BREAST DISEASE AND THE INTERNIST

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Breast disease is ubiquitous in women. All women will detect a lump in the breast at some point during their life. Most of these masses represent cyst formation and other benign proliferative changes. However, 1 out of 11 will eventually develop breast cancer (1). With this high incidence of malignancy it is obviously critical to be able to distinguish benign from neoplastic changes within the breast. Since advanced breast cancer is not curable, it would be ideal to be able to discriminate those individuals who are increased risk. The purpose of this discussion is to define what breast disease is, what is the risk that a women will develop breast cancer, and to develop a rationale approach to diagnosis, screening, and treatment of benign breast diseases.

I. Pathology of Benign Breast Disease

Classic approaches to benign disease have been to define each biopsy specimen as a morphologic entity (Table 1; Figures 1-10). The relative incidence in biopsy specimens indicates that almost all breast biopsies will have some of the elements of fibrocystic changes, particularly cyst formation (2). Most biopsies will have mixtures of these morphologic entities with typically only fibroadenomas being a pure pathologic entity. For the last 20 years pathologists have been trying to quantitate the proliferative changes in an effort to determine if these changes correlate these changes with the eventual development of breast cancer defining the risk of an individual woman developing breast cancer (2,3).

Table 1: Incidence of Benign Pathologic Entities in Biopsy Specimens

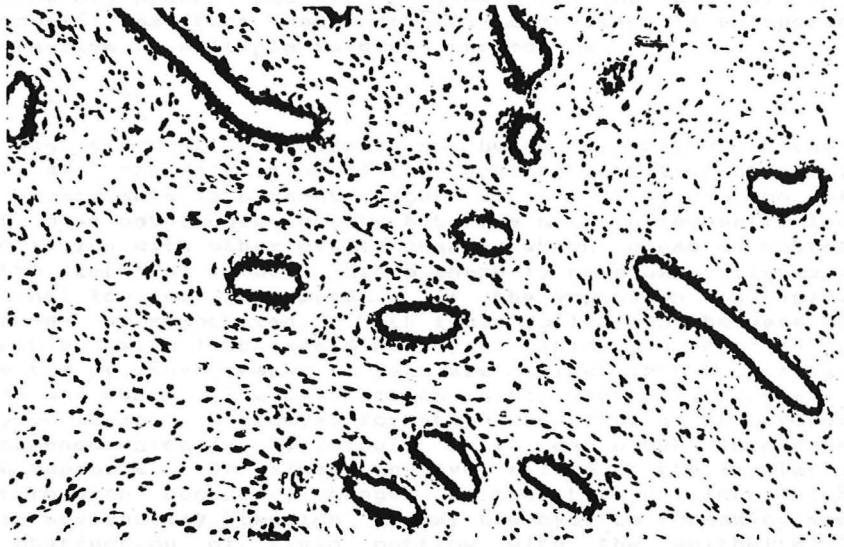
Histopathology	% Incidence
Fibroadenoma	11.5
Microcyst	32.1
Macrocyst	22.9
Papilloma	3.1
Apocrine metaplasia	27.8
Sclerosing adenosis	5.3
Duct ectasia	4.4
Lobular neoplasia	1.4

A. Fibroadenoma

Of the breast mastopathies fibroadenomas are most often seen as a distinct entity (Figure 1). There is typically a uniform proliferation of a fibroblastic connective tissue element; this may be hyalinized as well. When the latter occurs and in association with involution, calification may be detected. The epithelial component is variable in cellularity and mucinous character. Rarely, adipose tissue is found within the mass, but it can be

detected in association with a lobular element which is "trapped". Occasionally, other proliferative epithelial cystic changes are detected within fibroadenomas. This probably represents an encroachment or an encompassing of pre-existing cystic disease by the fibroadenoma. A less likely alternative, since the associations are haphazard and rare is that the glandular tissue proliferation accelerated by growth factors produced by the fibroadenoma.

Figure 1: Fibroadenoma



The entity occurs most frequently in young woman and is rarely seen in post menopausal women unless they are taking supplemental estrogens. With pregnancy fibroadenomas may grow in response to the hormonal stimulation while with menopause involution usually occurs. The incidence of the juvenile disease and possibly the adult form is greater in blacks (4,5). Fibroadenomas have been classified into juvenile and adult types. The adult type is usually a solitary lesion with a slow growth whereas the juvenile form is detected during puberty--frequently multiple and/or bilateral masses with a rapid growth potential. In reviewing adolescents with fibroadenomas Ashikari et al. found less than 10% were juvenile (4). The juvenile fibroadenoma and giant fibroadenoma are often confused with the malignant variant of cystosarcoma phyllodes resulting in inappropriate mastectomies when only careful surgical excision of the mass is required. Cysto-

sarcoma phylloides rarely occurs in adolescents and morphologically it requires the presence of mitotic figures and pleomorphic variation of the connective tissue component. These entities can not be distinguished on the basis of tumor size.

Fibroadenomas are usually palpable. They have a distinct morphologic appearance on mammogram of a well circumscribed a dense lesion with minimal distortion of the surrounding duct structures. Unless there is proliferative disease with atypia in association with the fibroadenoma, these lesions have no malignant potential. The treatment is usually surgical which usually requires removal of minimal normal breast tissue. When multiple lesions are present and with no growth of the lesions, once the diagnosis has been made careful observation is an appropriate alternative to multiple surgical procedures.

B. Cysts

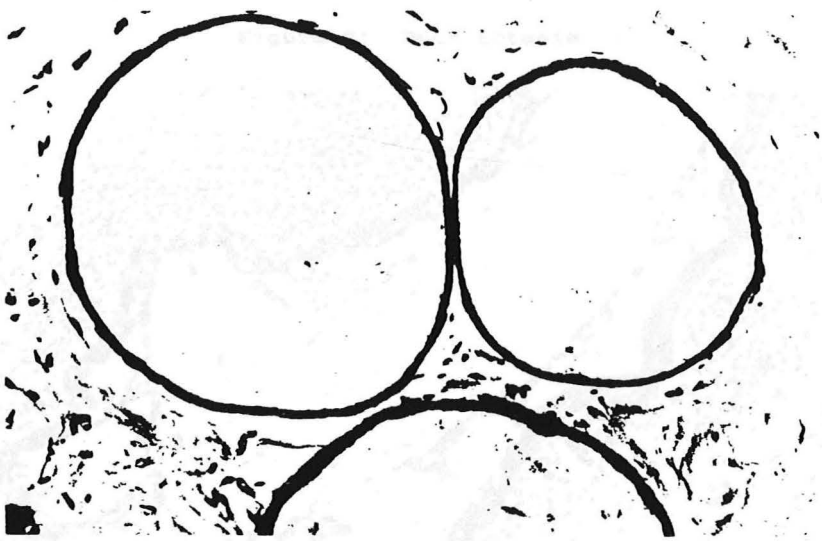
Although frequently considered to be an expansion of the duct, cysts are the dilitation of the terminal lobule when no epithelial hyperplasia is present (Figure 2) (6). They can be observed as a pure pathologic entity but are not infrequently found in association with other cystic changes which cause an obstruction of the terminal lobule. Since there is no elastic tissue in the terminal lobule, it expands. If the expansion is rapid, then pain may be associated. With fluid collection the mass becomes palpable. With long standing cyst fluid can calcify and be detected by mammography. Cysts are divided into two categories: micro and macro. The distinction is somewhat arbitrary and based only on size. Microcyst formation can occur as an involutional phenomenon which is physiologic or it can occur in conjunction with adenosis. It always involves a loss of the lobular architecture with secondary changes in the terminal lobules. Macrocysts are usually "tension" cysts; the cyst is formed by mechanical obstruction of fluid outflow with the epithelial lining unable to absorb fluid at the accumulated rate. The cause and the location of the obstruction includes all benign and malignant conditions. With fluid accumulation there is often loss of the the apocrine cell lining. Eventually, with resorption of the fluid there can be calcification. Obviously, an appropriately placed obstruction can cause microcystic dilatation as well.

Haagensen has stated that macrocysts are associated with an increased risk for the woman to develop breast cancer (7). Dupont and Page as well as others have found no attendent risk (2). Since the cyst does not occur spontaneously, i.e. some morphologic event has caused the dilatation--the other associated fibrocystic change are what effect the risk of developing a breast malignancy.

The primary treatment of cysts is needle aspiration. If the cystic mass does not completely resolve or the fluid rapidly

reaccumulates, surgical excision is required to prevent further fluid accumulation and to determine the cause of the fluid accumulation.

Figure 2: Cysts



C. Duct ectasia

Duct ectasia is characterized by dilatation and stasis of the ductal contents with an inflammatory reaction (Figure 3). It is not obvious whether the inflammatory component causes obstruction or an obstruction is associated with secondary infection and/or inflammation. The pathologic events leading to its development may be closely related with those causing traumatic fat necrosis. Its etiology may be associated with lactation and suckling but this has not been established (8). The entity can be construed as a variant of cyst disease with the obstruction occurring more proximal. Its occurrence rate may be as high as 30-40% (7). It can be distinguished from cyst disease by its proximal, subaerolar location, the association of nipple discharge, and the presence of ductal calcification.

Similar to pure cystic disease, duct ectasia has no association with an increased cancer risk. The major problem to the patient is the difficulty in discriminating the lesion from malignancy. the inflammatory response is often associated with a palpable lesion. When calcifications are present, these are not the ovoid

or round calcifications of cystic disease but the linear calcification of ducts similar to that observed in Paget's disease. Since the ectasia spreads retrograde from the site of the obstruction, the surgical procedure required may be significant requiring removal of a portion of the aerolar as well as the involved segment.

Figure 3: Duct Ectasia

D. Papilloma and Multiple Papillomas

A papilloma is a villous lesion with a fibrovascular core covered by an epithelial layer (Figure 4). Solitary papillomas are the most common cause of nipple discharge and bleeding. The lesion has a preference for larger ducts. These can be both microscopic as well as macroscopic with only about 50% being palpable. The distinction between benign and malignant lesions can be difficult requiring an assessment of the surrounding milleiu as well as more classic criteria for malignancy. Solitary papillomas are not associated with an increased risk of breast cancer (Table 2) (6). Multiple papillomas appear to have a significant risk associated with breast cancer and represent a true proliferative change associated with end organ response (7). As shown in the Table 2, the location and the symptoms of the associated lesions are very different. In addition there is also a high incidence of recurrence following local excision. Papillomatosis is a term

that has been used to describe the tongue like proliferation of epithelia within ductal structures. It can occur in association with a papilloma or independently, but it does not have the fibrovascular core of true papillomas. According to Azzopardi the term is an inappropriate misnomer representing an epithelial proliferation, epitheliosis (6).

Figure 4: Papilloma

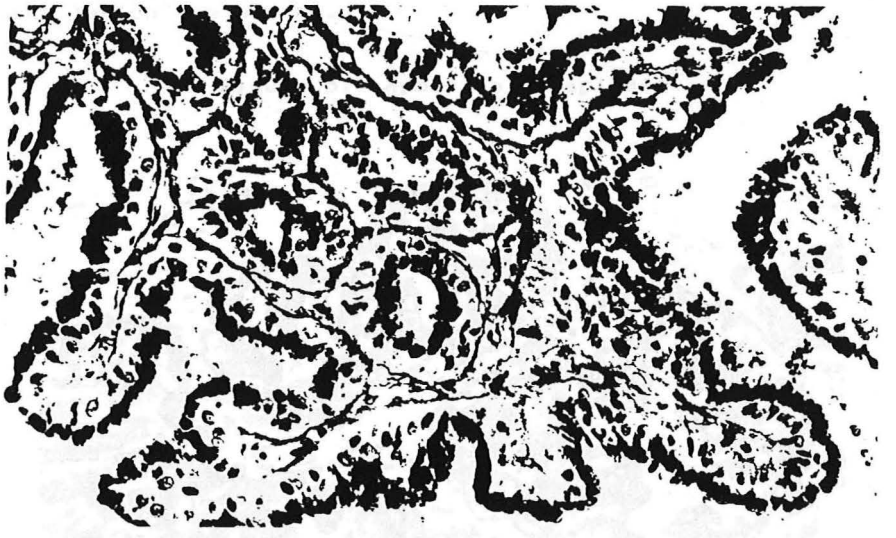


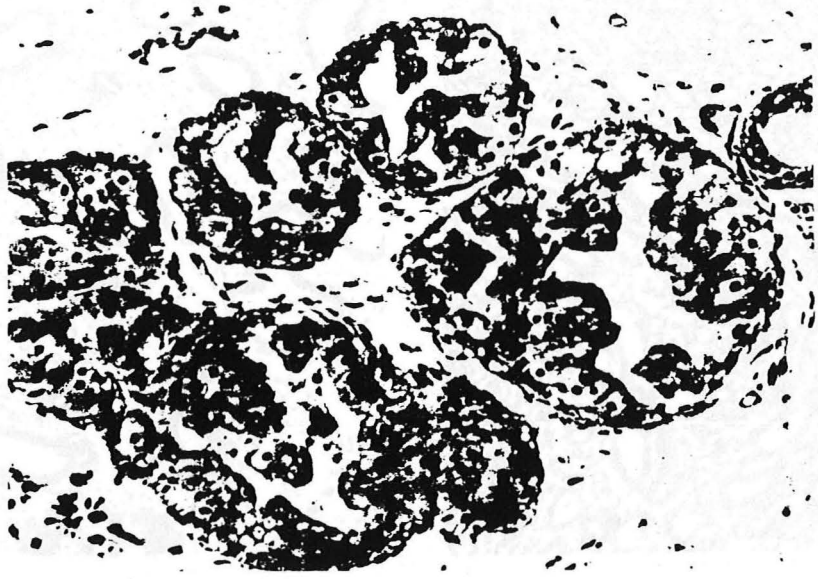
Table 2: Natural History of Papillomas and Multiple Papillomas

		Solitary Papilloma	Multiple Papilloma
1.	Clinical History		
	Age	48	40
	Nipple Discharge	Frequent	Infrequent
	Location	Subaerolar	More distal
	Bilaterality	Rare	25%
	Cancer Risk	None	4X
2.	Treatment	Local excision	Quadrantectomy or Simple mastectomy

E. Apocrine metaplasia

Apocrine metaplasia is a metaplastic change in the normal breast epithelial cell. It can be detected in both ductal and lobular epithelia (Figure 5). The pathologic finding is not often observed in association with sclerosing adenosis, duct ectasia or cystic disease. As it represents a proliferative change of epithelium, it has been shown to be associated with a minimum increased risk in the patients developing breast cancer. However, when it is present among more proliferative atypical changes, this is taken as evidence that the proliferative aspects of the lesion are benign.

Figure 5: Apocrine Metaplasia



F. Adenosis

There are two predominate forms of adenosis, with and without stromal proliferation. Blunt duct adenosis is defined by a highly organized hypertrophic process by which lobules give rise to two layered structures with blunt outlines (Figure 6). It typically effects all epithelial elements within the lobule. With the hypertrophy there is an apparent loss of secretory

activity. This entity is not confused with malignant changes in the epithelia and has no associated risk.

Figure 6: Blunt Duct Adenosis

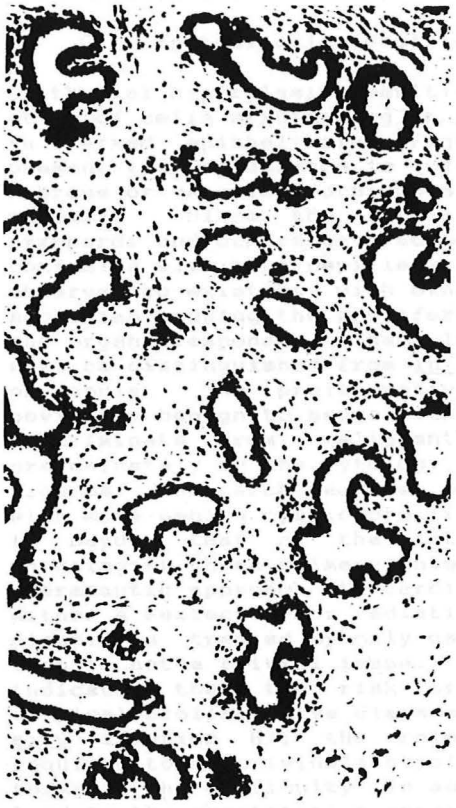
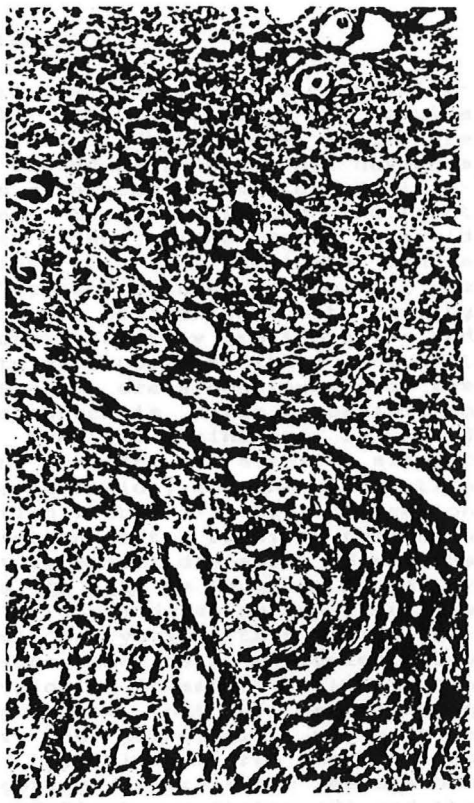


Figure 7: Sclerosing Adenosis



Sclerosing adenosis is adenosis associated with a stromal proliferation (Figure 7). It classically occurs in lobules but not infrequently evidence of ductal involvement is observed. Because of the reactive component the lesions can be palpable. The diagnosis may be difficult to discriminate from carcinoma; it often requires permanent sections for diagnosis. The diagnosis

of sclerosing adenosis is based on the more regular pattern of the cellular elements with in the fibrosis, the presence of two cell types requiring the identification of a myoid cell as well, and the absence on anaplastic changes with in the epithelial cells. The risk of the pure entity being associated with a malignancy is low, but probably greater than that of the normal population (8). When cellular atypia is observed, the risk is that attendent to the atypia.

G. Epitheliosis (Papillomatosis)

Epithelial hyperplasia resulting in semi-solid or solid proliferation of cells originating in small duct, ductules, and lobules is termed epitheliosis (Figure 8). When lumenal spaces are present the appearance is often pseudo-papillary, not having a fibrous or vascular core; this has give rise to the term papillomatosis. Since the latter term is anatomically incorrect Azzopardi and others have advocated using "epitheliosis" to avoid confusion with true papillary lesions (6). Epitheliosis can be observed co-existent with other "cystic" changes; suggesting the mechanism causing the proliferation may be identical with varying end organ response. These lesions are truly proliferative and must be distinguished from in situ carcinoma of either the duct or lobule. The proliferative changes are a continuum from the obviously benign to merge with that which is often impossible to discriminate from malignant. The discrimination is based predominately on the cytology, the presence of atypical mitotic figures, the architecture of fenestration, and the association with more benign cystic proliferation (Table 3). Its application is beyond that of the internist and often requires that of a pathologist whose primary interest is breast disease. Since the therapeutic approach to carcinoma in situ is usually treated by either a mastectomy or radiation therapy and benign proliferative disease is treated by only careful observation, this discrimination is not a trivial issue. Since the data presented below indicates that the risk of developing invasive carcinoma with atypical proliferative disease approaches that of carcinoma in situ (Section H), the role of the pathologist may only be required to discriminate atypical hyperplasia from more benign forms. The difficulty in segregating hyperplastic lesions has lead to the quantitative approach of Black and Chabon (3) and the discriptive approach of Page and his co-workers (2,9,10).

Figure 8: Epitheliosis

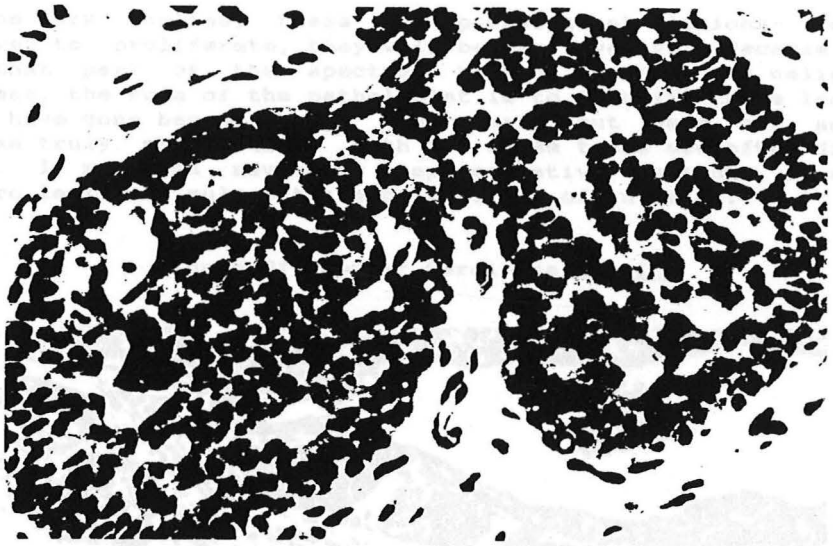


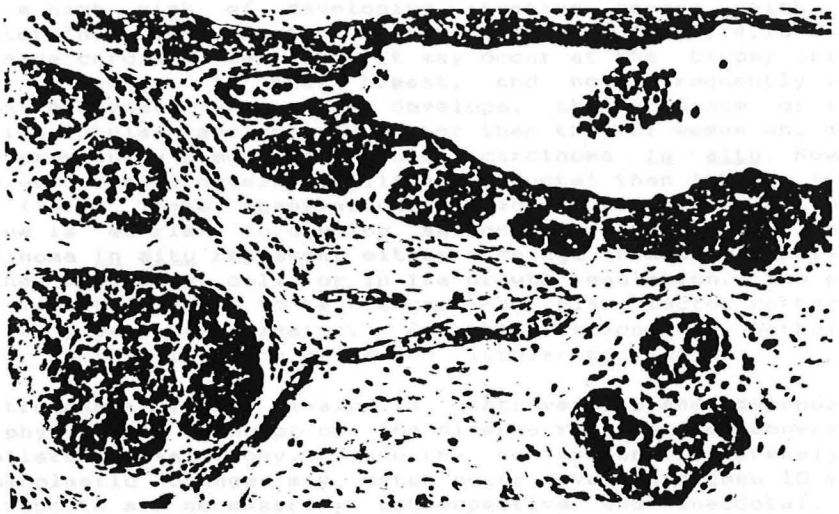
Table 3: Discrimination of Epitheliosis from Carcinoma <u>in</u> <u>situ</u>

	<u>Epitheliosis</u>	<u>Carcinoma in situ</u>
Cytology		
Cytoplasm	Bland, homogeneous	Variable
Nuclei	Ovoid, variable staining, with inconspicuous nucleoli	Rounded, hyperchromatic, monotonous
Fenestrations (when present)	Irregular	Regular
Atypical mitosis	None	May be present
Calcification	Infrequent	Common
Necrosis	Rare	Common
Hemorrhage	Rare	Occasional
Association with other cystic changes	Papillomas and apocrine metaplasia	Uncommon
Differentiation	Usually present	Absent

H. Carcinoma *in situ*

As the term implies, these are premalignant lesions--i.e. if allowed to proliferate, they will become invasive. Because they are that part of the spectrum between benign and malignant disease, the role of the pathologist is to identify those lesions that have gone beyond benign hyperplasia but have not as yet become truly neoplastic. Both of these tasks are often difficult. It requires reviewing representative sections from the entire lesion to rule out the possiblilty of invasion.

Figure 9: Lobular Carcinoma *in situ*



1. Lobular carcinoma *in situ* (lobular neoplasia)

When proliferative epithelial lesions cause distension of the terminal ductule with loss of the lumen, the diagnosis of lobular carcinoma *in situ* or neoplasia must be entertained (Figure 9). The cells are usually bland without hyperchromatic changes and usually uniform in size and shape, but occasionally more cellular atypia is observed. Although the lumen of the lobule is filled, in contradistinction to epitheliosis the cells do not appear tightly packed. The cells expand the lobule without evidence of extralobule invasion. Subsequently, cells appear to spread retrograde into the duct distorting but not destroying the normal architecture (This has been termed "Pagetoid spread") (11). This

again does not occur in other epithelial hyperplastic lesions. The distinction of these lesions from infiltrating carcinoma is based on the absense of evidence of invasion of the surrounding stroma. With invasion of the stroma the lobular or ductal appearance is often lost with only the loosely adherent cell remaining. Since there are no fibrotic reactions associated with the changes in the lobule and calcification does not occur, lobular neoplasia is usually not detected either by physical examination or mammography. It is often incidently detected in association with other cystic changes.

Not all lesions classified as lobular carcinoma in situ breast carcinoma will progress to malignancy. Lobular carcinoma in situ is probably not a premalignant lesion since it is only associated with a high risk of developing invasive cancer which is no greater than that of atypical hypreplasia (2,12,13,14,15). When invasive carcinoma develops, it may occur at the biopsy original site, elsewhere in that breast, and not infrequently in the opposite breast. When cancer develops, the incidence of infiltrating lobular carcinoma is higher than that of women who do not have previously diagnosed lobular carcinoma in situ. However, more woman still develop infiltrating ductal than lobular (65% vs 35%) (14). These observations indicate that the all breast tissue is at risk to develop malignant changes. Thus, lobular carcinoma in situ represent either a change in the responsiveness of the epithelial cell or in its growth regulation. The pathologic entity appears to be a significant risk factor rather than a true premalignant lesion. For these reasons many pathologist prefer that this lesion be termed "lobular neoplasia".

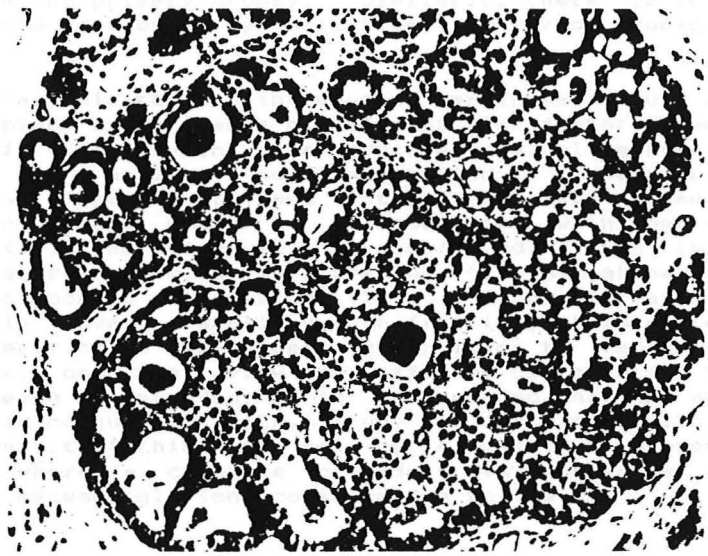
The treatment of this lesion is controversial and dependent on the physician's concept of the disease ranging from observation to bilateral mastectomy. Since the conversion from premalignant to neoplastic changes may often occur over more than 10 years, all reports are necessarily retrospective and anecdotal. The incidence of malignancy is approximately 25-30% which is not different from those with proliferative breast disease with atypia (2,14). As will be discussed in Section IV, the risk of developing malignancy appears to increase significantly when other risk factors are present such as family history. Our approach has been to view lobular neoplasia as a significant risk factor, reviewing each case individually in our Breast Evaluation Clinic and attempting to assess the woman's actual risk of developing breast cancer.

2. Intraductal carcinoma

Intraductal carcinoma have frankly malignant morphologic changes in the nuclei and cytoplasm (Table 3) (Figure 10). There is an association with necrosis and calcification. Pagetoid spread of the cells within the duct and into the terminal ductule. These findings help the pathologist discriminate carcinoma from

hyperplasia with atypia. Pagetoid spread can make for difficulty in discriminating this entity from lobular neoplasia.

Figure 10: Intraductal Carcinoma



The lesions occasionally present with a palpable mass, but more frequently are detected by mammography. The incidence of intraductal cancer in screening studies is far in access of that observed in unscreened patients (16,17); it presumably relates to the high incidence of microcalcifications within these lesions. Because the spread is often retrograde and involving the nipple, Paget's disease, there is an association with nipple discharge and bleeding.

Intraductal carcinomas are neoplastic--probably, all will become invasive at the site of detection if inadequately treated. The risk is the at the site of detection but it is also associated with bilaterality and multifocal disease (18,19). Therefore, it is a risk factor for developing disease elsewhere in addition to being a true malignancy. In fact the risk may be higher for developing invasive cancer elsewhere than when an infiltrating ductal cancer without intraductal elements has developed. The risk of invasive cancer being present in the setting of apparently only intraductal tumor is high. It requires that the biopsy specimen be thoroughly sampled, but the number of cuts is a practical consideration determined by the size of the lesion and the biopsy specimen (20). However, there is a risk of nodal

metastasis in specimens with no evidence of invasion which varies in the literature from 1 to 7% (21,22). This indicates that invasion cannot always be detected microscopically, but the wide discrepancy in the incidence of regional involvement probably reflects the enthusiasm of the pathologist for studying multiple cuts from the primary biopsy. Similarly, there is an incidence of patients developing systemic breast cancer of probably 3 to 5% (19).

These data indicate that intraductal carcinoma should be treated as a neoplasm as well as a significant risk factor. The standard therapy for this lesion is a modified radical mastectomy which includes an axillary node dissection. Lesser procedures, excisional biopsy, with and without axillary dissection, and radiation therapy appear to be associated with good short term results (23). Harris et al. have observed a high incidence of local recurrence with infiltrating tumors that have an intraductal component associated (24). Since intraductal tumors presumable have a small growth fraction, it is quite possible that these cells are less susceptible to radiation injury. Therefore, one must view the efficacy of radiation therapy in this disease as unproven; it is recommended that it should only be used in conjunction with a study and certainly, with the woman being aware that this may not be a curative procedure in a disease where a curative procedure is available and which requires exceedingly long conscientous follow-up.

II. Pathogenesis

Benign breast disease can best be described as a continuum of changes. It represents in its least proliferative component the response of breast epitlhelia to normal hormone secretions. With pregnancy and the approach of memonpause there is great abberation in the level of circulating estrogens and/or progestins. It is presumed that the epithelial changes are observed as a result of these hormonal changes imply that the fibrocystic changes are under physiologic control. Similar proliferative effects are observed in the postmenopausal woman taking estrogen supplementation for relief of menopausal symptoms and the prevention of osteoporosis. Thus, some benign mastopathies may be viewed as an endocrinopathies due to persistent estrogen stimulation with varying secretion of progestins (25,26). More recent data indicates that breast tissue is responsive to many growth factors as well as steroid hormones. Thus, other substances may be affecting proliferation by endocrine and/or autocrine means (27). The mechanism by which these are integrated into the pathogenesis of fibrocystic changes is unknown.

An alternative explanation of the pathogenesis, is that changes occur as result of a change in the breast epithelia responsiveness to a normal level of hormone--i.e. a change in end organ

response. The latter is clearly an attractive hypothesis which might be useful in explaining the more focal lesions. This event would be presumably associated with change in the response to hormones at the receptor level or as a receptor-gene interaction. If this were the mechanism of the more diffuse fibrocystic changes, one would have to postulate either a somatic or inherited genetic defect is effecting the entire breast.

III. Incidence

As mentioned above benign disease is ubiquitous, it is fair to say that every woman will have a palpable mass in her breast at some point during her life. This observation has lead the American Cancer Society to rename fiborcystic disease to fibrocystic changes (28,29). The actual incidence of the individual pathologic entities is not known as there has been no study combining biopsy results with autopsy findings. However, autopsy series suggest that at least 58% of all women have fibrocystic changes (30) and that probably this incidence does not decrease with age (31). The most recent data on relative incidence comes from Page and his co-workers, but this is based on that observed in breast biopsy specimens and not the incidence in the general population (Table 4) (2,9,10). Except for gross cysts and fibroadenomas these lesions rarely cause mass disease. Therefore, there is a bias in the incidence of biopsy related histology in that the lesion must be palpable or associated with abnormalities which necessitated the biopsy. This data is restricted to one cohort of women. There are biases based on the ethnic configuration, nutritional status, and age of the patient population as well. Hence, some lesions are more prevalent, such as fibroadenomas in blacks (6,7), which would effect the relative incidence of a histologic pattern. There is no data to suggest that the incidence of fibrocystic changes is effected by the character of the patient population.

Table 4: Breast Cancer Risk Associations with Benign Disease

Diagnosis	Cancer Incidence per 1,000
Cystic disease	2.8
Fibroadenoma	3.1
Adenosis	6.4
Metaplasia	3.2
Papillomatosis	7.5
ALL	3.2

IV. Associated Risk of Developing Breast Cancer

Many studies have indicated that women who have undergone a biopsy for fibrocystic disease have an increased risk for

developing breast cancer (2,9,32,33). The risk does not appear to be uniformly distributed among patients with fibrocystic changes. The likelihood of developing breast cancer appears to be related to the type of fibrocystic changes which is observed in association with other epidemiologic risk factors. Thus, it is critical for us to predict those women who are at higher risk so that they may be more extensively screened. If those individuals could be consistently identified, therapeutic intervention could be evaluated as means of preventing breast cancer.

A. Relative risk

To define the risk of developing a disease statisticians have developed the concept of relative risk (Figure 11) (34). Thus, for a pathologic entity the numerator would be the number of women with that entity of fibrocystic changes who eventually develop breast cancer divided by the incidence of that entity. That value would be divided by the incidence of breast cancer within the population without biopsy proof of that entity. Since the incidence of breast cancer is 1 of 11 or 3 per 10^4 per year, any entity with a greater incidence would have a risk higher than that of the population of women in the US. Other statistical methods have to be applied to prove that the calculated risk was significantly greater than that of women who do not have the diagnosis. Obviously, the calculation of relatively risk is greatly effected by the incidence in the two populations. Since these incidences have not as yet been defined, the calculated relative risk must be defined on the basis of the incidence of breast cancer among women in the US and not as those women without the pathologic entity.

Figure 11

Relative Risk

$$\frac{\text{Number with cancer among exposed population}}{\text{Number exposed population}} \div \frac{\text{Number with cancer among unexposed population}}{\text{Number unexposed population}}$$

B. Quantitation of Risk

Risk has been assessed on the basis of the histopathologic diagnosis (Table 1) (35). It was the general impression that this approach was not accurate since many biopsy specimens

contained mixtures of pathologic entities. Black and Chabon qauanitated the degree of duct atypia (2) demonstrating an even stronger association of atypia per se with the development of breast cancer (Table 5) (8). This association has been observed in many studies (8,33,35,36,37).

Table 5: Breast Cancer Risk Association with Benign Disease

Black-Chabon Score	Incidence per 1,000
1 or 2	2.5
3	3.6
4	9.9
5	21.1

Recent studies by Page and his co-workers have attempted to redefined atypia, pathologically separating hyperplasia from atypia and carcinoma in situ (2,9,10). The attempt is to use more modern criteria which appear to be consistent with the histiologic definitions of most breast pathologists. It is hoped that this will lead to a classification which is reproducible from study to study as well as in clinical practice. In doing so, they have defined the risk for proliferative benign breast disease and in particular proliferative breast disease with atypia (Table 6) (2,10). The overall incidence of the latter in their biopsy population is rare, about 5%. This population is probably analogous to those specimens with a Black-Chabon score of 4 or those with the entity of atypical lobular hyperplasia. The risk in these populations is greatly effected by the presence of other risk factors such as family history (Table 7). Family history appears to be an independent variable as it significantly effects the incidence of breast cancer in those with non-proliferative breast disease as well. Calcification within the biopsy specimen has no apparent effect on risk if observed in the absence of atypia. However, calcification with atypia was associated with a relative risk increase from 4.0 to 6.5 (Table 8) (2,38). If proliferative disease was observed in postmenopausal women, the relative risk was increased by at least two fold (Table 9). However, the absence of proliferative disease in this age group appeared to be protective reducing risk by 70%. Thus, using Page's criteria a group of women can be defined who are at risk with a subset who are at a very great risk for developing breast cancer. The incidence of breast cancer is such in these populations that they would be good candidates for therapeutic trials to determine if breast cancer can be prevented.

Table 6: The Effect of Proliferative Disease on Breast Cancer Risk

Histologic Changes	Incidence (%)	Relative Risk	P Values
ALL	100	1.5	<.0001
Non-proliferative	54.4	0.89	.51
Proliferative	43.4	1.9	<.0001
Without atypia	38.2	1.9	.003
With atypia	5.2	4.4	<.0001

Table 7: The Influence of Family History on Risk with Proliferative Disease

Histologic Changes	Family History	Relative Risk	P Values
ALL	-	1.4	.0007
	+	2.5	<.0001
Non-proliferative	-	0.86	.43
	+	1.2	.78
Proliferative	-	1.7	<.0001
	+	3.2	<.0001

Table 8: The Effect of Calcification on Risk with Proliferative Disease

Histologic Changes	Calcification	Relative Risk	P Values
ALL	+	1.8	.001
Non-proliferative	-	0.9	.59
	+	0.8	.66
Proliferative			
Without	-	1.5	.002
	+	1.9	.01
With	-	4.0	<.0001
	+	6.5	<.0001

Table 9: The Effect of Age in Association with Proliferative Disease on Breast Cancer Risk

Histologic Changes	Age	Relative Risk	P Values
Non-proliferative	20-45	0.99	.96
	46-55	0.83	.63
	>55	0.30	.21
Proliferative	20-45	1.9	<.0001
	46-55	1.9	.0002
	>55	2.2	.007

These finding were reviewed at a concensus meeting sponsored by the American Cancer Society and the College of American Pathologists entitled "Is 'fibrocystic disease' of the breast precancerous? (39). There conclusions are summarized below (Table 10) (40). They emphasized that "If the pathologic diagnosis, 'Fibrocystic Disease' is used, the component elements should be specified.

Table 10: Relative Risk for Invasive Breast Carcinoma Based on Pathologic Examination of Benign Breast Tissue

No Increased Risk
- Fibroadenoma
- Sclerosing adenosis
- Non-proliferative lesions
- Adenosis
- Apocrine metaplasia without atypia
- Cysts (macro and/or micro)
- Duct ectasia
- Fibrosis
- Hyperplasia without atypia (>2<4 epithelial cells in depth)
- Mastitis (inflammation)
- Periductal mastitis
- Squamous metaplasia

Slightly Increased Risk (1.5-2X)
- Hyperplasia without atypia, moderate or florid solid or papillary
- Papilloma with fibrovascular core, without atypia

Moderately Increased Risk (5X)

- Atypical hyperplasia
  - Ductal
  - Lobular

V. Diagnosis

A. Non-invasive Approaches

Breast examination whether by the patient or the health care professional can only detect a palpable mass. The ability of an individual to detect a mass is related to their experience and training. Although approximately 70-80% of all breast cancers are detected by the patient, it is probable that only a majority of fibrocystic changes are detected by the patient (41). More lesions should be detected by mammography since many of these lesions are not palpable. As with malignancies, non-invasive techniques are only suggestive of a diagnosis and require pathologic confirmation.

1. Breast Examination

The examination of the breast by the individual, breast self examination (BSE) or by the health care professional is important in diagnosing benign mastopathy. It is only useful, however, in the diagnosis of those lesions which will cause a mass effect such as fibroadenomas, macrocysts and sclerosing adenosis. These lesions are not associated with an increased risk of developing breast cancer. There importance as entities is that they must be discriminated from cancer. Physical examination does not discriminate benign from malignant growth. Changes on examination do not allow one to predict the risk of developing malignancy. Therefore, examination of the breast can only be viewed as part of the work-up to define whether benign or malignant breast disease is present. Its role is that of screening and primary detection. Guidelines for its use will be outlined in Section VI, Surveillance.

2. Mammography

Mammographic examination of the breast has the ability to define the parenchymal pattern as well as to detect mass lesions and calcification. The technique in its present state of the art encompasses both screen-film mammography and xeromammography. Both use conventional x irradiation to image the breast. There are differences in the dose of radiation to the patient, the means by which the image is collected, the quality of the image, the ease of magnification and the cost to the patient (Table 11). The newest versions of xeromammography requires dedicated equipment, uses less radiation and allows for magnification. The cost of the xeromammographic equipment and the special paper is significantly greater than the film techniques making it considerably more expensive for routine screening.

Table 11: Comparison of Mammography and Xeromammography

	Mammography	Xeromammography
Radiation dose	0.1-0.2 rad	0.5-0.8 rad
Film	X-ray film	Xerox paper
Equipment	Dedicated	General all purpose
Processor	film developer	Xerox processor
Contrast	stark	less broad
Compression	extreme required	moderate; avoidance of skin folds
Cost	Cheaper	
Magnification	Available	
Image Analysis		
Dense breasts	<	
Fatty breast	>	
Calcifications	=	
Chest wall	<	
Lateral	>	
Skin	<	
Lymph nodes	<	

Wolfe has developed a classification to characterize benign proliferative disease. He has divided mammographic findings into four patterns, N_1, P_1, P_2, and DY (Table 12, Figures 12-15) (42). There is considerable controversy as to the classification's reproducibility among radiologists and its predictive value for defining the population at risk with proliferative mastopathies (43,44,45,46,47). In addition changes in normal mammographic patterns associated with aging and hormone supplementation for either birth control or post menopausal symptoms have not been well defined (48,49,50).

Table 10: Correlation of Mammographic Findings with Breast Cancer Risk for Women

Group	Mammography	Median Age	Black-Chabon Score	Projected Tumors*
N1	Predominate Fat	48	1.21	1.0
P1	Prominent Ducts < 1/4th breast	52	1.67	1.9
P2	Prominent Ducts > 1/4th breast	50	2.50	9.6
DY	Mammary dysplasia	42	3.09	17.8

*Expected number of tumors per 1000 women over 3 years

Figure 12: N1 Breast

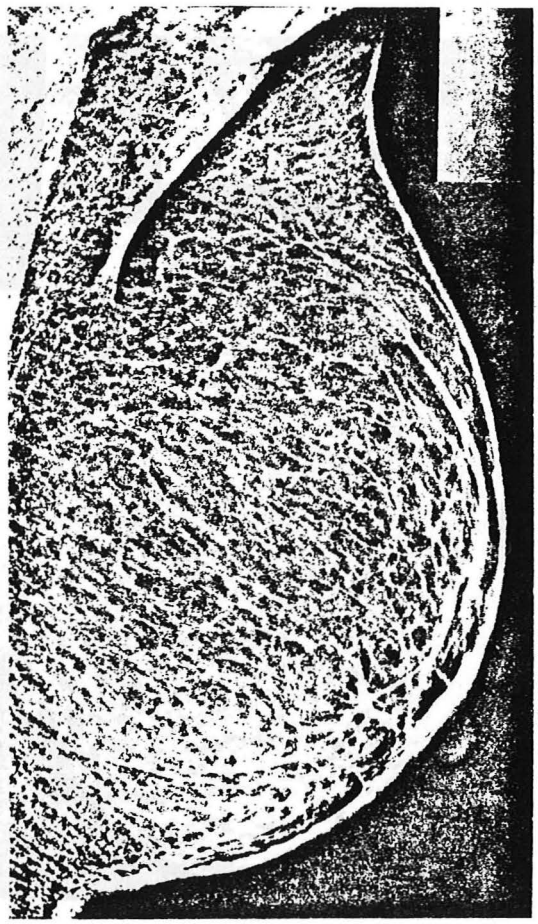


Figure 13: P1 Breast

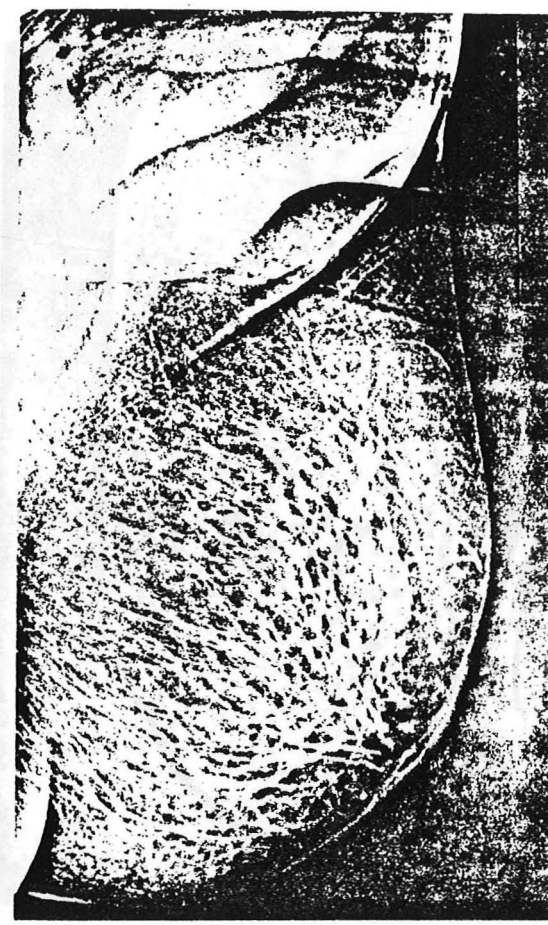


Figure 14: P2 Breast

Figure 15: DY Breast

3. Thermography and diaphonography

Thermography is capable of detecting changes in blood flow within a region of the breast. It will detect mass disease or vascular abnormalities. It does a much better job detecting superficial disease than disease deep within the parenchyma of the breast. Thus, the sensitivity is low (51,52,53,54). It also has low specificity with the results varying with the person doing the procedure and often not being reproducible either from institution to institution or from day to day (54). Investigators have specualted that the reason for this is due to variations in blood flow. Hence, a positive thermogram often means nothing. It does force the physician to do another test such as a mammogram or to repeat the thermogram increasing the cost of medical care. A negative study means that there is no detectable alteration in blood flow. The present recommendations of the American College of Radiology is that it is an experimental procedure (55). Similarly, diaphonography has no proven utility and must be considered an experimental procedure (55,56).

4. Ultrasound

Sonography has the ability to discriminate solid from cystic lesions and can detect calcium within lesions. The technique is not useful as a general approach to screening since the application of the probe is variable and to be complete the procedure is labor intensive and time consuming. The ability to detect an abnormality is dependent on the location within the breast as well as the changes with respect to the surrounding tissue. It can be very useful in localizing lesions and determining if a needle is within the cyst (51,57). However, sonography can not discriminate diffuse changes in the parenchyma. It also may be more useful in studying women with small breasts or masses near the chest wall. But its true utility appears to be in further describing a lesion which has been detected by another modality. Sonography will not prevent a more definitive procedure from being performed and it should only be used as an adjunct to another procedure.

5. Other Modalities

Computerized tomography and nuclear magnetic resonance imaging (MRI) are capable of detecting changes within breast tissue (51). These modalities may be more sensitive than mammography and sonography; MRI can detect changes in blood flow better than thermography. With improved technology the quality and sensitivity of MRI images will probably make it the best way to evaluate morphologic changes within the breast. Although these techniques might be able to detect smaller lesions, better identify parenchyma changes, and calcification, the cost of the procedure prevents their development. Both approaches are too labor and equipment intensive, too expensive for screening purposes. They

will not preclude additional diagnostic studies. It is possible that they might be of use in a specific setting where an invasive procedures is not an option. But this event would be exceedingly rare. It remains that they will most frequently detect breast lesions when they are being employed to define an abnormality within the thorax.

Nuclide imaging with non-specific probes has not utility indetecting breast lesions. Obviously, if there were monoclonal antibodies which could discriminate benign breast disease from malignant, these might be useful for imaging purposes (58). No antibodies has as yet been defined with these characteristics (58,59). In addition the smallest lesions consistently define with monoclonal antibody directed nuclide studies are in the range of 1 to 2 cm. This is clearly within the sensitivity of other modalities. Thus, the approach might be useful, but its utility is only speculative.

B. Invasive procedures

Only examination of breast tissue can define fibrocystic changes, identifyiang the morphologic changes and defining risk as described in Section IV. There are only three technical approaches: fine needle aspiration, needle biopsy, and open biopsy. Each approach has advantages and disadvantages with the specific applications being dictated by the clinical problem.

1. Fine needle aspiration (FNA)

Fine needle aspirations are coming more into vogue as a diagnostic procedure for the following reasons: 1) It can be done in the office or clinic without any extensive preparation; 2) the results are quickly obtained; 3) it is inexpensive; 4) it may be both diagnostic and therapeutic; 5) there is no associated morbidity to the patient. When the test is positive, whether the lesion be a benign cyst or a malignancy, FNA enables the physician to rapidly determine whether another procedure is required, and to discuss the alternatives with the patient. The indication for doing an FNA is that there be a palpable abnormality which does not require radiographic localization. The technique enables the physician to determine if the mass contains aspiratable fluid and to remove fluid and/or cells for cytologic analysis and bacteriologic culture. Occasionally, if the physician checks the needle a cellular plug will be present with enough tumor to make the diagnosis.

If there were monoclonal antibodies which were consistently associated with the progression to malignancy or the neoplastic state, cytologic examination might be more useful in separating atypia from malignancy.

The problems with needle aspiration relate to the physician's expectation. If serous cystic fluid is obtained, the patient must be closely followed to make sure that the fluid does not rapidly reaccumulate. The presence of benign epithelial breast cells is not helpful because of the potential for sampling error. The diagnosis of proliferative breast disease can not be made by FNA. In these situations an additional procedure is required. Interpretation requires proper smearing and fixation of the slides. The pathologist must have considerable experience with the procedure so that over-interpretation of the cytology is not an issue.

2. Needle biopsy

A needle biopsy has the advantage of obtaining histologic material. Again, there are problems with sampling, but the histologic interpretation may be more helpful than cytologic studies. The mass to be biopsied must be palpable and usually it is a solid mass from which fluid could not be aspirated. The procedure can be done in the office or clinic requiring little or no preparation. Occasionally, in tumors with significant scirrhous reaction, tissue may be difficult to obtain while the malignant cells as readily aspirated. When obtainable, multiple needle biopsies in a patient with advanced breast cancer can obviate the necessity for an open biopsy since adequate material can be obtained for receptor analysis and histologic examination.

3. Open biopsy

Open incisional or excisional biopsy remove the mass lesion or the abnormality identified by mammographic studies. If the mass is excised, there are no sampling errors associated. A diagnosis of breast abnormality present can be made from the specimen from which the malignant potential can determined. However, an open biopsy does not give information as to changes occuring elsewhere with the contralateral or ipselateral breast. In specimens with preneoplastic changes, it is always possible to miss the invasive cancer. The indications for its use are the following: 1) mass lesions which can not be definitively localized without imaging techniques; 2) cysts which do not completely resolve or rapidly recur; 3) dry or bloody needle aspirations; 4) inconclusive needle aspirations or needle biopsies; 5) eczematous changes of the nipple; 6) bleeding from the nipple; 7) previously diagnosed breast cancer the histology of which is associated with multi-centric or bilateral disease.

VI. Surveillance

The ACS and NCI at a joint concensus panel have made recommendation as to appropriate surveillance in women. These recommenda-

tions are tempered by the use of risk without defining those who are at risk (Table 13). In section IV we have defined the fibrocystic changes as they influence the risk of an individual woman developing breast cancer. An increased risk is found only in the association of histologic proven benign breast proliferative disease with atypia and not the presence of fibrocystic changes. Hence, any patient with biopsy proven atypia should be considered statistically to be at high risk for developing breast cancer (Table 10). In addition significant increased risk is associated with a maternal family history. This risk is greatly increased if the family member was premenopausal, had bilateral or multicentric breast cancer, or if more than one primary and/or second degree relatives are involved (60,61). The combination of risk appears to be greater than the individual risk and may be additive (2). Other risk factors such as age of the patient at the time of first pregancy, age at menopause, ethnic origin, etc. do not significantly increase risk to the level that these individual are at risk great enough to warrant close scrutiny.

A. Breast Examination

1. BSE

Seventy to eighty percent of breast masses used to detected by the patient. This percentage is probably slightly lower due to an increase in screening mammography. But it clearly is the most important screening and surveillance procedure (41,62). Many demonstration projects have shown the importance of BSE in detecting interval cancers (63,64,65,66). Most women believe they know how to exam their breast, but when confronted and requested to demonstrate how they preform BSE, the appropriate technique is usually suboptimal. Their performance of BSE appears to be sporadic. Thus, the major effort of the health professional is in education and supporting the relevance of BSE regardless of the woman's risk of developing breast cancer.

2. Physical examination

The recomendations for physical examination are yearly. Since the other screening recommendations require a yearly pelvic examination in most women, this examination is typical performed by the gynecologist or generalist. The BCDDP study showed that only 9% of breast cancers detected by the physician were not demonstrated on mammograms while 42% were found by mammography alone (67). Therefore, the role of the physician in breast screening is to examine the patient. But in reality they will have a greater impact on early detection by teaching breast self examination and by determining the need for mammographic screening.

B. Mammography

The ACS and NCI have made the following recommendations for minimal screening of woman (Table 13) (68). The level of surveillance was based on the HIP study (16,69) and the BCDDP results (67) on detecting primary and interval cancers. Screening mammography does detect smaller cancers (16,17). Since the radiation received per mammogram is 0.1-0.2 rads with modern equipment, it was felt that the associated radiation with regular screening was of no health risk to the individual. There is an attendent reduction in the pathological stage of the tumors in many studies (16,17,69,70). This has been translated into a survival benefit (69,71). The most remarkable results are the observations from the HIP study, showing that a single screening mammogram has a persistent effect on survival (69). This suggests that interval cancers although a problem in the high risk patient may not be as important in a large population. An alternative explanation is that once woman have been sensitized to the importance of screening it is continued throughout life. Unfortunately, epidemiologic data are not alvailable on the follow-up screening and routine medical care for the participants after 1963.

Table 13: Guidelines for Screening Mammography

Age	Frequency
35-40	Baseline
40-49	Biannual (yearly in high risk)
≥50	Yearly

Although the cost of the recommended screening procedures was considered, it did not influence the recommendations of the concensus. The cost of mammography in Dallas with at least two views ranges and including interpretation ranages from $50-150. At least 30 million American woman should have yearly screening mammography. The cost is approximately $3 billion per year to detect approximately 20,000 cancers. It has been estimated that there are at least four negative surgical procedures for every cancer and this may be a gross underestimination of the number of procedures being performed as a result of mammographic screening (72). An excisional biopsy costs approximately $1000 when physician and hospital costs are included and a needle aspiration can cost as much as $700 for a total cost of greater than $100 million per year. The total cost to detect 20,000 cancers per year is at least 3 billion dollars. Therefore, it is critical to determine if either fewer mammograms and/or fewer views are acceptable alternatives. The Swedish studies have concentrated on fewer views and biennial mammography (16) while Canadian national studies have utilized the American approach (73).

Clearly, less frequent screening impacts both on survival and the tumor stage at presentation. It is impossible to demonstrate that the results of these studies are significantly different. However, if they were, the difference could be ascribed to either the interval or the mammographic technique. Unfortunately, there has been no large randomized trial comparing these alternative approaches. Moskowitz has advocated that more frequent screening is necessary in the 5th decade and that less frequent screening may be necessary following menopause (54). His argument is based on the changes in breast parenchyma secondary to the hormonal variation during prior to menopause and on the involution of the breast parenchyma following menopause. Although his experience is significant, it must be evaluated in a large study controlling for the exogenous administration of estrogens to post menopausal women. Future recommendation for mammographic screening will probably be based on cost benefit analysis rather than optimal detection.

VII. Treatment

A. Medical management

Medical management has been predomnately employed in women who have proliferative breast disease with increased cyst formation, multiple fibroadenomas, and pain. As discussed below, some of the drugs have been shown to be effective in reducing proliferative changes on mammography and reducing the incidence of biopsies. There are no studies with biopsy material demonstrating that these agents have any efficacy in the treatment of proliferative breast disease with atypia. There are no studies demonstrating that they reduce the risk of developing breast cancer. Therefore, they can only be considered as a means to treat the symptoms and reduce the number of surgical procedures.

1. Hormonal intervention

Involutional changes in breast tissue are obvious with the development of menopause. This observation has been implicated in the genesis of benign breast disease and has been utilized in its treatment. Because proliferative breast disease was observed predominately in premenopausal women, there was considerable concern that oral contraceptives (BCP) would cause more proliferative disease and be a significant risk factor in breast cancer. There is no evidence to suggest BCP increase cancer risk (74,75). However, it has been noted that BCP significantly reduced the breast biopsy rate (74). Most studies have shown that the decrease is obseved after at least 1 year of therapy and may be maximal at two years. As these studies antedated the Wolfe mammographic classification, there is no data as to quantitative mammographic changes with BCP. There is controversy as to how long the protective effects last (74,75). It must be emphasized

that the BCP used in these studies contained significantly higher amounts of hormones than the present standard BCP. In addition to probably being more efficacious in proliferative breast disease, these combinations were associated with greater untoward effects such as water retention, weight gain, hypertension, CVA, etc. The effectiveness of newer BCPs needs to be quantitatively evaluated in benign proliferative disease. Considering their lack of side effects compared to other hormonal manipulations, a therapeutic trial may be warranted in an individual. The length of that trial should be at least one year with mammographic studies to document proliferative changes.

Hormones which effect estrogen and progesterone synthesis have been very effective in reducing proliferative breast disease. The efficacy of dannazol may be as high as 90% and the response rate is much quicker than with BCP being observed with four months (76,77). Most patients develop menstrual irregularities which cease with the cessation of the drug (78). Hirsuitism is also a frequent side effect which significantly limits dannazol's utility. The Horring study indicates that the relapse rate is significant with cessation of the drug with more than 50% recurring within 1 year (79,80). Tamoxifen which is a partial estrogen agonist may be a better agent. It probably has a slightly lower documented response rate of approximately 70% (81,82). The onset of improvement is approximately as rapid as with dannazol. Its only significant known side effects are the development of menstrual irregularities and menopausal symptoms. The use of Vitamin A or retinoids has been advocated as a means to reduce the risk of proliferative disease becoming malignant. Band et al. have reported that 50,000 U/day decreased proliferative changes by mammography in 5 of 12 women (83). The mechanism of this effect is not know; it could be either acting as a retinoid or by effecting steroidogenesis directly. To date there have been no quantitative studies using retinoic acid compounds. The prolactin inhibitor, bromocriptine, also seems to effectively reverse proliferative changes by mammography (81,84). It had originally been suggested this it would only be effective in women with high levels of prolactin, but studies indicated that the effect does not correlate with serum prolactin concentrations (84). Some investigators have been quite pleased with it, while others have found that the associated nausea and vomiting are limiting factors.

2. Caffeine

Early studies by Minton and co-workers indicated that caffeine withdrawl effectively decreased proliferative changes (85). These results have not withstood further investigation (86,87). There is no data other than anecdotal to suggest that caffeine, nicotine, or other dietary manipulation has any effect on

proliferative breast disease. We all recommend it to our patients because it is cheap and has only beneficial side effects. There is no data to support this approach.

3. Vitamin E

London had reported in a series of uncontrolled studies that vitamin E caused decrease in proliferative breast disease (88). However, in a recent double blind study with 128 patients three months of vitamin E administration caused no significant effect on breast proliferation (88). In evaluation of the participants hormonal profile only dehydroepiandosterone sulfate was significantly reduced in recipients of vitamin E. In view of the results with BCP it is possible that a 3 month trial was of inadequate duration, but the study had been designed on the basis of the early uncontrolled study.

Table 14: Medical Management of Benign Breast Disease

Mechanism	Drug	Effect	Side Effects
Antieastrogen	Danazol	60-90%	Menstrual irregularity Hirsutism
	Tamoxifen	70	Menstrual irregularity Menopausal symptoms
Antiprolactin	Bromocriptine	70	Nausea Vomiting
Estrogen Balance	Enovid	?	Water retention Hypertension CVA
Fatty acids	Vitamin E	none	
	Vitamin A	65	
Methylxanthine withdrawl		none	
Nicotine withdrawl		none	

B. Surgical management

Since hyperplastic proliferative diseases affect all breast tissue, another approach to reduce the risk of an indivdual's developing breast cancer is to remove the breast tissue. The most effective approach would be bilateral modified radical mastectomies. Most surgeons agree that this is somewhat aggressive for "pre-neoplastic" changes. The technique which is being advocated by most surgeons are either simple mastectomies or preferably, the total glandular mastectomy or subcutaneous mastectomy (89). Either approach allows for immediate reconstruction. These procedures remove at least 95% of all breast tissue including the nipple-aerolar complex as well as level I axillary nodes. The latter are necessary to make sure that the complete wing of the breast has been removed. It must be emphasized that the purpose of this approach is to remove all the breast tissue,

reducing the risk of breast cancer. The total glandular mastectomy is a technically difficult procedure fraught with post operative complications secondary to the vascular supply to the skin which remains intact. When complication occur the cosmetic result is poorer than with a lesser procedure. It must be emphasized that the purpose of this approach is to remove all the breast tissue, reducing the risk of breast cancer. This point should not be compromised to guarantee better cosmesis; the risks of complications and the alternatives must be explained to the patient.

Although there are significant numbers of patients that have been treated with this approach, it has not been used in a clinical trial. Hence, the number of patients that go on to develop breast cancer following total glandular mastectomies or lesser profilatic procedures is not known. This must be discussed with the patient prior to embarking on this approach.

The most difficult decision in treating hyperplastic breast disease is who should undergo these procedures (Table 15). When the lesion is unequivocal intraductal carcinoma, the appropriate therapy is at least an extended simple mastectomy and not a glandular mastectomy. If atypical changes are observed in the mastectomy specimen, profilactic surgery on the remaining breast is indicated. In cases of severe atypia or lobular neoplasia with atypia where one can estimate a relative risk of at least 3 fold that of normal woman, it should be considered and discussed with the patient. However, in cases of proliferative disease without atypia, in women with difficult breast to examine, and in women who have cancerophobia it should not be considered.

Table 15: Candidates for Profilactic Surgery

1. Biopsy proven atypical hyperplasia
   either lobular or ductal

2. Lobular neoplasia

3. Biopsy proven cancer in the contralateral breast associated with multifocal cancer

4. Women with multiple maternal family members with breast cancer

5. Combinations of #1-4

IX. Conclusions

Proliferative changes in the breast represents a spectruum of disease from the truly a benign to the frankly neoplastic. Its

ubiquitious nature and its attendent risk for the development of malignancy make it a major health problem. This protocol has attempted to define the risk of these changes becoming neoplastic, our ability to diagnose and characterize these lesions, and our therapeutic options. As it has been demnstrated above, the data is very difficult to analyze and the conclusions are often based on impressions. Treatment is often based on intuition and emotion. It is clear that the pathogenesis of the lesions needs to be further explored. Screening for breast cancer is incredibly expensive. Clinical trials are necessary to further define risk, to streamline screening, and to determine the efficacy of treatment. The goal is to approach breast disease and cancer rationally in the future.

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