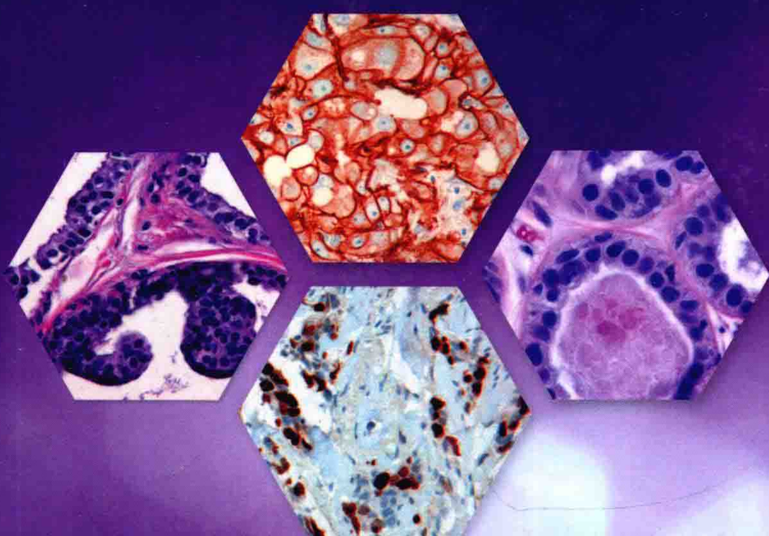
David J. Dabbs

Breast PATHOLOGY

BREAST PATHOLOGY



ELSEVIER
SAUNDERS

Breast Pathology

David J. Dabbs, MD
Professor and Chief of Pathology
Department of Pathology
Magee-Womens Hospital of UPMC
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

ELSEVIER
SAUNDERS

ELSEVIER
SAUNDERS

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

BREAST PATHOLOGY ISBN: 978-1-4377-0604-8

Library of Congress Cataloging-in-Publication Data

Dabbs, David J.
Breast pathology / David J. Dabbs.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4377-0604-8 (alk. paper)
I. Title
[DNLM: 1. Breast Neoplasms—pathology. 2. Breast—pathology. 3. Breast Diseases—pathology. WP 870]
616.99449—dc23 2011039822

Executive Content Strategist: William R. Schmitt
Senior Content Development Specialist: Kathryn DeFrancesco
Publishing Services Manager: Pat Joiner-Myers
Senior Project Manager: Joy Moore
Designer: Louis Forgione

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2

This Breast pathology textbook is dedicated to Breast pathologists across the globe who have contributed the abundance of information necessary to care for our patients.

This first edition is dedicated especially in honor of Edwin R. Fisher, MD, who passed away in March, 2008. Dr. Fisher was pathologist for the NSABP for nearly 50 years in Pittsburgh, Pennsylvania.

CONTRIBUTORS

D. Craig Allred, MD
Professor, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri
Predictive and Prognostic Marker Testing in Breast Pathology: Immunophenotypic Subclasses of Disease

Sunil Badve, MD, FRCPath
Professor, Department of Pathology and Laboratory Medicine, Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana
Sentinel Lymph Node Biopsy; Molecular-based Testing in Breast Disease for Therapeutic Decisions; Paget's Disease of the Breast

Frederick L. Baehner, MD
Assistant Professor of Clinical Pathology, Department of Pathology, University of California, San Francisco, San Francisco, California
Molecular-based Testing in Breast Disease for Therapeutic Decisions

Rohit Bhargava, MBBS
Associate Professor of Pathology, University of Pittsburgh; Co-Director of Surgical Pathology, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Predictive and Prognostic Marker Testing in Breast Pathology: Immunophenotypic Subclasses of Disease; Diagnostic Immunohistology of the Breast; Molecular Classification of Breast Carcinoma; Apocrine Carcinoma of the Breast; Pathology of Neoadjuvant Therapeutic Response of Breast Carcinoma

Werner Boecker, Dr.med.
Lecturer, Asklepius School of Medicine, Campus Hamburg Semmelweis University Budapest, Hamburg, Germany; Director Emeritus, Gerhard Domagk–Institute of Pathology, University of Müenster, Münster, North Rhine-Westphalia, Germany
Fibrocystic Change and Usual Epithelial Hyperplasia of Ductal Type

Mamatha Chivukula, MD
Associate Professor of Pathology, Department of Pathology, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Neoplasia of the Male Breast

Beth Z. Clark, MD
Assistant Professor of Pathology, Department of Pathology, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Adenosis and Microglandular Adenosis

David J. Dabbs, MD
Professor and Chief of Pathology, Department of Pathology, Magee-Womens Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Reactive and Inflammatory Conditions of the Breast; Patient Safety in Breast Pathology; Predictive and Prognostic Marker Testing in Breast Pathology: Immunophenotypic Subclasses of Disease; Diagnostic Immunohistology of the Breast; Adenosis and Microglandular Adenosis; Myoepithelial Lesions of the Breast; Fibrocystic Change and Usual Epithelial Hyperplasia of Ductal Type; Columnar Cell Alterations, Flat Epithelial Atypia, and Atypical Ductal Epithelial Hyperplasia; Lobular Neoplasia and Invasive Lobular Carcinoma; Metaplastic Breast Carcinoma; Pathology of Neoadjuvant Therapeutic Response of Breast Carcinoma; Neoplasia of the Male Breast

Ian O. Ellis, BM, BS, FRCPath
Professor of Cancer Pathology, Department of Histopathology, Nottingham City Hospital, Nottingham, United Kingdom
Ductal Carcinoma In Situ; Invasive Ductal Carcinoma of No Special Type and Histologic Grade

Nicole N. Esposito, MD
Assistant Professor, Department of Pathology and Cell Biology, University of South Florida College of Medicine; Chief of Breast and Gynecologic Pathology, James A. Haley Veterans Hospital, Tampa, Florida
Fibroepithelial Lesions; Papilloma and Papillary Lesions

Marie A. Ganott, MD
Associate Clinical Director, Breast Imaging, Department of Radiology, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Breast Imaging Modalities for Pathologists

Felipe C. Geyer, MD
Molecular Pathology Laboratory, The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London, United Kingdom; Division of Pathology, Hospital Israelita Albert Einstein, Instituto de Ensino e Pesquisa Israelita Albert Einstein, Sao Paulo, Brazil
Lobular Neoplasia and Invasive Lobular Carcinoma; Triple-Negative and Basal-like Carcinoma; Rare Breast Carcinomas: Adenoid Cystic Carcinoma, Neuroendocrine Carcinoma, Secretory Carcinoma, Carcinoma with Osteoclast-like Giant Cells, Lipid-Rich Carcinoma, and Glycogen-Rich Clear Cell Carcinoma

Christiane M. Hakim, MD
Associate Professor of Radiology, University of Pittsburgh; Assistant Chief, General Radiology, and Medical Director, Breast Imaging, Hillman Cancer Center, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Breast Imaging Modalities for Pathologists

Syed A. Hoda, MD
Professor, Weill Cornell Medical College; Attending Pathologist, New York Presbyterian Hospital–Weill Cornell Medical Center, New York, New York
Normal Breast and Developmental Disorders

Magali Lacroix-Triki, MD
Molecular Pathology Laboratory, The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London, United Kingdom; Biology and Pathology Department, Institut Claudius Regaud, Toulouse, France
Triple-Negative and Basal-like Carcinoma; Rare Breast Carcinomas: Adenoid Cystic Carcinoma, Neuroendocrine Carcinoma, Secretory Carcinoma, Carcinoma with Osteoclast-like Giant Cells, Lipid-Rich Carcinoma, and Glycogen-Rich Clear Cell Carcinoma

Shahla Masood, MD
Professor and Chair, Department of Pathology and Laboratory Medicine, University of Florida College of Medicine–Jacksonville; Medical Director and Chief of Pathology, Shands Jacksonville Breast Health Center, Jacksonville, Florida
Patient Safety in Breast Pathology

Syed K. Mohsin, MD
Pathologist, Department of Pathology, RMH Pathology Associates, Inc.; Head of Breast Pathology and Medical Director, Immunohistochemistry Laboratory, Department of Pathology, Riverside Methodist Hospital, Columbus, Ohio
Gross Examination of Breast Specimens; Radial Scar

Joseph T. Rabban, MD, MPH
Associate Professor and Assistant Director of Surgical Pathology Service, Department of Pathology, University of California, San Francisco, San Francisco, California
Mesenchymal Neoplasms of the Breast

Emad A. Rakha, MD, PhD, FRCPath
Clinical Associate Professor, University of Nottingham; Honorary Consultant Pathologist, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom
Ductal Carcinoma In Situ; Invasive Ductal Carcinoma of No Special Type and Histologic Grade

Jorge S. Reis-Filho, MD, PhD, FRCPath
Professor of Molecular Pathology, Institute of Cancer Research; Team Leader, Molecular Pathology Team, The Breakthrough Breast Cancer Research Centre, London, United Kingdom
Lobular Neoplasia and Invasive Lobular Carcinoma; Triple-Negative and Basal-like Carcinoma; Rare Breast Carcinomas: Adenoid Cystic Carcinoma, Neuroendocrine Carcinoma, Secretory Carcinoma, Carcinoma with Osteoclast-like Giant Cells, Lipid-Rich Carcinoma, and Glycogen-Rich Clear Cell Carcinoma

Christine G. Roth, MD
Assistant Professor, University of Pittsburgh School of Medicine; Assistant Professor, Division of Hematopathology, Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
Hematopoietic Tumors of the Breast

Reda S. Saad, MD, PhD, FRCPC
Associate Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto; Staff Pathologist, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada
Metastatic Tumors in the Breast

Sunati Sahoo, MD
Associate Professor of Pathology, University of Texas at Southwestern; Associate Professor, University of Texas Southwestern Medical Center, Dallas, Texas
Pathology of Neoadjuvant Therapeutic Response of Breast Carcinoma; Special Types of Breast Carcinoma: Tubular Carcinoma, Mucinous Carcinoma, Cribriform Carcinoma, Invasive Micropapillary Carcinoma, and Medullary Carcinoma

Sandra J. Shin, MD
Chief, Breast Pathology, and Associate Professor of Pathology and Laboratory Medicine, Weill Cornell Medical College; Attending Pathologist, New York Presbyterian Hospital, New York, New York
Nipple Adenoma (Florid Papillomatosis of the Nipple); Special Types of Breast Carcinoma: Tubular Carcinoma, Mucinous Carcinoma, Cribriform Carcinoma, Invasive Micropapillary Carcinoma, and Medullary Carcinoma; Mesenchymal Neoplasms of the Breast; Breast Tumors in Children and Adolescents

Jan F. Silverman, MD
Professor, Temple University School of Medicine; Professor, Drexel University College of Medicine; Chair and Director of Anatomic Pathology, Allegheny General Hospital, Pittsburgh, Pennsylvania
Metastatic Tumors in the Breast

Najwa Somani, MD, FRCPC
Assistant Professor, Department of Dermatology, and Associate Director of Dermatopathology, Indiana University School of Medicine; Staff Faculty, Indiana University Hospital, Indianapolis, Indiana
Paget's Disease of the Breast

Jules H. Sumkin, DO
Professor of Radiology, University of Pittsburgh; Chief, Radiology, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Breast Imaging Modalities for Pathologists

Steven H. Swerdlow, MD
Professor of Pathology, University of Pittsburgh School of Medicine; Director, Division of Hematopathology, University of Pittsburgh Medical Center–Presbyterian, Pittsburgh, Pennsylvania
Hematopoietic Tumors of the Breast

Victor G. Vogel, MD, MHS
Director, Cancer Institute, Geisinger Health System, Danville, Pennsylvania
Epidemiology of Breast Cancer

Amy Vogia, DO
Fellow in Breast Imaging, Department of Radiology, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania
Breast Imaging Modalities for Pathologists

Noel Weidner, MD
Senior Consulting Pathologist, Clarient Laboratories, Inc., Aliso Viejo, California
Reactive and Inflammatory Conditions of the Breast; Infections of the Breast; Myoepithelial Lesions of the Breast; Metaplastic Breast Carcinoma

Britta Weigelt, PhD
Postdoctoral Fellow, Cancer Research, UK London Research Institute, London, United Kingdom
Triple-Negative and Basal-like Carcinoma

Mark R. Wick, MD
Professor of Pathology, University of Virginia School of Medicine; Associate Director of Surgical Pathology, University of Virginia Health System, Charlottesville, Virginia
Tumors of the Mammary Skin

HOW TO USE THIS BOOK

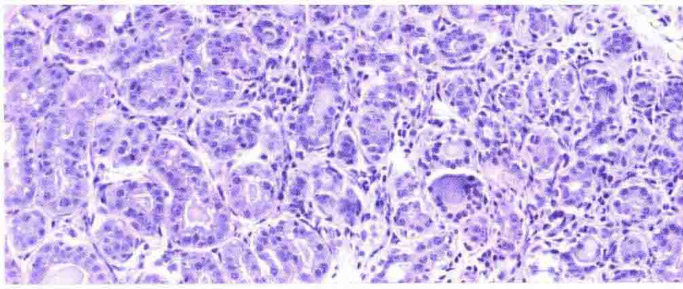
This is the first comprehensive pathology textbook on breast pathology with multiple international authors in the United States. The intent of this book is to draw on the expertise of breast pathologists in the United States and across the world. The authors are all highly distinguished breast pathologists at the forefront of their areas of particular interests in academic medicine.

As a result, it has been somewhat challenging to maintain uniformity in format in this text. In addition to the lesion-based chapter approach of this textbook, there are specialty areas that are covered intensely.

Each lesion/entity-based chapter follows a format that includes an introduction, clinical presentation, clinical imaging, gross pathology, microscopic pathology, treatment and prognosis, and differential diagnosis. The specialty-titled chapters are more didactic, and these include chapters such as normal breast and developmental disorders, epidemiology and breast cancer risk, patient safety in breast pathology, the gross examination of breast specimens, sentinel lymph node pathology, breast imaging modalities for pathologists, immunohistology of the breast, and the molecular-based tests that address current issues in the study of breast pathology. The intent of each chapter is to integrate traditional gross and microscopic findings along with imaging studies and current molecular information and paradigms for classification.

We sincerely hope that you will enjoy this book and find it to be useful in your practice. As always, I appreciate feedback and suggestions; send to dabbsihc@gmail.com.

CONTENTS



1

Normal Breast and Developmental Disorders

Syed A. Hoda

NORMAL BREAST

The breasts are the distinguishing feature of mammals and have evolved as milk-producing organs to provide appropriate nourishment to their offspring. There are other purported benefits of nursing. Physiologically, this act serves to help involute the uterus; psychologically, it helps to "bond" the mother and its offspring.[1] Other than the aforementioned functions of the breast, its intrinsic epigamic value cannot be overemphasized.

Embryology

Breast development in utero starts in the first trimester of gestation with multiple bilateral thickenings of the ectoderm on the ventral aspect of the fetus. This thickened ridge extends in a linear manner from the axilla to the groin, forming the so-called milk line (Figure 1-1). As fetal development proceeds, all except a pair of these thickenings, one on each side of the pectoral region, regress.[2–5]

In its earliest stages, the aforementioned thickening is caused by condensed mesenchymal tissue around an epithelial bud. Solid epithelial cord–like columns develop from the bud. Portions of dermis increasingly envelop the epithelial columns and develop into the connective tissue of the breast. More fibrocollagenous elements of the dermis extend into the developing breast and much later form the **suspensory ligaments of Cooper** (named after Astley Cooper, the English anatomist and surgeon, who described these structures in the 19th century). Gradually, the epithelial columns branch, canalize, and transform into ducts (and eventually into lobules). Thus, each column ultimately gives rise to a lobe of the breast. A "pit" in the epidermis forms at the convergence of the major (lactiferous) ducts, and shortly thereafter, its eversion forms the protuberant nipple (Figure 1-2).[6] Occasionally, the nipple may not evert, and this results in an inverted (or permanently retracted) nipple. This deformity may cause considerable difficulty in suckling.

In the third trimester, the developing mammary glands are responsive to maternal hormones and exhibit mild secretory changes. Upon delivery, the withdrawal of maternal hormones stimulates prolactin release, which initiates **colostrum** ("witch's milk") secretion. This occurs, to some degree, in approximately 90% of infants of both genders in the first few days after birth. Colostrum is actually composed of water, fat, and debris; it dissipates within a month or so of birth. During this time, and for a period of a few weeks thereafter, the breast is palpably enlarged. Until puberty, the breast tissue consists almost exclusively of major ducts.[7]

Gross Anatomy

The female breasts are rounded protuberances on either side of the anterior chest wall. The organ is present in rudimentary form in prepubertal girls, boys, and adult males. The bulk of female breast tissue overlies the pectoralis major muscle from the second to the sixth rib in the vertical axis and from the sternal edge to the midaxilla in the horizontal axis. Breast glandular tissue usually extends beyond these arbitrary boundaries. The

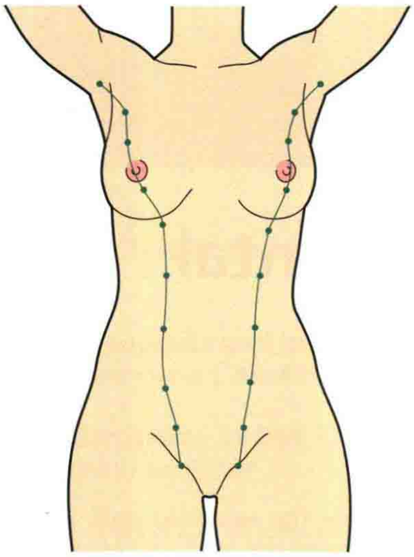


FIGURE 1-1 Schematic depiction of "the milk line." The milk line extends from the axilla to the inguinal region in the adult. Supernumerary nipples and/or breast tissue may persist anywhere along these lines.

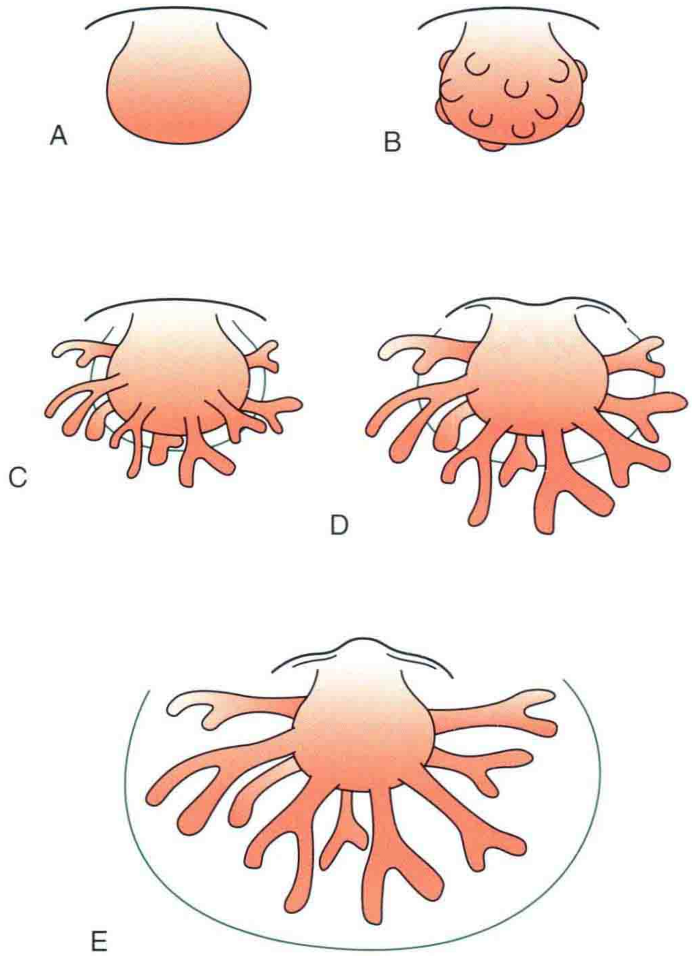


FIGURE 1-2 Embryonic development of the breast. Schematic depiction of developing mammary bud from that in a 6-week embryo to birth: epithelial primordium **(A)**, incipient duct formation **(B)**, early duct formation **(C)**, inverted nipple stage **(D)**, and elongation of ducts and eversion of nipple **(E)**. Area outlined in green depicts progressively growing connective tissue.

extension of breast tissue from the upper-outer quadrant into the axilla is eponymously referred to as the **tail of Spence** (after James Spence, a Scot surgeon of the 19th century). This "tail" can be difficult to envision on routine mammograms—and in earlier times, the patient was routinely placed in the so-called Cleopatra pose to allow such visualization.[8]

The breast is enveloped by fascial tissues. Anteriorly, there is superficial pectoral fascia. Posteriorly, there is deep pectoral fascia. These two layers of fascia blend with the cervical fascia superiorly and with that overlying the abdomen inferiorly. Fibrous bands (the aforementioned Cooper's ligaments), more numerous in the superior half of the breast, connect these two fascial layers. A "space" filled with loose connective tissue lies between the deep boundary of the breast and the fascia of underlying skeletal muscle. This retromammary space allows the breast some degree of movement over the underlying pectoral fascia. The fascia overlying the chest wall sometimes harbors breast glandular units. The glands rarely extend beyond this fascia into bands of underlying skeletal muscle. Such extension of breast glandular tissue into these deep structures is a normal anatomic feature that has clinical implications, for example, in modified radical mastectomies, which strive to remove as much of the breast glandular tissue as possible. Most mastectomies (short of the draconian radical mastectomies) are successful in removing no more than 90% of breast glandular tissue.

The **shape and size** of the breast depends not only upon genetic and racial factors but also upon age, diet, parity, and menopausal status of the individual. The breast can appear hemispherical, conical, pendulous, piriform, or thinned and flattened; however, typically, the breast is oval and hemispherical, with the long axis diagonally aligned over the chest. There is a distinct flattening of the superficial contour of the breast superior to the nipple.

The normal mature nonlactating female breast weighs approximately 200 g (±100 g).[9] The typical lactating breast may weigh more than 500 g. The average adult breast measures 12 cm in diameter and 6 cm in thickness. In a study of breast volume in 55 women, Smith and coworkers[10] found that the right breast was less voluminous: the mean for the right breast was 275 mL and that for the left breast was 290 mL. This discrepancy has been correlated to handedness. There is no correlation between breast mass and cancer risk because large breasts do not necessarily contain more glandular parenchyma.

The **nipple** being centrally located, and typically elevated from the surrounding areola, is the focal point of the skin of the breast. Its level in the thorax varies widely but, typically, overlies the fourth intercostal space in younger women. Both nipple and areola are pink, light brown, or darker (depending upon the general pigmentation of the body). These two structures are somewhat less pigmented in the nulliparous and become increasingly pigmented starting in the second month of pregnancy. The tinctorial change after pregnancy is irreversible.

Twelve to 20 minute rounded protuberances, representing prominent sebaceous gland units usually associated with a lactiferous duct, in the dermis, are present on the surface of the areola.[11] These protuberances are generally referred to as **Montgomery tubercles** (after Dr. William Montgomery, a 19th-century Irish obstetrician who described these structures, although it is possible that Morgagni, the 18th-century Italian anatomist, detailed the same structures much earlier). Montgomery's tubercles become prominent during pregnancy and lactation, reflecting the need for keeping the areola moist during feeding. The tubercles regress after menopause. Apocrine and sweat glands are also present in this area. Hair follicles are present at the edge of the areola. The presence of these glands and hair follicles may be involved in the pathogenesis of persistent subareolar abscesses.

Skin incisions for breast surgery are generally based on the knowledge of natural orientation of collagen fibers in the epidermis and dermis along the lines first described by Karl Langer, the 19th-century Austrian anatomist. Adherence to Langer's lines of skin orientation in making surgical incisions ensures minimal scarring and better cosmetic outcome.[12] These lines are based on mechanical principles rather than on any specific anatomic structures and are actually founded on the somewhat macabre premise of the direction in which the human cadaver's skin of a particular area will split if struck by a spike!

In the current TNM (tumor-node-metastasis) staging system, breast tumor of any size with direct extension to the chest wall and/or to the overlying skin with presence of nodules or ulceration is staged as T4. Invasion of the dermis by tumor does not qualify as T4.

Structure and Histology

Several collecting ducts, each of which drains a **mammary lobe,** open in the nipple. The lobes are arranged around the breast in a radial (spokelike) manner (Figure 1-3). Three-dimensional depictions of the breast lobe appear as cones—with its apex at the nipple and its base in the region of the deep fascia where most lobules reside.[13–16] Despite such depictions of mammary lobes in anatomy and pathology textbooks as discrete anatomic territories within the breast, the lobes grow intricately into one another around their edges and do not constitute distinct grossly identifiable entities. Thus, the lobes cannot be visually dissected during surgery. Notably, each duct system has a different anatomic extent: the larger ones may extend beyond a quadrant and the smaller may occupy much less than a quadrant. The lobes are independent systems; however, it is possible that a few lobes may interconnect at some level via ducts—although the evidence for this is rather dubious. Intraductal carcinoma extends in the long axis of the lobe along the duct system, utilizing the latter as a scaffold. Interlobar anastomosis, if it were to exist, could potentially allow intraductal carcinoma to spread beyond the primarily afflicted duct.

The nipple and areola are covered with **stratified squamous epithelium,** which is continuous with the surrounding skin over the breast. The opening of the collecting ducts at the nipple is typically plugged by keratinous

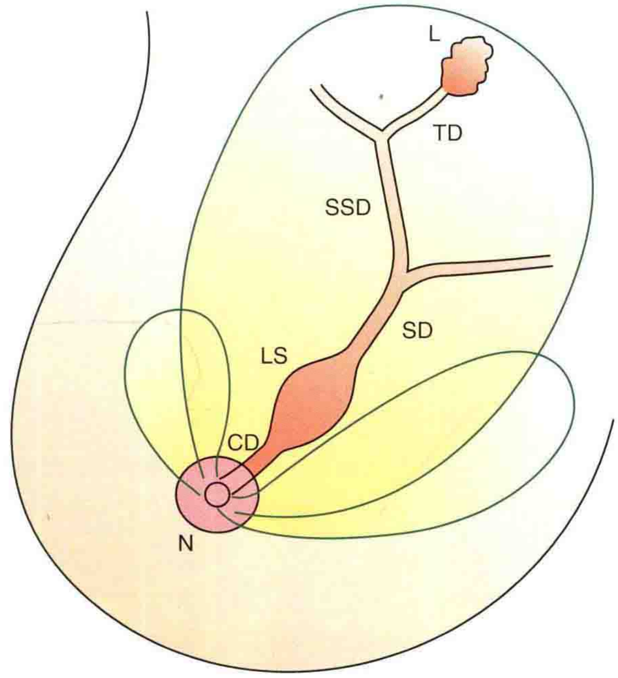


FIGURE 1-3 Sagittal section through the adult female breast. Three lobes are depicted in this diagram (all outlined in *green*). The central lobe shows its basic structure from the nipple (N). Depicted herein are collecting duct (CD), lactiferous sinus (LS), segmental duct (SD), subsegmental duct (SSD), terminal duct (TD), and lobule (L).

debris in the nonlactating breast. The squamous epithelium of the collecting ducts undergoes gradual transition to pseudostratified columnar epithelium and, finally, to cuboidal or low-columnar epithelium (Figure 1-4).

Approximately 20 **orifices of collecting ducts,** each representing a lobe of the breast, are present in the nipple. These orifices, which may be as few as 8 and as many as 24, are generally arranged as a central group and a peripheral group.[17] The deeper portion of the collecting ducts has a characteristically serrated contour for a variable distance before opening into its terminal portion. The latter portion has a relatively less convoluted and smoother profile. The lactiferous ducts in the nipple are surrounded by bundles of smooth muscle. The muscle fiber arrangement is principally circular, but some fibers are also arranged vertically, interlacing among collecting and lactiferous ducts. The circular muscle fibers cause nipple erection, readying it for suckling. By cyclic contraction, the vertically arrayed muscle bundles empty the lactiferous sinuses. There is virtually no adipose tissue immediately beneath the nipple and areola.

The portion of the **duct system** immediately below the collecting duct is the lactiferous sinus in which milk accumulates during lactation. This sinus communicates directly with segmental duct, which subdivides into subsegmental ducts, which in turn, subdivide into terminal ducts. The latter structures drain the lobule. Each lobe contains 20 to 40 lobules. The lobule is composed of groups of small glandular structures, the acini. The latter are the terminal portion of the duct system. The serially and dichotomously branching structure of the mammary gland, from the tubular-like collecting

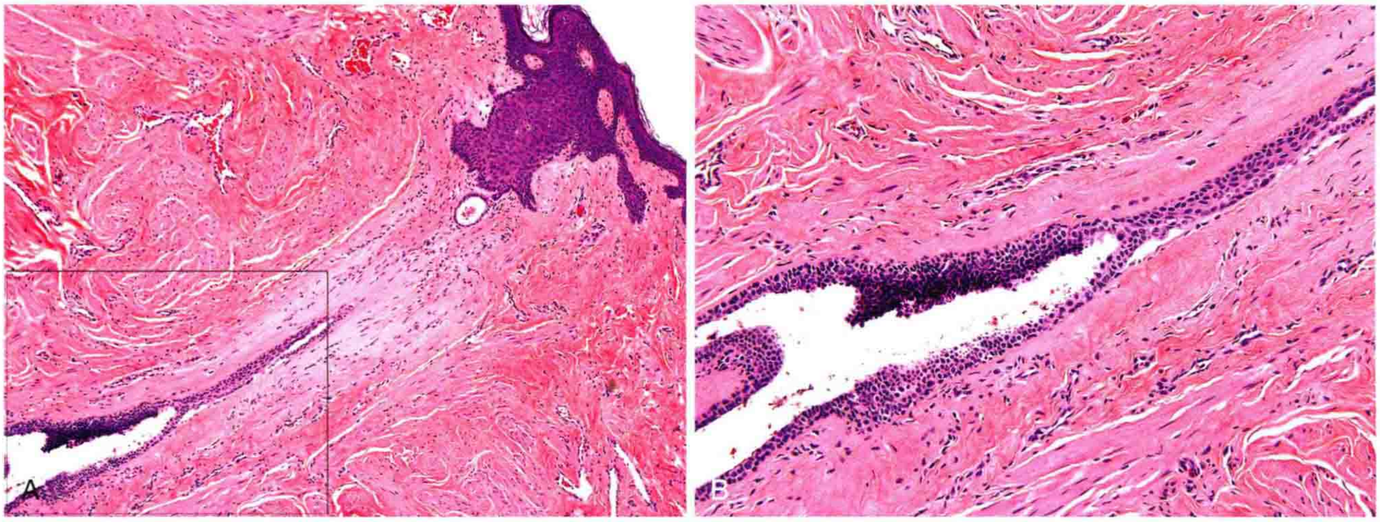


FIGURE 1-4 Vertical section through the nipple. **A,** A collecting duct is shown approaching the surface of the nipple (area in box is magnified in **B**). **B,** Squamous epithelium of the orifice undergoes gradual transition to the columnar epithelium of the collecting duct. **A** and **B,** Hematoxylin and eosin (H&E).

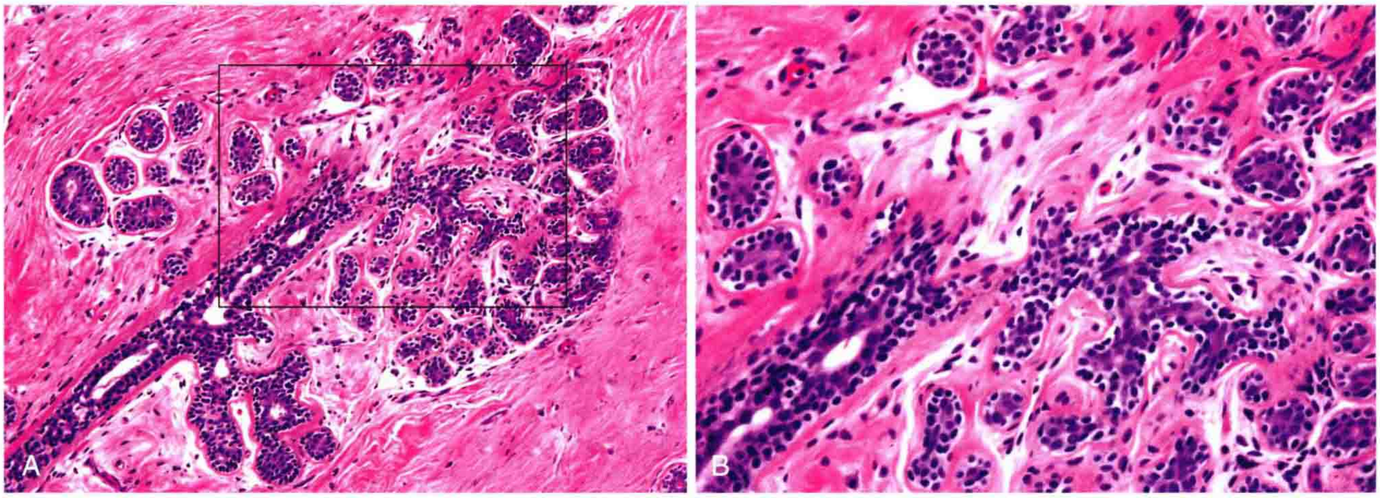


FIGURE 1-5 Terminal duct lobular unit (TDLU). **A,** The lobule is composed of multiple acini. Acini are on the right (area in box is magnified in **B**). **B,** The terminal duct on the left is seen exiting the lobule. Note inner epithelial layer (with denser cytoplasm) and outer myoepithelial layer (with clearer cytoplasm). **A** and **B,** H&E.

duct to the terminal acini, leads to its classification as a compound tubuloacinar (or tubulolobular) gland (Figure 1-5).

The **lobule** is inapparent to the naked eye on cut sections of breast tissue. However, with the aid of a magnifying lens, the lobules resemble minute drops of dew, and ducts may appear as linear streaks. The size of the "normal" lobule is extremely variable, as are the number of acini in each lobule. Each lobule consists of 10 to 100 (range 8–200) acini. The intralobular stroma consists of loose connective tissue and may also be populated by a mixed inflammatory cell infiltrate particularly in the secretory phase of the menstrual cycle. The lobule undergoes a variety of morphologic changes under various physiologic influences (Figure 1-6).

The fundamental glandular unit of the breast, and its most actively proliferating part, is the **terminal duct lobular unit** (TDLU). This unit comprises the lobule and its paired terminal duct. During pregnancy and lactation, the epithelial cells of the terminal ducts and lobules undergo secretory changes; and most disease processes of the breast arise from the TDLUs (including cysts, which may be the consequence of the "unfolding" of the terminal ducts and lobular units). Indeed, the only common lesion believed to be strictly of ductal origin may be the larger solitary intraductal papilloma (Table 1-1).

Except for the terminal portion of the collecting ducts, **low-columnar to cuboidal epithelium** lines almost the entire duct system of the breast; including the segmental ducts, subsegmental ducts, terminal ducts, and acini. This lining epithelium is supported on its basal surface by a distinct layer of myoepithelial cells. The basement membrane or basal lamina lies under the myoepithelial cells. External to the basement membrane is connective tissue.

Myoepithelial cells facilitate milk secretion via their contractile property, which is largely under the influence of oxytocin. Oxytocin receptors have been detected on the surface of myoepithelial cells,[18] and this hormone

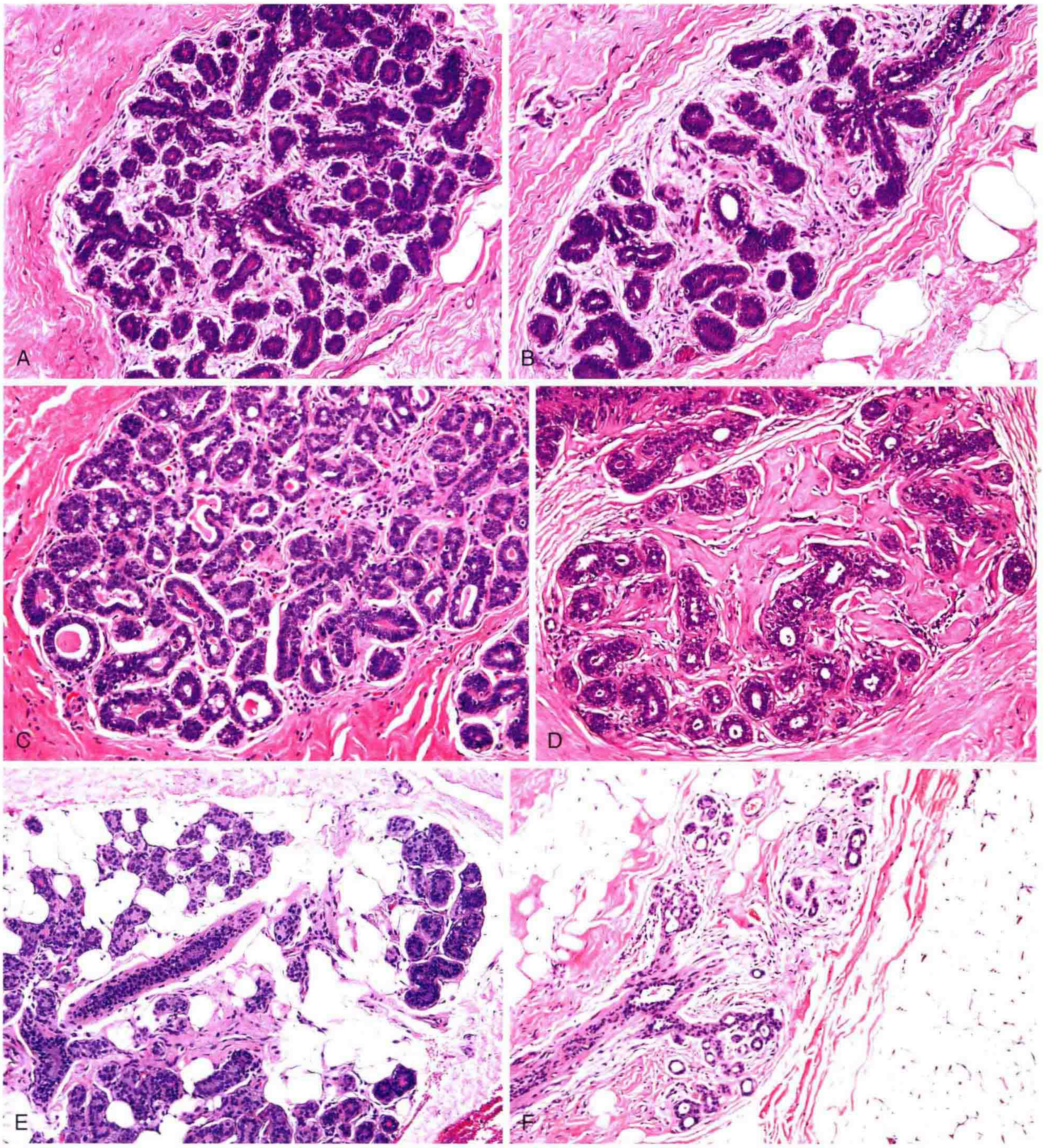


FIGURE 1-6 Mammary lobule at various physiologic stages. **A,** Lobule in an adult female breast, inactive. **B,** Lobule in early puberty; note the incipient development of the lobule. **C,** Lobule in the secretory phase of the menstrual cycle; note secretions in the glands. **D,** Lobule after menopause, with intralobular fibrosis. **E,** Lobule after menopause, with intralobular adipocytes. **F,** Lobule in the elderly; note glandular atrophy and relative prominence of myoepithelial cells. **A-F,** H&E.

is primarily responsible for the release of milk—a phenomenon called *milk let-down*.[19]

The myoepithelial cell layer is generally regarded as being spindle-shaped with usually inapparent cytoplasm. Indeed, in fine-needle aspiration cytology preparations, myoepithelial cells appear to be entirely devoid of cytoplasm (i.e., "naked"). The thin and compressed (**"bipolar"**) nuclei of these cells are oriented perpendicular to the long axis of the duct. Myoepithelial cells extend from collecting ducts to the tip of the acini and may occasionally appear prominent either de novo (Figure 1-7) or in certain physiologic (e.g., atrophy) and pathologic (postradiation, adenomyoepithelioma) situations. Myoepithelial cells are inapparent in certain lesions (e.g., in macrocysts, in which these cells get particularly stretched).

A variety of immunohistochemical stains can be used to demonstrate the presence of myoepithelium around

TABLE 1-1 Histologic Alterations in Breast Glands and Stroma during Various Phases of the Menstrual Cycle*

Proliferative Phase (Days 3–7)
Epithelial cells are small with dark, centrally located nuclei and eosinophilic cytoplasm. Myoepithelial cells are small. Glandular lumens are nondilated without secretions. Stroma is relatively dense. No epithelial mitoses are present.
Luteal Phase (Days 8–14)
Epithelial cells are larger with apical snouts. Rare epithelial mitoses are present. Glandular lumens are enlarged. Myoepithelial cells appear minimally vacuolated. Luminal secretions become evident. Stroma is edematous. Blood vessels are congested. Proliferation rate (as evidenced by Ki-67) is higher than in proliferative phase.
Secretory/Menstrual Phase (Days 15–22)
Epithelial cells have a high nuclear-to-cytoplasm ratio, with minute apical snouts. Epithelial mitoses are rare. Glandular lumens become smaller. Luminal secretions become less evident. Myoepithelial cells are highly vacuolated. Stroma is densely compact. Apoptotic figures are most numerous on day 28. Size of the lobule almost doubles from that in the early proliferative phase (from ~1 mm to nearly 2 mm).

*Histologic changes may vary widely within the breast, its quadrants, and even within lobules.

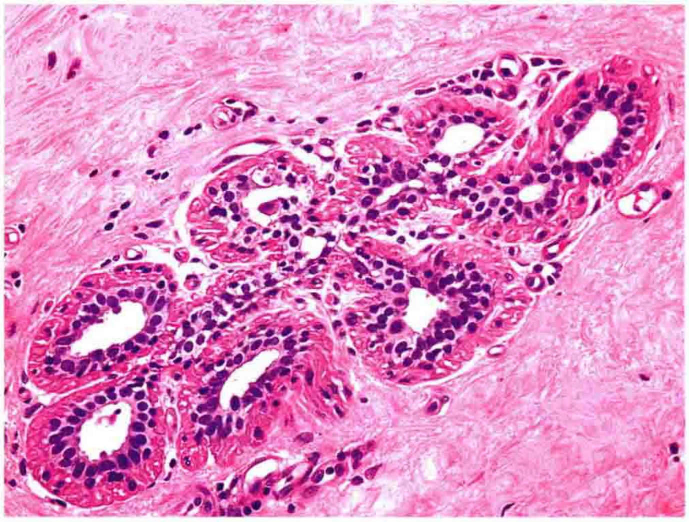


FIGURE 1-7 Prominent myoepithelial cells. The myoepithelial cells lie external to the epithelial cells and may occasionally appear prominent (myoid hyperplasia). H&E.

TABLE 1-2 Sites of Origin of Common Diseases in the Breast

From the Nipple
Paget's disease, florid papillomatosis of nipple (i.e., nipple adenoma)
From the Lactiferous Ducts
Subsclerosing duct hyperplasia, duct ectasia
From Segmental and Subsegmental Ducts
Solitary intraductal papilloma, duct ectasia
From the Terminal Duct Lobular Units
Cysts, epithelial hyperplasia, noninvasive and invasive carcinoma

ducts (Table 1-2 and Figure 1-8). The lack of myoepithelial cell layer around neoplastic glands is generally considered to be diagnostic of invasive carcinoma, barring special situations such as that encountered in microglandular adenosis[20,21] and solid-papillary carcinoma with smooth peripheral contours. Absence of myoepithelial cell layer has also been reported in some, but not all, apocrine cysts.[22] The use of double (or triple) immunolabeling with combinations of epithelial and myoepithelial immunostains is helpful in confirming early invasive carcinoma of breast (Figure 1-9).[23]

The **basement membrane**, composed of a relatively attenuated basal lamina, lies immediately outside of the myoepithelial cell layer and divides the glands from the stroma. The basement membrane can be highlighted using appropriate immunostains (e.g., laminin and collagen 4) or histochemical stains (reticulin and periodic acid–Schiff) (Figure 1-10). Stromal tissue lies beyond the basement membrane.

The mammary ducts and lobules are embedded within a variable **fibrous and fatty stroma.** The relative portions of glands and fibrous and adipose tissue vary with age and body habitus; however, stromal tissues make up the bulk of the breast in adult nonlactating and nonpregnant women. Adipose tissue is typically present in the interlobar stroma and not among lobules (at least not until atrophy ensues). The fibrous tissue assists in the mechanical coherence of the gland. The fibroblastic and myofibroblastic elements in the stroma of the breast often display a vaguely angiomatous appearance (hence, the term *pseudoangiomatous stromal hyperplasia)* (Figure 1-11). The volume-fraction of collagen-rich fibrous tissue is greater in younger adult women and accounts for the greater mammographic density therein.[24–26]

Apocrine cells are normal constituents of the glands of the breast in adult women, suggesting that this finding is a physiologic phenomenon (i.e., a normal line of metaplastic differentiation) rather than a pathologic finding.[27] The apocrine cells are typically pink and appear cuboidal or columnar and may exhibit a stubby apical snout (Figure 1-12).[28] Rarely, prominent apocrine granules may become evident—particularly at the apical portions of the cells (Figure 1-13). Cysts lined with apocrine epithelia typically bear calcium oxalate crystals, which may need polarizing microscopy to be

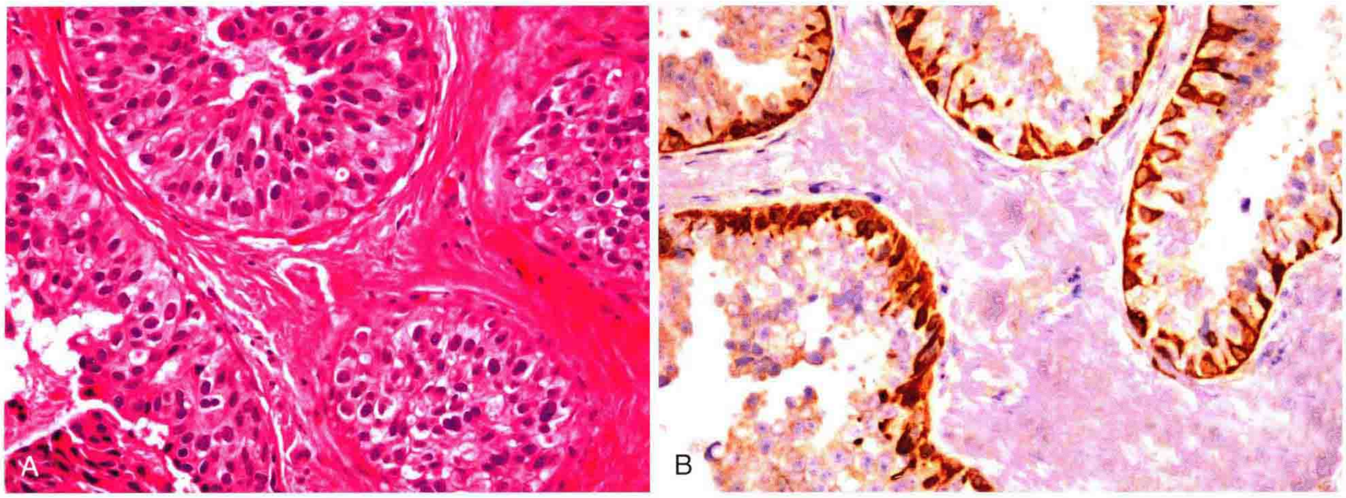


FIGURE 1-8 Myoepithelial immunostain (calponin) in ductal carcinoma in situ (DCIS). **A,** DCIS of solid and micropapillary types. H&E. **B,** Calponin immunostain demonstrates complete myoepithelial envelope around the neoplastic cells.

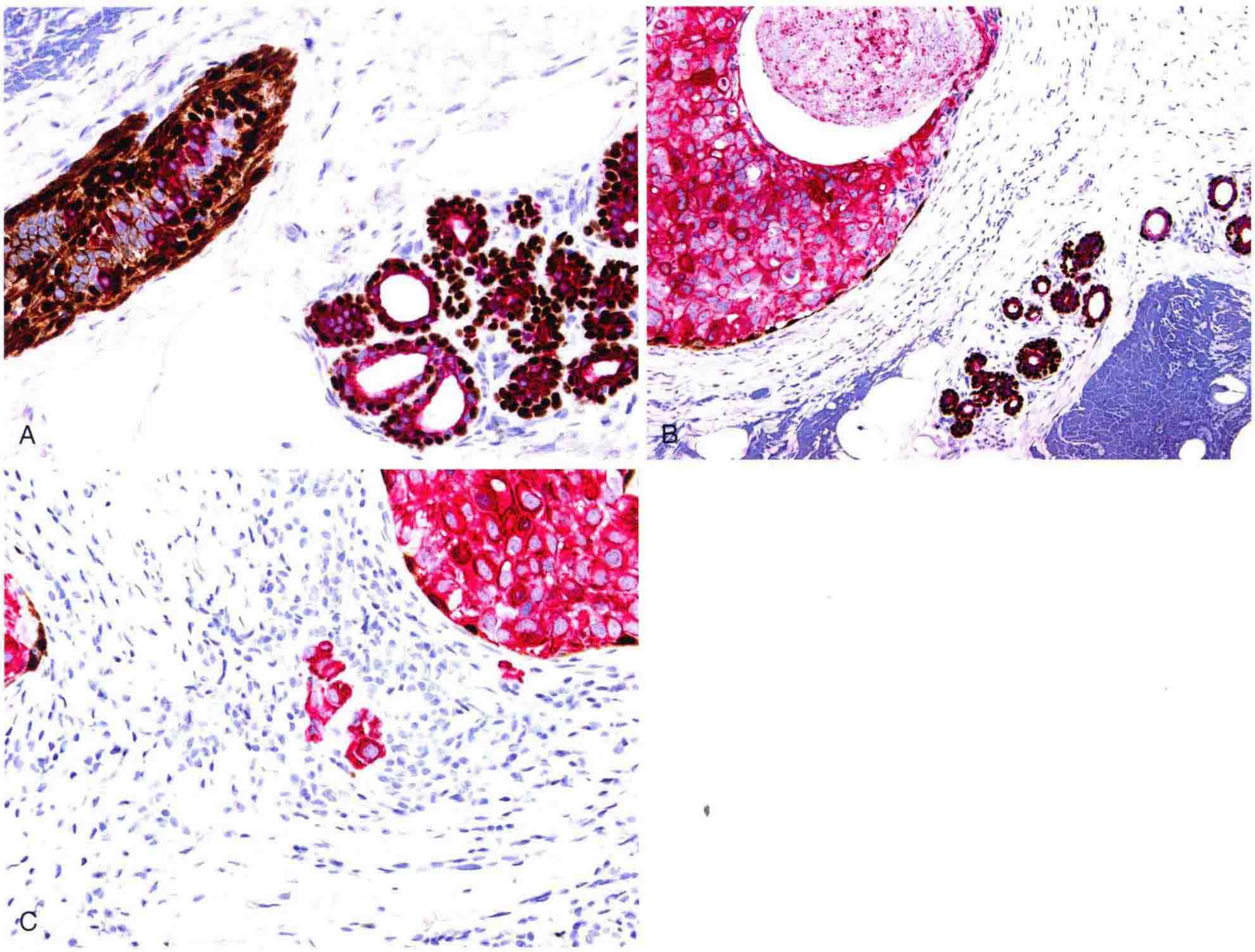


FIGURE 1-9 "Triple stain" highlights the myoepithelium and epithelium of mammary glands. The mammary ductal-lobular system is lined by a dual cell population: an inner epithelial cell layer and an outer myoepithelial cell layer. Red cytoplasmic immunostaining is seen in epithelial cells with cytokeratin. Brown cytoplasmic staining is observed in myoepithelial cells with myosin. Brown nuclear staining in myoepithelial cells is with p63. Shown here is a duct and an inactive lobule **(A),** ductal carcinoma in situ **(B),** and microinvasive carcinoma **(C center).** Note absence of myoepithelium around the cells of the microinvasive carcinoma. **A-C,** Triple immunostain: CK AE1/3 + myosin + p63.