

Time Interval Effect on Repeat Cervical Smear Results

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OBJECTIVE: Second cervical smears obtained at short time intervals often exhibit a lesser degree of abnormality than the first smear. We studied the effect of time interval between smears on diagnoses in two large, distinctive cohorts.

STUDY DESIGN: Patients with two or more satisfactory smears with at least one smear or a cervical biopsy showing atypical squamous cells of undetermined significance or greater were selected. Patients were divided

into four subsets by test intervals (days) (≤ 45 , 46–90, 91–120, > 120) and compared statistically.

RESULTS: The distribution of differences between results for the short-interval subsets (< 120) was significantly different ($P < .01$) from the interval subset > 120 days. At short intervals the results revealed loss of sensitivity in the second smear as compared to the initial smear and concurrent biopsies.

CONCLUSION: Rapidly repeated cervical smears show poor agreement with the biopsy and may be misleading. This effect is most pronounced when the interval is < 45 days. Colposcopists should consider whether concurrent smears shortly after an abnormal smear are worth performing, given the loss of sensitivity. (*Acta Cytol* 1997;41:269–276)

Keywords: cervical smears, follow-up studies, predictive value of tests, time factors.

A quality assurance study by our group suggested that when smears were obtained at intervals shorter than three months, the second smear tended to show a lesser degree of abnormality. Our study examined the cervical cytology-histology correlation by inclusion of the two most recent cervical smears. We also observed that this effect was less evident as the interval between smears increased.

This phenomenon was previously described by Koss.⁵⁻⁷ In his standard text on diagnostic cytology he stressed that cervical “*cytology was not always reliable* [italics his] during the follow-up period. . . . Negative smears were observed repeatedly even though there was excellent biopsy evidence that the lesion was present in the cervix epithelium at the time when the smear was obtained.”⁵

In studies by Koss and associates⁷ and by Richart and associates^{10,11} in the 1960s, a “close interval” was four months and not shorter than three. Koss, in 1989, stated, “It is singularly misleading to obtain

A cervical smear may be repeated too soon due to anxiety on the part of the clinician or the patient.

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a second smear within a few days or weeks after the first one, either to confirm the previous results or to clarify the diagnosis in "atypical" cases. For reasons unknown, the second sample may be completely negative in about 60% of patients with significant neoplastic lesions."⁶

Comparisons of different techniques should not be attempted by means of rapidly repeated smears.

A similar finding was described by Vooijs,¹⁶ who recommends that smears not be repeated within four weeks. While our own preliminary observations supported Koss⁵ and Vooijs,¹⁶ we did not find a detailed statistical study cited in their textbooks. Koss's 1963 study, which was a presentation of the natural history of carcinoma *in situ*, did not provide a detailed statistical picture of this phenomenon.⁷

Recent studies of cervical smear performance have utilized, or have proposed the utilization of, repeat smears at close intervals as "controls."^{12,14} We have also observed that in at least four institutions, it is standard practice for colposcopists to obtain a repeat smear, usually within a time interval of less than three months. These trends prompted our reexamination of the rapidly repeated smear.

Materials and Methods

Cytology and surgical pathology materials from two institutions were analyzed for this study. Pathology records from the Creighton University Medical Center (CUMC) were reviewed for the period from January 1, 1993, through October 1, 1994. Patients were selected for analysis if they had had two or more satisfactory cervical smears and at least one of the smears showed an abnormality of atypical squamous cells of undetermined significance (ASCUS) or greater. Patients were also included if they had had an abnormal cervical biopsy at or shortly after the second smear. Patients with only normal smears at annual intervals and patients with normal or inflammatory/reactive smears but no biopsy abnormalities were excluded. A second data set from northern California was obtained by reviewing the department records at the Permanente Medical Group Regional Laboratory (TPMG) using the above criteria for inclusion and coding but also specifically looking for a test interval of

< 120 days. Cervical biopsy and curettage results were included when available, but repeat smears were included without regard to any association with colposcopy. In each instance of an apparent discrepancy between the biopsy result and the cervical smear result, the slides were reviewed to verify that the discordance was due to sampling considerations and not to interpretive error. Data from the two institutions were examined as separate data sets.

Once the cases were verified to be correctly associated, the patient's identifying information was purged from the study file. The date and result of each cervical smear and biopsy were entered into a database program (Paradox, Borland International, Inc., Scott's Valley, California, U.S.A.) running on an Intel (Santa Barbara, California, U.S.A.) 486-based computer. The diagnoses were coded and grouped as follows: 1 = within normal limits, 5 = inflammatory and/or reactive changes, 10 = ASCUS or atypical glandular cells of undetermined significance, 20 = low grade squamous intraepithelial lesion (SIL) (LSIL), 30 = high grade SIL (HSIL), 40 = malignancy. The time interval between cervical smears and the difference between diagnoses for each smear pair were calculated. The smear pairs were divided according to test interval groups: (1) < 45 days (20th percentile), (2) 46–90 days (43rd percentile), (3) 91–120 days (54th percentile), and (4) > 120 days. These data were then exported to a statistics program (SPSS/PC+, SPSS, Chicago, Illinois, U.S.A.)⁹ for examination by means of frequency distributions, cross tabulations, correlation statistics of the two smear results and biopsies and the Mann-Whitney test. The data were also exported to a spreadsheet program (Quatro Pro, Borland) for the calculation of κ statistics, both weighted and unweighted, according to the methods described by Kramer and Feinstein.⁸

Results

The CUMC data yielded 278 cervical smear pairs. The interval between smears ranged from 4 to 539 days, with a median of 112 (Figure 1). The difference between diagnosis codes formed a parameter that ran the full range of possible values with a median and mode of zero. The Wilcoxon test, two-tailed, $P = .16$, indicated that the second result of each pair was not biased when compared to the first smear when the longer test interval pairs were included in the analysis of the entire data set. Visual inspection of the cross-tabulation or confusion ma-

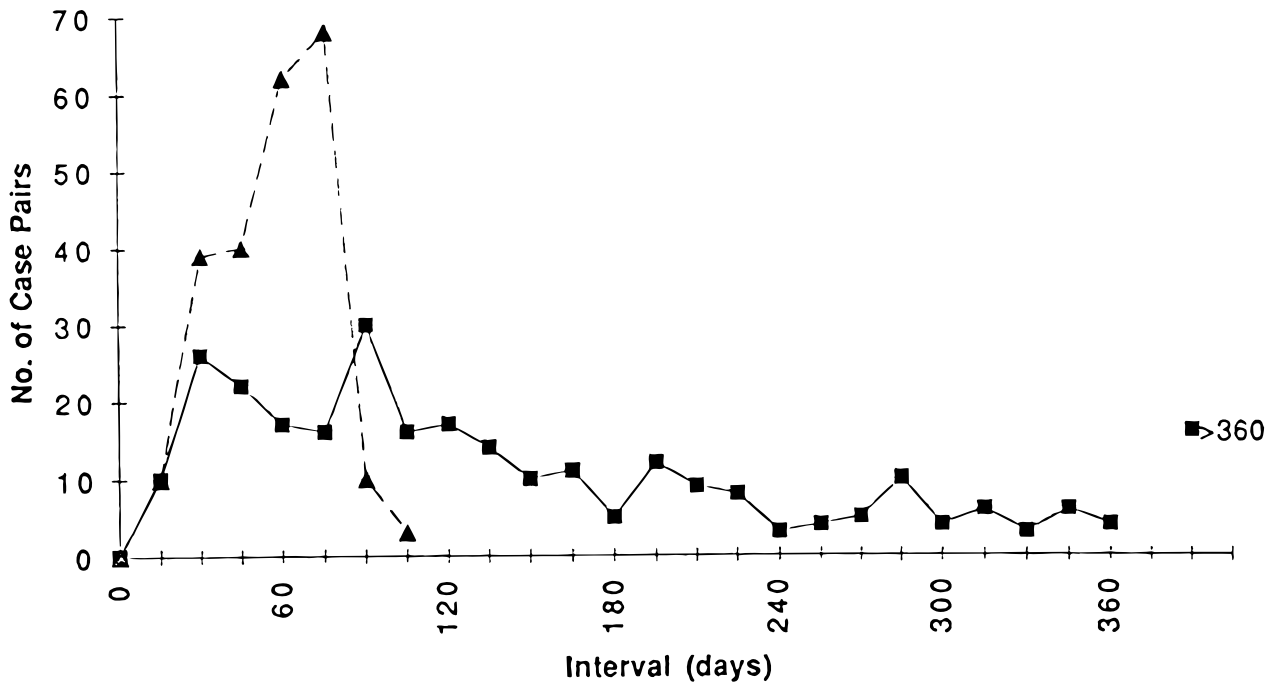


Figure 1 Interval between cervical smears. Frequency distribution showing the number of cervical smear pairs at each interval. The solid line is CUMC data. Noteworthy is the fact that half the pairs from CUMC were at intervals of < 120 days (actual median value, 112). The dotted line is TPMG data. The TPMG cases were selected for an interval of < 120 days. The graph breaks at greater than 360 days.

trix for the entire data set (Table I) demonstrated symmetry around the diagonal of concordance. These observations show that the sampling was sufficiently large, with enough data points for valid comparisons between interval groups. The number of pairs with repeats at < 112 days was equal to those > 112 days. The full data set did not manifest the same bias (loss of sensitivity in the second smear) seen in the short-interval groups (compare Tables I and III).

When the data were divided according to test interval groups—(1) < 45 days (20th percentile), (2) 46–90 days (43rd percentile), (3) 91–120 days (54th percentile), and (4) > 120 days—the distribution of values for the difference between diagnosis codes in each of the short-interval groups was different from the > 120 day group, as confirmed by the Mann-Whitney test ($P < .01$). Among the three short-interval groups there was no statistically significant difference in the distribution of differences between cervical smear results. They are treated as one group for the remainder of the analysis, with the exception of one observation: in the group < 45 days, the biopsies of dysplastic lesions showed a better correlation with the original smear than they did

with the repeat smear ($r = .493$ and $.057$, respectively). The discrepant cases included one HSIL and one carcinoma where the second cervical smear was “within normal limits.”

In the last subset (> 120 days, Table II), the confusion matrix is fairly symmetrical and similar to the entire data set. The correlation between the first and second cervical smear results for the first three groups was .30–.34 ($P < .05$), while for the fourth group it was .0071 ($P = .936$), and for the full data set it was .1592 ($P < .01$). The κ statistics, both weighted and unweighted, show agreement between the cervical smears that is better than chance but only “slightly” unweighted and “slightly to fairly” weighted, according to the classification scheme of Kramer and Feinstein.⁸ The degree of agreement between the biopsy and either cervical smear (weighted or not) was “poor” to “slight” for all groups except the group > 120 days, where agreement was “fair” (weighted). For comparison, cervical smear/cervical biopsy agreement at CUMC, as measured by κ and weighted κ statistics, was rated as “substantial.”

Table III provides a cross-tabulation of the cervical smears with an interval of < 120 days. The in-

Table I All Smear Pairs from CUMC

Smear1	Smear2 (n = 278)					
	WNL	Inflammatory and reactive	ASCUS/AGCUS	LSIL	HSIL	Carcinoma
WNL	20	4	12	35	6	
Inflammatory and reactive	6	3	3	14		
ASCUS/AGCUS	16	6	5	16	4	
LSIL	25	9	7	47	10	
HSIL	2	2	3	8	14	
Carcinoma	1					

Cross-tabulation comparing the second cervical smear result (Smear2) with the first cervical smear result (Smear1). Each of these cross-tabulations is read similarly. The instances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner, the diagonal of concordance (in boldface). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality. Values above and to the right of this diagonal show the number of instances where the second cervical smear showed a greater degree of abnormality. The numbers in italics are the cases that showed LSIL or higher on the first smear but less than LSIL on the repeat smear.

Total positive bias, 104.

Total negative bias, 85.

Agreement, 89.

stances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner: the diagonal of concordance (boldface numbers). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality than did the first. The numbers in italics are the 34 cases (23% of the pairs) that showed LSIL or higher on the first smear but less than LSIL on a repeat smear within 120 days. Twenty-four of these cases had biopsies performed at or shortly after the time of the second smear for comparison. There were 11 (46%) that showed dysplasia on the biopsy

in agreement with the first cervical smear in the face of a negative smear obtained prior to the biopsy. (Note: included are four cases of HSIL and one of carcinoma.) This reveals a sampling error in the second cervical smear, which is confirmed by review of the slides.

The TPMG data set consisted of 232 smear pairs selected within the interval range 5–120 days; the median was 53. The difference between diagnosis codes ran the full range of possible values with a median and mode of zero. By visual inspection (Table IV), the cross-tab for the TPMG data set was asymmetric around the diagonal of concordance, with the second cervical smear diagnoses tending to lesser values. The κ statistic (weighted or not) for

Table II Interval > 120 Days from CUMC

Smear1	Smear2 (n = 129)					
	WNL	Inflammatory and reactive	ASCUS/AGCUS	LSIL	HSIL	Carcinoma
WNL	7	2	9	27	6	
Inflammatory and reactive	2	3	1	8		
ASCUS/AGCUS	5	6	3	7	3	
LSIL	7	4	1	17	4	
HSIL		2	1	1	3	
Carcinoma						

Cross-tabulation comparing the second cervical smear result (Smear2) with the first cervical smear result (Smear1). Each of these cross-tabulations is read similarly. The instances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner, the diagonal of concordance (in boldface). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality. Values above and to the right of this diagonal show the number of instances where the second cervical smear showed a greater degree of abnormality. The numbers in italics are the cases that showed LSIL or higher on the first smear but less than LSIL on the repeat smear.

Total positive bias, 65.

Total negative bias, 29.

Agreement, 33.

Table III Interval < 120 Days from CUMC

Smear1	Smear2 (n = 149)					
	WNL	Inflammatory and reactive	ASCUS/AGCUS	LSIL	HSIL	Carcinoma
WNL	13	2	3	8		
Inflammatory and reactive	4		2	6		
ASCUS/AGCUS	11		2	9	1	
LSIL	<i>18</i>	5	6	30	6	
HSIL	2		2	7	11	
Carcinoma	1					

Cross-tabulation comparing the second cervical smear result (Smear2) with the first cervical smear result (Smear1). Each of these cross-tabulations is read similarly. The instances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner, the diagonal of concordance (in boldface). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality. Values above and to the right of this diagonal show the number of instances where the second cervical smear showed a greater degree of abnormality. The numbers in italics are the cases that showed LSIL or higher on the first smear but less than LSIL on the repeat smear.

Total positive bias, 37.
Total negative bias, 53.
Agreement, 56.

agreement between the two smears would be rated as "fair." The Wilcoxon test, one-tailed, was $P < .001$. The data were stratified by interval into groups of < 45, 46–90 and 91–120 days, but the groups were not significantly different from one another by the Mann-Whitney test ($P > .03$).

In the TPMG data set there were 56 cases (24% of the pairs; see numbers in italics, Table IV) that showed LSIL or higher on the first cervical smear and had less than LSIL on the second. Biopsy results were available for correlation in 10 of these cases, but in all except 1, the biopsy agreed with the *first* smear and not the second. Tables V and VI show the combined data for the two institutions at < 120 days and < 45 days, respectively.

Despite the geography, work volume and prac-

tice setting differences between institutions, the data for smears repeated at intervals of < 120 days are remarkably similar. Their cross-tabulations show a preponderance of values below the diagonal of concordance, their κ statistics show only fair agreement, and they include a sizable number of cases where a biopsy confirmed the abnormality of the first cervical smear when the repeat smear (usually concurrent with the biopsy) was negative.

Discussion

This study demonstrated that smears repeated at close intervals, < 120 days, lack sensitivity and may be quite misleading. This loss of diagnostic sensitivity occurs in two substantially different practice settings: a university medical center based on a fee-

Table IV Interval < 120 Days from TPMG

Smear1	Smear2 (n = 232)					
	WNL	Inflammatory and reactive	ASCUS/AGCUS	LSIL	HSIL	Carcinoma
WNL		2	1	2		
Inflammatory and reactive	2	3	1			
ASCUS/AGCUS	16	8	32	15	10	
LSIL	<i>12</i>	3	26	41	8	
HSIL	1	1	13	8	26	
Carcinoma						1

Cross-tabulation comparing the second cervical smear result (Smear2) with the first cervical smear result (Smear1). Each of these cross-tabulations is read similarly. The instances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner, the diagonal of concordance (in boldface). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality. Values above and to the right of this diagonal show the number of instances where the second cervical smear showed a greater degree of abnormality. The numbers in italics are the cases that showed LSIL or higher on the first smear but less than LSIL on the repeat smear.

Total positive bias, 40.
Total negative bias, 90.
Agreement, 102.

Table V Interval < 120 Days, CUMC and TPMG Combined

Smear1	Smear2 (n = 381)					
	WNL	Inflammatory and reactive	ASCUS/AGCUS	LSIL	HSIL	Carcinoma
WNL	13	4	4	10		
Inflammatory and reactive	6	3	3	6		
ASCUS/AGCUS	27	8	34	24	11	
LSIL	<i>30</i>	<i>8</i>	<i>32</i>	71	14	
HSIL	3	1	15	15	37	
Carcinoma	1					1

Cross-tabulation comparing the second cervical smear result (Smear2) with the first cervical smear result (Smear1). Each of these cross-tabulations is read similarly. The instances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner, the diagonal of concordance (in boldface). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality. Values above and to the right of this diagonal show the number of instances where the second cervical smear showed a greater degree of abnormality. The numbers in italics are the cases that showed LSIL or higher on the first smear but less than LSIL on the repeat smear.

Total positive bias, 77.

Total negative bias, 143.

Agreement, 158.

for-service referral practice and a large, primary care health maintenance organization. Our findings confirm the observations of Koss⁵⁻⁷ and Voojijis,¹⁶ who predicted that too short an interval between smears would result in errors.

These findings will seem to be contrary to the view of those who expect the second smear to show better agreement with the biopsy, especially when performed during the same colposcopy procedure. This expectation is especially erroneous when colposcopy is performed within 45 days of the original abnormal smear. Based on our data from two populations in two geographic areas, a clinician who relies on the negative result of a second cervical smear repeated within 120 days of a significantly abnormal first smear will incorrectly assume the absence of dysplasia in at least 46% of those cases. This is probably a minimal figure since it is known that the biopsy has less-than-perfect sensitivity due to sampling errors of its own.^{10,15}

There is another pervasive belief that holds that if an abnormal test is repeated and the result of the second test is normal, the first test must have been in error. Our findings indicate that cervical smears, when repeated at close intervals, are not independent observations but rather that the findings of the second are influenced by the performance of the previous test.

The primacy of colposcopy in the workup of cervical abnormalities appears to explain, or at least coincide with, the prevalence of rapidly repeated cytology. Reasons given for repeating the cervical smear at colposcopy include confirmation of the

findings of an outside institution, facilitation of a direct comparison with colposcopy and biopsy findings, and detection of new infections or changes in the grade of dysplasia.^{2,17}

Colposcopic-cytologic correlation is itself imperfect; that finding was recently and concisely illustrated by Tritz et al.¹⁵ The correlation is imperfect even in the special situation where colposcopy is used concurrently with cervical smears in the screening mode—i.e., not in the follow-up of abnormalities.¹ Most studies have examined repeat cytology as compared with colposcopic biopsy (and/or loop excisions) in the clinical context of a referral for an abnormal cervical smear.^{3,4,14,17,18}

Young and colleagues recently studied 414 patients with smears taken at the time of colposcopic biopsy, 165 of whom had previous smears in the same laboratory available for review.¹⁸ The mean interval between smears was 3.6 months (range, 1 week to 22 months). In 67 cases (41%) the initial and repeat cervical smears did not agree. In 46 of the 67, the repeat (colposcopy) smear was of lower grade (statistically significant by χ^2 test). The authors emphasized that the colposcopic smear was clinically helpful in only five cases (1.2%). Similarly, Wheelock and Kaminski¹⁷ found that smears taken at the time of colposcopy failed to disclose existing precancerous lesions in at least 69 patients in a series of 273 referrals for SIL. For false negative colposcopy smears the interval between smears is not stated specifically in either paper. These results support our findings.

In 1987, Jones et al⁴ reported on a study of 236 pa-

Table VI Interval < 45 Days, CUMC and TPMG Combined

Smear1	Smear2 (n = 145)					
	WNL	Inflammatory and reactive	ASCUS/AGCUS	LSIL	HSIL	Carcinoma
WNL	3	2	1	2		
Inflammatory and reactive	1	1	2	1		
ASCUS/AGCUS	9	2	12	11	4	
LSIL	8	4	10	32	5	
HSIL	1		5	7	20	1
Carcinoma	1					

Cross-tabulation comparing the second cervical smear result (Smear2) with the first cervical smear result (Smear1). Each of these cross-tabulations is read similarly. The instances where the two cervical smears agree form a diagonal from the upper left corner of the table to the lower right corner, the diagonal of concordance (in boldface). Values along this diagonal represent the number of case pairs in agreement for a given diagnosis. Values below and to the left of this diagonal show the number of instances where the second cervical smear showed a lesser degree of abnormality. Values above and to the right of this diagonal show the number of instances where the second cervical smear showed a greater degree of abnormality. The numbers in italics are the cases that showed LSIL or higher on the first smear but less than LSIL on the repeat smear.

Total positive bias, 27.
Total negative bias, 45.
Agreement, 68.

tients referred with “class II atypia.” The mean interval between repeats was 4.7 months (range, 3 weeks to 1 year). Fifty-eight patients (25%) had biopsy-proven SIL. Only 10 (17%) of these were evident on repeat cytologic smears. Most of the repeat smears were “benign,” and their data were not stratified by test interval. A short testing interval could account for at least some of the negative repeat smears.

Higgins et al³ examined multiple modalities, including repeat cervical smears, used to evaluate LSIL and HSIL on initial smears. Two hundred three patients had repeat cervical smears, and 188 of these also had colposcopy and loop excision. The repeat smears were “normal” in 53 (35%). Once again, the interval between smears may have played a role since all of the repeat smears were done in less than a four-month interval.

Sedlis and co-workers¹³ examined the limiting case of test interval when two smears were taken during the same gynecologic examination. They found that the first of the two smears documented 35% of the premalignant lesions seen on the second smear, while the second smear showed only 27% of the premalignant lesions found on the first smear. Neither smear found all the lesions, but the second smear was less sensitive than the first.

Tabbara and colleagues compared the adequacy of one-slide smears with two-slide smears in the detection of SILs.¹⁴ The study group (87 patients) had a one-slide repeat smear taken at the time of colposcopy, while the control group (85 patients) had a two-slide repeat smear. The authors concluded

that two-slide smears are better than one-slide smears, despite their acknowledgment that many of the one-slide smears were technically poor. Even though the interval between smears given for the two groups appear comparable, we are not told whether the nondiagnostic repeat smears in either group were distributed normally over the range of the test interval or if they were preponderantly on the short side of the median in one or both groups.

Our data and the studies cited point to a sampling problem in the second smear that is somehow related either to the fact that a prior smear was performed or to the concurrent colposcopy. The mechanisms underlying this loss of sensitivity in the second smear are not clear. Possible mechanisms that should be considered for further investigation include: (1) scraping by the first sampling may alter the neoplastic lesion (decreased size) for a time, rendering it less likely to be included in the second sample on a statistical basis; (2) after the first scraping, the abnormal cells may not exfoliate easily for a time; and (3) the repeat smear technique might be perfunctory due to a desire to avoid obscuring the colposcopic field with blood or to the belief that the colposcopic examination and biopsy are the main purpose of the procedure.

Recently, performance of the cervical smear has become an issue for investigation. Some investigators designing studies to compare one technique against another for efficacy in detecting cervical abnormalities have chosen to use repeat cervical smears with different techniques at close intervals

and to compare the results obtained.^{12,14} We have consistently found that the first and second cervical smears in such close interval pairs show a correlation, but a correlation is not enough. There is a distinct negative bias in the second smear result. Kappa statistics, which are a better test of agreement between cervical smear results, reveal this bias in the rapidly repeated second smear, even when the technique is the same. Cross-tabulations, such as those in Tables III–VI, also make this bias plainly visible. One must conclude that comparisons of different techniques should not be attempted by means of rapidly repeated smears.

Beyond its effect on study design, the presence of this bias towards decreased sensitivity suggests that a cervical smear may be repeated too soon due to anxiety on the part of the clinician or the patient. This second result may provide a false assurance that the first cervical result was in error, just as Koss warned^{5,6} and our study confirmed.

Although our study analyzed the performance of repeat cervical smears without regard for colposcopy, we recognize that many of these short-interval repeat smears are taken at the time of colposcopy as a test complementary to the biopsy. Our data do not speak directly to the efficacy of this practice. Our findings, together with the studies cited above, should lead practitioners to question whether there is any valid purpose to repeating the cervical smear at colposcopy.

When comparing cervical biopsy results with cervical smear results and reviewing apparent discrepancies, it is important to compare the biopsy results with both the concurrent smear and the immediately prior smear. One need review only those cases where *both* cervical smears are discrepant with the biopsy. This is especially true when the interval between smears is short.

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