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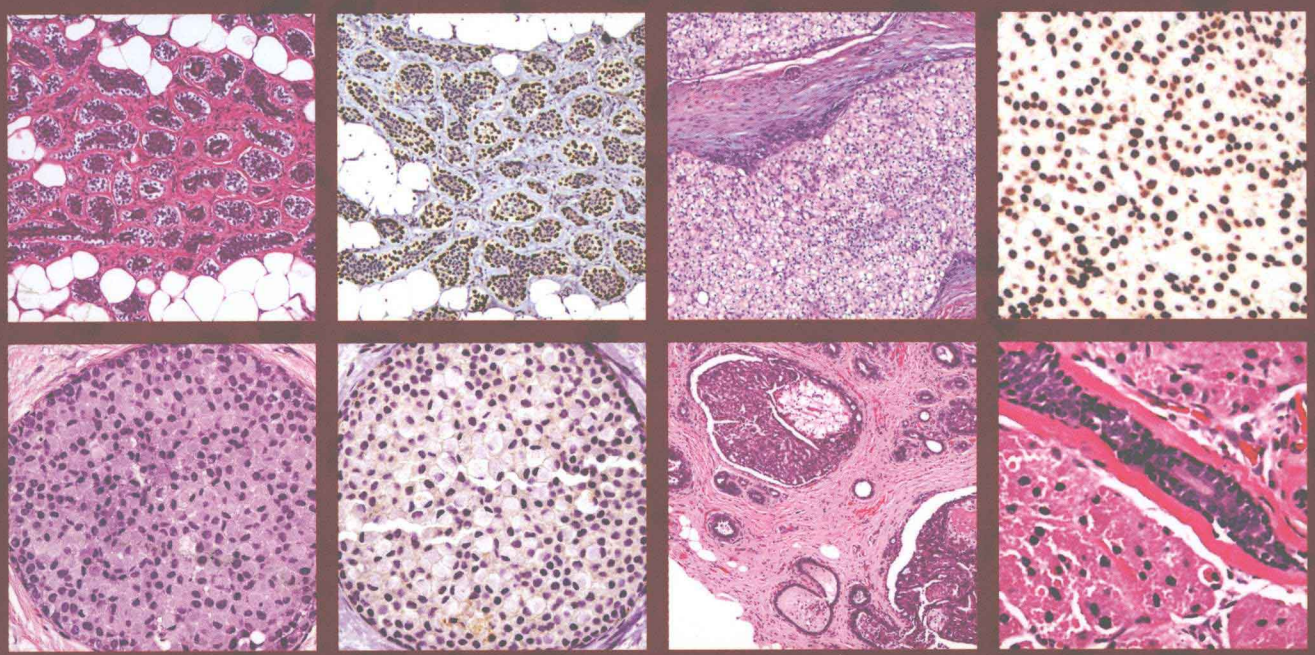
Breast Pathology

Diagnosis by Needle Core Biopsy

THIRD EDITION



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Wolters Kluwer Health | Lippincott Williams & Wilkins

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Cover images: Top Row: Myoepithelial hyperplasia in adenosis in fat; myoepithelial hyperplasia in adenosis in fat; myoepithelial cell nuclei are highlighted by the p63 immunostain; intraductal myoepithelial carcinoma; intraductal myoepithelial carcinoma with diffuse nuclear reactivity for p63. *Bottom Row:* Florid intraductal lobular carcinoma *in situ* composed of cells with cytoplasmic mucin; florid intraductal lobular carcinoma *in situ;* E-cadherin immunoreactivity is absent; granular cell tumor surrounding a duct; intraductal papillomas with histiocytes in fibrovascular stroma.

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In memory of
Flora Caspari and Paul Caspari, M.D.
Rose Rosen and Morris Rosen
and for
Mary Sue Rosen
Deborah, Madelyn, John
Jon, Karen, Jordan, Mitch
Stacy, James, Paige, Denis

In memory of
Rabia Hoda and Qamar Hoda
and for
Rana Hoda and Raza Hoda

Contents

Preface to First Edition (Updated)

Prior to the widespread implementation of breast conservation therapy, the role of the pathologist in breast cancer care was limited to making the diagnosis from tissue obtained by surgical biopsy and documenting the extent of the tumor after a mastectomy was performed. These two events typically centered around a single operative procedure in which the diagnosis made with a frozen section was followed by a mastectomy and axillary lymph node dissection. Presently, considerably more information is required to recommend breast cancer treatment that may employ more than one of the major existing therapeutic modalities: surgery, radiation, and chemotherapy. An important part of the data used for therapeutic decisions is generated by the pathologist using routine histopathologic procedures and immunohistochemistry.

The complex multifactorial description of breast pathology now considered to be standard practice has expanded the diagnostic report from a brief one- or two-line statement, such as "Infiltrating duct carcinoma, grade II; negative lymph nodes" to a catalogue of data one or more pages in length, often including many statements indicating the absence as well as the presence of features regarded as relevant to therapeutic decisions and to prognosis. A partial list of this information includes classification of the carcinoma, histologic grade, nuclear grade, tumor size, and statements about vascular invasion, the proportion of the in situ component in invasive lesions, subtype of in situ carcinoma, multifocality, and proximity of carcinoma to margins of excision. Immunohistochemistry is used to characterize distribution of estrogen and progesterone receptors, as well as other biomarkers and oncogene expression which are part of pathology reports. Proliferative activity may be estimated by the pathologist using immunohistochemistry.

Other advances have added to the complexity of the pathologist's role in breast cancer treatment. Primary among these is the widespread use of needle core biopsy procedures, especially for the diagnosis of nonpalpable mammographically detected lesions. Stereotactic needle core biopsy is an extremely valuable tool in planning breast conservation therapy because it can establish the diagnosis of nonpalpable lesions before operative surgical intervention. Needle core biopsy procedures often yield diagnostic samples, but in a significant number of cases the material obtained offers ambiguous findings that do not provide a specific diagnosis on which to base therapy. This is a limitation of the procedure and not a failure on the part of the pathologist or radiologist. When this situation arises, it is necessary for physicians caring for the patient to consider the entire clinical situation. This process of reflection is often referred to as "clinical correlation."

Many mammographically detected nonpalpable lesions present the pathologist with challenging diagnostic problems when excised intact and viewed in context with surrounding tissues. The appearance of such lesions in the incomplete and often disrupted form of needle core biopsy samples can substantially increase the degree of difficulty. The major differential diagnostic problems encountered in these specimens include:

- reactive changes vs. recurrent carcinoma after lumpectomy
- benign sclerosing lesions (radial scar) vs. infiltrating carcinoma
- papilloma vs. papillary carcinoma
- fibroadenoma vs. cystosarcoma
- atypical duct hyperplasia vs. intraductal carcinoma (DCIS)
- DCIS vs. DCIS with (micro)invasion
- spindle cell tumors (metaplastic carcinoma vs. sarcoma)
- vascular lesions (angioma vs. angiosarcoma)

Although self-evident, it is important to understand that the diagnosis made with a needle core biopsy specimen can only be based on the samples available to the pathologist and that these samples are not always representative of all of the pathologic findings in a given case. Consequently, carcinoma may be found in up to 50% of surgical biopsies after a needle core biopsy diagnosis of atypical hyperplasia, and microinvasion may be present in about 20% of surgical excisions after a needle core diagnosis of intraductal carcinoma. Three principles offer guidance in the use of the needle core biopsy procedure for the diagnosis and treatment of breast lesions:

- Anything can turn up.
- What you see is what you have and it may not be all there is.
- What you have may be all there is.

The emergence of the needle core biopsy procedure as a major diagnostic tool epitomizes the growing complexity of the interaction of radiologists, surgeons, and pathologists in the diagnosis and management of mammary diseases, especially in the era of breast conservation therapy. Specialization

in medicine has created circumstances in which the specialist physician is increasingly dependent on the assistance of colleagues who have acquired complementary expertise. This evolving situation has contributed to the team approach to disease management reflected in this volume. The intentional limited scope of this presentation, which focuses on diagnosis, does not permit inclusion of contributions from other important members of the team, including surgeons, radiotherapists, and medical oncologists who depend on these diagnoses to implement therapy.

Paul Peter Rosen, M.D.

Preface to Third Edition

This third edition of *Breast Pathology Diagnosis by Needle Core Biopsy* builds upon the two preceding volumes. A substantial number of images have been added, and a few images have been replaced. New and updated information is provided on laboratory procedures for processing needle core biopsy samples, the use of immunohistochemistry and molecular studies in the diagnosis of breast lesions, and differential diagnosis. The advantages and limitations of needle core biopsy sampling are emphasized throughout the text. New topics include basal-like and triple negative carcinoma.

As new information, references, and illustrations have been added, it has become necessary to omit selected references and text that appeared in the second edition to limit the book to a manageable size. As a consequence, we are no longer able to include chapters on the clinical aspects of imaging and needle core biopsy techniques that appeared in prior editions.

This edition has been thoroughly reviewed, rewritten, and subjected to rigorous scrutiny by the publisher's excellent staff at various stages in the production process. The choice of illustrations and references, the selection of data cited, and the conclusions expressed reflect the authors' experience and opinions.

Paul Peter Rosen, M.D.

Acknowledgments

The potential for the team approach to cancer treatment is epitomized in the management of patients with mammographically detected breast lesions, the most likely candidates for the needle core biopsy procedure. This effort draws upon the skills of mammographers, pathologists, and surgeons, as well as radiation therapists and medical oncologists. We are grateful to the hundreds of pathologists, surgeons, medical oncologists, and radiologists throughout the United States and abroad who contributed cases for pathology consultation that may be illustrated in this book, and to their patients.

The new illustrations in this book were taken from cases seen in consultation submitted from other institutions or diagnosed and treated at the New York-Presbyterian Hospital. Each specimen is vitally important to the individual from whom it was obtained, and we endeavor to provide a specific diagnosis that will contribute to the clinical care of that patient. This material is also a priceless resource for research and teaching. Thousands of adult women as well as many hundreds of men and children afflicted with breast diseases who cannot be recognized individually are acknowledged for their anonymous contributions to this and prior editions of *Breast Pathology, Diagnosis by Needle Core Biopsy.*

Knowledge gained in the course of providing this clinical service contributes to providing better care to patients with breast diseases. In this sense, each patient who has had a diagnosis made in the nearly 40 years of this consultation practice has participated in the academic undertaking and contributed to improving the diagnostic skill in breast pathology of hundreds of pathologists in training, to the benefit of still more individuals.

We also wish to recognize the superb support of the publisher for this project, most notably Marian Bellus, product manager, and Johnathan Pine as senior executive editor, from the earliest discussions of the concept for this third edition to the final publication.

We are indebted to Mary Sue Rosen for her loyal commitment, editorial assistance, and close attention to detail in preparing this manuscript. She is largely responsible for the timely completion of this edition.

All new photographic images in this edition were processed digitally by Ms. Patricia Kuharic in the Medical Arts Department of the Weill Cornell Medical College. We express our deep appreciation for her high professional standards that have made an essential contribution to this volume. We acknowledge with gratitude Daniel M. Knowles, M.D., the David D. Thompson, Professor of Pathology and Chairman of Pathology and Laboratory Medicine, for his continued support in establishing and fostering the growth of the Breast Pathology Consultation Service at the New York Presbyterian Hospital.

Introduction

Noninvasive techniques have been employed to study breast lesions since the beginning of the 20th century. The usefulness of this approach in the clinical setting has been dependent on technical advances that permitted the radiologist to detect lesions that were inapparent to the patient and physician, including clinically occult carcinomas. A consequence of this advance has been the need for a close working relationship between the practitioners of several medical specialties. The result is certainly one of the important examples of "team" management that requires the cooperative efforts of medical specialists to provide effective patient care.

Two methods of nonsurgical investigation of the breast were studied in the 1920s and early 1930s, namely, transillumination and radiography. As Cutler (1) reported, the idea for transillumination as a means of diagnosis "was first developed among the members of the laboratory staff of Memorial Hospital during the routine examination of breast specimens." Cutler also stated that "at the suggestion of Dr. Ewing, . . . Adair attempted to transilluminate breasts but encountered technical difficulties, chiefly due to the excessive heat developed by the transilluminating lamp." Although Cutler improved upon the light source, it is clear that transillumination offered little as a method of diagnosis except possibly as a way to distinguish between cystic and solid lesions. With widespread acceptance of needle aspiration of cysts, transillumination was abandoned and has now been replaced by ultrasonography.

The earliest radiologic studies of the breast reported in the United States in the 1930s by Fray and Warren, by Seabold, and by Lockwood were contemporaneous with similar investigations in Europe (2–7). When first employed clinically, it was apparent that roentgenography might prove helpful in the diagnosis of so-called early breast carcinoma. The definition of "early" has changed appreciably since this concept was introduced. This change is exemplified in a 1932 report by Fray and Warren (2) that described a 54-year-old woman who, on clinical examination, was thought to have chronic cystic mastitis. Roentgenologic examination revealed "a small area of dense tissue with irregular margins . . . in the left breast." The lesion proved on biopsy to be a carcinoma "the size of a walnut." It was concluded by the authors that the early status (of the tumor) was reflected not only by its small size but in the absence of macroscopic involvement of pectoral muscles. Today, the case described by Fray and Warren would be considered operable and potentially curable but not "early." Within a relatively short period, the term early has come to be used for lesions of microscopic dimensions, often detectable only by imaging techniques that include mammography, ultrasonography, and magnetic resonance imaging (MRI).

The initial mammography studies were met with skepticism. In 1931, Seabold (5) described the mammographic findings in a series of cases presented to the Philadelphia Academy of Surgery. The summary of the discussion that followed his report included the following comment:

> Dr. J. Stewart Rodman said that any attempt to make the diagnosis more exact is certainly praiseworthy. Being a surgeon, however, he is not sure but that sometimes x-ray men have somewhat vivid imaginations.... The clinical diagnosis of carcinoma of the breast and chronic cystic mastitis is not ordinarily difficult, and therefore until we have x-ray evidence of a more positive value we had best go a little slow in accepting evidence which is contrary to clinical findings.

Gunsett and Sichel (7) stated in 1934 that their x-ray images might be useful in some cases, but that radiologic distinctions between benign and malignant lesions were not precise enough to form a basis for surgical treatment. They concluded that mammography would not replace biopsy as a diagnostic procedure. The warning offered in these comments is applicable today. The clinician faced with a palpable abnormality in the breast should not depend only on mammography to decide whether biopsy is required. On the other hand, advances in clinical mammography and the development of stereotactic biopsy instruments have made it possible to detect and perform biopsies on nonpalpable lesions found by "x-ray men" who "have vivid imaginations" (5).

The need to relate radiologic findings to the histopathologic examination of breast tissue has been appreciated since the earliest x-ray images of the breast were obtained. In 1913 Albert Salomon (8), a surgeon at the University of Berlin, described a method for obtaining roentgenograms of serial sections of surgical breast specimens in order to correlate histologic observations with the specimen x-rays. The histologic appearance of calcification within a mammary carcinoma was described in his paper. Salomon may be credited with the first reported example of breast specimen radiography, and he deserves recognition for investigations that anticipated later developments in mammography and specimen radiography.

Detailed pathologic–radiologic correlations were carried out in the late 1920s by Dominguez (9–11) in Montevideo,

Uruguay. Dominguez was especially interested in studying the properties of calcifications in breast lesions. In addition to specimen radiography, he undertook biochemical analyses of the calcium content of breast tissue. Conway (12) described the clinical radiologic appearance of calcification in breast cysts and sarcomatous tumors, but failed to appreciate the potential usefulness of calcification as an x-ray marker for carcinoma. Lockwood (3) stressed the importance of correlating pathologic and radiologic findings, but did not obtain x-rays of specimens, and there was no mention of mammary calcification as an indicator of carcinoma in his report. Warren (6) described two cases thought roentgenologically to be carcinoma but reported to be benign on pathologic examination that "could not be studied because the specimens were thrown out before films could be made to locate the supposed small area of malignancy seen at the original examination."

The observations of Salomon, and later Dominguez, that calcium deposits in mammary carcinoma could be visualized radiologically remained largely unappreciated for nearly two decades. They were again brought to attention by Leborgne (13,14) in Montevideo who developed a technique for soft tissue roentgenography that made it possibly to identify small tumors and calcifications in clinical mammograms. He noted that "the roentgenographic study of the operative specimen also permitted the localization of the tiny calcifications for histopathologic study, and thus aided in finding a small cancer that would otherwise have been overlooked." As had Gershon-Cohen (15) some years earlier, Leborgne anticipated the role of mammography for detecting preclinical cancer:

> We firmly believe that the recognition and demonstration of this roentgenographic sign constitutes one of the easily observed aspects in which mammary cancer is presented, especially in its ductal form . . . and (is) therefore susceptible of detection in prophylactic examinations of women who do not yet present clinical tumor symptomology. With a systematic prophylactic roentgenographic examination of all women with antecedents of cancer in their family, we enter a new stage in the fight against mammary cancer.

The origin of modern needle core biopsy sampling of the breast to obtain a tissue specimen for histologic diagnosis is entwined with the history of needle aspiration biopsy and parallels the development of clinical mammography. Needles have been used to obtain samples for diagnosis from various anatomic sites since the middle of the 19th century (16). Needle aspiration sampling of the lung (17,18) and lymph nodes (19–21) was described by 1914. Many of the early biopsy attempts involved aspirating cells with a needle attached to a syringe. The aspirated blood and cellular material were expressed onto a slide and spread thinly to create a cytologic preparation.

The application of the needle aspiration biopsy technique to the diagnosis of neoplastic conditions attracted attention early in the 20th century. In 1921, Guthrie (22) reported that needle aspiration could be employed to evaluate the causes of lymph node enlargement. A method for aspirating cells from lymph nodes and the preparation of stained slides from this material was described in detail by Forkner (23) who also reported his experience using these samples for the diagnosis of cancer, including three women with adenocarcinoma in axillary lymph nodes (24).

The first concerted effort to employ the needle aspiration technique to the diagnosis of cancer was undertaken at Memorial Hospital in New York. In 1922, E.B. Ellis (25), a technician working under Dr. James Ewing, described cancer cells in cell block specimens of pleural fluid. Ellis concluded that "the diagnosis of cancer from direct smears is hazardous, but when one has made thin paraffin sections of suspected material and their evidence is fortified by some confirmatory clinical data, positive diagnosis may often be obtained." Four years later, Hayes Martin, a surgeon at Memorial Hospital, Fred Stewart, then the junior associate of Dr. Ewing, and Ellis began to use the aspiration biopsy technique in patients with head and neck cancer (26). In succeeding publications, they documented the applicability of the aspiration biopsy technique to a variety of tumors and defined the role of this procedure in the clinical management of cancer patients (27,28).

The Memorial Hospital technique proved to be the forerunner of what are now two largely separate methods of diagnosis: fine-needle aspiration (FNA) and needle core biopsy.

The specimens obtained by Martin and his clinical colleagues included disaggregated cells for cytologic examination, equivalent to FNA today, and fragments of tissue that they described as the clot, a counterpart of the modern needle core biopsy specimen. Ewing, Stewart, and their colleagues were not prepared to rely entirely on cytologic smears as evidenced by the importance they attached to the "clot," described in following commentary by Godwin (29):

> After the material is obtained in the syringe, the negative pressure is released to obviate splattering of the aspirate in the syringe. With the rake, the material is placed on several slides and gently smeared by approximating two slides and pulling them apart. The remaining material is placed on a small piece of blotting paper or fibrin foam and put in formalin for later paraffin section. This is designated as the clot.

The clot was "helpful in many instances where the smear is not diagnostic and in making a more definitive diagnosis as to the type of tumor" (29).

The system of aspirating tumors for diagnosis implemented at Memorial Hospital in the 1920s and 1930s evolved as a result of experience gained by the participants in this effort. In a later review, Godwin (30) observed:

> The interpretation of aspirates, as with other pathological material, is certainly not without pitfalls. It requires experience. It is necessary that a sufficient number of cases be available for both clinician and pathologist to maintain their efficiency. The pathologist must know the clinical setting, the normal cells of the region, and the nature of lesions to be anticipated in the area.

Technologic developments in imaging have played a major role in advancing the use of needles to obtain tissue samples from lesions in superficial and visceral locations. The impetus for improving needle biopsy techniques for breast lesions began with the increasing utilization of mammography in the 1960s and 1970s. The mammographic detection of nonpalpable lesions presented a diagnostic challenge to the radiologist, surgeon, and pathologist and led to the development of methods to localize nonpalpable lesions so that they could be found and excised by surgeons and sampled in the pathology laboratory. Various localizing procedures were introduced, employing needles, wires, dyes, and other markers placed in or near the lesion under mammographic or ultrasound guidance. After localization by the radiologist, the surgeon was guided by the marker. Radiographic examination of the specimen (specimen radiography) has been employed to confirm excision of a nonpalpable abnormality and to help the pathologist pinpoint the lesion for histologic examination (31–33). Specimen radiography has been particularly useful for lesions containing calcifications.

Under optimal conditions where a surgical biopsy was recommended for mammographic abnormalities with calcifications that were considered to be suspicious for carcinoma, 25% to 30% of the excised lesions proved to be carcinoma (32,33). Thus, for each patient with a biopsy sample that revealed carcinoma, three underwent surgical excision of a benign lesion. The surgical management of nonpalpable breast lesions without calcifications was more difficult because specimen radiography was not very reliable for confirming the adequacy of excision. The availability of the modern needle core biopsy procedure to sample nonpalpable mammographically detected lesions made it possible to avoid surgical biopsy in a substantial number of women. Friese et al. (34) analyzed Surveillance, Epidemiology, and End Results (SEER)-Medicare data for 45,542 patients with intraductal and invasive stage I–II breast carcinoma diagnosed between 1991 and 1999. The frequency of needle core biopsy as the first procedure increased from approximately 20% in 1991 to 30.9% in 1999 ($p < 0001$), and there was a concomitant decrease in initial surgical biopsy procedures. Women who had a needle core biopsy procedure initially tended to have fewer surgical procedures overall than those whose first biopsy specimen was obtained surgically.

The introduction of stereotaxic devices in the 1970s resulted in improved needle localization and made it possible to obtain needle biopsy samples from nonpalpable lesions more efficiently (35,36). One of the first papers described a "stereotaxic instrument" that facilitated "percutaneous needle biopsy of the breast for microscopic diagnosis" (37). The authors reported that "the sampling site can be located at a precision of ± 1 mm. The instrument can also be used for positioning of metal and dye indicators for guiding surgery and for post-operative identification of excised tumors." Linkage of this computer-guided localization system with the automated biopsy gun introduced in the 1980s (38) led to the development of modern stereotaxic core biopsy instruments (39). Ultrasound-guided core biopsy has proven to be particularly effective for nonpalpable lesions without calcifications. Stereotaxic MRI and ultrasound-guided core biopsy procedures are now widely used for the diagnosis of breast diseases. These technologies provide efficient methods for sampling small areas rapidly, with less morbidity and expense than surgical excision (40–42). Multifocal lesions are also accessible with this approach (43).

Needle core biopsy procedures provide the pathologist with tissue specimens that are processed to produce histologic sections. While satisfying the preference of surgical pathologists for a tissue sample rather than a cytology specimen, needle core biopsy samples create new diagnostic problems and challenges. To some extent, these difficulties arise from the partial view of a lesion in the core biopsy specimen. This problem can be compounded by the heterogeneous nature of some tumors such as papillary and fibroepithelial lesions as well as carcinomas (44). The context of surrounding tissue afforded by sections of surgical biopsy specimens, important in some instances, is largely lacking in needle core biopsy samples. Nonpalpable lesions are frequently small abnormalities that can be difficult to interpret even in a complete excisional biopsy specimen, and they should not be submitted for frozen section examination except in extraordinary circumstances (45).

False negative results for needle core biopsy samples are lower when specimens are obtained by using techniques that produce larger samples such as 11-gauge and vacuum-assisted instruments (46,47). Failure to sample a carcinoma that is present is more likely to occur in cases where the target is solely microcalicifications than a mass lesion (48). Consequently, intraductal carcinoma, especially the noncomedo type, is more likely to be missed than is invasive carcinoma. False-negative needle core biopsy samples can usually be appreciated prospectively because of discordance between the imaging studies for which the procedure was performed and the pathology diagnosis (49).

The accuracy of needle core biopsy sampling is so precise that imaging evidence of the target may be lost after the procedure, and in some cases the lesion itself may be entirely extirpated (50, 51). When all imaging evidence of carcinoma has been removed, up to nearly 80% of patients have residual carcinoma in a subsequent excisional biopsy. Lee et al. (52) reported that the MRI targeted lesion was completely extirpated in 30% of carcinomas diagnosed by MRI guided vacuum-assisted needle core biopsy. Nonetheless, 64% of patients whose MRI-detected lesion had been removed had residual carcinoma. Liberman et al. (53) found that the mammographic target was entirely removed in 100 of 214 (47%) carcinomas and that carcinomas remained in 79% of cases after complete removal of the imaging abnormality.

To assist the surgeon and pathologist in finding the site of a prior needle core biopsy where part or all of the lesion may have been removed, a clip may be placed in the biopsy

cavity at the conclusion of the procedure. Sometimes multiple clips are used to bracket a lesion or to mark more than one biopsy site. Clips of differing shapes are available and various types may be employed with mammographic, sonographic, or MRI-guided biopsy procedures (52,54,55). Migration of clips (56), extraction of the clip during a vacuum-assisted biopsy procedure (57), and loss of the clip during surgical excision (54) have been reported.

Relatively common diagnostic problems encountered in needle core biopsy specimens include the following: columnar cell lesions and atypical hyperplasia, radial sclerosing lesions and papillary tumors, lobular atypia, and lobular carcinoma in situ. Unusual tumors previously encountered only in surgical biopsy specimens such as pseudoangiomatous stromal hyperplasia, mucocele-like lesions, myofibroblastoma, metaplastic carcinoma, and hemangiomas are now the targets of stereotaxic needle core biopsy procedures (45,58). Today, virtually any lesion that occurs in the breast may appear on the pathologist's microscope in a needle core biopsy sample. The purpose of this book is to provide guidance in the interpretation of diagnosis of needle core specimens and the pathologic changes that occur in the breast as a result of these procedures.

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Pathology and the Origin of Specialization in Medicine

The development of modern medical specialism during the latter part of the nineteenth century and the early part of the present century . . . would hardly have taken place had not physicians accustomed themselves to the idea of distinct disease entities consisting of localized organic lesions connected with certain clinical pictures. . . . The development and application of a concept of localized pathology laid the groundwork for modern specialism by providing a number of foci of interest in the field of medicine. Each such focus of interest, that is, a disease or the diseases of an organ or region of the body, provided a nucleus around which could gather the results of clinical and pathological investigation.

On the technological side the influences represented in specialization manifest themselves in the multiplicity of technical skills, devices, and theories applied to the achievement of human aims in the field of medicine.

From *The Specialization of Medicine* by George Rosen, M.D., 1944

1 Anatomy and Physiologic Morphology

EMBRYOLOGY AND INFANTILE BREAST DEVELOPMENT

Mammary glands develop from mammary ridges or milk lines, thickenings of the epidermis that appear on the ventral surface of the 5-week fetus, extending from the axilla to the upper medial region of the thigh. In the human, much of the ridge does not grow further and disappears during fetal development. Persistence of segments of the milk line is the embryologic anlage for the development of ectopic mammary glandular tissue, which occurs most often at the extreme ends of the mammary ridge in the axilla or vulva. The development of the fetal breast is characterized by the differential expression of keratins 14, 18, and 19 and of actin in the breast ducts and lobular buds. Myoepithelial cells appear to arise from basal cells between weeks 23 and 28 of gestation (1). They contribute to the branching morphogenesis of the mammary gland by influencing the synthesis of basement membrane constitutents and growth factors (2). Endocrine and paracrine factors involved in fetal and neonatal mammary development were reviewed by Sternlicht (3).

In most girls, functional breast development does not begin until puberty. *Premature thelarche* is the unilateral or bilateral appearance of a discoid subareolar thickening before puberty. The incidence in white female infants and children up to 7 years old in the United States in 1980 was 20.8 per 100,000 (4). The nodular breast tissue formed in premature thelarche measuring 1.0 to 6.5 cm tends to regress slowly over the subsequent 6 months to 6 years (2). Excision of this tissue is inappropriate because of the resultant amastia after puberty. Premature thelarche has been associated with precocious puberty (5) but not with a predisposition to develop breast carcinoma (2).

Histologically, the breast tissue in premature thelarche resembles gynecomastia because it is characterized by epithelial hyperplasia in the duct system with a solid and micropapillary configuration. Growth and branching of the proliferating ducts results in an increased number of duct cross sections surrounded by moderately cellular stroma.

With the onset of cyclic estrogen and progesterone secretion at puberty, adolescent female breast development commences (Fig. 1.1). Growth of ducts and periductal stroma is estrogen dependent (6). Lobules are derived from solid masses of cells that form at the ends of terminal ducts. The greatest amount of breast glandular differentiation occurs during puberty, but the process may continue into the 20s and is enhanced by pregnancy (3). Most lobules in the mature breast are located in the fibrocollagenous stroma, but normal lobules may also be found in mammary adipose tissue (Fig. 1.2).

ANATOMY AND HISTOLOGY

The functional glandular and ductal elements are embedded in fibrofatty tissue that forms the bulk of the mammary gland. The relative proportions of fat and collagenous stroma vary greatly among individuals and with age. The combination of stromal and epithelial components is responsible for the radiographic appearance of breast structure in normal and pathologic states. Magnetic resonance imaging (MRI) provides a relatively precise method for discriminating between fatty and fibroglandular tissue in the breast. By comparing images obtained with mammography and MRI, Lee et al. (7) found a mean fat content of 42.5% (SD $\pm$ 30.3%) in mammograms and 66.5% (SD $\pm$ 18%) in MRI images. The ranges of fat content obtained by mammography and MRI imaging were 7.5% to 90% and 17% to 89%, respectively. The correlation coefficient for estimates of fat content obtained by both methods was 0.63, with the strongest correlation ($r = 0.81$) in postmenopausal women.

Each of the major lactiferous ducts terminates in and exits from the breast at the nipple via a secretory pore forming the lactiferous duct orifice. The squamocolumnar

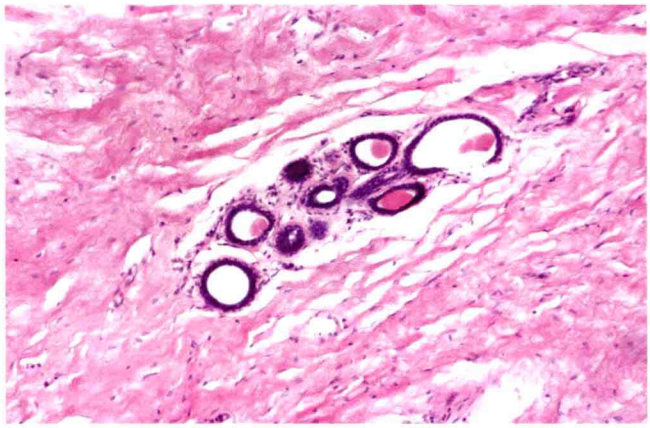

Figure 1.1 Immature breast. Breast tissue at the onset of puberty in an 11-year-old girl showing early lobular differentiation with glandular secretion and intralobular stroma.

junction, where the squamous epithelium joins the glandular duct epithelium, is normally distal to a dilated segment of the lactiferous duct, the lactiferous sinus, located just beneath the nipple surface. Extension of squamous epithelium into or below the lactiferous sinus is a pathologic condition termed *squamous metaplasia*. This may result in obstruction of the affected duct system.

Lactiferous ducts in the nipple are surrounded by circular and longitudinal arrays of smooth muscle fibers embedded in fibrocollagenous stroma. The lactiferous ducts extend distally from the nipple through a series of branches diminishing in caliber from the nipple to the terminal ductal–lobular units that are embedded in specialized, hormonally responsive stroma. Extralobular ducts are lined by cuboidal or columnar epithelium that is supported by myoepithelial cells, a basement membrane, and surrounding elastic fibers. In the nonlactating breast, the major ducts cut in cross section have contours marked by numerous folds or indentations that create a foliate or serrate border. The epithelium in the baylike pouches of the duct lumen can give rise to ductular branches. Fully formed lobules can originate directly from these pouches in lactiferous ducts in the nipple and in more distal segments of the mammary duct system (8).

The majority of the cells that form the duct epithelium are columnar or cuboidal cells lining the lumen. Their cytoplasm is endowed with abundant organelles involved in secretion. Myoepithelial cells lie between the epithelial layer and the basal lamina. The cytoplasm of the myoepithelial cells, distributed in a network of slender processes that invest the overlying epithelial cells, is rich in myofibrils. The histologic appearance and immunoreactivity of myoepithelial cells is variable, especially in pathologic conditions, and depends on the degree to which the myoid or epithelial phenotype is accentuated in a particular situation. Myoepithelial cells display nuclear reactivity for p63 that is the most useful marker for detecting these cells in normal and lesional tissue. However, epithelioid myoepithelial cells can have absent or reduced p63 reactivity.

The normal periductal stroma contains fibroblasts, elastic fibers, a sparse scattering of lymphocytes, plasma cells, mast cells, and histiocytes. Ochrocytes are periductal histiocytes with a cytoplasmic accumulation of lipofuscin pigment. These pigmented cells become more numerous in the postmenopausal breast and in association with inflammatory or proliferative conditions (9).

Mammary secretion originates in the lobules. These structures are composed of alveolar glands encompassed by specialized vascularized stroma. The alveoli are connected by intralobular ductules that combine to form a single terminal lobular duct that drains into the extralobular duct system. The resting lobular gland is lined by a single layer of cuboidal epithelial cells supported by loosely connected myoepithelial cells. The normal microscopic anatomy of the lobules is not constant because the structure and histologic appearance of the lobule in the mature breast are subject to changes associated with the menstrual cycle, pregnancy, lactation, exogenous hormone administration, aging, and the menopause. Furthermore, there is variation in the functional state of individual lobules regardless of physiologic circumstances, an observation

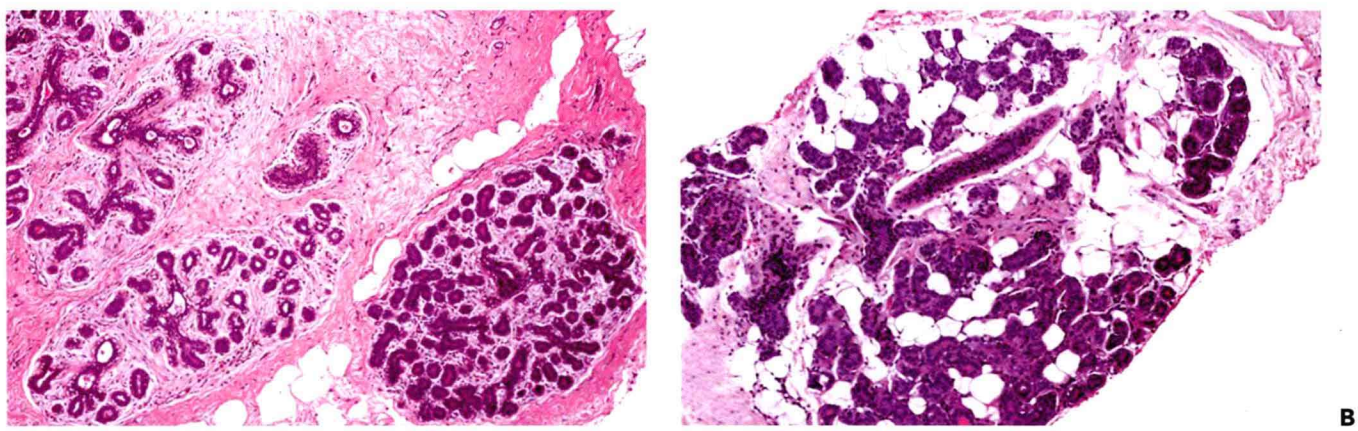

Figure 1.2 Normal lobules. A: A lobule in fibrocollagenous stroma. **B:** A lobule in mammary adipose tissue.

that suggests that individual lobules or regions of the breast have intrinsic differences in response to hormonal and other stimuli. This is reflected in the substantial variability in labeling indices, indicating different proliferative rates among lobules in a given individual (10). Immunoreactivity for hormone receptors is also variably expressed in lobules.

PHYSIOLOGIC MORPHOLOGY

Histologic cellular and structural alterations occur in the normal breast during the *menstrual cycle* (11). According to some authors, the *proliferative phase,* days 3 through 7, features the highest rate of epithelial mitoses and of apoptosis (12,13). Other investigators who defined this phase as days 0 to 5 reported that "apoptosis and mitosis were by and large absent in this phase" (11). Lobular glands at this time are lined by crowded, poorly oriented epithelial cells with little or no lumen formation and secretion. Myoepithelial cells are inconspicuous and difficult to distinguish from epithelial cells. The lobular stroma is relatively dense and hypovascular, with plump fibroblasts ringing lobular glands.

Mitoses and apoptic bodies are inconspicuous in the *follicular phase* (days 8–14). At this stage, the myoepithelial cells have a polygonal shape, clear cytoplasm, and become more apparent. Epithelial cells become columnar, with increasingly basophilic cytoplasm and basally oriented, darkly stained nuclei. An acinar lumen without secretion is evident.

During the *luteal phase,* comprising days 15 through 20, myoepithelial cells become more prominent following increased glycogen accumulation that results in cytoplasmic clearing. The glandular lumen is clearly defined by epithelial cells with basophilic cytoplasm. A small amount of secretion is present in a few glands. Edema and a mixed inflammatory cell infiltrate appear in the intralobular stroma. Mitoses and apoptotic bodies are infrequent.

The *secretory phase* corresponding to days 21 through 27 features heightened secretion with distension of glandular lumens by accumulated secretory material. The epithelium consists of columnar epithelial and myoepithelial cells with progressively clear cytoplasm. It is at this stage that mitoses and apoptotic bodies are most conspicuous with maximal intralobular edema and inflammation.

In the *menstrual phase,* comprising days 28 through 2, the stroma becomes compact with loss of intralobular edema. Lymphocytes, macrophages, and plasma cells are most conspicuous in the lobular stroma at this stage (12). Some glandular lumens remain and others appear collapsed. Mitotic activity is absent.

Improved ability to recognize menstrual cycle–related morphologic changes in the breast may become clinically useful in premenopausal women. At present, evidence suggesting that surgery performed during the luteal phase is prognostically advantageous (14,15) remains controversial (16,17). These observations have been based on retrospective reviews in which the reporting of menstrual cycle data was variously reliable. The status of breast tissue morphology can serve as a means of corroborating menstrual cycle information provided by the patients in future prospective studies. Needle core biopsy sampling might be used to obtain tissue for this purpose.

Estrogen and progesterone receptors are expressed in the nuclei of epithelial cells in the normal breast. Immunohistochemical staining reveals a higher proportion of positive nuclei in lobular than in ductal cells (18). Considerable heterogeneity exists in nuclear hormone–receptor activity among lobules with maximal expression in the follicular phase (19). No consistent menstrual cycle–related pattern has been found in the expression of estrogen and progesterone receptors in breast carcinomas that arise in premenopausal women (20,21).

Secretory changes associated with *pregnancy* occur unevenly throughout the breast (Fig. 1.3). There is progressive recruitment of lobules with successive pregnancies. Early in pregnancy, terminal ducts and lobules grow rapidly resulting in lobular enlargement with some coincidental depletion of the fibrofatty stroma (22,23). Stromal vascularity increases, accompanied by infiltration by mononuclear inflammatory cells. During the second and third trimesters, lobular growth progresses through the enlargement of cells as well as by cellular proliferation. The cytoplasm of lobular epithelial cells becomes vacuolated and secretion accumulates in lobular glands (Fig. 1.4). Lactation features markedly distended irregularly shaped lobular glands formed by cells with hyperchromatic nuclei (Fig. 1.5).

Hormonal alterations that occur during and after the *menopause* are manifested by a decrease in the cellularity and number of lobules, mainly as a result of epithelial atrophy. Coincidental with the loss of glandular epithelium, there is a tendency toward thickening of lobular basement membranes and collagenization of intralobular stroma.

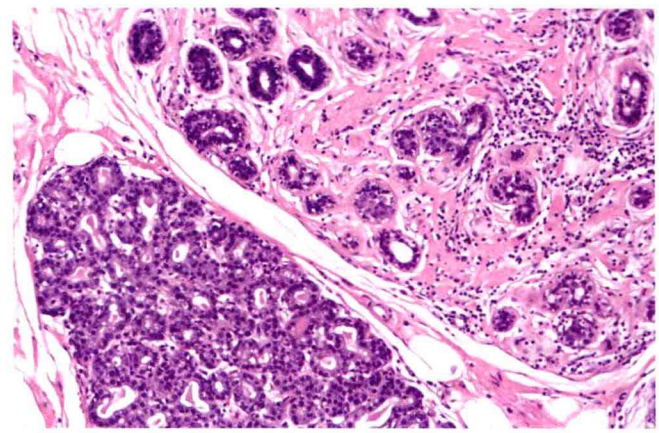

Figure 1.3 Lactational hyperplasia. This needle core biopsy specimen from a 31-year-old woman 34 weeks pregnant shows lactational hyperplasia in one lobule **(lower left)** and another unaltered lobule with fibroadenomatoid change.