SCREENING FOR GYNECOLOGIC MALIGNANCY -WHAT EVERY INTERNIST SHOULD KNOW

MEDICAL GRAND ROUNDS
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INTRODUCTION

The Pap Smear - Historical Perspectives

In the early 1920's, George Papanicolaou, a researcher studying the hormonal basis of the menstrual cycle, incidentally observed that tumor cells originating from the human cervix could be found in human vaginal smears.[1,2] At about the same time, a Rumanian pathologist, Aureli Babes published similar findings and suggested cytologic sampling as a technique for the diagnosis of cervical cancer.[2,3] Nothing substantial came of these discoveries until Papanicolaou in collaboration with Herbert Traut published a book in 1943 detailing the identification of tumor cells in vaginal pool specimens of patients with cancers of the cervix and endometrium, some not suspected clinically.[2,4] Subsequent study by J. Ernest Ayres resulted in samples being taken directly from the cervix with a wooden spatula.[2,5] Ayres and others also reported that malignant changes limited to the epithelium of the cervix (carcinoma in situ) could be identified in asymptomatic patients.[6,7] At that time, cervical cancer was a leading cause of cancer deaths and the concept of "screening" for early, treatable disease was heralded as a major breakthrough. The importance of these findings was also recognized and promoted by the American Cancer Society, originally established in 1913 by a group of concerned citizens attempting to decrease the mortality from cervical cancer.[8] Incidental impetus for annual cervical cytologic screening was provided by the advent in the 1960's of oral contraceptives. Since the latter could only be obtained by prescription, and most physicians required a pelvic examination and Pap smear prior to this, millions of young women were screened for cancer of the cervix.[9]

The purpose of these Grand Rounds is to summarize the current status of screening for cervical cancer, address remaining questions concerning the Pap smear regarding frequency of use, technique, and interpretation, and discuss the data that exists on office screening for other gynecologic malignancies including carcinomas of the ovary, endometrium, vagina and vulva.

Screening for Cervical Cancer - How does the Pap smear measure up?

Criteria for Screening - Criteria for a successful screening program have been outlined by several authors and include the following[10,13]:

1) the disease must have an asymptomatic period during which cases detected by screening can be expected to have an improved prognosis as compared to cases detected after symptoms occur

2) the disease must have serious consequences for the population

3) available screening techniques must be sensitive enough to make detection likely

4) screening techniques must be specific enough to make follow-up to differentiate between false positives and true negatives worth the expense and risk

5) the incidence of the disease must be sufficient to justify the cost of screening

Natural History

In order to address the first criterion it is necessary to review what is currently known about the natural history of cervical cancer. It is generally accepted that cervical cancer develops in a continuum from an early focus of dysplasia to carcinoma in situ to invasive cancer.[2,9,14,15] The frequency with which one stage progresses to the next and the time interval over which these changes occur has been the subject of considerable investigation, although it is important to remember that variations in histopathologic interpretation, possible alterations in the natural history by biopsy (i.e. elimination of lesions) and ethical problems related to observation of possible malignancy make this difficult.[15] Nonetheless, Stern reported that 6.4% of women followed prospectively with dysplasia progressed to invasive cancer each year. 32% demonstrated regression to normal.[16] Fox found that of 278 women followed with dysplasia and no biopsy, 60% progressed, 31% regressed and 9% remained unchanged.[17]

Another study in Japan followed a large group of women prospectively with cytology, colposcopy, and directed biopsy. Their results are summarized in the following table.[18]

NATURAL HISTORY OF CIN

LESION	NO. OF PATIENTS	REGRESSION (%)	NO CHANGE (%)	PROGRESSION (%)
MILD-MODERATE DYSPLASIA	151	63.6	26.5	9.9
SEVERE DYSPLASIA	74	58.1	25.7	16.4
SEVERE DYSPLASIA/ CIN	32	25.1	43.8	31.3
CA IN SITU	37	2.7	43.2	54.0

KURIHARA ET AL (1985)

Thus, while cervical cancer is preceded by premalignant lesions it appears that at most one in ten of the latter will progress to invasive cancer if left untreated.[2]

What is known about the transformation interval from dysplasia to invasive cancer? Richart and Barron reported a mean transition time from mild dysplasia to carcinoma in situ of 5.8 years. They calculated a mean duration of carcinoma in situ of 10 years but reported that 5% would become invasive in less than 3 years.[19] More recent studies from British Columbia suggest that these intervals may be even longer but could reflect the effects of biopsy, etc.[20] The general consensus is that 8 to 30 years are required for most carcinoma in situ to progress to invasive cancer.[14]

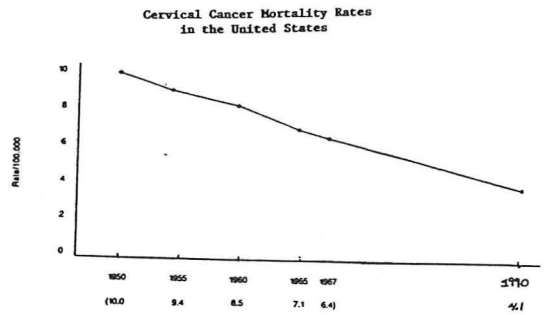
What is the evidence that prognosis can be improved by detection of asymptomatic lesions? The five year survival rate for carcinoma in situ is close to 100%.[14] This falls dramatically with more invasive lesions.[21]

Stage	5 Year Survival
Dysplasia and CIS	80%
Local Invasive	78%
Regional Invasive	43%

Thus early detection should improve prognosis and the evidence for this will be discussed shortly.

With regard to criteria 2 & 5, in 1990 the approximate number of new cervical

cancers in the United States was 13,500 with 6,000 deaths.[22] This however, represents a dramatic decline in mortality from the 1950's when the Pap smear was introduced (Figure 1).[9]



Adapted from Holler (1988)

At that time cervical cancer was a leading cause of cancer death in women. It remains world-wide the second most common cause of cancer death in women.[23]

<u>What is the sensitivity of the Pap smear for the detection of dysplasia and carcinoma in situ?</u> In the absence of controlled clinical trials the sensitivity of the Pap smear is difficult to evaluate.[24,25,26] Theoretically, one way to determine true sensitivity would be to colposcope and biopsy all negative cases which is obviously impossible. Alternatively all test negative subjects could be followed to determine how many invasive cancers eventually turned up among them, however, given the long intervals estimated for disease progression this would take more than a decade of follow-up. Nonetheless, several studies have attempted to determine the Pap smear's ability to detect neoplastic and pre-neoplastic lesions by retrospective review of prior Pap smears from patients ultimately diagnosed with abnormalities by Pap smear or biopsy (Table 2).[22,27-30] It is likely that true sensitivity is considerably lower.[24,31-33]

TABLE 2

SENSITIVITY OF THE PAP SMEAR

	TRUE POSITIVE	FALSE NEGATIVE/%	SENSITIVITY
VAN DER GRAFF ET AL (1987)	555	165/29.7	77.1
GAY ET AL (1985)	339	63/18.6	84.3
HUSAIN ET AL (1976)	168	25/14.9	87.0
RICHART AND VAILANT (1965)	273	3/1.1	98.6

ADAPTED FROM WILKINSON (1990)

Specificity refers to the proportion of non-diseased subjects in whom a test is appropriately negative. In the screening of asymptomatic persons this is as important as sensitivity because false positive tests require further evaluation that can be costly and morbid.[25] Although reliable data are lacking, a cohort study of women screened in British Columbia estimated specificity at 90%.[34] Tawa evaluated abnormal Pap smears in 3271 gynecology patients with colposcopy and biopsy and calculated a specificity of 99%.[31]

How then does the Pap smear measure up? It is safe to say that the incidence and mortality data to be discussed shortly have established the Pap smear's continued role as a screening tool. Its sensitivity, specificity, and cost, however, remain subjects of controversy, particularly with regard to issues such as who should be screened, how frequently should such screening occur, and how "abnormal" Pap smears should be handled.[14,15,19,22,24]

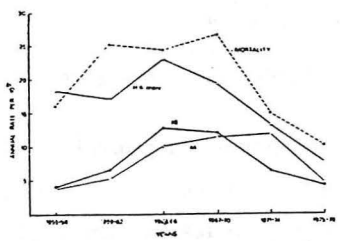
How "Effective" Has the Pap Smear Been?

There are 2 basic types of studies that can be initiated to evaluate screening programs, experimental and observational.[35,36] The former is typically termed the randomized controlled trial and is the method of choice as it alone produces an unbiased assessment of effect. When this is not possible, however, an observational approach may be necessary. One method is to examine the correlation between screening and the cancer mortality rate of several populations or of the same population at different times. However, simple correlation studies generally do not provide firm evidence of the benefits of a screening program.[36] With regard to cervical cancer, for example, a common error is to presume that the marked reduction in incidence of and mortality from invasive cancer in the US over

the past 30 years "prove" the effectiveness of the Pap smear. As Cole and Morrison have pointed out, mortality from cervical cancer is strongly and inversely related to socioeconomic status (and probably the likelihood of being screened) and was declining in many Western countries before Pap smear programs could have had any effect.[36]

A valid observational study should focus on a comparison of cancer incidence and mortality in a defined population before and after the introduction of a screening program. Time trends in incidence and mortality need to be examined and inter-area comparisons of intensively screened areas with non-screened areas need to be made. This also requires rapid introduction of the screening program and nearly full coverage of the population at risk. Reliable incidence and mortality data for at least a 10 year period prior to the onset of screening and which are predictable for the future need to be available.[35]

One study that meets these criteria was reported by Johannesson in 1982 from Iceland.[37] An organized screening program was begun in 1964 with one central screening clinic and cytopathology lab. Women were recalled by personal invitation every 2-3 years. By 1970, over 80% of the female population of Iceland under the age of 65 had been screened at least once, and by 1977 over 65% of women under the age of 75 had been screened at least twice. Figure 2 illustrates the effectiveness of the screening program.



. Changes over time in mortality and incidence of cervical cancer. The incidence is given by stage of disease. The rates given are the average annual age specific rates, in the age range 20–75.

From Johanneson et al (1982)

Importantly, it can be seen that the incidence and mortality from cervical cancer were actually increasing over a 10 year period prior to initiation of screening and

that the mortality among those under age 75 has fallen 60% and is paralleled by a fall in the incidence of stage II or greater tumors. Both the mortality rate and the incidence of advanced tumors were low among women with at least one negative smear and close to zero among women with two negative smears. The rates among unscreened women were only slightly higher than the rates before screening started. It is also important to note that survival for any given stage of cervical cancer remained the same for those diagnosed outside screening as it was before screening began. Such data, then, provide convincing evidence of success despite the lack of randomized controlled trials and have now been confirmed by a variety of similar studies in Finland, Scotland and British Columbia.[38-42]

Technical Aspects of the Pap Smear

As alluded to previously, it is estimated that the false negative rate for the Pap smear may exceed 30%.[2,14,22,24] Table 3 summarizes the causes of false negativety (i.e. a normal Pap smear in a woman with dysplasia or more severe lesions).[22]

Causes of False Negative
Cervical-Endocervical Cytology

Sample Error:	The diagnostic cells are not on the slide
Screening Error:	The cells are on the slide but are missed by the cytotechnologist in screening the smear
Interpretative Error:	The pathologist examined the cells in question and judged them benign when in fact, they were malignant

From Wilkinson (1990)

Sampling error may reflect inadequate technique and/or biologic factors that influence the shedding of cells. Systematic evaluation of "negative" smears in women subsequently diagnosed with lesions has demonstrated sampling error to be a significant problem accounting for the majority of false negative results in most series. Recently, Gay and Wilkinson have independently reported that approximately 60% of false negative smears are due to sample error.[22,27]

Obtaining the Sample

The method of obtaining the smear for cytologic evaluation is important.[2,9,15,22,26,26B]

(1) The patient should be instructed before coming to see the physician not to douche or insert any intravaginal drug or lubricant for at least 1 day before the examination.

(2) Cytological specimens should be obtained with a non-lubricated speculum prior to the bimanual examination.

(3) The cervix must be exposed with the speculum such that the os and exocervix are adequately visualized prior to sample taking.

(4) The endocervix and ectocervix should be sampled independently.

(5) A cytobrush or saline - moistened cotton - tipped applicator is inserted into the endocervical canal and twirled to collect a sample from the endocervix.

(6) The shaped end of a wooden or plastic spatula is rotated with pressure over the entire ectocervix (360 degrees).

(7) The samples are rapidly applied to one or two glass slides; the spatula by rotating the scraper end in swirls over the slide, the swab or brush by rolling over the slide.

(8) The slide is fixed prior to air drying by immersion in 95% ethyl alcohol or spraying with a fixative. "The thickness of the smear should be that after fixation newsprint cannot be read through the slide."[22]

Several of these steps deserve additional discussion. The majority of premalignant abnormalities and squamous cell cancers occur in the transformation zone where the squamous epithelium of the ectocervix meets the columnar epithelium of the endocervix at the squamocolumnar junction.[15] This junction is composed of metaplastic epithelium and in most adult women lies 8 to 13 mm proximal to the external cervical os. Age, parity, hormonal status and cryotherapy affect its location and in most women it migrates cranially throughout life making it more difficult to sample as the patient ages.[26,33] Traditionally, the moistened cotton swab has been used in addition to scraping with the spatula to ensure sampling of the transformation zone. In 1987, the Cytobrush was introduced in the United States and marketed as a tool for improving the yield of Pap smears. Several studies have reported that the use of such a device can increase effective sampling of the

transformation zone in many patients resulting in a decrease in inadequate samples up to 50%.[43-47] Additionally, studies have shown a significant increase in the proportion of Pap smears showing dysplasia or cancer when the Cytobrush was used.[48-49] Since the additional cost of this device is minimal and the only consequence to the patient is an increase in spotting after the procedure many do recommend its general use. These are currently available in the Parkland and Aston clinics and may well prove to be cost effective since they should significantly decrease the number of patients needing to be called back after an inadequate sample is obtained. While definitive data on this subject is lacking, it may be preferable to put the endocervical and ectocervical specimens on different slides simply to ensure that each sample is appropriately fixed prior to air drying although this increases the cost of the procedure.[2,15]

A vaginal pool specimen is no longer recommended in post-menopausal patients by many but not all authorities.[2,15] Such a specimen offers no additional yield for the diagnosis of cervical cancer, increases the workload for the cytology staff, and increases the cost of the test. Vaginal pool specimens have been recommended as a method to additionally screen for cancers of the endometrium, fallopian tube, ovary and vagina, however, the Pap smear is an insensitive and expensive screening tool used in this fashion, with no evidence that positive findings alter prognosis.[15] For patients exposed to DES, separate vaginal smears taken from the upper 2/3 of the vagina are recommended. Such patients should, however, be followed by a gynecologist.[50]

Quality Assurance in the Laboratory

It is estimated that approximately 40% of false negative Pap smears are secondary to laboratory errors. These include errors in screening or interpretation (Table 3).[2,22] Most laboratories that handle Pap smears are supervised by a cytopathologist but the actual screening of the smears is done by a cytotechnologist. Abnormal cells are marked on the slide and submitted to the cytopathologist for further review. A series of articles in the Wall Street Journal and other newspapers in 1987 drew attention to the lack of standardized qualifications for many of the personnel working in the laboratories. Additional questions were

raised as to how many slides a given individual could be expected to screen well in a 24 hour period. Prior to this, it was not infrequent for cytotechnologists to be paid on the basis of the number of smears screened. Even in laboratories where caps were placed on number of smears screened per day per person, overtime and moonlighting frequently exceeded these limits. The National Clinical Laboratory Improvements Act of 1988 addressed many of these issues. Only certified cytotechnologists are now allowed to screen smears. These persons have been trained at specialized schools for 1-2 years, and have passed an examination given by the American Society of Clinical Pathologists. A maximum of 80 slides are to be screened in a 24 hour period although this will be increased to 125 shortly. 10% re-screening of random negative slides by the pathologist is required for quality assurance purposes as well as re-screening of all slides in individuals with previously reported abnormalities. These measures should improve Pap smear screening, particularly in remote areas of Texas and other states.[51]

Evaluation of the Abnormal Pap Smear

One point needs to be emphasized prior to discussing interpretation of an abnormal Pap smear - lesions visible on examination need referral to a gynecologist for biopsy irrespective of Pap smear results. Smears taken directly from grossly evident cervical cancers yield a high false negative rate presumably because of necrosis and infection on the tumor surface.[2,52] Four methods of reporting cervical cytology are currently in use. These are the Pap system, the WHO system, the CIN system and the Bethesda system.[2,22,53,54] The latter system was developed in 1988 during a workshop sponsored by the National Cancer Institute with the goal being to develop concise, unambiguous and universal terminology.[53] The new system is summarized in Table 4.[22]

Important additions to the old format include:

- a statement regarding the adequacy of the specimen
- a categorization of normal vs abnormal with regard to the diagnosis of neoplasia
- a descriptive diagnosis, in some cases with recommendations regarding appropriate management.

Table 4

The 1988 Bethesda System for Reporting Cervical/Vaginal Cytological Diagnoses

Statement on Specimen Adequacy

Satisfactory for interpretation
Less than optimal
Unsatisfactory

Explanation for less than optimal/unsatisfactory specimen:

- —Scant cellularity
- —Poor fixation or preservation
- —Presence of foreign material (eg, lubricant)
- —Partially or completely obscuring inflammation
- —Partially or completely obscuring blood
- —Excessive cytolysis or autolysis
- —No endocervical component in a premenopausal woman who has a cervix
- —Not representative of the anatomic site
- —Other

General Categorization

Within normal limits
Other:
See descriptive diagnosis
Further action recommended

Descriptive Diagnoses

INFECTION
Fungal
Candida species
Other
Bacterial
Microorganisms morphologically consistent with *Gardnerella* species
Microorganisms morphologically consistent with *Actinomyces* species
Cellular changes suggestive of *Chlamydia* species infection, subject to confirmatory studies
Other
Protozoan
Trichomonas vaginalis
Other
Viral
Cellular changes associated with cytomegalovirus
Cellular changes associated with herpesvirus simplex
Other
(Note: for human papillomavirus [HPV], refer to "Epithelial Cell Abnormalities, Squamous Cell")
Other

REACTIVE AND REPARATIVE CHANGES
Inflammation
Associated cellular changes
Follicular cervicitis
Miscellaneous (as related to patient history)
Effects of therapy
Ionizing radiation
Chemotherapy
Effects of mechanical devices (eg, intrauterine contraceptive device)
Effects of nonsteroidal estrogen exposure (eg, diethylstilbestrol)
Other

EPITHELIAL CELL ABNORMALITIES
Squamous Cell
- Atypical squamous cells of undetermined significance (recommended follow-up and/or type of further investigation: specify)
- Squamous intraepithelial lesion (SIL) (comment on presence of cellular changes associated with HPV if applicable)
  - Low-grade squamous intraepithelial lesion, encompassing:
    - Cellular changes associated with HPV
    - Mild (slight) dysplasia/cervical intraepithelial neoplasia grade 1 (CIN 1)
  - High-grade squamous intraepithelial lesion, encompassing:
    - Moderate dysplasia/CIN 2
    - Severe dysplasia/CIN 3
    - Carcinoma in situ/CIN 3
- Squamous cell carcinoma

Glandular Cell
- Presence of endometrial cells in one of the following circumstances:
  Out of phase in a menstruating woman
  In a postmenopausal woman
  No menstrual history available
- Atypical glandular cells of undetermined significance (recommended follow-up and/or type of further investigation: specify)
  Endometrial
  Endocervical
  Not otherwise specified
- Adenocarcinoma
  Specify probable site of origin: endocervical, endometrial, extrauterine
  Not otherwise specified
- Other epithelial malignant neoplasm: specify

NONEPITHELIAL MALIGNANT NEOPLASM: SPECIFY

HORMONAL EVALUATION (APPLIES TO VAGINAL SMEARS ONLY)
- Hormonal pattern compatible with age and history
- Hormonal pattern incompatible with age and history: specify
- Hormonal evaluation not possible
  Cervical specimen
  Inflammation
  Insufficient patient history

OTHER

From Jama (1989)

Terminology differences between this and the prior Pap or WHO systems are summarized in Table 5.[22]

Nomenclature in Cervical Cytology

PAP System	WHO System	Bethesda System
Class I	Normal	Within normal limits
Class II	Atypical	Reactive or reparative change
Class III	Dysplasia	Squamous epithelial cell abnormality
		Atypical squamous cells of undetermined significance
		Squamous intraepithelial lesion
	Mild dysplasia	Low grade (includes HPV)
	Moderate dysplasia	High grade
	Severe dysplasia	High grade
Class IV	Carcinoma in situ	High grade
Class V	Invasive squamous cell carcinoma	Squamous cell carcinoma
Class V	Adenocarcinoma	Glandular cell abnormalities: Adenocarcinoma
Class V	—	Nonepithelial malignant neoplasm

From Wilkinson (1990)

The Bethesda system introduces two new terms: low grade and high grade squamous intraepithelial lesion. The former is the new designation for mild dysplasia, cervical intraepithelial neoplasm or CIN1 and cellular changes associated with the human papilloma virus. It also encompasses some of the Class III Paps. High grade squamous intraepithelial lesion includes the former moderate dysplasia to carcinoma in situ, or CIN2 to CIN3, or Class III - IV Paps.[54]

The old Class II/Atypical classification has been replaced with "Reactive and Reparative Change" encompassing inflammatory, therapeutic, or other effects which alter cellular findings but are not neoplastic. "Atypia" now only refers to changes of undetermined significance.[54]

Normal

95% of the Pap smears sent for interpretation will be normal. In these cases it is important to determine that the sample was adequate. This generally infers that the sample contained a reasonable number of cells not obscured by blood, inflammation or debris for interpretation. There should also be evidence that the transformation zone, the most frequent site of cervical cancer, was sampled. Thus, endocervical cells, endocervical mucus, or squamous metaplastic cells should be reported as present in all women with a cervix.[2,22,53] When a sample is inadequate, a new sample should be obtained. At least 1 month is required for cervical epithelium to be replenished following a Pap smear and samples repeated prior to this time will have a very high false negative rate.

Dysplasia

In the United States, it is the prevailing opinion that all SIL, that is dysplasia - mild, moderate, severe or carcinoma in situ requires referral to a gynecologist for culposcopic exam, biopsy and endocervical curettage.[2,15,22] Repeating the Pap smear at a short interval is not considered sufficient because of the significant false negative rate demonstrated on subsequent specimens.[2] Furthermore, there is considerable variability in how different pathologists read a given smear. Thus one pathologist's mild dysplasia can be read by another as marked or even carcinoma in situ.[2] However, the aforementioned recommendation is not the case in all other countries and reflects different views on the cost - benefit ratio of evaluating low grade abnormalities on the Pap smear. In 1982 the Canadian Task Force, for example, issued the following statement: "Women whose smears show mild dysplasia should have the smear repeated every 2 or 3 months, and if the dysplasia persists they should undergo culposcopic examination since significant dysplasia or carcinoma in situ is not uncommonly found in specimens obtained by culposcopically directed biopsy in such patients.[11,38] I believe further justification for evaluating mild dysplasia can be found in the report of the IARC Working Group on evaluation of cervical cancer screening programs.[55] This study, to be discussed shortly, represents the best data available to date on the protective effect of "negative" pap smears and is the basis of many recommendations regarding frequency of screening, etc. It makes sense that if we are to use this information to determine screening frequency we need to consider their definition of a positive smear. The latter includes any Class III Pap, that is any Pap showing evidence of dysplasia.

Atypical Squamous Cells

The appropriate management of patients with a Pap smear reported as "Atypical Squamous Cells" is a subject of controversy in the U.S. and elsewhere. Numerous studies have shown that there is an increased incidence of neoplasia, predominantly dysplasia but occasionally carcinoma in situ, in these patients.[56-60] Himmelstein, in a review of the literature, argues in favor of culposcopic examination following even a single atypical Pap smear. She cites data from Maier et al who prospectively evaluated 429 patients with atypia.[62] All patients underwent

colposcopy after a single smear with this diagnosis. 237 had abnormal exams and were biopsied, 86 patients demonstrating dysplasia. Of the latter, 36 were undetected on repeat smear. Almost identical data was reported by Davis using similar methodology.[63] The yield appears to be somewhat higher in patients with more than 2 positive results. Nonetheless, it is not clear that continued surveillance of such patients would not have been adequate to detect progressive abnormalities. Within our own institution one gynecologist follows patients yearly for atypia (his usual screening frequency) and recommends no further evaluation unless dysplastic changes occur; another recommends culposcopic examination after a second atypical result 3-4 months after the initial sample and treatment for "infection". The IARC Working Group considered an atypical Pap smear to be "positive" only if it was followed by a second atypical smear after 10 or more months or three consecutive smears were positive regardless of the time interval.[55] It is estimated that evaluation of all atypical Pap smears would double the frequency of culposcopic examinations being performed at a cost of $200.00 per examination.

Atypical Endometrial Cells

The Pap smear is a very insensitive screening tool for the diagnosis of endometrial cancer. Furthermore, the majority of the latter result in vaginal bleeding at curable stages of disease.[15] Nonetheless, an occasional adenocarcinoma of the endometrium will be detected in an asymptomatic patient by Pap smear. These represent no problem and should be referred to the gynecologist for definitive diagnosis (endometrial biopsy or D&C). It is unclear, however, what to do with the result "atypical endometrial cell". Cherkis performed a retrospective review of 175 women with such findings on Pap smear.[64] 20% had adenocarcinoma and this increased to 57% if only patients over 59 were included. 64% of those with cancer, however, were symptomatic and it is unclear how many more would have become symptomatic at early stages of disease. In the past, ACOG[50] has recommended endometrial biopsy in cases of atypical endometrial cells suspicious for cancer. At our institution some gynecologists react to this result even in an asymptomatic patient and others do not. At a minimum such results should lead the internist to review symptoms such as vaginal bleeding with the patient, and in my own practice

such patients will be referred to gynecology.

Human Papilloma Virus

In the past several years attention has become focused on HPV and its relationship to cervical cancer. Morphologic abnormalities in epithelial cells positive for HPV have been reported in up to 90% of women with invasive or intraepithelial neoplasia.[15,65-69] Moreover, pathologists note that it is frequently difficult to differentiate the cytologic abnormalities associated with HPV from cases of dysplasia where HPV cannot be isolated.[53] Because of this, the Bethesda workshop recommended that all HPV be included under the designation "low grade squamous intraepithelial lesion."[53] The latter implies that some degree of dysplasia is present and would therefore require that such a patient be referred for culposcopy. Occasionally a patient will be identified as positive for HPV but without any evidence of dysplasia. Once again gynecologists are divided as to the management of this problem. Some recommend yearly follow-up and others proceed directly to culposcopy.

Other Infections

There have been many papers published promoting the Pap smear as a diagnostic tool for other cervical and vaginal infections. An excellent review of this literature from a group at the CDC analyzed studies including more than 50 patients where culture was the gold standard and sufficient data was available to calculate the efficacy of the Pap smear.[76] For Chlamydia trachomatous data was primarily obtained from STD clinics and the sensitivity of the test ranged from 17% to 95% with a specificity of 61% to 100%. Positive predictive values ranged from 40% to 100% meaning that 40% to 100% of women with a cytologic diagnosis of infection actually had infection as determined by culture. Because of the correlation between Chlamydia and subsequent infertility and the frequency of negative cultures, many have recommended empiric treatment with doxycycline without further investigation and without establishing a reportable diagnosis.[77]

Predictive values of positive smears for vaginal mycoses and Hemophilus vaginalis range from 20% to 100% in patients with vaginitis, thus further evaluation or

treatment in asymptomatic patients, given the benign nature of the disease process, is not indicated.[76-77] In the one study reported of routine gynecology patients with smears positive for gonorrhea the predictive value was 87%.[76] Once again, given the potential complications associated with this diagnosis, culture and treatment (even if the latter is negative) are indicated.[77] The predictive value of a smear positive for Trichomonas vaginalis is higher at 81% to 100% however given the benign nature of the infection empiric treatment of the asymptomatic patient is not recommended and reevaluation is not necessary. Finally, with regard to Herpes Simplex, the predictive value ranges from 38% to 95%. In patients without visible lesions and without a prior history, serologic confirmation may be indicated because of its relevance to issues such as vaginal delivery in pregnancy, etc.[76,77]

Frequency of Screening

Frequency of screening in the general population is probably the most controversial topic with regard to Pap smears. In 1976 the Canadian Task Force (CTF) reviewed the effectiveness of the Pap smear screening program in Canada and concluded that annual cytologic screening was not necessary. They recommended that all sexually active women have two negative smears 1 year apart, then every 3-5 years for 15 years, and then every 5 years until age 60.[38] The American Cancer Society (ACS) agreed with their conclusion and in 1980 recommended that all asymptomatic women over age 20 and those under age 20 who are sexually active have a Pap smear annually for two negative examinations and then every one to three years until the age of 65. They recommended no further screening for cervical cancer after age 65.[78]

In 1982, the CTF reconvened and changed their recommendation to annual screening between the ages of 18 and 35 with an examination every 5 years between ages 35 and 60 and none thereafter, providing the patient had a prior history of normal smears. They concluded that the group of women between ages 18 and 35 constituted a high risk group, according to the known risk factors listed in Table 6, and merited more frequent screening. They also concluded that measures to improve the quality and sensitivity of screening programs to include women who have never been screened would be more effective in reducing

mortality from cervical cancer than increasing the frequency of screening.[38]

RISK FACTORS FOR CERVICAL CANCER

- ONSET OF COITUS AT AN EARLY AGE
- MULTIPLE SEXUAL PARTNERS
- A SEXUAL PARTNER WHO HAS HAD MULTIPLE SEXUAL PARTNERS
- HISTORY OF VENEREAL DISEASE, INCLUDING HERPES SIMPLEX
- CIGARETTE SMOKING
- LOWER SOCIOECONOMIC GROUP
- HISTORY OF CERVICAL HPV INFECTION
- HISTORY OF PRIOR CERVICAL INTRAEPITHELIAL NEOPLASIA

ADAPTED FROM WILKINSON (1990)

In 1986 Frame reviewed the ACS's recommendation and concurred with their judgement but recommended biannual screening because of concern that recommending screening every 3 years could result in an actual frequency less often than this.[14]

Most recently the ACS has recommended discontinuing an age limit for Pap smears to be obtained.[24] The U.S. Public Health Service Task Force recommended that Pap smears should begin with the onset of sexual activity and should be repeated every one to three years at the physician's discretion and may be discontinued at age 65 if previous smears have been normal.[24] It should be noted that the American College of Gynecology (ACOG) has continued to recommended yearly Pap smears in all women but concurred that individual physicians might choose longer intervals up to 3 years.[79]

Data on the efficacy of various screening intervals comes from retrospective studies and mathematical models. Eddy calculated the effectiveness of various screening intervals assuming a 50% sensitivity of the Pap smear and an 8 year duration of disease before becoming invasive in 95% of cases with 5% preceded by a preinvasive stage lasting 0-2 years.[80] Using this model in the age range, 35 to 64 years, he calculated the following results (Table 7) and concluded that screening every 3 years was cost-effective.

	Results of Revised Model*	
Screening frequency (yr)	Reduction in the cumulative rate†‡	No. of tests
1	93.9	30
2	92.7	15
3	91.0	10
5	85.75	6
10	63.9	3

* Age range, 35 to 64 years.
† Cumulative rate of invasive cervical cancer.
‡ Assuming screening begins at age 35, and that each woman has had a previous negative Pap smear.

Taken from Eddy (1987)

In 1986 the IARC Working Group reviewed screening programs in 8 countries and came to conclusions very similar to the model proposed by Eddy (Table 8).[55]

% Reduction in cumulative rate of invasive cervical cancer in women aged 35-64 with different frequencies of screening

Interval between screening (years)	% Reduction in cumulative incidence	No of tests
1	93·5	30
2	92·5	15
3	90·8	10
5	83·6	6
10	64·1	3

*Assuming that a woman is screened at age 35 and that she had also had at least one screen previously.

Taken from IARC Working Group Report (1986)

They commented that little was to be gained by screening every year rather than every two or even every three and noted that screening every 10 years, of interest only in countries where resources were scarce, still reduced the risk by nearly 2/3. They further commented: "In the context of public health this reduction should be compared with that achieved by screening 30% of the population every 3 years, an approach that screens the same number of women each year but reduces the incidence rate by less than 30%"

Since the safety of the Pap smear and the culposcopic examination performed to follow-up abnormalities are not an issue, cost has been the principal concern. Eddy has estimated this cost in Table 9 and it can be seen that this is not trivial. Moreover, because of various assumptions this is likely to significantly underestimate true cost.[80]

TABLE 9 Effect on Woman-Years of Life and Costs of Screening 100,000 Women: Results of Revised ACS Model

Screening frequency (yr)	Woman-years of life	Dollars
1	17,551	29,471,000
2	17,140	12,531,000
3	16,964	7,042,000
4	16,501	4,309,000
5	16,161	2,788,000
6	15,412	1,860,000
7	14,868	1,152,000
8	14,073	736,000
10	12,773	349,000

Taken from Eddy (1987)

How an individual physician decides to manage his patients will be variable although the public health implications of the above data are clear. It should be reinforced that women with previously abnormal smears, including dysplasia that has been successfully treated, constitute a special group for whom annual screening is important. Particularly if less frequent examinations are performed, recall of patients to facilitate compliance is necessary.

The elderly account for one-fourth of the incidence of invasive cervical cancer and 40% of the deaths. In one study where a single screening was offered to all women over age 65 (predominantly indigent patients), screening was calculated to be cost effective ($4,463 per year of life gained).[81] 75% of these women, however, had not been screened regularly (every 1-5 years) in the past. Thus, it is important to document an adequate history of normal regular Pap smears prior to discontinuing or decreasing the frequency of screening in the elderly.

There is also evidence that many opportunities for Pap smear screening are missed. This is especially true in the indigent population where patients are admitted to the hospital for a non-gynecologic problem and discharged without attention to routine health care maintenance. Particularly in otherwise healthy individuals this may represent their only contact with the health care system for several years. Thus it is important to review this with every patient during their hospitalization, indeed in several states it is now the law. It is also cost-effective to combine the gynecologic examination with other necessary health care whenever possible.[82-88]

Status-Post Hysterectomy

This issue has been frequently ignored in the various recommendations given. Everyone agrees it is important to establish the absence of residual cervix and the presence of a normal vaginal cuff on one exam. ACOG has stated that "the cost-effectiveness of cytologic screening for vaginal neoplasia after removal of the cervix for benign disease has not been demonstrated. In consideration of the well-being of the individual patient, however, periodic cytologic evaluation of the vagina is recommended at minimal intervals of 3-5 years."[79] The Canadian Task Force classified patients who have had a hysterectomy for benign disease as a group at "no risk" and felt they should not be included in a screening program.[38] Despite this it is not infrequent for physicians to continue annual or semi-annual screening. This makes little sense in my opinion. Such screening is thus being done for vaginal cancer and as we will discuss shortly there is no evidence that this is a sensitive screen or that this alters the prognosis of this infrequent disease. Since most gynecologists no longer do a vaginal pool specimen in patients with a cervix (thus not checking via Pap smear for vaginal cancer) it is unclear why this should be done post-hysterectomy. An occasonal paper in the literature refers to a slight increase in the incidence of vaginal cancer in patients who have had a hysterectomy for a benign problem but this is still a very small number.[89]

The general recommendation has been that patients undergoing a hysterectomy for cervical cancer or dysplasia be followed with yearly Pap smears of the vaginal cuff looking for recurrence/persistence of cervical disease and/or vaginal cancer. These patients have a 30% increased likelihood of subsequent vaginal cancer.[2,15,22,38,78,79]

Diethylstilbestrol - Exposed Patients

Cytologic examination should be initiated at the onset of menstration, by the age of 14 or when a patient exhibits symptoms, whichever occurs first. Such examinations should include smears from the upper 2/3 of the vagina as well as the cervix and should be repeated at 6 month - 1 year intervals.[79]

SCREENING FOR OVARIAN CANCER

Ovarian cancer, while less common than either cervical or endometrial cancer, is the leading cause of gynecologic cancer death in the United States. In 1989 there were approximately 20,000 new cases diagnosed with 12,000 deaths and it is estimated that 1 in every 70-100 American women will ultimately die from this disease.[90]

Despite advances in therapy, there has been only a limited improvement in overall prognosis. The American Cancer Society estimates that the 5-year survival rate for ovarian cancer has increased only 5% in the last 25 years, from 32% in 1960 to 37% in 1984.[91] The natural history of ovarian cancer is not well established but it appears to be a rapidly growing cancer with few early symptoms. Two-thirds of women have advanced (State III or IV) disease at the time of diagnosis.[90]

While there is no direct evidence that early diagnosis improves survival it is known that survival is strongly correlated to stage at diagnosis. The five-year survival rates quoted by Richardson et al in their 1985 review in the New England Journal of Medicine are as follows:

Stage 1	66%
2	45%
3	13%
4	4%

Recent studies however, indicate that the cure rate with aggressive treatment of Stage I lesions may approach 90%.[93] Such data suggest that an accurate method of early detection could result in a major improvement in survival.

Potential Screening Techniques

Screening methods that have been recommended to date include the periodic pelvic examination , the Pap smear, cytologic examination of peritoneal lavage fluid, serum tumor marker determination, and ultrasound examination, by either the transabdominal or transvaginal approach.

Periodic Pelvic Examination

The annual pelvic examination is often recommended as a screening test for ovarian cancer. In a recent consensus statement issued on Pap testing by the ACS, NCI, ACOG and others, the pelvic examination was recommended annually for all sexually active women or those over 18.[90] Although the frequency of Pap testing might be decreased after 3 normal annual smears, the organizations did not specifically discuss reducing the frequency of pelvic examinations. In the past, an annual pelvic examination has been recommended by ACOG, the ACS and the NCI.[90] Recently, Frame advised against this practice stating "the annual pelvic examination should not be recommended just because there is nothing better."[14] The U.S. Preventive Services Task Force came to the same conclusion noting that "it is clinically prudent to examine the uterine adnexa when performing gynecologic examinations for other reasons."[90] There are numerous comments in the literature stating that the pelvic examination is poor at detecting early stage disease,[90,94] and even ACOG has noted that "no available techniques are currently suitable for routine screening."[79] One older respective evaluation of an annual cancer screening program found a very low 5 year survival for cancer detected on pelvic examination.[95]

A more recent study used the pelvic examination in addition to other screening tools which will be discussed shortly. 1010 postmenopausal women recruited for an ovarian cancer screening program received a single pelvic examination. One 10cm Stage 1a ovarian cancer was detected, however, there were 27 additional abnormal examinations. In 17 of these patients ultrasound demonstrated normal ovaries. In the remaining 10 women with abnormal ultrasounds laparotomy yielded no malignancies. No additional malignancies were reported by participating subjects in response to questionaires sent out one year later. While the pelvic examination did detect the single ovarian cancer reported, the false positive rate was high and the sensitivity unclear since 1 year follow-up is not sufficient to exclude malignancy. Moreover, the size of this particular tumor facilitated diagnosis and is not representative of early ovarian cancer at large.[96] Thus, there exists little evidence that the pelvic examination is effective in detecting early treatable ovarian cancer and I concur with the recommendation of the U.S Preventive Services Task Force.

The Pap Smear

Anecdotal reports exist of ovarian cancer diagnosed by Pap smear testing but it is not considered a reliable screen for ovarian cancer. Sensitivities are reported between 10-40% but this at all stages of carcinomatosis.[90]

Peritoneal Lavage

Periodic culdocentesis for peritoneal cytologic study has proved impractical for routine screening because it is technically difficult, uncomfortable for patients and insensitive for the detection of early disease. McGowen et al performed culdocentesis on over 1000 asymptomatic women over age 35.[97] No positive results were obtained but in 2% of the patients perforation of the rectosigmoid occurred. Keetel et al reported that only 36% of patients with Stage Ia ovarian cancer had positive cytology when cul-de-sac aspiration was performed prior to surgery.[98]

Serum Tumor Markers

Serum tumor markers are frequently elevated in women with ovarian cancer. In 1981, Bast et al reported that a monoclonal antibody raised using an ovarian cancer cell line as an immunogen recognized a specific antigenic determinant CA125 in more than 80% of nonmucinous epithelial ovarian cancers.[99] Serum CA125 levels are measured with an immunoradiometric assay.[94,100] Antigens units are referenced to a standard preparation of CA125 from epithelial ovarian cancer cell cultures. Less than 0.3% of healthy women will have values greater than 65 u/ml and less than 1% greater than 35 u/ml.[94,100] Since the higher value limits the sensitivity of the test, in the clinical setting a serum level of CA125 greater than 35 u/ml is considered positive.

The rise and fall of CA125 levels have paralleled disease activity in more than 90% of cases where this has been monitored during treatment.[94] Moreover, CA125 levels returning to the normal range following treatment are associated with absence of disease or minimal residual disease at second look procedures.[94,100]

The usefulness of this marker as a screening test, however, is unclear. While disease outside the ovary (Stages II, III, IV) is associated with elevated levels in over 90% of cases, measurements taken at the time of laparoscopy indicate that CA125 is elevated in no more than one half of women with Stage 1 malignancies.[100] It is likely that the sensitivity of the test is significantly lower in asymptomatic women with preclinical Stage 1 disease. In one recent report, retrospective evaluation of blood obtained from women subsequently diagnosed with ovarian cancer yielded elevated CA125 levels in 15-20% of cases more than 2 years prior to diagnosis.[101]

Unfortunately lack of specificity is the major drawback to use of this technique alone as a screening tool.[90,94,100] CA125 has been reported to be elevated in 1% of healthy women and 6-40% of women with benign masses.[94] It has been suggested, however, that limiting the screening population to postmenopausal women would markedly decrease the frequency of false positive results since the incidence of disease increases progressively with age and the incidence of benign confounding conditions such as endometriosis decreases.[96,100] In one study of 1010 postmenopausal women screened with CA125 one early ovarian cancer was detected although at a level slightly below that usually determined to be abnormal.[96] In addition, both pelvic examination and ultrasound were abnormal in this case. However, 30 additional patients with benign disease had abnormal levels thus yielding a specificity of 97%. As the consequence of a positive screening test for ovarian cancer is surgery (laparoscopy or laparotomy) it has been suggested that a minimum positive predictive value of 10% should be required to even consider implementation of such a test. Simply put, this means that 9 false-positive tests would be generated for each case of ovarian cancer identified. Since the frequency of ovarian cancer in women over 45 is 1 in 2,500 per year, an annual screening test, even with 100% sensitivity, would require 99.6% specificity to meet this goal. Thus at present CA125 levels alone cannot be recommended as a screening tool.[96,100]

<u>Pelvic Ultrasound</u>

The use of real time pelvic ultrasound via the transabdominal or transvaginal approach as a screening tool for ovarian cancer has been investigated.[94] While the

positive predictive value for the absence of a pelvic mass exceeds 97%, differentiating benign from malignant lesions is more difficult.[94] Andolf et al screened 805 women ages 40-70 coming to an outpatient clinic for a variety of reasons. Pathologic findings were suspected in 83 patients on initial examination (via transabdominal scan) and were confirmed on repeat study in 50. 39 subsequently underwent surgery. Only 1 ovarian carcinoma and two borderline tumors were diagnosed; the former Stage III.[102]

Van Nagell et al recently reported their initial results from screening 1000 asymptomatic women age 40 or older with vaginal sonography.[103] The latter has been recommended because transabdominal studies can be time-consuming, expensive and involve significant patient preparation including filling the bladder before examination. Using $18cm^3$ and $8cm^3$ as the upper limits of normal ovarian volume in pre- and post-menopausal women, respectively, 31 patients (3.1%) had abnormal vaginal sonograms and 24 underwent exploratory laparotomy. Only one cancer was diagnosed and this was a metastatic ovarian cancer from a primary colon cancer that had been in remission for 2 years.

In the largest study reported to date, 14,356 ultrasound examinations performed over 3 years on 5,489 asymptomatic women over age 45 detected 5 ovarian cancers.[104] Sensitivity and specificity were calculated to be 100% and 94.6%, respectively, however because of the low incidence of disease, the positive predictive value of the test was only 2.6%. Thus, the routine screening of asymptomatic women cannot be recommended.

Multimodal Approach

In an effort to increase the specificity of screening tools a multimodal approach has been recommended. Jacobs et al has recently published data suggesting that specificity can increase markedly by combining vaginal examination, serum CA125 determinations and pelvic ultrasound.[96] Implementation of any such screening program, however will be expensive and must await confirmation that mortality does in fact decrease with early diagnosis.[14,90,94]

High Risk Groups

Another way to increase predictive value is to increase the incidence of disease in the screened population. Nulliparity or late-age at first pregnancy are known risk factors for ovarian cancer.[94] Women with a sister or mother with ovarian cancer are at 10 times the risk of the general population.[94] A family history of endometrial or breast cancer also increases risk as can a history of colon, lung or prostate cancer.[94] In the cancer family syndromes or breast/ovarian cancer syndromes the risk may approach 50%.[105] In such families screening with currently available techniques is probably warranted even in the absence of definitive data. Such patients should be referred for gynecologic follow-up.

ENDOMETRIAL CANCER

Endometrial cancer is now the most common gynecologic malignancy in women over the age of 45 with an incidence of more than 39,000 new cases per year. Risk factors include increasing age, obesity, infertility and estrogen use.[94]

Currently the ACS recommends that "high-risk" women should have an endometrial biopsy at menopause.[106] ACOG has concluded that "the cost-effectiveness of screening asymptomatic women for endometrial cancer and its precursors is very low and therefore unwarranted" although "high risk patients may require endometrial sampling."[79] At out institution biopsy is reserved for patients with abnormal vaginal bleeding or the rare case of an abnormal Pap smear.

Frame has noted that the natural history of endometrial cancer is important to any discussion of screening and prevention.[14] Endometrial cancer is felt to be the end result of changes of endometrial hyperplasia.[107] It is estimated that 5% of early cystic adenomatous hyperplasia, 12% of adenomatous hyperplasia, and 30% of atypical adenomatous hyperplasia will progress to cancer generally over many years. Thus, most cases of adenomatous hyperplasia do not become malignant.[108]

Endometrial cancer is also a highly treatable disease associated with an excellent

prognosis. Even without widespread screening 75% of cases are detected at Stage 1[108] with a 5-year survival of 90%, the overall 5-year survival being 79%. Over 80% of women with endometrial cancer have abnormal vaginal bleeding.[108]

The sensitivity of office endometrial biopsy for detecting adenomatous hyperplasia and cancer approximates that of D&C.[94] Nonetheless it is expensive (in excess of $100) and causes significant patient discomfort, particularly in older women. The only large study of endometrial screening in asymptomatic women was reported by Koss et al in 1986.[109] A cohort of 2586 women, 98% over age 45, were screened initially with 1567 returning for rescreening one year later and 187 for a third time. Approximately 86% of the women were able to be sampled adequately. 7 occult cancers were found for each 1000 patients screened, a rate higher than that seen in screening for cancer of the cervix. It is unclear, however, whether such screening would have any impact on mortality as most of these patients could be expected to become symptomatic prior to invasive disease. Furthermore, many patients found the examination uncomfortable and did not return for future screening. Thus it would appear that endometrial biopsy should generally be employed only in the presence of abnormal peri or postmenopausal vaginal bleeding.[14,79] Physicians should routinely question their patients regarding this symptom.

MALIGNANCIES OF THE VULVA AND VAGINA

Malignant tumors of the lower genital tract are uncommon and account for approximately 4% of all gynecologic malignancies. Squamous cell cancer is the most common vulvar malignancy with an incidence of 2.2 per 100,000 and an average age at diagnosis of 62 years. The majority of patients are symptomatic with vulvar pruritus, pain or bleeding, many for a long period prior to diagnosis. Carcinoma in situ may be entirely asymptomatic or associated with pruritus and the natual history is not well understood.[110] In one series only 4 of 102 patients subsequently developed invasive cancer.[111] Screening for this lesion has never been specifically recommended, nonetheless it is reasonable to inspect the vulva when performing a rectal or vaginal examination, with abnormalities referred for

biopsy. Other less frequent malignancies such as melanoma may also be detected by visual examination.

VAGINAL CANCER

Primary carcinomas of the vagina are infrequent and account for <2% of all gynecologic malignancies. Squamous cell cancer accounts for 80-90% of all vaginal cancers but adenocarcinoma, sarcoma and melanoma also occur.[110] Women with a prior history of DES exposure are at increased risk of cervical/vaginal adenocarcinoma, as previously discussed, as are women with a prior history of cervical cancer. There may be an increased risk following hysterectomy even for benign disease but this is not clear.[112] Occasionally vaginal cancer will be detected in an asymptomatic patient by visual inspection and/or Pap smear. Neither has been evaluated as a screening technique for early, non invasive disease, and the natural history of such lesions is not well understood.[110] Nonetheless, treatment with topical 5FU, lazer excision or surgical excision are indicated as some of these lesions will certainly progress. With regard to screening, there is no data that demonstrates the effectiveness of the physical examination or the Pap smear in reducing the risk of invasive vaginal cancer or the mortality from this disease. In my opinion, it is reasonable to examine the vagina when performing a pelvic examination and/or Pap smear for other reasons, although many gynecologists, including those at our institution, recommend yearly pelvic examinations.

Patients with a history of DES exposure, in particular, but also those with a history of cervical neoplasia constitute higher risk groups who should be followed by a gynecologist on a regular basis.

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