COUNCIL ON PHARMACY AND CHEMISTRY

REPORT TO THE COUNCIL

The Council has authorized publication of the following report from its Committee on Research.

ROBERT T. STORMONT, M.D., *Secretary.*

The Committee on Research, through its Subcommittee on Steroids and Cancer, is sponsoring a collaborative study on steroids and mammary cancer. Reports summarizing this work have been published (Estrogens and Androgens in Mammary Cancer, Report to the Council on Pharmacy and Chemistry, J. A. M. A. **140:***1214 [Aug. 13] 1949. Proceedings of the First Conference on Steroid Hormones and Mammary Cancer, Chicago, A. M. A. [April] 1949. Current Status of Hormone Therapy of Advanced Mammary Cancer, Report to the Council on Pharmacy and Chemistry,* J. A. M. A. **146:***471 [June 2] 1951).*

In the following report, the conclusions expressed are those of the authors and final conclusions of the Subcommittee must await evaluation of the studies now in progress.

PAUL L. WERMER, M.D., *Secretary.*

EFFECT OF TESTOSTERONE ON PATIENTS WITH BONE METASTASES

A METABOLIC STUDY, PARTICULARLY OF BREAST CARCINOMA

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In the past decade, hormonal therapy has been advocated in the palliative management of patients with metastatic breast carcinoma [1]; reports of temporary palliation have been published from many centers,[2] and a wide discrepancy between the incidence of subjective and objective improvement has been noted.

In a preceding paper,[3a] it was pointed out that metabolic studies are an important aid in defining the course of malignant disease, in gaging the effect of therapeutic agents, and in studying their mode of action. The mineral metabolism of patients with active osteolysis has been characterized by elevated urinary calcium and phosphorus excretions and negative balances.[3] At times, excessive rates of demineralization exceed the ability of the kidneys to excrete calcium, resulting in hypercalcemia.[3a] Conversely, patients with osteoblastic metastases have characteristically subnormal urinary calcium excretion and a tendency to maximal calcium retention.[4] On occasion, patients with osteolytic metastases may spontaneously have temporary phases of bone repair, evidenced by a metabolic behavior that approaches the calcium-retentive traits seen in osteoblastic cases.

The purpose of the present study is to observe the effect of testosterone on the metabolism of patients with osteolytic metastases secondary to breast carcinoma. If the hormone were to encourage the remineralization of osteolytic areas, the process would be evidenced by improvement in the mineral balances.

After metabolic studies in the pretreatment phase, testosterone was administered to six patients [5] with osteolytic metastases secondary to breast carcinoma. To assess whether the results attained were specific for breast carcinoma, a tumor that is presumed to be influenced by hormones, control studies were performed with patients having other types of malignancy. A patient with extensive osteolytic metastases secondary to leiomyosarcoma of the vulva was given testosterone. A male patient with multiple myeloma was given estrogen therapy initially and later testosterone. Finally, the effect of radiation castration was observed in a premenopausal patient with osteolytic metastases secondary to breast carcinoma.

The various effects observed are illustrated by the cases reported in this paper.

NITROGEN RETENTION INDUCED BY TESTOSTERONE WITH MINIMAL IMPROVEMENT IN CALCIUM BALANCE

Case 1, a 50-year-old white woman, had extensive osteolytic and pulmonary metastases secondary to leiomyosarcoma of the vulva that had been resected three years previously. Metastases, which progressed slowly, were noted a year later. At no time during the course of the disease were major complications, such as severe anemia, pathologic fracture, or hypercalcemia, noted.

Metabolic studies were conducted for a total of 153 days (fig. 1). At that time, the patient was ambulatory and in a fairly good nutritional state. The pretreatment phase lasted for 21 days, during which the patient was in slightly positive nitrogen and phosphorus balance and in negative calcium balance with a moderately elevated urinary calcium excretion.

Upon the administration of testosterone, a total of 2.25 gm. in 45 days, urinary nitrogen excretion dropped immediately, resulting in a highly positive nitrogen balance. The calcinuria was somewhat decreased, so that the calcium balance was slightly less negative.

The studies were then discontinued for 62 days during which time testosterone was not administered. In the first 15 days after the resumption of studies, the nitrogen and phosphorus balances were similar to those observed in the first pretreatment phase, but the urinary and fecal calcium values were lower than previously. Upon the additional administration of 1.8 gm. of testosterone in 36 days, an immediate drop in urinary nitrogen and phosphorus excretion was again noted, resulting in a positive nitrogen and phosphorus balance. The calcium excretion, however, showed no further change.

To observe the possible favorable effect of testosterone on the mineral balance if an adequate supply of calcium were furnished, the daily administration of testosterone was continued in conjunction with an increased calcium intake. In this patient the presumption did not prove to be correct. Although the anabolic effect of testosterone on the nitrogen metabolism was still clearly demonstrable, the urinary calcium remained uninfluenced. The calcium balance became positive but to an extent no greater than that observed when calcium intake was increased without the additional administration of testosterone.[3a] With increased fecal calcium elimination, more phosphorus was now excreted through the stool and the phosphorus balance became somewhat less positive. These changes are similar to those seen in patients on a similar dietary calcium:phosphorus ratio who did not receive testosterone.

This case illustrates a definite anabolic effect of testosterone on protein metabolism. It induced a total retention of 194 gm. of nitrogen corresponding to 1,213 gm. of protein. The patient gained only 1.2 kg. of body weight in this phase. No major changes were noted in the patient's clinical condition and laboratory data with the exception of roentgenograms which showed slow progression of osteolysis. No major improvement of the calcium metabolism was induced by testosterone.

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1. (*a*) Haddow, A.; Watkinson, J. M., and Patterson, E.: Influence of Synthetic Oestrogens upon Advanced Malignant Disease, Brit. M. J **2**: 393 (Sept. 23) 1944. (*b*) Hermann, J. B.; Adair, F. E., and Woodard, H. Q.: The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast. II. The Treatment of Osseous Metastases, Surgery **22**: 101 (July) 1947. (*c*) Nathanson, I. T.; Adair, F. E.; Allen, W., and Engle, E. T.: Estrogens and Androgens in Mammary Cancer: (A Progress Report of a Sub-Committee of the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry), J. A. M. A. **140**: 1214 (Aug. 13) 1949.

2. Proceedings of the First Conference on Steroid Hormones and Mammary Cancer: The Therapeutic Trials Committee of the Council on Pharmacy and Chemistry of the American Medical Association, Chicago, 1949.

3. (*a*) Laszlo, D.; Schulman, C. A.; Bellin, J.; Gottesman, E. D., and Schilling, A.: Mineral and Protein Metabolism in Osteolytic Metastases, J. A. M. A. **148**: 1027 (March 22) 1952. (*b*) Laszlo, D.: Mineral Metabolism in Metastatic Bone Cancer, Cancer Res. **9**: 614 (Oct.) 1949. (*c*) Laszlo, D.; Schulman, C. A.; Bellin, J.; Gottesman, E. D., and Schilling, A.: Metabolic Studies of Patients with Carcinoma of the Breast and the Effects of Testosterone Therapy, ibid. **10**: 230 (April) 1950.

MINERAL LOSS INDUCED BY TESTOSTERONE IN SPITE OF NITROGEN RETENTION

Case 2, a 57-year-old postmenopausal woman, had carcinoma of the left breast. Radical mastectomy, followed by radiotherapy, was performed and the patient was asymptomatic for four years, when extensive osteolytic metastases with spontaneous hypercalcemia developed. Testosterone was then administered but resulted only in temporary symptomatic improvement followed by progression of symptoms and findings. When admitted to the hospital, the patient was in hypercalcemic crisis. Testosterone was discontinued and intravenous fluid administration begun, resulting in a return of serum calcium and blood urea nitrogen values to normal levels, decrease in pain, and ambulation. At this time, the patient showed evidence of weight loss, masculinization, extensive osteolytic metastases with rib and vertebral fractures, diplopia, and blurred vision. The renal function, as measured by urinary concentration and urea clearance tests, was unimpaired.

Metabolic studies began two and one-half months after the discontinuation of testosterone and were conducted for nine periods totaling 54 days. The data are illustrated in figure 2. The pretreatment phase consisted of six periods, three on a low calcium intake and the next three on a higher calcium intake. In this phase, the nitrogen balance was in equilibrium. The phosphorus balances showed a retention on a low calcium intake which changed toward equilibrium on increased calcium intake. This change was mainly caused by an increase in fecal phosphorus and followed the trend which has already been described.[3a] The urinary calcium excretion was subnormal in the first three periods, indicating attempt at bone repair. In periods 4 to 6, the urinary calcium excretion tended to rise, but remained within normal limits. The calcium balance was only slightly negative on a low calcium intake. Minimal utilization (10%) of calcium gluconate was achieved in periods 4 to 6, resulting in only slight improvement of the calcium balance. The testosterone phase was clearly characterized by gradual decrease in urinary nitrogen and improvement in nitrogen balance. In contrast to the nitrogen retention was the mineral loss occurring during testosterone therapy. Hypercalcinuria occurred in the initial period of testosterone and increased progressively to excessive values accompanied by hyperphosphaturia. The excess urinary calcium and phosphorus loss approximated the ratio of these minerals in bone. The rate of mineral breakdown exceeded the urinary excretion, resulting in hypercalcemia. The calcium and phosphorus balances became progressively negative.

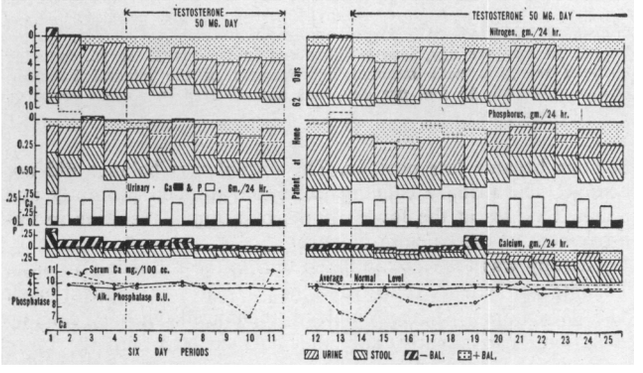

Fig. 1.—Metabolic data of a patient with leiomyosarcoma of the vulva and osteolytic metastases (case 1). All periods are for six days except periods 11 and 12 which are nine-day periods. Testosterone, 50 mg. per day, was administered in periods 5 to 11 and in periods 14 to 25, inducing nitrogen retention.

The metabolic data graph is charted according to Reifenstein, Albright, and Wells. Horizontal lines at zero in the balance graphs indicate the equilibrium between intake and output. Intake is charted from the zero line downward. Output is charted from the intake line upward toward the zero line. Interrupted lines in the phosphorus graph represent areas corresponding to the theoretical phosphorus retention or loss, calculated on the basis of theoretical N:P and Ca:P ratios. One unit of the phosphorus scale equals 15 units of the nitrogen scale and 2 units of the calcium scale.

Metabolic studies had to be discontinued for 11 days, at which time the serum calcium rose to 18.9 mg. per 100 cc. and the blood urea nitrogen to 74.8 mg. per 100 cc. Urinary collections were resumed for two periods when only intravenous feeding was feasible. Although a trend toward improvement in serum calcium and blood urea nitrogen levels was achieved, the patient died several days later of uremia. In the last period, almost 0.9 gm. of urinary calcium was excreted daily. At autopsy, marked nephrocalcinosis was found.

MINERAL AND NITROGEN LOSS INDUCED BY TESTOSTERONE

Case 3, a 47-year-old woman, underwent a left radical mastectomy two years prior to metabolic studies. Soon after the operation, osseous metastases were noted and the patient became bedridden with pain. The administration of 0.8 gm. of testosterone resulted in a cessation of menses but produced no symptomatic improvement. Subsequent radiotherapy to the lumbar spine and pelvis did not produce relief. Five months later, after a hypercalcemic crisis which improved after parenteral fluid was administered, testosterone therapy was reinstituted, the patient receiving a total of 4.1 gm. over a nine-month period. This therapy provoked hypercalcemia (15.1 mg. per 100 cc.), hypopotassemia (6.7 mg. per 100 cc.), nausea, vomiting, and dehydration. Testosterone was discontinued, and parenteral fluid and potassium were administered, resulting in a return to normal of the serum calcium and potassium within three weeks. However, anorexia and vomiting persisted, the blood urea nitrogen was 24.5 mg. per 100 cc., and the patient sustained a pathologic fracture of the left femur.

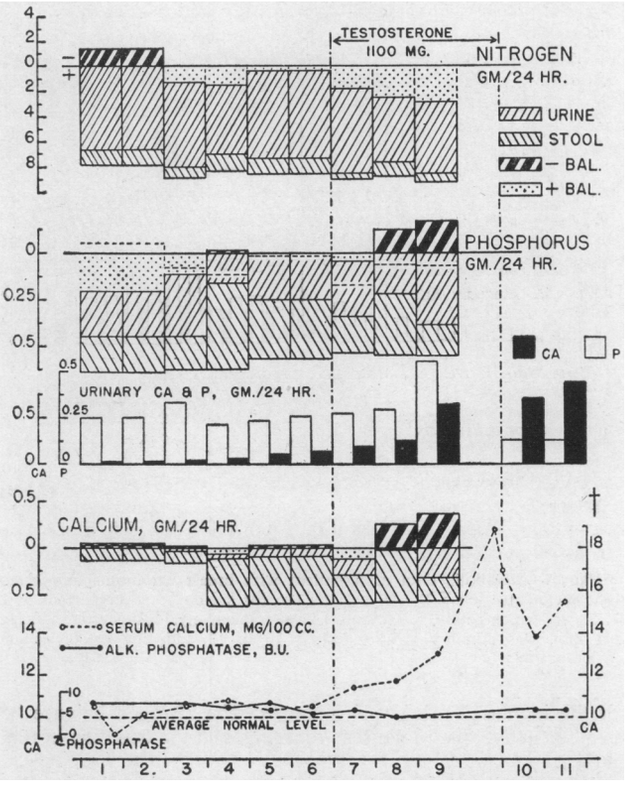

Fig. 2.—Metabolic data of a patient with breast carcinoma and osteolytic metastases (case 2). All periods are for six days. Testosterone, 50 mg. per day, was administered in periods 7 to 9, inducing hypercalcemia, nitrogen retention, and negativity of mineral balances.

Ten days later, at the time metabolic studies began, the patient had been bedridden for 22 months and was in poor nutri-

4. Aub, J. C.: Personal Communication to the author. Aub, J. C.; Tibbets, D. M., and Nathanson, I. T.: Metabolic Effects of Treatment of Carcinoma of the Prostate, Cancer Res. **7**: 723 (Nov.) 1947. Schilling, A.; Bellin, J.; Gottesman, E. D., and Laszlo, D.: Metabolic Studies of Patients with Carcinoma of the Prostate and the Effects of Stilbestrol Therapy, ibid. **10**: 239 (April) 1950. Schilling, A., and Laszlo, D.: The Effect of Diethylstilbestrol on the Calcium, Phosphorus and Nitrogen Metabolism of Prostatic Carcinoma, J. Clin. Investigation **29**: 918 (July) 1950.

5. These cases have been mentioned in a previous report as cases 3, 4, 6, 7, 8, and 9 (see footnote 3a). Cases 2 and 3 of this paper correspond to cases 8 and 9 of the previous report and are now described in detail as illustrative of the results obtained in this series.

tional state. The studies totaled 155 days, and are shown in figure 3. During the first five days of study, a moderately elevated calcinuria was noted. Later, urinary calcium excretion dropped toward subnormal values (as low as 20 mg. per day), calcium balance improved and was only slightly negative on a low calcium intake, and the patient was maintained in a state of nitrogen and phosphorus balance. The serum calcium was normal and the alkaline phosphatase elevated.

After 53 days of study, a total of 1.2 gm. of testosterone was administered intramuscularly in 24 days. Nine days after the institution of the hormone therapy, nausea and vomiting recurred, and the food and fluid intake decreased. Urinary calcium and phosphorus excretions rose rapidly. In the second period of hormone administration, the serum calcium rose to hypercalcemic levels and the alkaline phosphatase fell, indicating accelerated osteolysis. The average calcium balance during testosterone administration (–628) was five times that of the pretreatment periods (–129). The phosphorus balance, which was in equilibrium during the pretreatment phase, became negative because

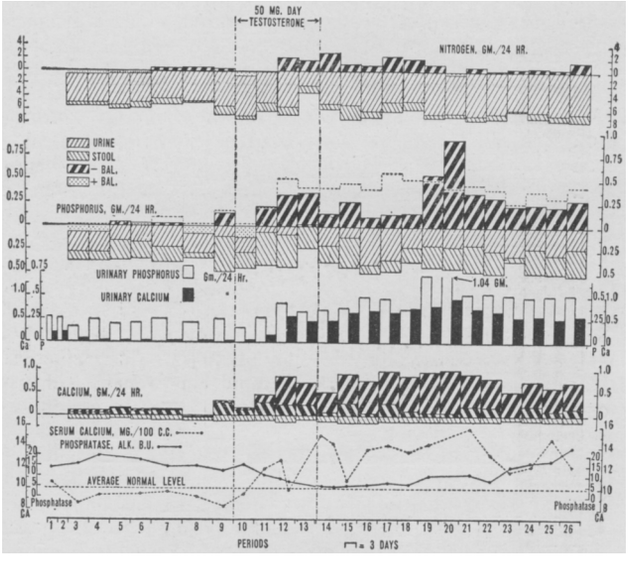

Fig. 3.—Metabolic data of a patient with breast carcinoma and osteolytic metastases (case 3) All periods are for six days except periods 1, 2, 7, and 8, which total 3, 2, 9, and 9 days respectively. Testosterone, 50 mg. per day, was administered in periods 10 to 13, inducing osteolysis and hypercalcemia.

of the increased urinary phosphorus. The nitrogen balance became negative due to nausea, vomiting, and the decrease in food intake.

With the discontinuation of testosterone, vomiting became less severe. However, the urinary calcium and phosphorus excretions increased still further, reaching a peak of 0.94 gm. and 1.043 gm. per day, respectively, six weeks after the discontinuation of testosterone. Clinically, during this phase, the patient showed a progressive downhill course. Accelerated tumor growth was evidenced by a rapidly enlarging nodular liver. Hypercalcemia, azotemia, and negative mineral balances persisted until death which occurred 12 weeks after the discontinuation of the hormonal therapy.

In summary, this case illustrates the metabolic behavior of a patient recovering from a previous hypercalcemic crisis induced by testosterone and in whom definite attempts at bone repair were observable. Reinstitution of testosterone induced another hypercalcemic crisis with excessive bone breakdown which persisted even after hormone therapy was stopped.

IMPROVEMENT IN CALCIUM BALANCE INDUCED BY DIETHYLSTILBESTROL; IMPROVEMENT IN NITROGEN BALANCE INDUCED BY TESTOSTERONE

Case 4, a 67-year-old white man, had multiple myeloma with extensive osteolysis. Ten weeks prior to the onset of metabolic studies, a compression fracture of the seventh thoracic vertebra caused paraplegia. A course of radiotherapy to the dorsal spine did not relieve pain nor did it improve the paraplegia.

Metabolic studies were performed for 288 days (fig. 4). In the four periods prior to treatment, the patient was in a state of positive nitrogen balance and of phosphorus equilibrium. The urinary calcium excretion was moderately elevated, averaging 0.212 gm. per day, and the balance was negative.

During the following 54 days, 15 mg. per day of diethylstilbestrol ("stilbestrol") was administered intramuscularly, totaling 0.81 gm. Urinary nitrogen excretion increased slightly and the

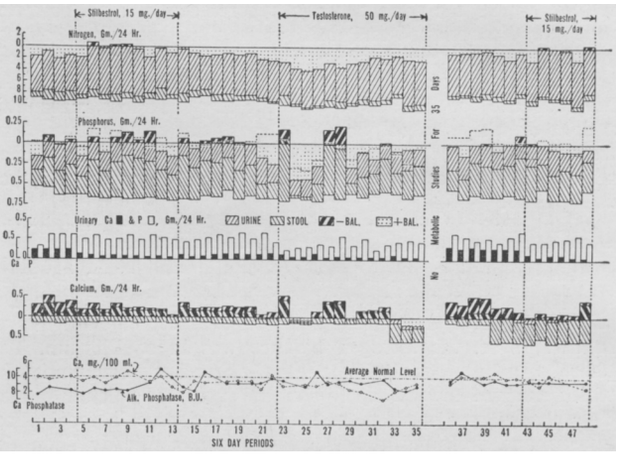

Fig. 4.—Metabolic data of a patient with multiple myeloma (case 4). All periods are for six days. Diethylstilbestrol, 15 mg. per day, was administered in periods 5 to 13 and improved the calcium balance. Testosterone, 50 mg. per day, was administered in periods 23 to 35, inducing nitrogen retention with minimal improvement in the mineral balances. Diethylstilbestrol, 15 mg. per day, was administered in periods 45 to 48 and improved the mineral balances.

balance became less positive. The phosphorus balance did not change. The urinary calcium excretion dropped promptly and reached values at the lowest limits of normal, resulting in improvement of the calcium balance.

Therapy was then discontinued during the following 54 days. The nitrogen balance returned to the previous pretreatment level. The phosphorus balance remained unchanged. Urinary calcium excretion rose slightly and the balance was slightly more negative.

For the following 60 days 50 mg. of testosterone was administered daily, totaling 3 gm. Urinary nitrogen excretion decreased promptly, greatly improving the nitrogen balance. Urinary calcium and phosphorus decreased slightly, resulting in minimal improvement of the mineral balance.

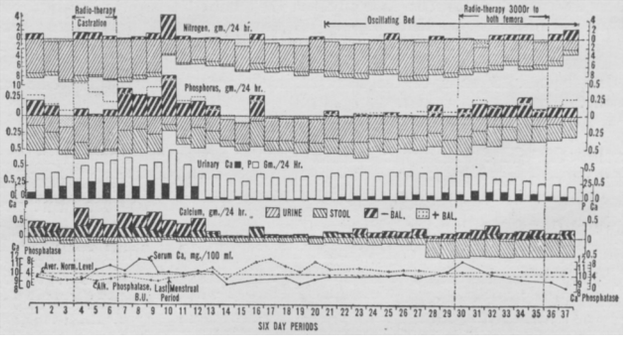

Fig. 5.—Metabolic data of a premenopausal patient with breast carcinoma (case 5). All periods are for six days except period 1, which was for nine days. Radiation castration induced an artificial menopause with improvement in the mineral balances. Subsequent radiotherapy to osteolytic areas in both femora achieved minimal improvement in the calcium balance.

In the succeeding 18 days of study, calcium gluconate was administered orally to increase the calcium intake, and testosterone administration was continued. The urinary nitrogen increased slightly, resulting in a somewhat less positive nitrogen balance. The phosphorus balance did not change significantly. The urinary calcium excretion did not change. However, ap-

proximately 80% of the increased calcium intake was retained, resulting in a reversal to positive calcium balance.

Studies were interrupted for 35 days, during which time no hormone was administered. Upon resumption of studies in period 36, the patient was found to have elevated urinary calcium excretion (0.281 gm. per day) and negative calcium balance, with the nitrogen and phosphorus approximately in balance. The oral administration of calcium gluconate did not change the calcinuria but improved the calcium balance with 45% utilization of the added calcium. When diethylstilbestrol was again administered, 0.54 gm. in 36 days, together with calcium gluconate, urinary calcium values decreased, calcium balance further improved, and utilization of the added calcium was 67%. As in the previous course of diethylstilbestrol therapy, the nitrogen excretion rose and the balance was less positive.

In summary, the data illustrate the metabolic behavior of a patient with advanced multiple myeloma and marked osteolysis. Diethylstilbestrol administration improved the calcium balance but only slightly affected nitrogen and phosphorus metabolism. Administration of testosterone improved nitrogen retention but had only minimal effect on calcium and phosphorus metabolism. However, supplementation of the calcium intake resulted in a high rate of utilization of the added calcium. After the effect of hormonal therapy had subsided, mineral catabolism was again evident. Subsequent administration of diethylstilbestrol was shown to achieve the same mineral anabolic effects as were obtained previously.

IMPROVEMENT IN MINERAL BALANCE INDUCED BY RADIATION CASTRATION

Case 5, a 38-year-old white woman, had extensive osteolytic metastases secondary to breast carcinoma. A radical mastectomy followed by radiotherapy was performed. Osteolytic metastases were noted one year later and the patient was admitted to the metabolic ward for further study.

Metabolic studies were performed for 225 days (fig. 5). The course of the patient can be divided into three distinct phases: (1) osteolytic crisis before castration (periods 1 to 13), (2) beneficial effects of castration with metabolic data suggestive of bone repair, and (3) recurrence of osteolytic activity.

In the first phase, excessive bone breakdown is clearly evidenced by high and continuously increasing urinary calcium and phosphorus excretion and a progressively more negative mineral balance. During period 9, the urinary calcium and phosphorus excretion reached a peak, with negative mineral balances. The excretion of calcium and phosphorus did not keep pace with the rapid rate of bone breakdown, resulting in hypercalcemia and hyperphosphatemia.

After 21 days of observation, radiotherapy was administered to achieve castration, 1,000 r to three pelvic portals. The patient's last menstrual period occurred in period 10. In period 13, 36 days after the completion of radiotherapy, a sudden improvement in the mineral balance occurred. The urinary calcium excretion dropped from 397 to 56 mg. per day, and progressively declined to subnormal levels. The calcium balance improved and became only slightly negative, as is normal with a low calcium intake. The nitrogen and phosphorus balance also improved. The attempt at bone repair is evidenced by a subnormal urinary calcium, a calcium balance approximating equilibrium even on a low calcium intake, and by rising serum alkaline phosphatase values.

This second phase, in which the patient experienced the greatest beneficial effect of castration, lasted 66 days. The urinary calcium and phosphorus excretion then increased progressively. The mineral balance became more negative, indicating renewed bone breakdown. In an attempt to improve the patient's calcium retention, she was placed on an oscillating bed and her low calcium diet was supplemented with calcium gluconate given orally. However, utilization of the supplemented calcium was only 21%, the urinary calcium continued to rise, and the calcium balance remained negative, despite the higher intake.

Because of the danger of pathologic fractures, radiotherapy, 3,000 r to both femora, was administered during periods 31 to 36. The urinary calcium and phosphorus continued to rise until period 35 and then began to fall slightly. Upon the completion of radiotherapy, the urinary mineral excretion improved still further, although the patient was still in negative calcium balance, even on a high calcium intake. It is to be noted that this second phase of osteolysis, occurring after castration, was not as severe as the osteolytic crisis seen while the patient was still menstruating.

In summary, this case illustrates the improvement in mineral metabolism upon radiation castration of a patient in an osteolytic crisis. This favorable effect, however, was only temporary, and further bone breakdown could not be prevented even with the aid of an oscillating bed and a higher calcium intake. Subsequent local radiotherapy at the beginning of a second osteolytic phase may have prevented, for a time, further excessive bone breakdown.

DISCUSSION

To observe some effects of malignancy on metabolism and evaluate the action of therapeutic agents, 42 patients were studied in the metabolic ward. Of this group, 24 patients had extensive osteolytic malignancy, 8 had osteoblastic metastases, 5 cancer patients had no bone metastases, and 5 patients had nonmalignant disease. Five cases in this series are reported here to illustrate certain points.

Previous reports [3] have presented data which show that active osteolysis secondary to malignancy is characterized by hypercalcinuria, hyperphosphaturia, and negative mineral balances. In cases of extremely rapid bone destruction, these metabolic trends are accentuated, the ability of the kidneys to excrete calcium is exceeded, and hypercalcemia results.[3a] It has been demonstrated [3a] that the mineral catabolism of osteolytic metastases is not specific for any one type of malignancy but is characteristic for all malignancies that cause bone destruction. Metabolic evidence has been presented showing that even advanced malignancy is characterized by periods of spontaneous remissions and exacerbations.[3a]

In bone metastases that cause an osteoblastic response, the metabolism is characterized by extremely low urinary calcium excretion and a calcium balance more positive than normal.[4] Data from this study indicate that improvement in osteolytic metastases is manifested by calcium and phosphorus metabolism that approaches normal and, with rapid bone repair, will even approximate the extreme calcium retention seen in osteoblastic cases.

The present study was conducted to evaluate the effect of hormonal therapy in patients with osteolytic metastases. In assessing the results obtained, an attempt will be made to differentiate between specific effect of the hormone on tumor and nonspecific effect on demineralizing bone. Previous metabolic studies have defined some factors that influence osteogenesis. The skeletal system of normal adults is in a dynamic equilibrium of resorption balanced by an equal rate of new bone formation.[6]

Some of the factors influencing osteogenesis are: (1) dietary intake of the building blocks of bone, (2) absorption from the intestinal tract into the blood stream, (3) utilization of the building blocks by the bone influenced by such endocrine factors as pituitary growth hormone,[7a] gonadal,[8] thyroid,[9] parathyroid,[10] and adrenocortical hormones,[7] (4) functional use of the skeleton,[11] and (5) excretion of minerals.[12]

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7. (*a*) Becks, H., and others: Antagonism of Pituitary Adrenocorticotrophic Hormone (ACTH) to the Action of Growth Hormone on the Osseous System of Hypophysectomized Rats, Endocrinology **34**: 311 (May) 1944. (*b*) Albright, F.: Cushing's Syndrome: Its Pathological Physiology, Its Relationship to the Adreno-Genital Syndrome, and its Connection with the Problem of the Reaction of the Body to Injurious Agents ("Alarm Reaction" of Selye), The Harvey Lectures **38**: 123, 1942-1943.

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Impairment of any of these factors can cause osteolytic bone disease characterized metabolically by hypercalcinuria, hyperphosphaturia, and negative mineral balances, similar to the data obtained in osteolytic malignancies. Metabolic studies have been reported for osteomalacia,[12] steatorrhea,[13] postmenopausal and senile osteoporosis,[14] hyperparathyroidism,[10] Cushing's disease,[13b] immobilization,[11] and renal rickets.[12]

In a number of these diseases, particularly in postmenopausal osteoporosis, androgen and estrogen therapy has induced improvement in calcium, phosphorus, and nitrogen metabolism.[14b] It has been noted that androgen has a significant protein anabolic effect, whereas estrogen induces predominantly mineral anabolism.

In patients with malignant bone disease, severe pain may cause immobilization, and osteoporosis from disuse is often a prominent feature. When gonadal hormones are administered to these patients, a favorable effect may be achieved on the osteoporosis, one that may be entirely nonspecific with respect to tumor growth.

For the purpose of this discussion, a specific effect on tumor shall be considered as one that causes inhibition or acceleration of tumor growth.

Experimental evidence has been advanced indicating that the incidence of mammary carcinoma in susceptible strains of mice is influenced by hormonal factors. This subject has been recently reviewed.[15] It has been demonstrated that ovariectomy decreased the incidence and delayed the appearance of mammary carcinoma in female mice of a susceptible strain[16]; similar results have been achieved by implantation of testes,[17] administration of testosterone,[18] and ovarian irradiation.[19] Ovarian grafts induced mammary cancer in castrated male mice of a susceptible strain and the incidence approximated that in females of that strain[20]; similar results have been achieved by administration of estrogen.[21] However, it must be stressed that these results are attained in mice of high mammary cancer strains. Androgens and estrogens apparently have no effect on the growth of a mammary tumor once it is established in a mouse.[15a]

13. Albright, F., and Stewart, J. D.: Hypovitaminosis of All Fat-Soluble Vitamins due to Steatorrhea; Report of a Case, New England J. Med. **223**: 239 (Aug. 15) 1940.

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24. Footnotes 1[c] and 2.

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Numerous clinical investigations have been conducted on the therapeutic effect of hormones in human breast cancer. Surgical or x-ray castration has resulted in clinical improvement of 20 to 56% of premenopausal women with breast carcinoma.[22] Castration has also resulted in improvement of some male patients with breast cancer.[23] Haddow and his collaborators reported great improvement in patients with advanced breast cancer receiving estrogen therapy, and serial biopsies of a few patients showed histological alterations suggesting regression of tumor cells.[1a]

The Committee on Research of the American Medical Association has undertaken to assemble the data of its cooperating investigators on the effects of steroid hormones in the treatment of breast cancer.[24] In a total of 285 patients with metastases treated with androgen, subjective improvement was noted in 62%. Objective improvement in soft tissue lesions was noted in about 20%. Objective improvement in osseous lesions was reported in 18%. In a total of 144 patients treated with estrogen, subjective improvement was reported in 60%. Objective improvement in soft tissue lesions was noted in 43%; a number of osseous lesions showed improvement.

However, there have also been clinical reports suggesting tumor promotion by hormones. Cancer of the breast has appeared in male[25] and female[26] patients receiving estrogens. Apparent acceleration of tumor growth was noted in patients with metastatic breast cancer receiving estrogen or androgen therapy.[27]

Case 1 is a study of the effect of testosterone in a patient with extensive osteolytic metastases secondary to leiomyosarcoma of the vulva. The androgen induced retention of protein and had a slight mineral-anabolic effect. Since this effect is similar to the one expected in a patient with postmenopausal osteoporosis, and since leiomyosarcoma is assumed to be a tumor that is not controlled by hormones, it may be assumed that the favorable effect of testosterone in this case is not a specific tumor-inhibiting effect.

Case 2 is a study of testosterone therapy in a postmenopausal patient with extensive osteolytic metastases secondary to breast carcinoma. Testosterone had the seemingly paradoxical effect of inducing nitrogen retention together with mineral loss causing hypercalcemia. If it were assumed that testosterone induced protein anabolism in tumor tissue, the accelerated rate of tumor growth in the osseous metastases would account for the increased bone breakdown.

Case 3 is a study of the effect of testosterone in a postmenopausal patient with osteolytic metastases secondary to breast carcinoma. The pretreatment phase illustrates a trend toward spontaneous bone repair in a patient with advanced malignancy. This favorable phase was interrupted by the administration of testosterone which promptly induced accelerated osteolysis and hypercalcemia. The accompanying protein catabolism was due to anorexia; the decreased food intake, nausea, and vomiting resulted from hypercalcemia. These catabolic factors outweighed whatever protein-anabolic effect the androgen might have had. As in the previous case, the osteolysis may have been caused by a tumor-promoting effect of testosterone. However, it must also be considered that the hormone may have had a direct mineral-catabolic effect as reported in mice by Gardner and Pfeiffer.[8]

Case 4 is a study of the effects of estrogen, and later androgen, in a patient with multiple myeloma. Estrogen induced mineral anabolism, but did not improve the nitrogen balance. Androgen promoted protein retention, but improved the calcium balance only slightly. This patient was paraplegic and bedridden at the onset of studies and considerable mineral catabolism could be attributable to osteoporosis of disuse. Since multiple myeloma is not considered to be a tumor that is hormonally controlled, the beneficial effects of hormone therapy cannot be considered to be due to tumor inhibition. As in case 1, the favorable effect achieved may not be assumed to be specific for tumor, but rather one of remineralization of osteoporotic areas.

It was reported previously[3a] that 30 to 40% of the ingested calcium gluconate was utilized in patients with osteolytic breast cancer metastases, a rate similar to that observed in normal persons.[28] In case 4, when calcium gluconate was administered

with testosterone, the rate of utilization was 80%, indicating the anabolic effect of testosterone. Tracer studies with radioactive calcium and phosphorus are planned to further elucidate this point.

Case 5 is a study of the effect of radiation castration in a premenopausal patient with extensive osteolytic metastases secondary to breast carcinoma. This artificial menopause induced a definite, but temporary, improvement in mineral and protein balance. It is likely that the palliation achieved was due to tumor inhibition caused by castration.

In none of the six patients with breast cancer who received testosterone during metabolic studies was a beneficial therapeutic effect achieved. Testosterone accelerated osteolysis and induced hypercalcemia in three cases. This small series cannot be used for a statistical evaluation of the efficacy of testosterone therapy. Since the purpose of the study was to define the mechanism when testosterone had an unfavorable action, four of the cases selected for study had previously had adverse effects from androgen therapy. Statistics have been submitted from other centers on the beneficial clinical effects of testosterone.[24]

From the data presented, it appears that testosterone therapy of advanced breast cancer may be most beneficial to those patients in whom it slows down tumor growth and induces recalcification of demineralized areas. A favorable response may also be expected from patients in whom the hormone improves the osteoporosis but does not affect the tumor. However, clinical and metabolic evidence is available to indicate that androgen or estrogen may accelerate tumor growth. In these instances, a more rapid downhill course may result from hormonal administration, with pain, anemia, hypercalcemia, tendency to fracture, and accelerated growth of metastases. There does not appear to be any specific criteria that will enable prediction of the therapeutic response to testosterone in a given patient with breast cancer. Therefore, precaution in the administration of hormonal therapy is indicated, with close clinical and laboratory follow-up.

SUMMARY

1. To study the action of testosterone under controlled conditions, metabolic experiments were performed in six patients with breast cancer with osteolytic metastases.

2. Control studies were also performed in three patients with extensive osteolytic malignancy. Testosterone was administered to a patient with leiomyosarcoma. Diethylstilbestrol, and later testosterone, was administered to a patient with multiple myeloma. A premenopausal breast cancer patient received x-ray castration.

3. Testosterone induced accelerated osteolysis and hypercalcemia in three patients with breast cancer.

4. Testosterone induced nitrogen retention in the patient with leiomyosarcoma, with minimal improvement in calcium balance.

5. Diethylstilbestrol improved the mineral balance of the patient with multiple myeloma. Testosterone induced nitrogen retention, with slight improvement of the mineral balance.

6. X-ray castration of the patient with breast cancer temporarily improved the mineral balance.

7. The mechanism of these favorable and unfavorable responses to alteration in the hormonal balance has been discussed.

Patient-Physician Relationship.—The essential ingredient of a lasting patient-physician relationship is time, time skilfully apportioned so that the garrulous are not allowed more nor the inarticulate allotted less. When we begin to hurry our patients the bond that is normally strengthened through listening and understanding is weakened. And when we introduce production line methods we are no longer physicians, just licensed pill-peddlers.

The sick sense being hurried and resent it. More than anything else they want us to grant them the warm sympathetic hearing they deserve. Denied this, they search elsewhere, anywhere, for an attentive ear.

To trim time solely to see more patients per day is to develop in the direction of greater mechanical efficiency and lesser diagnostic proficiency and the net result is that patient satisfaction shrinks as time spent is reduced.—W. S. Reveno, ℞ Time, q. s., *Detroit Medical News,* March 17, 1952.

COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION

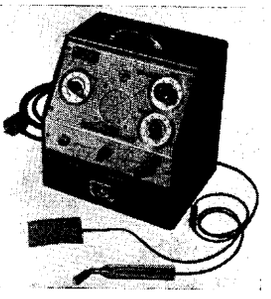
The Council on Physical Medicine and Rehabilitation has authorized publication of the following reports.

RALPH E. DE FOREST, M.D., *Secretary.*

SANBORN ELECTROPHRENIC RESPIRATOR ACCEPTED

Manufacturer: Sanborn Company, 39 Osborn St., Cambridge 39, Mass.

The Sanborn Electrophrenic Respirator is a generator of electric currents designed to stimulate the phrenic nerves and thus induce contractions of the diaphragm in apneic patients. It operates by connection with a source of 60-cycle alternating current at 115 volts. It is provided with a dispersive electrode which is applied to the patient's back and an active electrode which must be applied with pressure over the phrenic nerve in the neck. The electrical apparatus is housed in a portable case weighing 5.5 kg. (12 lb.) and measuring 25 by 24 by 20 cm. (10 by 9½ by 8 in.). Packed for shipping it measures 30.5 by 38 by 38 cm. (12 by 15 by 15 in.) and weighs 6.8 kg. (15 lb.). The foreign shipping weight is 15.9 kg.



Sanborn Electrophrenic Respirator

Evidence from sources acceptable to the Council indicated that even submaximal stimulation of one phrenic nerve by this device could provide adequate pulmonary ventilation, and that in the hands of properly trained persons under the supervision of a physician, especially under hospital conditions, the device was a means of supplying artificial respiration. Although the Council recognized the existence of certain difficulties in application of the method, the apparatus itself was found to be technically sound.

The Council on Physical Medicine and Rehabilitation voted to include the Sanborn Electrophrenic Respirator in its list of accepted devices with the express understanding that it should not be used for first aid by lay groups (such as fire departments) nor for the prolonged care of apneic patients, but that it is a satisfactory means of resuscitation when used under the direct supervision of a physician.

HEALTH RESORT FACILITIES OF WHITE SULPHUR COMPANY OF SHARON SPRINGS ACCEPTED

Operating Agency: White Sulphur Company of Sharon Springs, N. Y., Inc., Sharon Springs, N. Y.

The White Sulphur Company of Sharon Springs, N. Y., Inc., operates an extensive system of bathing establishments in Schoharie County. The distinctive natural resources is a mineral water containing a relatively high percentage of hydrogen sulfide. The management considers this institution essentially as a bathing establishment, there being no hospital connected with it. There is no laboratory and no roentgen ray department, and the physical therapy includes primarily baths, Scotch douches, and massages. Recreational facilities are offered both by the institution itself and by the community in cooperation with the institution.

The Council obtained evidence that the medical supervision was adequate and that the baths were not being exploited by cultists. Most of the patrons come without any desire for medical attention and without any expectation that the baths will give anything more than an enhanced feeling of well-being. The waters are not being promoted with therapeutic claims. The Council on Physical Medicine and Rehabilitation voted to include the Health Resort Facilities of the White Sulphur Company of Sharon Springs, N. Y., Inc., in its list of accepted health resorts.