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THE DIAGNOSIS OF CARCINOMA OF THE UTERINE CERVIX
BY CYTOLOGIC METHODS

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I. Introduction.

Carcinoma of the uterine cervix is one of the most common malignancies in women. An editorial in the Journal of the American Medical Association (34) states t at about 29,000 new cases of cervical carcinoma are diagnos d each year in the United States and that about 10,000 women in the United States die from cervical carcinoma each year. Lar son, et. al. (17) feel that only 5-8% of the United States' female population have cervical cytologic examinations. The editorial appearing in the Journal of the American Medical Association (34) states that the mortality from carcinoma of the cervix can be reduced from the present rate of 40% to about 5% by adequate examination of all women with cervical cytologic smears. This reduced mortality is accounted for by the superiority of the cure rate for in situ carcinomas as compared with invasive carcinoma. Green (11) points this out when he shows the approximate cure rate for in situ carcinoma to be 95-100%, for stage I to be 70-80%, for stage II to be 40-50%, for stage III to be 20-30%, and for stage IV to be 1-10%. These figures emphasize that we should strive to diagnose cervical carcinoma at the in situ stage and if this is not possible that the diagnosis should be made while the carcinoma is in the early invasive stage.

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In situ carcinoma of the uterine cervix has all the criteria of invasive carcinoma except it has not invaded through the basement membrane. The direct link between in situ and invasive carcinoma of the uterine cervix has not yet been established with absolute certainty but increasing cases are now documented in which in situ carcinoma has progressed to invasive carcinoma. No mass statistics are available since carcinoma in situ progresses slowly, and since most doctors are hesitant to wait until invasion occurs because of the increased mortality. Statistically, 4% of the in situ carcinomas become invasive in one year, 9% in five years, and 22% in 9 years. (24) Truly, there is nothing diagnostic by gross inspection of a cervix affected with carcinoma in situ. Most of the patients with in situ carcinoma (85%) (24) will have some abnormality, either a laceration, eversion, or erosion of the cervix. These are also common findings in patients who show only chronic cervicitis with biopsy. About 15% (24) of the patients with carcinoma in situ will have a cervix which appears grossly normal. At most, only 33% (24) of these women have had abnormal vaginal bleeding or post coital spotting. In the thirty's, when in situ carcinoma is very common, only 25% (24) of the women have noted vaginal bleeding or post coital spotting.

Since carcinoma in situ cannot be diagnosed accurately by clinical means, and since it is not practical to biopsy every abnormal cervix to rule out carcinoma in situ, the

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cytologic smear technique was developed by Papanicolaou and Traut in 1943. This technique has been greatly refined since its origin and is now a very valuable method of cancer detection. This paper is written to briefly describe the proper methods of obtaining, fixing, staining, and reporting such a slide and to extensively analyze statistically the correctness and accuracy of the reported diagnosis.

II. Techniques of the Cervical Cytologic Smear.

When should the smear be taken? Parker, et. al. (23) noted that 87 out of 485 (18%) of his patients with carcinoma in situ were below the age of 30 years. They also noted that in their obstetric patients, the average age for carcinoma in situ was 30 years. Scott and Ballard (29) with their records at the oncology office at McDonnald House, University Hospital of Cleveland, showed that 23 out of 181 patients (12.2%) had proven carcinoma in situ of the cervix below the age of 30 years. They point out that approximately one-third of the cervical dysplastic lesions can progress to carcinoma in situ over a period of 5-10 or more years. Carcinoma in situ, if untreated, can progress to invasive carcinoma over an equal period of time. (29) Therefore, it is generally assumed that cervical cytologic smears should be started at the age of 20 years and be taken at 2-year intervals in all women older than 20 years if they have negative smears. If the smears are atypical, the duration of the interval should be shorter. This is dictated by the individual case, but for atypical smears a repeat examination should be taken in 6 months to 1 year, and for dysplastic smears the

repeat should be taken in 3 months. The smears should be started before 20 years of age in all women who have had children.

For collection of the cervical cytologic smear the patient should be advised not to douche the day before or the day of the examination. The physician must have a speculum of appropriate caliber and standard length to properly visualize the cervix. It has been emphasized repeatedly that speculum lubricants should be avoided, but Krieger (19) feels this is not necessarily true. He states, "The important thing is to be careful not to traumatize the cervix when the speculum is spread." (19) Actually, the true contraindication to using speculum lubricants is that they interfere with fixation and staining of cells and therefore, should be avoided before taking the smear.

The three major ways of collecting a specimen are to utilize a cotton tipped applicator, Ayre spatula, or pipette. Various authorities emphasize different approaches. Scott (19) believes that the best and most comprehensive sampling can be obtained by aspiration of the cervical mucus plus scraping of the cervix about the external os. Furthermore, Scott and Ballard (29) believe that in certain women, particularly those who are post-menopausal or those who have had radiation therapy, cervical mucus may be very scant or absent, in which event material from the posterior vaginal fornix can be aspirated and properly identified on the laboratory request

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form. In reality Krieger (19) is probably correct when stating that the particular technique used to obtain the specimen is less important than the quality of the specimen obtained, the instructions to the patient not to douche prior to the examination, and the ability of the cytotechnician and pathologist to evaluate the prepared smears.

There are various fixatives used into which the smeared slide must be placed immediately after preparation. Probably the most commonly used fixative is equal parts of ether and 95% alcohol. Krieger (19) points out that a solution of 97 parts of 95% alcohol and 3 parts of glacial acetic acid is good. The smear should be allowed to be in the fixative for at least 20 minutes. After this they can be dried, separated with paper clips, placed together and sent to the laboratory. They should be accompanied by an appropriate requesition sheet and the various slides should be properly identified.

Once the slides are in the laboratory, they are stained. They are first hydrated and stained with aqueous soluble stains. Next they are cleared of the aqueous stains and then dehydrated. Finally, they are counter stained using aqueous insoluble stains. See Appendix II for the detailed staining procedure.

When the slides are mounted and labeled, they are ready for reading. In some laboratories specially trained cytotechnologists scan the smears, looking at atypical cells under high dry, and refer only the smears with atypical cells to the pathologist or cytologists. In other laboratories the pathologist looks at all

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the smears. The criteria to be fulfilled in reading the smears and diagnosing the various types of lesions is beyond the scope of this paper. This is the responsibility of the pathologist and takes years of training and experience. This paper will discuss the methods of reporting slides and the significance of the various categories, since this is necessary to understand before studying the statistical significance of the various reports.

III. Standardized Methods of Reporting Cytologic Smears.

In general there are two major methods of reporting smears. Most of the other systems are modifications of these two methods. One method is to report the findings in one of five different classes. The class 1 smears are considered negative and benign in all respects. The class 2 smears are probably benign, but have some atypical features. The class 3 smears are dysplastic and of a doubtful nature as to their malignancy. The class 4 smears contain cells which have some but not all of the criterial of malignancy. The class 5 smears contain cells with all of the criteria of malignancy.

The other method of reporting is to consolidate the five classes into three. In this method the classes 4 and 5 in the previous method of classification are consolidated. This can be done since the cervix is readily accessible to biopsy and since it must be biopsied for a class 4 smear in the other classification. Also in this method the class 1 and 2 are

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consolidated. This can be done since most of the smears in class 2 of the previous classification are of no consequence. All the systems have one class which is of a dysplastic or doubtful nature. This class contains all smears which have dysplastic but not truly malignant features. (Throughout this paper this class if referred to as a dysplastic or class 3 smear.) A certain percentage of the smears placed in the dysplastic category will ultimately prove to represent carcinoma. Graham (9) states that if a vaginal smear is called dysplastic, 14% of these patients will have malignant disease in the female genital tract. Most pathologists try to keep their reporting out of this dysplastic category since it is of little aid to the clinician.

Graham (9) also only places smears in the doubtful dysplastic category when they fulfill one of the following 8 criteria.

1) "A smear is called doubtful if only dyskaryotic cells are present; it remains in this category as long as this picture continues. This is the sole instance in which a smear on repeat is left in the doubtful category. It is reported as doubtful, dyskaryotic cells present.
2) "A frequent doubtful smear is that with marked cellular changes due to trichamonads. The changes may be so marked as to arouse grave suspicion of malignancy. One is not helped in the interpretation of the smears by the fact that 32% of the patients with invasive squamous cell carcinoma of the cervix also have trichomonads present. The infection should be treated and then the smear repeated. Usually on a repeat smear, if no more severe atypicalities are seen, the smear is called negative. The presence of parasites is always reported.

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3) "A smear that contains endometrial cells in a postmenopausal patient is an abnormal finding and is reported. The smear is called doubtful because of the association of endometrial hyperplasia with carcinoma of the endometrium. If no suspicious cells are encountered on repeat, the smear is called negative.

4) "A post-irradiation smear is called doubtful if cells that appear to be differentiated squamous cell carcinoma are encountered, but no definite undifferentiated cells can be found.

5) "A smear is called doubtful and repeated if the positive cells are considered to be the result of contamination. That is if they appear on a different focal level.

6) "A smear is called doubtful if only one or two malignant cells are found. The usual positive smear has a fair number of cancer cells. It is such an unusual occurence for only one or two to be present that it is safer to call the smear doubtful and repeat it.

7) "A vaginal smear is called doubtful and repeated if large numbers of either vacuolated basal cells or histiocytes are seen, but no malignant cells, since this picture is four times more frequent in positive smears than in negative ones.

8) "Finally, there are the smears in which the cytologist is actually in doubt about the malignant or benign character of the cells. The cells in these smears may have active nuclei with some clumping of chromatin. A common nucleus to see in this type of doubtful smear is one that has uneven distribution of nuclear material in one portion of the nucleus but even arrangement in the remaining portion. These nuclei are really the doubtful ones, since they are neither malignant or typically benign."

It is also important to note that radiation, chronic cervicitis, pregnancy, and healing from conization can all cause atypical cells. The pathologist should be notified of these facts with the requisition.

Different laboratories have different policies about trying to identify the source and stage of the malignancy if malignant

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cells are noted. Reagan (27, 28) and Patten (28) feel that wherever possible, the evidence should be evaluated in terms of the specific pathologic process which is believed to be present. For example, when they believe the cellular evidence to indicate carcinoma in situ, the report refers to "cellular changes consistent with those of carcinoma in situ." In their series of 127 consecutive patients having cellular changes consistent with those of in situ carcinoma, 120 (94.5%) were ultimately proved to have in situ carcinoma on histopathologic study. Reagan (28) further indicates that when it is impossible to make an interpretation of what, on the basis of the cellular evidence, is judged to be a significant reaction, the gynecologist can be informed as to the lesions which must be considered.

IV-a. Analysis of a Large Series of Routine Cervical Cytologic Examinations.

During the summer of 1963, all the abnormal slides recorded from cervical smears during the period from January 1, 1958, to July 1, 1962, were reviewed. The Physicians Laboratory, (Omaha, Nebraska) where these smears were reviewed, used a four class method for reporting their cytologic smears. This method utilized a form letter which was checked according to the findings of the various smears. The form letter was as follows:

☐ Atrophic pattern
☐ Moderate inflamatory background
☐ Heavy inflamatory background
☐ Bloody background present

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☐ Absence of abnormal or atypical cells. (Negative Examination)
☐ Atypical cells, probably associated with inflamation -
   request a repeat in 3 months.
☐ Atypical cells, recommend a repeat examination as soon as
   possible.
☐ Cells suspicious for malignancy--recommend a biopsy.
☐ Smear not satisfactory--please repeat at no additional
   charge.

In filling out this letter, the pathologist would first check two of the boxes to indicate the type of cells seen. If none of the conditions represented by these boxes were noted, this portion of the form would be left blank. Also, if some other condition was noted, which was not covered by these boxes, it would be noted by filling in the necessary information at the bottom of the letter. For example: If a woman had trichomonas and markedly atypical cells a note would be made on the bottom which would read "Atypical cells present probably due to the presence of trichomonads--recommend adequate treatment of the trichomonads and then a repeat smear." The bottom five classes of the form represented the actual impression. This utilized a four class method. Throughout this paper when this system is presented, the various classes will be referred to as negative, atypical, dysplastic, and suspicious. The negative and atypical classifications correlate with classes 1 and 2 of the 5 class system. The dysplastic class correlates with class 3, and the suspicious class correlates with a combined class 4 and 5 of the 5 class system.

In compiling the information for this series all of the suspicious smears were followed up with a form letter to the

patient's referring physician requesting the diagnosis of the biopsy. If the biopsy was diagnostic of malignancy, the stage and type of carcinoma was recorded. If the biopsy was negative, the tissue slides were obtained to see if the specimen was adequate to rule out carcinoma. The adequacy of the tissue specimens was determined by one of the pathologists on the staff. In a few instances the tissue sections were not obtained but the pathologic report from the various laboratories was noted. In this case, if the gross description represented a cold knife conization and if the laboratory was of a reputable name then the smears were considered to be adequate and truly negative. In a few other cases the tissue sections and pathologic report were not obtainable. If this was the case it was recorded. To try to correlate the relationship between atypical, dysplastic, and suspicious smears all patients having suspicious smears were checked through the files to see.if they had a record of a previous atypical or dysplastic smear. Also all patients with atypical or dysplastic smears were checked for two years previous and subsequent to see if they ever developed a suspicious smear. Follow-up letters were sent out on all women having dysplastic smears between June 1, 1961, and July 1, 1962. This follow-up letter was to determine if they had ever had the presence of carcinoma proven in some other laboratory.

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In compiling this series the point of interest was to
find out how many times suspicious smears were followed by
biopsies which showed no malignant findings. The next step
of interest was to determine whether or not the negative
biopsies were adequate to rule out carcinoma. Also, it was
of interest to note how often suspicious smears were followed
with biopsies positive for carcinoma. If the biopsies were
positive, the type and grade of carcinoma as evaluated by
microscopic tissue examination was recorded. With every
suspicious smear an attempt was made to determine how the
referring physician had followed up the smear. In an
occasional case the smear was not followed up due to religious
principle of the patient, bookkeeping errors, etc. If this
occurred, and the smear was inadequately followed up, the
information was noted and recorded. The dysplastic smears
were also studied to determine how often they were later
followed with a suspicious smear or biopsy.

Once the information was gathered it was tabulated.
(See table I, p. 19. If a patient had a dysplastic smear,
which continued to be dysplastic with repeat examination,
this was felt to be an inadequate follow-up. This point was
not made in the statistical record since there is no way of
knowing if the patient went to a second doctor or if the
original doctor sent his biopsies or repeat smears to a
second laboratory. If a patient had one or more dysplastic

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smears and was later followed with a negative smear or biopsy, it was considered an adequate examination. It was thus felt that any patient with a dysplastic smear should be followed with either repeat smears or adequate biopsy until carcinoma was either proven or disproven.

At the time of doing the study it was felt that a certain percentage of the patients with atypical smears would later be proven to have malignancy. No follow-up letters were sent on this class, but women who had atypical smears were followed through our files for as long as they continued to be atypical. However, if these women did not appear in the files or were negative for 2 consecutive years, they were no longer followed.

An attempt was made to ascertain the age of all women with abnormal smears. The patients were thus categorized as to age and the findings of the smear. The ages of the patients having biopsies were also obtained. These women were also categorized as to age and findings at time of biopsy. Eighty-five percent of the patients having abnormal smears were categorized as to findings and age. The fifteen percent having abnormal smears that were not classified as to age were either lost at the referring physician's office or were never obtained due to poor correspondence. One hundred percent of the patients with positive biopsies were also categorized as to age and biopsy results.

It should be noted that all the women having proven carcinoma by biopsy did not have suspicious smears. Some

of the positive biopsies were preceded by dysplastic smears.
Also some of the women with suspicious smears were never proven
to have malignancy. That is, they either had negative biopsies
or were not followed up with biopsies.

At no time was a patient found who had a negative smear
with proven carcinoma by another means. There is no way to
know if one is missing carcinoma, but upon entering each private
physician's office, for reviewing a smear, the question was asked
if any of their patients had been proven to have carcinoma after
having negative cervical cytologic smears. Even though this is
not a scientific method to arrive at information, it is felt to
be of value and is presented only for the interest of the reader.

After compilation of the material, the figures arrived at
were those in table I, p. 19. The figures are a direct
categorization of the results of individualized follow-up of
each smear. This study was performed in two different stages
by two different investigators. First, the suspicious smears
from January 1, 1958, to June 1, 1961, were reviewed by another
student and pathologist. Subsequently all the atypical and
doubtful smears as well as the suspicious smears from June 1,
1961, to July 1, 1962, were reviewed by myself.

The number of smears taken from January 1, 1958, to June 1,
1961, equaled 18,862, while the number taken from June 1, 1961,
to July 1, 1962, equaled 11,795. In compiling these figures,
the total number of cytologic smears done in the laboratory was

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multiplied times a ratio which was calculated by going through
3 sample months to determine what percentage of the smears were
from the cervix uteri. These figures include repeat smears on
women with previous atypical slides, etc. The correction ratio
was derived and found to be over 99%.

Since some of the suspicious smears were followed up by
another investigator prior to June 1, 1961, it was decided that
the suspicious smears should also be tabulated as two different
groups; one from January 1, 1958, to June 1, 1961, and the other
from June 1, 1961, to July 1, 1962. This was done to see if the
two investigators arrived at similar conclusions in the same
laboratory. (Also, it was done to see if the results of the
interpretation had changed over this period of time.) See
table II, p.20 for comparison of the two different time periods.

The large series included 30,657 smears. See table I, p. 19
Of this total 0.65% of the smears were suspicious, 0.40% were
dysplastic, and 0.62% were atypical. The remaining smears were
either completely negative, or represented inadequate smears
which could not be read. There is no way to know with certainty
what percent of the smears were inadequate for reading. Of the
patients with atypical smears, 3.1% of these later had carcinoma
demonstrated either by a biopsy or by a suspicious smear. No
carcinoma could be demonstrated in the remaining patients with
atypical smears although only 25.8% had negative repeat smears.
No follow-up letters were sent out to the patients with atypical
smears.

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The patients with dysplastic smears constituted 0.40% of the total number of smears taken. Of these 38.8% were followed with negative repeat smears, 21.5% were followed with 1 or more dysplastic smear, and 21.5% were followed with positive biopsies. 3.3% of the patients with dysplastic smears had positive biopsies but never had suspicious smears.

The patients with suspicious smears constituted 0.65% of the total number of smears taken. In 75.6% of these patients, carcinoma was demonstrated by biopsy. In the remaining smears, 16.9% were followed by negative biopsies, and 7.0% were never followed up by the referring physician. (The reason for not following these patients was usually due to religious principle or due to bookkeeping errors. Occasionally the patient would die of another cause before follow up could be obtained.) Of the negative biopsies 58.5% were found to be inadequate specimens when reviewed by our department of pathology. Also, 14.7% of the negative biopsies were never reviewed as to adequacy. (This was usually because the biopsy slides were never obtained.) Thus only 27% of the negative biopsies could be said to be adequate to rule out carcinoma with certainty. This would mean that only 4.6% of the suspicious smears were followed with biopsies which could definitely rule out carcinoma. The remaining suspicious smears which had negative biopsies may or may not have had malignancy of the cervix uteri.

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In the suspicious smears followed with positive biopsies,
52.7% of the biopsies showed carcinoma in situ of the uterine
cervix, 31.2% showed invasive squamous cell carcinoma of the
uterine cervix, 2.9% showed adenocarcinoma of the uterine
cervix, and 7.9% were reported as carcinoma of the uterine
cervix without diagnosis as to the type or grade of carcinoma.
6.3% of the biopsies following suspicious smears were diagnosed
to have endometrial carcinoma.

After dividing the patients with suspicious smears into
two sub-groups, it was found that from January 1, 1958, to
June 1, 1961, 18,862 cervical cytologic smears were examined.
(See table II, p. 20. Of these 0.67% were categorized as
suspicious smears. Positive cervical biopsies were present
in 81.0% of these suspicious smears. Of the positive biopsies,
50.0% were carcinoma in situ, 41.2% were invasive squamous cell
carcinoma, 2.9% were adenocarcinoma of the cervix, 6.8% were
endometrial carcinoma, and 1.0% were reported by the referring
physician as being diagnostic of carcinoma, but the type and
grade was not reported. 21.4% of the suspicious smears were
followed with negative biopsies. 96.8% of the negative biopsies
were reviewed as to adequacy and 59.2% of these were felt to be
inadequate to rule out carcinoma. 3.2% of the negative biopsies
were not reviewed as to accuracy of diagnosis because the biopsy
slides were not obtained for study. This means that only 5.5%
of the suspicious smears were later followed with negative
biopsies, which were adequate to rule out carcinoma. In this

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part of the series 6.4% of the patients with suspicious smears were never followed up by the referring physician to prove or disprove the presence of carcinoma.

In the portion of the series reviewing the suspicious smears taken from June 1, 1961, to July 1, 1962, 11,795 smears were examined. (See table II) Of these 0.52% were reported as being suspicious for malignancy. Positive cervical biopsies were present in 73.8% of these. Of the positive biopsies 60.0% were proven to have carcinoma in situ, 13.3% to have invasive squamous cell, 0% to have adenocarcinoma of the cervix, 4.5% to have cervical carcinoma, but the type and grade was not reported . Biopsies negative for carcinoma followed 14.7% of the suspicious smears. Of these 55.6% were felt to be inadequate to rule out carcinoma, and 11.1% were not reviewed as to accuracy. (This was again because the biopsy smears were not obtained.) Thus only 2% of the patients with suspicious smears were followed with adequate negative biopsies. In this part of the series 13.3% of the patients with suspicious smears were never followed by the referring physician. (The reason being the same as that cited above.)

Figure I, p. 21 visually demonstrates no significant difference in the age incidence of patients with atypical, dysplastic, or suspicious smears. Figure II, p. 22 shows no significant difference in the age of discovery of in situ compared to invasive carcinoma of the cervix. It also shows no significant second peak incidence around the time of the menopause for any type of carcinoma of the cervix.

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Table I. Results of the Cytologic Study Done at the Physicians Laboratory From January 1, 1958, to July 1, 1962.

Type of smear		Number	Percent
Suspicious Smears	Smears taken	201	—
	Smears followed with positive biopsies	152	75.6
	Positive biopsies diagnosed as carcinoma in situ	79	52.7
	Positive biopsies diagnosed as invasive sq. cell carcinoma	47	31.2
	Positive biopsies diagnosed as adenocarcinoma of cervix	3	2.0
	Positive biopsies diagnosed as endometrial carcinoma	9	6.3
	Positive biopsies type and grade not reported	12	7.9
	Smears followed with negative biopsies	36	16.9
	Negative biopsies felt to be inadequate	21	58.5
	Negative biopsies not reviewed as to adequacy	5	14.7
	Smears not followed by referring physician	14	7.0
Dysplastic Smears	Smears taken	121	—
	Smears followed with suspicious smears	23	19.0
	Smears followed with positive biopsies	26	21.5
	Smears followed with negative smears or biopsies	47	38.8
	Smears followed with one or more dysplastic smears	29	21.5
Atypical Smears	Smears taken	191	—
	Smears followed with suspicious smears or positive biopsies	6	3.1
	Smears followed with negative smears	48	25.8
	Total number of smears taken from 1-1-58, to 1-1-62	30,657	

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Table II. Comparison of the Suspicous Smears and Follow-up Biopsies Done Between January 1, 1958, to June 1, 1961, and June 1, 1961, to July 1, 1962.

| Type of Smear		Number of Occurences	Percent %
Suspicous Smears taken from January 1, 1958, to June 1, 1961.	Smears taken	126	—
	Smears followed with positive biopsies	102	81.0
	Positive biopsies diagnosed as invasive squamous cell carcinoma	42	41.2
	Positive biopsies diagnosed as carcinoma in situ	51	50.0
	Positive biopsies diagnosed as adenocarcinoma of cervix	3	2.9
	Smears later proven to have endometrial carcinoma	7	6.8
	Positive biopsies not reported as to type and grade	1	1.0
	Smears followed with negative biopsies	27	—
	Negative biopsies inadequate to rule out carcinoma	16	59.2
	Negative biopsies not reviewed as to adequacy	4	3.2
	Smears not followed by referring physician	8	6.4
	Total smears taken from January 1, 1958, to June 1, 1961	18,862	
Suspicous Smears taken from June 1, 1961, to July 1, 1962.	Smears taken	61	—
	Smears followed with positive biopsies	45	73.8
	Positive biopsies diagnosed as invasive squamous cell carcinoma	6	13.3
	Positive biopsies diagnosed as carcinoma in situ	27	60.0
	Positive biopsies diagnosed as Adenocarcinoma of cervix	0	0.0
	Smears later proven to have endometrial carcinoma	2	4.5
	Positive biopsies not reported as to type and grade	10	22.2
	Smears followed with negative biopsies	9	14.7
	Negative biopsies inadequate to rule out carcinoma	5	55.6
	Negative biopsies not reviewed as to adequacy	1	11.1
	Smears not followed by referring physician	6	13.3
	Total Smears taken from June 1, 1961, to July 1, 1962	11,745	
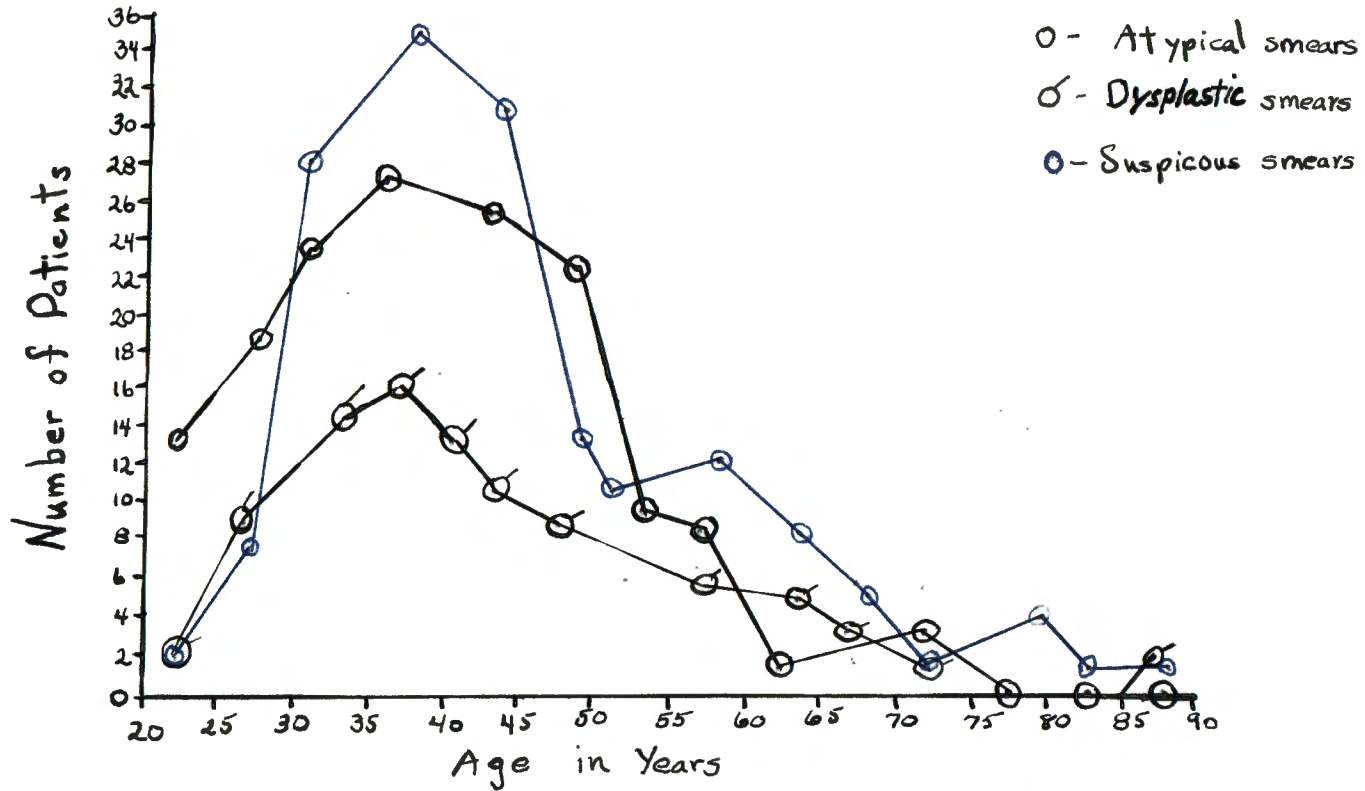
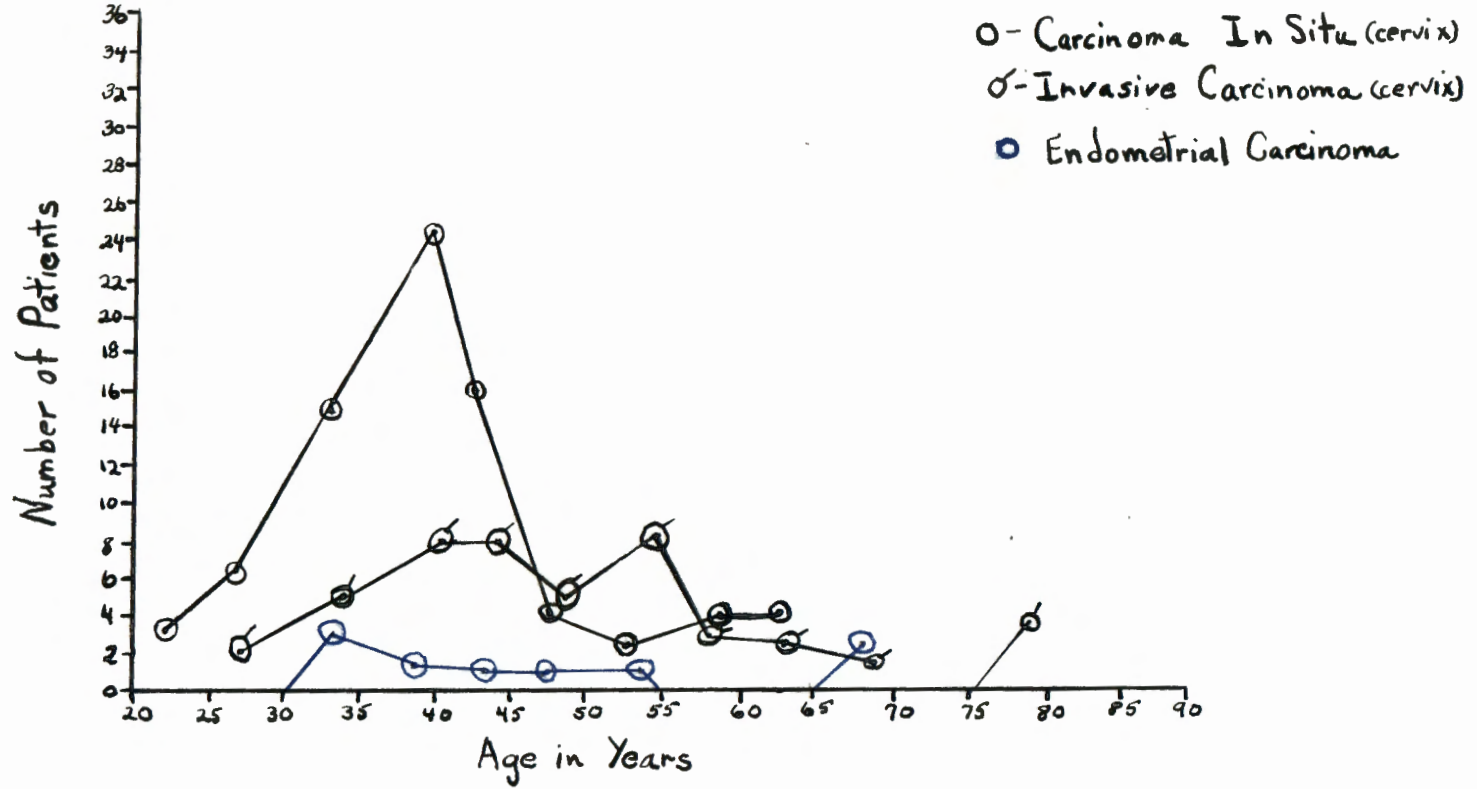Figure I. Age of Patients in Years Plotted against Number of Patients For Various Groups of Smears.

Figure II. Age of Patients in Years Plotted Against Their Types of Carcinoma.

O – Carcinoma In Situ (cervix)
♂ – Invasive Carcinoma (cervix)
O Endometrial Carcinoma

(22)

IV-b. Review of the Literature From 1956 Through 1964.

The general capabilities of cervical cytologic smears is evaluated by the following statements made by Emerson Day. (6) He considers the cytologic smear in its ability to diagnose carcinoma of the entire genital tract and thus states:

> "Exfoliative cytology rarely if ever is applicable in screening for cancer of the external genitalia. Here early diagnosis depends primarily on biopsy of suspicious areas of leukoplakia or kraurosis vulvae and of any tumors of external organs, glands, or related musous membrane and skin surfaces. Cytologic study of direct smears of suspicious surface lesions can occasionally be helpful, but in this use cytology is a diagnostic adjunct rather than a screening procedure.
> "Occasionally the routine vaginal aspiration smear reveals cells suspicious or positive for cancer which prove on subsequent diagnosis to originate from an unsuspected primary focus in the vagina. This occurred two times in 19,462 initial cancer detection examinations at the Strang Clinic (31) during the years 1956 to 1960, and has been reported occasionally in other screening programs.(4, 21, 25)
> "When incipient carcinoma of the vagina is present, study of exfoliated cells when collect in the vaginal pool is a highly effective screening device. However, the rarity of vaginal cancer relegates this achievement of cytology to the category of an unexpected dividend, effective when it occurs, but infrequent and therefore, relatively unimportant in screening programs.
> "The detedtion of cancer of the adnexa, principally the ovaries, by exfoliative cytology is similarly a dividend, but for opposite reasons. Here we are dealing with a much more frequent cancer, but one which is only indirectly accessible to standard cytologic techniques. Smears of peritoneal fluid or washings at time of laparotomy can be an effective diagnostic adjunct in adnexal carcinoma. However, only rarely do cells from an early unsuspected cancer of the ovary appear in routine screening smears. This has occurred twice in the Strang Clinic (31) experience and has been reported occasionally in other screening programs. (4, 8, 21)

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"There is, however, an indirect screening
application of vaginal-cervical cytology for
ovarian cancer. It occurs in the postmenopausal
woman who gives evidence of unusual estrogen
activity on standard smears. If this is unexplained
by a history of estrogen therapy, it suggests the
presence of a functioning ovarian tumor. The
follow-up of this lead, when well documented, has
led to the diagnosis of early ovarian cancer on
exploratory laparotomy in two instances in our
experience.
"Far and away the most important application
of exfoliative cytology is in screening for occult
cancer and precancerous lesions of the uterus. As
a screening method for the cervix, exfoliative
cytology approaches the ideal cancer detection
device, and, as experience accumulates, its
effectiveness for early cancer and precancer of
the endometrium is increasing."

Eleven major screening programs which together screened

615,927 women have been listed in the literature between 1955

and 1961. These articles did not list their data according

to the classification of the smears. They are presented to

point out the cancer detection rate by adequately following

up all class 2, 3, & 4 smears. (Throughout the remainder of

this paper, class 2, 3, & 4 as found in the literature will

be correlated with our atypical, dysplastic, and suspicious

smears, respectively.)

Tables III through VII (see Appendix I) include work

from these series. In table III the results of these 11

major series are listed to show the overall incidence of

histologically proven carcinoma on diagnostic follow-up of

women with some type of abnormality in their smears. The

results are listed in terms of absolute numbers and rates

per 1,000 women screened. As will be noted, a substantial

(24)

number of these carcinomas were unsuspected prior to the
cytologic report. This table shows that an average total
of 7.3 cases of carcinoma will be detected per 1,000 women
examined.

Table IV takes the results from 6 of these major screening
programs and lists it as to the method of obtaining the smear
and to the anatomical location of the carcinoma. The carcinoma
was considered detected if the smear was abnormal enough to
warrant further diagnostic procedure. The dominant carcinoma
detected by cervical or vaginal smear was squamous cell
carcinoma of the cervix; the average rate being 6 carcinomas
per 1,000 women examined, or 1 in every 167 women screened.
The incidence of carcinoma detection (using cervical or vaginal
smears) for the endometrium varied widely, the average rate
being 0.8 carcinomas per 1,000 women examined. The high rate
for the Wisconsin study (4) can be partially attributed to the
fact that the population was relatively old and to the special
attention devoted to endometrial cells in routine smears. The
experience for the detection of other pelvic carcinomas,
primarily vaginal and mixed tumors, similarly varied from
program to program with an average of 0.2 carcinomas per 1,000
women examined.

Tables IV and V seem to point out that various methods of
smear collection have a different detection rate for carcinomas
of various parts of the genital tract. From these tables the

(25)

apparent implications are that the vaginal aspiration is the best method of collection when looking for carcinoma of the endometrium; while the cervical smear is most effective for screening information about carcinomas of the cervix.

Tables V-A and V-B are taken from the Strang Clinic study. (31) In table V-A a series of 77 carcinomas in situ of the uterine cervix as proved by adequate biopsy were studied. In each of these the initial screening procedure was to do both a vaginal aspiration and cervical swab. In this series the vaginal aspiration smear was class 3 or 4 in 44.2% of the in situ carcinomas, while the cervical swab was class 3 or 4 in 97.4%. Also, this series points out that 18.2% of the vaginal smears were falsely negative for in situ carcinoma of the cervix while none of the cervical smears were falsely negative. This indicates that a vaginal smear will miss about one-sixth of the cervical carcinomas.

Table V-B is used to point out that the vaginal aspiration is superior in its ability to detect carcinoma of the uterine cavity. In patients with endometrial carcinoma the vaginal aspiration smear was a class 3 or 4 in 75.8% of the cases while the direct cervical swab was a class 3 or 4 in only 41.4% of the cases. The incidence of false negatives was 24.2% in the vaginal aspiration smears and 41.4% in the cervical swab smears. Day (6) points out that the detection rate for endometrial carcinoma using the cervical swab, is increased if the swab is inserted deep into the endocervical cannal while taking the smear. This technique will alter the

(26)

above percentages.

In a similar type study by Miller and VonHaam (21), the superiority of the cervical swab for cervical carcinoma was also demonstrated. This series found no difference between the cervical swab and vaginal aspiration in the detection of carcinoma of the endometrium. Hofmeister (13) points out that in his series, cervical or vaginal smears detected carcinoma of the endometrium only when symptoms were present. Day (6) indicates in his article that a smear technique is available which can be used to take smears directly from the endometrial cavity. He points out that this technique is superior to either the cervical swab or the vaginal aspiration for the detection of endometrial carcinoma. This topic is beyond the scope of this paper, but the reader is referred to Boschann's (2), Hecht's (12), and Jordan's (14, 15) articles for detailed discussions of endometrial cytology.

Table VI summarizes the degree of invasion of carcinoma of the cervix as demonstrated by the various programs listed. This table includes carcinomas that were diagnosed only by the initial smear. It is important to note that the overall ratio of in situ to invasive carcinoma is about 2.9 to 1. But it is more interesting to note that while this ratio is 0.6 to 1 in the Wisconsin group,(4) it is 24 to 1, in the Strang Clinic group. (31) This emphasizes the variability in cancer detection, which is probably related to age, racial,

(27)

and ethnic differences as well as the criteria used by the pathologist in differentiating between dysplasia and in situ carcinoma.

Table VII points out the different rate of cancer detection in 5 of the community programs. In all cases the rescreen patients were taken out of the same group reported upon in the initial statistics. There was a decreased percentage yield of both invasive and in situ carcinoma in the rescreen groups, but the decrease was noted to be more marked in the invasive group. This is compatible with our knowledge of the natural history of carcinoma of the cervix. It seems conceivable that with adequate screening of all the population, invasive carcinoma could be eliminated.

Reagan (26) quotes a series of 338,000 women who had initial cervical smears. He states that the detection rate of carcinoma in situ for the initial smear was 3.3 cases per 1,000 women, while the detection rate for invasive carcinoma of the cervix was 2.7 cases per 1,000. This has a high degree of correlation with the average detection rate per 1,000 in the five series reported in table VII. In this table, a total of 368,564 patients were studied. The average detection rate for carcinoma in situ of the cervix was 3.9 cases per 1,000 women while the detection rate for the invasive form was 2.7 cases per 1,000 women. In Reagan's report (26) he states that 20,000 of the initial 338,564

(28)

patients were followed with a second and a third smear. The
detection rate after the third smear for carcinoma in situ was
avout one-eighth the initial detection rate while that for the
invasive form was only about one-fourth the initial rate. This
would mean that after the third smear he was able to detect
only about 0.4 cases of carcinoma in situ per 1,000 women while
he was able to detect about 0.7 cases of invasive carcinoma per
1,000 women. This latter finding is in direct contradiction to
the conclusions drawn from the results listed in table VII.

Soule and Dahlin (33) list an initial detection rate of
7.5 cases of carcinoma per 1,000 patients examined in a series
of 110,000 cervical smears. 800% of these (.36 per 1,000
women examined) were infiltrating carcinomas of the cervix.
In their repeat group of smears they had a cancer detection
rate of 1.9 cases per 1,000 patients. They do not list their
smears as to whether the patients had one or more repeat smear.
They also do not categorize their patients as to in situ or
invasive carcimona of the cervix. In this series the rescreen
cancer detection rate was about one-fourth the initial pick
up rate.

Sedlis, et. al. (30) feel that you should detect 1.6
cases of carcinoma per 1,000 women for class 2 smears, 3.7
cases per thousand for class 3 smears, and 1.5 cases per
thousand for class 4 smears. This is summed to mean they
expect 6.8 cases of carcinoma in the female genital tract

(29)

per 1,000 women examined. This is compatible with the previous articles listed.

Ashe, Arey, and Williams (1) show the incidence of carcinoma in situ to be 7.6 cases per 1,000 women examined. They also show the incidence of squamous cell carcinoma to be 1.0 case per 1,000, and adenocarcinoma to be 0.82 case per 1,000. This means their detection rate for carcinoma of the genital tract is 9.5 cases per 1,000 women examined. Neither Ashe, et. al. nor Sedlis, et.al. state whether their detection rate was for the initial smear or whether it was for their whole series.

In the series presented in this thesis, the detection rate for all carcinomas of the genital tract discovered with initial and repeat smears was 6.3 cases per 1,000 smears taken. This figure is estimated to fall between 8 and 9 cases of carcinoma per 1,000 women examined. This is a comparable figure with these of other major series previously presented. See table VIII (see Appendix I) for a comparison of the detection rate of cancer of the genital tract by cytologic procedures as presented above.

Table IX (see Appendix I) compares the histologic diagnosis of biopsy of the cervix to the smear classification. This material represents the proportion of carcinomas found in each class of smear. In the series published by Sedlis, et. al. (30) a total of 71 in situ carcinomas, 52 invasive carcinomas, and 9 from other parts of the genital tract was

found. Of the in situ carcinomas about 12.7% were preceded
by class 2 smears, 73.3% by class 3 smears, and 14.1% by class
4 smears. In the invasive carcinomas detected 5.8% were
preceded by class 2 smears, 44.3% were preceded by class 3
smears, and 50.0% were preceded by class 4 smears. The
incidence of carcinoma in the class 2 smears was 5.0%. In the
class 3 smears, the incidence was 35.7% and in the class 4
smears it was 85.7%.

Maisel, et. al. (20) published a series with 133 in situ
carcinomas, 48 invasive carcinomas, and 13 carcinomas of other
parts of the genital tract. In their series they do not list
any follow-up of class 2 smears and evidently considered them
insignificantfor detection of carcinoma. Of their in situ
carcinomas 37.6% were preceded by class 3 smears and 62.4%
were preceded by class 4 smears. Of their invasive carcinomas
29.2% were preceded by class 3 smears and 70.8% by class 4
smears. The incidence of carcinoma in their class 3 smears
was 12.4% and in their class 4 smears was 75.4%.

Ashe, et. al. (1) reported on a total of 33 in situ
carcinomas. In their work 0.9% of the class 2 smears were
followed by biopsies positive for in situ carcinoma, 54.3%
of the class 3 smears were followed by biopsies positive
for in situ carcinoma, and none of the class 4 smears were
followed by biopsies positive for in situ carcinoma.

In the series presented in this paper 3.1% of the atypical
smears were followed with biopsies positive for carcinoma,

(31)

21.5% of the dysplastic smears were followed with positive
biopsies, and 75.6% of the suspicious smears were followed
by positive biopsies. No attempt was made to determine what
percentage of the positive biopsies following atypical and
dysplastic smears were diagnostic of in situ carcinoma.

This information presented in the above 4 series points
out that class 2 is not truly a negative category. Even
though it is impractical to biopsy all the patients with class
2 smears, the patient should be considered for biopsy if she
continues to have repeat class 2 smears. That is, if she
does not revert back to completely negative smears. It also
points out that class 3 smears are apparently followed by a
higher percentage of in situ carcinomas than are class 4
smears. Thus a patient with a class 3 smear should have a
biopsy to rule out in situ carcinoma of the cervix if we are
to be certain of not missing a significant number of carcinomas.
It also seems practical to conclude that if a patient has a
class 4 smear and a negative biopsy, extreme caution should be
used before accpeting the adequacy of the biopsy. If the
biopsy is accepted as adequate then carcinoma should be
suspected in other parts of the genital tract. This is the
safe approach and after all sites of carcinoma have been
ruled out then we can accept the class 4 smear as a false
positive. Lund (18) points out that we must have false
positive smears if we are to detect all the cases of carcinoma.
It is better to have a sensitive test since the biopsy is a very

specific test. Lund (18) also feels that if 20% of the class
4 smears are falsely positive, this is acceptable. In the
material reviewed in this paper it seems that a 20% incidence
of false positive smears is too high.

V. Summary.

If carcinoma of the cervix is discovered in the early
stages (stage 0 or 1) it is usually curable. The cervical
cytologic smear is at present the best means of making
the diagnosis while it is in the early stages. About 29,000
United States women are diagnosed to have cervical carcinoma
a year, and about one third this number die from it. Since
only 5-8% of the female population have routine cervical
cytologic smears it is felt that the mortality rate could
be greatly reduced if we had better population screening.

In this thesis the proper methods of collecting and
preparing a cervical cytologic smear are briefly described,
and the methods of reporting these smears are discussed in
detail. Also a series of 30,657 cervical vaginal smears from
a private physician's laboratory is presented and analyzed.
Finally this original work is compared with similar studies
reported in the literature. (from 1956 to 1965) All smears
are reported in one of 4 clases. The class 2 smears are
atypical, the class 3 smears are dysplastic, and the class
4 smears are suspicous for malignancy.

In studies where cervical biopsies and smears were
taken simultaneously it was found that for all the carcinomas
diagnosed by biopsy an average of 8% were preceded with class

2 smears, 44% were preceded with class 3 smears, and 48% were preceded with class 4 smears. In studies where the patient was first examined by smears and then, if indicated, followed with biopsies, the average incidence of carcinoma was found to be 4% in the class 2 smears, 23% in the class 3 smears, and 79% in the class 4 smears.

The average ratio of in situ to invasive carcinoma of the cervix detected by initial cervical vaginal smear is 1.8 to 1. This ratio is thought to increase if women have previously had negative smears but conflicting series are reported in the literature.

Cervical swab or cervical scrape smears are superior to vaginal aspiration smears in the detection of cervical carcinoma, but no consistency is noted in comparing the ability of the vaginal and cervical smears to detect endometrial carcinoma.

VI. Conclusions.

The cervical cytologic smear should be started at age 20 years and then taken at two year intervals. If the patient has had children it should be started earlier. All patients with class 2 smears should be followed with repeat smears at 6 month intervals until the smears are reported as negative. If the patient continues to have class 2 smears an adequate cervical biopsy should be taken to rule out carcinoma.

Patients having class 3 smears should either be followed with repeat smears at 3 month intervals or have adequate cervical biopsy to rule out carcinoma. If the class 3 smear is followed with negative repeat smears this can be considered an adequate follow-up, but if the patient continues to have subsiquent class 2 or 3 smears she should have an adequate cervical biopsy. This is because there is a high incidence of carcinoma following class 3 smears, and also because the proportion of carcinoma in situ is higher following class 3 smears, than following class 4 smears.

All patients having class 4 smears should be followed with adequate cervical biopsy to rule out carcinoma. If the biopsy is read as a negative biopsy extreme caution should be used before accepting the adequacy of the negative biopsy. If the biopsy is still considered adequate the physician must

diligently rule out all possible sites of carcinoma in the female genital tract before he can accept the smear as being falsely positive. (The incidence of false positive cervical smears is probably between 3 and 10% in good laboratories.)

The cervical smear should not be relied upon to rule out carcinoma of the endometrium. Its detection rate for endometrial carcinoma can be improved by inserting the swab deep into the endocervical canal but still the incidence of false negatives is too high to be used to rule out endometrial carcinoma. Because of these shortcomings the endometrial brush will probably become popular for diagnosis of endometrial carcinoma.

APPENDIX I

Table III.

Results of Screening
For Pelvic Carcinoma.(6)

Program	Number of Women	Carcinomas Detected		Clinically Unsuspected %
		Number	Rate/1000	
Mayo Clinic Rochester, Minn. (32)	139,503	987*	7.1	—
Ohio State Univ. Columbus(2)	113,258	453	4.0	72
Memphis, Tenn (8)	108,136	786	7.2	64
Madison, Wisconsin State Lab.(4)	65,163	750	11.5	43*
Mecklenberg County N.C.(16)	48,697	432	8.9	63
San Diego, Calif. (7)	33,746	359	10.6	—
Toledo Ohio (3)	29,687	292	9.8	34
Honolulu Hawii (25)	24,182	141	5.8	45+
Strang Clinic New York(31)	19,462	57	3.9	70
Floyd County, Ga.(22)	17,761	84*	4.8	73
Yates Clinic, Detroit, Mich(5)	15,832	151	9.6	43
Total	615,927	4,492	7.3	—

* cervix only

Table IV. Comparison of Methods Used and Anatomical Types of Carcinoma Detected. (6)

Program	Number of women	Method	Carcinomas Detected		Carcinomas of Cervix Detected		Carcinomas of Corpus Detected		Other carcinomas Detected	
			Number	Rate*	Number	Rate*	Number	Rate*	Number	Rate*
Ohio State Univ. Columbus (21)	113,758	Cervical Scrape and/or vaginal Asp.	453	4.0	388	3.4	49	0.4	16	0.1
Memphis, Tenn. (12)	108,136	Vaginal Asp.	780	7.3	724	6.7	49	0.4	20	0.2
Wisconsin State Lab. Madison (4)	65,163	Vaginal Asp.	750	11.5	548	8.4	154	2.4	43	0.7
San Diego, Calif (7)	33,746	Cervical scrape	359	10.6	343	10.1	16	0.5	—	—
Honoluu Hawii (25)	24,182	Vaginal Asp. and/or cervical Swab	141	5.8	134	5.5	2	0.1	5	0.2
Strange Clinic New York (31)	19,462	Vaginal Asp. and cervical swab	57	2.9	48	2.5	7	0.3	2	0.1
Total	364,447		2546	7.0	2185	6.0	275	0.8	86	0.2

* Rate per 1000

Table V. Cytologic Finding in 77
Patients with Carcinoma In Situ
of the Cervix and 29 Patients with
Adenocarcinoma of the Uterus.(6)

77 Patients with Carcinoma in situ of cervix seen at Strang Clinic (31)				29 Patients with Adenocarcinoma of endometrium Seen at Strang Clinic (31)				
V A Findings	Cervical Swab		Vaginal Aspiration		V B Findings	Cervical Swab		Vaginal Aspiration	
	NO.	%	NO.	%		NO.	%	NO.	%
Class 4	56	72.7	16	20.8	Class 4	5	17.2	16	55.1
Class 3	19	24.7	18	23.4	Class 3	7	24.2	6	20.7
Class 2	1	1.3	28	36.3	Class 2	5	17.2	0	—
Negative	0		14	18.2	Negative	12	41.4	7	24.2
Total	77	100.0	77	100.0	Total	29	100.0	29	100.0

* Taken from Strang Clinic Study

Table VI. Comparative Detection of In Situ and Invasive Carcinoma of The Cervix on Initial Screening.(6)

Group Doing the Study	Number of Women	Total Number Carcinoma of cervix		Carcinoma In Situ of Cervix			Invasive Carcinoma of Cervix		
		Number	Rate per 1000	Number	Rate per 1000	Percent Suspected	Number	Rate per 1000	Percent Suspected
Mayo Clinic Rochester, Minn (32)	139,503	987	7.1	897	6.4	—	90	0.7	—
Ohio State Univ. Columbus (21)	113,758	388	3.1	213	1.9	89	175	1.5	61
Memphis, Tenn (8)	108,136	724	6.7	393	3.6	90	331	3.1	30
Wisconsin State Lab Madison (4)	65,163	548	8.4	195	3.0	74	353	5.4	27
Mecklenberg County N.C. (16)	48,697	412	8.5	290	6.0	—	122	2.5	—
San Diego, Calif. (7)	33,746	336	10.0	259	7.7	—	77	2.3	—
Honolulu Hawii (25)	24,182	134	5.5	51	2.1	94	83	3.4	18
Strong Clinic (31)	19,462	48	25	46	2.4	90+	2	0.1	—
Floyd County Ga. (22)	17,761	84	4.8	56	3.2	92	28	1.6	35
Total	570,408	3661	6.4	3,400	4.2	—	1261	2.2	—

Table VII. Results of Rescreening Patients for Carcinoma of Cervix Uteri.(6)

Name of Study Group	Initial of Follow-up smear number	Number of Women	Carcinoma In Situ		Invasive Carcinoma	
			Number	Rate* per 1000	Number	Rate* per 1000
Memphis Tenn. (8)	First	108,136	393	3.6	331	3.1
	Second	32,728	72	2.2	9	0.3
Wisconsin State (4) Laboratory Madison	First	65,163	206	3.2	335	5.1
	Second	9,111	10	1.1	4	0.4
Floyd County Georgia (22)	First	17,761	56	3.2	28	1.6
	Second	4,482	12	2.7	4	0.9
Ohio State University Columbus (21)	First	113,758	213	1.9	175	1.5
	Second	44,009	40	0.9	7	0.2
	Third	16,137	2	0.1	2	0.1
San Diego Calif. (7)	First	33,746	265	7.8	78	2.3
	Second	9,725	34	3.5	2	0.2
	Third	4,213	6	1.4	–	–
	Fourth	1,654	–	–	1	0.6

* Rate per 1000 women examined with repeat smears

Table VIII. The Detection Rate of Cancer of The Female Genital Tract Using Cytologic Methods.

Name of Group Doing the Study	Cancer Detection Rate of initial Smear: cases per 1000*	Cancer Detection Rate of Repeat Smear: cases per 1000*	Cancer Detection Rate of Both Initial and Repeat smears cases per 1000*
Ohio State Univ. (21)	3.4	0.6	4.0
Memphis, Tenn. (8)	6.7	3.9	10.6
Wisconsin State Lab.(4)	8.4	3.1	11.5
San Diego, Calif. (7)	10.0	0.6	10.6
Honolulu, Hawii (25)	5.5	0.3	5.8
Strang Clinic N.Y.(31)	2.5	0.4	2.9
Reagan (26)	6.0	1.1	7.1
Soule and Dallin(33)	7.5	1.9	9.4
Sedlis et. AL. (30)	—	—	6.8
Ashe, Arey and Williams (1)	—	—	7.5
Physicians Lab. Omaha	—	—	6.3* +

* This is cases/1000 women in all cases except for the Physicians Laboratory which is cases/1000 smears. In the repeat smear group the rate is listed as cases per 1000 women. The women being the total number of women studied for the whole series.

+ 6.3 cases/1000 smears is estimated to be about 8-9 cases/1000 women examined.

Table IX. The Relationship Between the Grade of Cervical Cytologic Smear and the Presence of Carcinoma.

Name of Group Doing the Study	Diagnosis of smear using a class 1-4 classification	Number of patients or smears*	Number of In Situ Carcinoma of the cervix	Number of Invasive Carcinoma of the cervix	Number of other types of Carcinoma**	Number of Cervical Carcinoma type and grade not listed	Number of Benign Biopsies of the cervix	Number of Benign Biopsies called cervical dysplasia	Number of other Biopsies of the cervix
Sedlis Weingold Wilsey Stone	2	239(P)	9	3	0	0	75	17	58
	3	235(P)	52	23	9	0	116	61	55
	4	42(P)	10	26	0	0	2	2	0
(30)	Total	516(P)	71	52	9	0	193	80	113
Maisel Nelson Ott Morgenstern(20) Van Ravensby	2	–	–	–	–	–	–	–	–
	3	583(P)	50	14	8	0	434	47	387
	4	162(P)	83	34	5	0	38	26	12
	Total	745(P)	133	48	13	0	472	73	399
Ashe Arey Williams	2	111(P)	1	0	0	0	–	–	–
	3	59(P)	32	–	–	1	–	–	–
	4	12(P)	–	–	–	7	–	–	–
(1)	Total	182(P)	33	–	–	8	–	–	–
Physicians Laboratory Omaha Nebraska	Atypical	19(S)	–	–	–	6	–	–	–
	Dysplastic	121(S)	–	–	–	26	–	–	–
	Suspicous	201(S)	79	47	12	12	36*	–	–
	Total	513	79	47	12	44	36	–	–

** This includes all carcinomas that were not found in the cervix.

* If P appears after the number it represents number of patients but if s appears after the number it represents the number of smears.

* Of these 36 negative biopsies 21 were estimated by the pathologist to be inadequate to R10 carcinoma

APPENDIX II

Graham, et. al. (10) described the following method
of staining smears for cytologic interpretation. The
procedure is as follows:

1. 10 dips into 70% ethyl alcohol
2. 10 dips into 50% ethyl alcohol
3. 10 dips into distilled water
4. 3 minutes in Harris Alum Hematoxylin
5. 1 minute under running tap water
6. 1 minute in a diluted solution of Lithium carbonate
7. 1 minute under running tap water
8. 10 dips into 50% ethyl alcohol
9. 10 dips into 80% ethyl alcohol
10. 10 dips into 95% ethyl alcohol
11. 1 minute in Orange G-6
12. 10 dips in 95% ethyl alcohol
13. 10 dips in 95% ethyl alcohol
14. 2 minutes in E. A. 50
15. 10 dips in 95% ethyl alcohol
16. 10 dips in 95% ethyl alcohol
17. 10 dips in 95% ethyl alcohol
18. 4 minutes in absolute alcohol
19. 5 minutes in xylol

The slides are now mounted in neutral canada balsam.

Harris alum hematoxylin is made as follows:

hematoxylin	1 gm.
absolute alcohol	10 cc's
ammonium or potassium alum	20 gms.
distilled water	200 cc's
mercuric oxide	0.5 gms.

Orange G-6 is made as follows:

orange G (National Aniline & Chemical Co.)	100 cc's of a 0.5% solution in 95% ethyl alcohol
acid phosphotungtic (Merck)	0.015 gms.

E A-36 is made as follows:

light green S,F. yellowish (National Aniline and Chemical Co.)	0.5% solution in 95% ethyl alcohol 45 cc's
bismark brown (National Aniline and Chemical Co.)	0.5% Solution in 95% ethyl alcohol 45 cc's

eosin yellowish (National Aniline and Chemical Co.)	0.5% solution in 95% ethyl alcohol 45 cc's
acid phosphotugstic (Merk)	0.200 gms.
lithium carbonate saturated aqueous solution	1 drop

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BIBLIOGRAPHY

1. Ashe, J. R., Arey, J. V. and Williams, J. O.,
   The Abnormal Cytologic Smear, Am. J. Obst. Gynec.
   87:320-325, 1963.

2. Boschann, H. W., Endometrial Cytology, Cancer
   10:194, 1960.

3. Burns, E. L. and Gorski, T. W., Five-year Cure Rate
   of Clinically Occult and Suspected Uterine
   Carcinomas: A Community Cancer Detection Program,
   J.A.M.A. 166:568, 1958.

4. Calibresi, Paul, Arnold, N. V. and Stovall, W. D.,
   Cytologic Screening for Uterine Cancer Through
   Physicians Office, J.A.M.A. 168:243, 1958.

5. Dale, E. H. and others, The Role of Exfoliative
   Cytology in the Diagnosis of Carcinoma of the
   Cervix Uteri, Am. J. Obst. Gynec. 74:25, 1957.

6. Day, Emerson, Evaluation of Exfoliative Cytology
   as a Screening Method for Pelvic Cancer, Clinical
   Obst. and Gynec. 4:1183-1197, (Dec.) 1961.

7. Dunn, J. E. and others, Finding for Uterine Cancer
   From One or More Cytologic Examinations of 33,750
   Women, J. Nat. Cancer Inst. 23:507, 1959.

8. Erickson, C. C. et. al., Population Screening for
   Uterine Carcinoma by Vaginal Cytology: Preliminary
   Summary of Results of First Examination of 108,000
   Women and Second Testing of 33,000 Women, J.A.M.A.
   162:167, 1956.

9. Graham, R. M., The Cytologic Diagnosis of Cancer,
   2nd Ed. Philadelphia and London, W. B. Saunders Co.,
   1963, p. 331-334.

10. Graham, R. M. and others, The Cytologic Diagnosis of
    Cancer, 1st Ed., Philadelphia and London, W. B.
    Saunders Co., 1950, p. 209-211.

11. Green, T. H., Jr., Gynecology, Cited by: Nardi, G. L.
    and Zuidema, G. D., Surgery A Concise Guide To
    Clinical Practice, 1stEd., Boston, Little, Brown
    and Co., 1961, p. 659.

12. Hecht, E. L., The Endometrial Aspiration Smear:
    Research Status and Clinical Value, Am. J. Obst.
    Gynec. 71:819, 1956.

13. Hotmeister, F. J. and Barbo, D. M., Cancer Detection
    in Private Gynecological Practice: A Concluding
    Study, Obst. and Gynec. 23:386-391, 1964.

14. Jordan, M. J., Bader, G. M. and Nemazie, A. S.,
    Comparative Accuracy of Pre-operative Cytology
    and Histologic Diagnosis in Endometrial Lesions,
    Obst. and Gynec. 7:646, 1956.

15. _____, New Cannula for Obtaining Endometrial
    Material for Cytologic Study, Obst. and Gynec.
    8:611, 1956.

16. Kimmelstiel, Paul, Bos, J. F. and Nolen, Connaree,
    Community Survey for Uterine Cancer, Obst. and Gynec.
    11:688, 1958.

17. Larsson, Elizabeth and Webb, Alan, Cancer Survey:
    Experiences in Mass Screening of Cervical Smears,
    Obst. and Gynec. 22:630, 1963.

18. Lund, C. J., An Epitaph for Cervical Carcinoma,
    J.A.M.A. 175:298, 1961.

19. McCormack, L. J. and others, Symposium: Carcinoma
    of the Cervix - Technique of Methods for Diagnosis,
    Postgraduate Medicine 32:253-254, 1962.

20. Maisel, F. J. and others, Papanicolaou Smear, Biopsy
    and Conization of Cervix, Am. J. Obst. Gynec.
    86:931-936, 1962.

21. Miller, E. M. and VanHaam, E. A., A Comparison of
    the Vaginal Aspiration and Cervical Scraping
    Technique in the Screening Process for Uterine
    Cancer, Acta Cytol. 5:214, 1961.

22. Nieburgs, H. E. and others, Mass Screening of the
    Female Population of a County for Cervical Carcinoma,
    J.A.M.A. 164: 1546, 1957.

23. Parker, R. T., et. al. Intraepithelial (Stage O)
    Cancer of the Cervix, Am. J. Obst. Gynec. 80:693,
    1960. Cited by: Scott, R. B. and Ballard, L. A.,
    Cytology and Its Office Application as Viewed by
    the Clinician, Clinical Obst. and Gynec. 5:179-195
    (March) 1962.

24. Parson, Langdon and Sommers, S. C., Gynecology, 1st Ed., W. B. Saunders Co., 1962, pp. 682-700, pp. 887-947.

25. Quisenberry, W. B., Cytologic Detection of Cancer in Hawii, Postgraduate Medicine 21:179, 1957.

26. Reagan, J. W., Recent Advances in the Use of Cytological Studies in the Diagnosis of Cancer of the Uterus, Academy of Medicine of New Jersey Bulletin 8:210-217, (Dec.) 1962.

27. Reagan, J. W., and Hamonic, M. J., The Cellular Pathology in Carcinoma In Situ; A Cytohistopathological Correlation, Cancer 9:385, 1956.

28. Reagan, J. W., and Patten, S. F., Jr., Cytology and Its Application as Viewed by the Pathologist, Clinical Obst. and Gynec. 5:167-178 (March) 1962.

29. Scott, R. B. and Ballard, L. A., Cytology and Its Office Application as Viewed by the Clinician, Clinical Obst. and Gynec. 5:179-195 (March) 1962.

30. Sedlis, Alexander and others, Cytology Screening for Cervical Cancer in a Municipal Hospital, Cancer 17:152-158, 1964.

31. Simon, T. R., Durfee, G. R. and Ricci, A. G., The Value of the Vaginal Aspiration as Compared With the Cervical Swab Smear in the Detection of In Situ Carcinoma of the Cervix and Adenocarcinoma of the Fundus, Transactions of the Third Annual Meeting of the Inter-Society Cytology Council Cleveland, Inter-Society Cytology Council 1:10, 1955.

32. Soule, E. H. and Dablin, D. C., Cytodetection of Preclinical Carcinoma of the Cervix: 12 Years Experience With Initial Screening and Repeat Cervical Smears, Proc. Staff Mayo Clinic 35:508, 1960.

33. _____, Cytodetection of Preclinical Carcinoma of Cervix: 10 Years Experience With Initial Screening and Repeat Cervical Smears, Proc. Staff Meeting Mayo Clinic 34:1-8 (Jan. 7) 1959.

34. Talbott, J. H., Mayo, R. W. and Burgess, L. G., Carcinoma of the Cervix, J. A.M.A. 182:674, 1962.