THE DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX

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Of the malignant neoplasms occurring below the waistline, carcinoma of the cervix is the most frequent. Of 1779 carcinomata, specimens of which have been examined in the Laboratory of Obstetrics and Gynecology, University of Pennsylvania, 827 or 46.43 per cent had their origin in the cervix.

In a recent review by Keene and Kimbrough (1), of 479 of our cases from 1913 to 1926, cervical carcinoma shows a five-year mortality rate of 84.76 per cent. Ward’s, Healy’s, Schmitz’, and Heymann’s figures, quoting some of the most favorable, showed a mortality rate of approximately 75 per cent. Considering the figures of this country at large, the ultimate mortality rate is probably in the neighborhood of 90 per cent.

The five-year mortality rate in our early cases (Stage I, Schmitz classification) was 60.35 per cent. Even this average cannot be regarded as satisfactory, especially when it is remembered that only about 10 per cent of the cases are in this early stage when first seen, so that the real results become apparent.

Dietel and Steffan-Eisen (2) found that the group made up of intelligent patients sought medical advice earlier, and consequently gave better end-results than were secured among the more ignorant classes. These observers also found that the disease was more prevalent in the latter group, due doubtless to the fact that the former class receive more skilful obstetrical treatment. The higher birth-rate among the less privileged class may also influence this finding. Dietel and Steffan-Eisen found that among all gynecologic admissions uterine carcinomata made up 6.2 per cent of ward patients and 3.9 per cent of private cases.

At least half of the apparently favorable cases succumb within five years; in nine out of ten cases the mortality is much higher. For those interested in this subject numerous valuable statistics are available. In considering these it should be borne in mind that almost without
exception the figures have been compiled by those most skilled in the
treatment of the disease, and who possess the most complete armamen-
tarium for its practice. In other words, published statistics relating to
cancer usually represent the best results. Necessarily only a small
proportion of women suffering from carcinoma of the cervix are treated
under such favorable circumstances, and the mortality at large, there-
fore, is far greater than available statistics would indicate.

From our present knowledge—or lack of knowledge—of the etiology
of carcinoma and of the most acceptable method of treatment, it is evi-
dent that the most important factor in the prognosis is the stage of
advancement that the disease has reached. It is probable that the
veriest tyro could secure better results by performing a simple trache-
lectomy in early cases than the most experienced and skilful gyneco-
cologist could obtain by employing the most modern treatment in the
advanced cases. It is evident, therefore, that, until some more effective
method of dealing with carcinoma is discovered, prophylaxis and early
treatment are the two most important factors in dealing with this
disease.

Ninety per cent of cases of cervical carcinoma have their origin in
lacerated cervices. It is the cervicitis which always develops after
laceration which is the predisposing factor. Hunner (3) subjected
2895 cases of chronic cervicitis either to amputation or to cauterization,
and found, after a follow-up of ten years, that not a single case of car-
cinoma developed in the series. Bossi (4) has recorded equally good
results following plastic operations upon the cervix. Combined sta-
tistics of Pemberton, Smith et al., Smith, Bland, and Graves, as quoted
by Saltzstein and Topck (5), show that of 18,562 patients who were
treated by surgery or diathermy for cervical lesions, only 15 sub-
sequently developed cancer. The same authors quote statistics which
show that of 2,255 patients with carcinoma of the cervix only 33 had
received adequate treatment for chronic cervical lesions. Trachelec-
tomy is apparently a somewhat more effective method of securing
prophylaxis than either cauterization or trachelorrhaphy.

Periodic examinations of patients during the cancer age are un-
doubtedly of value, and, even if performed only once a year, would lead
to the discovery of at least a few early cases. The routine employment
of the iodine test (Schiller’s) and the use of the colposcope in suspicious
cases would tend to enhance the value of such examinations, as car-
cinoma could thus be recognized or suspected much earlier than by
the older methods alone. An important and additional advantage of
the periodic examination is its educational value.

The more thoroughly this disease is studied, the more evident be-
comes the necessity for early diagnosis. During the late stages the
diagnosis is made without difficulty, but during the early stages diag-
nosis is attended with uncertainty and positive recognition of the dis-
ease without the aid of the pathologist is usually impossible. In order
that an early diagnosis may be arrived at, the patient must submit to a
physical examination by a physician who is capable of recognizing the
disease, or who is at least sufficiently familiar with malignant conditions to become suspicious that carcinoma may be present, and who will take immediate steps to exclude or confirm the diagnosis.

A number of factors lead the patient to neglect seeking medical advice early in the disease. Among the most common of these are the inherent fear of cancer and the common belief that it is incurable, the mildness of the symptoms, and the fact that a discharge of some sort has probably been present for years, for, as stated previously, carcinoma rarely develops upon a normal cervix. A slight alteration in the character of the leukorrhea may be overlooked, or regarded as of no moment. Atypical bleeding is often attributed to a menopausal disturbance. The chief reason, however, that patients delay in seeking medical advice is probably the painless character of the early symp-
Incomprehensible as it may seem, one of the chief reasons why physicians fail to recognize the disease is their failure to make a pelvic examination.

In point of fact, during the early stages of the disease the symptoms are few, mild, insignificant, or entirely absent, and it is at this stage that it is much more insidious than most text-books would seem to indicate. As the disease progresses, the factors militating against diagnosis become less pronounced.

*Schiller's Iodine Test:* Two aids in the diagnosis of early carcinoma of the cervix have recently been developed; namely, the use of iodine potassium iodide solution in the form of Lugol's solution (iodine, 1; potassium iodide, 2; water, 300) and the employment of the colposcope. When Lugol's solution (Schiller's test) is to be used, the patient should be placed in the lithotomy position. The bladder should be empty. The foot of the examining table should be slightly elevated, and a vaginal speculum inserted, and the cervix exposed. The cervix and upper vagina should be cleansed of mucus or discharge and carefully inspected under good illumination. This is done for the purpose of making comparison after the stain has been applied. About half an ounce of Lugol's solution should then be instilled into the vagina, a small swab stick or a cotton pledget being used to insure that the iodine is brought in contact with the entire vaginal cervix. If this is not done, a fold of vaginal mucosa may occasionally overlap part of the cervix and prevent the uniform application of the solution. The iodine is permitted to remain for from thirty to sixty seconds. The table should then be lowered and the excess of iodine removed with cotton. The cervix should not be traumatized or scraped with a sharp instrument, as areas so traumatized fail to accept the iodine. The cervix should now be inspected thoroughly with the naked eye, and later with the aid of the colposcope. Some operators merely paint the exposed cervix with Lugol's solution. Whatever technic is employed, it is important that the solution actually reach all parts of the portio. The removal of excess cervical secretion insures uniform application and staining.

The information obtained as the result of this test is due to the work of Lahm (6), who showed that the normal superficial layers of the vaginal and cervical epithelium contain large quantities of glycogen, and therefore stain a deep mahogany brown with iodine in watery solution (Lugol's). Negative results, i.e., a uniform brown stain with no unstained areas, are a fairly positive indication that carcinoma is not present in the area which has been exposed to the iodine. A loss of staining properties occurs in the earliest stages of cancer. The most poorly differentiated tumors contain the least amount of glycogen. Simple erosions from which the investing epithelium has been denuded and erosions in the early stage of healing and covered with cuboidal epithelium do not stain. Although negative results, i.e., uniform staining, exclude carcinoma from areas that have been exposed to the action of the iodine solution, unstained areas are not positive evidence that carcinoma is present, but indicate points from which tissue should be
B'IOS. 2 A AND B. EXTREMELY EARLY SUPERFICIAL ADENOCARCINOMA OF THE CERVIX

The new growth has had its origin in a cervical gland. The surrounding squamous epithelium is normal. A moderate degree of inflammatory reaction surrounds the carcinoma. The deeper portion of the gland (not shown in the photomicrograph) was normal. × 80.
(P. N. 162292.)

The higher-power view shows gland formation with reduplication of glandular epithelium, and irregularity in size, shape, and staining properties of the cells. Here and there penetration of the basement membrane is seen. An occasional mitotic figure is present. × 150.
removed for microscopic examination. In other words, iodine-negativity and carcinoma are not always identical. What appears to be iodine-negative may be carcinoma or it may be merely hyperkeratosis, traumatic desquamation, or other benign lesion. Iodine-negativity can only attract attention to suspicious areas in which the epithelium is pathologically altered.

When the carcinoma is far advanced and definite necrosis has occurred, the necrotic area stains brown with the iodine. Surrounding this iodine-positive area, however, is a zone of iodine-negativity that is quite characteristic. As a matter of fact, by the time necrosis has occurred the disease is usually so far advanced that a diagnosis can be made with comparative certainty by clinical methods alone.

![Image](image.png)

**FIG. 3. EARLY EPIDERMID CARCINOMA OF THE CERVIX**

The carcinoma has had its origin at or near the point of transition between the columnar and squamous epithelium, and can be seen penetrating into two glands. A small epithelial pearl is present. While pearl formation in the cervix is suggestive, it is by no means diagnostic of carcinoma of this region. The area shown is not sufficiently characteristic to warrant a positive diagnosis of carcinoma. Frank carcinoma, however, was present in the immediate neighborhood. X 48. (P. N. 16156.)

Schiller (7) recommends that the scraped-off epithelium or excised cervical mucous membrane of the suspected area be tested by Best's carmine method for glycogen, and states that the presence of layers of large, typical, vesicular, superficial cells containing an abundance of glycogen is positive evidence against the presence of carcinoma. Pus stains a deep brown; areas of chronic cervicitis and traumatized areas accept the stain less positively than does normal epithelium. The cervix of the hypoplastic and atrophic individual stains lighter than does the normal mucosa of the normal individual (Graves, 8). Previous irradiation tends slightly to decrease the iodine-negativity in carcinoma. The author has repeatedly observed an increase in the
staining properties of cervical carcinomata two weeks after a single
treatment of 2400 mg. hrs. of radium. In these cases there was always
definite iodine-negativity, but it was not so marked as it was before
treatment.

The iodine test possesses the advantages that it is inexpensive and
that it requires but a few minutes, making it applicable in out-patient
work. Furthermore, it requires no elaborate armamentarium nor any
special knowledge for its effective use.

One of the chief weaknesses of biopsy lies in the fact that the tissue
may not be secured from the correct area, whereas the colposcope and
the iodine test are especially valuable in indicating this point.

Very early carcinoma is almost always superficial. Schiller (9)

![Image: Fig. 4. Benign ‘‘Epidermoidalization’’ at Point of Transition Between Squamous
and Columnar Epithelium]

The squamous epithelium is seen dipping into the stroma and into the cervical glands. However, the epithelium lacks malignant characteristics and the condition is clearly a benign one.

This type of lesion is sometimes incorrectly diagnosed ‘‘precancerous.’’ ‘‘Epidermoidalization’’ in this region probably is often a protective process. × 60. (P. N. 16188.)

strongly recommends the iodine test, and prefers to use a sharp curet
in place of the knife or punch with which biopsy specimens are ordi-
narily obtained. Babès (10) and Graves (8) also prefer scraping.
Curettage of the suspicious areas is in many cases preferable, as in this
way tissue can be secured from a number of areas with less mutilation
of the cervix than would occur as the result of multiple excisions.
Care must be observed to secure sufficient tissue for histologic examina-
tion. This is a very practical point. After the removal of tissue for
microscopic examination the denuded area should be touched with the
cautery, which tends to prevent dissemination and checks bleeding.

Early carcinomata situated within the canal may not be detected by
the iodine test, in which case additional methods for excluding the disease in this area are necessary. A modification of the John G. Clark test, i.e., the aseptic introduction, under sight, of a sterile sound into the canal and gentle manipulation of its point over the entire cervical mucosa, will almost always cause a slight trickling of blood to appear at the external os if a friable vascular lesion such as carcinoma is present. When this method is properly performed, negative results are practically conclusive, but when bleeding follows the test dilatation of the cervix, inspection, curettage, biopsy, and in some cases trachelectomy, are indicated to confirm the diagnosis.

The Colposcope: The colposcope, devised by H. Hinselmann of Hamburg and later modified by Preissecker and others, is a magnifying instrument of long focus with a powerful illuminating attachment employed in conjunction with a bivalve speculum for inspecting the upper vagina and cervix. The foreign instrument 1 gives an enlarged stereoscopic picture. An instrument devised for office work enlarges 10 times, whereas the more powerful instruments magnify up to 40 times. The latter are binocular coloscopes. Another foreign firm 2 has recently placed a binocular colposcope upon the market which magnifies 6 to 12 times at viewing distances of 10 to 25 cm. A smaller monococular instrument, made by an American firm, 3 may be attached to an ordinary Graves speculum, although the black speculum supplied with it is a distinct advantage in eliminating the glare and reflection which are present with the ordinary nickel instrument. With these instruments minute details and slight alterations from the normal are detectable; for example, extremely small ulcers, slight thickening or loss of transparency of the epithelium, and small areas of leukoplakia. Suspicious areas may thus be indicated, and from these tissue should be secured for microscopic examination. The colposcope may be employed with advantage both before and after the application of Lugol's solution.

Considerable experience is necessary in order to be able properly to interpret the pictures presented by the colposcope. At first the results are likely to be distinctly disappointing, but as experience increases and mental standards develop, so that the appearances of the different pictures are better understood, the amount of information acquired increases materially. Images secured with the aid of the colposcope should be compared with the microscopic pictures; in this way the investigator is enabled to build up for himself a series of mental colposcopic photographs much as the student in pathology does when he examines a series of histologic preparations with the microscope.

Viewed with the colposcope, cylindric and pavement epithelium can be distinguished. Preissecker (11) states that the pavement epithelium appears as a smooth, whitish to reddish or violet tissue, the color depending upon the degree of vascularity, its smooth glistening surface being its chief distinguishing feature. In many cases the vessels are

1 The colposcope manufactured by E. Leitz, Wetzlar.
2 Carl Zeiss, Jena.
3 Vaginal telescope manufactured by Cameron Surgical Specialty Co., Chicago.
FIGS. 5 A AND B. EPIDERMOID CARCINOMA OF THE CERVIX

The section shows the so-called carcinomatous "frosting" (an early superficial carcinomatous change). The cells in the carcinomatous zone show the usual characteristics of this neoplasm, and well defined carcinoma is present in the immediate neighborhood. × 80. (P. N. 9523.)

The lower photomicrograph is from another section of the tumor, showing definite carcinoma.
visible. Where they do not show through, as in Hinselmann’s (12) “tessellation,” a thin, normal epithelium is not present. The cylindric epithelium varies in color from a moderate to a deep red, and at a magnification of 10, small but definite papillæ are observable. The cylindric epithelium is not shiny. With stronger magnification the exits of the glands may be distinguished, with here and there droplets of mucus protruding from their openings. As compared to ectropion, the erosion has larger and more irregular papillæ, and hemorrhagic infiltration is often seen. Small collections of mucus may be present in the depressions. Ectropion is more regular and velvet-like in appearance. Erosions often exhibit signs of healing, whereas in ectropion one never

![Image](image_url)

**Fig. 6. Margin of an Early Epidermoid Carcinoma of the Cervix.**

To the right is the somewhat thickened layer of squamous epithelium, all the layers of which are well preserved. The basal layer exhibits considerable activity. To the left is the edge of the carcinoma which can be seen penetrating deeply into the underlying tissue. Here all regularity of layer formation is lost. Occasional mitotic figures are present. Although no marked hyperchromatosis is present, under higher magnification many nucleoli, which are in size out of proportion to the nuclei, can be observed. × 100. (P. N. 11575.)

sees the irregular, dull, yellow nodules representing cervical glands closed by healing pavement epithelium. The latter is characteristic of old healing erosions. Opacity and absence of vascularity suggest a thickening of the epithelium.

Schiller (13) has observed that, with the employment of the colposcope, minute areas of leukoplakia that cannot be detected with the naked eye become visible. These can be excised for histologic diagnosis. After an analysis of his cases, Schiller finds that many early cases have been discovered by the employment of the iodine test and the colposcope which could not otherwise have been recognized until considerably later. Emmert (14) also reports success in the detection of early carcinomata by the use of the colposcope. Niehaus (15)
THE DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX

recommends the iodine test. Preissecker (11) stresses the point that atypical epithelium recognized in the colposcope should be subjected to histologic examination in order to differentiate benign from early malignant lesions. Hinselmnnn (16) states that the transition from the healed erosion to carcinoma does not develop suddenly, but that the epithelium is altered before the malignant change occurs, and asserts that it is from this transitional zone that carcinoma is prone to develop. This altered epithelium can readily be differentiated from the normal epithelium by means of the colposcope. Chronic lesions, such as minute erosions or nodules, when situated at the point of transition from the striated to the columnar epithelium, are especially likely to undergo

![Image of early epidermoid carcinoma of the cervix]

Fig. 7. Early Epidermoid Carcinoma of the Cervix

Carcinomatous invasion of a cervical gland. The surface of the cervix is necrotic and the investing epithelium has been lost. The connective tissue is the seat of a dense inflammatory reaction. The epithelium of the carcinoma possesses the usual characteristics of this neoplasm, although the basement membrane of the gland is fairly well preserved. × 55. (P. N. 15385.)

carcinomatous change. With the colposcope a lesion 1 mm. in extent is magnified to 1 cm. or more. The advantages of this magnification are apparent.

Microscopic Diagnosis: Careful examination, including the use of Lugol's solution and the colposcope, is a distinct aid and may sometimes give conclusive evidence in the detection of carcinoma of the cervix; in all really early cases, however, the court of final resort is the microscope, employed by a competent pathologist.

The histologic diagnosis of carcinoma of the cervix is usually a simple matter. Excluding incompetence on the part of the pathologist, the chief reason for failure lies in not securing tissue from the proper site and therefore overlooking the presence of carcinoma. To the inexperienced this may seem unlikely, but as a matter of fact it is a dis-
tinct factor in the recognition of the really early cases. Carcinoma of
the cervix is prone to develop at or near the external os, the next most
frequent site being the canal, but the disease may spring from any part
of the cervical epithelium, including that situated in the depths of a
gland. As was previously stated, carcinoma rarely develops upon a
normal cervix; as a rule, lacerations, eversion, erosions, and hyper-
trophies are present. Eversions and erosions may simulate early car-
cinoma. Hypertrophy and edema increase the bulk of the organ. The
amount of tissue removed by an ordinary biopsy is necessarily small,
and hence impairs the reliability of the test. When a tumor is present
in the derma, as is often the case, and it is desired to determine whether
the neoplasm is benign or malignant, biopsy is satisfactory in almost all
cases, even when the new growth is a small one. When the cervix is
involved, however, a different state of affairs exists. Tissue for ex-
amination may readily be secured from a suspicious-looking erosion
upon the portio and be correctly diagnosed as benign by the pathologist
in cases in which a carcinoma is actually present in the canal or in an-
other portion of the cervix. Under such circumstances the carcinoma
may develop until it has reached the inoperable stage before it is recog-
nized, and then the surgeon, or more often the pathologist, will be cen-
sured for carelessness or for making an incorrect diagnosis. In such
cases the biopsy may actually be a deterrent to early treatment.

For cases of this type a high trachelectomy, performed preferably
with the endothermic knife, is the procedure of choice. Trachelectomy
possesses the following advantages: (1) All the tissue is available for
microscopic examination, which may be done under the most favorable
conditions, since sections may be secured from all suspicious areas.
(2) The operation is generally indicated, even in those cases in which it is pos-
sible by other methods positively to exclude carcinoma. A diseased
cervix is repaired, and the leukorrhea and other symptoms which it
causedit are relieved. (3) The operation serves as a prophylactic mea-
Sure against the subsequent development of carcinoma. (4) In the John
Goodrich Clark Clinic in cases of early cervical carcinoma amputation
of the cervix followed by irradiation has resulted in decidedly better
end-results than when irradiation alone was given; the former may in
itself be curative, although this method is not recommended. The
operation is practically free from mortality, and its only disadvantage
is the more prolonged convalescence that follows. This is not an argu-
ment against the value of biopsy, which is usually a satisfactory pro-
cedure, but is merely an effort to point out its limitations. When posi-
tive malignancy has been determined, biopsy is 100 per cent correct, but
when a negative result is obtained, as Stout (17) states, this "simply
means that no carcinoma has been found in the tissue examined and
nothing more."

Werner (18) very properly warns that neither curettage nor biopsy
THE DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX

The epithelium of the surface is thickened and exhibits a well defined predisposition to penetrate the glands. There is a tendency towards the development of a horny layer. The basalis and other layers are well defined and regular. The cervical glands are normal. Under low power (upper view) the picture is mildly suggestive of carcinoma. $\times 60$. (P. N. 16336.)

Under the higher magnification (lower view) the benign character of the thickened epithelium is apparent. Despite the tendency to penetrate, the regularity of the various layers, the absence of mitosis, and the lack of alteration in cellular morphology place this lesion clearly in the benign group. $\times 110$.

should be undertaken by the inexperienced. In addition to this warning, and at the risk of being accused of repetition, it may be stated that incompetence on the part of the pathologist not only nullifies the value of the test, but is actually a menace. In this connection it should be remembered that even a capable general pathologist may give unreliable information when asked to pass upon gynecologic specimens. Early carcinomas of the ovary, and especially granulosa-cell tumors, at times give rise to pathologic bleeding, and in cases in which examination of
the cervix and fundus has proved negative and no other probable cause for the bleeding can be discovered, this fact is worthy of consideration.

Trauma is undoubtedly a factor in causing the dissemination of carcinoma, but a skilfully performed biopsy or trachelectomy, especially if the cautery or endothermic knife is employed following the excision, is almost free from this danger, which certainly is not to be compared with the actual risk of delay in suspected cases. At the time when the trachelectomy is performed a diagnostic dilatation and curettage should be done in order to exclude carcinoma which may be situated higher in the uterine cavity, as well as other lesions in the body of the uterus which may have caused suspicious symptoms. It should be remembered that what has just been said refers to the diagnosis of extremely early Stage I carcinomata. These are the cases in which treatment offers a really good hope of permanent cure, and in which, therefore, early recognition is especially to be desired.

Of 827 cases of carcinoma of the cervix observed in the Gynecological Division of the Hospital of the University of Pennsylvania during the past twenty years, 94 have, according to the Schmitz classification, been Stage I cases. All classifications are more or less arbitrary, and among these 94 Stage I cases, 35 extremely early ones have been found and selected for study. In none of these has the macroscopic lesion been larger than 0.5 cm. in its greatest diameter. The symptomatology in this latter group was almost negligible. In 14.3 per cent the diagnosis was made clinically, and in an additional 54.3 per cent carcinoma was suspected; in the remaining 31.5 per cent the disease was unsuspected until the tissue was examined histologically. In one case the initial symptom was a massive hemorrhage, due to a carcinomatous erosion into an adventitious vein within the cervical canal. In none of the other cases were the symptoms marked, a slight metrorrhagia or leukorrhea being the most suggestive manifestation. The mildness, or in many cases the total absence, of symptoms was the chief characteristic elicited by an extremely careful scrutiny of the clinical findings in this group of cases. The five-year salvage was 85.8 per cent. Since in these early cases the diagnosis is dependent upon the histologic examination, a definition of the basis upon which such a diagnosis should be made is of vital importance.

Roughly speaking, the histologic diagnoses of all neoplasms may be grouped under three headings: (1) those in which the condition is positively malignant; (2) those in which the diagnosis is clearly benign; (3) those in which the question of malignancy is doubtful; i.e., those cases in which malignancy is suspected but in which the microscopic picture is insufficiently characteristic to form the basis for a positive diagnosis. The last group is a small one, and in proportion as the skill and experience of the pathologist increase, the group becomes smaller. Faulty histologic preparations, small amounts of tissue, sections secured from improper localities, and the so-called "precancerous" conditions account for the great majority of specimens which fall into the suspicious group. From a practical standpoint, and presuming that a
The surface is necrotic and has lost its normal investing epithelium. Well defined penetration of moderate sized masses of carcinoma cells is present. The surrounding tissue is edematous, rarefied, and infiltrated with inflammatory products. $\times 115$.

The higher magnification shows clearly the alteration in cellular morphology and general hodge-podge arrangement of the carcinoma cells. Most of these are moderate in size; many are vesicular and mitosis is frequent. $\times 300$. (P. N. 12934.)
careful study of the specimen has been made by a competent pathologist, the majority of these suspicious cases ultimately prove to be benign. Despite this fact, however, and because of the malignancy of carcinoma of the cervix, it is safer to treat such lesions as if they were malignant; this is particularly true in cases in which irradiation is selected as the treatment, since this carries so low a mortality rate.

It may be stated in passing that many cases which at first seem to belong to the suspicious group can be diagnosed definitely if more tissue is available for examination. Actual serial sections are rarely necessary, but it is advisable to secure a number of sections from different levels of the same block and prepare additional blocks if more tissue is available. Very frequently a single slide, often poorly prepared, and with no accompanying clinical data, is sent to the pathologist. From such a preparation a positive diagnosis often cannot be made.

Various criteria have been formulated as to what constitutes a histologic picture sufficiently characteristic to serve as a basis on which to make a diagnosis of carcinoma in its early stage. Valuable studies of the transition from the benign tissue to malignant neoplasm have been made by some of the foremost gynecologic pathologists.

It is well known that in certain laboratory animals the continued application of a suitable irritant will, in a proportion of tests, first produce a proliferation of cells and later terminate in the development of a benign neoplasm or a localized hypertrophy. If the treatment is con-

**Fig. 10. A Well Defined Group of Carcinoma Cells Filling a Gland Space of the Cervix**

There are necrosis and destruction of the normal surface epithelium, and a well defined inflammatory reaction is present. The basement membrane of the cervical gland is fairly well preserved, although the gland space is dilated by the invading mass of carcinoma cells. In general, these cells exhibit an abundance of nuclear material, while some of the basal-like layer is still preserved in the deeper portions of the carcinoma tissue. × 65. (P. N. 15385.)
continued, a change in the morphology and biologic behavior of the cells often takes place, invasive characteristics develop, and the lesion will extend beyond the treated area and often cause distant metastases; in other words, a carcinoma develops. It is probable, though not certain, that this is analogous to the development of carcinoma in man. This uncertainty militates somewhat against the value of such specimens as a means of studying the various stages in the development of the disease. As has previously been stated, it is a simple matter to define the histologic characteristics of carcinoma—invasion and alteration in cellular morphology—but it is difficult at times to determine these in a given specimen. These manifestations should usually both be present to

![Figure 11](image)

**FIG. 11. EARLY EPIDERMOID CARCINOMA OF THE CERVIX, SHOWING DIPPING DOWN OF THE CARCINOMATOUS EPITHELIUM, MARKED ALTERATION IN THE MORPHOLOGY OF THE BASAL LAYER WITH CONSIDERABLE HYPERCHROMATOSIS, MITOSIS AND AN ABUNDANCE OF NUCLEI AND NUCLEOLI**

From this field alone there might be some hesitancy in making the diagnosis of carcinoma. However, adjacent fields show unmistakable signs of malignancy. ×115. (P. N. 11449.)

warrant a positive diagnosis, but invasion and morphologic changes are so often matters of degree, that it is almost impossible to make a positive statement as to what is and what is not an extremely early carcinomatous growth. The experienced pathologist is usually able to make the distinction, but it is impossible to define the degree of cellular alterations upon which such a distinction is made. Sections taken from the immediate neighborhood of a malignant neoplasm often present suggestive but ill-defined histologic pictures, and in suspicious cases this is an additional reason for refusing to place dependence upon a single block of tissue. When only invasion or alteration of cellular morphology is present, the specimen may in some instances be regarded as suspicious, and often falls into the group of the so-called “precancerous” lesions.
Lahm (19) asserts that in specimens in which the carcinoma is still superficial, malignancy must be recognized by the alteration in the shape and function of the cells. In cell function the histotypic character of the cell grouping is included, as only a functionally normal cell can form typical groups. Heterotopia, infiltration, and destruction characterize malignancy, but if the cell function and shape are not altered, then carcinoma cannot be diagnosed with certainty in spite of the presence of heterotopia, infiltration, or even destruction.

Ribbert (quoted by Lahm) has drawn attention to the important rôle played by the condition of the surrounding tissue in the diagnosis of carcinoma. Loosening of the connective tissue, loss of collagenous and elastic fibers, and small round-celled infiltration constitute the fore-runners of carcinomatous infiltration (downgrowth). Proliferative processes occurring during embryonic development may resemble carcinoma. In these instances the epithelial proliferation is usually preceded by a connective-tissue reaction (mesenchymal thickening), apparently in order to prepare the way for deep invasion of the epithelium. In such cases the sub-epithelial changes may resemble those of carcinoma, but the malignant characteristic of the epithelium is lacking.

Even the most experienced gynecologic pathologists differ regarding the criteria on which to base a diagnosis of extremely early carcinoma. Frankl (quoted by Schiller, 20) formerly included as "initial" carcinomata only those cases in which the neoplasm was demonstrable microscopically in biopsy specimens, but which could not be found at operation. He later extended this group to include those cases in which the carcinoma was visible macroscopically, but in which the new growth was extremely small. Schiller (20) examined 135 cases operated upon for benign conditions and found early carcinoma in the portio in 4 cases (2.96 per cent). In another communication he describes 10 early cases, all extremely small superficial growths, only a few millimeters or a fraction of a millimeter in extent. In all of those cases in which it was possible to study the origin of the neoplasm it appeared to spring from the point of transition between the pavement and cylindrical epithelium, thus tending to confirm the earlier assertion of Schottländer and Kermauer (quoted by Schiller, 21) and Bailey (22) that cervical carcinoma usually has its origin in the transitional epithelium of the external os.

Leukoplakia is frequently followed by carcinomatous change, but leukoplakia of the cervix is relatively infrequent. Macroscopic examination reveals whitish, somewhat elevated, irregularly shaped areas, often only a few millimeters in diameter. Hinselmann (12, 16, 23, 24) and Hinselmann and Esser (25), in a number of papers devoted to the study of these lesions, stress their frequent "precancerous" character. Hinselmann emphasizes the value of the colposcope as a diagnostic aid, and is of the opinion that by its use leukoplakia can be recognized much earlier than with the naked eye, and adequate treatment can be instituted. Although leukoplakia of the cervix is generally thought to be infrequent, Hinselmann has been able to demonstrate this
lesion in about one per cent of all patients examined by means of the colposcope. If these conclusions are proved to be correct, it is obvious that this instrument offers a means of early diagnosis of cervical carcinoma as well as offering a method of prophylaxis against the disease providing leukoplakia is proved to predispose to carcinoma. Ries (26) recommends the routine employment of the instrument for life insurance examinations.

![Image](image_url)

**Fig. 12. Benign Epidermalization of Cervical Glands**

The squamous epithelium of the cervix is attenuated and shows a well defined horny layer. The normal columnar epithelium of the glands has been entirely replaced by squamous epithelium. Except for the unusual invasiveness of the epithelium, no malignant characteristic is present and the lesion is clearly benign. A marked edema and inflammatory reaction are present in the connective tissue. × 70. (P. N. 13836.)

Hinselmann (24) defines four types of leukoplakia and gives a detailed histologic description of the lesions, accompanied by many photomicrographs, as later detailed (see p. 322). He also describes a condition in the portio, which he designates as tesselation (“Felderung”), checkering, or partitioning of the mucosa, which is visible with the colposcope, usually with an enlargement of 10.5, although in the case of quite small tesselations an enlargement of 14 to 40 is necessary; he believes that these tesselations bear an intimate relation to and may constitute a basis for leukoplakia. Tesselation is not visible macroscop-
cally, but on colposcopic enlargement it appears as white, polyhedral patches surrounded by pink lines of unaltered cervical epithelium. It is claimed that tesselation is possible only in the presence of cylindric epithelium. Hinselmann (12) asserts that tesselation has often been found associated with leukoplakia in the portio.

Von Franqué (27) emphasizes the fact that as areas of leukoplakia cannot always be distinguished macroscopically from carcinomata, biopsy should be performed, preferably by making a wedge-shaped excision of the entire white area. He claims that many "precancerous" lesions in the vagina may also be recognized colposcopically, which cannot be detected with the naked eye.

Meyer (28) questions the frequent etiologic relationship between carcinoma and leukoplakia of the portio, and states that, just as in the vagina, these white areas consist of thickened layers of epithelium, a thickening especially of the stratum germinativum, the formation of prickle cells, and occasionally thickening of the stratum granulosum. Cornification may be present.

Schiller (20, 21) insists that the histology of the ordinary leuko-

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FIG. 13. SUSPICIOUS AREA, SHOWING SOME PENETRATION AND ALTERATION IN SHAPE, SIZE, AND STAINING PROPERTIES OF THE EPITHELIAL CELLS

These characteristics are not sufficiently pronounced to warrant a positive diagnosis. On account of the benign invasiveness of the squamous epithelium of the cervix, and the frequent alteration in morphology of the epithelium, due to inflammatory and other benign conditions, suspicious histologic pictures are frequently encountered in this area. Careful study of numerous areas, however, will nearly always permit a positive statement by the pathologist. Frank carcinoma was present in the neighborhood from which this section was taken. × 80. (P. N. 12362.)
plakia and of "precancerous" lesions differs, leukoplakia having a
horny layer which is absent in the "precancerous" stage, a point that
has frequently been observed by the author.

A study of six of the author's cases of early carcinoma of the cervix
shows that three were regarded as suspicious prior to operation, and
the remaining cases were discovered as the result of routine histologic
examination. In no case was the lesion over 6 mm. in its greatest
diameter. All the patients received radium treatment. In one of the

![Image](image)

**Fig. 14. Early Epidermoid Carcinoma of the Cervix, Showing Demarcation between Benign and Malignant Epithelium**

To the right is the thickened but benign squamous epithelium. At about the center of the picture is the clearly defined demarcation between the benign and the malignant epithelium. The latter shows a well preserved basal layer, although there are alterations in all the layers. The picture exhibits a striking contrast between the regular arrangement of the epithelium on the right and the malignant characteristics of the epithelium to the left of the center. × 80. (P. N. 8553.)

unsuspected cases death occurred from a recurrence of the disease. The remaining patients are well, four of them having survived beyond the five-year period. Histologically, all the growths were of the epidermoid type. All apparently began as an anaplastic atypia and polymorphism of the surface epithelium, and the transition from the normal, or in two cases benign thickening of the epithelium, was abrupt and well defined. All the neoplasms appeared to spring from or near the external os. Two showed their origin quite definitely from or very near the point of transition from the squamous epithelium to the true mucosa. The line of demarcation between the benign and malignant epithelium was usually oblique, as is shown in Figs. 15B and 17A. This marginal obliqueness is often present in advanced lesions, and has
been referred to by numerous observers. Schiller (20) believes that an explanation of the sudden transition and oblique delimitation is to be found only on the assumption of a continuous, progressive carcinomatous transformation of the basalis. He adds further that, theoretically, there is nothing to refute the belief that in the basalis carcinoma extends from one cell to another by assimilation. Schiller believes that in extremely early carcinomata penetration is entirely absent.

That epidermoid carcinoma usually originates on the surface of the cervix is fairly obvious. The layer of stratified squamous epithelium is normally moderately thin. Just what constitutes the earliest change in the transformation from normal to malignant epithelium is unknown, and, as previously stated, pathologists have formulated various criteria upon which they believe a positive diagnosis is justifiable. Of the two characteristics previously mentioned, namely, morphologic alteration and penetration, it is probable that the former precedes the latter, so that, upon theoretic grounds, Schiller’s contention that in extremely early cases penetration is entirely lacking is correct. Of the two manifestations, morphologic alteration is the most important. As, however, there is no specific test for carcinoma, it is apparent that the authenticity of some of the so-called extremely early cases, in which the diagnosis is dependent only upon the morphologic alteration of perhaps a very small group of cells, cannot be affirmed unless the patient subsequently succumbs to the disease, which is not usually the case. From a practical standpoint, therefore, the author prefers to designate many such cases as “suspicious” and not to include them as proved carcinomata, although in certain typical cases it is justifiable to make a positive diagnosis of carcinoma even if penetration is absent. Broders (29) asserts that the time has passed when epithelium can be regarded as non-cancerous, or at most only “precancerous,” because it is within the confines of the so-called basement membrane, and be considered as carcinomatous because it has penetrated beyond this barrier. He very properly stresses the point that it is upon the character of the epithelial cells, more than upon anything else, that the decision must rest. Beyond doubt the correctness of the diagnosis depends upon the judgment and experience of the pathologist, and these are conditions that cannot be accurately analyzed.

A study of the histologic sections in the writer’s group of cases has impressed upon him the importance of the following points in the recognition of early cases: The majority of the neoplasms appear to have their origin at or only slightly distal to the point of transition between the columnar and squamous epithelium. In none of the cases did the carcinoma appear to have originated from either a macroscopic or a microscopic ulcer.

Anaplastic atypia and polymorphism of the epithelium were present in all cases, and invasive tendencies were seen in almost all, but in none of them to as marked a degree as is the rule in advanced tumors. The transition to malignant epithelium was abrupt, sharply defined, and no
**Fig. 15 A. Invasion of a Cervical Gland by an Epidermoid Carcinoma of the Cervix**

Carcinomatous frosting invading a cervical gland and pushing off the columnar epithelium. × 115. (P. N. 9523.)

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**Fig. 15 B. Early Epidermoid Carcinoma of the Cervix, Showing Demarcation between Benign and Malignant Epithelium**

To the right is the clearly defined carcinomatous epithelium showing irregularity in size, shape, and staining properties of the cell, hyperchromatosis, nuclear abundance, mitosis, and penetration. It will be observed that the line of demarcation is sudden and clear cut. The obliquity is characteristic and results from the more rapid growth of the deeper layer of the carcinomatous epithelium. × 215. (P. N. 9523.)
intermediate stage was demonstrable. The line of demarcation was, as a rule, though not invariably, oblique, probably due to the more rapid growth of the deeper layers of the epithelium undergoing the carcinomatous change. This obliquity has been referred to by numerous observers (Schauenstein and Kermauner, Schottländer, Schiller, and others). In the early cases there was little displacement of tissue, and the sharp boundary lines between the epithelium and the connective tissue exhibited no marked deviation such as is seen in advanced neoplasms. Irregularity of this boundary line, i.e., a jagged line with penetration, not of fairly large groups of cells, but of individual cells or strings of cells, was not observed. Obviously, the earlier the malignant change, the less pronounced is the penetration.

Immediately beneath the new growth there was generally some inflammatory reaction. This inflammatory reaction was probably due, at least in part, to invasion by the carcinoma, and was a reaction of the stroma to this injury. This inflammatory manifestation is by no means diagnostic, but its presence is confirmatory (supportive) evidence. Rarefaction and loosening of the connective tissue were not observed to any marked degree; when present, they were probably incidental to or the result of concomitant edema or inflammatory reaction.

The normal superficial layer of the epithelium was often absent or unrecognizable. The prickle-cell layer exhibited extensive alteration. The individual cells were often oval or, at times, spindle-shaped. They resembled atypical basalis cells and were crowded together. The normal mutual flattening of the cells characteristic of epithelium was absent. The nuclei were irregular in size, but were generally large, round or oval, and deeply staining. Vesicular, multiple nuclei were sometimes observed. A moderate amount of mitosis was present. As a result of nuclear abundance, the protoplasm appeared to be reduced in amount.

Of even greater importance, perhaps, than the size of the nucleus is the relation it bears to the nucleoli. Karp (30) states that the nucleoli of carcinoma cells are considerably larger than are those of endothelial cells, the former measuring 4 to 12 μ. Of still greater importance than the actual size is the ratio between the size of the nucleus and that of the nucleoli. Karp finds that the area of the nucleus in endothelial cells is from 25 to 100 times as great as that of the nucleoli, whereas the nuclear area in tumor cells is only 4 to 20 times as large as that of the nucleoli. MacCarty (31) also stresses the relative enlargement of the nucleoli in carcinoma. At times quite large vacuoles are present in some tumor cells, but these are not usually observed in endothelial cells.

The basalis often shows marked and characteristic change. Thus it may be altered to such an extent as to be unrecognizable. The normal, single, palisade-like layer of slim oval cells may be converted into an irregular zone, often many cells deep, of round, oval, or irregular cells. Such cells may exhibit vesicular nuclei or may be tinctorially irregular. Mitotic figures are present. In many cases the malignant
change apparently originates in the basalis, with proliferation and irregularity. The cells are crowded together, irregular in size, shape, and staining characteristics; as a rule they are hyperchromatic and sometimes spindle-shaped. The nuclei are enlarged. Polymorphism and atypia are especially noticeable and characteristic in the nuclei, and nuclear abundance is also noted. The proliferating cells penetrate the connective tissue in small, bulbous or finger-like projections. Von-Franqué (32) has stressed the fact that in early neoplasms the first change is generally found in this layer (the basalis).

Schiller (21) describes the finding of intranuclear and paranuclear red inclusion bodies, which he considers the most important change in the surrounding epithelium. These red bodies exhibit a marked affinity for eosin, and may be the result of retrogressive metamorphosis. They were present in two of the cases studied by the author. The bodies were rather sparsely distributed—one or two in a field at most—and were easily recognizable by their brilliant red color.

Epithelial pearls, although common in the more adult types of epidermoid carcinoma of the cervix, are by no means diagnostic and may
be present in benign conditions. Lahm (19) believes that their presence does not even signify marked epithelial growth, but that they occur chiefly when regenerative processes become dominant. They may result from dysfunction of the epithelium. Epithelial pearls are suggestive, but not diagnostic, of carcinoma.

Simple papilloma, condyloma, hyperkeratosis, and hypertrophy may give rise to doubt regarding their benign character, especially when they are associated with chronic inflammatory processes; as a rule, however, they can be distinguished readily by the regular arrangement of the various layers of epithelium, particularly in the rete zone. Occasionally lacerations, with more or less local tumor-like infiltration, the result of long-standing inflammatory processes, are encountered and may simulate carcinoma. In such cases the character of the individual cells is the chief diagnostic feature. Staining for plasma cells with methyl-green pyronin is of value in differentiating between inflammatory and neoplastic tissue.

It must be remembered, however, that even early carcinoma, especially if growth is rapid, or if it originates, as it often does, upon an inflamed area, may be associated with many plasma cells. The tendency for benign squamous epithelium to invade glands and deeper layers of the underlying connective tissue often gives rise to diagnostic difficulties, but here again the regularity of the epithelium is the distinguishing feature. Epidermidalization is of frequent occurrence in cervical lesions and at times may lead to the formation of atypical growths, which occasionally give rise to confusing histologic pictures. "Epidermidalization" (Ruge and Veit) is the term used when the process leads to the formation of atypical epithelial overgrowths. This subject has been studied by Fluhmann (33), Meyer (34), L'Esperance (35), Ewing (36), Frank (37), and many others. In epidermidalization the layers of the epithelium are usually preserved, mitosis is rarely present, and the normal size, shape, and staining properties of the cells are generally dissimilar to the changes that occur in carcinoma.

Epidermidalization is a benign local tissue process, perhaps protective in origin, although five theories have been advanced regarding its origin (Fluhmann). At least one instance has been recorded of the condition affecting the uterine body of a newborn infant (Meyer, 38). The process is in no sense "precancerous." This statement is borne out by the frequency of epidermidalization in cervical mucous polypi, and the fact that not more than one per cent of these growths undergo carcinomatous change. Fluhmann (33) found epidermidalization in 59 cases of chronic cervicitis in a series of 1,195 specimens of diseased cervices, and in 29 of 100 cervical mucous polypi. Moglia (39) studied 72 cervical polypi and found metaplasia in 50. In none of the cases of cervical carcinoma studied by the author did the tumor apparently have its origin in epidermidalized tissue.

Leukoplakia, as previously stated, is a relatively infrequent lesion of the cervix. By the routine use of the colposcope many early cases can be recognized which would otherwise escape detection. Rogge (40)
Figs. 17 A and B. Early Epidermoid Carcinoma of the Cervix, Showing a Clear Cut Line of Demarcation between the Malignant and Benign Epithelium

This line is oblique due to the more rapid growth of deeper layers of the tumor. The cells of the latter exhibit the usual alterations in morphology characteristic of carcinoma. As is not unusual in some carcinomas, the basal layer is moderately well preserved. × 80.

In the higher-power photomicrograph (below) it will be observed that, despite the fact that there is as yet no marked penetration, the line of demarcation between the carcinomatous tissue and the stroma is more irregular than that of the benign epithelium, and that here and there small groups of cancer cells are tending to bud out into the stroma. The diagnosis, however, rests upon the alterations in the cellular morphology. Unmistakable carcinoma was present to the right of the area included in the photomicrograph. × 150. (P. N. 16171.)
has recorded the history of a case in which the entire portio was involved in leukoplakia. Its etiologic relationship to carcinoma is not known, but it appears to be a definite predisposing factor to the development of cancer. Haselhorst (41) has recently reported eight typical cases of leukoplakia and carcinoma of the portio. Kermauner (42) has observed two cases of leukoplakia, both associated with carcinoma. Macroscopically or with the aid of the colposcope the lesion appears in the form of white patches, usually of small size. The disease is prone to occur in association with erosions and eversion, and is often seen at the line of demarcation between the mucosa and pavement epithelium.

Histologically, these white areas usually consist of thickened epithelium, a thickening especially of the germinal layer, and the formation of prickle cells. More or less inflammatory reaction is usually present.

Hinselmann (24) divides leukoplakias into four types as follows:

I. Atypical cornifying epithelium.
II. Atypical cornifying epithelium with budding into the connective tissue.
III. Atypical cornifying carcinoid epithelium.
IV. Atypical cornifying carcinoid epithelium with (a) budding outward, (b) budding into the connective tissue.

He believes that Type I may develop into either Type III or Type IV. Meyer (28) is not in entire accord with Hinselmann’s views regarding leukoplakia.

Leukoplakia can readily be differentiated from carcinoma by the aid of the microscope in the hands of an experienced pathologist. On the other hand, when only minute bits of tissue are available for examination, confusion may result. Martzloff (43) emphasizes the importance of leukoplakia. He believes, furthermore, that the epithelial changes in some leukoplakic plaques possess all the cytologic characteristics of cancer, but lack the attribute of invasion (heterotopia). Kretschmer (44) stresses the periodic examination of women who have leukoplakia and of those in whom the disease has apparently been cured. This last is important, since leukoplakia tends to recur. This observer has found irradiation with radium the most effective and rapid method of curing the condition. Rogge (45) has observed two cases of leukoplakia of the cervix, both of which recurred after excision. Ries (26) believes that the colposcope is not only a great aid in diagnosis, but also that it is helpful in directing the treatment of erosions and other so-called “precancerous lesions” with the cautery. Emmert (14) describes the transition into carcinoma in a case of leukoplakia which was discovered by means of the colposcope in the clinic of Dr. F. J. Taussig.

Photomicrographs used in this article are by Mr. Basil Varian of the Department of Anatomy, University of Pennsylvania, through the courtesy of Dr. E. R. Clark, Professor of Anatomy.
THE DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX

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