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The Effects of Orchiectomy on Primary and Metastatic Carcinoma of the Breast

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For over two score years there has been an increasing interest in the effects of oophorectomy on mammary carcinoma, both primary and metastatic. For more than half of that period the medical literature on radiation therapy has seen a substantial increase in the bibliography on radiation castration for metastatic breast cancer, more especially as regards the effects of such a procedure on the secondary deposits in bone. The encouraging regressions of the skeletal metastases from mammary carcinoma following castration in women, still menstruating, have suggested the possibility that orchiectomy might retard or even cause regression of mammary cancer in the male—both in the primary and metastatic lesions. The latter experiment was begun more than two years ago at the Memorial Hospital and was noted in a preliminary report four months after the first patient was orchiectomized. Because of that result

other cases for such therapy by surgery have been collected.

In 1942 Farrow and Woodard¹ were led to observe the effects of the administration of androgens and estrogens on the serum calcium in patients with skeletal metastases from breast cancer. Impressed by the favorable results obtained in the retardation of the growth of osseous metastases in mammary carcinoma by radiation castration, they studied the effects of “chemical castration” by the injections of testosterone propionate. They found that the three patients who received such therapy had developed increased blood calcium in the urine. The chemical changes were accompanied by clinical and roentgenographic evidence of increased activity in the metastatic disease in bone. The administration of estrogens was found to produce a similar effect. They inferred, therefore, that the ability of the male and female sex hormones to cause hypercalcemia in such cases was due to the stimulation by the hormones of the growth of the metastatic tumor. However, this finding is at variance with the observations of Dobriner and of Abels² who administered to each of two patients a total of three

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grams of both crystalline testosterone and testosterone propionate without producing a stimulating effect on the primary or metastatic disease or increasing significantly the calcium level of the blood.

The observations that the use of androgens and estrogens in women with breast carcinoma was deleterious, the numerous favorable results in inoperable and metastatic carcinoma produced by X-ray castration and the older reports on surgical castration for inoperable breast cancer, suggested that castration be tried in males. Farrow and Adair³ observed the results of orchiectomy on osseous metastases from breast carcinoma. Their patient has been reported previously, but only four months after operation, and is the first of the six subjects in the present communication. Enough time has now elapsed to evaluate fully the overall effects of orchiectomy. At the time orchiectomy was performed the clinical classification of the six cases under report was primary operable, one; prophylactic, one; recurrent inoperable, one; primary inoperable, three.

The consent for orchiectomy, even in the elderly male with advanced breast cancer was most difficult to obtain. It appears to be a triumph of medical persuasion to obtain permission for this operation. Even an elderly male with the intense pain from osseous metastases was unwilling to undergo castration. The female who in her psychological make-up expects the climacteric at one time or another is more easily persuaded to submit to oophorectomy than is the male who rarely, if ever, expects a complete cessation of his sexual functions. It seems to be more difficult to obtain permission for castration in males suffering from mammary cancer than in malignant disease of the prostate.

The Clinical Results of Bilateral Orchiectomy

The following summary has been based on an analysis of the six patients who had bilateral orchiectomy and whose histories are analyzed in the Table.

To date no data on laboratory animals have been found which parallels the pres-

ent clinical study. If it did exist we believe that such studies would be inconclusive for we may reasonably infer that there exists at present no relationship between animal research and human experiment in such a problem.

We must call attention to the relatively small number of male patients with mammary cancer available in the clinic. From this group a smaller number have been considered suitable for the type of therapy under report. And from these few an even smaller group have been obtained who would consent to undergo surgical castration.

One may reason that if the procedure is of value in inoperable cases of male breast carcinoma, it might prove a beneficial form of therapy alone, or as an adjunct measure in the treatment of operable breast cancer in the male. We cannot as yet justify it.

Summary

In summarizing this group we may comment briefly on Case 2, the primary operable patient who became inoperable about seven months after radical mastectomy. He was treated with progynon after orchiectomy was refused and osseous metastasis had appeared. He had an associated cirrhosis of the liver. When the pain from the metastatic deposits in bone became unbearable he agreed to castration. The operation was performed under local anesthesia without incident, but the patient died suddenly three days after orchiectomy. Obviously the effects of castration could not be studied in this case.

In Case 5, the patient, a young man of 39 years admitted to the clinic with widespread disease of the skeletal system and intense pain, submitted to bilateral orchiectomy, surviving for four months. In the postcastration period there was no relief of pain and no evidence of reparative change in the skeletal metastases. It may be that his comparative youth, contrasted with the four older males in this group who have had favorable clinical responses, may be the reason for the unsatisfactory result. Cancer of the breast in the young, female or male, is always a formidable

TABLE.

Case	Clinical Classification	Mammary History	Pathology	Physical Findings on Admission	Treatment
1. M.S. Age 72, White, Italian, Catholic. Married, 2 children. Date of admission: 4-28-41	Primary inoperable, left	Ulcer of nipple, 4 mos. Mass 5 by 6 by 2 cm. Axillary nodes	2-9-42 Formal biopsy: infiltrating carcinoma — Grade II	Nipple and areola destroyed. Remained away 9 mo. after mastectomy was advised	None except orchiectomy
2. J.S. Age 75, White, English, Protestant. Married, 6 children. Date of admission: 6-10-41	Recurrent inoperable, right	Lump 1 yr. Mass 6 by 4 cm. Axillary nodes	7-1-43 Infiltrating carcinoma, Grade III. Multiple node metastases	Ulcerating lesion with involved nodes	Radical mastectomy 7-1-41. Progynon 228,000 R. U. 7-23. 8-18-42: orchiectomy
3. B.D. Age 65, White, Austrian, Jew. Married, 1 child. Date of admission: 4-13-42	Prophylactic, right	Local excision 15 years before axillary dissection, 2-23-42	2-23-42 Infiltrating duct carcinoma, Grade II	Granulating scar — radical axillary dissection. No recurrence.	Excision and axillary dissection elsewhere. Post-operative radiation and orchiectomy
4. A.I. Age 64, White, Irish, Catholic. Married, 1 child. Date of admission: 6-1-43	Primary operable, left	Lump in breast, 3 weeks. Hydrocele 3 years (bilateral)	6-12-43 Local excision: adenocarcinoma	Lump in left breast 2 cm. No nodes	None except local excision. Axillary dissection. Orchiectomy
5. E.S. Age 39, White, Irish, Catholic. Married, 2 children. Date of admission: 10-15-43	Primary inoperable, right	Lump 2 by 1½, right breast, 6 months. Loss of 8 lbs. Bilateral axillary nodes	10-18-43 Aspiration biopsy: carcinoma	Lesion with skin attachment. Several nodes. Back pain	None except orchiectomy
6. A.P. Age 63, White, German, Catholic. Married, 2 children. Date of admission: 2-1-43	Primary inoperable, left	Lump left breast 7 mo. duration, 5 by 4 cm. Slight nipple ulceration. Cutaneous nodules. Axillary mass 5 by 4 cm.	12-1-43 Aspiration biopsy: carcinoma	5 by 4 primary, 5 by 4 axillary mass. Cutaneous nodules	None except orchiectomy

Blood Chemistry						Pathological Report on Testes	Course	
X-ray Studies	Date	Cal-cium	Phos-phorus	Alkaline Phos-phatase	Date Castra-tion			
4-30-41, negative	2-5-42	10.5	3.62	5.9		Atrophy and interstitial cell hyper-plasia	Remarkable clinical regression of primary lesion with bone regeneration. Return to normal of blood chemistry. Questionable relapse.	
1-30-42, widespread					2-9-42			
4-4-42, no change	2-17-42	10.6	4.00	7.0				
5-28-42, rib fractures healed	5-25-42	11.0	4.20	11.1				
6-17-42, evidence of calcification	6-22-42	10.9	4.06	7.1				
6-22-42, 8-24-42, continued improvement	1-21-43	10.6	3.80	3.5				
5-24-43, no change	11-12-43	10.8	3.40	2.8				
3-17-44, no change	3-17-44	10.7	3.50	3.8				
5-25-44, ? reactivation	5-18-44	11.5	3.54	5.5		Slightly atrophic testes	Had cirrhosis of liver. Operative death 1-30-43. Estrogens reactivated?	
6-13-41, negative								
2-26-42, skull	2-26-42	11.2	2.39	5.4				
3-27-42, rib, spine, pelvis	6-18-42	10.9	3.89	7.6				
6-20-42, widespread								
7-17-42, increased	7-17-42	11.4	4.58	9.9				
8-7-42, increased	7-28-42	11.6	4.62	8.6				
12-28-42, increased right lung	8-17-42	14.4	3.80	10.9				
	1-18-43	11.8	4.40	11.6		1-27-43	Mild atrophy	Gain in weight of 40 pounds. No pain. X-rays show bone regeneration.
5-27-42, ? 12D., 1-3-4L.	6-1-42	10.3	2.92	4.2				
	8-10-42	10.2	3.10	4.8				
8-24-42, positive 12D; 1-2-3L.	4-8-43	11.4	4.18	4.7				
	4-30-43	10.3	3.56	6.6				
					5-8-43			
	7-12-43	10.8	3.10	3.7				
	2-7-44	11.8	3.39	2.6				
Chest negative. No symptoms of bone metastasis	NONE				6-12-43	Normal testes	Axilla not dissected until 10 months after excision. No metastasis.	
10-15-43, ribs	10-18-43	12.6	3.72	7.8		Essentially normal testes	Died April 4, 1944 of disease.	
11-22-43, skull and pelvis	11-22-43	11.4	5.24	8.1				
	12-9-43	15.2	5.12	13.7	12-8-43			
12-30-43, widespread	12-13-43	13.6	5.07	11.5				
2-21-44, increase	12-20-43	13.0	3.07	9.4				
3-20-44, increase	12-30-43	11.2	5.12	22.2				
	2-21-44	11.8	5.54	19.8				
	3-20-44	12.0	4.36	38.8				
10-1-43, pulmonary more marked on right	12-1-43	12.5	2.90	3.4		Slightly tubular atrophy. Spermatogenesis present. Interstitial cells normal	Breast tumor slightly smaller. Nodes unchanged. Pulmonary disease less. Pelvic metastases present on admission have not increased.	
	12-27-43	11.2	3.40	—				
	1-7-44	11.1	3.58	—	1-19-44			
3-1-44, increase	3-23-44	12.1	3.60	2.3				
3-31-44, decrease?	4-27-44	—	4.18	2.3				
5-24-44, pelvis positive. Lung less marked	5-5-44	12.2	3.52	4.0				

therapeutic problem. It may likewise be significant that his alkaline phosphatase was the highest preoperative value of any of the patients in this group—8.1 units. He also had the highest initial postoperative value of alkaline phosphatase—13.7 units. At no time did this reading approach the normal value and the last phosphatase determination showed a reading of 38.8 units. The procedure in this instance must be considered a clinical failure. Of the group of six castrates, he is the outstanding failure.

In Case 1, a 72-year-old male with widespread metastases to bone, was castrated on February 9, 1942. He had prompt relief from pain and has been comfortable since that time. Skeletal metastases have shown marked reparative change; all the pathological fractures in bone having healed with a firm callus which subsequently ossified. His general condition is good; he is in an excellent state of nutrition; the blood chemistry has returned to normal. One of the most striking results in this case has been the continued regression in the primary cancer of the left breast. The ulcerating tumor has now been completely replaced by a cicatrix. However, at the present time there is some question of reactivation especially in the skull. Twenty-eight months have elapsed since castration.

In Case 3, the patient submitted to castration on May 8, 1943, and was relieved promptly of the pain caused by metastases to the lower dorsal and lumbar vertebrae. While his blood chemistry never showed an abnormally high rise, his preoperative alkaline phosphatase of 6.6 units now is 2.6 units. X-ray films show evidence of bone regeneration. There has been a gain in weight. No evidence of local recurrence is noted nor are there new areas of metastasis and the pain has been completely relieved—a very gratifying clinical result 13 months after bilateral orchiectomy.

The third case with a favorable result has now gone one year after castration. He was the only primary operable patient in the group and his breast cancer was treated only by local excision and bilateral orchiectomy.

This unusual approach to the control of mammary carcinoma in the male has resulted in the following observations: (1) A radical axillary dissection 10 months after local excision and castration revealed no evidence of metastasis to the axillary nodes. (2) There has been no recurrence at the site of the local excision and the patient has not developed distant metastatic areas to date. However, one cannot be certain that local excision alone might have controlled the tumor process.

In Case 6, patient was castrated in January 1944, following the discovery of definite pulmonary metastases on his initial visit to the clinic. Five months after operation there has been a noticeable decrease in the extent and character of the pulmonary metastases. A single area of bone destruction in the crest of the right ilium has shown no further progression. The primary tumor in the breast has shown moderate healing and regression, but the axillary metastases have as yet shown no signs of alteration. There have been no significant changes in the blood chemistry. The patient has maintained his weight and is in good general condition.

Metabolic Effects of Orchiectomy

It is now a common observation that after orchiectomy, patients with carcinoma of the prostate which has metastasized to bone often show considerable clinical improvement. This benefit, as a rule, consists of a marked decrease of pain at the sites of skeletal metastases, increased appetite, gain in weight and muscular tone. Improvement of this nature, likewise, was noted to occur after operation in four of the six patients with breast cancer included in the present study.

The symptomatic change after orchiectomy most likely is related to the hormone imbalance effected by the surgical procedure. The nature of this imbalance is not, of course, clear, but it is reasonable to believe that metabolic changes are affected by a decreased androgen formation or overactivity of naturally occurring estrogens. The latter assumption appears

all the more likely since the administration of estrogens to patients with prostatic cancer metastatic to bone in many instances is attended by equal or better success than that induced by orchiectomy.⁴ Since the administration of certain estrogens and other related steroids apparently can induce characteristic metabolic changes, these alterations were sought for after orchiectomy in two of the six men with breast cancer and in an additional three patients with carcinoma of the prostate.

In particular, measurements were made of the effects of the surgical procedure on:

A. Fluid and electrolyte balance. Previous studies from this hospital have demonstrated that the administration of α -estradiol benzoate to women before and after the menopause and to men with prostatic cancer induces a significant rise in both extracellular water and plasma volume.⁵ It is interesting to note that a similar change results from the administration of large amounts of testosterone and testosterone propionate.⁶ However, from 12 to 18 days after orchiectomy no significant change had occurred in the volume of extracellular water or plasma in two patients with cancer of the breast and one patient with carcinoma of the prostate. Likewise, in the two remaining patients with prostatic carcinoma in whom these measurements were made only three months after operation, the values obtained were within normal limits. Furthermore, orchiectomy apparently had no persistent effect on the concentrations of sodium, potassium, calcium, bicarbonate, phosphate, or chloride in the serum of the patients studied.

B. Nitrogen balance and protein fabrication. The now well known effect of certain androgens (principally testosterone and testosterone propionate) to induce nitrogen retention⁷ suggested that a temporary negative nitrogen balance might be obtained in males subjected to castration. In a group of three individuals studied here (two with carcinoma of the breast and one with carcinoma of the prostate), nitrogen balance studies were made for from 12 to 18 days before and for a like period after operation. No change in ni-

trogen balance was found to have occurred in this time. The total circulating protein of these individuals, likewise, remained unaltered.

C. The urinary excretion of creatine. Since testosterone and methyl testosterone especially appear to exert a considerable influence on the urinary excretion of creatine⁸ there was reason to believe that this function might be effected by the castration. This was not found to be the case in the two patients with breast cancer and the one patient with carcinoma of the prostate. Likewise, the two other individuals with prostatic tumors excreted only normal amounts of creatine.

D. The utilization of carbohydrate. There is no satisfactory evidence that hormones particularly potent as androgens or estrogens exert an influence on carbohydrate metabolism as do corticosterone or certain other steroids of adrenal cortical origin. Nevertheless, it appeared to be of interest to ascertain whether or not the hormone imbalance conceived to occur after orchiectomy might be reflected in an unusual carbohydrate utilization.

Accordingly, two patients with carcinoma of the breast and one patient with carcinoma of the prostate were maintained on consistent diets as described by Thorne.⁹ When these subjects were in nitrogen balance, an estimation of their carbohydrate metabolism was obtained from their intravenous glucose tolerance curves both before and after orchiectomy. These measurements, made by the technique described by Thorne and associates,⁹ failed to indicate any change in carbohydrate utilization after operation.

Summary

It would appear, therefore, that of the metabolic phases measured, none changed significantly in the 12 to 18 days after orchiectomy in the patients studied. Changes known to be induced by testosterone or α -estradiol apparently do not occur simultaneously with clinical symptomatic improvement in patients subjected to orchiectomy.

Biochemical Effects of Orchiectomy

Before the blood chemical findings on the present cases are discussed, it will be well to review the general significance of chemical changes in patients with cancer metastatic to bone. Alkaline phosphatase is produced in large amounts in bones which are attempting to repair damage. When cancer of soft part origin metastasizes to bone, the bone may or may not respond to the injury with the production of new osseous tissue. When an attempt at repair is made, the alkaline phosphatase of the serum rises and the metastases are osteoplastic. When, as in the majority of bone metastases from carcinoma of the breast, no attempt at repair is made, the alkaline phosphatase of the serum remains normal, and the lesions are osteolytic. If the process of bone destruction is very rapid, the calcium and phosphorus of the serum may rise to high, or even dangerous, levels. Thus the alkaline phosphatase of the blood may be taken as an index of the rapidity of bone formation, and the calcium and phosphorus of the blood as an index of the rapidity of bone destruction.

We have shown elsewhere¹ that treatment with either testosterone propionate or with estrone caused an increase in the serum calcium of female patients with carcinoma of the breast metastatic to bone. The increase was apparently due to increased osteolysis caused by rapid growth of the tumor in the bone. It did not occur in patients with breast cancer who were without bone metastases.

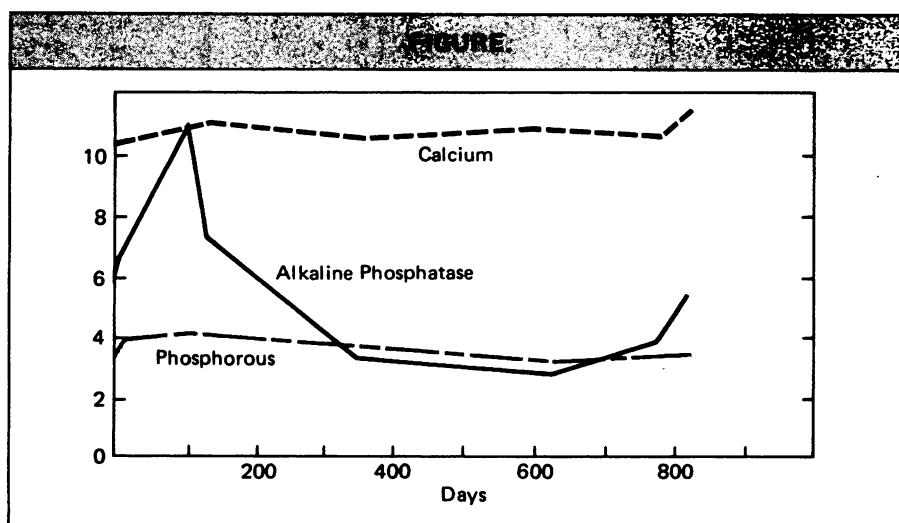
Several investigators^{4, 10, 11} have found that, when patients with carcinoma of the prostate metastatic to bone are orchiectomized, the serum alkaline phosphatase, which is usually elevated before treatment, rises still higher. In our series, this rise occurred in two-thirds of the cases. A similar rise was observed in patients treated with stilbestrol, but only in about one-fourth of the cases. The increase was temporary, persisting for only two or three months, and was followed by a drop to or below the initial level. The increase in the serum alkaline phosphatase was usually associated with an increase in the degree of osteoplasia of the bone lesions,

but in some patients this appeared to indicate healing, while in others the metastatic lesions became larger and more numerous.

It seems probable that the regenerative capacity of the injured bone is stimulated by some one of the many endocrine changes associated with castration. The effect is not confined to the male sex, since we have also seen it in female patients with carcinoma of the breast who have undergone either surgical or roentgen castration. The mechanism of this stimulation remains obscure.

Of the patients forming the subject of the present report, Case 1 showed changes in serum alkaline phosphatase very similar to those commonly seen in castrated patients with carcinoma of the prostate metastatic to bone. The alkaline phosphatase was slightly elevated at 5.9 units per 100 cubic centimeters before castration, began to rise immediately after operation, and reached 11.0 units in three and a half months. It then dropped, reaching normal in one year and remaining within normal limits for another year. There was no striking increase in the degree of osteoplasia of the bone lesions, but the process was arrested and some healing took place. The serum calcium and phosphorus were within normal limits throughout, indicating that the rate of bone destruction was never very rapid. At present, 28 months after castration, the serum alkaline phosphatase has risen slightly, and there are X-ray indications of possible relapse. The chemical changes are shown in the Figure.

In Case 2 there was considerable elevation of the serum alkaline phosphatase throughout the period of observation. The patient probably had cirrhosis of the liver, and, in liver disease, alkaline phosphatase may be retained in the blood, instead of being excreted in the bile, as it normally is. Hence, in this case, the level of serum alkaline phosphatase cannot be taken as an index of bone activity. The serum calcium, however, showed a highly significant rise during α -estradiol therapy. Before treatment the serum calcium was normal, varying between 10.9 and 11.4 milligrams per 100 cubic centimeters on three determinations. It began to rise immediately



on the beginning of treatment, and reached 14.4 milligrams per 100 cubic centimeters in two weeks. Treatment was then discontinued, and the calcium fell slowly to 11.0 milligrams. The rise in serum calcium was probably due to increased osteolysis caused by the acceleration of the growth of the metastatic tumor under the influence of α -estradiol.

In Case 3, patient showed occasional slight elevations in serum alkaline phosphatase and serum calcium, but the changes were too small to be significant.

In Case 5, patient showed, prior to castration, elevations in serum alkaline phosphatase (7.4 to 13.6 units per 100 c.c.), in serum phosphorus (3.2 to 5.1 mgm. per 100 c.c.), and in urinary excretion of calcium (420 to 580 mgm. every 24 hours). This appeared to indicate that osteolysis was rapid, as was also shown roentgenographically, but that some attempt at bone repair was being made. Immediately after castration there was a shift toward normal in all chemical findings, but this change lasted for only two weeks, after which there was a reversion to, or above, the former high levels. Simultaneously there was a deterioration in the clinical condition

of the patient. It is not clear whether the rise in alkaline phosphatase was a response to castration or whether it was caused by the increased activity of the metastatic deposits in the bones.

In Case 6, patient developed bone metastases late in the period of observation. His blood chemistry was normal except for a persistent borderline elevation in serum calcium. The elevation was too small to be considered definitely pathological.

Determinations of serum acid phosphatase were made at intervals on these patients, and no abnormalities were found. This was to be expected, since, as far as is known at present, serum acid phosphatase is never increased except in the presence of metastasizing carcinoma of the prostate.

Conclusion

We may summarize the clinical results of this study by stating that bilateral orchiectomy may have been responsible for the temporary regression of the primary lesion in two instances, quite striking in one of the cases. It has possibly prevented recurrence in the primary operable patient treat-

ed only by local excision, and may have prevented local recurrence in one other instance. The procedure has caused regression and repair in the secondary deposits in bone as well as in lung. The clinical regressions in this study compared with those reported for inoperable and metastatic carcinoma of the prostate have had in some cases the same dramatic cessation of pain caused by bone involvement. The clinical improvement has been as satisfactory and as long. In fact, we think this procedure for male breast cancer may parallel the striking results of orchiectomy for the advanced cases of prostatic cancer. One inoperable case has now survived 28 months after castration, and one 13 months. Both are in excellent states of nutrition and are free from pain. Two have lived for nearly six months with regression of their disease and give clinical promise of surviving for equally long periods. Two of the patients have shown definite reparative changes in metastatic deposits in bone, while one with a solitary area of bone involvement has shown no evidence of progression of the disease, nor have other areas developed since castration. This latter patient has had regression in the extent of his pulmonary metastases: in two instances the primary lesions have become smaller. The case of longest survival shows only a cicatrix, and the other, regression in the ulceration and in the cutaneous nodules. The latter patient has not survived long enough to evaluate properly the effect of orchiectomy on the breast tumor.

In the histological examination of the testes of the six orchiectomized patients, essentially normal gonads were found. The mammary cancer had not metastasized to the testicles. This is in striking contrast to the findings in 33 women who were castrated for therapeutic control of breast cancer. In this group, nine patients had mammary carcinoma metastatic to the ovaries.

The studies on two of the orchiectomized patients led to a conclusion that of the metabolic phases measured—(1) fluid and electrolyte balance; (2) nitrogen balance and serum protein fabrication; (3)

urinary excretion of creatine; and (4) the utilization of carbohydrate—none changed in 12 to 18 days after operation. This failure to demonstrate changes known to be induced by the administration of testosterone or α -estradiol, shows that these changes are not necessary to produce clinical symptomatic improvement.

In one castrated patient the same changes in the serum alkaline phosphatase were seen which were observed regularly in patients with carcinoma of the prostate metastatic to bone following orchiectomy. In two castrated patients there were no conspicuous changes in the calcium, phosphorus, or alkaline phosphatase of the serum, and in one the findings indicated continuing progress of the disease. In the patient treated with α -estradiol there was a rise in serum calcium similar to that found in female patients with bone metastases from carcinoma of the breast who have received estrogens. Thus, in this small series of patients, there is a marked lack of uniformity in the response to endocrine treatment of the blood changes caused by bone metastases. Further observation will be necessary before the cause of this variability can be determined.

We must call attention to the small number of cases under report. The value of the procedure will only be determined by observations on a larger group. @

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