Fibrocystic Disease of the Breast

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Pathogenesis of Fibrocystic Disease

In the phylogenetic development of man, a specialized sweat (apocrine) gland evolved into the complex mammary structure. The breast remains quiescent or infantile in the absence of ovarian function and begins to develop with the first stirring of ovarian activity. Estrogens stimulate fat deposition, stromal proliferation, and growth of the ductal system; later, in concert with progesterone, estrogens evoke the development of glandular acini and lobules. The mammary tree undergoes cyclic stimulation and regression, somewhat akin to the cyclic changes of the endometrium. Aside from estrogens and progesterone, other hormones (prolactin, growth hormone, corticotropin, androgens, thyroid, and insulin) play an important role in the preparation of the mammary gland for its destined role of galactopoiesis and lactation. Moreover, neural, nutritional, and psychologic factors also influence mammary development, structure, and function. Benign breast disease (BBD), of which fibrocystic disease (FCD) is by far the most common, results from an imbalance in estrogen-progestogen ratios or inappropriate target gland response to changing tides of hormonal stimulation. As a consequence, Stout believed that almost all women over 30 years of age, regardless of marital or lactational history, have affected mammary glands to a greater or lesser degree (1). Frantz et al. found histologic evidence of FCD in 54% of 225 postmortem examinations of so-called normal breasts (2).

Histologically, FCD may present as simple cystic glandular hyperplasia (Fig. 1A), adenosis (Fig. 1B), chronic cystic mastitis with apocrine metaplasia (Fig. 1C), and ductal papillomatosis (Fig. 1D). Fibroadenoma, a pseudoencapsulated tumor, is another variant (Fig. 1E).

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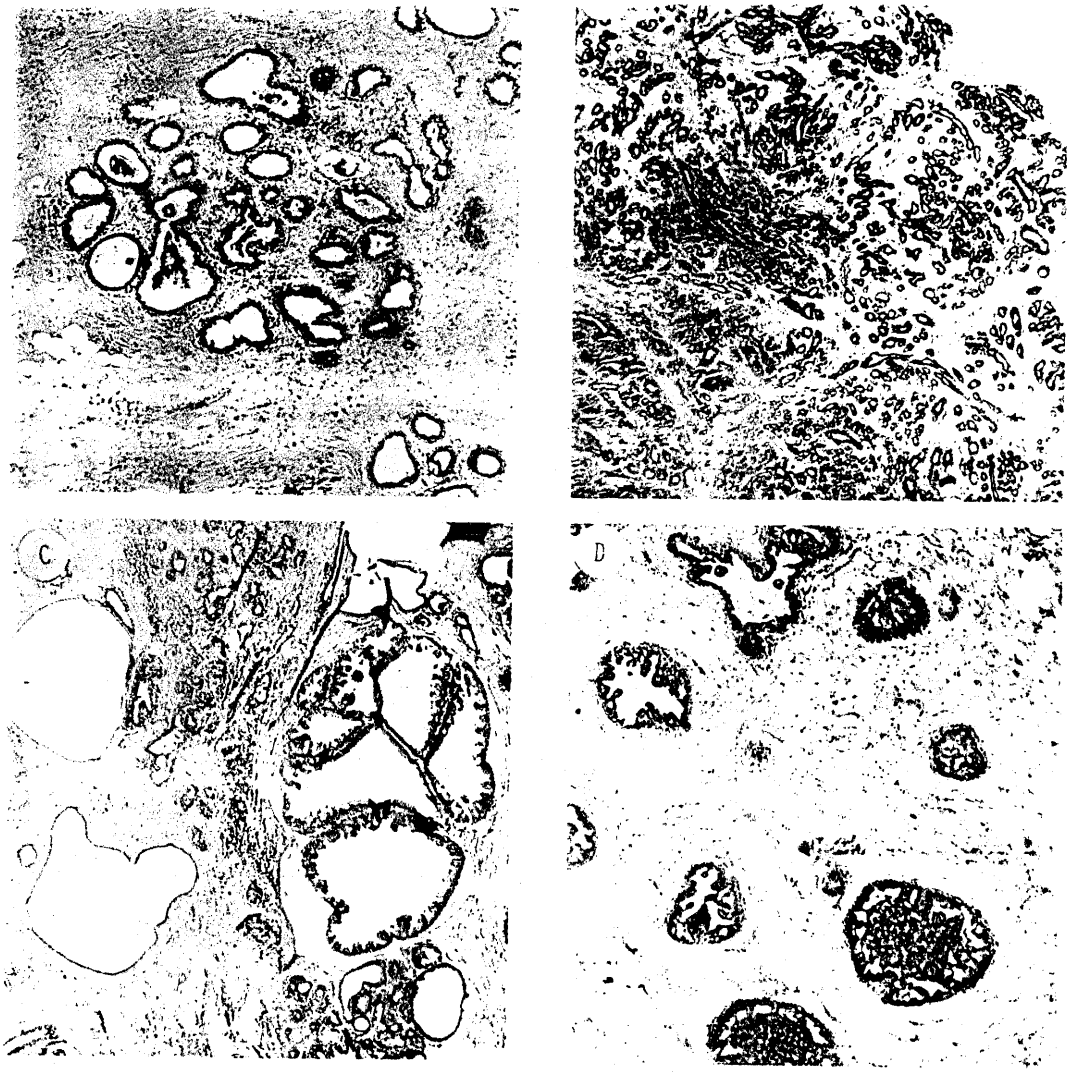
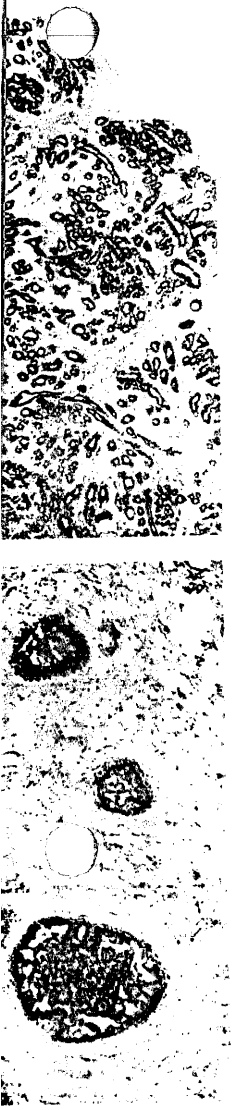


FIG. 1.A. *Cystic glandular hyperplasia,* **B.** *adenosis,* **C.** *chronic cystic mastitis with apocrine metaplasia,* **D.** *ductal papillomatosis,* **E.** *fibroadenoma, a pseudoencapsulated tumor.*

Experimental Studies

Experimental animal data yield some clues as to the etiology of FCD, although extrapolation to the human condition may not be appropriate.

1. Long-term administration of estrogens to virgin goats induced not only ductal proliferation with papillomatous epithelial outgrowths but also dilated alveoli (3).
2. Some of the abnormalities produced by chronic estrogen administration could be



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3. Certain progestogens, such as chlormadinone and depomedroxyprogesterone acetate (DMPA), may induce marked myoepithelial and glandular hyperplasia and, occasionally, neoplasia in beagle dogs but not in other dogs or other species of animals. DMPA proved innocuous when administered in massive doses to humans (5).
4. There is now a considerable amount of evidence that prolactin is important in tumor growth in some strains of rats and mice.
   a. Prior to using carcinogenic agents in rats, the administration of prolactin will diminish their capacity to tumor formation, but if given after the carcinoma is induced, the tumor will grow rapidly; if prolactin is then rapidly withdrawn, complete regression may take place (6).
   b. Chemically induced rat mammary carcinoma appears to be dependent on prolactin. Prolactin alone will stimulate tumor growth in the oophorectomized, adrenalectomized, hypophysectomized rat; estrogens will not (7).
   c. Estrogen-progestogen combinations (Enovid) will suppress carcinogen-induced mammary tumors in female rats (8).

Clinical Observations

1. The anovulatory female rarely develops severe FCD, as manifested by marked pain and lumpiness (9); however, others believe that the unopposed estrogens of anovulatory women probably promote breast pathology (10).
2. Oral contraceptives reduce the incidence of FCD and the frequency of mammary cancer in comparison with controls (11).
3. The administration of methyltestosterone, and at times testosterone, to males has resulted in nipple soreness and gynecomastia.
4. Cancer of the breast has occurred in two male transvestites who had been on estrogens (12). The development of mammary

Estrogens have been indicted as carcinogenic for the breast in humans based on animal studies in rodents. Geschiter and Hartman found no evidence that estrogens in extremely high doses over periods of 7 years and 7 months produced malignant changes in monkeys (14). Burch and Byrd concluded from a study of 511 estrogen-treated women followed for 9 or more years that the incidence of cancer of the breast was essentially the same as in a peer group (15). Hoover attempted to link exogenous estrogen replacement therapy to breast cancer in his review of menopausal women receiving estrogens in Gray's private practice (16). He found a slight increase that was not statistically significant except in women on estrogens for 10 or more years. Bland, in restudying the same series of patients and adding his own, arrived at a different conclusion: there was a slight decrease of mammary cancer rather than increase in estrogen-treated women (17). Gambrell and colleagues also found less mammary cancer in the estrogen-treated group than in non-estrogen users (18).

One of us (CN) reviewed the records of the senior author on women who had received continuous estrogens through implantation of estradiol-17β pellets from 1–21 years. There were two groups: one comprised 490 women of reproductive age from 16–44 who received estrogens and cyclic courses of progesterone for 18,480 cycles for an average of 1540 woman-years of therapy. No mammary cancers were encountered (Table 1) (19). The second group comprised 1058 women aged 45 and over who had received continuous estrogens for 9175 years (about half also received cyclic progestogens). Eleven mammary cancers were found, for an incidence in this perimenopausal group of 138.0:100,000 women-years. The expected incidence according to the tables of Cutler and Young in the Third National Cancer Survey was 239.3:100,000 woman-years (Table 2) (20). Incidentally, 197 patients had breast biopsies: 98 before and 99 after entering this study. Even if an equal number of women developed mammary cancer but were lost to follow-up, the frequency in our series was not significantly greater than that expected in a nontreated peer group. The incidence was much below the national average

TABLE 1. Age-Related Breast Cancer Incidence of Women on Continuous Estrogen Therapy for 1540 Women-Years

Age	No. of Women Treated	No. of Mammary Cancers	Cancer Incidence	Expected Incidence*
15–19	24	0	0:100,000	0.2:100,000
20–24	82	0	0:100,000	1.1:100,000
25–29	95	0	0:100,000	8.4:100,000
30–34	94	0	0:100,000	26.7:100,000
35–39	134	0	0:100,000	57.3:100,000
40–44	61	0	0:100,000	106.0:100,000
31.2	490	0	0:100,000	33.2:100,000

*Cutler SJ, Young JL, Jr. Third national cancer survey: Incidence data. Natl Cancer Inst Monogr 41, 1975.

alleged relationship between estrogen and mammary cancer has not been proved.

Risk of Mammary Cancer

The melancholy facts, however, are that 1 in 11 women in the United States will develop breast cancer in her lifetime; over 108,000 new cases could be expected in the year 1981; and the death rate from breast cancer has not improved over the past 40 years. There is an exponential increase in its incidence during reproductive years and in the postmenopausal period. The development of breast cancer is not a chance, random event that occurs throughout the population; various factors are credited with increasing the risk: family history, racial origin, nulliparity, obesity, high dietary intake, chronic psychologic stress, and fibrocystic disease of the breast.

Warren claimed that malignancy was 4.5 times greater in women who had been biopsied for FCD than in a normal female population (21). Cole and MacMahon reviewed the world literature and found the presence of FCD increased the risk of cancer by 2.64 times (22). Foote and Stewart studied the incidence of florid FCD in breasts amputated for cancer and noted five times more frequent hyperplasias in mammary cancer breasts than in biopsies for benign lesions (23). In a recent review, Van Bogaert conceded that mammary cancer is often preceded and accompanied by BBD or dysplasia and cited a 3- to 4.5-fold increase in cancer in those women who have had surgery for BBD in the past (24). Diametrically opposite views are also held that the relationship, if any, is a tenuous one (25).

What is FCD?

Fibrocystic disease is an exaggeration of the normal tissue response of the breast resulting from the ebb and flow of ovarian hormones. The response is not uniform and may vary considerably, depending on the hormonal milieu and individual idiosyncratic responses. FCD is characterized by pain and tenderness, most marked in the premenstrual period but later may continue throughout the cycle. The lumpiness or nodularity may be localized or generalized, unilateral or bilateral. These lesions differ from one another histologically, and, as a result, some one-half dozen varieties are listed under the rubric of benign breast disease—such as fibrocystic disease, mazoplasia, dysplasia, adenosis, sclerosing adenosis, ductal papillomatosis, apocrine metaplasia, chronic cystic mastitis (Schim-

TABLE 2. Age-Related Breast Cancer Incidence of Women on Continuous Estrogen Therapy for 9175 Women-Years

Age	No. of Women Treated	No. of Mammary Cancers	Cancer Incidence	Expected Incidence*
45–49	255	3	155:100,000	174:100,000
50–54	263	1	50:100,000	196:100,000
55–59	259	3	152:100,000	229:100,000
60–64	136	2	194:100,000	251:100,000
65–69	95	2	277:100,000	283:100,000
70	50	0	0:100,000	303:100,000
55.5	1058	11	138:100,000	293.3:100,000

*Cutler SJ, Young JL, Jr. Third national cancer survey: Incidence data. Natl Cancer Inst Monogr 41, 1975.

melbusch's disease), macrocystic disease (blue-domed cyst of Bloodgood), and myoepithelial hyperplasia (Reclus' disease).

Fibroadenomas are mobile, solid, well-defined, painless masses; intraductal papillomas usually manifest their presence with a unilateral watery, yellow, or bloody nipple discharge; duct ectasia manifests itself with a multicolored, commonly bilateral nipple discharge. The latter three entities, variants of the same inappropriate tissue responses are, as a rule, not responsive to hormonal manipulation. It is generally believed that FCD regresses with the onset of the menopause, but Rush and Kramer found that 69% of women 70 years of age or more have common hyperplastic lesions (26).

The Role of Hormones in FCD

Reported surveys showing that oral contraceptives lessen the incidence of FCD suggest that hormonal manipulation can effectively reduce the frequency of this disease and, perhaps in turn, the incidence of mammary cancer. The role of the various hormones in breast physiology is not entirely clear, but the following facts are on record. Estrogens are stimulatory to ductal growth, stromal proliferation, and prolactin production; in sufficient dosage, estrogens inhibit lactation; androgens stimulate apocrine glands; fluid aspirated from mammary cysts is rich in Δ^4-androstenedione and dehydroepiandrosterone (27). Androgens act at the critical period in fetal development to prevent mammary development (28). Antiandrogens administered at this time permit breast growth in males (29). Cyst fluid also contains higher levels of estriol, prolactin, and human chorionic gonadotropin (hCG) than are present in plasma (30, 31). Prolactin stimulates lactation and breast carcinoma but is also inhibitory since multiparas have less breast cancer. Thus, various hormonal preparations have been employed in the management of FCD, such as estrogens and androgens (32), progesterone (33), and danazol, a new steroidal agent related both to an androgen and a progestogen (17α-ethinyl testosterone and ethisterone) (34). Other modalities have been employed: bromocryptine (35), vitamin E (36), elimination of methylxanthines (coffee, tea, cola drinks, chocolate) (37), and an antiestrogen (tamoxifen) (38).

Diagnosis and Screening

Women complaining of breast pain, lumpiness, or both, or a nipple discharge that is serous, serosanguineous, or bloody should be subjected to a thorough manual breast examination. Cystic masses should be aspirated and the contents examined for cytologic atypia. It would seem important to find those women who are at greater risk of developing mammary cancer because of florid fibrocystic disease.

Common benign conditions cause breast hyperthermia. The severity of such a disorder is usually reflected in increased heat production, as measured by thermograms (the human skin emits infrared radiation). A recent advance, contact plate thermography, is based on the ability of liquid cholesterol crystals to change color under the influence of infrared rays. In most instances, abnormal thermal impressions precede radiologic changes in early carcinoma. In this respect, an abnormal thermal test in the absence of any palpable mass will identify patients in the high-risk category. Those with abnormal thermal impressions or with suspicious palpable densities should be subjected to xeromammograms and biopsies when indicated. It should be borne in mind that the average breast cancer is present for 6–8 years before it reaches the clinically palpable size of 1 cm. Xeromammograms can detect some breast cancers in this preclinical stage 1–2 years before they reach a clinically palpable size. While thermal tests are harmless and may be taken as often as necessary, mammograms are potentially dangerous because of the large doses of ionizing radiation and should be limited to no more than one exposure every 12–24 months, except in special cases. Biopsy of a suspicious lesion should never be deferred on the basis of a negative mammogram or thermal pattern (39).

Therapy and Prevention

It should be recalled that approximately 73% of all surgical procedures on the breast prove to be for benign breast disease (40). However, Humphrey demonstrated that 64% of women undergoing mastectomy for cancer had a previous biopsy revealing florid FCD 1–13 years earlier (41). Therefore, it is incumbent on us to determine whether reduction of nodosities by various modalities of therapy will result in a lessening of mammary cancer.

Fibrocystic disease should be medically managed unless a dominant lump develops, in which case a biopsy should be performed. Our 10 years' experience with a new steroidal agent, danazol, permits us to say that a 3- to 6-month trial of 100–400 mg/day will eliminate pain and nodosities in some 69% of women, and in another 30% the signs and symptoms will be considerably diminished (Table 3). The need for biopsy is frequently obviated; moreover, when multinodular breasts are encountered, a course of danazol enables the surgeon to direct his attention to the dominant nodule, i.e., the one that fails to regress satisfactorily following therapy. Danazol is not without trivial side effects, such as muscle cramps, oiliness of the skin, hot flashes, and occasional acne and mild hairiness. No serious untoward reactions have thus far been observed (Table 4) (42). Thermal studies often reveal a cooling of the breast following adequate therapy.

Conclusions

Recent reports indicate that women on estrogens or sequential estrogen-progesterone therapy are at no greater risk of developing mammary cancer than non-estrogen users. The findings that women on oral contraceptives have far less FCD than a peer group lends support to the long-held notion that this disturbance has some hormonal basis. The key to the problem may be a change in the hormonal milieu; thus, bromocryptine has proved effective by reducing prolactin levels and tamoxifen aids by neutralizing the action of estrogens. The administration of estrogens, testosterone, or progesterone often has proved effective.

The claim has been made that women with florid FCD are more prone to develop breast cancer. Women who are at greater risk may be identified with the help of thermography and mammography.

In recent years, danazol—an impeded androgen—has been found quite effective in the management of FCD. Only time will tell whether the amelioration of this disorder will lead to a decrease in the frequency of mammary cancer.

TABLE 3. Evaluation of Breast Nodularity in 130 Patients with Fibrocystic Breast Disease After Receiving 100–400 mg Danazol Therapy

Dosage	No. of Patients	Elimination	Decrease	No Change
100 mg	40	26	13	1
200 mg	55	36	19	0
400 mg	35	28	7	0
0 Total	130	90 (69.2%)	39 (30%)	1 (0.8%)

TABLE 4. Side Effects During Danazol Therapy

Side Effects	No. of Patients
Muscle cramps	19
Acne	15
Oily hair	12
Hot flashes	4
Nervousness	4
Weight gain	3
Hairiness	2
Increased libido	4
Edema	4
None	63
Total	130

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