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THE TREATMENT OF BENIGN BREAST DISEASE WITH DANAZOL*

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Benign breast disease, aside from fibroadenomas and intraductal papillomas, frequently responds favorably to hormonal therapy. Although the use of estrogen, androgens, and progestogens often proves useful, danazol, in our hands, was found more consistently effective. Danazol, an impeded androgen derived from a progestogen, 17α-ethinyltestosterone, was employed in doses of 100 to 400 mg/day for 3 to 6 months in the treatment of fibrocystic disease. This agent proved efficacious in eliminating nodularity in the majority of cases, with partial resolution in most of the others. Many women to whom surgery had been previously suggested were spared surgical interference because of a satisfactory response to danazol therapy.
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Benign breast disease (BBD) refers to a galaxy of pathophysiologic lesions resulting from progressive/regressive changes involving the component mammary structures, i.e., ducts, acini, stroma, and fat tissue. Fibrocystic disease is the most common of the BBD group and is believed to be an exaggeration and distortion of the cyclic changes that normally occur in the menstrual cycle. Depending on individual responsiveness to hormonal tides, a variety of histopathologic changes occur which have received different labels: mammary dysplasia, mazoplasia, chronic cystic mastitis, cyclic mastopathy, adenosis, sclerosing adenosis, adenofibroma, ductal papillomatosis, blue dome cyst of Bloodgood, myoepithelial hyperplasia of Reclus, and hyperplastic cystic disease of Schimmelbusch.

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These disorders—variants of fibrocystic disease, present alone or in combination, single or multiple, in one or both breasts—are frequently responsive to hormonal manipulation. Other lesions such as intracanalicular fibroadenoma, duct ectasia, and intraductal papilloma, which may or may not coexist with fibrocystic disease, also belong to the spectrum of BBD but are not hormone-responsive, nor, incidentally, are old sclerotic lesions of fibrocystic disease.

The precise incidence of BBD is not known but it is considerable. Bonte[1] reported that "8% of premenopausal women present excessive and irregular engorgement of nodularities, while another 8% have cystic disease, adenosis or fibrous disease." Of all breast lesions that come to surgery, about 73% are benign.[2] The purpose of this communication is to offer an alternative to surgery in the management of fibrocystic disease by the administration of danazol, a derivative of 17α-ethinyltestosterone. Danazol, an impeded androgen, is capable of suppressing the ovulatory luteinizing hormone surge,[3] interferes with gonadal steroidogenesis (both directly and indirectly),[4] dampens the gonadotropin response to luteinizing hormone-

TABLE 1. *Post-Therapy Evaluation of Breast Nodularity in Forty Patients Having Benign Cystic Breast Disease after Receiving 100 mg Danazol Therapy for 3 to 6 Months*

	Evaluation after				
	6 Mo	12 Mo	24 Mo	36 Mo	48 Mo
Elimination	26	25	26	27	7
Partial resolution	13	14	13	7	1
Unchanged	1	1	0	0	0
Total	40	40	39	34	8

releasing hormone[5] and is believed able to block estrogen and progesterone receptors at the breast tissue level.[6]

METHODS

The study was composed of two series of cases: one in which a dose of 100 mg of danazol/day was employed for 3 to 6 months in 40 women between the ages of 28 and 48 years who were seen because of breast nodularity with and without accompaniment of pain and tenderness. Almost all patients were seen at least at 6-month intervals for the first 2 years, and many of them for up to 4 years. Xeromammograms* were obtained whenever any suspicion of malignancy was entertained. If a cyst was suspected, aspiration was attempted and Papanicolaou smears were made if an aspirate was obtained. In the second series, doses of 200 mg/day were employed in 66 women and 400 mg/day in 95 women. The data reported here were furnished by a half-dozen investigators at a round table conference held in Washington, D. C., on May 14, 1979.

RESULTS

Our experience in the past has shown that many women with mastalgia and fibrocystic disease often respond in some measure to treatment with hormones such as estrogens, androgens, and progestogens. Most physicians, justly or unjustly, fear the use of estrogens in this disease because of possible exacerbation of the signs and symptoms or the aggravation of latent cancer. They avoid the administration of androgens because of possible virilizing effects, and others do not like progestogens because such agents often induce depression, tension, and emotional irritability.

While using danazol in the management of patients with endometriosis, we noted a lessening or elimination of nodosities, pain, and tenderness of coincidental fibrocystic disease. As a result of this observation, studies were undertaken by our group and others to note the effect of different dosage schedules of danazol on fibrocystic disease.[7, 8] Table 1 tabulates our results with a 100-mg dosage in 40 patients. At the end of 2 years, 39 of 40 patients returned for follow-up. We found that nodosities were eliminated in 26 patients, with partial resolution in 13.[9]

The results compare favorably with those achieved with 200-mg and 400-mg dosages (Table 2). In the latter group, the effectiveness of the drug seemed to parallel the onset of disturbances in menstrual pattern. For those on 200 mg/day for 6 months, a normal menstrual pattern was still present in 18% by the 5th month, whereas on 400 mg/day only 2% continued to have a normal cycle. The remainder either had scanty menses, irregular spotting, or complete amenorrhea. No improvement was noted in 9% of those on 200 mg/day or in 15% of those on 400 mg/day. It appears that poorer results were obtained with the larger dosage. The probable reason is that the 400-mg dose was employed in the more severe cases.

DISCUSSION

Optimal effectiveness of ductal development depends on estrogen; alveolar development on estrogen and progesterone. Prolactin, growth hormone, adrenocorticotropic hormone, corticoids, insulin, thyroxine, and androgens play facultative roles. In experimental animals, prolonged estrogen administration induces ductal hyperplasia with papillomatous outgrowths and stromal proliferation, whereas prolonged progesterone administration induces alveolar growth and some ductal development. Cystic alveoli may occur, depending on the ratio of estrogen to progesterone administered.[10, 11]

TABLE 2. *Fibrocystic Disease Response to Danazol at Completion of Medication Relative to Nodularity*[a]

Dosage	No. of patients	Elimination	Decrease	No change
200 mg	66	36 (54%)	24 (36%)	6 (9%)
400 mg	95	64 (67%)	16 (17%)	15 (16%)

[a]Material collected from data obtained at the Symposium on Fibrocystic Disease of the Breast, Washington, D. C., May 4, 1979.

*Xeromammography is a xeroradiographic technique developed by Xerox Corporation, El Segundo, Calif.; it yields a mammogram with the image produced on paper rather than X-ray film. The advantages are that in the physics of image production there is an edge-enhancement effect which makes small calcifications more readily visible, and a better image of the whole breast is obtained by this method.

TABLE 3. *Diurnal Prolactin Values in Two Women with Fibrocystic Disease*

Patient	Age	Serum prolactin level	
		4 A.M.	4 P.M.
		ng/ml	*ng/ml*
1	17	25.84	10.90
		19.84	4.72
2	41	39.03	28.88
		52.25	30.37[a]

[a]After 3 days of 400 mg of danazol.

TABLE 4. *Decrease in Prolactin Levels folowing Danazol, 400 mg/Day*

Patient	Control	2 Days	6 Days	30 Days	60 Days
	ng/ml	*ng/ml*	*ng/ml*	*ng/ml*	*ng/ml*
3	49.12			12.0	8.77
4	35.0	24.33	29.8	9.7	

Insofar as the human is concerned, the etiology of benign breast disease remains conjectural since human experimentation is not feasible. That cyclic hormonal changes play a role may be deduced from the report of Delarue and De Brux[12] of a young woman whose tuberculous fistula of the breast drained each month from day 18 and stopped with the onset of menses during an 8-month period of observation. Various authors have incriminated various hormones in the causation of fibrocystic mastopathy: disparate follicle-stimulating hormone/luteinizing hormone secretion, elevated estradiol levels, depressed progesterone production, low androgen levels,[13] and high prolactin levels.[14] Geller et al.[15] were not able to demonstrate a luteal deficiency in 63 ovulatory women with fibrocystic disease, but found an excessive prolactin response to thyrotropin-releasing hormone stimulation in 70% of cases.

This much is known about the etiology of BBD: estrogens stimulate prolactin production; increased prolactin shortens the life-span of the corpus luteum and lowers progesterone output; and low estrogen levels, as well as antiestrogens, reduce prolactin secretion. Our own limited studies have not been able to pinpoint any consistent variations in the hormonal profile. In most instances, serum prolactin levels and their diurnal rhythm were normal (Table 3). In some instances, however, moderately elevated prolactin levels were obtained, and a decrease in these levels followed danazol therapy (Table 4).

A consensus as to the etiology of BBD has never been reached, nor has there been an explanation of why various hormonal preparations may be effective. Despite the fact that estrogens are believed to be responsible for causation of benign breast disease, contrary to expectation several authors have found them often useful, whereas others prefer androgens.[16] The effectiveness of progestogens and oral contraceptives also has been reported. More recently, Ricciardi and Ianniruberto[17] have reported that the antiestrogen tamoxifen was promising. The protagonists of the theory that prolactin has much to do with the causation of fibrocystic disease are encouraged by the report of Montgomery et al.[18] that bromocriptine may be used to advantage.

CONCLUSIONS

Extensive trials with the new hormonal agent, danazol, indicate that the pain, tenderness, and lumpiness of BBD may be eliminated or greatly reduced, lessening the urgency of surgery. Intracanalicular fibroadenomas and intraductal papillomas are not responsive. The persistence of a dominant nodule after a 3-month course with this steroid could serve the surgeon well by pointing to the site where biopsy would prove informative. Danazol is a valuable addition to our therapeutic armamentarium for the conservative management of certain types of benign breast disease.

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