days later drowsiness and weakness occurred, followed by
anorexia and nausea. During the subsequent 10 days the stilbestrol was continued, but the patient became stuporous and incontinent of urine and feces. There was a marked increase in the calcium and phosphorus excretion; the serum calcium was 14.0 mg. per cent; serum phosphorus, 2.4 mg. per cent; NPN, 26.0 mg. per cent; and the van den Berg, 2.5 mg. per cent. Stilbestrol was omitted after 28 days of therapy. The patient died 2 days later.

Post mortem examination revealed extensive carcinoma of the right breast and skeleton. No cerebral lesions were present. The parathyroid glands and kidneys appeared normal on histologic examination.

Comment.—A delayed and essentially asymptomatic hypercalcemia occurred during testosterone therapy. The clinical status of the patient paralleled the chemical findings. The hypercalcemia and associated clinical findings may have been precipitated by testosterone therapy or may have occurred spontaneously. A shift in therapy to stilbestrol at the time of rapid progression of the process and hypercalcemia may have accentuated the disease and in turn contributed to the final result. On the other hand, it is conceivable that the established course of the disease was unaltered.

CASE IV

C. H., age 48. M.G.H. #52707 (Chart 5). One month after a left radical mastectomy in May, 1946, osteolytic metastases were detected in the left ilium. Irradiation of the ovaries was followed by relief of pain and apparent restoration of normal bone in the involved area for 15 months before the reappearance of symptoms.

Reactivation of the disease, evidenced by extensive osteolytic metastases, accompanied by severe back pain, weight loss, and debility became obvious in September, 1947. The patient became bedridden. Testosterone propionate was commenced at a dose level of 50 mg. intramuscularly, 3 times weekly. Complete relief of pain and rehabilitation occurred within 2 months. Therapy was discontinued after 5 months, since the clinical status remained constant and many bone lesions had calcified. Since the disease remained stationary, an attempt to obtain calcification of remaining osseous lesions was instituted by a second course of testosterone propionate, 50 mg. 3 times weekly, 4 months later. At this time the serum calcium was 10.3 mg. per cent and serum phosphorus, 3.7 mg. per cent. Two weeks later the patient was forced to bed because of anorexia and nausea. Vomiting began during the 4th week. X-rays then revealed an increase in the number and size of destructive bone lesions. The serum calcium was 15.2 mg. per cent, with accompanying hypercalcuria; serum phosphorus, 5.2 mg. per cent; NPN, 61 mg. per cent; and the total proteins 7.1 gm. per cent (Chart 5). The specific gravity of the urine was 1.010. The PSP excretion was 25 per cent in 2 hours. Since nausea and vomiting became increasingly severe, testosterone was omitted on the 42d day of the second course of therapy. Within 10 days, there was a disappearance of nausea and vomiting, and the serum calcium, phosphorus, and NPN fell to normal limits. Urinary studies revealed a diminishing hypercalcemia. The total protein remained between 6.2 and 6.6 gm. per cent. In an effort to study the hypercalcemia, a third course of testosterone propionate was attempted on August 11, 1948, employing the same dose. The patient remained asymptomatic until 2 weeks later, when severe nausea and vomiting recurred, and the hormone was again discontinued with relief of the gastrointestinal symptoms. The serum calcium just prior to omission of the hormone was normal, but the serum phosphorus had risen again to 4.6 mg. per cent. Through an error, serial serum calcium determinations were not made in an ensuing period, but studies of the urinary calcium excretion revealed significant elevations (Chart 5). During the succeeding 7 weeks, the patient was relatively free of pain but had recurrent and increasing nausea, vomiting, epigastric cramps, weakness, and weight loss. The 8th week after cessation of hormone therapy, a large nodular liver and large nodes were palpated in the abdomen and pelvis. The serum calcium increased to 11.8 mg. per cent, but the serum phosphorus and NPN rose rapidly to high levels. The patient died in uremia, November 9, 1948.
Post mortem examination revealed extensive metastatic cancer in the skeleton, liver, pelvic viscera, and abdominal lymph nodes. The disease produced complete obstruction of the ureters, with associated hydronephrosis. On histologic examination, scattered speckles of calcium deposits were seen in the renal tissues. The parathyroid glands appeared normal.

Comment.—Hypercalcemia did not occur during the initial course of androgen therapy, but was manifested during the second course of therapy and repeated in a third trial of the hormone. Evidence of temporary renal insufficiency during the hypercalcemia consisted of elevation of the non-protein nitrogen and inadequate PSP excretion. Though death was due to renal failure with terminal uremia, this apparently was the result of extensive pelvic metastases producing obstruction of both ureters. The calcium deposits in the kidneys secondary to hypercalcuria, in this instance, may have been a contributory cause of the renal insufficiency.

CASE V

A. F., age 61. M.G.H. #192478 (Chart 6). Two months after a left radical mastectomy, this woman developed back pain from osteolytic metastases in the spine. Diethylstilbestrol, 10 mg. daily, was started in December, 1946, and continued for 6 months. The pain decreased by the second month and was completely relieved by the fourth month. X-rays at this time revealed scattered calcifying bone lesions in the pelvis. However, during the 6th month of estrogen therapy, because of recurrent back pain and an increase in size of persistent osteolytic lesions in the spine and the appearance of additional osseous disease, stilbestrol was discontinued. Testosterone propionate, 50 mg. 3 times weekly, intramuscularly, was commenced immediately. The serum calcium was 8.6 mg. per cent; the serum phosphorus, 3.5 mg. per cent; and the NPN, 30 mg. per cent. Within 2 weeks the patient experienced relief of pain, an increased feeling of well-being, an increased appetite, and weight gain. After the 4th month the testosterone was omitted, since the patient was asymptomatic and the disease appeared static. The lesions remained unchanged on x-ray examination. During the ensuing 3 months the patient remained relatively comfortable, but excruciating pain recurred during the 4th month, and a second course of androgen therapy was started January 20, 1948. The serum calcium was 10.3 mg. per cent, and serum phosphorus, 4.7 mg. per cent. Two weeks later the patient developed moderate anorexia, nausea, vomiting, and abdominal distention. On the 18th day of the second course of therapy, the serum calcium (18.1 mg. per cent) and serum phosphorus (5.0 mg. per cent) were elevated (Chart 6). Vomiting and nausea had subsided by the 28th day of uninterrupted testosterone therapy. The serum calcium had returned to normal (calcium, 10.1 mg. per cent; phosphorus, 3.6 mg. per cent) by the 65th day of treatment. However, x-rays again revealed marked progression in the size and number of osteolytic metastases, and on the 70th day the nausea, vomiting, and back pain recurred and increased. On the 90th day of treatment, since the serum calcium was 15.2 mg. per cent, the testosterone was omitted. The patient was admitted to the hospital 7 days later, at which time the symptoms had subsided. Laboratory studies were:

![Chart 6. Case V: Hypercalcemia occurring during a second and third course of testosterone propionate (T. P.).](chart6.png)
remained normal, and the NPN varied from 30 to 78 mg. per cent.

Comment.—Though in the initial course of therapy the patient remained free of complications, the second and third courses of testosterone were accompanied by hypercalcemia. The occurrence of hypercalcemia and increased clinical manifestations, during the subsequent courses of testosterone therapy and partial recovery after discontinuance, suggest again that these symptoms are due to the blood calcium level rather than to increased growth rate of the tumor, about which we have no evidence.

CASE VI

D. F., age 56. P.H. #26605 (Chart 7). This incapacitated woman was seen on August 1, 1948, because of severe pain in the legs and back due to extensive osteolytic metastases from a cancer of the left breast. A spontaneous hypercalcemia due to extensive osseous metastases was evidenced by a serum calcium of 13.1 mg. per cent and serum phosphorus of 4.7 mg. per cent. Testosterone propionate, 100 mg. intramuscularly 3 times a week, was given for 18 days and then reduced to 50 mg. 3 times weekly. The serum calcium decreased to 11.2 mg. per cent, and the serum phosphorus fell to 2.6 mg. per cent. Within 1 month there was relief of pain, and the patient remained comparatively asymptomatic until the 88d day of therapy, when nausea and diplopia occurred. The therapy was omitted, and the nausea disappeared within 2 days. Testosterone was resumed after a 5-day interval. Four weeks later (120 days after the initiation of testosterone therapy), because of drowsiness and increasing pain, the patient was admitted to the Pondville Hospital with suspected hypercalcemia. Chemical studies on admission were serum calcium, 13.4 mg. per cent; serum phosphorus, 3.7 mg. per cent; NPN, 39.0 mg. per cent. Since these values were similar to the initial studies, hormone therapy was continued. Suddenly, 9 days later, the patient became very drowsy and nauseated. The serum calcium was 19.0 mg. per cent; serum phosphorus, 3.6 mg. per cent; and NPN, 57 mg. per cent (Chart 7). The testosterone was omitted immediately, and 250 cc. of 2.5 per cent sodium citrate was given intravenously by slow drip over a 4-hour period. By the next day the nausea and vomiting had disappeared; the serum calcium was 17.7 mg. per cent and the NPN 70 mg. per cent. During the ensuing 25 days the serum calcium and NPN gradually decreased to normal. Three months later the patient was ambulatory and nearly free of pain without medication or hormone therapy. However, the disease slowly progressed, and the patient died 6 months later.

Comment.—This case again demonstrates a delayed hypercalcemia during androgen therapy. In this instance, however, the more profound chemical changes appearing after clinical recognition of the syndrome were undoubtedly due to continu-

CASE VII

E. L., age 46. P.H. #27023 (Chart 8). This patient was admitted to the Pondville Hospital in November, 1948, 6 months after a radical mastectomy, because of extensive, progressing, cutaneous, pulmonary, and osseous metastases. There were no symptoms of spontaneous hypercalcemia. Testosterone propionate, 100 mg. intramuscularly every other day, was commenced on December 4, 1948. Blood chemical studies were in-
advertently omitted on admission, but 5 days later the serum calcium was 18.5 mg. per cent; serum phosphorus, 3.8 mg. per cent; NPN, 29 mg. per cent; and the total protein, 6.8 gm. per cent. Consequently, testosterone was omitted when these chemical findings were available. The patient was asymptomatic until the onset of nausea on the 8th day. The following day the patient was disoriented, comatose, and incontinent of urine and feces. The patient died on the 10th day when the serum calcium had risen to 25.7 mg. per cent and the serum phosphorus had decreased to 2.0 mg. per cent (Chart 8).

Comment.—This case illustrates the rapidity with which hypercalcemia may progress after testosterone therapy. Even though preliminary studies were omitted and spontaneous hypercalcemia may have been present, clinical manifestations did not appear until 8 days after initiation of therapy and 3 days after elevation of the serum calcium was demonstrated. The serum calcium levels in this patient were the highest recorded in our series. It is possible that with prompt recognition and therapeutic intervention with sodium citrate infusions and other measures, the end-result might have been delayed.

CASE VIII

A. R., age 55. M.G.H. #293271 (Chart 9). This patient was initially seen in September, 1944, with extensive cutaneous manifestations of recurrent breast cancer. X-ray therapy was given, followed by satisfactory responses, but local reaction appeared February, 1947. Consequently, therapy with diethylstilbestrol was instituted and continued from February to September, 1947, with excellent regression of the disease. The process remained quiet until July, 1948, when severe pain developed due to widespread osteolytic metastases forcing the patient to bed. The primary focus was inactive. Testosterone propionate, intramuscularly, was commenced at a dose level of 50 mg. 3 times weekly. The serum calcium and phosphorus were normal during the early course of therapy. An increased feeling of well-being and a decrease in pain were noted by the 3d month; but despite this the patient remained bedridden, and x-rays revealed progression of the disease. Two months later recurrent pain, nausea, and intermittent vomiting occurred. The serum calcium had gradually increased to 11.0 mg. per cent. During the 7th month of androgen therapy, new skin lesions were noted, nausea persisted, and the serum calcium had risen to 14.4 mg. per cent. Androgen therapy was discontinued 10 days later because of increasing symptoms and progression of the disease. Death occurred 10 days thereafter.

Comment.—In retrospect, it was noted that the serum calcium increased slowly during the period of androgen therapy. Immobilization of the patient and constant progression of the disease may have been the sole causes of the calcium rise. However, testosterone may have contributed to or precipitated the hypercalcemia. This case demonstrates that the symptoms of hypercalcemia may be subtle whether they occur spontaneously from advancing disease, metabolic shifts, or are induced by steroid therapy.

CASE IX

L. W., age 53. P.H. #23280. Three years after a radical mastectomy this woman became bedridden because of severe pain and debility from osseous metastases. Testosterone propionate, 50 mg., 3 times weekly, intramuscularly, was started on October 7, 1948. There was complete relief of pain, increase in strength, and mobilization of the patient within 6 weeks. However, at the end of the 8th week, severe pain recurred, and the patient was again confined to bed. Because of increasing drowsiness, nausea, and vomiting suggestive of hypercalcemia, this woman was admitted to the Pondville Hospital during the 11th week of treatment. The serum calcium was 15.1 mg. per cent; serum phosphorus, 3.3 mg. per cent; NPN, 43 mg. per cent; and the total protein, 7.0 gm. per cent. Three days later testosterone was omitted. After 7 days, the drowsiness had vanished, and the serum calcium had returned to normal. Other blood chemical measurements were likewise within normal range. The disease progressed, however, and death occurred 1 month later.

Comment.—Though the patient was initially subjectively improved, hypercalcemia developed after 10 weeks of testosterone therapy. Discontinuance of therapy was followed by disappearance of the hypercalcemia but progression of the disease. Although difficult to evaluate, it is con-
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The hypercalcemic state may have accelerated the later course of the disease.

CASE X

E. B., age 62. M.G.H. #609586 (Chart 10). Seventeen months after a right radical mastectomy, this woman developed osseous metastases in the pelvis. Pain in the leg was relieved by irradiation therapy. Three months later, extensive osseous and pulmonary metastases were demonstrated. Unfortunately, no preliminary chemical determinations were obtained.

The patient was given three injections of 50 mg. each of testosterone propionate, intramuscularly, on alternating days, beginning May 3, 1951. In conjunction with this, diethylstilbestrol was given for 5 consecutive days in daily doses of 10, 15, 15, 10, and 5 mg. On the 3rd day of therapy, nausea, belching, and epigastric distress occurred. The nausea increased in severity and persisted during the subsequent 6 days. Hormone therapy was discontinued the 5th day, and intravenous infusions were begun.

Drowsiness, which was noticed the 6th day, increased until the 9th day, at which time the patient was difficult to arouse, unco-operative, and incontinent. The serum calcium was 14.0 mg. per cent; serum phosphorus, 3.0 mg. per cent; NPN, 45 mg. per cent; serum sodium, 121.4 meq/liter; serum chloride, 76 meq/liter; serum potassium, 3.1 meq/liter; and CO₂, 39.2 meq/liter.

Because of the obvious hypercalcemia and moderate dehydration, further infusions were given. In addition, 500 cc. of 2.5 per cent sodium citrate were administered intravenously the 9th day, followed by 250 cc. on each of the 2 following days. Nausea disappeared, and the patient became more alert. The 12th day the patient appeared icteric. The serum calcium the 13th day was 16.3 mg. per cent, and the total van den Berg 1.8 (Chart 10). The Sulkowich test for urinary calcium was 3+. On the 14th day the patient was mentally alert, and the mental confusion disappeared gradually thereafter. Because the serum calcium was still 16.4 mg. per cent on the 15th day, 250 cc. of 2.5 per cent sodium citrate was again administered and the dose repeated 3 days later.

The 21st day the serum calcium was 10.2 mg. per cent, and other serum chemistries were normal. The urinary calcium was 1+. On the 44th day the serum calcium was 8.8 mg. per cent; serum phosphorus, 2.4 mg. per cent; and NPN, 21 mg. per cent. No further hormone therapy was given. Despite x-ray irradiation, there was progression of the disease during the ensuing 6 months.

Comment.—This illustrates again the rapidity of onset of hypercalcemia that may occur with even small doses of hormone and the necessity to recognize the condition early and to combat dehydration. Since this was the third case in which bilirubinemia occurred without known liver disease, this may well be a characteristic of the hypercalcemia syndrome.

CASE XI

L. T., age 54. M.G.H. #734994 (Chart 11). Two months following a right radical mastectomy for carcinoma of the breast, this woman complained of acute low back pain. Roentgenological examination revealed a metastatic lesion in the eleventh thoracic vertebra. The alkaline phosphatase was 3.5 units (Bodansky) per cent and the NPN, 95 mg. per cent.

Testolactone, 50 mg. 3 times a week, intramuscularly, was begun on July 31, 1951. One week later the serum calcium was 7.1 mg. per cent; serum phosphorus, 2.9 mg. per cent; and alkaline phosphatase, 3.9 units per cent. Because there was no relief of back pain after 2 months of therapy, testolactone was discontinued. Three weeks later the back pain increased, and a 2-cm. hard node could be palpated in the right supraclavicular area. The alkaline phosphatase was 13.7 units per cent. No serum calcium determination was done.

Because of the increase in back pain, testosterone propionate, 100 mg. 3 times a week, intramuscularly, was commenced on October 17, 1951. Diminution of back pain occurred the first 2 weeks of therapy. The 3rd week a sudden increase in pain forced the patient to bed and was followed by anorexia and drowsiness. On admission to the hospital, 3 weeks after testosterone therapy was begun and 2 days after the last injection, the patient was nauseated, lethargic, and sweating profusely. The supraclavicular node was un-
changed. Roentgenological examination revealed diffuse osteolytic lesions in the spine and pelvis. The vertebral lesion in T-11, however, appeared dense. The serum calcium was 13.0 mg. per cent; serum phosphorus, 4.3 mg. per cent; alkaline phosphatase, 16.5 units per cent; total protein, 6.3 gm. per cent; and NPN, 100 mg. per cent (Chart 11). A Sulikowich test for urinary calcium was 3+. Analysis of spinal fluid revealed a calcium of 5.6 mg. per cent; phosphorus, 1.4 mg. per cent; and total protein, 52 mg. per cent. The serum electrolytes and van den Berg were normal.

Intravenous fluids were administered daily for 4 days. On the 2d hospital day, 250 cc. of 2.5 per cent sodium citrate were given intravenously. On the 4th hospital day, the patient was alert and no longer nauseated. The serum calcium was 11.2 mg.

CHART 11.—Case XI: Hypercalcemia during testosterone therapy. A second course of therapy was accompanied by an increase of serum alkaline phosphatase to 71.0 B.U. per cent without evidence of liver disease.

Because of the widespread metastases and persistent back pain, and in an attempt to study further this syndrome of hypercalcemia, testosterone propionate, 100 mg. intramuscularly on alternate days, was begun the 13th hospital day. The serum calcium was 8.9 mg. per cent; alkaline phosphatase, 57.2 units per cent; and urinary calcium excretion, 46 mg. in 24 hours (calcium intake was 250 mg. daily). No change in the serum calcium or phosphorus followed. The alkaline phosphatase rose steadily to 71.2 units per cent by the 23d hospital day (Chart 11). The liver could not be palpated, nor was jaundice observed. The NPN was 21 mg. per cent, and the PSP excretion subsided, reinstitution of androgen therapy resulted in a striking reduction of urinary calcium and a temporary elevation of alkaline phosphatase to 71.2 units per cent.

DISCUSSION

Varying degrees of elevation of the serum and urinary calcium may occur in association with osteolytic metastases. These increases are found particularly in patients with breast cancer in which the metastases are predominantly osteolytic (11, 28). By contrast, the serum and urinary calcium are seldom increased in metastatic prostatic cancer where the osseous lesions are usually of the osteoblastic type, or in the rare breast cancer with osteoblastic metastases. When profound increases in calcium levels occur in the presence of osseous metastases, they are almost invariably accompanied by characteristic signs and symptoms. This extreme state may be designated as the "spontaneous hypercalcemic syndrome." Intermediate variations in the chemical and clinical
findings are more common. Under these circumstances, the symptoms and signs are usually subtle or absent. The diagnosis as a rule is made only by laboratory studies. Thus, it is often difficult to detect clinically the hypercalcemic state in its early stages, though it occurs spontaneously in 12–14 per cent of untreated patients with osseous metastases from breast cancer (34).

It appears from the present study and other reports that an “induced hypercalcemic syndrome” may occur in association with steroid hormone therapy for osseous metastases from breast cancer (1, 19, 28, 34). Clinically, this is characterized by apathy, anorexia, nausea, vomiting, and drowsiness. In severe hypercalcemia weight loss, dehydration, disorientation, stupor, coma, vascular collapse, and death may occur.

In our experience, no cases clinically free of skeletal metastases have developed hypercalcemia during hormonal therapy. This is consistent with other reports and indicates that “induced” hypercalcemia does not occur in the absence of osseous involvement. Estrogenic hormones seldom produced hypercalcemia in patients with osseous metastatic lesions from breast cancer, whereas the occurrence of this syndrome during androgen therapy, although infrequent, was more common. With the use of either hormone, the development of the symptoms described above in patients with demonstrable osseous metastases from breast cancer should be considered as presumptive evidence of an impending hypercalcemia, even though the laboratory findings are within normal limits. Absence of x-ray evidence of osseous metastases or atypical laboratory data, however, does not completely exclude the possibility of hypercalcemia, since the defects are not always detectable. If hypercalcemia should occur during hormone administration without clinical evidence of osseous disease, the question of such involvement should be raised. Similarly, we consider an elevation of the serum alkaline phosphatase during hormone therapy in the absence of detectable liver disease presumptive evidence of osseous involvement. This indicates increased osteoblastic activity (bone repair) and may be of diagnostic significance.

Anorexia, nausea, vomiting, and apathy are fairly common early symptoms in patients with nonmalignant diseases treated with large doses of estrogens and are occasionally seen with androgen therapy (21). This is even true when an osseous disease such as osteoporosis is the primary reason for the treatment. There is no convincing evidence to indicate that the symptoms are due to hypercalcemia so that they must be attributed to some other action of the hormones. The mechanism is not known, but it has been demonstrated that steroid hormones, when used in sufficient amounts, are anesthetic in animals, which would help explain the drowsiness (33). In any event, the nausea, vomiting, diarrhea, and apathy that occur during hormone therapy of breast cancer in the absence of x-ray or laboratory evidence of osseous metastases may be due to hormone actions other than those causing hypercalcemia.

In the present series of eleven patients with advanced breast cancer, hypercalcemia occurred early in the course of hormone therapy in four. Five patients developed hypercalcemia at later periods during androgen therapy. Two patients who had an initial favorable response with testosterone therapy rapidly developed the syndrome during subsequent trials of the hormone for reactivation of the disease after rest periods (Cases IV and V). Three patients apparently died because of hypercalcemia, seven died from progression of the cancer and one is alive (Table 1).

Laboratory studies of the “induced” hypercalcemic state revealed an increase in serum and urinary calcium excretion and a negative calcium balance. Serum phosphorus levels were more variable. During steroid hormone administration in two patients without obvious renal impairment, the serum phosphorus decreased with a corresponding increase in urinary phosphorus. In one of these patients (Case I) the sequence of events was similar to that following the administration of parathyroid hormone in that an initial increase in urinary phosphorus was followed by a fall in serum phosphorus, a rise in serum calcium and hypercalcuria. In four patients with renal damage, as determined by an elevated NPN and impaired PSP excretion, the serum phosphorus was elevated. In five patients without evidence of renal disease the serum phosphorus was normal (Table 1).

The excretion of excessive amounts of calcium by the kidneys may be followed by calcinosis of renal tubules and deposition of calcium in glomerular tufts with resulting progressive renal damage (11, 12, 19). This impairment of renal function may become so marked that azotemia follows. Hypercalcemia and hypercalcuria, apparently induced by steroid hormone therapy, were accompanied by induced renal insufficiency in four patients, as judged by elevated serum NPN, impaired PSP excretion, and other routine tests. In one of these women (Case V), permanent renal damage resulted. Post mortem examination of the kidneys of another patient (Case IV) with

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*I. T. Nathanson and B. J. Kennedy, unpublished data.
renal insufficiency demonstrated scattered calcium deposits (12). Based on the usual criteria, six patients suffered no renal damage during hypercalcemia and the renal status of all the patients was apparently normal initially. It should be stressed, however, that other and more specific tests of renal function were not routinely performed. Hence, subtle abnormalities may not have been detected.

Elevation of the serum bilirubin occurred in three cases (Cases I, III, and X) during the period of hypercalcemia. This might possibly be explained by red blood cell hemolysis or by increased viscosity of the blood (7, 25). There was no evidence of hepatic failure to account for the bilirubinemia.

Since the serum total protein was normal in all cases, the elevation of serum calcium would appear to be due to an increase in diffusible calcium, unbound to protein, and therefore capable of passing through tissue membranes.

The constancy of cerebrospinal fluid calcium is well known. The cerebrospinal fluid calcium is apparently in ionized form and identical with the diffusible fraction of serum calcium. The usual association between values for cerebrospinal fluid calcium and diffusible serum calcium is lost under conditions of abnormal serum calcium concentrations (25). In Case XI, the cerebrospinal fluid calcium was 5.6 mg. per cent (normal, 4.5–5.6 mg. per cent) when the serum calcium was 13.0 mg. per cent and 4.5 mg. per cent when the serum calcium was 9.3 mg. per cent. In this case the calcium of the cerebrospinal fluid paralleled the serum calcium but still remained within normal limits.

The following speculations have been considered in an attempt to explain the mechanism of action of steroid hormones in the production of hypercalcemia in patients with advanced breast cancer and osseous metastases:

1. Barriers may be removed that permit the metastatic tumor to grow unhindered, to be followed by marked demineralization of bone which results in an increase of serum and urinary calcium excretion (26–28).

2. The hormone may produce acceleration of tumor growth, resulting in more rapid destruction of bone and flooding of the blood stream with calcium (18).

3. Immobilization of an active individual may lead to continued bone absorption at a normal rate, decrease of bone formation, hypercalcemia, hypercalcuria, and even renal impairment. This has been observed particularly in children during periods of sudden immobilization of the extremities due to fractures or paralysis and in immobilized patients with osteitis deformans (5, 6). The degree of hypercalcemia depends on the discrepancy between demineralization and bone formation.

Immobilization may be involved in the hypercalcemia and hypercalcuria of patients with breast cancer treated with hormones. Six of these patients were already bedridden. Three were less active than normally, but were not confined to bed (Cases I, IX, and XI). Hypercalcemia developed in two ambulatory patients (Cases III

<table>
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<th>Hormone</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>NPN</th>
<th>Calcium</th>
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<tr>
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<td>Stilbestrol</td>
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<td>++</td>
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<tr>
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<td>0</td>
<td>++</td>
<td>++</td>
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</tr>
<tr>
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<td>0</td>
<td>++</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Progression</td>
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</table>
and IV), but the symptoms of the syndrome forced them to bed. Hence, immobilization does not appear to be the sole factor involved, but may contribute significantly to the alterations observed.

4. Prolonged ingestion of vitamin D may produce a syndrome of hypercalcemia and tissue calcification (10, 14). However, the sequence of events in vitamin D toxicity maintains a hypercalcemia for longer than that seen in hormonetreated patients with advanced breast cancer. None of these patients received supplementary vitamin D.

5. In one case (Case I) the metabolic effects during stilbestrol therapy closely resembled those produced by the administration of parathyroid extract, even to the sequence in which they occurred (4). However, the parathyroid glands of those patients who succumbed to hypercalcemia appeared normal at post mortem examination.

6. A “spontaneous hypercalcemia” may occur in patients with extensive osteolytic metastases from various neoplasms, particularly breast cancer (15). The “induced hypercalcemic syndrome” of hormone therapy does not appear to be solely accounted for by spontaneous occurrences, since it occurred during the initiation of hormone therapy and in other cases was reproducible on re-institution of hormone therapy. Furthermore, the rapidity of onset in some cases is in contrast to the slower development of spontaneous hypercalcemia.

Management of “induced hypercalcemia.”—The occurrence of hypercalcemia as a complication of hormone therapy of breast cancer does not contra-indicate its general use. Nor does the presence of a spontaneous elevation of serum calcium preclude hormone therapy. It is unusual for such hypercalcemia to be made worse by hormone treatment, and a decrease in the serum calcium level after commencing therapy is usually noted. Frequent serum calcium and phosphorus determinations and renal function studies prior to and during hormone therapy may detect early alterations before the clinical symptoms of induced hypercalcemia occur. Mobilization promotes or maintains the normal stress stimulus to osteoblastic activity.

Once hypercalcemia is manifest, discontinuance of the hormone may be followed by a decrease of the serum calcium and disappearance of azotemia. Most important is adequate parenteral fluid to prevent severe dehydration and measures to correct the electrolyte imbalances that occur. A low calcium diet aids the reduction of the serum calcium. A further measure is the use of sodium citrate to reduce temporarily the amount of ionized calcium in the blood by formation of a soluble, non-ionized calcium citrate complex (23). For this purpose, 250 cc. of 2.5 per cent sodium citrate can be administered intravenously and repeated in 4-6 hours if improvement does not occur, or to the point of developing a Chvostek sign of impending tetany. Caution must be exercised in regard to the total amount of sodium citrate given in a day. In this regard, knowledge of the state of renal function is imperative, since, if it is impaired, an alkalois may be produced. This in itself may be as serious as the hypercalcemia. In some cases the measures advocated may be of no avail. The recent use of chelating agents may prove important in controlling the high blood calcium acutely though this has not been adequately delineated clinically.  

SUMMARY

1. Hypercalcemia is a potential serious complication during androgenic and estrogenic hormone therapy of patients with advanced breast cancer and obvious osseous metastases.

2. Eleven cases of hypercalcemia occurring during steroid hormone administration are presented.

3. Metabolic studies of patients with “induced hypercalcemia” demonstrated an elevated serum calcium, hypercalcuria, altered serum and urinary phosphorus levels and occasionally renal insufficiency.

4. Immobilization, possible acceleration of tumor growth, and removal of barriers to the spread of cancer cells may contribute to the development of the hypercalcemia. The resemblance to the metabolic effects of parathyroid hormone is described in one case.

5. The detection and management of hypercalcemia are an essential part of steroid hormone therapy of advanced breast cancer.

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