Precancerous Lesions and their Detection and Diagnosis

L. G. Koss

This meeting marks almost to the day the 21st anniversary of my involvement in cytology. When as a young pathologist I first decided to explore this field, the views of my then superiors and contemporaries were decidedly negative.

Nevertheless I moved on to the Memorial Hospital where I met Dr. PAPANICOLAOU, who was then consultant in cytology. He used to come twice a week to the dark and uncomfortable little laboratory in the basement of the Strang Cancer Prevention Clinic building and review some of the more interesting cases. PAPANICOLAOU was an anatomist who knew little pathology and lived in mortal fear of a diagnostic mistake. He was therefore very cautious and, rather than commit himself to a definitive diagnosis, elected to render his opinions as "classes" of smears. He rarely committed himself to a classification higher than Class IV (presumable cancer), unless the evidence was absolutely overwhelming. His favored diagnosis on abnormal smears was "Class III" or suspicious; that he soon subdivided into Class III A and III B, to indicate a lesser or greater degree of suspicion.

PAPANICOLAOU made many basic contributions to the recognition of carcinoma in situ and related lesions of the uterine cervix and other organs. He observed that cells from the earliest precancerous lesions of cervix epithelium are quite different from cells of carcinoma in situ and from cells of invasive carcinoma. To describe the cells from the earliest lesions he coined the term "dyskaryosis" to define cells with a cancerous nucleus and a nearly normal cytoplasm.

He also made many basic contributions to the cytology of other organs. His Atlas [18] is a remarkable compendium of cells and cell types, a massive accumulation of experience, not always well correlated with histologic findings, but forever a monument to the power of perception and observation of GEORGE NICHOLAS PAPANICOLAOU.

The Uterine Cervix

It is perhaps of interest to note that PAPANICOLAOU cannot claim priority to the most widely used application of cytology, detection of cancer of the uterine cervix. The credit here goes to a Roumanian pathologist, AURELI BABES who, some months before PAPANICOLAOU, published an article on diagnosis of cancer of the cervix by smears [1]. Whether the credit goes to PAPANICOLAOU or to BABES is immaterial in view of the successful application of cytology to the detection of precancerous states of the cervix. Carcinoma in situ of the cervix prior to 1950 was a rarity observed only in a few specialized institutions either as a result of colposcopy or of a chance biopsy; now it is a common pathologic entity. In fact, to many of the younger
generation of pathologists in the United States invasive cancer of the cervix has become a rarity, whereas they may observe carcinoma in situ on a daily basis.

No significant doubt remains in the minds of serious observers of carcinoma in situ that the lesion, if untreated, will progress in many but not all cases to invasive carcinoma of cervix. For instance, Kottmeier observed 34 patients with this disease without treatment; 25 of them developed invasive cervix cancer within a follow-up period of 2 to 21 years [13].

The question still unresolved in the minds of many is that of definitions. About 10 years ago, an international committee of experts arbitrarily defined carcinoma in situ of the cervix as a lesion without surface differentiation. Nothing could be further from the truth, as any working pathologist will attest. Carcinoma in situ of the cervix is by definition a lesion that looks like cancer and hence is capable of differentiation and keratin formation [6]. In its most recent deliberations the WHO committee on uterine tumors fortunately recognized this fact and soon hopefully the old definition will be permanently discarded.

Another, more significant problem pertains to the lesions of lesser degree of abnormality that cannot qualify as carcinomas in situ. These lesions are characterized better by their cytologic abnormalities than by the histologic patterns; the latter may be inconspicuous and require a practiced eye for recognition.

These lesions have received various names from "atypisches Epithel" to anaplasia, dysplasia or borderline lesions. For a long time all major significance was denied to these lesions. Careful studies disclosed, however, that such lesions are in equal measure precursors of invasive cancer of the cervix as the more classical carcinoma in situ [7, 12].

Our own investigation [12] conducted for over 10 years in New York City, disclosed several important facts about carcinoma in situ and borderline lesions (mild and moderate dysplasia), some of which may be summarized as follows:

1. A simple punch biopsy may significantly alter the distribution and natural history of these lesions. As a consequence, post-biopsy studies of these lesions do not reflect their true behavior.

2. Histologic or cytologic patterns do not lend themselves to prognostication. Any epithelial lesion with nuclear abnormalities may lead to carcinoma in situ or to invasive carcinoma of the cervix.

3. If followed under uniform conditions of observation, carcinoma in situ and dysplasia show strikingly similar behavior patterns with an approximately equal percentage of lesions disappearing after biopsy. The progression of mild and moderate dysplasia to carcinoma in situ occurred in 40% of cases.

Similar conclusions pertaining to dysplasia as a progressive lesion were reached by Richart and Barron [20]. Stern and Neely [27] pointed out that women with dysplasia have a 1,600 times greater chance of developing carcinoma in situ than women without this disease. It has also been documented that dysplasias have an abnormal chromosomal makeup, akin to that of invasive carcinoma [26].

4. Perhaps the most important lesson from the study of carcinoma in situ and related lesions of the uterine cervix pertains to the natural history of precancerous states and cancer in man. It has been clearly shown that cancer is not the acute disease that it once was thought to be. On the contrary, the slow and unpredictable progression of the precancerous epithelial lesions that may last as long as 20 years