HORMONE THERAPY IN MALIGNANCIES

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HORMONE therapy in the treatment of cancer is useful for two purposes: (1) as a palliative in incurable cases; (2) for study of the behavior of cancer in an attempt to understand its natural history. It is never curative and for that reason should not be depended upon when surgical removal of the primary lesion can be accomplished before metastases have occurred. There are perhaps some exceptions to this rule; for example, as a therapeutic measure for patients severely ill with some other incurable ailment or in the aged patient whose life expectancy is limited. This therapy may be dangerous if misused. Its action is not well understood. Even though cures are not produced it may, nevertheless, relieve pain, improve health temporarily, and prolong life in some patients.

Hormonal therapy may be regarded solely as hormonal administration or it may be accepted as indicating manipulation or withdrawal of existing hormones in some cases. We shall consider both aspects briefly in relation to breast and prostatic cancer.

Castration and Cancer of the Breast in Women

As early as 1886, Sir George Beatson[1] recommended oophorectomy as a treatment for cancer of the female breast. Adair[2] has recently estimated that it is useful in 15 to 30 per cent of patients with recurrent or metastatic disease. Little or no response is to be found in lymph gland metastases or in the primary tumor. X-ray castration may be capable of causing definite regression in pulmonary metastases temporarily. A good result brings relief from pain, increase in appetite and weight, regression of bone metastases and, occasionally, pulmonary metastases. Although always transient, desirable effects may persist for a year.

Castration of men for cancer of the male breast is often followed by good results.[3,4,5,6,7] It is claimed that such effects are even more striking than for carcinoma of the prostate. Interestingly, in contrast to women who are more likely to obtain the best results in younger years, men are more often benefited by this treatment if they are over 60.

Administration of Estrogens for Breast Cancer

Haddow,[8] in 1944, used trichlorphenyl ethylene, triphenyl methyl ethylene and stilbestrol in 73 patients with breast cancer. With the first compound there were good responses in 10 of 22 patients treated and, with stilbestrol, improvement in 5 of 14 treated, or approximately half of the patients in each group.

In 1944, 10 British observers[9] reported their results with estrogens in the treatment of 168 cases of mammary cancer. The most striking fact arising from the study was that the response proved vastly superior in women over 60 years of age. This observation is supported by the most recent report of the Therapeutic Trials Committee's Subcommittee on steroids.[10]

My observations regarding the use of steroids[11] in the treatment of breast cancer are based on the results of many investigators among whom are Adair,[2] Farrow,[3] Nathanson,[12,13] Huggins,[14] and Vest[15] in this country, and Haddow,[8] Fergusson[16] and others in England. In addition, I have relied upon the most recent report on the subject for many of my statistics. This is the third analysis of all cases treated by participating investigators under the direction of the Subcommittee on Steroids and Cancer of the American Medical Association. The data were analyzed under the supervision of Dr. Walton Van Winkle October 27, 1950.

Regarding the Choice of Estrogen

Stilbestrol has been used extensively and, in general, is more practical because it is effective orally and is inexpensive. In addition, there is little to suggest the superiority of any other estrogen. Among 695 patients treated with various steroids, it appeared that ethinyl estradiol had a better effect in causing regression of soft tissue lesions; even here it is not certain that its advantage of 67 per cent compared to 53 per cent for stilbestrol would not have been less obvious had dosages been equalized.

An attempt has been made to determine the optimum dose. With stilbestrol, subjective improvement is much greater after the total dose has reached 2.0 Gm. than with lower doses. Objective changes in the primary lesion, soft tissue and bony lesions require larger total doses. In these cases good results are about doubled when the dose rises over 4.0 Gm. total. It is obvious that, when the commoner dose of 15 mg. per day is used, it takes 4 months to reach 2.0 Gm. and 8 months to reach 4.0 Gm. Patients treated for more than 6 months have, on the whole, done decidedly better than those treated for a lesser interval. Here again it is difficult to know whether the amount of the drug is the important factor or whether, for example, patients with milder disease live longer independent of treatment. The facts suggest that doses as large as 30 mg. per day or more are worthy of a trial.

In considering estrogen therapy for cancer of the breast (table 1) age is such an important factor that it is useless to consider treatment in a patient under 50 years of age, skeletal lesions being of the utmost consequence. No example of improvement in skeletal metastasis has been seen following estrogen therapy in a premenopausal woman. Before the menopause, estrogen has no advantage over androgens in controlling soft tissue lesions which are greatly influenced in about 23 per cent of patients by either testosterone or stilbestrol. However, after the menopause conditions change, primary and other soft tissue lesions respond much better to estrogens than to androgens.

Regression or healing of bone metastases is obvious after androgens in only

Table 1

REGRESSION OF BONE LESIONS COMPARED TO SOFT TISSUE LESIONS BEFORE AND AFTER MENOPAUSE

Preparation	Bone Lesions		Soft Tissue Lesions	
	Per Cent Premen.	Regression Postmen.	Per Cent Premen.	Regression Postmen.
Testosterone propionate	10%	14%	24%	22%
Diethylstilbestrol		14%	22%	53%
Ethinyl estradiol		10%		67%
Premarin		16%		44%

Table 2

RELATION OF AGE TO SURVIVAL IN BREAST CANCER

Mean Time from Admission to Death		
Age	Estrogen	Testosterone
20 - 29		9.0
30 - 39	10.0	8.5
40 - 49	7.6	7.5
50 - 59	9.7	9.2
60 - 69	9.1	9.3
70 - 79	10.6	7.4
80 - 89	12.3	
Mean	9.8 mos.	8.5 mos.

10 per cent of premenopausal patients and subsequent to androgen or estrogen therapy in about 15 per cent of patients having experienced the menopause.

One of the most striking clinical changes is the healing of large ulcerating carcinomata. In some patients the healing is complete with epithelialization and a contracture of tissue suggesting cicatrix formation. Almost complete disappearance of lung metastases, according to x-ray, may be demonstrated following estrogen therapy. In some, surprisingly, improvement continues many months after cessation of treatment even though little change had been evident during therapy (fig. 1a and b).

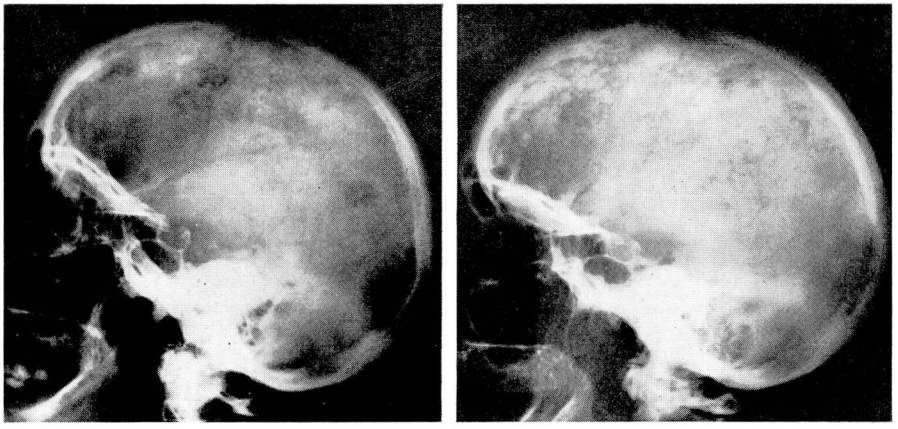
The individual response is difficult if not impossible to predict, and apparently is not related closely to the type of carcinoma present.

Life expectancy varies greatly after initiation of therapy. With estrogens, it relates to the age of the patient, the older person having a greater period of survival; with testosterone this is not apparent (table 2).

A year's survival time is considered to be a reasonable estimate, although some patients live 25 months or longer. Interestingly, the persons who have survived the longest are those with lung metastases which have regressed.

Common untoward effects of stilbestrol, some of which may at times interfere with its use, are listed in table 3 together with the approximate frequencies of occurrence. Despite preconceived opinion, further studies have shown that the various estrogens differ little in these respects.

Hypercalcemia occurs with estrogen therapy less frequently than with androgen therapy. Serum calcium levels should be determined in any patient for whom steroid hormone therapy is indicated, as hypercalcemia may appear or increase or, in some cases, diminish and disappear during therapy (graphs 1 and 2). As the calcium falls alkaline phosphatase may rise, indicating bone healing. It may be suspected clinically if nausea, vomiting, headache, or



(a) (b)

FIG. 1. (a) Metastases to skull from carcinoma of breast following methyl testosterone, 300 mg. three times a week for 18 months, plus stilbestrol, 15 mg. daily for 3 months. (b) Striking diminution in metastases 6 months after withdrawal of steroid therapy.

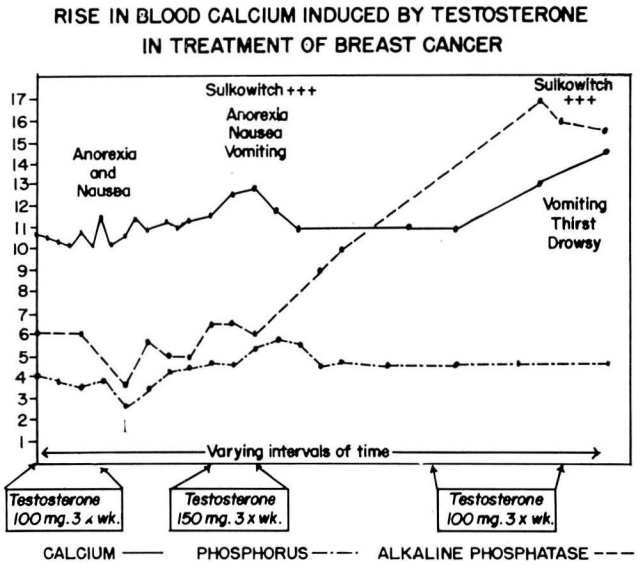
polyuria are present. It is aggravated by skeletal immobilization during severe pain, and lessened when activity is permissible due to relief of pain. It is usually associated with bony metastases but may occur in cases in which no skeletal lesions are evident. Unlike the hypercalcemia of hyperparathyroidism or vitamin D intoxication, serum calcium may reach levels as high as 20 or more with no ascribable symptoms.

Estrogen is utilized primarily for inoperable breast cancer in postmenopausal women with soft tissue or lung metastases. There is little difference in the effectiveness of various estrogens; however ethinyl estradiol may be slightly superior. A minimum of 4 Gm. should be prescribed over a period of 6 months.

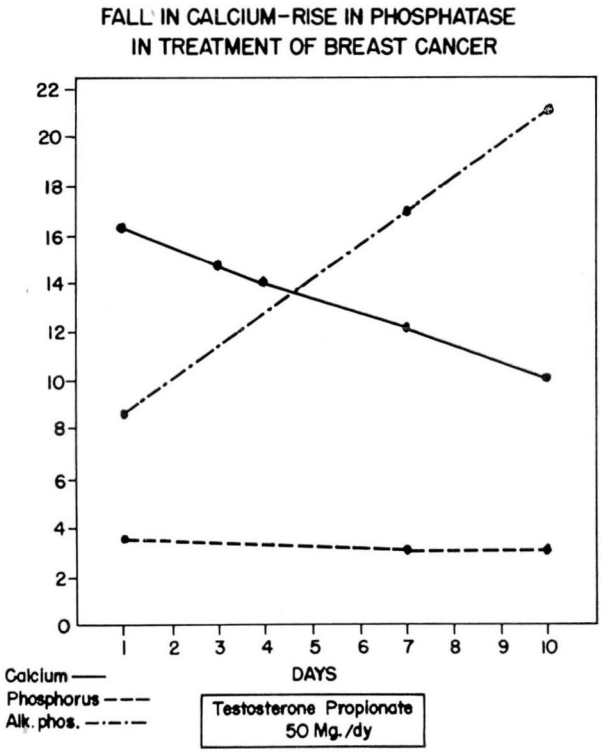
Administration of Androgens for Breast Cancer

In general, androgens have been found more useful than estrogens in the treatment of bony lesions, although soft tissue lesions are sometimes significantly benefited by androgens. As with estrogens, the result to be expected in a given patient is impossible to predict. Symptomatic response is frequently dramatic, and pain severe enough to require morphine has been almost completely relieved within 2 days in some patients. In others, persistent use of testosterone may not be followed by a good response until the hormone has been continued for 8 to 10 weeks. It is also interesting that in some instances improvement may continue for months after withdrawal of the drug.

Among the most impressive changes following testosterone therapy is the alteration in roentgen appearance of skeletal metastases. The pain may disappear with no visible change in the lesions, or the demineralized area may



Graph 1



Graph 2

become dense; even more exceptional are signs suggestive of healing in some lesions and of progression in adjacent ones. Occasionally, the entire process appears to progress with increased vigor under therapy. In some elderly patients soft tissue lesions and lung metastases may regress definitely during testosterone therapy.

During therapy, it is suggested that the levels of alkaline phosphatase in the blood be checked accurately. An increase of three to five times the original level may be seen which indicates healing of the lesions. The serum calcium should always be measured before beginning therapy and, if it is noticeably increased, treatment should be withheld or given with caution. Hypercalcemia during therapy has been found in about 10 per cent of testosterone-treated patients as compared to 3 per cent of those under estrogen therapy.

The subjective response to androgens in premenopausal women is distinctly greater than with estrogens. This is often an important consideration; even though a woman may not live longer or have a more definite objective improvement, nevertheless the androgens may give a sense of vigor and well-being which add greatly to her comfort during the months she does live.

Table 4 demonstrates the relative value of estrogens and androgens in

bringing about subjective improvement in women before and after menopause.

Interestingly, recent studies have shown that methyl testosterone given orally is just as effective in the doses used as testosterone propionate injected intramuscularly. The dose required, however, is large; i. e. a minimum of 200 mg. per day, or a dose supplying a total of 30 Gm. within 5 months. The optimum dose of testosterone propionate appears to be 50 mg. intramuscularly three times per week—a dose which supplies a total of 3.0 Gm. in 3 or 4 months' time. Larger doses have not proved more effective.

There are always undesirable effects to be expected with testosterone therapy, and the patient must be warned of these and allowed to accept or reject the treatment as she wishes. Undesirable effects which have been observed include those in the dose range advised in table 5.

Increased libido may be so intense as to be decidedly bothersome. However this symptom is noted with less frequency on extremely high doses of testosterone than with smaller ones. In patients receiving 75 mg. per week, the symptom is present in 36 per cent. It appears in 27 per cent of those receiving 150 mg. per week, and in only 19 per cent receiving 600 mg. per week.

Testosterone is used principally for inoperable mammary cancer in premenopausal women and in women with bone lesions at any age. The optimum dose is 150 mg. per week. Before abandoning the possibility of response, a minimum dose of 3 Gm. in 3 months should be prescribed.

Irradiation of the breast or metastatic lesions prior to steroid therapy lessens the sensitivity of the lesion to the steroid effects. Although Garland[17] et al recently investigated this problem, their results are inconclusive on combined irradiation and steroid therapy as an asset or detriment to a comfortable life. It was their impression that such treatment should be used serially and not simultaneously.

Castration for Prostatic Cancer

The intimate relationship of androgens to prostatic cancer was illustrated by Moore[18] who examined the prostates of 252 men who died between the ages 41 and 90 and found 20 per cent malignant. The same author, after careful search, was unable to find any record of prostatic carcinoma in a patient who had eunuchoidism or any evidence of benign hypertrophy among 28 careful autopsies on men who had eunuchoidism, eunuchism, or pituitary infantilism arising before the age of 40.

Since 1935, interest has steadily increased regarding the relationship between hormones and prostatic cancer. At that time Kutscher and Wolbergs[19] isolated prostatic phosphatase and showed that it was active in acid solution. In 1936, Gutman and Sproul[20] discovered that acid phosphatase existed in metastases from prostatic carcinoma, and it was demonstrated that this substance did not exist in the infant prostate although present normally in the adult.

Since that time, the estimation of acid phosphatase in the blood has become

Table 3

SIDE EFFECTS OF STILBESTROL IN PER CENT

	Per Cent
Pigmentation areolae	46
Nausea	33
Edema	33
Bleeding	26
Vomiting	19
Incontinence	10
Hypercalcemia	3

Table 4

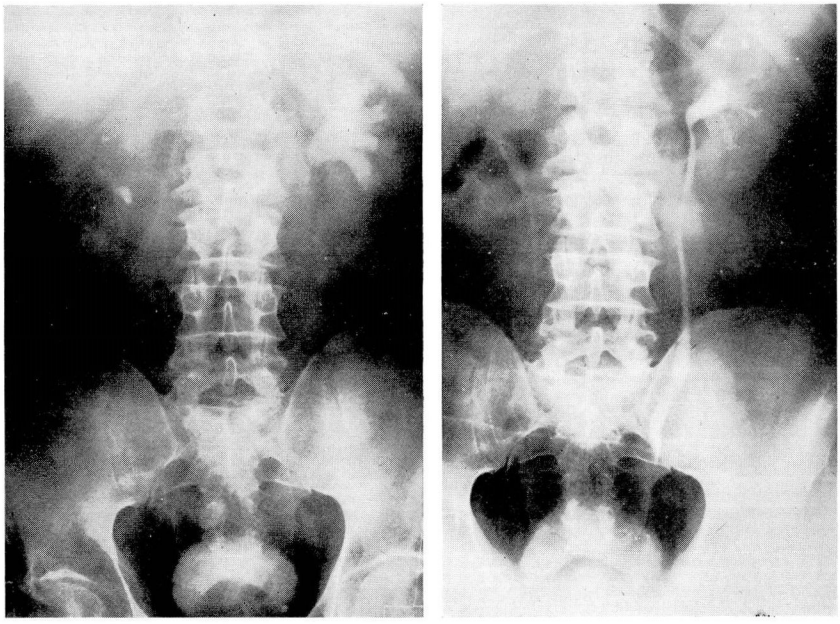
SUBJECTIVE RESPONSE TO STEROIDS IN BREAST CANCER
(740 Cases)

	Per Cent Relieved	
	Premen.	Postmen.
Testosterone propionate	51%	58%
Methyl testosterone		53%
Diethylstilbestrol	11%	39%
Ethinyl estradiol		59%

Table 5

SIDE EFFECTS OF TESTOSTERONE

With a dose of 150 mg. per week	
	Per Cent
Voice change	69
Hirsutism	65
Edema	29
Acne	29
Increased libido	27
Flushing	22
Nausea	12
Hypercalcemia	8
Vomiting	6



(a) (b)

FIG. 2. (a) Shows left hydronephrosis due to obstruction at ureterovesicle junction. Metastatic glands. (b) Marked improvement in left hydronephrosis after 4.0 mg. of stilbestrol daily for 30 days.

a diagnostic procedure of considerable value in the spread of carcinoma of the prostate. Dean[21] states that there is an increase in acid phosphatase in 73 per cent of patients in whom prostatic cancer has grown through the gland capsule. Metastases may be present, however, in some cases in which the acid phosphatase level is normal. Alkaline phosphatase, conversely, is high in nearly all cases of metastases of prostatic cancer to the bone, indicating the activity of bone defense. It may be high also in liver disease.

The experimental work of Huggins[11] has served as a great impetus in this field. Especially impressive was his demonstration that, in dogs in which the prostate was isolated from the bladder, androgen treatment caused a metaplasia of the prostate cells simulating cancer while estrogen treatment restored the gland to normal.

Following this, orchiectomy became a popular treatment for cancer of the prostate in patients in whom complete excision of the growth did not seem feasible.

Although many reports are available, only three will be mentioned. Dean[21] recorded the results of 31 cases treated by castration and followed for 6 months. The immediate effects were startling. Almost without exception, pain disappeared within 48 hours; appetite improved, weight increased, strength returned and soft tissue and lung metastases disappeared. The prostatic size

diminished little. Some improvement in skeletal metatases was seen. The acid phosphatase levels were elevated in 19 of 26 patients in whom this estimation was made while in 16 it fell promptly. Alkaline phosphatase tended to rise. After an average period of improvement lasting about 8 months relapses occurred.

Huggins[11] reported 5 year results of the treatment of prostatic cancer by orchiectomy in 20 cases in which 4 had no clinical or laboratory evidence of cancer and 1 had slowly advancing disease. All these patients had had widespread metastases and elevated serum phosphatase levels at the time of orchiectomy. After 5 years the phosphatase levels were normal and the skeletal metastases had disappeared or were equivocal.

Vest[15] has compared the survival rate in two groups of 74 patients, one group having undergone castration. Data from a 6 year follow-up study indicates that the total fatalities in the noncastration group totaled 82 per cent as contrasted with 43 per cent in the castration group.

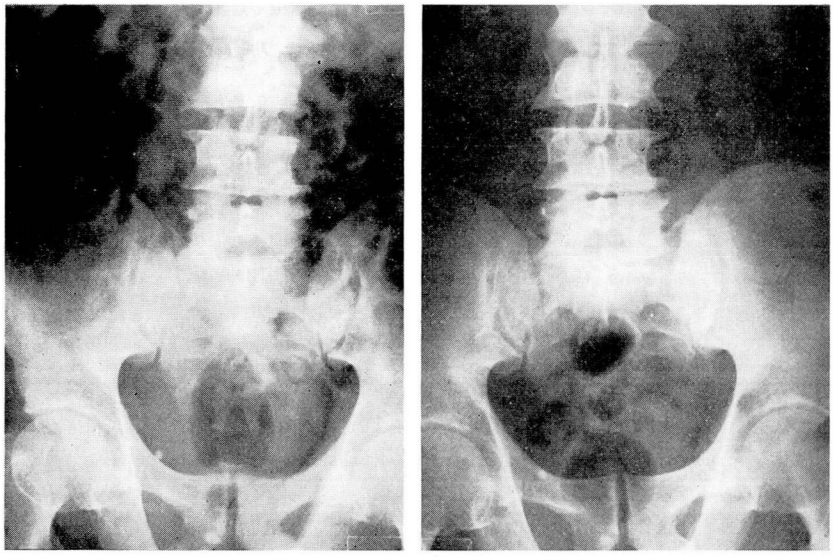
Studies of hormone excretion are interesting in relation to castration. Gonadotrophins rise to high levels, estrogens tend to fall and, most significant, 17-ketosteroids after an initial fall tend to rise above pretreatment levels.[22,23] This suggests that the adrenal androgens increase, a condition which may be connected with the occurrence of a common exacerbation. However, no rise in 17-ketosteroids follows the use of estrogens under similar circumstances.

Estrogens in Prostatic Cancer

Stilbestrol, or other estrogen therapy in inoperable prostatic cancer, has largely supplanted castration. The dosage varies widely. In our experience 2.0 mg. per day was insufficient to lower urinary gonadotrophins to below normal, although 6 mg. per day did so satisfactorily. Theoretically, it is highly desirable to lower pituitary gonadotrophin production in order to remove stimulus to androgen production. Whether or not doses of 30 mg. per day are more satisfactory than 10 mg. has not been clearly demonstrated.

Undesirable effects include impotence, severe irreversible damage to the testes (fig. 2a and b) and gynecomastia. It would seem highly inadvisable to withdraw estrogens after testicular damage has been brought about because pituitary hyperactivity would ensue and probably increase the output of adrenal androgens. It is advisable, therefore, once having started stilbestrol to continue it. Occasionally, nausea or vomiting, muscle pains or edema interfere with therapy. The accompanying mammary hypertrophy[24,25,26,27] may give rise to carcinoma which, when it occurs, is usually bilateral.

Results are slower than those following castration. Symptoms are often well-controlled when due to metastases and, although the size of the prostate may not alter significantly, lymphatic glands may be reduced in such a way as to relieve ureteral obstruction (fig. 3a and b). The common osteolytic lesions of the hip and spine apparently become denser and the bone outlines more normal in appearance. Dense osteoblastic lesions may disappear as may large osteolytic lesions in the skull, even on such small doses as 2.0 mg. per day.



(a) (b)

FIG. 3. (a) Extensive skeletal metastases from carcinoma of prostate. (b) Striking diminution in evidence of metastases after 21 months of stilbestrol therapy (total dosage 1649 mg.)

Such small doses, however, are considered undesirable.

An interesting comparison of estrogens and orchiectomy in prostatic cancer has been made by Nesbit.[28] In a large number of his patients demonstrating no metastases when first seen, orchiectomy plus stilbestrol therapy was definitely more valuable than either alone. The combined procedure was followed by a survival rate of 66 per cent in 3 weeks, whereas either method used alone resulted in a survival rate of only half the patients treated. In untreated patients, only 22 per cent lived for 3 years.

In patients in whom metastases were evident on first observation, stilbestrol did not produce results as satisfactory as those following orchiectomy alone or orchiectomy plus estrogen therapy. When metastases were present, combined orchiectomy and estrogen therapy were little better than orchiectomy alone.

During treatment it is interesting to follow the serum calcium, phosphorus and phosphatase levels. Acid phosphatase is elevated in about 75 per cent of cases, especially when the cancer has escaped beyond the prostatic capsule. In the course of improved cases the levels often fall to normal and, in the event of improvement of skeletal lesions, there may be a several-fold increase in the levels of alkaline phosphatase. Relapse occurs in most instances after 7 or 8 months of treatment. In older men the condition, even though cured, is kept in such complete control that the patient outlives his cancer to succumb to some other disorder.

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