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Carcinoma in situ of the cervix : a statistical study and general discussion

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CARCINOMA IN SITU OF THE CERVIX: A STATISTICAL STUDY
AND GENERAL DISCUSSION

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Doctor of Medicine

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INTRODUCTION AND PURPOSE

The purpose of this study, undertaken at the University of Nebraska College of Medicine and its affiliated hospital and gynecologic clinic, is to evaluate certain types of diagnostic procedures for early detection of carcinoma of the uterine cervix.

This treatise is divided into three distinct sections:

- I A statistical study of detection techniques for carcinoma of the cervix among patients at University Hospital and its out-patient clinic.
- II Incidence of carcinoma in situ of the cervix-- a review of the literature.
- III A general discussion of the nature of carcinoma in situ--its detection and treatment.

PART I
A STATISTICAL STUDY OF DETECTION TECHNIQUES FOR
CARCINOMA OF THE CERVIX AMONG PATIENTS
AT UNIVERSITY HOSPITAL AND ITS
OUT-PATIENT CLINIC

Today the serious nature of cervical carcinoma is attested by the fact that it ranks second only to carcinoma of the breast as a cause of death from malignant diseases among females.

Historically speaking, carcinoma of the cervix has been recognized as a grave and insidious disease for more than a century. Seventy-five years ago Baille (1) wrote: "This disease (ulcer of the cervix) is certainly as formidable as cancer because it terminates fatally, but its progress is different from that of cancer in any other part of the body."

In 1932, Broders (2) described and named the disease "carcinoma in situ" of the cervix, breast, skin, colon and larynx.

By definition, he said, carcinoma in situ is a cytologically malignant lesion that has not broken through the normal barrier that separates epithelium from underlying stroma. And in the cervix, he stated, the earliest changes (often by a process of creeping replacement) involve the mucous glands in the area of the external os.

This glandular involvement, he continued, does not imply invasion with resultant metastasis but often simply constitutes a problem of interpretation because practically all cervical carcinomas begin in the squamous epithelium at the squamo columnar junction.

Hinselmann (3) feels that the growth into cervical glands should not be considered as genuine invasive growth. It often

will occur in such thick strands that it is no more a mere filling of the glandular lumen but an expanding growth. This process may appear quite like invasive carcinoma. From these deep growing cones a really destructive growth may start.

Another important step in detecting early cervical carcinoma was developed by Papanicolaou (4). He theorized that carcinoma, growing on a free surface, such as that of the cervix, exfoliated certain cellular elements which are identifiable from microscopic studies of secretive smears and scrapings from the areas involved.

His experiments demonstrated that material shed from the cervical surface where carcinoma in situ was present afforded an apt basis for diagnosis.

His studies of patients showed that discovery and early diagnosis of carcinoma in situ by cytologic smear technique resulted in increased salvage.

* * *

This study was stimulated by an effort to evaluate the experience of the University of Nebraska in employing the vaginal smear as one means of detecting early cervical carcinoma.

The nature of University Hospital and its clinic should be borne in mind in considering the statistics presented.

Because University Hospital is a state-supported institution treating largely charity cases, the socio-economic status

of the majority of the patients precludes getting an accurate cross-section of the population in general.

Most of the patients treated are in the lower-income group and follow the generally-known environmental pattern which predisposes to large numbers of pregnancies, and toward delaying seeking medical advice until symptoms often reach alarming proportions.

* * *

CLINICAL DATA

Material

The departments of Obstetrics and Gynecology at the University of Nebraska Hospital in co-operation with the department of Cytology at the College of Medicine began to evaluate the cervical smear in 1948 and since then smears have been obtained routinely on new and referred patients at both University Hospital and its out-patient gynecologic clinic. This study covers the years 1950 through 1951.

Since January 1, 1950, 2,023 cervical smears have been examined by newer cytologic techniques. This study reviews the records of 49 patients screened in this manner. Diagnosis subsequently proved that these patients had carcinoma of the cervix although in approximately half of the patients cervixes did not initially exhibit lesions which were believed by the examining

physicians to be carcinoma.

* * *

Age Grouping

The ages of the patients in this group of 49 patients ranged from 25 to 73 years and were distributed by five-year intervals as shown in Table I. Figures show the spread of patients is fairly even between the ages of 25 and 50 years but there is a smaller but clearly significant group over 50 years of age.

The average age of 15 patients who had early invasive carcinoma was 48 years with a range of 28 to 73 years. In the smaller group of 8 patients whose cervical carcinomas proved to be in situ the average age was 37 years with a range from 28 to 62 years.

These figures are substantially in agreement with those arrived at by Jones, Galvin and Telinde (5) who by reviewing the literature cited the average age for invasive carcinoma as 48 years.

Galvin and Telinde (6) reported the average age of 75 women with carcinoma in situ as 37.1 years. Young, Hertig and Armstrong (7) reported an average age of 38 years for carcinoma in situ.

TABLE I

Age, Years	Patients
Under 251
25-29.6
30-34.7
35-39.7
40-44.3
45-49.6
50-54.4
55-59.4
60-64.4
65-69.3
70 and over.4

ABNORMAL CELLS IN VAGINAL SMEARS OF 49 PATIENTS

* * *

Number of Pregnancies

Of the 49 patients all are or have been married. Two had never been pregnant; the remainder had had one or more full-term pregnancies as shown in Table II.

Of the 47 patients who had several full-term pregnancies, 10 had had 6 to 9 full-term pregnancies and two had had between 10 and 15 full-term pregnancies. Three patients of known low

mentality were unable to state how many full-term pregnancies they had had.

TABLE II

Number of Pregnancies	Patients
No Pregnancies	2
1-3 Pregnancies	12
4-5 Pregnancies	13
6-9 Pregnancies	10
10-15 Pregnancies	2
Several Pregnancies, Exact Number Unknown . . .	3

NUMBER OF FULL-TERM PREGNANCIES IN PATIENTS
WITH CERVICAL CARCINOMA--42 PATIENTS*

(* Histories and charts of seven patients did not indicate the number of pregnancies.)

The foregoing figures serve to emphasize the belief on the part of most gynecologists that the traumatism of childbirth, notably lacerations with eversion of the cervix and erosions of the cervix, are important factors in the etiology of cervical carcinoma.(8)

* * *

Nature of Complaint

Next an analysis was undertaken to determine how many of

the 49 patients had gynecologic symptoms which might have been indicative of pelvic disease.

Fourteen patients had no recorded symptoms suggestive of gynecologic disease while two patients entered the clinic for sterility studies.

Histories of abnormal discharge or bleeding taken from the 33 remaining patients at least suggested the presence of a neoplasm of the genital tract.

* * *

Examination of the Cervix

The cervixes of 5 patients of the 49 were reported on examination as appearing normal. Vaginal stenosis prevented inspection of the cervixes of 3 patients at the time the smear was obtained.

Cervical lesions of 13 patients were said to be minimal and did not appear significant. Cervixes of 28 patients exhibited lesions which appeared to be clinically significant to merit the description: angry, denuded, friable, granular, rough, or reddened.

* * *

Evaluation of the Vaginal Smear

In a further attempt to learn the value of the smear method in detecting unsuspected cervical carcinoma, the 49 patients were divided into groups in accordance with indications for

biopsy. In 31 cases the appearance of the cervix alone justified the securing of a biopsy specimen.

In 17 cases a smear alone was taken at the time of first examination, the specimen for biopsy being secured later as a result of a positive or suspicious report on the smear.

In four instances the biopsy was performed in the patient's home city prior to her referral to University Hospital.

* * *

Extension of Lesions

The next stage in the study was to determine the final stage of extension of each lesion which was detected by smear or biopsy.

The League of Nations classification of carcinoma of the uterine cervix recognizes four stages. However, the International classification includes five stages. They are(9) :

- | | |
|-----------|---|
| Stage 0 | Carcinoma in situ--also known as pre-invasive carcinoma. |
| Stage I | The carcinoma is strictly confined to the cervix. |
| Stage II | The carcinoma extends beyond the cervix but has not reached the pelvis wall.
The carcinoma involves the vagina but not the lower third. |
| Stage III | The carcinoma has reached the pelvic wall (On rectal examination no cancer-free space is found between the tumor and the pelvic wall.)
The carcinoma involves the lower third of the vagina. |

Stage IV The carcinoma involves the bladder or the rectum, or both, or has extended beyond the limits previously described.

Eight patients of the 49 studied were classified as having squamous cell carcinoma of the cervix, Stage 0, that is, carcinoma in situ.

Fifteen patients were Stage I. However, at least 2 of the 15 lesions were placed in this category after conization of the cervical canal or other procedures had disclosed what the surgical pathologist termed early or very early infiltration.

In 12 cases the stage was listed as II; nine cases, Stage III and five cases, Stage IV. Three additional patients had adenocarcinoma of the cervix and endocervix.

* * *

Analysis of Initial Smear

Graphic analysis of the initial smear is shown in Tables III and IV. In 5 cases the result of the initial smear was termed suspicious and in one case negative (plus one probable malignant and one malignant) while biopsy revealed in each instance squamous cell carcinoma in situ.

The one positive smear in the group of 8 in situ patients remained positive on two successive occasions while a second smear taken on the patient with an initial negative finding proved positive.

Of the 15 patients who were classified as Stage I, initial smears of 8 were termed malignant; 3, probable malignant, and 3, suspicious.

TABLE III

Reported	Number of Cases
Malignant1
Probable Malignant1
Suspicious5
Negative1

INITIAL SMEAR IN CARCINOMA IN SITU
(Group of 8 Patients)

TABLE IV

Reported	Number of Cases
Malignant8
Probable Malignant4
Suspicious3

INITIAL SMEAR IN STAGE I CARCINOMA
(Group of 15 Patients)

* * *

Treatment

Though a consideration of treatment may not rightly belong in a presentation dealing only with diagnostic technique it still may be of interest to briefly discuss final disposition of the

49 patients included in this study.

Of 8 patients whose lesions were proved to be of Stage 0, 4 were subjected to total abdominal hysterectomy; 3 to x-ray and radium treatment, and 1 to radium therapy followed by surgical operation.

Of the 15 patients whose lesions were Stage I, one underwent cervical amputation; 13 received x-ray and radium treatment only and 1 was treated with irradiation followed by cervical amputation.

All 12 of the patients whose carcinomas were Stage II, received x-ray and radium therapy and in two instances surgery was also performed. The three patients with adenocarcinoma of the cervix and endocervix were treated by total abdominal hysterectomy.

* * *

DISCUSSION

Assuming that the diagnostic techniques used at University Hospital for the detection of carcinoma of the cervix in situ are highly valuable another question arises. Namely--whether and following what time interval are these observed cytological changes followed by the development of clinical carcinoma in the organ involved?

While this study does not indicate that carcinoma in situ and invasive carcinoma of the cervix are one and the same, two pieces of circumstantial evidence seem to point in that direction .

1. Analysis shows an average age differential of 11 years between patients who exhibit carcinoma in situ and overt carcinoma of the cervix--seemingly indicating that the lesions at least remain intraepithelial during this time interval. This age differential is in basic agreement with other studies made of these diseases.
2. The fact that all of the 49 patients studied had been married and most had several full-term pregnancies correlates with the known fact that invasive carcinoma of the cervix is a rarity among unmarried women.

The evidence in point 1 is in basic agreement with a recent summarization of available literature on the subject by Jones, Galvin and TeLinde (5). Their findings are as follows:

1. Documentary evidence concerning 40 patients revealed that cervical carcinomas in situ, which under observation or by accident, were allowed to progress eventually manifested themselves in invasive lesions.
2. An average differential between in situ and invasive carcinoma was reported at 10 years.

3. Galvin and associates in reviewing biopsies on 13 patients who subsequently had clinical carcinoma of the cervix found in 11 instances that changes now recognized as carcinoma in situ were present in tissue originally removed. One specimen exhibited basal cell hyperactivity and the remaining specimens had been denuded of epithelium.

The TeLinde report, however, also shows nine examples where carcinoma in situ seemingly reverted to normal. On the other hand one must not exclude the possibility that biopsy especially if followed by cauterization for hemostasis did not destroy all of the original lesion.

* * *

CONCLUSION

Importance of the cervical smear when clinically applied is aptly illustrated in the records of Dahlin, Mussey and Dokerty (10). Excluding obstetrical patients, the group made cervical smears of 5,459 of 7,960 new patients. Of these 52 or about 1 per cent proved to be shedding malignant cells from clinically undetected carcinoma of the cervix. Smears from only two patients (or 1 in 2,700) were false negatives which might have led to dismissal if detection had not been made.

University Hospital records of 1950-51 indicate a higher

incidence of diagnosis by cervical smear. Of 2,023 consecutive smears, 49 or 2.4 per cent revealed cervical carcinoma.

Eight cases of carcinoma in situ found represent an incidence of 0.4 per cent of smears taken and 16.3 per cent of the total cases of carcinoma.

Of the 8 patients who were later proven to have carcinoma in situ only two gave positive smears on the first occasion. The remainder were reported as suspicious (Grade III) or highly suspicious (Grade IV). In three of these patients abnormal cells were never found.

In 5 of the 8 patients the first biopsy was reported positive for non-invasive carcinoma. Additional biopsies on the remaining patients were ultimately positive.

The statistics seem to afford ample evidence of the efficacy of the vaginal smear as a method of diagnosing pre-invasive and invasive carcinoma which may be asymptomatic or clinically undetected.

PART II
INCIDENCE OF CARCINOMA IN SITU OF THE CERVIX:
A REVIEW OF THE LITERATURE

While the actual incidence of carcinoma in situ is unknown, introduction of cytological techniques has resulted in the lesion being identified and diagnosed with more frequency than in the past. Studies substantiating this fact have been made at several hospitals and clinics throughout the country.

Results of these studies, reported below, show that the incidence of carcinoma in situ varies greatly depending upon the source and type of material evaluated.

* * *

UNIVERSITY HOSPITALS--CLEVELAND, OHIO

The Gynecological Service of the University Hospitals at Cleveland, O., (11) during 1952 treated 63 squamous cell carcinomas of which 12, or 19 per cent, were intraepidermal carcinomas which with one exception were initially diagnosed by means of the cervical smear.

* * *

FREE HOSPITAL FOR WOMEN

Illustrative of the fact that the incidence of carcinoma in situ varies is a 1949 study made by Young, Hertig and Armstrong (7) at the Free Hospital for Women. Incidence was reported at 0.84 per cent of 2,262 cervixes examined by biopsy in 1946. On the other hand, Pund and Auerbach (12) found an incidence of 3.9 per cent of 1,200 clinically benign cervixes examined at the same hospital, also in 1946.

A third study at the Free Hospital in 1946 showed an incidence of 1.15 per cent on biopsies from 955 clinically diseased cervixes of ambulatory patients.

* * *

NEW YORK STATE ANALYSIS

An analysis made in New York State showed an incidence of 34.3 per hundred thousand, or 0.034 per cent, of the total female population according to figures reported by Haagensen and quoted by Corscaden (13).

* * *

STRANG PREVENTION CLINIC

Scapier (14) reports 26 cases of intraepithelial carcinoma among 10,800 new female patients, 20 years of age and older, attending the Strang Prevention Clinic of the Memorial Center for Cancer and Allied Diseases.

Only five additional cases were found in a comparable series of 9,500 return patients, previously screened by cytological and other diagnostic methods. All 31 cases were confirmed by biopsy although only 20 cervixes showed persistence of the same lesion after surgical removal.

Thus the incidence of cervical intraepithelial carcinoma in a series of 20,300 presumably well patients attending a cancer detection clinic showed an incidence of 1.5 per thousand or 0.15 per cent.

BARNARD FREE SKIN HOSPITAL AND
WASHINGTON UNIVERSITY-BARNES HOSPITAL

Frerichs, Sherman, Ruch and Monat (15) have analyzed 1,327 staged cases of squamous cell carcinoma of the cervix. Patients were from the Barnard Free Skin and Cancer Hospital and the Washington University-Barnes Hospital.

The Barnard study showed an increasing percentage of early cervical cancer due to greater pickup of in situ cases by newer techniques. The change ranged from 9 per cent of all new cases seen in 1949 to 15 per cent in 1950. Studies at the Washington University-Barnes Hospital showed no such findings but did indicate a growing percentage in detection of Stage I lesions.

Both analyses revealed that some 40 per cent of all new cervical cancer cases are either Stage 0 or Stage I.

While the total incidence of Stages 0, I and II showed no noteworthy change, the total of Stages 0 and I increased sharply thus indicating that cases are being detected before Stage II is reached.

* * *

UNIVERSITY OF IOWA HOSPITALS

One of the most extensive analyses of carcinoma in situ is that made at the State University of Iowa Hospitals in Iowa City by Krausher, Moore and Pettis (16). The study, covering all cases of uterine cervical cancer treated from 1940 through 1949

attempts to determine whether there has been any significant change in the extent of lesions and whether new diagnostic techniques have been effective.

Findings, plotted in Table V, indicate that during the period between 1940 through 1942, 185 new cases of cervical carcinoma were treated while in the second period (1947 through 1949) 226 cases were detected (exclusive of 23 cases of carcinoma in situ). The number of biopsies doubled during the second

Carcinomas in situ were for the most part discovered in patients from whom cytological smears revealed abnormal cells suggestive of malignancy.

The group concluded that the significant increase in the number of carcinomas detected reflects the efficacy of educational measures and the widespread use of newer diagnostic techniques thus proving the effectiveness of the latter.

The study states: "The percentage of cases belonging to Stage I under the League of Nations classification was on the average more than twice as great in the latter period. Further study of Table V, however, shows that the increase of Stage I was at the expense of Stage II cases, since the number of women with lesions in Stages III and IV remained relatively stable.

"Inclusion of carcinoma in situ (Stage 0) with Stage I cases accentuates this difference. Every effort has been made

to standardize clinical classifications and an attempt has been made to place borderline cases in the higher rather than the lower stage."

YEAR	0	PER CENT OF NEW CASES LEAGUE CLASSIFICATION					TOTAL BIOPSIES	TOTAL NEW CASES
		I	O&I	II	III	IV		
1940	-	16.4	16.4	57.3	21.3	4.9	134	61
1941	-	14.7	14.7	72.1	9.8	3.3	215	61
1942	-	12.7	12.7	69.8	14.2	3.2	162	63
1947	1.5	28.5	30.0	39.2	25.4	6.6	235	63
1948	14.9	30.8	45.7	31.8	18.8	3.7	423	107
1949	7.5	34.1	41.6	32.9	15.2	10.1	370	79

TABLE V
INCIDENCE AND STAGES OF CARCINOMA OF THE CERVIX
AT STATE UNIVERSITY OF IOWA HOSPITALS

The Iowa City group contributes the increase in diagnosis of early stage cancer to the following favorable conditions:

1. Women are appreciating the significance of early symptoms of cervical carcinoma (vaginal bleeding and discharge) and are seeking medical advice earlier.
2. Physicians are realizing that abnormal vaginal

bleeding or discharges, especially in women over 40 years of age should be assumed to mean cancer until some other acceptable explanation can be found.

3. This mere thinking of cancer automatically leads to the utilization of cytologic smears and biopsies or to referral to some institution experienced in carrying out these examinations.

* * *

WRIGHT AND BRISTOL

One of the more recent studies on detection of carcinoma was that made by Wright and Bristol (17) who limit their practice to obstetrics and gynecology.

From March 1, 1950 to June 28, 1951, 383 Papanicolaou smears were taken, for the most part from those patients with minor cervical pathology such as erosions, polyps, chronic cervicitis, and a history of abnormal vaginal bleeding.

In 6 of the 383 cases a diagnosis of carcinoma was made by the smear method. Of the six, diagnosis was confirmed by biopsy in five cases. Two cases proved to be early invasive carcinoma and three were intraepithelial carcinoma.

One false positive was reported.

THE MAYO CLINIC

A 1952 survey made by Dahlin, Mussey and Dockerty (10) at the sections of Obstetrics and Gynecology at the Mayo Clinic showed the following results:

1. Since August 1, 1950, routine smears were made on all new and referred patients with the exception of obstetrical patients and women less than 30 years of age whose cervixes were apparently normal.
2. Cases of 92 of the first 10 thousand patients screened were reviewed and all of these patients were subsequently proved to have cervical carcinoma.
3. 73 patients were shown to have carcinoma in situ, their average age being 42.1 years. 11 patients with early invasive carcinoma showed an average age of 47.8 years. Only 13 patients of the 92 came to the clinic complaining of gynecologic symptoms, thus again indicating the value of the smear technique in early detection.

* * *

CONCLUSION

The foregoing studies plus that made at the University of Nebraska Hospital attest the efficacy of the cervical smear as

a diagnostic technique. However, the results do not intend to imply that the smear should replace the biopsy.

Biopsy should always be employed following the finding of positive or equivocal smears before any definite treatment is prescribed.

It is also important that during this verification procedure (except when the tissue specimen includes a completely conized cervical canal plus the squamocolumnar junction) the post biopsy cautery be applied with utmost caution and reluctance.

As Dahlin (10) writes: "All too often the bone fide evidence of carcinoma of the cervix in situ has ascended in the smoke of such burnt offerings."

PART III

A GENERAL DISCUSSION OF THE NATURE OF CARCINOMA IN SITU--

ITS DETECTION AND TREATMENT

What is now called carcinoma in situ of the cervix has in the past been designated:

1. Incipient Carcinoma
2. Non-invasive Carcinoma
3. Pre-invasive Carcinoma
4. Intramucosal Carcinoma
5. Bowen's Disease of the Cervix
6. Superficial Non-Invasive Carcinoma
7. Intraepithelial Carcinoma

To a great extent all of these classifications may be termed misnomers because the accepted definition of carcinoma itself does not fit the conditions paramount in "in situ" cases. That definition states that carcinoma is an epithelial neoplasm which invades, metastasizes and ultimately kills its host unless prevented from doing so by therapeutic measures.

If it weren't for the fact that the word "precancerous" is in ill repute perhaps the best description for the lesion would be "precancerous anaplasia" which really describes the situation more accurately than does "carcinoma in situ".

* * *

FIRST RECOGNITION

Chronologically speaking, Rubin (18) is thought to be the first to have recognized the type of lesion called carcinoma in situ. In 1910 he presented a paper based on a study of three

patients. In one of the three he found a cervical carcinoma which appeared to be limited to the mucosa, accompanied by atypical epithelial proliferations. The latter he designated as the most essential diagnostic sign of malignancy.

He concluded: "The important criteria of malignancy in these early cases lie not so much in the relation of the cell nests to the stroma, the depth or the extent of epithelial invasion or evidences of surrounding inflammatory changes, as in the intrinsic morphology of the epithelial cells."

Since 1910 pathologists and physicians in increasing numbers are coming to accept the premise that this type of lesion is the first step in the morphologic sequence through which the squamous cells of the cervix progress before they become invasive.

A later writer, Meyer (19) is in basic agreement with Rubin. Refusing to accept the term, carcinoma in situ, Meyer instead attempted to carefully define the earliest characteristic changes which were recognizable as carcinoma.

Patients having such lesions were subjected to repeated biopsies until an incontestable diagnosis could be made. By collecting such data Meyer was able to define histologic characteristics of early malignancy.

* * *

HISTOLOGIC CHANGES

These histologic changes usually begin in the squamous

epithelium at the junction of the portio and endocervix. Foote and Stewart (20) have proved this point by a careful study using multiple block examinations of 27 pathological specimens of intraepithelial carcinoma of the cervix. Their analysis showed that the origin of the lesion is concentrated in the critical area centering at and about the external os, at the junction of the squamous and endocervical epithelium.

It is interesting to note that in one of the cases studied Foote and Stewart concluded that the carcinoma was present in two separate areas of the cervix and interpreted the evidence as signaling two independent primary growths.

In conclusion Foote and Stewart stated that it was impossible to tell with the naked eye where an intraepithelial carcinoma was located in a given cervix but they state that biopsies taken at the squamo columnar junction at four sites equally distributed around the periphery probably result in diagnosis of the great majority of cases.

In further reporting his studies of histologic changes in cervical carcinoma, Meyer (19) reports: "A study of very early squamous cell carcinomas leads to the conclusion that they arise always from squamous epithelium and always from basal cells. In most cases the carcinoma arises at the margin of an old erosion."

In only one case, Meyer states, has he seen a very small squamous cell carcinoma which seemed to arise within an erosion.

And he further says he has never seen a squamous cell carcinoma of the cervix which did not arise from the surface epithelium. He also says that "transitions from benign epidermization to carcinoma are unknown."

His report continues: "Cervical polyps, in spite of being covered by ripe squamous epithelium and exposed to irritation, do not become carcinomatous. This is probably due to the fact that there is no older squamous epithelium surrounding the area of epidermization to serve, as in the cervix, for the tissue of origin of the carcinoma."

* * *

PATHOLOGY OF CARCINOMA IN SITU

Carcinoma in situ presents five definite problems.

1. Are the lesions which are designated in situ really carcinomas?
2. Is this an early form of invasive carcinoma?
3. Is this an irreversible lesion?
4. What is the relationship of changes seen in pregnancy to carcinoma in situ?
5. What is the relationship of the changes seen in trichomonas infection to carcinoma in situ?

An accurate diagnosis of carcinoma requires the following:

1. Inability of the cells to differentiate into layers.
2. Irregularity of the cell and nuclear form.
3. Staining characteristics.
4. Abnormalities of mitosis.

It should also be noted that these changes do not have to involve the whole depth of the epithelium before malignancy can be diagnosed.

Certain cervical lesions fall below these obvious specifications. Often these have uninvolved epithelium above them, the absence of which is likely to be the result of artificial trauma at the time of biopsy. A malignant cervical tumor spreads along the basal epithelium at its margin, replacing the epithelium as it invades. The greater growth potential in more advanced growths often causes the tumor to move forward in the epithelium in a large mass.

In early tumors carcinoma cells which have established themselves in the basal layer proceed to proliferate and produce more and more layers which thicken with less overlying normal epithelium toward the center of the lesion. A careful scanning of these contact areas between normal and malignant cells shows sections where tumor cells are destroying normal cells.

The premise that carcinoma in situ is irreversibly within biologic limits and goes on to become carcinoma of the cervix (unless destroyed or surgically removed) is based on the following observations by Hertig and Young (21):

1. The incidence of carcinoma in situ, while varying slightly from clinic to clinic is comparable to that of squamous carcinoma of the cervix, but
2. The age at which it appears is on the average some years earlier than that of cervical carcinoma.
3. Carcinoma in situ and carcinoma of the cervix are, respectively, one-sixth (14) and one-fifth (22) as common in Jewish as in non-Jewish women.
4. A significant and increasing number of patients with morphologically diagnosed carcinoma in situ have been allowed, either wittingly or unwittingly, to progress to cervical carcinoma within a period ranging from 11 months to 13 years.
5. As carcinoma in situ progresses through its successive stages of surface involvement and mucous gland involvement, to early but definite stromal invasion, the associated vaginal exfoliative cytology becomes increasingly more positive for cancer.
6. Carcinoma of the cervix nearly always can be shown

to possess an in situ pattern of the surface epithelium at the periphery of the invasive carcinoma.

* * *

DIAGNOSTIC CRITERIA

Despite the increasing frequency of carcinoma in situ definite diagnostic criteria through smears and sections aren't nearly as well established as diagnostic methods for invasive carcinoma.

However, many studies show that the cervical smear in cases of carcinoma in situ is often positive. Young (21), Scapier (14), Bickel and Culbertson (23) and others have shown by employing the smear technique the efficacy of this method in detecting or confirming pre-invasive carcinoma.

Studies by Achenbach, Johnstone and Hertig (24) show that initial examination of the first smear revealed malignant cells in 70 per cent of 60 cases. And later when tissue diagnosis became known the smears were re-examined with 82 per cent revealed as positive.

Reicher (25) made a study of 3,500 vaginal smears and found an overall malignancy incidence of 2.4 per cent. However, he also adds that if a patient has a genital tract cancer, the vaginal smear has an 89 per cent chance of picking it up; on the other hand, any given patient with a positive smear has an

82 per cent chance of having cancer and an 18 per cent chance of having a benign lesion.

Foote and Li (26) found similar results in a study of 18 proven cases of carcinoma in situ. They found positive results in 14 smears of the cervix while finding positive cells in only 9 vaginal smear specimens.

Kulcsar (27) by use of the surface cell biopsy method, detected cancer cells in 93 of 100 specimens obtained from 20 patients with early carcinoma. He also reports that the cellular content of the vaginal pool contained neoplastic cells in 55 out of 100 specimens.

Achenbach, Johnstone and Hertig (24) were able to identify 45 out of 60 proven carcinoma in situ cases when cellular content was collected from the vaginal pool.

In a more recent study, Reagen (27) reported scrapings of the uterine cervixes of 54 patients with carcinoma in situ revealed anaplastic cells in 50 cases. However, he found that material aspirated from the vaginal pool revealed tumor cells in only 43 of 54 patients.

His findings point up the necessity of examining cervical scrapings rather than the vaginal pool in diagnosing cases of unsuspected carcinoma. These studies also emphasize that direct cervical smear or cell scraping considerably reduced the number of questionable smears and in effect reduced the

necessity for taking repeated smears.

Studies by Papanicolaou and Traut (4) show that cells most commonly confused with those derived from carcinoma in situ have one feature in common: Namely, they possess variable degrees of alteration in the nuclear-cytoplasmic ratio.

They interpreted such cells as evidence of "superficial dyskeratosis" and found that such cells are more common in specimens obtained by scraping the uterine cervix, stating, however, that such cells do occur in aspirated material from the posterior vaginal fornix.

Further studies revealed that tissue spreads taken during the post-menopausal period may contain dense numbers of atrophic cells of parabasal type. The presence of such cells, however, is not thought in any way to exclude the possibility of carcinoma.

Papanicolaou and Traut also found that cervical lesions which histopathologically are characterized by acanthosis may also present confusing cell types, the most common of these being condyloma, with leukoplakia less frequently noted.

In the presence of squamous cell metaplasia, they found that cells in the cervical specimen are so constantly present that there can be little doubt as to their origin--although they aren't confined to this lesion alone.

They concluded that inflammation of the uterine cervix regardless of its cause may produce cytological changes, essen-

tially due to degeneration. And they say that only in the presence of acute gonorrhoeal cervicitis are cytological alterations sufficient to be confused with carcinoma.

Pregnancy, trichomonas infection and certain other factors may also cause morphological changes which are apt to cause an erroneous diagnosis of carcinoma in situ. In certain cases changes are inconspicuous and are characterized by moderate nuclear activation with perinuclear vacuoles and increased cytoplasmic acidophilia.

In other cases trichomonas infection is associated with nuclear abnormalities of marked degree such as hyperchromatism, prominence of nucleoli and thickening of nuclear membrane.

* * *

COURSE OF UNTREATED CARCINOMA IN SITU

Little definite information is available on the course of untreated carcinoma in situ of the cervix.

In a three-year study by Scapier (14) 31 cases of carcinoma in situ were diagnosed histologically, representing an incidence of 2.4 cases per 1,000 new patients.

In addition to these 31 cases there were 7 cases seen which suggested spontaneous regression based upon cytological studies. Four of these 7 had two or more positive smears revealing cells with malignant features of the intraepithelial type, followed by two or more negative smears over a period of eight to 24

months. The remaining three cases showed malignant features on a single smear only, followed by two or more negative smears.

Biopsies in all seven cases were reported as negative for cancer. Therefore, it is assumed that these biopsies did not constitute therapy.

Serial sections were not performed, however, leaving the possibility that a minute focus of carcinoma was removed at the time of biopsy.

The question therefore follows: Did spontaneous regression occur in these seven cases? Smears in each instance revealed cells characteristic of intraepithelial carcinoma. In this type of carcinoma focus is confined to the squamous epithelium thus natural desquamation of the epithelium could account for the lesion's disappearance.

* * *

AGE DIFFERENTIAL

If carcinoma in situ is the pre-invasive stage of cervical carcinoma, the age of the patient in whom the former appears should be younger on the average than that of the patient with invasive carcinoma.

This fact is confirmed by Young, Hertig and Armstrong (7) who in 1949 reviewed the literature and cited the average ages of carcinoma in situ and squamous carcinoma as 38.7 and 48 years, respectively. This is shown graphically in Table VI.

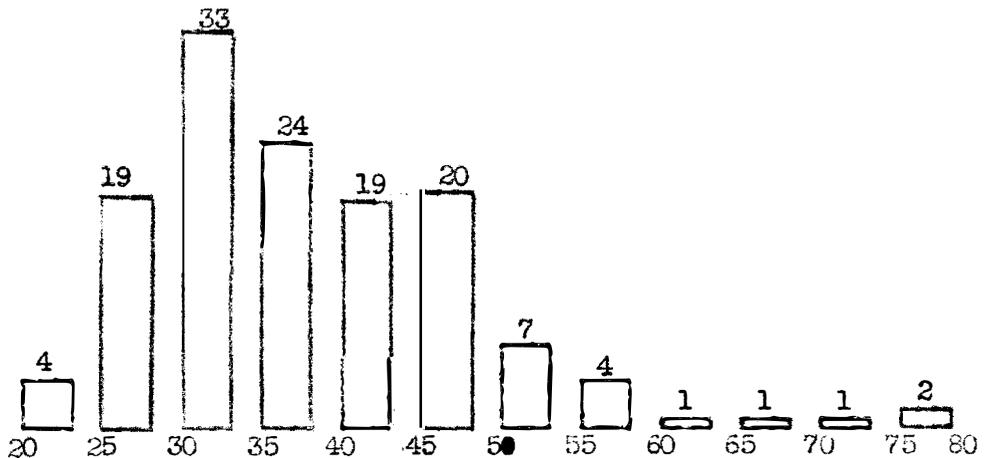


TABLE VI

AGE DISTRIBUTION OF 135 CASES OF CARCINOMA IN SITU

Studies of the age incidence of carcinoma in situ are based, however, on relatively small numbers of cases. For example:

1. Young, Hertig and Armstrong (7) reviewed the literature in 1949 and found only 16 cases of carcinoma in situ progressing to squamous carcinoma.
2. Jones, Galvin and TeLinde (5) in a recent review of the literature found only 40 cases including those of Young and associates.

Thus the concept that carcinoma in situ becomes invasive carcinoma rests on a small number of patients. And in our present state of knowledge if lesions diagnosed as in situ

don't resemble the lesion ultimately shown to be invasive then one seems justified in suspecting the original lesion may have been misdiagnosed.

If one admits the possibility of early invasion at the time of original biopsy then the possibility of the lesions becoming invasive cannot be ruled out because in no instance was the entire cervix available for study. Thus absolute scientific proof that in situ carcinoma precedes invasive carcinoma may never be forthcoming since to rule out early invasion one must have the entire cervix but to prove the ultimate invasiveness of the process the cervix must be left in.

* * *

TREATMENT OF CARCINOMA IN SITU

Treatment of carcinoma in situ is best expressed in a questionnaire compiled by Davis (28). His findings are summarized in Chart VII.

TABLE VII

QUESTIONNAIRE ON CARCINOMA IN SITU

Carl Henry Davis, M.D.

Replies of 70 Members of the American Gynecological Society and/or American Association of Obstetrics, Gynecology and Abdominal Surgery.

	Yes	No	Other
1. (a) Do you classify cancer in situ as cervical cancer?	66	4	

	Yes	No	Other	
(b) Do you consider cancer in situ as the pre-invasive stage of genuine cervical cancer?	47	1	Uncertain	17
2. (a) Do you believe spontaneous regression of cancer in situ occurs?	14	34	Uncertain	22
(b) Do you believe cancer in situ may regress during or after pregnancy?	17	22	Uncertain	18
(c) In how many cases have you observed spontaneous regression?			None	48
			1 or 2	3
			3 plus	1
			Probable	2
3. Do you use routine cytology prior to biopsy?	39	25	Frequently	9
4. What type of biopsy is performed?				
(a) Single punch or radial	6			
(b) Multiple punch	23			
(c) Ring biopsy	23			
(d) All three according to case	6			
(e) Multiple punch or ring	10			
(f) Cutting current	2			
5. With repeated positive cytology and negative pathological report, do you consider this definite evidence that there is no malignancy or do you require more adequate sectioning of the tissue submitted?			Continue study	69
			No malignancy	1

6. What treatment do you consider adequate for cancer in situ of the cervix uteri?

- | | |
|---|----|
| (a) Electro conization and coagulation | 2 |
| (b) Cervical amputation | 2 |
| (c) Total hysterectomy | 26 |
| (d) Radical surgery | 3 |
| (e) Treatment varies with age | 40 |
| (f) Radiation | 1 |
| (g) Radiation and radical surgery | 3 |
| (h) Vaginal hysterectomy where possible | 1 |
| (i) Radical operation not indicated | 13 |

	Yes	No	Other
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7. Do you believe cancer in situ should be studied by means of frequently repeated cytology, surgery withheld?

10	26	Only during pregnancy	6
		Uncertain	4
		Follow 6-a, b, or c	
		further cytology and biopsy	4

8. Have you or do you know of anyone who has found evidence of an involved lymph gland where careful examination of cervical tissue revealed only carcinoma in situ?

By hearsay	6
Don't know	1

SUMMARY

1. During the two years, 1950 and 1951, a total of 2,023 vaginal smears were taken on patients at University Hospital and its clinics. A total of 49 proven malignancies of the cervix were thus detected. Of these, 8 were Stage 0; 15 were Stage I.
2. The average age of the eight patients with carcinoma in situ was 11 years younger than that of the patients with invasive carcinoma.
3. Papanicolaou smears were taken on all the patients and were reported as malignant in two of the eight in situ cases. In Stage I cases, the smears were reported as malignant in 12 of the 15 cases.
4. The Stage 0 cases were treated by total abdominal hysterectomy in four cases and by x-ray and radium in three cases. Of the Stage I cases, 13 were treated by x-ray and radium.
5. The incidence of carcinoma in situ varies from 0.15 to 3.9 per cent according to the literature.
6. While the total incidence of Stages 0, I and II has not changed appreciably, the total of Stages 0 and I has increased, but at the expense of Stages II and III.
7. Early carcinoma of the cervix may be confused cytologically with non-malignant lesions such as trichomonas infection, pregnancy and leukoplakia.

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* * *

CONCLUSION

With present methods of therapy for carcinoma of the cervix, early diagnosis still remains the most important weapon in the reduction of mortality from this disease.

Since early carcinoma of the cervix often cannot be recognized grossly, one seems justified in concluding that adequate and competent cytologic techniques represent the greatest advance to date in the early detection and control of this type of malignancy. Use of these techniques can direct the clinician to diagnosis through the use of the biopsy.

Admittedly a routine vaginal smear on every female is impractical but smears should be taken on every questionable case and if reported suspicious or malignant, biopsy is the procedure of choice.

Use of the punch biopsy, however, is based upon the

knowledge that it can and will be followed by repeated cytologic studies and by cold-knife biopsies of the cervixes of those patients who, despite negative tissue reports on punch biopsy specimens, continue to show epithelial atypism in cytologic smears.

In this way more early cases of carcinoma of the cervix will be detected. And since the evidence seems to point to the fact that carcinoma in situ ultimately progresses to clinical carcinoma, it is desirable to treat these early lesions as soon as possible. Perhaps, if a patient who today has invasive carcinoma had been subjected to cytologic studies at a hospital or clinic five to 10 years ago, she would not now be a victim of malignancy.

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