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A REVIEW OF THE LITERATURE ON CARCINOMA IN SITU
OF THE UTERINE CERVIX

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In mankind's ageless conflict against cancer, painfully slow, often imperceptible advances have been made. Yet modern science with all its magnificent implements for research, detection, and treatment is often futile against these dreaded malignancies, since many are so insidious that they become evident even to the most careful study only after they have become widespread and incurable. Early detection has long been a vital problem in this struggle. One early lesion of interest in the last few years is carcinoma in situ of the uterine cervix.

Carcinoma in situ of the uterine cervix as described by various writers consists of malignant epithelial cells found in or near the position occupied by their ancestors before the ancestors underwent malignant transformation. These changes appear to begin in the basal layer, but are sometimes initially found in the more superficial layers of the epithelium. The changes described are variations in the size and shape of the nuclei with a tendency for increased size, irregular shapes, and hyperchromatism. A loss of a distinct nuclear membrane and a peculiar granularity were described. Many contain large or even multiple nucleoli. Mitotic figures are present and some

are abnormal. There is a loss of polarity and the orderly pattern of the epithelium is disturbed. There is a general agreement among writers that this change begins at the portio vaginalis of the cervix at the junction of the squamous and columnar epithelium, and that the spread is laterally, but mainly upward into the endocervix, the process over-riding or displacing the normal columnar epithelium. There is also regularly described a thickening of the epithelium and especially a broadening and elongation of the rete Malpighii. The lesion characteristically grows into the glands of the endocervix and many think that it is from extensions through these glands that the lesion becomes invasive. The lesion then is a malignant change in the squamous epithelium without evidence of invasion of the stroma. It has been called noninvasive potential carcinoma, Bowen's disease of the cervix, incipient carcinoma, pre-invasive carcinoma, superficial noninvasive intraepithelial carcinoma, intraepithelial carcinoma, epithelial restlessness, psuedomalignancy, covert cancer, latent cancer, and many other synonyms.

Rubin (1) 1910 was the first American to describe cancer in the preclinical stage, or what he called incipient latent carcinoma. He expounded the idea that malignancy depended upon the intrinsic morphology of the epithelial cells rather than upon its invasiveness. He credits his teacher,

Schottlaender with the first description of the lesion, but others give credit to Borst-Wurzburg who published a description in 1904, some years before Schottlaender, and still others to Kermauner who wrote at about the same time as Schottlaender.

Cullen (2) 1921 studying sections of a cervix removed for endometrial hyperplasia, found malignant-like changes in a greatly thickened epithelium with very minimal invasion of the stroma. Little else was written until the early thirties when numerous gynecologists discovered these early stages of carcinoma. There was a widespread reluctance on the part of most gynecologists and pathologists to admit that these anaplastic and malignant changes in the epithelium could be malignant without evidence of invasion, cell nests in the stroma, and the typical inflammatory changes.

Among the early writers who thought the condition malignant were Pemberton and Smith (3) who in 1929 reviewed sections of a case of invasive carcinoma of the cervix, previously diagnosed as a benign cervix after a trachelorrhaphy four years before. This review revealed malignant changes in the epithelium with mitotic figures and loss of differentiation, but no signs of invasion. Dr. Frank B. Mallory and other noted pathologists reviewed these slides but considered it benign despite the neoplastic changes, because they considered invasiveness to be a requisite of malignancy.

Broders (4,5) 1932 first used the term carcinoma in situ for this malignant change limited to the epithelial layers. He argued that a lesion be classed as malignant or nonmalignant upon its cytology rather than on its position.

Te Linde (6) 1933 was one of the many men to consider the lesion benign though he described malignant changes in several cases of carcinoma in situ. He belabored men for indiscriminate hysterectomies on such a diagnosis. He was only one of many that Schiller of Vienna influenced to change their minds about the malignancy of this lesion after he came to this country in 1933.

Schiller (7) 1933 wrote extensively on carcinoma of the cervix and developed the iodine test for the selection of biopsy sites. He considered carcinoma in situ to be malignant and was instrumental in this concept becoming widespread. He pointed out that early carcinoma may be entirely asymptomatic, and noted the similarity of the epithelium bordering an invasive carcinoma and that seen in early carcinoma or carcinoma in situ. He pointed out the similarity of Bowen's dermatosis of the skin and carcinoma in situ. Schiller is one of many writers to object to the term "precancerous" as applied to carcinoma in situ, since it implies that the lesion may or may not become malignant, and is used quite loosely to include lesions that only

rarely become malignant. Schiller (8) argued that this condition was an early malignancy beginning in the epithelium and showing only changes in cytological character and not histological conditions such as downgrowths and invasion.

Smith and Pemberton (9) 1934 reviewed sections on three patients who had had trachelorrhaphies for various causes and later developed cancer of the cervix. Upon review of these sections, the diagnoses were changed to carcinoma in situ. These trachelorrhaphies had been performed three to twelve years previously. These men also report a case of a patient diagnosed as carcinoma in situ by biopsy, who was followed closely and in eleven months developed an early invasive carcinoma. This patient had a high cervical amputation, and the sections showed early carcinoma with minimal invasiveness. The patient is apparently cured eleven years later.

Schmitz and Benjamin (10) 1934 describe a case followed without treatment. The cervix was amputated for chronic cervicitis and serial sections revealed neoplastic changes confined to a hyperplastic epithelium. The case was diagnosed as an early epidermoid cancer, but no treatment other than the amputation was done. In ten months the patient had frank cancer of the stump by biopsy. The patient was apparently cured by radium therapy.

Stevenson and Scipiades (11) 1938 report a case diagnosed by biopsy as an intraepithelial cancer and followed eight years and one month before clinical cancer developed. They have several cases that were adequately treated for this lesion or with whom they have lost contact. One of their cases was diagnosed by biopsy as noninvasive cancer and died of other causes three years later. Serial sections of this cervix showed early carcinoma with minimal invasion. At that time, these men had eighteen cases of carcinoma in their series, obtained from a study of four thousand cervixes by serial section. Excluded were any that showed any evidence of invasion. The results were checked by Schiller and Emil Novak. In this series of eighteen, all but one was parous, nine had leukorrhea, seven had metorrhagia, two had post-coital bleeding, thirteen showed cervical erosions or lacerations, and four were hypertrophied.

Schiller (12) 1938 reported three cases of typical carcinomatous change in the cervical epithelium and penetration into the glands a maximum of 1.2 millimeters. These were untreated and sixteen months, eighteen months, and nine years later there was little change in these superficial carcinomas. He believes the period of surface growth is prolonged and that months and years pass before invasion takes place. He advises routine cervical biopsy as a means of increasing the per cent of cures of cervical carcinoma.

Younge (13) 1939 had two cases to report in addition to the sixteen cases reported by Smith and Pemberton from the Free Hospital for Women, Brookline, Massachusetts. These two cases developed invasive carcinoma two and one-sixth and three and one-third years after the original biopsies were diagnosed as benign, but upon review definitely show the picture of preinvasive carcinoma. Tracy B. Mallory in a discussion following this report, admits that the gynecologists at Brookline had taught the pathologists a lesson. He was speaking of Smith, Pemberton and Younge.

Martzloff (14) 1940 doubts the malignancy of any lesion without invasion, but decries the hard and fast attitude taken in borderline cases that noninvasive carcinomatoid changes are or are not definitely carcinoma. He believes that these cases should be treated regardless of what you believe as to its malignancy to eliminate the danger of an incurable malignancy.

Knight (15) 1943 reviewed seventeen cases of what he calls superficial epitheliomas. In eleven of these cases, carcinoma was unsuspected. These lesions were at or just within the internal os and extended up into the cervical canal. In none of these cases, had the stroma been invaded to any extent. He believes it is impossible to tell microscopically when rapid growth and invasion will become manifest, and recommends complete hysterectomy or curretage with radium and X-ray.

Te Linde (16) 1943 had a series of eleven cases of early invasive carcinoma. The average age of these patients was only thirty-six. In each case, diagnosis by biopsy showed only epithelial changes, but in all cases, the removed sections showed early invasion of the stroma.

Rubin (17) 1945 reported a case of carcinoma in situ who refused treatment. No further biopsies were obtainable but there was no gross evidence of carcinoma seven years later.

Taylor and Guyer (18) 1946 reported a case of a fifty year old woman who in 1938 had a cervical biopsy called epithelioma, and a second biopsy called chronic cervicitis. Six years and ten months later a diagnosis of a Stage I carcinoma was made. Upon review of the previous biopsies it was agreed that there was sufficient variation in cytology to justify a diagnosis of carcinoma in situ.

Pund and Auerbach (19) 1946 reported one of the largest and most reliable series up to that time. They made a diagnosis of carcinoma in situ in forty-seven cases or 3.9% of twelve hundred clinically benign cervixes examined after complete hysterectomies. This study based on whole cervixes, the sections so cut that only the minutest lesions could have escaped detection. The average age of this group was 36.6 years. The gross appearances of the cervixes varied widely. Seventy-one per cent had describable deformities,

but various cervical diseases were present excluding a possible relationship between the gross lesion and carcinoma. These lesions were located entirely on the gland bearing portion of the cervical lining, at or near the junction of the squamous and columnar epithelium. In general the extension was to displace the columnar epithelium of the endocervical lining. The line of advancement was abrupt as often as it was oblique. The change seemed to arise from the basal cells. The least vertical measurement was three millimeters and the maximum about two centimeters. These men recommend total hysterectomy for this lesion.

Goldberger (20) 1947 had a case that had no pelvic symptoms but showed a sugar frosting lesion on the cervix about one-half inch in diameter. A wedge biopsy revealed leukoplakia with marked cell irregularities and mitoses. No infiltration of the stroma could be demonstrated. A high cervical amputation was done, and sections of the removed cervix showed pronounced papillae which dipped into the connective tissue. There was marked anaplasia of the basalis layer with irregular cells and nuclei. There was a loss of polarity and mitotic figures but no break through the basement membrane by the abnormal cells was found. The patient was well with a normal appearing stump six months later.

Pund, Neffles, Caldwell, and Nieburgs (21) 1948 added nineteen cases of carcinoma in situ to the forty-seven cases reported by Pund in 1946. Carcinoma was not suspected in any of these cases which were entirely asymptomatic. Total hysterectomy was the treatment of choice. One of these cases was untreated and developed advanced carcinoma four years and nine months after the initial biopsy.

Ayre (22) 1947 produced a cancer-like lesion of the cervix near the squamous and columnar epithelial junction by the administration of estrogen to a vitamin deficient girl of twenty-five. In some cases of early cervical cancer, a low thiamine and riboflavin level has been found.

Foote and Stewart (23) 1948 believe that some cases of carcinoma in situ are not available to punch biopsy because they are mainly in the endocervix. They suggest biopsies anteriorly, posteriorly, and laterally and curettage as a possible means of discovering more of these early lesions. They reported twenty-seven cases in their series. Eleven of these cases had no symptoms and in twenty there was no suspicion of carcinoma.

Wespi (24) 1949 reported thirty-six cases, seventy-eight per cent of which had no symptoms. In reviewing slides of one hundred sixteen cases of carcinoma of the cervix, thirty one cases were found that showed carcinoma in situ changes at the margin of the frank carcinomas. He reported three cases

of carcinoma in situ developing into invasive carcinoma, but he has also followed some forty-five cases for over five years that have not developed invasive carcinoma in that time. He favors a careful macroscopic examination employing the Schiller stain, and the routine use of a colposcope.

Galvin and Te Linde (25) 1949 believe that carcinoma in situ is preceded by basal cell activity, and believe that it should serve as a warning for repeated biopsy. These men collected seventy-five cases of carcinoma in situ by biopsy, but in fifty-five of these cases a more careful study revealed invasion. In twenty, however, only carcinoma in situ was found. Fifty-eight per cent of these seventy-five cases had irregular vaginal bleeding but this was mainly post coital spotting. These men recommend total hysterectomy, but if the woman is desirous of bearing children, she is followed with routine examinations. They have six cases followed in such a manner for more than five years.

Diddle, Ashworth, Brown, and Bronstad (26) 1949 reported seventeen cases. The average age was 36.2 years, and seldom were there any associated symptoms. They have followed two of these cases over six years and the lesions have remained localized and have not developed invasiveness.

Younge, Hertig, and Armstrong (27) 1949 summarized the one hundred thirty-five cases found at the Free Hospital for Women, Brookline, Massachusetts. At this hospital it is the

practice to biopsy every eroded, everted, or positive Schiller stained cervix, and fifty-eight of these cases were collected in this manner. Forty-two were diagnosed at the time of conservative pelvic operations, and thirty-five others were found by routine sections after pelvic surgery. They believe the frequency with which these lesions are being found is increasing because more routine biopsies are being done. In ten years at the Free Hospital, the incidence has remained about the same. In 1937 two cases were discovered in one hundred fifty-one biopsies or 1.32%. In 1946 eleven cases in nine hundred fifty-five biopsies or an incidence of 1.15%. These men place the incidence of invasive carcinoma of the cervix at 3.3%, and thus the incidence of carcinoma in situ approaches but does not exceed the incidence of invasive carcinoma. The age of these patients was 38.6 years or 9.3 years less than the accepted age of forty-eight years for frank carcinoma. Twenty-three of these patients were less than thirty years old. Forty-six per cent of these patients had no symptoms relative to the cervix. Twenty-four per cent had leukorrhea, and thirty per cent had abnormal bleeding, usually post coital. Ninety-four of these cervixes were regarded as normal.

In thirty-one of these cases, seventy-one per cent had positive papanicolaou smears on repeated attempts. These men as well as Novak (28) 1949 and others do not believe

that carcinoma in situ can be distinguished from invasive cancer on vaginal smears. However, Nieburgs and Pund (29) 1949 believe that there are "specific cells" of carcinoma in situ on papanicolaou smears in a high percentage of cases. Novak believes that a simple but complete hysterectomy is the treatment of choice but since this lesion is found in such a young age group preservation of fertility would be desirable. Six of the patients of the series from the Free Hospital recieved cauterization as treatment and have become pregnant since. Of this series of one hundred thirty-five only four died of cancer of the cervix and three of these were originally misdiagnosed.

Another of these cases showed a mildly eroded cervix, and a biopsy revealed carcinoma in situ, but in the operating room the cervix appeared so normal that in the opinion of the surgeon no treatment was necessary. Six and one-half months later a biopsy from the same area was positive to the Schiller test and a biopsy showed carcinoma in situ. Eleven months later, another biopsy and curretment was done and fragments of carcinoma with pegs of stromal invasion were found. The cervix was amputated and serial blocks showed a small invasive carcinoma five millimeters in the greatest diameter at the site of the original carcinoma in situ. These men now have sixty-nine cases diagnosed by biopsy as carcinoma of the cervix in situ that have been

followed with routine examinations for at least five years with little evidence of progression.

Piper (30) 1949 reported the thirty-two cases of carcinoma in situ collected at the Mayo Clinic from 1932 to 1946. These were diagnosed by biopsy. Eighteen had pelvic symptoms, but fourteen had no symptoms at all. Twenty-eight had hysterectomies, three had a dilatation and curettage plus radiation and one patient was not treated at the clinic. Two died of heart disease but the rest are alive and have had no recurrence of carcinoma.

Novak (29) 1949 noted that the endocrine stimulation of pregnancy caused hyperplasia, basal cell hyperactivity, changes in the nuclear size, and increased mitoses of the cells of the endocervix giving a picture similar to carcinoma in situ, but which disappeared after involution of the uterus postpartum. Te Linde does not make the diagnosis of carcinoma in situ during pregnancy due to these changes.

Danforth (31) 1950 reported that forty-five per cent of biopsies of pregnant cervixes showed deviation from the normal including a higher incidence of inflammation than in the non-pregnant, increased mitoses, basal cell hyperactivity, thickening of the squamous epithelium, considerable variation in cell size and nuclear size, and increased hyperchromatism. These changes can be found in normal non-pregnant cervixes but seem to be increased during pregnancy and since they

are similar to changes in carcinoma in situ, this diagnosis should probably not be made on pregnant women. These changes are thought to be due to intense endocrine stimulation and revert to normal soon after delivery. Hellman and Te Linde confirm this work and insist that invasiveness is necessary to make a diagnosis of malignancy in a pregnant cervix. These changes and their relationship to carcinoma in situ have not yet been properly evaluated.

Jones (32) 1950 described a case of a forty-six year old woman first seen in 1939 with a vaginal discharge and an eroded and lacerated cervix. The cervix did not seem to heal and was cauterized three times electrically and twice with silver nitrate in a period of about a year. A conization was done but did not heal properly and was cauterized twice more in the next eleven months. In March 1939, a biopsy and rebiopsy revealed benign epithelial hyperplasia. Several more examinations were carried out and the cervix seemed to be healed although the discharge more or less persisted for the next nine years. There was an episode of a bloody discharge in May 1949 and on one other occasion. In January 1950, a friable area on the posterior cervical lip was noted and after a conization the diagnosis of an invasive carcinoma was made.

In summary, carcinoma in situ of the cervix is a lesion confined to the epithelial layer of the cervix but showing

all malignant changes except invasiveness. There are some thirty-one cases now reported in which invasive carcinoma developed from carcinoma in situ. There are, however, some one hundred twenty cases that have been followed at least five years without the development of invasive carcinoma. There are also a number of cases where the diagnosis was made by biopsy in which no further evidence could be found on repeated biopsies. This has been explained on the basis that the entire lesion was removed at the time of the original biopsy. It is unknown how many of these diagnoses were made on pregnant uteri. There is, therefore, no unanimity on the subject, but most men are convinced that the process is definitely malignant and will develop into frank or invasive cancer in a matter of time. It is generally conceded that the diagnosis should not be made during pregnancy.

The average age of the victims is some eight to twelve years less than the average age for invasive carcinoma of the cervix. Symptoms are absent or minimal in most cases. Many of the cases are picked up on routine smears and biopsies, both of which are invaluable in the detection of early carcinoma. There are many who favor routine pelvic examinations on all women over thirty-five years of age. Almost all agree that the treatment of choice is a simple total hysterectomy. If the woman is young and wishes to bear children, cauterization

can be done and the patient followed carefully. Some men suggest carefully following all cases of carcinoma in situ in premenopausal women. The rate of cure is almost one hundred per cent and discovery of such a lesion is a great service.

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