Relationship of Fibrocystic Disease to Carcinoma of the Breast *

CHARLES M. KARPAS,** M.D., HENRY P. LEIS,*** M.D., ABRAHAM OPPENHEIM,† M.D., WALTER L. MERSHEIMER,†† M.D.

From the Departments of Surgery and Pathology, New York Medical College-Flower & Fifth Ave. Hospitals

PATIENTS with clinically detectable and histologically proved fibrocystic disease subsequently develop mammary carcinoma at three to four times the expected breast cancer rate of the general population. This increased incidence has been reported by Warren,[26] Haagenson [11] and others.[3, 5, 15, 18] In mastectomy specimens removed for cancer, microscopic evidence of fibrocystic disease appears in a larger percentage of instances than in breasts with no malignant lesions. McCarthy and Mensing [20] found fibrocystic changes associated with cancer of the breast in 100 per cent of cases investigated, while the incidence in other studies has ranged from 56 [19] to 80 per cent.[24] Although the clinical correlation may not be conclusive, the relationship of fibrocystic disease to breast cancer does not appear to be fortuitous.

The relationship of estrogenic stimulation and the development of breast cancer is complex and controversial. Although the effects in women are difficult to evaluate, extensive studies in experimental animals show that the administration of estrogen results in fibrocystic disease and that prolonged usage can lead to progressive hyperplastic changes and cancer.[1, 4, 12, 13]

Whether or not there is a correlation between all morphologic types of fibrocystic disease and cancer of the breast or only with certain histologic variants has been questioned. Terms used to describe various entities in fibrocystic disease are micro- or macrocysts, apocrine epithelium, blunt duct adenosis, florid adenosis, sclerosing adenosis and proliferative changes. The latter consists of epithelial hyperplasia with or without papillomatosis and atypism. It is this varient of fibrocystic disease that many observers consider significant in relationship to cancer.

Foote and Stewart [10] suggested that papillary hyperplasia, which in some individuals becomes cytologically atypical, plays a role in the development of human breast cancer. Humphrey and Swerdlow [14] found a statistically significant correlation between large duct epithelial hyperplastic changes and an increased incidence of carcinoma. In a study of 282 patients with fibrocystic disease followed for an average of 9.6 years, Davis, Simons and Davis [7] conclude that fibrocystic disease without intraductal epithelial hyperplasia did not appear to be related to carcinoma, while with hyperplasia, the incidence of carcinoma was three times the usual rate. Leis and Bowers [17] be-

* Submitted for publication June 21, 1964.

Study supported through a grant from the New York City, Department of Health and conducted as a co-operative effort with the Division of Cancer Control and Research.

** Chairman, Department of Pathology, Beekman-Downtown Hospital; former Associate Prof. of Pathology, New York Medical College-Metropolitan Medical Center.

*** Associate Clinical Prof. of Surgery, New York Medical College-Metropolitan Medical Center.

† Assistant Clinical Prof. of Surgery, New York Medical College-Metropolitan Medical Center; Director, Division of Cancer Control and Research, New York City, Department of Health.

†† Prof. and Chairman, Department of Surgery, New York Medical College-Metropolitan Medical Center.

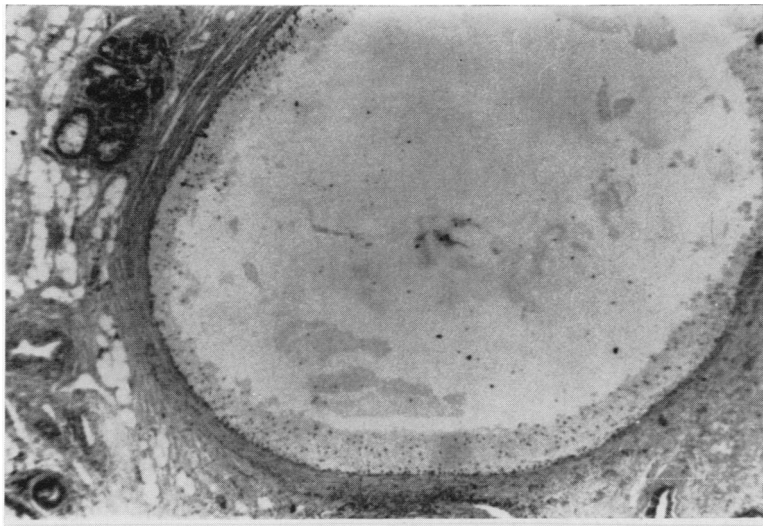

FIG. 1. Cystic structure lined by flattened epithelial cells associated with a wall of condensed fibrous tissue (× 40).

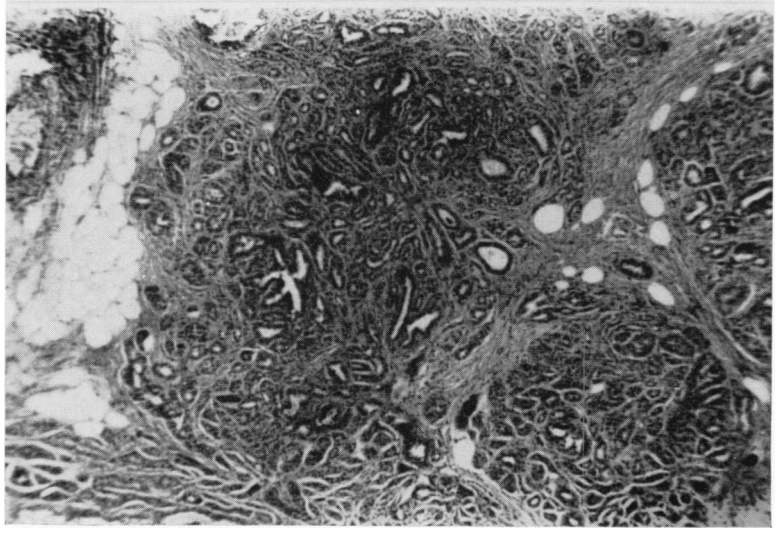

FIG. 2. Adenosis; a proliferation of glandular and ductal structures conforming to a lobular pattern (× 40).

lieve that fibrocystic disease showing atypical hyperplasia is definitely a premalignant lesion. Furthermore, McLaughlin *et al.*[21] consider those cases showing more progressive changes with some degree of nuclear irregularity and hyperchromatism to be a noninvasive form of cancer. This concept of "early carcinoma" is supported by Cutler.[6]

The degree and frequency of intraductal epithelial proliferation is higher in surgically removed breasts than in breasts with no malignancy studied post mortem.[23] Tellem *et al.*[25] found that atypical hyperplasia was seen seven times more frequently in cancerous breasts than in benign excisional biopsy specimens. In addition, the more extensive the epithelial proliferation, the higher the incidence of node metastases.

The purpose of this investigation is to evaluate further the relationship of proliferative changes to the development of human breast cancer in 645 patients over a 5-year period. Initial morphologic findings of fibrocystic disease in patients with malignant and benign lesions of the breast are presented.

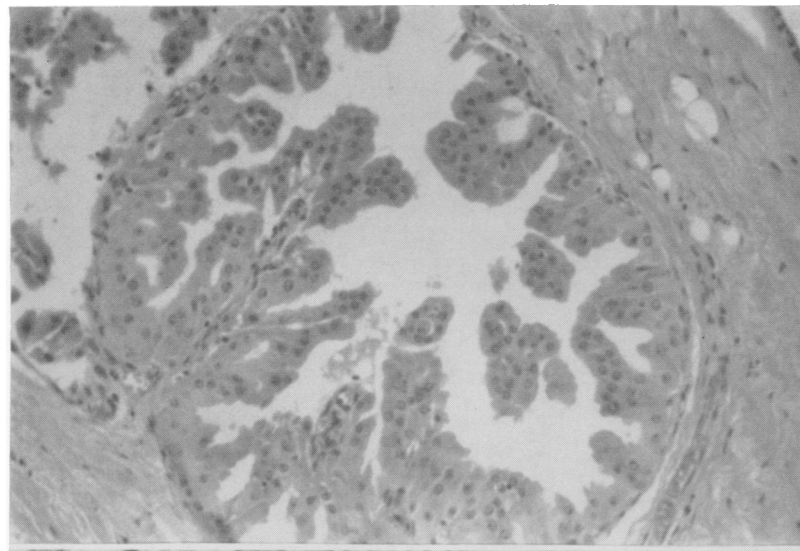

FIG. 3. A dilated duct lined by apocrine type cells. Note the "knobby" appearance of the free cytoplasmic margins (× 150).

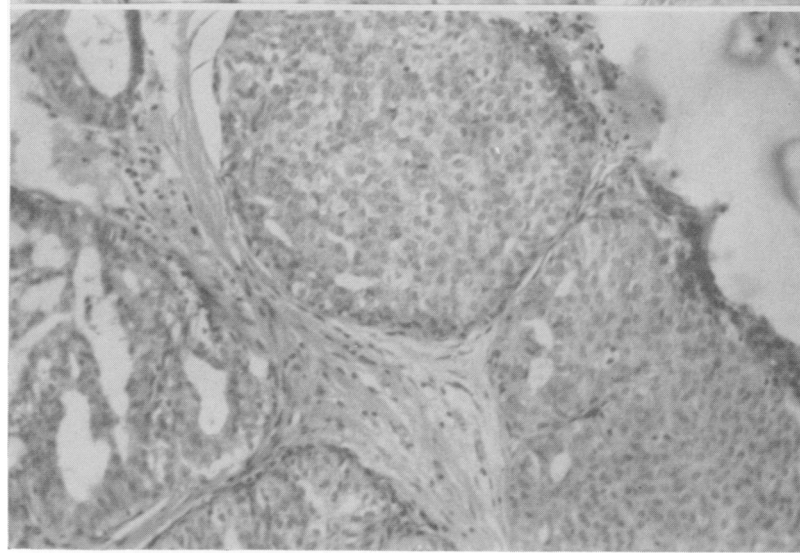

FIG. 4. Epithelial hyperplasia. The lumen is completely obliterated by uniform appearing epithelial (× 200).

Material and Methods

From July 1, 1948 through December 31, 1952, 838 consecutive cases of breast lesions operated on at Flower & Fifth Avenue Hospitals were reviewed. Of this series 119 were omitted because insufficient tissue was available for study or clinical information was inadequate. Of the remaining 719 cases 74 were fibroadenomas, leaving a total of 645 which were evaluated for various histologic types of fibrocystic changes in malignant and nonmalignant cases. In 226 patients the diagnosis was malignant lesions. No cases were included in which a lesion was removed for specific inflammatory conditions, and breast lesions treated by irradiation were similarly excluded.

The histologic variants of fibrocystic disease tabulated in this study are defined as follows:

1) *Cysts* (Fig. 1): dilated ducts lined by flattened epithelium which may or may not be replaced by a fibrous wall. Cysts not visible to the naked eye but noted microscopically were scored as "minimal" change.

2) *Adenosis* (Fig. 2): a proliferation of ducts and acini associated with an increase

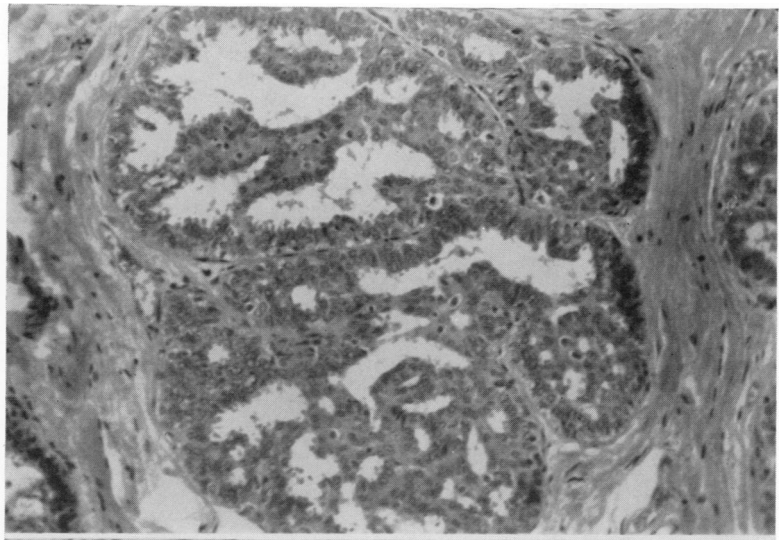

FIG. 5. Papillomatosis; papillary epithelial proliferations associated with thin connective tissue stalks projecting into the lumen of the ducts (× 150).

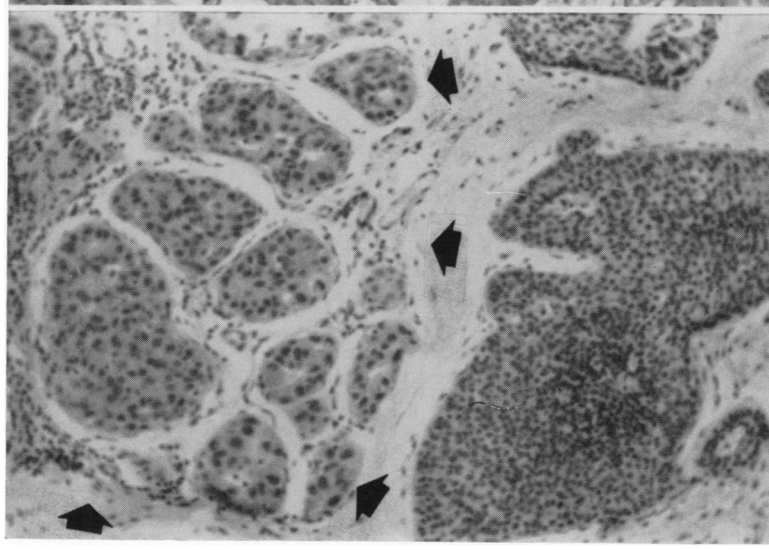

FIG. 6. Arrows indicates a focus of *in situ* carcinoma immediately adjacent to atypical epithelial hyperplasia seen on the right (× 100).

of cellularity but conforming to a lobular pattern (florid stage). With progressive fibrosis there appears to be distortion of the lobular architecture and sclerosis of the epithelial elements. Since the florid stage was obscured by varying degrees of fibrosis, this variant was *not* tabulated under proliferative changes.

3) *Apocrine epithelium* (Fig. 3): elements appearing as glandular or cystic structures or both. The lining epithelium is columnar and contains a characteristic eosinophilic cytoplasm and a small basal nucleus. The free cytoplastim margins are "knobby" in appearance.

4) *Epithelial hyperplasia* (Fig. 4): an exuberant proliferation of duct epithelia which appears several layers thick and may appear to completely obliterate the lumen. Atypical epithelial changes are characterized by those proliferative processes exhibing nuclear irregularity, loss of polarity and mitotic activity in varying degrees.

5) *Papillomatosis* (Fig. 5): papillary epithelial proliferations projecting from the ductal epithelium in a regular manner.

TABLE 1. *Tabulation of Proliferative, Nonproliferative and Minimal Changes in Patients with Nonmalignant Lesions of the Breast*

Age in Decades	No. Cases	Proliferative Changes: Total No.	Total %	Atypical No.	Atypical %	Adenosis No.	Adenosis %	Cysts & Apocrine Epithelia No.	Cysts & Apocrine Epithelia %	Minimal Changes No.	Minimal Changes %
10–19	3	1	33%	—	—	—	—	1	33%	1	33%
20–29	46	5	11%	—	—	25	54%	20	43%	6	13%
30–39	96	21	22%	2	2%	35	37%	54	56%	28	29%
40–49	196	64	32%	1	0.5%	66	34%	130	66%	52	27%
50–59	61	14	23%	1	2%	17	28%	37	61%	14	23%
60–69	11	2	18%	—	—	1	9%	5	45%	5	45%
70–79	3	2	67%	—	—	2	67%	3	100%	—	—
80+	3	1	33%	—	—	2	67%	2	67%	—	—
Total	419	110	26%	4	1%	148	35%	252	60%	106	25%

Atypical changes are similar to those described under epithelial hyperplasia.

The histologic variants of fibrocystic disease were placed in three major groups:

1) *Proliferative:* papillomatosis and epithelial hyperplasia with or without atypical cellular changes.

2) *Non-proliferative:* a) adenosis, including all stages from florid to sclerosing, and b) cyst and apocrine epithelia.

3) *Minimal changes:* those lesions in which the proliferative or nonproliferative entities were quantitatively considered slight. Malignant lesions associated with minimal fibrocystic disease, atrophic breasts or no apparent associated changes were also scored as "minimal changes."

The various histologic entities of fibrocystic disease were graded initially as slight, moderate and marked. Since the classification of quantitative changes was either difficult or occasionally arbitrary, moderate and marked changes were considered together. On the other hand, when combined proliferative or nonproliferative changes were interpreted as slight, the lesions were tabulated as "minimal."

Results

Tables 1 and 2 compare the various components of fibrocystic disease, according to age group in decades, in patients with malignant and nonmalignant lesions of the breast. The distribution of proliferative

TABEL 2. *Tabulation of Proliferative, Nonproliferative and Minimal Changes in Patients with Malignant Lesions of the Breast*

Age in Decades	No. Cases	Proliferative Changes: Total No.	Total %	Atypical No.	Atypical %	Adenosis No.	Adenosis %	Cysts & Apocrine Epithelia No.	Cysts & Apocrine Epithelia %	Minimal Changes No.	Minimal Changes %
10–19	—	—	—	—	—	—	—	—	—	—	—
20–29	3	—	—	—	—	—	—	1	33%	2	67%
30–39	36	8	22%	5	14%	6	17%	7	19%	19	53%
40–49	71	24	34%	15	21%	12	17%	13	18%	39	55%
50–59	60	11	18%	6	10%	3	5%	7	12%	42	70%
60–69	38	5	13%	3	8%	2	5%	3	8%	31	82%
70–79	14	3	21%	2	14%	—	—	2	14%	10	71%
80+	4	1	25%	1	25%	—	—	—	—	3	75%
Total	226	52	23%	32	14%	23	9%	33	15%	146	65%

TABLE 3. *Comparison of Atypical Changes in Patients with Malignant and Nonmalignant Lesions of the Breast*

Breast Lesions	No. Cases with Proliferative Changes	No. Cases with Atypical Changes	% Atypical Changes
Noncancerous	110	4	4%
Cancerous	52	32	62%

changes are similar in each group with the peak incidence in the 5th decade. The seemingly high percentages among older age groups, especially in the 8th decade of patients with nonmalignant disease, may reflect the small number of cases and therefore are not considered as significant.

A salient feature in our studies is the degree of atypical changes in breasts with malignant as compared to nonmalignant lesions. Fourteen per cent of the former group showed moderate to marked atypical epithelial proliferation in contrast to one per cent of the group with nonmalignant disease. The significance of cellular atypia can be further appreciated by comparing the incidence to the total number of proliferative changes, *per se* (Table 3). Thirty-two (62%) of 52 patients with breast malignancy who had proliferative morphologic variants exhibit appreciable histologic evidence of atypical epithelial changes while only 4 per cent of patients with nonmalignant lesions of the breast with proliferations showed any significant degree of atypia.

Formation of cysts and apocrine epithelial proliferation reach a peak incidence in the fifth and sixth decades, followed by gradual decrease. In patients with malignant lesions of the breast, however, the peak incidence appears to be in the fourth and fifth decades. This difference in time of occurrence is statistically insignificant, however, and may be accounted for, in part, by the nature of the definition of "minimal changes." It is significant that the latter group was characterized largely by the cystic and apocrine epithelial variants. Furthermore, in advanced decades the limited number of cases nullify the validity of seemingly disproportionate changes.

In contrast to cysts and apocrine epithelia, the incidence of adenosis is higher in the earlier decades and decreases significantly with age. It is again apparent that the number of patients in the eighth and ninth decades is too small for any statistically significant evaluation.

"Minimal" changes, including atrophic breasts, were observed in 146 patients (65%) with cancer of the breast, compared to only 106 (25%) with no breast cancer. Therefore, in the remaining 80 patients with breast cancer, proliferative changes could be demonstrated in only 52 (65%) while proliferative changes occurred in 110 of 313 patients (35%) with nonmalignant lesions of the breast.

Comparison of the various components of fibrocystic disease in breasts with and without malignant lesions reveal that 1) there is a relative increase in proliferative changes in patients with cancer of the breast and 2) the proliferative changes are represented by an appreciably large population of atypical epithelial elements.

Discussion

Statistical analysis has indicated a higher incidence of mammary carcinoma in patients previously operated upon for benign lesions then is seen in women without previous breast operations. This increased frequency is subject to varying interpretations since many cases are never treated and many patients are not seen by any physicians, the latter confirmed by the high incidence of fibrocystic disease seen at autopsy. A second complicating factor in correlating breast cancer with fibrocystic disease is that the latter includes several histologic variants. An analysis of the morphologic variants yields a more meaningful conclusion for correlating cancer of the breast with fibrocystic disease. Our findings, as well as those of other investigators, indicate

that there is a relationship between the rare form of fibrocystic disease showing atypical epithelial hyperplasia and cancer.

The demonstration of atypical cellular proliferations coexisting with malignant breast lesions parallels similar conditions in other organs. In assessing the biologic significance of cellular atypism, one can only speculate about its premalignant nature in terms of a time and spatial relationship. Inasmuch as the ducts and glands of the breast are composed of epithelial cells which normally have a high turnover rate, it is not difficult to predict that this rate would be increased by an abnormal exposure to a chronic stimulus. A further possibility is that the epithelial elements could have a low threshold to an apparently physiologic hormonal stimulation. Regardless of this possible "cause and effect" hormonal relationship, these proliferating cells may not only fail to replicate into mature secretory elements, but they may give rise to atypical forms. As these forms accumulate, an atypical hyperplasia results. Although the future of these atypical cells cannot be predicted, it is possible that this progressive disarrangement of structure may convert the atypia into a cancer. The high frequency of atypical hyperplasia in the presence of breast cancer, especially in regions adjacent to foci of intraductal carcinoma (Fig. 6), is one argument in favor of the premalignant potential of such proliferations.

Atypical hyperplasia occurs rarely in the absence of cancer of the breast. Despite the hypothesis that cancer may develop in a step-wise manner, preceeded by various stages of cellular atypism, one cannot predict whether atypical lesions will proceed further or regress. However, the surgeon must be aware of the biologic potential of the type of fibrocystic disease showing atypical proliferation in the breast with a benign lesion. To assume that these lesions are without neoplastic potential would be unfortunate and contradictory to the principles of early cancer detection. On the other hand, when a tumor is excised and reported as benign fibrocystic disease it is mandatory for the pathology report to be specific as to the histologic type of this disease; it then becomes the surgeon's responsibility to determine the future care of the patient. He must be cognizant of the multiple pathologic entities that comprise the all-inclusive term, fibrocystic disease.

With increasing popularity of diagnostic aids, most notably soft tissue mammography,[2, 8] in the study of diseases of the breast, many physicians may be misled by reports indicating no evidence of malignancy. A surgical biopsy should be performed on any dominant area or mass in the breast except in the case of a superficial cyst where aspiration may offer a definitive treatment. Because of the appreciable number of "false negatives" with mammography and other diagnostic aids, they cannot be considered absolutely reliable, even when combined with clinical examination. Histologic evidence should ultimately determine whether a dominant area or mass in the breast is benign or malignant.

Minimum requirements for proper management of patients with such lesions should include: 1) monthly self examinations of the breast by the patient, 2) periodic careful breast examination at least every 4 months by a physician, 3) the use of soft tissue mammography and other diagnostic aids at yearly intervals or more often as indicated and 4) the immediate biopsy of any slightly suspected areas.

Some authorities believe that when this rare form of fibrocystic disease is diagnosed some definite form of operation should be entertained, especially if there is a familial history of breast cancer.[9, 16, 21] Simple wide excision or even unilateral simple mastectomy would not be considered adequate since these lesions tend to be bilateral and multiple throughout the breast tissue. The only definitive surgical procedure offering

adequate protection would be bilateral simple mastectomy or bilateral adenomammectomy as developed by Rice and Strickler.[22] This latter procedure removes most of the parenchymatous breast tissue without the mutilation associated with simple mastectomy.

A more definitive conclusion regarding the possible premalignant nature of the proliferative lesions in fibrocystic disease requires an extended follow-up period. The authors are presently formulating such an investigation.

Summary

Of 645 patients with breast lesions operated upon at Flower & Fifth Avenue Hospitals over a 5½-year period, 226 were diagnosed as having malignant lesions.

Histologic varients of fibrocystic disease in patients with malignant and non-malignant lesions of the breast were classified in three major categories: proliferative (papillomatosis and epithelial hyperplasia), nonproliferative (adenoses, cysts and apocrine epithelia) and "minimal" changes (atrophy or proliferative or nonproliferative entities, or both, quantitatively considered slight).

The results of this study indicate that 1) there is a relative increase in proliferative changes in breasts with malignant lesions and 2) these proliferative changes are represented by an appreciable large population of atypical epithelial elements.

The significance of atypical hyperplasia as a premalignant lesion and its management in patients with nonmalignant lesions of the breast is discussed.

References

1. Astwood, E. B. and C. F. Geschickter: Changes in the Mammary Glands of the Rat Produced by Various Glandular Preparations. Arch. Surg., **36**:672, 1938.
2. Berger, S. M. and J. Gershon-Cohen: The Roentgenographic Diagnosis of Carcinoma of the Breast. J. Int. Coll. Surg., **36**:750, 1961.
3. Behrend, A.: Cystic Disease of the Breast: Its Relation to the Development of Carcinoma. J. Int. Coll. Surg., **40**:549, 1963.
4. Burrows, H.: A Comparison of the Changes Induced by some Pure Estrogenic Compounds in the Mammae and Testes of Mice. J. Path. Bact., **42**:161, 1936.
5. Clagett, O. T., N. C. Plimpton and G. T. Root: Lesions of the Breast: The Relationship of Benign Lesions to Carcinoma. Surgery, **15**:413, 1944.
6. Cutler, M.: Tumors of the Breast. Philadelphia, J. B. Lippincott Co., 1962.
7. Davis, H. H., M. Simons and J. B. Davis: Cystic Disease and Carcinoma of the Breast. Bull. Soc. Int. Chir., **5**:1, 1960.
8. Egan, R. L.: Experience with Mammography in a Tumor Institution. Radiology, **75**:894, 1960.
9. Farrow, J. H.: Treatment of Chronic Mastitis. Tumors of the Breast, Chest and Esophagus. Pack, G. T. and I. M. Ariel, ed. New York, Paul B. Hoeber, Inc., 1960. p. 60.
10. Foote, F. W. and F. W. Steward: Comparative Studies of Cancerous Versus Non-Cancerous Breasts. II. Role of so-called Chronic Cystic Mastitis in Mammary Carcinogenesis, Influence of Certain Hormones on Human Breast Structure. Ann. Surg., **121**:197, 1945.
11. Haagensen, C. D.: Diseases of the Breast. Philadelphia, W. B. Saunders Co., 1956.
12. Haagensen, C. D. and H. T. Randall: Production of Mammary Carcinoma in Mice by Estrogens. Arch. Path., **33**:411, 1942.
13. Herman, J. and O. F. Krehbiel: The Influence of Hormones on Breast Hyperplasia and Tumor Growths in White Rats. Amer. J. Cancer, **27**:450, 1936.
14. Humphrey, L. and M. Swerdlow: Relationship of Benign Breast Disease to Carcinoma of the Breast. Surgery, **52**:841, 1962.
15. Kiaer, W.: Relation of Fibroadenomatosis (Chronic Mastitis) to Cancer of the Breast. Copenhagen, Ejnar Munksgaard, 1954.
16. Leis, H. P., Jr.: Fibrocystic Disease of the Breast. J. Med. Ass. Alabama, **32**:97, 1962.
17. Leis, H. P., Jr. and W. F. Bowers: Premalignant Lesions of the Breast. Western J. Surg. Gynec. Obstet., **72**:171, 1964.
18. Lewison, E. F. and J. G. Lyons, Jr.: Relationship Between Benign Breast Disease and Cancer. Arch. Surg., **66**:94, 1953.
19. Logie, J. W.: Mastopathia Cystica and Mammary Carcinoma. Canc. Res., **2**:394, 1942.
20. McCarthy, W. C. and E. H. Mensing: The Relationship between Chronic Mastitis and Carcinoma of the Breast. Collected Papers of the Mayo Clinic. Mellish, W. B. ed. Philadelphia, W. B. Saunders Co., 1915. p. 7.
21. McLaughlin, C. W., Jr., J. R. Schenken and J. X. Tamisiea: A Study of Precancerous Epithelial Hyperplasia and Noninvasive Papillary Carcinoma of the Breast. Ann. Surg., **153**:735, 1961.
22. Rice, C. O. and J. H. Strickler: Adenomammectomy for Benign Breast Lesions. Surg. Gynec. & Obstet., **93**:759, 1951.
23. Ryan, J. A. and C. J. Coady: Ductal Proliferation in Breast Cancer. Canad. J. Surg., **5**:12, 1962.
24. Stout, A. P.: Human Cancer. Philadelphia, Lea & Febiger, 1932.
25. Tellem, M., L. Prive and D. Meranze: Four-Quadrant Study of Breasts Removed for Carcinoma. Cancer, **15**:10, 1962.
26. Warren, S.: The Relation of "Chronic Mastitis" to Carcinoma of the Breast. Surg. Gynec. & Obstet., **71**:257, 1940.