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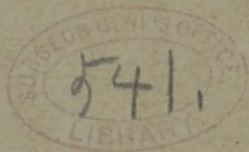
MALIGNANT ADENOMA OF
THE UTERUS

BY

WILLIAM S. STONE, M. D.,

ALUMNI FELLOW IN PATHOLOGY, COLLEGE OF PHYSICIANS AND SURGEONS;
ASSISTANT IN THE DEPARTMENT OF DISEASES OF WOMEN,
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MALIGNANT ADENOMA OF THE UTERUS.*

THE class of new growths to which the term adenoma has been applied offers a field for study of much pathological and clinical interest. Some of these neoplasms present histological forms which differ but little from the more marked grades of glandular hypertrophy and hyperplasia. Other forms, although presenting certain anatomical distinctions, do not differ at all from other malignant new growths, either in their clinical history, their mode and rapidity of growth, or in their tendency to recurrence.

Adenomata, we know, occur in many different organs, as, for example, the thyroid gland, liver, kidney, intestine, mamma, ovary, and uterus. The uterus offers a good example of an organ in which they frequently display their malignant qualities. The uterine mucosa, too, is so frequently the seat of extensive glandular hyperplasia, that it is often from curettings hard to distinguish these anatomical changes from those of a tumor.

Waldeyer (1), writing in 1867, characterized adenoma as a reproduction of glands of the normal type, in which the epithelial cells were regularly arranged on a distinct membrana propria. We know now that this definition might apply to hyperplasia, and Waldeyer not having ex-

* The writer has carried out this work in the Pathological Laboratory of the College of Physicians and Surgeons, and is indebted to Dr. G. C. Freeborn for many timely suggestions, and for the use of the slide from which Drawing 2 is made. For the specimens and clinical material the writer is also greatly indebted to Professor G. M. Tuttle and Dr. E. B. Cragin.

amined any adenomata of the uterus, the particular class which we call malignant adenomata was not included in his description.

In the latest times, Delafield and Prudden (2) describe the adenomata in general as benign tumors, but mention the occurrence of malignant adenomata in certain organs, and place them on the border line between adenomata and carcinomata.

As most of the reported cases of adenoma of the uterus contain meagre descriptions of their anatomical structure, and as the exact nature of the tumors has been variously interpreted, there is much uncertainty as to the identity of some of these cases with the neoplasms now described as malignant adenoma.

Coe (3) has written twice upon the subject, giving an historical *résumé* of cases reported, and adding three cases of his own. His conclusions are: "The term benign adenoma of the uterus is a misnomer; neither glandular hyperplasia nor adenoid polypus is adenoma; the only true adenoma of the uterus is essentially malignant adenoma, anatomically, because it invades deeper structures, and clinically, because it recurs after removal, and eventually assumes a more malignant character. Malignant adenoma at first is not identical with adeno-carcinoma, but is an initial stage of it; endometritis glandularis hyperplastica is not adenoma, because the mucosa is generally hypertrophied without marked proliferation of pre-existing glands, and the process is confined to the mucous layer and proliferation is always typical." With regard to diagnosis and treatment, he states that rapid recurrence after recutting should suggest malignant adenoma rather than glandular hyperplasia, although the disease may have existed for a long time and the curettings may not present the anatomical structure of a malignant neoplasm.

Ruge and Veit (4) described malignant adenoma of the uterus, and, although they suggested that it might be a transitional form between glandular hyperplasia and cancer, never had seen cases which could prove this relation.

Pozzi (5) says: "Lesions may begin as a slight glandular endometritis, may become, if inveterate, a glandular endometritis of the most pronounced type (typical benign ade-

noma); may then degenerate into an atypical malignant adenoma, and this is the first stage of cancer." He makes the difference between benign and malignant adenoma to depend upon the presence in the former of a single layer of epithelium, a certain amount of normal interglandular tissue, and a clear line between the glandular and muscular layers.

Schröder (6) maintains that no sharp distinction between glandular hyperplasia and adenoma can be made; that there are extreme forms of the latter which suggest malignancy, and frequently go over into cancer.

Fürst (7) is very extreme in his suggestions for treatment. Although he regards glandular hyperplasia as benign, he does not think it is wise to be content with curetting, but "to strive for excision, as the new formation inclines to malignant degeneration."

C. Ruge (8) uses the terms benign and malignant adenoma. By the former he understands simple glandular hyperplasia. "In malignant adenoma there are changes in the entire uterine tissue. Metastases occur in other organs. Solid cell processes invade the deeper parts to a greater extent than is common in cancer." These last changes are certainly those of true cancer.

Lander and Abel (9) use the terms simple adenoma, meaning glandular hyperplasia, in contradistinction to malignant adenoma. They consider the amount of relatively unchanged interglandular tissue as the best guide in distinguishing the two forms.

Ziegler (10) considers adenomata of mucous membrane in general as not sharply differing from cancer.

Williams (11) thinks adenoma in the uterus is probably always malignant.

J. Veit (12) says: "There is a gradual transition from adenoma to cancer."

Cushing (13) describes malignant adenoma of the uterus as "an adenomatous thickening of the mucous membrane of the body of the uterus in elderly women, which finally degenerates into carcinoma."

The majority of writers, then, classify the marked cases of chronic endometritis with glandular hyperplasia among the adenomata. So long as the reproduction of

the glands conforms perfectly to the normal gland type, they speak of them as benign. When the numerical increase becomes excessive, and the epithelium tends to form in several layers; when the interglandular tissue becomes scanty, and the tissue consists almost entirely of new-formed glands, and inroads are made into neighboring tissues, they are called malignant. Furthermore, the latter form of lesion is generally considered as the initial stage of cancer. In other words, simply hypertrophy and hyperplasia are not distinguished from the changes existing in a well defined tumor. Many writers, too, wrongly speak of malignant degeneration of a tumor, using the term degeneration in the same way that it is used in speaking of fatty or amyloid degeneration.

Before taking up the four cases which the present writer has to offer as examples of malignant adenoma of the uterus, it was thought that it might be useful to give a general description of the curettings from nine cases of well-marked adenomatous hyperplasia.

In these nine cases of adenomatous hyperplasia, the increase in the size and the number of the glands was very well marked. The epithelium, for the most part, consisted of one layer resting on a distinct membrana propria. The stroma was considerable in amount and showed in some cases the changes of a simple exudative inflammation, while in others there was the formation of new connective tissue. In other words, the glandular hyperplasia seemed to be simply a part of or a result of an ordinary chronic inflammation of the mucous membrane. Fig. 1 represents the condition in one of these cases.

The ages of these patients from which the curettings were taken range from twenty eight to forty-seven. The most marked condition was in a patient of thirty-eight years. Five of the cases had been curetted before with relief for from six months to two years. Two of the cases were thought to be malignant clinically, because of their loss of flesh and poor general condition. This cachexia could readily be ascribed to the severe and protracted hæmorrhages from which they had suffered. There were no appearances in these curettings which would warrant their classification among the neoplasms or suggest malignancy.

The possibility of their future development into a malignant new growth can not be denied, but in the writer's experience thorough curetting and appropriate after-treatment cure most cases of chronic endometritis with glandular hyperplasia.

The curettings of two other cases, representing a more serious condition, have been very recently examined. In both of them the larger part of the curettings show simply

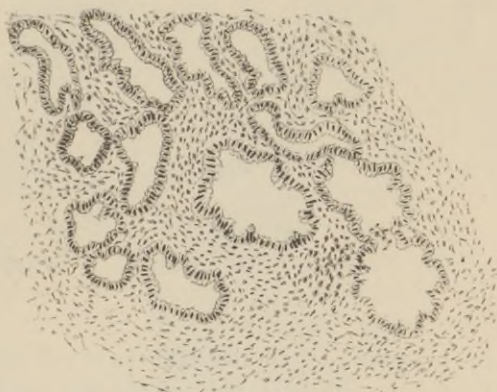


FIG. 1.

a glandular hyperplasia; but there are a few places in one case where there is an excessive numerical increase of glands and proliferation of the lining epithelium into several layers, with a very small amount of intervening stroma. In all parts a severe exudative inflammation is in progress, leucocytes almost filling the lumina of the glands. We have here, then, a beginning malignant adenoma. In a few places in the other case there are alveoli filled with regularly arranged epithelium, and with no trace of normal gland structure left. There is no exudative inflammation present, and glandular hyperplasia is not so well marked. In this case there is certainly a beginning carcinoma.

In both of these latter cases we have a simple benign process coexisting with a certain amount of excessive and lawless growth. We might interpret these changes as representing different steps of the same process if we knew certainly that they did not begin independently of each other.

Fig. 2 represents a section of some curettings showing coexistence of adenoma and carcinoma. On the left are seen the enlarged glands lying close together. The epithelium has proliferated into several layers, but the



FIG. 2.

gland type is preserved. On the right the alveoli are completely filled with epithelium, and we have true cancer.

In contrast to the previous conditions, the writer wishes to describe four cases of well-marked malignant adenoma.

CASE I.—Patient, forty-eight years of age, had had three children, the last one fourteen years ago. Her menstruation had always been regular until two years and a half before admission to the hospital. Since then she has flowed almost continuously, and has lost flesh rapidly for seven months, and during the last four months has suffered from severe pains in the lower part of abdomen and back.

Examination.—Patient is pale and thin. Palpation reveals a hard, smooth tumor in the median line of the lower part of abdomen, reaching to the umbilicus above. Bimanual examination shows the tumor to be an enlarged uterus. The cervix is short, soft, and the external os admits one finger. Behind and to the left of the uterus is a hard, immovable tumor, which with the uterus completely fills the pelvis and lower part of abdomen.

Patient was curetted, and, a large amount of fleshy material having been scraped out, the entire uterus and tumor behind, with an indurated portion of the vaginal wall, were removed through the abdomen. The uterus externally resembles in its

form one at full term of pregnancy, its cervix having almost disappeared. It measures from fundus to external os seven inches, and across the fundus between the tubal openings four inches. The interior is completely lined by a soft, irregular new growth, having elevations which project like polypi into the uterine cavity (see Fig. 3). One half of the uterine wall, which measures an inch and three quarters in thickness, consists of the new growth.



FIG. 3.

The other tumor, which apparently originated from the left ovary, is nearly circular in form, with a somewhat irregular surface, and measures four inches in diameter. It is solid throughout, its cut section being of a yellowish-white color, not exactly homogeneous in structure, but traversed by numerous bands of slightly paler color than the rest of the tissue. The apparently normal left tube runs over the tumor. The right ovary and tube are normal.

Sections were cut from different portions of the uterine wall, ovarian tumor, left tube, and broad ligament, and stained with hæmatoxylin and eosin and with picro-acid fuchsine.

The left tube and broad ligament show no invasion by the new growth. One half of the uterine wall consists of a mass

of alveoli closely packed together, with a scanty supply of intervening stroma, resembling in structure the normal uterine glands. The alveoli are generally lined with two or more layers of epithelium. A lumen is always present, although some of the alveoli contain a large number of leucocytes. The hypertrophied muscular layer is irregularly invaded by this adenomatous growth.

Fig. 4 is a photograph with a low power of a section of the new growth. Fig. 5 is a drawing of the same with high power.

The excised portions of the vaginal wall also consist of this same adenomatous growth, the alveoli resembling normal glands and showing no true carcinomatous structure.



FIG. 4.

The ovarian tumor consists of a mass of alveoli, some of them having the epithelium regularly arranged like normal glands, others being filled with epithelial cells and leaving no trace of normal gland structure. Between the alveoli is a stroma consisting of irregularly branching trabeculæ with a smooth, homogeneous appearance, resembling hyaline degeneration. A few connective-tissue cells are seen in the trabeculæ, especially in the larger ones near the periphery of the tumor, and none of the chemical tests for hyalin degeneration give the

proper reaction, so that these trabeculæ, although closely resembling hyalin degeneration in many places, are thought to consist of very dense connective tissue.



FIG. 5.

Diagnosis of the uterine tumor is malignant adenoma; of the ovarian tumor, adeno-carcinoma.

CASE II.—A single woman, aged fifty-four, had suffered from irregular uterine hæmorrhages, increasing size of abdomen, loss of flesh, and poor general health for two years. Examination of abdomen shows a hard, irregular-shaped tumor completely filling the lower half of abdomen and pelvis.

Laparotomy revealed a large uterus filled with fibro-myomata, attached to the left of which, by means of the tube and numerous adhesions, was a soft, friable mass about the size of an orange. The entire uterus and tumor were removed.

The large subperitoneal fibro-myomata, measuring about four inches in diameter, are situated at the fundus. Numerous small ones are situated in the uterine wall. One small pedunculated fibroid, attached to the fundus and having a shaggy covering, projects into the uterine canal. The uterine canal measures four inches and a half from fundus to external os and is lined by a soft, irregular growth, particularly at about the middle of the body.

The ovarian tumor consists of a rather firm central mass covered by a very soft papillomatous outgrowth. Microscopic examination of the subperitoneal fibroids shows the structure of an ordinary fibro-myoma. The pedunculated submucous tu-

mor consists of a large number of well-formed glands with considerable intervening stroma. The entire body of the uterus is lined internally by an adenomatous growth, in all respects resembling the growths in the uterus in Case I, except that it is not so extensive. The growth in many places has superficially invaded the muscular coat.

Diagnosis is malignant adenoma occurring in a uterus the seat of multiple fibro-myomata.

The ovarian tumor consists of a papillary fibrous framework covered by a mass of alveoli, some of which preserve the normal gland structure, while others are simply masses of epithelial cells.

CASE III.—A married woman, aged sixty-nine, had been suffering from irregular uterine hæmorrhages for over a year, and had been curetted three times. The diagnosis of the first curettings had been simple adenoma; of the third, malignant adenoma.

Uterus was removed *per vaginam*. It measures four inches from fundus to external os and two inches and a half across the fundus between the tubal openings. The interior of the uterine body is covered by an irregular growth, not so extensively as the first case, but much more so than the second. At the fundus the uterine wall is an inch in thickness and chiefly consists of this new growth. In one place only an eighth of an inch of muscular tissue remains. Near the internal os the growth has not encroached upon the muscular tissue so extensively, and the cervix is not at all invaded.

Microscopical examination of the growth shows it to have the same structure as in the other two cases. There are irregular invasions into the muscular tissue, and here and there, deep in the muscular coat, isolated patches of glands are found, conforming in general to normal utricular glands.

There are no evidences that the new growth has gone beyond the uterus, although in one place, at the fundus, it has very closely approached the peritoneal coat.

Diagnosis is malignant adenoma.

CASE IV.—A married woman, aged forty, had suffered from pain in the back and iliac regions for three years. During the six months previous to her admission to the hospital pain had become much worse and she had rapidly lost flesh, and for three months had had a foul discharge. Menstruation had been normal.

Examination under ether revealed an enlarged uterus, retroverted and adherent. Both appendages were prolapsed and adherent to the uterus. A hard mass was felt on each side of the uterus. Microscopic examination of the curettings removed at the time of the examination under ether show a great mass

of glands lined by several layers of epithelium, but always preserving a general adenomatous structure.

On account of the infiltration on the sides of the uterus extirpation was not attempted. Patient died two months later. No post-mortem examination was made.

In this case, of course, it is impossible to be certain that there was no carcinomatous growth in or about the uterus, but a large amount of material was removed at the curettings which only showed the structure of malignant adenoma.

These four cases, as examples of malignant adenoma of the uterus, present some interesting points. The anatomical structure of the new growth in all of them is the same.

They all present more active and destructive changes than do cases of simple glandular hyperplasia, and they all differ anatomically from cases of cancer. Cases I and II are interesting because the adenomatous growth in the uterus is associated with carcinoma in the ovary.

Case II was interesting because of the association of the new growth with a uterus filled with fibr-omyomata.

Cases I and III show well the encroachment of the new growth upon the neighboring tissue and the preservation of the gland type in these invasions. Even in Case I, where the adenomatous growth has spread beyond the uterus, the invaded parts of the vaginal wall consist of glands more nearly like normal uterine glands than those in the uterus. In all of the cases the cervical mucous membrane was not invaded.

Summary.—There occurs in the uterine mucous membrane a moderate glandular hypertrophy and hyperplasia, associated with chronic inflammation, which is entirely distinct from any tumors in the same region. The glands are simply more tortuous and more numerous, and the lumen is larger, but their general structure is the same as that of normal utricular glands.

More marked examples of glandular hyperplasia occur which often simulate clinically malignant neoplasms. They often occur near the menopause, may cause severe hæmorrhages, and impair the general health. Sometimes they have to be curetted several times before the condition disappears.

Anatomically these latter cases are characterized by an excessive number of glands, but the epithelium does not show any marked tendency toward proliferation, and there is still a large amount of stroma left in which inflammatory changes are going on. There is an increased number of stroma cells and an infiltration with leucocytes; there are new blood-vessels, and oftentimes interstitial hæmorrhages occur. The whole picture is one of inflammation, in which the glands are increasing in number simply as part of the general inflammation.

Some of these more marked cases probably do become malignant, and therefore a careful microscopical examination of all curettings should be made.

Although a positive diagnosis between adenomatous hyperplasia and adenoma may not always be made from the curettings, yet it is possible in the large majority of cases to form a conclusion of sufficient accuracy.

Adenomata occurring in the uterine mucosa are tumors consisting almost entirely of glands which conform in general to the normal gland type. There is very little interglandular tissue, and, while there may be an inflammation going on, it is entirely subsidiary to the main process—*i. e.*, growth of new glands. The epithelium lining the alveoli shows a tendency to proliferate, but a lumen or the suggestion of a lumen exists.

Adenomata in the uterus are always malignant, because they invade neighboring tissues and recur unless completely removed.

Adenoma in the uterus, although it may represent a transitional step between simple glandular hyperplasia and carcinoma, certainly often develops to a high degree without losing the anatomical characteristics of adenoma.

Adenoma usually, perhaps always, begins in the body of the uterus, and does not involve the cervical mucous membrane; and, while it invades the muscular layers and eventually goes beyond the uterus, it remains confined to the mucous membrane longer than carcinoma does. It might be described as spreading around in the mucous membrane rather than burrowing through the different layers, and thus quickly involving other parts.

Compared with carcinoma of the uterus clinically, we

find that adenoma of the uterus usually occurs later in life than carcinoma, and lasts longer without causing cachexia. Frequently we get a history of irregular hæmorrhages for several years, during which time the patient has been cuttred several times without permanent relief. Pain and discharge are not such prominent symptoms in adenoma as in carcinoma. The enlargement of the uterus is more marked in adenoma.

The prognosis in adenoma after removal is better than in carcinoma, because from its manner of growth complete extirpation of the growth is more certain.

The treatment for adenoma of the uterus should be the same as for carcinoma.

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