INTERNATIONAL ACHIEVEMENT MONOGRAPH

# THE BREAST

INTERNATIONAL ACADEMY OF PATHOLOGY MONOGRAPH

# The Breast

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# The Breast

INTERNATIONAL ACADEMY OF PATHOLOGY

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# Foreword

This is the 25th monograph in the series Monographs in Pathology initiated by the International Academy of Pathology in 1959. The various chapters are based on presentations for the Long Course entitled "The Breast" given on March 2, 1983, at the time of the 72nd Annual Meeting of the United States-Canadian Division.

The monograph allows for a more extensive treatment of each subject than was possible at the time of presentation of the course and has the additional advantage of including references which can serve as a means of convenient access to the recent literature. The aim is to present, in brief form, information on breast lesions that frequently present difficult diagnostic problems.

The directors of the course have gathered an impressive faculty who are the authors of the various chapters of this monograph.

The Academy wishes to express its appreciation to Dr. Robert W. McDivitt, Dr. Harold A. Oberman, and Dr. Luciano Ozzello, to the other distinguished contributors to this monograph, and to the publisher, Williams & Wilkins, for their valuable support and cooperation.

NATHAN KAUFMAN, M.D.
*Series Editor*

# Preface

This monograph is based on manuscripts prepared in conjunction with presentations given at the 1983 I.A.P. Long Course on Breast. In most instances chapters contain additional information that was not presented at the Long Course due to limitations in time. Each chapter attempts to present a summary of current information pertaining to a specific topic that otherwise would be difficult to obtain without an extensive search of the literature. In selecting topics for presentation, the editors have assumed that readers are competent histopathologists; therefore, there is no attempt to teach the rudiments of diagnostic breast pathology or to provide an atlas of unusual lesions. This is contained in other available publications. Discussions of histopathology are, therefore, limited to difficult, and at times borderline, lesions that most frequently have proved troublesome for experienced pathologists. One will also note that considerable emphasis is placed on information derived from new investigative techniques that have greatly expanded our understanding of the relationship of morphology to the natural history of disease. We believe that this information is important and necessary for pathologists who collaborate with their clinical colleagues in the diagnosis and management of breast disease. Some of these techniques also provide ancillary methodologies aimed at improving the accuracy of both diagnoses and prognostic evaluations.

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# Contents


Foreword by *Nathan Kaufman* ..... v
Preface by *Robert W. McDivitt, Harold A. Oberman, and Luciano Ozzello* . vii
Contributors ..... ix
1. Benign Breast Lesions Confused with Carcinoma . *Harold A. Oberman* 1
2. Diagnostic Imaging of the Breast ..... *H. Stephen Gallager* 34
3. Cell Kinetic Analysis of Human Breast Carcinomas . . . *John S. Meyer* 45
4. Lobular Carcinoma *In Situ* and Intraductal Carcinoma of the Breast ..... *Paul Peter Rosen* 59
5. Benign and Malignant Proliferations of the Mammary Epithelium: Ultrastructural Observations ..... *Luciano Ozzello* 106
6. Breast Cancer Multicentricity ..... *Robert W. McDivitt* 139
7. Steroid Receptors in Breast Cancer ..... *Eugene R. DeSombre* 149
8. Pathological Parameters Useful in Predicting Prognosis for Patients with Breast Cancer ..... *Robert V. P. Hutter* 175
9. Needle Biopsy of the Breast ..... *Rosemary R. Millis* 186
Index ..... 205

Chapter 1

# Benign Breast Lesions Confused with Carcinoma

HAROLD A. OBERMAN

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While many benign or inflammatory lesions of the breast may produce a lump or a nipple discharge *clinically* indistinguishable from carcinoma, a lesser number of these conditions occasion difficulty in *microscopic* differentiation from malignant neoplasms. The most common diagnostic problem confronting the pathologist interpreting breast biopsies, as reflected by consultation requests submitted to the author, is the differentiation of intraductal epithelial hyperplasia and intraductal carcinoma. The distinctions between intraductal papilloma and noninvasive papillary carcinoma and between atypical lobular hyperplasia and lobular carcinoma *in situ* are also common diagnostic problems. These often are borderline lesions wherein the pathologist is acutely aware of the basic nature of the lesion.

A miscellaneous group of lesions remains, clearly benign, whose microscopic pattern may entrap the unwary pathologist in an improper diagnosis of carcinoma. These may be considered the antithesis of malignant neoplasms with a deceptively indolent pattern, such as tubular carcinoma, which may be mistakenly interpreted as benign. While the number of lesions which might be considered in this presentation could be lengthy, depending upon the diagnostic creativity of the pathologist, the following discussion will confine itself to those benign epithelial lesions which most commonly occasion difficulty in differentiation from malignancy as perceived in an active consultation practice.

It must be emphasized that the pathologist always must see microscopically convincing evidence of carcinoma before making that diagnosis. The finding of an unusual microscopic growth pattern, seemingly at odds with one's previous experience, should not result in a diagnosis of malignancy. As in all aspects of surgical pathology, a thin, well-stained section will often clarify a nettlesome lesion. Appreciation of the overall pattern of the lesion through use of the low power objective is essential, with the high power objective primarily serving a confirmatory function.

Clinical information, such as age of the patient, gross appearance of the lesion, and symptomatic manifestations, is as important in ensuring accurate interpretation of breast biopsies as it is in ensuring that of biopsies of other areas. For example, the rare occurrence of carcinoma of the breast in women under the age of 25 years should heighten the threshold for that diagnosis in biopsies examined from patients of that age. Similarly, one may question the need for frozen section examination of a sharply circumscribed lesion excised from the breast of a teenager, as these will most commonly be adenofibromas. Confusion of epithelial hyperplasia with carcinoma in such tumors, considering the rarity of the latter

diagnosis, suggests that final interpretation should await examination of permanent sections.

## PREMATURE THELARCHE

Breast enlargement usually commences shortly before, or at the time of, menarche. In some children breast enlargement antedates puberty by several years and commonly involves only one breast. This may result in confusion with a clinically significant lesion and may occasion needless operative intervention.[55]

The error of excising such a physiologic variant may be compounded if the pathologist is unaware of the extent of intraductal epithelial proliferation in prepubertal breast enlargement, as it may occasion the unfortunate misdiagnosis of malignancy. Accordingly, it should be appreciated that cancer of the breast is extremely rare in the first two decades of life and, especially in prepubertal children, usually presents with the relatively indolent secretory growth pattern.[39]

Figure 1.1 represents the degree of proliferative activity which may occur in premature thelarche. In this case a 5-year-old girl presented with a 2-cm mass in her left breast. The "mass" was excised, and the lesion was misdiagnosed as intraductal carcinoma. Two cell types are involved in the proliferative process, and neither a cribriform growth pattern nor significant cellular atypism is evident. This pattern is not dissimilar from that occasionally seen in gynecomastia, wherein the hyperplastic process also may cause confusion with intraductal carcinoma.

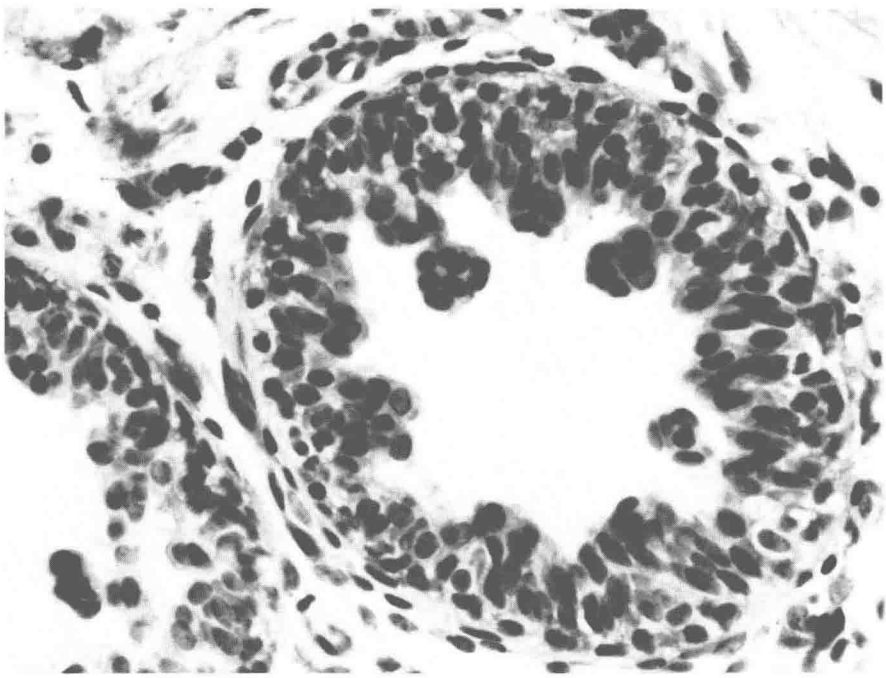

FIG. 1.1. Intraductal epithelial proliferation in breast of 5-year-old girl, mistakenly diagnosed as carcinoma. H & E, × 330.

## INFARCTS OF BREAST

Mammary infarcts may occasion both clinical and microscopic confusion with carcinoma. Most of these lesions occur in intraductal papillomas, in adenofibromas, or in pregnancy or lactation. In addition, there have been isolated reports of coagulation necrosis of breast associated with panarteritis and of hemorrhagic necrosis of breast tissue and overlying skin in patients receiving anticoagulants.[34, 47] Most mammary infarcts are solitary lesions; however, infarction of bilateral or multiple adenofibromas has been reported by Pambakian and Tighe[42] and by Majmudar and Rosales-Quintana.[33]

Most infarcts present as circumscribed nodules, or as multinodular lesions, usually measuring up to 4 cm in greatest dimension. Approximately one-third of these lesions are painful, and a greater number are tender to palpation. To cause further concern, there may be enlargement of axillary lymph nodes, as was the case in four of the six patients reported by Delarue and Redon (6).

The microscopic changes which cause the greatest interpretive difficulty in mammary infarcts present at the margin of the lesion (Fig. 1.2). The compressed and distorted ducts in this area, associated with the inflammation and organization of the infarct, may occasion difficulty in diagnosis, especially on frozen section.[46] It is important to recognize the two-cell type of epithelial investment of viable mammary ducts in this location, and to appreciate that, as in infarcts in other areas, there can be modification of the usual microscopic arrangement of such ducts. Moreover, most often in infarcts of intraductal papillomas, there can occasionally be squamous metaplasia of the ductal epithelium.

The possible confusion of these lesions with carcinoma was underscored by Delarue and Redon, who noted that four of their six patients with this lesion underwent mastectomy without the benefit of biopsy or frozen section examination. This aggressive treatment was related to the clinical impression of malignancy, occasioned by the hardness and fixation of the lesion and the enlarged axillary lymph nodes. Newman and Kahn[37]emphasized the possibility of misdiagnosis of the infarct as necrotic carcinoma. While the outlines of necrotic ducts may simulate carcinoma, sections taken from the viable periphery of such lesions will reveal their true nature. It must be recalled that occasional carcinomas manifest extensive coagulation necrosis. When a small biopsy specimen contains only necrotic tissue, it is important to obtain additional tissue in an effort to examine viable ducts at the margin of the lesion.

Infarction of breast tissue in pregnancy or lactation was first reported by Hasson and Pope in 1961,[22] and this was shortly followed by a report of 10 cases by Wilkinson and Green 3 years later.[58] The latter authors' presumption that these lesions occurred in adenomas or in fibroadenomas was challenged subsequently by Lucey,[29] who considered them to be hyperplastic lobules. It is difficult to determine whether the infarcts occurring in pregnancy or lactation represent infarcts of preexisting adenofibromas or localized coagulation necrosis in hyperplastic lobules. The so-called "lactational adenoma" likely represents confluent hyperplastic lobules. The circumscription of these lesions certainly suggests the presence of a preexisting adenofibroma; however, typical adenofibromatous tissue often cannot be discerned.

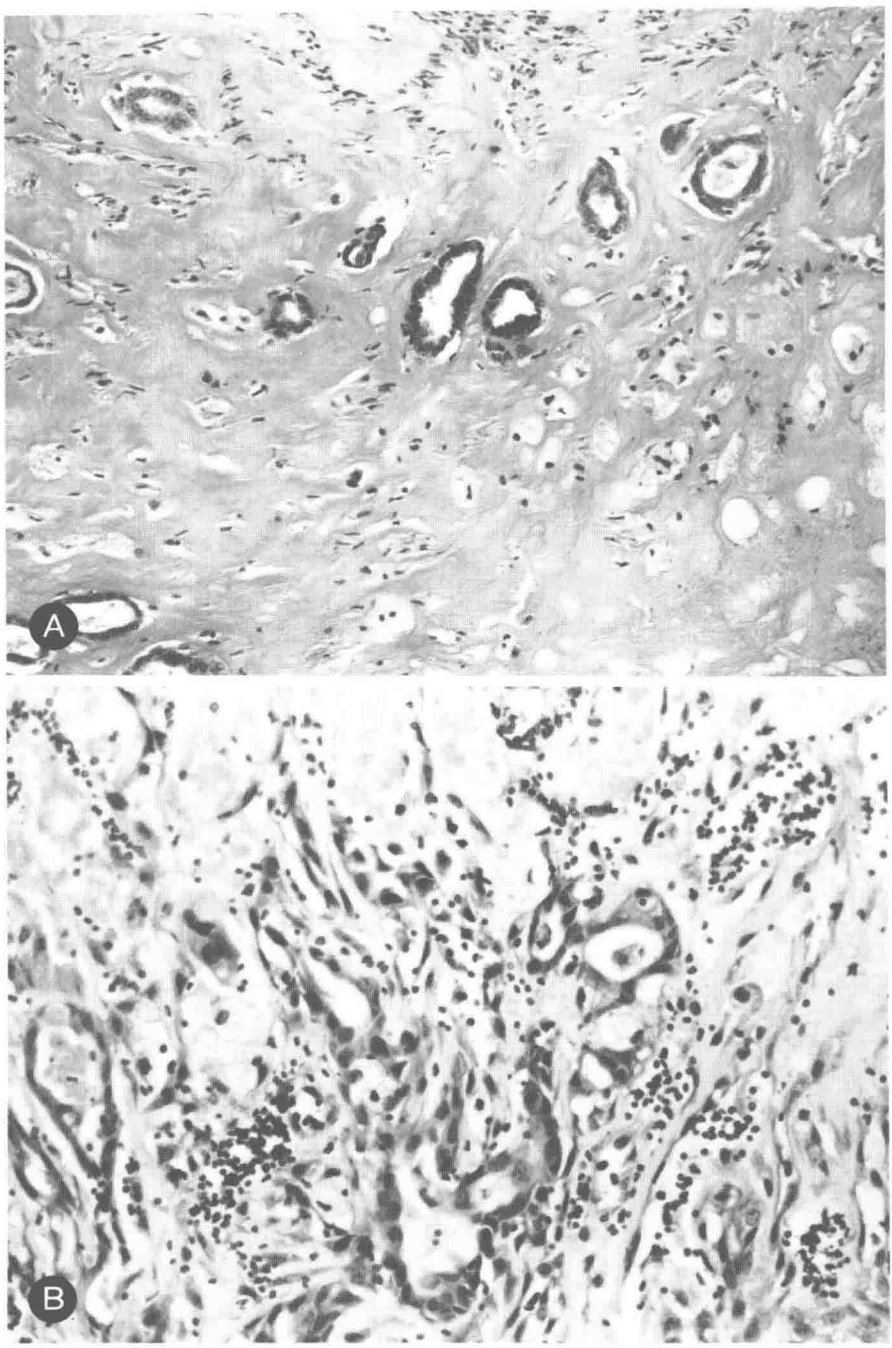


FIG. 1.2. (*A*) Haphazard arrangement of ducts at margin of infarct. H & E, × 132. (*B*) Distortion of ducts adjacent to capillary proliferation at margin of infarct. H & E, × 208.

Infarction of adenofibromas, in the absence of pregnancy, is uncommon. Newman and Kahn[37] could find only five cases in the extensive files of their institution. While some authors have been unable to demonstrate vascular occlusion in infarcts in either adenofibromas or in association with pregnancy, Newman and Kahn found thrombotic occlusion of small arteries in two of their lesions. However, they acknowledged that these small thrombi could have been a result of, rather than a cause of, the infarct. Similarly, Lucey[29] identified vascular occlusion in three of his five patients with infarcts associated with pregnancy. This supports the concept that the infarcts result from vascular occlusion rather than from lesional growth outstripping the blood supply to the area. Focal coagulation necrosis of intraductal papillomas usually is not associated with discernible vascular occlusion.

An unusual example of infarction causing clinical confusion with carcinoma was reported by Robitaille *et al.*[47] In this instance the axillary tail of the breast was infarcted, apparently related to nonspecific panarteritis. The patient presented with a large circumscribed mass, unrelated to a preexisting lesion. Vasculitis of both arteries and veins was prominent, with predominant arterial involvement consisting of lesions of different ages.

## ADENOFIBROMA

Although this lesion rarely causes histopathological confusion with carcinoma, some uncommon variants may cause concern in differential diagnosis. These include foci of adenosis and intraductal epithelial hyperplasia as well as juvenile expressions of the lesion. Infarcts in adenofibromas, which also may pose diagnostic difficulty, have been discussed above.

Manifestations of fibrocystic disease in an adenofibroma are rather common. A study done some years ago in our laboratory revealed that half of such lesions contained one or more of the elements of fibrocystic disease (41). Apocrine epithelium was seen in one-third of the tumors, intraductal epithelial hyperplasia was evident in 22%, and adenosis was seen in 7%. While these changes usually are inconspicuous, on occasion adenosis dominates the microscopic pattern of the tumor (Fig. 1.3). In such instances, especially when there is considerable compression of the ducts, the appearance may simulate invasive carcinoma. The circumscription of the lesion, most evident grossly, the presence of occasional foci of compressed and elongated ducts typical of an adenofibroma, and the maintenance of a biphasic cell population in the ducts in areas of adenosis should resolve the diagostic problem. As in adenosis elsewhere in the breast, microcalcification is common and usually is intraductal (Fig. 1.4).

Less common is the presence of intraductal epithelial hyperplasia in an adenofibroma. Because of unfamiliarity with this manifestation, it may result in confusion with carcinoma (Fig. 1.5). The criteria for this diagnosis in these tumors do not differ from those applied elsewhere in the breast. At one time an etiologic relation was postulated between such changes and oral contraceptive use.[15] However, Fechner[11] indicated that this was inappropriate and that such changes occurred independently of such medication. Intraductal carcinoma in adenofibromas most often is a manifestation of multicentric disease in the breast.

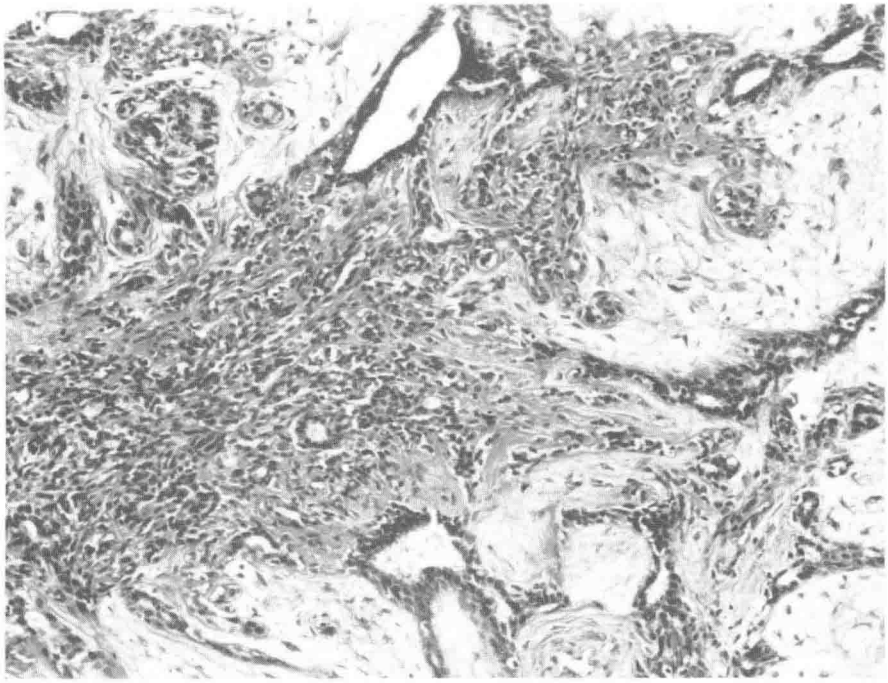

FIG. 1.3. Focal adenosis in an adenofibroma. H & E, × 133.

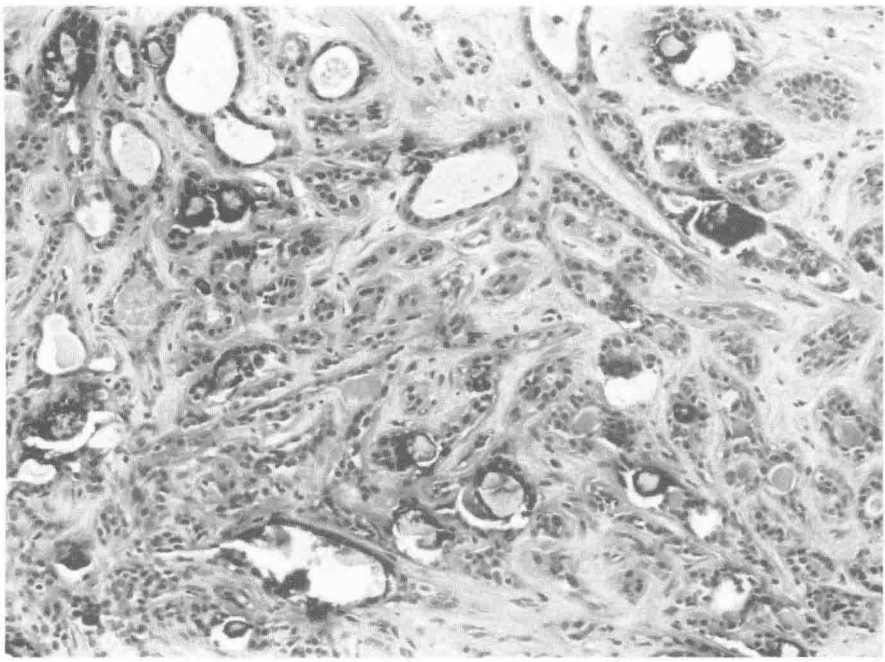

FIG. 1.4. Adenosis with microcalcification in an adenofibroma. H & E, × 133.

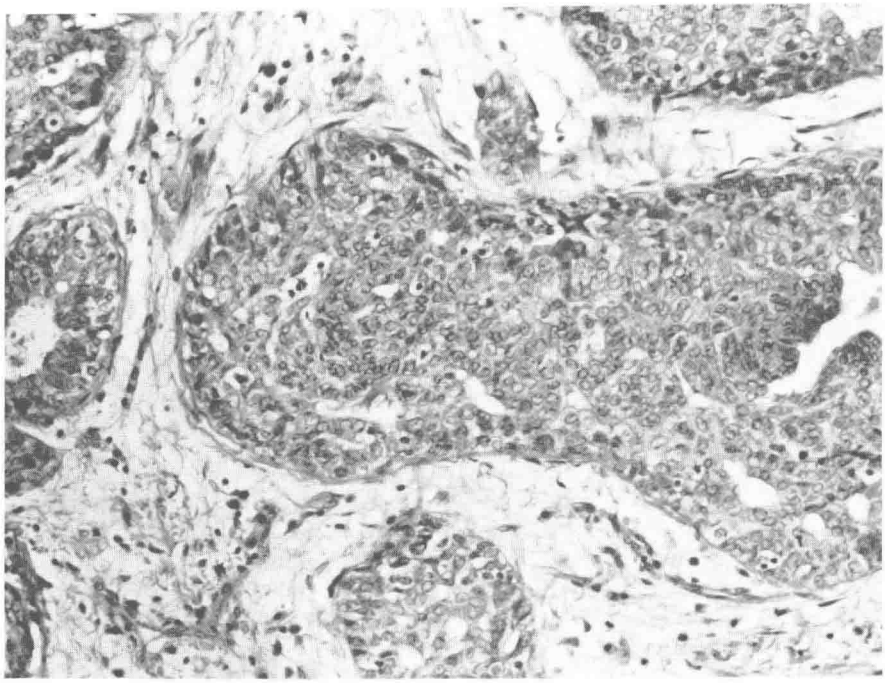

FIG. 1.5. Intraductal epithelial hyperplasia in an adenofibroma. H & E, × 165.

Since the adenofibroma is a derivative of the mammary lobule,[7] it is not surprising that lobular carcinoma *in situ* is the most common form of carcinoma to arise in these tumors.[14] Both forms of primary carcinoma in adenofibromas are rare. The author has seen three examples of intraductal carcinoma and five of lobular carcinoma *in situ*, primary in adenofibromas.

Tubular adenomas of the breast have been considered variants of adenofibromas,[24] but recently this relationship has been questioned.[23] These lesions may be distinguished from the so-called "lactational adenoma."[43] Tubular adenomas lack the usual relationship between stroma and epithelium seen in adenofibromas, with associated compression and elongation of ducts; however, the circumscription of the lesion is maintained. Whereas adenofibromas are characterized ultrastructurally by merging of the epithelial-stromal junction with the stroma of the tumor, the ultrastructural features of a tubular adenoma are characteristic of the normal breast.[23] In contrast to adenofibromas with prominent adenosis, the ducts in the tubular adenoma consistently are of uniform size and shape, regardless of the plane of section, while the former lesions manifest variation of ducts (Fig. 1.6). The uniformity of ducts, maintenance of a biphasic cell population, and the circumscription of the lesion distinguishes this variant from tubular carcinoma.

A pattern of adenofibroma often seen in adolescents may result in both clinical and microscopic diagnostic confusion with malignancy. "Juvenile" adenofibromas, in contrast to the typical adenofibroma, may occasion clinical concern

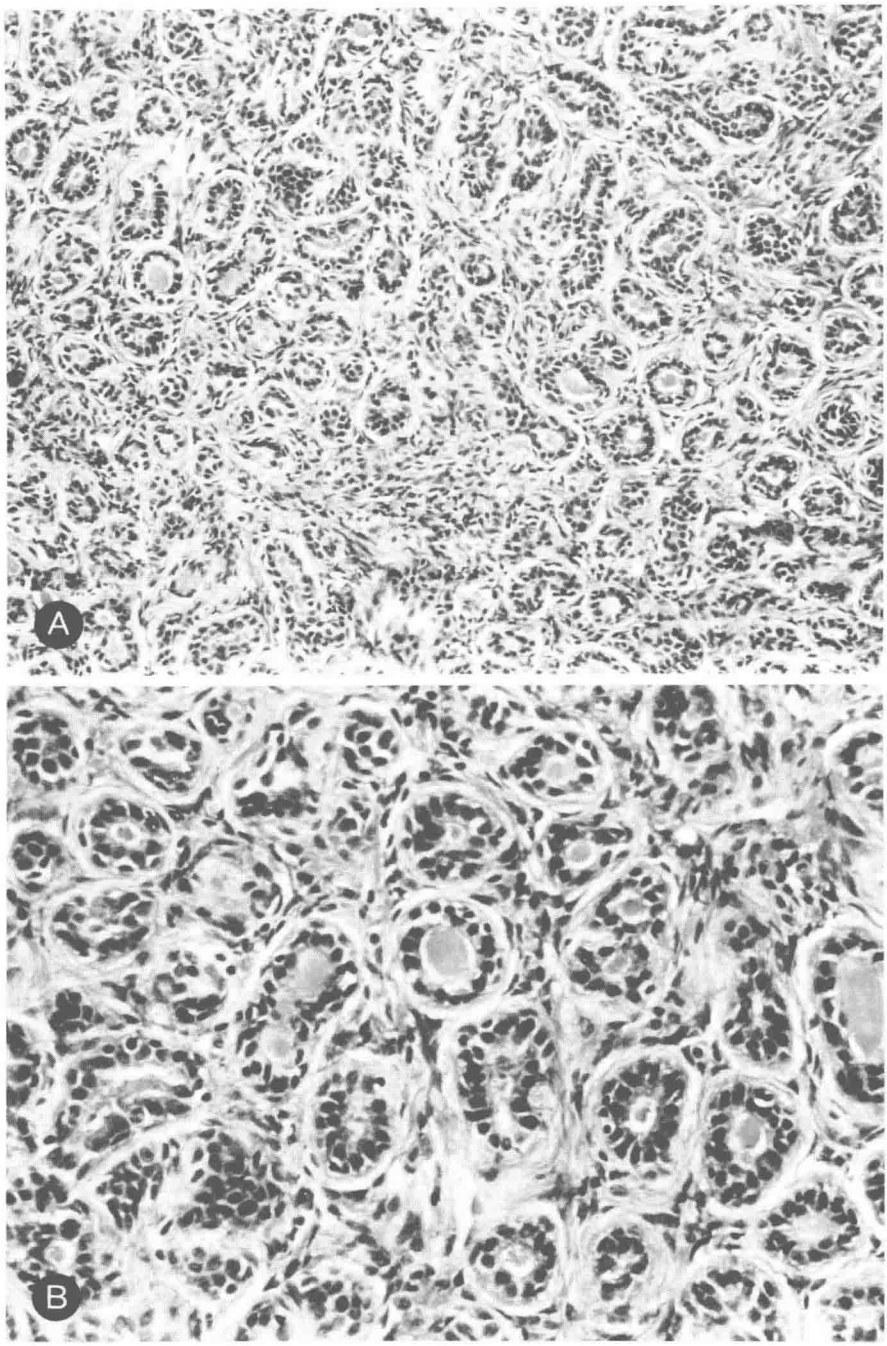


FIG. 1.6. (*A*) Uniformity of ducts in tubular adenoma. H & E, × 132. (*B*) Ducts of tubular adenoma lined by double cell layer. H & E, × 208.