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The changing concepts of early carcinoma of the uterine cervix

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With 1 plate

The scientific interest in the problems of carcinoma of the uterine cervix has perhaps never been as great, as it is today. The principal reason for this situation, especially in the United States, is a widespread application of the methods of exfoliative cytology as a medium of screening large groups of women for incipient cervical cancer. At the Strang Clinic of Memorial Center for Cancer and Allied Diseases many thousands of apparently healthy persons are examined at yearly intervals for evidence of neoplasm. A thorough clinical and cytological examination of the genital tract of all female patients is an integral part of the visit to the clinic.

Early in 1951 a long range follow-up program was established to evaluate lesions of the uterine cervix which were difficult to classify on pathologic and cytologic bases. The purpose of this program is to increase our understanding of the early morphologic epithelial changes related to or leading to cancer. It is hoped that eventually some light will be shed on the entire obscure field of spontaneous human carcinogenesis. This unfinished study has contributed considerable material pertaining to abnormalities of the cervical epithelium. The accumulated material consists of smears and biopsies taken at frequent intervals. The use of smears in preference to biopsies has been especially rewarding. The smears, in trained hands, have allowed a very adequate interpretation of the status of the cervical epithelium without disturbing the actual disease process. However, no case was followed on cytological grounds alone and where indicated, all cytological findings were confirmed by biopsies.

The material thus obtained is especially interesting because with very few exceptions the lesions were observed in patients with no clinical complaints or symptoms, except, perhaps, cancerophobia, which prompted them to undergo the initial cancer detection examination.

The present contribution, honoring Prof. HANS BLUNTSCHLI, has as its purpose to present and discuss briefly some of the broad problems that have emerged during the past several years of work on cervix cancer. The following points appear to be especially worthy of consideration:

1. What is an early cervix cancer?
2. Does in-situ carcinoma of the cervix inevitably lead to invasive cancer?
3. Is cervix cancer a preventable disease?

The question as to what constitutes an early cancer of the uterine cervix is an ambiguous one: early, of course, implies cancer of short duration. However, the term is often applied to a lesion that is small in size; or because it is superficially located; or because it is easily and successfully excised. Practically nothing is known concerning the interval between the actual beginning of the disease and its first clinical manifestations. It is apparent from our work that localized forms of cervix cancer are usually entirely asymptomatic and that their discovery is either the result of an accident or a systematic search for such lesions. It is also evident that the change from a localized form of carcinoma, especially the so-called in-situ carcinoma, to an invasive or infiltrative form is in the majority of cases the result of an exceedingly slow process. Moreover, it appears that not all of these localized manifestations of malignant transformation of the epithelium will invariably progress to a more classical form of cancer. In fact, after several years of observation of approximately 60 patients with lesions morphologically approaching in-situ carcinoma, only one case progressed to invasive carcinoma. It can not be sufficiently emphasized that these patients were for the most part totally asymptomatic and that therefore the lesions were probably of shorter duration than those reported by other observers. In a sizable proportion of our group of patients a complete disappearance of the epithelial lesions was noted, and no trace of it could be detected either on multiple cytologic examinations and biopsies of the cervix or on serial sectioning of cervices removed in some cases. In several cases, on the other hand the lesions have remained stationary.

Thus, what is early cancer of the uterine cervix? Is it in-situ carcinoma? Apparently not necessarily so. Is in-situ carcinoma a lesion which, as Dr. FRED W. STEWART put it, «cancer because it looks like one»? Sure-

ly, in-situ carcinoma looks like cancer yet it apparently does not fulfill one especially important criterion of malignant tumors, namely, it apparently lacks the ability of uncontrollable autonomous growth. It appears to this author that in-situ carcinoma is a lesion which can live in a state of symbiosis with healthy cervical epithelium, in a sort of equilibrium that may either remain stationary or change in favor of either health or disease. One could imagine two athletes with arms interlocked in an effort to tip each other over. The fight may end in a draw or in the victory of either one of the strugglers. Yet, even though the athletes remain apparently immobile their bulging muscles testify to their effort. The morphologists can not at the present time detect any evidence of struggle in the cervical epithelium, nor can they explain the disparite behavior of in-situ carcinoma. It is very likely that the laws governing the state of epithelial equilibrium or its disruption vary from individual to individual. It is also probable that the problem of early cervical cancer will have as many answers as there are patterns of tissue reactivity and individual response to disease. What may morphologically appear as an early carcinoma may constitute the threat of death to one patient and may be an insignificant lesion to another. The secret probably remains with individual response to disease, not with the disease itself. I do not believe that the time will ever come when the future behaviour of in-situ carcinoma will be decided on morphological grounds alone. The purely morphological approach appears to be a «blind alley» and an entirely new dynamic approach is needed to elucidate the peculiar behavior of such lesions.

The problem is somewhat different in regard to borderline lesions, variously called atypical metaplasia, dysplasia, etc. These are, generally speaking, lesions which do not fulfill the general criteria of localized cancer. Perhaps one could say, that they do not quite look like cancer, and yet represent definite deviations from the normal epithelial pattern. The question is whether these lesions precede the appearance of carcinoma and constitute a step in the direction of carcinogenesis, whether they are harmless deviations from normal epithelium destined to disappear after an ephemeral existence, or whether they are an evidence of epithelial defense against some carcinogenic agents. In an effort to put some order into this confused field of epithelial morphology, Grace Durfee and the author (1956) isolated one group of atypical epithelial lesions characterized mainly by the presence of large cells with vacuolated cytoplasm. Because of the cavitary appearance of the cytoplasm the

term of «koilocytotic atypia» was chosen to define the lesion (Fig. 1, 2, 3). Several years of observation suggest that the majority of uncomplicated «koilocytotic atypia» will eventually regress. However, occasionally an association of similar lesions with either in-situ or invasive carcinoma has been observed. Thus, the initial questions remain only partially answered. At this point one could say that such atypias can be best interpreted as a warning that cancer may be present elsewhere in the cervical epithelium. They should not be considered as either cancerous or precancerous in nature. Presumable it will take many more years to elucidate the various morphological patterns of atypical epithelium and correlate these lesions with their subsequent behavior. It is probable, however, that the behavior of morphologically identical atypical lesions will vary from patient to patient, as is the case in carcinoma in-situ.

In view of this variation in morphology, can we ever hope to prevent cancer of the cervix? The experience of this author points to the fact that although not all in-situ carcinomas become invasive, all invasive cervical cancers go through a stage of «in-situ carcinoma». Carcinoma in-situ is a curable lesion. Thus, by prompt detection of all cases of in-situ carcinoma one can hope to eliminate cancer of the cervix as a cause of death. I believe that the eradication of cervix cancer as a cause of death could be accomplished by a thorough yearly examination of the female population. Cytologic examination of the female genital tract has the advantage of allowing detection of endocervical and endometrial lesions as well as those of the portio. The interpretation of smears requires special training but the initial screening can be readily accomplished by lay screeners under the supervision of a cytopathologist. Training enough people for this task is simply a question of ecomomics. It can be done and I hope it will be done in the near future.

It is probable that the unpredictable behaviour of in-situ carcinoma of the cervix finds it's counterpart in other organs. As HAMPERL (1954) pointed out, the prostate offers the best example of it's kind. The very high percentage of occult prostatic cancers found in autopsy material is probably best explained by the considerable attention devoted to the investigation of this small organ. Occult and silent localized cancers of other organs are indeed not an infrequent autopsy finding. One is tempted therefore to anticipate that the silent, localized cancers are perhaps not at all as rare as hitherto thought, but perhaps, with appropriate search, could be found in ever increasing numbers. Is cancer in general a much more frequent disease than previously anticipated? Do only a

certain percentage of all malignant transformations of tissue reach the invasive stage? The answers are not available at this point but it would be worth while to make a concentrated effort to answer these questions.

References

HAMPERL, H., KAUFMAN, C., and OBER, K. G. (1954): Histologische Untersuchungen an der cervix schwangerer Frauen. Arch. Gynäkol. *184*: 181—280, 1954.

KOSS, L. G., and DURFEE, G. R. (1956): Unusual patterns of squamous epithelium of the uterine cervix: Cytologic and pathologic study of koilocytotic atypia. Ann. N. Y. Acad. Sciences *63*, 1245—1261, 1956.

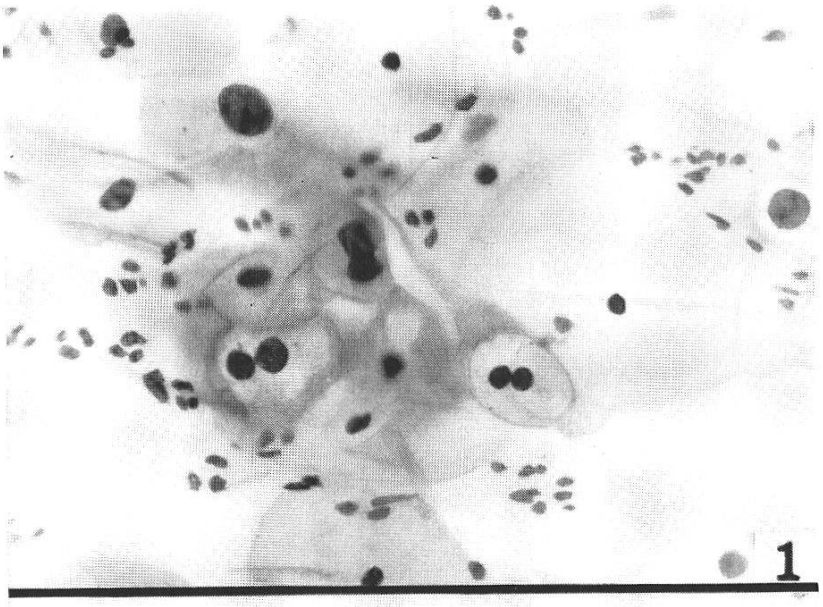
Captions for Figures

Fig. 1 Cluster of exfoliated squamous cells displaying the characteristic features of koilocytotic atypia: slightly hyperchromatic and frequently multiple nuclei and a centrally translucent cytoplasm with dense periphery. (Papanicolaou stain, 360x.)

Fig. 2 A single exfoliated superficial squamous cell with slightly enlarged and hyperchromatic nucleus and centrally translucent cytoplasm of a cavity appearance. Such cells are characterically associated with koilocytotic atypia. (Papanicolaou stain 360x.)

Fig. 3 Section of a biopsy of cervix displaying the characteristic features of koilocytotic atypia. It is obvious that this tissue pattern should not be confused with cancer. (Hematoxylin and Eosin, 225x.)

Plate 1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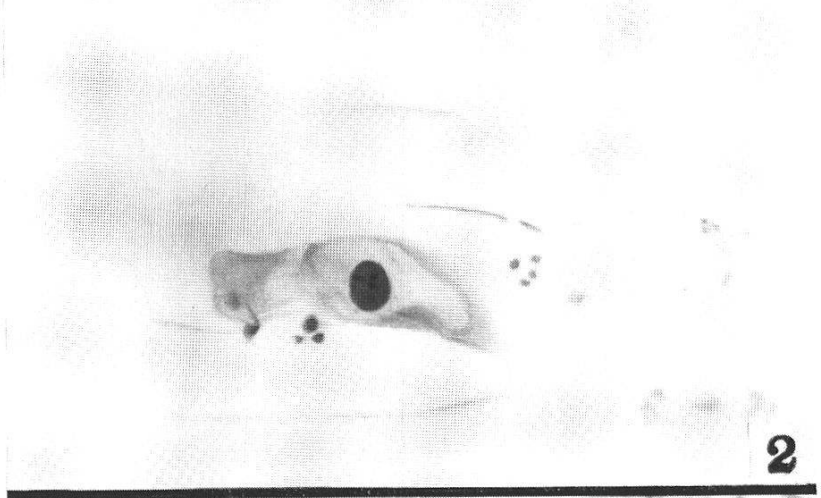
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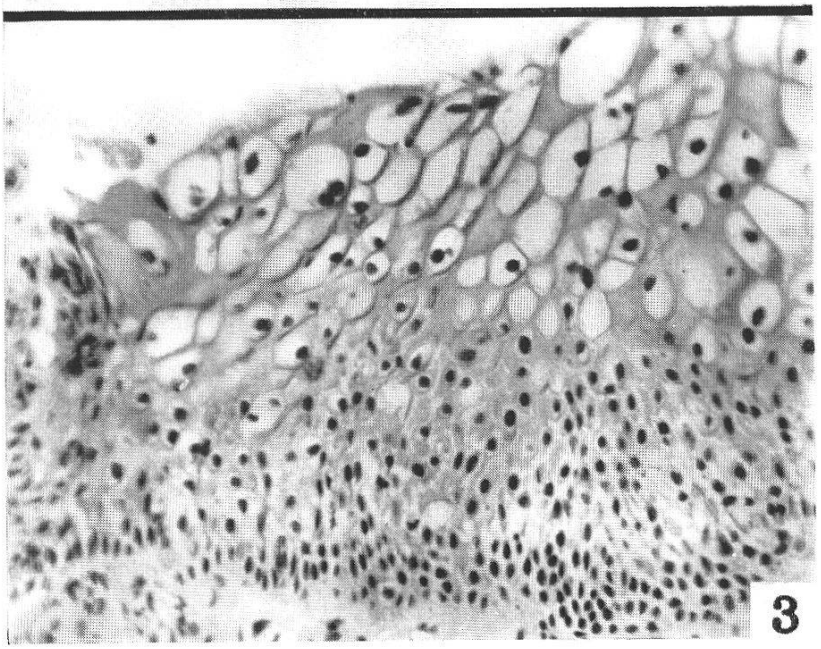
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