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Progesterone Insufficiency in Benign Breast Disease

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Benign breast disease no longer poses only the problem of differential diagnosis with breast cancer. An estradiol to progesterone imbalance is the leading risk factor for breast cancer. Moreover women suffering from benign mastopathy have a two- to four-fold risk of breast cancer compared to normal women.

Benign breast disease deserves close attention when we are studying the pathophysiology of breast cancer, and may indeed be considered an important intermediary stage in the evolution from normal breast to carcinoma in view of reported epidemiological, pathological, and hormonal data (5,13,23,61).

It seems reasonable to consider benign breast disease not only as a restrictive entity limited to histopathological and mammographical characteristics, but it is now more appropriate to have an overall view of this disease in terms of hormone dependency and of hormonal milieu permitting the development of breast lesions with different steps of cellular alterations.

HORMONE DEPENDENCY OF THE NORMAL MAMMARY GLAND

Previous findings of specific receptors for estradiol and progesterone in breast cancer (38–40) and in benign breast disease (31,41,42,60) classified the mammary gland as hormone-dependent. Nevertheless, the hormone dependency of breast tissue has been less explored than that of uterus. Morphologically, estradiol is the hormone initially responsible for (a) differentiation and development of the ductal epithelium (15), and (b) increasing mitotic activity in the cylindric cells of the internal layer of the ducts (28,48,51,52). The connective tissue around the ducts is also very sensitive to the action of estrogen. Under estrogen stimulation, it secretes a watery mucoid substance that has a tendency toward hyalinization (1,3).

Progesterone acts, in the breast as well as in the endometrium, as both a complement and an antagonist to estradiol. Synergistically with estrogens, it acts on the distal part of the duct, favoring differentiation into acini. It therefore ensures the organization of the mammary gland for its secretory function (58). But pro-

gesterone is also an antiestrogen that can antagonize the action of estradiol on duct cells by changing the proliferative effect of estrogens into a mitotic resting stage and cellular differentiation (75). Biochemical evidence of the antiestrogenic action of progesterone—particularly its ability to decrease the concentration of estradiol receptors—has been observed recently in human mammary tissue (31), as it was in the endometrium (72).

In human physiology, the existence of harmonious ovarian cyclic function ensures perfect mammary development. In particular, the presence every month of a corpus luteum that secretes a sufficient quantity of progesterone for a normal duration of time permits a coherent organization of the galactophoric system and of the adjacent connective tissue.

EXPERIMENTAL DATA

Many investigations have shown that the mammary gland of different species reacts differently to estrogen when the hormone is administered in physiologic or supraphysiologic doses. Bässler (3) showed that large doses of estrogen administered for long periods to castrated female rats induced proliferation and dilatation of the lobules in the glandular tissue, with formation of cysts and overgrowth of the epithelium. In addition, estrogen provoked an increase in circumcanalicular and intralobular connective tissue.

The time sequence of mammary morphologic alteration after the administration of estradiol to female rats is the following: epithelial proliferation, secretion, dilatation of ducts, formation of cysts, and fibrosis. These changes observed under the effects of supraphysiologic doses of estrogen seem to be comparable to human fibrocystic disease (15,51,52). On the contrary, when estradiol is administered to castrated female rats in combination with progesterone, complete and proper development of the mammary gland is observed when the ratio between estrogen and progesterone is adequate. Cowie et al. (12) found in castrated goats that hexoestriol and progesterone combined resulted in uniform development and secretion when the dose of estrogen remained slight (0.25 mg/day). An increase in the estrogen dose to 1 mg/day produced cysts and epithelial proliferation. The antagonistic activities of estrogen and progesterone on connective tissue are also well documented. Whereas the injection of estrogen into some animals induces an increase in the mucopolysaccharide content, particularly the hyaluronic acid content, in all connective tissues, progesterone appears to have the opposite effect (3,18).

OVARIAN FUNCTION IN WOMEN WITH BENIGN BREAST DISEASE

Between 1972 and 1978, 550 patients with various benign breast diseases have been observed in our department. In addition to clinical, mammographic, thermographic, and cytologic examinations, an endocrine study was carried out on each patient. First, the basal body temperature (BBT) was recorded for two consecutive

months, then the endocrine function
patients was evaluated.

Among the 550 patients seen for
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241 patients had either anovulatory
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months, then the endocrine function of the corpus luteum in the case of ovulating patients was evaluated.

Among the 550 patients seen for breast diseases, we paid particular attention to 309 patients who had apparent ovulatory cycles. This presumption was based on BBT measurements showing a nadir followed by a luteal plateau lasting for 8 to 12 days. The length of the cycles studied varied between 24 and 40 days. The other 241 patients had either anovulatory cycles or had cycles of more than 40 days and clear evidence of an ovulatory disorder. In a first study, 109 women between 18 and 40 years of age were investigated (68). They had different sorts of benign breast disease, but all were suffering from mastodynia at the time of the investigation. One blood sample for progesterone and estradiol radioimmunoassay was collected from each of the 109 patients between the first and the last day of the luteal phase. The same assays were carried out on 50 normal women (Fig. 1). In the group of patients, the daily values of plasma progesterone were significantly lower than those of normal women ($p < 0.001$), whereas no significant difference was noted between plasma estradiol levels of patients and normal women.

In another study on 184 patients (69), blood samples were taken on 3 different days of the luteal phase. The plasma was pooled, and then estradiol and progesterone were assayed. The results provide the mean values of estradiol and progesterone over 3 days. As regards plasma progesterone, the observed values were lower than normal. When the 184 patients were divided into 5 groups according to clinical features (Fig. 2), plasma progesterone was uniformly low, without significant differences from one group of patients to another.

Plasma estradiol levels were in the normal range in patient groups I, II, and III (respectively, isolated mastodynia, cysts, and fibrocystic disease). However, they were significantly higher than in the normal women ($p < 0.01$) in groups IV and V (respectively, patients with fibroadenomas and patients with increased breast nodularity).

In order to investigate if a correlation between plasma progesterone and estradiol levels existed during the luteal phase, the ratio of mean plasma progesterone to mean estradiol level observed during the luteal phase [P.E.L.: progesterone (P)/estradiol (E_2) during luteal phase] was calculated as follows:

$$\text{P.E.L.} = \frac{\text{P (pg/ml)}}{\text{E}_2\text{ (pg/ml)}} \times 0.01$$

In the 50 normal women, the P.E.L. ratio was 1.58 ± 0.14, whereas in an entire group of 184 patients, this ratio was significantly lower: 0.66 ± 0.03, $p < 0.001$ (Fig. 3). This P.E.L. ratio was also established for each group of patients. The highest ratio was found for the patients with cystic mastitis, and the lowest was observed in the patients with isolated mastodynia.

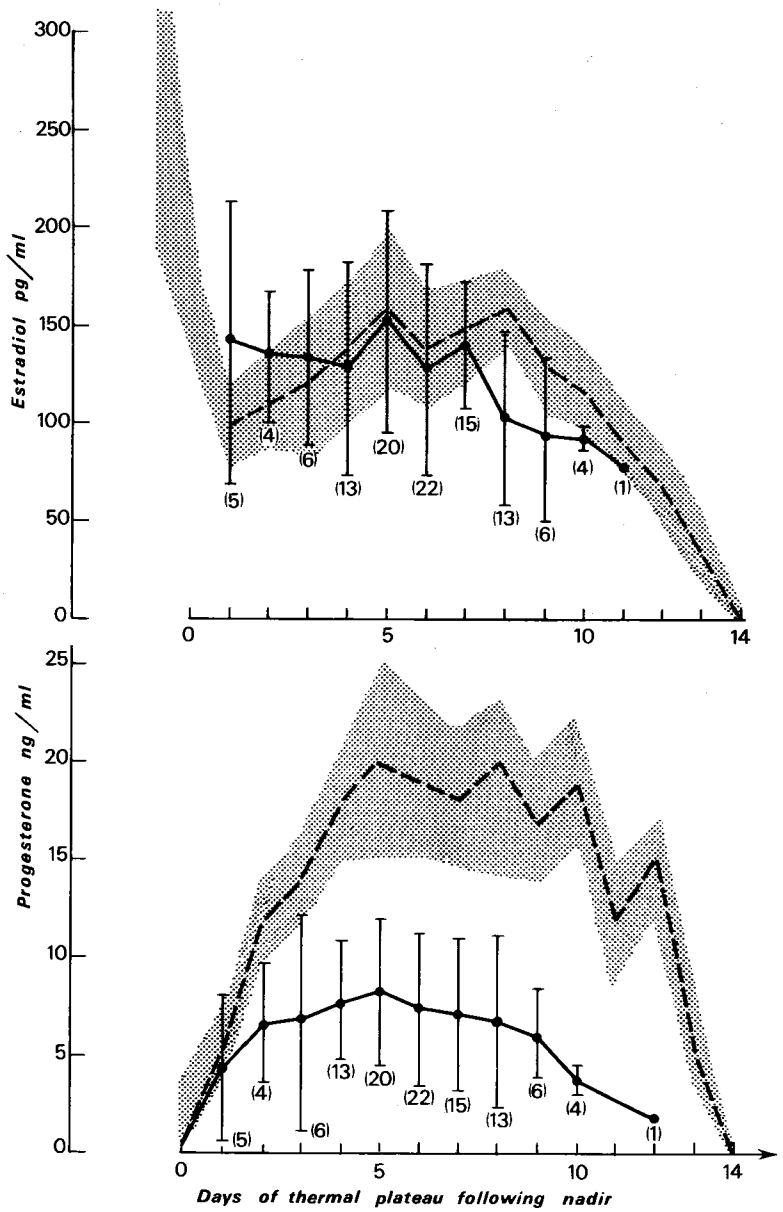

FIG. 1. Mean ± SE for plasma estradiol and progesterone values in 109 patients with benign breast disease studied from day 1 to day 12 of the thermal plateau. In parenthesis: number of determinations per day. Shaded area: mean ± SE for plasma estradiol and progesterone values in 50 normal women studied at the same time in the menstrual cycle. (From Sitruk-Ware et al., ref. 68.)

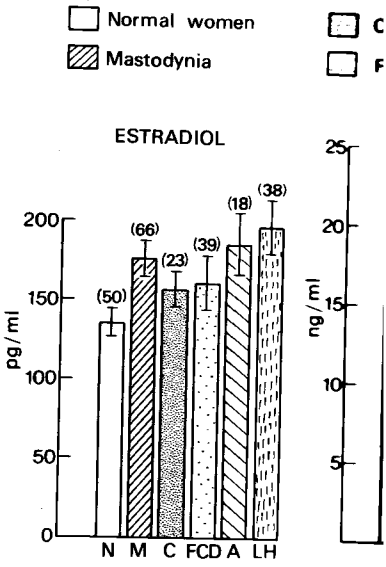

FIG. 2. Plasma levels of estradiol, prog
groups of patients with mastodynia (M), is
enomas (A), and increased nodularity of bc
(From Mauvais-Jarvis et al., ref. 52.)

ESTRADIOL AND PROGESTE
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High-affinity binding of estradiol and
methods previously described (41,42).

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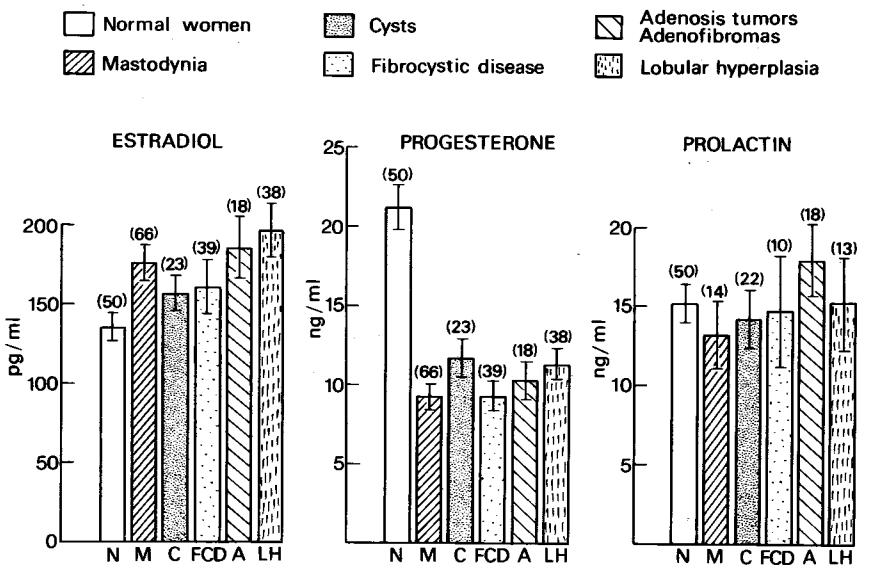

FIG. 2. Plasma levels of estradiol, progesterone, and prolactin during the luteal phase in groups of patients with mastodynia (M), isolated cysts (C), fibrocystic disease (FCD), fibroadenomas (A), and increased nodularity of both breasts (LH) compared to 50 normal women (N). (From Mauvais-Jarvis et al., ref. 52.)

ESTRADIOL AND PROGESTERONE RECEPTORS (ER and PR) IN BENIGN BREAST DISEASE

There is little information concerning the presence of receptors in benign breast disease (31,35,41,42), mainly because of the fact that the breast is a very heterogeneous tissue in which receptive structures (ducts and acini) are spread into connective tissue. Therefore, it was interesting to look for the receptors only in the receptive cells of breast tumors obtained surgically and carefully isolated from connective tissue. The fibroadenomas were obtained surgically at mid follicular phase (sixth to tenth day of the cycle).

The cellular density of the tumor was assessed by determination of the relative proportion of epithelial and stromal cells. Three degrees of cellular density were distinguished. In type I, the proliferation of the acinar epithelial cells was predominant and fibrosis practically absent; in type III, the fibrosis was so predominant that the original lobular proliferation could scarcely be recognized as a fibroadenoma. In type II, microscopic features were intermediate between types I and III. High-affinity binding of estradiol and progesterone were determined according to methods previously described (41,42).

The highest concentration in cytosolic estradiol receptor (ER_c) was found in fibroadenomas with a very marked cellular density (41.2 ± 24.0 fmoles/mg protein) (Fig. 4). In fibroadenomas which had an intermediate type II cellular density, the mean ER_c level was 18.7 ± 11.4 fmoles/mg protein, whereas in fibroadenomas with predominant fibrosis (type III), the mean ER_c level was lower than 5 fmoles/mg

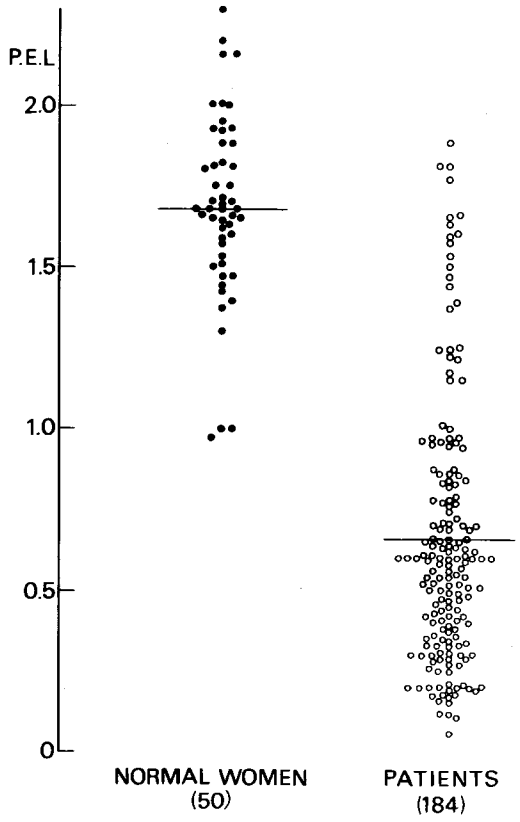

FIG. 3. Plasma progesterone to estradiol levels during the luteal phase (P.E.L.) in 184 patients (○) compared to 50 normal women (●). (From Sitruk-Ware et al., ref. 69.)

protein. Moreover, the greatest concentrations of estradiol binding sites were observed in young patients and in recently developed lesions (Fig. 5). A similar observation was made by Rosen et al. (61) in a short series of 23 fibroadenomas.

The cytosolic progesterone receptor (PR_c) levels (Fig. 4) were constantly elevated in fibroadenomas with high cellular density. PR_c levels were low in fibroadenomas with low epithelial cellularity (type III), but they were also low in fibroadenomas with midepithelial cellularity (type II).

It is important to note that breast tissue was obtained at midfollicular phase. At this period of the cycle, estradiol production is elevated and there is no substantial secretion of progesterone by the ovary. These two conditions are necessary for active synthesis of PR and no translocation to the nucleus.

Also it should be emphasized that in the 24 type II fibroadenomas, the low PR_c levels contrasted with still considerable ER_c levels, even though the extent of sclerosis was not yet sufficient to explain the disappearance of the progesterone receptor. Since PR is considered one of the best indices of estrogen dependence, and because its presence proves cellular differentiation and functional capacity, the

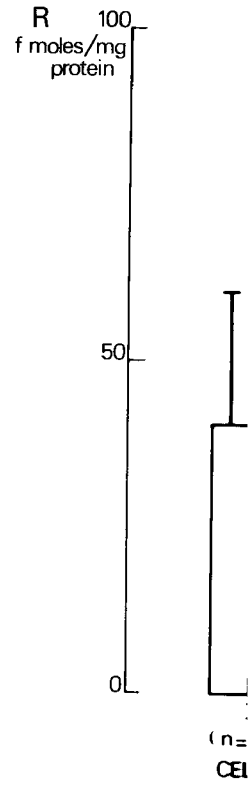

FIG. 4. Cytosol estradiol binding sites (ER
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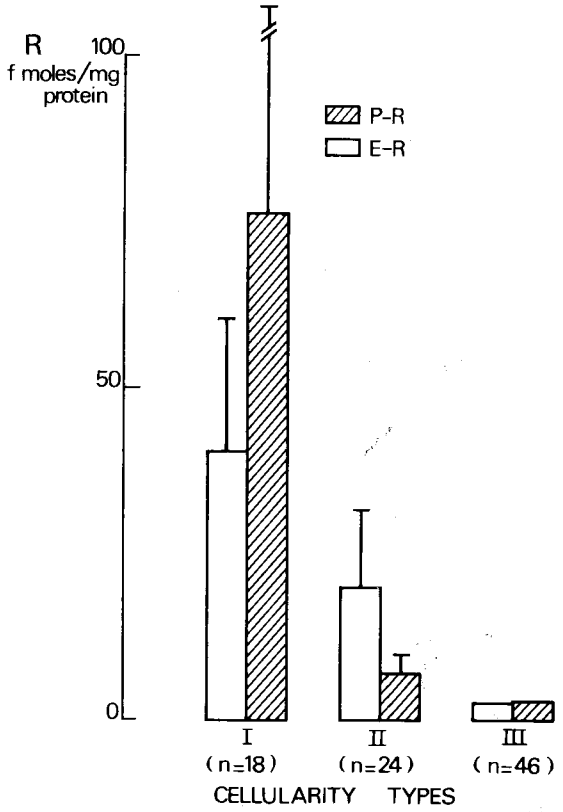

FIG. 4. Cytosol estradiol binding sites (ER) and progesterone binding sites (PR) in three groups of fibroadenomas according to their epithelial cell density: high in group I (n = 18), intermediate in group II (n = 24), and low in group III (n = 46). (From Martin et al., ref. 42.)

disappearance of PR_c from these fibroadenomas suggests the loss of hormone dependence and the onset of a dedifferentiation process.

The presence of estradiol and progesterone receptors in the fibroadenomas with great cellular density provides additional support to the hypothesis that benign breast diseases are estrogen-dependent. Previously, Cortes-Gallegos et al. (11) found a higher concentration of estradiol in breast tissue from patients with benign breast disease than in normal breast tissue. It was therefore fruitful to study the changes in ER and PR content in fibroadenomas according to the phase of the menstrual cycle and to determine the variations in the subcellular localization of receptors (31). In fibroadenomas with high cellular density and scarce fibrosis, cyclic changes in the distribution of cytosolic and nuclear receptors of estradiol (ER_c and ER_n) and progesterone (PR_c and PR_n) are similar to those noted in the human endometrium (4,9,25). These findings suggest that receptors in both tissues are under the control of cyclic ovarian secretion. Indeed, during the follicular phase (Fig. 6), the increase in ovarian secretion seems to be responsible for a progressive increase in cytosolic

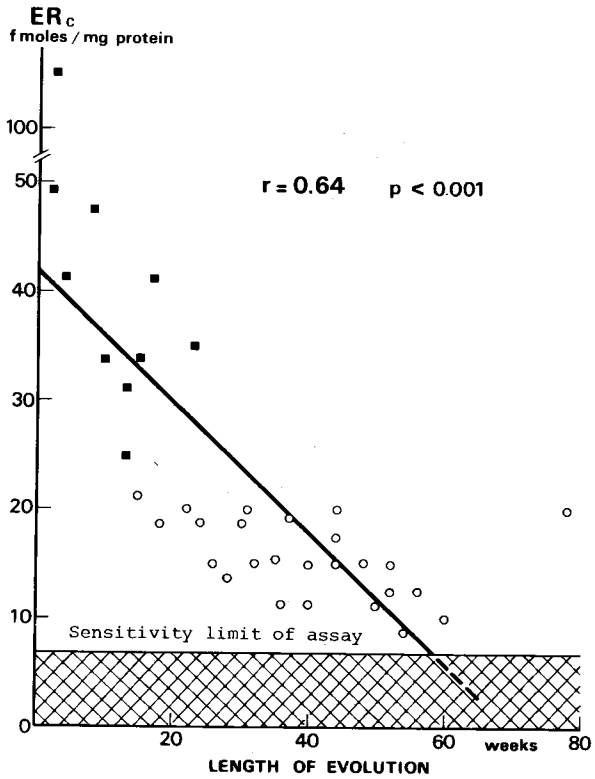

FIG. 5. Linear correlation ($p < 0.001$) between the estradiol cytosol binding sites (ERc) calculated from Scatchard plots after DCC exchange assays (ERc = Y); and the length of the firboadenoma evolution between discovery and surgery (x) in 11 patients with fibroadenoma of high epithelial cellularity (■), and 24 patients with firboadenoma of mid epithelial cellularity (○). ERc = 7fmoles/mg protein is the limit of sensitivity of the assay.

and nuclear ER, since estradiol stimulates synthesis of its own receptor (6,63). During the same phase of the menstrual cycle, the higher ER level in the nucleus as compared to the cytosol may also be explained by the increase in plasma estradiol and the translocation of the ER complex from the cytosol to the nucleus (19).

During the luteal phase, the decrease in ER_c and ER_n probably reflects the action of progesterone secreted by the corpus luteum, since progesterone is known to inhibit ER synthesis (20,27).

Moreover, the variations in PR_c and PR_n levels noted in fibroadenomas throughout the menstrual cycle (Fig. 7) give valuable information on the hormone-dependency of PR. The estrogen-dependency of PR (33,59) is reflected by its high level at the end of the follicular phase. The translocation of PR from the cytosol to the nucleus at the beginning of the luteal phase seems to be attributable mainly to the occurrence of progesterone secretion (76). The decrease in PR levels during the luteal phase probably reflects the inhibition by progesterone of its own receptor (53). The moderate increase in PR_c noted at the end of the luteal phase may be explained either by the decrease in plasma progesterone at the end of the luteal phase, or by

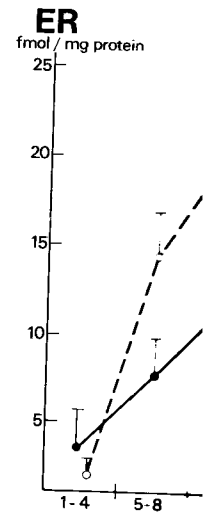

FIG. 6. Variations in ER_c (●——●) the different phases of the menstrual 4 or more). (From Kuttenn et al., ref. 31

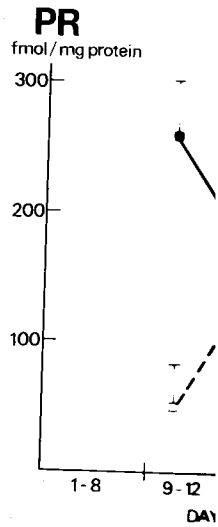

FIG. 7. Variations in PR_c (■——■) during the different phases of the menstr = 4 or more). (From Kuttenn et al., ref. 3

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In addition, it is interesting to not tribution to cytosolic and nuclear re broadenomas removed from women tr

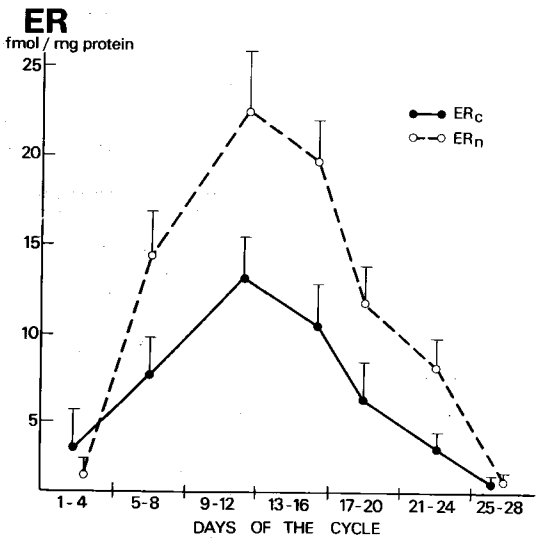

FIG. 6. Variations in ER_c (●——●) and ER_n (○- - - -○) levels in 34 fibroadenomas during the different phases of the menstrual cycle. Each point represents the mean ± SE (n = 4 or more). (From Kuttenn et al., ref. 31.)

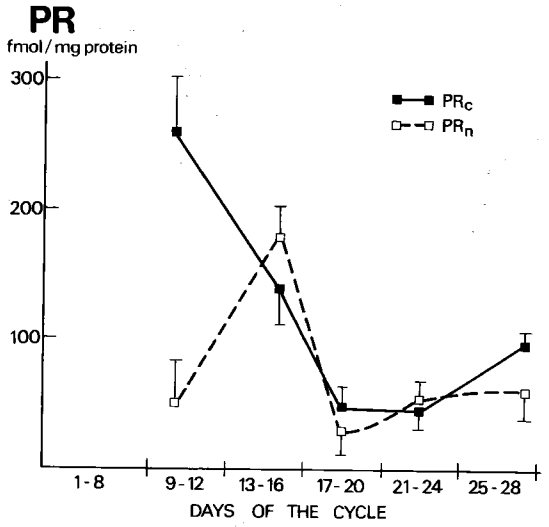

FIG. 7. Variations in PR_c (■——■) and PR_n (□- - - -□) levels in 26 fibroadenomas during the different phases of the menstrual cycle. Each point represents the mean ± SE (n = 4 or more). (From Kuttenn et al., ref. 31).

the frequent luteal insufficiency noted in these patients (46–52). Milgrom et al. (53) observed similar PR cyclic variations in rat endometrium.

In addition, it is interesting to note the variations in the concentration and distribution to cytosolic and nuclear receptors of estradiol with progesterone in fibroadenomas removed from women treated with progestagen or estrogen–progestagen

combinations (Fig. 8). The results observed prove the sensitivity of recently developed fibroadenomas to exogenous steroid (49, 51,52,70). When estrogen–progestagen combinations are well balanced, they induce a cell distribution of PR similar to that observed during a normal luteal phase. The correction of luteal insufficiency in patients with fibroadenomas induces a PR translocation into the nucleus which warrants the efficiency of this treatment.

Not only are receptors sensitive to secretory hormonal variations throughout the menstrual cycle and to progestin administration, but the 17β-hydroxysteroid dehydrogenase enzyme (E_2DH) which converts E_2 into E_1 also exists in the breast (21) as well as in the endometrium (73). This enzyme is interesting since E_1 is less active than E_2: ER has a lower affinity for E_1, and the complex thus formed dissociates more rapidly. Therefore, the intracellular concentration of E_2 and the response of the mammary gland to circulating estrogens can be expected to be regulated by the tissue levels of E_2DH. In breast tissue as in the endometrium (73), E_2DH is progesterone-dependent: it increases during the luteal phase, and under progesterone or progestagen treatment (21).

These data provide the biochemical basis of fibroadenoma regression, which may occur during progestagen therapy (49,70).

PATHOPHYSIOLOGICAL INTERPRETATION OF THE HORMONAL ABNORMALITIES OBSERVED IN WOMEN WITH BENIGN BREAST DISEASES

Considering the ovarian function in women with benign breast disease, it appears likely that in most cases these patients have an inadequate corpus luteum function.

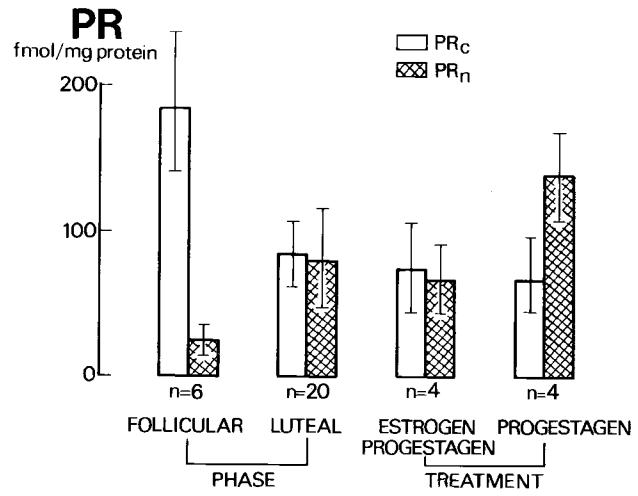

FIG. 8. Parallel study of PR levels (mean ± SE) in the cytosol (▭) and the nuclear fraction (▨) of fibroadenomas from women being treated by estrogen–progestagen combination or progestagen alone, compared to PR levels during the follicular and the luteal phases of the menstrual cycle. (From Kuttenn et al., ref. 31.)

as observed by Sherman and Korenman in oligomenorrheic and infertile women (64,66) and by Backström et al. (2) in premenstrual tension.

The frequency with which an inadequate corpus luteum is observed in women with benign breast disease should warn the practitioner that in judging the functional quality of the corpus luteum, he cannot be satisfied with a mere appreciation of a biphasic basal body temperature curve. Only a ratio of plasma progesterone to plasma estradiol levels in a presumed luteal phase can give objective information on luteal function (69).

Patients with recent lesions characterized histologically by marked cellularity with little fibrosis have high levels of both plasma estradiol and receptors of estradiol and progesterone in breast tissue. However, in old lesions, there is neither elevated plasma estradiol concentrations nor detectable steroid receptors in the tissue. These data may account for the remarkable effect of the treatment by progesterone and progestins in recent benign breast lesions where cellular hyperplasia is predominant and fibrosis still absent, such as isolated mastodynia, recent fibroadenomas, and increased nodularity of both breasts (48,52,69). In fact, this treatment requires the presence of progesterone receptors to be effective. In old lesions with much fibrosis, there are no steroid receptors or only a small concentration of estradiol receptors.

The persistent estrogenic stimulation of breast tissue without the moderating, and perhaps protective, effects of progesterone noted in patients with benign breast diseases suggests the possibility that an estradiol versus progesterone imbalance may play a role in the development of female genital tract dystrophies. This assumption concerning the pathogenesis of endometrial hyperplasia and adenocarcinoma is well documented. Our observations support the hypothesis that a similar hormonal stimulus may provide a propitious setting in the mammary gland for the development of benign lesions (51,67).

The Concept of "Dysovulation"

The role of the central nervous system in provoking abnormalities of corpus luteum function observed in women with breast diseases is very likely. Inadequate corpus luteum and anovulatory cycles are essentially related to an abnormality in gonadotropin secretion (64). Anovulatory or "dysovulatory" cycles may occur in women at any time during their reproductive life, but they are most common immediately after menarche and before menopause, both periods being characterized by a particularly high incidence of benign breast diseases (46,52).

But ovulation can also be disturbed at any time during reproductive life. Its cyclical hypothalamic regulation is complex, and in some women and some families, it is extremely sensitive to psychological and sensorial stimuli. Emotions, aggressions, certain events in sentimental, family, or professional life (unequally perceived) can also interfere with ovulatory regulation (32,43,44,50,52).

The Role of Hyperprolactinemia

In our opinion, the role of prolactin oversecretion in the development of benign breast disease lesions might be only indirect (Fig. 9). The role of this pituitary

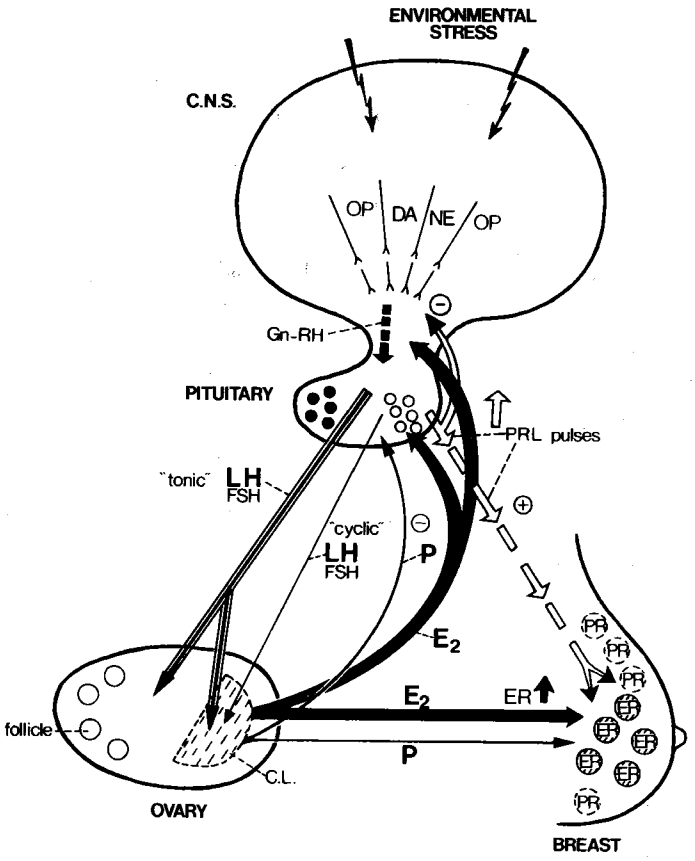

FIG. 9. A proposed interpretation of the pathophysiology of benign breast disease. Inadequate corpus luteum (CL) results from an abnormal discharge of "tonic" LH and FSH. As a result, an estradiol (E_2) versus progesterone (P) imbalance is created. This imbalance acts at two levels: the mammary gland, by increasing the level of estradiol receptor (ER); and the hypothalamus and pituitary gland by exaggerating the secretory pulses of prolactin (PRL) in response to various stimuli. PRL, in turn, have two possible actions: a negative feedback action on GnRH production. and an increase in formation of ER.

polypeptide hormone in the genesis of mammary tumor in mice is well known (54). In women, prolactin does not seem to act as directly on triggering the human mastopathy process, and in physiological conditions, prolactin is rather a factor of cell differentiation, particularly during the first full-term pregnancy (Table 2).

However, in certain pathological conditions such as progesterone deficiency with unopposed estrogen, an intermittent secretion of prolactin could occur in the form of pulses provoked by stress of any kind (22,55). A series of experimental data suggests that stress does not act directly on pituitary prolactin secretion but indirectly by increasing β-endorphin secretion. The central nervous system β-endorphin in turn decreases the hypothalamic dopamine turnover (77). Moreover, in women. prolactin production during TRH testing has been found to increase in the case of

TABLE 1. *Hypoth*

Pathophysiology
Inappropriate gonadotropin se
Etiology
Physiological
perimenarche
perimenopause
Pathological
environmental conditions
psychological disturbance
individual predisposing fac
Pathological Consequenc
Hormonal
Decreased production of p
phase, with normal or inc
unopposed estrogen effe
Cellular
Increased cellular multiplica
Clinical
Premenstrual tension
Menstrual disorders
Hypofertility
Benign breast diseases

From Mauvais-Jarvis et al., ref. 5

TABLE 2. *Effects of sex ho*

Estradiol	Es
↓	
Progesterone	Pr
↓	
Prolactin	De t
↓	
Proper differentiation of terminal ductule cells	Incr re

dysovulation with unopposed estroge
persecretion of prolactin could accen
adequate corpus luteum (29). In add
could increase estradiol synthesis in
C_3H mice induce mammary tumor
Coezy and Rochefort (10) observed a
these experimental conditions.

Finally, it has been observed that
certain species of animals (26). Therefo
whatsoever unopposed by a cyclical a

TABLE 1. *Hypothesis on the mechanism of dysovulation*

Dysovulation
Pathophysiology
Inappropriate gonadotropin secretion due to a central catecholamine dysfunction
Etiology
Physiological
perimenarche
perimenopause
Pathological
environmental conditions
psychological disturbances
individual predisposing factors
Pathological Consequences
Hormonal
Decreased production of progesterone during the luteal phase, with normal or increased estradiol secretion: unopposed estrogen effect
Cellular
Increased cellular multiplication
Clinical
Premenstrual tension
Menstrual disorders
Hypofertility
Benign breast diseases

From Mauvais-Jarvis et al., ref. 52.

TABLE 2. *Effects of sex hormones on mammary cell differentiation*

Estradiol	Estradiol	Progesterone lacking
↓	⇅	←
Progesterone	Prolactin	
↓	↓	
Prolactin	Dedifferentiation of terminal ductules	
↓	+	
Proper differentiation of terminal ductule cells	Increase in estradiol receptors in breast	

dysovulation with unopposed estrogen (56). Such an intermittent stress-related hypersecretion of prolactin could accentuate or induce dysovulation and thus an inadequate corpus luteum (29). In addition, even slight hypersecretion of prolactin could increase estradiol synthesis in the mammary gland itself; pituitary grafts on C_3H mice induce mammary tumor (10), probably owing to hyperprolactinemia. Coezy and Rochefort (10) observed an increase in cytosolic estradiol receptors in these experimental conditions.

Finally, it has been observed that progesterone inhibits prolactin secretion in certain species of animals (26). Therefore, it is likely that any type of hyperestrogeny whatsoever unopposed by a cyclical adequate secretion of progesterone may favor

an intermittent hyperprolactinemia, especially in the case of stress. This hyperprolactinemia could itself favor dysovulation and participate in creating a vicious circle which will eventually increase breast cell multiplication.

RELATIONSHIP BETWEEN BENIGN BREAST DISEASE AND BREAST CANCER

The exact evaluation of the predisposing role of benign breast disease in cancer remains extremely imprecise. The only useful studies concern cystic disease, which increases the risk of cancer approximately two- to four-fold (7,13,24,75). A recent study from the Mayo Clinic (17) showed that most cancers observed in patients with a previous history of cystic disease became clinically apparent five to ten years after the benign disease was diagnosed. This observation was made in women 40 to 49 years old when their cancer was diagnosed. It confirms the notion of a large time interval between the appearance of benign dystrophy and cancer, which takes into account the likely tumor doubling time. With regard to the association mechanism between cancer and cystic mastitis, MacMahon et al. (37) give two explanations: (a) the cystic disease itself is a premalignant condition that either predisposes to neoplastic change or is an early manifestation of malignant change, or (b) benign and malignant breast diseases have etiologic factors in common—perhaps a particular hormone pattern.

Recently, Bulbrook et al. (8) reported the level of plasma estradiol and progesterone in women with varying degrees of breast cancer risk. In premenopausal women, these authors noted that increased risk of breast cancer correlated with subnormal plasma progesterone values in the luteal phase of the menstrual cycle. Plasma estradiol values do not vary with risk. Another approach to the problem consists in the examination of the hormonal status of women with breast cancer. Breast cancer, as well as endometrial cancer, is considered to be a hormone-dependent malignancy. In some women, changes in the hormonal environment of the neoplasia have succeeded in temporarily slowing down or arresting the cancerous growth.

The risk of breast cancer increases with age. Incidence rises between the ages of 25 and 45 and levels off between 45 to 55. Thereafter, the curve of incidence resumes its upward course. Accordingly, peaks of breast cancer incidence between ages 45 to 49 and approximatley 65 to 70 have been suggested (16). Thus, the first peak of breast cancer incidence has been related to the ovarian estrogen disturbance of the perimenarchial period also called "first estrogen window" by Korenman (29), whereas the increase in breast cancer incidence after age 60 is thought to be due to a perimenopausal stimulus ("second estrogen window"). This stimulus might be either of adrenocortical origin (16,67), in particular an increase in the conversion of androstenedione to estrone in extraglandular tissue (62), or attributable to the intake of exogenous estrogen by postmenopausal women (25). The risk factors for breast cancer are well known, but they are generally interpreted in different ways. Sherman and Korenman (65) on the one hand, and our group on the other hand

(52) have suggested that the main known risk factors for breast cancer may be interpreted in the same way. Both interpretations are based on the postulate that in terms of epidemiology, "unopposed estrogen effect" or "estrogen windows" (29) are carcinogenic and that adequate progesterone secretion by corpus luteum has a protecting effect against breast cancer development (29,52). Thus, by comparing the particular environment of benign breast diseases to factors considered to confer high risk for breast cancer, we concluded (52) that the following factors might be interpreted as reflecting an abnormal regulation of the female reproductive cycle (51): early menarche and late menopause; nulliparity and late age at first pregnancy; familial risk factors; ethnic risk factors; urinary estrogen abnormalities; and urinary androgen excretion abnormalities.

BENIGN BREAST DISEASE AND "THE PILL"

Considering all the data obtained from the investigation of patients with benign breast disease, it appears likely that benign breast disease occurs in a context of unopposed estrogen. Thus, dysovulation should be explored and hyperestrogeny corrected, but above all, iatrogenic induced hyperestrogeny should be avoided!

Whereas estrogen used alone as a substitutive therapy for menopause increases the frequency of BBD, estrogen–progestagen pills do not increase the rate of BBD as far as pills containing 50 μg of ethinyl estradiol are concerned (74). Such pills could even have a protective effect, mostly when they are used for more than 2 years. However, the women who continue oral contraceptive use for more than two years are those who experience no side effects, particularly no mastodynia. Therefore there is a bias of selection. In the study of the Royal College of General Practitioners, BBD frequency under estrogen–progestagen contraceptives appears inversely correlated to the progestagen/estrogen ratio in the pill (62).

Concerning breast cancer, Lees et al. found that prolonged contraceptive use in women with a history of benign breast disease increased the risk of cancer ninefold (34). Similarly, Brinton et al. reported a higher rate of cancer in long-term users with a history of benign mastopathy (7). The risk of oral contraceptives in women with altered mammary cells or intermediary cells seems evident, based on the work Li Volsi et al. (36). In a retrospective study on pathological analysis of 205 cases of fibrocystic disease, these authors observed that oral contraceptives appeared to protect against cancer only in patients with fibrocystic disease devoid of cell atypia, whereas they increased the risk of cancer in the case of cellular atypia. Lastly, Pike et al. (57) emphasized the increased risk of cancer in two particular circumstances: (a) antecedents of BBD, and (b) use of oral contraceptives before the first full term pregnancy, that is, during the first estrogen window. In this respect, great caution should be the rule concerning estrogen/progestagen minipills containing 30 μg of ethinyl estradiol. With the use of such compounds, some gonadotropic activity persists thus providing partial ovarian follicular maturation. The consequent estradiol level remains between 50 and 120 pg/ml (71) and acts in addition to the synthetic estrogens of the oral contraceptive.

Women with high endogenous estradiol levels under minipills often have symptoms of hyperestrogeny, such as mastodynia. Hyperestrogeny, if prolonged, presents an actual cellular risk for the breast. Therefore, occurrence of such symptoms is an indication that the minipill must be stopped. Moreover, it is striking to note the frequency of benign breast disease in less than 20-year-old women under "mini" or sequential pills. Since the higher the progestin dose, the lower the mastopathy rates (62), caution should be the rule concerning the risk of the minipill producing hyperestrogeny during the period of maximal cell growth.

TREATMENT OF BENIGN BREAST DISEASE WITH PROGESTERONE AND PROGESTINS

A total of 380 patients with benign breast disease and with a hormonal profile characteristic of an inadequate luteal phase or anovulatory cycle have been treated in our department by progesterone and progestins. This treatment was prescribed in order to correct the defect in the ovarian secretion of progesterone. It began 7 years ago and is presently being followed up (49,52).

The 380 patients in whom a progestagen treatment was undertaken had mammary symptoms of varying type and importance. Some had only one symptom; most had an association of symptoms.

In order to evaluate more precisely the effects of treatment, it seemed more objective to estimate the results obtained in relation to a given mammary symptom instead of calculating the results obtained on a group of symptoms. Under these circumstances, this study concerned 620 symptom manifestations observed in 380 patients. The symptoms manifested were the following: 249 cases of isolated mastodynia; 115 cases of increased nodularity of the breasts which did not disappear after menstruation; 63 cases of fibrocystic disease; 122 cases of isolated cysts authenticated by mammography followed by needle aspiration; and 71 cases of fibroadenoma demonstrated by mammography with negative needle aspiration.

Treatment Scheme

All patients were treated with sequential oral administration of progestins and progesterone applied topically to both breasts. The progestin was Lynestrenol, 10 mg/day, from day 10 to 25 of the menstrual cycle. The duration of this treatment varied from 9 months to 4 years. The percutaneous application of progesterone consisted of an alcohol water gel in which the steroid was dissolved; 50 mg of progesterone was applied to the breast daily.

It has been demonstrated previously that topically applied radioactive progesterone can be absorbed through the skin (45). Labeled metabolites (pregnandiol and allopregnandiol) were recovered in the 48-hr urine after percutaneous administration of the precursor (45). We had also calculated that percutaneous absorption of the steroid was only 10%. Therefore, the daily administration of 50 mg of progesterone might result in a local concentration of 5 mg of active progesterone.

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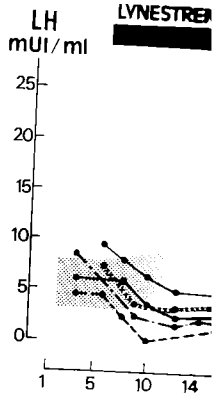

FIG. 10. Daily plasma luteinizing hor
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Treatment, edited by W. L. McGuire, p. 7

Recent *in vitro* studies confirm the presence of significantly higher levels of progesterone in breast than in peripheral blood afer percutaneous administration of this steroid (14). In addition, the high fat solubility of progesterone is responsible for a prolonged local retention of the steroid, whereas, owing to an extensive *in situ* metabolism of progesterone in the breast, there is no systemic effect of the steroid, in particular, no significant modification in endometrial histology and no breakthrough bleeding (70). De Boever et al. (14) also found no increase in plasma progesterone after percutaneous application of the steroid, despite its high local concentrations in the mammary gland. For all these reasons, percutaneous progesterone was administered every day, including during the menstrual period.

The fact that progesterone is continuously present inside the breast might produce a permanent antiestrogenic effect, which competes with the possible presence of a high local estradiol concentration (11). In addition, the administration of 10 mg a day of Lynestrenol results in a substantial decrease in gonadotropin secretion and in plasma estradiol. This result is of importance because Lynestrenol was also used in young women for its contraceptive effect (30,49; Fig.10).

Results

Results obtained by combined progesterone–Lynestrenol treatment on 620 symptoms observed in the diverse mastopathies are given in Table 3. The therapeutic results of hormonal treatment of benign breast disease were expressed as follows.

The beneficial effects consisted of a complete disappearance of breast pain and tenderness, in particular during the premenstrual period. Mammary glands became supple, and nodularities disappeared. On mammography, the results obtained were less clear, and there was always a disparity between clinical and radiologic results.

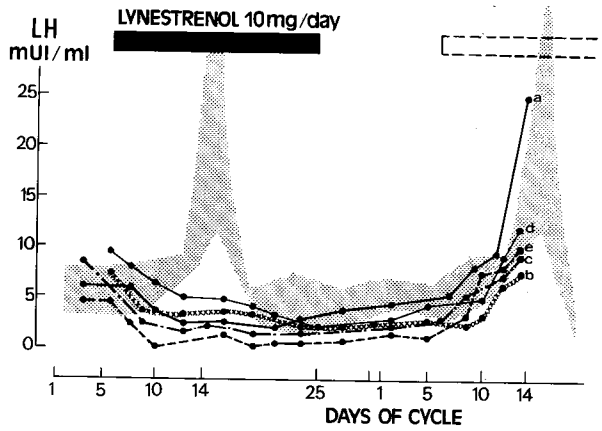

FIG. 10. Daily plasma luteinizing hormone (LH) levels of 5 normal women during the administration of 10 mg Lynestrenol from day 5 to day 25 of the menstrual cycle. The shaded area represents the untreated cycle in 50 normal women. [From: P. Mauvais-Jarvis, R. Sitruk-Ware, and F. Kuttenn (1981): Benign Breast Disease. In: Breast Cancer: Advances in Research and Treatment, edited by W. L. McGuire, p. 74. Plenum Press, New York. Reprinted with permission.]

TABLE 3. *Results obtained after treatment of 380 patients with 620 mammary symptoms— treatment: 50 mg percutaneous progesterone applied daily to the breast plus sequential administration of 70 mg lynestrenol 15 days/cycle.*

	Isolated mastodynia 234 cases	Increased nodularity 70 cases	Isolated cysts 38 cases	Chronic fibrocystic disease 56 cases	Fibroadenomas 52 cases
Good results	96%	85%	50%	10%	50%
Failures	4%	15%	50%	90%	50%

It is difficult to obtain comparable X-rays in two consecutive examinations. Also, edema is not easily visualized on mammography, whereas indelible intralobular sclerosis—thicker than glandular tissue—masks the modification of glandular tissue, owing to hormonal treatment. By contrast, there was a very clear improvement in vascular imaging after treatment, as shown by thermography. The total improvement in breast pain and tenderness was observed from the very beginning of the treatment in 96% of the 249 cases of mastodynia.

The 4% failure was observed when this symptom was associated with fibrocystic disease or cysts. In the patients with fibrocystic disease, only 10% improved with the treatment. In these cases microcysts disappeared and did not develop again during the course of treatment. The cysts treated first by needle aspiration did not reappear during the hormonal treatment in 50% of the cases. Eighty-five percent of fibroadenomas were improved in the cases of increased nodularity of the breasts. In these cases the lesions completely disappeared, and in the remaining 15% no improvement was observed. In the latter cases the lesions had been present for many years and were far larger than in the cases where the treatment was effective.

The higher percentage of positive results was obtained with this treatment on symptoms ascribable to recent lesions, in particular in the case of isolated mastodynia in which treatment was also invariably effective. The results of this treatment were remarkable also in the cases in which increased nodularity of the breasts had recently appeared, and in which sclerosis was either absent or only slight.

Some positive results also were obtained in "young" fibroadenomas. This confirms our *in vitro* data showing that estradiol and progesterone receptors were found only in fibroadenomas with considerable cellularity and no fibrosis (41,42). A correlation could be found between the presence of progesterone receptors in "young" fibroadenomas and the response to hormonal treatment.

The hormonal treatment of benign breast diseases is effective if it is begun very early in the course of the disease, particularly in cases in which unopposed estrogen action is responsible only for edema and reversible glandular hyperplasia. For these reasons, we believe that mastodynia is not a physiological event but is probably the first symptom of hyperestrogenic milieu inside the breast (48). Moreover, benign breast disease must not only be treated at the beginning of its history but should also be treated for a long time, particularly in cases in which the disease is associated with another risk factor for breast cancer.

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SUMMARY

It seems likely that benign breast disease is induced by a hormonal environment characterized by an unopposed estrogen effect owing mainly to inadequate lutal function. The *in vitro* presence of estradiol and progesterone receptors in lesions with epithelial cell proliferation gives additional support to such a hypothesis. Thus, recent lesions may be treated successfully by the administration of progesterone and progestins to correct the systemic and local hormonal insufficiencies.

There is no proof that the same hormonal environment plays a major role in the development of breast cancer. There is only indirect evidence that favors a pathophysiological interpretation of human breast cancer epidemiology in terms of luteal insufficiency. However, it is obvious that there is no danger in considering the lack of progesterone secretion as a common risk factor for development of both benign breast diseases and cancer. The side effects resulting from treatment by progesterone and progestins are minor or negligible. Only early and lengthy treatment of a large cohort of patients, either with benign breast diseases or with high risk of developing breast cancer, may confirm that speculation.

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Benign Breast Le

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Problems related to the repro
increasing attention in the last fe
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From January 1971 through Oc
Gynecology II of University of R
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graphic evaluation, best avoided in
because it had been performed els

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and testosterone were measured in
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elsewhere (2). Number of patients
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In a parallel study on nonobese eut
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