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Follow-up of previously negative cervical smears : a 5-year follow-up of cervical smears of 750 private patients

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THE FOLLOW-UP OF PREVIOUSLY NEGATIVE
CERVICAL SMEARS
A 5 Year Follow-up of Cervical Smears
of 750 Private Patients

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I. INTRODUCTION:

Methods of diagnosis and treatment of cancer in recent years have advanced rapidly. However, in most patients, even with new methods of diagnosis and treatment, the total salvage from carcinoma is far from desirable, for by the time the cancer is clinically recognizable, local extension and distant metastases have taken place. This unfortunate occurrence is due either to the rapid invasiveness of the cancer after its unsuspected or unavailable location, where it smolders many years before detection.

The uterine cervix is the second most common site of cancer in American women; accounting for 10% of all newly diagnosed cancer, 10% of the total cancer deaths, and 1600 deaths in American women every year. This large number of carcinomas originates from the surface epithelium of this small organ.

It has now become almost universally accepted, that the Stage-0, or intraepithelial carcinoma is the precursor of invasive carcinoma, and that it may remain dormant for many years before becoming malignant. The cure rate of intraepithelial carcinoma treated by total hysterectomy is stated by most authors to approach, if not equal 100%. Even total excision by a wide cone

biopsy is from 85% or more curative according to some authors. (1) From this we can reasonably conclude that the mortality from this relatively frequent and highly destructive carcinoma could be almost, if not entirely eliminated, if all cases could be discovered in the pre-invasive state. The exact duration of dormancy of the pre-invasive lesion has not been ascertained, but most authors place the average at between five and ten years. (2) What is not known, is the frequency with which intraepithelial carcinoma becomes invasive in a relatively short time following its origin, say under one or two years. (3) If this were known, a rational approach could be developed as to the length of time which could be safely allowed between successive cytologic screening procedures on women with previously negative cervical cytology. This of course, is quite difficult to compute because of the almost universal practice of surgically excising the intraepithelial carcinoma as soon as it is diagnosed. Furthermore, the diagnosis of intraepithelial carcinoma cannot be definitely made without cone biopsy of the cervix to establish that the suspected non-invasive lesion is not merely a peripheral portion of a nearby invasive lesion, as is commonly seen.

The purpose of this paper is to attempt to determine if possible, how carcinoma of the cervix can be diagnosed early, and thus be cured. Cytologic screening is assumed to be an inseparable part of such a program. An attempt will be made to determine how frequently cytologic screening should be done in relation to known benign cervical pathology. In doing this, possible predisposing factors of carcinoma of the cervix, duration of intraepithelial carcinoma, and age specific incidence will be discussed.

II. HISTORY:

Carcinoma in situ was first described by Rubin, (4) who in 1910, reported two cases in which the tissue in question appeared identical in cellular detail to that of carcinoma of the cervix, but with no invasion of stromal tissues. He described this lesion as incipient carcinoma. Shortly after this in 1912, Schottlander and Kermauner (5) reported the similarity between carcinoma in situ and nests of cells in the epithelium at the periphery of invasive cervical carcinoma. In 1937, Schiller (6) described these as identical with the invasive carcinoma, except for an intact basement membrane. Until recently, much controversy has existed over the significance of carcinoma in situ; whether it was a

completely benign lesion; or if the lesion invariably became invasive. Over 40 cases have been reported in the literature in which carcinoma in situ has been followed and observed to progress into invasive cervical carcinoma. It is now generally agreed that many carcinomas in situ are potentially invasive, but the frequency with which these actually become malignant, or the frequency with which invasive carcinoma is preceded by carcinoma in situ for a clinically significant duration is not known.

III. METHODS OF DIAGNOSIS:

Twenty-five years ago the diagnosis of cervical carcinoma was usually made by biopsy of grossly visible lesions. The public education program was dedicated toward having women see their physician at the first sign of abnormal vaginal bleeding. In view of the frequent absence of symptoms in association with carcinoma in situ; and relatively frequent paucity of symptoms in the earlier stages of invasive carcinoma; it is not surprising that most cases were picked up in the later stages, and that the cure rate was discouragingly low.

Histologic diagnosis of tissue biopsy is the only method by which the final diagnosis of carcinoma of the cervix can be made. Only by this method can the

source of malignant cells be identified; invasiveness of the cells, and extent of the lesion be defined. This method possesses several real disadvantages when considered as a screening procedure. The two most important disadvantages of biopsy are the high cost, and the question of where to biopsy when no lesion is grossly visible.

The Schiller test has been used fairly extensively in the past, and to a lesser extent today; for the diagnosis of cervical carcinoma. The basis for the test is the failure of some abnormal cervical cells to take the iodine stain because of their lack of glycogen content. Cervical carcinoma, leukoplakia, erosions, and ulcerations fail to take the iodine stain, and areas of chronic cervicitis take the stain poorly. The lesions must then be biopsied for histologic diagnosis. The Schiller test is effective in detecting malignancies, but so many non-malignant lesions appear indistinguishable from carcinoma; a great many false negative biopsies must be performed. Hunter (7) found that in 152 cervixes which had a positive Schiller test, 22 had cervical carcinoma. The Schiller test is useful in pointing out an area to biopsy; but is inferior to the cervical smear for cervical cancer screening, and is not widely utilized today.

Early in the 1900's Papanicolaou was assaying the effects of female hormones on vaginal and cervical epithelium by studying the exfoliated cells in the vaginal pool. Although he occasionally hinted as to the possibility of cancer detection, he did not report this aspect of his studies until 1928, when he described the characteristics of exfoliated malignant cells. His work went almost unrecognized until 1943, when he published his famous monograph. (8) Since then, interest in vaginal cytology has rapidly spread, and is now utilized to a great extent throughout the world as a screening procedure. Unfortunately, vaginal cytology was held by some, to be a procedure competitive with cervical biopsy. But as experience with cytology broadened, it gradually evolved as an invaluable compliment to the biopsy - both possessing assets the other lacked. In contrast to the biopsy, cytologic studies are relatively inexpensive, and by its nature is in effect a surface biopsy of the cervix, part of the vagina, and in many cases of the endometrium.

Cytology, however, cannot show the origin of the cells, and the extent of the lesion, the latter especially important in diagnosing carcinoma in situ.

Cytologic methods have been well-suited for

mass screening programs, the positive smears supplemented by a biopsy. In a recent review of the literature by Collings, (9) 40 series representing 196,389 women were compiled to determine the accuracy of cytology smears. The overall accuracy of cytology smears was 94.3% in detecting carcinoma. The 5.7% of false negatives were usually from far advanced, clinically recognizable lesions which shed necrotic degenerate cells, or from very early lesions not yet desquamating many cells.

(9)

The case records of 157 patients in whom cervical carcinoma was discovered in the years 1951 to 1957, inclusive, at the University of Nebraska Hospital were reviewed to see if any previous negative cervical cytological smears had been taken. Three cases were found in which previous negative smears were reported; two cases four years prior to detection of carcinoma, one case one year before. These slides were re-examined, and all were considered "Suspicious for Malignancy." These three false negatives represent an incidence of 2%; much lower than an average of the 40 series reported by Collings in 1955. Undoubtedly, the rate of false negatives in this series would have been much higher if more previous smears had been done.

Various techniques have been proposed for the collection of desquamated cells. In his monograph in 1943, Papanicolaou suggested collecting secretions from the posterior fornix by a bulb syringe attached to a glass pipette. (8) This was endorsed by Graham, because this pool contains an abundant supply of endometrial cells, thus increasing the number of endometrial carcinomas incidently diagnosed. (10) Ayre in 1946, believing that surface scrapings of the cervix at the squamo columnar would yield a higher accuracy of the cytologic smear, designed a wooden spatula for this purpose. (11) Brunschwig, in 1954 reported the use of a specially prepared tampon for the "self collection" of vaginal secretions. The results from this method are very satisfactory, and may prove very useful in mass screening tests, as they require a minimum of professional time. (12) It has been emphasized that these screening procedures should not replace careful periodic pelvic examinations. (Nieburgs) (13)

Other methods of diagnosis include phase contrast microscopy, colposcopy, and colpomicroscopy, as reported by Antoine. These are all useful adjuncts in diagnosis, but are not adaptable for mass screening procedures. (14)

IV. PREDISPOSING FACTORS TO CARCINOMA OF CERVIX:

It has long been known that the frequency of carcinoma of the cervix varies significantly between certain groups of people. This variation occurs not only along racial lines, but varies as to age, parity, exposure to intercourse, and incidence of cervical infection. These factors are important both as to a possible prevention of carcinoma of the cervix, and as regards the intensity with which a particular group of women should be followed to discover carcinoma in its earliest stages.

There are many reports of the racial difference in the incidence of cervical cancer. Jewish women have been shown to have an incidence $1/6$ that of other white women in the United States. The incidence of carcinoma in situ is similar - $1/5$ as common in Jewish women. The Moslems and Fiji Islanders also have a low incidence; whereas the orientals have a much higher incidence of carcinoma of the cervix as compared with white American females. As many as 40% of newly diagnosed cases of carcinoma are of the cervix in some reports from the orient. Many factors have been reported to be responsible for this difference of incidence, such as the relative frequency of chronic cervicitis; differences of diet;

use of coal tar douches; age of first coitus; number of pregnancies; circumcision of the male; and hereditary factors. The Moslems, Jews, and Fiji Islanders, each of whom have a low incidence of carcinoma of the cervix, uniformly practice circumcision of the male. (15) The exact significance of this is not known. Poor penile hygiene is much more frequent in non-circumcised males. Some authors believe that this is related to carcinoma of the cervix by causing chronic cervicitis in the female; others believe that the smegma itself is carcinogenic. It is a significant fact that carcinoma of the penis is also more common in uncircumcised males.

Chronic cervicitis is believed by some to be an important predisposing factor to carcinoma of the cervix. Gognan treated and cured 3,000 cases of chronic cervicitis, and during the time of his follow-up, found no carcinomas of the cervix. He believes that this may account for the low incidence of cervical carcinoma in nulliparous females. Karnoky similarly cured 5,000 cases of carcinoma of the cervix in a follow-up study. Pemberton and Smith found the same to be true in 1,408 cases of cervicitis which they cauterized. Phaneuf biopsied 100 patients with advanced cervicitis, and found that 10% showed carcinoma. Wynder, in his study

says that the incidence of chronic cervicitis, and of carcinoma of the cervix correlates well with the exposure to intercourse; and that after this factor is eliminated, he could find no significant variation between the incidences of cervical carcinoma between nulliparous and parous women. Towne reviewed the records of 13,000 nuns for a 20 year period, and found only 6 cases of cervical malignancy; (16) Gaynors, in a similar review failed to find a single case of cervical cancer among the histories of the 13,000 nuns that he reviewed. Conversely, Pajel from Denmark, found that prostitutes had four times the normal incidence of cervical cancer. Cervical carcinoma has been found more frequently in women with syphilis; but Wynder believes that this is secondary to the increased exposure to coitus in women with syphilis. Wynder further found a higher incidence of cervical carcinoma in women who married early, or who had their first coitus at an early age, as well as women who had multiple marriages. He believes that these factors represent an increased exposure to intercourse. He further states that exposure by more than one male may increase the incidence of carcinoma. (15)

These factors present strong evidence to support the common notion that sexual intercourse predis-

poses to chronic cervicitis, which in turn predisposes the patient to carcinoma of the cervix.

Many other factors are proposed to predispose to carcinoma of the cervix. Ayre found that in 50 patients with cervical neoplasm, 90% had excessive tissue estrogens. (15) Nieburgs, however found that of premenopausal patients with carcinoma of the cervix, 71% showed decreased estrogens, but post-menopausal cancer patients showed increased estrogens. (17)

Lombard and Patter feel that lacerations of the cervix predispose to malignancy. They found that 26% of cancer patient but only 13.2% of negative controls had laceration of the cervix. They further report that the use of the coal tar douche may account for the rather high incidence of cervical cancer in native Italians. Smith, however points out that Jewish women use a similar douche, and they have a very low rate of cervical cancer. Khanalker believes that dietary variations may account for the differences of incidence between various ethnic groups. Housdorff reports a correlation between cervical carcinoma, and irritative vaginal discharge. Wynder could find no correlation between cervical cancer and the age of menarche, method of delivery, irritative discharge, frequency of douch-

ing, or a history of gonococcal infection. (15)

Although all of the factors predisposing to cervical carcinoma, and the exact relationships of the previously mentioned factors which seem to predispose to cervical carcinoma are uncertain, it seems reasonable to assume that accurate diagnosis and adequate treatment of cervicitis, as well as such factors as circumcision of the male, and promotion of good penile hygiene should to some degree reduce the incidence of cervical carcinoma. Women with resistant, or low grade chronic infections, should be followed with periodic cytologic smears in anticipation of neoplastic change.

V. LIFE HISTORY OF CARCINOMA OF THE CERVIX:

In attempting to determine how frequently women should be screened for maximum efficiency of detection, it is necessary to consider the life history of carcinoma of the cervix. Some of the possible predisposing factors have been previously listed. These irritative factors incite epithelial hyperactivity, which in some cases, apparently progress through some mechanism now unknown, to malignancy. This remains in a non-invasive state for considerable, but variable time before becoming invasive. There are many cases reported in the literature, in which Stage-0 lesions

were followed until they became malignant. There is considerable variation in the duration of the "latent period" from time of detection, until becoming malignant. This is understandable, as the cases were detected in different stages of development; some just after inception, others just prior to becoming invasive. Also, the latent period undoubtedly varies considerably from case to case. If we would consider that about as many of these cases were detected early as were detected late, these variations would balance each other, and the average duration of the non-invasive carcinoma cases would represent $1/2$ of the duration of the average Stage-0 carcinoma. From this method, it can be seen from Table 1, the life span of Stage-0 carcinoma is on the average, 11 years, before becoming invasive. The range is 6 months to 16 years and 8 months.

As was previously mentioned, it is difficult to diagnose carcinoma in situ, to exclude invasive carcinoma and yet leave the lesion to progress into invasive carcinoma. Some of the cases which progressed early to invasiveness may have been invasive when first detected; and others seemingly lying dormant for many years, may have actually been destroyed by the initial diagnostic procedure, the invasive carcinoma arising from a new

T A B L E I

REPORTED CASES OF STAGE-0 CERVICAL CARCINOMA BECOMING INVASIVE

Smith & Pemberton (18)	1.	37 mo.	
	2.	57 mo.	
	3.	73 mo.	
	4.	150 mo.	
Schmitz & Benjamin (18)	5.	9 mo.	
Schiller (18)	6.	60 mo.) --approx.
	7.	60 mo.	
	8.	60 mo.	
Stevenson & Scapiades (18)	9.	108 mo.	
	10.	36 mo.	
Younge (18)	11.	26 mo.	
	12.	40 mo.	
Knight (18)	13.	36 mo.	
	14.	59 mo.	
Taylor & Gieger (18)	15.	84 mo.	
Goldburger & Mintz (18)	16.	72 mo.	
Pund, et al (18)	17.	45 mo.	
Younge, et al (18)	18.	11 mo.	
TeLinde & Galven (18)	19.	6 mo.	
Scheffey (18)	20.	108 mo.	
Wespi (18)	21.	36 mo.	
	22.	120 mo.	
	23.	102 mo.	
Hinselman (18)	24.	48 mo.	
	25.	36 mo.	
Hagelhorst (18)	26.	60 mo.	
Jones (18)	27.	118 mo.	
Anderson (18)	28.	118 mo.	
	29.	47 mo.	
	30.	15 mo.	
Galvin, et al (18)	31.	93 mo.	
	32.	43 mo.	
	33.	74 mo.	
	34.	178 mo.	
	35.	68 mo.	
	36.	12 mo.	
	37.	200 mo.	
	38.	84 mo.	
Carson & Gall (19)	39.	24 mo.	
	40.	60 mo.	
	41.	114 mo.	
Diddle (20)	42.	48 mo.	
	43.	18 mo.	
	44.	76 mo.	
Average Duration		66.6 mo.	

T A B L E I (Cont'd)

The average duration is 66.6 months, which represents $1/2$ life span of the average Stage-0 carcinoma. The life span would then average 133.6 months, or 11.1 years. The range is from 6 months to 200 months.

87% of the cases are over two years, 82% are over three years, and 64% are over four years duration.

carcinoma in situ many years later. It is impossible to evaluate these possibilities at present. In spite of these possibilities for error, the average duration of carcinoma in situ, calculated by this method, compares closely with the duration arrived at by subtracting the average age of carcinoma in situ patients from the average age of patients with invasive carcinoma, as will be shown.

Table II is a compilation of ten series from the literature; comparing the average age of patients with carcinoma in situ, and with invasive cervical carcinoma, and thus indirectly arriving at the average duration of carcinoma in situ. As can be seen from Table II, the average age of carcinoma in situ patients is 36.3 years; and that for invasive carcinoma is 46.1 years. The average duration of carcinoma in situ as calculated by this method is 9.8 years. These results are similar to those of Hertig and Younge; who found the average age of carcinoma in situ patients to be 36.7 years, and of invasive carcinoma to be 48 years, or an average duration of 11.3 years. (29) The average duration of carcinoma in situ as estimated by this method is seen to be very similar to the results in Table I, where the average duration is calculated to be 11.1 years.

T A B L E II

	YEAR	NO. CASES:		AV. AGE:		RANGE:	
		ST-0*	INV.‡	ST-0	INV.	ST-0	INV.
Dahlin (21)	1955	243	24	42.1	49.7	15-75	35-75
Dahlin (22)	1952	73	11	42.1	47.8	25-69	34-76
Carter (23)	1952	126	226	38.9	48.4	- -	- -
Diddle (20)	1949	17	--	36.2	43.5	- -	- -
Nieburgs (17)	1951	100	100	39.2	50.3	- -	- -
Cuyler (24)	1951	94	--	36.7	48.2	- -	- -
Achenbach (25)	1951	60	--	35.2	--	22-59	- -
Haynes (26)	1952	--	--	34.6	40.8	19-	21-
Peterson (27)	1952	30	--	38.7	--	22-67	- -
Pund (28)	1946	47	50	36.6	48.6	23-56	- -
Howard (29)	1951	14	--	47.	--	- -	- -
<u>Total</u>		904	511	<u>36.27</u>	<u>46.2</u>		

*ST-0 = Stage-0

‡INV. = Invasive

Although the duration of in situ carcinoma is important, knowing the relative frequency in different age groups will aid in deciding which age groups to screen more intensely. Carter, et al (23) in reviewing 151 cases of intraepithelial carcinoma, and 566 cases of invasive cervical carcinoma found the age distribution to be as is shown in Table III. From Table III can be seen that about 80% of the cases of intraepithelial carcinoma occur between the ages of 25 and 50. One important feature, as shown by Table III, is that 20% of the cases occur under the age of 30. Achenbach, (25) in a review of 60 cases of carcinoma in situ, found that 25% of the cases were under 30 years of age. If carcinoma of the cervix is to be adequately controlled, women in the 20-30 year age group must be screened. The women who are between 30 and 45 years, in which about 55% of the cases occur, must be screened more intensely.

Mass cytologic screening procedures for cervical carcinoma have been utilized for over five years, and reports are starting to be published on follow-ups of women with previously negative Papanicolaou smears.

Martin, et al (31) in 1953, screened 11,000 patients, and found 105 cases of carcinoma of the cervix. In 6,060 patients who were screened again a year or more

T A B L E III

FROM CARTER (23)

CA. IN SITU - TOTAL 115 PTS. INVASIVE CA. - TOTAL 556 PTS.

	NUMBER	PERCENT		NUMBER	PERCENT
20-24	12	7.9	} 20%	4	.7
25-29	20	13.2		24	4.2
30-34	27	17.8	} --77.3%	58	10.2
35-39	28	18.5		74	13.1
40-44	27	17.8		65	11.5
45-49	15	10.0		90	16.0
50-54	7	5.0		80	14.1
55-59	9	6.0		71	12.5
60-64	2	1.3		42	7.4
65-69	3	2.		28	4.9
70-74	0	0.		17	3.0
75-79	1	0.7		6	1.1
80-84	0	0.		6	1.1
85-89	0	0.		1	.2

later, he found no cases of carcinoma of the cervix. He concludes that yearly screening is not necessary, and suggests extending the interval to two or more years.

VI. REVIEW OF 768 PRIVATE PATIENTS FIRST SCREENED DURING 1949, 1950, AND 1951 FROM THE PRACTICE OF DR'S. McGOOGAN, KOVARIK, KROUPA and VROMAN.

The records of 768 patients who had cervical cytologic smears taken in the years 1949, 1950, and 1951 were reviewed. (See Table IV) Among these patients, 18 cases of cervical carcinoma were detected in the initial smear, 6 non-invasive, and 12 invasive. This is a total incidence of 2.3%. 1.54% for invasive carcinoma, and .77% for carcinoma in situ.

Of the 768 patients, 350 were followed for two or more years with subsequent cervical smears, and no carcinoma was detected. 298 of the 350 patients had cervical smears five years or more after the initial smear was taken. One case of invasive carcinoma was detected in this group. This patient was 53 years old when first seen in 1950. She had had pelvic irradiation in 1933 for menstrual difficulties, and had no menses since. Cervical cytology in 1950 was reported as negative. In 1956 a repeat smear was performed, and reported

T A B L E IV

REVIEW OF 768 PRIVATE PATIENTS
 FIRST SCREENED IN THE YEARS 1949, 1950 & 1951
 FROM THE PRACTICE OF DR'S. McGOOGAN, KOVARIK, KROUPA & VROMAN

AGE GROUP	TOTAL PTS.	CA. DETECTED IN FIRST SCREENING		2 YR.	5 YR.	CA. DETECTED IN LAST SCREENING	SUSPICIOUS PROVED NEG.	SUSPICIOUS NOT FOLLOWED	BIOPSY OR TISSUE DIAGNOSIS
		CIS.*	INVASIVE						
20-29	130	1	1	6	31	0	2	-	13
30-39	307	4	5	18	122	0	5	9	64
40-49	217	1	1	22	91	0	9	1	56
50-59	77	0	2	3	31	1	2	1	10
60-69	35	-	2	3	3	0	0	0	6
70-79	2	-	1	-	-	-	-	-	1
TOTAL	768	6	12	52	298	1	18	11	150
PERCENT.		.77%	1.54%			.3%			
AVERAGE AGE		35	47						

22

*CIS= Carcinoma in situ

as "suspicious for malignant cells". Cervical biopsy was done a week later, which was reported as "poorly differentiated squamous cell carcinoma of the cervix". Whether the first smear was a false negative, or the lesion actually developed during the five year follow-up period is impossible to determine. If this was a recently developed neoplasm, it would represent an incidence of cervical carcinoma of about .3% in previously negative women, as compared with an incidence of 2.3% for unscreened women. These results are similar to those reported by Martin, et al (31) as previously mentioned.

Twenty-nine suspicious smears were reported; 18 which were proved negative by subsequent studies. 11 suspicious smears were in the group in which no follow-up was possible.

Tissue diagnosis was done in 150 of the patients in this series, either by biopsy, or following hysterectomy for benign causes. There were no histologic diagnoses of cervical carcinoma that were not first diagnosed by cervical smears. As far as is known, there were no false negative cervical smears in the survey.

Although the number of cases of carcinoma which were detected was too few to be statistically significant in considering age distribution, the average age

of carcinoma in situ was 35 years, and the average age of invasive carcinoma was 47 years, which is similar to the figures as calculated in Tables I and II.

VII. CONCLUSIONS:

Women are now being subjected to mass cervical cytologic screening in many localities. The program is destined for expansion, as the value of such a program is recognized by the public, and as facilities and cytologists become more generally available.

As more and more women are screened and found to have non-malignant cervicies, the problem of how often to re-screen these negative women for a combination of greatest cancer detection, and greatest efficiency presents itself. These smears must be made often enough to pick up any false negative smears which might have been made, and to detect invasive carcinoma which may arise from a previously negative cervix. Examples of three known false negative smears found in 157 cervical cancer patients at the University of Nebraska Hospital were cited. (31) It is reasonable to assume that the incidence of false negative reports will decrease as experience in Cytology is gained.

Carcinoma in situ has been shown by several methods to last on the average, about 10 years, before

becoming invasive.

The average woman could be screened for carcinoma every ten years, and all carcinoma detected would be in the in situ stage. However, a certain percent of Stage-0 carcinomas become invasive prior to the ten year average. Furthermore, it has not been established that some cases of cervical carcinoma do not have a latent Stage-0 stage, but progress rapidly to invasion. The latter group if present, is believed to be small.

In Table I, it is seen that of the 44 cases of carcinoma in situ, 87% became invasive in two or more years, 82% in three or more years, and 64% in four or more years. This is calculated from the actual time reported for invasiveness to occur. Since the average of these cases were detected about half-way in their course toward malignancy, these percentages are undoubtedly much higher. However, it is impossible to apply averages to single cases. If smears were taken at three year intervals, 82% of the cases of carcinoma would be detected in the non-invasive state, according to these figures. The remaining 18% would be detected in the invasive state by cytologic screening, or brought to a physician by their symptoms. Those with Stage I or II lesions would then be given five year cures at rates of

about 80% or 55% respectively. (Holly) (32) Thus, by this method, the cure rate of cervical carcinoma would conceivably be over 90%.

Without doubt, the more frequently cervical cytologic studies are done, the higher will be the percentage of diagnosis in the non-invasive state. It is most important for a patient to have an initial negative cervical smear. Being placed in the group of having a normal cervix, a woman has a much lower chance of having cervical carcinoma when the next smear is taken. This is illustrated by Martin's work, and a review of 768 private patients, as shown in Table IV. Martin concludes from his study, that cervical smears could be taken at intervals of two years or more, instead of every year, as is commonly practiced.

The age of specific incidence of cervical carcinoma is important in determining how frequently women should be screened. From 25-30% of carcinoma in situ are reported to occur in women under 30 years of age. This indicates that women in this age group must be screened, if adequate detection is to be obtained. The incidence is highest in the ages between 30 and 45, so this group should be screened more intensely.

The factors which possibly predispose to cervical carcinoma must also be considered in deciding how

often smears should be done. Virginal women have been shown to have a much lower incidence of cervical carcinoma than their non-virginal sisters; and according to the work of Towne and Gaynor, may need to be seldom, if ever screened. According to Wynder, the incidence of cervical carcinoma is related closely to exposure to intercourse. He believes that the apparently higher incidence of cervical cancer in parous women is merely a reflection of the exposure to intercourse. From this, one may infer that married nulliparous women (and certain of the unmarried ones) should be screened as frequently as parous women.

Cervical carcinoma has been reported to be more common in patients with chronic cervicitis. Probably the best course in this respect is in a preventative aspect by adequately treating the cervicitis, as reported by many authors. If adequate treatment is not possible, these women should be followed more closely than women with normal cervixes.

It must be remembered that although cervical carcinoma occurs relatively frequently, and is a serious threat to the host's existence, it is only one aspect of the patient's health. At our present state of knowledge, the only way to control the disease is to screen women

intermittantly throughout most of their life. This must be approached in a manner which is acceptable to the patient financially, and in such a way as to avoid undue cancer-consciousness. If, instead of having patients return at yearly intervals to have their "cervix checked", cervical screening were integrated into a complete examination every three to five years, perhaps better overall good results could be obtained. Thus, a patient would be screened for other diseases, many of which are more common, and ultimately more lethal than carcinoma of the cervix. The interval between subsequent cervical smears must be individualized to the patient; as to her age, marital status, and pathology found in the cervix.

There are presently many studies being performed in mass cytologic screening procedures, which will undoubtedly reveal much more information in the near future.

VIII. SUMMARY:

1. A brief history of carcinoma in situ of the cervix, and evolvement to present day status was presented.
2. A resume' of methods of diagnosis with emphasis on those methods especially adaptable to mass cervical cytologic screening was discussed.
3. The predisposing factors of cervical carcinoma as reported by several authors, both in the light of prevention of malignant change by adequate treatment, and close surveillance of women who possess these "pre-cancerous" entities.
4. The Life History of Carcinoma in Situ was discussed. An attempt was made to determine the average and range of the duration of the non-invasive carcinoma. Forty-four cases from the literature were presented in which carcinoma in situ was observed to progress to invasiveness. The average duration of these cases as reported, was assumed to represent one-half the average duration of carcinoma in situ. The average age of patients with carcinoma in situ was compared with the average age of patients with invasive carcinoma as determined by the compilation of eleven series reported in the literature. The difference between these ages was assumed to repre-

sent the average duration of the average case of carcinoma in situ. As calculated by this method, carcinoma in situ remained non-invasive for a period of time very close to that as determined by the average time taken for those cases of intraepithelial observed to progress to invasiveness, or about 10 years.

5. A series of 768 private patients of Drs. McGoogan, Kroupa, Kovarik, and Vroman who had initial cervical cytology in the years 1949-1951 were presented, 350 of these patients had a two year follow-up, and 298 had a five year follow-up. Eighteen cervical carcinomas were picked up on the initial smear, and only one carcinoma on a five year follow-up. Cytologic screening was thus shown to be valuable, resulting in a much lower incidence of cervical carcinoma in previously screened women.
6. The conclusions reached were that cervical cytology, as a screening procedure, could be done as infrequently as 3-5 years, and still maintain a high percentage of early diagnosis. Women in their 20's should be screened, but five year intervals should be sufficient, since the frequency of cervical malignancy is low in this age group. Women in the 30-50 age group, where the incidence is decidedly higher,

should be screened at three year intervals. At any time when cervical pathology such as cervicitis is encountered, the patient should be adequately treated or followed more closely with cytologic studies. The three to five year cervical screening should not be considered an entity in itself, but should be incorporated into general check-up, thus treating the patient as a whole.

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