

GRAY

DYSPLASIA, CARCINOMA IN SITU AND
MICRO-INVASIVE CARCINOMA OF THE CERVIX

THOMAS

DYSPLASIA, CARCINOMA IN SITU AND MICRO-INVASIVE CARCINOMA OF THE CERVIX UTERI

Compiled by

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Dedicated to the Memory of
DR. GEORGE N. PAPANICOLAOU
and
DR. WALTER SCHILLER

PREFACE

PROFESSOR WALTER SCHILLER visited the Gynecological Pathological Laboratory of The Johns Hopkins Hospital in 1934. At that time he demonstrated the lesion of intraepithelial carcinoma of the cervix uteri in sections, which he had originally described some seven years earlier. As a neophyte in the laboratory, I was tremendously impressed by his concept. Although a few individuals had made reference to intraepithelial lesions in earlier years, it was Schiller who crystallized the understanding of the preinvasive lesions which has extended the practice of modern gynecology to an extraordinary degree. Thereafter, the lesion was reported at increasingly frequent intervals as more biopsies were performed, particularly in this country, but it was the science of cytology, introduced by Papanicolaou and Trout in 1943, which presented a method for the more frequent detection of preinvasive carcinoma.

From 1953 to 1956, in the course of examining approximately 6,000 patients, 1,585 cervixes which showed eversion and eversive cervicitis of moderate or marked degree were biopsied by us. Twelve cases of carcinoma in situ were discovered by this routine. From 1956 to 1959, in 5,155 patients, the Papanicolaou smear was obtained from each, and twenty-six cases of carcinoma in situ were found, primarily by means of the smear but confirmed by biopsy and conization of the cervix. This dramatically emphasized the value of cytology.

The volume of the literature devoted to the preinvasive and early invasive lesions of the cervix has increased rapidly; in the last few years very many papers have been published. Numerous investigators have concentrated their efforts to the study of these epithelial changes.

Distinguished pathologists and clinicians have accepted invitations to write chapters for this book which summarize the recent knowledge of the early lesions, and which present in addition their own original investigations. At the conclusion I have taken the liberty to emphasize certain facets of diagnosis, treatment, and research. The great scientific achievements that have come from the work of Schiller and Papanicolaou must be applied accurately.

The contributors to this book have been most generous, and their efforts are tremendously appreciated. As always, the publisher has been helpful in every detail and has prepared a beautiful book. Again, I am personally indebted to Mr. Payne Thomas, who has followed in the footsteps of his distinguished father, and to Mr. Warren H. Green, the esteemed Editor of Charles C Thomas, Publisher.

LAMAN A. GRAY, M.D.

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**DYSPLASIA, CARCINOMA IN SITU,
AND MICRO-INVASIVE
CARCINOMA OF THE CERVIX UTERI**

INTRODUCTION

LAMAN A. GRAY, M.D.

ONE OF THE greatest advances of our time in the entire field of medicine has been the description and understanding of preinvasive and extremely early malignant lesions in the cervix uteri, particularly enunciated by the brilliant work of Schiller, and made possible to be discovered readily by the science of diagnostic cytology originated by Papanicolaou. Knowledge of this field of pathology, of clinical diagnosis, and of definitive treatment is available throughout the world, but has yet to be universally applied. There are some differences of opinion, but actually one comes to the interpretation of the activity and future of small lesions involving relatively few cells; undoubtedly further research and study will clarify the prognostic implication of the appearance of these cells in these early lesions.

The Papanicolaou cytologic technique was dramatically placed before the profession in the beautiful monograph by Papanicolaou and Trout in 1943. This unfortunate time found most of the gynecologists in alien work, or they were so overburdened by routine obstetrics and gynecology in civilian practice that they could give little time to the study of this technique and its application in clinical practice. It seemed at the time that perhaps the study of desquamated cells was impractical and it seemed doubtful that many would achieve proficiency in the interpretation of the meaning of those cells shed into the va-

gina from the cervix and endometrium. Following the war there was increase in interest in this technique, but by 1949 to 1951, that activity had diminished greatly, and some university centers were discontinuing cytologic study because it seemed too expensive for the value obtained. A few medical centers and investigators continued to make great contributions in this field. Then in 1951, the Memphis, Tennessee Project was underwritten by the United States Public Health Service under the direction of Dr. Cyrus Erickson. A few years later in 1956, a similar program was begun in Louisville, Kentucky under Dr. William Christopherson, and in a few other areas in the country. These projects demonstrated the complete practicability and the necessity for the application of the Papanicolaou cytologic technique to the study of every female patient, certainly after the age of eighteen years. Reference to these projects does not mean that other workers throughout the country had not developed extremely proficient laboratories in the Papanicolaou technique, but on the other hand, in many localities the techniques employed were imperfect and the interpretations were not dependable. In part, this was because the pathologists were well oriented in tissue pathology, and did not fully accept the value of cytology. The development and training of cytologic screeners and the cytopathologists caused this technique to become extremely accurate in

screening and in aiding in diagnosis. Unfortunately, more than half of the women in this country have never had a cervical cytologic study performed. The properly interpreted cytologic study in this field of medicine becomes one of the more accurate diagnostic procedures in medicine.

The anatomy of the human cervix is being considered in a different light in recent years, especially since Fluhmann has indicated that there are not true glands in the endocervix, but merely clefts. The older literature has indicated that true glands of the tubular racemose type are present. The embryologic changes in the cervix relate undoubtedly to the future lesions that may appear in adult life. The progress of the squamous epithelium up into the endocervical canal, its regression or propulsion back to the external os, and the residue of these mobile cells undoubtedly must have some relation to inflammatory and neoplastic lesions.

Eversions of the endocervical epithelium and inflammation in this area are intimately related to metaplastic and dysplastic changes in the reserve cells and squamous epithelium. The possible effects of these inflammatory changes on preinvasive neoplasms are necessarily important.

The reserve cell has become the focus of an intensive investigation in all laboratories concerned with the problem of carcinoma of the cervix. Its embryologic origin, its sensitivity to inflammations and hormones, and finally its possibility of development in adult life into either mucous secreting epithelium or glycogen-containing squamous epithelium are factors which may be related to the development of carcinoma. This cell has been implicated as the origin of

the majority of carcinomas of the cervix. Allusions to the reserve cell, with its multiple capabilities, are repeated throughout the recent literature.

The early lesions must be defined, and their progressive nature must be understood when possible. The descriptive meaning of each term must be clarified for communication and elucidation.

Recent studies of the chemical changes in the vaginal secretions and in the cervical cells offer a new field of investigation which undoubtedly will progress in many directions. The intensive research of preinvasive and invasive cancer cells with very high magnification with light microscopy and electron microscopy reveals details of the cytoplasm, nucleus, and chromosomes which indicate some specific findings in the relation to the static and the invasive carcinoma.

The accuracy and details of the cytologic technique have become so refined as to be almost specific in diagnosis, although the cytopathologist continues to insist on histologic proof of a diagnosis. In reverse, the histopathologist must make certain that his findings will correlate with the cytology, or further histologic study is necessary.

Knowledge of the gross appearance of the early lesions of the cervix has been neglected or considered of superficial importance. On the other hand, much can be learned from clinical observation. This includes not only inspection, but also the use of the Schiller test. Colposcopy and the newer colpomicroscopy make the clinical examination more complete.

The progression of dysplasia of the cervix to carcinoma in situ, and from there to microinvasive carcinoma and massive occult invasion of the cervix re-

presents a basic concept in gynecological pathology. The relation of dysplasia evidently is an inconstant one, whereas the later lesions are more intimately progressive. The concepts of clinical treatment of dysplasia, carcinoma in situ and microinvasive carcinoma are reasonably unanimous, except for the latter. It becomes a problem for the pathologist to determine how often early invasion extends beyond the uterus and metastasizes to the lymph nodes.

The pregnancy problem appears to be clarifying itself, as one realizes that specific changes do occur due to the hyper-hormonal stimulation of the mucous glands, reserve cells, and squamous epithelium. These hyperplasias may even suggest dysplasias, but it is becoming apparent that true carcinoma in situ is a constant lesion in the pregnant or non-pregnant as a rule.

More publications which clarify the life history of dysplasia of the cervix, carcinoma in situ, microinvasive carcinoma, and clinical carcinoma of the cervix are appearing constantly. The relations of these lesions are being known; the reversibility, the time intervals involved, and the effects of physiologic processes are being studied carefully and reported in detail. Do these lesions follow in sequence? Are they preceded by reserve cell changes so that even earlier preinvasive forms may be known? Should microinvasive carcinoma be made a separate group? Does the latter merit radical treatment or conservative treatment? Should this term be completely omitted from the literature? In this book the reader will see some differences of opinion, but viewing the whole problem, there are well established guideposts for the present, and some exciting new ideas for our future consideration.

THE CERVIX UTERI

C. FREDERIC FLUHMANN, M.D.

THE CERVIX or neck is the lower portion of the uterus and is cylindrical in shape but tapers off at its inferior extremity. The cervix enters the vault of the vagina and the points of reflection of the vaginal wall divide it into an upper part, the *supravaginalis*, and a lower, the *portio vaginalis*, which are approximately of the same length. The vaginal mucosa is attached to the periphery of the cervix and, as it is reflected toward the front, the sides, and the back, the vault forms the fornices which are useful for purposes of description. The supravaginal portion is in close apposition to the bladder in front, but posteriorly it is covered by peritoneum which is continued on to the posterior vaginal wall and eventually is reflected over the rectum. The portio vaginalis points into the vagina and is usually directed toward the posterior wall but this may vary according to the relationship between the corpus and the cervix. The cervix is more firmly held by its ligamentous connections but may incline backward, forward, or laterally as the corpus is anteverted, retroverted, or lateroverted. There may also be some modification in the direction of the portio vaginalis according to the relationship between the longitudinal axis of the corpus and cervix. The corpus is bent forward at its junction with the cervix when the uterus is in a state of *anteflexion* but when it is directed posteriorly it is in

retroflexion and when toward the sides of the pelvis it is in *lateroflexion*.

The canal of the cervix measures 2.5 to 3 cm. long, is fusiform in shape, flattened from front to back, and slightly dilated in its middle third. The average transverse diameter at its widest point is 7 mm. and sagittally about 4 mm. It is continuous with the uterine cavity above the *internal os*, the narrowest portion of the uterine cavity. The *external os* is the opening in the portio vaginalis which connects the cervical canal with the vagina. It is usually nearly circular but often is represented by a small transverse slit and many variations may be seen in women who have borne children and suffered cervical lacerations extending in different directions. When it is a small oval opening, as in young girls, it formerly was referred to as the *os tincae* because of its supposed resemblance to a tench's mouth—and since few gynecologists are well versed in the lore of ichthyology it might be added that a tench is a fresh-water fish allied to the carp. The part of the portio vaginalis in front of the external os is known as the *labium anterius* or anterior lip, and behind is the *labium posterius* or posterior lip. Since the posterior vaginal fornix is deeper than the anterior fornix, the posterior lip appears longer than the anterior lip, but this is an illusion brought about by the difference in the levels at which the vagina is reflected from the anterior and posterior walls of the cervix.

My thanks are due to Mr. James Brodale for illustrations 8 and 9.

The cervical mucosa is involved in grossly visible folds which in the past have been described wrongly as composed of a regular pattern. They were known as *plicae palmatae* and it was stated that they consist of from one to four longitudinal folds or rugae from which emanate smaller accessory folds directed obliquely toward the internal os. Their arrangement was said to resemble the trunk

and branches of a tree and hence they acquired the name "arbor vitae."

This description is another of the anatomic myths associated with the cervix and an inspection of the endocervical mucosa either grossly or with a lens shows that there is no regular pattern of arborization. As seen in the examples in Figure 1 there is a very great dissimilarity in the configuration of the folds and grooves

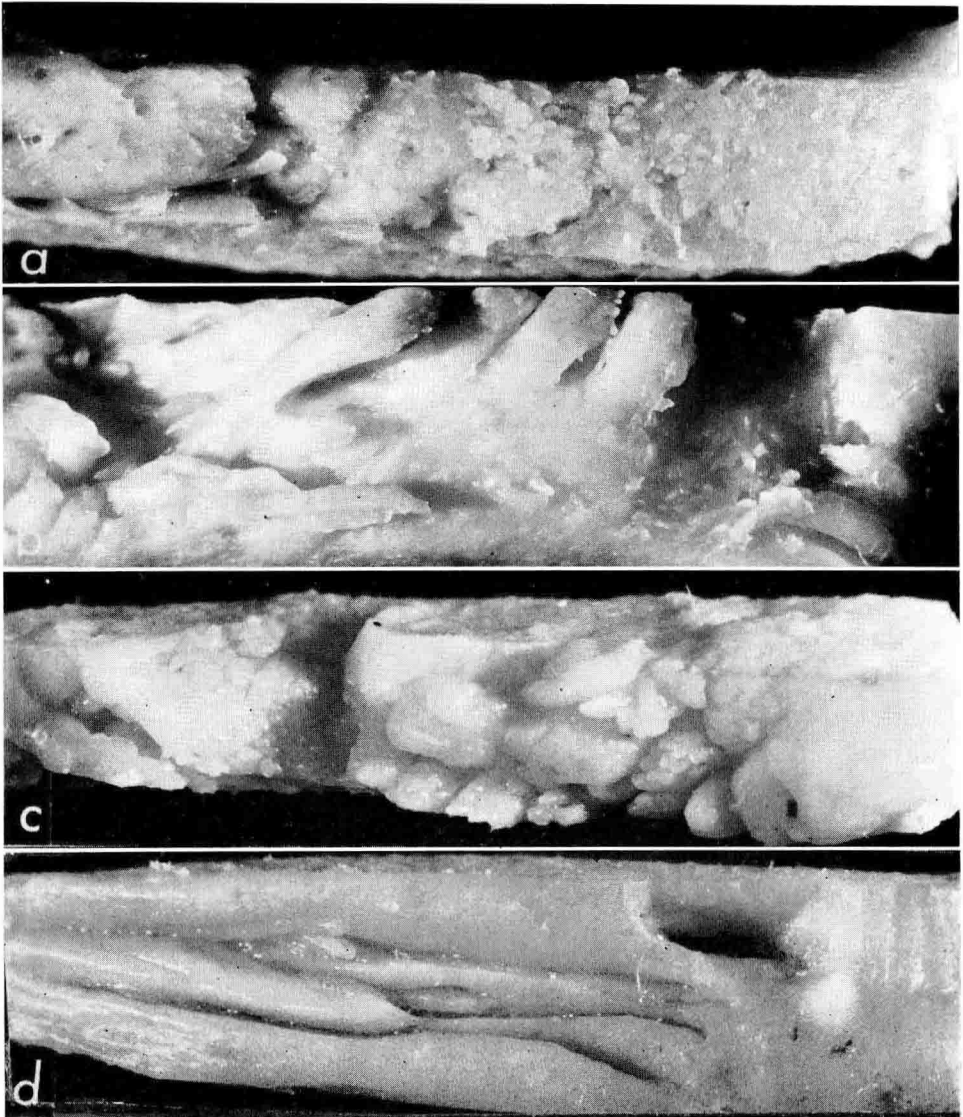


Fig. 1. Surface markings, or so-called *plicae palmatae*, of the cervical canal. X4. (From Fluhmann.⁹)

and no consistent arrangement can be determined. The grooves vary in length, width, and depth. They may extend for as little as fractions of a millimeter to as much as 1.5 cm. and in width they may be of microscopic dimensions or measure up to 1 mm. Their depth in the nonpregnant woman as determined from microscopic sections reaches a maximum of approximately 3 mm., namely the depth of the whole mucosa. They may course in all directions and be straight or curved. This arrangement is important as it corresponds to the clefts which make up the glandular structures of the cervix uteri.

The division between the corpus uteri and the cervix is of significance especially in any discussion of the lower uterine segment in obstetrical problems. According to Aschoff² the isthmus is a manifest part of the uterus with distinct histologic characteristics and it lies between two clearly defined points. The first is the *anatomic internal os*, which marks the lower boundary of the corpus uteri. It is a point of constriction which can be recognized either by visual inspection of a gross specimen, or it can be identified by passing a sound through the intact cervix and noting the distance from the external os to the lower border of the narrowing. At a distance varying from 6 to 10 mm. below this point is the *histologic internal os* which corresponds to the histologic junction of the mucosa of the isthmus and the cervix, while the *isthmus uteri* itself is defined as the region lying between these two ora (Fig. 2).

Danforth^{3,4} has cast doubt on the validity of this classic description and given us a new concept (Fig. 2). According to his findings the isthmus is not a separate entity but merely the lower part of the corpus uteri. This area may still be termed the isthmus, but it is variable in

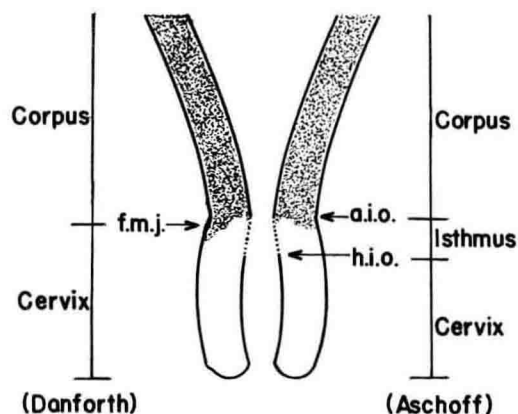


Fig. 2. The classic concept of Aschoff is that the isthmus is a specialized portion of the uterus with a distinct mucosa. The upper border corresponds to the constricted area of the uterus and the junction of the endometrium and the isthmic mucosa and is known as the "anatomic internal os" (a.i.o.). The lower border of the isthmus is located at the junction of the isthmic and cervical epithelia and is known as the "histologic internal os" (h.i.o.).

According to Danforth the uterus is divided into a corpus and cervix at the junction of the muscle of the corpus and the fibrous tissue of the cervix, the fibromuscular junction (f.m.j.). This is a variable point but corresponds to the narrowing of the uterus and consequently may be regarded as the internal os. The isthmus is held to be merely an area of attenuated endometrium of variable size immediately above the junction with the cervical mucosa.

width and location and does not have any relation with uterine muscle function. Since the cervix itself is composed chiefly of fibrous tissue, the important anatomic point is the *fibromuscular junction*, the junction between the muscle of the corpus and the fibrous tissue of the cervix. It is sometimes abrupt but it may be gradual and occur almost imperceptibly over the course of 5 to 10 mm. The fibromuscular junction also corresponds to the constricted portion of the uterus, but it is unrelated to the histologic variations of the

mucosa nor the junction of the endocervical and endometrial epithelia.

HISTOLOGY

The main substance of the cervix is composed mainly of fibrous tissue, although there is a variable but small number of smooth muscle fibres. The surface of the portio vaginalis is covered by squamous epithelium identical and continuous with that of the vagina, while the canal is lined by a columnar epithelium different from that of the endometrium. The transition from one type of mucosa to the other in the region of the external os has been given as occurring at a sharp "junction" in all classic descriptions of these structures. Actually in most instances there is a zone of variable width between the squamous and columnar epithelia which represents a "transformation" or "transitional" area. It is composed of cellular components which have been termed "epidermidization," "squamous metaplasia," or "squamous prosoplasia" and interpreted as a pathologic process. The frequency of this occurrence, however, calls for a departure from this concept and this epithelium should be considered as a normal constituent of the cervical mucosa. On the other hand there is a fairly well-defined junction between the columnar epithelium of the endometrium and that of the endocervix at a point near the fibromuscular junction.

Squamous Epithelium. The covering of the portio vaginalis (ectocervix) is a stratified squamous epithelium, but complete cornification does not take place as a rule and keratinization occurs only as the result of prolonged irritation. There are five layers or zones of cells, according to the original description of Dierks⁵ (Fig. 3).

Zone 1. The lowermost layer consists

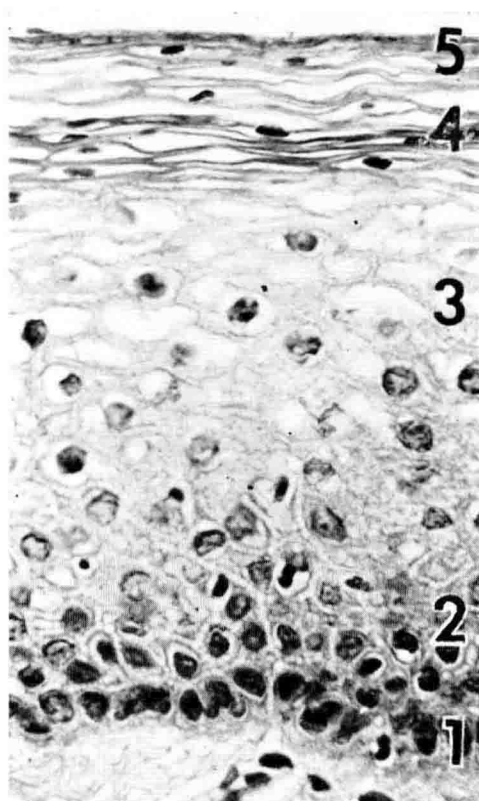


Fig. 3 The five zones of the squamous epithelium of the ectocervix. (1) Basal. (2) Parabasal. (3) Clear. (4) Condensation. (5) Cornified x550. (From Fluhmann.¹)

of a single compact row of small cylindrical cells with relatively large nuclei. They are usually referred to as basal cells, but they are also called germinal cells, inner basal zone, or stratum cylindricum.

Zone 2. This area is composed of several thick layers of polyhedral cells with fairly large nuclei and distinct intercellular bridges. They have been called prickle cells, parabasal cells, spinal cells, and the stratum spinosum profundum.

Zone 3. The third zone is known as the clear zone, light zone, intermediate zone, navicular zone, or stratum spinosum superficiale. The cells are larger, moderately flat, highly vacuolated, with