Proliferative Breast Disease: Diagnosis and Implications

M. H. Skolnick *et al.* (*1*) obtained specimens by multiple fine-needle aspiration from the breasts of women with and without a family history of breast cancer. They assessed the prevalence of certain cytologic changes in these groups of women, which they labeled proliferative breast disease (PBD). Skolnick *et al.*'s use of this term is unfortunate because PBD is a well-recognized histologic diagnosis (*2, 3*) of changes that bear only a slight and untested resemblance to the cytologic findings in (*1*). In order to avoid confusion, we will hereafter use PBD in its conventional sense.

Although PBD is consistently associated with increased breast cancer risk (*4*), studies have not been performed which show that cytologic abnormalities or similarly defined patterns have such an association. Skolnick *et al.* cite three papers that discuss fine-needle aspiration criteria for hyperplastic or proliferative lesions of the breast. One of these (*5*) states, "The limitations of [fine-needle aspiration] for diagnosing mild-to-moderate atypical hyperplasia appear to be greater than those of surgical biopsy since we were not able to define cytologic changes diagnostic for this lesion." Thus it is not clear why Skolnick *et al.* conclude that cytologic abnormalities are a significant risk factor for breast cancer. Their use of the term PBD to describe their findings could result in a demand for needle aspirations in asymptomatic women, the clinical value of which is unproved.

It is possible that the cytologic results of Skolnick *et al.* were affected by nonresponse bias. Case patients had numerous relatives with breast cancer. Controls were women related by marriage to the case subjects. Skolnick *et al.* do not state how many eligible controls were available, but, because there were 103 case subjects, the number was potentially large. Only 31 women volunteered to serve as control subjects, probably because this meant undergoing eight passes of a needle in each of eight sites within the breasts. It seems likely that participating controls differed from nonparticipants with respect to their concern about breast cancer and other factors associated with breast cancer risk. One of these factors is age; the average age of controls was 6 years greater than that of case subjects (52 versus 46 years). This is important because cytologic changes in the breast epithelium usually become less prominent soon after menopause or in the years immediately preceding it. Thus it is plausible that the different prevalence of cytologic abnormalities among cases and controls was attributable to differences in ages between the groups.

Skolnick *et al.* found that cytologic abnormalities were only 2.6 times more common in women with family histories of breast cancer than in women without such a history. Using the more conventional and stringent two-sided test, and removing the two women with suspicious mammograms (and, indeed, cancer) from the numerator, we calculate P to be 0.06, rather than the reported 0.02. This weak association links the cancer risk already known to be present because of family history with a cytologic finding of unknown significance. A "lesion" must be shown to be linked to a verifiable clinical outcome, such as cancer development or death from cancer, if it is to be denoted as a valid risk factor.

In our cohort of more than 10,000 women who underwent benign breast biopsy (*2*) we found no association between PBD without atypia and a first degree family history of breast cancer; the prevalence of these lesions was 27% and 29% in women with and without such a history, respectively. Women with this family history did, however, have a higher prevalence of atypical hyperplasia than did women without this history (4.8% and 3.9%, respectively, P = 0.02, two-tailed). Because family history and atypical hyperplasia have a highly synergistic effect on breast cancer risk (*2*), it would be appropriate to look for these lesions in women with family members who have developed breast cancer. This, however, cannot be done by fine-needle aspiration.

DAVID L. PAGE
Department of Pathology, Vanderbilt University School of Medicine, Nashville, TN 37232
WILLIAM D. DUPONT
Department of Preventive Medicine, Division of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN 37232

REFERENCES

1. M. H. Skolnick *et al.*, *Science* **250**, 1715 (1990).
2. D. L. Page, W. D. Dupont, L. W. Rogers, M. S. Rados, *Cancer* **55**, 2698 (1985); W. D. Dupont and D. L. Page, *N. Engl. J. Med.* **312**, 146 (1985).
3. C. L. Carter, D. K. Corle, M. S. Micozzi, A. Schatzkin, P. R. Taylor, *Am. J. Epidemiol.* **128**, 467 (1988); F. A. Tavassoli and H. J. Norris, *Cancer* **65**, 518 (1990).
4. W. D. Dupont and D. L. Page, *Am. J. Epidemiol.* **125**, 769 (1987).
5. M. Bibbo *et al.*, *Acta Cytol.* **32**, 193 (1988).

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Response: Page and Dupont suggest that we have misused the term "proliferative breast disease" (PBD), in part because we did not take our samples from histologic sections. Because we preferred to use a less invasive procedure on clinically normal women, we undertook cytomorphologic examination of specimens obtained by systematic fine-needle aspiration.

The lesions we found appear to represent the same process as those described as PBD on the basis of examinations of histologic sections. Bibbo *et al.* (*1*) state that they could not define cytomorphologic criteria that were concordant with mild-to-moderate atypical hyperplasia defined histologically. However, their histologic and cytologic diagnoses were concordant for *severe* atypical hyperplasia. Their results revealed a continuum of changes between proliferative lesions. There is disagreement among histopathologists about the subclassification of a specific lesion and about the criteria to be used in diagnosis. The consistency of subclassification does not affect our reported findings, as we made no attempt to subclassify atypical hyperplasia. Masood *et al.* (*2*) examined the cytologic diagnosis of proliferative and nonproliferative breast disease in mammographically guided fine-needle aspirates and reported that "A high degree of concordance (90% to 99%) was found between the cytologic findings and the histologic diagnosis. This study suggests that it is possible to apply a cytologic grading system to further subclassify benign breast disease and to distinguish these forms from neoplastic lesions."

Terminology aside, one pathologist performed a blind evaluation of the aspirates in our study using consistent cytologic criteria that describe cellular proliferation (*3*). A parsimonious explanation for our results is that PBD is a phenotypic expression of a susceptibility allele in these kindreds. We therefore chose not to create a new and potentially confusing term. Inherited PBD will eventually be defined genotypically by specific DNA sequences at specific loci, and phenotypically by molecular analysis of expression of specific oncogenes, the inactivation of specific tumor suppressor genes, and quantitative histologic and cytologic analysis.

If there had been nonresponse bias in our

sampling, it would mean that women with occult proliferative lesions in the control group pool preferentially refused to volunteer for our study. This seems unlikely. The difference in cytologic results was significant when corrected for age, as indicated in our reference 19. Page and DuPont suggest that we should have removed from the experimental group the two patients with PBD in whom breast cancer was detected during our study. We reported that, in one case, PBD was detected 1 year before the diagnosis of cancer and, in the other, the classification of PBD (on the basis of fine-needle aspirates) was made independent of the suspicion of cancer (as detected by mammography). Such individuals should be considered as affected with PBD in genetic and statistical analysis. These examples strengthen our contention that cytologic analysis can be an effective diagnostic tool in studies of genetic susceptibility to breast cancer. We used a one-tailed test of significance because our hypothesis stated that "PBD is more frequent in the clinically normal relatives of two closely related women with breast cancer than in controls." A two-tailed test, which would be appropriate for detecting positive or negative associations between PBD and breast cancer, also revealed a significant correlation ($P < 0.04$).

We would like to reemphasize that systematic sampling of the breast by fine-needle aspiration is strictly a research tool, and we discourage its use as a clinical screening method for asymptomatic women. We have no specific clinical recommendations to make to women who have histologically or cytologically defined PBD (*4*) other than to follow established screening guidelines.

MARK SKOLNICK
C. JAY MARSHALL
WILLIAM MCWHORTER
DAVID GOLDGAR
LISA CANNON-ALBRIGHT
JOHN H. WARD
HARMON EYRE
University of Utah Medical Center, Salt Lake City, UT 84132
G. BERRY SCHUMANN
University of Alberta, Edmonton T6G 2R7, Canada
D. TIM BISHOP
Imperial Cancer Research Fund, Leeds LS2 9LU, United Kingdom

REFERENCES

1. M. Bibbo *et al.*, *Acta. Cytol.* **32**, 193 (1988).
2. S. Masood *et al.*, *ibid.* **34**, 715 (1990).
3. C. J. Marshall *et al.*, *Am. J. Clin. Pathol.* **95**, 157 (1991).
4. W. D. Dupont and D. Page, *N. Engl. J. Med.* **312**, 146 (1985).

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Critical Velocity of Stick-Slip Motion

In a recent report (*1*), we presented simulations of stick-slip motion in boundary lubrication. To mimic experiments (*2*), we considered a molecularly thin film confined between atomically flat, solid walls. A shear stress was applied to the top wall by attaching it, through a spring, to a stage translating at constant velocity. At high velocities, the top wall slid at a uniform rate. Below a critical velocity, v_c, jerky motion occurred; the two walls alternately stuck together and slipped past each other. This "stick-slip" motion is a generic phenomenon observed in such disparate systems as squeaky hinges, milling machines, and violin bows (*3*). In this comment, we reconsider the factors which determine v_c.

Our simulations showed that stick-slip motion in thin films resulted from transitions between ordered static and disordered sliding states of the film. For a film of simple spherical molecules, the two states were crystalline and fluid. The periodic potential of the static, solid walls crystallized the film at a temperature above the bulk melting temperature. Under a sufficiently large shear stress, this crystalline state became unstable and the film melted (*4*). The walls were then free to slip past each other and release the stress. When the stress in the molten film dropped below a critical value, there was spontaneous recrystallization. We found that v_c coincided with the velocity of the wall just before recrystallization; the molten sliding state was unstable below this velocity.

An upper bound on v_c is provided by the lattice constant of the wall divided by the relaxation time required for the film to order. The spherical molecules used in our simulation crystallized rapidly, and v_c was about one-tenth the speed of sound. Critical velocities in experiments are roughly eight orders of magnitude smaller. Measured relaxation times in thin films are also six to eight orders of magnitude larger (*5*). We attributed both effects to the slowing of intramolecular dynamics in confined spaces and began studies of short chain molecules that had internal degrees of freedom (*6*). Unexpectedly, the values of v_c did not decrease substantially with increasing chain length. While some relaxation times grew rapidly with chain length, locking of the films into a static glassy state only required rapid, monomer-scale rearrangements. The factors which determine the observed v_c are entirely different from those that determine the longest relaxation times.

In order for the moving wall to stop, its kinetic energy must be converted into potential energy in the film. The maximum potential energy that can be stored in the film scales as the static frictional force (or yield stress), F_s, times the lattice constant of the wall, σ. Equating this to the kinetic energy at V_c, we find $v_c = c\sqrt{\sigma F_s/M}$, where c is a numerical factor and M is the mass of the moving wall. This mass was 14 orders of magnitude larger in experiments than in our simulations. We have completed new simulations which confirm that v_c scales as $M^{-1/2}$ when other parameters are held fixed. The value of c varies from about 0.05 to 0.5, depending on load, commensurability of wall and fluid, and the crystalline alignment of the walls. The largest values of c were only found for epitaxial fluid densities and aligned walls. Neither condition is satisfied in typical experiments. Taking experimental values of $F_s \sim 20$mN, $\sigma \sim 5$Å, $M \sim 0.02$ kg, and $v_c \sim 2$ μm/s, we find $c \approx 0.1$. This is well within the range of theoretical values.

The other conclusions of our report (*1*) remain essentially unchanged. In particular, the stick-slip motion becomes irregular and intermittant as v approaches v_c. As v increases, the degree of order required to absorb the kinetic energy increases, and it becomes increasingly unlikely that the film will achieve this degree of order and stick. These results and the changes introduced by molecular structure will be presented in a longer paper (*6*).

MARK O. ROBBINS
Department of Physics and Astronomy, Johns Hopkins University, Baltimore, MD 21218
PETER A. THOMPSON
Exxon Research and Engineering Co., Route 22 East, Annandale, NJ 08801

REFERENCES AND NOTES

1. P. A. Thompson and M. O. Robbins, *Science* **250**, 792 (1990).
2. M. L. Gee, P. M. McGuiggan, J. N. Israelachvili, A. M. Homola, *J. Chem. Phys.* **93**, 1895 (1990).
3. E. Rabinowicz, *Friction and Wear of Materials* (Wiley, New York, 1965).
4. Shear-melting transitions have been studied in the weak crystals formed by colloidal suspensions [B. J. Ackerson and N. A. Clark, *Phys. Rev. Lett.* **46**, 123 (1981); M. J. Stevens and M. O. Robbins, *ibid.* **66**, 3004 (1991)].
5. J. Van Alsten and S. Granick, *ibid.* **61**, 2570 (1988); *Tribol. Trans.* **33**, 436 (1990).
6. P. A. Thompson, G. S. Grest, M. O. Robbins, in preparation.
7. Support from NSF grant DMR-8553271 and the Pittsburgh Suppercomputer Center is gratefully acknowledged. M.O.R. also acknowledges support from the Sloan Foundation.

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