

# TREATMENT OF CANCER OF THE BREAST IN PREMENOPAUSAL PATIENTS WITH RADICAL AMPUTATION AND BILATERAL OOPHORECTOMY\*

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THAT THE OUTLOOK for cure of carcinoma of the breast is more discouraging in young women than in those in the postmenopausal period has been rather generally accepted. Sittenfeld<sup>1</sup> states: "Every cancer worker realizes that cancer of the breast in a woman under 40 years of age is a highly malignant disease and notwithstanding the most thorough surgical excision and large doses of radiant energy, the end-results are very grave and disappointing." Ewing<sup>2</sup> has stated: "Before 30 years of age mammary cancer is extremely fatal, so that some surgeons prefer not to operate during this period."

The relationship of the endocrines to certain types of cancer seems to be definitely established. When, in 1932, Lacassagne<sup>3</sup> induced mammary carcinoma in male mice by injections of estrone benzoate it was apparent that an important step forward had been made in the understanding of the causes of mammary cancer. This led to a variety of interesting findings concerning the general effects of the estrogens on neoplasms. Likewise, Huggins<sup>4</sup> and his coworkers have established in their experimental and clinical work on cancer of the prostate a definite relationship with male sex hormone. Whatever may be the explanation of the benefits of orchiectomy on cancer of the prostate, and they certainly exist in many cases, it would seem that an analogy might apply to bilateral oophorectomy in cancer of the mammary gland.

Shimkin<sup>5</sup> states: "It was found that mammary tumors occurred more frequently in breeding than in nonbreeding mice. In some strains, the incidence of tumors is proportional to the number of pregnancies undergone by the mice. Loeb<sup>6</sup> further demonstrated that the incidence of tumors can be radically reduced by ovariectomy, and that the incidence is related to the age of the animal at the time of ovariectomy. Cori,<sup>7</sup> and W. S. Murray,<sup>8</sup> substantiated these findings, and the latter succeeded in obtaining mammary tumors in castrated male mice bearing ovarian grafts."

"With the advent of chemically isolated estrogens, numerous investigators reported the appearance of mammary tumors in male mice injected with these compounds. The work was rapidly expanded and elaborated. The most important conclusion was that estrogens would elicit mammary tumors in males of strains in which females developed such tumors spontaneously, and in approximately the same incidence. Males of strains in which the tumor incidence was

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extremely low did not develop a mammary cancer no matter how strenuously they were treated with estrogens. This would indicate that the strains known to be readily susceptible to cancer of the breast, whether male or female, would develop cancer of the breast by injections of estrogens."

Mammary carcinoma in male mice of susceptible strains has been developed with all the natural and synthetic estrogenic compounds that have been studied. The list includes estradine, estrone, estriol, quilenin and their benzoates, diethylstilbestrol, *etc.* The carcinogenic activity of these substances seemed to be related to the amount of estrogen in physiologic units rather than to chemical structure or other properties of the substance injected. They could be administered subcutaneously, intramuscularly, or orally with the same results, depending on the physiologic activity by the particular route employed. The administration had to be continued for a prolonged period, eight weeks or more, if carcinoma was to be developed at a later period. Compounds having rapid elimination and consequently a shorter period of activity had to be given in larger doses and administered over a longer period than those compounds given as subcutaneously implanted pellets.

The site, the growth, and the histologic appearance of the mammary tumors developed in castrated mice injected with estrogens correspond in every detail with the description of the spontaneous adenocarcinomas in female mice of the same strain.

Using rats of the Long-Evans hooded strain, in which only four fibroadenomas had been seen in 15 years, Nelson<sup>9</sup> reported the induction of 68 carcinomas of the breast in 103 animals. He gave daily injections of 50 *gamma* of diethylstilbestrol, or subcutaneously implanted pellets of diethylstilbestrol. Metastases developed in 33 rats, which were classified as: duct carcinoma, 13; adenocarcinoma, 8; duct and adenocarcinoma, 13; and carcinoma simplex, 5. He found that both male and female rats were equally susceptible to the induction of tumors. Numerous other workers have repeated the experiments, using the same strain of rats, with essentially the same results.

Geschickter<sup>10</sup> injected a number of castrated rabbits with daily doses of 0.5 or 1.0 mg. of dimethylstilbestrol. Three rabbits developed papillary cystadenoma of the breast in 10 to 15 months, and in one this progressed to carcinoma within 20 months.

In earlier investigations by Loeb<sup>11</sup> it was shown that there is a direct quantitative relationship between the duration of the action of endogenous ovarian hormones and the incidence of carcinoma of the mammary gland in mice; the longer the endogenous hormones were allowed to act, the greater the incidence of carcinoma. It was also shown by Lathrop and Loeb<sup>12</sup> that the latent period preceding the appearance of carcinoma of the mammary gland was in a similar way related to the duration of the action of the endogenous hormones; the longer the endogenous hormones were allowed to act, the shorter the latent period.

It follows from their earlier experiments that removal of the action of

ovarian hormones at a period of life when the mice had passed the onset of sexual maturity was effective in diminishing the incidence of mammary carcinoma and in increasing the latent period.

Shimkin further states: "It is abundantly clear that in all species, carcinoma of the mammary gland is the end-result of an intricate, prolonged interaction and combination of at least several factors or complexes of factors. In all species, a degree of genetic susceptibility and a degree of hormonal stimulation are essential, and the process can be modified by numerous secondary influences of internal and external environment."

What seems to be the double rôle of estrin in the causal and in the formal genesis of mammary cancer resembles what might be the relationship between androgenic substances from the testicle and cancer of the prostate. The beneficial results of removing the ovaries along with a radical operation for cancer of the breast may be attributed to the withdrawal of a causal genesis, to the removal of a formal genesis, or to a combination of both of these factors. The recurrences of cancer of the breast after a radical operation are doubtless due to cancer cells that have been left. The small amount that remains, however, would be stimulated by estrogenic substances. As there have been cases in which cancer of the breast receded, at least temporarily, after removal of the ovaries, with no other treatment, it would seem that there may be a mass relationship. That is, the effect of withdrawing estrogenic stimuli might be greater if there are only a few cancer cells than if there is a large amount. With only a few remaining cancer cells, however, this unfavorable influence of withdrawing the stimulating effect of estrin should be more deleterious and create an unfavorable soil for their existence.

In women who have previously had cancer in one breast, the increase of ovarian activity in pregnancy appears to promote mammary cancer in the remaining breast. Trout<sup>13</sup> collected 15 instances of pregnancy subsequent to a radical operation for mammary cancer, in 13 of which there was prompt development of very malignant carcinoma in the remaining breast. Wintz<sup>14</sup> reported seven instances of pregnancy after radical operation for mammary cancer, with fatal cancer then occurring in the remaining breast.

Ultimate results from the treatment of cancer of the breast in young women were most disappointing. J. Shelton Horsley found this to be true in his cases prior to 1937. Of nine patients under 36 years of age upon whom a radical operation was performed by him at St. Elizabeth's Hospital in the period from September 1, 1922 to November 1, 1937, five died of recurrence. The marked difference in the results obtained in this younger age-group, as compared with those in older patients, and the results of experimental work already referred to, caused J. Shelton Horsley<sup>15</sup> to adopt the procedure of removing both ovaries whenever a radical operation is done for cancer of the breast in women in the premenopausal period.

Four years after he did the first bilateral oophorectomy associated with radical amputation of the breast, which was on November 19, 1937, the splendid report of Huggins on castration for cancer of the prostate appeared. His

work seems to confirm the wisdom of bilateral oophorectomy in premenopausal women whenever a radical operation is done for cancer of the breast. This procedure apparently was first suggested by Schinzinger,<sup>16</sup> although according to his article, he did not carry it out. He is said to have discussed this also before the Surgical Congress in Berlin on April 25, 1899. Doubtless, it has been performed by other surgeons, although there does not seem to be any systematic record of a number of cases.

At first a bilateral oophorectomy was done with radical operation for cancer of the breast only on patients under 40 years of age. Later, this was extended to all patients in the premenopausal stage. The desirability of having both ovaries removed along with the radical operation is, of course, first explained to the patient.

Since beginning this method of treating cancer of the breast, numerous investigators have reported excellent results by roentgenologic or surgical castration in patients with extensive carcinoma in both the pre- and postmenopausal periods. Ritvo and Peterson<sup>17</sup> reported definite regression of osseous metastases from carcinoma of the breast following ovarian sterilization by roentgenologic treatment. With regression of the metastases there was also marked relief of pain, which was quite similar to the relief of pain in patients with osseous metastases from carcinoma of the prostate.

Treves, *et al.*<sup>18</sup> reported regression of a primary lesion in two cases following bilateral oophorectomy and improvement in another case. They also noted clinical regression in metastases in both the lung and bone, and in several cases there was dramatic relief of pain immediately following castration. Recently, Adair and Herrmann<sup>19</sup> have reported using large amounts of testosterone propionate in treatment of advanced carcinoma of the breast. They reported 11 cases treated, with improvement in four cases associated with relief of pain; no improvement in four cases; and three cases were still under treatment when their report was made. Three of the four cases reported in detail were in their fourth decade, and all of them seemed to show improvement, with a sense of well-being, definite gain in weight, and clinical and roentgenologic evidence of regression of the neoplasms. Two of these three cases were menstruating when the injections of testosterone were started, and after injections developed amenorrhea.

J. Shelton Horsley presented the results up to November 1, 1943, of his cases of radical amputation of the breast with bilateral oophorectomy. A further report on this work is given in the following Tables. In addition to the results obtained on patients in the premenopausal stage, Table I shows results from all cases of cancer of the breast admitted to St. Elizabeth's Hospital between November 1, 1937 and November 1, 1946. These statistics are shown so that the comparison in the different age-groups may be noted.

In Table I there is a total of 170 cases, showing living and no recurrence 108, living with recurrence four, and 54 deaths. Of the dead, 36 were from recurrence, 11 from causes unknown—some of which undoubtedly were from metastases, and seven from causes other than metastases.

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Table II includes only those cases without oophorectomy, but five of these cases had sterilization by roentgen-ray. There is a total of 131 cases, with no recurrence in 78; living, with local recurrence three. Total deaths were 46, of which 29 were definitely from recurrence; 11 from causes unknown; and six from causes other than metastases.

TABLE I  
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*All cases admitted to St. Elizabeth's Hospital, Richmond, Virginia  
between November 1, 1937 and November 1, 1946*

Total cases.....	170	
No recurrence.....	108 (63.5%)	
Recurrence and living.....	4 (2.4%)	
Dead:.....	54 (31.7%)	
From recurrence.....	36 (21.2%)	
Causes other than metastases... ..	7 (4.1%)	
Cause unknown.....	11 (6.4%)	
Follow-up incomplete.....	4 (2.4%)	

TABLE II  
CANCER OF THE BREAST WITHOUT OOPHORECTOMY

*November 1, 1937 to November 1, 1946*

All cases without oophorectomy.....	131	
No recurrence.....	78 (59.5%)	
Recurrence and living.....	3 (2.3%)	
Dead:.....	46 (35.1%)	
From recurrence.....	29 (22.1%)	
Causes other than metastases... ..	6 (4.6%)	
Cause unknown.....	11 (8.4%)	
Follow-up incomplete.....	4 (3.1%)	

TABLE III  
CANCER OF THE BREAST WITHOUT OOPHORECTOMY

*November 1, 1937 to November 1, 1946*

Cases traced.....	127	
No recurrence:.....	78 (61.4%)	
Oldest patient—77 years of age		
Youngest patient—28 years of age		
Under 35 years of age—2		
Under 40 years of age—5		
Recurrence and living:.....	3 (2.4%)	
Local, after 3 years—1 age 49		
Local, after 2 years—1 age 66		
Local, after 5 years—1 age 35		
Dead:		
From recurrence.....	29 (22.9%)	46 (36.2%)
Causes other than metastases... ..	6 (4.7%)	
Cause unknown.....	11 (8.6%)	

Table II is further broken down into Table III, and it will be noted that in patients without recurrence there were several still in the premenopausal stage—two under 35 years of age and five under 40 years of age. Of these five, none had roentgen-ray treatment over the ovaries for one reason or

another, the chief one being a low-grade type of malignancy with either an intraductal or mucoid type in which sterilization seems to be of less value. There are three cases living, with local recurrence, one of whom was in the premenopausal stage at the time of operation and was sterilized by roentgen-ray. However, six months after the first roentgen-ray sterilization, she began menstruating and had to receive roentgen-ray therapy over the ovaries on two other occasions before a complete and final suppression of menstruation was effected. All three recurrence and living cases have had local excision of the recurrent nodules, and recent examinations showed no evidence of further trouble.

Of the 29 deaths from known recurrence, eight cases were in the premenopausal period. One case, age 34, was so extensive that only a diagnostic biopsy was done; three other cases had only the radical operation, and all died within two years. The remaining four cases had roentgen-ray sterilization in addition to the radical operation. Of these four cases, one died after two years, one after four, one after five, and one after nine years. It was because of incomplete castration by roentgen-ray, two of them requiring further roentgen-ray treatment over the ovaries six months later, that it was decided surgical sterilization was the procedure of choice when castration was indicated, with radical amputation of the breast for cancer.

TABLE IV  
RESULTS THREE AND FIVE YEARS AFTER OPERATION IN CASES WITHOUT OOPHORECTOMY

	Operated Upon 3, or more, Years	Operated Upon 5, or more, Years
Total cases.....	97	62
Living:.....	55 (56.6%)	28 (45.1%)
No recurrence.....	53 (45.6%)	27 (43.5%)
Local recurrence.....	2 (2.0%)	1 (1.6%)
Dead:.....	42 (43.3%)	34 (54.8%)
From recurrence.....	28 (28.8%)	23 (37.1%)
Causes other than metastases	4 (4.2%)	4 (6.4%)
Cause unknown.....	10 (10.3%)	7 (11.3%)

Realizing that many of these cases have been of recent origin, and a true index of cures is not given in the preceding Tables, the recent cases were eliminated. Table IV gives the results of those without oophorectomy operated upon three years, or more, and five years, or more. There is a total of 62 that have been operated upon five years, or more, of which 28, or 45.1 per cent, are still living. One of these—the patient who had roentgen-ray castration, as mentioned in Table IV—has a local recurrence. There are 34, or 54.8 per cent, dead. Of this number, 23, or 37 per cent, died from recurrence; seven, or 11 per cent, from causes undetermined; and four, or 6 per cent, from causes other than recurrence. Assuming that all of the deaths whose exact cause is not known were from recurrence, there would be a total of 30 deaths, or only 48.4 per cent. Of the patients operated upon three, or more, years ago, which include the cases operated upon five years ago, or more, there is a total of 97; 55, or 56.6 per cent, of whom are still living. Two of these have had

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local recurrence, but at present there is no evidence of any further metastasis. Of these 97, 42, or 43.3 per cent, have died—28 from recurrence, ten from causes undetermined, and four from causes other than recurrence.

TABLE V  
CANCER OF BREAST WITH OOPHORECTOMY  
*November 1, 1937 to November 1, 1946*

All cases with bilateral oophorectomy.....	39	
Living:.....	31 (79.5%)	
No recurrence:.....	30 (76.9%)	
Oldest patient—50 years of age		
Youngest patient—28 years of age		
Average age—40.6 years		
Under 35 years of age—4		
Under 40 years of age—14		
Recurrence:		
Local, after 4.5 years—age 43.....	1 (2.5%)	
Dead:.....	8 (20.5%)	
From recurrence:.....	7 (18.0%)	
After 6 months—1 age 28, bilateral, with metastases to axillae at time of operation		
After 1 year—1 age 38, metastasis to bone		
1 age 38, local metastasis		
1 age 44, extensive axillary involvement at time of operation		
After 2 years—1 age 43, metastasis to lung		
After 3 years—1 age 33, metastasis to bone		
After 5 years—1 age 38, metastasis to lung		
From causes other than recurrence.....	1 (2.5%)	
Age 30, from peritonitis 5 years after operation. Autopsy showed no recurrence		

Table V includes all cases in which bilateral oophorectomy was done at the time of operation, with a total of 39. There have been no recurrences in 30; local recurrence in one; and eight deaths, seven of which were from recurrence and one from causes other than metastasis. The oldest of the living patients was 50 and the youngest 28 at the time of operation. The average age was 40.6 years. There were four under 35 years of age and 14 under 40 years of age. There is one living who has had a local recurrence, the original operation having been done 4.5 years ago, when she was 43 years of age. She has had several recurrences in the skin, occurring at about yearly intervals, the last one being a little over a month ago. The patient at present seems to be in excellent condition, and there is no indication of other metastases. There were eight deaths in the series, seven of which were from definite recurrence and one from general peritonitis following intestinal obstruction five years after the original operation. Necropsy in this case revealed no evidence of recurrence of the malignancy. One case, 28 years old at the time of operation, who had extensive cancer of both breasts, with metastases in both axillae, died six months after operation. The other six cases died of metastasis—three, one year after operation; one, two years after operation; one, three years after operation; and one, five years after operation.

Table VI shows cases three and five years after the original operation, with bilateral oophorectomy. Thirteen cases were operated upon five years ago, or more, and of these, ten are living without recurrence, and one had local skin

recurrence. This gives a percentage of 76.9 living without recurrence after five years. There is a total of 26 that were operated upon three or more years ago, with one local recurrence, as shown in the five-year cases. There were five deaths from recurrence, giving 76.9 per cent of three-year cures, which is the same as that noted in the five-year, or more, cases.

TABLE VI  
RESULTS THREE AND FIVE YEARS AFTER OPERATION IN CASES WITH OOPHORECTOMY

	Operated Upon 3 or more Years	Operated Upon 5 or more Years
Total cases.....	26	13
No recurrence.....	20 (76.9%)	10 (76.9%)
Local recurrence.....	1 (3.8%)	1 (7.7%)
Dead from recurrence.....	5 (19.3%)	2 (15.4%)

While this paper is primarily concerned with the results obtained in cancer of the breast cases in the premenopausal stage treated by radical amputation and oophorectomy, we have reviewed in some detail the results obtained in all cases of cancer of the breast admitted to St. Elizabeth's Hospital during this nine-year period. This is done so that the results in those cases without oophorectomy, and mostly in the postmenopausal period, may be compared with those in the premenopausal period, with oophorectomy. This comparison should be significant, as it covers the same period of time, all operations were done by one of three surgeons, and the same operative procedure was used. It will be noted in the five-year "cures" that there were 43.5 per cent in those cases without oophorectomy as compared with 76.9 per cent in those of the premenopausal period with oophorectomy. The same results were observed in the three-year cases in the latter group.

This series of cases, combining bilateral oophorectomy with radical amputation of the breast, is too small to be conclusive, but, in our hands, the results have been outstanding, considering the discouraging reports before oophorectomy was done with the radical amputation. The results are much better than those obtained when roentgen-ray castration was tried, though our few cases treated with roentgen-ray were better than those without either method.

There might be further improvement by the administration of testosterone propionate even after oophorectomy. The recent reports of Adair and Herrmann show that fair results are also obtained by such injections in elderly patients past the menopause with extensive metastases. We have not yet tried these injections either with or without oophorectomy. There have been several reports on the use of testosterone propionate injections without oophorectomy with good results, but as this would be a prolonged procedure it would seem that oophorectomy would be more certain and less hazardous. The objection to the use of the male hormone is quite similar to that of roentgen-ray castration. In some patients sterilization is not complete and the size of the injection or radiation often has to be increased before the desired results are obtained. It is this delay and uncertainty in effecting complete suppression of the female hormone that makes these methods unsatisfactory. Numerous other



factors are involved in the development of breast cancer, such as heredity, the milk factor, *etc.*, as have been shown in experimental and clinical research, but surgical castration of those patients in the premenopausal stage with radical amputation of the breast is a step forward in the right direction.

SUMMARY

1. A brief review of the recent literature on the influence of female hormone on breast cancer has been given.

2. Results obtained by radical amputation of the breast and bilateral oophorectomy in cancer of the breast in premenopausal cases are given, showing 76.9 per cent of cases living without recurrence in both three- and five-year postoperative periods.

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