Endometrial Cells and the Papanicolaou Test

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The *end* or purpose of the Papanicolaou (Pap) test is to prevent deaths due to squamous cell carcinoma (SCC) of the cervix. It works for the following reasons: (1) Cervical SCC and its precursor lesions occur over a relatively small area that often can be visualized and can be sampled easily. (2) Precursor lesions of SCC have cytomorphologic changes that can be recognized consistently by pathologists. (3) There is a significant lag time between the development of a recognizable precursor lesion and the development of an invasive malignancy. (4) Precursor lesions and early malignancies can be treated adequately, and invasive SCC can be prevented.

Because of the cytology, anatomy, and biology of cervical SCC, the Pap test has contributed to the marked decline in deaths due to cervical SCC in the United States. Once the leading cause of cancer death among women in the United States, it now ranks eighth, with only 4,500 to 5,000 deaths resulting from cervical SCC per year in the United States. This is despite the fact that infection by the virus necessary for its development is likely as prevalent as ever.

Although the Pap test already had shown itself to be extremely effective, it was somewhat hindered, even throughout the 1980s, by a lack of consistent nomenclature. As truly the first step in cervical SCC prevention, this lack of a uniform nomenclature made further triaging somewhat complicated for clinicians. Pap test results and nomenclature varied from institution to institution and even from individual to individual. Test result reporting also was hindered by a lack of standardization of the criteria for adequacy.

The Bethesda system (TBS) was developed in 1988 and eventually published in 1994 after a second meeting of a National Cancer Institute working group.[1,2] The stated goals in the introduction to the 1994 monograph were as follows: (1) to provide uniform terminology that would facilitate communication between the laboratory and the clinician and (2) to provide precise criteria for both diagnostic terms and for the descriptors of specimen adequacy.

Throughout the early 1990s, TBS came to be implemented in most US laboratories for the reporting of Pap test results.[3] With the standardization of Pap test interpretations, evidence-based treatment guidelines eventually were developed.[4] Furthermore, standardization also accomplished other goals of TBS by facilitating research into the epidemiology, biology, and pathology of cervical disease and by providing reliable data for national and international statistical analyses and comparisons. TBS is responsible for much of our increased understanding of cervical SCC during the past decade and is, at least in part, responsible for much of the rich data that have emerged from larger trials studying the proper treatment and even prevention of cervical SCC.

Arguably the most important accomplishment of TBS was standardizing adequacy requirements and the criteria and nomenclature for the interpretation of squamous intraepithelial lesions. TBS, however, also standardized the reporting of other lesions, including infectious and glandular abnormalities. Recommendations also were given for the reporting of normal-appearing endometrial cells when present in Pap smears from postmenopausal women, when the cells were found to be "out of phase," and when a menstrual history was not provided.[1] The 1994 monograph recommended that cytologically benign endometrial cells in Pap smears from postmenopausal women should be reported under the category *epithelial cell abnormalities*.[2] The monograph stated, "The presence of endometrial cells, epithelial or stromal, even

when normal in appearance, in a postmenopausal woman not on hormonal therapy must be explained."[1]

The reason for this reporting was rather pragmatic. Postmenopausal women should not, theoretically, shed endometrial cells. Furthermore, although a true prospective trial had not been performed (and still has not), a number of studies had shown that women with endometrial cancer were more likely to have had endometrial cells in a previous Pap smear than women with benign follow-up and that women with endometrial cells in their Pap smears were, when follow-up was available, more likely to be diagnosed with endometrial pathology.[5-8]

Most studies that have reported such findings, however, are problematic for a number of reasons. Most, including the studies presented in this and other journals during the past year, require tissue follow-up as a starting point or an end point.[5-14] This creates a significant selection bias because Pap smears with and without endometrial cells most commonly do not have tissue follow-up. Should cases without tissue follow-up be considered benign because in all likelihood they are? Still, studies that regard the absence of follow-up as benign obviously would be problematic because many laboratories receive Pap tests from patients who will have tissue follow-up interpreted elsewhere.

Further complicating the matter have been the widespread use of postmenopausal hormone therapy and the introduction and now near universal conversion to liquid-based Pap technologies during the past decade. These technologies have proven superior to conventional technologies in a number of ways, one of which is that the brushes used with them are more likely to sample the transition zone adequately and to procure endocervical cells. However, because of this, these brushes also may be more likely to sample the lower uterine segment and endometrial cells may be more common with these specimens.[10] Also, with liquid-based Pap tests, cytopathologists seem to be better at differentiating benign from atypical and malignant glandular cells, and the cytologic interpretations of *atypical glandular cells of undetermined significance* and *adenocarcinoma* now seem to have better positive predictive values than they did with conventional Pap tests.[15] Thus, it would seem that benign-appearing endometrial cells in Pap tests today are unlikely to mean what they did 20 or even 10 years ago.

It seems that if endometrial cells are to mean anything in Pap tests, clinical context is paramount. For a premenopausal woman or any woman younger than 40 years, they are likely to mean very little because the prevalence of endometrial carcinoma in either of these populations is low and Pap tests from these women commonly show benign endometrial cells. Conversely, although they may be shown to correlate with endometrial pathology for postmenopausal women who are symptomatic, they still may have little *meaning* as these women would undergo tissue sampling of their endometria regardless of their Pap test results. For this reason, many studies, including a study in this issue of the *Journal* by Browne et al,[12] have specifically investigated or mentioned the meaning of endometrial cells in Pap tests from asymptomatic, postmenopausal women. Browne et al state that 3 of 6 women in their study who had had endometrial cells in their Pap tests and later were found to have endometrial cancer had been postmenopausal and asymptomatic and 2 had even been premenopausal and asymptomatic! Why did these women undergo sampling? Was it because of their Pap results? Why did the other 625 presumably asymptomatic women not undergo sampling?

Even if turns out to be true that a postmenopausal woman with a Pap test showing endometrial cells may be more likely to have endometrial carcinoma or a putative precursor lesion than a comparable woman without endometrial cells in her Pap test, the prospective meaning and usefulness of reporting are not as obvious. What is needed is the *true* positive predictive value of the finding, especially as it is related to other clinical findings and risk factors. However, the prospective study necessary for such information seems unlikely to be done. If it were, it then could be determined whether such a predictive value was sufficient to warrant different patient treatment or follow-up. Would a 1% or even 5% risk for endometrial pathology warrant subsequent biopsy for all patients or some select cohort?

The authors and participants in TBS 2001 grappled with these issues and made some modifications to the suggested reporting of benign endometrial cells in Pap tests.[16] The authors first acknowledged that the overall clinical context is extremely important and generally is not known by the cytopathologist at the time of interpretation of the Pap test. For this reason, TBS 2001 suggested that endometrial cells be reported when found in Pap tests of women older than 40 years. (The authors also suggest an appended comment if the cells are present during the first half of a cycle from a woman with a given date of last menstruation.) Because the meaning of these cells is not clear, the finding is no longer to be interpreted as an *epithelial cell abnormality* but instead is reported under the heading *other*. In a way, they also dealt with the likely increased numbers of endometrial cells that will be found with increased sampling of the lower uterine segment by liquid-based techniques and stated that "…only exfoliated, intact endometrial cells should be reported…" drawing a distinction between the supposedly meaningful exfoliated endometrial cells and those that are "abraded."[16]

Because of the near universal acceptance of TBS, TBS 2001 has quickly come to be the standard of care for the reporting of Pap test results. A benefit of this is that data have quickly emerged regarding the reporting of endometrial cells in women older than 40 years. Although early results are mixed, it seems probable that identification of these cells in most clinical

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contexts will have little meaning and will not drive clinicians to implement different therapies. Browne et al[12] show that twice as many endometrial cancers were found to be associated with endometrial cells reported on Pap tests since their implementation of TBS 2001, whereas the reporting of endometrial cells increased by 5 times! Thus, although the sensitivity of the test has improved, the overall predictive value has decreased with the implementation of TBS 2001.

The Pap test obviously will never work as a screening test for endometrial adenocarcinoma or its possible precursor lesions. The endometrium is not adequately sampled by the Pap test and may be difficult to adequately sample even with specifically designed endometrial brushes. Furthermore, shed endometrial cells seem to have little positive predictive value for the identification of women with endometrial adenocarcinoma or putative precursor lesions. Even when the endometrium is sampled with an endometrial brush, the cytologic diagnosis of endometrial adenocarcinoma is difficult and may not prove to be reproducible. The identification of putative precursor lesions is even more difficult. Furthermore, we do not know the true lag time between the development of the putative precursor asymptomatic lesions of the endometrium and the development of endometrial adenocarcinoma. Nor do we know whether we can treat early lesions in such a way as to lower the eventual death rate from endometrial adenocarcinoma.

TBS 2001 will assist in the generation of data regarding the use of reporting benign endometrial cells. If benign endometrial cells in Pap tests correlate at all (which they likely will) with the presence or later diagnosis of endometrial adenocarcinoma in any patient cohort, it is hard to imagine that we will be able to exclude the finding from our cytology reports. Although such reporting may slightly increase the number of women who undergo endometrial biopsy, the worry that this reporting will cause undue treatment of asymptomatic women probably is unfounded, and some clinicians seem to state that they simply ignore the finding.[16,17] The purpose of reporting the cells, however, is to provide one more tool to the clinician who treats women in whom endometrial adenocarcinoma may develop. Whether, when, and how such reporting will be of assistance remains to be shown.

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