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## Results of the routine use of the vaginal smear in the detection of uterine cancer in a private obstetrics and gynecology practice

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RESULTS OF THE ROUTINE USE OF THE VAGINAL SMEAR  
IN THE DETECTION OF UTERINE CANCER IN A PRIVATE  
OBSTETRICS AND GYNECOLOGY PRACTICE

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## Introduction

In the years 1955, 1956, and 1957; there were over 8,000 deaths due to cancer of the cervix uteri in the United States.<sup>16</sup> Cancer of the cervix ranks second only to cancer of the breast in frequency of a malignancy occurring in the female population. As an example, in New York State; exclusive of New York City; the incidence of carcinoma of the cervix was 32 per 100,000 persons in the general population in the years 1942-1947.<sup>10</sup> With these figures in mind, much research and study has been directed towards eradicating this disease as a relatively common cause of death among the female population.

Five year cure rates for cancer of the cervix approach 100% in the so called "in situ" lesions and 0% in the stage IV lesions. Because of this, one may imply that if all lesions were discovered in the "in situ" stage deaths due to carcinoma of the cervix could be eliminated. Until a "cure" for cancer is discovered, it appears that the best method for attacking the problem is that of early detection. Since the report of Papanicolaou on the use of vaginal smears in the diagnosis of uterine cancer, his method is being employed more and more in clinics and hospitals throughout the coun-

try.<sup>21</sup> It is likewise spreading to various medical centers of the world.

There is little argument as to the place of this procedure in screening for cancer of the cervix. As more and more experience is being gained in the interpretation of the slides, more reliance is being placed on their actual diagnostic value. In some instances, surgery has been carried out with an ultimate diagnosis of a malignancy even in the face of a negative biopsy.

It is not the purpose of this paper to resolve the economic feasibility of this procedure as a screening test, but rather to present the results of the routine use of the vaginal smear in an obstetrics and gynecology practice and to discuss some of the pros and cons of their use.

## Historical Background

Much is owed to George N. Papanicolaou for his exhaustive study of the science of exfoliative cytology. The following historical information is extracted from a report by Dr. Papanicolaou to the Joint Program Committee of the International Union Against Cancer and the American Cancer Institute.<sup>22</sup>

The earliest report on the microscopic examination of a body fluid is, presumably, that of Donne in 1838 on fresh smears prepared from human colostrum. Wallsche, in 1843, was presumably the first to observe tissue fragments of malignant growths expectorated from the respiratory tract.

The observations of Poushet in 1847 are the earliest on record concerning exfoliative cytology of the female genital tract. He, however, confined his studies to normal cytology. Little was then reported concerning exfoliative cytology in diagnosis of uterine cancer until Papanicolaou's initial suggestions in 1928. Little heed was paid to preliminary reports on the diagnostic value of vaginal smears in carcinoma of the uterus until 1941. Since that time, however, much research has been carried out along these lines.

## General Aspects of the Use of the Smears

Results were obtained from the routine use of the vaginal smear by four specialists in obstetrics and gynecology and one general practitioner. The slides in all instances were read by one of the specialists who had received special training in their interpretation. For all practical purposes, the practice is representative of a specialty obstetrics and gynecology practice in Omaha, Nebraska.

The type of patients seen must for the most part be considered of average to above average economic strata. Patients for all practical purposes are white. It is estimated that approximately 12% of the practice is Jewish. No estimate was made for those submitted by the general practitioner included in this survey. However the number of specimens submitted constituted a small percentage of the total number examined.

The minimum age of patients from whom slides were obtained was 18 years. In general, it is the policy to obtain smears from all married women regardless of age and all single women over 25 years of age. It is also the general practice to obtain smears on all new obstetrics patients and to repeat these smears on the routine

six week post partum check up. An attempt is made to repeat the slides at yearly intervals, though this is obviously difficult to do as is generally found. The years covered in this survey are 1957-1960.



## Techniques of Obtaining Smears and Staining

In the method of obtaining smears as originally proposed by Papanicolaou, a thin glass pipette equipped with a suction bulb was inserted into the vagina with the bulb depressed. The bulb was then released and the pipette moved from side to side in the vagina as the pipette was withdrawn.<sup>23</sup> Since this method was introduced, several different methods for obtaining material for cytological study have been proposed; among these are, aspirating the vaginal pool, aspirating the endocervical canal, and scraping the squamo-columnar junction. In addition, various combinations of the preceding methods have been suggested. It is felt by the majority of authorities that the vaginal pool is so diluted as not to offer sufficient material for study. On the other hand, individuals feel that a specimen obtained from this source is more representative of the entire female genital tract and thus offers a better chance to detect malignancies in more remote locations of the tract.

In this study, smears were obtained by the method as devised by Ayre using the "spatula" of his design. By employing this method, the cervix is visualized by use of the vaginal speculum and material for study

obtained by scraping of the cervical os; care being exercised to obtain material from the squamo-columnar junction. Material thus obtained is immediately smeared on a common glass slide and fixed in a solution of equal parts ether and 95% alcohol before any drying can occur. It is important that patients do not douche, bathe or insert any material in the vagina prior to the taking of the smear. Slides so obtained are left in the fixative solution for a period of 5-15 min. If slides are allowed to remain a half hour, it is felt they may be withdrawn from the solution, air-dried, and then mailed without significant loss of staining properties. Other methods for fixing slides have also been devised with similar success. Care should be taken when mailing slides that the surfaces of slides do not rub together. This is prevented by placing an ordinary paper clip on each slide.

Slides are stained by the method as devised by Papanicolaou, with some slight modifications.<sup>19</sup> These are essentially the reduction of the number of alcohol baths. The principal stain employed is EA 50, though EA 36 is employed by many simply by preference. The most important aspect of staining is that of obtaining adequate nuclear detail. Some individuals have

adopted the method of simply staining the slides with methylene blue, others read the slides without benefit of stain, reading them as they come from the fixative solution.

With the partial exception of adenoma malignum, which originates on the gland-bearing mucosa of the endocervix and in the endometrium, all types of carcinoma of the uterus (including the very early stages of the disease) have a common characteristic, namely, they are exfoliative growths. By this is meant that they are constantly shedding superficially placed cells.<sup>15</sup> This statement serves to illustrate the basis on which exfoliative cytology is useful in the diagnosis of uterine cancer.

It should be mentioned here, that research is now in progress in other areas as to the use of acridine orange as a staining material. It is felt by some that the use of this dye will ultimately speed the process of screening though not necessarily increase the accuracy of interpretation. Other efforts are directed at the development of a satisfactory mechanical or electronic instrument for the preliminary screening of a great bulk of slides as found in total population screening.

Slides in this office are read and classified by

the standards as suggested by Papanicolaou and are reviewed below.<sup>20</sup>

Class

I	Negative	Absence of atypical or abnormal cells.
II	Negative	Atypical cells present but without abnormal features.
III	Suspicious	Cells with abnormal features suggestive of but not conclusive for malignancy.
IV	Positive	Cells and cell clusters fairly conclusive for malignancy.
V	Positive	Cells and cell clusters conclusive for malignancy.

As a general rule, a report of anything but a negative slide calls for at least a repeat smear. In the case of positive smears or persistent suspicious smears, cervical biopsy is mandatory. In general, a punch biopsy or wedge biopsy of the cervix is done if invasive carcinoma is suspected by gross appearance of the cervix. The cold knife cone is used for more complete pathological study in suspected in situ lesions. As more lesions are now being discovered in the in situ or early invasive stages, more cone biopsies are now being done than previously.

## Results of Smears

The data as will be presented here is the result of 3,430 smears on 2,416 women. Initial classification of these slides is given in Table I. It is to be noted that all smears have been counted even though in some instances they are smears which have been taken following biopsy proving malignancy. Of the 3,460 smears, 1,044 represent repeat examinations. In this study, no attempt was made to determine how many women were actually reexamined following an initial negative examination, realizing that this information may be of some value.

Table I  
Results of Initial Examination  
of 2,416 Women

Class	Number	% of Total
I& II	2,300	95.15
III	92	3.81
IV	16	.66
V	8	.33
		99.95

These results indicated a somewhat higher rate of positive or suspicious smears than has been found in the Memphis, Tennessee study of 108,100 women.<sup>7</sup> However, one must remember that considerable bias is present in

a study such as this. One of the most important of these points is that the majority of patients screened in this survey came to the office with some sort of complaint referable to the genital tract. Also, a number of the patients, from whom smears were taken, were referred with some type of suspicious lesion. These two factors alone would serve to increase the number of suspicious or positive findings significantly.

Of the women who were initially Class III (suspicious), 66 or 71.7% subsequently had punch biopsy, wedge biopsy, cold cone, D & C, or hysterectomy. The majority of women initially Class III, had an ultimate diagnosis of a benign lesion of one form or another. A subsequent diagnosis of a malignancy was made in 15 or 22.7% of those who had tissue specimens submitted for study. One other case was an obvious cancer of the rectum. A breakdown of these results are found in Table 2. One other individual who was initially Class III converted to a Class IV which on biopsy proved to be a severe chronic cervicitis. This result will be included as a false positive finding.

Table 2  
**Subsequent Tissue Diagnosis of 66  
 Women Initially Class III**

Lesions	Number	% of Total
Benign Lesions (Includes cervicitis, basal cell hyperplasia, leukoplakia, and hydatid- form mole)	51	77.30
Endometrial Carcinoma	4	6.06
Carcinoma of the Cervix	9	13.63
Invasive	3	4.54
In Situ	6	9.09
Cystadenocarcinoma of Ovary	1	1.52
Metastatic Carcinoma of Rectum	1	1.52

Initial examination revealed 16 Class IV slides and 8 Class V slides. These represent 0.66% and 0.33% of the total number of women examined. Tissue studies were subsequently carried out in all the women of this group. Results of tissue examination are recorded in Table 3. In this study, we have considered all of the carcinomas of the endometrium to have been suspected. This is done because we consider all post menopausal women who bleed as having endometrial carcinoma until proven otherwise. Also because of this, a negative smear in the face of post-menopausal bleeding is not considered adequate. For this reason, we do not believe the

Papanicolaou smear is of much material value in the diagnosis of the great majority of cancers of the endometrium.

Table 3  
Results of Tissue Study in Those  
Women Class IV and Class V

<u>Class IV Lesion</u>	<u>16 Cases No.</u>	<u>%</u>
Adenocarcinoma of Endometrium	2	12.50
Recurrent CA of Vulva	1	6.25
Carcinoma of the Cervix	9	56.20
Invasive	9	56.20
False Positive	4	25.00
<u>Class V Lesion</u>	<u>8 Cases No.</u>	<u>%</u>
Carcinoma of the Cervix	8	100.00
Invasive	8	100.00

Of the 17 carcinomas of the cervix which gave positive smears, 10 or 59% were suspected. In all cases but one there was some symptom or physical finding referable to the female genital tract. It should be pointed out that the decision as to whether a lesion is suspected or not is a rather ambiguous point in that one should suspect a malignancy in all cases where a gross lesion is seen. This is not to imply that all



lesions of the cervix need tissue study but they at least should be suspected. The majority of cervical lesions visualized are in all probability benign, but this does not relieve the physician of the responsibility of proving them to be so.

Of the 1,014 repeat examinations, 17 or 1.67% were found to have smears other than Class I or Class II. Class III was the most frequent class converted to, occurring in 14 or 82.5% of the cases. Two patients or 11.8% converted to Class IV and one or 5.7% converted to a Class V smear. One of the patients who converted to a Class III had previously been diagnosed as having an invasive carcinoma of the cervix and treated for it. This same patient subsequently converted to a Class IV smear and ultimately died of her disease. Of the patients converting to Class III smears, other than the patient just mentioned, only 1 or 7.15% of those converting was subsequently proved to have a malignancy, this being an adenocarcinoma of the endometrium.

One of the patients converting to Class IV had been referred in with a diagnosis of endometrial cancer. The other patient was subsequently proven by tissue study to have an invasive carcinoma of the cervix.

The one patient who converted to a Class V smear has an interesting history. This patient had been seen by one of the participating physicians over a period of about 20 years. Several years prior to the time that a positive smear had been found, her physician had been suspicious of the way the cervix had appeared at physical examination. Because of this, the patient was hospitalized and cervical cone done. Results of this examination were negative. Because of this history and a positive vaginal smear, the patient was hospitalized and a laporatomy carried out. Results of this examination were much more revealing. It was found that the patient had a papillary serous cystadenocarcinoma of the ovary metastatic to the cervix.

One of the interesting aspects of those patients converting to a suspicious or frankly positive smear is to observe the class smear immediately preceding the suspicious or positive smear. In this study, the most frequent preceding class is a Class II smear. This occurred in 12 or 70.6% of the 17 patients converting to other than negative smears. This finding was also noted by Dunn in his examinations of more than 33,000 women of whom 9,000 plus were examined a second time.<sup>6</sup>

This may, as Dunn says, be partly due to the predominance of older aged patients in the Class II smear group.

Another interesting aspect of this study, is the age distribution in the various suspicious and positive classes. This distribution is presented in Table 4.

Table 4

<u>Age Range</u>	<u>Number</u>	<u>% of Total</u>
<u>Class III</u>	<u>105 cases</u>	
20-29	29	27.6
30-39	30	28.5
40-49	20	19.0
50-59	18	17.1
60 plus	8	7.6
<u>Class IV</u>	<u>18 cases</u>	
20-29	2	11.1
30-39	5	27.8
40-49	4	22.2
50-59	3	16.6
60 plus	4	22.2
<u>Class V</u>	<u>9 cases</u>	
20-29	0	00.00
30-39	1	11.2
40-49	4	44.4
50-59	2	22.2
60 plus	2	22.2

It can be seen that the peak age for each class rises as the slides pass from the suspicious to the definitely positive classes. This is probably to be expected as the incidence of atypical cells probably increases as the age of the patient increases.

Table 5 below summarizes the overall results of the study.

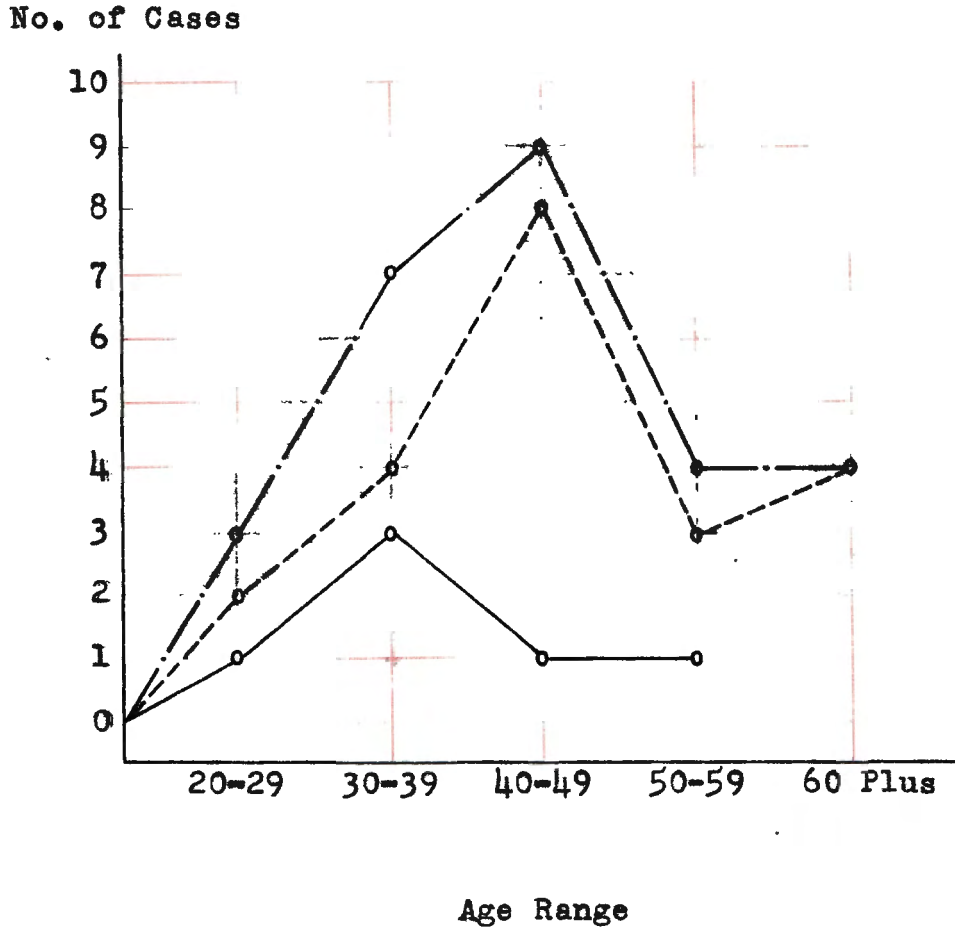
Table 5  
Overall Results of 3,430  
Smears of 2,416 women

Lesion	No.	% of Smears	% of Women Examined	Rate Per 1,000 Women
Carcinoma of Endometrium	7	00.24	00.29	2.9
Carcinoma of Cervix	27	00.79	01.12	11.2
a. Invasive	21-78% of total			8.7
b. In Situ	6-22% of total			2.5
Recurrent CA of Vulva	1	00.02	00.04	0.4
Serous Cyst-adenocarcinoma of Ovary	1	00.02	00.04	0.4
Metastatic Carcinoma of Rectum	2	00.04	00.08	0.8

As previously stated, all carcinomas of the endometrium have been considered suspect for the reasons stated. The cystadenocarcinoma of the ovary was not suspected. Of the carcinomas of the cervix, none of the in-situ lesions were suspected; and 9 or 42.8% of the invasive lesions were unsuspected. All other lesions listed, unless otherwise stated, were considered suspect.

The age distribution of the carcinomas of the cervix present another interesting aspect of this problem. These are presented in Graph I.

Graph I  
Age Distribution of  
Carcinomas of the Cervix



Total Cases      .....  
 Invasive          .....  
 In Situ            .....

Realizing that the number of cases found is too small to be significant, the peak incidences are comparable

to all the reports that were studied. In all of the reports studied, it was found that the peak age range for the in situ lesions is in the 30-39 year group. The incidence of invasive lesions rises after the age of 40 years. Here, however, our figures are too small to be of comparative value; however, the peak is reached at the 40-49 year age range.

## General Comments on Results

The number of women examined and the total number of smears examined are not of great enough magnitude to be considered statistically significant. However, we do feel that the results are at least illustrative of the findings to be expected in a comparable type of practice with a comparable patient load. We do not mean to imply that these results can be referred to the general population.

The patients who are represented by the data presented in this paper must be considered a special population universe. First, the majority of these patients are consulting an obstetrics and gynecologic specialist. Secondly, the greatest number of the patients come to the physician with some kind of complaint even though it be a suspected pregnancy. In addition, the patients studied are not representative of all the various economic levels as found in the general population. This, in the past, has been found to be a significant point, in that the greatest number of cervical malignancies have been found in the lower income levels.

The number of cervical malignancies found in this study are generally higher than those found in total population screening for carcinoma of the cervix. We account for this on the basis that the majority of the patients cannot be considered as well individuals. Secondly, a number of the patients who were found to have a malignancy of the female genital tract were referred by other physicians because of symptoms of gynecologic significance.

The number of suspicious smears is somewhat higher in this study than is actually necessary. One of the physicians covered by this study has requested that the slightest indication of suspicion makes the whole slide reportable as a Class III smear. This then causes some slides that might have otherwise been reported as Class I or Class II to be reported as Class III, thus increasing the number of such smears above the actual level.

Another point in the evaluation of a diagnostic procedure is that of the number of false positive and false negative reports. In this series, we do not have any of the so-called false negative results. It is, in our estimation, rather difficult to define the so-called false negative report, other than it represents



a single or multiple number of slides all of which are negative but subsequent tissue diagnosis is a malignancy. In none of our cases of cancer was there a vaginal smear of less than Class III. Thus, we cannot report a percentage of false negative results. We have, however, found a small number of false positive smears. These amounted to 5 or 0.14% of the total number of slides examined. All of these were revealed on initial examination and resulted in 0.24% of such examinations being reported as false positives. In general, false positives have occurred in other surveys from 0 to 30%. The number of so-called false negatives is generally reported as being less than 5% of the total smears examined. If the criteria for malignancy is made more rigid, the number of false positive smears will fall; but,, on the other hand, the number of false negatives will rise. It is felt that a false positive report is much more desirable than a false negative, the reason for this being obvious.

One other point that has been raised in the evaluation of this procedure is that of the cost of carrying it out. The cost of cytologic examination has varied from \$0.90 to \$3.00 in total population screening.<sup>7</sup>

The price to the patient in this study is generally a standard \$5.00. The cost of doing the examination has not been estimated. In this study, 1.12 women for every 100 examined were found to have a carcinoma of the cervix. Therefore, approximately \$500.00 was spent by the patients for every one case of cervical malignancy found. One may argue that this is a large amount of money to spend in finding one case of cervical carcinoma. To those patients who were found to be free of malignancy, this may be so; but to that one individual in whom the malignancy was discovered early enough that a cure could be brought about, the cost could have been a hundred times greater and still be very much worth the initial cost. Therefore, we do not feel that too much emphasis should be placed on the cost of the examination in a private practice. This, however, does not hold true when one is considering total population screening by vaginal smear where the cost is borne by the tax payers.

## General Aspects of Total Population Screening by Vaginal Smears

The results of total population screening for carcinoma of the cervix by use of the vaginal smear are only now coming to the point of being of any great significance. The largest of these surveys for which preliminary results have been reported is that being conducted by Cyrus C. Erickson in Memphis Shelby County Tennessee under the auspices of the National Cancer Institute.<sup>8,9</sup> In this series, the results of which will be given later, 108,000 women have been examined at least once.

As was stated at the beginning of this paper, some 8,000 women die of cancer of the cervix in the United States each year. According to one author,<sup>1</sup> in 1944 there was a total of 26,000 lives lost due to uterine cancer in the United States. This figure obviously includes deaths due to fundal carcinoma in addition to that of the cervix. Combined deaths due to carcinoma of the cervix uteri and corpus uteri in 1957, as a comparison, amounted to 9,840 deaths.<sup>16</sup> One can thus see that over the past twenty plus years the death rate due to uterine cancer has been drastically reduced.

The reason for this, in all likelihood, is due to a combination of better therapy, early detection, and public education. Because of this, cancer of the uterus seems to be one type of malignancy that may, with proper education leading to early detection, almost be eliminated. The National Cancer Institute as a result has begun several pilot studies in total population screening for cancer of the cervix by use of the vaginal smear. This can be compared to the periodic chest x-ray to detect early pulmonary tuberculosis.

The first of these studies set up to evaluate the cytologic technique as an aide in the diagnosis of cancer of the cervix was in Hot Springs, Arkansas in 1947.<sup>15</sup> In this study, a cancer detection clinic was set up in conjunction with a previously established treatment center for venereal diseases. In this series, all females in the cancer age admitted to the venereal disease center were routinely given an examination directed primarily to diagnosis of malignant disease. In this study, there was a high incidence of syphilis, 91%, and the group was largely negro, 93.2%. Thus, the results cannot be referred to the general population.

The largest study of the vaginal smear technique

was undertaken in Memphis Shelby County Tennessee in 1952.<sup>8,9</sup> To date, some 108,000 women have been examined at least one time. Source of cytologic tests has been both from private patients as well as from health department, hospital, and temporary annual clinics arranged for genital cytology screening in industrial and business sites. In this study, a massive program of public education was undertaken to get women to come in for the tests even though symptoms were not present. The method of obtaining material for smears was by vaginal aspiration. A significant argument for the obtaining of smears by this method was that no instrumentation was necessary. This in itself would, they believed, attract a larger number of women. Some 50% of the smears were sent in by some 300 participating private physicians while the other 50% were sent in by the special clinics which were set up.

The method of obtaining smears has varied among the various studies set up. These are summarized in Table 6.

Table 6  
Summary of Methods of  
Obtaining Vaginal Smears

Location of Study	Method of Obtaining Smear
1. Memphis, Tennessee	Vaginal aspiration
2. Springfield, Mass.	Aspiration of vaginal pool and cervical canal
3. Madison, Wisconsin	Self obtained vaginal aspiration
4. Hot Springs, Ga.	Cervical scraping with Ayre spatula
5. Charlotte, N.C.	One by aspiration of vaginal pool and one by spatula from cervix.
6. Floyd, Co., Ga.	Self obtained vaginal aspiration, or direct from endocervical canal with cotton swab.
7. San Diego, Calif.	Speculum exam with cervical scraping.

Ease of obtaining the smear is a big factor in the number of women who can ultimately be induced to undergo the examination. Much can be said for the self obtained specimen in that the patient can obtain the specimen in her own home without use of instruments. Various methods have been developed for the patient to obtain smears herself. Among these, are the pipette with bulb for aspiration and various types of tampons.

Direct examination of the vagina and cervix and obtaining smears by direct visualization is still considered the ideal method of examination. However, as a mass screening technique, this method is not economically or physically practical. It would require a tremendous number of physicians doing nothing else and, in addition, a tremendous amount of money.

In all the studies conducted, all reports of results are reported directly to the physician chosen by the patient. The method of reporting smears varied from study to study, but in general all slides were classified, with slight modifications, according to Papanicolaou's original classification. A common method of reporting was that of negative, suspicious, and positive. As in our study, diagnosis was final only after adequate tissue study. Generally, cold knife cone is recommended where initial biopsy is inconclusive or borderline, and to rule out invasive lesions or guide subsequent therapy.

Results of Larger Studies  
of Total Population Screening

Memphis Shelby Co., Tennessee

This survey conducted by Cyrus C. Erickson and group under auspices of the National Cancer Institute was begun in July, 1952.<sup>8,9</sup> This plan was designed to examine as many women as possible by one vaginal smear and repeat the smear at yearly intervals for a 3-year period; and in all women with significant cytologic findings, to obtain and examine adequate biopsies. The source of these tests has been previously stated, but, briefly, they came from private as well as public clinics. The cytology laboratory in the University of Tennessee Cancer Research Building was the center for examining all smears. This laboratory included personnel trained for conducting the cytologic screening and reporting examinations. The laboratories were set up to handle some 1,000-1,800 smears per week. Initially in this study, two-thirds of the patients were from hospital clinics, school clinics, and industries. At the time the report was written in 1958, fifty percent of smears were from private patients.

Prior to undertaking the study, in the years 1951



and 1950 there was a total 498 malignancies of the female genital tract reported for the resident female population in Shelby County. In the first 60,000 women examined by cytological study in the period July, 1952 to June, 1954, there was a total of 492 cases of invasive cancer of the uterus and intraepithelial cancers of the cervix found. In addition, 15 cases of cancer of other parts of the genital tract were found. In this series, obvious cases of cancer were eliminated from the final total. All of these cases were confirmed by cervical biopsy. A total of 304 women were biopsied as a direct result of cytologic finding in the first 60,000 women examined. Of this group, 235 or 77% were found to have intraepithelial cancer and 61 or 19% were found to have invasive cancer of the uterus.

The results of the examination of 108,136 women once are even more significant. These are illustrated in Table 1 as compiled by Erickson. Generally, in 983 of each 1,000 women examined in the first screening, no evidence of cancer or significant abnormality was found; while 17 of each 1,000 were advised to have other study by biopsy. Seventy-seven percent of those for whom biopsies were requested did return for biopsy.

Table 1  
 Pathological Findings in 1,453 of 1,842 Women  
 for Whom Biopsies Were Recommended as a Result of  
 Examination of Vaginal Smears of 108,136 Women.<sup>8</sup>

Lesion	No.	% of 108,136 Women
Invasive Uterine CA	373	0.34
Cancer of Cervix	331	0.31
Cancer of Corpus	42	0.04
Other Genital Cancer	20	0.02
Intraepithelial cancer of cervix	393	0.36
Total Invasive CA and IE Cancer	786	0.73
Atypical Metaplasia	141	0.13
Findings Normal	<u>479</u>	<u>0.44</u>
Total	1,406	1.30

Of these 13 women per 1,000 examined, 8.6 were found to have some pathological change, 7.3 had intraepithelial carcinoma or invasive cancer and the remaining 1.3 showed a marked degree of atypical change that was considered to be a borderline lesion or possible intraepithelial carcinoma. An interesting point here is that 36% of the women with invasive cancer were non-residents of Shelby County though they constituted only 13% of the women who were examined.

One half of the cancers found were in negroes who constituted 33.3% of the surveyed population. This

rate was expected as a morbidity study for uterine cancer for this area for 1950 and 1951 had shown approximately this same ratio of negroes to whites with cancer of the uterus.

Fifty-nine percent of the total number of cases of invasive and intraepithelial cancer were unsuspected. Of this figure, 90% of the intraepithelial cancers and 30% of invasive cancers respectively were unsuspected. Studies of age incidence showed that the peak incidence of intraepithelial cancer occurred from 30-34 years and invasive cancers in the 50-54 year age group.

In a group of 32,728 women rescreened, 244 or 69% of those for whom biopsy was recommended were biopsied. Eighty-three cancers of the uterus were found representing 72 intraepithelial cancers, 9 invasive cancers, and 2 fundal cancers. An interesting comparison is the following: In the first screening, 3.6 intraepithelial cancers were found per 1,000 women examined and 3.1 invasive cancers per 1,000 women examined. In the second screening of each 1,000 women, 2.2 had intraepithelial carcinoma and 0.3 had invasive carcinoma. This would seem to have a bearing on the theory that the intraepithelial lesion is a precursor of the invasive lesion.

According to calculations as reported by Erikson, more than a fourfold increase in case findings resulted from this screening as compared to those found with the methods previously used. San Diego, California.<sup>6</sup>

The women studied in this group were all seen by private physicians in private practice. Two-thirds were patients of obstetrics and gynecology specialists of the Gynob Group, San Diego, and the remainder were from physicians using Gynob cytology laboratory facilities. Smears were obtained by cervical scrapings. Four women from the initial 33,750 examined were excluded because they were known to have cervical cancer.

Cytologic findings suggestive of malignancy were found in 774 women examined, or a rate of 22.9 per 1,000; of these, 259 patients were found to have intra-epithelial carcinoma of the cervix and 77 were found to have invasive carcinoma. Prevalence rates for such positive cytology reach a high point in the 30-39 year age group. This, as will be noted again later, compares favorably with our own small study. Class III, as in our study, was also the most frequent positive cytology, Class III being considered positive in that it is not a definite negative classification.

In this study also, the prevalence of intra-epithelial lesions increases with age reaching a maximum in the 30-39 year age range. Prevalence rates for invasive cervical cancer increase consistently up to the age of 70 years. The greatest majority of those classified as Class III or more were subsequently biopsied. An interesting point is that the majority of cancers associated with a Class III smear were of the intraepithelial type. Fundal cancer, on the other hand, was most often associated with a Class IV or V smear. About 50% of those with Class IV or V smears had intraepithelial cancer. Class IV smears were found to be associated with some form of malignancy in 73% of cases, and for those with Class V smears, about 90% had some form of malignancy. The 77 patients with invasive cancer had Class IV or V smears in 96% of the cases.

Of those eligible, 9,725 women or 40% underwent a second examination. An interesting point is again observed here. The bulk of those with positive cytology now fall in the Class III smear. Those who were initially Class I show a marked reduction in the incidence of positive cytology on repeat smears (5.1 per 1,000) compared to the prevalence at initial

examination (22.9 per 1,000). The group that was Class II initially shows a higher incidence of positive cytology (33.8 per 1,000). On the average, women who had Class II cytology initially returned for reexamination a little sooner than the women who were Class I initially (16.9 months versus 12.8 months). Here is a point of bias that may be related to the motivation of women returning for reexamination. A remarkable finding is that the incidence of carcinoma in situ in the reexamined Class II group is over 1 3/4 times the initial prevalence rate (13.8 versus 7.8).

The two cases of invasive carcinoma in the second screening were in the Class I initially. The interval before final diagnosis was made was 32 months in each case.

The total percentages of known missed cases resulting from cytology: 6 cases in situ missed - 2.3%, 1 case invasive - 1.3%, and 2 cases fundal - 12.5%.

The number of women who returned for a third examination was 4,213; 19 or 4 per 1,000 had positive cytology, of these, 4 or 0.8 per 1,000 had in situ carcinoma. The number of women who returned for a fourth examination was 1,654; one cancer of the fundus and one early invasive lesion were found. Of the 450

returning for a fifth examination and 135 for a sixth examination, only one had a Class III cytology and this was not shown to be a cancer.

Madison, Wisconsin.<sup>4</sup>

This study was conducted on a so-called mail order basis. Upon request, the State Laboratory of Hygiene provides for any physician, clinic, or hospital in Wisconsin complete kits with the necessary equipment to collect vaginal smears and return by mail. Slides were stained by the Papanicolaou method. Suspicious or positive interpretations indicated that biopsy was required for definitive diagnosis.

The population involved in this study was largely devoid of negroes and Jews. Also, the population was predominantly rural and thus tended to remain relatively stable. The total number of women in the state, exclusive of Milwaukee County, 20 years of age or older, varied from 785,000 to 832,000 for the period studied.

The number of women examined at least once in this study was 65,163, and 9,111 women were examined a second time. Of 814 biopsies requested, tissue diagnosis was obtained in 726 cases, or 90%. In all, about 5% of the women studied were known to have had tissue examination.

The prevalence rate for epidermoid carcinoma was found to be 8.3 per 1,000 women. A total of 541 carcinomas of the cervix were found. Of this total, 206 were in situ and 335 were invasive lesions. Of the 206 in situ lesions, 195 were detected by vaginal smear, and 323 of the invasive lesions were detected by vaginal smear. The remainder were considered as known false negatives. In addition, 158 adenocarcinomas of the corpus, 26 adenocarcinomas of the cervix, 2 carcinomas of the vagina, 2 carcinomas of the ovary, and 2 carcinomas of the tubes were found.

On rescreening 9,111 women a second time after an interval of not less than 10 months from original examination, positive tissue diagnosis was reported in 23 cases. In this group, 10 in situ and 4 invasive carcinomas of the cervix were found. In addition, 9 adenocarcinomas of the endometrium were found.

It was determined that 27% of the invasive and 74% of the in situ lesions were considered unsuspected. In this report, a definition of unsuspected is not given, and thus, one cannot rely too much on these figures.

Charlotte, N.C.<sup>13</sup>

In this study, 63,905 examinations of genital smears, representing the findings in 48,697 women, were



made. The majority of these smears were taken in a private physician's office. Method of taking smears has previously been given.

Of the white female population 21 years and over, 30.4% were examined in one year. Prevalence of uterine cancer in this series was 0.89%. Clinically unsuspected cases were 56%, which represents 67.1% of in situ lesions and 28.2% of invasive lesions. Peak incidence of invasive cancer occurred in the 51-60 age group, and in the 31-50 year age range for in situ lesions.

#### Floyd County, Ga.<sup>7</sup>

This county was chosen for a study because of its relatively static female population of 15,000-20,000 women above 19 years of age.

This study was interesting in that part of the smears were obtained by the examining physician and some were self obtained. The figures are 17,761 and 2,472, respectively. The women who underwent a repeat examination numbered 4,482. The length of follow up ranged from 6 months to 4 years. Routine examinations were carried out in a special cancer detection center for indigent persons. A public health nurse was engaged to assist in examination of all employees

in the cotton mills and other factories. Smears were taken routinely by 27 physicians in Floyd County.

Examinations were conducted between 1951 and 1955. Of the 17,761 women examined, 16,604 were white and 1,157 were negro. Of the repeat examinations, 234 were negroes. Of the initially screened women, 117 had smears which showed cancer cells, representing a rate of 6.6 per 1,000. Confirmation had been obtained in 84, or 4.7 per 1,000. Carcinoma in situ was found in 56 women, or 3.9 per 1,000, and invasive carcinoma was found in 28, or 1.6 per 1,000. Two cases of in situ cancers were found in women 19 years of age.

In this series, as differs from the majority of others, the largest number of cases was found in the 41-50 age group, 5.5 per 1,000, and over 60, 5.8 per 1,000. The highest incidence of invasive cancer was found in the over 60 age group. In this series, it is reported that 35% of the invasive lesions were unsuspected and 92% of the in situ lesions were unsuspected. The highest incidence of malignancy was found in the negro population, but their number was considered too small to be significant.

The number of white patients reexamined was 4,482. Only those who had a follow up at intervals of 6

months or more are included. Those who developed cervical carcinoma in a period of 6 months or less after their first negative examinations are omitted. Of this reexamined group, 12 developed carcinoma in situ and 4 developed early invasive lesions. This represents an average of 3.5 per 1,000 which developed during an average period of 25.3 months. This suggested that 1.68 per 1,000 new cases developed in the population group every year.

Of the 11,000 kits distributed for self-obtaining of smears, 2,472 were returned in 2 months. Of these, 28% were considered unsatisfactory as they did not contain endocervical cells; 6.2 per 1,000 were requested to have biopsies on the basis of malignant cells found on the slides.

In this study, the average age of patients with in situ lesions was 39, with early invasion 41.6, and with frank invasion 47.8.

Los Angeles, Calif.<sup>27</sup>

This study was carried out in a cancer detection center. In 1950, 36% of women seen were smeared on the basis of a visible lesion; whereas, in 1955, 98% of women attending the clinic were smeared. Over a 6 year period, 39,157 women were studied out of 53,667

new patients. Discovery rate in all stages was 4.3 per 1,000 population and 12.1 per 1000 smears in 1950 compared to 5.4 and 5.5, respectively, in 1955. In 1950, the discovery rate for in situ carcinoma was 0.86 per 1,000 population and 2.4 per 1,000 patients examined. The corresponding figures in 1955 were 3.0 and 3.1. In sampling all new patients, new patient discovery rate increased to 7.1 per 1,000 in 1955 from 2.5 in 1951. Average age for in situ lesions was 43.3 and for stage 1, 51.3. For stage 2-4 lesions, the average age was 57.6. The modal for each of these was 30-39, 40-49, and 50-59, respectively.

Overall, vaginal smear examination of 39,387 women from 1950 to 1955, inclusive, yielded 303 proven cases of genital cancer. Of these, 241 were squamous cell carcinomas of the cervix.

Columbus, Ohio<sup>28</sup>

In a two-year study of vaginal aspiration and/or cervical smear, a total of 60,184 women were examined. Of these, 205 were found to have a malignancy of the genital tract; 82 of these were in situ cancers and 94 invasive cervical lesions.

A summary of the results of examinations on some 608,200 women is given by Raymond F. Kaiser<sup>11</sup>. This is

a report of those studies set up under the National Cancer Institute, whose goal is the cytologic examination of at least 700,000 women once.

Table 1  
Results of First Cytologic  
Examination of 608,200 Women<sup>12</sup>

Result	No.Exam.	%
Unsatisfactory	5,660	0.9
Negative	578,640	95.2
Atypical	18,430	3.0
Suspicious	4,010	0.7
Positive	1,460	0.2

Table 2  
Proved Cancers Detected as a Result of  
First Cytological Exam of 608,200 Women<sup>12</sup>

Type Uterine Cancer	No. Patients	Rate per 1,000
In situ Cancer of Cervix	1,490	2.45
Invasive Cancer of Cervix	910	1.50
Cancer of Corpus	130	0.21
Cancer of Other Sites of Female Reproductive Tract	55	0.09

Table 3  
Uterine Cancers Diagnosed Microscopically  
Following First Cytological Examination<sup>12</sup>

Project	No. Screened	In Situ	Invasive
Memphis	108,136	393	373
Madison	65,163	206	335
Columbus	37,540	31	52
San Diego	33,746	259	77
Louisville	12,000	41	60
Hot Springs	3,224	32	35

### Comparison of Smaller Survey to Total Population Screening.

There is no real point in comparing the method of obtaining smears, as that in a private practice will of necessity be different because of physical and financial facilities. The methods of staining and fixing slides are, with minor variations, quite similar.

The discovery rate for invasive carcinoma of the cervix in this study is somewhat higher than that reported in the results of some 608,000 women. I believe this can be accounted for on the basis of the type of patient being studied in the smaller study. The bias involved here could easily account for this discrepancy. The majority of patients involved in our study have come to the physician with some complaint, and thus the possibility of a cancer being discovered is much greater than in the so-called well female being examined routinely. The incidence of in situ lesions in this study is strikingly similar to that found in the population screening. The difference amounting to only 0.01 per 1,000 women being examined. I believe this is logical in that the in situ lesion is more often picked

up in the asymptomatic women, than is the invasive lesion, and thus, the type of individual with this lesion is more apt to be similar in both studies. This is based on the assumption that both are probably asymptomatic.

The prevalence of the invasive carcinoma and in situ carcinoma in the various age ranges are, for all practical purposes, the same. These results seem to be quite well established at this time and need no further comment.

It is interesting then, that the only difference of any consequence between the two types of study is the difference in the rate of invasive carcinomas being found per 1,000 patients examined. This is the type of lesion one would expect to disappear from the population for the most part if every woman over 20 years, particularly those who are married, were routinely examined, at least once per year.

Another point of comparison between the smaller survey, which we have reported, and the larger survey, is that of the greater incidence of the positive smear in the women previously Class II. This report, however, was made only in the San Diego, California study.

## Summary

In this report, a study was made of the routine use of the vaginal smear over a period of about four years in an obstetrics and gynecology group. Included in this data are smears taken by one general practitioner using the cytologic facilities of the specialty practice.

During this period, a total of 3,430 examinations were made on 2,416 females. Of this group, a total of 116 women had suspicious or positive smears on initial examination. All of the women with positive smears and 71% of the women with suspicious smears underwent tissue study. Repeat examinations were carried out on 1,014 patients, and a total of 17 additional women had smears which were suspicious or positive. As a direct result of or with the aid of the vaginal smear, a total of 27 carcinomas of the cervix were found. This represents 11.2 cases per 1,000 women examined. Of this group, 21 or 78% had invasive lesions, and 6 or 22% had in situ lesions. These two groups represent 8.7 and 2.5 cases per 1,000 women examined, respectively. In addition, 7 carcinomas of the endometrium and 1 cystadenocarcinoma of the ovary were found.



Of the 27 carcinomas of the cervix, 55% were considered unsuspected. None of the in situ carcinomas were suspected, and 42.8% of the invasive lesions were considered unsuspected. All of the endometrial cancers were considered suspect for one reason or the other.

The peak incidence of in situ carcinoma was found to occur in the 30-39 year age group, and the invasive peak occurred in the 40-49 year age group.

An interesting observation was made in that the woman who was initially Class II was most apt to convert to suspicious or positive smears. This occurred in 70% of those women converting to these classes of smears.

It was also found that the most common reason for a woman to have a Class III smear was the presence of some type of cervicitis. In this study, no so-called false negatives were found. A total of 5 false positive smears was found. This amounted to 0.14% of the total smears examined.

A review of several large screening studies with use of the vaginal smear was made. Of some 608,200 women examined at least once, about 39 per 1,000 women

examined were found to have atypical, suspicious, or positive smears. Of this same group, 2.45 per 1,000 women examined were found to have in situ cancer of the cervix, and 1.50 per 1,000 women examined were found to have invasive cancer of the cervix. An additional 0.21 women per 1,000 were found to have cancer of other sites of the female genital tract.

The incidence of carcinoma in situ was found to be highest in the 30-39 year age group, and that for invasive carcinoma increased from the 40-49 year age group upwards.

It was also found that the incidence of carcinoma of the cervix was highest in the negro population studied, but that the number examined was not large enough to be considered significant, at least in this report.

In the larger studies, it was also found that upwards of 90% of the in situ lesions were considered unsuspected prior to vaginal cytology. Figures for invasive cancer of the cervix ranged up to 30% being unsuspected.

It was concluded that the greatest value of the routine vaginal smear is in the detection of in situ carcinoma of the cervix. Also, the age at which

examination should be started is a matter of individual opinion, but in general, all women over the age of 25 should be examined. The frequency at which these examinations should be carried out is still in question.

## Conclusions

When one is confronted with a mass of figures, such as have been reported, it is difficult to arrive at a definite conclusion as to what has been proven. The principal purpose of the first part of this paper was to report, as objectively as possible, the findings of routine vaginal smears on patients as commonly seen in an obstetrics and gynecologic practice as seen in Omaha, Nebraska. The second part has been devoted to presenting findings reported for larger numbers of patients in different circumstances.

On the negative side, I do not believe that one can, with any honesty, say that the routine use of the vaginal smear is not of value. In our study, some 11.2 cases of cervical cancer per 1,000 women examined were discovered as a result, at least in part, by the use of the routine vaginal smear. As no study was made in this series as to the case finding rate prior to installation of the routine smear, no conclusion can be arrived at as far as the increase in case finding is concerned. In the one large series where this was reported, there was a fourfold increase in the case

finding rate for cancer of the cervix. This is significant.

The real value of routine screening is not in finding the far advanced cancers but in finding the so-called in situ cancers which reach their peak in the relatively young 30-39 year age group. It is with this type of lesion where treatment at the present time is most gratifying, approaching a 100% five year cure rate. This is the group in which symptoms are most often absent and in which the patient is least apt to come to her physician for examination because of symptoms. Also, in this type of lesion, clinical findings are so often absent that a potential death dealing lesion would be missed if it were not for the vaginal smear giving suspicious or positive results. Granted, not enough information is available at present concerning the prevalence of the in situ cancers prior to the institution of the routine vaginal smear. Evidence is, however, apparent that the number of such lesions found has increased since institution of the vaginal smear. Also, the studies in which a large number of women have been examined twice or more have shown a marked decrease in the number of invasive cancers of the cervix being discovered on

reexamination. This indicates that following the initial examination, the incidence of invasive cancers should fall progressively as the number of reexaminations increases. In fact, following the initial screening of a population, assuming that the interval is not too long, no more invasive lesions should be found in this same population upon reexamination. Therefore, I am of the opinion that if all women would be faithfully examined at periodic intervals, deaths due to cancer of the cervix could be eliminated for all practical purposes.

One may argue that the expense involved in such an examination is not worth the number of cases of malignancy found. This may be true in the individual who undergoes repeated examinations with negative results, but to the one individual in which a cancer is found in a "curable stage", the value of the examination has been priceless. I believe, for this reason, that the true monetary value of the test is a matter of individual opinion, for who can say what the value of a life saved is. I do not believe that the average private patient undergoing this examination would begrudge the cost of the examination were she truly aware of the real value of early detection

of cancer of the uterus, the cervix in particular. This road could be made smoother by an adequate program of public education, similar to that concerning cigarettes and lung cancer, with the added incentive that cancer of the cervix is quite curable in the early stage.

The routine use of the vaginal smear will also be of value in determining the relationship of intra-epithelial cancer and frankly invasive cancer of the uterus. Actually, the only absolute way that this can be proven is to watch the progression of an intra-epithelial lesion to a frankly invasive cancer. In this country, I do not believe that this will ever be attempted, at least until the more advanced cancers can be cured in a higher percentage of cases.

Not enough attention, at least in the majority of studies, has been paid to determining the findings in relation to socio-economic level, race, creed, and parity of the patients in whom cancer is found. This data would be of further value in determining exactly in which groups routine screening would be of the greatest value. Many studies have shown a higher incidence of cancer of the cervix in negroes and a lower incidence in the Jewish population. However, in

the statistical studies of data concerning results of total population screening for cervical cancer, these figures have not been tabulated in a significant number of studies.

In all the studies, it has been shown that the greatest majority of the intraepithelial lesions have been unsuspected upon clinical examination of the female genital tract. In our series, none of the six in situ carcinomas of the cervix were suspected. In the Memphis study, the corresponding figure was 90%. This leaves little doubt as to the value of the vaginal smear in detection of this type of cancer. One must assume, however, that the examining physician truly felt that there was no indication of malignancy at the time of the examination clinically.

Generally, I conclude that the routine use of the vaginal smear in an obstetrics and gynecology practice in Omaha has produced enough proven cases of cancer of the cervix to be of value. This is true particularly in the case of intraepithelial lesions, where 100% were found as a direct result of positive or suspicious Papanicolaou smears. Concerning the invasive lesions, this is still questionable though some 42% were considered unsuspected prior to taking a



vaginal smear. It is questionable as to whether or not these would have been discovered if smears had not been taken. In the larger studies, this same point has been made; here, results have varied up to 90% of the intraepithelial lesions being unsuspected. The greatest value of the smear, therefore, lies in the discovery of the very earliest truly malignant lesion.

As far as what is the minimum age or other conditions under which smears should be taken, I do not feel this has as yet been clearly resolved; cases of cancer have been found in females as young as 19 years of age. In general, I would conclude that 25 years or over is an acceptable age at which to start routine screening, as the incidence of positive smears increases at least from this point upward. The final decision, however, still will rest with the examining physician and what his clinical impressions are.

The data as so far collected in the larger screening does not appear applicable to the total population at the present time. There have not been a significant number of examinations, and secondly, numerous points of bias exist. In essence, not enough of the total female population has had an equal

opportunity of being examined by the vaginal smear.

I conclude that there is little doubt as to the value of routine screening both in private practice and in the total population. The only question which remains to be resolved is that of whether or not examination of more specific population groups might not be more fruitful. One of these groups seems to be fairly well established, this being the female negro, where at least in one large study there was found a much higher incidence of positive findings.

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