THE BIOLOGY OF CARCINOMA IN THE CERVIX UTERI [1]

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Five years ago a paper was presented before the American Association of Obstetricians, Gynecologists and Abdominal Surgeons entitled "A Study of Twelve Hundred Cervices." Since then, over 500 additional cervices have been studied, attention being focused more especially upon the biological behavior of cervical cells under normal and neoplastic conditions.

Normal Standards

Histologically the stratified epithelium and subepithelial stroma of the vagina is a modified cutaneous tissue with an abrupt transition to columnar epithelium within the cervical canal. The branched (elkhorn) mucous glands furnish an abundant secretion, which serves as a protection against both infection and friction.

The endocervical canal is closed by mucus except as it is opened periodically by menstrual activity or reproductive function. The thirty or more years of recurring activity and the changes of senescence tend to alter the precisely adjusted cellular parts. This decidual, atrophic, involutional process is dependent upon a balanced withdrawal of endocrine influences and progressive lessening of the blood supply for all cells alike. The scant muscle parts give place to relatively dominating connective tissue. Even the well defined, persisting, stratified epithelial layer narrows, and the polarity of the cells becomes progressively indifferent. The germinative or basal layer of cells is the last to surrender its vitality because of its advantageous contact with the stromal transportation of blood, lymph and tissue hormones.

It is obvious that when normal structural and physiological criteria are kept in mind, biological deviations may be more clearly defined. Certain major changes may reasonably have some bearing upon the development of carcinoma in the cervix uteri, as developmental defects, malformations, vascular and degenerative changes, inflammatory and metabolic disturbances, trauma, endocrine imbalance, disturbed cellular adjustments, and benign neoplasms. These will be discussed in reverse order.

Benign Neoplasms

From a study of more than 1700 cervices the influence of benign growths does not appear to be of great significance for the development of carcinoma. Polyps were not infrequent in this series and a small number of cervical myomata were seen. The coincidental occurrence of fundal myoma and cervical carcinoma was observed a number of times. Endometrial and endo-

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cervical hyperplasias were quite numerous. Associated with these benign growths were irregularities of blood supply and lymph drainage, hormone variations, malformations, metabolic inflammatory and degenerative changes. *In vitro,* maintenance of growing tumor tissue is greatly aided by emulsions of embryonic or immature tissues. Benign new growth may seemingly contribute a comparable environment, but this setting is not ideal for the initiation of malignancy.

Disturbed Cellular Adjustments

Experience with tissue cultures has established the fact that a single cell will not grow when isolated from other cells of its kind. Furthermore, physiological function of specifically differentiated cells fails when the developmental process does not carry them to their normal body positions. This law is illustrated by the incompletely descended testicle; that part of the testicle just outside the scrotum fails to function, while the part within is normal. With abnormal cellular arrangement in the cervix, many cells are unable to attain complete differentiation; protective function is undeveloped, sensitivity is increased, the effects of extrinsic irritation are more severe, and the embryonic cells are stimulated to increased growth.

It may be pointed out that the great majority of women having lacerated cervices with striking cell maladjustments do not develop carcinoma. With equally good logic it may be said that all who have diseases are not liable to their complications, but in a certain percentage of patients these complications do occur and prove fatal. Without the diseases, there would have been no complications. Similarly lacerations predispose to infection, increased secretion, irritation, irregular blood supply, changed lymphatic drainage, and lowered resistance.

Endocrine Imbalance

The cultivation of tissues has demonstrated the existence of substances which control cell growth. The only known source of such substances is living tissue, and the richest of these is the embryo, due doubtless to its content of growth hormone substances. Growth of malignant tissue in the cervix is more virulent in young than in old patients and in those in whom the hormone is high than in those in whom it is low.

The tissue fields of growth hormonal activity in the human adult are comparatively few, especially after the child-bearing period. The cervix uteri at this time is undergoing senescent changes though it does not become completely decidual. Its minor functions continue; local stimuli and irritations do not cease; cellular adjustments are frequently difficult; erosions, infections, hypertrophy, hyperplasia, cornification, ulceration, old traumata prevail, associated with old or recent efforts at local tissue repair.

Three types of cells are chiefly concerned in restoring the cervical lesion to normal: young stratified and glandular epithelial cells, and young connective-tissue stromal cells. But little concern should be given to a repair process if its needed provisions are met and results are accomplished in the usual time. If, on the contrary, factors of interference are present and remain active for

an extended period—perhaps five or ten years—there is created a parallel with the experimental or occupational interval required to produce carcinoma.

It is clear that the maintenance of normal characters in tissues is dependent on a normal environment and upon normal stimuli. Endocrine imbalance of sexual organs is now commonly recognized by hyperplasia of epithelial structures. The gonadotropic hormone in the urine is more often associated with malignant than with benign tumors of the genital tract. It is often observed that partial or complete loss of ovarian function following the menopause, or operative removal of the ovaries, is followed by an excretion of considerable amounts of urinary gonadotropic hormone.

Growth impulse is present in all hyperplasias of any adult age, with the single exception of retrogressive states. Hyperplasias predispose to malignancy; hormone imbalance is an important stimulus to hyperplasia, and its continuation beyond the menopause therefore becomes a specific liability.

Traumatic, Vascular, Degenerative, Malformative, and Metabolic Disturbances

The group of changes described by the terms traumatic, vascular, degenerative, malformative, and metabolic represents a progressive series of pathological events. There has been in the last few years some tendency to belittle or deny the opinion that lacerations, infections, and their attending sequelae have anything to do with the causation of malignant growth in the cervix. The phenomena, it is said, have been like circumstantial evidence, suspicious but without proof. Strongly convincing data have been presented, however, indicating that these lesions may act as provoking causes for malignant change. Loeb and Corner (quoted by McLeod), for example, have shown that, while the corpus luteum is developing deciduomata will form on the mucosal surface of the uterus if mere scratching of the mucosa is produced.

Robson defines plasticity as " the capacity for receiving structural impressions from mechanical, chemical, and physical factors of environment, which express themselves in the alterations of the mode of growth, density, proportions, color and other structural details. Such modifications may be produced either by reactions to specific factors, or they may be passively received by the organism." Plasticity, as defined above, is strikingly variable in all forms of life, from the simple to the most complex. Variability in the multiplication of bacteria is well known. The plasticity of adult tissues, especially cutaneous and mucosal structures, is familiar to all observers.

In a large number of gross and microscopic sections studied in the past ten years, the variability in the plasticity of the uterine cervix has been impressive, especially so far as the germinative or basal cells of the stratified layer and its underlying stromal connective-tissue cells are concerned. Known irritants that will produce experimental carcinoma and sarcoma include animal parasites, coal tar, lubricating oil, soot, arsenic, light, heat and x-rays.

When tissue is grown *in vitro*, a supply of activating substance must be assured. Growth *in vivo* occurs for one of the following reasons: (1) accomplishment of differentiation or maturity; (2) repair of tissue loss, (3) response to stimuli. In physiological and structural attempts at repair of the cervix, all

three reasons for growth are present. The development of malignancy at the site of repair signifies an excessive abnormal response to stimuli and failure in differentiation and repair.

In vitro, tissue growth is promoted by embryo extract up to a proportion of 40 per cent, and it is out of this substance that new cells are nourished. Leukocytic extract is also capable of promoting growth. The cell of all cells that is most easily grown *in vitro* and *in vivo* is the fibroblast. This fact, coupled with another, that it is omnipresent in malignant disease of the cervix, goes far in explaining the embryonic support of the malignant growth. Yet its presence is primarily for the purpose of repair in the parts injured. Continued irritation demands continued repair, hence a chronic infection is part of a vicious circle. Young fibroblastic ingrowth is followed often by new capillaries and spread of the malignant process.

It is an established fact in tar carcinoma that a considerable proportion of animals die from the toxic effects of the tar, showing nephritis, hepatitis, bone marrow changes, myocardial degeneration, and pneumonia. One might suspect that toxins are present in all causes of malignancies.

Malignant tissue contains more lactic acid than normal tissue, due to the type of oxidation processes in the cell. Calcium is reduced, potassium is increased; the lecithin-cholesterol ratio is high; permeability and electrical conductivity of the involved area are enhanced. Glucose oxidation is to a large extent lost. The foregoing changes are closely comparable to those of inflammation; therefore but little new has been learned by metabolic studies. The contrast in normal and carcinomatous cervical tissues obtained by staining with Lugol's solution depends upon the reduction of glycogen in the carcinomatous parts, which appear whitish in contrast with the dark brown of the normal tissues.

Developmental Defects

Failure in complete development of the uterus yields liabilities of considerable significance: function may be irregular or suppressed, general resistance to infection may be lowered, a predisposition to severe laceration or rupture may exist, and the danger of malignancy is increased. A second factor is doubtless provided by the cells produced to repair injury or to resist long-continued infection. Growth of cells in an environment of maturity, especially in the higher vertebrates, is relatively uncommon. Ability to repair a tissue with cells like those destroyed is limited, and a universal repair material of young connective tissue is generally utilized. Otherwise a holding stroma, together with epithelial or other cells, is used in a very limited way.

Cutaneous and mucous surfaces furnish the best examples of repair in the adult human body, and none receive more injuries and need more repair than the cervix uteri. Repair processes after lacerations, when observed microscopically, exhibit inflammation, production of fibroblasts, filling in of the gaping area by descended cervical glands, and bridging between the separated ends of the stratified epithelium by new generations of epithelial cells derived from the maternal or basal cells. A few of the advance cells in this bridging process change their polarity and are seen in single file and with their axes parallel to

the stromal or to the glandular surface. As stratification develops, the right-angle position of the cells is restored.

A striking difference in the stratified epithelium of the repair process and the old or primary epithelium is the persistence of slightly modified hyperchromatic basal cells in the mid-zone of the layer, suggesting delayed maturation. This phenomenon is most pronounced when there is underlying infiltration of leukocytes, abundant production of fibroblasts, and maladjustments of stromal to epithelial cells. It is in just this type of field that there is found an increased number of immature epithelial and stromal cells. In the majority of instances maturation is later accomplished, inflammation subsides, excess of stroma is absorbed, and repair with scarring is completed.

It is in this type of tissue change that the great majority of the 266 malignancies occurred in the series of over 1700 cervices studied. Carcinoma ultimately changes all three layers of the stratified epithelial cells until all distinction is lost. The evenly placed picket-fence arrangement of the basal cells on the upper surface of the stroma gives way to cells of irregular shape which have no systematic fixation to the basement line. In the normal stratified epithelium, division of cells is seldom observed and the few cells making this change are confined almost exclusively to the immediate zone of the basal cells; in carcinoma, on the other hand the cells divide freely at all levels of the layer, they appear almost equally vital and well stained, and show marked variation in size and form.

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