

Interobserver Variability in the Classification of Proliferative Breast Lesions by Fine-Needle Aspiration: Results of the Papanicolaou Society of Cytopathology Study

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This study evaluates the applicability of the published cytologic criteria in the categorization of proliferative breast lesions by assessing the diagnostic accuracy and interobserver reproducibility of a panel of experts. Twelve breast fine-needle aspiration (FNA) specimens of biopsy-proven nonproliferative breast lesion (NPL) (1 case), proliferative lesions without atypia (PL) (7 cases), proliferative lesion with atypia (PLA) (1 case), and low-nuclear grade ductal carcinoma in situ (DCIS) (3 cases) were selected. Six FNAs were Papanicolaou (PAP) and 6 were Diff-Quik-stained (DQ). Six expert cytopathologists classified the smears using a summary of published criteria as a guideline. All 6 participants rendered the same cytologic diagnosis in 2/12 (16%) cases. The agreement among the 6 raters was low ($Kappa = 0.35$). Cytohistologic correlation was achieved in 26/72 (36%) FNA diagnoses. The

correlation of the PAP-stained cases was better than the DQ: 17/36 (47%) PAP and 9/36 (25%) DQ correlated. Improving the correlation was achieved by amalgamation of NPL and PL into "low risk" and PLA and DCIS into "high risk" categories: 47/72 (65%) FNA diagnoses then correlated with histology [29/36 (81%) PAP and 18/36 (50%) DQ]. We conclude that the cytologic criteria of proliferative breast lesions need to be further defined and assessed. Consideration should be given to minimizing the number of diagnostic categories and adopting a terminology that has a direct effect on patient management. Diagn. Cytopathol. 1998;18:150-165. © 1998 Wiley-Liss, Inc.

Key Words: fine-needle aspiration of breast; proliferative ductal lesions; classification; interobserver reproducibility

Proliferative breast disease is a morphologic continuum that includes hyperplasia without atypia, hyperplasia with atypia, and carcinoma in situ. The categorization of these lesions is valuable in identifying women at an increased risk for the subsequent development of breast cancer.¹⁻³

With the increasing frequency of fine-needle aspiration (FNA) of mammographically detected breast lesions, cytopathologists are often faced with the challenge of distinguishing the entities in the continuum of proliferative disease. Several articles have advocated the usefulness of various cytologic criteria to distinguish nonproliferative breast lesions, proliferative lesions with and without atypia, and carcinoma in situ.⁴⁻¹⁰ However, the utility of the proposed criteria has not been adequately tested or universally accepted.

The purpose of this study is to evaluate the applicability of the published cytologic criteria in the categorization of nonproliferative breast lesions (NPL), proliferative lesions without atypia (PL), proliferative lesions with atypia (PLA), and low-nuclear grade ductal carcinoma in situ (DCIS) by

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Table I. Guidelines for the Classification of Proliferative Breast Lesions

Nonproliferative breast lesion
 Cytologic grading score 6–10
 Low to medium cellularity
 Epithelial cells arranged in monolayered cohesive clusters

Proliferative breast lesion
 Cytologic grading score 11–14
 Cellular yield higher than NPL
 Complex or cribriform arrangement of epithelial cells
 Intercellular spaces are regular or irregular, cellular streaming or nuclear spindling with overlap
 Cells are uniform or have variation in size and shape
 Bland chromatin pattern
 A relatively small number of single epithelial cells may be present. These cells closely resemble those of the benign epithelial cell groups
 Admixture of nonproliferative epithelium, apocrine cells, and stromal cells

Low nuclear grade ductal carcinoma in situ
 Cytologic grading score 19–24
 High cellular yield
 Monomorphic population of small to intermediate epithelial cells arranged singly or in clusters
 Three-dimensional cell clusters having papillary, solid, or cribriform (regular round/oval spaces with surrounding uniform rounded cells) pattern
 Myoepithelial cells within epithelial cell clusters are absent
 Absence of admixed benign cellular elements
 Presence of many single epithelial cells
 Individual cells are polygonal or cuboidal with round-to-oval nuclei and occasional small nucleoli

Proliferative breast lesion with atypia
 Cytologic grading score 15–18
 Ductal epithelium architecturally and/or cytologically similar to the low nuclear grade DCIS *but*:
 Single epithelial cells usually few or absent
 Scantly cellular sample
 Admixture with a large component of benign epithelium

Table II. Comparison of the Histologic Diagnoses to the Cytologic Diagnoses Rendered by the Six Participants^a

Case no.	Histologic Dx	Cytologic Dx					
		Pathologist					
		A	B	C	D	E	F
1	PL	NPL	PL	PL	NPL	PL	PL
2	DCIS	<u>DCIS</u>	<u>DCIS</u>	<u>DCIS</u>	<u>DCIS</u>	<u>DCIS</u>	<u>DCIS</u>
3	PL	<u>PL</u>	<u>PL</u>	<u>PL</u>	<u>NPL</u>	<u>PL</u>	<u>NPL</u>
4	PL	<u>DCIS</u>	<u>DCIS</u>	<u>PLA</u>	DCIS	<u>DCIS</u>	DCIS
5	DCIS	PL	PLA	<u>DCIS</u>	PLA	<u>DCIS</u>	<u>DCIS</u>
6	PL	NPL	NPL	<u>NPL</u>	NPL	<u>NPL</u>	<u>NPL</u>
7	DCIS	PL	PLA	PLA	PLA	<u>DCIS</u>	<u>DCIS</u>
8	NPL	PLA	PLA	PLA	PL	<u>PLA</u>	<u>PLA</u>
9	PL	DCIS	NPL	PLA	PLA	PL	DCIS
10	PL	NPL	<u>PL</u>	PLA	<u>PL</u>	<u>PL</u>	<u>PL</u>
11	PL	PLA	<u>PLA</u>	PLA	<u>PLA</u>	<u>PL</u>	<u>PLA</u>
12	PLA	PL	DCIS	DCIS	PL	<u>DCIS</u>	<u>PLA</u>

^aNPL = nonproliferative lesion; PL = proliferative lesion without atypia; PLA = proliferative lesion with atypia; DCIS = low-nuclear grade ductal carcinoma in situ. The correlating cytologic and histologic diagnoses are underlined. Case nos. 1–6 are Papanicolaou-stained FNA, case nos. 7–12 are Diff-Quik-stained FNA.

assessing the diagnostic accuracy and interobserver diagnostic reproducibility among experts in the field.

Materials and Methods

Twelve breast FNA specimens (6 Papanicolaou and 6 Diff-Quik-stained) were selected for the study. The selection did not consist

of a consecutive series of proliferative lesions and was aimed at including a spectrum of lesions, some of which were likely to cause diagnostic difficulties. The cases were provided from the files of The George Washington University and the University of Virginia Health Science Center. All cases had a subsequent excisional biopsy of the aspirated lesion. The possibility of

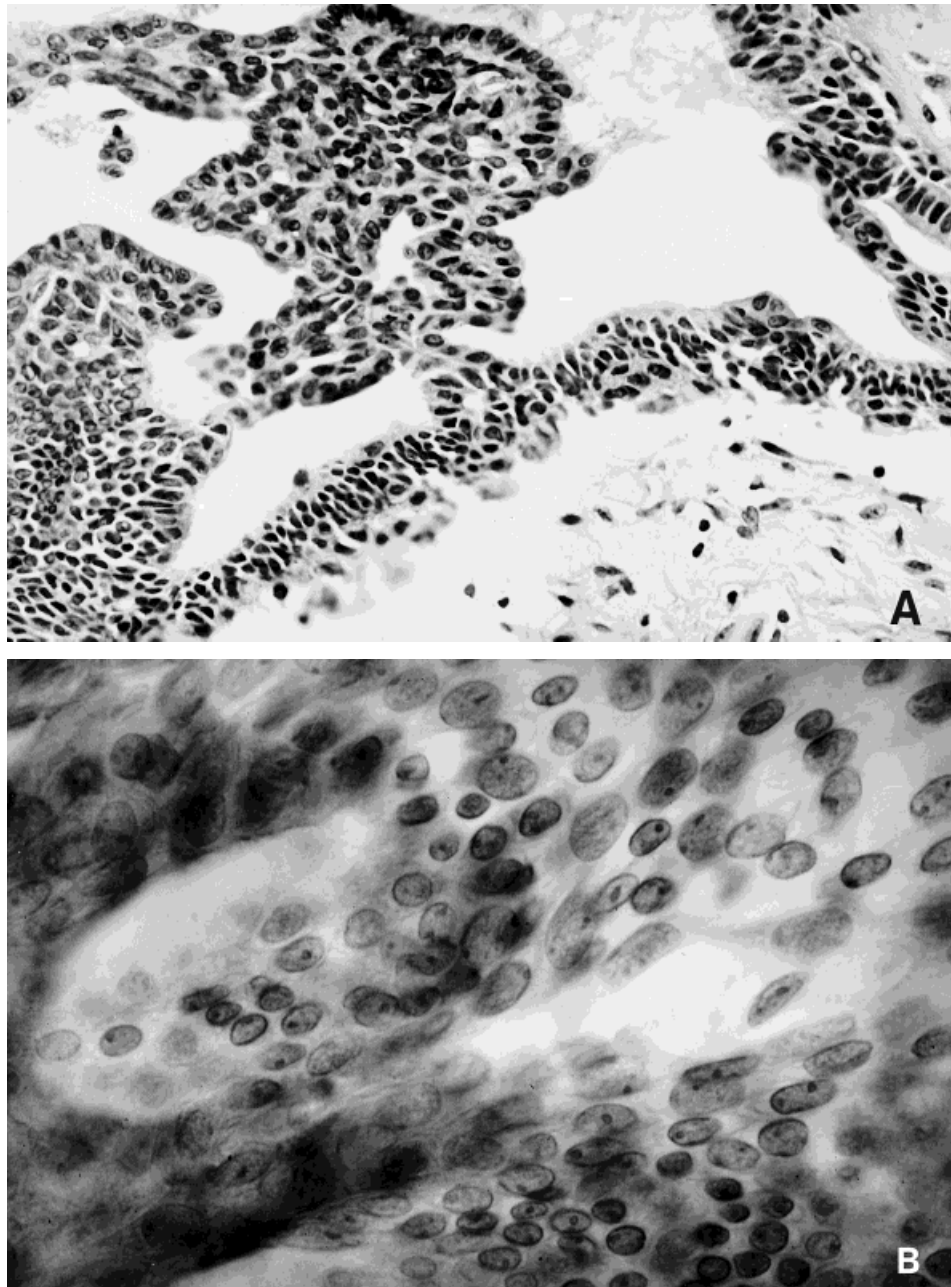


Fig. 1. Case 1. Palpable proliferative lesion. **A:** Histologic section. Ductal hyperplasia without atypia (hematoxylin and eosin stain, $\times 400$). **B:** Smears displaying sheets of epithelial cells with good polarity, regular nuclei, and fine chromatin. Cellular spindling and the outline of a lumen are noted (Papanicolaou stain, $\times 1,000$).

sampling error was excluded based on cytohistologic correlation and/or the presence of a needle tract within the biopsy specimen. The histologic sections of all cases were reviewed and classified by Dr. Steven G. Silverberg.

Six pathologists with expertise in the field of breast FNA (W.J.F., A.R.F., S.M., T.R.M., N.S., H.H.W.) reviewed the smears and were asked to classify the lesions into one of four categories: NPL, PL, PLA, or DCIS. The participants were

provided with a summary of published cytologic criteria to use as a guideline (Table I) and with two pertinent references (Masood et al.⁸ and Sneige and Staerke⁹).

The provided summary of cytologic criteria was compiled from the published literature⁴⁻¹⁰ and was mostly derived from Masood et al.⁸ and Sneige and Staerke⁹ articles. Both architectural and cytologic features were included: cellularity, cell composition (duct epithelium, apocrine metaplasia,

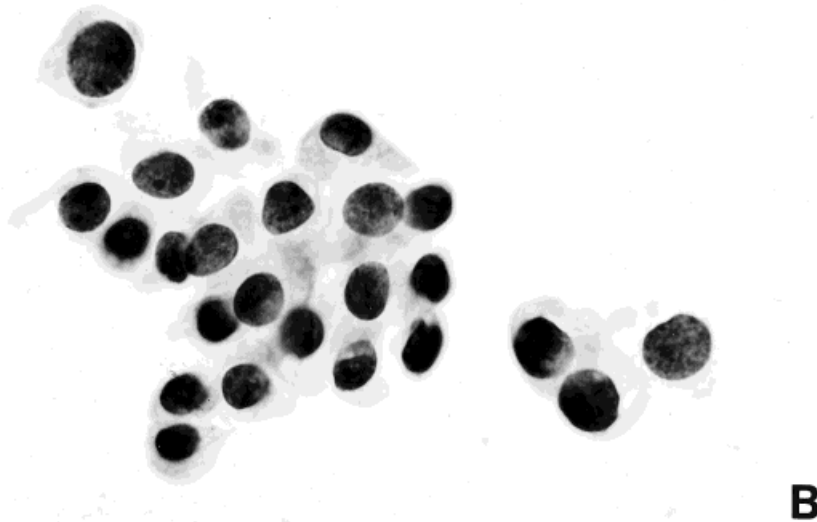
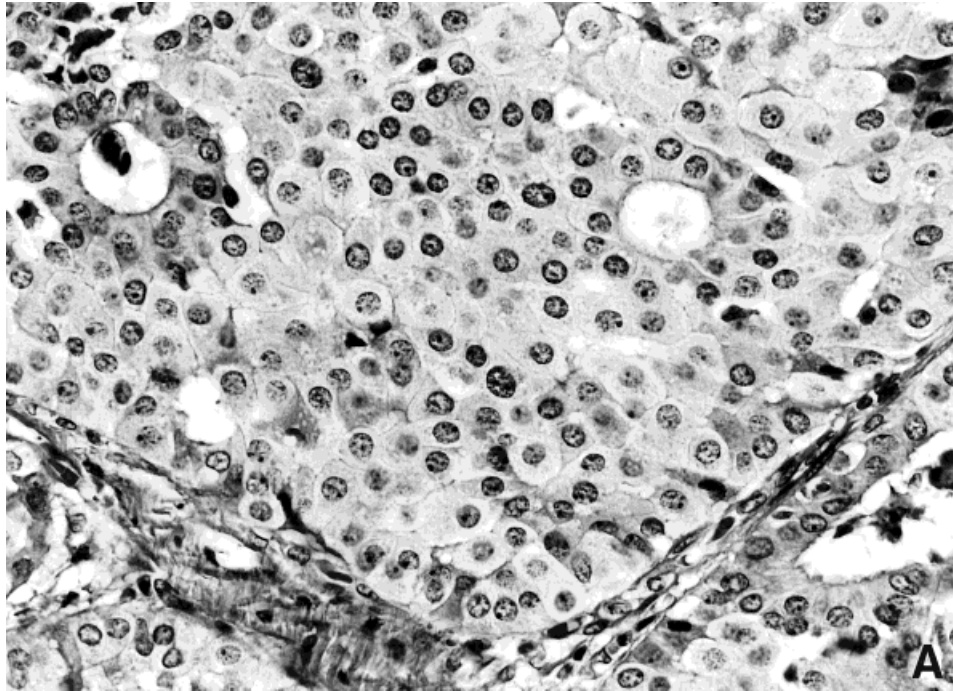


Fig. 2. Case 2. Palpable ductal carcinoma in situ. **A:** Histologic section. Ductal carcinoma in situ, low nuclear grade (hematoxylin and eosin stain, $\times 1,000$). **B:** Cellular smear showing poorly cohesive clusters of ductal cells with enlarged pleomorphic, hyperchromatic nuclei and prominent nucleoli. No myoepithelial cells present (Papanicolaou stain, $\times 1,000$).

myoepithelial cells, stromal cells), architectural pattern, number of single epithelial cells, and nuclear features. The cytologic scoring system proposed by Masood et al.,⁸ in which the classification was based on a score derived from the sum of six values, was also included. The system consisted, briefly, of a value of 1 to 4 given for each of

the following features: cellular arrangement, cellular pleomorphism, presence of myoepithelial cells, anisonucleosis, nucleoli and chromatin clumping. The purpose of the study was not to compare various systems, i.e., cytologic scoring vs. architectural, therefore, the participants were not instructed in the application of these guidelines nor required to

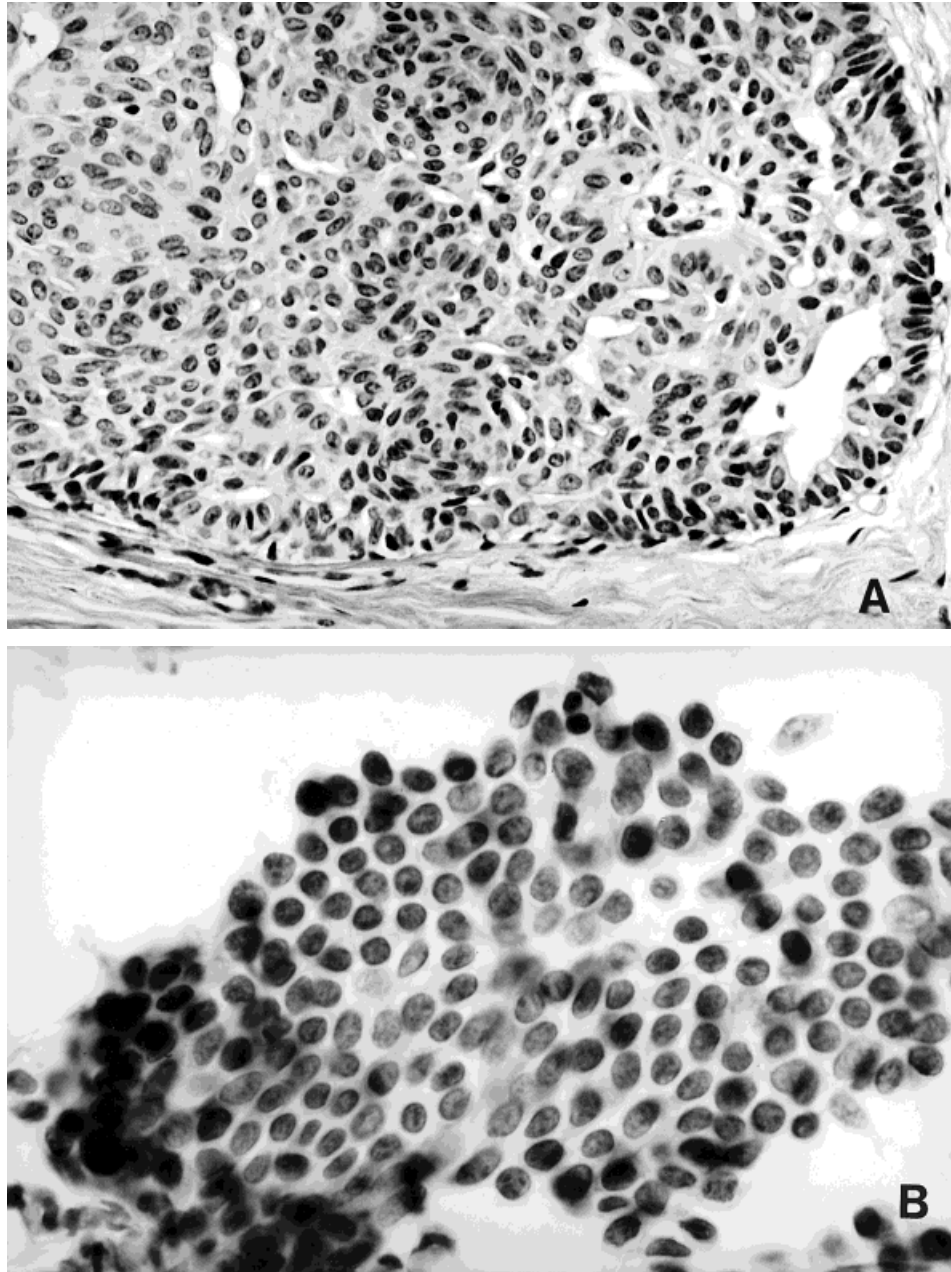


Fig. 3. Case 3. Palpable proliferative lesion. **A:** Histologic section. Ductal hyperplasia without atypia (hematoxylin and eosin stain, $\times 400$). **B:** Smear displaying cohesive sheets of regular ductal cells with interspersed myoepithelial cells (Papanicolaou stain, $\times 1,000$).

use both systems. The design of the study was aimed at simulating the current situation of most cytopathologists in that assessment is based on reading and interpreting various published criteria combined with personal experience.

The level of interobserver agreement was tested using kappa statistics. To determine whether agreement varied by type of lesion, the extent of agreement among raters in distinguishing each type of lesion from all the others combined was assessed. The cytohistologic correlation and

the comparison of the Papanicolaou and Diff-Quik-stained results were determined.

Results

The age of the patients ranged from 37 to 77 years. Nine lesions were palpable and three were nonpalpable and were aspirated under radiologic guidance. The histologic classification of the breast biopsies was: NPL (1 case), PL (7 cases), PLA (1 case), and DCIS (3 cases). In all twelve cases there was complete agree-

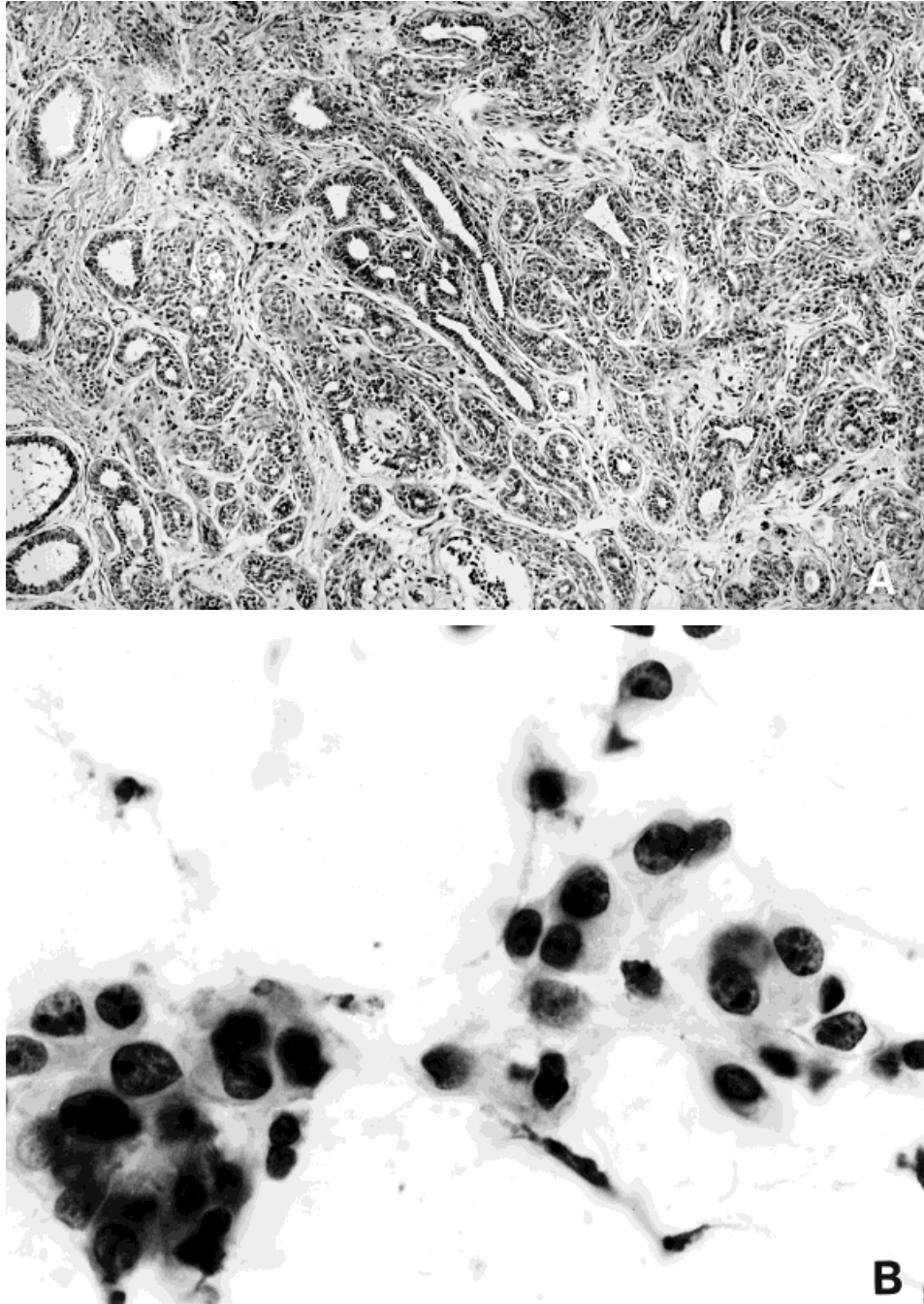


Fig. 4. Case 4. Nonpalpable 0.5-cm lesion. **A:** Histologic section. Ductal hyperplasia without atypia and adenosis (hematoxylin and eosin stain, $\times 200$). **B:** Highly cellular smear showing poorly cohesive clusters of ductal cells with enlarged pleomorphic nuclei, coarse chromatin, and prominent nucleoli. Note the resemblance with Figure 2B (Papanicolaou stain, $\times 1,000$).

ment between the original and the review diagnosis, which highlights the fact that the histologic classification of the selected cases was not controversial.

Cytohistic Correlation

The comparison of the histologic diagnoses with the cytologic diagnoses rendered by the six pathologists is presented

in Table II. One case was correctly diagnosed by all six participants (case 2, DCIS). Three cases were correctly classified by 4/6 participants (cases 1, 3, 10), one case was correctly classified by 3/6 participants (case 5), one case was correctly classified by 2/6 (case 7), and three cases were correctly classified by 1/6 (cases 9, 11, 12). The remaining three cases (nos. 4, 6, 8) were incorrectly classified by all 6

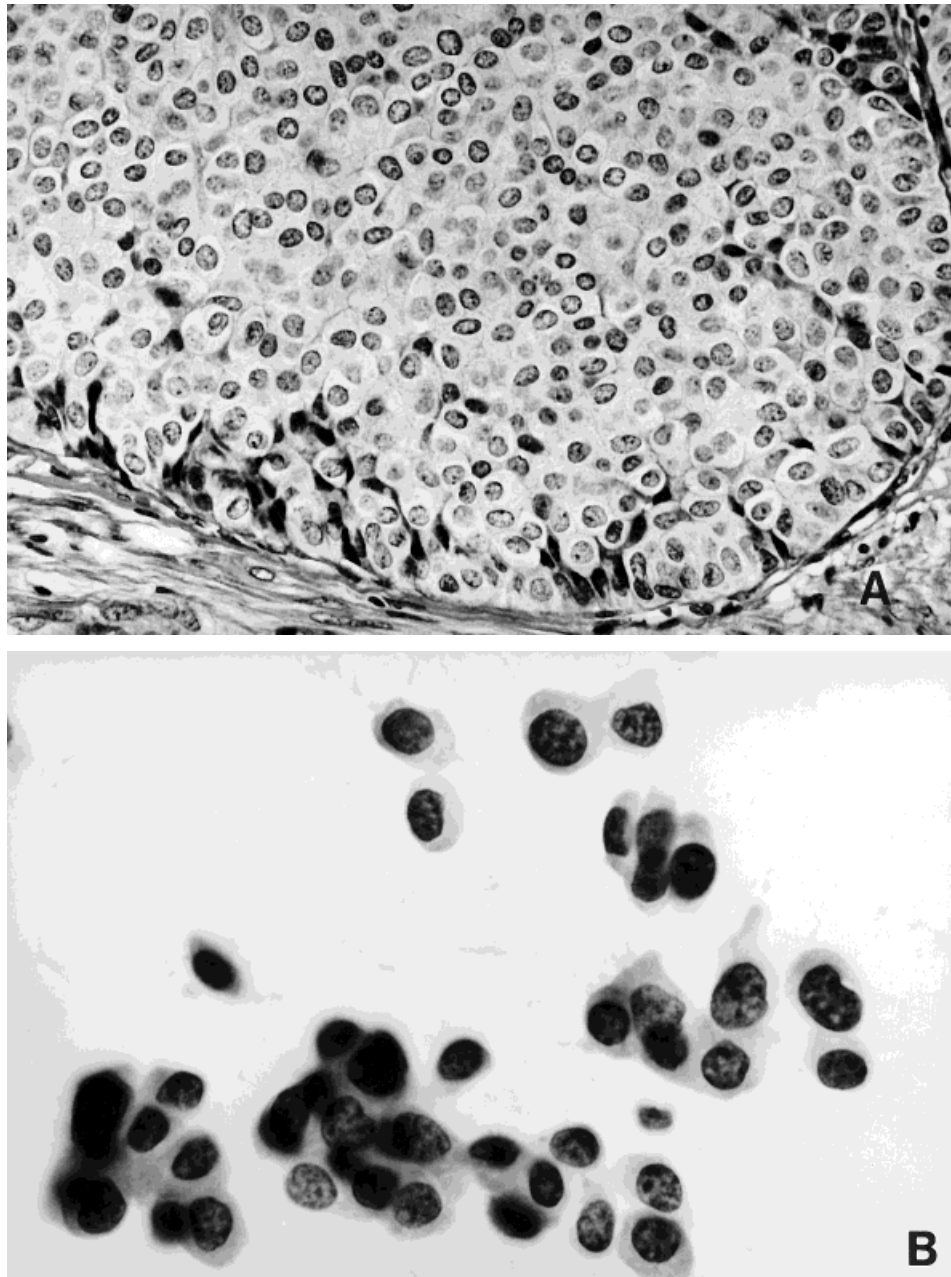


Fig. 5. Case 5. Nonpalpable 0.9-cm lesion. **A:** Histologic section. Ductal carcinoma in situ solid and cribriform type (hematoxylin and eosin stain, $\times 400$). **B:** Cellular smear showing poorly cohesive clusters and single epithelial cells with enlarged pleomorphic nuclei, clumped chromatin, and irregular nuclear membranes (Papanicolaou stain, $\times 1,000$).

participants. The cytology and corresponding histology of the study cases are illustrated in Figures 1–12.

Overall, 26/72 (36%) rendered cytologic diagnoses correlated with the histologic classification. When the results were tabulated according to the type of stain (Papanicolaou vs. Diff-Quik-stained FNA), histologic correlation was achieved in 17/36 (47%) and 9/36 (25%) of the cytologic diagnoses, respectively.

Interobserver Reproducibility

All six participants rendered the same cytologic diagnosis in 2/12 (16%) cases (nos. 2, 6), only one of which correlated with the histologic diagnosis. The FNA diagnoses were within one degree of difference among the participants in 5/12 (42%) cases (nos. 1, 3, 4, 8, 11) and within two degrees of difference in 4/12 (33%) cases (nos. 5, 7, 10, 12). The FNA diagnoses ranged from NPL to DCIS in 1/12 (8%) case (no. 9).

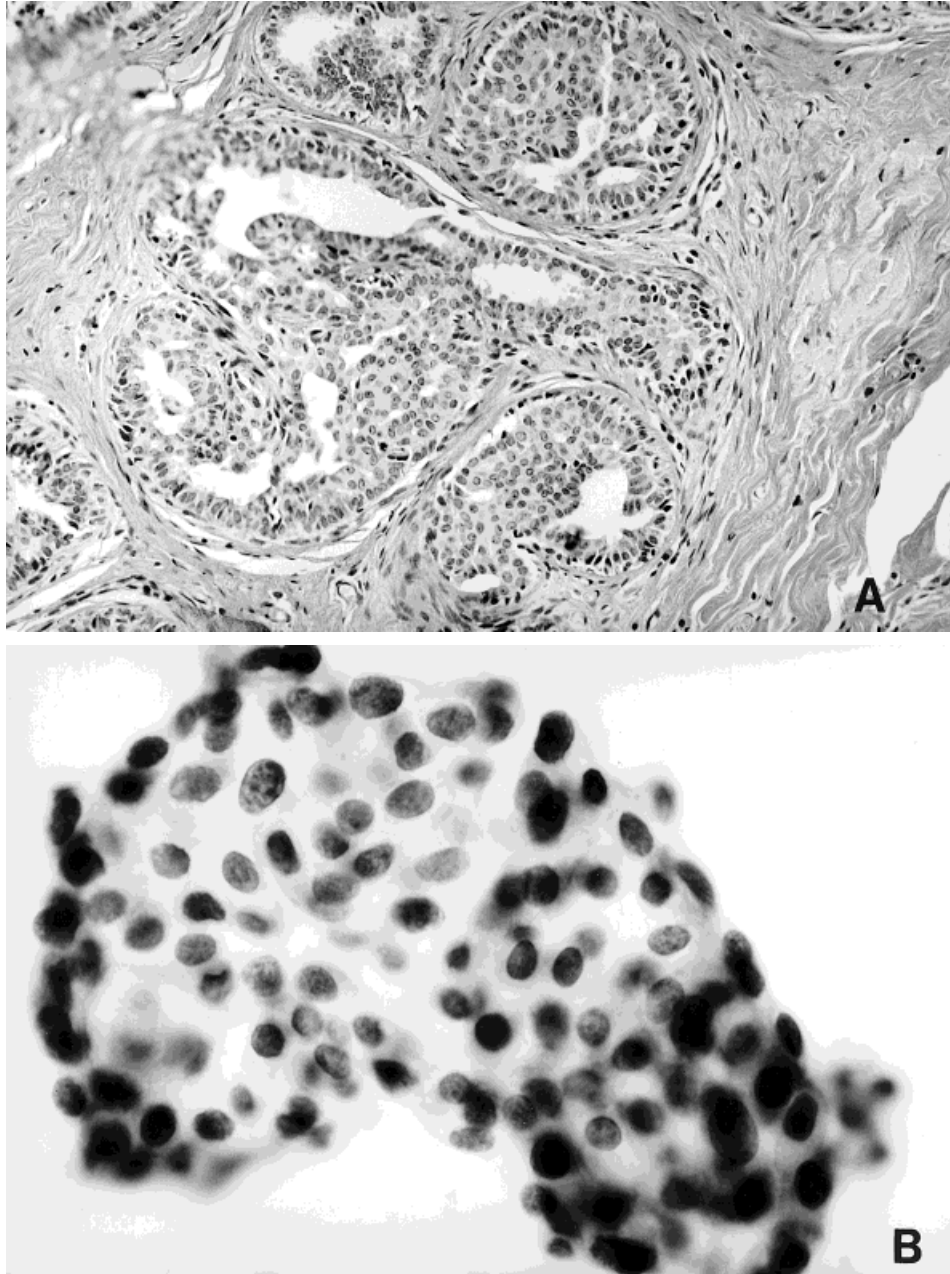


Fig. 6. Case 6. Nonpalpable ill-defined lesion. **A:** Histologic section. Ductal hyperplasia without atypia (hematoxylin and eosin stain, $\times 200$). **B:** Smear showing tightly cohesive clusters of ductal cells with slight variability in nuclear size and interspersed myoepithelial cells. No particular architectural pattern is appreciated (Papanicolaou stain, $\times 1,000$).

Overall the agreement among the 6 raters in categorizing the lesions was low ($\text{Kappa} = 0.35$). The extent of agreement varied according to the lesion, with low agreement in the diagnoses of PL ($\text{kappa} = 0.18$) to a moderate level of agreement ($\text{Kappa} = 0.48$) in the diagnoses of NPL and DCIS.

Minimizing the number of diagnostic categories, without compromising patient management, is likely to improve the cytohistologic correlation and interobserver reproducibility. Since NPL and PL may be managed conservatively, they

were combined into “low risk lesions,” while PLA and DCIS, which need to be biopsied, were combined into “high risk lesions.” The results of implementing this classification are presented in Table III. Overall, 47/72 (65%) rendered cytologic diagnoses correlated with the histologic classification. When the results were tabulated according to the type of stain (Papanicolaou vs. Diff-Quik-stained FNA), they showed that 29/36 (81%) and 18/36 (50%) rendered cytologic diagnoses correlated with the histologic classification,

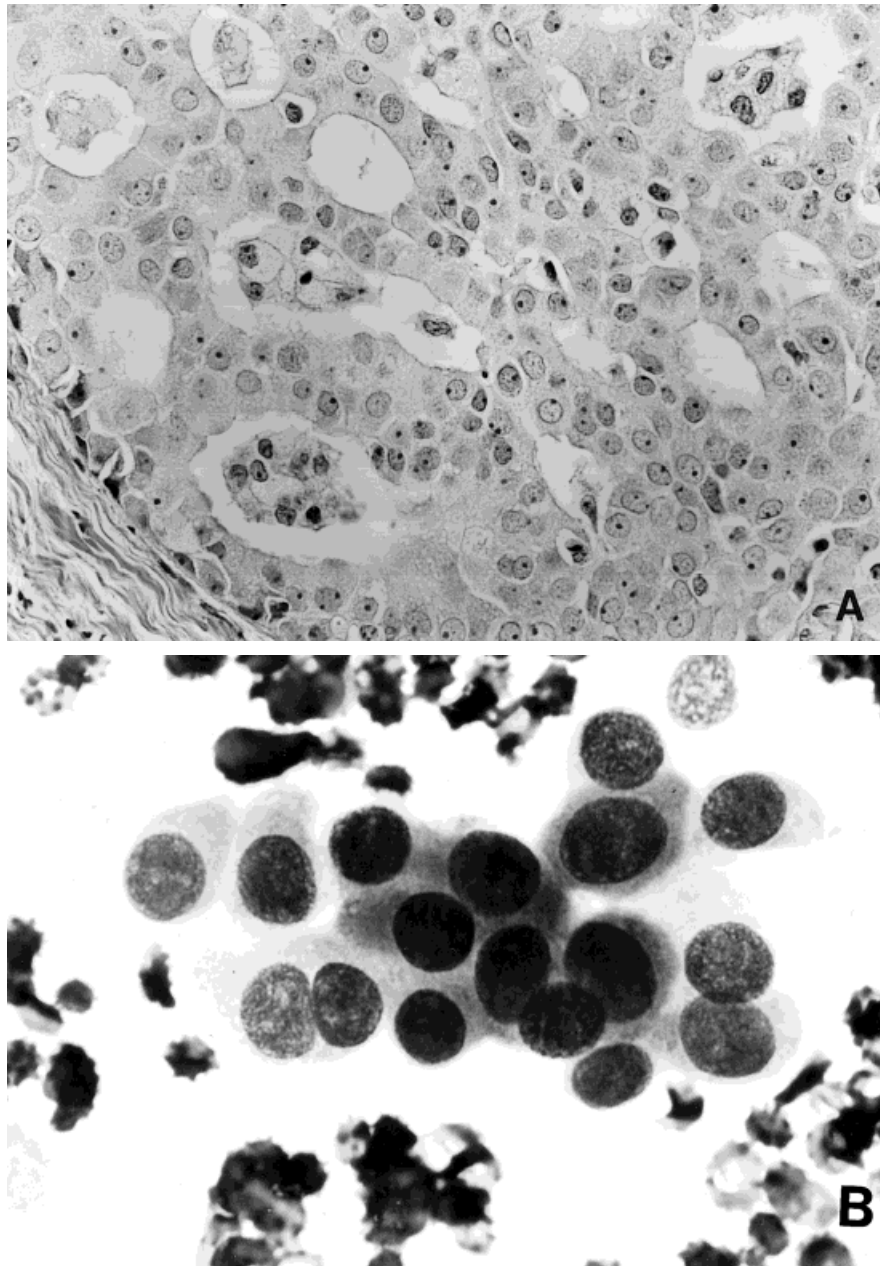


Fig. 7. Case 7. Palpable lesion. **A:** Histologic section. Extensive ductal carcinoma in situ, solid and cribriform type (hematoxylin and eosin stain, $\times 400$). **B:** Bloody smear showing many small clusters of ductal epithelial cells, some loosely cohesive, with nuclear enlargement and dense well-defined cytoplasm (Diff-Quik, $\times 1,000$).

respectively. Of the 25 noncorrelating diagnoses, 21 were overcalled cytologically (6 Papanicolaou and 15 Diff-Quik-stained) and 4 were undercalled (1 Papanicolaou and 3 Diff-Quik-stained). Decreasing the number of diagnostic categories also improves the interobserver reproducibility. All six participants rendered the same diagnosis in 5/12 (41%) cases, four of which correlated with the histology and one (case 4) did not.

Discussion

Intraductal proliferative lesions of the breast reflect a spectrum of changes that ranges from physiologic alterations to in situ carcinoma. The risk of developing subsequent invasive breast carcinoma is stratified according to the degree of epithelial proliferation and atypia.^{1,2,11} The risk is 1.5–2-fold in women with proliferative lesions without atypia, 4–5-fold in women with proliferative lesions with

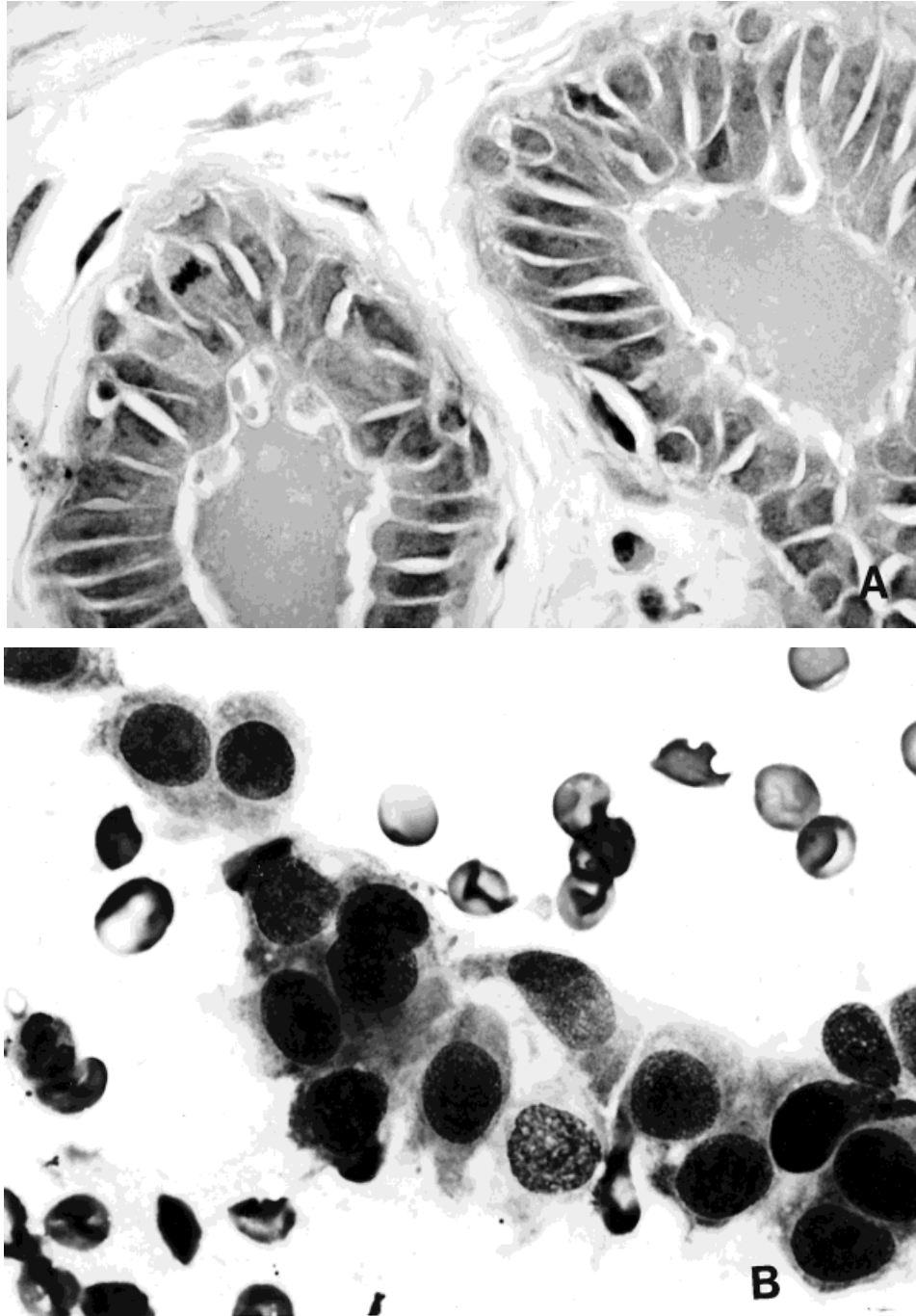


Fig. 8. Case 8. Palpable nonproliferative lesion. **A:** Histologic section revealed a needle tract and nonproliferative ductal and lobular units. Note the nuclear enlargement and mitotic activity (hematoxylin and eosin stain, $\times 400$). **B:** Cellular smears displaying loosely cohesive clusters of epithelial cells with nuclear enlargement and pleomorphism (Diff-Quik, $\times 1,000$).

atypia, and 8–10-fold in women with carcinoma in situ. Histologic criteria that allow the distinction of these various proliferative lesions are established.^{12,13}

The increasing utilization of screening mammography has led to an increase in the detection of benign proliferative

lesions and carcinomas in situ either by the appearance of a nonpalpable new density or the presence of clustered microcalcifications. These occult lesions reveal a high proportion of prognostically significant abnormalities. Rubin et al.¹⁴ showed that 20% of nonpalpable breast masses

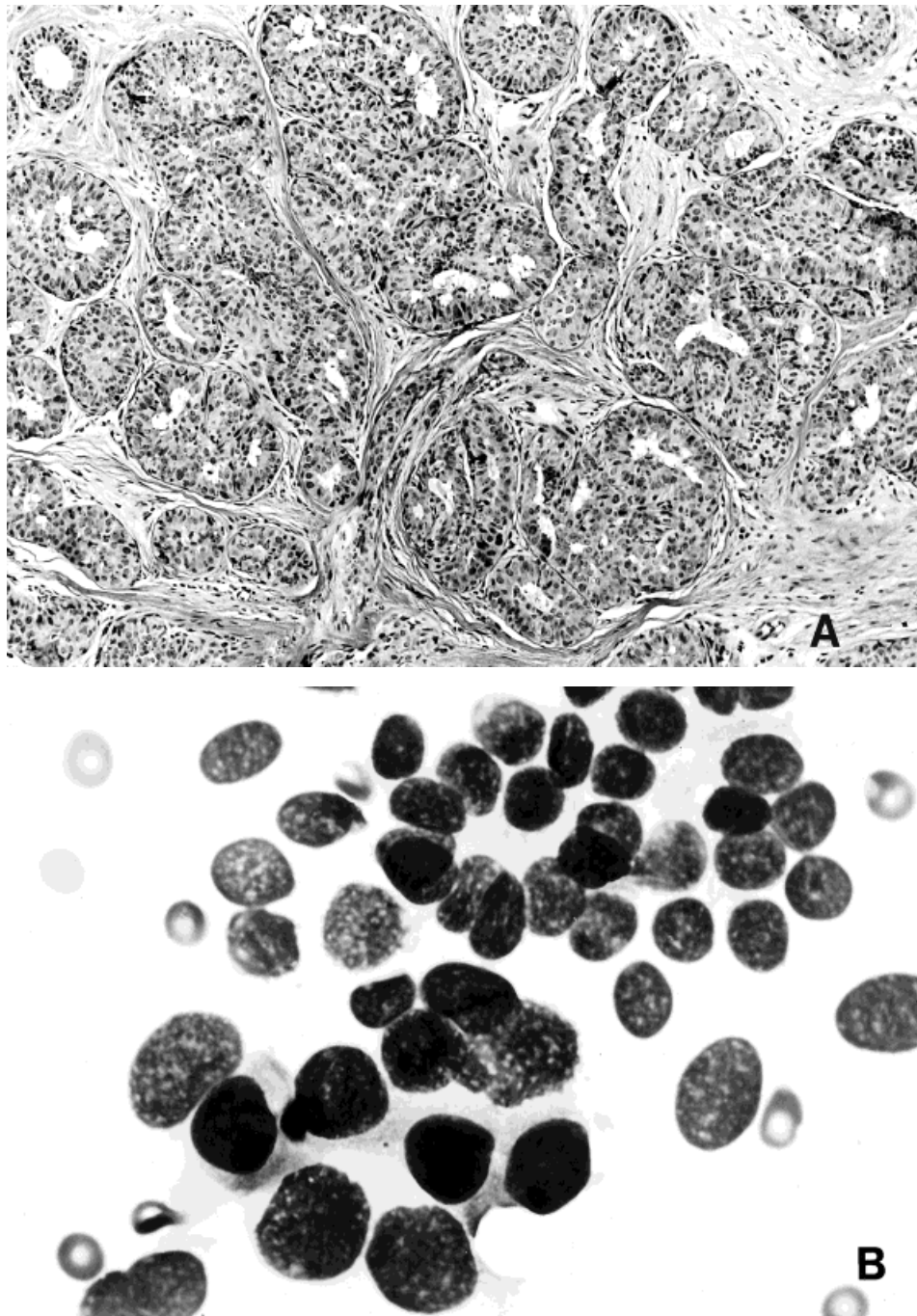


Fig. 9. Case 9. Palpable proliferative lesion. **A:** Histologic section. Ductal hyperplasia without atypia (hematoxylin and eosin stain, $\times 200$). **B:** Cellular smears displaying loosely cohesive clusters of epithelial cells with nuclear enlargement, overlap, and pleomorphism. Acinar arrangement is noted (Diff-Quik, $\times 1,000$).

were malignant (55% in situ) and 10% revealed atypical ductal hyperplasia. Rosenberg et al.¹⁵ found that among 927 cases, 29% were malignant and 35% were proliferative lesions. As a result, the pathologist may be increasingly faced with the challenge of interpreting these lesions cytologically.

The reliability of cytologic criteria in separating benign from malignant breast lesions is well established. Recently,

several studies have addressed the ability of cytomorphology to diagnose NPL, PL, PLA, and DCIS.^{4-10,16-18} These studies resulted in variable degrees of success. Masood et al.^{7,8} assessed the reliability of a cytological scoring system, on Papanicolaou-stained smears, in a prospective study of 100 mammographically guided FNAs of nonpalpable breast lesions. The results showed a high degree of concordance

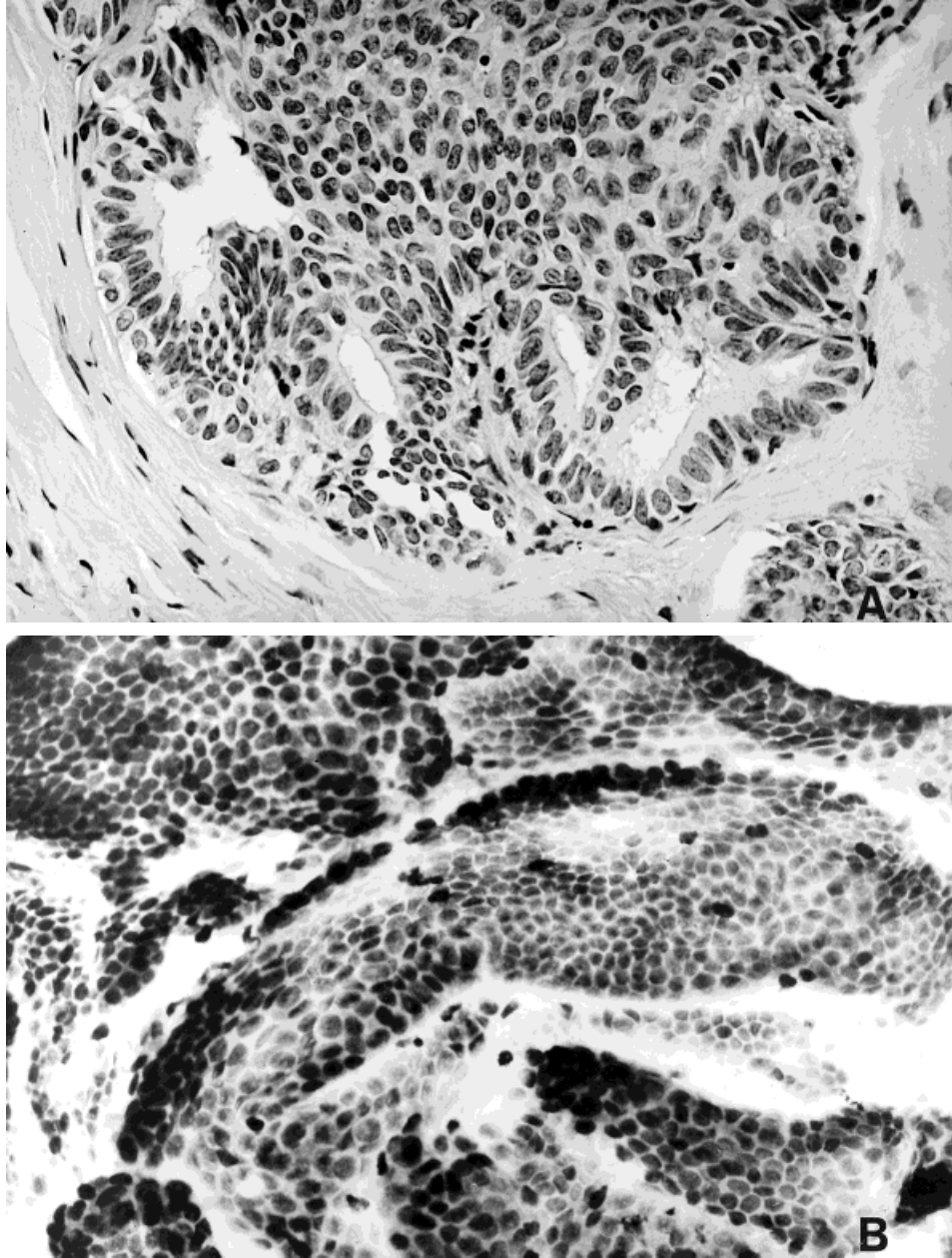


Fig. 10. Case 10. Palpable proliferative lesion. **A:** Histologic section. Ductal hyperplasia without atypia (hematoxylin and eosin stain, $\times 400$). **B:** Highly cellular smear displaying large sheets of ductal epithelium with slit-like spaces. Nuclear polarity is preserved and myoepithelial cells are present within the cells groups (Diff-Quik, $\times 1,000$).

between the cytologic interpretation and the histologic diagnosis rendered on the needle localization biopsies. Masood et al.¹⁹ also applied their cytologic grading system to evaluate 156 palpable breast lesions and showed a diagnostic accuracy of 95% despite the heterogeneity of sampling in palpable, particularly large lesions.

Sneige and Staerkel⁹ introduced the concept of using architectural features cytologically and concluded that the application of both cytologic and architectural criteria is

more reliable than cytology alone in separating proliferative breast lesions. Similarly, Dawson et al.⁵ showed that applying both architectural and cytologic criteria enhanced diagnostic accuracy. Cytologically, the architectural features of proliferative breast lesions may be apparent in the larger tissue fragments and recapitulate the histologic appearance of these lesions. Slit-like lumens, swirling and streaming, are noted in PL; round spaces may be seen in PL, PLA, and cribriform DCIS; rigid sublumens and a micropapillary

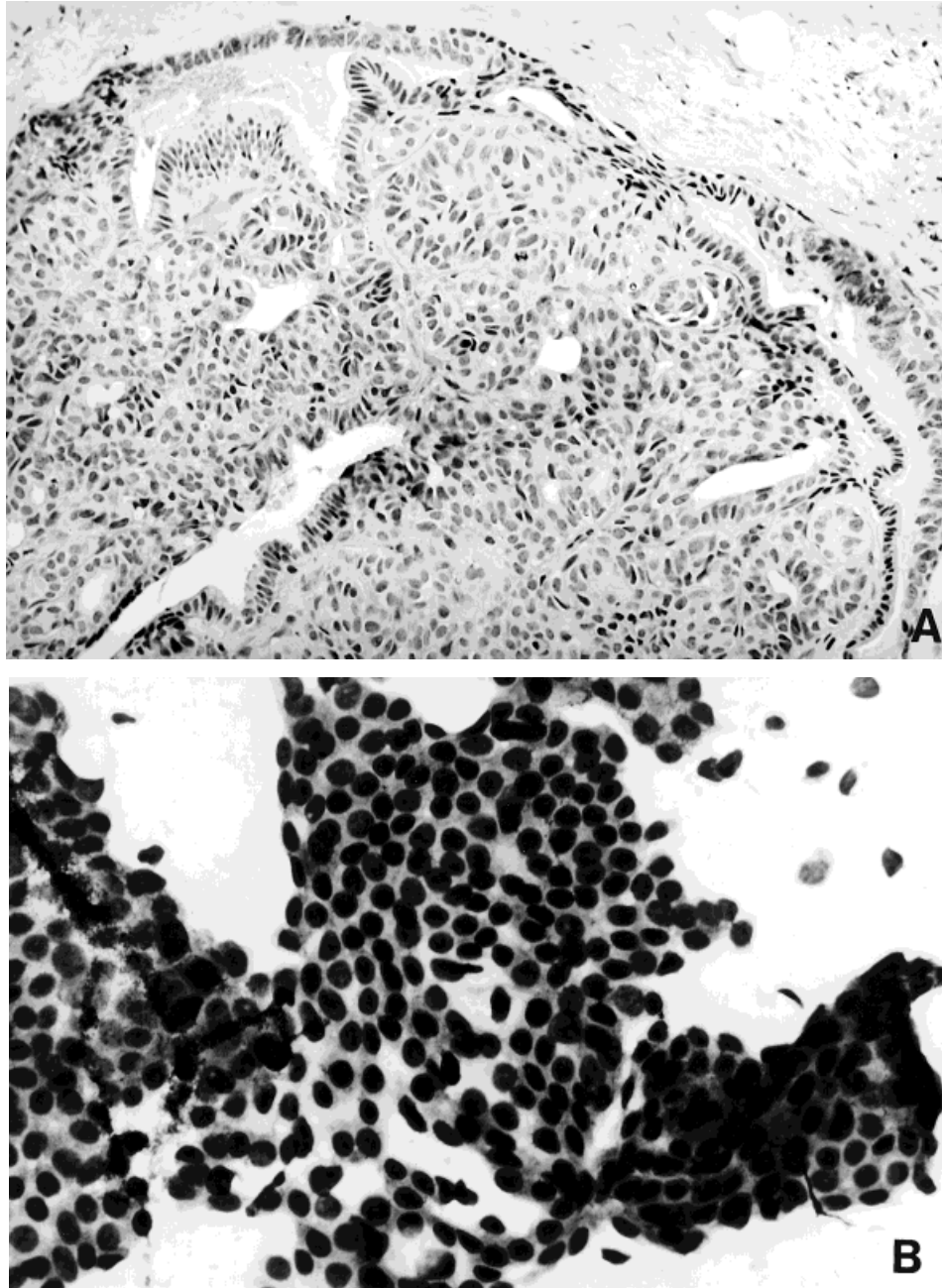


Fig. 11. Case 11. Palpable proliferative lesion. **A:** Histologic section. Ductal hyperplasia without atypia (hematoxylin and eosin stain, $\times 200$). **B:** Highly cellular smear displaying large sheets of epithelial cells with complex architecture. Focal nuclear enlargement is present (Diff-Quik, $\times 1,000$).

architecture are features suggestive of DCIS. Thomas et al.¹⁰ demonstrated that experience and fine-tuning of cytologic criteria increased the concordance with the histologic findings. All of these studies emphasize the importance of adequate sampling to minimize, in particular, underdiagnoses.

In the current study, the agreement among the six raters in categorizing the 12 lesions was low (Kappa = 0.35). All six participants rendered the same diagnosis in only 2/12 cases. The extent of agreement varied according to the lesion, with

low agreement in the diagnoses of PL (kappa = 0.18) to a moderate level of agreement (Kappa = 0.48) in the diagnoses of NPL and DCIS. Since there is a substantial degree of subjectivity and interobserver variability in classifying proliferative breast lesions histologically, it is reasonable to expect the same and even greater difficulty cytologically.^{20,21} Interobserver variation in the interpretation of borderline lesions in many body sites is well recognized. A good example is the poor reproducibility of the diagnosis of

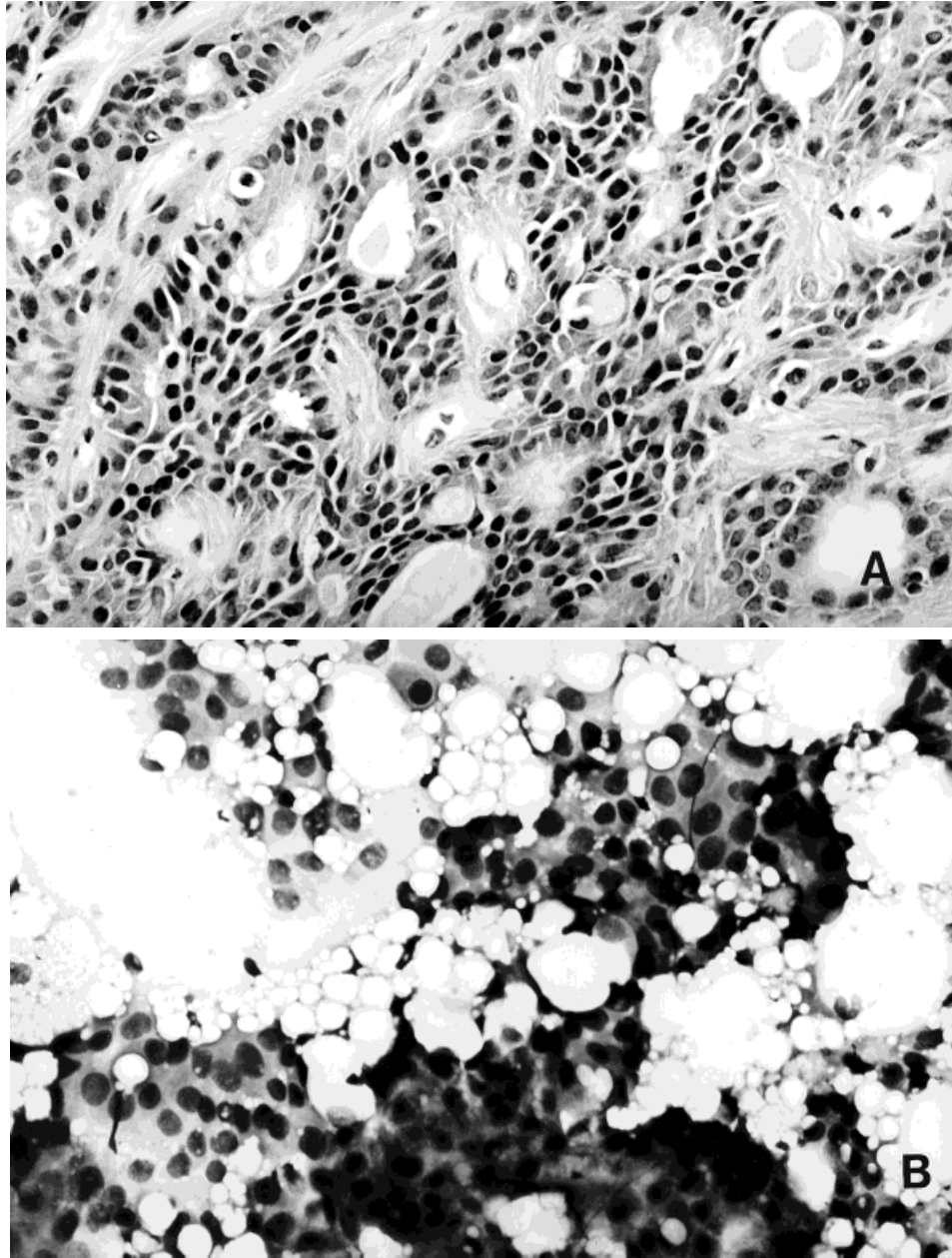


Fig. 12. Case 12. Palpable 0.9-cm superficial lesion. **A:** Histologic section. Atypical ductal hyperplasia (hematoxylin and eosin stain, $\times 400$). **B:** Highly cellular smear displaying large loosely cohesive clusters and single epithelial cells showing nuclear enlargement and pleomorphism (Diff-Quik, $\times 400$).

atypical squamous cells of undetermined significance (ASCUS) in cervical smears, despite the fact that criteria for ASCUS have been published.^{22,23}

Exact cytohistologic correlation was achieved in only 26/72 (36%) FNA diagnoses in the present study. This is probably due to overlap in the cytologic criteria between diagnostic categories and a significant element of subjectivity in applying these criteria. The cytohistologic correlation of the Papanicolaou-stained cases was better than that of the Diff-Quik-stained: 17/36 (47%) vs. 9/36 (25%). The differ-

ence in the results may be explained by the fact that most studies have proposed criteria based, at least in part, on alcohol-fixed, Papanicolaou-stained preparations.^{6,7} Chromatin detail is not as well preserved and is more difficult to evaluate in air-dried preparations. In addition, nuclear enlargement, pleomorphism, and overlap, reported as useful criteria, may be exaggerated in air-dried preparations and may lead to overcalls. Although in most cases it is sufficient and most cost effective for the laboratories to make either air-dried Diff-Quik-stained or alcohol-fixed Papanicolaou-

Table III. Comparison of the Histologic and Cytologic Diagnoses Rendered by the Six Participants Using the Categories Low- and High-Risk Lesions^a

Case no.	Histologic Dx	Cytologic Dx					
		Pathologist					
		A	B	C	D	E	F
1	PL	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>
2	DCIS	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>
3	PL	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>
4	PL	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>
5	DCIS	LR	HR	HR	HR	HR	HR
6	PL	LR	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>	<u>LR</u>
7	DCIS	<u>LR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>	<u>HR</u>
8	NPL	HR	<u>HR</u>	<u>HR</u>	<u>LR</u>	<u>HR</u>	<u>HR</u>
9	PL	HR	<u>LR</u>	HR	<u>HR</u>	<u>LR</u>	HR
10	PL	<u>LR</u>	<u>LR</u>	HR	<u>LR</u>	<u>LR</u>	<u>LR</u>
11	PL	<u>HR</u>	<u>HR</u>	HR	<u>HR</u>	<u>LR</u>	<u>HR</u>
12	PLA	LR	<u>HR</u>	<u>HR</u>	LR	<u>HR</u>	<u>HR</u>

^aNPL = nonproliferative lesion; PL = proliferative lesion without atypia; PLA = proliferative lesion with atypia; DCIS = low-nuclear grade ductal carcinoma in situ; LR = low-risk lesion; HR = high-risk lesion. The correlating cytologic and histologic diagnoses are underlined. Case nos. 1–6 are Papanicolaou-stained FNA, cases 7–12 are Diff-Quik-stained FNA.

stained preparations, the combination of both types of preparation affords more information than either one alone since these stains highlight different features of cytoplasm, background material, and nuclei.²⁴

It is important for the pathologist to recognize that the cytomorphology of NPL, the benign end of the spectrum, varies. NPL causes no diagnostic problem when the smears consist of small, uniform epithelial cells arranged in a honeycomb pattern, have regular nuclei with fine chromatin pattern, and reveal myoepithelial cells within the epithelial clusters. However, it has been shown that a certain degree of cellular atypia may be seen in NPL and that the cytologic features of NPL and PL overlap.^{17,18} Maygarden et al.¹⁸ found no cytologic feature that reached statistical significance in distinguishing NPL and PL. Frost et al.¹⁷ found that only the presence of a swirling pattern reached statistical significance in distinguishing between the two entities and concluded that the overlap in cytologic features between NPL and PL makes their distinction difficult in cytologic sampling. Cytologic atypia, such as mild nuclear enlargement, crowding and overlapping, and distinct nucleoli in ductal and lobular epithelium, may occur during the secretory phase of the menstrual cycle and is reported as a source of diagnostic error.²⁵ Aspirates of radial scar may simulate those of carcinoma and are a source of false-positive results.^{26,27}

DCIS, the other end of the spectrum of proliferative lesions, also presents with variable cytologic features. The findings vary according to the subtype of DCIS (comedo, solid, micropapillary, papillary, and cribriform). There are distinct cytological differences between comedo and noncomedo DCIS. The diagnosis of carcinoma in comedo DCIS

usually presents little difficulty since the features of malignancy are quite evident, but the ability of FNA to distinguish between a pure DCIS and an invasive tumor is limited.^{6,28,29} On the other hand, the ability of cytologic material to distinguish noncomedo DCIS from proliferative breast disease is also limited.^{28,30–32} Smears are frequently interpreted as benign, inconclusive, or suspicious due to the low cellularity, minimal cytologic atypia, or absence of cellular dissociation.

Our findings underscore the difficulty in applying the histologic categorization of proliferative breast lesions to FNA samples. Moreover, the focal nature of these lesions further complicates the cytologic interpretation. For instance, PLA is often present in the midst of fibrocystic changes or is associated with DCIS,³³ and adjacent benign or malignant elements may predominate in the smears. The results of this study support the concept that, even assuming that the cytologic sample is representative of the most severe lesion, only a broader categorization that has an impact on patient management may be possible cytologically. By reducing the number of diagnostic categories to two—“low risk” consisting of NPL and PL and “high risk” consisting of PLA and DCIS—the cytohistologic correlation and the interobserver reproducibility improved. Forty-seven of 72 (65%) FNA diagnoses correlated with the histology. Twenty-nine of 36 (81%) correlating diagnoses were from Papanicolaou-stained and 18/36 (50%) from Diff-Quik-stained cases. The majority of the noncorrelating diagnoses (21/25) were overcalls of the FNA (6 Papanicolaou-stained and 15 Diff-Quik-stained). The remaining 4/25 noncorrelating diagnoses were undercalls (1 Papanicolaou-stained, 3 Diff-Quik-stained). By using a two-tiered classification system, interobserver reproducibility increased from 16 to 41%.

On September 9–10, 1996, the National Cancer Institute of the National Institutes of Health sponsored a workshop dedicated to the development of a standardized uniform approach to breast FNA.²⁴ The “Diagnostic Terminology Subcommittee,” co-chaired by Drs. Shahla Masood and Nour Sneige, recommended classifying FNA of breast lesions into one of five categories: unsatisfactory, benign, indeterminate/atypical, suspicious/probably malignant, and malignant. NPL and PL were included in the “benign” category, while PLA and low-grade carcinoma would fall into either the “indeterminate/atypical” or the “suspicious/probably malignant” category. This recommendation recognized the difficulties in subclassifying nonproliferative and proliferative lesions and concurred with the conclusion of our study that the classification should be limited to two diagnostic categories that have a direct impact on patient management. The cytologic diagnosis of “benign” lesion should be correlated with the clinical and imaging characteristics, i.e., the so-called “triple diagnosis method.” Patients with “benign triplets” results can be followed clinically within a 6-month interval. In contrast, tissue biopsy is

recommended to establish the exact nature of a lesion classified in the “indeterminate/atypical” category.

The categorization of proliferative breast lesions by FNA remains a challenge to the pathologist and the cytologic criteria need to be further defined and assessed. Decreasing the number of diagnostic categories is likely to improve the correlation between the cytologic and histologic diagnoses without compromising patient management. “Low risk lesions” (which encompass NPL and PL) may be managed conservatively and “high risk lesions” (which encompass PLA and noncomedo DCIS) need to be biopsied.

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