THE USE OF SEX HORMONES IN CANCER

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FOR more than a century it has been known that the only hope for cancer depends on the complete destruction or removal of the tumor cells. Consequently, when metastases have occurred cure is difficult, if not impossible, unless some method such as chemotherapy can be adapted to the task. Chemotherapy for cancer is not new; chemical treatment was employed in many forms even before the advent of modern surgery. Recently many substances have been tried experimentally for their effects upon the development of malignant tissues.[1] It seems just to say, however, that sex hormones have shown more promise than any other form of chemotherapy.

Hormonal treatment of cancer is not without grave dangers, especially if it is used in improperly selected cases. The treatment is palliative, not curative. In carefully selected cases, however, it may relieve pain, improve health, and prolong life in some patients. The mode of action of the hormones under consideration is incompletely understood, and the apparent inconsistency of results is totally unexplained. Even though cures are not produced a study of the relationship of hormones to cancer offers hope of explaining the previously mysterious natural history of the disease.

For the following statements I have drawn heavily upon the recent literature especially on the work of such investigators as Adair,[2] Farrow,[3] Nathanson,[4] Huggins,[5] and Vest[6] in this country, Haddow,[7] Fergusson,[8] and others in England.

Hormones and the Breast

The breast from birth to old age is constantly subject to endocrine factors of control. From experimental evidence we know that the duct system is developed chiefly under the action of estrogens, and progesterone acting simultaneously with estrogens is an important factor in producing lobular growth. The effect of pituitary lactogenic hormone on the production of milk has been extensively studied.

Many changes in the breast may occur under physiologic influences. These include the breast hypertrophy and production of "witch's milk" in the newborn; the frequent breast hypertrophy in puberal boys and normal breast growth in puberal girls; the cyclic changes in the female breast during the menstrual cycle; the changes in pregnancy, lactation, and of the climacteric and senescence. On the pathologic side we recognize profound changes in the breast frequently in association with certain ovarian or testicular tumors, in some tumors of the pituitary and adrenal cortex, as well as breast hypertrophy in cirrhosis of the liver, in certain instances of malnutrition, and during stilbestrol therapy for prostatic cancer. Under some circumstances mammary

enlargement occurs in association with testicular failure as well as in eunuchoid men treated with testosterone.

Although the menstrual cycle has never been shown to have any definite effect upon breast cancer, the disease frequently tends to advance with great rapidity during pregnancy and lactation. It is suspected that this is due in part, at least, to the changes in breast structure. There are a few reports of the development of human breast cancer following prolonged administration of estrogen, but as yet no proof of etiology is forthcoming. Certainly with the widespread use of estrogens one would expect more reports of breast cancer after their use if they were important as a cause.

Castration and Breast Cancer

Castration as an adjunct to the treatment of breast cancer was suggested independently by Schinzinger[9] in 1889 and by Sir George Beatson[10] in 1886. The results of such treatments have been reexamined recently. According to Adair,[11] transient beneficial response may be expected in 15 to 30 per cent of castrated patients who have advanced recurrent or metastatic disease, and little or no response is to be expected in the primary tumor or in lymph gland metastases. The patients who improve are almost entirely in the premenopausal group. X-ray castration may produce good results (fig. 1). In some in whom it fails the failure is suspected to be due to incomplete cas-

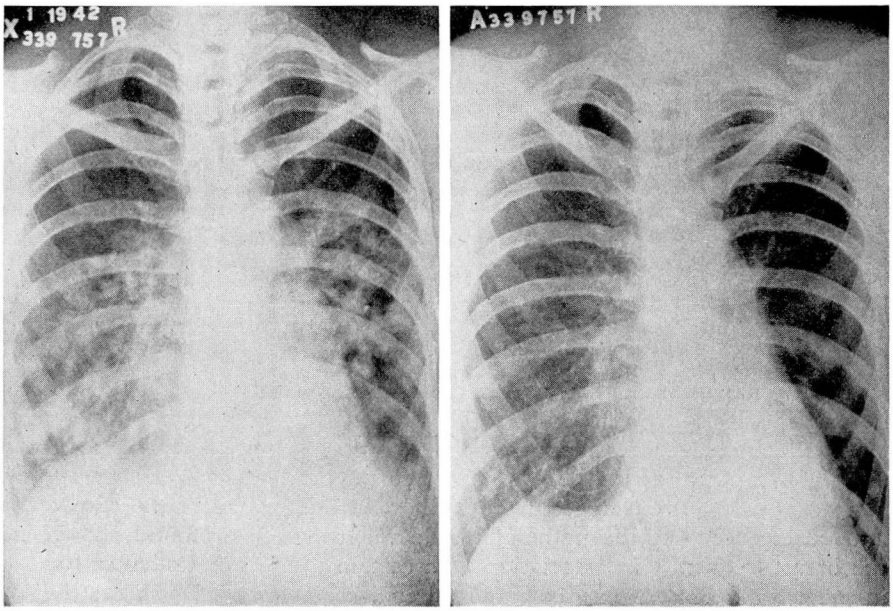


FIG. 1. Regression of metastases from breast cancer in a woman 42 years old. Six months following x-ray therapy to ovarian region. Total skin dose 1650 r.

tration effects of the x-ray. A good result is manifested by relief of pain, increase in appetite and weight, regression of bone metastases, and occasionally pulmonary metastases. Unfortunately, beneficial response is transient.

Administration of Estrogens

When it was discovered that certain carcinogenic hydrocarbons influenced the growth of experimental malignant lesions,[1] some of these substances were tried in cases of human breast cancer. It may appear absurd that the excessive rate of growth of malignant breast tissue should be decelerated by substances which at one time accelerated the development of the same tissues, but such is the case. Haddow[7] reported the results in 73 cases treated with triphenyl clorethylene, triphenylmethylethylene, and stilbestrol, all estrogens. With trichlorphenylethylene there was a favorable response in 10 of 22 patients treated, and with stilbestrol there was improvement in 5 of 14 patients treated, approximately half the patients in each group. The results were similar in both groups, namely, transient retardation or regression of the local growth with evidence of prevention of metastases.

Ten British observers have reported the value of estrogens in the therapy of breast cancer[12] on a group of 168 patients treated with stilbestrol for advanced disease. A summary of their results is presented here in tabular form.

TABLE 1
Stilbestrol in Mammary Cancer
168 Cases

Age	Under 60—100 Patients			Over 60—68 Patients		
Results of treatment in per cent of patients treated	Not improved	Improved	Spectacular improvement	Not improved	Improved	Spectacular improvement
	86	14	1	60	40	7

This table shows that striking improvement is uncommon and is limited to individuals over 60 years of age, a point of singular importance in the selection of patients.

In discussing these results, E. C. Dodds[12] made several timely suggestions: (1) that the sense of well-being be discounted and separated from actual response of the tumor; (2) that heavier doses be tried; (3) that other estrogens, such as hexestrol and dienestrol, are worth trying, and (4) that a rigid series of controls be established.

Dosage. Stilbestrol is the most widely used estrogen. The results mentioned have been obtained with oral doses of 5 to 30 mg. per day. Other synthetic estrogens, such as dienestrol and ethinyl estradiol, are being tried, but I have seen no reports of the results. To my knowledge, doisynolic acid has not been used.

Undesirable side effects of estrogen therapy may include loss of appetite, nausea, vomiting, diarrhea, and sometimes edema, which may be important when the myocardium is impaired. Menorrhagia is likely to supervene when high dosage is long continued.

Results. Good results include regression of the primary tumor, of soft tissue recurrences, and of lymph gland and pulmonary metastases. Pain from skeletal metastases may be relieved, but favorable response in them otherwise is doubtful. There is great individual variation in response, but in all instances improvement is transient.

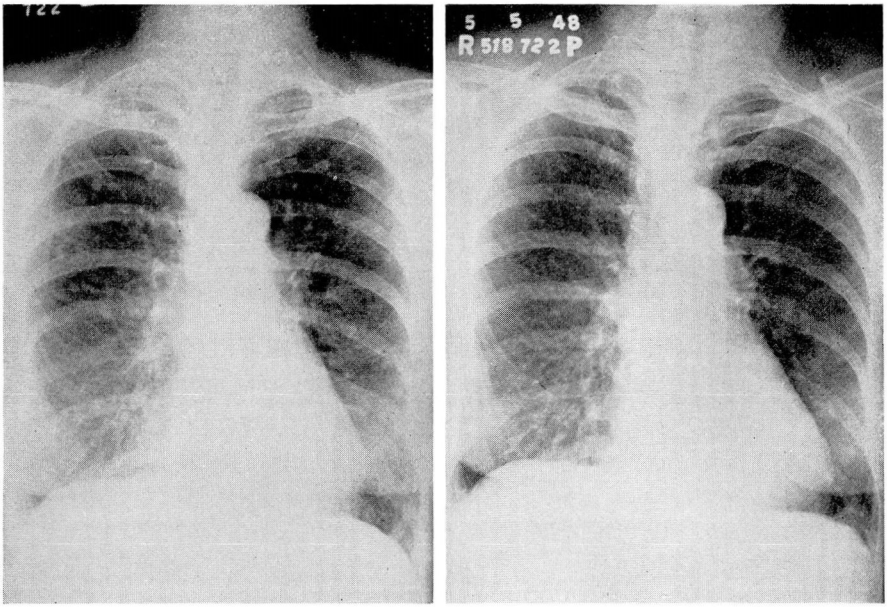


Fig. 2. Woman aged 70. Gradual but continuing decrease in pulmonary metastases from carcinoma of the breast. Eleven months after therapy with testosterone. Dose 100 mg. per day six times per week.

Dangers. The chief danger of estrogen therapy is that growth of an existing cancer may be accelerated in younger women. The Sub-committee on Therapeutic Trials of the Council on Pharmacy and Chemistry of the A.M.A.[13] warns, "Any patient who still menstruates or who has menstruated within five years should definitely not receive estrogen therapy, as it accelerates the rate of growth of the carcinoma. In no case should estrogen therapy replace radical surgery in treatment of breast cancer."

In summary, estrogens may be considered useful palliative agents for the treatment of soft tissue manifestations of advanced cancer of the breast in some older women.

The Effect of Androgens on Breast Cancer

Experimental and clinical observations regarding the effect of androgens on breast cancer have all been made within the past seven or eight years.

Results. In general, androgens have been found most useful in younger patients and in those who have skeletal metastases. As with estrogens the results are inconsistent, and there is great individual variation. Reports show that soft tissue metastases are influenced relatively little, as a rule, although again exceptions appear. One of my patients at the age of 70 had a large recurrent soft tissue mass in the subaxillary area. During testosterone therapy, 50 mg. per day over a ten-week period, this soft tissue mass disappeared till it could not be palpated, and there was a pronounced decrease in roentgenologic evidence of pulmonary metastases.

Farrow[14] mentions 2 patients, ages 37 and 60 years, respectively, who developed hypercalcemia, extension of metastases, rapid decline, and death following 400 mg. of testosterone in eight days and 250 mg. of testosterone in ten days.

Adair and Herrmann[2] reported 11 patients (women) who received doses of 50 to 200 mg. of testosterone propionate two or three times weekly. The largest total dose was 3975 mg. Four of the 11 showed improvement. In 3 recalcification of skeletal metastases was demonstrated, while in 1 hypercalcemia developed.

Symptomatic response may be dramatic. We have seen severe pain from spinal metastases disappear in two days; usually it is one to three weeks during which time a sense of strength and well-being, increased appetite, and ability to sleep without sedation appear.

Among the most impressive changes following testosterone therapy is a change in the roentgenologic appearance of skeletal metastases. In some patients areas of demineralization become denser, suggesting deposition of new bone. In some pain may disappear without any evident change in the secondary lesions. In others there may be roentgenologic evidence of remineralization, in some metastases, while other lesions in the same patient appear to increase in size and decrease in density. Unfortunately, in some patients the entire disease appears to take on increased vigor during therapy.

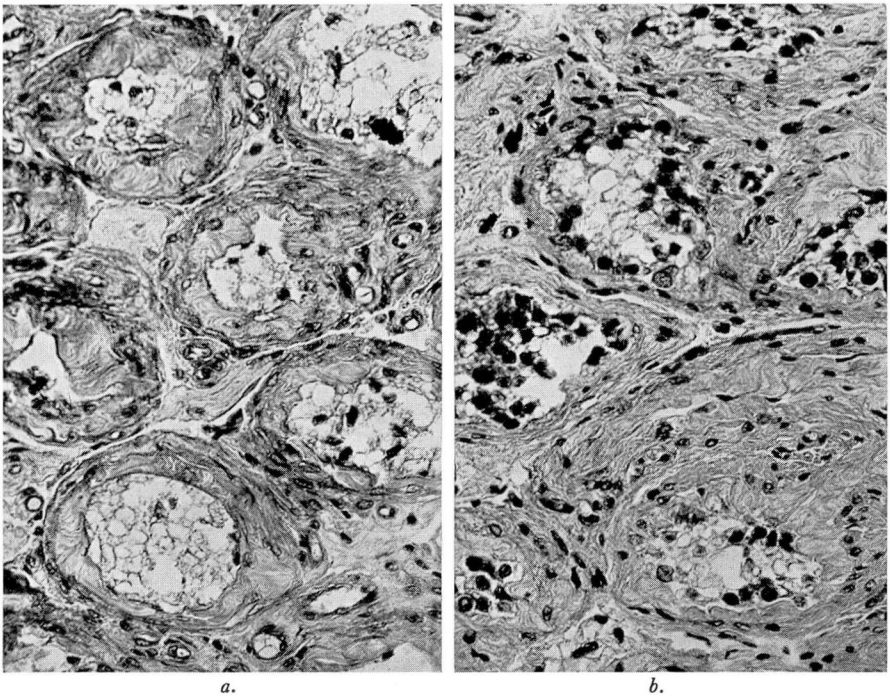
In a few patients soft tissue masses may disappear as in the patient represented in the accompanying chest x-rays (fig. 2). She received 300 mg. per week for thirteen months and is continuing to show a decrease in pulmonary metastases. During this interval a large axillary mass has completely disappeared. A small primary lesion remains palpable.

It is interesting to follow the alkaline phosphatase levels. Increases of three to five times the pretreatment range suggests healing of bony lesions. The mode of action of androgens has not been definitely ascertained but may be partially the production of other effects, such as a more direct action on cellular metabolism, in the older group.

In 20 cases we have treated, the results have been approximately as follows: In 3 symptomatic response was dramatic, and in 6 others improvement was

good, a total of 9 improved. In one of these there was definite improvement in soft tissue and pulmonary metastases. In another pain disappeared and there were striking changes in skeletal metastases, and in the third prompt to complete relief of pain from bony metastases. In the remaining 11, 3 declined rapidly and died, 1 is in extremis. In 2 the present status is unknown, and 1 was not improving and testosterone was replaced by estrogen. The remaining 4 patients have been under treatment too short a time to judge their progress.

Dosage. The dose of testosterone propionate used has varied. Earlier doses of 5 to 25 mg. were used. We have used 50 to 100 mg. six times a week in some, and in 2 patients 200 mg. daily over a period of two weeks. We have set no limit to the duration of treatment, being guided by the patient's progress only.



a. *b.*

Fig. 3. (a) Carcinoma of prostate with metastases to testes in patient aged 73. Stilbestrol therapy 2.0-4.0 mg. per day over twenty month period. (2880 mg.) (b) Patient aged 70. Twenty-five months after stilbestrol therapy 1.0-3.0 mg. per day. (1650 mg.)

Undesirable Effects. Weight gain is a common accompaniment of testosterone administration. In one of our patients, this feature caused massive painful swelling of an already swollen arm, such swelling of the neck as to make coughing and swallowing almost impossible, as well as pronounced swelling of the external genitals. Because of this, treatment was discontinued.

Nausea, headache, and malaise suggest hypercalcemia. The serum calcium should always be examined. If it is high testosterone should be given with extreme caution, if it rises to levels of 13 or above it usually should be withdrawn. Although we have seen a decline in serum calcium levels during therapy in 1 patient.

The voice usually deepens, rather extensive acne may appear, the growth of a fuzzy beard may necessitate shaving, and, even in women over 70, sexual libido may be excessively increased.

Castration for Cancer of the Male Breast

Favorable responses in carcinoma of the male breast following castration have been reported. Treves and associates[15] have reported 7 cases with a good response in 6. Strangely enough, in contrast to women, the men who showed the best results after castration were 63 years of age or older. A good response to orchiectomy has included partial regression of the primary tumor and osseous metastases. Treves believes that the effects of castration in carcinoma of the male breast may parallel the brilliant results obtained in carcinoma of the prostate following similar treatment.

Striking improvement in the local appearance in a case of cancer of the male breast twenty-two months after castration is shown by Nathanson.[16] Farrow[14] cites the case of a man in whom pronounced improvement in the primary tumor and increased density of skeletal metastases followed orchiectomy during a period of four months of postoperative observation.

Sex Hormones and Prostatic Cancer

The development and physiologic activity of the prostate gland is largely influenced by androgens. The prostate of the eunuch remains very small, its epithelium flat, and its acini almost devoid of secretion; the prostate of the adult castrate undergoes a marked reduction in size, and the acinar epithelium becomes extremely atrophic. The intimate relationship of androgens to prostatic cancer was illustrated by Moore,[17] who examined the prostates of 252 men who died between the ages of 41 and 90 and found 20 per cent malignant; yet the same author after careful search was unable to find any record of prostatic carcinoma in a patient who had eunuchoidism, eunuchism, or pituitary infantilism arising before the age of 40.

Since 1935 there has been a steadily mounting interest in the relationship between hormones and prostatic cancer. In 1935 Kutscher and Wolbergs[18] isolated prostatic phosphatase and showed that it was active in acid solution. In 1936 Gutman and Sproul[19] discovered that acid phosphatase existed in metastases from prostatic carcinoma, and it was shown that this substance did not exist in the infant prostate but was present in the adult and in the cancerous prostate.

Since that time the estimation of acid phosphatase in the blood has become a common diagnostic procedure in the estimation of the spread of carcinoma

of the prostate. Dean[20] 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, on the other hand, 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 certain liver diseases.

The experimental work of Huggins[21] also 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 prostatic cells simulating cancer, and estrogen treatment returned 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. Many reports are available; only 3 will be mentioned here. Dean reported the results of 31 cases treated by castration and followed for six months. The immediate results were startling. Almost without exception pain disappeared within forty-eight hours. The appetite became good, weight increased, strength returned. Soft tissue and lung metastases disappeared. The prostatic size diminished little. Some improvement in skeletal metastases was seen. The acid phosphatase levels were elevated in 19 of 26 patients in whom this estimation was made, and in 16 it fell promptly. Alkaline phosphatase tended to rise. After an average period of improvement of about eight months relapses occurred.

Huggins reported five-year results of the treatment of prostatic cancer by orchiectomy in 20 cases in which 4 had no clinical or laboratory evidence of

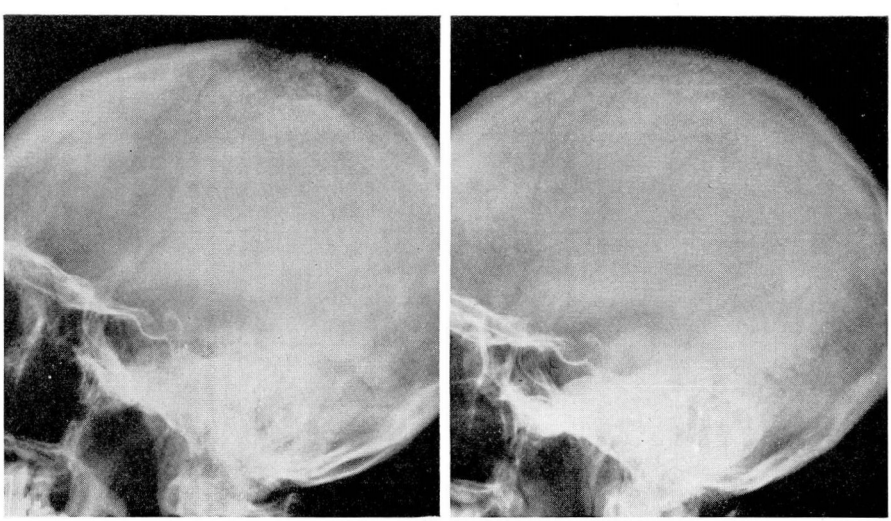


FIG. 4. Carcinoma of prostate. Age 56. After ten months' treatment with stilbestrol 2 mg. per day.

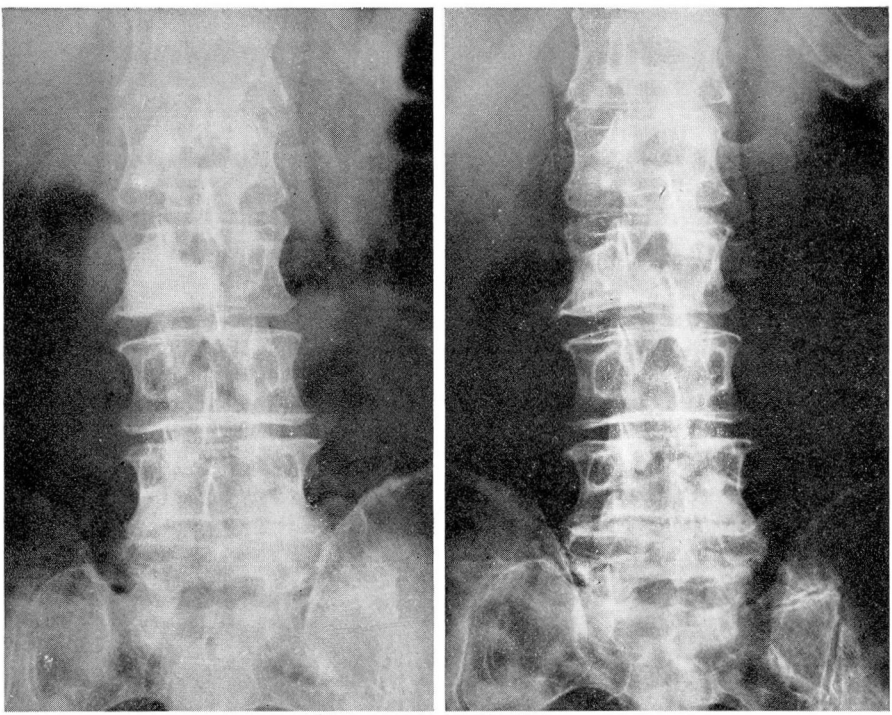


FIG. 5. Carcinoma of prostate in 78 year old patient. Changes following three years, two months stilbestrol therapy 2-3 mg. per day. Alk. phos. 2.2—acid phos. 1.4.

cancer and 1 had slowly advancing disease. All these 5 patients had had widespread metastases and elevated serum phosphatase levels at the time of orchiectomy. After five years the phosphatase levels were normal and the skeletal metastases had disappeared or were equivocal.

Vest[22] has compared the survival rate in 2 groups of 74 patients, 1 group having castration, the other not. Data from a six-year follow-up study indicates that the total dead in the noncastration group is 82 per cent, while the total dead in the castration group is 43 per cent.

Studies of hormone excretion are interesting in relation to castration. Gonadotropins rise to high levels, estrogens tend to fall, and most interesting and significant is the fact that 17-ketosteroids after an initial fall tend to rise above pretreatment levels.[23] This suggests that the adrenal androgens increase, and the suspicion arises that this may be connected with the common exacerbation which occurs. It is interesting, therefore, that no rise in 17-ketosteroids may follow the use of estrogens under similar circumstances. Also it is to be anticipated that stilbestrol therapy once started and causing severe testicular damage will in turn cause a pituitary hyperactivity greater than that before treatment if stilbestrol is subsequently discontinued.

Estrogens in Prostatic Cancer

More recently the trend has been away from castration and toward estrogen therapy for inoperable prostatic cancer. The mechanism of its action, as shown by hormone excretion studies, is quite different from that of castration. When stilbestrol is given the urinary estrogens rise by virtue of the excretion of the administered drug, urinary gonadotropin levels fall, and androgen levels, as judged by urinary 17-ketosteroids, fall. In 9 patients studied by Dean the pretreatment level of 17-ketosteroids averaged 8.9 mg. of androsterone equivalent, and the post-treatment level after doses of 2 to 5 mg. per day of stilbestrol averaged 5.4 mg.

Profound degenerative changes occur in the testis. The gametogenic elements atrophy, the basement membrane becomes thickened, and repeated biopsies have shown a decline in the apparent activity of the Leydig cells (fig. 3, a and b).

Dosage. Stilbestrol is commonly used in this country in doses of 1 to 5 mg. per day, while in England some workers[24] have given as much as 30 mg. per day. I am inclined to believe that 3 mg. per day or less is likely not to be fully effective, since we have found 3 patients taking 2.0 mg. daily in whom the gonadotrophins were not depressed below normal range. Increase of stilbestrol dosage to 5.0 and 6.0 mg. per day, respectively, depressed urinary gonadotropins to subnormal levels of less than 6 mouse units per day (table 2).

TABLE 2

Hormone Assays in Relation to Stilbestrol Therapy in Prostatic Cancer

Age	Stilbestrol Daily Dose mg.	Duration of Therapy	Other Treatment	Urinary gonadotropins m.u. per day	Urinary 17-K.S. mg. ketonic
73	1.0	4 mos.	Resection	6	
67	2.0	6 mos.	Castration	26-52	
71	2.0	6 mos.		26-52	4.8
	6.0	3 wks.		6	5.8
63	2.0	3 mos.		13-26	
	5.0	2 mos.		6	

(Normal urinary gonadotropins 13-105 mouse units daily)

Results. In general the results of treatment with stilbestrol, though slower, are otherwise equal or superior to those following castration. Symptoms are as well controlled, and in many instances large osteolytic lesions become densely remineralized (fig. 4). Osteoblastic lesions may become more dense, but whether or not this means healing in terms of cancer growth is not easy to determine by roentgenologic appearance. After a period of seven or eight months' improvement most patients have had relapses. In one case of osteoblastic

metastases of the spine, the patient outlived his prostatic carcinoma to die a cardiac death at the age of 78 years (fig. 5).

The untoward effects of stilbestrol therapy in men may include nausea, vomiting, and in some muscle pains and edema. Complete impotence is the rule, the nipples and areolae become dark, and a rather striking degree of gynecomastia appears. Malignant tumors of the interstitial cells of the testis have been reported in the estrogen-treated mouse,[25] but nothing comparable to this has been suggested in man.

Castration and estrogen treatment for prostatic cancer is palliative, not curative. It is a useful adjunct to treatment in properly selected cases but should never replace surgery where surgery holds any promise of a cure. At the present time it must be considered experimental and a hopeful approach to new avenues of study.

To quote Alexander Haddow[26], "It is indeed true that those who have considered the matter most thoroughly are under the least illusion as to its practicability. That the subject will continue to be investigated, quite regardless of success, is, however, equally true and it must therefore be our duty to stimulate the process as far as possible, while at the same time never failing to underline its inherent and therefore inescapable difficulties. The slight advances of the past few years are, however, more than were accomplished in any previous period, and it is surprisingly likely—and very much to be hoped for—that a review such as the present will comparatively soon be out of date."

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