THE NATURAL HISTORY OF CARCINOMA *IN SITU* OF THE CERVIX UTERI

BY

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THE natural history of squamous cell carcinoma *in situ* of the cervix begins with minor histological atypicalities arising at the junction where the two types of cervical epithelium meet. The degree of atypicality increases and slowly progresses through a spectrum of changes from minor dysplasia, to major dysplasia, to carcinoma *in situ*, to carcinoma *in situ* with early stromal invasion, to occult or micro-carcinoma and then on to clinical invasive cervical cancer. This knowledge concerning the natural history of carcinoma *in situ* of the cervix was acquired over a period of many years. It resulted from the work of many different investigators. It was pieced together by numerous clinical observations and detailed histological and cytological studies. The histological progression has never and can never be observed to take place in a single case, because a biopsy specimen cannot be grafted back into its original location. A sceptic, therefore, can always question the concept. But, as Stewart (1957) said: "Every infiltrative cervix cancer must come from an *in situ* cancer there being no other thing it can come from, this irrespective of various doubts cast on the relationship." The accumulation of this knowledge can be divided into two eras: before and after Papanicolaou.

The pre-Papanicolaou era began 78 years ago in London in the year 1886 when Williams (1888) described for the first time carcinoma *in situ* of the uterine cervix. He said in his Harveian Lecture: "This is the earliest condition of undoubted cancer of the portio vaginalis which I have met with, and it is the earliest condition which is recognizable as cancer. It is superficial and remains superficial for a long time." What more can be said about the natural history of this lesion even today?

Fourteen years later, in 1900, Cullen first described the surface coating of carcinomatous epithelium adjacent to invasive cancer of the cervix. In 1910, Rubin, not aware of Williams' earlier report, described a case of carcinoma *in situ* and concluded that this superficial neoplastic epithelium was the earliest stage of squamous carcinoma of the cervix. The classical work of Schottlaender and Kermauner (1912) again stressed the presence of neoplastic epithelium on the surface of the cervix at the periphery of some invasive cervical cancers. One of their students, Schiller (1927), deserves most of the credit for focusing the attention of gynaecologists on this lesion when he wrote about the early diagnosis of cervical cancer. He not only reported detailed histological studies, but also described the iodine staining test which now bears his name.

In 1929 and 1934 Pemberton and Smith of the Free Hospital for Women published papers on very early cervical cancer. They reported retrospective observations in which carcinoma *in situ* progressed to invasive cancer in a few cases. At that time, in spite of the fact that the lesion had been described by numerous observers for nearly 50 years, there was great reluctance on the part of pathologists to make the diagnosis of malignancy in the absence of invasion. Because of this reluctance, Pemberton urged in 1934 that prospective studies should be carried out at the Free Hospital for Women in order to learn more about the natural history of carcinoma *in situ*. In 1938 the first deliberate experiment allowing *in situ* cancer to progress to invasive cancer was concluded (Younge *et al.*, 1949). That same year at the Free Hospital for Women a patient died of invasive cancer whose biopsies taken eight years before showed, on re-

examination, carcinoma *in situ*. By 1938, at the Free Hospital for Women, *in situ* cancer had been observed to progress to invasive cancer in seven patients. The time interval varied from 11 months to 12 years. Consequently, because we were convinced of the relationship, prospective experiments were discontinued; instead, methods of treatment of carcinoma *in situ* were investigated and dysplastic lesions were studied prospectively. It was learned that, if carcinoma *in situ* and its surrounding atypical epithelium were either removed completely by surgery or destroyed by cauterization, preservation of reproductive function was possible, whilst the treatment was adequate and safe. It was also learned that when a screening biopsy showed carcinoma *in situ* further investigation usually revealed more carcinoma *in situ*, occasionally only dysplasia, and very rarely invasive cancer. Occasionally no trace was found in the hysterectomy specimen because the pre-operative biopsies had removed the entire lesion. To date there has been only one recurrence following the treatment of carcinoma *in situ* at the Free Hospital for Women (Younge, 1958). This occurred at the vaginal apex where dysplasia was present at the point of surgical excision, and the recurrence, an invasive lesion one centimeter in diameter, was precisely at that area. Irradiation treatment given twelve years ago has been successful to date.

Stoddard in a very thorough review of the literature in 1952 reported 42 well-documented cases in which carcinoma *in situ* progressed to invasive cervical cancer. This type of inconclusive clinical research is no longer popular or necessary, although the final outcome of Petersen's (1956) cases in Denmark is eagerly awaited. His latest report indicates that about 30 per cent of his cases develop invasive cancer within ten years; all have been subjected to biopsy one or more times.

Considerable confusion existed in the late pre-Papanicolaou era in the early 1940s as to whether or not replacement of the endocervical epithelium in glands meant invasive cancer. Te Linde (1946) thought that it did, whilst many others did not. Their teaching, however, led to the belief that pure carcinoma *in situ* was a rare condition because gland involvement is the usual finding. There is general agreement now that endocervical gland involvement is not stromal invasion. The debate between Hertig and Younge and McKelvey in 1952 ended all doubts about the malignant nature of carcinoma *in situ*. The only questions that remained after that debate were: (1) Should carcinoma *in situ* be classified as a stage 1 lesion and treated accordingly as recommended by McKelvey (1952), or should it be classified as a stage 0 lesion requiring less radical therapy? (2) Does squamous cell carcinoma *in situ* arise from the squamous epithelium of the portio or from the reserve cell (subcolumnar cell) of the endocervical epithelium? Nearly all students of this subject agree that carcinoma *in situ* does not require radical cancer therapy. Also, there is almost universal agreement that the lesion begins in the transitional zone between the portio and cervical canal. There is strong support for the view that squamous cell carcinoma *in situ* arises in some cases from the reserve cell (Johnson *et al.*, 1964).

Although Papanicolaou and Traut's great contribution to the field of cancer detection was published in 1943, its full impact did not occur until at least ten years later when cytology was generally accepted. During the early post-Papanicolaou era the problem of the clinical and pathological significance of dysplasia became apparent. It was essential to determine its significance because it was being found with increasing frequency on vaginal smears. McKay *et al.* (1959) reviewed all such cases found at the Free Hospital for Women between 1945 and 1954. They found 243 cases of which 129 had been followed adequately. From the literature and including five of their own cases, they found 23 examples of dysplasia that progressed to cancer; 18 were *in situ*, and 5 invasive. The age incidence of dysplasia, its frequent association with carcinoma *in situ* and invasive cancer, its incidence as a routine finding in hysterectomy specimens and its reported rate of regression, persistence or progression as reported by Reagan *et al.* (1955) and Galvin *et al.* (1955), led Fluhmann (1961) to conclude: "On the basis of these generalizations it seems justified to accept dysplasia as a lesion which bears a relationship to carcinoma *in situ* very similar to that of carcinoma *in situ* toward invasive cancer. The co-existence of these lesions and the fact that

dysplasia, at least in some cases, progresses to pre-invasive cancer is good evidence that it should be considered representing potential neoplastic fields."

The post-Papanicolaou era began with the widespread use of exfoliative cytology. About this time, Antoine and Gruenberger (1949) developed the colpomicroscope which made *in vivo* cytological observations possible. Thus, the tools were available for the prospective study of the natural history of undisturbed pre-invasive lesions of the cervix. Wong *et al.* (1961) and later Okagaki *et al.* (1962b) found it was necessary, however, to develop a cytological method for excluding carcinoma *in situ* within the cervical canal where it could not be visualized by colpomicroscopy. This was essential in order to follow patients safely where the cytological findings were consistent with dysplasia without resorting to histological confirmation. Wied *et al.* (1962) reported that the cytological accuracy in differentiating between dysplasia, carcinoma *in situ* and invasive cancer was nearly 90 per cent in his laboratory. Okagaki *et al.* (1962a) at the Free Hospital for Women found by differential cell counts that the accuracy of cytology in distinguishing dysplasia from carcinoma *in situ* was 97·5 per cent. In a prospective colpomicroscopic study of 80 patients with suspicious cytological findings, Lerch *et al.*, (1963) reported progression from dysplasia to carcinoma *in situ* in two cases within two years. Biopsies were not done until carcinoma *in situ* was suspected by one method or the other; the findings were confirmed by serial block sections of the hysterectomy specimens. Richart is continuing this type of study at Columbia University.

At the Strang Prevention Clinic, a division of the Memorial Hospital for Cancer and Allied Diseases in New York City, Jordan, Bader and Day (1964) conducted a prospective study of 379 patients with cervical lesions ranging from mild dysplasia to unequivocal carcinoma *in situ*. Their patients were followed clinically, cytologically and histologically. In eight patients the lesion progressed from major dysplasia to carcinoma *in situ* after periods ranging from six months to five years. In three patients *in situ* carcinoma progressed to microscopic invasive cancer after intervals of 15 months, 2 years and 5 years respectively. Of 180 patients with carcinoma *in situ*: 88 had definitive treatment; 54 had diagnostic treatment, usually conization; and 38 untreated patients have been under observation for intervals ranging from three months to eleven years. They correctly state that "there is really no way to study the life history of carcinoma *in situ* without minimal interference with the lesion". None of their 104 patients with minor dysplasia showed progression to more severe lesions during the period of observation. The cytological differentiation between minor atypia and major atypia, should therefore, be our goal so that the life history of pre-malignant lesions can be studied and unnecessary major diagnostic procedures because of suspicious smears avoided.

The post-Papanicolaou era has also been characterized by attempts at population screening. Statistical studies of these screening projects give us perhaps the best view of the natural history of pre-malignant lesions.

Bryans, Boyes and Fidler (1964) reported the results of screening 265,950 women in British Columbia over a period of 14 years. In 1955 invasive cancer was found in 10·2 per 1,000 and carcinoma *in situ* in 4·4 per 1,000 women screened. In 1962 invasive cancer was found in 0·7, and carcinoma *in situ* in 2·8 per 1,000. Even more striking was the incidence of invasive cancer in the previously screened population compared with the unscreened. In 1962, 3·5 invasive carcinomas were found per 100,000 of the female population, compared with 24·1 in the unscreened. They concluded that "the three stages of pre-clinical carcinoma—*in situ* carcinoma, *in situ* carcinoma with microscopic foci of invasion, and occult invasive carcinoma—are sequential phases of a single disease process, which can in some cases lead to clinical invasive carcinoma".

In Louisville, Kentucky, Christopherson *et al.* (1962) has conducted an annual screening programme since 1956. Approximately 60,000 women have been examined cytologically each year. After the third year, there has been no case of invasive cervical cancer among those screened annually and a steady rate of one carcinoma *in situ* for every 2,000 women screened for the past eight years. The Louisville study has also demonstrated that a low socio-

economic status but not the racial background, is a contributory factor to the high incidence of cervical cancer in all its phases from dysplasia to invasion.

Thus, the population studies in British Columbia and Louisville, Kentucky, prove beyond a reasonable doubt that, when the cancer spectrum is stopped at the *in situ* stage invasive cancer of the cervix can be eliminated from a population. The best and most economical method of disrupting the natural history of cervical cancer is to employ routine cytology in the female population over the age of 20.

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