Detection, Diagnostic Evaluation and Treatment of Dysplasia and Early Carcinoma of the Cervix

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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. There can be no doubt that these changes resulted from the increase in screening for preclinical cervical neoplasia. 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 related to cytologic screening is a more complicated problem and one surrounded by some controversy. The number of cases of recurrent and/or persistent carcinoma of the cervix referred to Downstate Medical Center from other institutions has not declined during this period. Clearly the physician must be aware not only of the importance of cytologic screening but also 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 associates and by Boyes 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 stage, 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 cytological smear has proven to be the most easily applied, most economical, and most effective tool yet devised. The occurrence of squamous cell cervix cancer and its precursors is confined almost exclusively to those women who have had sexual intercourse, and a higher relative risk is

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associated with early sexual experience and promiscuity. Although the peak incidence rates occur in the 20-30 year olds, while the earlier precursors, frequently termed dysplasia, may 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. Taking into consideration the available facts relating to 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 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. Similarly, the self-taken irrigation sample is not recommended since it has a high false negative rate, and it is believed that the patient should have a careful speculum and pelvic examination performed when the smear is taken. (The self-taken irrigation technique is now under study by the National Cancer Institute for use in those patients who cannot be reached by the usual cervical cytologic screening exam.)

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 encourages a lack of discipline which at times leads 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. Re-

| Year | Moderate Dysplasia | Severe Dysplasia | Carcinoma In Situ |
|------|--------------------|------------------|-------------------|
| 1957 | —                  | —                | 13                |
| 1958 | 1                  | 6                | 32                |
| 1959 | 7                  | 13               | 37                |
| 1960 | 4                  | 14               | 49                |
| 1961 | 11                 | 17               | 16                |
| 1962 | 6                  | 17               | 24                |
| 1963 | 6                  | 11               | 29                |
| 1964 | 4                  | 12               | 25                |
| 1965 | 3                  | 13               | 19                |
| 1966 | 3                  | 4                | 31                |
| 1967 | 14                 | 20               | 74                |
| 1968 | 16                 | 23               | 84                |
| 1969 | 11                 | 16               | 91                |
| 1970 | 12                 | 26               | 77                |
| 1971 | 31                 | 53               | 94                |
| 1972 | 52                 | 87               | 120               |
| 1973 | 74                 | 150              | 95                |
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.

gardless of the reporting system, the factor which 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 the report he receives irrespective of the classification which 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, 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 intradepthelial 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 which are found in neoplastic epithelium and 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 punctation. 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 out-patient management protocol. In addition, highly abnormal vascular forms regularly accompany invasive cervical cancer 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 an out-patient evaluation and management program are beyond the scope of this article but are covered in detail in several recent 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. Very few clinicians in practice will have adequate numbers of abnormal smears to maintain the skill needed to perform colposcopy accurately. That there is a definite limitation to the accuracy of the colposcope in precisely subclassifying cervical intraepithelial lesions is shown in Table 4, where error rates are shown.

In an out-patient management 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 appropriately 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 coloscope; (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 staining technique has a significant false positive and false negative rate. 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

| Authors          | Number Of Cases | Microinvasion Missed |
|------------------|-----------------|----------------------|
| Stafi & Mattingly| 217             | 5 (2.3%)             |
| Krumholz & Knapp| 60              | 2 (3%)               |
| Crapanzano       | 143             | 4 (2.8%)             |
Fig. 1. Cervical Smear Flow Chart
Colposcopy and Skilled Colposcopist Available

- Normal
  - Repeat at 1 year intervals
- Atypical
  - Treat cervicitis
  - Repeat smear at 3 months
  - Normal
  - Repeat smear at 3 months
- Abnormality seen
  - Directed punch biopsy
  - Cm (dysplasia/in situ)
    - Treat by appropriate means
    - Follow up smears and exams for life
    - If pregnancy desired
  - Smear at 3 month intervals
  - Definitive treatment
    - Surgery or radiation for definitive treatment
    - Follow up smears and exams for life
  - Metastatic survey and exam for staging
    - Surgery or radiation for definitive treatment
    - Follow up smears and exams for life
- Suspicious-Positive (Dysplasia/in situ)
  - No lesion present
  - Biopsy of lesion
    - Colposcopy
      - Follow colposcopy as shown under suspicious positive smears
        - Metastatic survey and exam for staging
          - Surgery or radiation for definitive treatment
            - Follow up smears and exams for life
  - Lesion present
    - Lesion present
    - Colposcopy
      - Follow colposcopy as shown under suspicious positive smears
Fig. 2. Cervical Smear Flow Chart

Colposcopy Not Available

- **Normal**
  - Repeat at 1 year intervals
  - Atypical
    - Treat cervicitis
    - Repeat smear at 3 months

- **Suspicious-Positive** (Dysplasia/in situ)
  - No lesion present
  - Lesion present
    - Biopsy of lesion
    - Any degree of dysplasia or carcinoma

- **Positive** (Invasive)
  - No lesion present
  - Lesion present
    - Apply Lugol’s solution to stain cervix
    - Follow outline for Lugol’s under suspicious smears

- **Abnormality seen**
  - Biopsy of lesion
    - Moderate to severe dysplasia or carcinoma
      - Repeat smear at 3 months
      - Directed punch biopsy and endocervical curettage
    - Mild dysplasia
      - Repeat smear at 3 months

- **Conization**
  - Mild or moderate dysplasia
    - Repeat smears at 6 month intervals
    - Severe dysplasia or carcinoma
      - If pregnancy desired
      - Follow up smears and exams for life
  - Definitive surgery
    - Smears at 3 month intervals
    - Metastatic survey and exam for staging
    - If pregnancy desired
    - Follow up smears and exams for life

- **Invasive carcinoma**
  - In situ carcinoma
    - Surgery or radiation for definitive treatment
    - Repeat smears at 3 month intervals
    - Follow up smears and exams for life

- **In situ carcinoma**
  - Conization

- **Conization**
  - Repeat smears at 6 month intervals
  - Severe dysplasia or carcinoma
    - If pregnancy desired
    - Follow up smears and exams for life

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recommended because of its lack of specificity.

The tissues removed by endocervical curettage and punch biopsy are most easily oriented if one of the small square curets and punch biopsy instruments such as the Kevorkian, are used. Those tools, 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 required for outpatient evaluation, 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 cancer 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 at least 50 percent of the canal should be removed. This should be followed by a curettage of the remaining endocervical canal.

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

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 dilatation of the cervix is performed. The main complication of conization is bleeding. However, if the procedure is done carefully, bleeding should occur infrequently.

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 suspected, 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 nonpregnant patient. If a skilled colposcopist and cytologist 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 invasive cancer and whose colposcopic findings confirm an earlier lesion.

Although cytologic screening is the most important procedure to discover unsuspected cancer of the cervix, a punch biopsy of the cervix at the time of emptying the uterus for an abortion has led to the finding 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. This 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 of the local lesion. This constitutes step one and until this is completed, one 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, he is prepared to proceed with the other indicated pretreatment studies.

Dysplasia and Carcinoma in Situ (Cervical Intraepithelial Neoplasia)

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 II A

Table 5 gives the International Classification of carcinoma of the cervix. Stage I is now subdivided into Stage IA and IB. Stage IIA carcinoma of the cervix includes only the very earliest of Stage II cases; more specifically, those cases with minimal 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 seriously be considered. The hazards of radical surgery in Stage IIB cases are such that it has been discontinued in most clinics.

The pretreatment evaluation of patients with invasive carcinoma of the cervix should be the same regardless of the stage of the disease. This requires a thorough investigation for evidence of metastatic spread. These 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 must 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 pa-
Fig. 3. Slight dysplasia or CIN Grade 1. Undifferentiated neoplastic cells up to one-third the thickness of the epithelium.

Fig. 4. Moderate dysplasia or CIN Grade 2. One-third to two-thirds the thickness of the epithelium is occupied by undifferentiated neoplastic cells.
Fig. 5. Severe dysplasia or CIN Grade 3. Over two-thirds the thickness of the epithelium is occupied by undifferentiated neoplastic cells.

Fig. 6. Carcinoma in situ or CIN Grade 3. The entire epithelium is composed of undifferentiated neoplastic cells.
tient'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. Aside from the usual battery of liver chemistries, we feel that it is important to carry out the BSP test, which is the most sensitive of all the liver function tests usually available.

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 the lateral extension of the disease into the paracervical ligaments.13 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 Dysplasia

With refinement of the techniques previously described to detect cervical intraepithelial neoplasia and the addition of epidemiological and laboratory stud-

| Table 5. International Classification Cervical Carcinoma |
|--------------------------------------------------------|
| STAGE 0  Carcinoma in situ, intraepithelial carcinoma. |
| STAGE I  Carcinoma confined to the cervix (extension to the corpus should be disregarded.) |
| Stage 1a Microinvasive carcinoma (early stromal invasion). |
| Stage 1b All other cases of Stage I. Occult cancer should be marked “occ.” |
| STAGE 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 parametrial involvement. |
| Stage IIb Obvious parametrial involvement. |
| STAGE 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. |
| STAGE 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. |
ies, 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.\textsuperscript{14, 15} Cervical neoplasia originates as a focal event at the squamocolumnar junction which histologically consists of an area of altered cell growth characterized principally by cytological 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 glycogen, and an increase in cell turnover rates.\textsuperscript{16}

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 cervical intraepithelial neoplasia (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 stages of cervical intraepithelial neoplasia, 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.

In the report by Hall and Walton,\textsuperscript{17} for example, 206 cases were followed from one to 14 years. The results are shown in Tables 6 and 7. 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. Those cases with a slight or mild degree of dysplasia regressed 62.2 percent of the time, while 13.4 percent progressed. On the other hand, those with marked or severe dysplasia regressed only 19.1 percent of the time whereas 33.3 percent progressed. Table 7 demonstrates the number of cases that progressed to carcinoma in situ. Most important is the fact that seven cases of 24 originally found to have marked dysplasia ultimately developed carcinoma in situ. In other words, 29.1 percent, or roughly three out of every 10 patients with marked dysplasia, when followed, ultimately developed carcinoma in situ. Also important in this discussion is the fact that these patients are, on the average, significantly younger than patients with carcinoma in situ or invasive carcinoma. This group of 206 patients had a median age of 25.6, in keeping with the concept of dysplasia as a forerunner of carcinoma of the cervix and suggesting that the carcinogenic factors require a longer period of time to produce the change to carcinoma. Further support for this concept comes from Stern's\textsuperscript{18} finding that the majority of new cases of cancer originate in a population of women with dysplasia.

The 532 women followed by Richart and Barron\textsuperscript{19} 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. In addition, this study demonstrated that there is a proportion of patients in each group who fail to progress to the next higher group but that one cannot predict what the subsequent behavior of a lesion will be based on its previous course.

Cervical intraepithelial neoplasia 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 cancer precursors form a continuum, the subsets of which can only be distinguished by arbitrarily set limits.20

If a patient has a lesion whose distribution makes it amenable to local management and she is in the hands of physicians skilled in such out-patient management procedures, treatment may be undertaken as an office procedure. The problem should be explained in detail to the patient; she should be instructed as to the necessity for 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, conization or even hysterectomy may be indicated, particularly if the patient does not wish to have additional 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 cryotherapy21 and electrocoagulation22 as a means of treating the dysplasias have begun to appear in increasing numbers. It must be emphasized again that an out-patient 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. At the present time, the use of out-patient modalities should be regarded as clinical investigation in progress and should be reserved for centers in which such studies can be undertaken safely and evaluated.

Stage O Carcinoma (in Situ)

Carcinoma in situ or cervical intraepithelial neoplasia 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. The most compelling studies were those reported by Peterson and Funck-Brentano. Peterson reported on 127 patients with carcinoma in situ who were followed without definitive treatment in the Radium Center at Copenhagen. They found that invasive carcinoma developed in 22 percent of the patients at the end of five years, and in 33 percent at the end of nine years 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 cervix cancer precursors, it has commonly been considered separately because of its importance in the classical literature on this disease, because it tends to occupy a larger area, particularly in the endocervical canal, than lower grade lesions and because the patient with carcinoma in situ statistically 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 Brooklyn 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 series had not been pregnant, it allows one to calculate in the individual case the latest that sexual activity may have begun.

Although patients with carcinoma in situ (CIN Grade 3) may be treated in an out-patient oriented management program as described for patients with dysplasia, the risks of error are greater and, hence, greater skill and experience are required. If highly skilled and experienced colposcopists, cytologists and pathologists are not available, diagnostic conization or hysterectomy are the procedures of choice. The patient who desires further childbearing should have a full explanation of the problem and may be allowed to proceed to have more 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 is 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.

There is still some debate as to whether conventional conization is an adequate therapeutic measure, largely because of the reports that approximately one in three patients in whom a conization is performed will have a recurrence or persistence of carcinoma in
situ and potential progression to invasive carcinoma. In view of this statistic, it has frequently been recommended that in the absence of special diagnostic techniques, conization be followed by hysterectomy, generally with a vaginal cuff. Way has reported a 21 percent incidence of involvement of the vaginal cuff by carcinoma in situ when the upper third of the vagina is removed with the uterus and when that vaginal cuff is studied by serial sections. Others have shown involvement of the vaginal mucosa as well, but colposcopic studies have failed to confirm these data. Way states that the recurrence rate is at least three times greater after total hysterectomy than after modified radical hysterectomy.

A most important consideration in a discussion of methods of treatment for carcinoma in situ is the length of follow-up because of the lag period or incubation period, which some feel is, on the average, 10 years between the onset of carcinoma in situ and its transformation to invasive carcinoma. Equally important is the fact that there are no statistics available showing that a significantly large number of patients have been followed for over 10 years after surgery consisting of a total abdominal hysterectomy but not including a 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 O cervical cancer may be treated by simple 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 an in situ carcinoma, which represents no threat for metastasis, to a frankly invasive carcinoma that may spread from the cervical stroma to adjacent tissues and lymphatics. 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 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 synonyms for "microinvasive" carcinoma; the term is variously defined as stromal invasion to a depth beneath the basement membrane of one mm., three to four mm., five mm., and nine mm. Usually, the five mm. figure is used, probably as a result of Mestwerdt's original description of a "microcarcinoma," a squamous cell carcinoma invading stroma with the greatest diameter being less than five mm. Most studies conclude that if the diagnosis of microinvasive carcinoma is made, the patient may be treated safely by total hysterectomy similar to Stage O 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 five 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 which ultimately led to the diagnosis of Stage O 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 cancer, the patient was treated by radical hysterectomy and pelvic lymphadenectomy. Study of the uterine specimen revealed no residual cancer and all nodes were negative for metastasis. 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. 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 "superficial" 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 to 89 layers of the small cell type. Obviously, five 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 0.7 mm. To illustrate the above measurements a normal cervix of a uterus that was removed for benign disease is shown in Figure 7. Note that measurements are in millimeters from the surface of the ectocervix and endocervix and not from the basement membrane. Figures 8 and 9 represent higher magnifications of the same cervix and clearly demonstrate the vascular spaces within an area of only 1.42 mm. and 0.5 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 five mm. constitutes signifi-
cant 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 millimeter 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 is available regarding diagnostic methods, treatment and long-term follow-up, stromal invasion by squamous cell carcinoma greater than one millimeter should be classified as frankly invasive cancer, Stage IB, and treated by radical surgery or radiotherapy. Stromal invasion less than one millimeter with absence of demonstrable vascular penetration by malignant cells may be classified as Stage IA and treated like Stage 0 carcinoma.
References
1. Christopherson, W. M.; Parker, J. E.; Mendez, W. M.; and Lundin, P. E., Jr.: Cervix cancer death rates and mass cytologic screening. Cancer 26: 808-811, 1970.
2. Boyes, D. A.: The British Columbia screening program. Obstet. Gynecol. Surv. 24: 1005-1011, 1969.
3. Barron, B. A. and Richart, R. M.: An epidemiologic study of cervical neoplastic disease. Based on a self-selected sample of 7,000 women in Barbados. West Indies. Cancer 27: 978-986, 1971.
4. Richart, R. M., and Vailant, H. W.: Influence of cell collection techniques upon cytologic diagnosis. Cancer 18: 1474-1478, 1965.
5. Richart, R. M., and Vailant, H. W.: The irritation smear: false-negative rates in a population with cervical neoplasia. J. A. M. A. 192: 199-202, 1965.
6. Copplestone, R. M.; Fuxe, E., and Reid, B.: Colposcopy: A Scientific and Practical Approach to the Cervix in Health and Disease. Springfield, Ill.: C. C. Thomas, 1971.
7. Kolstad, P., and Staff, A.: Atlas of Colposcopy. Baltimore: University Park Press, 1972.
8. Staff, A., and Mattingly, R. F.: Colposcopic diagnosis of cervical neoplasia. Obstet. Gynecol. 41: 168-176, 1973.
9. Krumholz, B. A., and Knapp, R. C.: Colposcopic selection of biopsy sites. Obstet. Gynecol. 39: 22-26, 1972.
10. Crapanzano, J. T.: Office diagnosis in patients with abnormal cervicovaginal cytoscans: Correlation of colposcopic biopsy and cytologic findings. Amer. J. Obstet. Gynecol. 113: 967-972, 1972.
11. Dolan, T. E.: Personal communication.
12. Averette, H. E.; Nasser, N.; Yankow, S. L., and Little, W. A.: Cervical conization in pregnancy. Amer. J. Obstet. Gynecol. 106: 543-549, 1970.
13. Nelson, J. H., Jr.: Atlas for Radical Pelvic Surgery. New York: Appleton-Century-Crofts, 1969.
14. Richart, R. M.: A radiographic analysis of cellular proliferation in dysplasia and carcinoma in situ of the uterine cervix. Amer. J. Obstet. Gynecol. 86: 925-930, 1963.
15. Averette, H. E.; Weinstein, G. D., and Frost, P.: Autoradiographic analysis of cell proliferation kinetics in human genital premalignant lesions. J. Normal cervix and vagina. Amer. J. Obstet. Gynecol. 108: 8-17, 1970.
16. Richart, R. M.: Natural history of cervical intraepithelial neoplasia. Clin. Obstet. Gynecol. 10: 748-784, 1967.
17. Hall, J. E., and Walton, L.: Dysplasia of the cervix: A prospective study of 206 cases. Amer. J. Obstet. Gynecol. 100: 662-671, 1968.
18. Stern, E., and Neely, P. M.: Carcinoma and dysplasia of the cervix: A comparison of rates for new and returning populations. Acta Cytol. (Baltimore) 7: 357-361, 1963.
19. Richart, R. M., and Barron, B. A.: A follow-up study of patients with cervical dysplasia. Amer. J. Obstet. Gynecol. 105: 386-393, 1969.
20. Richart, R. M.: Cervical intraepithelial neoplasia: A review. In: Sommers, S. C. (ed.): Pathology Annual. New York: Appleton-Century-Crofts, 1973.
21. Townsend, D. E., and Ostergard, D. R.: Cryocauterization for preinvasive cervical neoplasia. J. Reprod. Med. 6: 171-176, 1971.
22. Richart, R. M., and Sciarr, J. J.: Treatment of cervical dysplasia by outpatient electrodacauterization. Amer. J. Obstet. Gynecol. 101: 200-205, 1968.
23. Petersen, O.: Spontaneous course of cervical precancerous conditions. Amer. J. Obstet. Gynecol. 72: 1063-1071, 1956.
24. Funck-Brentano, P.: The present problem of intraepithelial epithelioma of the uterine cervix. J. Obstet. Gynecol. (Paris) 59: 5-17, 1969. (Fre).
25. Hall, J. E.; Boyce, J. G., and Nelson, J. H., Jr.: Carcinoma in situ of the cervix uteri: A study of 409 patients. Obstet. Gynecol. 34: 221-225, 1969.
26. Devereux, W. P., and Edwards, C. L.: Carcinoma in situ of the cervix. The applicability of diagnostic and treatment methods in 632 cases. Amer. J. Obstet. Gynecol. 98: 497-508, 1967.
27. Fidler, H. K.; Boyes, D. A., and Lock, D. R.: Intra-epithelial carcinoma of the cervix. 214 cases, with emphasis on investigation by cytology and cone biopsy. Canad. Med. Ass. J. 77: 79-85, 1957.
28. Masel, F. J., et al.: Papanicolaou smear, biopsy and conization of cervix. An evaluation of their reliability in the diagnosis of cervical cancer. Amer. J. Obstet. Gynecol. 86: 931-936, 1963.
29. Pederson, B. L., and Jeffries, F. W.: Cervical carcinoma in situ: A study of 144 patients. Obstet. Gynecol. 26: 725-730, 1965.
30. Schiffer, M. A., et al.: Cervical conization for diagnosis and treatment of carcinoma in situ. Amer. J. Obstet. Gynecol. 93: 889-895, 1965.
31. Schulman, H., and Cavanagh, D.: Intraepithelial carcinoma of the cervix. The predictability of residual carcinoma in the uterus from the microscopic study of the margins of the cone biopsy specimen. Cancer 14: 795-800, 1961.
32. Silbar, E. L., and Woodruff, J. D.: Evaluation of biopsy, cone and hysterectomy sequence in intraepithelial carcinoma of the cervix. Obstet. Gynecol. 27: 89-97, 1966.
33. Way, S.; Henningan, M., and Wright, V. C.: Some experiences with pre-invasive and micro-invasive carcinoma of the cervix. J. Obstet. Gynaec. Brit. Comm. 75: 593-602, 1968.
34. Te Linde, R. W.: Operative Gynecology. Philadelphia: J. B. Lippincott Co., 1962, p. 907.
35. Younge, P. A.: The conservative treatment of carcinoma in situ of the cervix. Proc. 2nd Nat. Cancer Conf. 1: 668-678, 1952.
36. Dukas, R. C.; Yon, J. L., Jr.; Ford, J. H., and Averette, H. E.: Carcinoma of the cervix and pregnancy. Obstet. Gynecol. Oncol. 1: 283-289, 1973.
37. Ullery, J. C.; Boutsels, J. G., and Botschner, A. C.: Microinvasive carcinoma of the cervix. Obstet. Gynecol. 26: 866-875, 1965.
38. Frick, H. C.; Janovski, N. A.; Gusberg, S. B., and Taylor, H. C.: Early invasive cancer of the cervix. Amer. J. Obstet. Gynecol. 85: 925-939, 1963.
39. Morton, D. G.: Incipient carcinoma of the cervix. Amer. J. Obstet. Gynecol. 90: 64-72, 1964.
40. Margulis, R. R.; Ely, C. W., Jr., and Ladd, J. E.: Diagnosis and management of stage IA (microinvasive) carcinoma of the cervix. Obstet. Gynecol. 29: 529-538, 1967.
41. Tarkington, C. N.; Tweeddale, D. N., and Rodick, J. W.: Microinvasive carcinoma of the cervix. Southern Med. J. 62: 1000-1002, 1969.
42. Musse, E.; Soule, E. H., and Welch, J. S.: Microinvasive carcinoma of the cervix. Late results of operative treatment in 91 cases. Amer. J. Obstet. Gynecol. 104: 738-744, 1969.
43. Gray, L. A.: Dysplasia, Carcinoma in Situ and Micro-Invasive Carcinoma of the Cervix Uteri. Springfield, Ill.: C. C. Thomas, 1964. 162 p.