

Lactation Induced by Luteotrophin in Women with Mammary Cancer. Growth of the Breast of the Human Male Following Estrogenic Treatment*

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In this paper functional maturity of mammary epithelium will be defined as the capacity of the cells to secrete, and it may be determined by a simple method—by the production of milk following the administration of luteotrophin. It is known that functional maturity of the breast is never achieved in the absence of appropriate hormones or artificial substances with a similar physiologic activity. Recognition of physiologic maturity is of some significance, since it is known that certain mammary cancers are dependent on endocrine activity since they regress when the appropriate hormonal sources are removed or inactivated. In the observations to be presented luteotrophin was employed as a stimulus for mammary secretion in patients with cancer of the breast, and the results throw new light on the physiology of women bearing this neoplasm. We shall also describe conditions which resulted in the induction of physiologic maturity in the human male, since knowledge of the action of hormones on the human breast is vague.

As the barest outline of the factors known to be necessary for the development of milk-secreting tissue, it is known that estrogenic substances (1) are essential to this process as is also a protein (12), the lactogenic hormone, luteotrophin, which induces milk formation in the breast which has been already prepared to a mature state. An enhancement of growth of the mammary epithelium occurs when other steroids are supplied in addition to estrogenic agents; among these synergistic steroids are progesterone (3) and testosterone (2, 11, 13).¹

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¹ Lactation has been observed repeatedly in this laboratory following the combined administration of androgenic and

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The effects of luteotrophin on the breast of women *post partum* has been extensively investigated, but otherwise few observations have been made in the human. Werner (14) administered a crude pituitary extract containing luteotrophin to eight castrate women 21–35 years of age; lactation was not observed, although in one woman “a few drops of colostrum-like fluid” could be expressed from the breasts. Goldzieher (4) treated menstrual disorders in women with luteotrophin, but mammary secretion was not described by him.

PROCEDURE

Luteotrophin,² dissolved in physiological saline made slightly alkaline (pH 9) with sodium hydroxide, was injected subcutaneously in daily amounts of 500 International Units; the solutions were freshly prepared, and the injections were continued for 7 days only.

The mammary secretion was considered to be milk when there appeared from the nipple a white opaque fluid crammed with fat droplets, staining red with Sudan III, without leukocytes other than colostrum corpuscles; the fluid was always examined with a microscope. Milk was obtained by manual expression of the breast or by suction with a breast pump.

This series comprised 21 female patients who had disseminated mammary cancer, and all had been subjected to unilateral mastectomy. There were also three men with advanced prostatic carcinoma who had been treated for therapeutic purposes with oral diethylstilbestrol for 20 months, 2, and 6 years, respectively. There were eight persons without mammary or prostatic cancers who served as controls.

In each case of mammary cancer a biopsy of the breast was obtained for histological purposes, the material being stained with Sudan III.³ Subsequent to the luteotrophin in-

estrogenic substances to immature dogs. For example, dog 8-45, age 123 days, was given injections of testosterone propionate, 20 mg. daily for 210 days, and during the last 75 days of this treatment, with diethylstilbestrol, 0.5 mg., in addition; luteotrophin, 250 I.U. was then injected on each of two consecutive days, and copious lactation occurred on the 3d day.

² We are indebted to E. R. Squibb & Sons, New York, N.Y., and to Professor C. H. Li of the University of California for generous gifts of luteotrophin.

³ The histologic preparations were made under the direction of Professor Eleanor Humphreys, of the University of Chicago, to whom we are indebted.

jections all the women with mammary cancer were subjected to combined adrenalectomy and oöphorectomy in one sitting. After about 1 week following the surgical procedures, the final maintenance dosage of cortisone acetate (50 mg/day) was instituted and continued in all the subjects.

OBSERVATIONS

Lactation, when it occurred, was never profuse; it varied from a tiny drop to *ca.* 0.5 cc. from each breast. Clear colostrum was not observed, and the mammary secretion was always milk, as defined above.

Mammary growth in the human male.—Estrogenic substances had been administered to three men in the treatment of disseminated prostate cancer for many months; after luteotrophin injection two lactated and one did not lactate.

W. N. (reported in brief earlier [5]), age 64, had taken diethylstilbestrol, 20 mg/day, orally for 2 years, after which interval sub-areolar button-like masses of mammary tissue could be palpated bilaterally; luteotrophin was then injected for 5 days, and milk was expressed from the breast on the 6th day. Orchiectomy was then performed, and both luteotrophin and estrogenic substances were discontinued. This man continued to lactate for 7 years when the formation of milk gradually ceased.

In the case of A. W., age 62, diethylstilbestrol (5–15 mg/day) had been ingested for 20 months after bilateral orchiectomy; the breasts became slightly enlarged. Luteotrophin was injected, and lactation occurred on the 7th day. A biopsy of the breast showed moderately well developed mammary ducts and alveoli containing milk. In the case of E. G., age 59, diethylstilbestrol (5 mg/day) was ingested almost continuously for 6 years; this resulted in the development of large pendulous breasts, but no lactation occurred after injections of luteotrophin.

Onset of lactation after luteotrophin.—Lactation occurred on day 3 of the injection series in one patient, on day 6 in seven patients, and on day 7 in eight patients.

Lactation in humans without cancer.—Luteotrophin was administered to two normal males, age 51 and 59, and to four normal females, age 34–59, and none lactated. However, lactation occurred in a healthy woman, age 66, and it lasted more than 4 months. Similarly, lactation was induced in a nulliparous ovariectomized woman with cystic disease of the breasts, but here milk persisted for only 10 days.

Lactation in certain women with mammary cancer.—Luteotrophin was injected in twelve women with advanced cancer of the breast, and in all these women lactation occurred (Fig. 1). Men-

struation had ceased in all (Table 1). One of these patients had not been treated with hormones; ten women had received testosterone for long periods of time; estradiol had been administered in one case. The range of age was 36–64 years; three patients were, respectively, ages 58, 60, and 64. In two patients oöphorectomy had been performed some years before testing with luteotrophin. Three of the women had not had pregnancies.

A biopsy of the breast was performed in each of these women, and histological examination revealed Sudanophilic fat droplets in the alveolar cells and in the lumina of the ducts. Among the twelve patients, carcinoma was found in five in the remaining lactating breast; in two cases these cancerous cells had traces of lipid secretory activity, the product resembling milk. In nine cases the primary tumor consisted largely or entirely of alveoli lined with one layer of neoplastic cells, which we designate adenocarcinoma. In three cases there was no morphologic "differentiation." The range of weight of both adrenal glands of individuals in this group was 3.2–10.3 gm.; the median weight was 8.0 gm.

All the patients in this category were subjected to removal of the ovaries and adrenal glands in one sitting (7), life being sustained with cortisone (6). In four patients lactation ceased within 1 week following the operation. In seven patients lactation was very prolonged, in four of these women persisting more than 7 months (Table 1), although luteotrophin was not supplied exogenously.

Failure of certain women with mammary cancer to lactate following luteotrophin.—There were nine women in this category (Table 2). None of these patients possessed menstruation; all had been treated with testosterone. There were no patients with unmixed mammary adenocarcinoma in this group, and four of the primary tumors lacked "cytologic differentiation." The range of adrenal weight was 6.2–9.4 gm.; the median weight was 7.9 gm.

Failure to suppress lactation in women with mammary cancer.—We attempted to suppress the lactation which had been induced with luteotrophin in three women with mammary cancer who had persistent secretion of milk following removal of the ovaries and the adrenal glands; none of the measures was efficacious.

The patient, K. A., received testosterone propionate, 50 mg. daily, by intramuscular injection for 21 days; she continued to lactate. Progesterone, 100 mg. daily, was injected intramuscularly for 22 days; lactation remained.

The patient, M. S., received diethylstilbestrol,

5 mg. daily, by intramuscular injection for 51 days; lactation was uninfluenced.

The patient, R. B., received diethylstilbestrol, 5 mg. daily, by intramuscular injection for 47 days. Then she was given methyltestosterone, 30 mg. daily, by mouth for 58 days. Neither treatment caused the secretion of milk to stop.

DISCUSSION

It must be emphasized that lactation was not copious in any of the humans when it had been induced by luteotrophin; merely small amounts of milk were obtained. It was apparent, however, from the histological studies of the mammary tissue obtained by biopsy that the secretion of

milk in any quantity was a criterion of maturity of mammary epithelium.

In the goat and guinea pig it is known that estrogenic substances can induce mammary maturity without the intervention of exogenous synergistic steroids. In the experiments of Lewis and Turner (9) diethylstilbestrol was implanted in two castrate male goats; one of these animals failed to lactate, while the other produced a small quantity of milk without luteotrophin injections. They obtained small amounts of milk from a male kid similarly treated. Nelson (10) found that estrone induced mammary growth with, later, lactation in the male guinea pig. Our observations demonstrate that diethylstilbestrol ingested for

TABLE 1
AGE, HORMONAL STATUS, TYPE OF MAMMARY CANCER, AND DURATION OF LACTATION
FOLLOWING LUTEOTROPHIN ADMINISTRATION

CASE	MENOPAUSE		CAUSE OF MENOPAUSE	HORMONAL TREATMENT, TYPE AND DURATION	CLASSIFICATION OF MAMMARY CANCER	DURATION OF LACTATION
	Age (yr.)	Age (yr.)				
1. E. M.	47	42	Surgical	Testosterone (14 months)	Adenocarcinoma	7+ months
2. G. M.	58	52	Spontaneous	Testosterone (14 months)	Adenocarcinoma	7+ "
3. K. A.	49	48	Irradiation	Testosterone (9 months)	Poorly differentiated adenocarcinoma	6+ "
4. R. B.	47	46	Irradiation	Testosterone (3 months)	Mixed ductal and adenocarcinoma	6+ "
5. M. S.	36	35	Irradiation	Testosterone (8 months)	Undifferentiated	4 "
6. M. H.	45	45	Surgical	Testosterone (1 month)	Undifferentiated	3 "
7. T. G.	64	47	Spontaneous	Estradiol (6 months)	Adenocarcinoma	1 week
8. L. W.	60	47	Spontaneous	None	Ductal and adenocarcinoma	4+ months
9. M. E.	46	40	Irradiation	Testosterone (28 months)	Ductal and adenocarcinoma	1 week
10. A. B.	49	46	Irradiation	Testosterone (24 months)	Undifferentiated	1 "
11. E. B.	49	49	Spontaneous	Testosterone (4 years)	Adenocarcinoma	1 "
12. M. B.	49	49	Irradiation	Testosterone (12 months)	Adenocarcinoma	—

TABLE 2
AGE, HORMONAL STATUS, AND TYPE OF MAMMARY CANCER OF PATIENTS WHO DID NOT
LACTATE FOLLOWING LUTEOTROPHIN ADMINISTRATION

CASE	MENOPAUSE		CAUSE OF MENOPAUSE	HORMONAL TREATMENT, TYPE AND DURATION	CLASSIFICATION OF MAMMARY CANCER
	Age (yr.)	Age (yr.)			
1. A. C.	52	48	Irradiation	Testosterone (6 months)	Undifferentiated
2. E. P.	46	42	Spontaneous	Testosterone (2 weeks)	Undifferentiated
3. M. M.	48	44	Irradiation	Testosterone (4 months)	—
4. E. B.	53	52	Irradiation	Testosterone (12 months)	Undifferentiated
5. A. M.	32	31	Surgical	Testosterone (7 months)	Ductal and adenocarcinoma
6. E. L.	32	32	Irradiation	Testosterone (6 months)	Undifferentiated
7. F. P.	54	47	Surgical	Testosterone (5 months)	Ductal and adenocarcinoma
8. M. W.	50	50	Irradiation	Testosterone (5½ months)	Ductal and adenocarcinoma
9. K. M.	55	50	Irradiation	Testosterone (12 months)	Undifferentiated and very poorly differentiated adenocarcinoma

prolonged periods of time can induce maturity of the breast in certain elderly human males. However, the human male differs from the animals just described in that spontaneous lactation was not observed; the injection of luteotrophin was necessary for milk formation.

The duration of lactation induced by luteotrophin was impressive, since milk commonly persisted for many months—and in one male for 7 years. The mechanism whereby this type of lactation is maintained for such long periods of time is at present unknown; we know that milk continues to be secreted both in the presence of the adrenal glands and in the absence of these structures and the gonads as well. Observations (8) have been made on experimental animals which are analogous to the clinical findings; most dogs with spontaneous mammary cancer possess lactation, and this characteristic persists for many months, at least, despite the removal of the adrenal glands and the ovaries.

SUMMARY

The breast of the human male can be induced to grow to a functionally mature state by the administration of estrogenic substances without additional exogenous steroid synergists. Spontaneous lactation was not observed in these men, but it was induced by luteotrophin.

The formation of milk in any amount by the breast is a criterion of functional maturity of the mammary epithelium. Luteotrophin induced the secretion of small amounts of milk in a group of women with mammary cancer and in a number of healthy women as well, and, in addition, in two human males to whom estrogenic substances had been administered for therapeutic purposes. Lactation did not occur in two normal males.

Many patients with carcinoma of the breast, even those in the 7th decade, secreted milk when the mammary gland was challenged with luteotrophin, despite the menopause and earlier removal of the ovaries; the primary mammary cancer in most of these women was adenocarcinoma. Other women with cancer of the breast failed to lactate when treated with luteotrophin; the primary neoplasm in most of these patients was undifferentiated.

A potential secretory capacity can be retained by the breasts of the human female in senility.

The prolonged administration of testosterone

did not cause functional atrophy of mammary epithelium.

When lactation was induced in human beings, the secretion often persisted for many months; it lasted for 7 years in one man. In certain women with mammary cancer lactation ceased abruptly following the removal of the ovaries and adrenal glands, while in others it persisted. In three women with this persistent lactation, the secretion of milk was not stopped by the administration of diethylstilbestrol, testosterone, or progesterone.

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FIG. 1.—Milk which appeared following expression of the breast in a woman, age 58, with mammary cancer, following the injection of luteotrophin for 6 days.

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