The Correlation of Histologic Changes in the Human Breast With the Menstrual Cycle

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Histologic changes in the normal human mammary gland associated with the menstrual cycle were sought in tissues derived from a defined population of patients undergoing subcutaneous mastectomy or reduction mammoplasty for reasons other than neoplasia. Ninety patients were selected for their regular menstrual cycling, abstinence from hormone use, and absence of disease which might influence pituitary-ovarian cycling. Morphologic changes in the mammary stromal and epithelial components were identified as they related to specific pituitary-ovarian events, and histologic criteria were identified that allowed reproducible morphologic categorization of the mammary gland into five specific phases: proliferative (Days 3–7); follicular phase of differentiation (Days 8–14); luteal phase of differentiation (Days 15–20); secretory (Days 21–27); and menstrual (Days 28–2). Double-blind reviews of tissues confirmed the validity and the reproducibility of these histologic criteria in identifying the menstrual phase. The findings further characterize the morphologic correlates of hormone responsiveness of the normal human mammary gland. The recognition of menstrual-cycle-dependent histologic changes may be expected to provide a basis for extending the interpretation of the morphologic characteristics of the breast in surgically acquired specimens that may be associated with hormonal aberrations. (Am J Pathol 1981, 104:23–34)

A DESCRIPTION OF HISTOLOGIC CHANGES in human endometrial tissues correlating with the menstrual cycle was first published by Hitschmann and Adler in 1908.[1] Subsequently similar menstrual-phase-associated histologic variations were defined for the fallopian tube,[2] cervix,[3] and vagina.[4] Although the breast is known to be hormonally responsive, attempts to define histologic changes associated with the menstrual cycle have resulted in inconsistent reports concerning the existence, nature, and extent of such alterations. Most studies describing the morphology of the mammary gland at different phases of the menstrual cycle were published before the hormonal physiologic characteristics of the ovary were understood.

The ability to interpret the data of many previously published reports has been compromised by the use of postmortem specimens or biopsies acquired from patients with irregular menstrual cycles and/or debilitating disease. Other studies have included tissues derived from breasts resected for malignancy that may be associated with epithelial proliferative changes.[5] In describing breast tissue response to ovarian cycling, semiquantitative analyses have been attempted, principally utilizing specimens from patients of differing age and parity. The influence of aberrations in pituitary-ovarian-adrenal function on the physiologic state of the breast dictates that tissues used for the identification of histologic variations associated with the menstrual cycle be derived from a population of women in good health, with regular menstrual cycles, for whom accurate menstrual dates are known and who have abstained from exogenous hormone use. Fanger met these criteria in his study of ultrastructural changes occurring in the breast during the menstrual cycle.[6] In this study little emphasis was placed on the light-microscopic features of these tissues.

Sex steroids and selected peptide hormones have been shown to have profound effects on mammary gland morphology in animal model systems.[7] These

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studies, along with the elucidation of the physiology of lactation[8] and the biochemistry of sex-steroid hormone receptors[9] have affirmed the sex-steroid responsiveness of the breast. The human breast may therefore be expected to reflect hormonal status, not only in pregnancy, but also during the regular periodic cycling of ovarian estrogen and progesterone secretion. Therefore, breast tissue from a population of patients undergoing subcutaneous mastectomy or reduction mammoplasty was studied in an attempt to define the histologic features of mammary stromal and epithelial elements that might allow reproducible categorization of breast tissues into specific phases reflecting the effect of ovarian–pituitary cycling (menstruation).

Materials and Methods

Patient Selection

One hundred seventy-three women underwent bilateral reduction mammoplasty or subcutaneous mastectomy at Duke Medical Center between August 1, 1978 and December 1, 1980, for indications other than neoplasia. These patients were interviewed preoperatively by experienced epidemiologists, and 90 patients were selected because of their history of regular menstrual cycling, abstinence from use of hormones or hormone-containing preparations, no debilitating disease, no use of medications that might influence pituitary–ovarian function, and accurate recall of menstrual dates. The ages of these women ranged from 16 to 51 years, with a mean of 35 years and a standard deviation of 9 years. There was uniform distribution of patient age and parity within each of the phases of menstrual cycle, as determined by chi-square analysis. With a single exception, none of the women had given birth within 2 years of their breast operation. A majority of the women had histories of 28-day menstrual cycles. Menstrual dates from the remaining were normalized to a 28-day cycle. The frequency distribution of cases within the menstrual cycle is shown in Figure 1. All days were represented except Days 4 and 19.

Tissue Preparation

The mammary glands were obtained from the operating room in the fresh state with sutures placed for orientation and identification of the subareolar region. The breasts were sectioned at 3-mm intervals in the sagittal plane and were examined with a stereomicroscope using transillumination and epi-illumination at 4–50 × magnification. Areas for embedding were selected as previously described.[5] Tissues were fixed in 0.1 M phosphate, 4% formaldehyde, pH 7.2, overnight; dehydrated in serial alcohols to xylene; and embedded in paraffin. Sections were prepared at 6–8 μ, deparaffinized, and stained with hematoxylin and eosin.

Morphologic Studies

Five sections were examined from each breast (10 sections/case). The proportion of tissue that deviated from normal ductular-lobular patterns was noted. The tissues contained some evidence of simple fibrocystic disease (<10% of lobular-alveolar units involved) in 39 cases, fibrocystic disease with epithelial proliferative change in 11 cases, and no deviation from normal in 40 cases. The normal cases and those cases containing simple fibrocystic tissues were found to be distributed uniformly within the cycle. The eleven cases with epithelial proliferative changes were eliminated from the study. The remaining cases were examined for their most consistent attributes, and morphologic criteria were established for specific menstrual phases. Subsequent to the establishment of these criteria, case materials were reviewed independently by two observers without knowledge of the menstrual dates in order to test interobserver variability in assigning the tissue to a specific menstrual date and phase. A second review of each case by one of these observers was carried out to test intraobserver variability. To further test these criteria for menstrual phase assignment, three pathologists performed independent double-blind reviews of 2 randomly selected cases from each phase.

Results

Morphologic changes were observed in the breast in both the epithelial and stromal components. While changes occurred on a daily basis, these were subtle and subject to interobserver and intraobserver variation in interpretation. We were, however, able to generate criteria that define five phases of morphologic response to ovarian cycling and that allow accurate, reproducible interpretations of histologic patterns as specific to a given phase. These morphologic alterations follow the sequence as outlined (Table 1) and discussed below.

Phase I—Proliferative (Days 3–7)

This phase was most characteristically identified by the presence of mitotic figures among the acinar epithelium (Figure 2C). Day 3 contained only occasional mitoses, while Days 5, 6, and 7 contained, on the aver-

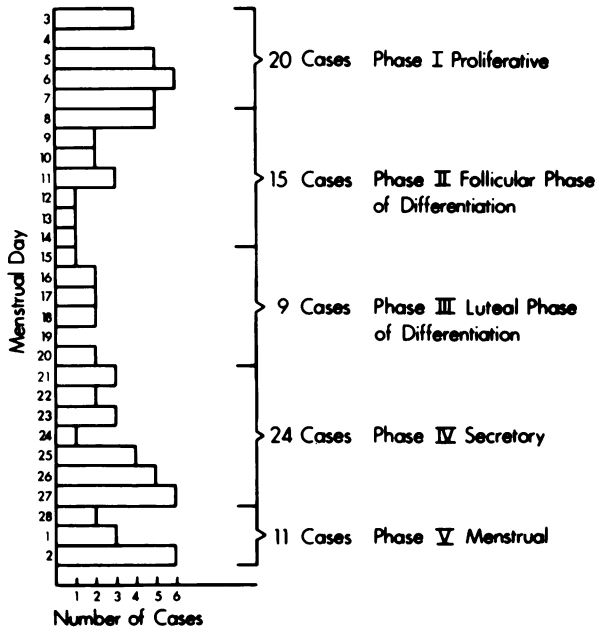

Figure 1—Distribution of case material within the normalized 28-day menstrual cycle. The case distribution and number relative to the day of menstruation are shown. The cases are uniformly distributed among the 5 phases.

age, 4, 14, and 2 per 10 high-power fields, respectively. The observation of significant numbers of mitoses was specific for Phase I, but not absolutely sensitive. The lobules contained acini and ductular components that were composed of a dominant single cell type. These cells lined the acini with the appearance of 2–3 cell layers due to the absence of distinct stratification (Figure 2C). At this phase the acinar epithelial cell was characterized by its polygonal shape; homogeneous eosinophilic pale cytoplasm; round, centrally placed nucleus with prominent nucleoli; poorly defined cell borders; and relatively little orientation to the lumen. Numerous apoptotic cell figures were seen. The acinar-ductular lumen was tight and in many cases closed. In acini with luminal space there was rarely secretory product within the glandular space and no evidence of active secretion. The lobules were sharply demarcated from the homogeneous collagenous stroma by dense, cellular mantle tissue with plump fibroblasts (Figure 2A and B). Plasma cell infiltrates of the mantle tissue were frequently observed.

Phase II—Follicular Phase of Differentiation (Days 8–14)

In this phase there was no longer a single dominant epithelial cell type. Two morphologically distinct cells became apparent in addition to the single dominant cell present in Phase I. These two cell types included: 1) a basal cell with clear cytoplasm and small hyperchromatic nucleus (distinguished from the apoptotic cell with pyknotic nucleus) and 2) a columnar luminal cell with more basophilic cytoplasm and a basally situated darkly staining nucleus (Figure 3C). The luminal cells were more radially oriented, and the acinar lumen became defined by the borders of these cells. The lumen contained minimal secretion with little evidence of active secretion. The intralobular mantle tissue remained dense, appearing more collagenous and less cellular than in Phase I. The lobule continued to be sharply demarcated from the interlobular connective tissue (Figure 3A and B). Acinar components were well defined by an increasingly prominent basal lamina. Mitotic figures were rare.

Phase III—Luteal Phase of Differentiation (Days 15–20)

The lobules in this phase were characterized by acini and ductular epithelium of three dominant cell types: 1) columnar, basophilic cells bordering the lumen; 2) pale, eosinophilic cells, usually basal; and 3) clear ballooned cells with small, comma-shaped nuclei in a basal position (Figure 4C). The vacuolization and ballooning of the basal cell layer was the hallmark of the onset of this phase. The lumen was enlarged and more rounded and defined than in previous phases. Active secretion was not apparent, although secretory product could be seen in the lumen. The intralobular stroma loosened, and the basal lamina became less prominent than in Phase II (Figure 4A and B). Mitotic figures were not seen.

Phase IV—Secretory Phase (Days 21–27)

The acini in this phase were characterized by true apocrine secretion from the luminal epithelial cells into a large, often distended lumen. The basal cells remained vacuolated, and pale eosinophilic cells remained present in an intermediate or basal position (Figure 5C). Also conspicuous in this phase were alterations occurring in the stromal elements. The mantle tissue became frankly edematous, with prominent fluid-filled spaces, which separated adjoining acini and disrupted the lobular border (Figure 5A and B). This was in sharp contrast to the well-defined lobular borders characteristic of earlier phases of the cycle. Large congested venous spaces were present within the intralobular mantle tissue as well. The basal lamina was thin and attenuated.

Phase V—Menstrual Phase (Days 28–2)

Two morphologically distinct epithelial acinar cell

Table 1—Morphologic Criteria for Phase Assignment

			Epithelium			
	Stroma	Lumen	Cell types	Orientation of epithelial cells	Mitoses	Active secretion
Phase I Days 3-7	Dense, cellular	Tight	Single predominant pale eosinophilic cell	No stratification apparent	Present, average 4/10 HPF	None
Phase II Days 8-14	Dense, cellular-collagenous	Defined	1) Luminal columnar basophilic cell 2) Intermediate pale cell 3)Basal clear cell with hyperchromatic nucleus (myoepithelial)	Radial around lumen	Rare	None
Phase III Days 15-20	Loose, broken	Open with some secretion	1) Luminal basophilic cell 2) Intermediate pale cell 3) Prominent vacuolization of basal clear cell (myoepithelial)	Radial around lumen	Absent	None
Phase IV Days 21-27	Loose, edematous	Open with secretion	1) Luminal basophilic cell 2) Intermediate pale cell 3) Prominent vacuolization of basal clear cell (myoepithelial)	Radial around lumen	Absent	Active apocrine secretion from luminal cell
Phase V Days 28-2	Dense, cellular	Distended with secretion	1) Luminal basophilic cell with scant cytoplasm 2) Extensive vacuolization of basal cells	Radial around lumen	Absent	Rare

types remained apparent in this phase. Basal cells with ballooned, clear cytoplasm supported luminal cells that were characterized by scant basophilic cytoplasm and nuclei that indented distended lumens, creating a hobnailed appearance (Figure 6B and C). The lumen on occasion was observed to be greatly distended and filled with eosinophilic, granular secretions. The morphologic appearance suggested that active secretion had abated. The stroma was compact and cellular, often containing mononuclear inflammatory cells (Figure 6A). No mitotic activity was apparent.

Testing of Morphologic Criteria

For phase assignment of an individual case, each specific morphologic component was graded and evaluated by the criteria generated for each menstrual phase (Table 1). These components were evaluated in sequence, consisting of 1) intralobular stromal density and cellularity; 2) acinar epithelial cell types, including morphologic characteristics of luminal cells and vacuolization of basal cells; 3) presence of mitoses; and 4) evidence of apocrine secretion. Phase assignment independently by two of the authors (P.V. and K.M.) of case material resulted in an interobserver variability of 15% with correct phase assignment of 85% and 77%. The correct or adjacent phase was assigned in 92% and 88% of cases. Intraobserver variability was 7%. Assignment in a double-blind manner by three of the authors (K.M., S.V., B.F.) of two randomly selected cases from each phase resulted in an interobserver variability of 17%, with correct phase assignment in 83% of reviews. The correct or adjacent phase was assigned in 93% of reviews. Interestingly, one case was assigned to the same incorrect but adjacent phase by all observers.

Discussion

Morphologic criteria have been identified that allow reproducible categorization of morphologic characteristics of the mammary gland into phases that correlate with ovarian hormonal cycling. While numerous reports describe the physiology of lactation and the effects of exogenous estrogen and progesterone on the mammary glands of experimental animals,[7] many consider the interpartum human breast as a resting gland. This idea is in conflict with historical investigations,[10-16] ultrastructural findings,[6] and the cyclic morphologic changes of the breast described in the present study.

Rosenberg was the first to describe a cycle of histologic changes consisting of premenstrual lobular-alveolar proliferation and postmenstrual "regression"

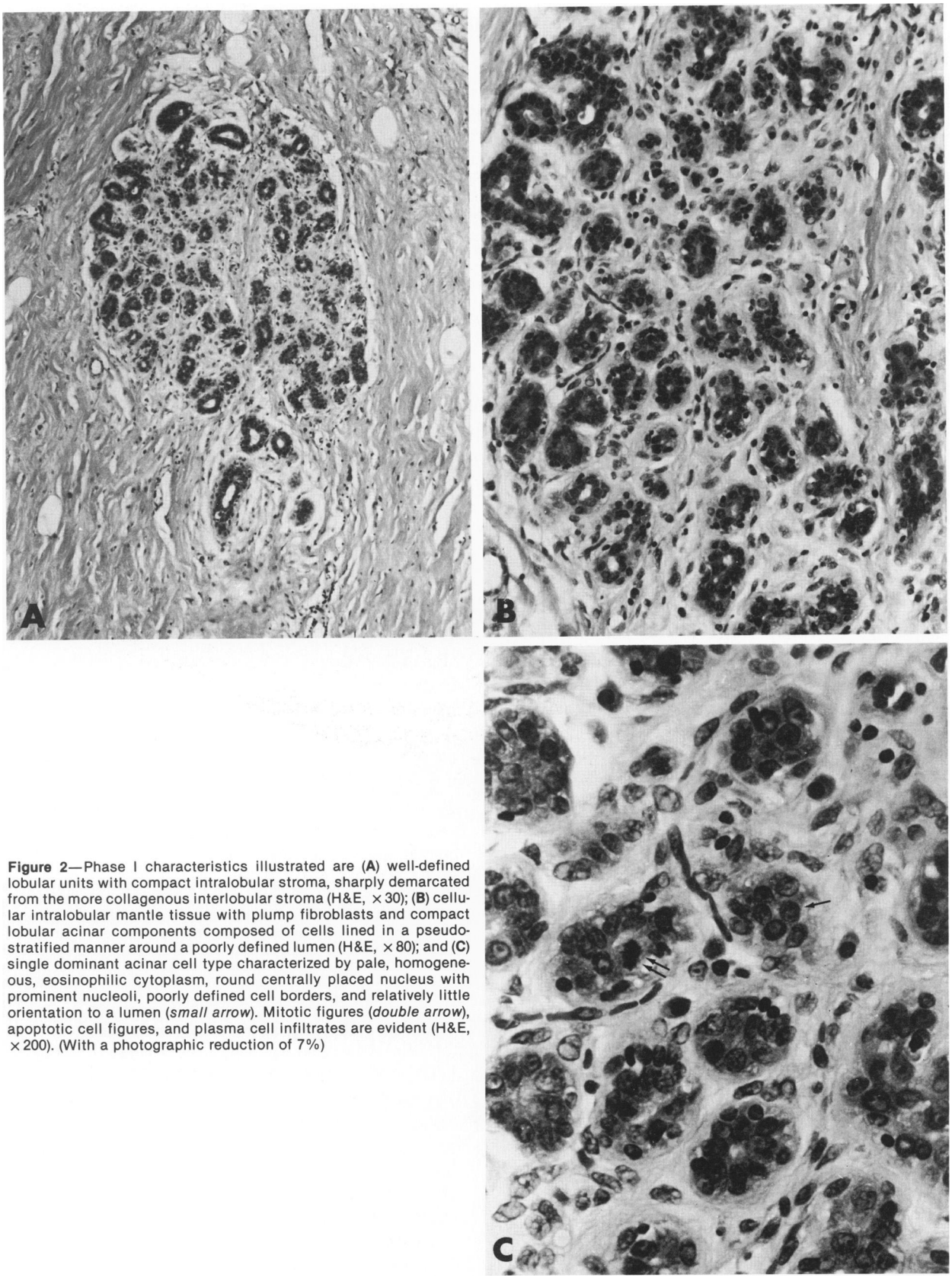

Figure 2—Phase I characteristics illustrated are (**A**) well-defined lobular units with compact intralobular stroma, sharply demarcated from the more collagenous interlobular stroma (H&E, ×30); (**B**) cellular intralobular mantle tissue with plump fibroblasts and compact lobular acinar components composed of cells lined in a pseudostratified manner around a poorly defined lumen (H&E, ×80); and (**C**) single dominant acinar cell type characterized by pale, homogeneous, eosinophilic cytoplasm, round centrally placed nucleus with prominent nucleoli, poorly defined cell borders, and relatively little orientation to a lumen (*small arrow*). Mitotic figures (*double arrow*), apoptotic cell figures, and plasma cell infiltrates are evident (H&E, ×200). (With a photographic reduction of 7%)

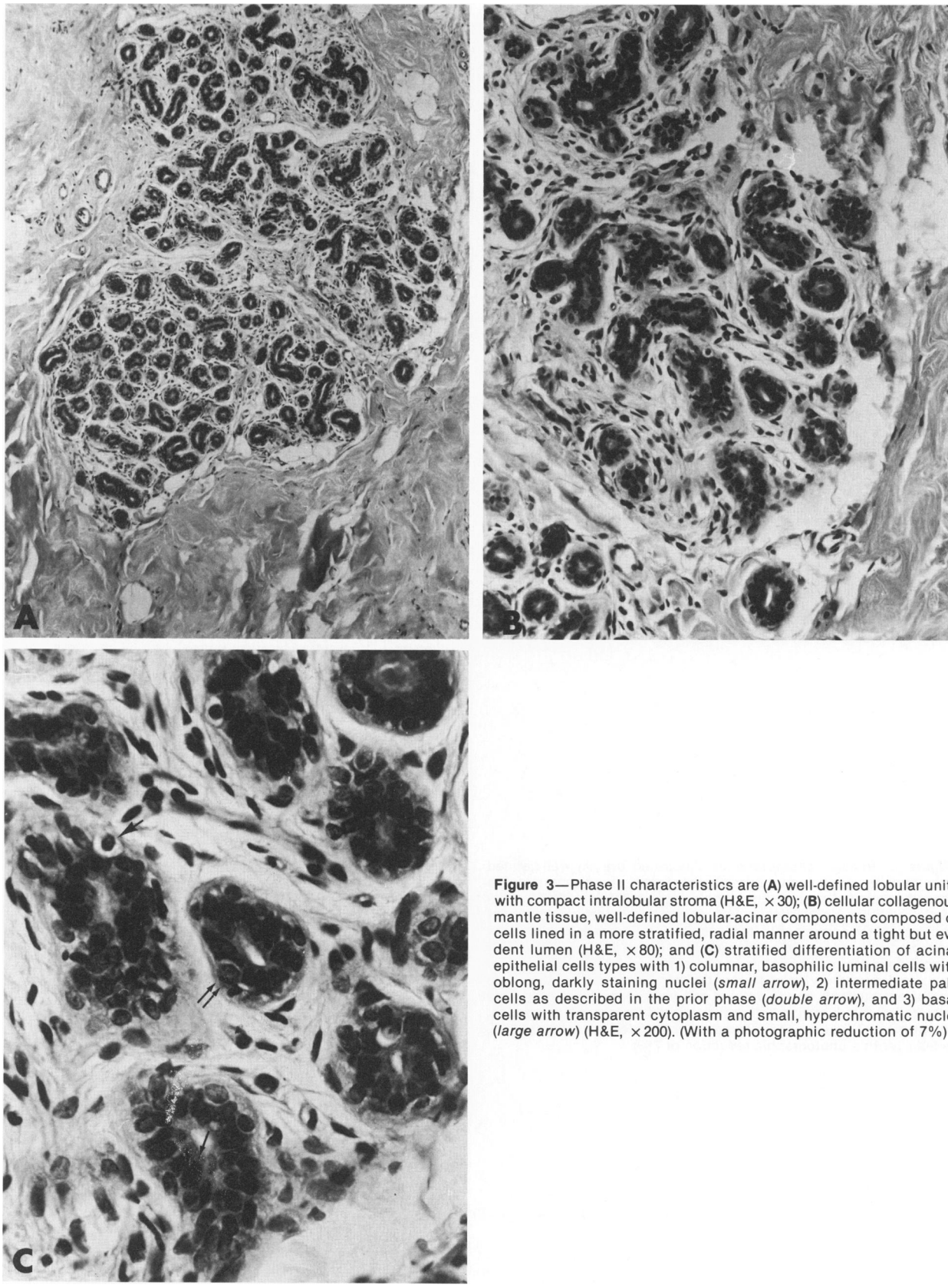

Figure 3—Phase II characteristics are (**A**) well-defined lobular units with compact intralobular stroma (H&E, ×30); (**B**) cellular collagenous mantle tissue, well-defined lobular-acinar components composed of cells lined in a more stratified, radial manner around a tight but evident lumen (H&E, ×80); and (**C**) stratified differentiation of acinar epithelial cells types with 1) columnar, basophilic luminal cells with oblong, darkly staining nuclei (*small arrow*), 2) intermediate pale cells as described in the prior phase (*double arrow*), and 3) basal cells with transparent cytoplasm and small, hyperchromatic nuclei (*large arrow*) (H&E, ×200). (With a photographic reduction of 7%)

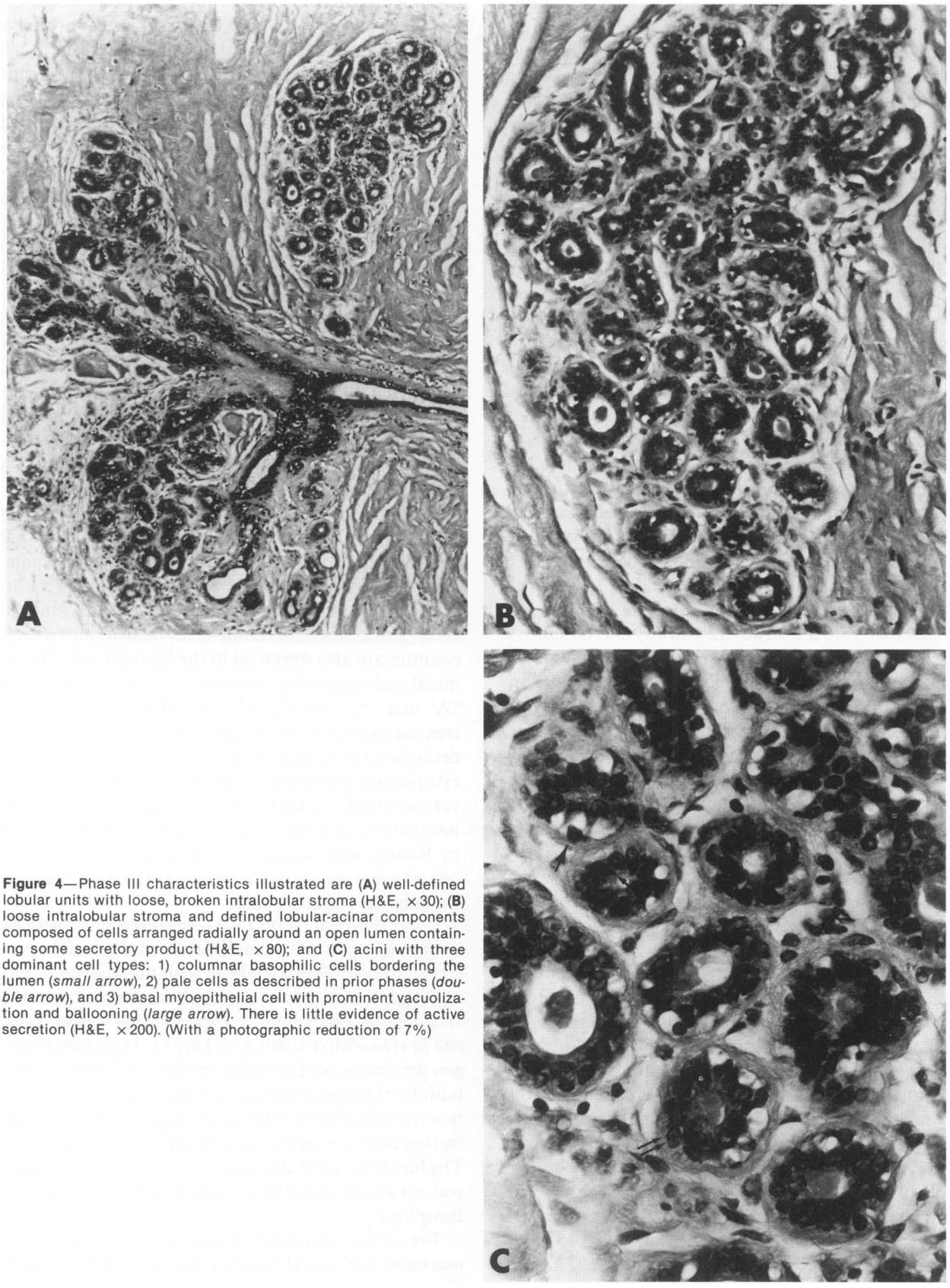

Figure 4—Phase III characteristics illustrated are (**A**) well-defined lobular units with loose, broken intralobular stroma (H&E, ×30); (**B**) loose intralobular stroma and defined lobular-acinar components composed of cells arranged radially around an open lumen containing some secretory product (H&E, ×80); and (**C**) acini with three dominant cell types: 1) columnar basophilic cells bordering the lumen (*small arrow*), 2) pale cells as described in prior phases (*double arrow*), and 3) basal myoepithelial cell with prominent vacuolization and ballooning (*large arrow*). There is little evidence of active secretion (H&E, ×200). (With a photographic reduction of 7%)

with atrophy of the glandular tissue.[10] This observation was based on material acquired at autopsy. Centeno[13] and Polano[15] supported these observations, likening the premenstrual breast to the breast during the first months of pregnancy with lobular-alveolar proliferation and acini filled with secretions. Other investigators have defined changes during the menstrual cycle, emphasizing the connective tissue elements, considering epithelial alterations as secondary.[11,12] The principle changes considered were the premenstrual loosening of the intralobular connective tissue. Diekman[11] and Moskowitz[12] emphasized premenstrual lobular-alveolar dilation as opposed to proliferation, the latter describing a "true apocrine secretion." Both deemphasized postmenstrual regression, in contrast to Rosenberg's descriptions. A compact mantle tissue in the postmenstrual period with a "fixing" of the glandular fields was noted by both groups.

Speert, in an attempt to resolve conflicting data from previous studies and avoid the problems inherent in the use of human tissue, studied the rhesus monkey.[17] Sequential biopsies were obtained from the breast of each animal, with ovulation confirmed by laparotomy. With the use of this study design, a premenstrual lobular enlargement secondary to acinar dilation and stromal edema was appreciated.

Geschicter, in a study of 22 autopsy and 68 surgical specimens, described menstrual changes in two phases.[16] The first phase, a period of "regression" from Day 1 to Day 8, was characterized by atrophy of the epithelium, closing of alveolar lumen, condensation of intralobular stroma, and a variable inflammatory infiltrate. The second phase of the cycle was considered proliferative in nature and was characterized by lobular-alveolar budding, accumulation of secretion, and stromal edema. Haagensen, on the basis of a semiquantitative study of surgical specimens, was not able to define a statistically significant difference in the phases of the menstrual cycle for particular morphologic components.[18]

Our findings, based on a defined patient population, are in agreement with some, but in contrast to other, published findings. Menstrual-cycle–related ultrastructural features described by Fanger et al are in agreement with, and are complemented by, our observations. Menstrual-phase–specific morphologic features can be seen in both the epithelial and stromal elements. We observed postmenstrual proliferation and differentiation as opposed to reports of "interval regression." While the lobules and their acinar components became more compact, the phase-specific finding of mitotic activity observed from Day 3 to Day 7 suggest this phase as one of epithelial proliferation. Such proliferation of mammary epithelium has been documented in animal experiments to occur under the influence of rising serum estrogen.[7] This proliferative activity is characterized by an irregular increase in cell layers with epithelial elements which may protrude into the lumen. Following and/or concommitant with proliferation is a radial organization and stratified differentiation of epithelial cells. The result is a columnar basophilic luminal cell supported by a polygonal, pale eosinophilic cell and a basally situated cell with transparent cytoplasm and a small, comma-shaped nucleus. This differentiation of the epithelial cells observed in the present study is similar to that reported by Bassler in human breast tissue in response to exogenous estrogens[19–20] as well as the differentiation observed by Radnor in the developing mouse mamma.[21] Menstruation-dependent ultrastructural cytodifferentiation in the human breast was also described by Fanger.[6] The basophilia of the luminal cell correlates with increasing RNA and increased ribosome content observed by electron microscopy; a morphologic expression of the increased transcriptional and secondary translational activity in response to estrogen stimulation. Estrogen administration has been shown to produce similar findings in the mammary gland and uterus in experimental animal model systems.[22–23] Increased stainable chromatin, nuclear enlargement, and migration of the nucleus into a basal position are also observed in the luminal cell. The luminal and supporting cells appear to correspond to the "A" and "B" cells described by Bassler.[7] The basal, transparent cell is the myoepithelial cell, its cytoplasm depleted of glycogen during fixation. Bassler reports cytoplasmic filaments in the "B" or "chief" cell, observations which support it as a "precursor" for both the luminal cell and the myoepithelial cell. Observations by Radnor also suggest the existence of a progenitor cell which gives rise to the myoepithelial basal cell and the luminal secretory cells.

In our material, Days 15–21 were associated with an intense cytoplasmic vacuolization of the basal myoepithelial cell. This correlates with the known effects of progesterone on the glycogen content of cultured endometrial epithelium.[24] Progesterone serum levels rise *in vivo* with ovulation on Day 14. Increased glycogen deposition is observed in the postovulatory epithelium by electron microscopy.[6] The extraction of routine fixation would result in the myoepithelial vacuolization observed in formalin-fixed histologic sections. The lumen of acini and ducts were enlarged, but there was no apical budding to suggest active secretion in this phase.

The active "secretory" phase, Days 21–27, was remarkable for apical budding from the luminal cell. This also appears to be a progestational effect, resem-

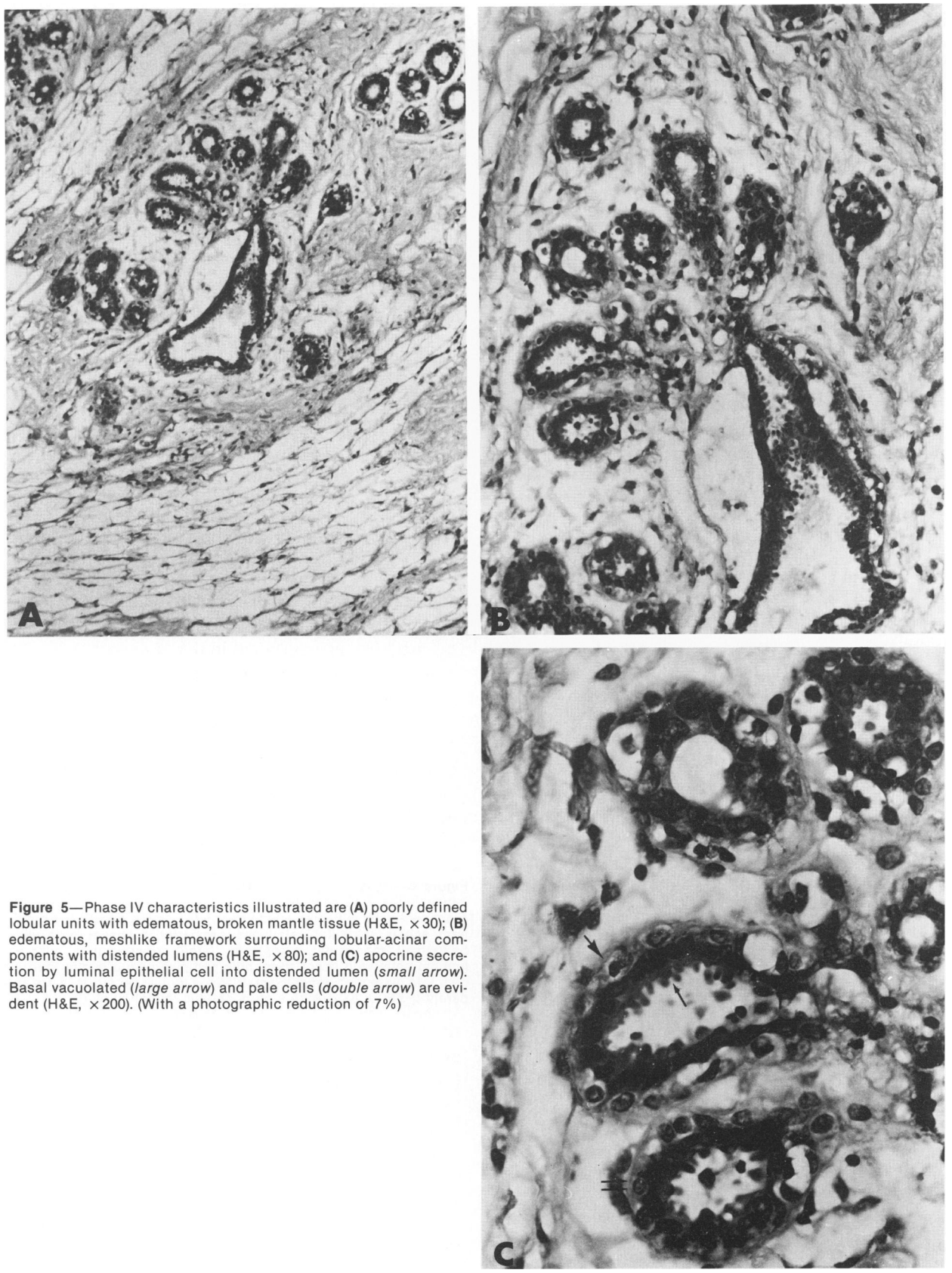

Figure 5—Phase IV characteristics illustrated are (**A**) poorly defined lobular units with edematous, broken mantle tissue (H&E, ×30); (**B**) edematous, meshlike framework surrounding lobular-acinar components with distended lumens (H&E, ×80); and (**C**) apocrine secretion by luminal epithelial cell into distended lumen (*small arrow*). Basal vacuolated (*large arrow*) and pale cells (*double arrow*) are evident (H&E, ×200). (With a photographic reduction of 7%)

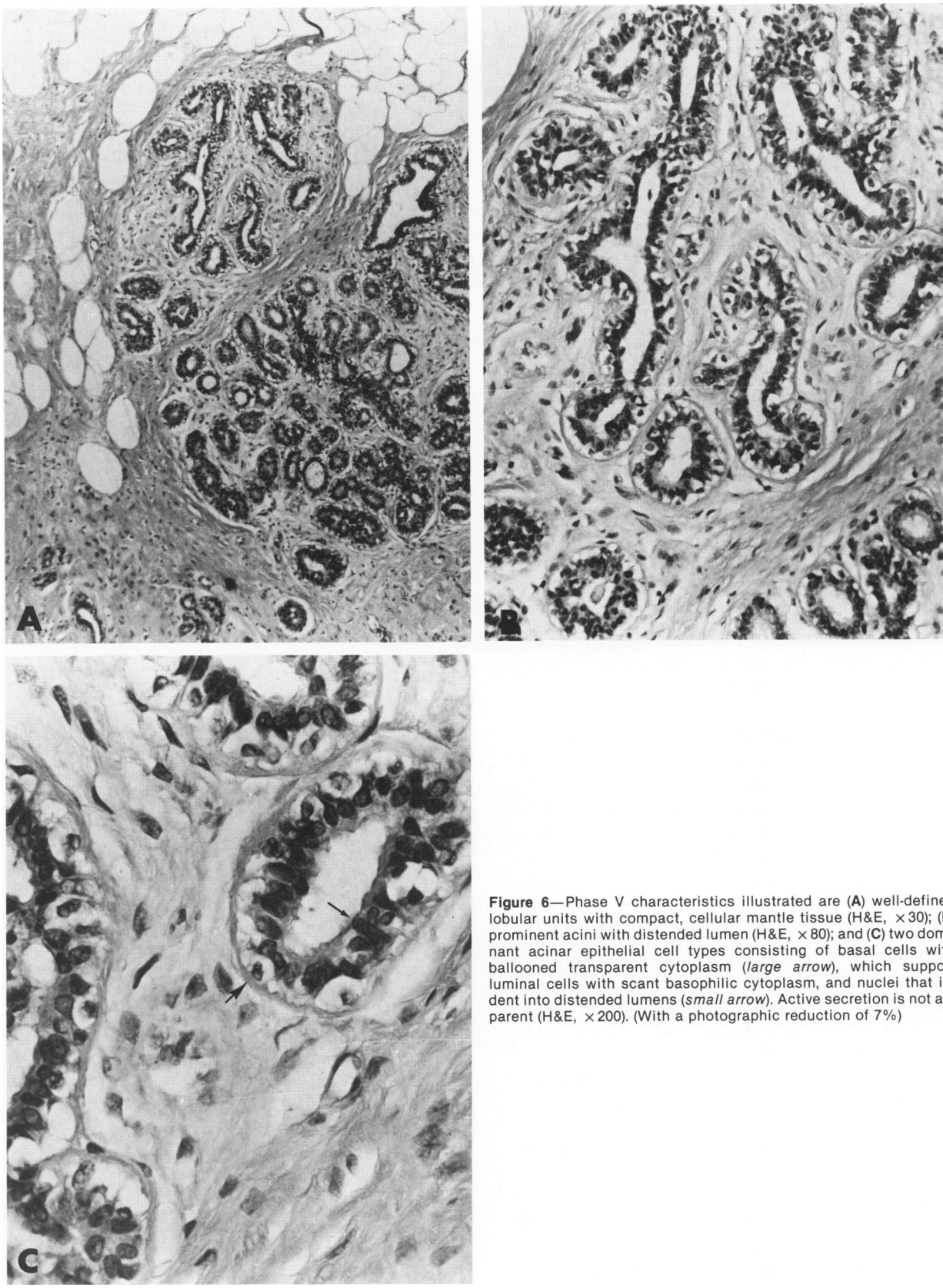

Figure 6—Phase V characteristics illustrated are (**A**) well-defined lobular units with compact, cellular mantle tissue (H&E, ×30); (**B**) prominent acini with distended lumen (H&E, ×80); and (**C**) two dominant acinar epithelial cell types consisting of basal cells with ballooned transparent cytoplasm (*large arrow*), which support luminal cells with scant basophilic cytoplasm, and nuclei that indent into distended lumens (*small arrow*). Active secretion is not apparent (H&E, ×200). (With a photographic reduction of 7%)

bling closely findings reported following progestin administration to estrogen-primed goats.[25] Ultrastructural changes including a marked increase in rough endoplasmic reticulum and secretory vacuoles support this phase as one of active protein synthesis and secretion.[6] The onset of intralobular stromal edema and venous congestion resulting in a meshlike framework separating and distorting the lobular acinar units was also a prominent feature of this phase. The edema formation may be attributed to sex-steroid–induced histamine effect on the mammary microcirculation.[26,27] An increase in the acid mucopolysaccharide content of the intralobular stroma has been demonstrated during this phase of the menstrual cycle[28] and may also account for the alteration in connective tissue structure. The resulting lobular-acinar hypertrophy secondary to epithelial enlargement, dilatation of acinar lumen, and stromal edema may account for the symptomatic breast engorgement often noted by women during this phase of their menstrual cycle. Evidence of epithelial proliferation was not characteristic of this phase, mitoses rarely having been seen.

During menstruation apocrine budding abated, but the acinar lumen remained distended with secretions. The luminal basophilic cell had scant cytoplasm, presumably lost during apocrine secretion. The basal layer of cells were extensively vacuolated, and the intralobular stroma appeared as a more dense cellular, well-demarcated structure. As the tissue reentered the proliferative phase, the luminal cells became less basophilic, basal cell vacuolization diminished, acinar lumens were less dilated, and the cycle was reinitiated.

We found, as have others, that different lobules within the same breast may vary in morphologic appearance. Placing a specimen within a phase required that the most consistent morphology among a population of lobules within several sections be determined. Proper fixation and avoidance of areas containing fibrocystic lesions were important when one was identifying a dominant morphologic pattern among the ductular-lobular units. Lobules that varied from the dominant pattern often expressed the morphologic features of the adjacent phase. While a morphologic picture determined by all criteria was important, several features were more consistently observed than others. We found significant numbers of mitotic figures and apocrine secretion to be specific for the proliferative (follicular) and secretory (luteal) phases, respectively.

Utilizing surgically obtained whole mastectomy specimens from patients interviewed by experienced epidemiologists has allowed us to avoid several factors that compromised earlier studies. Some problems, however, are inherent in obtaining adequate tissue for study. While almost half of our specimens contained no pathologic changes in any sections, others did display some evidence of fibrocystic change in some sections (<10% of ductular-lobular units). Although women were chosen for their regular menstrual cycles, recent studies have indicated an increased likelihood of hormonal aberration in patients with fibrocystic disease.[29] Because sequential breast biopsy of a single patient was not feasible, we compared breasts from patients with differing age and parity. This precludes precise quantitative description of the menstrual changes but does allow for credible qualitative criteria. The interviewing of patients prior to the time of surgery has been shown to be a reasonable means of obtaining menstrual dates based on comparison. Concomitant endometrial biopsy would be more precise but was not feasible.

This study defined histologic criteria that further characterize the hormone responsiveness of the normal human breast *in vivo*. The reproducibility of these observations was shown with double-blind trials. Our findings may be expected to provide a basis for more precise interpretation of morphologic aspects of the breast observed in surgically acquired specimens and to add to the understanding of the mechanism of hormone-associated alterations in the human breast.

References

1. Hitschmann F, Adler L: Der Bau der Uterusschleimhaut des Geschlechtsreifen weibes mit besönderer Berucksichtigung der Menstruation. Monatssch Geburtshilfe Gynaekol 1908, 27:1–82
2. Novak E, Everett HS: Cyclical and other variations in the tubal epithelium. Am J Obstet Gynecol 1928, 16:449
3. Duperroy C: Morphological study of the endocervical mucosa in relation to the menstrual cycle and to leucorrhea. Gynecologia 1951, 131:73–86
4. Geist SH: Cyclical changes in vaginal mucous membrane. Surg Gynecol Obstet 1930, 51:848–851
5. McCarthy KS Jr, Kesteron GHD, Wilkinson WE, Georgiade NG: Histopathologic study of subcutaneous mastectomy specimens from patients with carcinoma of the contralateral breast. Surg Gynecol Obstet 1978, 147: 682–686
6. Fanger H, Ree HJ: Cyclic changes of human mammary gland epithelium in relation to the menstrual cycle-an ultrastructural study. Cancer 1974, 34:571–585
7. Bassler R: The morphology of hormone induced structural changes in the female breast. Curr Top Pathol 1970, 53:1–89
8. Voherr H: The Breast: Morphology, Physiology and Lactation. New York, Academic Press, 1974
9. McCarty KS Jr, McCarty KS Sr: Steroid hormone receptors in the regulation of differentiation. Am J Pathol 1977, 86:704–774
10. Rosenberg A: Über Menstruelle durch das Corpus luteum bedingte Mammaveränderungen. Frankfurt Z Pathol 1922, 27:466–506
11. Diekmann H: Über die Histologie der Brustdruse bei

gestortem und ungestörtem Menstruationsablauf. Virchows Arch (Pathol Anat) 1925, 256:321-356
12. Moskowitz L: Über den monatlichen Zyklus der Brustdru. Arch Klin Chir 1926, 142:374-418
13. Centeno J: Über die cyklischen Veränderungen der weiblichen Brustdruse: Beitrage zur pathologischen Anatomie und zur allgemeinen Pathologie 1927, 78: 594-617
14. Kückens H: Zur Frage der zyklischen Veränderungen der Mamma und des menschlichen Scheidenepithels. Z Geburtshilfe Gynaekol 1929, 96:55-76
15. Polano O: Untersuchungen über die zyklischen Veränderungen der weiblichen Brust während der Geschlechtsreife. Z Gerburtshilfe Gynaekol 1924, 87: 363-372
16. Geschicter CF: Diseases of the Breast. 2nd edition. Philadelphia, J. B. Lippincott, 1947
17. Speert H: Rhesus monkey—A preliminary report. Surg Gynecol Obstet 1941, 73:388-390
18. Haagensen CD: Diseases of the Breast. Philadelphia, W. B. Saunders Company, 1971, pp 57-62
19. Bassler R, Schafer A: Elektronen mikroskopische Cytomorphologie der Gynäkomastie. Virchows Arch (Pathol Anat) 1969, 348:356-373
20. Bassler R, Schafer A: Elektronen mikroskopische und experimentelle Untersuchungen zur Morphologie der Gynäkomastie. Verh Dtsch Ges Pathol 1968, 52:491-498
21. Radnor CJP: Myoepithelial cell differentiation in rat mammary glands. J Anat 1972, 3:381-398
22. Bassler R, Forssmann W: Experimenteller Strukturwandel der Drüsenzelle durch Hormonwirkung. Verh Dtsch Ges Pathol 1964, 48:240-244
23. Segal SJ, Scher W: Estrogens, muclic acids and protein synthesis in uterine metabolism, Cellular Biology of the Uterus. Edited by RM Wynn. Amsterdam, North Holland, 1967
24. Hughes EC, Demers LM, Csermely T, Jones DB: Organ culture of human endometrium—Effect of ovarian steroids. Am J Obstet Gynecol 1969, 105: 707-720
25. Benson GK, Cowie AT, Cox CP, Folley SJ, Hosking ZD: Relative efficiency of hexosterol and progestrone as oily solution and as crystalline suspensions in inducing mammary growth and lactation in early and late ovariectomized goats. J Endocr 1965, 31:157-164
26. Zeppa R: Vascular response of the breast to estrogen. J Clin Endocrinol Metab 1969, 29:695-700
27. Zeppa R, Womach NA: The role of histamine release in chronic cystic mastitis. Surgery 1962, 52:195-201
28. Ozzello L, Speer FD: The mucopolysaccharides in the normal and diseased breast. Am J Pathol 1958, 34:993-1099
29. Golinger RC: Hormones and the pathophysiology of fibrocystic mastopathy. Surg Gynecol Obstet 1971, 146: 273-285

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