Detection, Diagnostic Evaluation and Treatment of Dysplasia, Carcinoma In Situ and Early Invasive Cervical Carcinoma

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Dysplasia, in situ and early invasive carcinoma of the cervix are becoming an increasingly important part of the problem of cervical cancer. The mounting frequency with which these diagnoses are made is directly related to the increased use of the Papanicolaou smear technique. This fact is reflected in Table 1. At the same time, a significant decrease in the number of new patients with Stage II and Stage III invasive cancer was noted. Whether this is directly related to cytologic screening is a more complicated problem and one surrounded by some controversy. Clearly the physician must be aware not only of the importance of cytologic screening but also of the details of how to carry it out. He must also understand the meaning of cytologic reports so that he knows which patients require further investigation. Finally, he should educate himself concerning the investigation that is indicated and see that it is done either by himself, if he is qualified, or by someone who is trained in this field. The purpose of this article is to outline the detection, diagnosis and treatment of these early cervical lesions.

Detection

It is strongly suggested by the studies of Christopherson and associates1 and by Boyes2 that the detection and eradication of dysplasia and carcinoma in situ (cervical intraepithelial neoplasia) in a population will prevent the subsequent development of invasive cervical carcinoma and lead to a dramatic fall in death rates from that disease. Due to the lack of clinical signs or symptoms in the intraepithelial phases, routine surveillance techniques are required to detect these early lesions and, although a number of different screening techniques have been suggested over the years, the cytologic smear has proven to be the most easily applied, economical, and effective tool yet devised.

The occurrence of squamous cell carcinoma of the cervix and its precursors is confined almost exclusively to those women who have had sexual intercourse, and a higher relative risk is associated with early sexual experience and multiple sexual partners.3 Although the peak in the age-specific prevalence of carcinoma in situ falls in the 30-40 year age group, the peak incidence rates occur in the 20-30 year olds, while the earliest precursor, termed mild dysplasia or CIN, grade I, may

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be seen in the teens. In general, the earlier intraepithelial lesions are easier to eradicate than the later ones and a premium is placed on early detection not only of precursor lesions, but of the earliest lesions within the spectrum. In light of current knowledge about epidemiology, natural history and management, it is clear that cytologic screening is a mandatory part of any preventive medical program, and that women should be screened regularly when they begin sexual activity, at whatever age. The choice of a screening interval depends upon many complex factors but is generally chosen to be one year. The optimal cytologic sample should include both a cervical scraping and a sample from the cervical canal, the latter obtained using either an external os aspirator or a cotton-tipped applicator stick. The utilization of a vaginal pool sample as the only source of cells is unacceptable due to its high false negative rate (Table 2).

The cytology report is given in a variety of ways ranging from a simple positive-negative to a narrative statement of the nature of the lesion to be anticipated. A numerical classification when used without an accompanying narrative diagnosis encourages a lack of discipline that may at times lead to inaccurate reporting. An acceptable reporting system should include a narrative when numbers are used. An example of this type of reporting system is presented in Table 3. Regardless of the reporting system, the factor that is probably of greatest importance is good communication between the cytologist and the clinician. It is the responsibility of the clinician to know the implications of
### TABLE 2
CYTOLOGICAL FALSE NEGATIVE RATES IN PATIENTS WITH CERVICAL NEOPLASIA

| Collection Technique | Carcinoma in situ or Invasion % False Negative | Dysplasia % False Negative |
|----------------------|-----------------------------------------------|---------------------------|
| External os aspiration | 4                                             | 17                        |
| Cervical scraping     | 6                                             | 28                        |
| Vaginal Pool aspiration | 45                                           | 63                        |

### TABLE 3
CLASSIFICATION OF CERVICAL SMEARS

| Class | Description |
|-------|-------------|
| Class I | Smear normal. No abnormal cells. |
| Class II | Atypical cells present below the level of cervical neoplasia. |
| Class III | Smear contains abnormal cells consistent with dysplasia. |
| Class IV | Smear contains abnormal cells consistent with carcinoma in situ. |
| Class V | Smear contains abnormal cells consistent with invasive carcinoma of squamous cell origin. |

### TABLE 4
COLPOSCOPIC PREDICTABILITY

| Authors                | Microinvasion or Invasion Missed |
|------------------------|----------------------------------|
|                        | Negative ECC                  | Positive ECC               |
| Ronk et al 1977\(^7\)  | 2 of 87 (2.3%)                 | 13 of 59 (22.0%)           |
| Townsend et al 1970\(^8\) | 0 of 26 (0.0%)                 | 8 of 50 (16.0%)            |
| Chanen & Hollyock 1974\(^9\) | 0 of 224 (0.0%)               | 9 of 162 (5.5%)            |
the report he receives, irrespective of the classification that is used, and to monitor the quality of the service he receives.

**Colposcopy and Biopsy Techniques**

The colposcope has been in use for more than 40 years—until recently, principally in Europe and South America. It provides a well-lighted, magnified stereoscopic view of the cervix and its utilization in the evaluation of the cervix is increasing rapidly in the United States. Cervical intraepithelial neoplasia begins in the transformation zone, that area of the cervix in which native columnar epithelium is replaced by squamous epithelium. The colposcopic evaluation of the transformation zone and of the endocervical canal is a useful procedure in the evaluation of a patient with an abnormal cervical smear. Colposcopy is not recommended as a screening technique. It is too time-consuming and expensive for use on a large scale. Cytology is the screening method of choice.

In the colposcopic evaluation of the patient with an abnormal smear the cervix is bathed with a three percent acetic acid solution to accentuate the topographic and vascular alterations that are found in neoplastic epithelium and that serve to differentiate it from the normal or metaplastic areas. The alterations accompanying neoplasia include areas of white epithelium and abnormal vascular patterns referred to as mosaic or punctuation. Although these colposcopic changes are not diagnostic of cervical neoplasia, their presence is highly correlated with disease and a study of their grade and distribution is useful in delineating the lesion prior to conization or as a part of an outpatient management protocol. In addition, highly abnormal vascular forms regularly accompany invasive cervical carcinoma and a highly skilled colposcopist can identify areas of invasion within an intraepithelial neoplasm. Colposcopy should not be regarded as a definitive diagnostic technique, however, but as an additional tool for the evaluation of the cervix and for identifying areas to be biopsied.

The details of colposcopic technique and particularly its use as part of a diagnostic evaluation and management program are beyond the scope of this article but are covered in detail in several texts. Colposcopy requires constant practice to achieve and retain a high level of accuracy. The use of colposcopy is best suited to an institutional setting where significant numbers of abnormal smears are obtained. Few clinicians in solo practice will have adequate numbers of abnormal smears to maintain the skill needed to perform colposcopy accurately. It is clear that there is a definite limit to the accuracy of the colposcope in precisely subclassifying cervical intraepithelial lesions as demonstrated in Table 4, where error rates are shown. To minimize the error rate, extensive biopsies and endocervical curettage should be done routinely in the patient with an abnormal smear.

In any therapy protocol the critical factor is the ability to rule out the presence of invasive disease and in skilled hands the need for diagnostic conization may be reduced. In the evaluation of the patient with an abnormal smear, colposcopy is extremely useful, but a conization must be performed if: (1) there is no colposcopically visible lesion and the abnormal tissue is thought to be in the canal; (2) the entire lesion cannot be seen with the colposcope; (3) the patient is considered an inappropriate candidate, e.g., one deemed unreliable in follow-up; (4) when a diagnosis of microinvasion is made on a colposcopic biopsy; and (5) the colposcopically directed biopsies fail to explain the cytology. The corollary of the last indication for conization is that the clinician who undertakes a colposcopic diagnosis and management program must have access to a very high quality cytology and histology consultation service in order to detect invasive cancer. In those patients with an abnormal smear and no visible lesion, the biopsies should be performed under colposcopic control if possible (Fig. 1). If colposcopy is not available, the application of Lugol's iodine solution is helpful in delineating biopsy sites (Fig. 2). As pointed out above for colposcopy, the Lugol's technique has a signifi-
cervical conization.

Alternatively, the physician can carry out a conization. Regardless of the biopsy technique used, a complete evaluation should include a carefully performed endocervical curettage above the cervical biopsy. The so-called four quadrant biopsy technique cannot be recommended because of its lack of accuracy.

The tissues removed by endocervical curettage and punch biopsy are most easily oriented if one of the small square curettes and punch biopsy instruments, such as the Kevorkian, are used. Those instruments, especially designed for superficial cervical biopsies, produce minimal bleeding and lend themselves to an office procedure.

To obtain the maximum information from the biopsy specimens, the clinician should place all the curetted material, including blood, mucus and tissue fragments on a small piece of paper towel prior to fixation and should prepare the biopsy specimens similarly, taking care to orient the tissue on the towel so that the plane of the epithelium is perpendicular to the plane of the towel. Bleeding is not usually a problem if the proper biopsy instruments are used, but if it does occur, simple pressure or the application of Monsell’s solution is adequate for its control.

In the absence of the availability of the instruments or skills described above, the patient with a smear consistent with cervical neoplasia, in whom a diagnosis of invasive carcinoma has not been established by punch biopsy, should be further evaluated by cervical conization.

A diagnostic conization should be performed with a cold knife and not by electrocautery, for the latter may destroy tissue at the cut edge and, since the only malignant tissue present may be at this point, the diagnosis may be missed. The portio incision for the conization procedure should lie outside the transformation zone so as to include all potentially neoplastic tissue in the specimen and, if the endocervical margin is not chosen colposcopically, at least 50-75 percent of the canal should be removed. This should be followed by a curettage of the remaining endocervical canal.

The neoplastic epithelium separates easily from the underlying stroma in many cases, and the diagnostic tissue may be lost due to trauma. Therefore, it is best to avoid vaginal preparation with sponges. The conization should be prepared for by an antiseptic douche the night before surgery, and then a gentle antiseptic douche again when the patient is on the operating table and ready for the procedure. The conization should be done before the dilatation of the cervix is performed. In the past, the two main complications of conization have been stenosis and late hemorrhage. Stenosis can be prevented in virtually all patients by sounding the endocervical canal at two weeks and six weeks after the conization. Late hemorrhage characteristically occurred at approximately eight to 10 days after surgery when the absorbable sutures were weakened and “let go.” The development of newer synthetic absorbable sutures that retain tensile strength for much longer periods of time has virtually eliminated late hemorrhage as a complication of the cone biopsy.

The tissue obtained by conization must be examined completely. This requires many sections taken at frequent and regular intervals throughout the entire specimen.

A positive cervical smear in pregnancy suggestive of carcinoma must be pursued as though the patient were not pregnant. Averette and associates have shown that conization does not predispose to abortion. In general, it is better to avoid anesthesia during the first 10 weeks of pregnancy when organogenesis occurs. If an invasive carcinoma is likely, however, one should not delay. The cone specimen should be “more shallow” during pregnancy. “More shallow” in this instance means that it should not extend as far up the canal as in the non-pregnant patient. If a skilled cytologist and colposcopist are available, the carefully selected patient may be followed through pregnancy without a conization and re-evaluated and treated postpartum. The “carefully selected” patient in this instance is one whose cytologic smear does not suggest
Fig. 1. Cervical smear flow chart when colposcopy and skilled colposcopist are available.
Fig. 2. Cervical smear flow chart when colposcopy is not available.
invasive carcinoma and whose colposcopic findings are compatible with an earlier lesion.

Although cytologic screening is the most important procedure employed to discover unsuspected carcinoma of the cervix, a punch biopsy of the cervix at the time of emptying the uterus for an abortion has led to the detection of many cases of cancer. If a lesion of the cervix is present, it should be biopsied, but if no lesion is present, the specimen should be obtained from the transformation zone and include the squamocolumnar junction if it is accessible. Cervical neoplasia begins at the squamocolumnar junction of the transformation zone and extends into that zone on the exposed portion of the cervix. The application of three percent acetic acid to the portio may be helpful in delineating the transformation zone if it is not obvious.

Pretreatment Evaluation

The basic principle in pretreatment evaluation of any cancer can be stated simply: know the extent of the disease as accurately as possible before treatment is considered. The axiom applies in all cases of pelvic cancer but is critical in cervical carcinoma.

The foregoing discussion has been directed at accurately determining the extent and severity of the local lesion. This constitutes step one and until this is completed, the physician should not proceed with treatment. Only after step one will the clinician know whether he/she is dealing with dysplasia, carcinoma in situ, or invasive carcinoma of the cervix. Knowing the nature of the local lesion, one is prepared to proceed with the other indicated pretreatment studies.

Dysplasia and Carcinoma In Situ (Cervical Intraepithelial Neoplasia) (Table 5)

When a diagnosis of intraepithelial neoplasia has been properly established, it can be said with confidence that the danger of an unexpected finding of invasive carcinoma has been eliminated. Therefore, it is not necessary to carry out diagnostic studies for evidence of metastatic disease. One must decide upon the therapy and evaluate the general health of the patient to make certain that whatever therapy is selected is within the capacity of that patient to withstand.

Stages I and IIA

Table 6 gives the International Classification of carcinoma of the cervix. Stage I is now subdivided into Stages IA and IB. Stage IIA carcinoma of the cervix includes only the very earliest of Stage II cases; more specifically, those cases with spread of the disease from the cervix onto the vaginal mucosa. Stage IIA is included under this discussion of early carcinoma of the cervix because up through and including Stage IIA carcinoma of the cervix there is an option available to the clinician insofar as treatment is concerned. Beyond Stage IIA it is the general consensus that radiation therapy is the only form of treatment that should be seriously considered. Beyond Stage IIA radical surgery cannot eradicate the disease except in a small proportion of cases and is to be condemned.
The pretreatment evaluation of patients with invasive carcinoma of the cervix should be the same regardless of the stage of the disease, and requires a thorough investigation for evidence of metastatic spread. Studies should be directed first at the structures immediately surrounding the cervix because this disease spreads mainly by direct extension. Therefore, cystoscopic examination is important to rule out direct extension to the base of the bladder and also to rule out any unassociated but significant bladder pathology. The ureters, which lie in close lateral proximity to the cervix, should be examined by intravenous pyelography before treatment. For the same reason, proctoscopic and sigmoidoscopic examinations should be carried out on all patients with invasive carcinoma of the cervix. Barium enema is not done except in patients over the age of 40 or in patients with symptoms suggestive of colon disease. Finally, chest x-ray and skeletal x-rays are done to rule out possible distant metastases to those sites. Blood chemistries are done with two purposes in mind. The first is to add to the overall evaluation of the patient's general health and, therefore, a blood urea nitrogen and fasting blood sugar are obtained. Second, liver chemistries are obtained to detect any latent liver disease and also to serve as a baseline during and after therapy.

The final, and perhaps the most important, step in pretreatment evaluation is that of the pelvic examination to describe in detail any deviation from normal. The speculum examination is important to visualize the cervix and the extent of any lesion that may be present. The rectovaginal examination is the critical part of the pelvic examination since it permits the palpation of extension of the disease into the paracervical ligaments. Nelson and associates, Averette and associates, and others have shown a significant error in clinical staging; however, it remains the most important step in the estimate of extent of disease and choice of therapy. Palpation of induration of the paracervical ligaments is not difficult, but the International Classification specifically states that there must be nodular induration in order to consider it extension of the cancer.

By breaking the pelvic examination down into those three basic components, namely, speculum examination, bimanual and rectovaginal examinations, one can see and palpate the extent of the local lesion. When this procedure is combined with the previously described diagnostic studies, the individual case can be placed in the proper stage of the International Classification. Then, but not before, a treatment regimen may be considered.

**Treatment—Cervical Intraepithelial Neoplasia (CIN)**

**Dysplasia**

With refinement of the techniques previously described to detect cervical intraepithelial neoplasia (CIN), and the addition of epidemiological and laboratory studies, the concepts regarding the development of cervical cancer have been modified in recent years. An understanding of the disease process and its implications is essential to the clinician who determines therapy. Normally, in cervical squamous epithelium, the generative or mitotic compartment is confined to the basal and lower parabasal cell layers. Cervical neoplasia originates as a focal event at the squamocolumnar junction, histologically an area of altered cell growth characterized principally by cytologic pleomorphism involving the full thickness of the epithelium. There are alterations in cell-cell contacts, a decrease in the production of specialized cell products, such as glyco- gen, and an increase in cell turnover rates.

The various degrees of dysplasia or intraepithelial neoplasia are distinguished by the extent to which the full thickness of the epithelium is composed of undifferentiated neoplastic cells. If such cells occupy the lower one-third of the epithelium, the lesion is referred to as CIN Grade 1, or mild dysplasia (Fig. 3); if they occupy up to two-thirds of the thickness of the epithelium, the term moderate dysplasia, or CIN Grade 2 (Fig. 4) is used; and if the undifferentiated neoplastic cells reach almost to the surface, the lesion is referred
to as severe dysplasia, or CIN Grade 3 (Fig. 5). When the entire epithelium is composed of undifferentiated neoplastic cells, it is generally diagnosed as carcinoma in situ, or CIN Grade 3 (Fig. 6).

Cervical intraepithelial neoplasia forms a continuum beginning with mild dysplasia and ending with invasive carcinoma, but there remains some controversy over the definitions of the early stages of this spectrum of disease and over the natural history of its subsets. It is generally agreed that patients with the earlier grades of CIN (the dysplasias) may have one of three courses, namely, regression, persistence or progression to carcinoma in situ, or invasive carcinoma. Furthermore, it has consistently been reported that the risk of progression to more significant stages of the disease increases with decreasing differentiation.

The fate of CIN depends upon many factors, the most important of which are the histological grade and how the lesion is defined. Many authors have performed prospective clinical follow-up studies.

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**TABLE 6**

**INTERNATIONAL CLASSIFICATION CERVICAL CARCINOMA**

| STAGE | Description |
|-------|-------------|
| 0     | Carcinoma in situ, intraepithelial carcinoma. |
| I     | Carcinoma confined to the cervix (extension to the corpus should be disregarded). |
| Stage Ia | Microinvasive carcinoma (early stromal invasion). |
| Stage Ib | All other cases of Stage I. Occult cancer should be marked "occ." |
| II    | The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina, but not the lower third. |
| Stage IIa | No obvious parametrical involvement. |
| Stage IIb | Obvious parametrical involvement. |
| III   | The carcinoma has extended to the pelvic wall. On rectal examination there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydro-nephrosis or non-functioning kidney. |
| Stage IIIa | No extension to the pelvic wall. |
| Stage IIIb | Extension to the pelvic wall and/or hydro-nephrosis or non-functioning kidney. |
| IV    | The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bulous edema does not classify as Stage IV. |
| Stage IVa | Spread of the growth to adjacent organs. |
| Stage IVb | Spread to distant organs. |
Although the rates of progression and regression have varied, most have concluded that the entire spectrum of CIN places the patient at risk but that the risk is higher with increasing histological grade. As the lesion loses its differentiated features it is less likely to regress and more likely to progress.

In the report by Hall and Walton,19 for example, 206 cases were followed from one to 14 years. The results are shown in Tables 7 and 8. The cases were differentiated morphologically into slight, moderate and marked degrees of dysplasia, and the subsequent course was directly related to the degree of dysplasia. Their study suggested that the carcinogenic factors require a longer period of time to produce the change to carcinoma. Further support for this concept comes from Stern's20 finding that the majority of new cases of cancer originate in a population of women with dysplasia.

The 532 women followed by Richart and Barron21 all had dysplasia ascertained by three separate abnormal smears and followed without biopsy—an important difference when compared to Hall and Walton's report. Richart and Barron confirmed that dysplasia is a significant lesion but reported much higher progression rates than Hall and Walton and very few spontaneous regressions (Table 9). The increased progression rates are thought to be due to the absence of biopsies, which by itself may cure early lesions. This study also demonstrated that there is a proportion of patients in each group who fail to progress to the next higher group, and that based on its previ-
I. CIN has been studied with regard to cell turnover times, behavior in tissue cultures, fine structure and cell biology, and these have all confirmed the thesis that the cervical carcinoma precursors form a continuum, the subsets of which can only be distinguished by arbitrarily set limits.

If a patient has a small lesion whose distribution makes it amenable to excision by conservative biopsy methods and is in the hands of physicians skilled in such procedures, treatment may be undertaken by this means. In general, as shown by Rome and associates, the more severe grades of dysplasia are more extensive and consequently require more extensive treatment methods. The problem should be explained in detail to the patient; she should be instructed as to the necessity of regular follow-up examinations with cervical smears, and she should be a reliable follow-up candidate (Figs. 1 and 2).

In cases in which the lesion is extensive, making local therapy difficult or impossible, conization or even hysterectomy may be indicated, particularly if the patient does not wish to have children or if infertility is present on the basis of tubal obstruction. Whatever course of treatment is recommended, patients with dysplasia (cervical intraepithelial neoplasia), regardless of its degree, should be followed after treatment is completed in the same manner as the patient who has been treated for invasive carcinoma.

Reports of the use of cryotherapy and electrocoagulation as a means of...
treat the dysplasias have begun to appear in increasing numbers. It must be emphasized again that a conservative approach to the management of this disease requires the utmost skill on the part of the cytologist, pathologist, and clinician and that unless such skills are available, there is a strong possibility of incorrect management. Sevin and associates\(^2\) have recently reported on eight patients with invasive cervical carcinoma occurring after cryotherapy was used to treat presumably preinvasive lesions. Three patients had normal cytology prior to the use of cryotherapy. Five patients had abnormal cytology, and four of the five had inadequate evaluations prior to the use of cryosurgery. In addition to the problem of inadequate evaluations, the long-term effectiveness of cryotherapy has not been demonstrated. It is now under investigation. Until more data are available, outpatient methods should be reserved for office practices and centers in which such studies can be undertaken safely and evaluated.

### Stage 0 Carcinoma of the Cervix (in situ) or CIN Grade 3

Carcinoma in situ, or CIN Grade 3, is widely accepted as a precursor of invasive carcinoma. This is based on two general types of evidence: first, the finding of carcinoma in situ and invasive carcinoma simultaneously in the same cervix; and second, the development of invasive carcinoma in patients followed without treatment after a diagnosis of carcinoma in situ has been made. Peterson\(^3\) and Funck-Brentano\(^4\) studied the development of invasive carcinoma in patients followed without treatment after a diagnosis of carcinoma in situ had been made. Peterson reported on 127 patients with carcinoma in situ who were followed without definitive treatment in the Radium Center at Copenhagen. Invasive carcinoma developed in 22 percent of follow-up. Beyond nine years, the number of patients available for follow-up was too small to be significant. Such studies are no longer reported because it is no longer acceptable to follow patients without treatment unless childbearing is an important consideration. Although carcinoma in situ (CIN Grade 3) is considered to be part of the continuum of precursors of cervical carcinoma, it has commonly been considered separately because: (1) it has an important place in the classical literature on this disease; (2) it tends to occupy a larger area, particularly in the endocervical canal, than lower grade lesions; and (3) the patient with carcinoma in situ statis-

| Degree of Dysplasia | Regressed (%) | Persisted (%) | Progressed (%) |
|---------------------|--------------|--------------|---------------|
| Slight              | 62.2         | 24.4         | 13.4          |
| Moderate            | 32.9         | 48.7         | 18.4          |
| Marked              | 19.1         | 47.6         | 33.3          |

### TABLE 7

**BIOLOGICAL SIGNIFICANCE ACCORDING TO SEVERITY OF DYSPLASIA**\(^5\)

1. **JOURNAL FOR CLINICIANS**
### TABLE 8
**INCIDENCE OF CARCINOMA IN SITU**

| Degree of dysplasia | Number of cases of dysplasia | Cases of carcinoma in situ from dysplasia |
|---------------------|-----------------------------|----------------------------------------|
| Slight              | 97                          | Number | Percent |
| Moderate            | 85                          | 11     | 12.9    |
| Marked              | 24                          | 7      | 29.1    |

### TABLE 9
**PROJECTED PROPORTION OF PATIENTS BY SMEAR CLASS HAVING PROGRESSION TO CARCINOMA IN SITU**

Graphical representation of the progression rates to carcinoma in situ of patients with entering diagnoses of 3 (very mild dysplasia), 3A (mild dysplasia), 3B (moderate dysplasia), and 3C (severe dysplasia) and for all dysplasias. Dotted lines represent medians where each follow-up examination is 8 months.
tically has a greater risk of invasion occurring in a shorter period of time.

The findings in 402 cases of carcinoma in situ detected at Downstate Medical Center reflect those reported by other clinics. Patients with carcinoma in situ are, for the most part, from the lowest socioeconomic group. The patient with carcinoma in situ is characteristically one who began sexual activity at an early age. This is reflected in the Downstate series by the fact that 89.7 percent of patients were married, separated, divorced or widowed. Their marital status is concrete evidence of sexual activity and when tied to the fact that only 4.9 percent of the patients had not been pregnant, it allows one to calculate for the individual the latest that sexual activity may have begun.

The patient who desires childbearing should have a full explanation of the problem and may be allowed to proceed to have children, provided she is willing to undergo regular follow-up examinations including cervical smears at three month intervals. If the patient’s past obstetrical history indicates a long-standing problem of infertility, it may be advisable for her to undergo hysterectomy. If the patient is known to follow instructions poorly and to be a poor follow-up candidate, then serious consideration should be given to advising surgery.

Although there is still debate as to whether conventional conization is an adequate therapeutic measure, series are being accumulated in which conization alone is utilized for treatment, and the early results are encouraging. However, the patient so treated must be reliable and available to follow-up to be safely treated by conization alone since Kolstad et al have shown that the recurrence rate is significant. If a hysterectomy is performed the vagina should first be examined colposcopically, or by Lugol’s iodine, to determine whether the CIN extends to or past the fornix. In the absence of demonstrable vaginal disease there is evidence to suggest that the removal of the upper third of the vagina is not beneficial, even though Way and others have reported a substantial proportion of patients with vaginal involvement. It is important to note that there are no publications in which a large number of pa-
patients have been followed for over ten years after total abdominal hysterectomy with no vaginal cuff. Final judgment must be reserved on the adequacy of this form of treatment. Total abdominal hysterectomy is, without question, the most commonly used form of definitive treatment.

Stage IA (Microinvasive) Carcinoma

Although most reports indicate that Stage 0 cervical carcinoma may be treated by conservative means, considerable controversy exists regarding the diagnosis and management of Stage IA cervical cancer. Most agree that it is the earliest stage in the transition of cervical intraepithelial neoplasia to invasive carcinoma and represents no threat of metastasis. With respect to treatment, the crux of the problem seems to be how much infiltration into the stroma is permissible so that simple methods may be utilized rather than the radical radiotherapy or surgery required for a more advanced carcinoma.

In recent years, confusion has resulted from numerous reports on “microinvasive” or “superficially invasive” carcinoma, largely because many fail to define the extent to which infiltration has progressed from the in situ stage. For example, we have noted 18 definitions for “microinvasive” carcinoma; the term is variously defined as stromal invasion to a depth beneath the basement membrane of one mm, \(0.15\) mm, three to four mm, and five mm. Most studies conclude that if the diagnosis of microinvasive carcinoma is made, the patient may be treated safely by total hysterectomy, as is done for Stage 0 carcinoma. Some authors add qualifications such as evidence of lymphatic vascular penetration by squamous carcinoma as a reason for disqualifying a lesion as microinvasive, irrespective of the depth of stromal invasion. Others report that lymphatic penetration is unimportant in the diagnosis of microinvasion. Also, it should be noted that pelvic lymph node metastases have been reported with stromal invasion of less than three mm.

At the University of Miami School of Medicine, interest in microinvasive carcinoma developed as a result of expansion of a cytologic screening program to detect preclinical cervical neoplasia. In 1957, 6,139 Pap smears were obtained that ultimately led to the diagnosis of Stage 0 carcinoma in 19 patients, when a cone biopsy of the cervix was done for suspicious or positive cervical cytology. The cone biopsy of one patient contained a small focus of several squamous cells penetrating the basement membrane, which was interpreted as “superficially invasive” carcinoma of the cervix. Since the diagnosis was invasive carcinoma, the patient was treated by radical hysterectomy and pelvic lymphadenectomy. Study of the operative specimen revealed no residual cancer and all nodes were negative for metastases. In 1960, 13,312 Pap smears led to the diagnosis of in situ carcinoma in 166 cone specimens and “superficially invasive” carcinoma in 16 patients. All patients with invasive carcinoma were treated by radical surgery or radiotherapy. When it became apparent by 1961 that none of the 36 patients classified as having “superficially invasive” carcinoma...
had lymph nodes that contained metastatic carcinoma and the uterine specimen frequently contained no residual carcinoma, it was decided to revise the plan of therapy. Thereafter, all patients demonstrating invasion of the cervical stroma less than one mm were treated by total abdominal hysterectomy with a wide vaginal cuff. In addition, pelvic lymphadenectomy was done so that lymph nodes could be examined for possible metastasis. After 87 consecutive lymphadenectomies without lymph node metastasis, it was concluded that treatment for "superficially invasive" carcinoma would include only total abdominal hysterectomy with a wide vaginal cuff, without pelvic lymphadenectomy. To date, no patient treated in this manner has demonstrated any evidence of recurrent or persistent cervical carcinoma.

From the foregoing, it seems evident that the literature on diagnosis, management and prognosis for microinvasive or "superficially invasive" carcinoma of the cervix creates confusion and dilemma. Unfortunately, it is not possible to diagnose microinvasion except by histologic examination. It is unlikely that all observers actually measured the depth of stromal invasion; certainly, most reports fail to mention the method by which depth of invasion was measured. Initially, at the University of Miami, histologic specimens were designated merely as "superficially" or "deeply" invasive. Since it appeared that many observers diagnosed microinvasion when they saw a few cells beneath the basement membrane and estimated the number of millimeters of cell penetration into the stroma, it seemed of interest to measure accurately cell diameters and epithelial thickness in human cervical tissues to clearly indicate what one, two, five, or more millimeters of penetration represented. Using precisely calibrated optics, it was found that the average diameter of squamous cancer cells of the "large" type was 16.5 microns; of the "small" type, 11.2 microns. At 1,000 microns to the millimeter, penetration of the basement membrane to a one mm depth is equivalent to 66 cell layers of the large cell type and 89 layers of the small cell type. Obviously, three mm of stromal invasion represents more than a few cells beneath the basement membrane. Similar measurements were made of the squamous epithelial thickness in 10 patients with normal ovulatory cycles. The epithelial thickness varied from 0.20 mm to 0.32 mm with an average thickness of 0.26 mm. Also, measurements were made of the epithelial thickness in 10 patients with carcinoma in situ. Here the average width was 0.41 mm with a range of 0.26 to 0.70 mm. To illustrate the above measurements, a normal cervix of a uterus that was removed for benign disease is shown in Fig. 7. Note that measurements are in millimeters from the surface of the ectocervix and not from the basement membrane. Figs. 8 and 9 represent higher magnifications of the same cervix and clearly demonstrate vascular spaces within an area of only 1.42 mm and 0.50 mm beneath the basement membrane.

It should therefore be evident that microscopic invasion of squamous cell carcinoma beneath the basement membrane to a depth of three mm constitutes significant invasion of the cervical stroma — significant not only in cell counts and epithelial thickness, but also in the fact that the stroma is abundantly supplied with blood vessels and lymphatics which easily could be invaded by carcinoma. Certainly, one mm or more of stromal invasion indicates a greater degree of cancer than is recognized as microinvasive cancer by most pathologists, who are usually concerned with a "few cells" penetrating the basement membrane.

The present authors believe that until more data are available regarding diagnostic methods, treatment and long-term follow-up, stromal invasion by squamous cell carcinoma greater than one mm should be classified as frankly invasive carcinoma, Stage IB (occult), and treated by radical surgery or radiotherapy. Stromal invasion less than one mm, with absence of demonstrable vascular penetration by malignant cells, may be classified as Stage IA and treated like Stage 0 carcinoma.
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THE PLANNING OF SCIENCE

We have to face, in whatever discomfort, the real possibility that the level of insight into the mechanisms of today's unsolved diseases—schizophrenia, for instance, or cancer, or stroke—is comparable to the situation for infectious disease in 1875, with similarly crucial bits of information still unencountered. We could be that far away, in the work to be done if not in the years to be lived through. If this is the prospect, or anything like this, all ideas about better ways to speed things up should be given open-minded, close scrutiny.

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