THE DIAGNOSIS AND DETECTION OF BREAST DISEASE

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To Rosemary, Jean, Nancy, Sandi, Doris, Abby, Betty, Virginia, Scotty, Ann, Mary, Rosie, Kelley, Janet and all the women with breast disease who have taught us so much, we dedicate this book.

Preface

This book represents for us the culmination of a longstanding collaboration predicated on the belief that patients are best served when physicians work as a team. We have therefore written this book to emphasize the importance of the team approach to the diagnosis of breast diseases. We believe that it is important for the treating physicians from different disciplines to be aware of the diagnostic pitfalls that each face. This is both the purpose in writing this type of book and what we hope is its most important message. The completion of this book is difficult for us. The relocation of one of us (CBS) to a new institution marks the end of a professional collaboration begun in 1980. While our working relationship will of necessity be diminished by this move, our personal respect and friendship will endure.

This book is also the product of the work of a large number of individuals besides ourselves. We are extremely grateful to all of them for their help and their expertise which has enabled us to complete this project. We would like to thank our co-authors for their hard work in producing chapters that make the book truly a team effort. Thanks are extended to Diana Kimball, Debra Martin, and Retha Higgs for capable secretarial help with numerous manuscript revisions. Joy Stoll and Sandi Jaros were generous with their help in finding cases and materials for photographs and in literature searches. We are indebted to Richard Geissler, Gary McClure and William Gill for excellent photographic support. Richard Gersony is responsible for the magnificent illustrations that we feel enhance the book greatly. The staff of the film library in the Department of Diagnostic Radiology helped identify and find cases, and Sylvia Valle, one of our supervisory histotechnologists, willingly prepared high-quality slides from old blocks. A number of colleagues contributed unusual cases that we did not have in our own departments. We are extremely grateful to these individuals, whose names are cited in the book with their cases. We would also like to thank our colleagues at the University of Kentucky Medical Center and particularly the cytotechnologists, histotechnologists, and radiologic technologists who have worked with us over the years in the diagnosis of breast disease for the patients at our medical center. We would also like to thank our editors at Mosby, Susan Gay, Sandra Clark, and Vicki Hoenigke, who worked with us on this project from initial conception to final product with help when needed and nudging when appropriate. Most especially we would like to thank our families, and in particular our husbands, Dr. Michael Stelling and Dr. Ralph Powell. Without their understanding and support this book could not have been written.

Finally, as the dedication states, we would like to thank and pay tribute to our patients with breast disease. They are responsible for teaching us much of what we write here and are indeed the reason for this book.

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Carol B. Stelling, M.D.

Contents

PART I

Technical and Clinical Aspects of Breast Diagnosis

CHAPTER 1

The Normal Breast: Structure, Function, and Epidemiology

Deborah E. Powell

The human mammary gland arises in the embryo along two lines, called the milk lines, which extend on the anterior chest from the level of the axillae to the groin. Usually only two glands develop, one on each side of the anterior thorax. However, accessory breast tissue may be found at any point along the milk line, and in rare instances tumors can arise in this accessory tissue or the tissue can respond to hormonal stimulation with hypertrophy and formation of a mass (Fig. 1-1, A and B).

The human breast is a type of apocrine sweat gland, modified for the secretion of milk. It is a hormonally responsive tissue that usually develops identically in both the male and female until puberty. At this time, stimulated by hormones primarily from the pituitary gland and ovary, the female breast develops and the male breast does not undergo similar developmental changes.

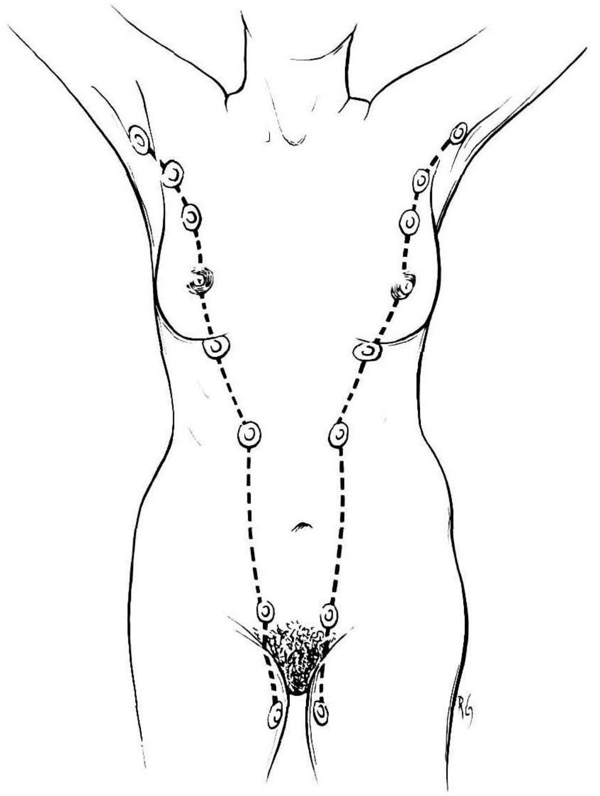
STRUCTURE OF THE FEMALE BREAST

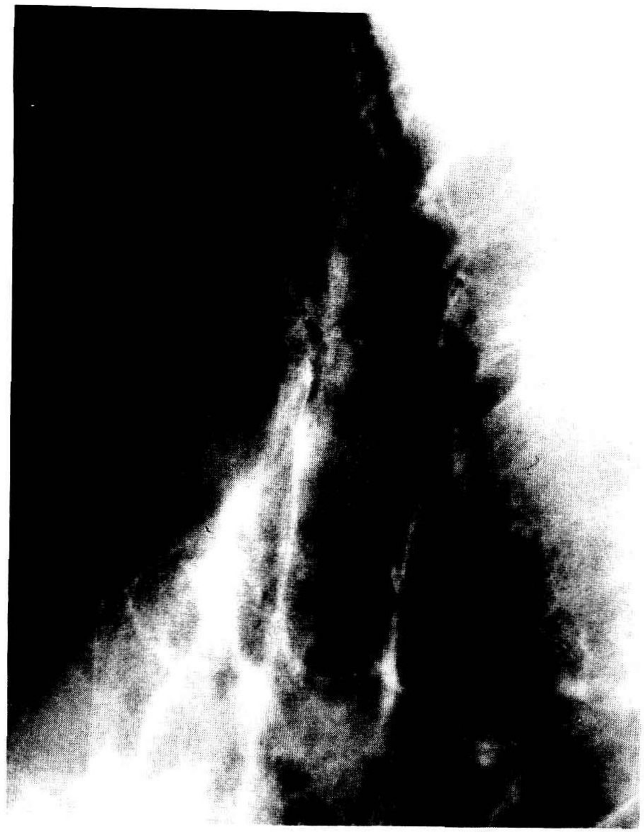
The mammary glands are located in the superficial fascia of the anterior chest wall.[3-5] The suspensory ligaments of Cooper anchor the breast to the underlying pectoralis major muscle fascia and to the overlying dermis. A lateral projection of the gland, the axillary tail of Spence, may extend for a variable distance into the axilla (Fig. 1-2, A and B).[1] The blood supply to the breast is primarily from the internal mammary and lateral thoracic arteries. The lymphatic drainage is to pectoral, axillary, and subclavicular lymph nodes predominantly; however, internal mammary lymph nodes may drain medial portions of the breast. Occasionally, lymph nodes are found within the mammary parenchyma, especially laterally (Fig. 1-3).

The female breast, after puberty, is composed of glandular and ductal elements embedded within varying amounts of fibrous and adipose tissue. The glandular elements or lobules consist of small secretory ductules and acini. These are the terminal units of a system of branching ducts that ramify as subdivisions from the large lactiferous ducts.[4] Approximately 20 to 25 major lactiferous ducts empty into the nipple. Before opening into the nipple, each lactiferous duct dilates to form the lactiferous sinus, located approximately 1 cm beneath the nipple. The nipple and areola are covered by pigmented epithelium. These structures are richly supplied by nerves and blood vessels and contain bands of smooth muscle. In the nipple these bands are oriented parallel to the lactiferous ducts and in a circular pattern near the base of the nipple. Contraction of this smooth muscle causes erection of the nipple. On the areola are found small, raised nodules referred to as tubercles of Montgomery. These nodules contain sebaceous glands not associated with hair follicles and glands of Montgomery.[2] The glands of Montgomery function during lactation and represent true secreting structures, similar to the secretory units found in the breast. Their ducts are coiled, however, before they dilate into a lactiferous sinus. These lactiferous ducts, often accompanied by sebaceous glands, form the tubercles of Montgomery on the areolar surface (Fig. 1-4).

At their point of origin at the nipple, the lactiferous ducts are lined by a keratinizing squamous epithelium. Usually the opening of the ducts in the nonpregnant female is blocked by a keratin plug. At or above the level of the lactiferous sinus, the duct lining becomes a cuboidal epithelium with a prominent underlying basement membrane. Between the epithelium and the basement membrane is a discontinuous layer of myoepithelial cells (Fig. 1-5). This lining of cuboidal lumi-

A

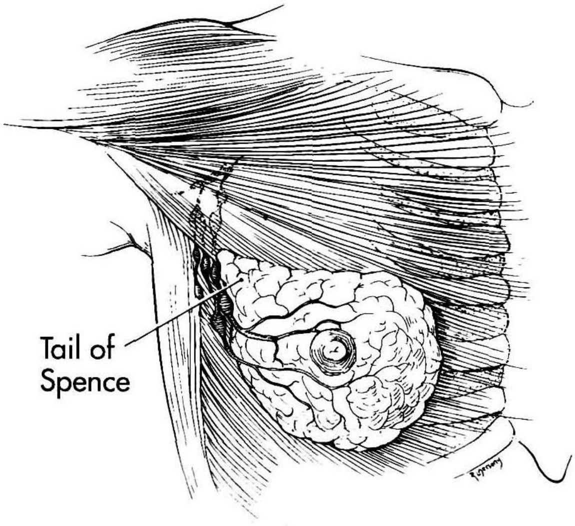




B

Fig. 1-1 **A,** Diagrammatic representation of the embryonic milk lines illustrating sites at which accessory breast tissue and supernumerary nipples can arise. **B,** A supernumerary nipple projects from the skin surface in the tail of the breast in this oblique projection. A ductal structure extends from the axillary parenchyma to the nipple.

A



B

Fig. 1-2 A, Diagrammatic representation of the axillary tail of Spence. Note the location of the lymph nodes which may occasionally be found within the breast parenchyma in this region. **B,** Breast parenchyma in the low axillary area represents normal axillary breast tissue *(arrow)*.

Fig. 1-3 Normal lymph nodes with fatty hilum located in breast tissue and projected over pectoral muscle.

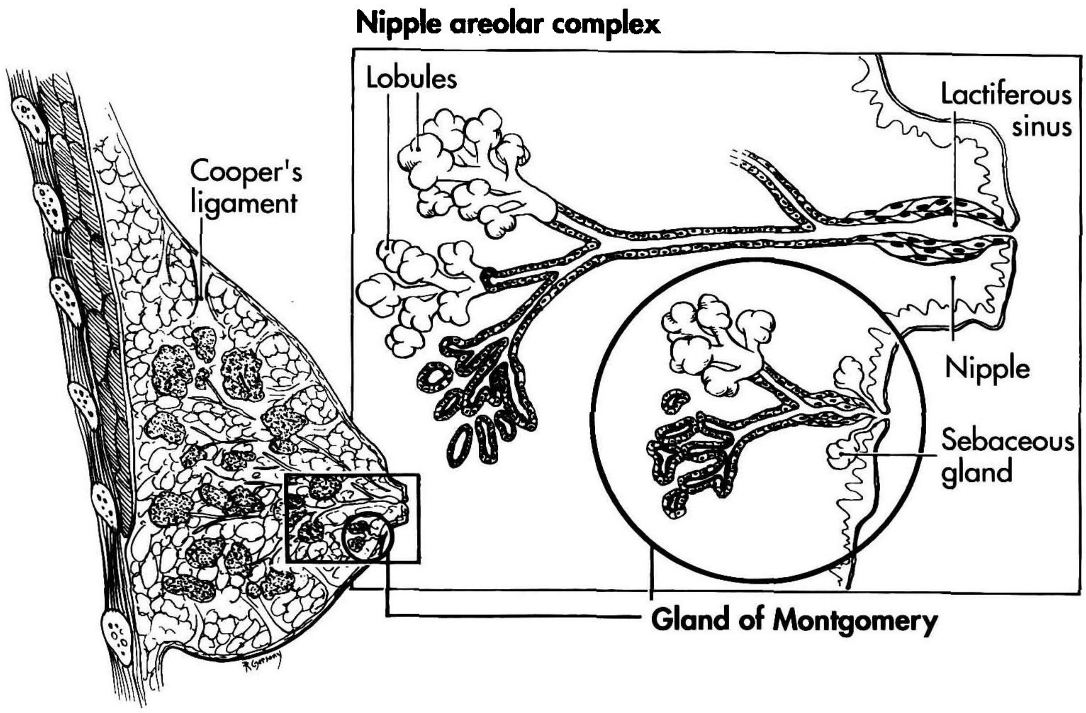


Fig. 1-4 Diagrammatic representation of the breast and the nipple-areolar complex. Both the main duct system extending from the nipple to the lobular units and the glands of Montgomery, which terminate on the areola, are illustrated. The main lactiferous ducts dilate beneath the nipple epithelium to form the lactiferous sinus. To this point, the duct is lined by stratified squamous epithelium. More distal, the ducts are lined by a double layer of epithelial and myoepithelial cells. The ducts of the glands of Montgomery are associated with sebaceous glands as they empty onto the surface of the areola at the tubercle of Montgomery. The most superficial portion of this duct structure is coiled and then dilates slightly before branching. The glands of Montgomery terminate in small secretory structures, similar to the true lobules.

Fig. 1-5 Photomicrograph of small mammary ducts illustrates the two-layered cell lining. The darker stained epithelial cells are located closer to the lumen, whereas the pale staining vacuolated myoepithelial cells are located adjacent to the surrounding stroma.

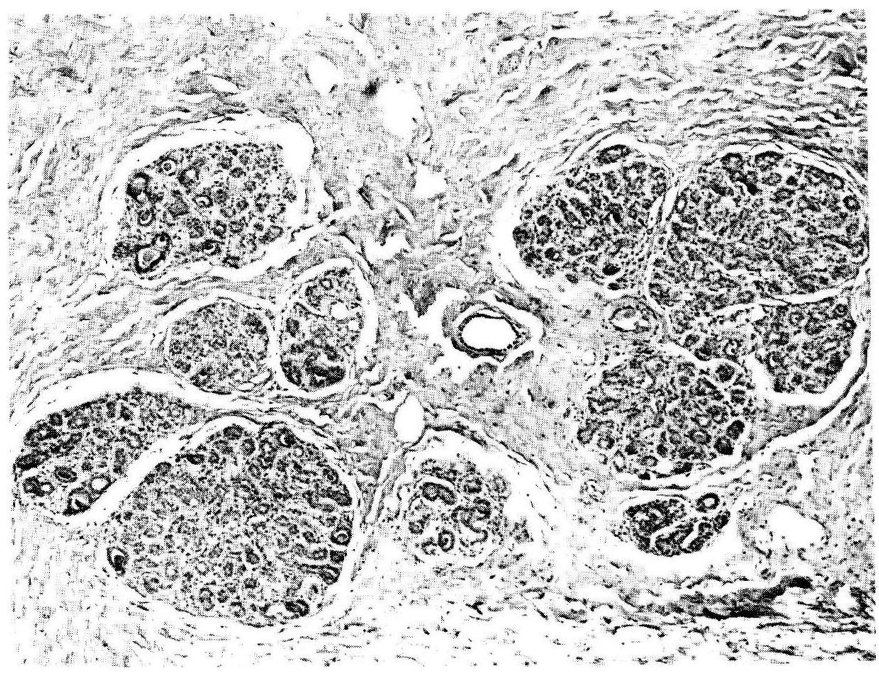


Fig. 1-6 This low-power photomicrograph of a lobule illustrates the centrally located terminal duct and the peripherally arranged clusters of small glandular structures grouped within a loose fibrovascular stroma. The stroma exterior to the lobule and the terminal duct is composed of collagen-rich connective tissue.

nal epithelium, myoepithelium, and basement membrane extends down to the level of the secretory units of the breast.[3] The epithelium may undergo changes under the influence of hormones, particularly estrogen and progesterone, in a cyclic fashion during the female reproductive years, as will be discussed later. The terminal acinar units of the breast are also lined by cuboidal epithelium, underlying myoepithelium, and basement membrane. These small groupings of acinar structures are referred to as lobules, and an alveolar or terminal duct is usually identified centrally within the lobular unit (Fig. 1-6). The individual terminal units of the lobule are contained within a specialized connective tissue, which is loose and highly cellular, termed the perilobular stroma. This lobular connective tissue has a rich capillary network but contains little to no fat (Fig. 1-7,A–C). Outside the lobule, the parenchyma of the breast consists of a mix of dense fibrous paucicel-

A

B

C

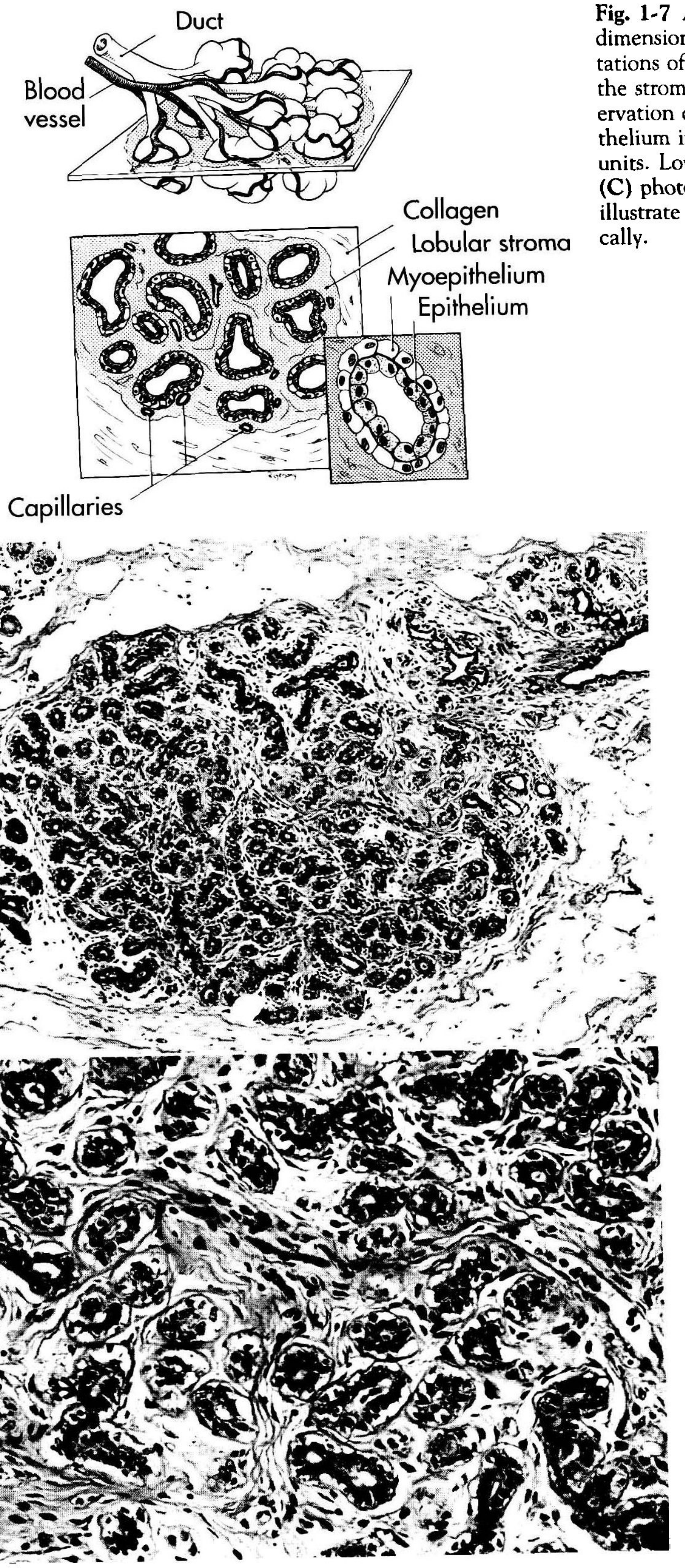


Fig. 1-7 A, Diagrammatic three-dimensional cross-sectional representations of the lobule, emphasizing the stromal vascularity and the preservation of the double-layered epithelium into the most distal lobular units. Low **(B)** and higher power **(C)** photomicrographs of the lobule illustrate these features histologically.

lular connective tissue and mature adipose tissue in which small blood vessels can be identified.

FUNCTION OF THE FEMALE BREAST

The female breast undergoes striking hormonally mediated changes at menarche or shortly before.[8,13] The production in the ovaries of estrogen followed by progesterone stimulates the growth of the breast parenchyma. Other hormones such as growth hormone, thyroxine, and insulin also play a role in this process. There is elongation and branching of the duct system with the development of terminal buds into rudimentary lobular structures. Fat deposition, vascularization, and change in volume of the connective tissue parenchyma also occur at this time, and these latter changes are important for increase in size and protrusion of the breast disk. Changes in nipple and areola also occur, consisting mainly of increased size and pigmentation. Occasionally there is a marked increase in volume of one or both breasts during puberty, which is referred to as pubertal hyperplasia. This is contrasted with giant fibroadenoma in Chapter 9. The formation of the lobule is accentuated by pregnancy when the lobules become fully differentiated.

Several studies have been published on changes that occur in the epithelial cells and in the perilobular stroma during the menstrual cycle.[6,10,14] In the follicular phase of the cycle the acini are small, with no evidence of active secretion by the radially oriented cells lining the lumina. The lobular stroma is compact, with relatively few lymphocytes and little edema or metachromasia. Epithelial cells are shown to undergo some evidence of cytoplasmic blebbing during the early luteal phases of the menstrual cycle without evidence of active secretion, whereas myoepithelial cells become strikingly vacuolated. True apocrine secretion into a distended lumen is seen in the latter half of the luteal phase. There is an increase in epithelial mitotic figures close to the beginning of menstruation followed by an increase in cell death (apoptosis) at the time of menses, which extends into the early part of the follicular phase. During the luteal phase the perilobular stroma becomes more edematous, and lymphocytic infiltration and metachromasia peak at the time of menses (Fig. 1-8).

The breast becomes fully differentiated during pregnancy and lactation, and the terminal lobular units are most affected during this physiologic state. Several histologic changes occur in the terminal ducts and lobules with enlargement and formation of new lobular units early in pregnancy. By the end of the second trimester of pregnancy, secretory changes are well developed and the cuboidal luminal epithelial cells show evidence of vacuolization. Accumulation of fat droplets occurs within the cytoplasm of the epithelium of the lobules during the third trimester. The lobules undergo striking hyperplasia to occupy most of the breast parenchyma during this time, with a decrease in the interlobular connective tissue. Finally, the expanded lobular units show marked distention of their lumina by colostrum (Fig. 1-9, A–C).

After lactation, the breast undergoes involutional changes, which may take several months. Some of these changes are probably due to a reduction in prolactin levels, but the role of mechanical and vascular stimuli on this involution is not understood well. However, the lobular units become more compact and lose the luminal secretions, and the interlobular stroma once again becomes more prominent.[3] This pattern is referred to as the resting lobule. Some patients who are not pregnant or lactating have been found to have these same secretory changes in breast biopsies, often in a focal distribution.[11,12] These changes, often referred to as focal pregnancy-like changes, may be associated with exogenous hormones such as oral contraceptives as well as other medication.[7]

After menopause, the breast undergoes involution and atrophy, which involves primarily parenchymal elements of the breast, particularly the lobule (Fig. 1-10). Parenchymal cells undergo atrophy and fibrosis, and hyalinization of the stroma of the lobule as well as the lobular elements themselves is seen. Concomitantly, there is an increase in adipose tissue within the breast and a decrease in both fibrous connective tissue and elastic tissue (Fig. 1-11, *A* and *B*). Ultimately, much of the breast consists of adipose tissue and some hyalinized fibrous stroma with small ductal elements and occasionally a few lobular units, which may show microcystic change of the terminal ductules. Occasionally, persistence of lobules is seen in breasts of postmenopausal women who are not receiving exogenous hormones.[9] This latter finding is considered by some to represent evidence of endogenous hormone secretion. It is considered to be a risk factor for subsequent development of carcinoma by some authors.[15]

HORMONES AND THE FEMALE BREAST

As mentioned, the mammary gland is a hormonally responsive organ. The female breast is most impressively influenced by estrogen and progesterone, but several other hormones also affect the mammary gland, especially during lactation. Estrogen produced chiefly by the ovary is important for the increased size of the breast during puberty

A

B

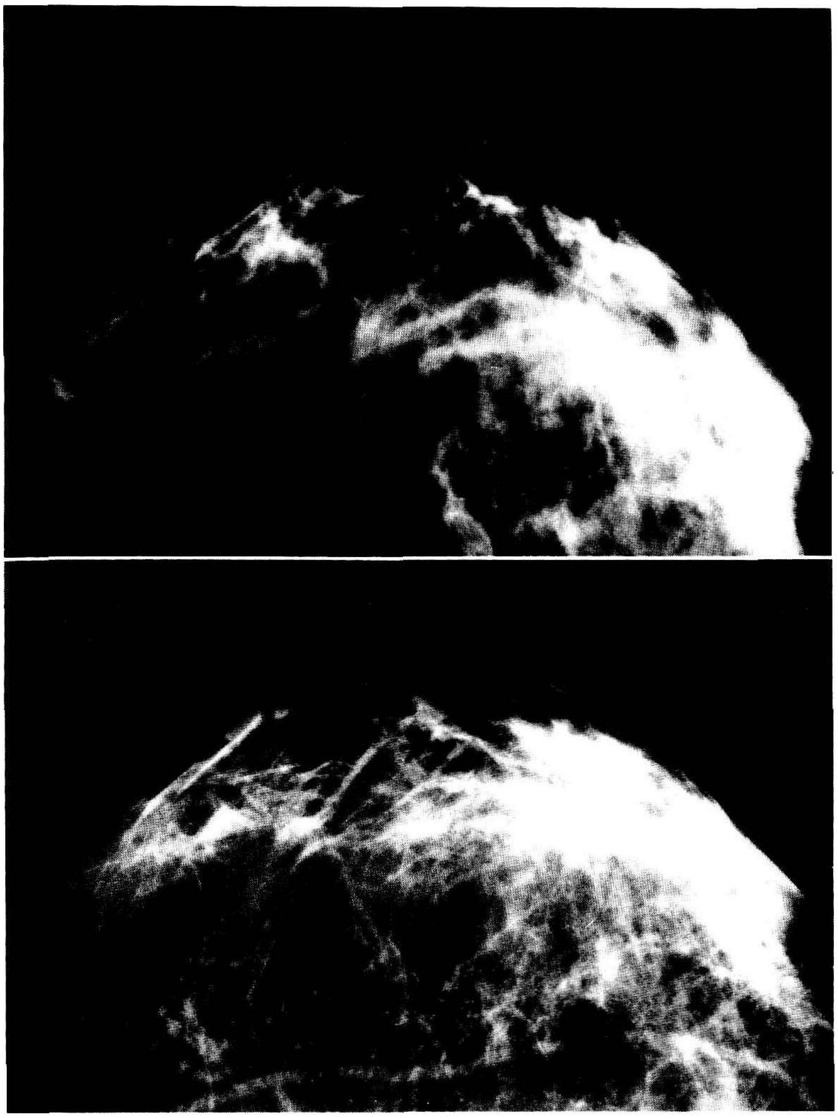


Fig. 1-8 Monthly cyclic changes. Numerous vague densities in the breast become more prominent in the premenstrual phase **(A)** as compared with midcycle **(B)**. This variability is seldom noted radiographically.

and again in pregnancy, when estrogen is produced by the placenta as well. Estrogen promotes fat deposition and growth of both stroma and the duct system of the breast. Progesterone, also from the ovary, stimulates growth of the lobules and acini. Progesterone also causes an increase in interstitial fluid in the breast, particularly in the perilobular stroma. During pregnancy, progesterone from the placenta stimulates marked increase in lobules, in both size and number, and is responsible for secretory modifications in the cytoplasm of the acinar cells. Other hormones (insulin, growth hormone, glucocorticoids, and prolactin) are important for the growth of the duct system of the breast.

Although the lobule of the breast is prepared for lactation by progesterone, prolactin is necessary for lactation to occur. Lactation in the pregnant female is inhibited by estrogen and progesterone produced by the placenta, despite the fact that serum prolactin levels rise during pregnancy to 10 times that of the nonpregnant state. However, after delivery, with loss of placental estrogen and progesterone, lactation is stimulated by the high serum prolactin. Growth hormone, glucocorticoids, and parathyroid hormone are required for proper composition of the milk, and oxytocin, which stimulates myoepithelial cell contraction, permits the ejection of milk from the acini.

At the cellular level, estrogen and progesterone function by binding to specific receptor proteins.[20] These, with other steroid hormone receptor proteins, are members of a supergene family—the nuclear hormone receptor family—which in addition to the steroid receptors includes receptors for vitamin D, thyroid hormone, and retinoic acid.[17] The estrogen and progesterone receptors are con-

A

B

C

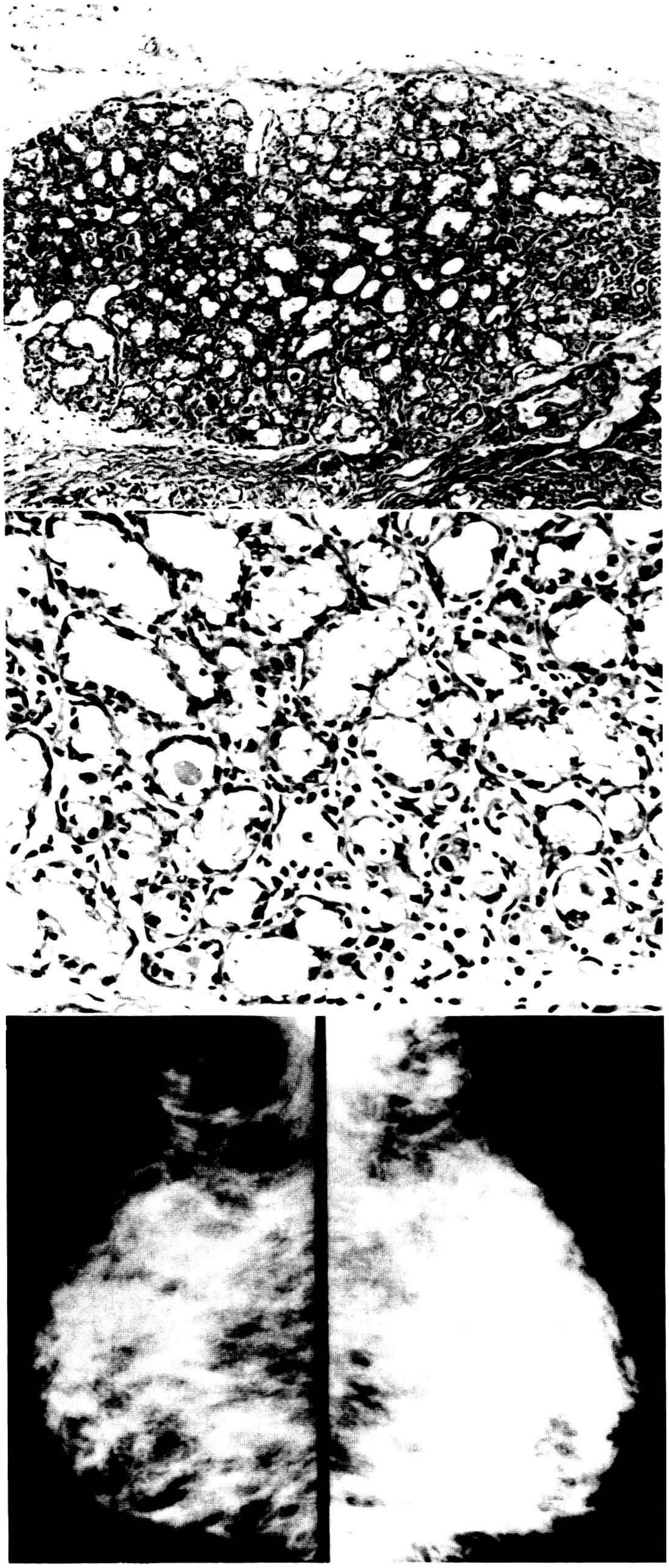


Fig. 1-9 A, During the last trimester of pregnancy there is marked hyperplasia of the lobules, with striking expansion in their size. **B,** The vacuolization of the cytoplasm of the lobular epithelial cells that occurs during the third trimester is illustrated in this photomicrograph, which also illustrates the distention of the gland lumens by secretory material. **C,** During pregnancy the mammary parenchyma is extremely dense, lowering the sensitivity of mammography. Note presence of axillary breast tissue.