CHAPTER II

BACKGROUND

Carcinoma in situe (CIS) may be defined as an intraepithelial lesion with cytologic atypia similar to that seen in invasive carcinoma but without evidence of invasion into the stroma. These atypical cells extend through the entire thickness of the epithelium and have enlarged, pleomorphic nuclei with dense, coarse chromatin and scant cytoplasm. The polarity of the cells as well as the polarity of the epithelium, i.e., the normal surface maturation and differentiation, is lost. Various degrees of parakeratosis may be seen.(Briggs, 1979)

Lesions composed of similar atypical cells but that retain some degree of surface maturation have been referred to as "dysplasias" by Reagan (1969). Dysplastic epithelium spans a range of severity, from mild loss of polarity, a high degree of cellular differentiation, and few mitoses (mild dysplasia), to a lesion resembling carcinoma in situ in its marked cytologic, nuclear atypia and increased mitotic activity but retaining some degree of epithelial polarization (severe dysplasia). In many cases, pathological differentiation of carcinoma in situ from severe dysplasia may be very difficult

and may hinge on minimal cellular flattening in the most superficial cell layers of the epithelium.

The suggestion that these lesions represent a continuum of change that begins with mild dysplasia and advances through carcinoma in situ led Richart (1969) to introduce the concept of cervical intraepithelial neoplasia (CIN), with the following four classification: "CIN I" indicates mild dysplasia, "CIN II" indicates moderate dysplasia, and "CIN III" indicates severe dysplasia and carcinoma in situ. Evidence in support of Richart's classification of these lesions as a spectrum of one disease entity came from the finding of aneuploid changes (the same chromosomal changes usually found associated with malignant tumors but not with benign tumors) in the nuclei of dysplastic cells (Richart, 1963). Autoradiographic studies (Richart, 1963) have demonstrated a steady increase in the mitotic activity of these lesions that corresponds exactly to the degree of histologic differentiation and maturation present, this observation is consistent with the postulate of the cervical intraepithelial neoplasia represents stages in a continuum of disease.

Diagnosis of Cervical Neoplasia

A. Cytology.

The outstanding contribution of recent decades to the field of cancer detection is that of the George Papanicolaou. In studying cells exfoliated from the female

genital tract. Papanicolaou (1920) noted characteristic cellular changes associated with cervical carcinoma. These cellular abnormalities include anomalies of staining reaction, pleomorphism, nuclear irregularity, hyperchromasia, the presence of multiple nucleoli, and an increased nuclear-cytoplasmic ratio. Supported by many important discoveries (Papapnicolaou and Traut, 1943; Roberts, 1964) Papanicolaou's cytologic technique (the Pap test) has been accepted as a cancer screening measure.

1. Papanicolaou's classification of the cytologic findings consisted of five grades: (Papanicolaou, 1943)

I. Benign

II. Atypical benign

III. Suspect

IV. Probably positive

V. Positive

Although this classification applied to invasive cancer, it became apparent that it was possible to detect and identify specific abnormalities associated with carcinoma in situ and dysplasia by cytologic examination. It is the practice in many laboratories to evaluate dysplasia and carcinoma in situ with the class III and class IV designations, respectively (Seybold and Johnson, 1971).

2. Technique of Obtaining Cervical Smears

(Kistner,1986)

The following equipment is needed:

1. Clean glass (microscope) slides with frosted ends permit easy labelling the patient's name in pencil and also identify the "right side" or smeared side of the slide.

2. Glass pipettes measuring about 8 inc. in length and having a slight curve, with a capillary opening,or cotton swab for adequate sampling of the cervical secretion.

3. Rubber suction bulb (1-oz or 2-oz size), with an opening that fits snugly over the pipette.

4. Spatula to be used for cervical scraping and smearing.

5. For fixative, any one of the following dehydrating agents can be used:

a. Half-and-half mixture of 95% ethyl alcohol and ether.

b. Plain 95% alcohol or lesser dilutions to 75%

c. 75% to 95% methyl alcohol.

d. 75% to 95% isopropyl alcohol or commercially available cytologic fixative agents.

Smears are obtained prior to digital pelvic examination with the patient in the lithotomy position and without lubricants, which would spoil the staining characteristics of the cells. Smear must not be obtained within 12 to 24 hours after douching because douchers will dilute and wet the cells. The glass pipette (or cotton swab) is used to aspirate the endocervical secretions, which are then blown out (or spread out) on the slide by compressing the

aspiration bulb firmly, thereby creating a fine film. The slide is immediately fixed by immersion into a small stoppered bottle containing any fixatives or sprayed with the commercially available fixatives. The spatula is then used to scrape the portio of cervix circumferentially at the area of the transformation zone and the slide is rapidly smeared and fixed. Fixation is complete in 15 to 30 minutes, after that the slide may be dried and then secured in a cardboard or wooden holder for transportation. Immediate fixation is possible with a cytologic fixative containing methyl alcohol, acetone, and polyethylene glycol.

B. Biopsy and Histologic Diagnosis.

Clinicians have depended on the Papanicolaou smear as a screening method for detection of cervical neoplasia. Serial sampling over time provides a longitudinal look at the cervix, decreasing the impact of isolated false-negative smears. The Papanicolaou smear must remain a screening technique. Biopsy and histologic diagnosis remain the cornerstones in the management of cervical neoplasia.(Griffiths and Younge, 1969).

A targeting technique developed by Schiller in 1938 now known as the "Schiller's test" may be used to "highlight" cervical abnormalities, making them visible for biopsy. A solution of sodium iodine reacts with glycogen to stain the normal squamous epithelium of the cervix and vagina to dark-brown color. Nonstaining or Schiller positive areas stand out from the dark background will represent surfaces

lacking glycogen which include columnar epithelium, true pathologic erosions, immature metaplastic epithelium and neoplastic lesions.

C. COLPOSCOPY

Colposcopy has superb Shiller's technique in most centers as the initial step in evaluating abnormal Papanicolaou' smears because biopsy has high false negative rate (Townsend, Ostergurd and Mishell, 1970). Hinselman developed the colposcope in 1925 in an attempt to localize small ulcerations that theorized to represent small cervical neoplasm. He found that the low power magnification of the colposcope (x 6 to x 40) revealed not only the neoplastic cervical epithelium but also alterations of the underlying stromal vasculature resulting from the neoplastic process. The degree of alterations in vascular pattern, in intercapillary distance, in surface color and in texture was found to correlate well with the severity of the neoplastic process (Coppleson and Pixley, 1981).

Adequate Colposcopic Evaluation (satisfactory colposcopy) requires complete visualization of the transformation zone at the lesion in question as well as correlation between the cytologic and histologic diagnosis and clinical impression of the colposcopist. Endocervical curettage should be performed as part of every colposcopic examination (Urcoyo, Rome and Nelson, 1977). **Almost 90% of 24 women with abnormal cytologic findings could have adequate evaluation with colposcopy.**

Colposcopic examination composes of colposcopic impression of the lesion seen under colposcope and histopathology result of cervical tissue gained from biopsy guided by colposcope -called colposcopic directed biopsy (Koldstad and Stafl, 1976). By criteria of Koldstad, the colposcopists can predict the histology grading of lesion when they see the lesion under colposcope but the colposcopic impression can not be the diagnostic result of colposcopy because the accuracy of prediction is not high enough (only 78 % to 85 %) (Koldstad and Stafl, 1976; Benedet and Boyes, 1976). They are all accepted that histopathology result of cervical tissue gained from colposcopic directed biopsy is the diagnostic result of colposcopy because of its high accuracy (up to 98 %)(Kirkup and Shirly, 1980).

In some situation, Richart (1966) found that in some group of patients, the histopathology results of colposcopic directed biopsy were more severe than conization results. He stated that colposcopic directed biopsy would induce regression in the remaining lesion or colposcopic directed biopsy removed all minute severe foci of cervical neoplasia from the cervix. By these reasons, there had no severe lesion left in the cervix when pathologists examined the cone specimens. Benedet and Boyes (1976) also found that 8% of the patients in their study had colposcopic directed biopsy results more severe than conization results. In their study, The final histopathology diagnosis did not come only from conization but combined with result of colposcopic directed biopsy.

Many studies (Koldstad and Stafl, 1972; Coppleson, Pixcy and Ried, 1975; Bruke and Mathews, 1977) have shown that colposcopic directed biopsy has a high accuracy to detect cervical neoplasia in abnormal Pap smear patients. The accuracy ranges between 90% to 98%. By using colposcopy in experienced hands, the rate of diagnostic conization in abnormal Pap smear women can be reduced significantly (Townsend, Ostergard and Mishell, 1970).

Technique of Cervical Biopsy (by colposcopic directed biopsy or Shiller's technique) (Kistner,1986)

The cervix is visualized by a speculum with adequate illumination. Wiping the cervix with dry gauze frequently causes bleeding, so that the cervix should be cleansed with a cotton swab or cotton ball soaked in an alkaline astringent solution (Alkalol) or aqueous benzalkonium chloride (Zephiran), or 3% acetic acid. After that colposcopy will be performed.(Schiller staining is mandatory for targeting the abnormal cervical lesion if colposcopy is not available.) A rectangular biopsy specimen is obtained by using a Kevorkian or Younge biopsy punch, and the cervical tissue is immediately fixed in 5% formalin solution. Post biopsy bleeding may be controlled by pressing, cauterizing with silver nitrate or ferrous subsulfate (Monsel's solution), packing with surgical gauze or suturing as required. The patient is instructed to avoid douching, tampons use, and sexual intercourse for two weeks after biopsy. Although the procedure is painless, a paracervical block with lidocaine or

chloroprocaine (Nesacaine) may be used. Endocervical curettage may be added by vigorously curetting the canal with a narrow curette, after cervical dilation.

D. Cervical conization

Although colposcopic directed biopsy has high accuracy and can substitute the need of diagnostic conization in majority of cases, cervical conization still remains the gold standard for some situation. A properly performed conization removes the entire transformation zone and virtually the entire endocervical canal, providing the pathologists with the maximum amount of tissue to absolutely rule out invasive carcinoma. Drawbacks of this procedure include the need for anesthesia and a hospital stay, a complication rate (primarily post operative hemorrhage) approaching 10% in most series (Claman, 1974) and possible adverse effects on future fertility (Chao, McCaffray and Todd, 1969). For these reasons the vast majority of all patients may be completely and adequately evaluated for cervical neoplasia by colposcopy, but it is important that the clinicians must be assured that invasive cancer has been ruled out before consideration to give conservative treatment such as cryosurgery laser vaporization. So conization is required to rule out invasion if the following conditions are not met (Chao, 1969).

1. Lesion seen colposcopically must be limited to the portio of the cervix without extension into the endocervical canal.

2. The entire transformation zone must be visualized.

3. Results of endocervical curettage must be negative for neoplasia.

4. Biopsies and cytologic examination must reveal intraepithelial disease only.

5. Cytologic and histologic diagnoses must correlate.

Technique of Conization (Kistner, 1986)

Under adequate general anesthesia, the patient is placed in the dorsal (supine) lithotomy position. The vagina and perineum are gently prepared with povidone-io-dine (Betadine) to avoid bacterial infection from vaginal flora. After the bladder has been catheterized, an pelvic examination is performed to rule out existing pelvic disease. A weighted retractor is placed in the posterior fornix, a Sims retractor is placed anteriorly, then cervix is visualized. Colposcopy or Schiller's test is performed to delineate the extent of disease on the portio of cervix. A tenaculum is placed on the portio of cervix anteriorly, above the planned limit of the cone biopsy. Lateral-angle sutures are placed into the stroma of the cervix at the 3 o'clock and 9 o'clock positions to ligate the descending branches of the uterine artery. These sutures are left long (for tying at the end of the procedure). The body of the cervix is infiltrated with a dilute solution of vasopressin in saline (20 units in 20 ml), or Marcaine hydrochloride (bupivacaine) epinephrine 1:200,000 which aids

in homeostasis.

The mucosa is incised circumferentially maintaining in 2 to 3 mm beyond the lesion (as delineated by colposcopy or Schiller's staining). A cone shaped specimen in a length of 1.5 to 1.8 cm is carefully excised encircling the endocervical canal. Care is taken to avoid prematurely entering the canal, since neoplastic tissue might then be left behind . A uterine sound may be placed within the canal to aid the dissection. Manipulation of the mucosa of the specimen should be avoided. Traction may be attained by placing sutures within the stroma of the cone specimen or by grasping the area with forceps. A suture is placed at the 12 o'clock position in the stroma of the specimen to aid the pathologic orientation. The uterus is then sounded and dilated, then an endometrial sample is taken as desired.

Bleeding is usually minimal with this technique, however, persistent bleeding points may be electrocauterized or ligated with size 0 chromic sutures in a figure-of-eight pattern. The canal is then packed with Surgical gauze, which is gently tied into place with the long ends of the lateral sutures. The patient is usually observed overnight and then discharged home with instructions to avoid douching, use of tampons, and intercourse for two weeks.