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BENIGN BREAST DISEASE
AN UPDATE

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PART I – BENIGN BREAST DISEASE (BBD)

INTRODUCTION

Benign breast disease includes several heterogeneous conditions of various origins, like non epithelial lesions such as fibromas and lipomas, inflammatory lesions, and epithelial lesions often termed "fibrocystic disease". This last – and especially its gross cystic variant – is the most common disease among benign conditons, its incidence being similar to that of breast cancer. However, it is worth pointing out that the actual incidence of benign breast disease may be overestimated by clinically mistaking near-normal nodules for dysplastic lesions.

In the '70s and early '80s, most studies stated that the risk of developing brast cancer in women with fibrocystic disease was 2 to 20 times higher than in the general population, according to different Authors ([1, 4]).

This finding prompted the publication of a large number of papers concerning fibrocystic disease covering a broad range of topics from risk factors to hormonal involvement and possible different treatments.

NOMENCLATURE AND CLASSIFICATION

The main problem related to benign breast disease has been, and perhaps still remains, the type of nomenclature most suitable and the development of an accurate, workable definition, especially as the affliction involves a polymorphous pathological situation which can evolve in time.

For this reason the attempt to constrain the wide range of benign breast lesions to a single definition has resulted over the years in various classifications, each giving different importance to the different aspects of the pathological situation involved.

Thus, the disease has been defined as fibroadenosis, adenoma with cyst formation, chronic cystic mastitis, chronic mastitis, cystic hyperplasia, epithelial dysplasia, mastopathia cystica and mazoplasia. The term "mazoplasia" has been used to define a proliferation of periductal and periacinous fibrous connective tissue, as well as being used as a synonym for mastalgia, a term which underlines the presence of pain, but has no pathological content.

The terms "chronic mastitis" and "cystic mastitis" are incorrect, in that they include flogosis, which is often absent.

The term "fibroadenosis" is not the best definition either, as fibrosis, although present, is not the main characteristic of the disease.

Even the term "fibrocystic mastopathia" and "cystic breast disease", the latter proposed by Haagensen ([3]) and widely used in the last ten years, is often discarded today.

At present, the WHO proposes the term of mammary dysplasia ([5]), which on the one hand has the advantage of introducing no element with morphological meaning, such as cyst and connective proliferation, but on the other is limited by a lack of explicative content. However, this limit is shared by all the definitions describing different morphological changes.

Hence, it can be said that currently no satisfactory classifications of BBD exists.

Although a new classification has been proposed for the various pathological entities traditionally defined as BBD (Tab. 1) ([6]).

The rationale of this classification is based on the notion that many histological lesions described as BBDs can be regarded as simple aberrations or disorders of normal development, clinical changes and involution

Table 1. – *Classification of benign breast lesions.*

Fertile years	*Normal processes*	*Benign disorders*	*Benign breast disease*
Development	ductal development	nipple inversion single duct obstruction	mammillary duct fistula
	lobular development stromal devolopment	fibroadenoma juvenile hypertrophy	giant fibroadenoma
Cyclical changes	hormonal activity	mastalgia nodularity focal diffuse	
	epithelial activity	benign papilloma	
Pregnancy and lactation	epithelial hyperplasia	blood nipple discharge galactocele	
Involution	lobular involution	cysts - sclerosing adenosis	
	ductal involution	nipple retraction duct ectasia	periductal mastitis with suppuration
	involutional epithelial	simple hyperplasia	lobular hyperplasia with atypia
	hyperplasia	micropapillomatosis	ductal hyperplasia with atypia

(Hughes, 1987)

Table 2. – *Classification of fibrocystic disease.*

A)	Paraphysiological, clinically undetectable non cancer-predisposing forms:
	Blind duct
	Microcystis (size <3 mm)
	Apocrine metaplasia
B)	Clinically undetectable non cancer-predisposing forms:
	Adenosis
	Papillomatosis
C)	Clinically detectable, non cancer-predisposing forms:
	Fibrous mastopathy
	Isolated intraductal papilloma
D)	Clinically undetectable cancer-predisposing forms:
	In situ lobular carcinoma
E)	Clinically detectable and cancer-predisposing forms:
	Multiple intraductal papilloma
	Macrocysts (size >3 mm)

(Haagensen, 1981)

of the breast during female life. The majority of these morphological changes can determine mammary tension and nodularity ([6]).

The main difference between this classification and Haagensen's ([3]), the most reliable in recent years, is that the former overcomes the concept of the risk of developing malignancies linked to certain histological lesions (Tab. 2).

Prognostic criteria have been abandoned in favour of a strictly descriptive criterion extended to histological patterns as well as clinical aspects, and related to the morphology of the normal breast and its changes during reproductive years.

Although this proposal should be evaluated in the light of all present knowledge of BBD, it is in any case a valuable attempt to clarify a subject which still remains very unclear.

For a clinical point of view, fibrocystic disease has been defined as " a condition where palpable masses are present in the breast, usually associated with pain and tension, which change during the menstrual cycle and tend to worsen progressively until menopause ([17]) ".

On the basis of this definition, about 50% of fertile women clinically display fibrocystic disease ([8]).

The majority of these masses are physiological nodularities that follow the changing hormonal pattern in different phases of the menstrual cycle.

Within a particular woman the fact that size and tension, as well as the associated pain, can change in a clinically relevant manner within the space of time, highlights that the response of breast epithelium and stroma to hormonal stimuli, though physiological, changes in time both quantitatively and qualitatively ([8]).

No objective parameters exists to draw the line between physiological changes and disease. Until now, the difference between the two has been classified arbitrarily and is based on the doctor's evaluation of very subjective elements such as size, consistency of the lesion and the pain sometimes complained of by the patient ([8]).

BBD AND THE RISK OF BREAST CANCER

Numerous studies involving women without clinical evidence of disease during their life-time, have revealed that in breast biopsies 50 to 90% of women show pathological signs of fibrocystic disease, the proportion varying from Author to Author ([9, 10]).

On the basis of this finding, the pathological differences between a normal and a fibrocystic breast become no longer qualitative but only quantitative.

Lesions, up to date considered to be signs of FCD, have lost their role as distinct histological entities and are now considered to be representative of a range of conditions based on an imbalance between hormonal stimulus and local response.

Thus, it is impossible to establish the point where both clinically and histologically a normal condition becomes a disease. Today, a process seen clinically in 50% and histologically in 90% of women cannot justifiably be termed a disease.

The pre-malignant potential of fibrocystic disease or the greater susceptibility to breast cancer of patients with fibrocystic disease has often been reported in literature.

Although, many studies report a 2-4-fold increased risk compared to the control population ([11, 14]), it should be underlined that BBD is often referred to generically without referring to a specific pathological situation.

In addition, more recent studies do not confirm these findings, and here the risk is deemed not to be generically ascribable to BBD but to be attributable to certain rare specific histological patterns ([15]).

Regarding the association between FCD and breast cancer, it has become evident that in distinguishing between hyperplasia and neoplasia,

the most crucial variables are the degree and particular characteristics of the epithelial hyperplasia.

Dupont and Page [15] divided benign breast lesions into 3 main prognostic histological categories: non-proliferative disease and 2 types of proliferative lesions, proliferative disease without hyperplasia and atypical hyperplasia.

Non-proliferative lesions include: mild hyperplasia, cysts, calcifications and fibroadenoma. Simple proliferative lesions include: moderate hyperplasia, papilloma, ductal involvement with atypical lobular hyperplasia and sclerosing adenosis [15].

Atypical hyperplasia, on the other hand, is the most severe proliferative lesion and includes both ductal and lobular atypia.

These atypical hyperplastic lesions have some features of the " in situ " carcinoma, but are not sufficient for the diagnosis of cancer. Thus, they are defined as borderline lesions [15].

One of the most interesting findings of the study by Dupont and Page is that 70% of women who underwent biopsy could be reassured, as their lesions were non-proliferative and thus their risk of developing cancer was not increased [15].

The remaining 30%, on the other hand, had proliferative lesions, which double the risk of developing cancer. However, of this 30%, 26% of the lesions were simple hyperplasia and only 4% were atypical and therefore regarded as borderline [15] (Tab. 3).

Table 3. – *Benign lesions observed i n 10542 consecutive biopsies.*

Non proliferative lesions	69.7%
Proliferative lesions without atypia	26.7%
Proliferative lesions with atypia	3.6%

(Dupont and Page, 1985)

Women with atypical proliferative lesions have a 5-fold increased risk of cancer compared to the remaining female population. Their risk is comparable to the risk of patients already treated for controlateral breast cancer [15] (Tab. 4).

One interesting aspect is the relationship between breast cancer familiarity and different pathological pictures. While a positive familiarity involves only a slight increase in the risk (r.r. 1.2, confidence interval 0.43-3.1) where lesions are non-proliferative, the association between po-

Table 4. – *Relative risk of breast cancer in women with proliferative disease and in those without proliferative lesions.*

	RR	IC	P
Non proliferative lesions	0.89	0.6 - 1.3	0.51
Proliferative lesions	1.9	1.6 - 2.3	<0.0001
Proliferative lesions Without atypia	1.6	1.3 - 2	0.0001
Proliferative lesions With atypia	4.4	3.1 - 6.3	<0.0001

(Dupont and Page, 1985)

sitive familiarity and atypical proliferative lesions has an r.r. of 8.9 (confidence interval 4.8-17), which is 11-fold higher than in women with non-proliferative lesions and negative familiarity (r.r. 0.86, confidence interval 0.59-1.3) ([15]).

The risk for women harbouring breast cysts is not increased, unless they have a positive familiarity for breast cancer, in which case, the r.r. is increased 3-fold ([15]).

Only 2% and 4% of women with non-proliferative lesions and similar proliferative lesions, and 8% and 20% of women with atypical lesions, with negative and positive familiarity respectively, developed invasive cancer in 15 years ([15]).

These findings show that the majority of women (96.4%) who underwent a biopsy for fibrocystic disease were not at risk of breast cancer, and that the risk of breast cancer was increased only in women (3.6%) with histologically atypical cell hyperplasia.

It should emphasised that the histological patterns associated with an increased risk of breast cancer, such as atypical hyperplasia, do not arise from nodularity or masses; their discovery always being accidental, and occurring when a biopsy is performed for any other breast disease.

Furthermore, about half of the cancers in women at risk due to the presence of an atypical breast lesion develop in the contralateral breast, compared to the breast where the atypical lesion was diagnosed ([8]). This means that these lesions cannot be regarded as premalignant, as this definition implies an evolution potential towards cancer which has not been observed.

It is better regarded as a risk factor which, like other known risk factors such as age and familiarity, suggests a need to monitor the patient more attentively.

RISK FACTORS OF FIBROCYSTIC DISEASE

The great number of epidemiological studies on fibrocystic disease do not allow an exact definition of its risk factors and their relationship with the risk factors of mammary carcinoma.

Data on incidence and prevalence are not available, when no such information has been collected during a screening programme. Thus, risk factors can only be derived from case-control studies.

While no relationship has been seen with age at menarche, age at first pregnancy and age at menopause, some studies have revealed a lower risk in women with high parity ([16, 17]).

The role of other factors such as socioeconomical level, diet and life style is still subject to debate.

Women belonging to lower socioeconomical classes appear to be at lower risk of fibrocystic disease. Furthermore, an inverse relationship has been found with body weight; in women with a body weight higher than 65 kilos the risk is 40% lower than in women with a body weight lower than 55 kilos ([16]).

In addition, it is worth while mentioning the increase in risk, quoted by some Authors, as a function of a diet rich in methylxantines and present in high amounts in tea, coffee, chocolate and Coca Cola ([18]).

However, as methylxantine consumption is related to several factors such as life style, social status, working conditions, further studies are necessary to support the validity of this finding.

In a recent study, risk factors for fibrocystic disease have been examined separately in pre- and post-menopausal women ([19]).

With regard to demographic variables; an increased risk of fibrocystic disease has been shown in pre-menopausal women belonging to higher socio-economic classes and in Jewish women. Regarding reproductive variables, no relationship to fibrocystic disease has been observed, apart from a slight decrease in the risk, along with the increasing parity (Tab. 5) ([19]).

The increased risk for the other variables examined should be evaluated with caution, as women with fibrocystic disease are more likely to practise breast self examination, to have had a history of previous BBD and to report a positive familiarity for breast cancer, compared to controls.

These women are regarded as at risk for breast disease, both because of a positive familiarity and because of previous breast disease. As a consequence, they are likely to undergo more frequent clinical examinations than a control group. Hence, the diagnosis of fibrocystic disease is more

Table 5. – *Risk factors for fibrocystic disease.*

		Premenopause	Postmenopause
Demographic variables:			
– Race (white/black)		1.3	0.9
– Socioeconomical status		2	2.9
– Jewish religion		1.8	1.3
Reproductive variables:			
– Nulliparous		1	0.9
– Number of live-born children:	1 - 2	1	1
	2 - 4	0.7	1.5
	>5	0.6	1.6
– Age at menarche		1	1
– Age at menopause			1.4
Other variables:			
– Breast self-examination		1.7	
– Yearly clinical examination			1.2
– Previous benign breast disease		2.4	5.5
– Positive familiarity for breast cancer (mother-sister)		2.1	1.4
– Tubal sterilization			0.1
– Previous smokers		1.2	0.6
– Smokers		0.8	0.4

(Berkowitz, 1985)

frequent ([20]). An increased risk has also been observed in post-menopausal women of higher socio-economic classes, although no reproductive variable seems to be associated with an increase of the risk, except for a positive trend with an increasing number of children ([19]). Among the other variables examined, while a positive relationship has been found with a positive history of previous BBD, a negative trend has been shown with tubal sterilization and cigarette smoking ([19]).

No relationship has been shown between degree of atypia and pre- or post-menopausal status, when the relationship between risk factors and degree of atypia of the breast lesion was examined. In premenopausal women, the highest degree of atypia was shown by a trend test to be associated with low parity and advanced age at first pregnancy, while no association was found with regard to the other variables. The highest degree of atypia is associated with advanced age at first pregnancy, even in postmenopausal women, whereas the premenopause, the group of post-menopausal patients with high atypia have a higher number of living children ([19]).

Moreover, the association between the type of pathological lesion according to Haagensen's classification, and various risk factors has been studied. Micro and macrocysts, adenosis and sclerosing adenosis are significantly more frequent in premenopausal women. Macrocysts and sclerosing adenosis are more frequent in white women, while papillary hyperplasia or papillomatosis are more frequent in Jewish women and women belonging to higher socio-economic classes [19].

In premenopausal women, no positive association was shown with the other variables, apart from a strong negative association between the Quetelet index and macrocysts and sclerosing adenosis. Whereas in postmenopausal women a positive relationship has been shown between the above mentioned lesions and a positive history of breast cancer in mother and sister, this association has not been shown in premenopausal women, and no relationship seems to exist between the Quetelet index and papillomatosis or papillary hyperplasia in premenopausal women [19].

Some differences in the distribution of risk factors in pre- and postmenopausal women can be easily explained, while others are more difficult to understand [19]. For example, the finding that breast self-examination and positive familiarity for carcinoma are risk factors for FCD in premenopause, and not in postmenopause, may be due to the fact that younger women undergo more frequent mammary biopsies in the case of positive family history for mammary carcinoma [20]. On the contrary, it is not easy to explain the negative association between tubal sterilization and fibrocystic disease, which is evident in postmenopausal women only, though hormonal changes and disorders of the menstrual cycle resulting from this operation are reported in literature [21, 22].

Though some risk factors seem similar to those of mammary carcinoma, for example socio-economic status in pre and postmenopause, women of the Jewish religion and low parity in premenopause, late menopause in postmenopause; the lack of definite association between age at menarche, age at the first pregnancy and FCD seems to suggest that no etiological relationship exists between fibrocystic disease and mammary carcinoma.

ORAL CONTRACEPTION AND BBD

Several epidemiological studies have evaluated the relationship between BBD and oral contraception.

A review of 17 studies undertaken in the period 1972-1981 showed that the use of oral contraception reduces the relative risk of developing BBD [13].

While some studies do not report the duration of use of the oral contraception, others suggest that reduced risk is shown only when oral contraceptives are used for one year at least, according to some Authors, and four years at least according to others [13].

A prospective study on more than 17,000 women showed that the protective effect of estrogen-progestagens lasts exclusively during administration and for one year after withdrawal. The risk tends to decrease with increasing use; a 50% decrease in the risk is observed after 6 or more years of the use of oral contraception [16] .

The conclusions of a study on 228 women with histologically proven BBD, compared with 285 women hospitalized with acute events of non-mammary origin were similar. A protective effect is seen during estro-progestagen administration, and the risk of the development of BBD in women using oral contraceptives is reduced the longer the period of treatment [23].

The risk of BBD in oral contraception users one year after withdrawal and in non-users was similar; moreover, no relationship was observed with duration of use and no rebound effect was reported at withdrawal. The protective effect attributed to estrogen-progestagens is evident for FCD only (r.r.=0.2, confidence interval 0.1-0.6) [23], and is practically nil for other forms of benign pathologies such as fibroadenomas and papillomas.

At present, the pharmacological mechanisms through which estroprogestagens prevent the development of BBD are not known.

Histopathological studies on benign lesions have not yet shown any significant difference between oral contraceptive users and non-users [24].

As the Royal College of General Practitioners hypothesized [25] and the Oxford Family Planning study confirmed [26], the effect could be linked to the dosage of progestagen, or even more likely estroprogestagens might act to prevent the hormonal fluctuations of menstrual cycles. Furthermore, this last hypothesis would explain the rapid disappearance of the protective effect after withdrawal.

Possibility it is not the histological picture which alters, but the symptomatological one, thus attention is not directed towards the status of the gland.

THE IMPLICATIONS OF THE HORMONAL ASPECTS OF BBD

BBD has been associated with a number of hormonal dysfunctions [27]:

1) increased estrogen levels (due to increased endogenous estrogens or to exogenous administration);

2) luteal inadequacy;
3) prolactin increase;
4) decrease in thyroid function;
5) androgen excess.

While the level of circulating estrogens in premenopausal women is similar in healthy and BBD women, progesterone levels are often reduced in BBD [28].

However, the response of breast tissue to varying hormonal levels is fundamental, especially when, at a given hormone circulating level, only one breast or only part of a breast may be affected by BBD.

Hyperestrogenism was the first etiopathogenetic hypothesis proposed to explain BBD [28]. This hypothesis derives from breast morphological changes observed during the phases of the menstrual cycle; ductal ectasia and stromal inhibition occur from ovulation to the premenstrual phase. According to the majority of Authors, ductal proliferation and ectasia are almost exclusively estrogen-dependent [29, 30]. For this reason, fibrocystic disease has been supposed to be the result of a prolonged, though moderate, hyperestrogenism and altered estrogenic stimulation leading to a proliferative response, which can produce structural disorganisation [31, 32]: although increased circulating or urinary estrogen levels have never been shown in BBD women [28, 33, 63], while a progestinic deficiency has often been reported [28, 37]. Hyperestrogenism, however, is not necessarily absolute; it can be relative, that is, due both to a decreased progesterone secretion and to a too short luteal phase [35, 38, 39, 40, 41].

There is much data in favour of this hypothesis, not least in the evidence of more frequent irregular menstruation, oligomenorrhea, anovulatory cycles, in BBD patients when compared to controls. Irregular menstruation is present in 20%, 10% and 8% of BBD patients, patients with carcinoma and controls respectively [41]. Menstrual cycles in BBD patients are longer than in breast cancer patients (Tab. 6) [41]». Two percent of breast cancer patients have menstrual cycles of 30 days or longer, whereas 20% of patients with BBD and 28% of the controls exhibited no such

Table 6. – *Duration of menstrual cycle.*

Patients	Days	Range
Cancer	26.4	20-30
Benign disease	27.9	21.45
Controls	28.6	19.90

(Olsson, 1983)

long cycles ([41]). Short menstrual cycles of less than 21 days are more frequent in breast cancer patients (20%) than in controls (4%) ([41]).

These data support the hypothesis that hypoluteinisation is more frequently associated with BBD, as it can be responsible for both long and short cycles. On the other hand, hyperestrogenism, most frequently the cause of short cycles, is associated with mammary carcinoma ([41]). PEL index (progesterone/estrogen in luteal P (pg/ml)/E2 (pg/ml)$\times$0.01) ([28]) has been proposed for the quantification of progesterone deficiency. However the PEL index is not free from criticism, both because this index takes into account estrogen and progesterone only, in a multiple hormonal target organ such as the breast, and because of the unlimited number of samples necessary for correct evaluation of the index, on account of the rapidly fluctuating sex hormone levels ([27]).

Salivary progesterone has been measured with the aim of solving the problem, the advantage being that progesterone in salivary samples is free and not bound to plasma proteins, and thus is biologically active. Salivary progesterone was measured at 9a.m. and 9p.m. during the luteal phase: no differences were demonstrated in patients with breast cancer, BBD patients and controls ([42]). Another advantage is that this is easy to perform, and painless, thus multiple samples can be obtained, reducing the bias introduced by circadian fluctuations ([43]). As far as fluctuations are concerned, the only difference between the above mentioned groups was that the progesterone levels of the controls and previous BBD patients were significantly higher in the evening than in the morning samples, this difference not being found in patients with breast cancer ([42]).

Increased prolactin levels were shown in BBD women, such as epiphenomenon of spontaneous hyperprolactinemic poussées and/or an increased prolactin secreting response to specific stimuli ([36, 44]). In fact, prolactin plasma levels obtained in different groups of BBD women with a single sampling per patient were similar to prolactin levels in controls ([45]).

Hyperprolactinemia in BBD women became evident only when chronobiological fluctuations of the hormone were taken into account, that is to say daily fluctuations in the different phases of the menstrual cycle and circadian fluctuations of the hormone. In single sampling, prolactin values were similar in BBD women and controls ([46, 47]).

In the time span of 24 hours, prolactin values vary considerably and when circadian levels are studied higher levels are found after midnight, during nocturnal hours. In BBD patients circadian rhythms are changed as well as circannual one ([49]), moreover, prolactin levels in the luteal phase are higher than in the follicular phase, especially in the morning ([33, 34, 44, 50]).

The more marked prolactin peak shown in BBD patients in the nocturnal hours, has been defined as amplitude-hyper-prolactinemia ([51]).

It is interesting to point out that the situation is similar in hypertension, both experimental and in men, where amplitude-hypertension is an early stage of blood pressure increase in labile essential hypertension, and is the intermediate stage between normotensive and hypertensive disease ([52]).

Hence, nocturnal amplitude is proposed as being an evolution phase of fibrocystic disease, passing from simple mastalgia, with or without nodularty, to epithelial proliferation and fibrosis ([53]). For now however, only the fact that women with BBD show an altered pattern of pituitarian release that manifests itself in nocturnal hyper-prolactinemia, associated possibly with high diurnal values ([54]) has been demonstrated.

To summarize, BBD is characterized by an increase of prolactinemic response to various physiological and pharmacological conditions rather than by an increase of basal prolactin levels. Indeed, the increase of prolactin during the night is seen following the administration of dopaminergic drugs and TRH ([55, 56]). I. v. administration of TRH 200 mg in BBD women results in prolactin hypersecretion, with TRH levels similar to controls ([51, 57]).

At present, the mechanisms responsible for the increased prolactin response in patients compared to controls have not been explained (Fig. 2) ([72]).

Estrogen may modulate prolactin secretion: 1) at hypothalamic level, by suppressing TIDA, which has an inhibitory dopaminergic control on anterior pituitary lactototropic cells ([58]); 2) by suppressing pituitary cell sensitivity to dopamine (DA) ([59]); 3) by modifying the extra prolactinemic response without affecting basal secretion ([60]). Hence, hyperestrogenism is a hyperprolactinizing factor: estradiol may possibly affect dopamine by being metabolized to 2-hydroxyestradiol, the latter having a higher affinity for dopaminergic receptors ([61, 62]).

It has been proposed that the TRH test may have a predictive value clinically for the selection of patients with mastalgia who will respond to bromocryptine ([63]). As for the mechanism which produces hyperprolactinemia after TRH stimulation in BBD patients, a connection wth hyperestrogenism has been hypothesized in this group of patients ([27]). TRH induced hyperprolactinemia could actually be higher in patients with unopposed estrogen effect, hence independently from breast disease ([64]), as in patients with anovulatory cycles, where TRH stimulation induces hyperprolactinemia, and bromocryptine can restore ovulation ([65]). However, in many studies increased estrogen levels have not been found in patients in whom prolactin levels increased after TRH administration. It is therefore possi-

ble that induced hyperprolactinemia is independent from hyperestrogenism ([66]).

Hyperestrogenism has been regarded as the main factor responsible for epithelial hyperplasia of breast cells as well as the factor responsible for hyperprolactinemia ([66]).

In rodents estrogens produce a rapid increase in PRL levels via a decrease in dopaminergic inhibition ([58, 60]).

However, this hypothesis has recently been rejected by in vitro studies by Bethea ([3, 4]), in which estrogens decreased the sensitivity of pituitary cells to dopaminergic stimuli in rats, whilst primates cells responded with an increased sensitivity to dopamine in the presence of estrogens ([67, 68]). E2 administration can increase the level of dopamine inhibition on prolactin synthesis in vivo both in men and monkeys ([69]), and a decrease of prolactin basal levels following E2 administration has been shown in some women ([70]).

A possible explanation is that estrogen induced prolactin activates the short feed-back mechanism on hypothalamic dopaminergic activity, besides increasing the sensitivity of prolactin producing pituitary cells to increased dopamine levels ([6]). On the contrary, in non-hyperprolactinemic women with a reduced dopaminergic activity, estrogens induce a further PRL increase, unopposed by the reduced dopamine activity ([71]). In other words, estrogen induced hyperprolactin is opposed by an increased dopaminergic activity in normal-condition subjects, in addition, progesterone can exert a complementary action with regard to the inhibition of PRL release in the luteal phase ([72]).

These complicated neuroendocrine relationships may explain the negligible plasmatic changes in PRL during normal menstrual cycles, in spite of the wide fluctuations in estrogen levels ([66]).

Returning to BBD patients, the estrogen-dopamine ratio may be responsible for hyperprolactinemia as well as for the increased prolactinemic response to different stimuli, independently of the absolute values of plasma estrogen levels ([66]).

Endogenous opioids, for example, by provoking a stimulation of dopamine turnover may cause an increase in prolactin levels ([73, 74]). This hypothesis is supported by the fact that endogenous opioid antagonists, such as noloxone, can inhibit the prolactinemic response to stress ([75]).

Furthermore, it is possible that, especially in young women with the initial stages of BBD, or even more likely women suffering from simple cyclic mastalgia, related hyperestrogenism following luteal failure may result in an increase in the inhibitory effect of dopamine thereby maintaining normal prolactin levels ([35]).

Progesterone seems to inhibit prolactin release in experiments performed both in vivo in animals and in vitro, at concentrations which correspond to the luteal phase [72, 76]. However, this prolactin suppression has not yet been demonstrated in humans [27].

Luteal failure can result in a relative hyperestrogenism, which in turn suppresses dopaminergic drive, with resulting hyperprolactinemia [27].

Mammary PRL can induce estrogen and prolactin receptors, which results in a stimulation of cell proliferation [72].

Heavy, chronic, but not sporadic, stress can produce hormonal imbalance, which can induce the breast morphological changes seen in BBD (Fig. 3) [27]. PRL increase induced by endogenous opioids is the most direct effect of stress. Beta-endorfin may cause inhibition of the TIDA system [78, 79] at the hypothalamic level, though a direct action on pituitary lactotrope cells cannot be excluded, which would result in a decreased responsivity to dopamine [80]. Both the above mentioned mechanisms would result in hyperprolactinemia.

ACTH dependent steroidogenesis stimulation is another stress mechanism which can interfere with breast hormonal control, resulting in an increase in circulating levels of glycocorticoids and adrenal androgens [27]. Androgen excess can increase androgenic activity due to peripheral androgen-estrogen conversion. Anyway, the breast is a target organ for androgens, in fact dehydroepiandrosterone sulphate levels are often elevated in fluid aspirated from breast cysts [81, 82].

Glycocorticoids amplify the mitogenic and lactogenic effects of prolactin in the breast [72, 83]. Hyperprolactinemia can increase adrenal DEAS secretion [84, 85], possibly through an increase of ACTH [85].

Hence, stress may act on the etiopathogenesis of BBD via mechanisms similar to the already mentioned ones, that is to say hyperprolactinemia and increased levels of adrenal androgens (Fig. 3).

Taking an overall prospective, the possible causes of BBD can be considered as being a series of predisposing factors linked together in such a way that they influence one another reciprocally.

SEX HORMONES IN NIPPLE ASPIRATION FLUID

The presence of sex hormones in nipple aspiration fluid has also been studied, in order to obtain more detailed information about steroid metabolism in breast cells.

In a Finnish study on women, aged 20 to 69, free from breast diseases, estrogen levels in nipple aspiration fluid were found to be higher than plasma levels, although no age-related change was observed [85].

DEAS in fluid aspirated from nipples of women with BBD and breast cancer have been found not differ from controls, while plasma DEAS levels in patients with breast disease have been found to be lower than in the reference group ([86, 88]).

On the contrary, testosterone levels in aspiration fluid have been found to be higher in breast cancer patients compared to controls, In fact, it is well known that the testosterone production rate is higher in cancerous than in healthy tissue ([89, 90]).

It is not yet completely clear however if progesterone levels are lower in BBD or breast cancer patients. Recently, it has been shown that the concentration of Progesterone is higher in nipple aspiration fluid compared to plasma, especially in the luteal phase ([91]).

Prolactin has also been measured in nipple fluid and its values are higher in fibrocystic disease and/or mastalgia compared to controls ([92]). This finding could explain the effectiveness of bromocryptine treatment, even if limited to the period of administration, in patients with mastalgia and normal prolactinemia ([93]).

Biologically active PRL levels in nipple secretions, measured with Nb2 rat lymphoma cells, appears higher in BBD patients, whereas the hormone seems to be biologically inert in controls ([94]).

At this point two hypotheses may be proposed: in fluid aspirated from the nipples of women free from BBD, a special configuration of the hormone is present which makes it biologically inactive, or else an inhibitor is present, which abolishes its biological activity, without preventing the identification of the hormone with RIA ([95]).

Epidermal growth factor (EGF) has been shown in maternal milk ([96]), breast cancer cells ([97]) and in some cases seems to stimulate cell growth ([98]), as is the case in cyst fluid ([99]). EGF is not, however, present in nipple aspiration fluid in the majority of healthy women (it was shown in 3 cases out of 10 only) while it is measurable in most of women with BBD (6 cases out of 7) ([95]).

The possible role of EGF in patients with fibrocystic disease is still under investigation. Owing to its presence in the breast tissue of patients with cancer, it possibly has a role as a biological marker identifying the elevated risk of developing cancer ([100]).

MAMMARY MORPHOLOGICAL CHANGES IN THE MENSTRUAL CYCLE

Authors do not even agree about morphological changes induced by hormone secretion in different phases of the menstrual cycle.

Initially, Rosemburg described a premenstrual hypertrophy of breast cells and a menstrual regression ([101]).

Other Authors, on the contrary, have asserted that cyclic breast tissue changes are more evident in the connective tissue than in the acinous epithelium ([102, 103]).

Others deny the existence of menstrual cycle dependent morphological changes, and regard the breast outside pregnancy as a quiescent gland ([104–106]).

More recently, Ferguson (1981) reported an increase in the level of mitotic activity during the luteal phase of the cycle, namely a mitotic activity peak, characterized by mitosis and apoptosis, occurring on days 25 and 28 of the cycle ([107]). Vogel, at the same time examined breast tissue from mastectomies and mastoplasties and reported a mitotic activity peak during the proliferative phase of the menstrual cycle, between the 3rd and the 7th day ([108]).

The great disagreement in literature can be attributed to the heterogeneous lobular development both within and among patients, and to the difficulties in obtaining sufficient tissue for performing accurate morphological evaluations in normal women whose menstrual cycle features are known ([109]).

Mammary epithelium and lobular connective tissue heterogeneity is overcome only by examining multiple sections of the same breast; in this way, specific morphological changes can also be ascribed to different phases of the menstrual cycle. In fact it has become evident by comparing tissue samples from fertile and postmenopausal women that some morphological changes are linked to differences in estrogen and progesterone secretion ([6]). Recently Longacre, in her studies on necroscopic human tissue showed that the dynamics of mammary epithelium are characteristic of the second half of the cycle ([109]); indeed, the mitotic peak in the breast occurs on days 23-25 of the cycle, in contrast to the endometrium. This finding gives evidence for a progesterone effect or a combined effect of estrogen and progesterone on mitotic activity ([109]).

These findings have been confirmed using 3H-thymidine: a low labelling index is associated with a rapid increase in DNA synthesis in the follicular phase on the 22nd day of the cycle ([110, 111]).

In the luteal phase, epithelial morphological changes have been shown to be associated with changes of the connective tissue: stromal oedema gradually increasing during the secretory phase and peaking at the 23rd-25th day of the cycle. Connective tissue oedema is ascribed to sex hormones, which provoke a hystamine-like effect in mammary circulation ([109]).

Mucopolysaccharide accumulation may be due to endothelial cells, as shown in human and mouse mammary tissue ([112]) as well as in estrogen-stimulated fibroblasts ([112]).

Besides estrogens, the possible role of progesterone has been more recently taken into consideration: in fact, mucopolysaccharide accumulation becomes evident in the luteal phase of the cycle, while it is negligible in its first half ([109]).

The functional significance of the cyclical changes in connective tissue has not yet been completely elucidated. As interactions between collagen, mucopolysaccharides and the embrional morphogenesis of glandular epithelium have been shown ([114]) it could be suggested that connective tissue changes may have a modulating effect on the cyclic proliferation of glandular epithelium ([109]).

Lobules are small (maximum size=1.06) and with few, (8 to 40, average 23.3) terminal duct acina in the proliferative phase ([109]). The epithelium content of terminal ducts is low and consits of polygonal cells with central nuclei. Mitotic events are rare (0-0.5 per lobule).

In the first part of the luteal phase, 16th to 20th day, the number of terminal ducts increases (range 17-55, average 42.8) and the size of the lobule increases parallely (1.24 mm).

Mitosis remain a sporadic event from days 16 to 20 (0-0.5 per lobule) ([109]).

The maximum development of lobules occurs in the second part of the luteal phase, and they reach a size of 1.82 mm; the number of lobules per acinus reaches the value of 67.7. Each lobule contains 1.1 to 1.3 randomly distributed mitotic figures ([109]).

Cyclic changes the of mammary epithelium do not seem to be affected either by age or by parity ([109]).

No cyclical morphological changes in the epithelium and connective tissue have been seen to occur in fibrocystic areas. However, they do occur in the normal tissue surrounding the lesion and do not differ from healthy breast ([109]). The apoptosis peak occurs 3 days after the mitosis peak, possibly because apoptosis is recognizable for 18 hours, while mitosis is recognizable for 3 hours only ([107]).

At present, the role of sex hormones on mitosis and apoptosis has not yet been completely elucidated. As maximal mitotic activity occurs together with a peak in progesterone and the second estrogen peak (22nd and 23rd day), it is possible that mitotic activity can be induced by progesterone or by a synergic action of estrogen and progesterone. It is interesting to note that mitosis does not increase concurrently with the first estrogen peak at the 14th day of the cycle ([107]). However, the morphological changes

of the endometrium, a target tissue for sex hormones, are completely different from those of mammary tissue; indeed, in the endometrium the mitosis peak occurs in the proliferative phase of the cycle, when estrogen activity is maximal ([109]).

Apoptosis occurs in the second part of the luteal phase, both in the endometrium and the breast; thus, apoptosis is likely to be the response of estrogen and progesterone levels which occurs before menstrual bleeding ([107]).

BIOCHEMISTRY OF FLUID ASPIRATED FROM BREAST CYSTS

The study of cyst fluid has always been based upon the rationale, referred to by the Authors themselves, of an increased risk of breast carcinoma in women harbouring breast cysts, (the risk being 3-4-fold increased) ([3, 4, 115, 117]).

In reality this increased risk has not been demonstrated, notwithstanding the positive familiarity for breast cancer ([15]).

Thus, breast cysts cannot be regarded as premalignant lesions, as neoplastic lesions have never been shown within a cyst, and in the cases of macrocyst-cancer association, the cancer develops far from the cyst or even in the contralateral breast ([15]).

In any case, cyst fluid has been studied for years, with the object of identifying a hypothetical subpopulation at a higher risk of carcinoma, based on the biochemical characterization of fluid aspirated from cysts. Hence, different breast cyst subpopulations have been identified on the basis of different electrolyte and hormone concentrations in aspirated fluid.

The electrolyte status has been perhaps the most studied aspect; in 1973 Fleisher found a higher potassium content in cyst fluid than in plasma ([118]). A few years later, a higher cation content was found in cyst fluid than in the plasma compartment: the "anion gap" which occurs, due to an insufficient concentration of inorganic anions (Cl- and HCO3-), being balanced by the negative valences of proteins and organic anions, as in the intracellular compartment ([119]).

More recently attention has been turned to the concentrations of Na^+ and K^+ and in particular to the inverse proportions of these ions in cyst fluid which allows these cysts to be divided into three groups: I) cysts with high K^+ and low Na^+; II) cysts with low K^+ and high Na^+; III) cysts with intermediate levels of the two electrolites ([120–122]). From this, three types of classification have been derived (Tab. 7). The difference between the classification systems are small: initially Bradlow ([120]) used the absolute

Table 7. – *Classification of breast cysts.*

I)	K^+	>100 mEq/l;	Na^+	<50 mEq/l
II)	K^+	<50 mEq/l;	Na^+	>100 mEq/l
III)	K^+ and Na^+	<100 mEq/l;		>50 mEq/l
				(by Bradlow, 1983)
I)	K^+/Na^+	>1		
II)	K^+/Na^+	<0.25		
III)	K^+/Na^+	>0.25 <1		
				(by Miller, 1983)
I)	K^+/Na^+	>1.5		
II)	K^+/Na^+	<0.66		
III)	K^+/Na^+	>0.66 <1.5		
				(Dogliotti, 1986)

values of K^+ and Na^+ concentrations as the discriminating criteria, while groups were defined by K^+/Na^+ ratio in later classifications. This approach has the advantage of excluding not even the small group of cysts with K^+ and Na^+ levels higher or lower than 50 or 100 mEq/1. The different cut-off level proposed by Dogliotti's classification ([122]) would allow a reduction of the number of cases classified in the third group, thus enabling a better comparison of cysts with high and low K^+ content. Type I and Type II cysts are more frequent in fertile and menopausal years respectively ([122]). The two main types of cysts differ in terms of hydrogen and chlorine ion concentration: K^+ and H^+ concentrations are higher in group I, while Na^+ and Cl-concentrations are higher in group II ([122]).

Furthermore, a vast range of both proteic and steroid hormones have been identified in cyst fluid (Tab. 8 and 9) ([27, 123–125]). Cyst fluid contains high concentrations of thyroid hormones, especially free triidotyronine (T3) and thyroxine (T4) ([124]). Moreover, an inverse relationship links FT3 and PRL, suggesting a possible synergistic effect of the hormones in the breast, though actual data are limited to animals, where an interaction has been shown to exist between thyroid hormones and prolactin in mammary lobular-alveolar development ([126]).

No significant difference appears to exist between cyst fluid and the plasmatic compartment with respect to levels of steroid hormones, even if there is no agreement in literature (Tab. 10) ([37, 124, 125]).

Dehydroepiandrosterone sulphate (DEA-S) and sulphoconjugated estrone (E-S) seem to be the two most interesting steroids in breast cysts. The former DEA-S seems to accumulate in cyst fluid, for which two possible

Table 8. – *Pituitary hormones in cyst fluid.*

		No.	Mean value	Range
GSH	g/ml	40	1.1	0-4.2
TSH	mIU/ml	45	2.3	0.5-6.8
FSH	mIU/ml	50	2.1	0-6.6
LH	mIU/l	40	3.3	0-8.4
PRL	ng/ml	412	5.6	1-41.6

(Angeli, 1987)

Table 9. – *Thyroid hormones in cyst fluid.*

		No.	Mean value	Range
T3	nmol/l	225	7.37	0.61-41.16
T4	nmol/l	98	20.56	2.57-59.12
fT3	pmol/l	164	111.21	7.98-296.46
fT4	pmol/l	162	123.39	7.06-524.42
rT3	nmol/l	50	4.91	2.15-11.98

(Angeli, 1987)

origins have been proposed: 1) DEA-S is the only molecule which can transfer significant radioactivity levels from outside into the cyst, given the plasmatic origin of the steroid; 2) the synthesis might occur locally by apocrine lining cells of the cyst wall ([125]). High DEA-S concentrations have been shown in the secretion of apocrine extra-mammary glands, for example axillary sweat glands ([127]). Apocrine glands in breast cysts can be

Table 10. – *Steroid hormones in cyst fluid.*

		No.	Mean value	Range
Aldosterone	pmol/l	54	95.7	4.7-208.1
Androstenedione	nmol/l	69	95.7	0.69-23.92
Cortisol	nmol/l	285	99.3	11.03-336.58
DHA	nmol/l	75	26.7	1.21-102.28
DHAS	mmol/l	409	97.2	1.29-115.43
Estradiol	pmol/l	182	403.8	36.7-1652.1
Estrone	pmol/l	76	314.3	36.9-2441-18
Progesterone	nmol/l	266	40.7	2.54-103.67
Testosterone	nmol/l	124	4.2	1.04-13.17
17-OH-Progest.	nmol/l	133	14.8	1.51-24.81

(Angeli, 1987)

defined as steroid androgen receptors and/or predictors, when taking into account the high cyst levels of DEA-S and the relationship between androgens and apocrine secretion ([125]).

Moreover, a positive correlation between DEA-S and intracystic concentrations of K^+ and a negative correlation between DEA-S and Na^+ have bben demonstrated (Fig. 5) ([120, 122, 128]). Hence, group I and II cysts tend to have high and low DEA-S levels respectively, suggesting that apocrine differentiation of lining epithelium is more evident in the first group ([129]).

Apocrine cells have been shown in 84% and 64% only of fluid aspirated from type I and type II cysts respectively ([124]).

Sulphoconjugated estrogen are another group of hormones with a high tendency for intracyst accumulation. Estrone sulphate (E1-S) reaches intracystic concentrations 20 fold higher than in plasma; even estradiol sulphate (E2-S), which is normally absent in plasma, has been measured in cyst fluid (Tab. 11). ([125]).

Table 11. – *Estrogen in cyst fluid.*

pg/ml	E1	E2	E1SO4	E2SO4
Mean	66	96	9620	2740
Range	8-204	37-240	2240-2100	1060-4590
Range in female	30-300	37-710	470 foll.	—
Plasma			890 lut.	
Number of samples	40	40	35	35

(Bradlow, 1983)

As far as estrogens in cyst fluid are concerned, a local synthesis from steroid precursors is required, in that test with labelled steroids have excluded the possibility of an active transport mechanism from plasma ([125, 130]).

Estrone-3-sulphate (E1-S), a 18-C molecule, has been shown to be derived from the peripheral sulphoconjugation of free estrogens, estrone and estradiol ([131]).

It is essential that the role of proteic hormonal carriers should be taken into account, in order to more accurately define the active role of the numerous hormones isolated in BFC. The binding capacity of intracystic hormonal carriers is markedly lower than in plasma, about one tenth on average. As a result, hormonal concentrations even lower than those found in plasma may actually have important biological effects.

Moreover, the hormonal action would be greatly facilitated by a hypothetical lower affinity of the intracystic ligand compared to the plasmatic one [132].

Besides hormone binding proteins, the protein content of cyst fluid is inconstant, being, on average, about one third of circulating levels [133].

Proteins and enzymes, (LDH, alkaline phosphatase, amylase, lipase, gamma-GT, beta-glucuronidase), small amounts ofalbumin and high glycoproteins levels have been shown to be responsible for the characteristic viscosity of BCF [133].

Higher levels of proteins of thrombocytic origin, such as beta-thromboglobuline and thrombospondine, have been shown in group II cysts, as well as non-secretory IgA (7S), while secretory form (11S) prevails in group I cysts [134].

GCDFP-15 (gross cystic disease fluid protein 15000 Dalton) is a specific protein of cyst fluid [135, 137]. It has also been shown to be present in axillary and perineal apocrine gland secretion and in the plasma of some patients with metastatic breast cancer [3, 136]. GCDFP-15 levels seem to be higher in those cysts in which lactalbumin is not measurable; this protein is thought to express the degree of cellular differentiation in cyst epithelium [137]. A positive relationship has been shown between GCDFP-15 and EMA, an epithelial membrane antigen which is expressed by breast cells and a possible marker for epithelial hyperplasia. Another possible relationship has been found between GCDFP-15 and EGF, the growth factor which is always measurable in cyst fluid, even though at varying degrees [137].

Furthermore, many cancer associated antigens have been found in cyst fluid, such as CEA and CA 125, which are prevalent in group II cysts [124, 128, 138], alpha-fetoprotein, which seems prevalent in group I cysts, and also BHCG [139].

CONCLUSIONS

The various pathological features of benign breast disease often raise a series of doubts and unsolved problems concerning hormonal involvement, the risk of developing breast cancer and risk factors.

As for fibrocystic disease, which is the most common aspect of benign breast disease, it is now interpreted as a dysendocrine condition - this view being supported by epidemiological observations, presence of bilateral lesions, clinical course and success of hormonal therapy. The hormone profile underlying a slowly progressing disease developing after years of proliferative activity, implies a complex pathogenesis and only slight changes from " normality ". The basic endocrine disorder should be considered as

multifactorial; it is likely to differ between individuals and, during the course of the disease, within the same subject. The effect of the various hormones on breast tissue should not simply be estimated as depending on their plasma concentrations; other factors are to be considered, such as the amount of hormones produced following the various stimuli, their transport mechanisms, vascular and extravascular distribution, cell-receptor interactions, target cell metabolic response, metabolization, and loss of specific biologic activity. Moreover, hormones interact with each other: for instance, prolactin responds to the various stimuli depending on estrogen concentrations.

The estrogen hypothesis, according to which fibrocystic disease is caused by mild but long-lasting hyperestrogenisms, is still the most widely accepted. Excessive estrogen stimulation leads to slow tissue proliferation, with consequent structure disorganisation. Relative hyperestrogenism may also occur, which is not necessarily linked to increased estrogen release but rather to reduced progesterone secretion. This condition causes high blood prolactin levels, with consequent flares, and/or results in enhanced blood prolactin response to specific stimuli.

Specific factors such as stress, for instance, may lead to increased blood prolactin concentrations by reducing dopaminergic tone, or to an unopposed estrogen effect by increasing ACTH,induced adrenal steroidogenesis.

The etiopathogenetic mechanisms of benign breast disease are complex and still only partially clear, as also the possible relationship between benign disease and risk of developing breast carcinoma.

In this regard, the medical attitude has markedly changed over the past few years: the alarmism of the '70s – when benign lesions were often thought to be premalignant – is over, and only proliferative lesions with atypia are now considered at risk for carcinoma. These, in fact, cause a 5-fold increase in the risk of developing breast cancer in comparison to the control population. It is worth recalling that such cases only account for 4% of biopsies; the majority of patients undergoing biopsy may thus be reassured that their lesions will not evolve into a malignancy. A full clinical examination and a proper use of diagnostic tools, including mammography and cytologic examination after needle biopsy, will reduce the number of unnecessary biopsies. Besides, scar tissue hampers the sensitivity of mammography: a useless bioptic examination heightens the cost-to-benefit ratio, by increasing costs, causing the patient the stress of the operation and reducing the reliability of postoperative breast monitoring.

PART II – MEDICAL TREATMENT OF FIBROCYSTIC DISEASE

INTRODUCTION

The literature of the past ten years is rich in articles regarding the medical treatment of fibrocystic disease, in which the need to treat the disease is emphasised, as is its association with an increased risk of breast cancer.

However, more recent data show that fibrocystic disease is not associated with an increased risk of breast cancer, except in some specific histological cases, found in 4% of breast biopsies. The relative risk in this subgroup of patients is 3.5 (c.i.: 2.0 - 5.5) and increases up to 8.9 (c.i.: 4.0 - 17) if the atypical proliferative lesion is associated with a family history of cancer.

It is particularly interesting to note that the histological patterns, (essentially different forms of atypical hyperplasia), associated with an increased risk of breast cancer, usually do not result in nodes or thickening. In addition, their finding is frequently accidental, following a biopsy performed for another disease, which by itself does not suggest than an increased risk exists.

The fact that these lesions are not clinically identifiable proposes the further problem that their true incidence cannot actually be quantified.

Moreover, the lesions in themselves are poor cancer predictors; at the most they are generic risk markers. It has in fact been shown that half of the cancers seen in women at risk occur in the contralateral breast, compared to the breast in which the biopsy showed the atypical lesion ([8]).

Nevertheless, several therapies have been used to treat this disorder, which at present may be regarded as a non-disease.

In the course of the past few years, acupuncture, auricolotherapy, combined coumarin-rutin, A and E vitamins, decreased intake of xanthines in the diet have all been used. Recently, hormonal therapy has been introduced, stimulated by the recently acquired knowledge of the endocrine pathogenesis of some forms of the disorder.

In any case, the optimal drug is far from being identified. Moreover, there is no agreement in literature as to which mastopathies are best suited to medical treatment, when the treatment should be started, its objective and how the response should be evaluated.

The therapy is usually aimed at correcting the functional hormonal imbalance with is considered to be the basis of the clinical and symptomatological findings. In some cases mastopathy is only the epithenomenon of an altered hormonal environment, in others the symptomatology occurs in patients free from noticeable hormonal changes.

While in the former the treatment is guided by the type and size of hormonal imbalance, in the latter it is aimed at controlling the disease through direct intervention against an etiopathological factor whose existence cannot be demonstrated in each single case.

Subjective symptoms, (mastalgia and breast tension), improve above all, but even some objective symptoms, (nodularity, breast tenderness or stiffness) can show a response, even if in longer time spans. However, in most studies the evaluation of the response is restricted to recovery from symptoms, without taking into consideration the possible histological changes due to treatment. Moreover, the importance of the placebo effect should be pointed out when evaluating the response, as it can be important in a disease where the emotional-anxious component does have a noticeable weight, as in breast disease.

However, many papers regarding the treatment of breast cystic disease can be found in literature. They have been analysed by us according to an objective procedure, in order to enable the reader to repeat the analysis according to our parameters or, if desired, to different ones, provided that they are objectively defined ([140-143]).

EVALUATION CRITERIA OF THE LITERATURE EXAMINED

Analysis was performed on papers written in French, English and Italian, published in the period 1-1-75 - 31-3-86, and reported in Index Medicus under the key words " Benign breast disease and medical therapy ".

Only original clinical studies and not reviews have been taken into account.

In addition, clinical studies available in the libraries of Pharmaceutical firms, published in the same period, even if not reported by Index Medicus (8 papers) were analysed (danazol 238-242; bromocryptine 243-260; percutaneous progesterone 261-274; other drugs 275).

The evaluation criteria of selected papers were as follows:

1) Type of study:

Randomisation: the only randomisation techniques judged as valid were those in which a sealed envelope containing the randomisation was

provided, (although today even this system is to be avoided), or a randomisation scheme via telephone, coordinated from the centre where the data is subsequently validated, at the moment that a patient assessed as eligible, is registered as participating in the study, were considered as valid. Techniques based upon dates of birth, data sheet number, date of entry, and generally on elements which could allow bias to be introduced, consciously or not, by the investigator involved, by avoiding placing certain patients, whom they consider personally better suited to a therapy other than that to which the randomisation scheme would allocate them, into the study were excluded from the analysis.

Blindness: a double blind design is the best choice, performed with the administration of a placebo or another drug whose appearance and packaging cannot be distinguished from the drug in study, identifiable by means of a symbol, unknown to the investigator or the patient.

This may not always be possible, particularly with drugs such as danazol and bromocryptine, drugs which have side effects making them easily identifiable from placebo. In these cases, studies with at least a single blind design were classified as valid.

Observational studies without a reference group were examined separately. Such studies are less informative since it is not possible to assume what proportion of the observed effect is due to placebo effect and what proportion to the drug. The above considerations are valid both in the evaluation of therapeutical effectiveness and of the undesired side effects of the therapy. It should be pointed out that the possible "carry over" effect of the first drug is often not taken in account when evaluating the response to therapy in placebo-drug or drug-drug cross-over studies.

2) The nations in which the studies were carried out:

Dividing the trials by drug, the country in which the trials took place, within or outside Italy, was taken into account in order to determine whether a different approach to the treatment of fibrocystic disease exists in different countries.

3) Size of the sample:

This is an important element when giving weight to the observed effect, apart from the effect on the possible statistical significance of the study.

4) Diagnostic procedures:

As discussed in the introduction, an agreement on the significance of the term of "fibrocystic disease" is lacking, thus a distinction has been made between studies considering subjective symptoms, studies referring to the objective clinical situation, studies reporting instrumental findings such as thermography, echotomography and mammography, and studies referring to histological findings in lesions.

5) Definition of the hormonal status of the sample:

As already reported, fibrocystic mastopathy can occur both in women free from hormonal imbalances, and in women with concurrent hormonal disorders related to or affecting the clinical status of the breast.

Studies were divided into the following separate groups:

– no reported data on the hormonal status;

– definition of menopausal status and clinical features of menstrual cycle only;

– assessment of the hormonal status with hormonal assays.

6) Dosage and duration of the treatment:

Daily dose and duration of the treatment are reported for each drug, in order to evaluate differences related to the two variables in different studies and the resulting relationship with therapeutical effectiveness.

7) Evaluation of the aims of the study:

The possible aims of a study investigating the treatment of cystic breast disease include the reduction of the risk of cancer, any change in instrumental findings, the reduction of clinical symptoms (particularly tenderness and nodularity) and of subjective symptoms.

For each of these end-points, the way in which the results were expressed was taken into account qualitatively or quantitatively, and in the latter case, whether objective and hence reproduceable scales were employed.

8) Duration of the response:

Not only the proportion and degree of response was taken into account, but also the duration of the response; from this certain problems emerged regarding the expression of the data. The majority of the Authors give no data on follow up, and the response to the therapy was evaluated during the period of drug administration only. In those studies in which the

response after withdrawal was evaluated, many confine themselves to merely stating that therapeutical effectiveness was maintained "for some time" "in some patients", and only a few of them give details regarding the proportion of patients and the size of the response at different observation times.

9) Compliance with treatment:

As certain drugs have considerable side effects, it is important to know the degree of treatment compliance. Compliance is an extremely important parameter, but it is often reported in a superficial and incomplete manner. In addition, Authors vary greatly, at the point of data analysis, in the way in which patients who have suspended treatment are considered, independently from the reason driving them to do so.

The calculation of drop-outs from the original group of patients is the only acceptable way of correctly analysing results; the analysis should be performed according to the "intention to treat" principle, and reasons for withdrawals should be listed in detail; in reality, drop-outs are often excluded from calculations and information about the reasons for withdrawal are often lacking, or, even worse, the only statement provided is that the treatment was tolerated well enough.

10) Choice of the reference group:

When the type of study has allowed it, selection criteria of controls have been analysed e.g. therapy/no therapy, placebo or other drugs than the drug in study. These evaluation criteria were chosen on the basis of what is usually done as a preliminary step when a meta-analysis of literature is performed. They are arbitrary, nevertheless they are unequivocal and objective, thus allowing everybody to repeat the analysis on the same papers or others chosen with different criteria. Moreover, the criteria may serve as a foundation upon which to select other criteria in order to undertake a more profound criticism of any particular aspect of the review.

RESULTS OF THE REVIEW

85 papers were selected on the basis of the above criteria: 21 of which concerned danazol ([144–159]; [238–242]), 32 bromocryptine ([160–173]), 16 percutaneous progesterone ([174, 175, 261–274]), 4 vitamins ([176–179]), 4 tamoxifen ([180–183]) and 8 other drugs ([184–190, 275]).

In the following assessment, 88 studies out of 85 papers are examined, as one paper on progesterone [268] and 2 papers on danazol [147, 239] included 2 clinical studies each.

24 of 32 studies on bromocriptine [162-164, 168, 169, 171, 173, 243, 250, 252, 260], 11 studies of 17 on progesterone [262-267, 269, 273], 1 study each on vitamins [177] and tamoxifen [180] and 2 studies on other drugs [185, 190] are Italian, while studies on danazol were all carried out in other countries (Tab. 12).

Table 12. – *Distribution of studies according to drug and country.*

	Total number of studies	Italian	Foreign
Danazol	23	—	23
Bromocryptine	32	24	8
Perc. progesterone	17	11	6
Vitamins	4	1	3
Tamoxifen	4	1	3
Other drugs	8	1	7
Total	88	38	50

Perc. progest.: percutaneous progesterone.

In the group defined as " other drugs ", therapies reported in a very small number of studies (no more than 2 per drug) were included (Table 13). The 438 patients included in this group were treated with therapies ranging from acupuncture to tamoxifen, thyroid hormones to mechanical means such as " made to measure brassières ", coumarin plus rutin given by different routes of administration, to reduced intake of dietary xanthines. Only one of the studies on reduced intake of xanthines is rando-

Table 13. – *Other therapies for BBD.*

	Total number of studies	Total number of patients
Acupuncture	1	5
Coumarin + Rutin	1	20
Thyroid hormone	1	19
Oral progesterone	2	75
Measured brassière	1	114
Reduced xanthines	2	205
Total	8	438

mised [188], the other 7 [184–187, 189–190, 275] are observational and only 2 of them [184, 189] have a control group. This group of studies was excluded from further analysis, due to the small number of patients treated with the same drug.

On reviewing the last 10 years of literature on medical treatment of cystic disease, the first finding which strikes the reader is that most of the studies are observational. When single drugs are examined, only 8 studies of the 23 concerning danazol [146–148, 150, 154–155, 158, 240] 5 of 32 concerning bromocryptine [160, 161, 165, 256, 269], 2 of 17 [268, 273] concerning percutaneous progesterone and 2 out of 4 concerning vitamins [178, 179] and tamoxifen [180, 182] are randomised (Tab. 14).

Table 14. – *Distribution of clinical studies according to drug.*

Drug	Observational	Experimental	Total
Danazol	15	8	23
Bromocryptine	27	5	32
Perc. progest.	15	2	17
Tamoxifen	2	2	4
Vitamins	2	2	4
Total	61	19	80

Perc. progest.: percutaneous progesterone.

If, then, the quality of the randomization of the controlled clinical trials is evauated, it is seen that randomization criteria were not defined in the studies regarding progesterone and vitamins. Randomization criteria were defined and have been judged as fair in 2 studies only out of 5 concerning bromocryptine [160, 165], in 3 [150, 154, 155] out of 8 trials on danazol, and in the 2 randomised studies on tamoxifen [180, 182]. Thus, in a total of 19 randomised studies, 14 double blind studies [146–148, 150, 154, 155, 160, 161, 165, 178, 179, 256, 268, 273] and 4 open studies [158, 240, 259] only 7 can be regarded as correctly randomised.

Among all non-randomized studies, 49 are without a control group and only 12 with, however the selection criteria were not defined; 2 [157, 172] were carried out versus placebo, 9 [166, 168, 169, 239, 249, 253, 270, 274] versus another drug and 1 [272] versus placebo and another drug in two arms (Tab. 15).

70% of controlled clinical trials were reported both by Index Medicus and Current Contents. When the observational studies were considered, the proportion reported in Current Contents (32%) was about 10% less than Index Medicus (44%) (Tab. 16).

Table 15. – *Distribution of observational studies according to drug.*

	Without reference group	With reference group		Total
		vs pl.	vs drug	
Danazol	12	1	2	15
Bromocryptine	21	1	5	27
Perc. progest.	12	1*	3*	15*
Tamoxifen	2	–	–	2
Vitamins	2	–	–	2
Total	49	3*	10*	61*

Perc. progest.: percutaneous progesterone.

* 1 study with one arm vs placebo and one arm vs drug.

Table 16. – *Distribution of studies according to drug, randomisation and review.*

	Random			Non random		
	No.	IM	CC	No.	IM	CC
Danazol	8	7	6	15	10	10
Bromocryptine	5	3	3	27	11	5
Perc. progest.	2	–	–	15	2	2
Tamoxifen	2	2	2	2	2	2
Vitamins	2	2	2	2	2	1
Total	19	14	13	61	27	20

Perc. progest.: percutaneous progesterone

IM: Index Medicus; CC: Current Contents.

When randomised studies were compared with non-randomised ones, according to the total number of examined patients, only 22% of women proved to have been examined in controlled clinical trials (Tab. 17).

The average number of patients per study and the type of drug in randomised studies is identical to non-randomised, and it is not particularly restricted to the bromocryptine studies, where the average number of treated patients falls to 35 in randomised studies. The situation is the opposite for percutaneous progesterone, where a high number of patients per study (X=233) were treated corresponding to an equally high number of non-randomised studies (Tab. 18).

The diagnosis of fibrocystic disease may well be clinical or instrumental in all the studies; however, objective inclusion criteria are never clearly defined. In addition the deciding factors employed in differentiating bet-

Table 17. – *Distribution of patients in randomised and non-randomised studies according to drug.*

	Non R No. pts.	R No. pts.	Total
Danazol	2062	1393	3455
Bromocryptine	1382	175	1557
Perc. progest.	3497	147	3644
Tamoxifen	45	138	168
Vitamins	72	205	277
Total	7058	2058	9116

Perc. progest.: percutaneous progesterone.
Non R: non-randomised studies; R: randomised studies.

Table 18. – *Average number of patients in randomised and non-randomised studies according to drug.*

	Random			Non random		
	No. St.	X Pt/St	Range	No. St.	X Pt/St	Range
Danazol	8	174	6-514	15	137	16-958
Bromocryptine	5	35	10-72	27	51	7-192
Perc. progest.	2	73	50-97	15	233	20-1375
Tamoxifen	2	69	60-78	2	22	14-31
Vitamins	2	102	73-132	2	36	12-60

Perc. progest.: percutaneous progesterone.
X Pt/St: Average number of patients for studies.

ween cyclic mastalgia and nodularity via echographic and thermographic findings were not stated.

In a few studies, 13 ([160, 162, 164, 167, 168, 173, 244, 247, 249, 251, 259, 260]) on bromocryptine, 1 ([153]) on danazol, 1 ([179]) on vitamins and 1 ([180]) on tamoxifen, the diagnosis of mastopathia was confirmed via histological assay (Tab. 19).

Table 19. – *Proportion of patients with histological diagnosis according to drug.*

	Number of studies	% examined patients
Danazol	1/23	22%
Bromocryptine	13/32	7 studies: ? 6 studies: 11-83%
Perc. progest.	0/17	
Tomoxifen	1/4	89%
Vitamins	1/4	?

Perc. progest.: percutaneous progesterone.

However, it is often impossible to refer back to the number of patients per study who have undergone biopsy: as for bromocryptine, for example, in 7 studies [160, 167, 173, 244, 247, 259, 269] biopsy is said to have been performed in "some patients", in the remaining 6 studies the proportion of histologically evaluated patients is extremely variable, 11 to 89%.

28% of studies were not randomized [145, 149, 161, 159, 166, 169, 170, 174, 175, 239, 251, 261, 264, 268] and 42% [147, 154, 165, 158, 178, 240, 268] of the randomised studies do not take into account the hormonal status of the examined population.

In 18 studies, 7 randomised [146, 148, 150, 179, 256, 259, 273] and 11 non randomised [114, 152, 156, 176, 241, 242, 269, 270, 272, 274] studies the patients hormonal status is simply characterized on the basis of their menopausal status and the regularity of menstrual bleeding. These criteria are not sufficient to define hormonal changes such as hyperestrogenism, anovulatory cycles, etc.

In 4 randomised studies out of 19 [160, 161, 165] and in 33 non randomized studies out of 61 [147, 153, 157, 162–164, 167–169, 171–173, 238, 243–250, 252, 254, 255, 257, 258, 260, 262, 263, 265–267, 271] hormonal status of patients is defined with hormonal assays. The majority of the studies on bromocryptine (26/33) belong to this last group (Tab. 20).

Table 20. – *Definition of hormonal status of the sample.*

	Not defined		Clinically defined		Defined with horm. assay	
	R	Non R	R	Non R	R	Non R
Danazol	5/8	6/15	3/8	5/15	0/8	4/15
Bromocryptine	0/15	4/27	2/5	0/27	3/5	23/27
Perc. progest.	1/2	5/15	1/2	4/15	0/2	6/15
Tamoxifen	1/2	2/2	0/2	0/2	1/2	0/2
Vitamins	1/2	0/2	1/2	2/2	0/2	0/2
Total	8/9	17/61	7/19	11/61	4/19	33/61

Perc. progest.: percutaneous progesterone.
R: Randomised studies. Non R: non-randomised studies.

The studies conducted upon patients with fibrocystic disease not associated with hormonal disorders represent 46% of the studies in which some hormonal variables are assessed [147, 157, 162, 164, 167–169, 172, 180, 246, 249, 252, 255, 257, 258, 266] (Tab. 21).

However, it should be underlined that only one study in this group concerning tamoxifen is randomised [180], whilst the remaining studies are observational.

Table 21. – *Studies in patients free from hormonal disorders.*

	No. studies random	No. studies non random	Total
Danazol	–	3	3
Bromocryptine	–	12	12
Perc. progest.	–	1	1
Tamoxifen	1	0	1
Total	1	16	17

Perc. progest.: percutaneous progesterone.

In 2 studies on danazol [153, 238], 14 on bromocryptine [160, 161, 163, 165, 171, 173, 244, 245, 247, 248, 250, 254, 256, 260,] and 4 on percutaneous progesterone [262, 263, 267, 271] patients with a normal hormonal profile and patients with hormonal disorders such as hyperprolactinemia, polycystic ovaries, excessive estrogen secretion not balanced by progesterone, as in anovulatory cycles and in luteal failure, have not been stratified but are evaluated as one group (Tab. 22).

Table 22. – *Number of studies evaluating patients with normal and changed hormonal status in the same sample (range of % of studied patients).*

Drug	Normal	Hyper-PRL	PCO	Hyperestr.	Total
Danazol	2 (53-57)	–	–	2 (43-47)	2
Bromocryptine	12 (18-90)	11 (10-78)	4 (11-100)	1 (53)	14
Perc. progest.	3 (38-83)	–	1 (25)	4 (14-100)	4

PCO: polycystosis; Hyperestr.: hyperestrogenism.
Perc. progest.: percutaneous progesterone.

This is an important item in the assessment of the response. Clearly, in the case of a hormonal disorder the drug will give a better response than placebo, but these patients cannot be regarded as a representative sample of the true population of women suffering from BBD.

Authors do not agree even about the dosage of the drug to be given: the dosage of danazol varies more than 10 fold in different studies, the situation of percutaneous progesterone is extreme, with 1000 fold dosage variations (Tab. 24).

The duration of the treatment is also very variable, even in patients participating in the same study. The greatest variability is seen for danazol

Table 23. – *Daily dose in therapy of benign breast disease.*

Drug	Range
Danazol	50 - 800 mg
Bromocryptine	2.5 - 7.5 mg
Perc. progest.	5 - 500 mg
Tamoxifen	10 - 20 mg
Vitamin A	90000 UI
Vitamin E	150 UI

Perc. progest: percutaneous progesterone.

Table 24. – *Duration of treatment according to drug irrespective of type of study.*

Drug	X (months)	Range (months)
Danazol	4	0.5 - 10
Bromocryptine	3.3	1 - 6
Perc. progest.	5.3	1 - 24
Tamoxifen	3.2	3 - 4
Vitamins	2.5	2 - 3

Perc. progest.: percutaneous progesterone.

and percutaneous progesterone (Tab. 24). The longest treatment period does not exceed 2 years, even when considering complete studies. It is in any case surprising that patients given therapy for 15 days can be regarded as evaluable.

In no study whether randomised or not, are valuation criteria objectively and clearly defined. The only attempt made is a visual scale for the definition of pain, used in some cross-over studies versus placebo: 3 with danazol and 1 with bromocryptine ([165]).

Interestingly, in almost all of the studies ([148, 154, 155]) an increased risk of carcinoma in BBD patients is referred to, though none of them considered by defining as an end-point worthy of assessment, the possible decrease in this risk as a result of the therapy, even if in the long term. This should be considered seriously when a cost/benefit assessment of treatment is undertaken.

Following these premises, when response evaluation criteria were assessed in individual studies (Tab. 25) it was seen that the assessment was uniquely subjective and based on symptom variations referred by patients in 13 studies out of 80, 3 randomised ([160, 182, 268]), and 10 non-randomised ([157, 166, 168, 170, 183, 240, 247, 262, 271, 272]). In 2 randomised studies ([149, 156,]) the response

Table 25. – *Response evaluation criteria in randomised and non-randomised studies.*

	No. R	No. non R	Total
Subjective	3	10	13
Clinical	–	2	2
Subjective + Clinical	8	24	32
Instrumental	–	2	2
Clinical ± Instrumental	1	1	2
Subjective + Clinical ± Instrumental	7	22	29
Total	19	61	80

R: randomised studies; non R: non-randomised studies.

evaluation was only clinical; in 32, 8 randomised ([146, 147, 154, 155, 158, 160, 161, 240]) and 24 non-randomised ([145, 151–153, 162, 173, 174, 181, 238, 239, 242, 248–251, 256, 258, 261, 263]), studies the response evaluation was based upon subjective and clinical findings, but usually it was not possible to determine the weight given to the variables in the response evaluation. In 2 (1 randomised ([179]) and one non-randomised ([156])) studies the response evaluation was both clinical and instrumental and finally in 29 (7 randomised ([148, 150, 178, 180, 256, 259, 273]), and 22 non-randomised ([147, 151–153, 162, 173, 174, 181, 238, 239, 243, 246, 252, 253, 257, 260, 267, 268, 272, 274]) studies the evaluation of the response was based on subjective, clinical and instrumental findings.

Previous remarks, concerning the different instruments used for the quantitative assessment of response to treatment and the resulting impossibility of comparing results from different studies, are well founded regard in this too.

In Tab. 26 the elements of the evaluation of the response have been divided according to treatment, evaluation criteria and type of study. In

Table 26. – *Response evaluation criteria according to treatment and drug.*

	Subjective		Objective		Instrumental	
	R	non R	R	non R	R	non R
Danazol	8/8	12/15	8/8	13/15	2/8	4/15
Bromocryptine	5/5	27/27	4/5	22/27	2/5	12/27
Perc. progest.	2/2	13/15	1/2	11/15	1/2	7/15
Tamoxifen	2/2	2/2	1/2	1/2	1/2	0/2
Vitamins	1/2	2/2	2/2	2/2	2/2	2/2

R: randomised studies; non R: non-randomised studies.
Perc. progest.: percutaneous progesterone.

Table 27. – *Response percent range according to treatment.*

	Subjective		Objective		Instrumental	
	R	non R	R	non R	R	non R
Danazol	50-82 (?)	43-100 (?)	54-89 (?)	40-100 (?)	74	29-85
Bromocryptine	80-100 (?)	57-100	61-80	14-100 (?)	23-60 (?)	0-78 (?)
Perc. progest.	72-92	0-96 (?)	11	0-75 (?)	0	0-93 (?)
Tamoxifen	71	70-87	71	87	71	–
Vitamins	40	47-92	0-49	42-47	0	8-78
Placebo	10-50	10-33	0.53	NE	0-21	NE

(?): one study, at least, does not define the proportion of responders.
NE: not evaluated; Perc. progest.: percutaneous progesterone.

the following table (Tab. 27) the highest and the lowest percentage values of observed responses are reported, when available. The symbol " ? " indicates the presence in the studies referred to in that column, of certain studies, at least one, in which no numerical data is given, but in which the information is limited to vague statements regarding a general improvement in an undefined number of patients.

It is interesting to point out how placebo produces a subjective and objective response in more than 50% of cases in randomised studies, even when patients have hormonal disorders which could be attributable to the breast symptoms.

The duration of the response is another element which is seldom assessed ([180, 181]) (Tab. 28). 23 of 80 studies only report the duration of the response after therapy withdrawal. Not all of them report the proportion of patients in whom the response lasted for the period of time taken into consideration.

The longest duration of response was 12 months in the 2 studies on bromocryptine ([162, 251]), 12 months in 1 study on tamoxifen ([180]) and 8 months in 1 study on vitamins ([176]). One of the 3 studies on danazol ([238]) reports the results up to 24 months and 2 studies ([149, 156]) up to 24 months after therapy withdrawal, but the proportion of patients with this follow-up is less than 50% of the patients in the study.

The problem of drop-out is rarely taken into consideration. Only 20 out of 32 studies on bromocryptine ([160–166, 168–170, 172, 173, 244, 247, 248, 250, 253, 259, 260]), 14 of 23 studies on danazol ([145, 147, 148, 150, 152, 153, 155, 157, 159, 239, 242]), 3 out of 4 studies on vitamins ([177–179]) and 3 of 4 studies on tamoxifen ([181–183]) report

Table 28. – *Duration of the response according to treatment irrespective of the type of study.*

	No. st. Tot.	<3 M No. st.	3-6 M No. st.	>6 M No. st.	Not ev. No. st.
Danazol	23	3 ?-91%	5 19-100%	3 90-100%	12
Bromocryptine	32	4 ?-91%	2 ?-100%	2 ?-70%	24
Perc. progest.	17	1 ?	–	–	16
Tamoxifen	4	1 80%	–	1 95%	2
Vitamins	4	–	–	1 100%	3
Total	80	9	7	7	57

M: months; No. st.: number of studies; Not ev.: not evaluable.
( ): responder-patients percent; Perc. progest.: percutaneous progesterone.

Table 29. – *Compliance evaluation irrespective of the type of study.*

		% Drop-outs			
	No. st.	% Tot.	% Tox.	% Not eff.	% Not def.
Danazol	14/23	10.3	5.9	0.003	4.4
Bromocryptine	20/32	8.9	4.2	—	4.7
Perc. progest.	5/17	0.009	—	—	—
Tamoxifen	3/4	0	7.8	—	—
Vitamins	3/4	9.6	1.4	—	8.2

% Tox.: % Toxicity; Not eff.: not effective; Not def.: Not defined.
Perc. progest.: percutaneous progesterone.

data regarding the number of drop-outs accordings to varying reasons. A proportion of 10% of drop-outs for danazol and a little lower for vitamins and bromocryptine can, however, be derived from the fragmentary data provided.

All drop-outs in tamoxifen studies, half of the drop-outs in danazol and bromocryptine studies and 1.4% only of drop-outs in vitamin studies are due to toxicity. Percutaneous Progesterone drop-outs were very few, but this finding cannot be considered to be very reliable, due to the restricted number of studies analysing this variable.

In a high proportion of drop-outs, (about 50% for danazol and bromocryptine, 80% for vitamins) published data do not report the reasons.

Table 30. – *Drug administered to reference group; randomised studies.*

Drug	No. st.	No. pts.	Response Subject.	Object.	Instrum.
Hiruroid	1	77	45%	20%	NE
Phytormone	1	83	65%	19%	NE
Bromocryptine	2	161	47-60%	NE-70%	NE
Primrose oil	1	92	45%	NE	NE
Oral progest.	3	161	9-63%	NE-70%	NE-0%
Placebo	8	197	10-50%	0.53%	0-21%

No. st.: number of studies; No. pts.: number of patients; Subject.: subjective; Object: objective; Instrum.: instrumental; NE: not evaluated.

Table 31. – *Drugs administered to reference group; non randomised studies.*

Drug	No. st.	No. pts.	Response Subject.	Object.	Instrum.
Perc. progest.	1	350	53%	NE	NE
Oral progest.	1	270	76%	NE	NE
Auriculopuncture	1	130	84%	NE	NE
Tamoxifen	2	90	81-88%	NE-64%	NE
Danazol	1	20	70%	NE	NE
Methergolin	2	21	0-10%	0%	NE
Vitamins	2	42	3-14%	0%	NE
Bromocryptine	2	76	NE-81%	NE	NE-92%
Placebo	2	72	10-83%	NE	NE

No. st.: number of studies; No. pts.: number of patients; NE: not evaluated; Subject.: subjective; Object.: objective; Instrum.: instraumental.
Perc. progest.: percutaneous progesterone.

The allocation of drop-outs is an important aspect of the statistical evaluation of results, especially as Authors tend to eliminate them from their calculations, thus introducing a bias in favour of the therapy.

Referring to response to the treatment of fibrocystic disease, the percentage of patients who responded in the randomised studies was compared to the percentage in the non-randomised studies with regard to the drugs used as control in the studies with a control group (Tab. 30 & 31).

A highly heterogeneous ensemble of control drugs was used in both study groups: from auriculo-therapy to primrose oil, while placebo was used only in 2 non-randomised and in 8 ([147, 150, 157, 178, 179, 256, 268, 272, 273]) randomised studies, (44%). For these drugs, usually the subjective response but rarely the clinical response was assessed. Response to treatment according

to instrumental parameters was assessed in 3 studies only ([150, 256, 259]), as far as placebo is concerned, in 1 study where oral progesterone was used as the control drug ([259]) and in 1 study where the control drug was bromocryptine ([270]).

The proportion of responders to different drugs was remarkably different, and even in this regard the lack of definition of clear response evaluation criteria does not allow conclusions to be drawn.

Preliminary data on the first 266 patients included in a randomised, double blind, placebo controlled, multicentric study on bromocryptine in cyclic mastalgia carried out in 13 European countries have been published ([276]). Patients were treated with bromocryptine 2.5 mg/day or placebo for 3 months; After 3 months responders would continue treatment for a further 3 months; non-responders would be followed up for 6 months, in order to evaluate the possible reappearance of symptoms after the withdrawal of therapy. Follow-up data are not yet available.

A CRITICAL COMMENT ON THE AUTHORS' CONCLUSIONS

From the great number of figures reported so far, above all, the poor reliability of published studies has been revealed. The reasons are many, and in order to give an objective picture the studies were intentionally examined in detail, and according to well defined and expressed criteria, instead of merely reporting the Author's conclusions about different treatments.

Published studies on the medical therapy of BBD do not include the premises actually necessary to answer the questions regarding the best treatment to be used, and whether the cost/benefit ratio of the treatment is favourable for the patient. The intrinsic limits of the examined studies are many, in particular the following emerge:

– high number of non controlled clinical trials, with non-reproduceable, hence unreliable results;

– invalid randomization schemes in randomised studies;

– limited number of patients per study;

– diagnosis based upon clinical examination seldom confirmed via instrumental diagnosis;

– lack of histological confirmation of disease and remission;

– response-evaluation assigned to the subjective judgement of clinician or patient;

– response evaluation quantified as the "majority", "a certain number", "a good proportion", of patients;

– duration of the treatment: extremely variable even within the same study;

– evaluating of side effect given in descriptive terms such as " good tolerance ";

– lack of information regarding the number of drop-outs, which was often excluded from the evaluation of the response.

Following these premises, it seemed of value to comment upon the Author's comments regarding the effectiveness of evaluated treatments, reported at the end of each study.

All the studies, both randomised and not randomised, concerning percutaneous progesterone, judge it to be a " good therapy " for mastalgia, both simple and associated with fibrocystic disease. However, in the two randomised studies, the possible effect of the drug was not evaluated. In fact, favourable responses of breast symptoms to placebo were recorded as being 24% and 49% ([268, 273]) respectively.

The conclusions drawn by the French Authors ([174, 175]) on progesterone are much more satisfactory. Mastalgia being defined as the first sign of relative hyperestrogenism which could be responsible for pathological changes of the breast through various stages resulting possibly in BBD and eventually in cancer. Hence, the use of percutaneous progesterone in the case of mastalgia and its association with systemic progesterone for long periods, months or years, in the presence of fibrocystic disease may prevent breast cancer.

In reality none of the studies report data about the risk of breast cancer in treated patients compared to any type of controls; thus, the reduction of the risk, if any, cannot be calculated; a calculation which must be performed if this conclusion is to be considered scientific evidence rather than a generic assumption based on no reliable proof.

There is no agreement about the effectiveness of bromocryptine in the therapy of BBD in literature, and the Authors of randomised studies come to quite different conclusions compared to the Authors of non-randomised ones.

In 2 randomised, double blind, cross over, placebo controlled studies, Durning and Mansel ([161, 165]) conclude that the use of bromocryptine should be restricted to the few cases of simple or BBD associated cyclic mastalgia, ([165]), the severity of which affects the daily activities of the patient. Durning points out that well known side effects of the drug result in an unfavourable cost/beneft ratio in women with milder symptoms.

Furthermore, the placebo effect of any treatment makes the assessment of results difficult.

In two other randomised studies ([256, 259]), where the randomization criteria are not defined, bromocryptine is favourably evaluated, due to the high proportion of subjective, clinical, as well as instrumental responses.

However, even in this case, the positive assessment of the drug is not reported in association with a definition of the evaluation of the response. The Authors themselves underline that the restricted number of cases and the significant proportion of responses with placebo ([256]), render further investigations essential before the real therapeutic effect of bromocryptine, its mechanism of action and long term efficacy, which at present are unclear, can be determined.

On the basis of the preliminary findings of the European multicentric study, Mansel *et al.* conclude that bromocryptine can reduce breast pain, though the placebo effect of any treatment cannot be neglected. Bromocryptine appears to be a more effective symptomatic drug than placebo. The findings of the study suggest that the classification of patients according to breast symptoms could be simpler than those done according to pathology. Actually, symptoms were similar in all European centres, despite differences in BBD classification by different clinicians.

Non-randomised studies reach even more favourable conclusions, claiming that bromocryptine is an excellent "symptomatic therapy" in BBD patients, but no Author evaluates bromocryptine's benefits against its possible side effects.

Moreover, some Authors ([243, 254, 260]) attribute to this drug a possible antineoplastic effect. In this case too, as previously reported for percutaneous progesterone, the conclusion in drawn without any scentific demonstration.

In these studies, the influence of hormonal treatments on all the activities of the hypothalamus-pituitary-gonadal-breast axis are often not taken into consideration; thus, even if the use of the drug is justified for correcting hormonal imbalances resulting in BBD, its administration must be arbitrary in BBD patients without detectable hormonal disorders, at least until the relationship has been completely elucidated between prolactin and BBD and possible biochemical-enzymatic changes induced by antiprolactin drugs in breast glands.

As far as danazol is concerned, all the Authors of the 8 randomised studies point out that the majority (85%) of the patients with mastalgia associated with a clinical picture of BBD accept and tolerate such symptoms when they are reassured about the benign nature of their condition. In this light danazol becomes a drug to be used only in the case of such severe mastalgia that it affects the daily life of the suffering patient.

In contrast to certain Authors ([146, 147, 150, 154]) who regard the drug's side effect as mild compared to the benefits, others ([158, 240]) point out that the side effects restrict its use, and that the drugs which are best tolerated by patients must become the first choice for therapy, considering that the remission of a symptom is the objective, and that this effect is often restricted to the administration period, or lasts for a few months after withdrawal from the therapy.

In order to evaluate even indirectly the cost/benefit ratio, it would valuable to know how many responders accepted or spontaneously asked to repeat the treatment at the end of the treatment period. However these data are not reported in this nor in the remaining groups of studies, concerning both danazol and other drugs.

The group of non randomised studies do not even take into account the cost/benefit ratio and only a few Authors ([152, 153, 159, 242]) mention the side effects of the therapy. Side effects are regarded as " mild ", but how can the term " mild " be evaluated when the cost of the treatment is not compared to its benefits? The Authors of this group of studies agree that danazol is a drug capable of reducing mastalgia and nodularity in fibrocystic disease. Some of them ([144, 238, 241]) consider that the response to the drug therapy can reassure patients and physicians about the benign nature of the disease; on the other hand, it is thought advisable to perform biopsies on mammary lumps which do not change with therapy, as this in itself may represent an element for suspecting the presence of a carcinoma.

However, there is no data regarding how many cancers it has been possible to diagnose ex-adjuvantibus with these therapies. Although Humphrey ([152]) points out that providing reassurance that the disease is benign is the best therapy for patients with symptomatic and clinical evidence of fibrocystic disease, he concludes that the antigonodatropinic action of danazol should anyway prevent the development and progression of a breast cancer in women given such therapy.

Greenblatt ([149]) also attributes an "antineoplastic" activity to danazol and considers that the reduction or disappearance of nodularity following therapy can reduce the risk of neoplasms. As in the case of bromocryptine and percutaneous progesterone, this assumption is neither confirmed nor refuted by any study comparing danazol with control groups.

In only one randomised study is the use of tamoxifen in BBD advised. Actually, according to Shoobon ([181]), pain disappears in almost all cases; side effects (hot flushes, vaginal bleeding) are regarded as slight compared to the benefits. The Authors of the remaining 3 studies ([180, 182, 183]) do not agree; side effects are regarded as more important, and in the randomised

study by Fentiman ([182]) drop-outs due to drug toxicity reach about 8%. Moreover, the lack of knowledge of the mechanism of action of Tamoxifen leaves open many questions regarding its use in BBD. It is not known if the reduction of pain, seen in all the studies should be ascribed to a peripheral action of the drug on breast tissue, or to a central action on the hypothalamus-pituitary-ovary axis mediated by prolactin or other hormones. The characteristics of responsive patients cannot be predicted and the long-term effects of Tamoxifen are not known ([180]). Fentiman points out that Tamoxifen increases sex hormone binding protein levels in postmenopausal women, and this in turn causes a reduction in the level of free estradiol. It is not known whether this effect occurs also in premenopausal women, and whether the possible estradiol reduction results in a decreased risk of breast carcinoma, or in an increased loss of bone mineral content with an increased risk of pathological freactures due to osteoporosis ([183]).

CONCLUSIONS

The analysis of the literature of the past ten years concerning the different aspects of medical treatment of fibrocystic disease has not permitted conclusions to be drawn.

While awaiting further experimental studies allowing a greater understanding of the etiopathogenesis of the disease, as well as defining which clinical signs of the " disease " should be treated and when, it is possible to make some proposals of a practical nature, based on the available data.

Fibrocystic disease is very frequent in the female population, occurring in many forms and degrees from physological to pathological. In the light of this it does not seem valid to term a disorder, which also affects 50% of pre-menopausal women, as a " disease ". A systemic hormonal treatment is clearly advisable in cases where mastalgia, tenderness and nodularity are an epiphenomenon of hormonal imbalance, the treatment being aimed at restoring the normal function of the hypothalamus-pituitary-gonadal-breast axis.

Where only subjective and objective breast symptoms are present, it is our opinion that reassurance of the patient by the physician should be the first line therapy.

This is very often sufficient to remove the anxiety linked to mammary disease and render the typical BBD symptoms acceptable to the patient.

In cases where symptomatology is so severe as to interfere with normal activities, medical treatment does appear to be justified. One should not

forget that any reduction in the degree of the symptoms is the main aim of therapy in these cases, therefore the evaluation of cost/benefit ratio should guide choice of treatment.

The high number of drop-outs seen with the majority of drugs should induce reflection, especially when it is considered that they occur in clinical studies, that is to say in patients who, theoretically at least, were prepared to enter a trial and were in some way motivated to carry on the treatment by the investigators themselves.

On the basis of the findings of recent studies, it is no longer possible to support the concept of the preneoplastic role of BBD and the possibility of preventing cancer by its treatment. On the other hand, drug therapy has never been shown to modify the histological picture of the breast. BBD can only be associated with an increased relative risk of developing a cancer in the presence of specific histological patterns, encountered in not more than 4% of all breast biopsies. The finding of these lesions, notably atypical hyperplasia, is completely accidental, as they are not associated with clinically detectable breast nodules or thickening.

Faced with the above situations, it is impossible to propose solutions free of criticism: no drugs able to modify significantly the risk of carcinoma are known; retinoids, which were expected to be very useful in the past, cannot be readily used, due to their high toxicity. No drug commonly used in BBD has been shown to affect this risk; aggressive surgery, such as bilateral subcutaneous mastectomy with subsequent prothesis, seems excessive when preservative techniques are employed for small invasive cancers.

Clinical and instrumental surveillance may prove insufficient in preventing a delayed diagnosis of invasive cancer, but at present it seems the only practical solution, in view of the fact that BBD cannot be regarded as a precancerous lesion or a cancer-associated disorder, and perhaps not even a disease.

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