Letters to the Editor

CORRESPONDENCE RE: SHERMAN ME, TABBARA SO, SCOTT DR, KURMAN RJ, GLASS AG, MANOS MM, ET AL. "ASCUS, RULE OUT HSIL": CYTOLOGIC FEATURES, HISTOLOGIC CORRELATES, AND HUMAN PAPILLOMAVIRUS DETECTION. MOD PATHOL 1999;12:335–42.

To the Editor: The principal problems with this article are the use of the term *ASCUS* and the interpretation of cytologic evidence. I address both issues.

The term *ASCUS* (atypical squamous cells of unknown significance) was created by the Bethesda System to replace the previously used terms, such as *atypia*, to describe trivial cytologic abnormalities that are very difficult or impossible to interpret. The emphasis is on the words *unknown significance,* and that should preclude the use of this term in situations in which a disease process is suspected. Unfortunately, the term has become dogma: any cervical smear that, in the judgment of the pathologist, is not conclusively normal or abnormal is thrown into the all-inclusive category of ASCUS. Dogmas are bad for science and may be bad for patients. In the context of this article, the use of the term *ASCUS* is, in my judgment, inappropriate and fails to reflect the diagnostic reality. How can ASCUS be used to "rule out HSIL"? What kind of message does it convey to the clinician and the patient? If the smear contains scanty evidence of HSIL, perhaps insufficient to establish a conclusive diagnosis, this fact should be clearly stated, the smear should be considered "suspicious," and the use of the term *ASCUS* in that context should be avoided at all cost. The patients should be immediately referred for colposcopy and biopsies. Most clinicians would react to the diagnosis of ASCUS by repeating the smear within a few weeks. As has been repeatedly shown, the "repeat" smear may fail to reveal confirmatory cytologic evidence of disease in 30 to 40% of patients, sometimes with disastrous results (1, 2). I do not believe that it was the primary intent of the Bethesda System to consider ASCUS as an excuse to avoid diagnostic responsibility. The phrase, "ASCUS, rule out HSIL," is a disservice to patients and to the community of pathologists. It is clear that in this regard, the interpretation and usage of the Bethesda System is totally inadequate as it does not reflect the day-to-day reality.

As far as the cytologic evidence is concerned, not having reviewed the smears or the biopsies personally, I cannot comment on all of the actual findings. However, the photographs of the four cases used to illustrate the article show clearly small cancer cells singly and in clusters. Thus, at least these four cases should have been diagnosed *unequivocally* as HSIL. In Table 1 of the article, the cytologic criteria used in the study were listed. Some of them, such as "atypical immature metaplasia," a term advocated by some observers, represent small cancer cells that mimic small metaplastic cells, as has been previously stated (1). Other findings, such as "tissue fragments" (shown in Fig. 1A of the article) are the old-fashioned so-called "syncytia" or microbiopsies of cancer that must be recognized as such by careful analysis of the edge of the cluster. The authors will find appropriate illustrations and descriptions in previously published works, none of which was cited (1–3). The authors could have used this study to *teach* the readers what should *not* be designated as ASCUS but instead, in a lengthy discussion, justified the diagnoses by citing other contributions that were just as disturbing as this one. There is nothing more difficult in pathology than the interpretation of the cytology of the uterine cervix, and revising and restructuring the experience accumulated over the past half century is not necessarily useful or valid, although it does produce papers. As experts, the authors could have taken this opportunity to redress some of the misconceptions and limitations imposed by a rigid diagnostic system that clearly requires adjustments.

A final comment has to do with human papillomavirus typing and its value as an adjunct to cytology. The test was supposed to separate women who are at risk from women who are not at risk. In this study at least, the test failed to live up to these expectations, as shown in Table 2 of the article. It is hoped that future results of this complex and costly study will better justify the time and effort.

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In reply: We thank Dr. Koss for his interest in our recent article analyzing the proposed cytologic category of "ASCUS, rule out HSIL."

We agree that patients who receive a diagnosis of "ASCUS, rule out HSIL" should be considered for immediate colposcopy because these patients have a relatively high frequency of underlying biopsy-confirmed high-grade CIN as compared with women with ASCUS, unqualified. This is in fact the major conclusion of our study and the basis for our recommendation that pathologists subclassify ASCUS as "rule out LSIL" or "rule out HSIL" rather than as favor a reactive process or favor a lesion as is currently suggested in The Bethesda System guidelines (1).

Many women diagnosed with "ASCUS, rule out HSIL" do not have biopsy-confirmed high-grade CIN. In clinical practice, it would be harmful simply to classify all of these women as HSIL because this would result in unnecessary treatment and morbidity for many of these women. Unfortunately, the diagnostic reproducibility of cervical cytologic diagnoses remains at best imperfect and at worst irreproducible, despite the publication of numerous books and atlases. Many of the cases included in this report were selected because one reviewer independently diagnosed HSIL and another diagnosed ASCUS. We sympathize with Dr. Koss's criticism of our uncertainty in diagnosing these smears, but classifying a single published photograph out of context is very different from diagnosing an entire cytologic slide. In fact, this underscores the difficulty in trying to improve cytologic diagnosis; acquisition of skill is highly experiential and even "experts" frequently disagree, sometimes widely. Differential diagnoses such as reactive metaplasia Vs HSIL or "atypical repair" Vs fragments of HSIL will remain with us forever, and "expert" opinions on individual cases are not always accurate or enlightening. However, providing the practicing cytopathologist with a means to communicate a significant level of concern about a case without committing to a definitive diagnosis is very useful. It flags a case for immediate colposcopy but permits a reevaluation and correlation of the findings if a biopsy-confirmed lesion is not found. In contrast, a definitive diagnosis of HSIL would mandate treatment in most settings, even without histologic confirmation.

In the past, difficult cytologic diagnoses often could not be clarified because our sole source of truth was the opinions of "experts," even though these pathologists often disagreed in such cases. Because it has been demonstrated that essentially all cervical carcinomas contain oncogenic HPV types (2), the significance of various cytologic diagnoses now can be objectively assessed by comparing the proportion of cases that are HPV positive in these different categories. We attempted to correlate cytologic diagnoses with HPV detection in this study, but our analysis was limited by the unavailability of specimens for virologic testing from many patients at diagnosis. It is erroneous to attempt to use the results of our study to evaluate the utility of HPV testing for clinical management. The utility of HPV testing for colposcopy triage has been suggested in several recent studies designed to address this issue (3, 4) and will be analyzed more definitively in the National Cancer Institute ASCUS LSIL Triage Study (ALTS).

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