Chapter 8
CANCER OF THE UTERUS

According to the vital statistics for the United States for 1947, cancer of the uterus was responsible for 18.1 per cent of all female deaths from cancer. During that year 17,455 women died of uterine cancer. Eleanor J. Macdonald, Research Statistician of the Cancer Division of the Connecticut State Department of Health, estimated that, in 1950, physicians in the United States would see 17,066 new cases of cancer by speculum examination. In 1946 uterine cancer was responsible for 14.5 per cent of cancer deaths in the female population, the figure being identical to that of deaths from breast cancer; hence, these two share the sinister distinction of leading in the cancer deaths in women. Kamperman found cancer of the uterus in 4 per cent of all gynecologic cases. In an analysis of 2,832 malignancies of the female pelvis seen at the University Hospital of the University of Michigan, Norman F. Miller found that 81 per cent were uterine.

ETIOLOGY OF CANCER

The underlying cause of cancer is still a mystery, but through the combined efforts of geneticists, chemists, biologists, bacteriologists, pathologists, and clinicians new facts concerning normal and abnormal growth are being discovered.

In experimental animals it has been amply shown that certain strains are resistant to the development of specific types of carcinoma while other strains will almost invariably develop it. Geneticists have been able to produce mutations and cancer by using various carcinogenic agents. Certain types of cancer in man, such as retinoblastoma, are known to be inherited, while others which are potentially malignant, such as multiple polyposis, are thought to be inherited. Certain families in which there is a high concentration of certain types of neoplasms will tend to have a higher incidence of this particular cancer than is found in the population as a whole. Wassink found this to be true of mothers and sisters of patients with breast cancer. Macklin, in a statistical study, found that "male relatives of breast cancer patients who have cancer appear to have prostatic cancer in greater percentage than do male relatives with cancer who are related to patients with cancer elsewhere than in the breast." These findings certainly do not indicate that every member of a cancer family will develop cancer but should cause such individuals to have regular checkup examinations so that early deviations from normal may be discovered. Murphy, in his study, *Heredity in Uterine Cancer,* concluded that though heredity is an important factor in the development of uterine cancer, the incidence of breast cancer was not linked to the incidence of uterine cancer.

The part played by heredity in the occurrence of multiple cancer in the same individual is still not clear in the human species, though numerous families with cancer in their background four generations back have been reported. A family history in multiple cancer cases was found to be present in 28.6 per cent by Hurt and Broders, 26.6 per cent by Stalker, Phillips, and Pemberton, and 26 per cent by Barrett, Miller, and Fessenmeyer.

The occurrence of six primary cancers in one patient was recently reported by Ettinger et al. Slaughter found that multiple primary carcinomas occur in 3.9 per cent of all carcinoma cases. Of 1,900 patients observed in the Massachusetts Cancer Program, 117 patients developed a second primary malignant tumor whereas the expected occurrence would have been between eighty and eighty-five. Warren and Gates state that the statistical expectancy of multiple primary malignancy should be around 6 per 1,000, whereas the observed incidence is 37 per 1,000, indicating, according to him, a definite tissue susceptibility. Marrangoni and McKenna found an incidence of 2.4 per cent of multiple carcinomas of the female genital tract in 618 cases of cancer of the female genitals.

The fine balance between cellular anabolism and catabolism with its physical and chemical and enzymatic reactions is being intensively studied by means of numerous techniques, including the use of tagged atoms. The influence of general nutrition on cancer development in mice was studied by Tannenbaum. By restricting just the caloric intake in mice the incidence of four types of malignant tumors was significantly reduced. A review of insurance statistics suggests that the person of average weight is less apt to develop cancer than is the obese individual. The influence of endogenous and exogenous agents as factors in the production of abnormal cell growth is now well recognized. Those of importance in uterine cancer will be discussed later.

Since Peyton Rous in 1911 succeeded in causing sarcoma in chickens by injecting a cell-free extract of tumor tissue, the role of viruses in production of cancer has been intensively studied. Bittner has shown that the "milk factor" is responsible for the vertical transmission of mammary cancer in mice. Mice were removed from their mothers immediately after birth and given to a foster mother to suckle. It was found that mice of high cancer strain nursed by foster mothers of a low cancer strain had a low incidence of mammary cancer, and conversely mice of a low cancer strain nursed by foster mothers of a high cancer strain had a high incidence of mammary cancer. Horne found that in human beings this vertical transmission did not occur in daughters of women who had breast cancer. Gye and his co-workers found that desiccation and freezing of carcinomatous tissue did not remove the active virus which they claim is responsible for the transmission of cancer; but Russell and Wynne in a critical review of Gye's experiments state that the only method which ensures an absence of viable cells is to pass the material through a filter too small to permit passage of cells. Passey et al. have shown that intact tumor cells can survive freezing and desiccation.

Gregory identified the cancer virus in Berkefeld filtrates by means of the electron microscope in over 1,000 cancer specimens and has never found it in normal tissue or in that of benign tumors. In a more recent article he

presents cases of advanced cancer treated by a filtrate of *B. subtilis* Tracy I, which he calls tracin. Under the electron microscope he demonstrated the antibiotic action of the subtilis bacilli on the cancer virus. If the excellent results he reports can be duplicated by others, it will certainly change our ideas on the origin of cancer.

A large number of carcinogens have been described, which under certain conditions will cause cancer. The reactions caused within the cell which result in carcinoma are still not known. Many of these substances occur in the body normally and some, for example, estrogens, are used in treatment of various conditions.

With this brief sketch one can see that the problem of the cause of cancer is a many sided one; however, it is probable that with the teamwork of scientists in many fields the answer will soon be found.

Cancer of the uterus includes malignant growths of the cervix and malignant growths of the corpus uteri. Cancer of these two parts of the uterus differs so much in structure and in the problems of diagnosis and treatment that it is advisable to consider them separately. The malignancy occurs as carcinoma or sarcoma.

The subject of this chapter then may be divided into three parts, as follows:

Carcinoma of the Cervix Uteri

> Squamous-Cell Carcinoma (Epithelioma)
> Cylindrical-Cell Carcinoma (Adenocarcinoma)

Carcinoma of the Corpus Uteri

> Endometrial Carcinoma
> Chorionepithelioma

Sarcoma of the Uterus (Cervix and Corpus)

CARCINOMA OF THE CERVIX UTERI

This term signifies malignant disease of epithelial origin, situated in the cervix. It may arise from the squamous epithelium covering the vaginal surface of the cervix, in which case it is a squamous-cell carcinoma or "epithelioma." It may arise from the glandular epithelium in the interior of the cervix, in which case it is a cylindrical-cell carcinoma and is ordinarily designated adenocarcinoma. The cervix is the most frequent site of cancer of the uterus. Frankl states that 89 per cent are located there. Cullen in a strict analysis of his 128 cases of carcinoma of the uterus found that 93 (73 per cent) were in the cervix. In more recent series, the University of Michigan gives 81 per cent, University of Rio de Janeiro 95 per cent, McGill University, Montreal, about 78 per cent.

ETIOLOGY OF CERVICAL CANCER

Though the underlying cause of cervix cancer has not yet been discovered, some contributing factors have been identified, including age, chronic irritation, certain types of endocrine imbalance, and certain vitamin deficiencies.

In regard to age, invasive carcinoma is most common between the ages

of forty to fifty, the average being forty-six. With early noninvasive carcinoma, which is now recognized as the earliest stage of carcinoma, the average age is 36.6 years. Waters reported a case in a seven-month-old infant; Baber et al. recently reported one in a fifteen-month-old baby; and three cases in the first year of life were reported by Heckel, two of which occurred on his service. Those occurring in early life are usually adenocarcinomas. Salvadore di Palma, in a series of 1,637 cancers of the cervix, had two in patients between 90 and 95 years of age. Sadugor and Palmer have an excellent summary of age, incidence, and distribution of cancer of the cervix in a series of 4,652 cases.

Race seems to be important, for in all studies carcinoma of the cervix is less common in Jewish women than it is in the non-Jewish group. The figures vary in different studies, but the disease is from five to twelve times more frequent in the non-Jewish group. At Mount Sinai Hospital in New York, Weiner, Burke, and Goldberger found the ratio to be five times, and at Mount Sinai Hospital in Chicago, Rothman, Rapoport, and Davidsohn found it to be nine times more frequent in the non-Jewish women. The reason for this apparent partial immunity is not known. Some think it is due to the custom of refraining from coitus for seven days after menstruation and others attribute it to the custom of early circumcision. Plaut and Kohn-Speyer showed that human penile smegma contained a carcinogenic agent which lent weight to the latter theory, but Khanolkar is quoted by Kennaway as finding that among Indian religious groups the Moslems who practice circumcision have the second highest incidence of cervical carcinoma while the Indian Christians, most of whom are not circumcised, have the lowest incidence, or almost half of that of the Moslem group.

Di Palma found a high incidence of cervical carcinoma among Negroes at the New York City Cancer Institute and Clinic, but in a statistical review of malignancy in the Negro, Robinson concluded that under comparable situations and similar environment malignancy behaves the same as in other races.

Maliphant made a careful statistical study of the effect of marriage and childbearing on the relative risk of contracting cervical cancer. In his series of 1,200 cases with cervical cancer 98.5 per cent of the patients were married. He concludes: "The figures showing the relative risks run by the three groups indicate that when a woman has reached the age of 35 or more her risk of contracting cancer of the cervix is twice as great if she has been married, and ten times as great if she has also had children, than if she were single." Contrary to the findings of Deelman that the incidence of carcinoma does not rise with multiple pregnancies, Maliphant found that the relative risk increases slightly with each confinement, so that the woman who has had six or more children is twice as apt to develop cervical carcinoma as one who has had only one child.

That the damage to the cervix and the consequent chronic cervicitis is probably the main factor seems to be indicated by numerous studies attacking the problem from different angles. A recent excellent statistical report on a study of the incidence of cervical carcinoma among nuns was made by Gagnon. He surveyed the medical files of an annual average of 13,000 nuns covering

a twenty-year period. In this group there were no cervical carcinomas. He then collected all of the cases of uterine carcinomas in nuns from the files of several large pathological laboratories and centers for radiologic treatment for a period covering twelve to twenty years. In these he found 19 cases of corpus cancer and three cases of cervical cancer occurring in nuns. According to the index of frequency of six cervical to one corpus cancer reported by Meigs, there should have been 114 cases of cervical cancer discovered. In a third study Gagnon noted the occurrence of all types of malignancies in an annual average of 3,280 nuns for a twenty-year period, and though there were 130 malignant tumors of all organs, including two of the corpus uteri, there were no cervical carcinomas.

It is well known that chronic cervicitis occasionally develops in virgins, hence it would be expected that cancer would occasionally also develop in such a cervix. As Gagnon readily admits, chronic cervicitis is certainly not the only factor, for heredity, acquired constitutional states, viruses, enzymes, deficiencies, and biochemical and hormonal influences all play their part, and these are probably especially important in those rare cases of carcinoma occurring in apparently normal cervices.

Another angle to this problem is the question as to whether curing of the cervicitis prevents the development of cervical carcinoma. Craig reported that in 2,895 cases of chronic cervicitis adequately treated no carcinomas developed in ten years of observation. In over a thousand cases in which a wide conization for extensive cervicitis was done (reported by R. J. Crossen), there were no subsequent cervical carcinomas during the period of observation from two to fourteen years. In a summary of several series of adequately treated cervicitis cases comprising 18,562 cases, Saltzstein and Topcik found only 15 cases which had developed cervical cancer, whereas in a series of 2,255 cervical cancer cases only 33 had received adequate treatment for the pre-existing chronic cervicitis.

With this wealth of statistical proof that chronic cervicitis is an important predisposing factor in the development of cervical carcinoma, it is hoped that the statements still found in some textbooks to the effect that the proof of its importance is still lacking, will be deleted from future editions.

The role of estrogens in the development of cervical cancer was investigated by Edgar Allen and Gardner. These workers were able to produce cervical carcinoma in experimental animals (mice) by administration of large doses of estrogens plus trauma to the cervix. Ayre claims that vitamin B deficiency, plus an excess of estrogen and cervicitis, may indirectly cause carcinoma in the cervix. Hofbauer feels that the predisposition of multiparous women to the development of cervical cancer during the early premenopausal period is the result of a disturbance of balance between hypophyseal and ovarian activity associated with an altered condition of their receptor, e.g., the cervix or endometrium.

The role of leukoplakia of the cervix in the development of carcinoma was reviewed by Shiller. He points out that the word "leukoplakia" merely conveys an optic impression which the examiner gets either by examination with the naked eye or with the colposcope. The two types of leukoplakia as

seen through the speculum can be differentiated only by microscopic examination. The type described by Hinselmann is a hyperkeratosis formed through excessive cornification of the cervical epithelium and this type rarely gives rise to carcinoma. The other type seen through the speculum as a whitish area when examined microscopically is discovered to be an early non-invasive or early invasive carcinoma. Hence the importance of microscopic examination in all suspected cases, and, since Hinselmann cites six cases in which the hyperkeratotic type eventuated in cancer, removal of the entire area seems indicated.

Ayre has suggested that the etiological factor in the causation of cervical cancer is a disordered growth response to inflammation in the presence of excessive estrogen and a deficiency of the vitamin B complex. Greene points out, however, that in patients with carcinoma of the cervix, the incidence of hyperplasia of the endometrium, which should be common if there was an excess of estrogen, is very low. A discussion of the endocrine factors in cervical carcinoma is given in a recent article by Nieburgs, and the reader is referred to this article for further information on this subject.
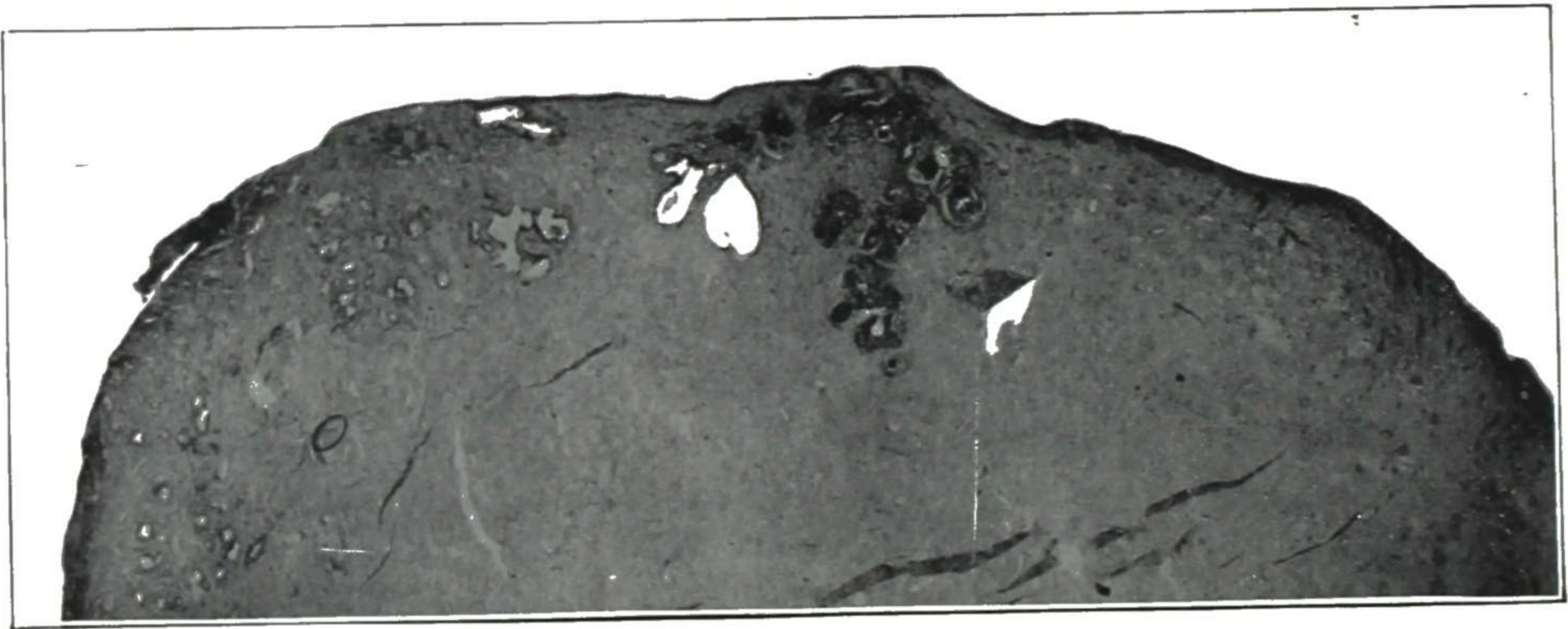

Fig. 645.—Section of a small squamous-cell carcinoma of the cervix. Section of the entire width of the cervix. At the left is seen the wall of the canal, with cervical mucosa and glands. At the upper left angle is the external os, and some distance out from the external os is the carcinoma. It is situated in an area of old erosion, remnants of the glandlike depressions being still present under the surface. Surface inspection of this cervix would show only an area of irritation—nothing suggestive of the sinister activity going on underneath. Gyn. Lab.

Squamous-Cell Carcinoma.—The squamous-cell cancer of the cervix originates from the squamous epithelial cells covering the vaginal portion. Arising from that part of the cervix known as the "portio vaginalis," it is sometimes spoken of as "cancer of the portio." The squamous-cell type is by far the most frequent, running in different series from 80 to 90 per cent of all cervical carcinomas.

It is now known that the disease begins with a change in the cell layers and the cells themselves in the epithelium and that these changes may precede invasion by many years. The cervical surface at this stage may have a normal appearance or may show chronic cervicitis, but there are no changes detectable by the naked eye which would indicate that a beginning cancer is present. At some later date the basement membrane is penetrated and invasion occurs as shown in Fig. 645.

PATHOLOGY

Cancer of the uterus is, in the beginning, essentially a local process. The apparently independent growths appearing later in various organs are simply metastases from the primary tumor. The important bearing of this on treatment is apparent.

Carcinoma of the cervix occurs in two forms: squamous-cell carcinoma (epithelioma) arising from the vaginal surface of the cervix, and the cylindrical-cell carcinoma (adenocarcinoma) arising from the glandular epithelium of the cervical canal.
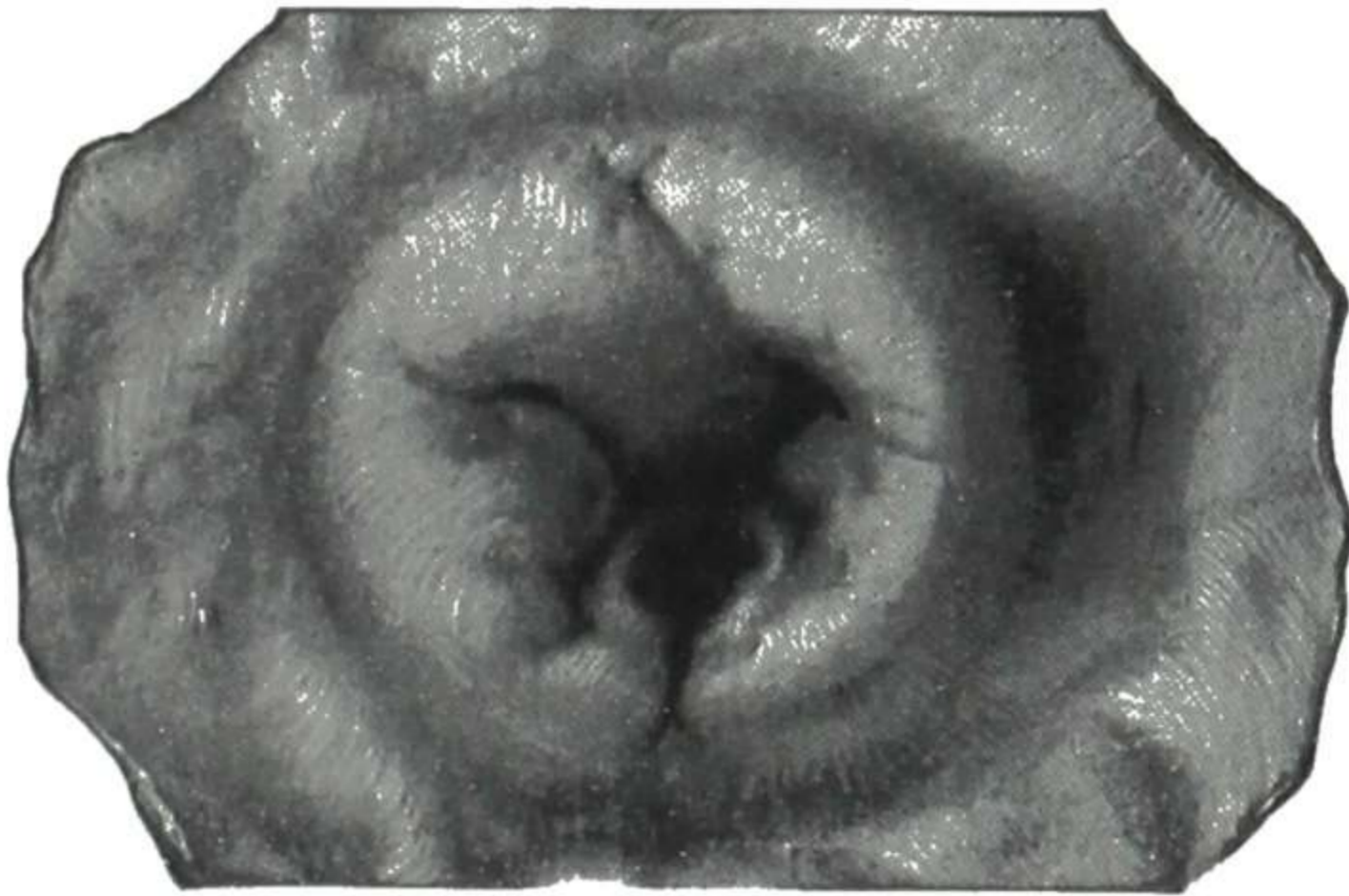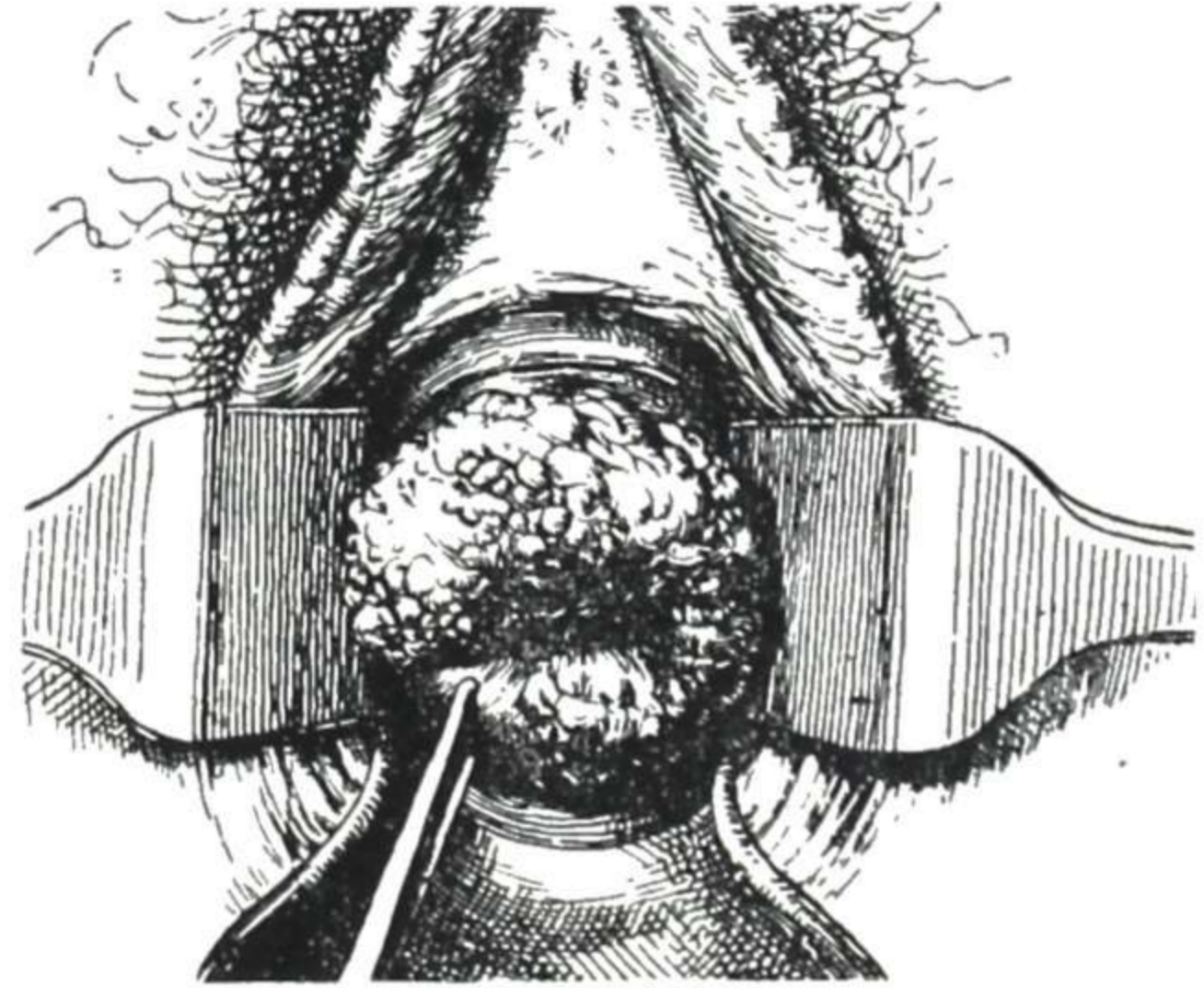

Fig. 646.

Fig. 647.

Fig. 646.—Drawing from a specimen of squamous carcinoma, or epithelioma, of the cervix. Notice that it has begun at one of the angles of the stellate tear. Gyn. Lab.

Fig. 647.—Epithelioma of the cervix, appearing as a papillary growth. (From Kelly: Operative Gynecology.)
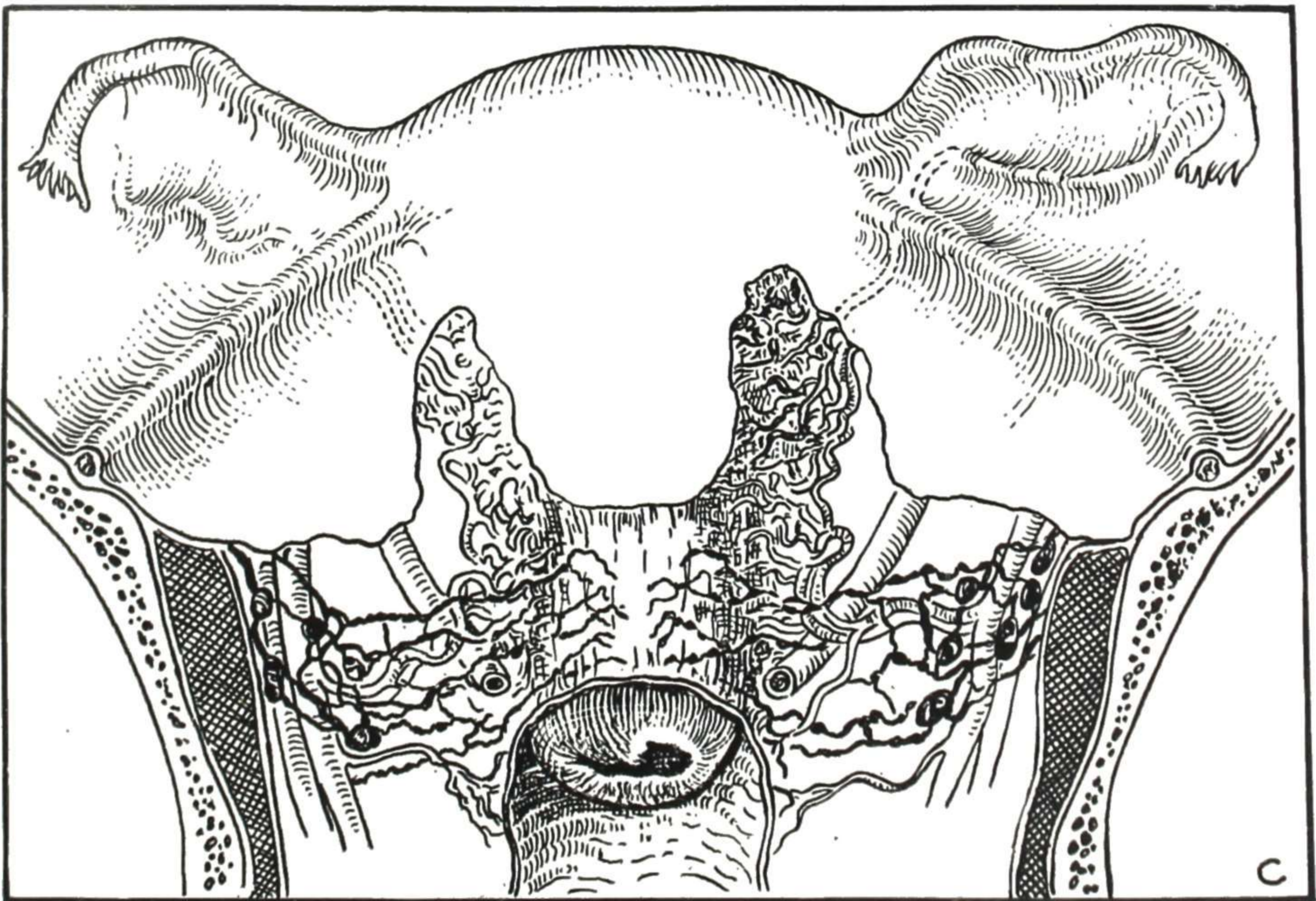

Fig. 648.—Early extension to deep-lying structures at the pelvic wall, as here indicated, *before* troublesome symptoms appear, is the cause of the high percentage of advanced cases found at first examination and the low percentage of cures.
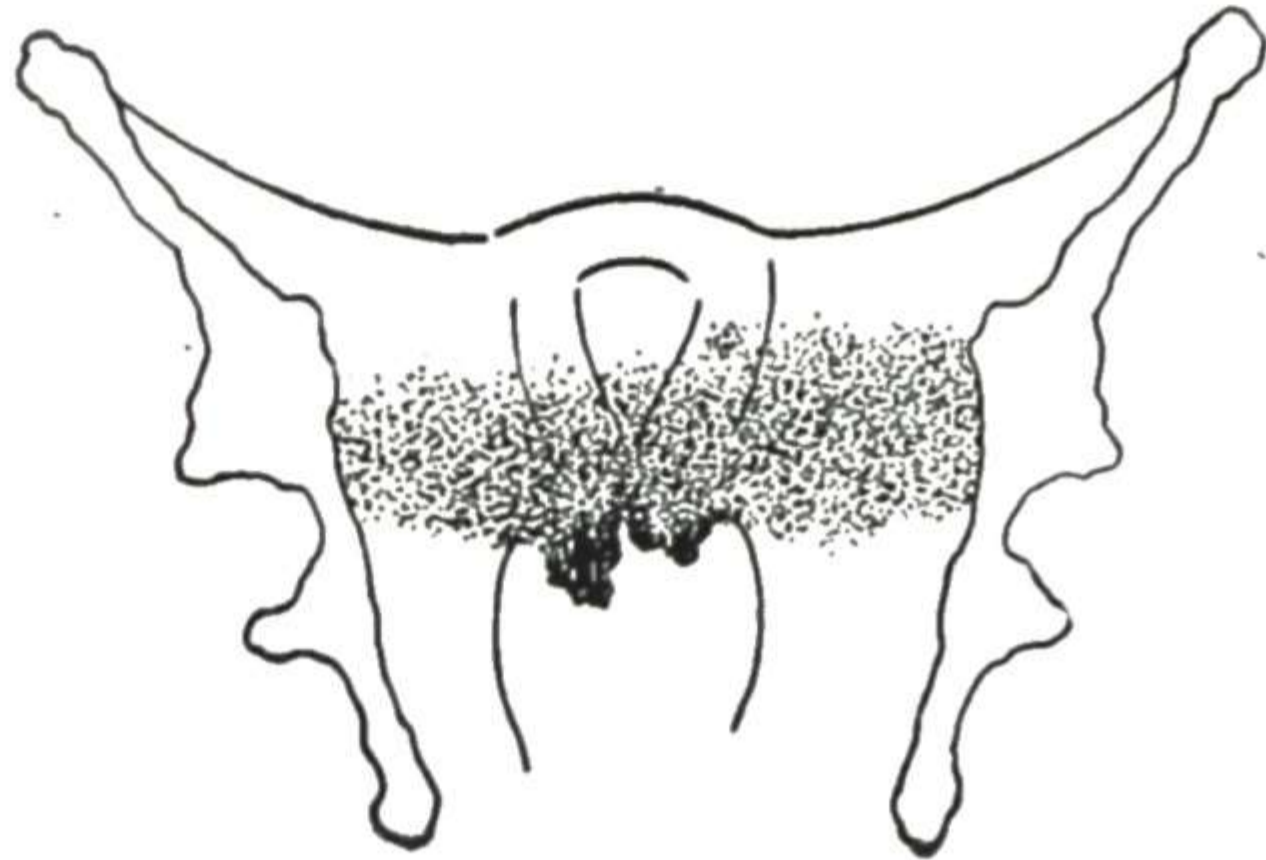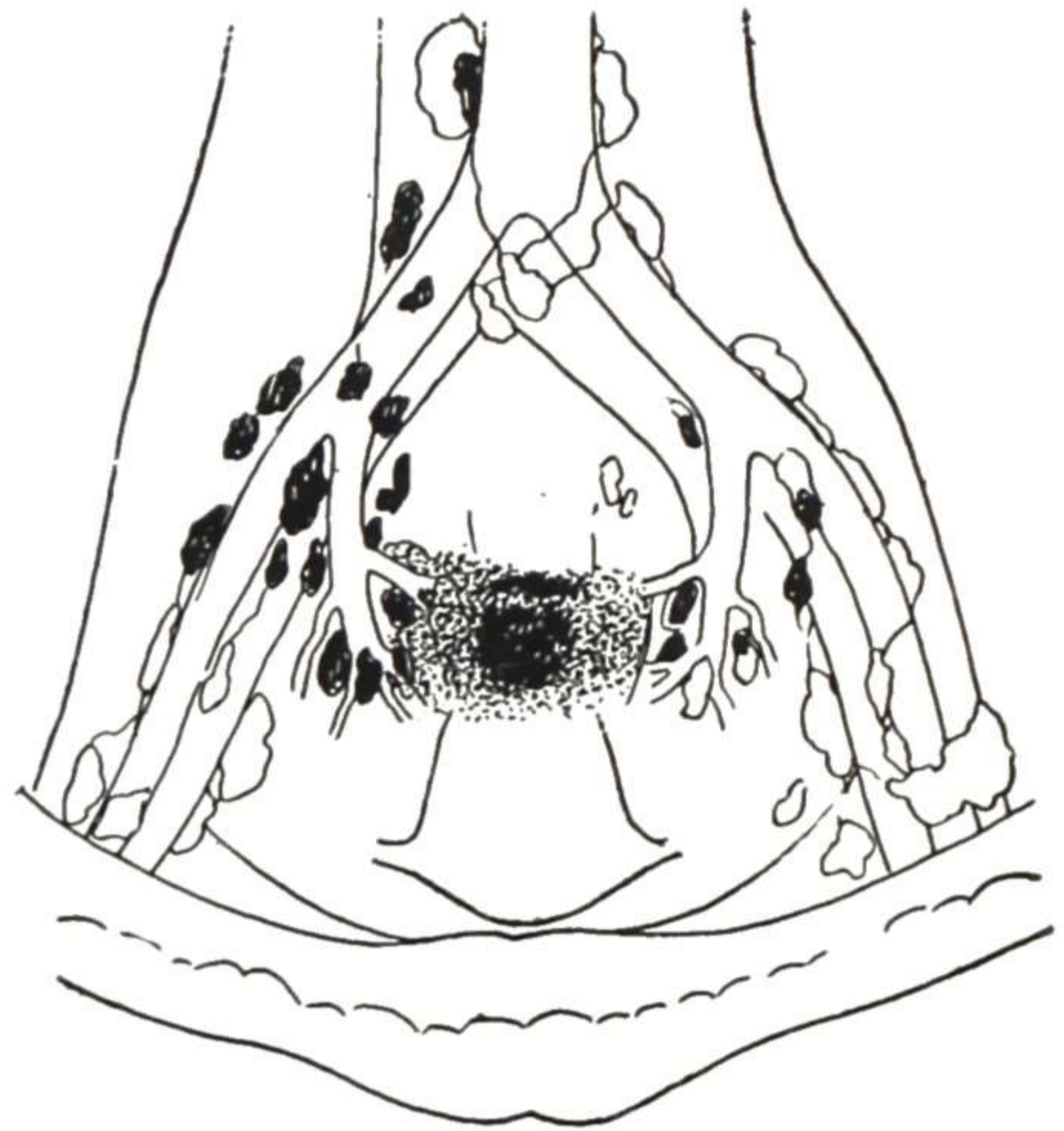
Fig. 649.

Fig. 650.

Figs. 649 and 650.—Diagrammatic representation of pelvic extension of carcinoma of cervix uteri. Fig. 649. Parametrial involvement extending out to the pelvic wall on each side. Fig. 650. Involvement of the pelvic lymph glands. The general location of the different groups of glands is indicated by the dim outlines, and the involved portions by the dark areas. The internal iliac (hypogastric) group are usually the first involved.
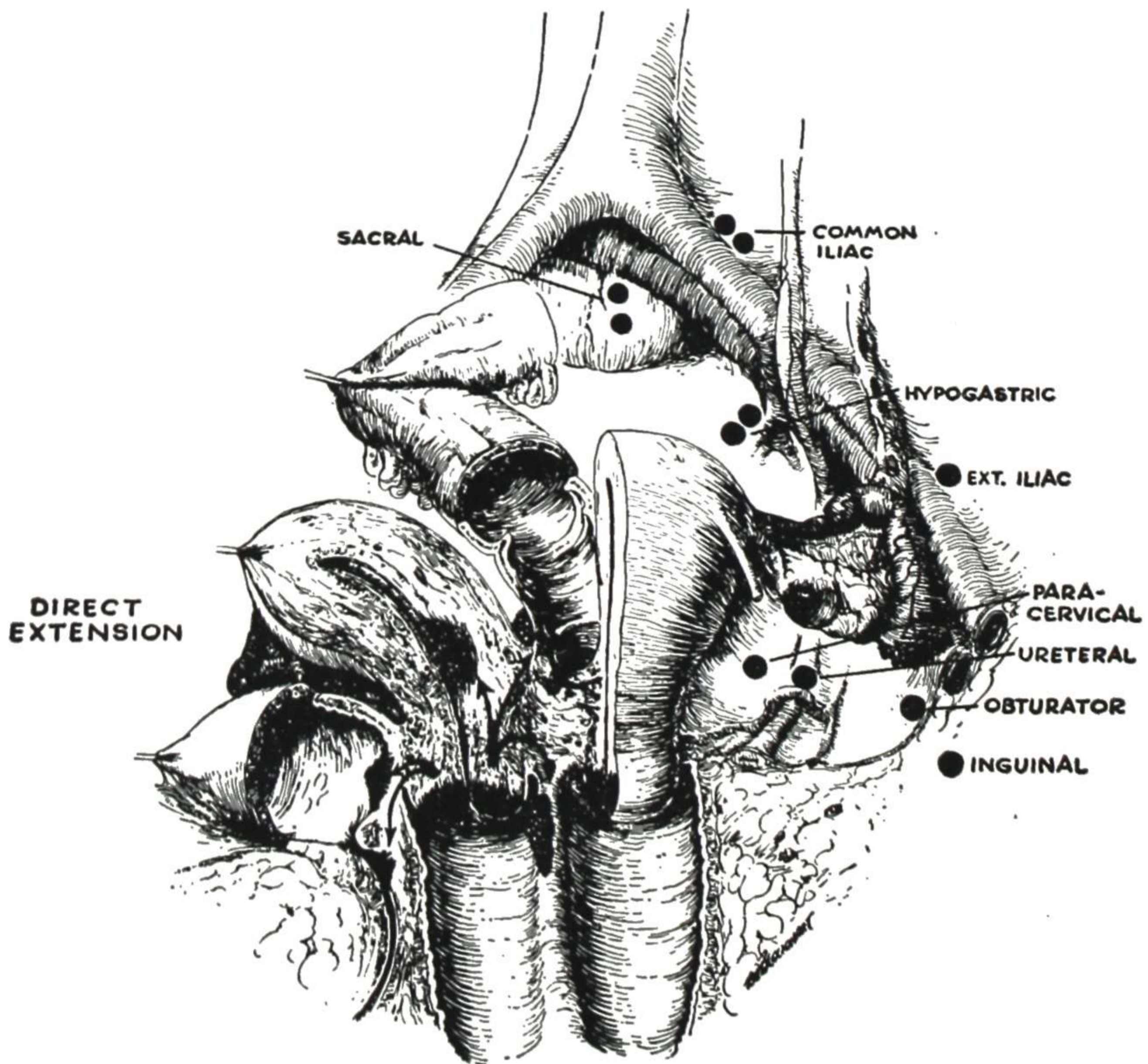

Fig. 651.—Spread of cervical carcinoma by the lymphatics and direct extension. (From Henriksen: Radiology, June, 1950.)

Gross Pathology

As the process continues, the carcinomatous infiltration, with the opposing round-celled (leukocyte and lymphocyte) infiltration, penetrates deeper into the tissues, and the small area of induration gradually increases in extent. A small abrasion or ulcer appears (Fig. 646), or there may be a raised papillary area (Fig. 647). This usually bleeds slightly when touched. Frequently the
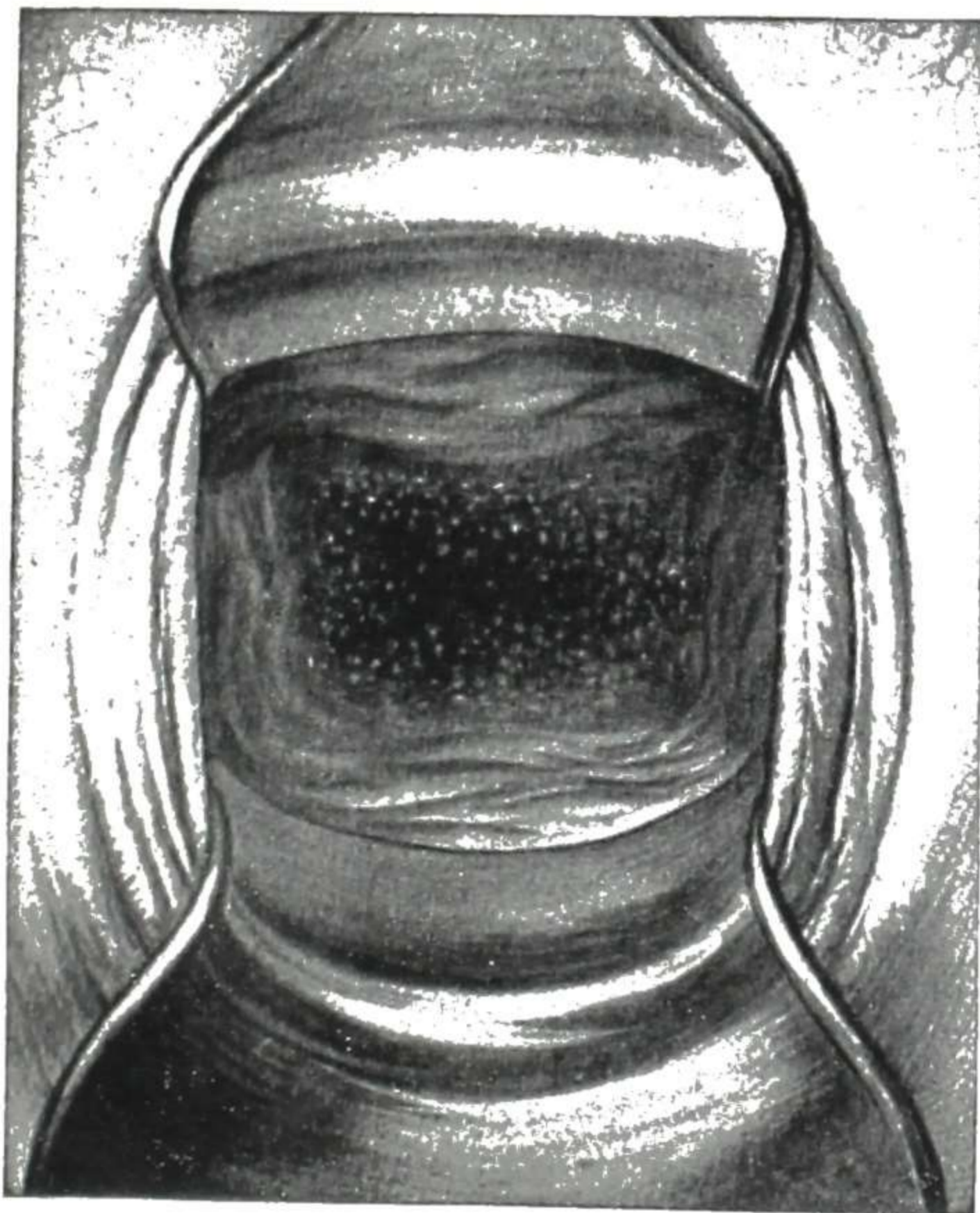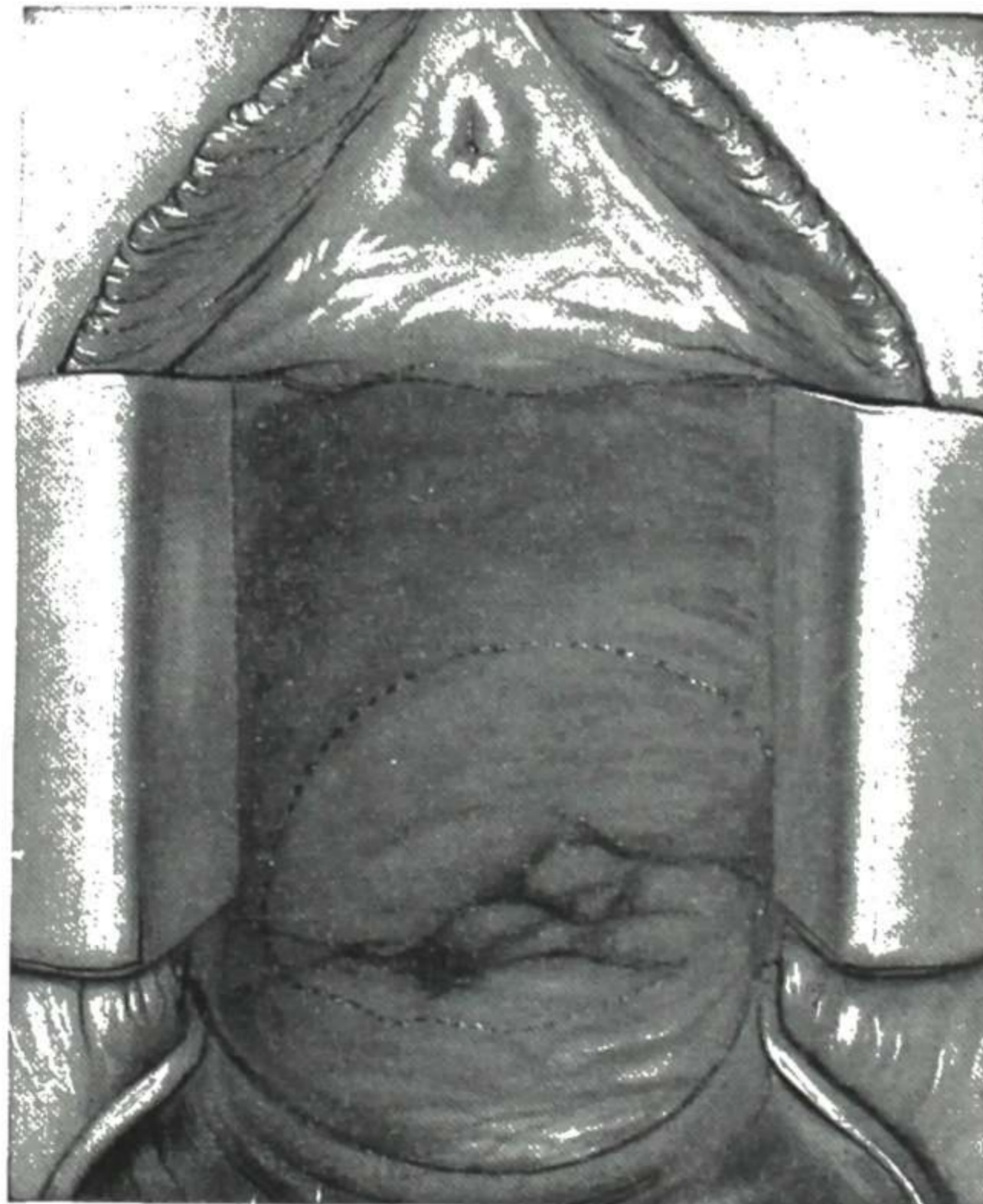

Fig. 652.

Fig. 653.

Fig. 652.—Epithelioma of the cervix. The cervix has been destroyed, leaving only an area of cancerous ulceration at the top of the vagina.

Fig. 653.—Epithelioma of the cervix. The cervix has been destroyed and the affected area has been drawn in by the gradual contraction of the infiltrated tissues, until no cancerous tissue can be seen. Palpation, however, shows that there is infiltration of the area enclosed within the dotted line.

(From Kelly: Operative Gynecology.)

Non-treated   *Treated*

39% UTERUS ———————————— UTERUS 17%

30% BLADDER WALL ———————— BLADDER WALL 20%

19% BLADDER ———————————— BLADDER 21%

0.8% URETHRA ———————————— URETHRA 1.8%

32% VAGINA ————————————— VAGINA 20%

24% RECTUM ————————————— RECTUM 18%
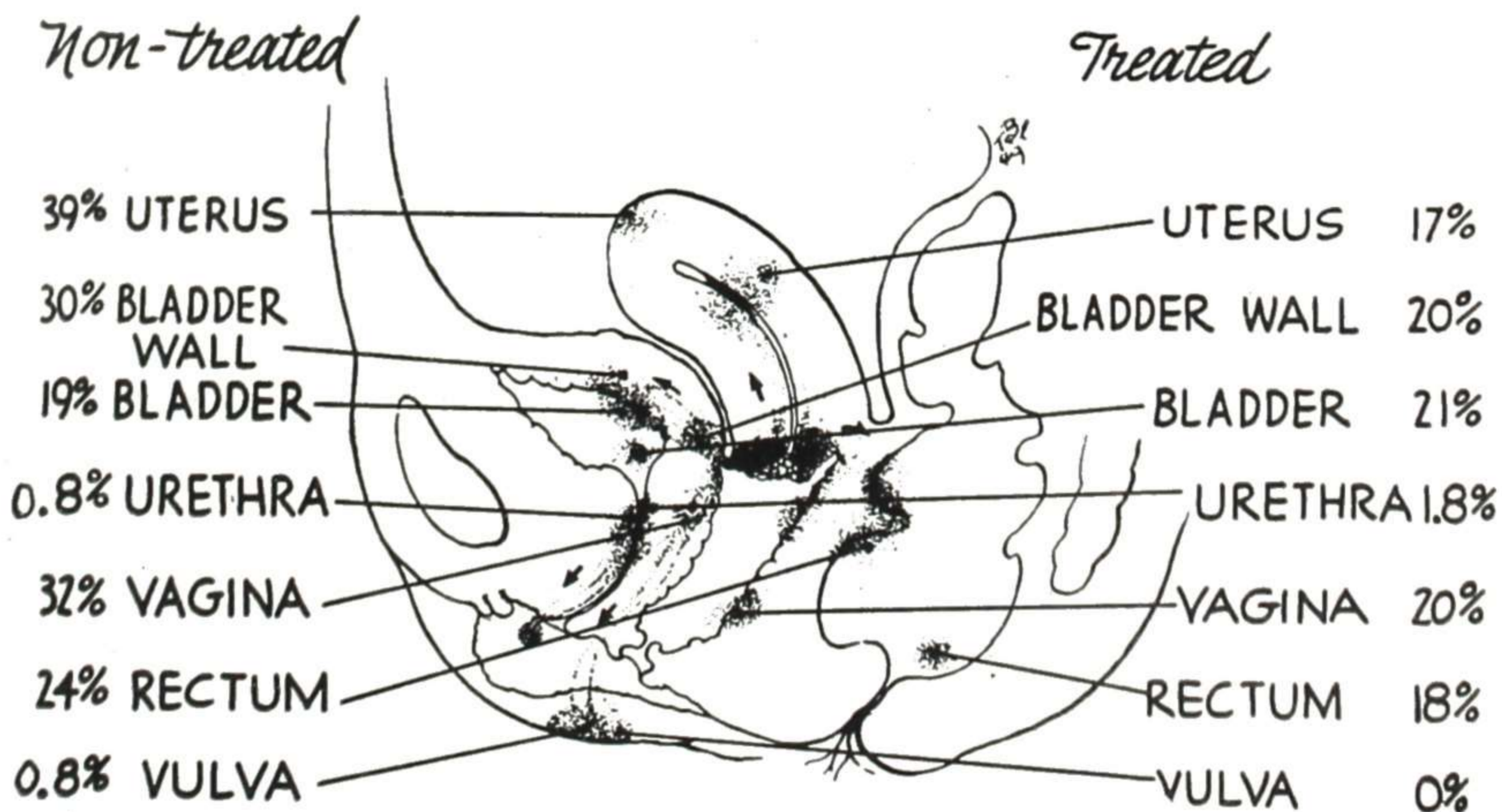
0.8% VULVA —————————————— VULVA 0%

Fig. 654.—Incidence of organ involvement in 154 nontreated and 202 treated cases of cervical carcinoma. (From Henriksen: Radiology, June, 1950.)

first evidence of anything wrong noticed by the patient is this slight streak of blood or spot after coitus or after extra walking or other exertion. Already the disease has penetrated deeply into the cervix and out into the parametrium, as indicated in Fig. 648.

As the disease extends in the cervix, infiltration becomes appreciable on palpation, and more ulceration (which may be mistaken for laceration or erosion) may be seen through the speculum. The disease is continuously progressive, the destructive cells penetrating more and more of the surrounding healthy tissues and to adjacent lymph vessels and glands, until there is a continuous mass of cancer tissue blocking the pelvis as in Fig. 649, with extensions to higher pelvic and abdominal glands (Figs. 650 and 651).
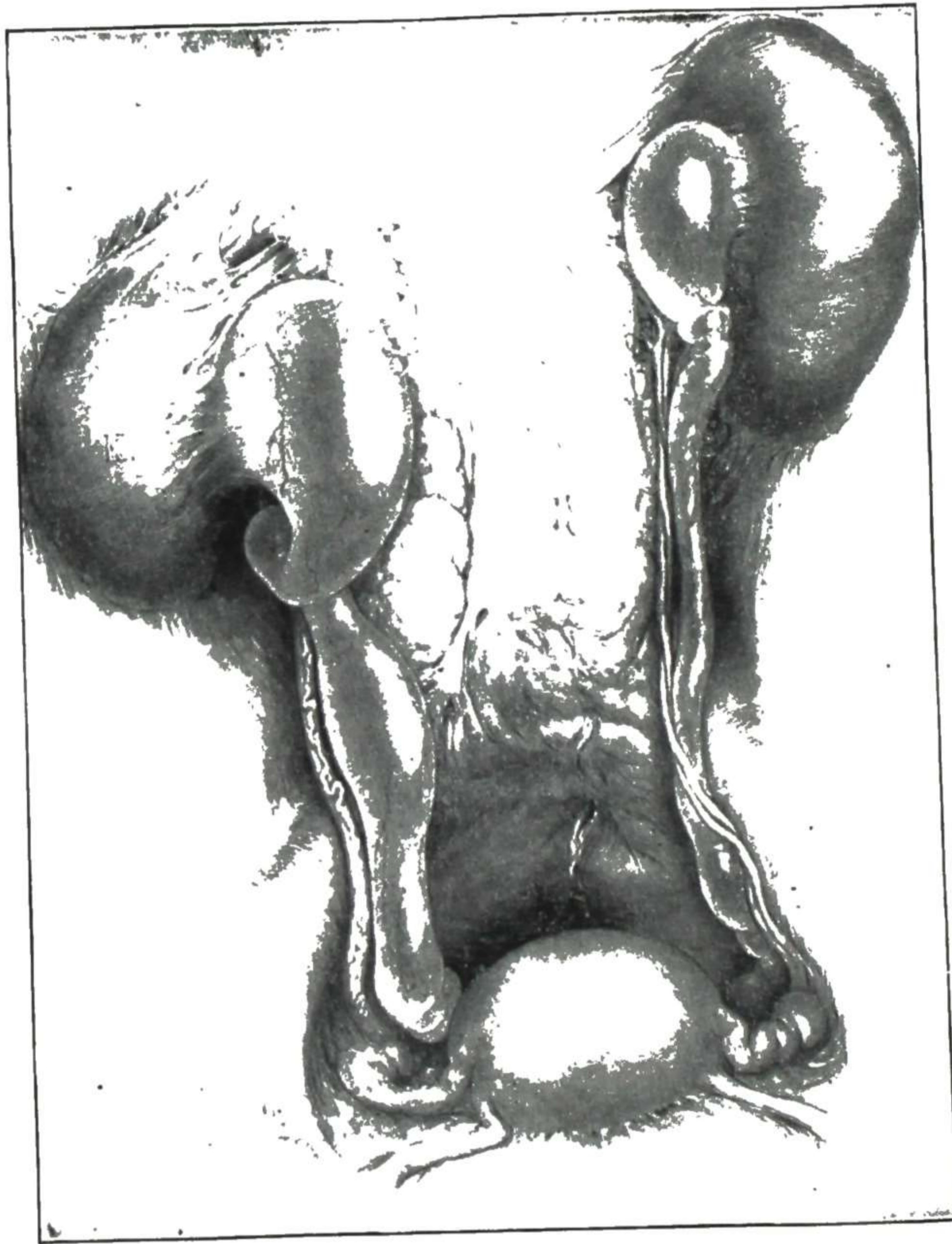

Fig. 655.—Case of carcinoma of cervix uteri in which the parametrial involvement has obstructed the uterus, causing serious dilatation of them and of the kidney pelves. (From Kelly: Operative Gynecology.)

If there is much ulceration the cervix may be destroyed, its location at the vaginal vault being occupied by a granulating cavity as in Fig. 652. On the other hand, particularly in the aged with very slow-growing epitheliomas, the formation of contracting scar tissue may so draw in the affected region that it cannot be seen. In such a case it can be appreciated only by palpation, which reveals induration at the vaginal vault (Fig. 653). All this time the growth is extending out into the parametrial tissues toward the adjacent

organs and the pelvic wall. Fig. 654, by Hendriksen, shows the incidence of involvement of surrounding structures.

In certain cases the carcinomatous ulceration extends into the bladder and into the rectum, causing leakage of the contents of those organs into the vagina. In the later stages there may be compression of the pelvic nerves and vessels, causing severe suffering and persistent edema of the lower extremities. Compression of the ureters with back-pressure destruction of the kidneys, as in Fig. 655, is a frequent terminal condition.

A **clinical classification** into **stages** is required for recording the extent of the disease in each case, along with the treatment measures employed and the results attained. The same classification should be used by all workers. A uniform classification in stages representing the extent of involvement is imperative for comparison of results of various methods of treatment. The classification of the Cancer Committee of the League of Nations is satisfactory; it is already in rather general use and is the only classification likely to come into universal use. It groups the cases of cancer of the cervix into the following five stages, representing the different stages of the disease.

Resolution Adopted on Classifications of Cervical Cancer

''Whereas, the so-called League of Nations' Classification of Carcinoma of the Uterine Cervix is now in common use in many countries, but is not used exclusively in the U. S. A., it is desirable that this Classification, or an acceptable modification thereof, be adopted universally in order to reach a common ground of understanding. Therefore, a committee of duly appointed representatives of the Section of Obstetrics and Gynecology of the A. M. A., the Am. Ass'n of Obstetricians, Gynecologists, and Abdominal Surgeons, and the Amer. Gynecological Society, meeting in session with the Editorial Committee of the Annual Report on the Results of Radiotherapy in Carcinoma of the Uterine Cervix on the occasion of the International and 4th American Congress on Obstetrics and Gynecology at New York City on May 14-19, 1950, has agreed to propose the following modification of the Classification adopted by the Health Organization of the League of Nations in 1937:

''Stage 0.—Carcinoma *in situ;* also known as preinvasive carcinoma, intraepithelial carcinoma and similar conditions.

''Stage I.—The carcinoma is strictly confined to the cervix.

''Stage II.—The carcinoma extends beyond the cervix, but has not reached the pelvic wall. The carcinoma involves the vagina, but not the lower third.

''Stage III.—The carcinoma has reached the pelvic wall. (On rectal examination, no 'cancer-free' space is found between the tumor and the pelvic wall.) The carcinoma involves the lower third of the vagina.

''Stage IV.—The carcinoma involves the bladder or the rectum, or both, or has extended beyond the limits previously described.

''Be it resolved that this Classification be termed the International Classification of the Stages of Carcinoma of the Uterine Cervix, and that all organizations concerned with the problem on hand be approached to consider its adoption.''

In the case of each patient, the evidences of the extent of involvement should be worked out sufficiently to permit accurate assignment to class. Accuracy is enhanced by deciding definitely as to the class at the time of examination and then recording the decision. This obviates the difficulty encountered when trying later to classify a borderline case with some needed detail missing. This accurate classification is best made during examination under

the analgesia for the radium implantation. Deep rectal palpation of the broad ligament of each side is most helpful in determining the fact and the extent of parametrial involvement.

For emphasis, it is well to repeat that a universal international classification is imperative for accurate comparison of the results of the various methods of treatment. If anyone wishes to divide further one or more of the stages in reporting his cases, there is no objection to that—provided the subgroups are clearly defined and do not extend beyond the stage divided.

Some tumors have a tendency to grow in an everting manner, forming a sessile or pedunculated cauliflower-like mass with little underlying involvement, while the other type invades early with little external protrusion; these are designated inverting carcinomas. The difference in prognosis of these two types is discussed later.

Associated diseases also add to the pathological picture in some cases. The advanced ulcerating growths are nearly always infected and may present sloughs at the vaginal vault. If the cervical canal is blocked, there may be *pyometra* above, with a thinned-out uterine wall. The inflammatory complications add much to the patient's distress and to the difficulties of palliative treatment.

Myoma may be a complication, as shown in Fig. 603. *Pregnancy* is sometimes a complication. Carcinoma of the cervix may appear while the patient is pregnant, or occasionally pregnancy may take place in the early stage of carcinoma of the cervix. In either case the effect of pregnancy is to hasten the progress of the carcinoma. The softening of the tissues and the congestion associated with pregnancy seem to favor rapid extension of the malignant disease.

The duration of invasive carcinoma of the cervix is variable, the limits ordinarily being from one to three years. The duration depends somewhat on the kind of tumor (the softer the tumor, the more rapid the growth), upon the age of the patient (the younger the patient, the more rapid the growth), and upon the proximity to childbirth—those carcinomas appearing within one year after parturition progress very rapidly.

These are only general rules, to which there are, of course, exceptions.

Microscopic Pathology

The microscopic findings of early noninvasive carcinoma of the cervix are shown in Figs. 656 to 658; this condition is discussed at length later in this chapter.

The characteristic "pearl" formation is shown in Fig. 659, and carcinoma cells growing into a cervical gland in Fig. 660.

The pathological classification as to cell types was done by Broders and by Martzloff, in the hope that the degree of cellular maturity might offer some help in deciding on the best method of treatment. The three grades used by Martzloff are shown (Figs. 661 to 663); he found that in the cases treated surgically the spinal-cell type offered the best prognosis and the spindle-cell type the worst. For cases treated by radiation no correlation between cell types and prognosis has been found. Galvin, in summarizing a

Fig. 656.—Early squamous carcinoma of cervix. Section through a diagnostic clipping from a suspicious area on the cervix. Gyn. Lab.
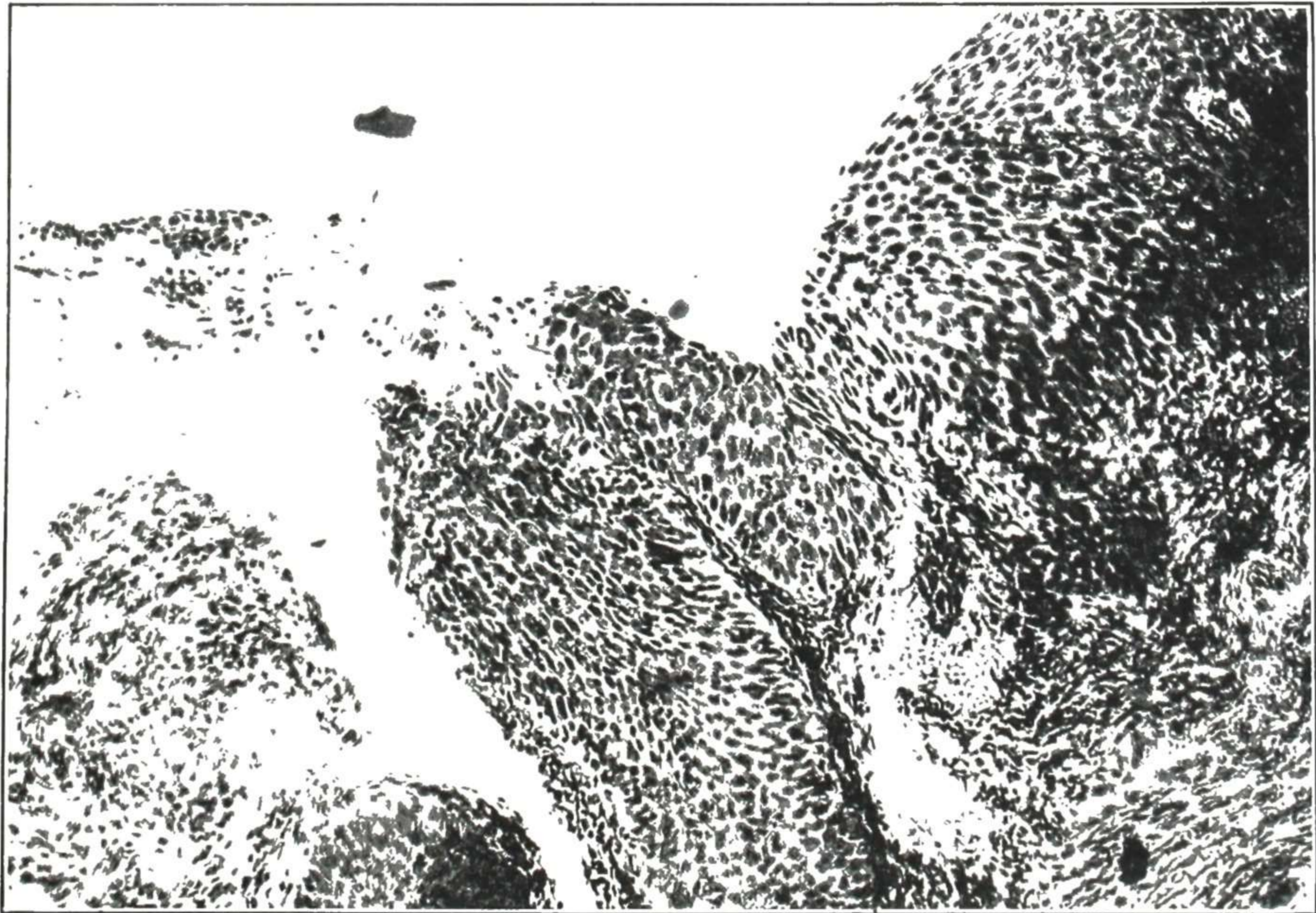

Fig. 657.—Another view of Fig. 656, showing the distinct junction line of the abnormal epithelium with the fairly normal, at the upper right portion of the field; also illustrating the peculiar bud of abnormal cells with its own blood supply. Gyn. Lab.

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The pathological classification as to cell types was done by Broders and by Martzloff, in the hope that the degree of cellular maturity might offer some help in deciding on the best method of treatment. The three grades used by Martzloff are shown (Figs. 661 to 663); he found that in the cases treated surgically the spinal-cell type offered the best prognosis and the spindle-cell type the worst. For cases treated by radiation no correlation between cell types and prognosis has been found. Galvin, in summarizing a

Mode of Extension

The fact that cancer in many cases remains localized for years is now a well-established fact. Two general types of extension are seen clinically: the inverting type, which extends into the surrounding tissues early, and the everting type, which grows into the vaginal cavity and forms a cauliflower-like tumor. As will be pointed out later, the type of growth has a bearing on prognosis. The spread is usually by direct extension along the lines of least resistance and is limited to some extent by fascial planes; hence the first extension is usually laterally into the broad ligaments. Anteriorly and posteriorly these planes protect the bladder and rectum until late in the course of the disease. Most of the early spread is in the base of the broad ligament, a fact which aids in classification of the extent of the disease by palpation. Later dispersion of the carcinoma is through the lymphatics, and as a rule those near the uterus are involved first and those along the pelvic wall later, though it has been found that there may be involvement of distal glands with normal proximal glands. The distribution of lymphatic involvement found on autopsy in 26 nontreated cases of cervical carcinoma reported by Henriksen is shown in Fig. 664.
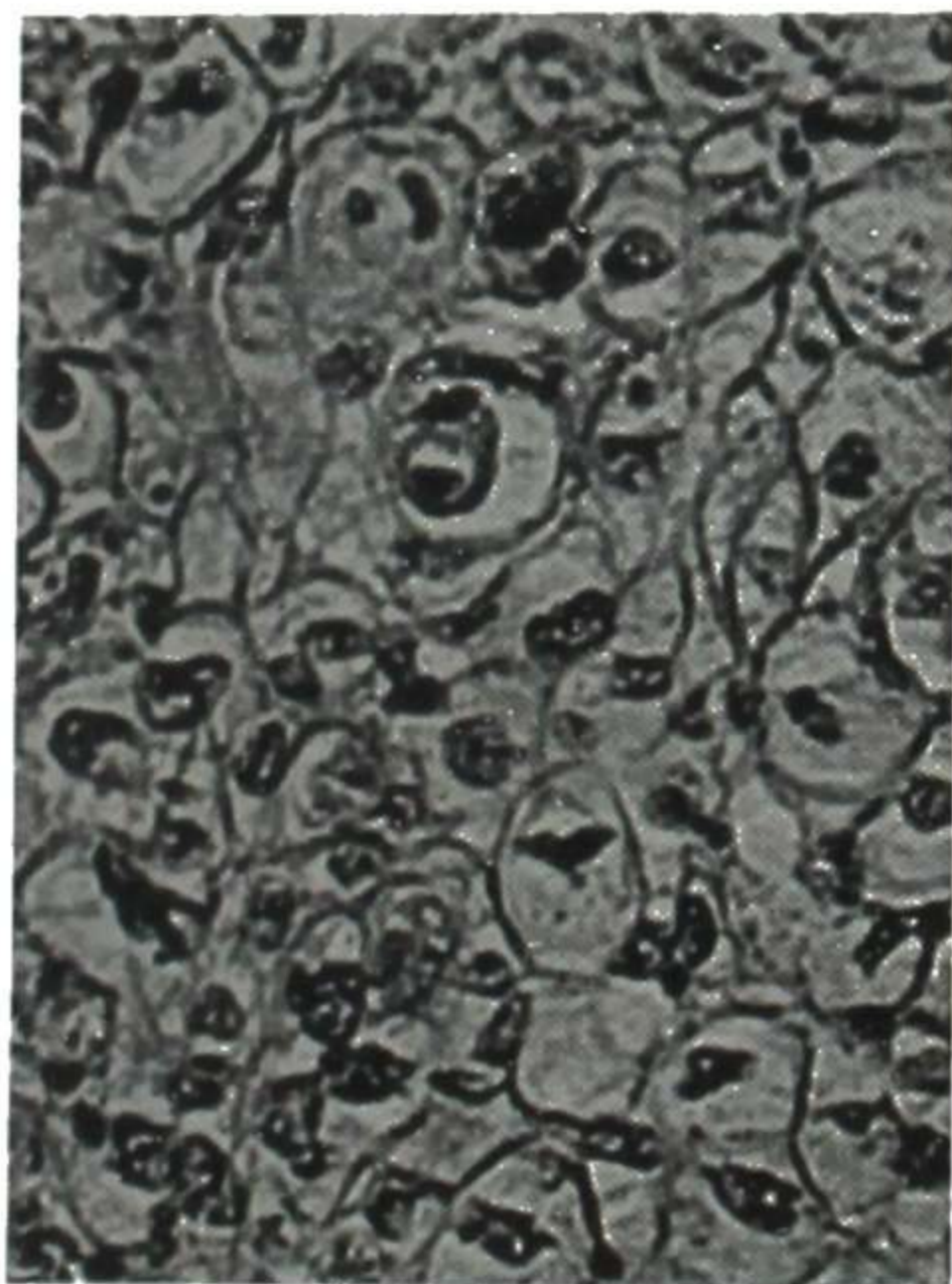

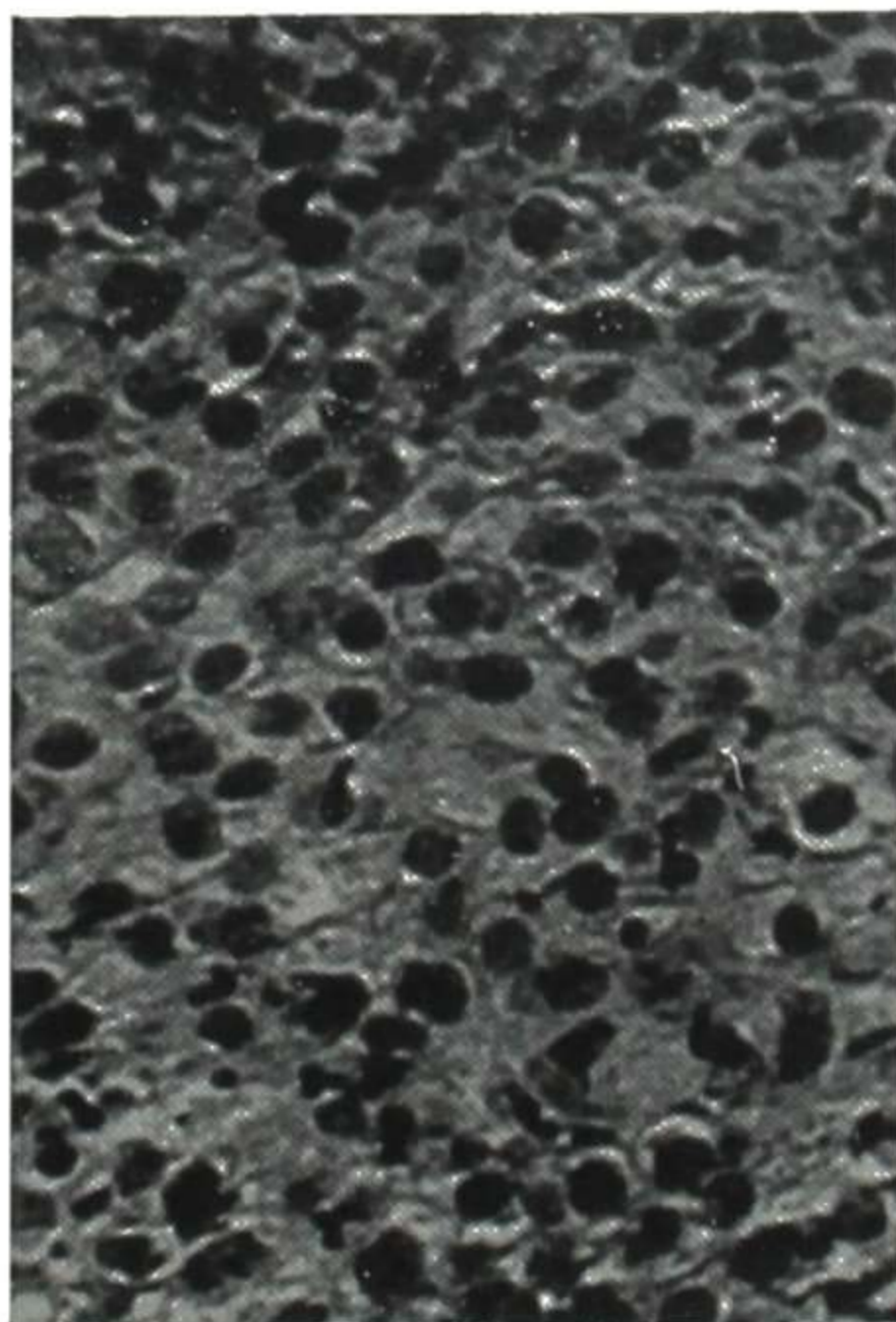Fig. 661.   Fig. 662.   Fig. 663.
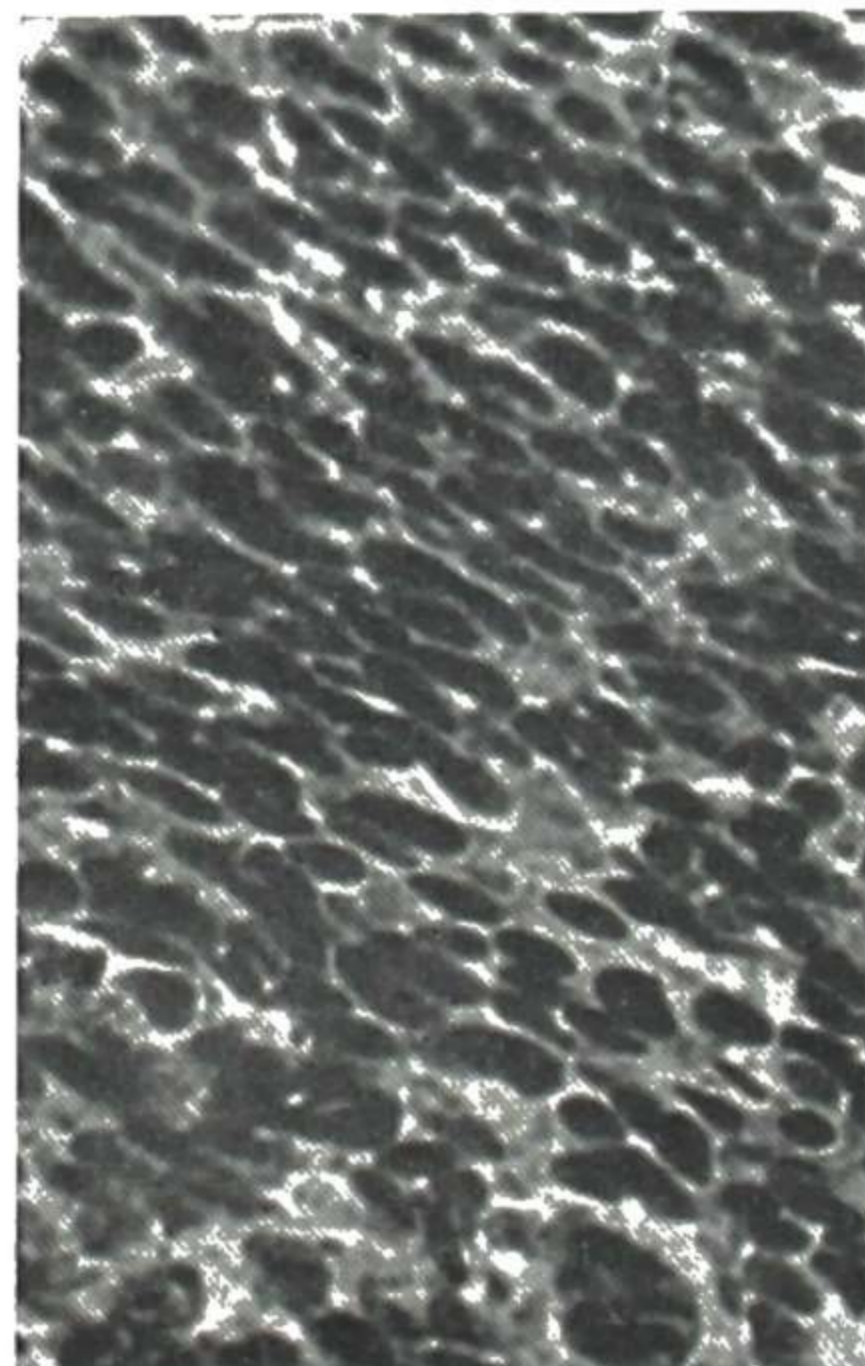
Fig. 661.—Squamous-cell carcinoma of the cervix. Grade I (spinal-cell type). Gyn. Lab.
Fig. 662.—Squamous-cell carcinoma of the cervix. Grade II (transitional-cell type). Gyn. Lab.
Fig. 663.—Squamous-cell carcinoma of the cervix. Grade III (fat spindle-cell type). Gyn. Lab.

In extension **by the blood stream,** some carcinoma cells penetrate into a blood vessel, are caught in the current, and are carried to distant organs, where they lodge and grow and form metastatic tumors. In whatever kind of tissue these metastatic growths are situated, they reproduce the structure of the parent growth.

Henriksen states that the frequency of distant metastases is not widely appreciated; he found 32.5 per cent of distant metastases in untreated cases

and 37.8 per cent in treated cases. The most common site of the distant metastases was the liver, with the bone, lung, and bowel involved in that order. The bone most frequently involved was the vertebra.

Tissue Reaction to Invasion

As the carcinoma cells multiply and invade the surrounding normal tissue, certain resistance mechanisms occur in the surrounding tissue similar to those which occur in the case of infection. Whether this resistance reaction is due to the advancing carcinoma cells or to the infection which always accompanies the carcinomatous invasion is not known, but both factors are probably responsible. At first there is a wall of leukocytes and round cells
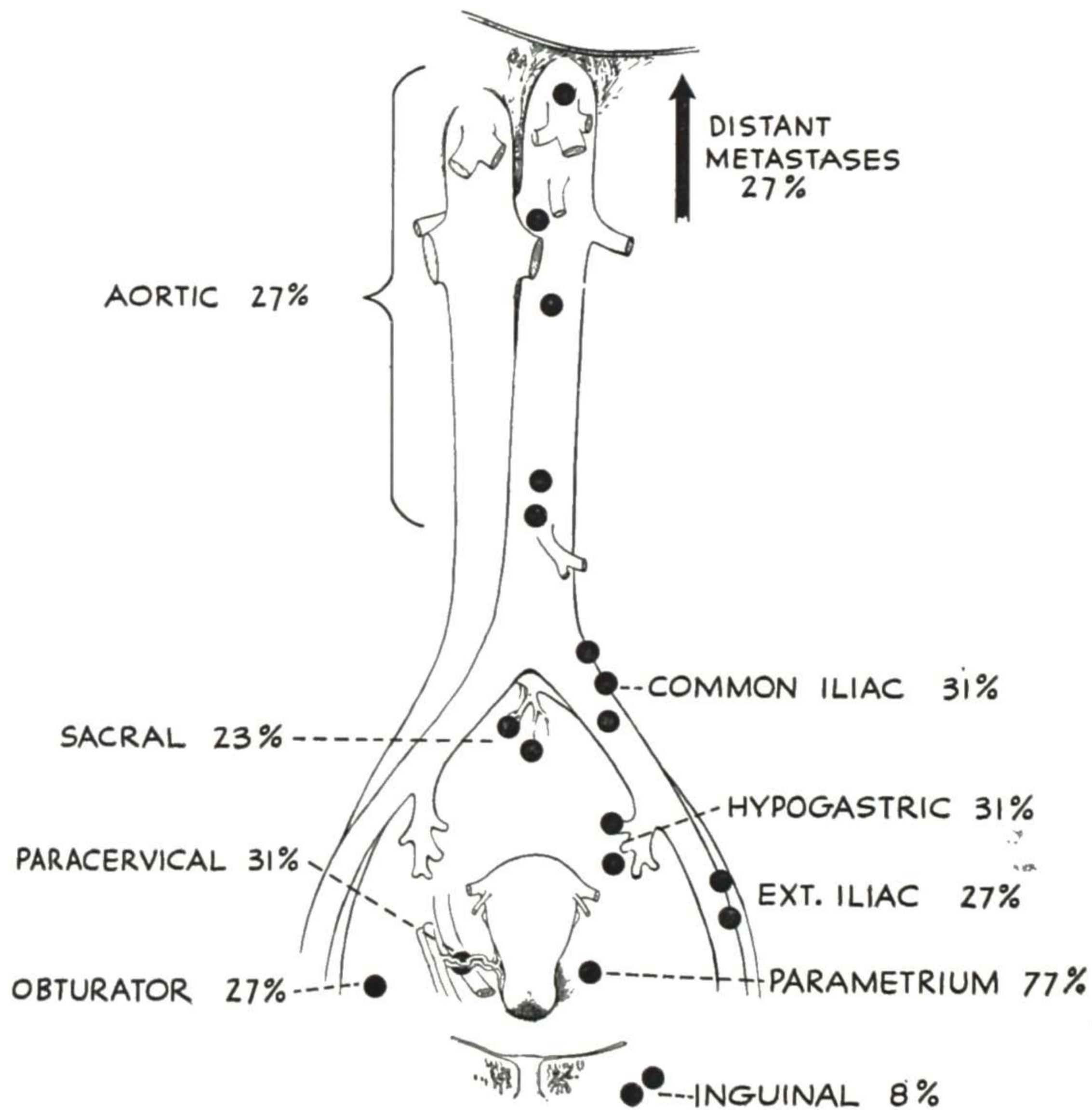

Fig. 664.—Incidence of node group involvement in twenty-six nontreated cases of cervical carcinoma. (From Henriksen: Am. J. Obst. & Gynec., November, 1949.)

surrounding the area, and later fibroblasts also help in the attempt to resist and wall off the growth. The induration felt on examination is due to a combination of these factors and the infection present. As will be noted later, the effect of local radiation is reduced by this infected bed, hence as a rule x-ray treatment is given before radium is used locally.

INTRA-EPITHELIAL CARCINOMA OF THE CERVIX

The possibility of detecting early changes in normal tissue which would eventually result in malignant invasion was, until recently, denied by most pathologists. There was general agreement that cancer had no infancy nor adolescence but that there was a sudden metamorphosis from a normal cell to

a malignant one. This process was a very rapid one and the criterion which determined whether or not the condition was benign or malignant was penetration of the basement membrane and invasion of the underlying tissue.

Research in animals demonstrated that many factors are involved in the development of malignant change in normal tissue. It was also shown that
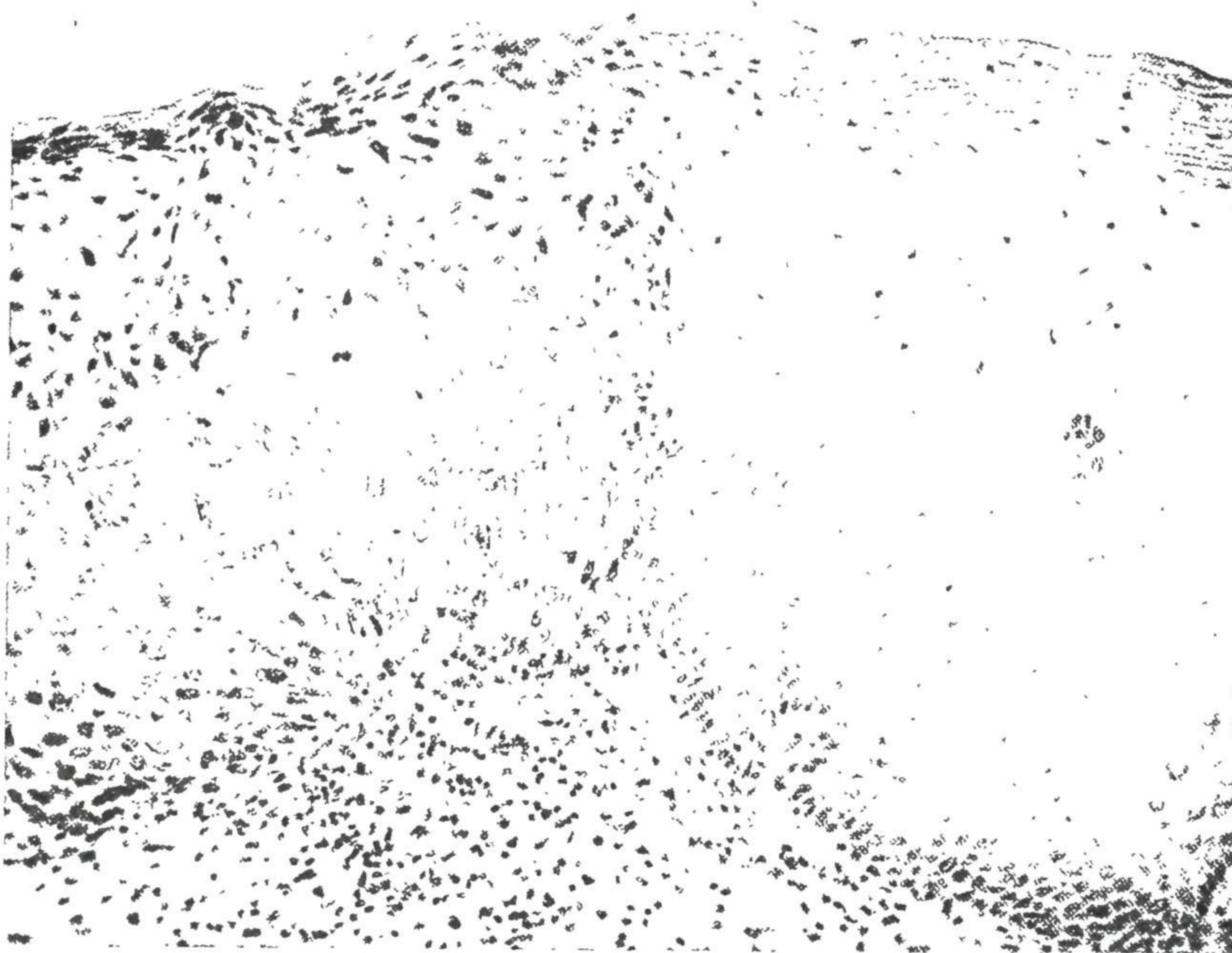

Fig. 665.—Demonstrating an abrupt perpendicular change between abnormal and normal epithelium. (From Galvin: Radiology, June, 1950.)

Fig. 666.   Fig. 667.
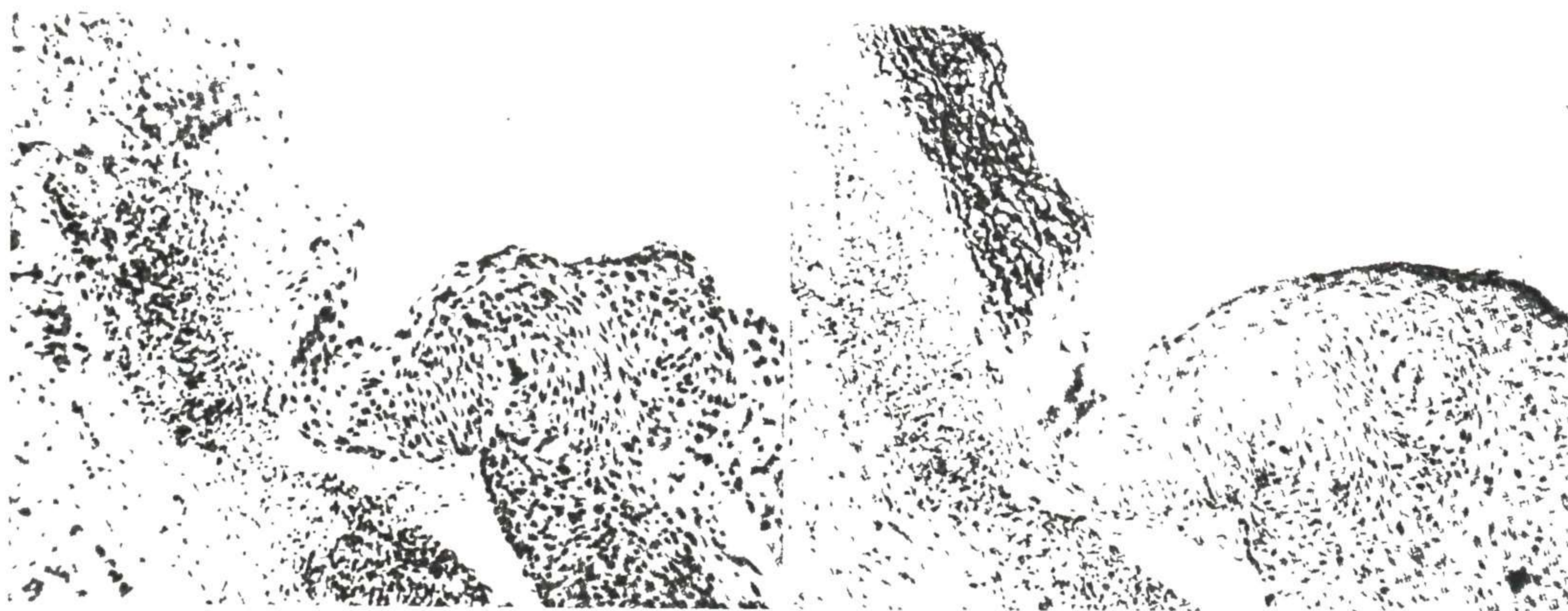
Fig. 666.—The carcinoma in situ is seen to the right, the normal epithelium on the left. Demarcation is by the short oblique line of Schiller. (Hematoxylin and eosin stain.)

Fig. 667.—The PAS reaction has been applied to the field corresponding to Fig. 666. The total absence of glycogen in the hyperactive area to the right is demonstrated.

(From McManus and Findley: Surg., Gynec. & Obst.)

when a carcinogenic agent is used, it must act over a long period of time before invasion occurs. During this latent period the tissue does undergo changes, such as hyperplasia, which can be detected microscopically.
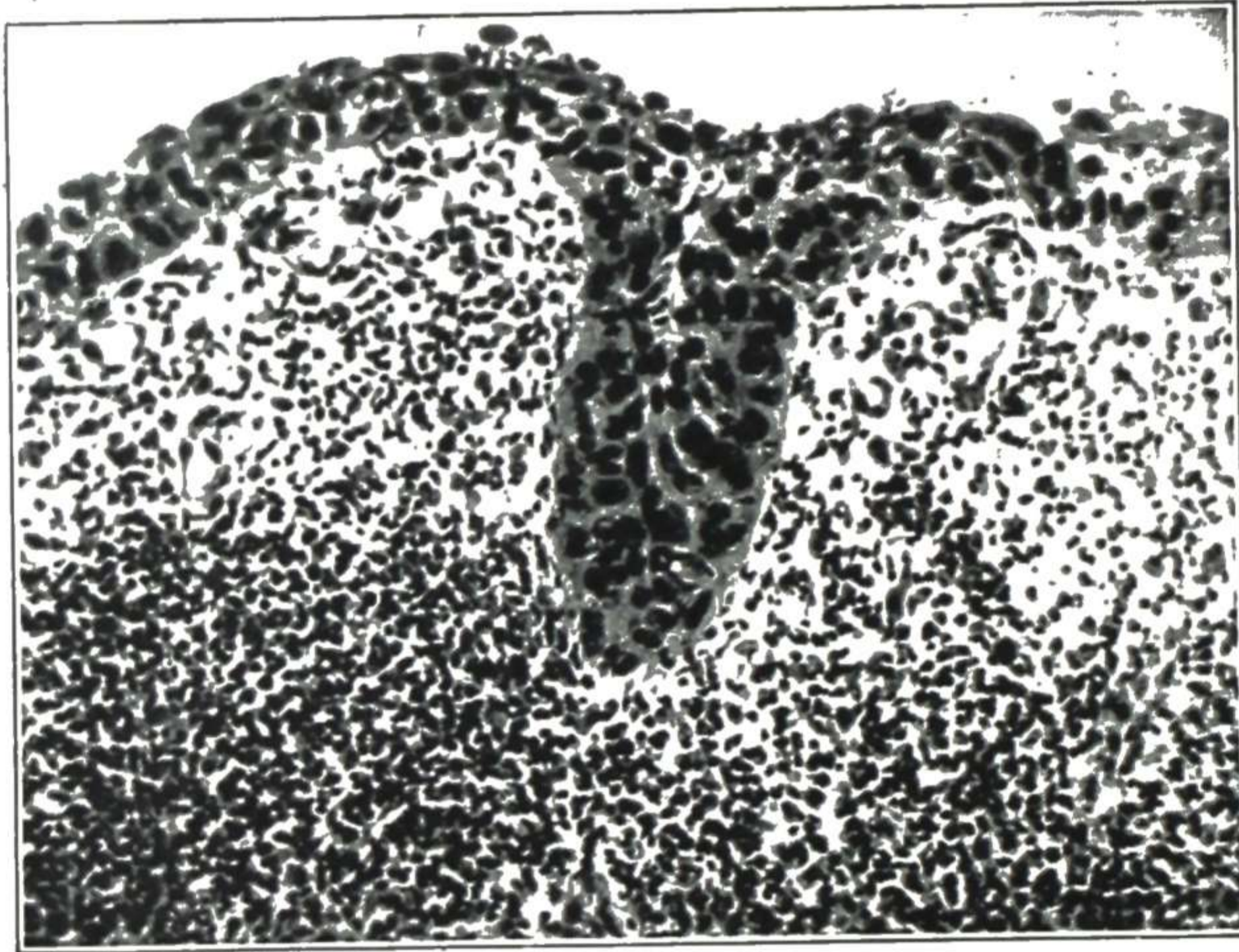

Fig. 668.—Squamous-cell carcinoma in situ of the uterine cervix, in which the carcinomatous cells have replaced the normal cells and are appearing to function in a protective manner. There is no penetration of the so-called basement membrane; therefore, according to older teaching, the growth would be considered noncarcinomatous, or, at most, only precarcinomatous. (From Broders: J. A. M. A.)
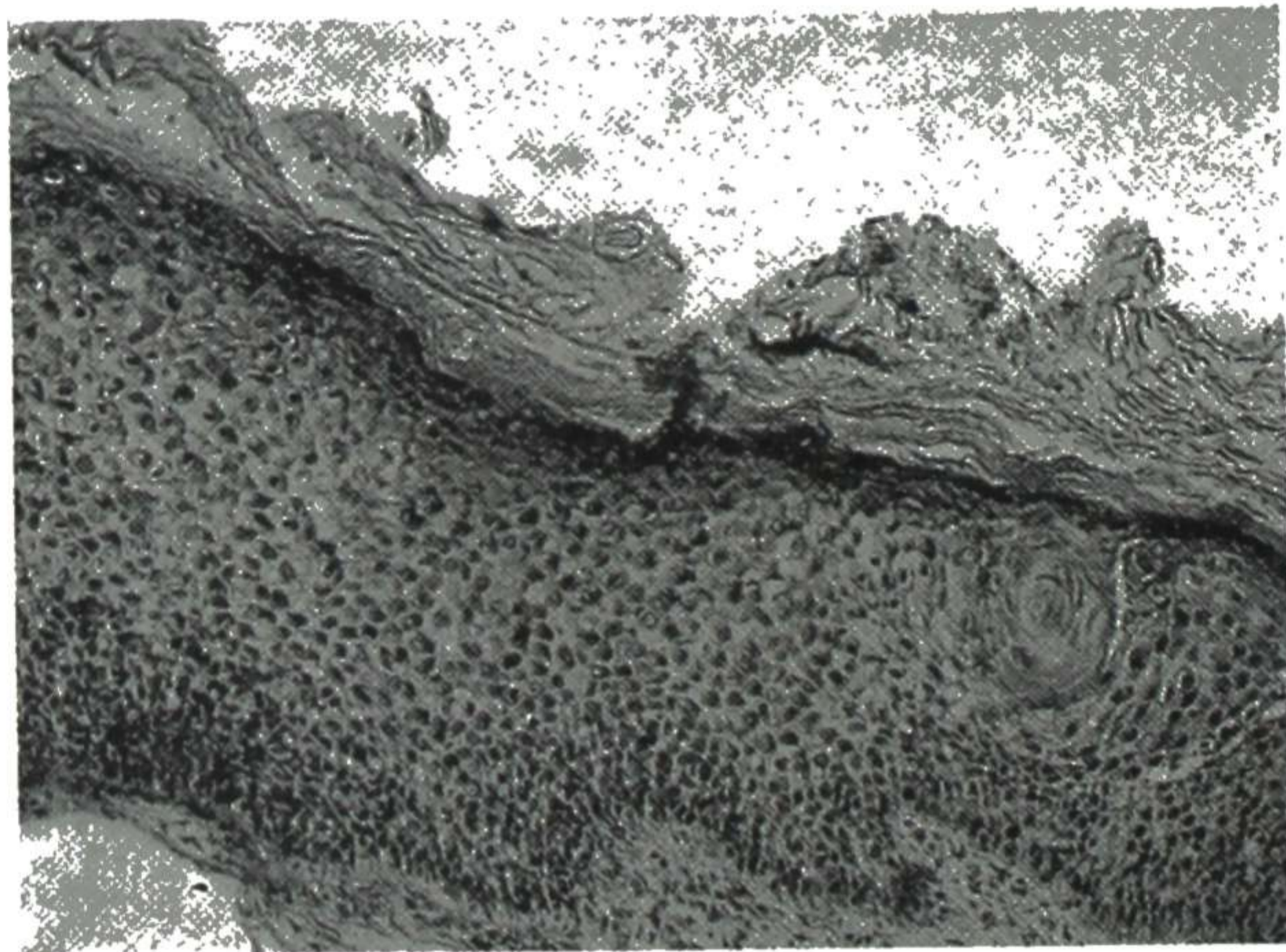
Fig. 669.—Intra-epithelial carcinoma, without invasiveness but with loss of normal stratification, hyperkeratosis, an attempt at pearl formation and definite anaplastic cell changes, with frequent mitosis. This picture is often spoken of as Bowen's disease of the cervix, from an assumed analogy with Bowen's disease of the skin. (From Novak: J. A. M. A., April 3, 1937.)

Clinically the dermatologists have for years recognized that certain skin diseases such as Bowen's disease, leukoplakia of the vulva, and certain papillomas will in a large percentage of the cases develop into cancer. It is not surprising that dermatologists should be among the first to use the term precancerous, for they were able to observe the process of carcinogenesis in the skin. For many years these changes of hyperplasia or atrophy and other

cellular changes were considered peculiar to the skin and many eminent pathologists maintained that no such progressive pathologic changes preceded the development of cancer in other organs.

Cramer, in an article on "The Origin of Cancer in Man, sums up the evidence for the existence of precancerous conditions in man as follows: "Since it has been demonstrated experimentally that carcinogens, to produce their effect, require prolonged periods of time during which the tissue on which they act undergoes a series of pathologic changes, and since, as explained previously, the characteristic age incidence of spontaneous cancer in man and animals finds an explanation in the long period of induction, the existence of a precancerous condition has established itself as a fairly general phenomenon in the origin of cancer. It has encouraged clinicians and pathologists to search for such conditions in different organs."
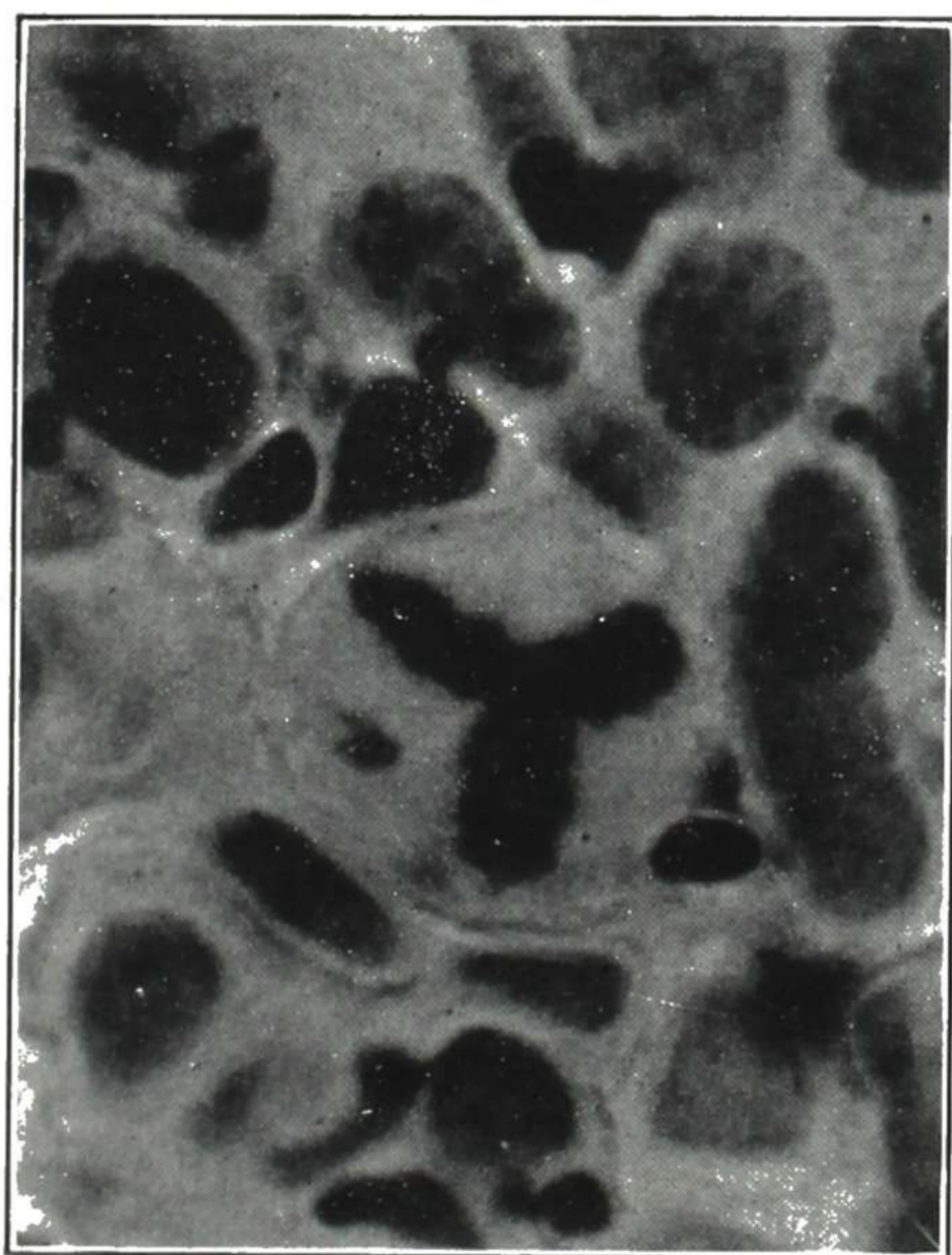

Fig. 670.—Abnormal mitoses. The photomicrograph to the left shows the so-called "Y" type of mitosis, and the one to the right shows the "H" type. In the case presenting these mitoses, the specimen consisted only of scrapings from the suspicious area of the cervix, and there was no piece of tissue large enough to show relations. The diagnosis had to be made from the cell characteristics, and these abnormal mitoses aided materially in the diagnosis of malignancy. The condition proved to be a squamous-cell carcinoma. Gyn. Lab.

The history of intra-epithelial carcinoma of the cervix is not new, for as early as 1908 Shottländer and Kermauner noted that a surface layer of malignant cells was frequently found at the periphery of an invading carcinoma, and they felt that this was the process by which the carcinoma advanced. Norris emphasized the sharp line of demarcation between the normal epithelium and the early malignant stage (Fig. 665). The fact that the malignant cells do not contain glycogen is shown in Figs. 666 and 667, taken from an article by McManus and Findley. Shiller after an exhaustive study concluded that intra-epithelial carcinoma was the precursor of invasive carcinoma. Broders in 1932 described the so-called carcinoma in situ in which the normal

Fig. 671.
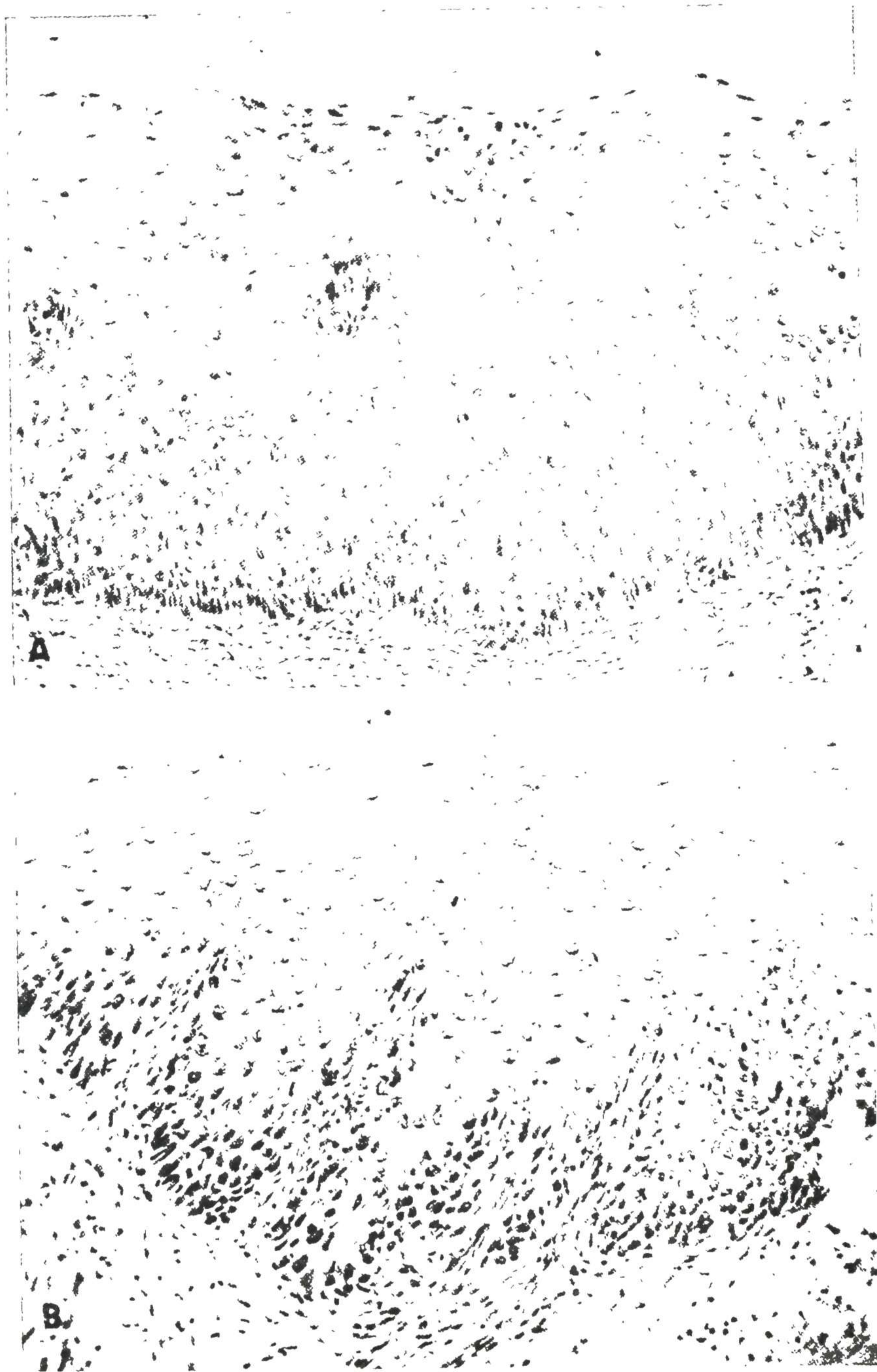
Fig. 672.

Figs. 671 to 674.—Successive biopsies taken over a period of fourteen months in a case in which invasive carcinoma eventually developed.   (From Galvin: Radiology, June, 1950.)

Fig. 671.—First biopsy shows basal cell hyperactivity.

Fig. 672.—Three months later, same condition but more marked.
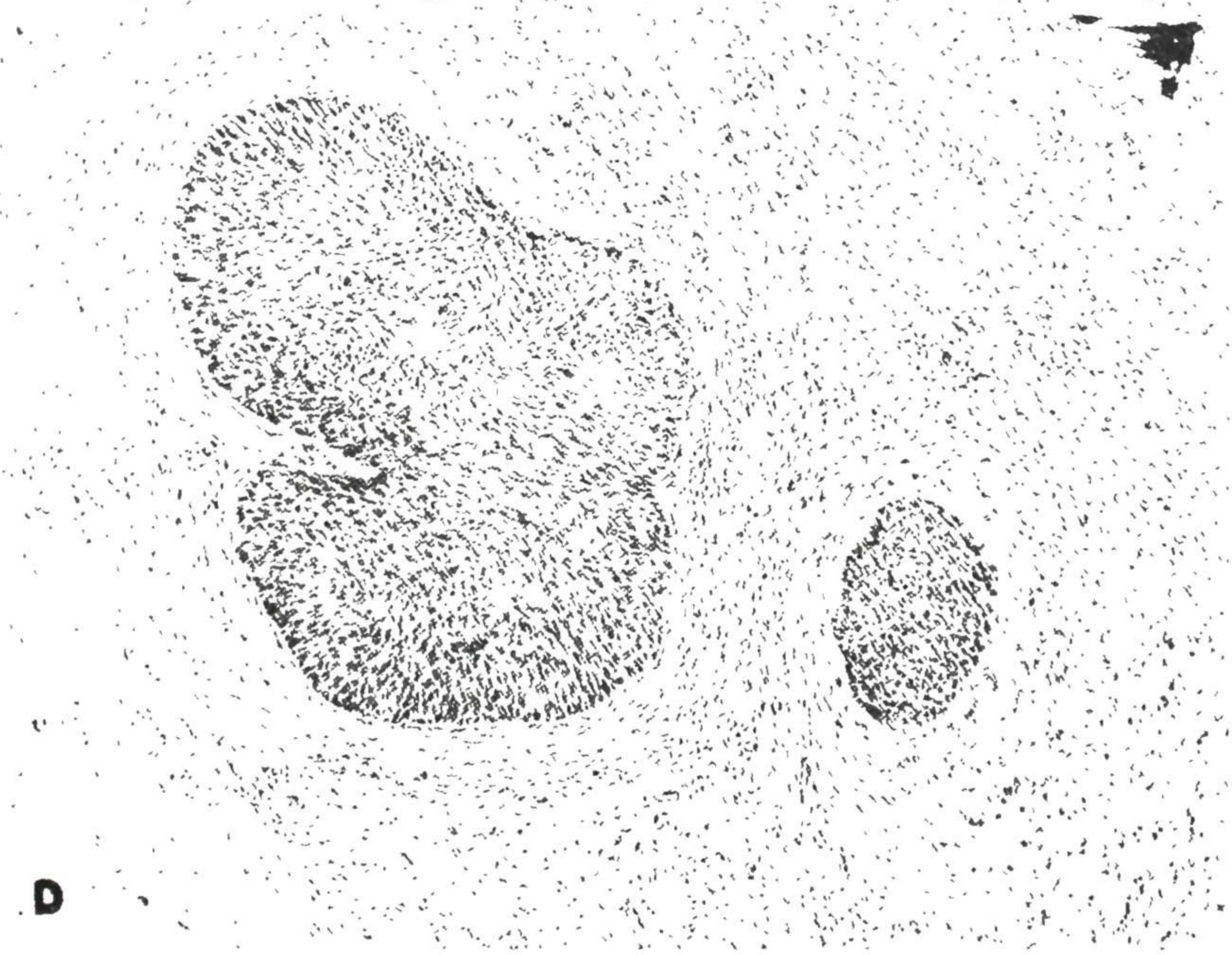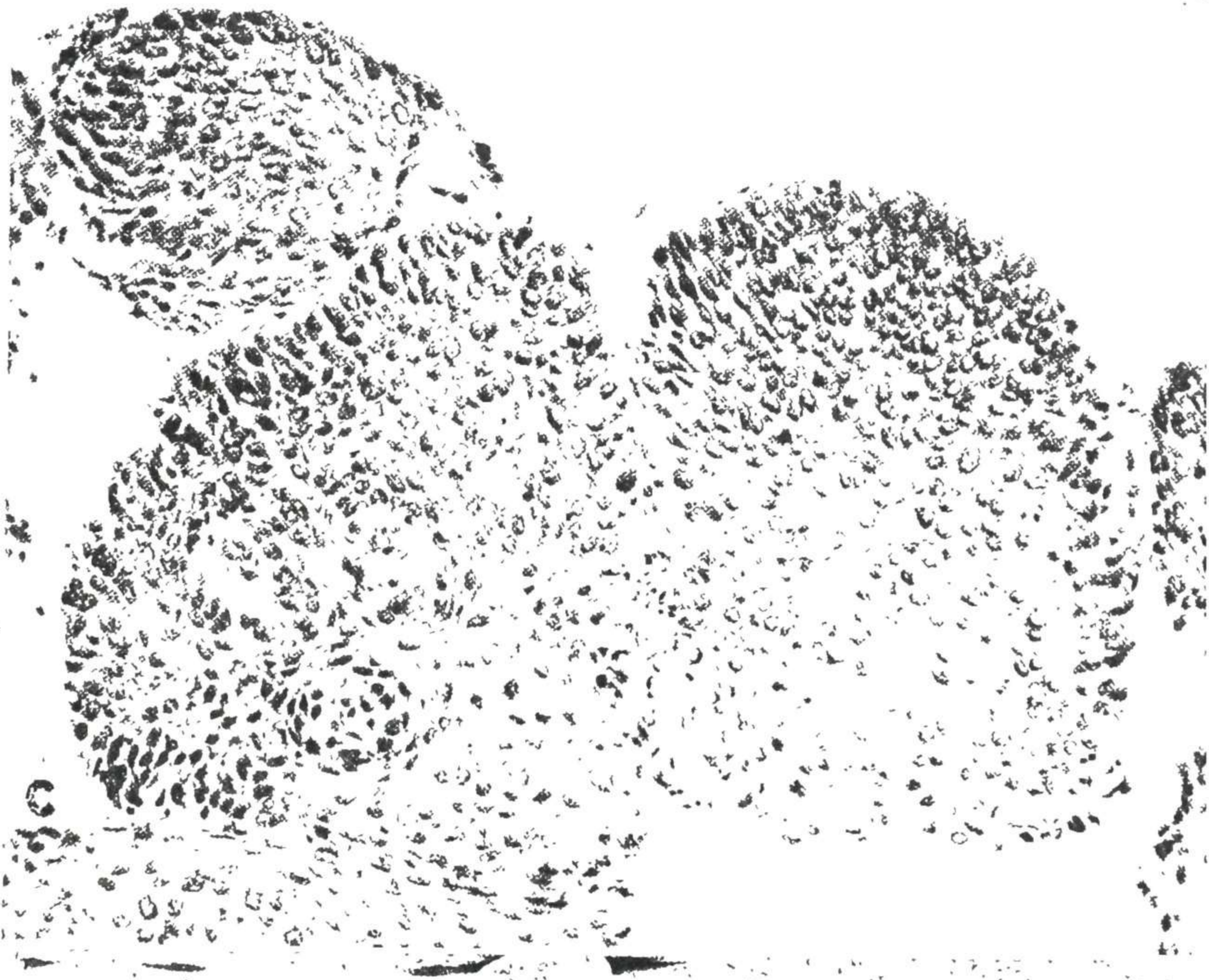
Fig. 673.

Fig. 674.

Fig. 673.—Seven months after original biopsy, definite intracellular carcinoma.

Fig. 674.—Fourteen months after original biopsy, islands of carcinomatous tissue deep in cervical stroma.

Fig. 671.
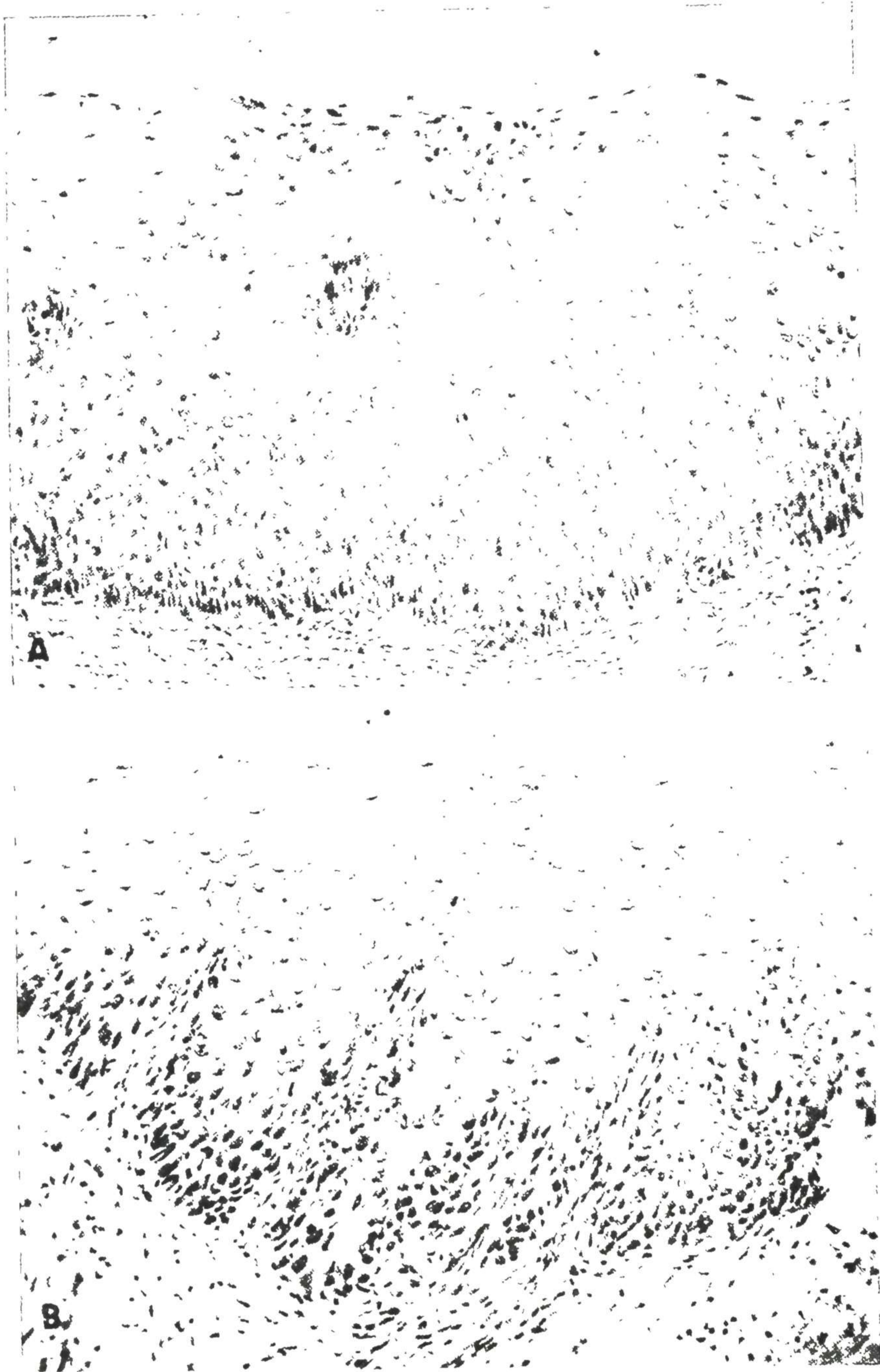
Fig. 672.

Figs. 671 to 674.—Successive biopsies taken over a period of fourteen months in a case in which invasive carcinoma eventually developed. (From Galvin: Radiology, June, 1950.)

Fig. 671.—First biopsy shows basal cell hyperactivity.

Fig. 672.—Three months later, same condition but more marked.

Fig. 673.

Fig. 674.

Fig. 673.—Seven months after original biopsy, definite intracellular carcinoma.
Fig. 674.—Fourteen months after original biopsy, islands of carcinomatous tissue deep in cervical stroma.

The causes for mistakes in interpretations of intra-epithelial carcinoma have been investigated by Edmund R. Novak and Galvin. In the gynecological patho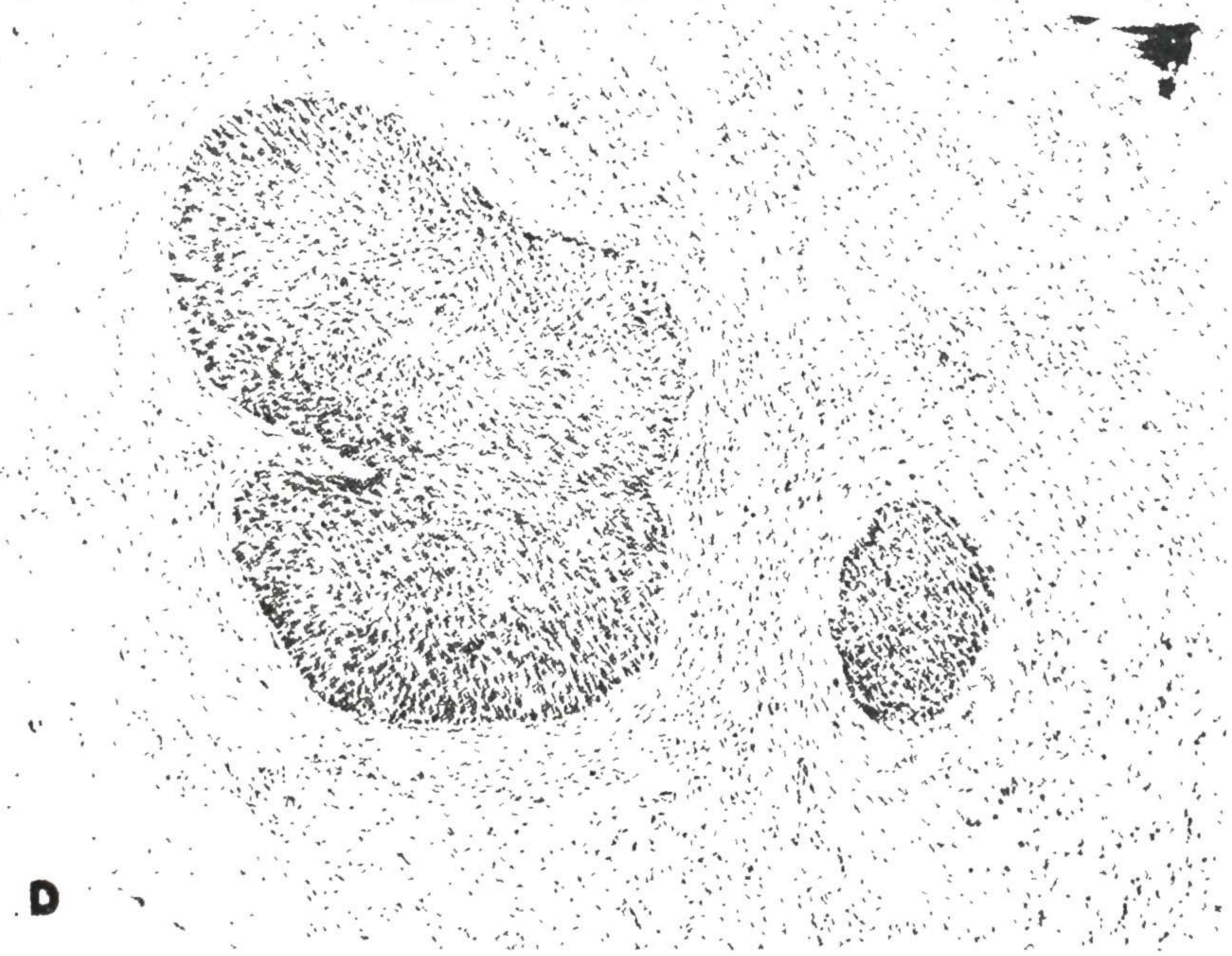logy department at Johns Hopkins Hospital they found twenty-five cases in which the preoperative diagnosis of intra-epithelial carcinoma was not confirmed by laparotomy, and they emphasize the importance of establishing the diagnosis beyond a doubt before instituting radical therapy.

EARLY DIAGNOSIS

It is estimated that in the year 1950 there were 17,066 new cases of uterine cancer seen in this country. Although we are making slow advance in the salvage from this disease by improvement in treatment, early diagnosis is the real keystone to any sizable reduction in mortality of cervical carcinoma; from 75 to 90 per cent of the early cases can be saved by adequate treatment.

What then has been the cause of the delay in early diagnosis? This problem was the subject of an exhaustive study made by a group of physicians in Philadelphia, composed of specialists and general practitioners. A report on this study of 1,140 cases of pelvic cancer was made by Howson and Montgomery. It was found that there was a delay of a month or more in 71.8 per cent of the cases of pelvic cancer. The patient delay, which is counted as the time elapsed between the appearance of the first symptom to the securing of medical advice, amounted, in the case of cervical cancer, to 56 per cent of the total causes for delay. Thanks to the excellent programs of the American Cancer Society and allied organizations, including the national and local medical societies, the patient is being educated to the fact that local evidence of cancer may exist for months or even years before symptoms appear. Patients are beginning to appreciate the importance of a pelvic examination twice a year as a safeguard against conditions leading to carcinoma. The checkup is especially important in the danger zone between the ages of forty and sixty years, but it is also important in younger women who have had children, for we now know that cervical cancer can occur at any age, and non-invasive carcinoma occurs at an average age of thirty-six years.

Let us assume that the enlightened patient has presented herself for examination. The problem of early diagnosis is now up to the physician, and the patient's future depends not only upon his knowledge and ability but also upon his scientific curiosity and perseverance in carrying out a thorough search for conditions which may indicate carcinoma or predispose to its development. The degree to which we as physicians have failed to assume this responsibility is brought out by the fact that, in the study mentioned, the physician was wholly responsible for the delay in the diagnosis of cervical carcinoma in 14.9 per cent of the cases and he shared responsibility with the patient in 12.9 per cent, making a total of 27.8 per cent. The average duration of the physician delay was 7.4 months. The appalling fact that the delay was due to a failure to examine the patient vaginally in 49.3 per cent of the cases shows where the emphasis must be placed if the results are to be improved. It is interesting to note that the general practitioners were not the only ones responsible for delay, for there were 28 cases of delay on the services of the Philadelphia hospitals,

From this study and from similar studies made in other centers, it is evident that the weak spot in the attack on the problem is the period of silent growth in the undiscovered lesion before therapy is instituted. What can we as physicians do to correct our failure in this prevention program? The obvious answer is, first and above all, to include an adequate pelvic examination in every case. This can be done by any physician who has a speculum, a good light, a healthy curiosity, and an earnest desire to give the patient the full benefit of his knowledge. It is easy for gynecologists to give lengthy papers on this subject with a full discussion of numerous techniques for early diagnosis of cervical carcinoma, together with statistics, but this leaves the average physician not only confused but also frustrated, with the result that he does nothing about it.

It is important to know that in large centers where routine smears for uterine cancer have been taken on all patients, the accuracy of diagnosis runs as high as 98 per cent. Many unsuspected cases of early noninvasive cervical carcinoma have been discovered. From a practical standpoint it is also important to add that because of cost and lack of nationwide facilities this test at the present time cannot be applied to the population as a whole. If in the future these diagnostic centers can be made a part of state and municipal public health programs as the Wassermann laboratories are at present, screening of the entire population may become a reality. Until such a time as this ideal is realized, we should have a practical plan of attack which can be used today by any physician.

Plan of Examination

First, let me reiterate that we will never know the condition of the pelvis if we do not do a pelvic examination; as mentioned, 51 per cent of the neglected cases might have been saved if the physician had taken the pains to look at the cervix. Rectal and rectovaginal examination should also be done, as induration in the parametrium may indicate malignancy in the canal which cannot be seen on the surface of the cervix.

In determining the diagnostic procedures to be done, let us divide the types of cervices seen through the speculum into three groups: the normal-appearing cervix; the cervix having a small erosion, eversion, or superficial cysts; and, last, the cervix with extensive cervicitis and deep cysts.

A. Normal-Appearing Cervix.—In cases with a normal-appearing cervix a smear is indicated under the following circumstances:

1. Persistent discharge.
2. Spotting at irregular intervals.
3. Bleeding when surface or canal of cervix is wiped with cotton swab.
4. An unusual incidence of cancer in family history.
5. Request for a smear.

If such a plan is followed in cases with a normal-appearing cervix, most of the early unsuspected cases of cancer will be discovered and certainly the number of such cases missed would be less than the number of false negative reports which one would obtain with routine smears in every case.

B. Small Erosions, Eversions, or Superficial Cysts.—This second group includes those cases in which there is some visible lesion requiring office treatment, such as eversion, erosion, or a few superficial Nabothian cysts. In this group we should also have definite indications for special diagnostic procedures.

A smear or a biopsy or both are indicated in this group of cases under the following circumstances:

1. Any of the special conditions enumerated under the normal-appearing cervix.

2. Cervical lesions which do not clear up promptly under treatment.

3. Suspicious areas should be biopsied, with the full understanding as to the limitations of a biopsy. The Shiller test aids in determining the area to be biopsied and multiple biopsies are preferred.

4. Cases requiring repeated treatments should be handled as outlined under the third group of cases.

C. Extensive Cervicitis With Deep Involvement.—In this third group are the cases of extensive chronic cervicitis and those cases which do not respond to ordinary office treatments. These cases should have an excision of the entire involved area either by the knife, such as a Sturmdorf operation, or by wide conization and suture. We prefer wide conization and have found no need for a "cold biopsy" in these cases. If the proper setting of the high frequency current is used and the cutting is done rapidly, the tissue is excellent for microscopic examination.

Regardless of the method used, the purpose of the procedure is to obtain all of the tissue for examination, including the junction of the squamous and columnar epithelium, and at the same time to remove the chronically infected tissue with its cancer-potential factors. The advantage of this procedure in reducing the incidence of cancer will be discussed later under Prevention.

Diagnostic Techniques

Smear.—There are several methods of obtaining and preparing the material for a vaginal smear, and the one used will depend upon the facilities available.

If the available laboratory is accustomed to the paraffin section technique, there are several methods which may be used to obtain the tissue. The area about the external os may be scraped with a tongue depressor or, if preferred, special scrapers have been designed by Ayre and by Novak for removing the superficial cells in this area. Doyle has designed a vaginal spoon which is left in the vagina overnight so as to obtain a "total uterine sample." Gladstone obtains a specimen by rubbing the cervical surface briskly with a piece of "Gelfoam."

Regardless of the method, the tissue obtained is placed in formalin for fixation and then blocked in paraffin, cut, and stained as usual (Fig. 676).

If facilities for diagnosis of a Papanicolaou smear are available, the smear may be taken in several ways. A specimen of the secretion from the vagina or the cervical canal can be aspirated by a syringe, or any of the methods mentioned above may be used except Gelfoam. A thin smear is made on a

clean, dry slide, and this is dropped immediately, while still moist, into a solution containing equal parts of 95 per cent ethyl alcohol and ether.

If no laboratory is available the slide may be mailed to a diagnostic center. For mailing, the slide is left in the ether-alcohol solution for twenty-four hours, then removed, and while still wet a large drop of glycerin is placed on the smear and a second slide is pressed firmly over the smear. The slides can then be placed in a container and mailed, together with a history of the case.

Fremont-Smith and Ruth Graham have recently reviewed the literature up to 1951 in regard to the use of the vaginal smear as a screening test. In 704 consecutive new women patients coming to the office of an internist, pelvic cancer was detected by the vaginal smear in 10 cases (1.4 per cent).

Biopsy.—This may be taken with any of the numerous types of instruments used for this work. It is important to take several specimens from dif-
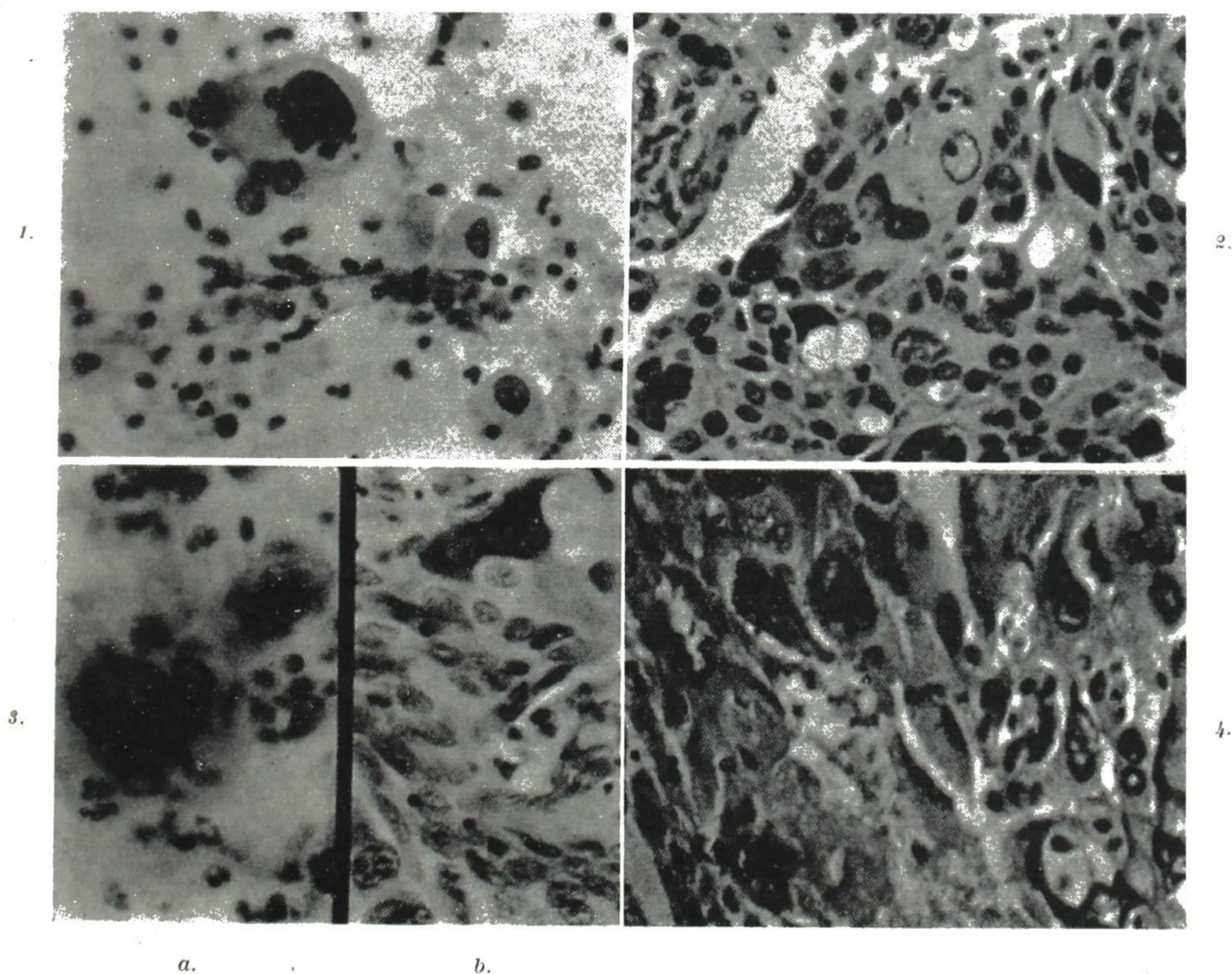
Fig. 676.—*1*, Cervical cytology smear showing cancer cells aspirated from the external os in a case of squamous carcinoma of the cervix. Note the extreme nuclear variability.

2, Tissue biopsy in same case of squamous carcinoma of cervix. Observe the same cellular variability as seen in the smear.

3, a, Cervical cytology smear in case of 26-year-old woman admitted to the ward bleeding. Note bizarre cell with nuclear multilobulation.

3, b, Tissue biopsy from same case of squamous carcinoma of cervix showing the same types of cells in the tissue.

4, Centrifuge cytology technique showing large numbers of malignant cells segregated by the centrifuge. This is not a biopsy but simply an aspiration of the cervical secretions. (High power.)

(From Ayre: Am. J. Obst. & Gynec., June, 1946.)

ferent areas in the junction between the squamous epithelium of the portio and the cuboidal epithelium of the cervical canal.

The details of smear and biopsy are more fully discussed in Chapter 11. The important point in diagnosis is to have a practical plan of examination with definite indications for smear or biopsy and to use it in daily practice.

PATHOLOGY OF ADENOCARCINOMA

This type of cancer of the cervix arises from the columnar epithelium lining of the cervical canal and its glands. In a recent review of 15,476 cases of cervical carcinoma collected from the literature, Hepler et al. found that 4.5 per cent were primary adenocarcinomas of the cervix.

Fig. 677. Fig. 678. Fig. 679.
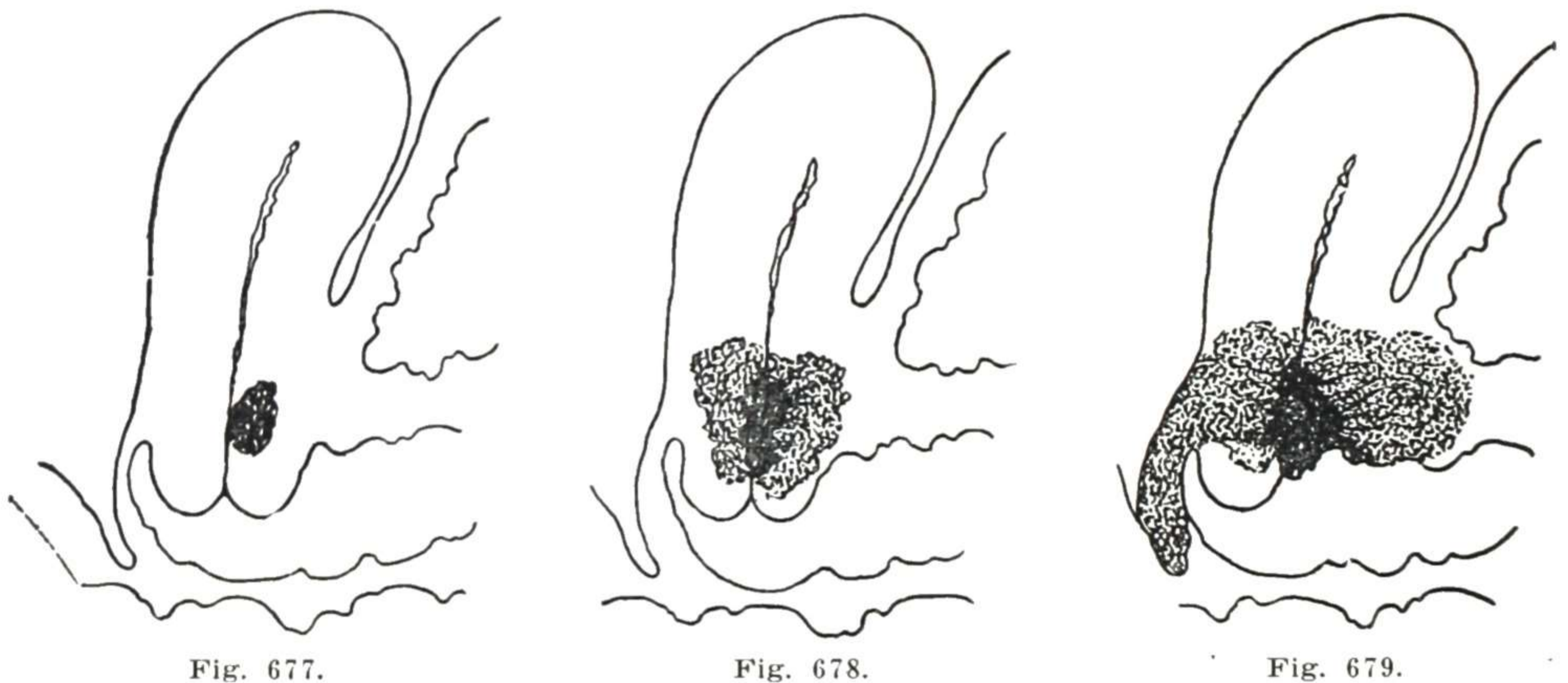
Figs. 677 to 679.—Progressive development of an adenocarcinoma of the cervix. Fig. 677 originates from a gland within the cervix, in contradistinction to squamous carcinoma which originates from the squamous epithelium on the vaginal portion. Fig. 678, Extension throughout the greater part of the cervix. Fig. 679, Extensive involvement of pericervical tissues.

As adenocarcinoma is inside the cervix (Figs. 677 to 679), its presence is not appreciated until it has advanced sufficiently to cause bleeding or discharge which leads to investigation inside the cervix. The disease runs much the same general course as described for squamous-cell carcinoma, the cancer cells penetrating deeper and deeper into the cervix and out into the parametrium. After a time the cancer may extend to the external os, as a small swelling or as a papillary projection. The induration gradually extends and in time the pelvis becomes occupied by a firm fixed mass of infiltrated tissues, involving the parametrium to the pelvic wall and the rectum and the bladder. In some cases the ureters are gripped and constricted. Various stages in adenocarcinoma are shown in Figs. 677 to 682. Occasionally the cervical canal becomes completely blocked, with pyometra above from the accompanying infection.

Microscopic Pathology.—Adenocarcinoma of the cervix arises from the cylindrical cells lining the interior of the cervix and forming the cervical glands. It may then in the beginning be located near the external os in the cervical canal or in any part of a gland extending deeply into the cervical wall. As the cell columns penetrate the underlying tissues, the cells assume

Fig. 680.
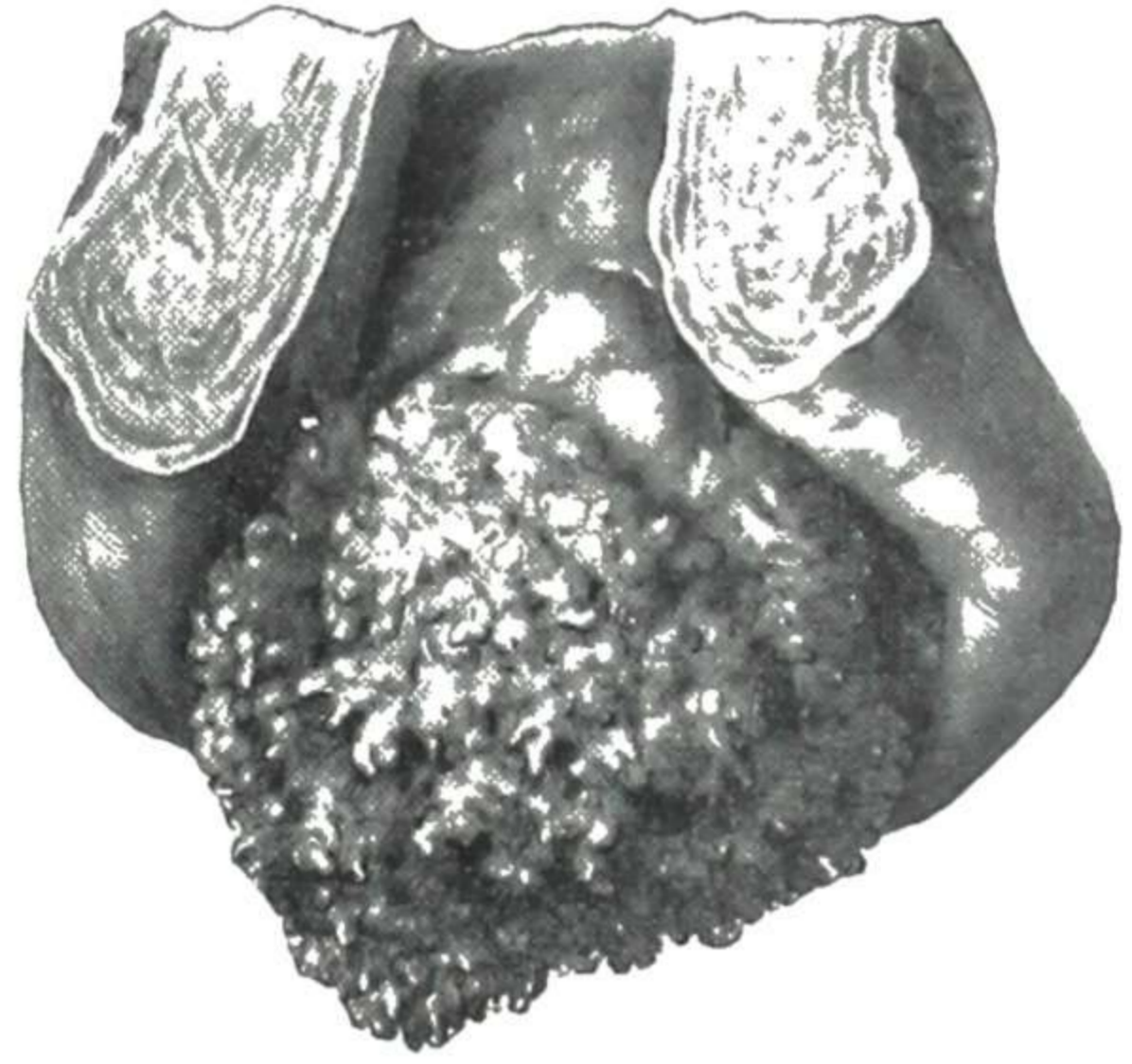
Fig. 681.

Fig. 680.—Adenocarcinoma of the interior of the cervix. A small swelling at the widened external os. (From Sampson: Bull. Johns Hopkins Hosp.)

Fig. 681.—Drawing from an adenocarcinoma of the cervix forming a small projecting papillary mass. Part of the cervix has been removed to show the connection of the papillary mass with the cervical wall. Gyn. Lab.
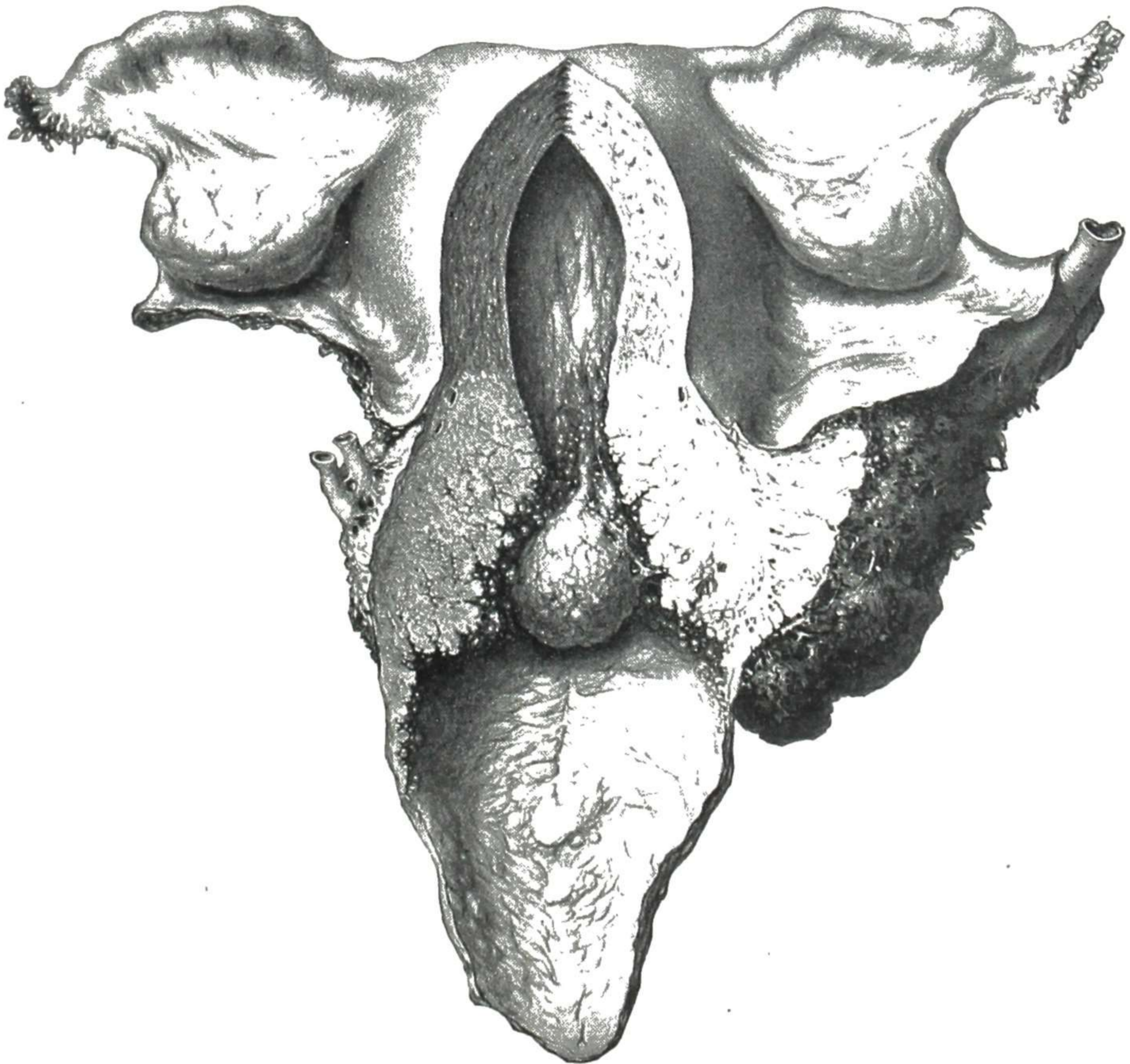
Fig. 682.—Still more advanced carcinoma of cervix (adenocarcinoma), ureters involved. (From Kelly: Operative Gynecology.)

e cervix uteri.   This photomicrograph is from the growing
and the carcinomatous glands in the same field.   Gyn. Lab.

ers metastasize early, because they are endophytic
ophytic (outgrowing on the surface).

noma creates a special diagnostic problem in that it
ch area is not visible on speculum examination. If
al show of blood or a discharge, with nothing about
e of cervix to account for it, the solution of the prob-
nely, to carry out fractional curettage and coniza-
e treatment for the bleeding or discharge, whether
rium or the cervical mucosa, and at the same time
or determining with certainty whether or not there
r location.

The other phase of this diagnostic problem is furnished by the patient who comes simply for a safety check-over and has no bleeding or discharge or other evidence of trouble in vagina or uterus. Of course we have been inclined hitherto to feel that, with the vagina and vaginal portion of the cervix free of irritation on inspection and no indication of trouble higher, we could safely assure the patient of normal conditions. But developments have raised a serious doubt.

If, on wiping the cervical canal with a cotton swab, bleeding occurs in patients who are not in the premenstrual period, a smear is indicated. The Papanicolaou or the Doyle method is used, and if there is still doubt a fractional curettage with conization is indicated. By these the early noninvasive lesions may be discovered.

TREATMENT

In this volume only an outline of the principles of treatment will be given; a more complete and detailed discussion is given in *Operative Gynecology.*

In 1934 Dr. H. S. Crossen was requested to submit an article on the radical operation for cancer of the cervix. This he declined to do because he felt that emphasis on this type of treatment would merely help to undo the immense amount of painstaking effort that he and others had done to convince doctors in general that radiation of cervical carcinoma had supplanted operation as the best method of treatment. In response to his refusal, Dr. Livingston, the Editor of the *American Journal of Surgery,* then asked him to write an editorial on the treatment of cancer of the cervix; the editorial is given below. It should be remembered that this was written before we had the many recent aids to abdominal surgery, such as antibiotics and blood banks.

The most important advance in the treatment of cancer of the cervix is the shift from operation to irradiation. This change has been going on gradually for some years, and is now almost complete among the leaders in gynecologic work. Even those few who still employ radical operation do not depend on the operation but use irradiation also in some form to reach the outlying cancer cells.

Despite the variety of classifications used and the consequent difficulties of critical comparison of results from operation and from irradiation, there is already apparent a definite statistical balance of cure-rate in favor of irradiation. And that is only part of the story. The radical operation has been developed practically to its limit, while irradiation is young and still developing rapidly. Again, irradiation can rescue many patients who have passed far beyond the reach of operation. Again, when depending on radical operation it is necessary in even the earliest case of cancer of the cervix to subject the patient to very grave risk, whereas with irradiation the patient is given a better chance of cure with much less risk in all stages.

My conclusions in this important matter were not reached hastily, but through critical study and a long experience of practical participation in radical operative treatment and in radical irradiation treatment for this disease. I deal with the subject from the standpoint of the practicing surgeon, anxious to give his patient every possible chance for life. There should be no antagonism of the surgeon to radium. It is simply another helpful instrument added to his armamentarium.

Effective irradiation treatment of cancer of the cervix is serious and hazardous surgical work. The shift of instruments from the knife to the more deeply penetrating radium does not lessen the surgical responsibility. If the dosage employed is too large for the particular conditions present in the pelvis, serious injury to important organs may result. If the dosage is too small, the patient is not given the chance for life to which she is entitled. The maximum dosage possible in a given case depends on a number of factors, in-

cluding the location and size of the cancerous mass, the amount of involvement of each of the organs in the immediate vicinity, the extent and direction of ulceration, and the amount of fixation of the bladder and rectum by the carcinomatous infiltration. The accurate determination of these conditions and the utilization of that knowledge in effective radium treatment require a large amount of experience and skill in pelvic work. While in some situations the radiologist without special local knowledge may give effective radium treatments, in carcinoma of the cervix conditions are such that the most effective treatment can be given only by one with special gynecologic training as well as radium training. His special knowledge of pelvic anatomy and pathology and his training in accurate pelvic palpation and diagnosis must all be utilized in the supreme effort to reach the marginal cancer cells with effective radiation.

There is a tendency among the inexperienced to regard the use of radium lightly. This tendency is encouraged by some of the radium-rental instructions given by commercial companies, which presume to fit the recipient for the safe and effective use of this dangerous instrument. It would be as reasonable to suppose that instructions issued with a scalpel would fit the recipient to use it safely and effectively in the eradication of cancer. Radium is as potent as the knife, and in inexperienced hands may produce as disastrous results, either in the form of injury to adjacent organs or as failure to save a life which might have been saved by effective use.

Of course, irradiation treatment does not exclude any work with the knife which may be helpful. In special conditions some vaginal operation or abdominal operation may permit more advantageous placing of the radium in its various forms. The important point in regard to any operative work employed is that it should supplement irradiation and not displace it. Another important point is that any experimental work, not established by a record of five-year cures, should be presented as experimental only. Otherwise it may be accepted and used by the uninitiated as an established method of cure.

The most pressing problem just now is to bring the benefits of radical irradiation treatment to patients generally. The spread into general practice of this most effective treatment for this disease is very slow. There are reasons for this. In the first place, cancer of the cervix is very deceptive as to the extent of the lesion and the depth of penetration. What appears to be an early cancer of the uterus is really already a cancer of the outlying pelvic structures, for whose elimination hysterectomy as ordinarily performed is but a futile gesture.

A second stumbling block to the general adoption of the most effective treatment is that many physicians find it difficult to understand how any other treatment could be more effective than operative removal. Now, while operative removal is effective as far as it goes, in most cases of cancer of the cervix it cannot go far enough to remove the outlying cancer cells. When only one patient in four can be saved by the most radical operation by the most experienced pelvic surgeons, what chance of cure has the patient with this widespread disease when subjected to operation by an operator inexperienced in this deep work in this difficult situation? The result as a rule is removal of little more than the uterus, leaving the deeper portions of the growth to progress and eventually cause death. Dependence on such incomplete operation deprives the patient of the chance for life which modern treatment would give her.

The treatment given patients with cancer of the cervix in any community is determined largely by the surgeons of that community. In every case the decision as to the type of treatment is a serious matter, for it may mean the difference between life and death for that patient. Hence the importance of the clear presentation, by the educational agencies of the profession, of the superiority of expert radical irradiation for this disease.

It seems to me that the clearness of such educational presentation and its effect in securing such treatment for these patients are both diminished by coincident attractive delineation of the radical operation, with its wealth of pictorial detail which appeals so strongly to the uninitiated. Actions speak louder than words, and my feeling as to the importance of this matter is shown by my declining . . . an invitation to present the radical operation for the symposium in this issue.

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The other phase of this diagnostic problem is furnished by the patient who comes simply for a safety check-over and has no bleeding or discharge or other evidence of trouble in vagina or uterus. Of course we have been inclined hitherto to feel that, with the vagina and vaginal portion of the cervix free of irritation on inspection and no indication of trouble higher, we could safely assure the patient of normal conditions. But developments have raised a serious doubt.

If, on wiping the cervical canal with a cotton swab, bleeding occurs in patients who are not in the premenstrual period, a smear is indicated. The Papanicolaou or the Doyle method is used, and if there is still doubt a fractional curettage with conization is indicated. By these the early noninvasive lesions may be discovered.

TREATMENT

In this volume only an outline of the principles of treatment will be given; a more complete and detailed discussion is given in *Operative Gynecology*.

In 1934 Dr. H. S. Crossen was requested to submit an article on the radical operation for cancer of the cervix. This he declined to do because he felt that emphasis on this type of treatment would merely help to undo the immense amount of painstaking effort that he and others had done to convince doctors in general that radiation of cervical carcinoma had supplanted operation as the best method of treatment. In response to his refusal, Dr. Livingston, the Editor of the *American Journal of Surgery,* then asked him to write an editorial on the treatment of cancer of the cervix; the editorial is given below. It should be remembered that this was written before we had the many recent aids to abdominal surgery, such as antibiotics and blood banks.

The most important advance in the treatment of cancer of the cervix is the shift from operation to irradiation. This change has been going on gradually for some years, and is now almost complete among the leaders in gynecologic work. Even those few who still employ radical operation do not depend on the operation but use irradiation also in some form to reach the outlying cancer cells.

Despite the variety of classifications used and the consequent difficulties of critical comparison of results from operation and from irradiation, there is already apparent a definite statistical balance of cure-rate in favor of irradiation. And that is only part of the story. The radical operation has been developed practically to its limit, while irradiation is young and still developing rapidly. Again, irradiation can rescue many patients who have passed far beyond the reach of operation. Again, when depending on radical operation it is necessary in even the earliest case of cancer of the cervix to subject the patient to very grave risk, whereas with irradiation the patient is given a better chance of cure with much less risk in all stages.

My conclusions in this important matter were not reached hastily, but through critical study and a long experience of practical participation in radical operative treatment and in radical irradiation treatment for this disease. I deal with the subject from the standpoint of the practicing surgeon, anxious to give his patient every possible chance for life. There should be no antagonism of the surgeon to radium. It is simply another helpful instrument added to his armamentarium.

Effective irradiation treatment of cancer of the cervix is serious and hazardous surgical work. The shift of instruments from the knife to the more deeply penetrating radium does not lessen the surgical responsibility. If the dosage employed is too large for the particular conditions present in the pelvis, serious injury to important organs may result. If the dosage is too small, the patient is not given the chance for life to which she is entitled. The maximum dosage possible in a given case depends on a number of factors, in-

cluding the location and size of the cancerous mass, the amount of involvement of each of the organs in the immediate vicinity, the extent and direction of ulceration, and the amount of fixation of the bladder and rectum by the carcinomatous infiltration. The accurate determination of these conditions and the utilization of that knowledge in effective radium treatment require a large amount of experience and skill in pelvic work. While in some situations the radiologist without special local knowledge may give effective radium treatments, in carcinoma of the cervix conditions are such that the most effective treatment can be given only by one with special gynecologic training as well as radium training. His special knowledge of pelvic anatomy and pathology and his training in accurate pelvic palpation and diagnosis must all be utilized in the supreme effort to reach the marginal cancer cells with effective radiation.

There is a tendency among the inexperienced to regard the use of radium lightly. This tendency is encouraged by some of the radium-rental instructions given by commercial companies, which presume to fit the recipient for the safe and effective use of this dangerous instrument. It would be as reasonable to suppose that instructions issued with a scalpel would fit the recipient to use it safely and effectively in the eradication of cancer. Radium is as potent as the knife, and in inexperienced hands may produce as disastrous results, either in the form of injury to adjacent organs or as failure to save a life which might have been saved by effective use.

Of course, irradiation treatment does not exclude any work with the knife which may be helpful. In special conditions some vaginal operation or abdominal operation may permit more advantageous placing of the radium in its various forms. The important point in regard to any operative work employed is that it should supplement irradiation and not displace it. Another important point is that any experimental work, not established by a record of five-year cures, should be presented as experimental only. Otherwise it may be accepted and used by the uninitiated as an established method of cure.

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erable cases. His five-year results in 100 cases reported in the *American Journal of Obstetrics and Gynecology,* October, 1951, will be discussed later.

Another problem which has arisen since this editorial is the treatment of the group 0, early noninvasive, cases. The varying opinoins on this topic will also be discussed later in this chapter.

RADIATION THERAPY

Principles of Radiation Therapy of Cervical Cancer

A. N. ARNESON, M.D.

Prior to the discovery of x-rays and radium clinical observations had shown that prognosis in cancer varied with certain factors other than recognized extent of involvement. The type of tissue in which the tumor originates may, for example, affect the outlook to be expected. Furthermore, cancer of similar structures in different individuals may follow life histories that are distinctly different. It is obvious that variations in tendency toward spread are largely responsible for the differences noted in clinical behavior. One of the older observations upon biologic properties had to do with gross architecture assumed by a particular lesion. Everting types of growth generally present a more favorable outlook than those with tendency toward spread by direct invasion into surrounding structures. It is possible that the invasive qualities of some tumors increase risk of lymphatic and vascular dispersion, but with the advent of radiotherapy it soon became evident that the everting growths were of a quality more responsive to irradiation.

Infection is also a factor to be considered in the control of cancer. All such lesions present an inflammatory reaction of some degree. Severe infection may produce local sequelae or generalized effects that prolong convalescence or may bear a definite relationship to the end result obtained. The adverse action of infection is chiefly upon the host, but it may also affect tumor. Dr. W. B. Coley observed occasional spontaneous regression, notably in certain soft tissue sarcomas after severe episodes of erysipelas. Those experiences prompted development of a "toxin" bearing his name in one of the early attempts at chemotherapy.

The relation of tumor and host is complex. Both tissues involve the same parent stock of cells, but each is antagonistic to the other. The tumor follows a destructive course bent upon spread by invasion and dispersion. Normal tissues attempt to restrain and neutralize the invader by methods similar to those applied to any foreign irritant. The tendency toward spread makes necessary the radical measures applied in treatment. The therapeutic procedure is always traumatic, whether performed by excision, by radiotherapy, or by chemotherapy. In every instance there is damage to normal tissues, following which there must be repair. The degree of injury to the host limits the extent of the therapeutic measure to be applied. Radiotherapy in particular depends upon recovery of normal tissues and their neutralizing effects upon the tumor.

Evidence of the traumatic effects of radiation can be visualized in such phenomena as erythema, inflammatory changes, and contracture due to scar

tissue formation. There are many complex physiochemical effects induced by absorption of radiation that are more subtle in action and less easily visualized. Some of those effects can be seen microscopically in serial biopsies taken after the application of x-rays, radium, or other radioactive materials (Arneson and Stewart[1]; Healy and Arneson[2]). Degenerative changes occur in tumor cells, but the end point at which cellular death occurs has not been established. One can only postulate upon whether a tumor cell will recover or go on to destruction following a given degree of recognizable trauma. Components of the tumor bed represent some of the normal tissues of the host. The alterations there consist chiefly in the production of fibrosis and ischemia. It is important that those alterations proceed in an orderly fashion if good regression of tumor is to be attained. Excessive injury can result in radiation necrosis with removal of the normal mechanism of restraint by the host. The nature of the tumor bed also affects the degree of regression attained. If prior to irradiation there is considerable fibroblastic response and relatively marked ischemia, there is lesser opportunity for tumor bed alteration than in the case of soft spongy lesions with rich blood supply. The more sclerotic lesions are, therefore, less sensitive to irradiation.

Infection may complicate the response of a lesion to treatment. Clinical experience has shown that markedly infected tumors are more difficult to control. Solution of that problem is not to be found in increase in dose, however, because the infected tumor bed shows greater suspectibility to damage. Biopsy of a severely infected cancer usually shows in the tumor cells alterations similar to those found after application of small amounts of radiation. Those changes are response to injury induced by infection. The assumption can then be made that living in a traumatic environment develops adjustment or tolerance to the injury induced by irradiation. That is not the case with the tumor bed, however, which presents a lower threshold to radiation necrosis. Processes of trauma and recovery are not fully understood (Duffy, Arneson, and Vohe[4]; MacComb and Quimby[5]). Experience has shown that different tissues present variations in susceptibility to injury and in ability for repair. The risk of concomitant damage from both infection and radiation exceeding limits of repair presents the most valid explanation for the greater difficulty encountered in controlling infected lesions. It is, therefore, important that attempts at eliminating infection be undertaken at the beginning of irradiation. It is possible to control much of the infection present in the tumor by the use of external roentgen irradiation. The small dose reaching the tumor each day will lessen the existing infection without producing untoward damage. It should be noted, however, that any acute inflammatory process may show exacerbation and result in abscess formation. Risk of those sequelae is greater for radium treatment due to the instrumentation involved and to the relatively higher intensity of irradiation. For those reasons there is general agreement that treatment should be started with a course of x-rays.

The relative amount of radiation reaching various depths is made greater by increase in distance between irradiating source and surface to which treatment is applied. For that reason the amount of radiation arriving at lateral aspects of the pelvis is apt to be greater for x-rays applied externally, than for radium applied within the uterine cavity or within the vagina. In clinical

practice it is difficult to treat adequately the lateral pelvic nodes without producing untoward damage to normal tissues. In the combined use of x-rays and radium each is intended to supplement the other in the attempt to deliver an adequate dose to the entire tumor-bearing region. The local area about the cervix can be controlled by radium alone. The contribution from x-rays in that region is relatively less important. Fletcher has described an elaborate scheme of roentgen treatment aimed at increasing the parametrial dose without overexposing the cervix, bladder, and rectum. The two methods of irradiation cannot be considered independent entities. Each is complementary to the other, and usually there is some advantage to be gained by choosing total doses that will permit a continuous course of irradiation. To interpose an inactive period for recovery of normal tissues may allow untoward recovery of tumor.

It is obvious that one must have knowledge of the amount of radiation required for tumor control. Of equal importance, however, is the tolerance of normal tissues. In addition to tumor bed, the principal normal structures subject to injury include bowel, bladder, vaginal mucosa and skin. The range in dose between lethal tumor effects and untoward damage may be small. For that reason it is important that the total dose be distributed with as much homogeneity as possible, and throughout a volume of tissue corresponding to the normal pathways of spread. For any given dose the biologic effect varies with intensity, and also for the quality of radiation employed. All physical factors of the exposure are important, but with those data an expression of dose in air roentgens for x-rays or in milligram hours for radium does not present an easily determined estimate of the dose arriving at any particular point. Tumor and normal tissue dose can be rather well defined by tissue roentgens for x-rays and gamma roentgens for radium.

There is little homogeneity of irradiation for an intracavitary application of radium made by means of a tandem arrangement of tubes introduced into the uterine cavity. There is rapid falling off in dose at short distances away. The loss in intensity is such that very little radiation will reach the outer margins of the cervix and uterus even for the enormous quantities falling upon tissues immediately adjacent to the tandem (Fig. 684). The distribution of radiation is improved by means of vaginal applicators used in conjunction with the intrauterine sources (Arneson[7]) (Fig. 685). Radium tubes located in the lateral vaginal fornices carry the radiation somewhat more lateralward toward the parametria rather than toward the bladder and rectum. Much of the improvement in distribution is due to the greater distance that can be used in the vagina. Several applicators have been devised to keep the radium tubes a centimeter or more away from the adjacent vaginal wall. As a result there is loss in intensity that must be compensated for by an increase in exposure time, but, there is also improvement in relative depth dose. A tube of radium held by an applicator at 1.0 cm. distance from the vaginal wall will deliver per milligram hour very much less radiation against the fornix than would a tube lying directly upon the mucosal surface. For the same biologic effect there must be increase in the total milligram hours of exposure. The improvement in depth dose does not, however, follow directly the inverse square law applied to external application of x-rays. A tube of radium will

CERVICAL CANCER - RESULTS AND COMPLICATIONS

206 patients followed 5 years - 1921-1936

Radium by tandem alone   3,000 - 5,000 mghrs

A - 5,000 - 7,000 7r
B - 1,000 - 1,500 7r
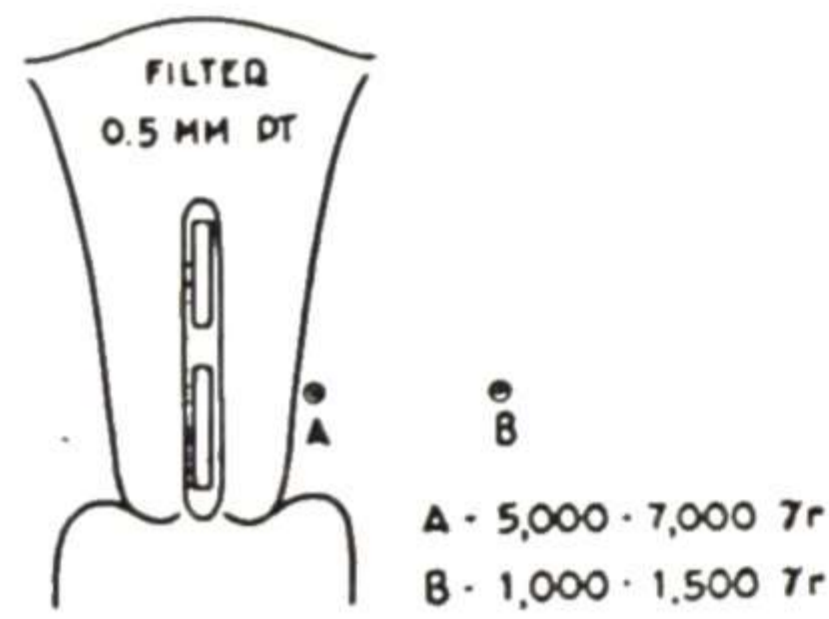
STAGE	NUMBER OF PATIENTS	5 YR SURVIVAL PER CENT	COMPLICATIONS PER CENT
I	22	55	40
II	81	42	47
III	84	6	70
IV	19	0	80
	206	24	57

Fig. 684.—Radium doses arriving at specified points, clinical results, and incidence of complications for method of treatment used from 1921 to 1936. (From Arneson: New Orleans M. & S. J., December, 1951.)

CERVICAL CANCER - RESULTS AND COMPLICATIONS

245 patients followed 5 years - 1937-1947

Radium by tandem and vaginal sources - 5,000 mghrs

A - 7,000 7r
B - 1,900 7r
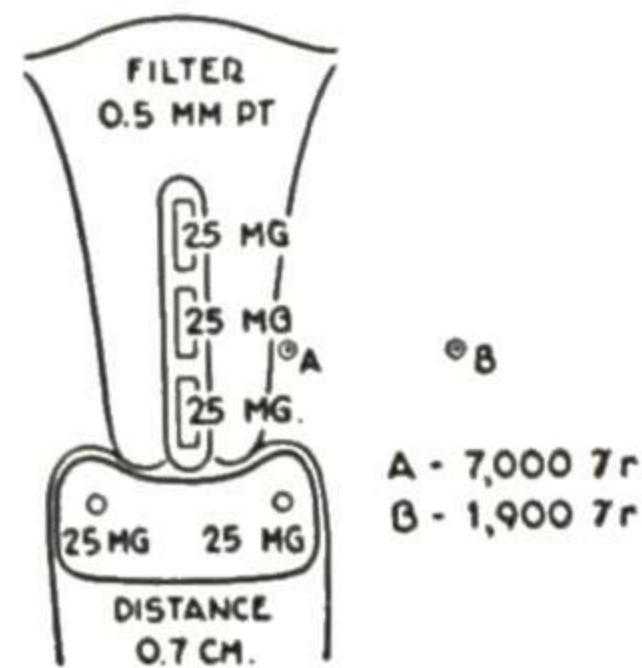
STAGE	NUMBER OF PATIENTS	5 YEAR SURVIVAL PER CENT	COMPLICATIONS PER CENT
I	42	60	36
II	113	44	25
III	76	11	22
IV	14	0	31
	245	35	27

Fig. 685.—Radium doses arriving at specified points, clinical results, and incidence of complications for method of treatment used from 1937 to 1947. (From Arneson: New Orleans M. &. S. J., December, 1951.)

not act as a point source due to the relatively close range at which it is used in relation to its active length. In points along a line perpendicular to the middle of the tube, radiation from the ends of the source will travel greater distances than will photons from nearer the central portion. The inverse square law cannot be applied directly unless calculations are made for a series of points along the tube. Calculations of that order are tedious, and the data can be obtained more conveniently from tables published to show the amount of radiation arriving at various points for different physical factors of treatment such as milligram-hours exposure, radium-surface distance, length of source, filter, etc. These are given in *Physics of Radiation* by Glasser et al.,[8] and in *Radiation Dosage, the Manchester System*, by Meredith.[9]
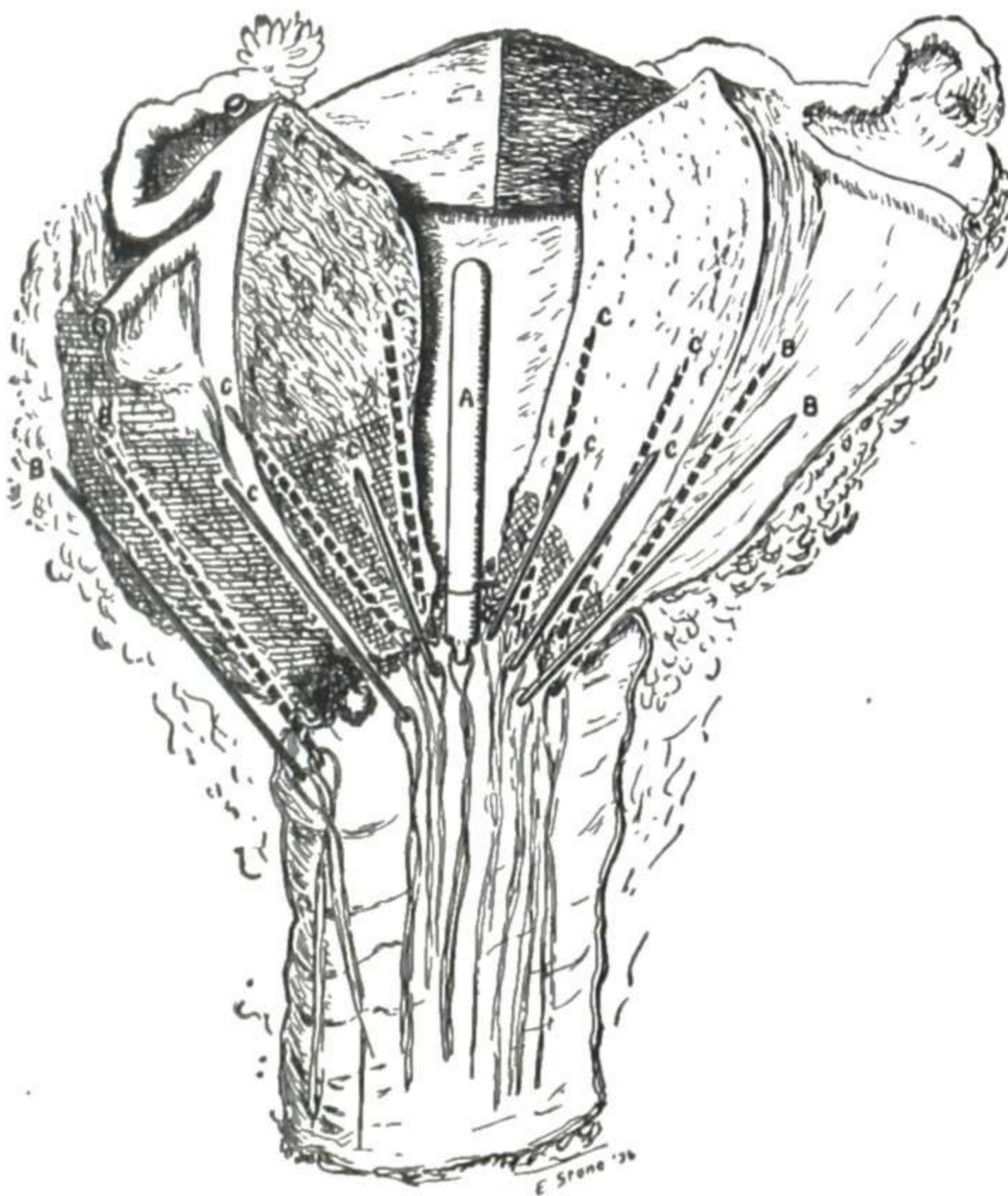
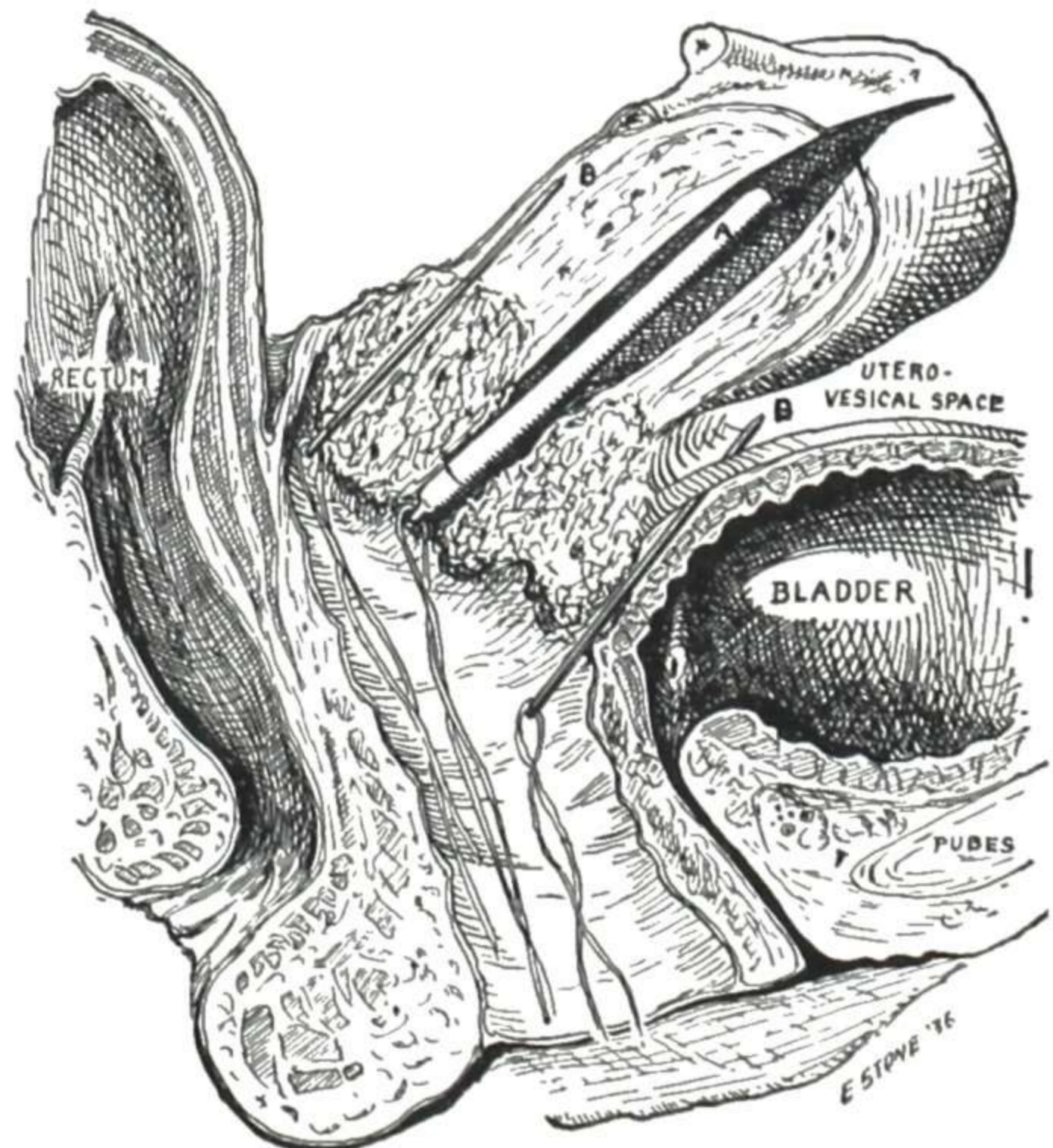Parametrial Invasion   Tumor of Cervix

Fig. 686.

Fig. 687.

Fig. 686.—Lined area indicates advancing parametrial invasion, and the cross-hatched area, the cervical tumor. *B*, indicates the 3 mg. needles and *C*, the 2 mg. needles. The dotted needles are posterior to the midline of the cervix.

Fig. 687.—Method of inserting needles anteriorly and posteriorly.

(From Pitts and Waterman: Surg., Gynec. & Obst.)

It would appear that one should select an applicator giving as much distance as possible. That is accomplished only by increase in bulk. Size of the applicator to be used is determined by space available in the vagina. Preliminary roentgen irradiation results in some contracture. For that reason a number of authors recommend that vaginal radium be applied as early as is practical in the course of irradiation. Radium can also be applied interstitially by introducing needles into the paracervical and parametrial tissues (Arneson and Hauptmann[10]; Corscaden et al.[11]; Waterman et al.[12]) (Figs. 686 and 687). That method has not been adopted widely, and in some clinics it has been abandoned after unsuccessful results. The untoward sequelae that have occurred have been due largely to the use of needles of too high in-

tensity. The sources should not be stronger than 1.0 mg. radium per 1.0 cm. active length. The use of low intensity needles has not resulted in an incidence of sequelae greater than that following more standard methods of irradiation. The increase in number of irradiating sources produces greater "cross fire." The contribution from a particular needle or tube becomes less in relation to the total dose. Somewhat more homogeneity is attained, but for any pelvic treatment the distribution of radiation remains irregular, with considerable range in dose between the "hot" and "cold" spots. It should be noted again that specification of dose in milligram-hours carries no information upon the amount of radiation arriving at the tumor or upon normal tissues. Those data can be given only in gamma roentgens, and for any specified dose the biologic effect will vary with the intensity of treatment.

The Manchester System of radium dosage has evolved a method specifying dose at certain points for indicating the whole dose delivered in treatment of cervical cancer.[9] Selection of those points has been made upon the basis of critical importance in relation to tumor as well as normal tissues, and upon the feasibility of indicating distribution of radiation throughout the region in question. One point is in the paracervical triangle, which was shown by Tod[13] to be of critical importance because overexposure is responsible for many of the sequelae that may follow irradiation. That point, designated as "A," is located 2.0 cm. deep to the vaginal mucosa, and 2.0 cm. lateral to the cervical canal. Point "B" is located at the same level, but at a distance 3.0 cm. lateralward. It falls somewhere near the primary group of nodes in the iliac and obturator fossae. It is of particular significance due to the difficulty encountered in attempting to deliver an adequate dose into that region. The specification of dose employed in the Manchester System is not perfect, and several authors have suggested modifications in selection of points. It is the one most frequently used, however, and the system of dosage presents a fundamental advance in the treatment of cervical cancer.

The Manchester System utilizes a differential loading of various applicators. Unity of radium strength can be established at about 5.0 or perhaps 10.0 milligrams. For an intrauterine tandem of two or more linear sources, one unit is used at the cervical end, and strengths of two units are used for each linear source located more deeply in the uterine canal. Vaginal radium is applied by means of ovoids, one being placed in each lateral vaginal fornix. Equatorial diameters of the ovoids range from 2.0 to 3.0 centimeters. The radium treatment distance is the radius of the ovoid. Selection of ovoid to be used is dependent upon space in the vaginal vault. Those of the smallest diameter are loaded with three units of radium, but approximately five units are employed in the largest (Fig. 688).

Data are not precise upon doses lethal for tumor or upon tolerance levels for normal tissues. The amount of radiation required for control of epidermoid carcinoma of the cervix is estimated to be on the order of 6,000 roentgens if applied within a period of 10 to 14 days, and about 8,000 roentgens if administered over a period of 21 to 28 days. Tolerance of the paracervical triangle for the same periods of time appears to be on the order of 7,000 to 9,000 roentgens. The rectum has about the same tolerance, but the bladder

may withstand slightly greater amounts. The vaginal mucous membrane has excellent ability for recovery, but not more than half the dose at "A" should be applied through that entry (Fig. 689). The remaining half of the total

INTRAUTERINE TANDEM
Tubes 2.0 cm. length

VAGINAL OVOIDS
Spacer 1.0 cm.

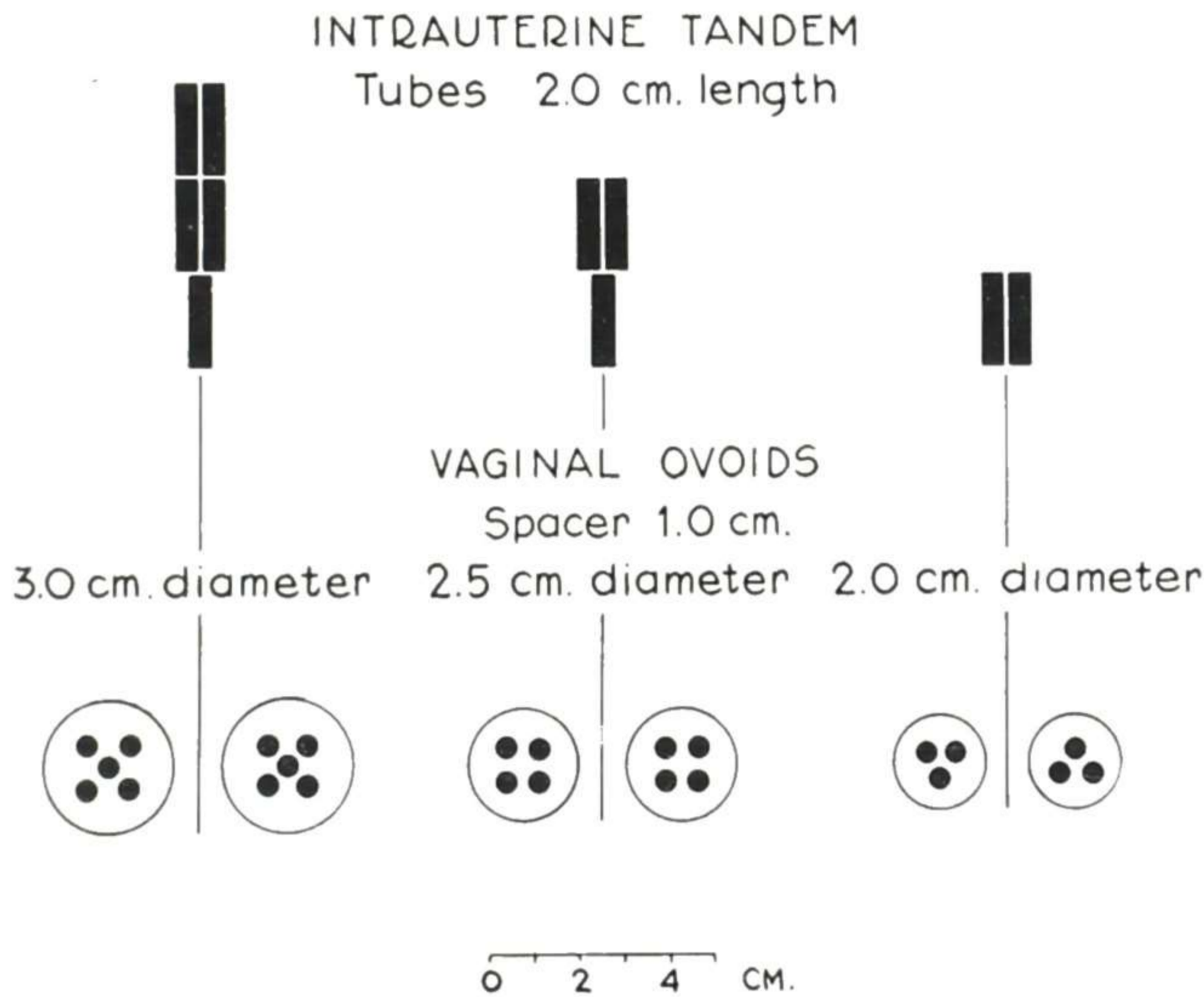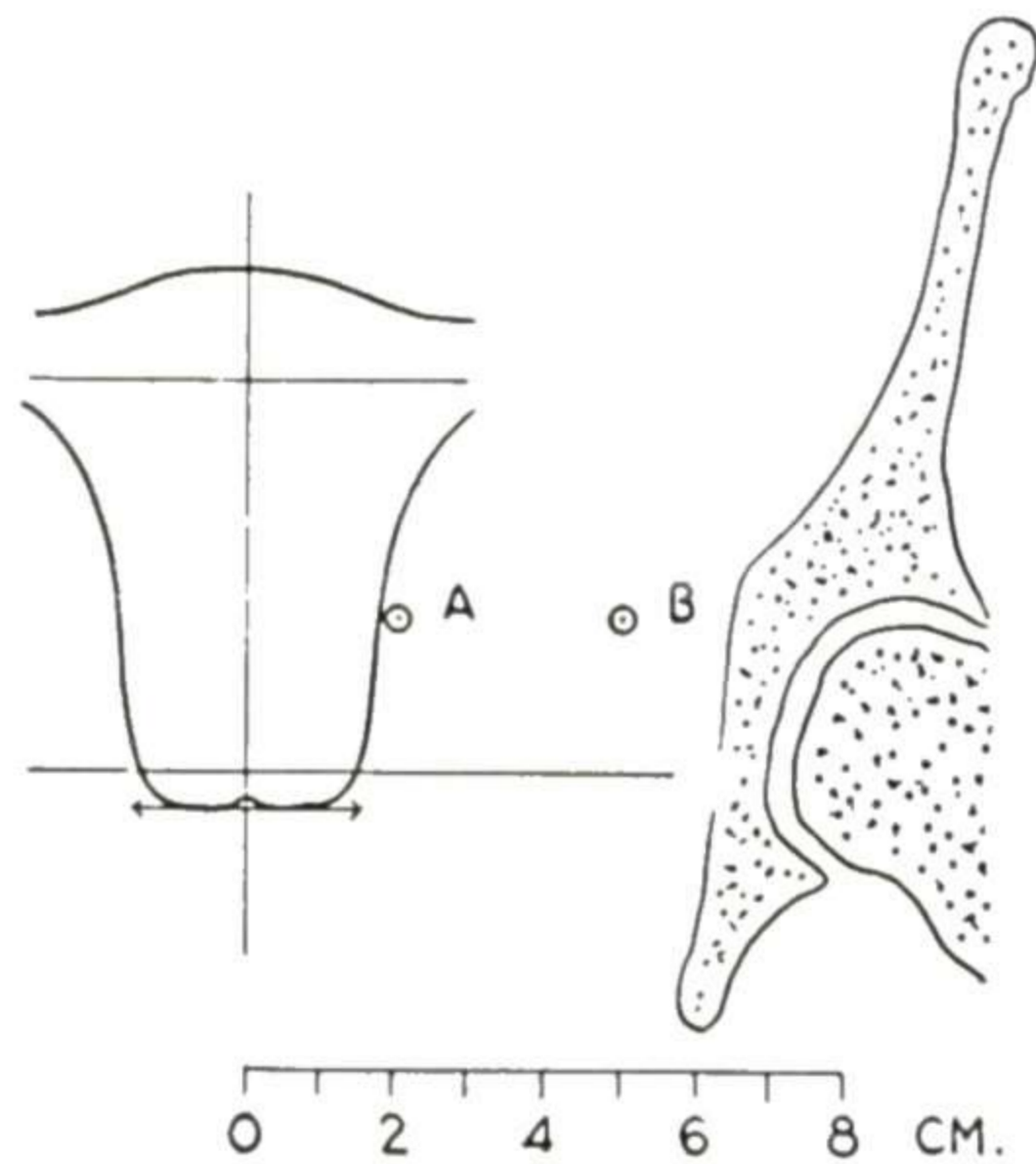3.0 cm. diameter   2.5 cm. diameter   2.0 cm. diameter

0   2   4   CM.

Fig. 688.—Cancer of cervix—radium treatment. Diagrammatic representation of variations in strength of radium tubes used for intracavity treatment in the Manchester System of radium dosage. (From Arneson: Progress in Gynecology, Vol. II, 1950.)

0   2   4   6   8   CM.

POINT "A" RECEIVES 200r PER 1.0 MG. IN UNIT EACH 24 HRS.

5.0 MG. UNITS DELIVER 1,000r AT "A" IN 24 HRS.

USING FROM 8 TO 15 UNITS EMPLOYS 960-1,800 MG·HRS. PER DAY

FOR APPROXIMATELY 4,400 MG·HRS. POINT "B" RECEIVES 1,000r,

OR ABOUT 0.2 TO 0.4 DOSE AT "A".

Fig. 689.—Cancer of cervix—radium treatment. Diagrammatic representation of dose falling at specified points for different intensities of irradiation (Manchester System). (From Arneson: Progress in Gynecology, Vol. II, 1950.)

dose at "A" should be contributed by the intrauterine tandem and other sources. The cervix and uterus have remarkable tolerance, exceeding that of other points by a factor of 3 or 4.

With variation in length of intrauterine tandem and in size of vaginal ovoid there must be a wide range in number of milligram-hours radium employed. If unit strength is 5.0 milligrams radium, the dose per 24 hours may range from about 1,000 milligram-hours to 1,800 milligram-hours radiation.

Fig. 690.—Colpostat with handle, in closed and open positions. (From Ter-Pogossian, Sherman, and Arneson: Am. J. Obst. & Gynec., October, 1952.)
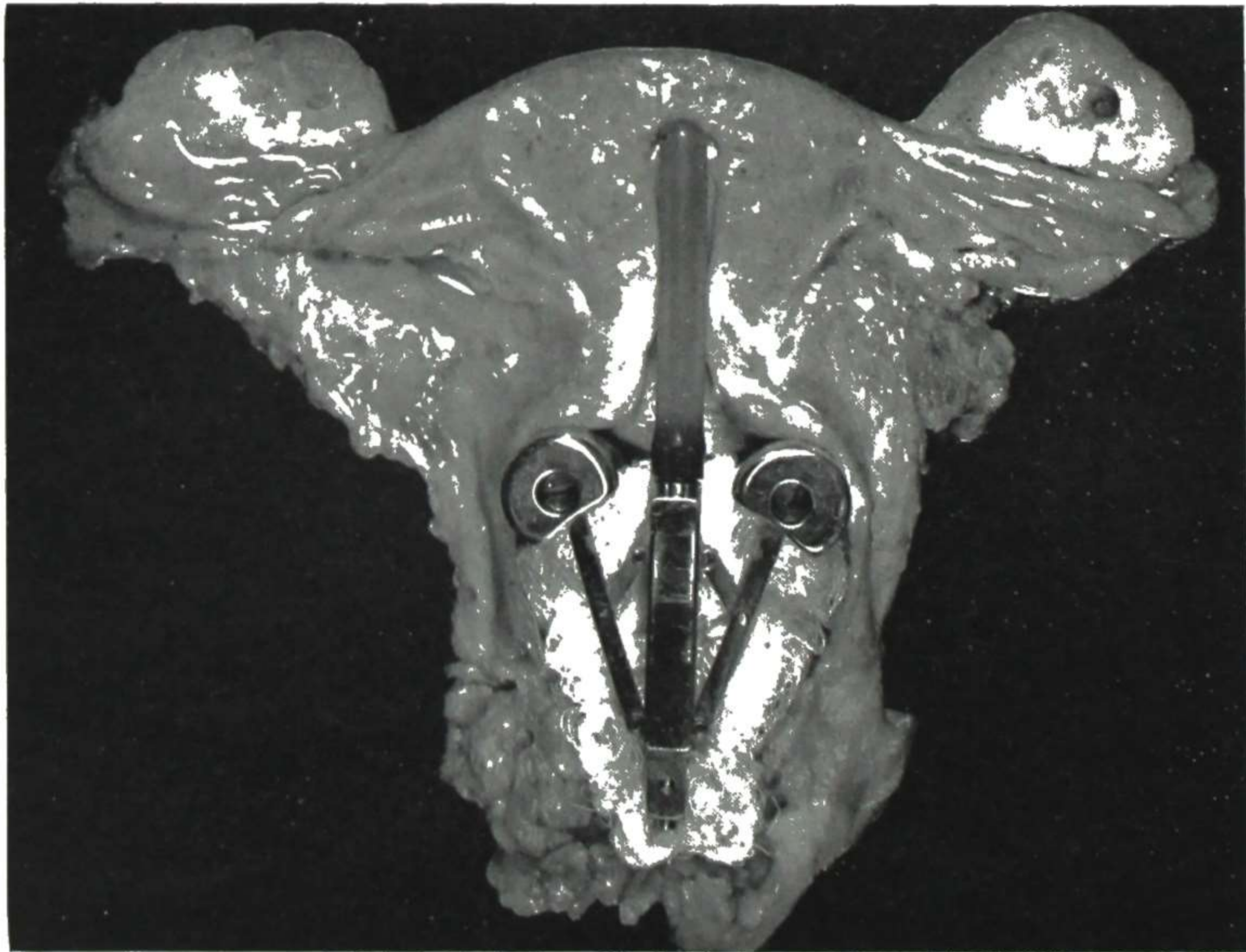

Fig. 691.—Cross-sectional view of a uterus with colpostat in place showing vaginal packing. (From Ter-Pogossian, Sherman, and Arneson: Am. J. Obst. & Gynec., October, 1952.)

For almost any suitable arrangement of sources the dose falling at "A" will be about 1,000 gamma roentgens during that period. Thus the treatment might be continued for a total of about six days or divided into two sittings given a week or so apart for a little more than three days each. To illustrate the discrepancy between doses arriving at "A" and at "B," it should be noted that approximately 4,400 milligram-hours radiation are required for 1,000 gamma roentgens at the latter point. That is approximately 0.2 to 0.4 the dose at "A."

[An expanding fixed tandem-ovoids colpostat recently described by Ter-Pogossian et al. offers promise of overcoming some of the disadvantages of other methods of radium application. This is shown in Figs. 690 and 691. Because of the fixed relationship of the ovoids to the tandem the cervix always maintains a predetermined ideal geometrical position, and because of this the so-called "hot spots" in the surrounding normal tissues are avoided. It can be inserted and removed easily and has been found to maintain its position in the vagina over many hours without much discomfort to the patient].*
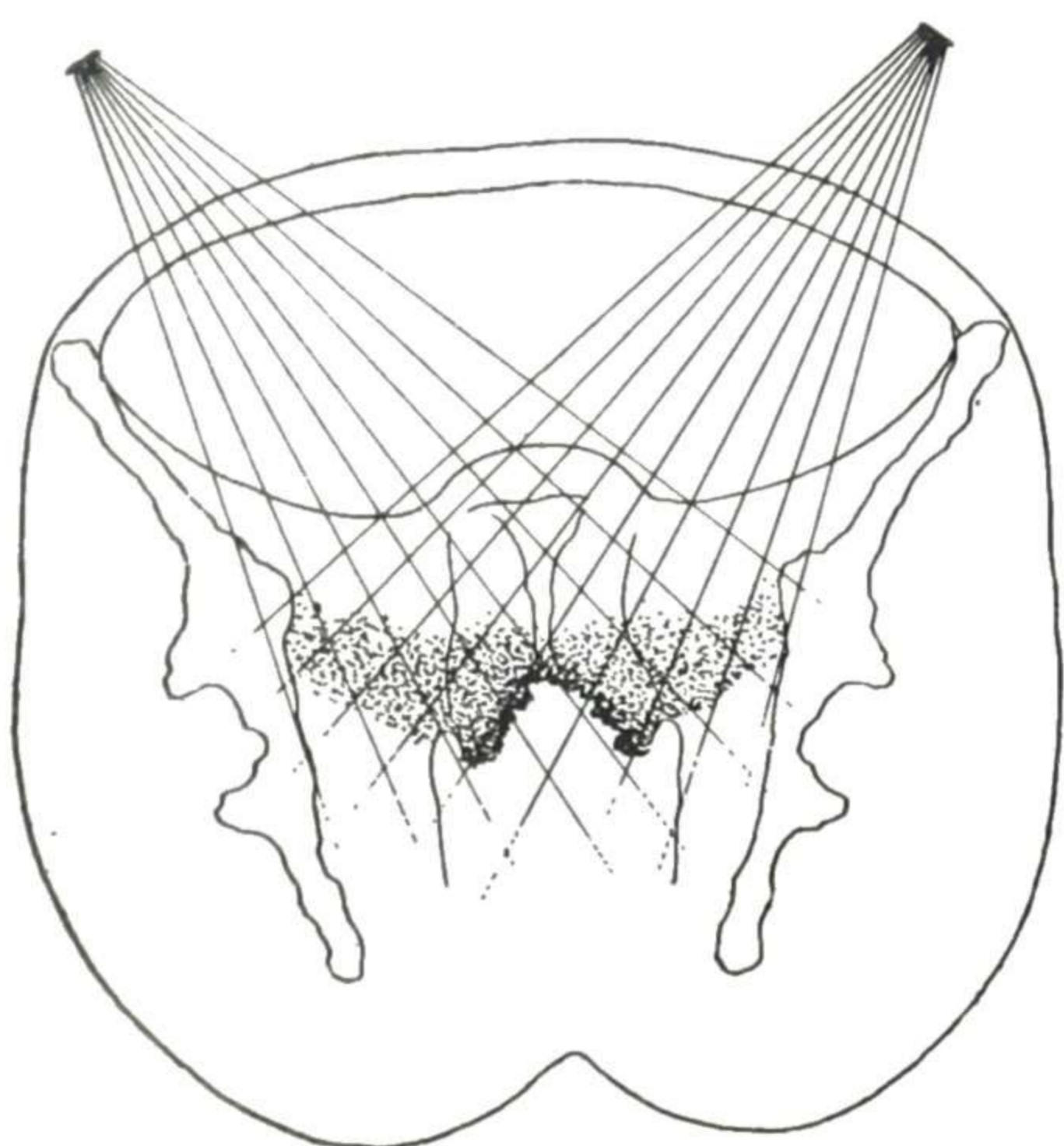

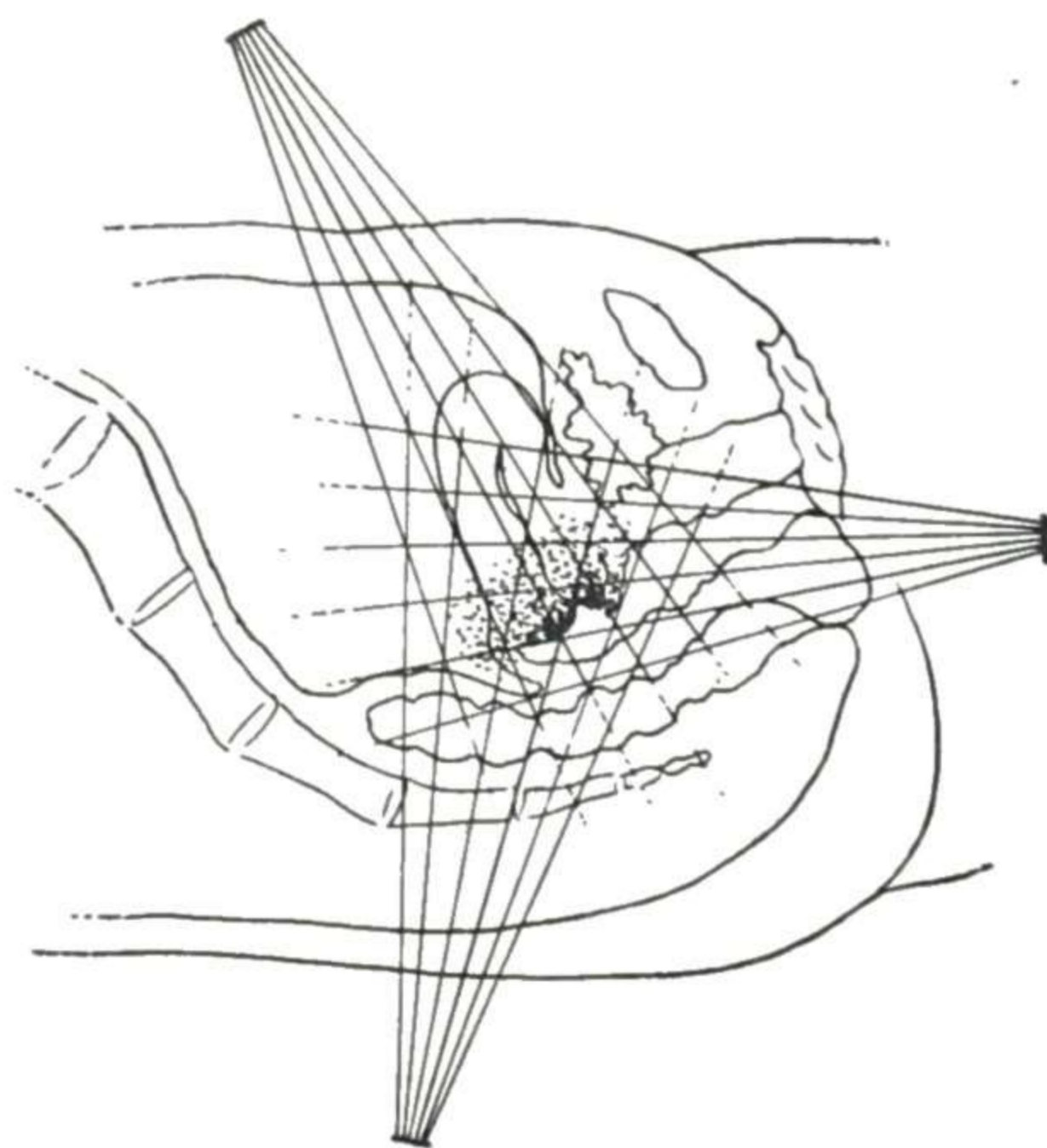Fig. 692.   Fig. 693.

Figs. 692 and 693.—X-ray treatment of carcinoma of cervix uteri. In order to place sufficient dosage in the cancer area without injury to the overlying skin, extensive cross firing is necessary, and the use of many ports of entry, one after another. Fig. 692 indicates successive steps in firing through lateral portions of the abdomen. Fig. 693 indicates other ports of entry—the central abdomen, the sacral region, and the pelvic outlet. Improvements in technique have now made practical x-ray treatment through a vaginal tube.

The Swedish technique employed at the Radiumhemmet has been followed for many years without any radical modification. The method is described by Kottmeier[14] and places more importance upon dose contributed by the intrauterine tandem. Vaginal radium is applied by means of a variety of trays, plaques, and sledges. A modified form of the Stockholm technique is used by Lederman[15] at the Royal Cancer Hospital. Ernst[16] has devised an expandible vaginal applicator rigidly attached to an intrauterine tandem. All of those methods share two features in common: Multiple sources of irradiation are employed, and in each instance the attempt is made to expand the vagina and

*Author's comment.

carry tubes of radium as far lateralward as possible. An effective means for increasing the number of sources and for increasing the effective dose lateral to the uterus is the use of radium needles introduced directly into paracervical and parametrial tissues. For any method, however, it is rarely possible to deliver an adequate dose at point "B" by means of radium alone. Some form of supplementary treatment must be employed for irradiation of the entire tumor-bearing region. The method generally used is external roentgen irradiation (Figs. 692 and 693). If radium is to be applied it is essential that the central pelvis be protected from excessive exposure to x-rays. The scheme devised by Fletcher is aimed at increasing the parametrial dose without overexposure to the bladder, cervix and rectum. In many clinics treatment is begun with external irradiation. The principal gain for that procedure is the decrease in infection that follows the application of x-rays. There is, however, contracture of the vagina that may lessen the distention that can be accomplished in the vault. For that reason some authors prefer to apply radium, at least in the vagina, as early as possible in the course of irradiation.

Emphasis should be given the importance of carefully planned irradiation in the treatment of cervical cancer. That is not intended to imply that a program established at the outset should be completed regardless of reaction in the patient. Individualization is essential.

Objections to irradiation have been made upon the basis of untoward sequelae, and upon lack of tumor control. Those failures are due largely to the empirical methods that have been followed. For any radical procedure it is impossible to eliminate all risk, but most radiation injuries are due to overexposure and to improper clinical judgment. Persistent or reappearing disease in the cervical region has the same etiology. The use of radiographs taken routinely to study the arrangement of radium will often reveal inadequacies or errors that can be corrected in subsequent applications. The reward for detail is both immediate and remote. The clinician will experience a decline in sequelae among his patients and will be gratified years later to find a greater percentage alive and well.

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Sherman, Bonebrake, and Allen in recent experimental work have injected radioactive gold into the parametrium. They had previously shown in rabbits that the colloidal gold was taken up by the lymphatics and reached the primary and secondary lymph nodes. The number of cases treated so far and the length of time since treatment do not permit of any conclusions as to the ultimate result, but it has been shown that the parametrium and regional lymphatics can be irradiated adequately by this method.

For details on the various techniques of radiation therapy the reader is referred to the authors' book on *Operative Gynecology.*

OPERATIVE TREATMENT

Operative treatment is used either alone or in combination with radiation therapy, and the type of operative treatment used depends upon the stage of the disease, condition of the patient, and other factors.

In the group 0 cases of early noninvasive carcinoma the treatment advised by different men varies from cautery or conization of the cervix, simple complete hysterectomy, wide complete hysterectomy with preservation of the ovaries (Te Linde), Wertheim hysterectomy (Meigs), and radiation therapy. There have not been enough of these cases followed for a sufficient length of time to know which is the proper method of treatment. Before relying on anything but radical therapy one must be positive that there is no invasion present. Galvin and Te Linde obtained the cervix either by wide conization or by hysterectomy in 75 cases which had been diagnosed as intra-epithelial carcinoma by them from a biopsy specimen. In this group of 75 cases of supposed early noninvasive carcinoma, invasion was discovered in the removed specimen in 55 of the cases. Of the remaining 20 cases, ten showed carcinoma in situ and the remaining ten showed no abnormality. From these findings it is evident that one should be absolutely sure of the diagnosis before instituting therapy, and with the high incidence of proved unsuspected invasion most of the cases should be given the accepted treatment for invasive carcinoma. The only exception should be in the young woman in whom no invasion is found on wide conization or Sturmdorf operation, and in such cases complete hysterectomy with preservation of the ovaries may prove to be the treatment of choice. Hoge and also Schmitz have reported good results using this treatment. Carter et al. give a summary on a follow-up of 151 patients with cancer in situ and also a report on the questionnaire on this subject sent out by the American Gynecological Society.

Time alone will determine which is to be the preferred treatment.

With the improvements made in modern surgery, Meigs decided to re-evaluate the surgical treatment of invasive cervical carcinoma. His technique combined the wide parametrial dissection with the lymphadenectomy advocated by Taussig. With the exception of two cases, only Stage I and Stage II cases which were good operative risks were selected by Meigs for his report on his five-year results with the radical operation in one hundred cases. In going over the pathology 15 cases were excluded, 13 were found to be preinvasive carcinoma, and 2 endometrial carcinoma; hence there were only 85 cases in which the results were given. In Stage I cases 80.7 per cent were alive and in Stage II cases 60.7 per cent were alive after five years. Meigs has

shown beyond doubt that this operation done by one specially trained in its performance results in no greater surgical mortality than would be expected in any radical pelvic operation. His results are comparable to those obtained by men equally trained in radition therapy. The report of McKelvey of 81 per cent cures in Stage I demonstrates what can be done when the radiation patient is given pre- and postoperative therapy commensurate with that given the operative case.

Some years ago Taussig added the operation of lymphadenectomy in cases that had been radiated, based upon the idea that radiation did not effect lymph node metastases. The subsequent work of Morton, Henriksen, and Sherman Ruch, and Monat, all confirm the fact that the percentage of positive nodes found is appreciably less in patients who have received radiation than in those who have not. Willis Brown and his co-workers have recently shown that 5,000 to 6,000 "tissue roentgens" will eradicate carcinoma in radiosensitive lymph nodes, when delivered in five to six weeks. Morton, after considerable experience with lymphadenectomy concluded that as the results with radiation improved, the operation for lymphadenectomy would no longer be indicated.

In hopeless cases, due to extension of the disease or irreparable radiation damage, Brunschwig advocated exentration with removal of the bladder and rectum. In cases of this type where there are fecal or vesical fistulae or where pain is a serious factor, this operation does offer at least temporary relief. Within our group at Washington University, Dr. Eugene M. Bricker has done 25 cases with cervical carcinoma, and though there is a primary mortality of about 20 per cent, the patients who survive the operation have all had a marked relief of symptoms. The eventual prognosis as to survival will, of course, not be known for some years.

In a survey of treatment of cervical carcinoma made in 1949 by Hoge, replies were received from 77 accredited medical schools. In Stage I cases 66 per cent used radiation alone, 19.5 per cent used radiation and surgery, and only 1.3 per cent used surgery alone; 13 per cent used multiple methods. In the Stage II cases 90.9 per cent of the schools used radiation alone; this clearly shows that radiation is still the preferred method of treatment.

PROGNOSIS

The results of adequate treatment whether by radiation or surgery depend upon the stage of the disease and, to some extent, upon the clinical type of the growth. In the Stage I cases, five-year cures vary from 70 to 80 per cent; Stage II cases, from 40 to 55 per cent; Stage III cases, from 10 to 20 per cent; and Stage IV cases, from 0 to 5 per cent. It has long been felt that the everting type of growth offered a better prognosis than the inverting type of growth and this has been shown statistically by the excellent report of Arneson (see page 549, table taken from his article).

The effect of lymph node metastases on prognosis in cervical carcinoma was studied by Sherman and Ruch. In 253 patients from Barnard Free Skin and Cancer and Barnes Hospitals with Stages I and II cervical carcinoma, 21.7 per cent of the cases were found to have positive nodes. Of those patients having positive nodes only 10.9 per cent survived, whereas of those with negative nodes 52 per cent survived five years.

CANCER OF CERVIX UTERI, 1935-1942

(Primary Cases—Absolute Statistics)

Relation Gross Appearance to End Results in Different Clinical Groups

CLINICAL GROUP	PATIENTS	GROSS APPEARANCE				TOTAL	PER CENT
		EVERTING	INFIL-TRATING	CRATERED	UNCLASSI-FIED		
I	Number	9	10	1	2	22	13
	5-year	7	7	1	1	16	72.7
II	Number	29	14	16	0	59	34
	5-year	21	1	9	0	31	52.5
III	Number	18	25	20	1	64	37
	5-year	3	2	3	0	8	12.5
IV	Number	13	3	12	0	28	16
	5-year	0	0	0	0	0	0
Total	Number	69	52	49	3	173	
	5-year	31	10	13	1	55	31.8

Five-year survival rates for cervical cancer in different stages of clinical advance. The patients are divided numerically according to gross appearance of lesion. (From Arneson: J. Tennessee M. A. **41:** 195, 1948.

In a recent article Ruth Graham correlated the end results in cervical carcinomas that had been followed by means of vaginal smears, in order to determine the prognostic value of cytology. The absolute prognostic accuracy in a group of 73 patients five years after irradiation was 75 per cent; the relative accuracy was 80 per cent. J. B. Graham and Meigs emphasize the value of cytology for earlier detection of recurrences.

The statistics on five-year survivals from the clinical service at Barnes Hospital and from the private practice of Arneson and of the authors' private cases are shown in the accompanying tables (pages 550 and 551).

Scheffey et al., in a twenty-five-year evaluation of treatment of cervical carcinoma, reported a steady improvement in the percentage of five-year survivals. The most recent period, 1942 to 1946, was 47.6 per cent.

Late complications following radiation have recently been reviewed by White and Finn, and a summary of our knowledge concerning acute radiation injuries has been reported by Hempelmann. Many of these complications associated with infection have been reduced through the use of antibiotics. The causes of death in cancer of the cervix were given by Auster and Sala in a detailed analysis of 124 cases.

PREVENTION

The importance of chronic cervicitis as an etiologic factor in cervical carcinoma has been fully discussed under etiology and the importance of regular examination and the technique of detection are given in detail under Early Diagnosis; hence they will not be repeated here. Prevention of cervical carcinoma can be summed up briefly by restating the fact that removal of the entire gland-bearing area of the cervix together with a wide area of the surrounding involved tissue will prevent the future development of carcinoma in close to 100 per cent of the cases and give adequate tissue for microscopic examination so as to rule out preinvasive or invasive carcinoma. This can be done by wide conization, the Sturmdorf operation, or amputation of the cer-

Cancer of Cervix Uteri, 1935-1946

Results of Treatment

(Dr. A. N. Arneson and Clinic Service at Barnes Hospital)

YEAR	NO. OF PATIENTS TREATED	ALIVE WITHOUT EVIDENCE OF DISEASE AFTER PERIOD OF OBSERVATION OF YEARS						ALIVE BUT NOT CURED AFTER PERIOD OF OBSERVATION OF YEARS						DIED OF CANCER DURING PERIOD OF OBSERVATION OF YEARS						LOST SIGHT OF DURING PERIOD OF OBSERVATION OF YEARS						DIED FROM INTERCURRENT DISEASE DURING PERIOD OF OBSERVATION OF YEARS					
		5	6	7	8	9	10	5	6	7	8	9	10	5	6	7	8	9	10	5	6	7	8	9	10	5	6	7	8	9	10
1935	23	6	5	5	5	5	5	0	0	0	0	0	0	16	16	16	16	16	16	1	1	1	1	1	1	0	0	1	1	1	1
1936	23	7	7	7	7	7	7	0	0	0	0	0	0	13	13	13	13	13	13	3	3	3	3	3	3	0	0	0	0	0	0
1937	18	4	4	3	3	3	2	0	0	0	0	0	1	12	12	12	12	12	12	2	2	2	2	2	2	0	0	1	1	1	1
1938	17	6	6	5	5	4	4	0	0	0	0	0	0	8	8	9	9	9	9	3	3	3	3	4	4	1	1	1	1	1	1
1939	30	9	8	8	8	7	6	0	1	0	0	1	0	19	19	20	20	20	20	1	1	1	1	1	2	1	1	1	1	1	1
1940	40	17	17	17	17	15	13	0	0	0	0	0	1	17	17	17	18	18	18	5	5	5	5	6	8	0	1	1	1	1	1
1941	29	13	11	11	11	10	7	0	0	0	0	0	0	14	14	14	14	14	14	2	3	3	3	3	6	1	1	1	1	1	1
1942	41	21	20	17	15	11		2	1	0	0	1		11	12	14	15	15		5	6	6	8	12		0	2	2	2	2	
1943	27	10	10	9	5			1	1	1	1			10	11	12	13			6	5	7	9			2	2	2	0		
1944	29	11	9	6				2	1	1				12	13	13				2	4	7				0	1	2			
1945	44	22	20					2	1					18	18					2	3					2	1				
1946	52	24						1						21						3						3					
Total	373	150					40.2%	7						171						35					9.3%	10					

CANCER OF CERVIX UTERI, 1935-1946

RESULTS OF TREATMENT

(Dr. H. S. Crossen and Dr. R. J. Crossen)

YEAR	NO. OF PATIENTS TREATED	ALIVE WITHOUT EVIDENCE OF DISEASE AFTER A PERIOD OF OBSERVATION OF — YEARS						ALIVE BUT NOT CURED AFTER A PERIOD OF OBSERVATION OF — YEARS						DIED OF CANCER DURING A PERIOD OF OBSERVATION OF — YEARS						LOST SIGHT OF DURING A PERIOD OF OBSERVATION OF — YEARS						DIED FROM INTERCURRENT DISEASE DURING A PERIOD OF OBSERVATION OF — YEARS					
		5	6	7	8	9	10	5	6	7	8	9	10	5	6	7	8	9	10	5	6	7	8	9	10	5	6	7	8	9	10
1935	13	6	5	5	4	4	4	1	1	1	1	1	1	6	6	6	6	6	6	0	0	0	0	0	0	0	0	0	0	0	1
1936	14	8	7	6	6	6	6	0	0	0	0	0	0	5	5	5	5	5	5	0	0	0	0	0	0	0	1	1	1	1	1
1937	12	5	3	2	2	2	2	0	0	0	0	0	0	7	7	9	9	9	9	0	0	0	0	0	0	1	1	1	1	1	1
1938	14	7	7	7	7	7	7	0	0	0	0	0	0	7	7	7	7	7	7	0	0	0	0	0	0	0	1	1	1	1	1
1939	11	8	8	8	8	8	8	0	0	0	0	0	0	2	2	2	2	2	2	1	1	1	1	1	1	0	0	0	0	0	0
1940	5	3	3	3	3	3	3	0	0	0	0	0	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
1941	8	3	3	2	2	2	2	1	0	0	0	0	0	4	4	4	4	4	4	0	0	0	0	0	0	0	1	1	1	1	1
1942	6	3	2	2	2	2	2	0	1	0	0	0	0	3	3	3	3	3	4	0	0	0	0	0	0	0	0	0	0	0	0
1943	11	2	1	0	0			0	0	0	0			9	9	9	9			0	0	0	0			0	0	0	1		
1944	15	7	5	5	4			0	0	0	0			6	6	6				2	2	2				0	0	1			
1945	11	4	4	4				0	0	0				6	6					1	2					0	0				
1946	9	5	4					0	0					3						1						0					
Total	129	61					47.2%	2						59						5					3.8%	2					

vix, and the method selected will depend upon the age of the patient and the technique desired by the operator. The procedures and results have been previously given in Chapter 6.

When hysterectomy is indicated for some benign condition, the operation should include the cervix wherever possible, and if, for some reason, the cervix cannot be removed, it should be coned out at the time even though it appears grossly normal. The reason behind this is the increasing number of early carcinomas which are being discovered in apparently normal cervices, detected by the various cytological tests and by biopsy and conization, and the incidence (4 per cent) of carcinoma in the cervical stump.

PREGNANCY WITH CERVIX CANCER

The incidence of carcinoma of the cervix occurring in pregnancy varies in selected series from 0.0075 per cent (Chalfant) to about 0.05 per cent found by Emge. Gross, at the Kiel University Clinic, found 120 cervical carcinomas in 224,080 pregnancies, or 0.053 per cent. If, on the other hand, we consider the number of pregnancies complicating carcinoma of the cervix, the figures vary from 0.70 to 2.66 per cent.

Until recent years the importance of regular inspection of the cervix during pregnancy was not fully appreciated. Since the studies of Fluhmann and others, the importance of careful observation with smears and biopsies, if indicated, is evident; but, as Novak has pointed out, one must be extremely careful in the pathological interpretation of these cases. During pregnancy, due to the excessive estrogenic stimulation, there are many microscopic changes found in the cervix which simulate early malignancy, but these changes revert to normal at conclusion of the pregnancy. An excellent review of these changes is given by Carrow and Greene.

The guiding principle in the treatment of proved carcinoma in pregnancy is to treat the carcinoma. There are, of course, not only varying ages of pregnancy to be considered, but also varying stages of carcinomatous extension. Any combination of these two may be present in any given case, so a consideration of both factors guides one in determining the best treatment for the particular case.

There is no unanimity of opinion as to the management of cervical cancer complicated by pregnancy. The advice varies from full radiation with hysterotomy or cesarean section to radical hysterectomy and lymphadenectomy. W. O. Johnson uses radiation plus radical hysterectomy.

Under four months, radiation usually causes death and expulsion of the conceptus, and this may be followed by adequate radium and x-ray therapy. If abortion does not occur, hysterotomy is preferable to dilating the cervix to complete the abortion.

When the pregnancy is between four and seven months the treatment depends upon the mother's desire for a living child and the stage of the pregnancy. With an early lesion in a pregnancy just short of viability in a mother very desirious of offspring, 3,000 mg.hr. of properly screened radium should be given. There should be a distance of at least 5 cm. between the radium and the head of the fetus. External version and Trendelenburg position during radiation are advisable for protection of the child. This plan does not harm

the fetus at this stage and may hold the carcinoma in check long enough to permit the delivery of a viable fetus. As soon as the child's chance of surviving is fairly good, a cesarean section is done to rescue the fetus. Following this, radiation should be given as for any like case of carcinoma.

When the mother has children and the urgent indication is to save her to take care of them, adequate radium and x-ray radiation should be given at the outset. This usually causes death of the fetus, and delivery is completed later, usually by cesarean section.

In pregnancy between seven months and full term in which there is an early lesion of the cervix, the treatment of choice is a cesarean section followed by adequate radiation. When the lesion is more advanced, moderate radiation is given first, followed by section and then adequate radiation. This plan helps to reduce the operative risk by reducing the accompanying infection and by causing some regression of the carcinoma.

At or near term, cesarean section followed by full radiation therapy is the method of choice.

Radiation therapy has given best results in a series reported by Baer and the recent one reported by Hirst. In early operable cases, W. O. Johnson prefers radiation plus radical hysterectomy, as do Maino, Broders, and Mussey. Until the five-year results of a larger number of these cases is determined, the treatment cannot be standardized. Each case is a problem in itself and the treatment used will depend upon other factors as well as the proficiency of the physician in the use of radiation or surgery.

CARCINOMA OF THE CORPUS UTERI

Carcinoma of the corpus uteri constitutes a distinct class, having better prognosis than carcinoma of the cervix. It begins in the endometrium; consequently the tumor tissue is accessible to the curette at a very early stage. The growth is for a long time confined to the tissues immediately about the uterine cavity, the extension to the periuterine tissue being slow—hence the chance of cure is much better. Carcinoma of the corpus comprises 10 to 15 per cent of all uterine cancers.

ETIOLOGY

The etiology of adenocarcinoma of the endometrium has been approached from many angles, and most men who have investigated this field agree that estrogenic stimulation over a prolonged period of time, in women genetically predisposed to cancer, can initiate carcinogenesis.

The avenues of approach to this problem from the clinical side have included studies of delayed menopause, cases in which there is a combination of feminizing mesenchymomas of the ovary and endometrial carcinoma, association of endometrial hyperplasia with endometrial carcinoma, case reports of endometrial carcinoma following prolonged use of estrogenic medication, and, finally, the fact that in a large percentage of the endometrial carcinoma cases there is clinical evidence of polyglandular dysfunction and hyperestrinism.

In regard to late menopause, Crossen and Hobbs in 1935 found that 60 per cent of 89 endometrial cancer cases menstruated past the age of fifty, whereas only 15 per cent of 2,291 supposedly normal cases reported by Krieger

menstruated past fifty years. In a series reported by Randall, late menopause was also four times as frequent in the fundal carcinoma cases as it was in the normal ones. Morrin has reported similar findings from the material at the Barnard Skin and Cancer Hospital. This would seem to indicate that prolonged stimulation of the endometrium by endogenous estrogen into the period of life when the endometrium is usually atrophic may be one etiologic factor in the initiation of the carcinomatous process.

Ingram and Novak collected fifty cases of adenocarcinoma of the endometrium in association with estrogen producing feminizing mesenchymomas of the ovary and added four cases of their own. Novak brought out the interesting fact that 29 of the 54 patients had thecomas in spite of the fact that these ovarian tumors have a much lower incidence than granulosa-cell tumors. Since their report there have been an additional thirteen cases reported by Dockerty and Mussey. Hertig estimated that 18 to 20 per cent of granulosa-cell tumors of the ovary have an associated carcinoma of the endometrium. Dockerty found that 27 per cent of his cases in the postmenopausal period had this combination. Three of the patients reported by Dockerty and Mussey had also a carcinoma of the breast and in one case it was bilateral. These findings confirm the idea expressed by Loeb many years ago that the estrogenic substance must act over a long period of time in order to initiate the carcinomatous changes.

It has been well established that unopposed estrogenic stimulation will cause a characteristic cystic glandular hyperplasia of the endometrium, but the relationship between hyperplasia and adenocarcinoma of the endometrium has for many years been a moot question. Novak and Yui found a glandular hyperplasia of the endometrium accompanying 25 per cent of their endometrial carcinoma cases, and from their studies they concluded that there was a developmental relationship between this type of endometrial hyperplasia and carcinoma. The report of Gusberg confirms their findings. There have been a number of reports of carcinoma developing in patients in whom previous curettages had shown a hyperplasia; the most recent is that of Bastiaanse. The association of myoma with adenocarcinoma of the endometrium has long been known. Tannhauser found that uteri containing endometrial carcinoma were considerably larger than was usual in this age group of patients. He attributes this to hypertrophy of the myometrium. Wissner and Young had noted this muscle hypertrophy previously in cases with endometrial hyperplasia, and they felt that excessive estrogenic stimulation was the probable etiologic factor in both conditions.

Since the well-documented case of adenocarcinoma of the endometrium following prolonged medication reported by Fremont-Smith et al., 17 cases of endometrial carcinoma following estrogenic therapy have been reported, in most of whom prior curettage had shown none to be present. In all cases the therapy extended over long periods of time and the total dose was large. Fremont-Smith's patient was followed for eighteen years and had had a total of 292 mg. of estradiol, 1,085 mg. Premarin, and 18 mg. diethylstilbestrol, all in the preceding period of eight years. Two years prior to the finding of adenocarcinoma of the endometrium a curettage had revealed an endometrial hyperplasia. Edmund Novak reported a patient recently who had been given 1 mg. of stilbestrol daily for twelve years. We have had a case in a 35-year-

old patient who was given an estrogenic "shot" three times a week for two years by her family physician; since this type of carcinoma is rare at this age, the estrogenic medication may have been an etiologic factor.

Fig. 694.—Photomicrograph showing the effect on the endometrium of weekly injections of 200 R. U. of estrogen for a period of seven months, in a 24½-month-old C.B.A. mouse. At A is an area in which the glands are proliferating rapidly. There is very little intervening stroma and the glands invade the underlying stroma deeply. (From Crossen: South. M. J., June, 1946.)
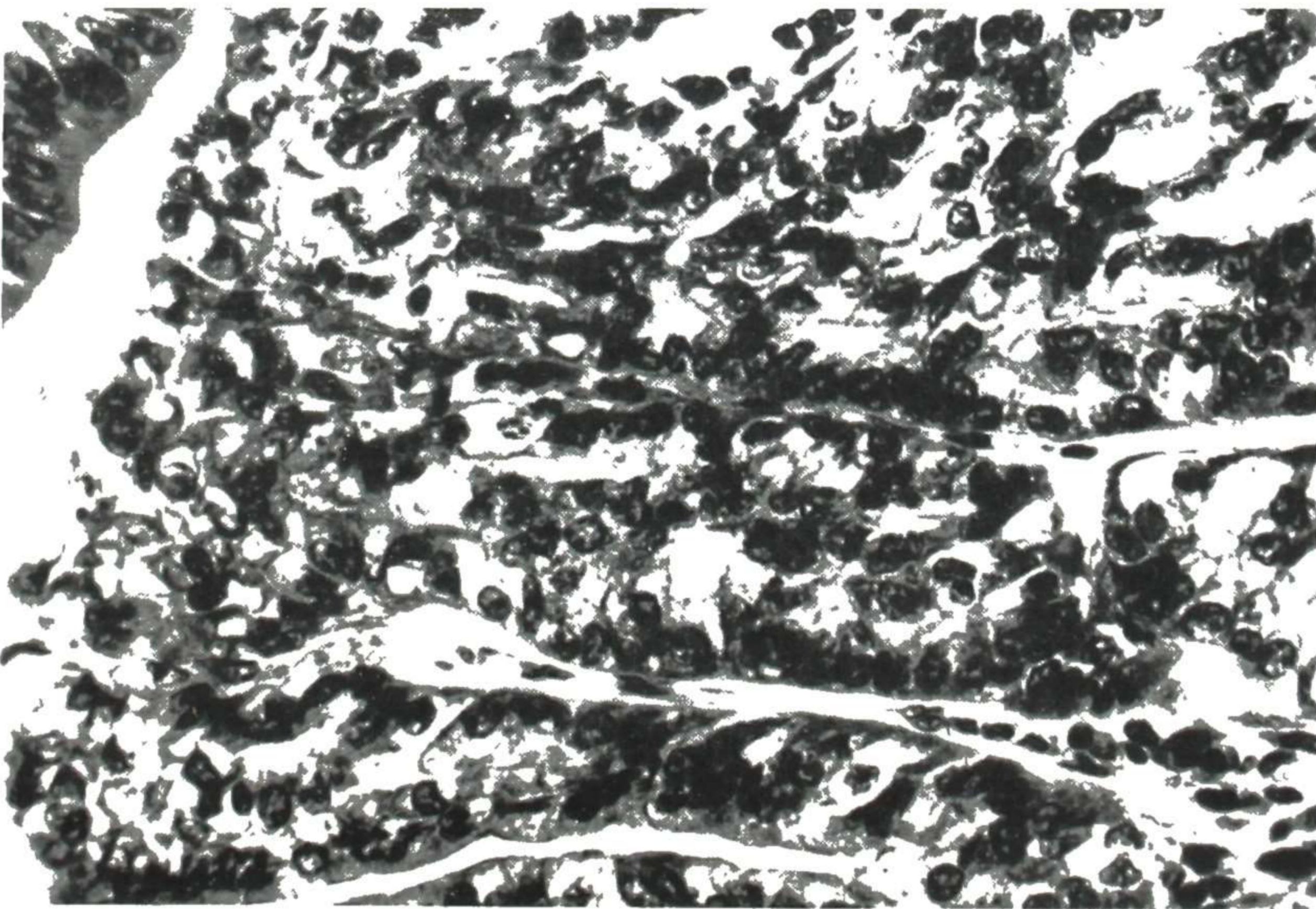
Fig. 695.—High power of the same area shown in Fig. 694. (From Crossen: South. M. J., June, 1946.)

The relation of estrogens to carcinogenesis has been extensively studied in experimental work in animals. Allen and Gardner were the first to produce

cervical carcinoma in mice by estrogen administration, and this work was confirmed by Miller and Pybus in 1942.

Endometrial carcinoma is common in rabbits. Greene and Saxton reported 83 in their rabbits, and they believe that there is abundant evidence that excessive estrogenic stimulation was the main factor involved. So far as Dr. Loeb and I have been able to find, there have been no instances reported of endometrial carcinoma occurring in mice, nor has it ever been induced in mice experimentally. Since most of the experimental work had been done in young mice and it had always been our feeling that age was an important factor in the development of carcinoma, we decided to see what prolonged administration would do to the endometrium in old mice. Dr. Loeb was good enough to give us some old mice which he had been using to study changes caused by aging. Figs. 694 and 695 show our results. This was diagnosed as carcinoma by Otto Schwarz and by Loeb, but later Loeb decided that since there was no way of prophesying as to whether or not this lesion might not have receded if the estrogen had been discontinued, we reported it merely as an unusual degree of endometrial stimulation and hyperplasia. In his extensive investigative work in this field, Loeb had never seen changes of this extent in mice.


Fig. 696.—Opened uterus showing the large polyp protruding from the endometrium and through the cervix ((approximately natural size). (From Crossen and Suntzeff: Arch. Path., December, 1950.)

In monkeys spontaneous malignant tumors are rare and there are none reported occurring in the cervix or endometrium. Cystic hyperplasia of the endometrium and metaplasia of the cervical epithelium have been produced by estrogen administration but until recently there have been no tumors of any kind produced in monkeys. In 1941, I was able to obtain a menopausal monkey and, in collaboration with Dr. Suntzeff, administered estradiol and progesterone over a period of three years. Pelvic examination and curettage at the start of the experiment showed the uterus and endometrium to be nor-

mal. The polypoid benign growth which was produced was about a fourth the size of the uterus. The polyps and the hyperplastic endometrium can be seen in Figs. 696 and 697.

A.
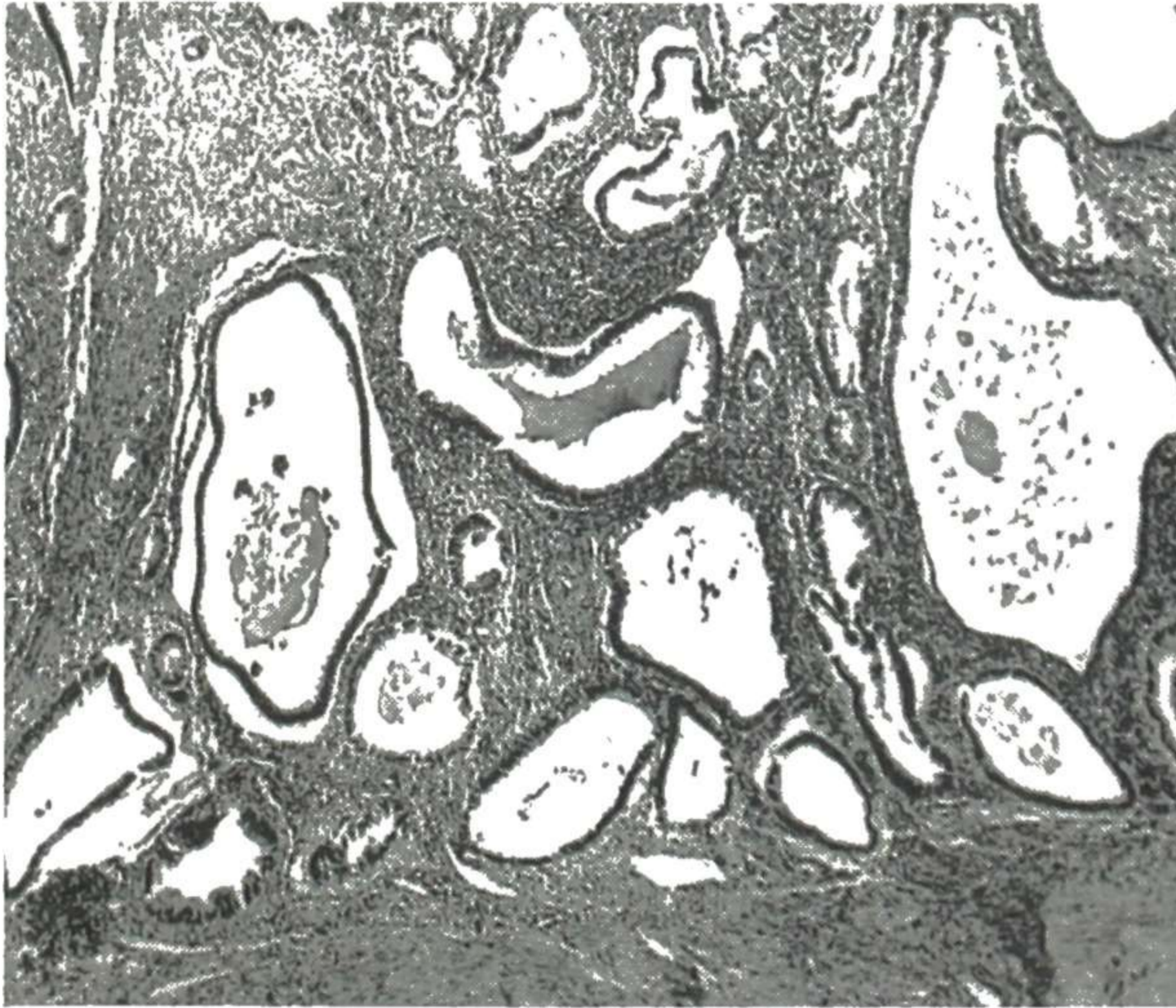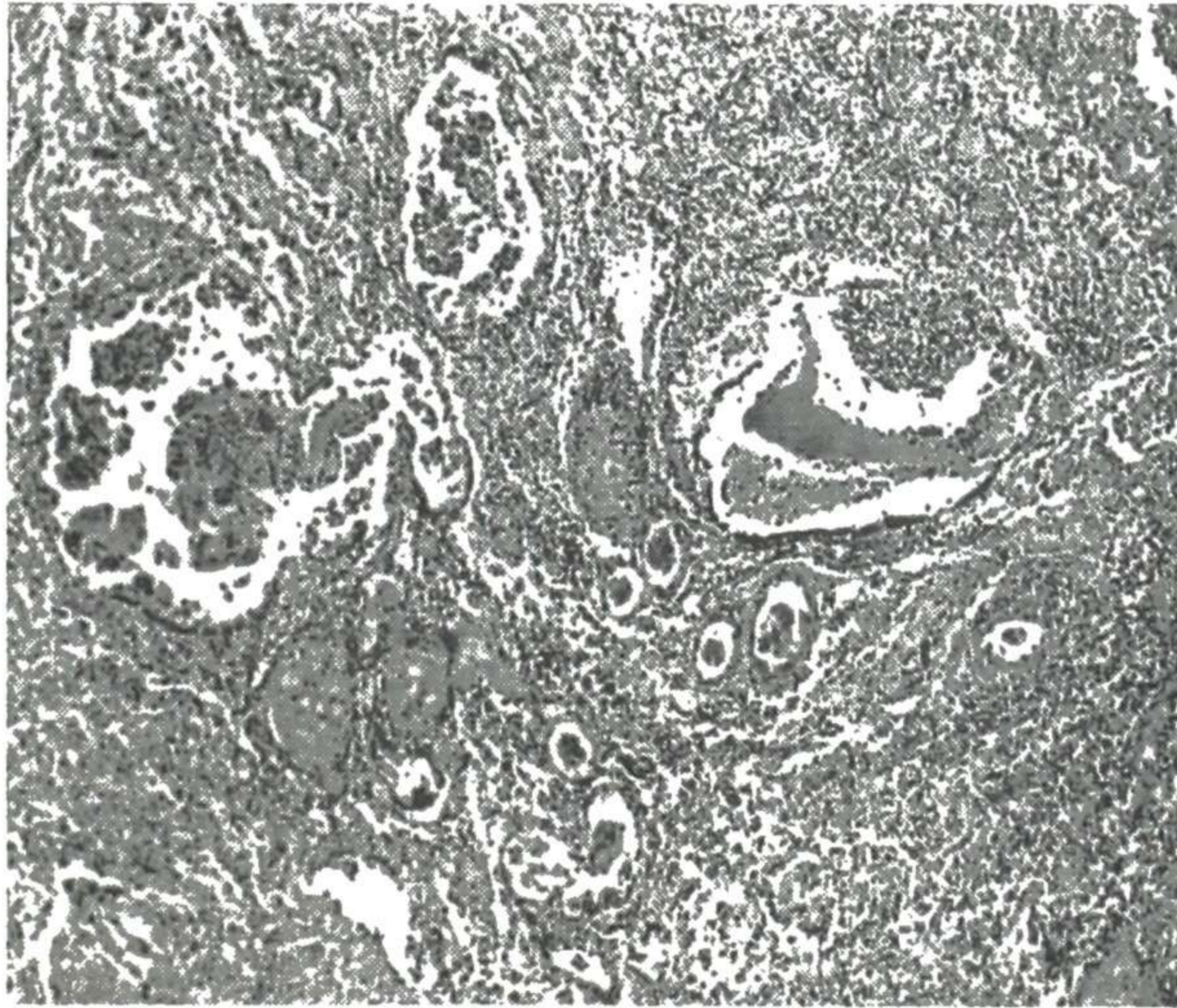
B.

Fig. 697.—*A*, Photomicrograph of an area from the adenomatous polyp (medium power magnification). *B*, Photomicrograph of endometrial hyperplasia, Swiss cheese pattern (medium power magnification). In the upper right field can be seen a group of hypertrophied vessels. (From Crossen and Suntzeff: Arch. Path., December, 1950.)

Though one cannot state positively that estrogens are carcinogenic in women, from this wealth of circumstantial and experimental evidence it would seem logical to conclude that estrogens should be used clinically only on definite indications and then only in small doses over short periods of time. Great caution should be exercised in menopausal women with a family history of cancer, endocrine dysfunction, or delayed menopause.

Other Clinical Factors

In regard to age, the decade for most frequent occurrence of corpus cancer is from fifty to sixty years, thus differing from cervix cancer which occurs most frequently in the decade forty to fifty years. Randall in 330 proved cases of endometrial carcinoma admitted to the University of Iowa Hospitals found that three-fourths fell in the age group 50 to 69 years, and the average age when the diagnosis was made was 58.8 years. Palmer et al. in 957 cases found the peak at the age period of 55 to 59 years, whereas Corscaden found the peak period between 50 and 55 years, a little lower than in most series. In recent years it has been repeatedly shown that carcinoma of the fundus is more common than was formerly supposed in younger women; the incidence occurring under forty varies from 5 per cent in a series reported by Speert, to 2.1 per cent in a study of 1,694 cases reported by Dockerty.

In regard to parity Wilson concludes that it has no etiological importance, though in our series and in that of Corscaden 38 per cent were nulliparous. In the younger women a high incidence of sterility was noted in the various series reported by Speert, by Sommers, and by Dockerty. This fits in with the high incidence of menstrual and other endocrine disturbances in these younger patients.

Several studies indicate that in some cases of endometrial carcinoma rather typical changes are found in the ovary. Woll and associates found stromal hyperplasia of the ovarian cortex in 92 per cent of the patients having endometrial carcinoma, whereas only 42 per cent of a control group showed this ovarian hyperplasia. In addition to this finding, Sommers, Hertig. and Bengloff found ovarian changes similar to those found in cases with the Stein-Leventhal syndrome. Shaw and Dastur in 24 ovaries removed from 48 cases of endometrial cancer found groups of hilus cells which they felt arose from the endothelium of the blood vessels.

There is probably no single factor responsible for the development of endometrial carcinoma, but endocrine dysfunction with excess estrin, plus genetic predisposition, aging tissue, or tissue with disturbed nutritional balance are factors frequently associated with these cases.

PATHOLOGY

Gross.—In carcinoma of the corpus (endometrial carcinoma), the uterus may or may not be larger than normal. As this cancer occurs most frequently between the ages of fifty and sixty years, the uterus, in the early stage of the carcinoma, may be senile and considerably smaller than a normal adult uterus. As the disease advances, the uterus enlarges progressively, and as the process penetrates the wall, adjacent structures become involved. The myometrial hyperplasia described by Tannhauser has previously been mentioned. This progressive involvement is indicated in Figs. 698 to 700. Gross specimens of the disease in different steps of development are shown in Figs. 701 to 703.

Microscopic.—The microscopic characteristics of carcinoma of the endometrium are shown in Fig. 704, *A* and *B*. Endometrial carcinomas are graded into four classes, representing graduations in structure from the mature glandular form of mild malignancy to the immature solid form of great malig-

nancy. This grading was suggested by Mahle, on the basis of MacCarty's standard of cell differentiation. Healy has done much helpful work in clinical application of the grading and in developing its general use, and his name is frequently attached to this grading system, though in his writings he gives full credit to Mahle.
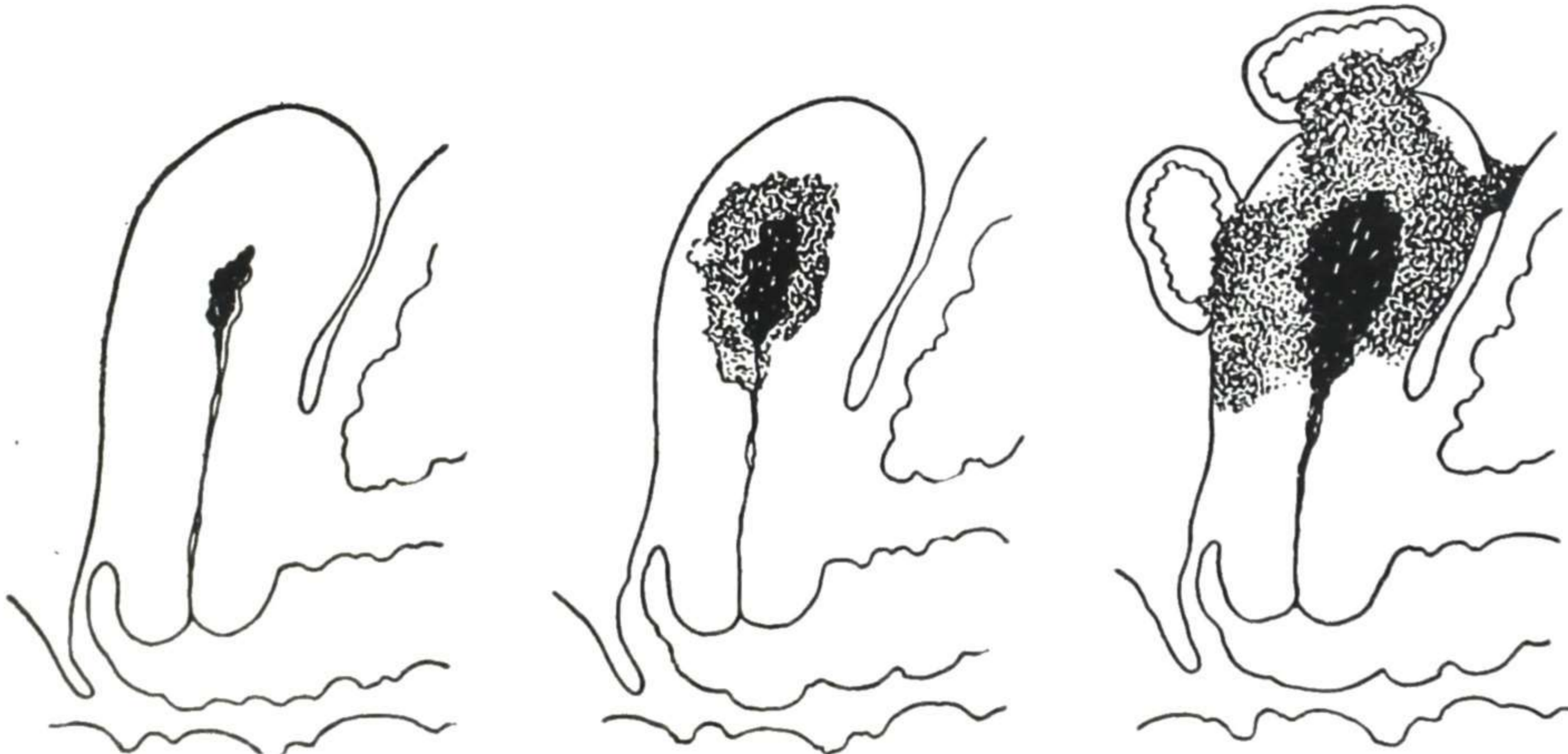

Fig. 698.　　　　Fig. 699.　　　　Fig. 700.

Figs. 698 to 700.—Progressive development of carcinoma of the corpus uteri. Fig. 698, Carcinoma of the corpus begins in the endometrium. Fig. 699, Extensive involvement of the uterine wall. Fig. 700, Extension through the uterine wall and involvement of adjacent structures.
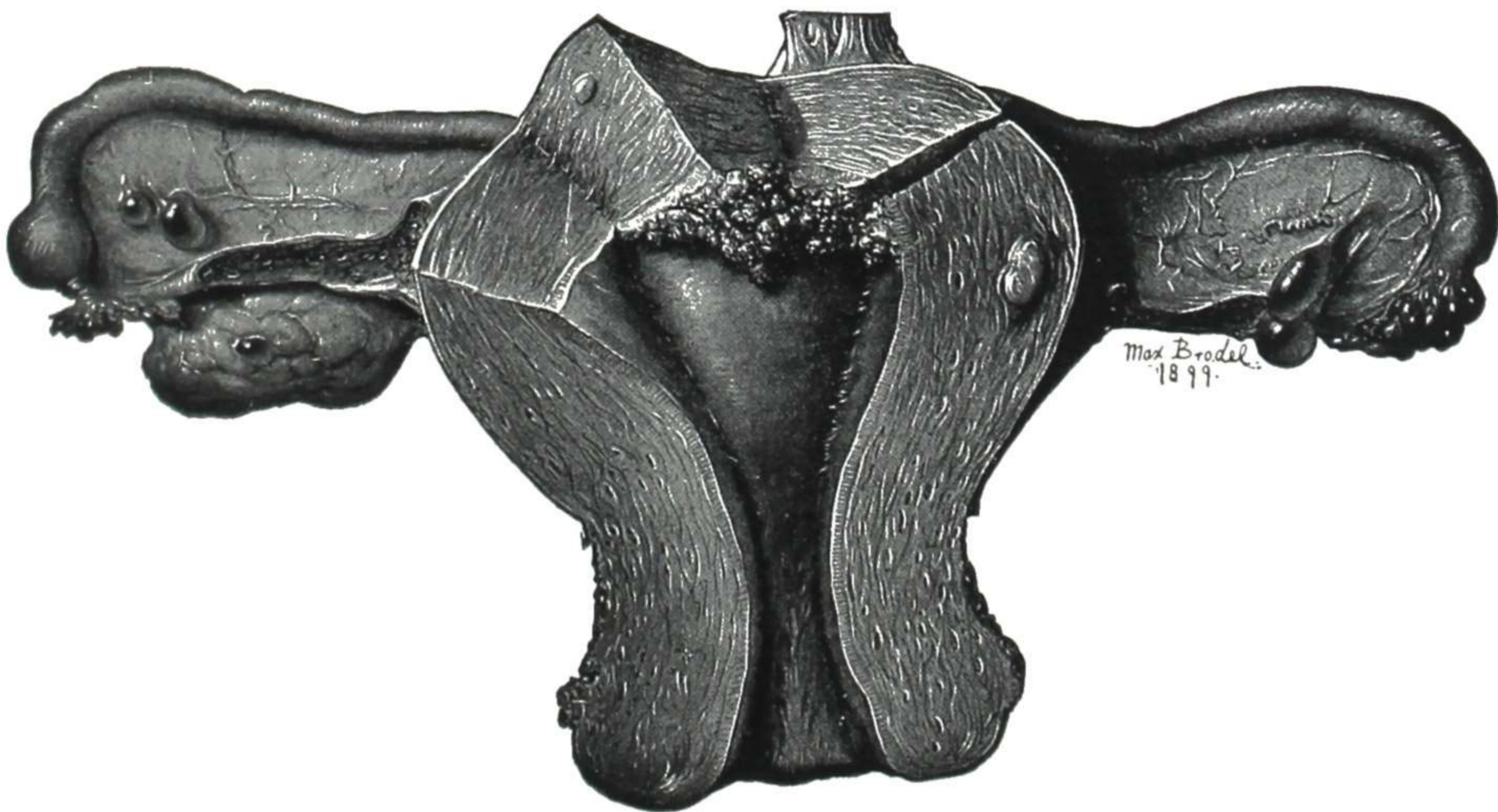
Fig. 701.—Beginning carcinoma of the corpus uteri. There is no external sign of the growth at this stage, except an occasional streak of blood in the leukorrheal discharge. The diagnosis must be made by curettage. (From Cullen: Cancer of the Uterus.)

In connection with the fact that this grading is based on the extent of departure from normal gland forms, it may be noted that endometrial hyperplasia represents a type of endometrial structure lying between normal endometrium and carcinoma of Grade I. In fact, the diagnosis in a doubtful case consists usually in determining whether the condition is hyperplasia or begin-
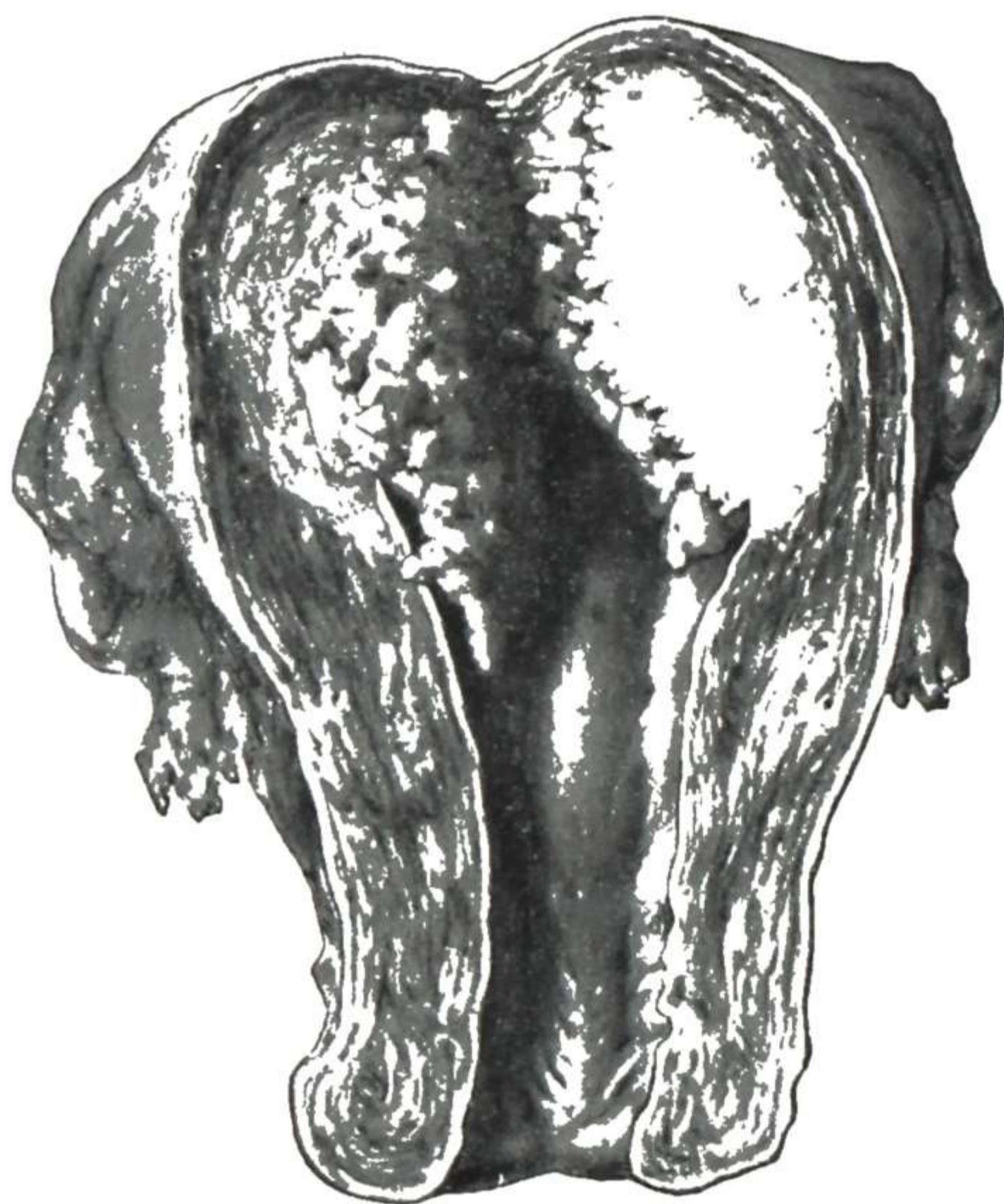
Fig. 702.

Fig. 703.

Fig. 702.—Drawing from a specimen of a comparatively early carcinoma of the corpus uteri. Gyn. Lab.

Fig. 703.—Drawing from a specimen of a more advanced carcinoma of the corpus. The growth has invaded the muscular wall extensively, but the peritoneal covering of the uterus is not yet involved. Gyn. Lab.

A.

B.

Fig. 704.—Diagnostic curettings, under low power (*A*) and high power (*B*). Gyn Lab.

Fig. 705.   Fig. 706.

Fig. 705.—Endometrial hyperplasia, for comparison with endometrial carcinoma, Grade I. Gyn. Lab.

Fig. 706.—Higher power of the endometrial hyperplasia shown in Fig. 705. Gyn. Lab.
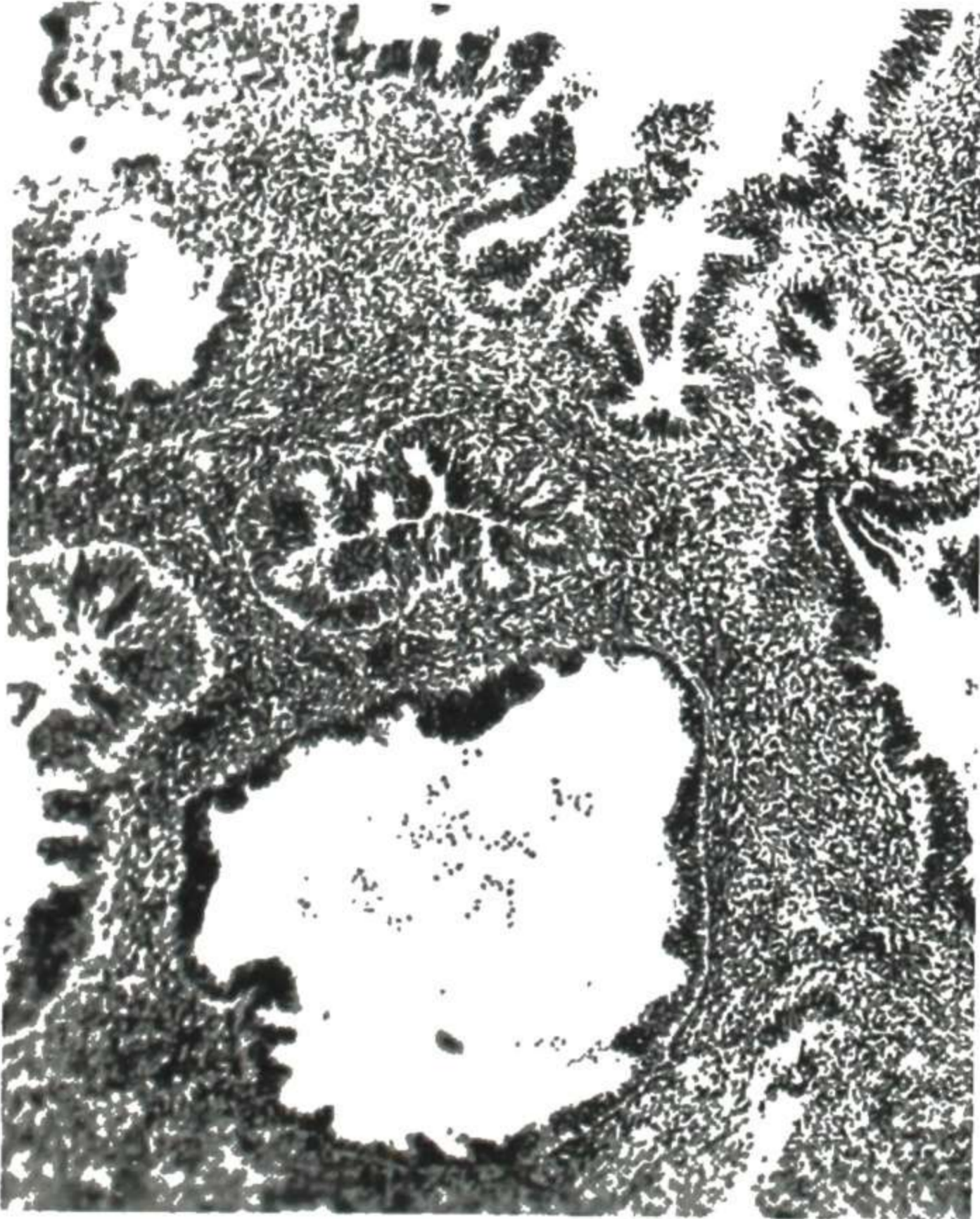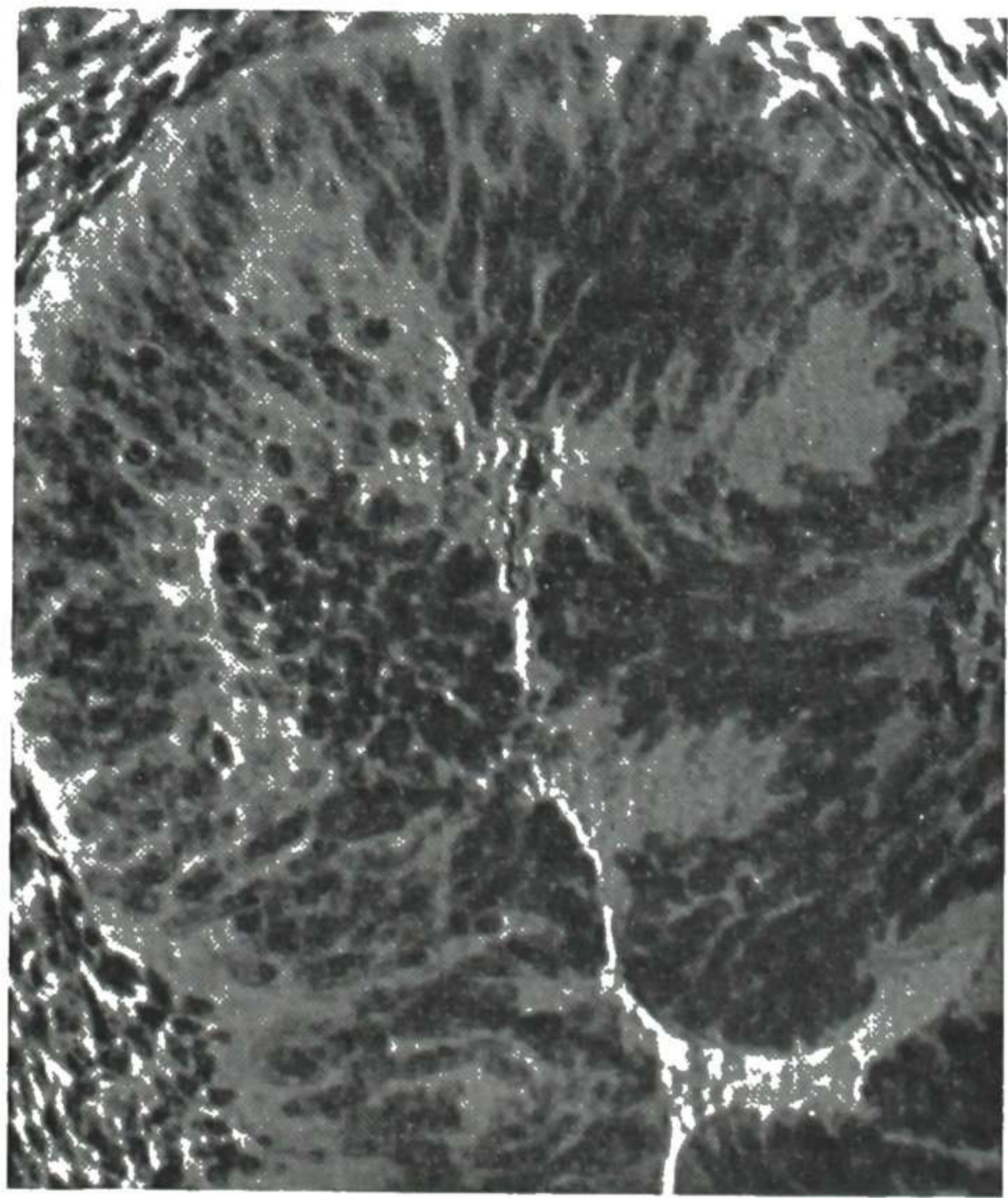

Fig. 707.   Fig. 708.

Fig. 707.—Endometrial carcinoma, Grade I. Note the well-developed glandular character and resemblance to hyperplasia, except for the abnormal piling-up of the epithelium and the character of the cells. Gyn. Lab.

Fig. 708.—Higher power of Fig. 707, showing details of the cells and their arrangement. Gyn. Lab.

ning cancer. Consequently the characteristics of hyperplasia are shown (Figs. 705 and 706) along with those of carcinoma, Grade I.

An interesting fact in connection with the slides showing hyperplasia and those showing carcinoma of Grade I is that they are from the same patient. One year after she was curetted and the hyperplasia found, symptoms returned requiring another curettage and the carcinoma of Grade I was found.

The points cited in the following differentiation into grades are largely from Healy's clear description:

Grade I (Figs. 707 and 708). Papillary Adenoma Malignum. This is a characteristic form in which the growth is superficial and entirely papillary. The papillae are low, the cells are not very atypical, and there is no infiltration. As the cells are not multiplying rapidly, the glands are well formed. Some cases are extremely difficult to distinguish from adenomatoid endometritis. It is in this histologic type that cures following curettage have been observed.

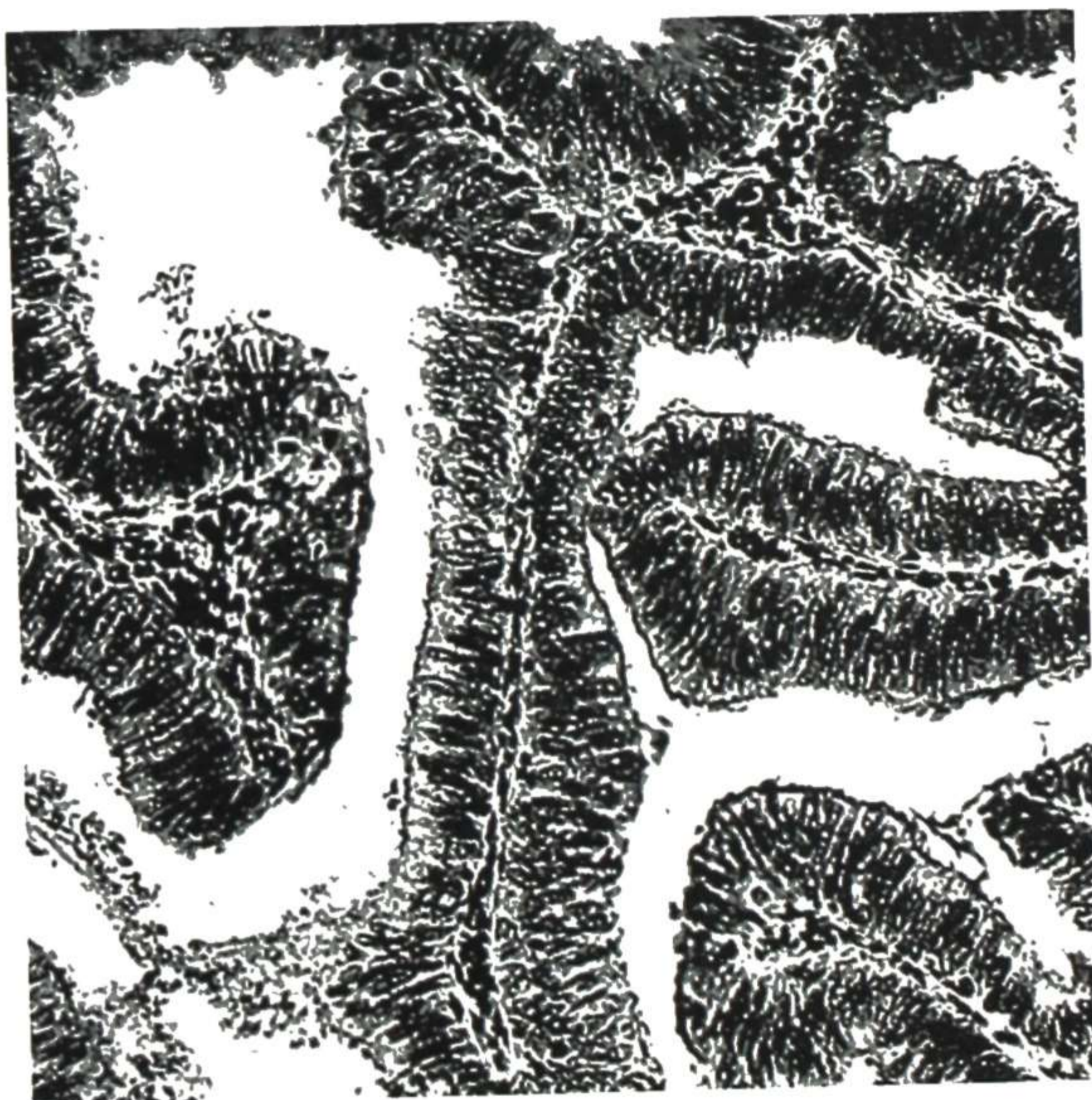Fig. 709.   Fig. 710.

Fig. 709.—Endometrial carcinoma, Grade II. Notice the increasing departure from normal gland characteristics, as explained in the text. Gyn. Lab.

Fig. 710.—Higher power of Fig. 709, showing details of the erratic cell activity. Gyn. Lab.

Grade II (Figs. 709 and 710). Adenoma Malignum. This group comprises those cases in which the uterine glands are markedly enlarged and elongated. They are often thrown into folds and convolutions to form inside papillae. The cells are cuboidal or cylindrical and are arranged in compact layers about the gland lumen. The nuclei are very hyperchromatic, giving to the stained section a dark appearance. Mitoses are often abundant. The entire tumor appears to be composed of giant glands encroaching upon the interglandular connective tissue. The stroma is thus scant and adjacent glands come in direct contact. The polarity of the tissues is everywhere maintained. As Lindsay has emphasized, if at any point the cells show a tendency to form solid masses and infiltrate the stroma, the tumor should be classed as adenocarcinoma.

Grade III (Figs. 711 and 712). Adenocarcinoma. Adenocarcinoma includes all cases in which the tumor forms solid masses of cells which grow in cords and columns. There is definite loss of polarity with infiltration of the stroma. Signs of anaplasia are more marked

than in adenoma malignum. The cells are more atypical. Not infrequently portions of the tumor show adenoma malignum and other parts adenocarcinoma. These tumors are classed as adenocarcinoma. Although the growth is more atypical than in adenoma malignum, the glandular arrangement is still maintained.

Grade IV (Figs. 713 and 714). Diffuse (Embryonal Anaplastic) Carcinoma. This group is characterized by a complete loss of polarity. The glandular arrangement is entirely lost. The growth is diffuse and is composed of small round and polyhedral cells, closely
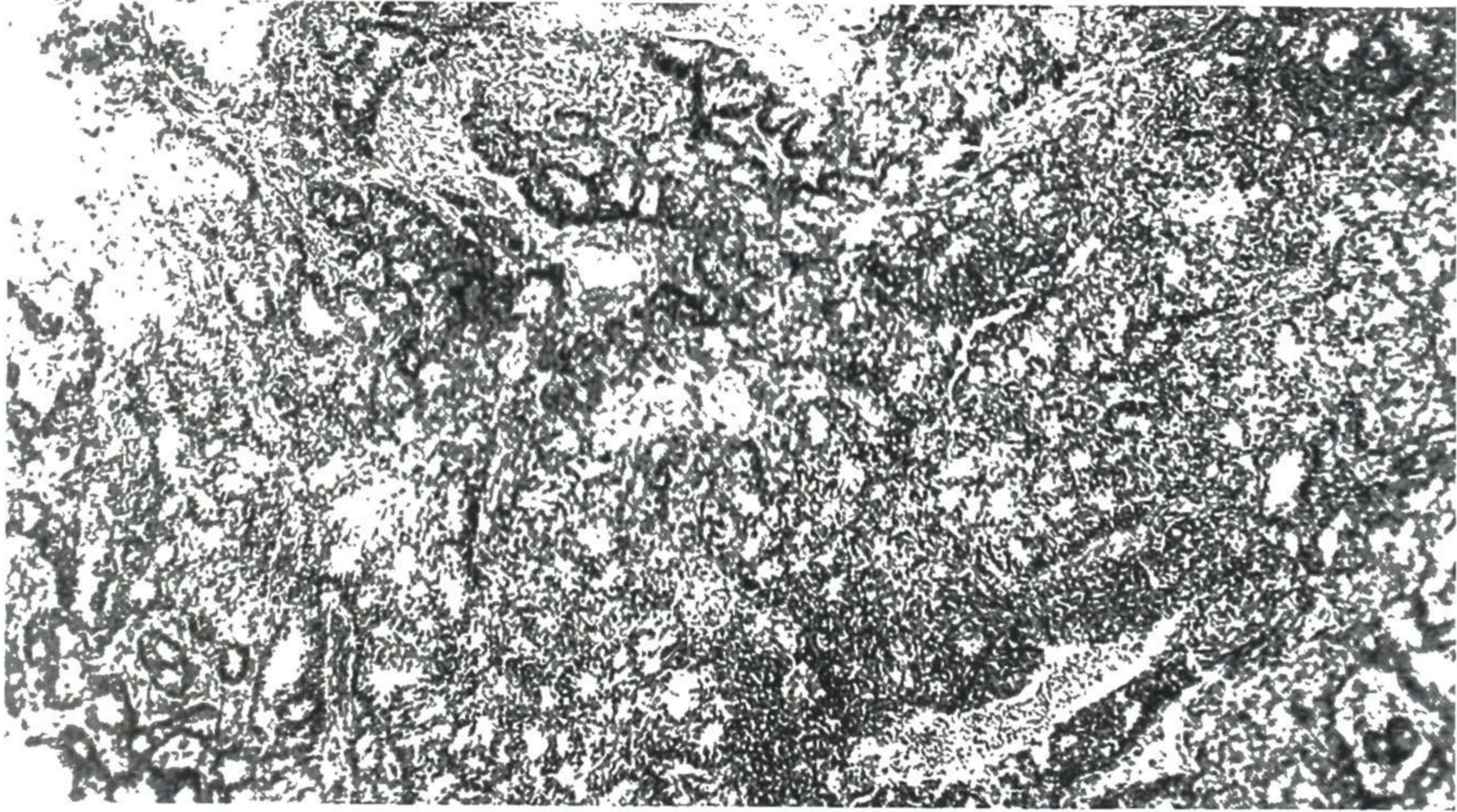

Fig. 711.—Endometrial carcinoma, Grade III. Shows the increasing tendency to solid invasion, but there are still irregular gland patterns. Gyn. Lab.
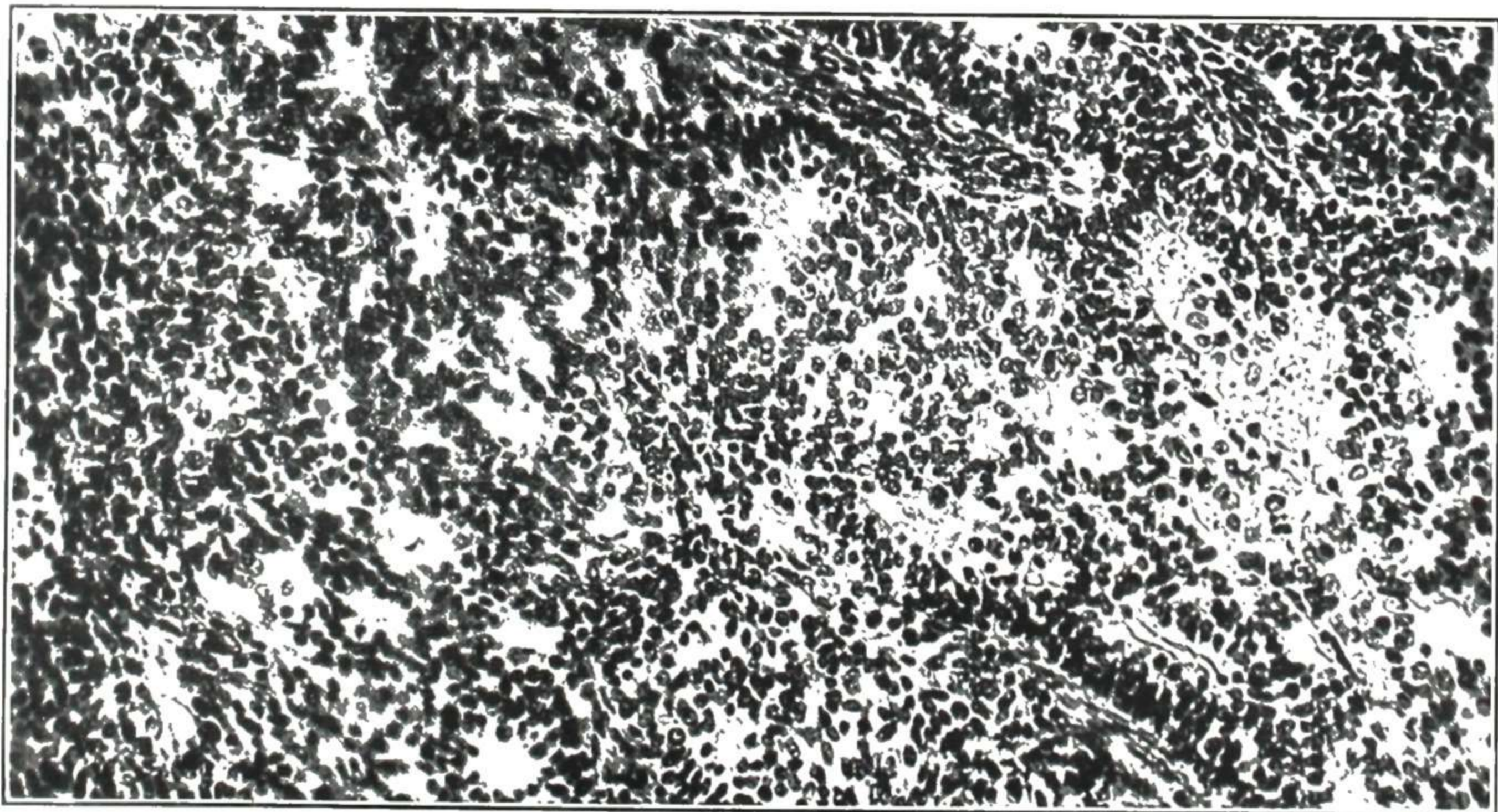

Fig. 712.—High power of Fig. 711. Gyn. Lab.

packed, growing in sheets and cords. The nuclei are small and hyperchromatic and the cytoplasm is scanty. There are marked signs of anaplasia. There is complete loss of differentiation. Mitoses are very abundant. The histologic structure often closely resembles anaplastic epidermoid carcinoma of the cervix from which it may be difficult to distinguish microscopically. Fig. 715 shows mixed grades in carcinoma of the endometrium, Grades I and IV.
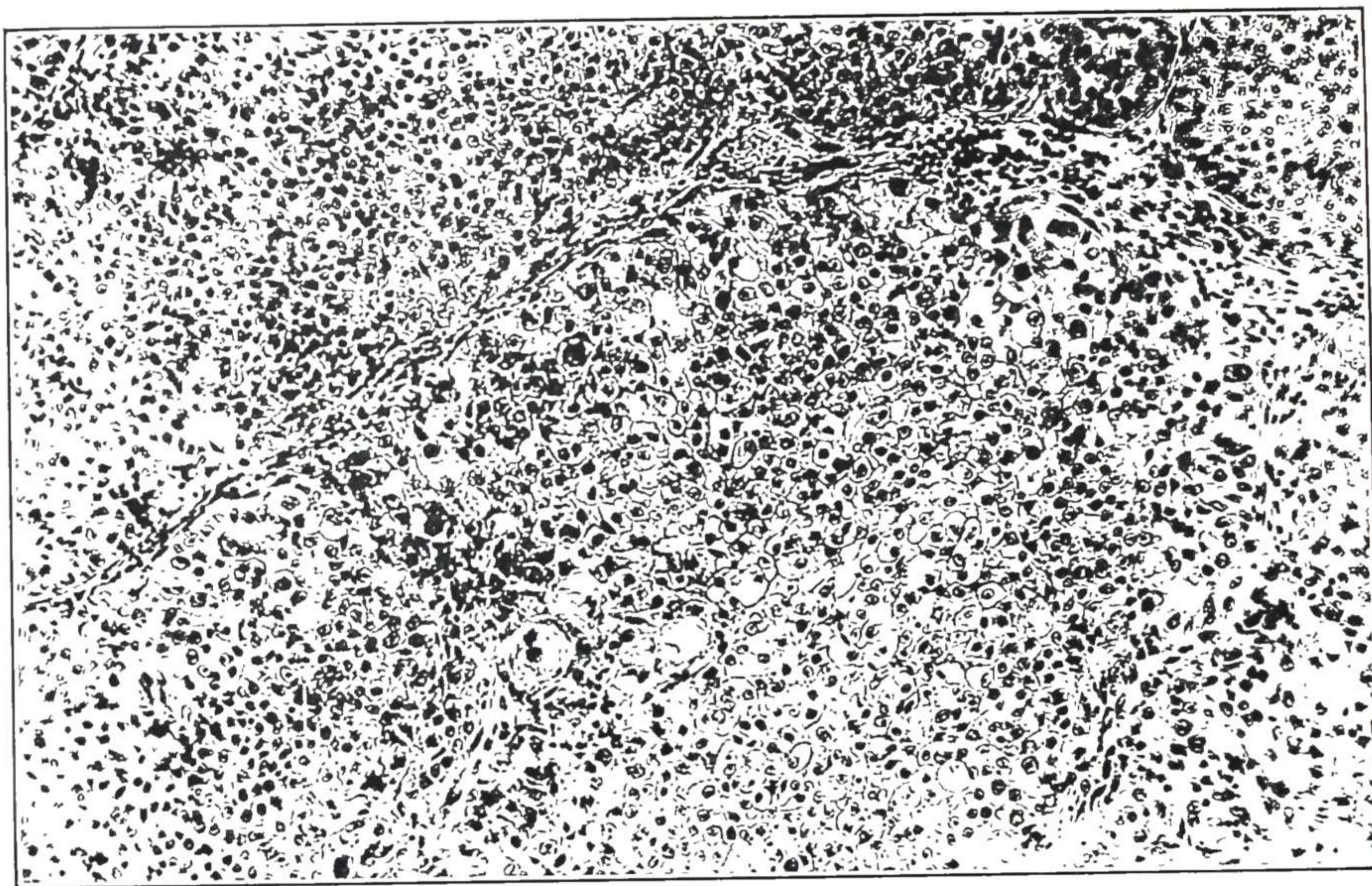
Fig. 713.—Endometrial carcinoma, Grade IV. The malignant cell change has advanced to the point of solid invasion, with only an occasional suggestion of gland tendency. Gyn. Lab.
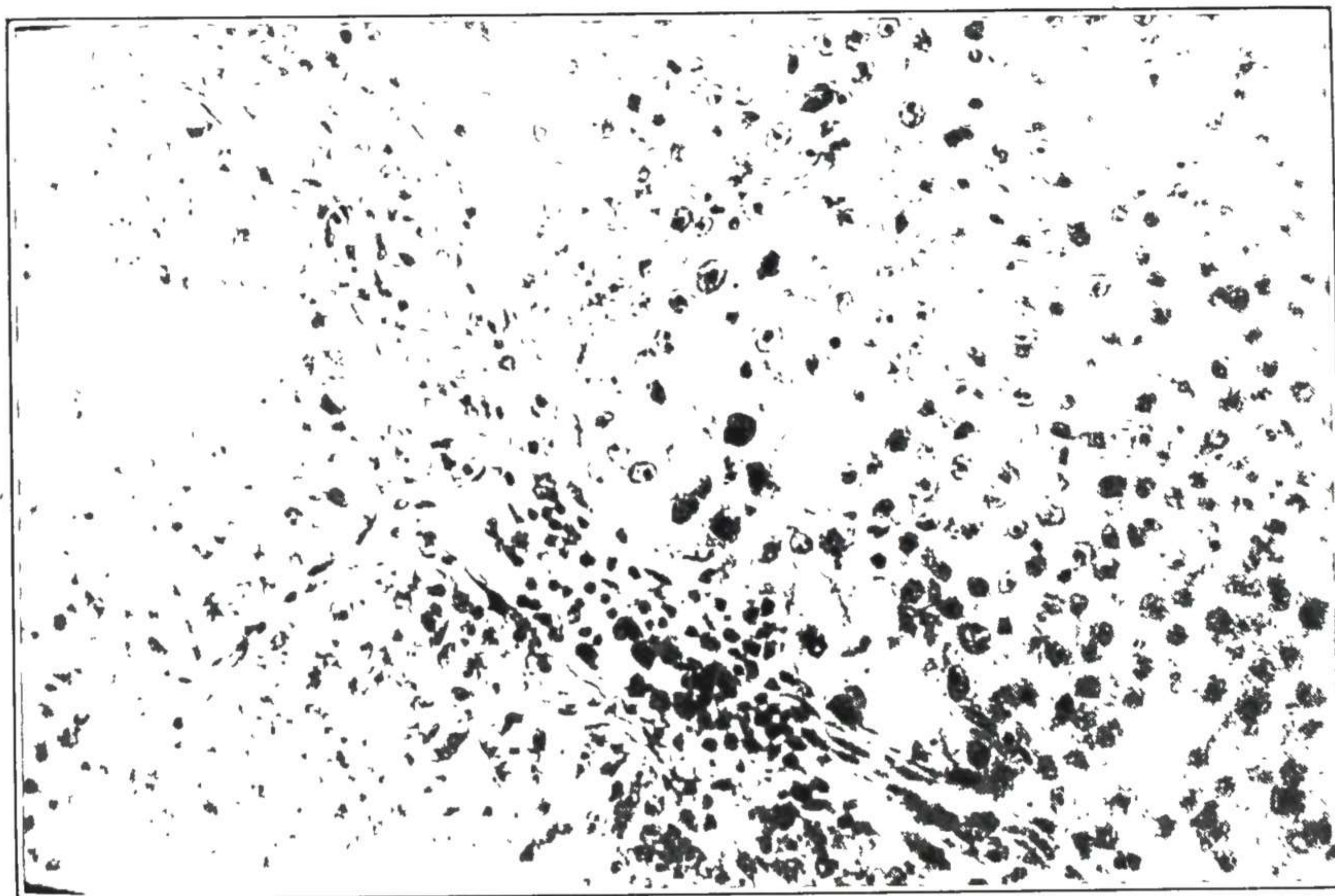

Fig. 714.—High power of Fig. 713, showing character of the cells.

The malignancy of these grades increases from group one to group four, and the response to radiation is in the reverse order.

Epidermization, described and illustrated in connection with the diagnostic problems of cervix cancer, occurs also in the endometrium. It is not frequent in this situation and is probably due, as a rule, to metaplasia or to "rests" of embryonal cells which retain the power to develop into the squamous type.

Fluhmann states that he found only six cases in the literature, including his own. Novak states that it is probably not so rare. Hintze reported nine cases.
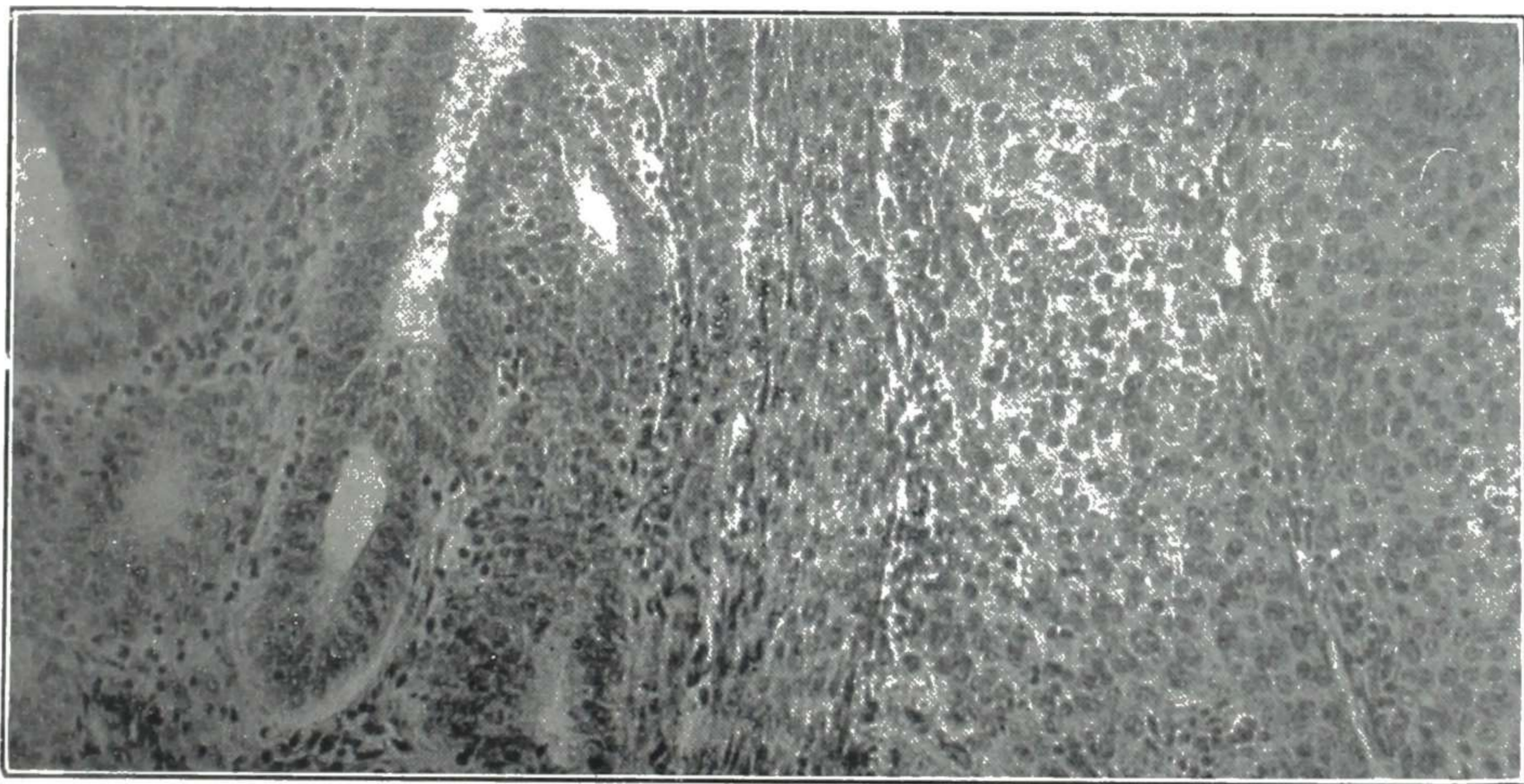

Fig. 715.—Adenocarcinoma of the endometrium, showing different grades in the same specimen. Grade I left and Grade IV right.

Novak feels that the condition is essentially benign and states that seven of Hintze's patients were cured by simple curettage and have remained well from two to five years after operation. Motyloff has recently reviewed this subject and reported a similar case which was followed for five years. His case eventually developed cholesteometra, which he feels is the end result of heteroplastic differentiation of the basal cells and probably not metaplasia. Fig. 716 shows surface epidermization of the endometrium overlying an adenomyoma, and Fig. 717 shows the epidermization in the deeper glands. Fig. 718 shows metaplasia in an adenocarcinoma.

Metastases.—The adenocarcinomas of the corpus are relatively slow growing as cancer goes, and they usually metastasize late from Grades I and II. Grades III and IV grow more rapidly, and the prognosis is much more grave. Finn found that the rate of recurrence in the undifferentiated type of endometrial carcinoma was five times as frequent as it was in the well-differentiated type. He found that the most frequent nodes involved were the aortic, iliac, and inguinal groups. The most common site of recurrence was the vagina, an important point in treatment. In his persistent or recurrent cases, 56 per cent recurred in one year, 69 per cent in two years, and 85 per cent in three years.

Fig. 716.—Squamous "metaplasia" or "epidermization" of the surface epithelium in a case of hyperplasia of the endometrium and adenomyoma. This is a purely benign change.
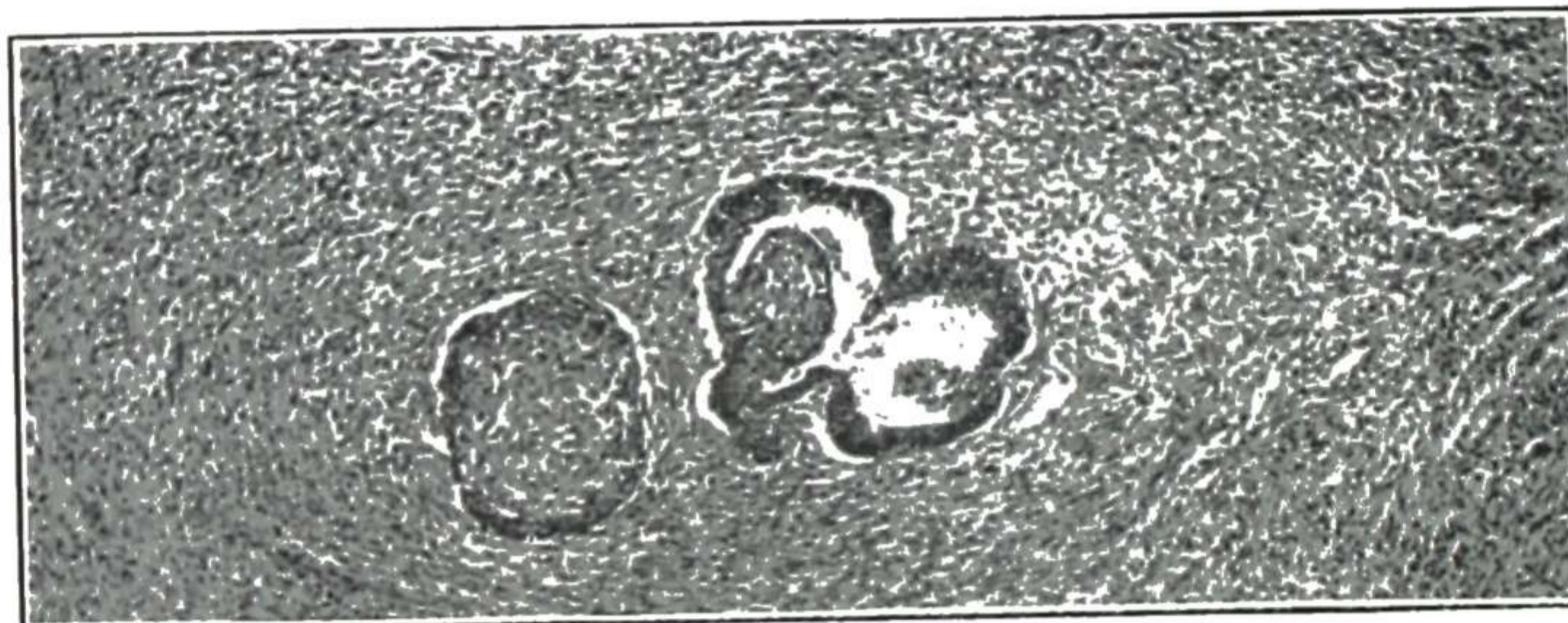

Fig. 717.—"Epidermization" of deeper lying gland epithelium of adenomyoma in same case. These changes, formerly considered as evidence of malignancy, are now looked upon as definitely benign (see text).

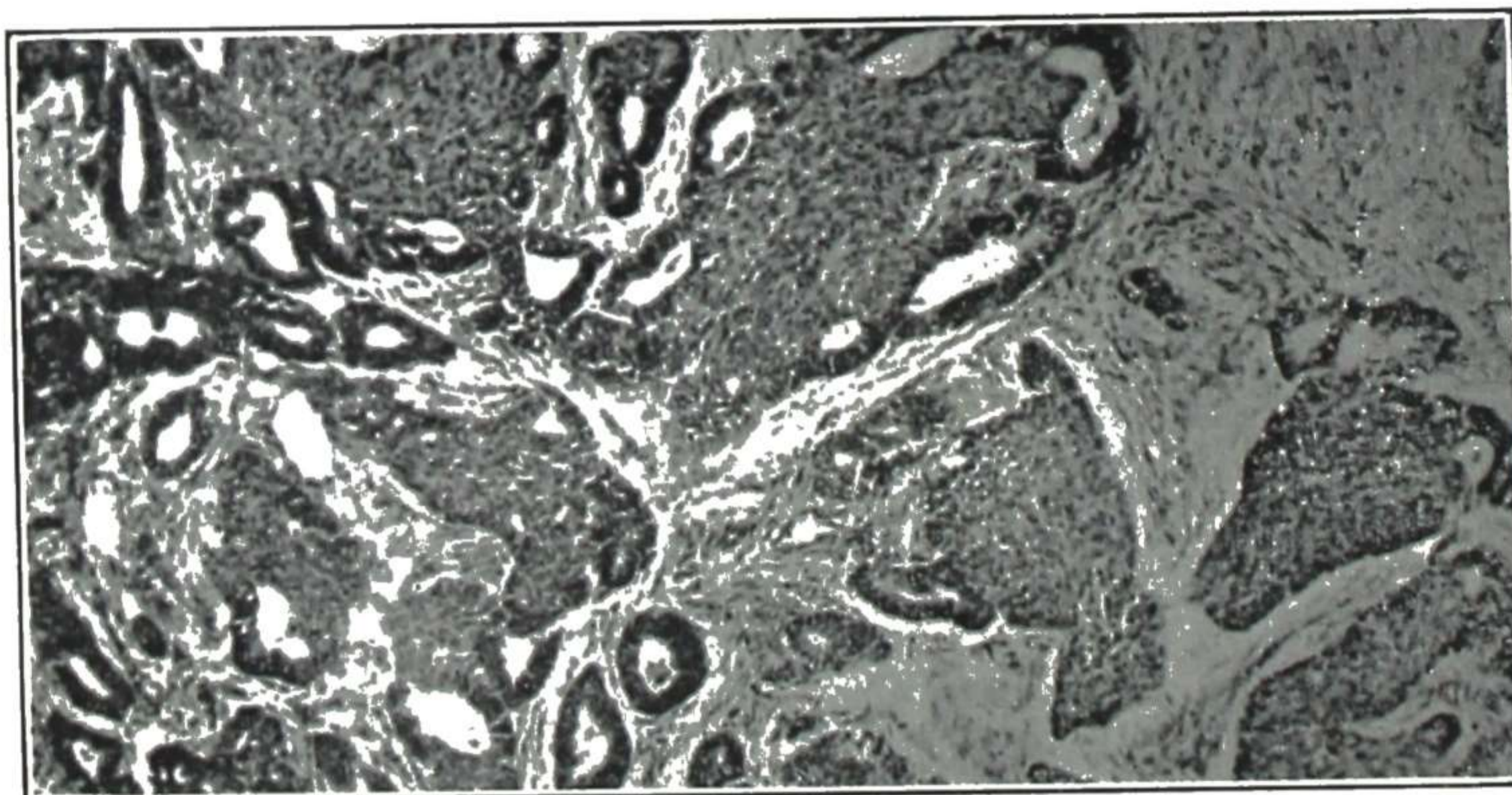Fig. 718.—Extensive squamous metaplasia in an adenocarcinoma of the uterus. Here there is no doubt of the transition from a primary gland carcinoma, but in other areas the squamous change is so extensive that the primary character of the tumor is blotted out. Such cases have in the past often been wrongly interpreted as combinations of squamous cell and adenocarcinoma.

(Figs. 716 to 718 from Novak: Am. J. Obst. & Gynec.)

SYMPTOMS AND DIAGNOSIS

As is evident from the discussion under Etiology, there are certain characteristics which are common to the woman who is prone to develop endometrial cancer.

She is usually obese and has a history of endocrine dysfunction often evidenced in menstrual disturbances of a type associated with excessive estrogen secretion. Corscaden and Gusberg found that women with endometrial carcinoma weighed on an average of 18 pounds more than those with cervical carcinoma. These patients are frequently single and, if married, the incidence of sterility is high. Diabetes is not uncommon in these patients; it was present in 11 per cent of Scheffey's cases, and Palmer found it to be almost seventeen times as frequent in cases with fundal carcinoma as it was in the same age group in the general population.

Bleeding is the symptom which usually causes the patient to seek medical advice; in younger women this may occur as excessive flow with intermenstrual spotting; in older women it is usually a recurrence of bleeding after a period of cessation for months or years. Late or delayed menopause was found to be four times as frequent in these cases as in normal cases. Bleeding was the first symptom in 90 per cent of the cases, and in the remaining 10 per cent vaginal discharge was the complaint. Fortunately, due to the fragile nature of the endometrium, the surface over the early lesion is easily broken so that bleeding or serosanguineous discharge usually occurs while the growth is still limited to the endometrium, and if the physician recognizes the warning signal and acts accordingly, a fairly early diagnosis results. The conclusive proof of endometrial carcinoma depends upon a microscopic examination of the curettings, though a vaginal smear is a valuable aid in indicating the need for further confirmation. Whether the smear is positive or negative, if there is abnormal bleeding which does not respond to therapy in a woman past thirty-five years of age, curettage is indicated from a therapeutic as well as a diagnostic standpoint.

A technique described by Heyman has, in his hands, given more information on the size and location of the tumor than has simple curettage. Before dilating the cervix, the lower portion of the cervical canal and area near the external os are scraped with a small curette. After measuring the uterine cavity with a sound, the cervical os is dilated to the size of a No. 8 Hegar dilator; then a uterine canal forceps (similar to a narrow sponge forceps) is introduced and kept closed until it reaches the fundus, at which time it is opened, closed, and withdrawn. This procedure is repeated in several areas of the fundus. Next the area of the upper cervix up to and including the internal os is curetted, and finally curettage of the entire fundus is done. The tissue obtained from each of the three different areas is preserved separately, and in this way some idea as to the distribution of the carcinoma is obtained, and any polyps missed by the curette are usually discovered with the dressing forceps technique.

Very often in these bleeding cases there is also chronic cervicitis, which is an additional reason for urging the curettage, as the chronic cervicitis may be taken care of at the same time by conization. The curettage is effective

treatment for the endometrial bleeding, and the conization removes the menace of chronic irritation in the cervix. All tissue removed is subjected to microscopic investigation, which gives definite information as to what process is going on in both cervix and corpus and whether or not there is any complicating malignancy.

Uteroscopy with special endoscopic tubes has been used in these cases, as has also x-ray visualization of the endometrial irregularities by injecting opaque material. These measures combined with special instruments for clipping off specimens of such irregularities for cancer diagnosis may have a strong visual and technical appeal to the uninitiated—so strong as possibly to obscure other important features of the situation. Hence it may be well to call attention to certain points in this connection. This method is *contraindicated* on account of the *danger* and also on account of the *inaccuracy* or inadequate handling of the diagnostic problem. The danger of the injected fluid carrying carcinoma cells into the peritoneal cavity has been mentioned. Sampson has demonstrated the transfer of cells from the endometrium through the tubes from slighter causes than injection, and in carcinoma such transportation by injected fluid might have serious results.

In regard to inaccuracy, this method seems to be a reversion to the old unsatisfactory plan employed in suspicious cervix cases, namely, excision of a small specimen and if no cancer is found then waiting and perhaps another specimen excision later as conditions develop. This has now been superseded by a more adequate method which consists of excision of the whole involved area. Thus all the involved tissue is secured for microscopic investigation, so that negative findings really exclude cancer, and at the same time there is effective treatment for the nonmalignant lesion which stops the chronic irritation. Fortunately, in corpus cancer gynecologists started with the thorough method of removing the whole diseased endometrium by curettage and submitting it all to microscopic examination. To do less would seem a backward step in diagnosis. Again, a bleeding uterus needs treatment as well as investigation, and removal of the diseased endometrium by curettage furnishes this.

The vaginal smear has been discussed in the early part of this chapter and also in Chapter 2 on Diagnosis. In cases suspected of endometrial carcinoma the material is obtained by means of an Asepto syringe from the external os, and the vagina or the Doyle spoon can be used for a total uterine sample. Where facilities are available, this is a very valuable aid in discovering which case needs further investigation. In some reported cases of proved carcinoma the smear has continued positive in spite of a negative curettage, and in a case of a patient who had had a LeFort operation it offered the only clue to a cervical carcinoma behind the repair.

Clinical Classification.—An item of diagnostic importance is the extent of the disease. While pathologic grading of carcinoma of the corpus according to cell type and arrangement is now on a firm basis and proving useful, clinical classification on a practical basis has been delayed. A dependable clinical classification of cases of carcinoma of the corpus into stages of progress is a complicated matter, much more complicated than appears on the surface. It has been delayed by difficulties not found in carcinoma of the cervix. In cervix cancer the location and extent of the marked infiltration can be determined by palpation, and the depth of the vaginal and cervical ulcerations are open to easy and accurate inspection. Not so in corpus cancer, where the various stages of extension into the thick uterine wall defy palpation and inspection, and can be outlined only after the uterus is removed.

CLINICAL RECOGNITION OF STAGES.—Clinical recognition or identification of the stage in a particular case is useful in two ways, namely, in accurate re-

porting of the case and in selection of treatment for the patient. Identification of the stage of involvement for case reporting is a comparatively simple matter, because the report is made after treatment, and hence, in most cases the uterus is out and available for sectioning. Identification of the stage of involvement for the selection of treatment is a much more difficult matter, for it must be made before the uterus is removed.

Heyman divides his cases into three clinical groups for the purpose of treatment:

1. Those clinically operable in which it can be determined from examination, both bimanual and curettage, that the cancer can be removed, the patient's general condition being such that she can withstand the operative work.

2. Those technically operable but in which operation is contraindicated either because of patient's general condition or because of old age or pronounced adiposity.

3. Those inoperable because of extent of disease as determined by pelvic examination and x-ray. The difficulties of an accurate estimate before operation are evident, for the enlargement of the uterus felt could be due to carcinoma, myoma, or adenomyoma. The involvement of the adnexa could be due to old infection, endometriosis, or other benign conditions.

The reliable and uniform grouping of these cases into clinical stages representing extent of growth is absolutely necessary for the evaluation of treatment results. In comparing the results of different methods of treatment, the comparison must be made between cases of the same approximate extent of involvement, i.e., early cases to early cases, medium advanced to medium advanced, and late cases to late cases. Otherwise there may be erroneous conclusions as to the efficacy of the different treatment methods.

Such classification requires careful examination and accurate recording of findings before operation, of gross findings at operation, and then of gross findings in the laboratory. This division into stages representing extent of growth must of course be founded on a solid *pathologic* basis. That is, the clinical stages cannot be defined by symptoms but must represent definite extent of growth as determined by examination at operation and in the laboratory. Hence, the stages of the classification to be made before operation as a guide to treatment must be defined in terms of pathologic extent which can be accurately determined only after operation. This paradox shows very well the vicious circle of difficulties encountered, and the reason why the solution of this important problem has been so long delayed.

Having identified the difficulties, we are in a better position to attack the problem successfully. In the first place, it is clear that the stage-classification made before operation cannot be accurate, only approximate. But by utilization of all the factors which help toward accuracy, the preoperative classification may be made to approximate so closely the actual extent as to be of material assistance in the selection of treatment for that patient. The first task is to define the stages in terms of pathologic extent; and the second and more difficult task is to devise a plan of recognizing the stages approximately before operation.

THE STAGES.—The division of a continuous process into stages necessitates dealing with borderline areas about which there may be differences of opinion

as to preferable assignment. The important thing, however, is not exactly where the lines of division are placed but that they should be placed definitely somewhere, and then that this definite classification be used in all clinical work and in all reports of cases. The following classification into stages is definite and practical, and stands the test of application in the examining room and at

Fig. 719. Fig. 720. Fig. 721.

Figs. 719 to 723.—Show the clinical stages of corpus cancer, as detailed in the text.
Fig. 719.—First stage. Endometrium only involved.
Fig. 720.—Second stage. The myometrium involved, but not beyond the middle.
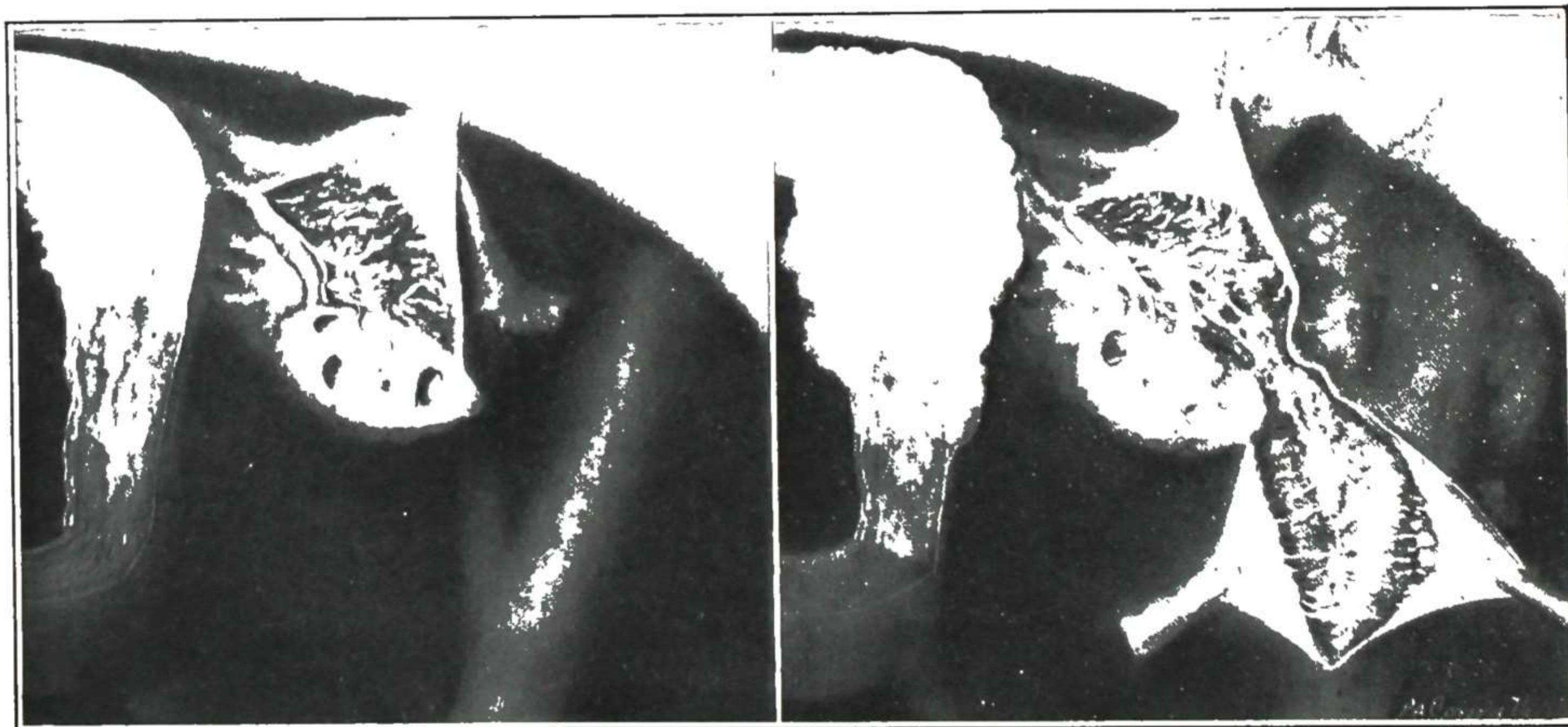Fig. 721.—Third stage. Myometrium extensively involved (past middle).

Fig. 722. Fig. 723.

Fig. 722.—Fourth stage. Involvement of adjacent removable structures (in this case the ovary).
Fig. 723.—Fifth stage. Involvement of irremovable structures (in this case the deep pelvic glands), but the primary tumor mass may still be removed.

the operating table and in the laboratory. Each of these stages was selected with two points in view: first, to have its limits correspond with anatomic lines as far as practicable so as to be well defined and easily described, and second,

to have it recognizable clinically before operation as far as possible with the various helps available. The six stages, each representing a definite extent of involvement, are as follows:

Stage I: Endometrium alone involved (Fig. 719).

Stage II: Definite involvement of the muscular wall, but not beyond its middle (Fig. 720).

Stage III: Extension to the outer half of the uterine wall, but not beyond the borders of the uterus (Fig. 721). This includes extension to the peritoneal coat with possible areas of adhesive peritonitis, but without carcinomatous involvement of the adhesions.

Stage IV: Extension to surrounding structures but not beyond removable ones, such as adnexa and adjacent portions of the broad ligaments (Fig. 722). There may or may not be extensive intestinal or other peritoneal adhesions, but no extension of carcinoma cells into such adhesions.

Stage V: Extension into structures not advisable to remove, but removal of the original tumor is still practicable. The carcinomatous extension may be into an adherent coil of intestine or an adherent area of bladder wall, or it may be along the broad-ligament lymphatics into the deep structures of the pelvic wall (Fig. 723).
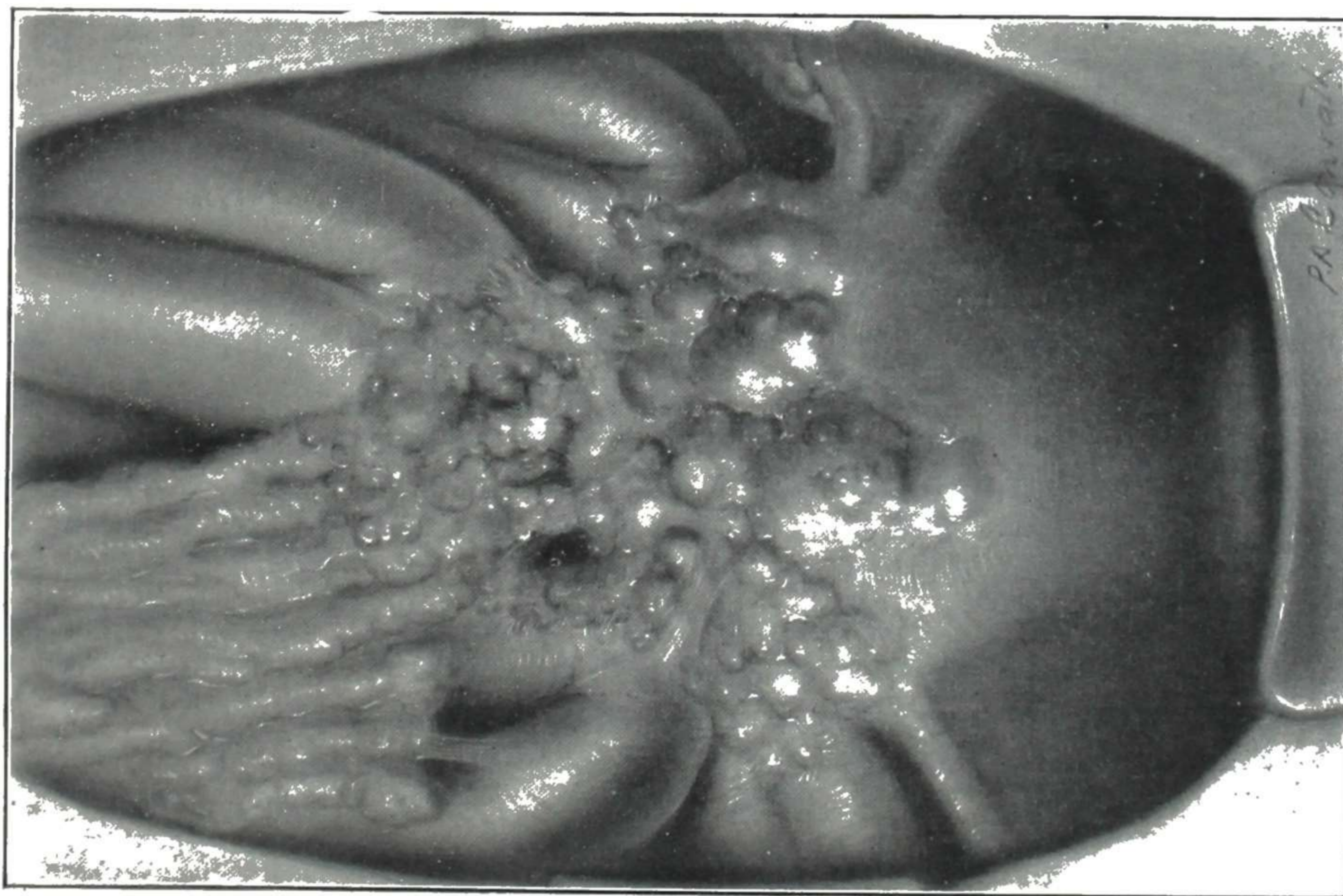

Fig. 724.—Sixth stage. Involvement of surrounding structures to such an extent as to preclude even palliative removal of the main tumor mass.

Stage VI: There is such extensive involvement of surrounding structures that not even the main tumor mass can be safely removed (Fig. 724).

There are a number of factors concerned in the early identification of the stage of involvement, early enough to be of assistance in deciding what treatment to give the patient. These factors are as follows: history of the case, pelvic examination, curettage exploration of cavity and deep pelvic palpation under anesthesia, microscopic examination of curettings, and special examination methods, including gastrointestinal x-ray and cystoscopic examination. Each of these factors is considered in detail in the article in which this subject is presented ("Clinical Classification of Cases of Carcinoma of Corpus Uteri," by H. S. Crossen) along with the following summary. The grouping is into six stages, each stage representing an extent of involvement within fairly definite anatomic limits. The limits are capable of recognition and easy designation by the combination of operative and laboratory examinations.

Stages III, IV, V, and VI may ordinarily be recognized at operation, and Stages I, II, III, and IV may be recognized in the laboratory. The laboratory examination may identify even Stage V by critical examination of the gross specimen and selection of blocks at its margin where the cancerous extension to irremovable tissue was cut across in the operation.

Each stage has also a clinical significance of its own, bearing on treatment or prognosis, as explained in detail later when dealing with treatment for the different stages.

Why six stages? Six stages may at first thought seem a rather large number. It seemed so to us, and much study was given to trying to reduce the number. But carefully considered from the standpoint of accurate definition of each stage and the classification's usefulness in clinical and laboratory work, the six stages were found necessary. A reduction in number by combining any two of them was unsatisfactory. For example, if Stage I included I and II and the operator received a laboratory report stating ''Corpus carcinoma, clinical Stage I,'' he would at once wish to know whether or or not it had extended to the muscular wall, because of the difference in clinical significance. If Stage II were extended to include all muscular involvement, neither the clinician nor the pathologist would be satisfied with that broad designation, for each would wish to have stated clearly whether the cancer involved only a small part of the muscular wall or extended into the outer half. The same objection applies to any combination of two stages, and still more to any combination of three. Careful critical study of the six stages in practical application to clinical and pathologic work shows that each stage represents a definite step in the progress of the cancerous infiltration and is of importance to the clinician in treatment and prognosis.

Finn has reviewed (1951) the eight suggested methods of classification, including that adopted by the American College of Surgeons. He has cut the number of stages in the Crossen classification to five and has included Stages V and VI in his Stage 5. In addition to this he gives the histologic grade: Grade A, well differentiated; Grade B, intermediate; and Grade C, poorly differentiated; for instance, a tumor classified as Stage I, Grade A, denotes a well-differentiated tumor confined to the endometrium.

To my mind this classification offers an improvement over previous ones for it gives a definite conception of the amount of extension plus the histologic estimate of cellular differentiation.

In conclusion it is my conviction that the only way in which results reported by various centers can be compared is to have a general acceptance of one method of classification by all workers in this field.

TREATMENT

The treatment of carcinoma of the corpus differs from that of carcinoma of the cervix in that the operation is still an important factor in the handling of corpus cancer. Radiation is used in all cases, and is our sole reliance in the inoperable cases. In the ordinary case, however, operation is added to the radiation. There are certain special features in corpus cancer which make operation more effective than in cervix cancer. For example, in carcinoma of the corpus the growth starts in the endometrium, hence, bleeding occurs early. This causes the patient to seek medical advice, leading to early examination and curettage and diagnosis of malignancy. Also, there is not the silent deep penetration of cancer cells to irremovable structures before outward clinical manifestation, as so often happens in carcinoma of the cervix. Again, the anatomical relations of the corpus uteri are such that the first lymphatic extensions of the growth may be easily removed, by excision of adnexa and associated portion of broad ligaments with contained vessels, while removal of

the lymphatic extensions from the cervix necessitates deep dissection and removal of the parametrium beyond the ureters—a prolonged and exhausting operation with very high mortality. Javert and others have advised a radical Wertheim hysterectomy, but because the spread is to the lumbar nodes and not the hypogastric or obturator nodes it is difficult to see how this could offer any advantage over simple, wide and complete hysterectomy with a good cuff of vagina. Randall, Mirick, and Wieben found no advantage in their series.

In addition to the features rendering corpus cancer more favorable for operation than cervix cancer, there are conditions which render it less favorable for radium treatment. Its high location in the uterus puts it out of reach of direct palpation and increases the difficulties of determining the exact location of the malignant area and the extent and direction of its progress. These difficulties interfere with accurate application of the radium for safe maximum effect. This combination of conditions makes it advisable to employ operation in addition to radiation, except in cases where there is some serious operative contraindication.

Another principle of treatment is to secure radiation-devitalization of the cancer cells *before* the general tissue disturbance of operative removal. Such devitalization effect lessens virulence and diminishes the chance of cancer cell implantation-metastasis from the operation. It also eliminates the infective uterine discharge, and thus diminishes the danger of peritonitis following the hysterectomy.

An important technical feature in effective radium treatment for corpus cancer is distribution of the radium capsules in the uterine cavity and their maintenance in position and their certain removal. The reason for distributing the radium in several centers, instead of in a simple tandem as for myoma, is to enable the heavier dosage required for carcinoma to be given without causing point-devitalization and sloughing. It is a difficult problem on which considerable work has been done. Schmitz devised a Y-shaped applicator, whereas Heyman packs the fundus with multiple capsules as do most of the workers in this field. Nolan and Arneson devised an instrument for introducing the intrauterine capsules (Figs. 725 and 726); it has some similarity to that used by Heyman.

Dr. H. S. Crossen devised a very satisfactory form of wire distributor for this purpose. The experimental and clinical details concerning it will be found in the article, ''Advances in the Treatment of Cancer of the Corpus Uteri.'' The distributor is shown in Fig. 728, the method of introducing and keeping it in place in Fig 727. The advantages of this type of applicator are: they are easily adjustable to any size cavity; anyone can make them from a piece of malleable wire; they keep the radium source where it has been placed. However, it is more difficult to use than the packing method.

The vaginal packing of petrolatum gauze is the same as that used in radium treatment for myoma, and the method of removal is the same (Figs. 622 to 627). The matter of ensuring removal of all radium capsules placed in the uterine cavity is not as simple as may appear at first thought. In a reported case an overlooked radium capsule gradually worked through the uterine wall and penetrated the intestine, eventually causing death.

Heyman in 1947 reported results with radiation alone that compared favorably with those obtained by hysterectomy or by radiation plus hysterectomy, and he now resorts to operation only in the cases which do not respond
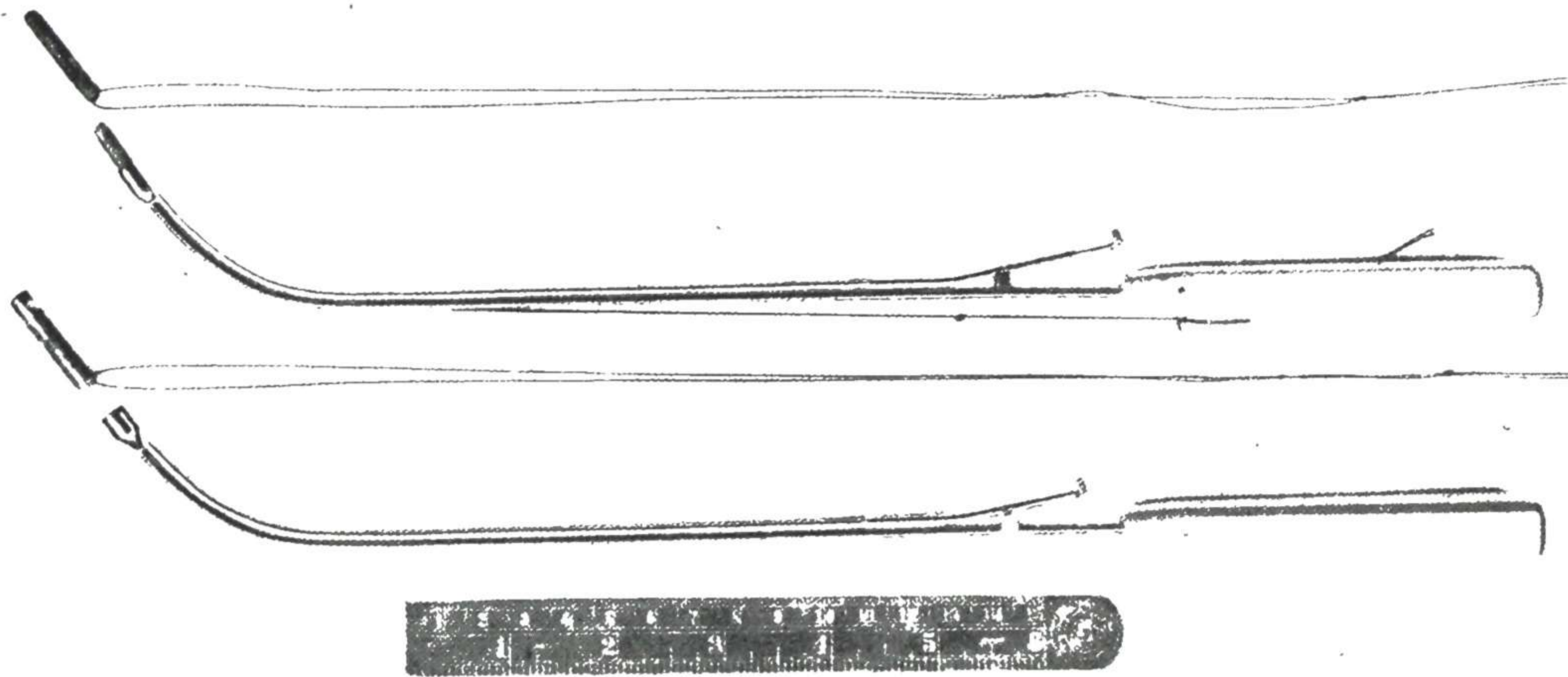

Fig. 725.—Instruments used for inserting tubes of radium into the uterus.   (From Nolan and Arneson: Am. J. Roentgenol., April, 1943.)
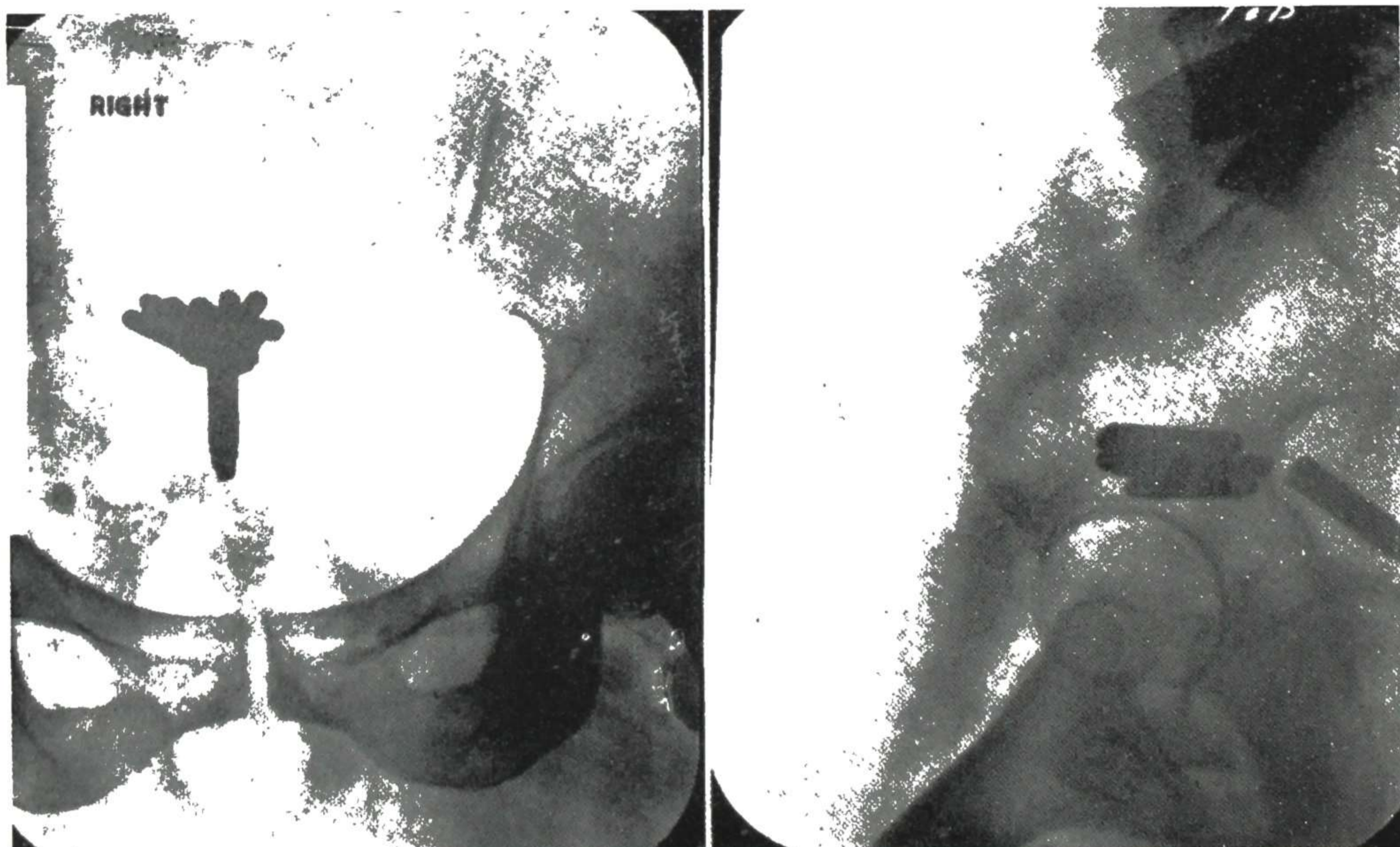

Fig. 726.—Multiple sources of radium within a uterus somewhat larger than average. A capsule of greater external diameter is located in the cervix. By that means the canal is kept dilated for safe removal of the deeper tubes. The source in the cervix is of greater radium strength than those in the upper part of the uterus. (From Nolan and Arneson: Am. J. Roentgenol., April, 1943.)

to radiation. In this country most workers advocate preoperative radiation followed by hysterectomy. Miller employed preoperative x-ray with excellent results, and Schmitz uses all three methods. The improvement of results re-

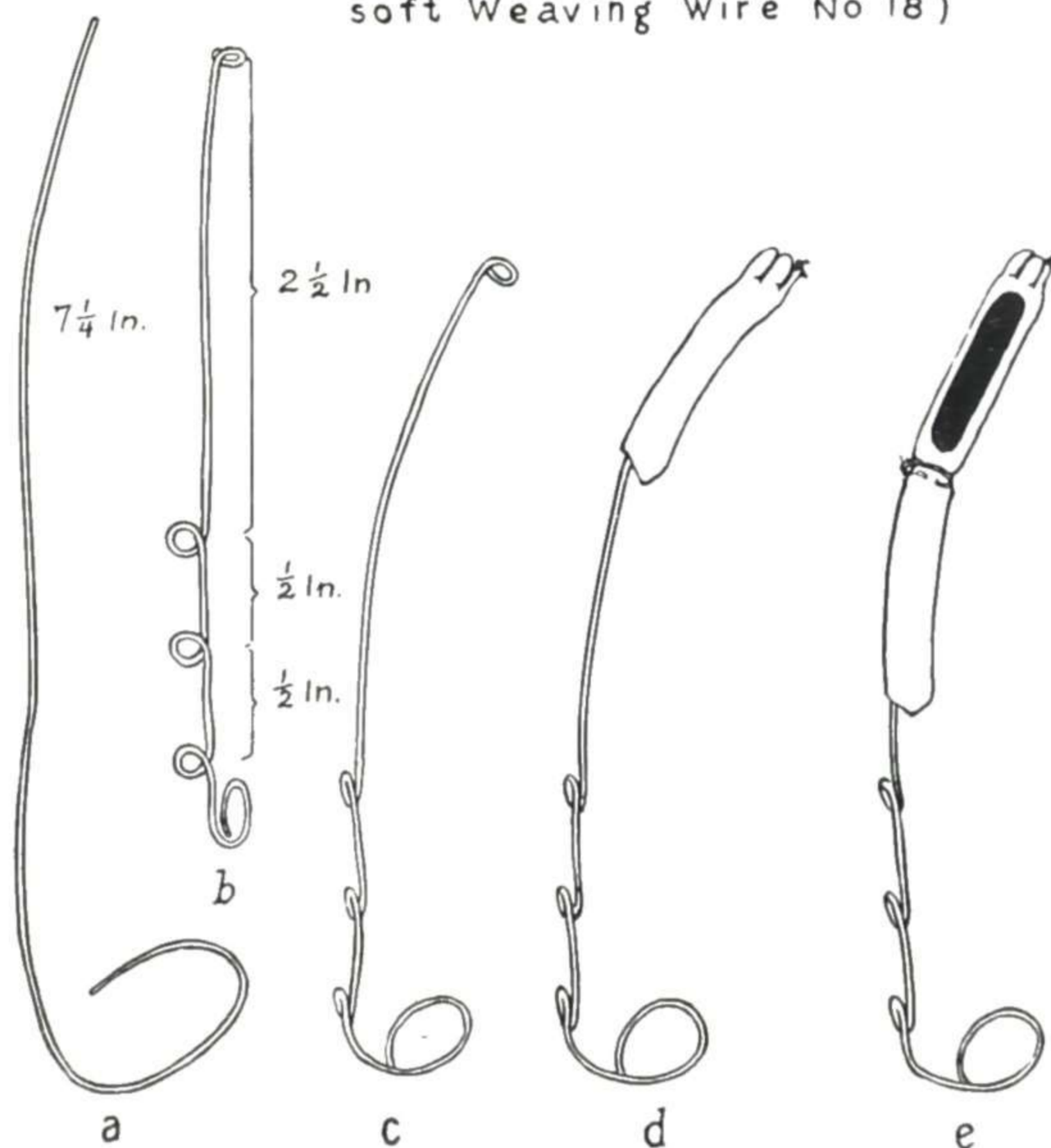Special Wire Distributor (Made of soft Weaving Wire No 18)

Fig. 727.—Details of the wire distributor devised by Crossen. *a,* The piece of pliable wire, 7¼ inches long, of which the distributor is made. *b,* The completed distributor turned so as to show the three eyes for adjustment to uterine cavities of different length. *c,* A general view showing the loop handle at right angle to the row of eyes and also the eye at the inner end to which the tubing is stitched. *d,* Rubber tubing for a single capsule in place and stitched securely to the eye at the end of the wire. *e,* A two capsule length of tubing in place and one capsule fastened in it. (From Crossen: J. Missouri M. A.)
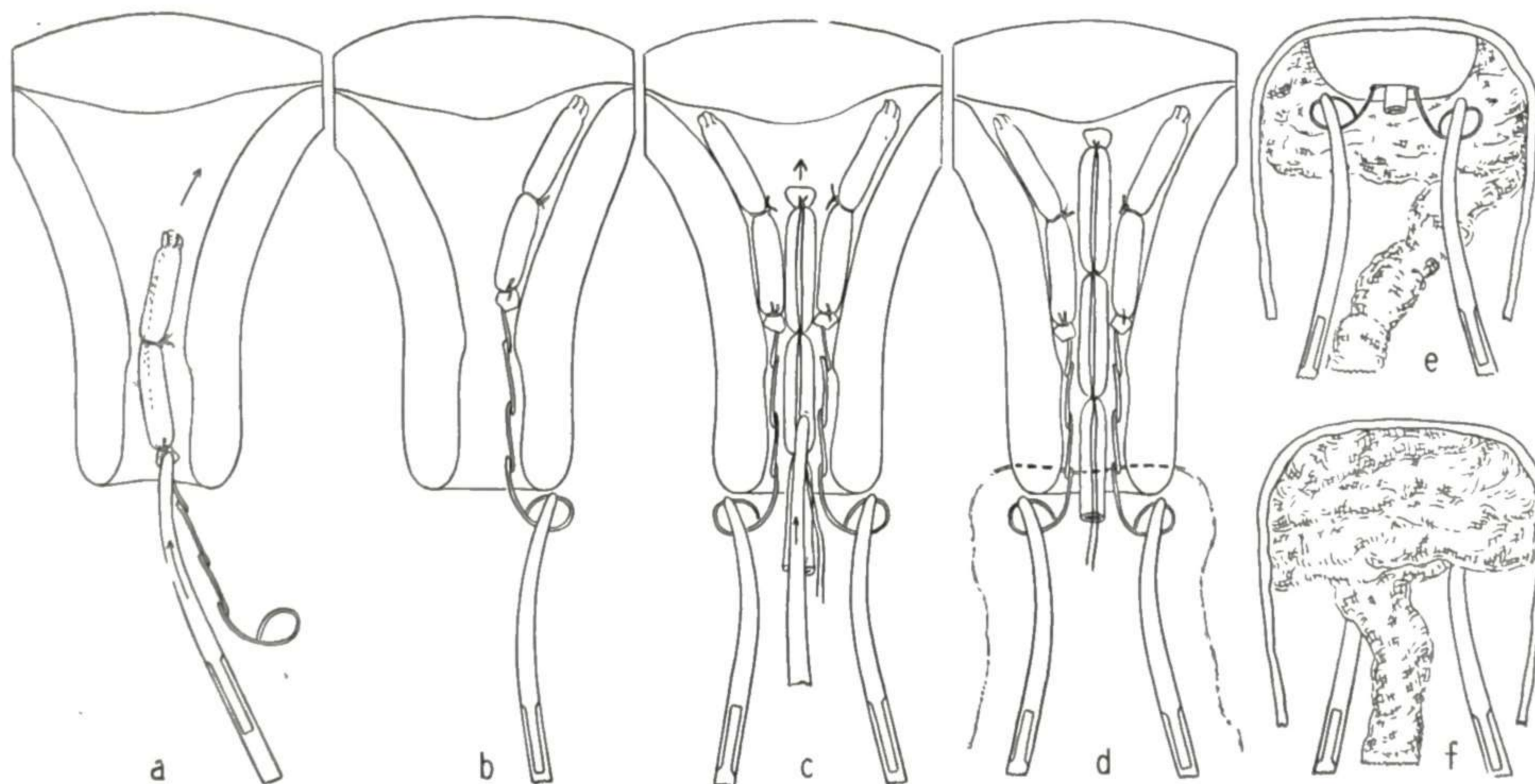
Introducing and Fastening the Wire Distributor.

Fig. 728.—Details of the introduction and fastening of the distributor as explained in the text. *a,* The distributor is grasped about the middle with a strong Kelly forceps and introduced through the dilated cervix as shown. *b,* The distributor in place and held firmly by an assistant with the Kelly forceps clamped on the handle. *c,* The two distributors in place and held by forceps while the tandem is being introduced between them. The firm forceps hold on the distributors is maintained until the suture, which passes through the cervix and an eye of each distributor and the tandem tubing, is in place as in *d,* and also until the petrolatum gauze packing is in place back of the cervix (*e*) and in front of the cervix and extends down beyond the distributor handles as in *f.* The forceps are then removed and the long suture is tied over the packing. (From Crossen: J. Missouri M. A.)

ported in many series indicates that the combination of radiation and hysterectomy is the method of choice, reserving radiation alone for those cases in which operation is for some reason contraindicated.

The cure rate in the operable cases varies in different series from 50 to 90 per cent. Heyman, in 316 cases treated by the new radium packing method, with hysterectomy in the cases not controlled by radiation, had a relative five-year cure rate of 64.9 per cent. Scheffey in a series of patients in which he used the so-called "planned technic" obtained a 91.2 per cent five-year cure.

In regard to prognosis, histologically the prognosis improves with the maturity of the cell type. Arneson found that when the tumor was completely destroyed in the removed uterus, the outlook was excellent; and Schmitz, in his series of superficial carcinomas where no evidence of the disease was found in the removed uterus, reported his cure rate as 80 per cent.

PREVENTION OF CORPUS CANCER

Is there any factor entering into the causation of corpus cancer (endometrial carcinoma) which we can modify by treatment? There seems to be such a factor in association with delayed menopause. Delayed menopause and late menopause are terms used to designate that condition in which the permanent cessation of menstruation is delayed beyond the normal age. This delay is due to prolonged erratic ovarian activity and is frequently accompanied with endometrial hyperplasia.

The relationship of this undue endometrial activity in the age of declining function to the onset of endometrial carcinoma is an important subject. An analysis of the work on this subject has been given under Etiology, and sufficient evidence has been collected to indicate that endometrial hyperplasia or the factors causing it in delayed menopause should warn one of a definite tendency to endometrial carcinoma.

In the clinical analysis of bleeding at the menopause age it is necessary to consider all cases of late uterine bleeding, whether or not presenting the rhythmic character of menstruation. In giving the history, patients usually regard any recurring bleeding as menstrual flow and an appearance of blood after cessation as a return of menstruation.

Accepting this composite group for investigation, pelvic examination will show the cases in which the late bleeding is due to a demonstrable local lesion, such as carcinoma of the cervix or corpus, uterine myoma, ovarian tumor, or a tumor or inflammation of some adjacent structure. Further investigation will identify the cases presenting some extrapelvic disease which may be the cause of the bleeding, such as blood dyscrasia or cardiovascular-renal hypertension or thyroid disorder.

There remains a small group of cases presenting no evident genital lesion nor extragenital disease to account for the bleeding, and in which the bleeding simulates more or less the menstrual rhythm. This is a most interesting group, presenting unsolved problems in pelvic physiology and pathology. The patients are past the usual age for normal ovarian functioning and yet they present evidence of endometrial activity dependent on ovarian activity.

Are these cases simply examples of unusual disparity between the age in years and the age in physical changes, and consequently due to run a normal

course to a later menopause? Are they, on the other hand, cases representing an irregularity of functional decline which may impose a pathological influence on the cell activity of the involuting endometrium? We have given considerable thought to this interesting problem and its practical bearings, and some features were presented in an article by Crossen and Hobbs. The ramifications of the subject are extensive and space consuming, but the practical conclusions from our study may be stated as follows:

1. Delayed menopause, especially when delayed to the age of fifty years, means some pathological condition, either in structural change or in cell activity. The influence of persisting irregular ovarian activity on the cells of the involuting endometrium tend to erratic cell activity, thereby favoring cancer development. In our series of 89 cases of cancer of the corpus uteri, there were 30 in which there was an interval of over three years between the menopause and the clinical appearance of the endometrial carcinoma. In these 30 cases the menopause occurred at the age of fifty years or later in 22, or 70 per cent.

2. Endometrial hyperplasia in the endometrium of involutionary age seems to represent a step in the pathological progress from normal endometrium to carcinoma. Hyperplasia is a very frequent finding at curettage for bleeding in this age period when carcinoma is most common. In our series of cases of endometrial carcinoma a few of the patients had been curetted, in their home town or elsewhere, one or two years previously. In 3 such cases the slides of the previous curettings were available for study and each of them showed definite hyperplasia at that time. Here, in this one series of cases, there were 3 instances in which curetting showed benign hyperplasia and another curetting one to two years later showed endometrial carcinoma; there are many other such cases reported. There was also an interesting specimen of a double uterus in which one horn showed endometrial hyperplasia and the other horn endometrial carcinoma.

3. Delayed menopause, especially when delayed to the age of fifty years, is an indication of aberrant endometrial activity and a warning of a tendency to endometrial malignancy. Consequently, appropriate treatment should be employed to stop the aberrant endometrial activity.

4. Appropriate treatment consists usually of curettage (to stop the bleeding temporarily and to furnish tissue for microscopic study), conization of the cervix if needed for chronic cervicitis, and radium treatment to stop the erratic endometrial and ovarian activity. If there is no malignancy in the curettings or in the cervical tissue, the treatment outlined is usually sufficient to prevent further trouble. If the microscopic investigation of the curettings shows that endometrial carcinoma has already developed, then radical measures for that must be employed.

Several series of cases have been reported on carcinoma following a radiotherapeutic menopause; Speert and also Corscaden, Fertig, and Gusberg found that from three to three and one-half times as many of these women developed subsequent endometrial carcinoma as occurred in patients with a normal menopause. Corscaden points out that this figure is about the same as that found by Randall in women whose menopause was characterized by abnormal bleeding in which there was no radiation used for inducing menopause. He concludes that 9.6 per cent of women who have excessive bleeding at the menopause will develop cancer of the endometrium. These statistics have caused some men to advise hysterectomy in every case. Crossen and Crossen (1947) reported a "Critical Analysis in Five Hundred Cases of Radiation Therapy in Uterine Myoma." The radium treatment was in all cases accompanied by a curettage, and in most of them a conization of the cervix was also done. Twenty-three endometrial carcinomas were discovered on the primary curettage. In many of the reported series, curettage was not done, especially in

patients receiving x-ray therapy, hence one is unable to state definitely that carcinoma was not present when the therapy was given. This is, of course, a very important point and it may account for the high percentage of post-irradiation carcinomas in some of the reports. The results in our series are given in the table on page 491. It shows that in myoma cases endometrial cancer was more than twice as frequent in the nonradiated as in the radiated cases. These figures cannot be applied to cases in which radium is given to stop the menses in patients with a delayed menopause, but at least they would indicate that the radiation therapy is not the factor causing subsequent cancer of the endometrium. I am inclined to agree with Corscaden that factors behind the abnormal bleeding at the menopause are the important ones in the development of postmenopausal carcinoma.

In actual practice the cases of benign bleeding should be individualized; if the patient has a family history of cancer, or has a so-called bloody menopause, or has a uterus which can easily be removed by vaginal hysterectomy, and is a good operative risk, hysterectomy is the procedure of choice. In a patient with a small uterus, whose only symptom is recurring periods after fifty years of age, radium will certainly give an excellent result with little future risk. Also in poor-risk patients or patients who refuse operation, radiation may be a lifesaver. Irradiation for benign conditions is used in selected cases by Scheffey, Novak, Schmitz, and others. Schmitz states, in his discussion of a paper on "Sarcoma of the Uterus" by MacFarlane, that irradiation for benign menopausal bleeding is the treatment of choice in their clinic, and he brings out the important point that recurrence of bleeding is an indication for hysterectomy rather than for re-irradiation.

Individualization in selecting the proper method of treatment applies as well in younger women whether they have a myoma or persistent abnormal menstruation without myoma. In those under forty, hysterectomy is usually preferable; in those above that age irradiation may be used with excellent results in properly selected cases. When hysterectomy is done, it should be a total hysterectomy, and the uterus should be opened and inspected for malignancy as soon as it is removed so that a complete operation may be done if carcinoma or sarcoma is discovered. If one uses definitive selection of treatment in these benign conditions and follows this with routine checkup examinations as in normal women, the immediate and future risk of death from endometrial cancer should be almost nil.

CHORIONEPITHELIOMA*

Chorionepithelioma is a peculiar form of carcinoma arising from the fetal cells covering the chorionic villi. A striking feature is the early penetration of blood vessels resulting in the hemorrhagic character and appearance of the growth, as shown in Fig. 729. This blood vessel penetration leads also to early metastases to distant organs, which makes it an exceedingly fatal growth.

Although, as Marchand demonstrated in his classical description of this condition in 1895, the origin of these tumors is from the fetal villi, they may

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*"Chorionepithelioma" more definitely identifies the origin of this growth directly from the chorion, and this spelling may eventually prevail. Synonyms: Chorioepithelioma and Choriocarcinoma.

Fig. 729.—A chorionepithelioma of the uterus, showing the hemorrhagic character of the growth as it projects into the uterine cavity and penetrates into the uterine wall. Gyn. Lab.

be metaplastic decidual cells. Park and Lees have recently contended that the cells seen on the fetal side of the fibrinoid layer of Nitabuch, dividing the decidua from the trophoblast, may either be metaplastic decidual cells or fetal cells under maternal influence. About 50 per cent of the cases are preceded by a hydatidiform mole, 25 per cent by an abortion, and the rest of the cases occur after a normal pregnancy. Since the incidence of hydatidiform mole is approximately one in 2,000 pregnancies, it can be seen that chorionepithelioma is a very rare disease, as probably less than 2 per cent of hydatidiform moles become malignant.
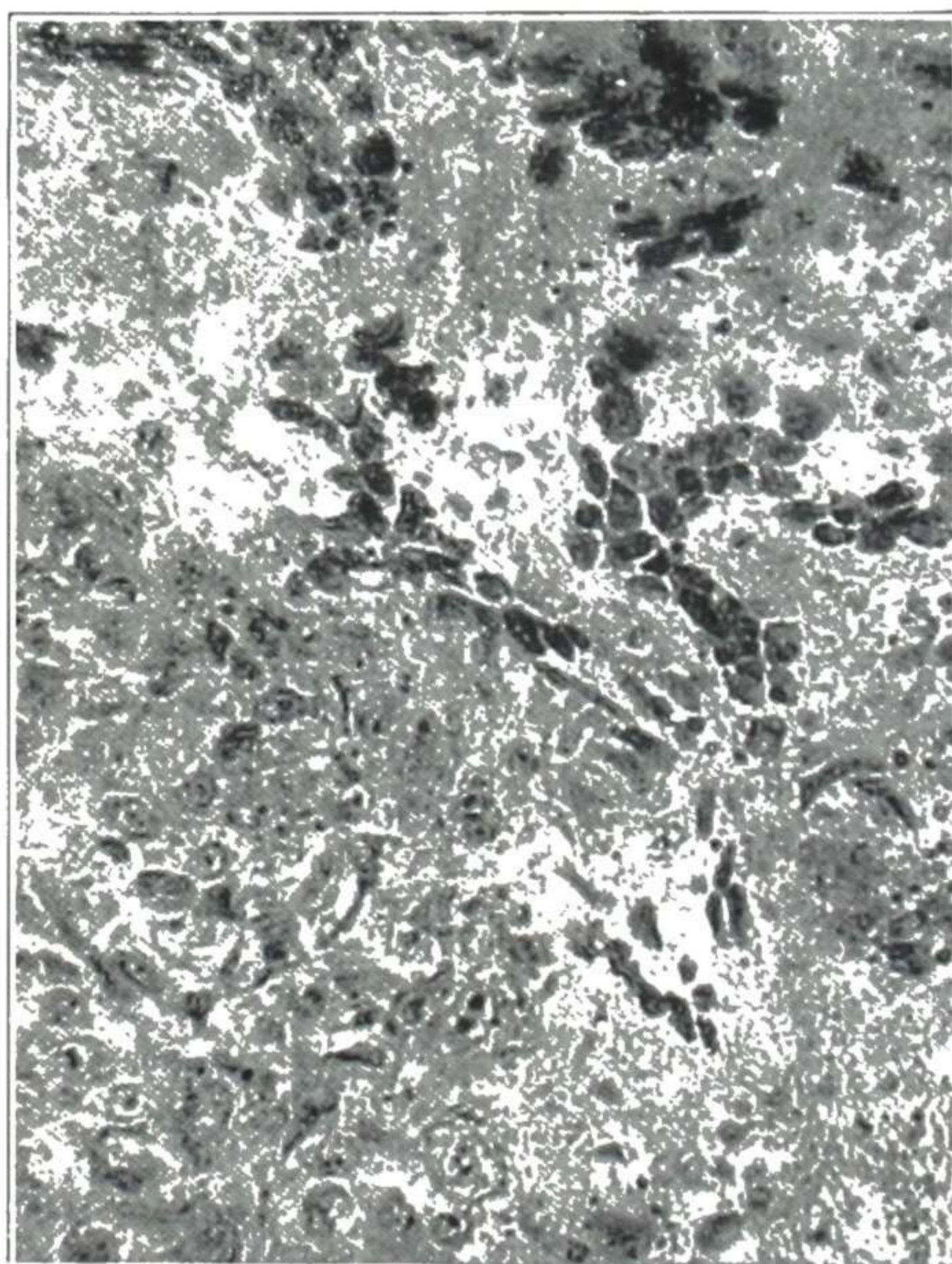

Fig. 730.

Fig. 731.

Fig. 730.—Another case of chorionepithelioma of the uterus, showing extensive involvement of the corpus uteri and a metastatic growth in the cervix. Gyn. Lab.

Fig. 731.—High power, from the specimen shown in Fig. 730. Shows syncytial cells and Langhans' cells. The latter are shown particularly well, as large light-staining cells in contrast to the darker syncytial cells. Gyn. Lab.

Care should be taken to exclude this type of growth whenever there is persistent bleeding coming on some weeks or months after confinement or miscarriage.

Pathology.—Grossly these lesions appear as a dark hemorrhagic tumor, whether found in the uterine wall or elsewhere. On microscopic examination trophoblastic cells are found growing in a disorganized manner into the surrounding tissue. As Novak has pointed out, villi are rarely found in the true choriocarcinoma as they are usually blotted out by the extensive necrosis and

hemorrhage associated with these growths. The characteristic cellular features of chorionepithelioma are shown in Figs. 730 and 731.

Because of the invasive nature of trophoblastic tissue in normal pregnancy, the mere fact that invasion is found is of no significance. The maternal organism seems to have an inhibiting effect which controls this invasion in normal cases. Even when, as has been shown, these elements are transported to distant organs, in normal pregnancy they usually disappear. The final decision as to malignancy, according to Novak, must be made on microscopic examination. He finds that in a frank case of choriocarcinoma the diagnosis offers no problem, but in the borderline case he admits that it is impossible to be sure of the malignancy of the lesion. For more complete discussions of the problems involved, the reader is referred to papers by Novak, by Hertig and Sheldon, and by Park and Lees.

There is a group of cases in which the tumor composed of apparently malignant trophoblastic cells remains localized. These tumors are classified by Park and Lees as localized choriomas and include the carcinoma-in-situ of Hertig and the chorioadenoma destruens described by Ewing. These metastasize late and when removed early show a high rate of cure. The fact that such tumors may lie dormant and then revive and metastasize widely is evidenced by reports of cases of death from extensive chorionepithelioma occurring many years after a pregnancy.

Enlargement of the ovaries due to multiple lutein cysts is frequently associated with both hydatidiform mole and chorionepithelioma, and in the past this has led to erroneous diagnoses of ovarian tumors, often with tragic results. Since the fundamental work of Aschheim and Zondek on the chorionic-gonadotropin levels in pregnancy, and the frequent finding of unusually high blood levels in hydatidiform mole and chorionepithelioma, we realize that enlarged cystic ovaries are due to the excessive stimulation of this hormone.

Diagnosis.—A large percentage of chorionepitheliomas are preceded by hydatidiform mole, hence symptoms of this condition are usually present. The uterus is larger than expected for the duration of the pregnancy. Uterine infection is not uncommon. Symptoms of toxemia such as hyperemesis or pre-eclampsia are frequent and they occur in the latter part of the first trimester or, more rarely, in the early part of the second trimester. Bleeding is the most common symptom, and occasionally grapelike masses are passed, confirming the diagnosis (Figs. 732 and 733).

Occasionally a metastatic lesion in the vaginal wall will give the first clue to the diagnosis. In a recent case occurring during pregnancy reported by MacRae, the first symptom was intractable vaginal bleeding from a mulberry-like necrotic lesion in the vaginal wall. Another unusual case, shown in Fig. 734, was reported by Wilson. This instructive case is of unusual interest because a year and a half elapsed after the removal of an hydatidiform mole before there was any evidence of chorionepithelioma. The Friedman test became negative promptly and remained so up to the time mentioned. The patient had periodic examinations and was in good health. About two months after the last examination she was admitted to the hospital, critically ill and with a history of cough and bloody sputum for the past week, and died in five days of generalized chorionepithelioma.

Persistent or recurrent bleeding after a pregnancy of any kind calls for investigation, but this is especially true after a molar pregnancy. Such was the history of the specimen shown in Figs. 730 and 731. This patient was first seen some months after the expulsion of a large hydatidiform mole. The immediate cause of the consultation was repeated uterine hemorrhage, difficult to control. Curettage gave tissue that showed malignant disease of the corpus uteri. A hysterectomy was done, and sectioning of the removed uterus showed a typical chorionepithelioma.

As metastases occur early, one or more of the metastatic growths may overshadow the primary uterine trouble, causing it to be overlooked. In a suspected case of chorionepithelioma, x-ray examination of the lungs should be carried out to see if any metastases are there. Also, any disturbance of other organs should be investigated with the idea that it may be metastatic from a chorionepithelioma not yet large enough to produce pelvic symptoms.
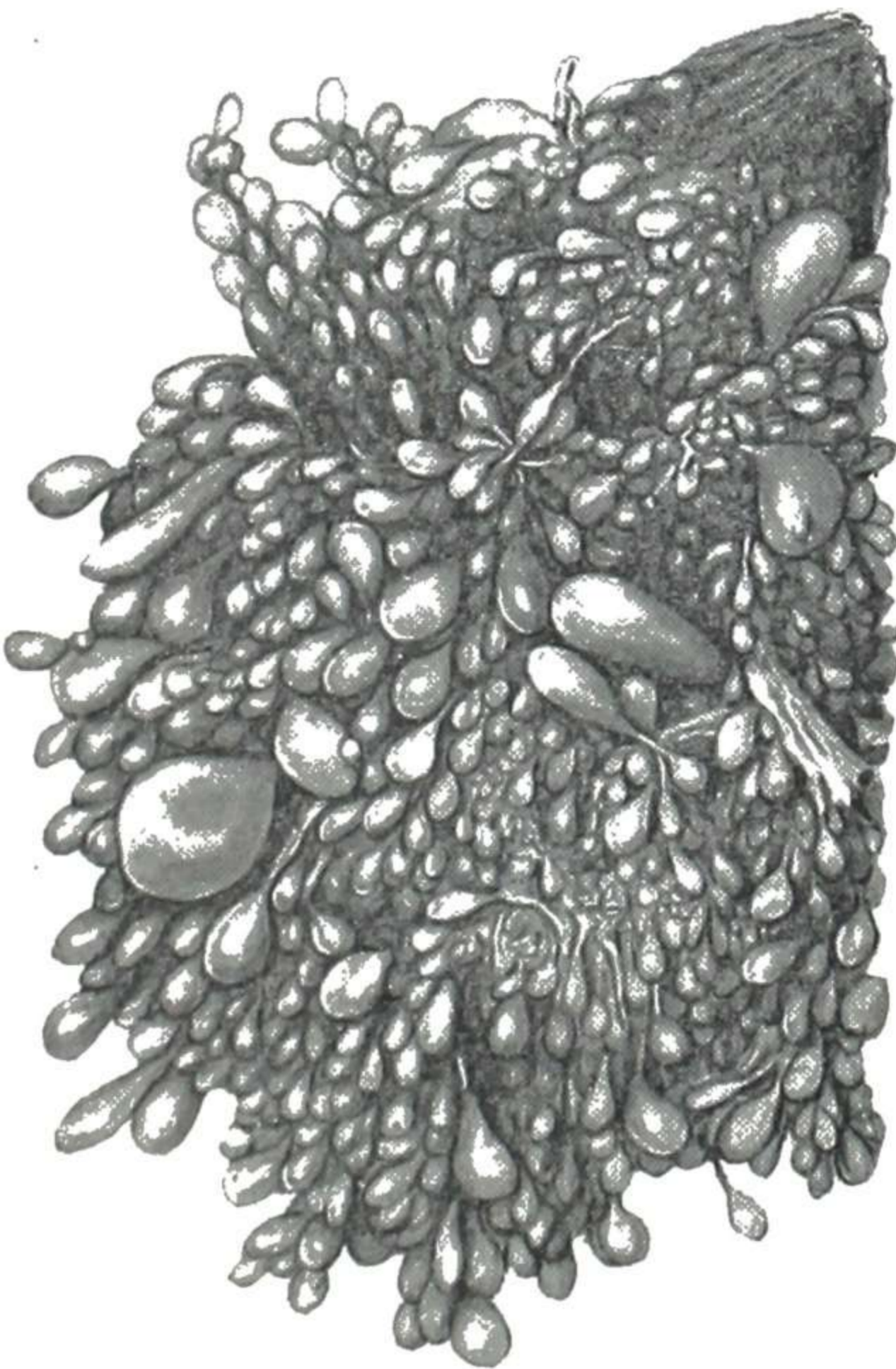

Fig. 732.

Fig. 733.

Fig. 732.—Showing the cystic character of an hydatidiform mole, from which most chorionepitheliomas originate. Vesicles may break off the mole and come away with the bloody discharge, which is often present, and search for them in a suspicious case may aid in diagnosis. Gyn. Lab.

Fig. 733.—Lung metastases from a chorionepithelioma of the uterus. Gyn. Lab.

Further investigation includes: (a) quantitative Aschheim-Zondek or frog tests repeated frequently to see if the level is rising or falling and if the levels correspond with those found for the stage of pregnancy; (b) search for hydatidiform cysts in the vaginal discharge; (c) x-ray for fetal bone shadows after the fourth month and of the lungs for metastatic nodules; (d) exploration of the uterine cavity if the bleeding is excessive or the clinical and laboratory findings point clearly to the presence of a mole. In deciding on this last step one should remember that multiple pregnancy will also cause an unusually

large uterus and a high gonadotropic titer. In a patient of ours who had had a mole with a previous pregnancy, we were suspicious of another mole because of an abnormally large uterus, high titer, and bleeding; we emptied the uterus only to discover that it had contained a triplet pregnancy.

Great caution must be employed in performing the curettage lest the uterus be perforated. Although it is of great value in establishing the diagnosis of hydatidiform mole, it may be of doubtful value in chorionepithelioma, for not infrequently the malignant fetal elements are found only in the muscular wall of the uterus.

Fig. 734.—A small chorionepithelioma deep in the wall of the uterus at the fundus, with metastatic nodules in the vaginal wall. (From Wilson: Tr. Am. Gynec. Soc.)

In chorionepithelioma, the Aschheim-Zondek test (with its modifications) assumes importance in diagnosis. In a case with suggestive signs and symptoms a level higher than the usual limits for the stage of pregnancy should make one suspicious. If intra- and extrauterine pregnancy and hydatidiform mole can be ruled out, frequent quantitative tests may be the only index of abnormal chorionic activity. A persistently positive test six to eight weeks after delivery of a mole (or even a normal pregnancy) indicates that there are active fetal elements present. A curettage would help to rule out persistent remnants within the cavity of the uterus but not in the wall of the uterus. When the test is positive, Hertig recommends biweekly quantitative

determinations, and, if the level shows a persistent rise and the other clinical evidence warrants it, hysterectomy should be done. As noted above, there are many pitfalls which can be encountered in the interpretation of this test, but with full knowledge of these the test is a valuable adjunct in diagnosis and an aid in determining treatment and prognosis.

Dr. Seymour Monat supplied me with the chart shown in Fig. 735, which represents the concentration of serum gonadotrophic hormone in 18 cases of hydatidiform mole compared with normal pregnancy. He states: "While the curves show the average concentration of gonadotrophin it is important to remember that individual values may vary greatly from the mean. Thus Schoenbeck has reported readings of 3,000,000 units and more in a case of twins at the 65th day, while, on the other hand, several of the moles in our series had extremely low levels, especially if they were encapsulated by a layer of clots.

What this curve should demonstrate is that, in general, moles tend to run much higher levels long after the 70th day of pregnancy, which represents the point of maximum titer in normal single pregnancies. Multiple pregnancies, though not so extensively studied, tend to follow much the same curve, though the titer is somewhat higher and may persist for a few days longer than in single pregnancies."

The fact that the chorionepithelioma may occur with a normal pregnancy should be kept in mind. MacRae recently reviewed the literature of such cases and reported one of his own in which bleeding from a vaginal metastasis led to the diagnosis. Sheares has also had a similar case.

Concerning the troublesome and sometimes misleading variations in prolan output in hydatidiform mole and chorionepithelioma, the following conclusions were reached by Payne in hormone studies in the presence of hydatidiform mole and chorionepithelioma.

The curve of prolan concentrations during normal pregnancy serves as a valuable standard for comparison in the interpretation of abnormal concentrations that are prone to occur in the presence of hydatidiform mole and chorionepithelioma.

Analyses of the clinical picture, the prolan values, and the pathological findings of hydatidiform mole disclose that any of 4 types of molar activity may be encountered. Since each type presents distinctive clinical and hormonal characteristics, both aspects must be considered in its identification.

Following molar evacuation, regularly spaced hormone titrations for a year are necessary to differentiate between recovery and the development of chorionepithelioma. An increase in prolan values denotes the presence of malignant degeneration or intervening pregnancy, while a gradual decline or the lack of an increase, even over a considerable period of time, indicates the absence of chorionepithelioma.

In the diagnosis of chorionepithelioma, repeated quantitative prolan titrations are invaluable. The final decision does not rest upon a single qualitative or quantitative determination but upon the demonstration of increased values over a short period of observation.

Following treatment for chorionepithelioma, quantitative hormone studies are useful both as a prognostic aid and as a guide to subsequent treatment.

H. Acosta-Sison of Manila found that the triad of history, bleeding, and enlargement was more significant in arriving at a correct diagnosis of chorionepithelioma than were gonadotrophic levels or curettage. She found that the history of expelled products of conception, abnormal bleeding, and the finding

QUANTITATIVE CHORIONIC GONADOTROPHIN TITER IN 16 CASES OF HYDATIDIFORM MOLE, COMPARED TO TITER IN NORMAL PREGNANCY.
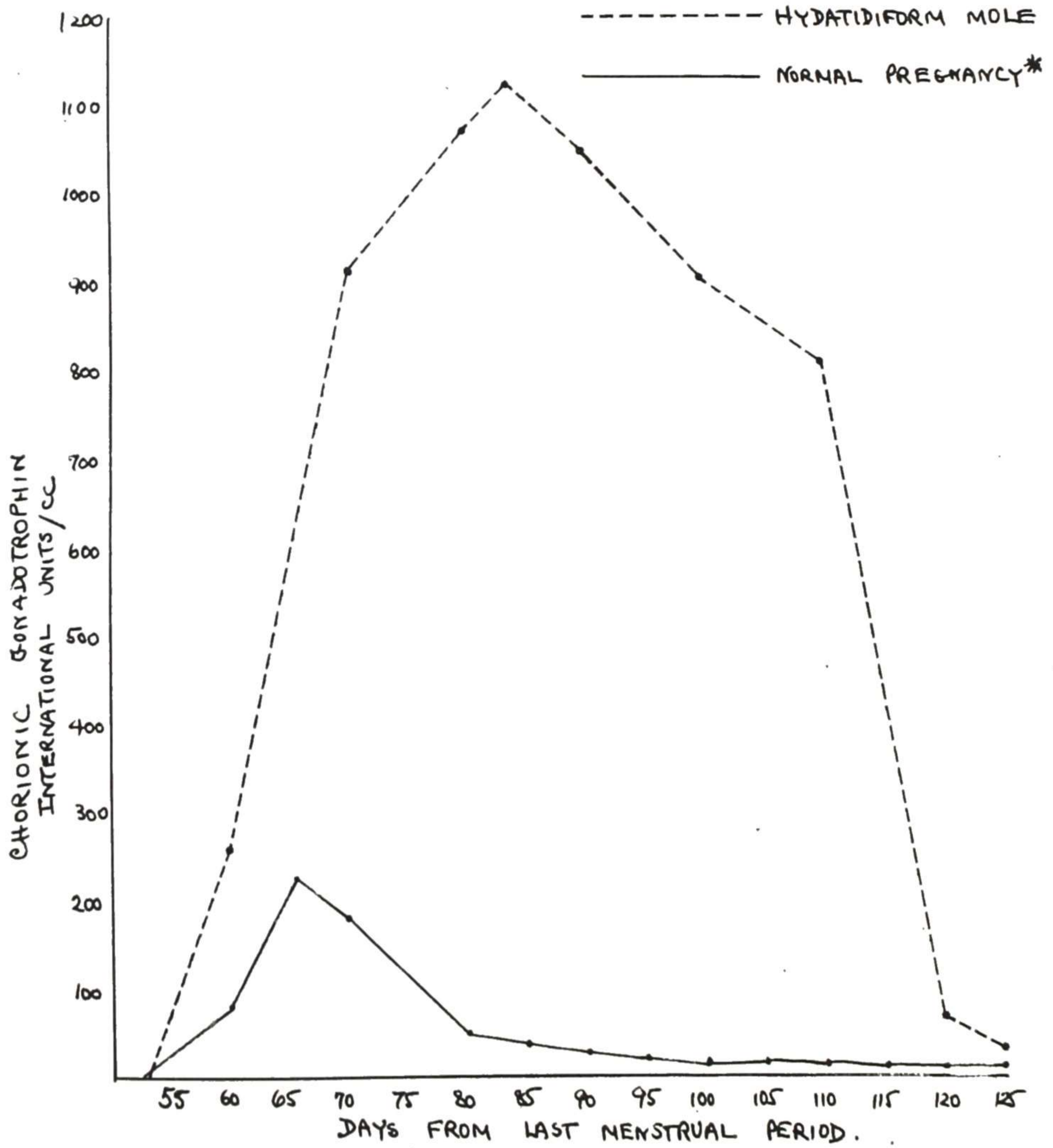
* HASKINS AND SHERMAN; J. CLIN. ENDOCRINOLOGY, APRIL, 1952. VOL. XII no. 4.

Fig. 735.

of an enlarged boggy uterus led to a correct diagnosis in 43 of her 70 collected cases. In 15 of the remaining cases this triad was present but the diagnosis was missed.

In a personal communication, B. H. Sheares of the University of Malaya states that, in addition to this triad, he looks for enlargement of the ovaries and has also found that these patients usually have a sustained elevated basal body temperature.

Treatment.—Though chorionepithelioma may metastasize early and run a rapid course to death, the operative treatment has not now the almost hopeless outlook of earlier years. There are two factors responsible for this improved outlook. Operative treatment has shown that some of the fairly advanced tumors are still localized and may be cured by hysterectomy.

The other factor, and the main one in the improved outlook, is the possibility of early diagnosis by careful watching and the employment of the means mentioned under Diagnosis.

Recent reports of interesting cases of chorionepithelioma have been made by Sutherland, Kistner, Mohler and McConnell, and by Rashbaum et al., the latter being a report of a primary cervical choriocarcinoma.*

SARCOMA OF THE UTERUS

A sarcoma is a malignant growth arising from any tissue in the uterus which has a mesodermal ancestry. It can arise from connective tissue or muscle elements whether they are in the wall of the blood vessels, muscle tissue of the uterine wall, myomas, or even from the endometrium.

It is not especially associated with childbearing, and though more common between the ages of thirty and sixty, certain types are found almost exclusively in childhood.

The incidence of this disease is fortunately very low; Finn in a recent article found that sarcoma of the uterus comprised 0.15 per cent of 22,539 admissions in the Women's Clinic of the New York Hospital over a sixteen-year period. Novak found 59 cases from a total of 26,973 gynecologic specimens seen in his laboratory over a twenty-five-year period.

The ratio of sarcoma to all pelvic malignancies is between 3 and 5 per cent, and the ratio to uterine carcinomas varies; in a summary of eight series collected by Thornton and Carter, the ratio was from 1.1 to 3.6 per cent. It was found that in these eight series the ratio of myomas to sarcomas averaged 0.99 per cent, MacFarlane in Montreal found this ratio in his series to be 0.81 per cent, while Murray and Weitzner at the Harlem Hospital in New York had an incidence of 0.36 per cent. Fenton and Burke found that the twenty-six sarcomas occurring on the ward service of the Mount Sinai Hospital comprised 5.5 per cent of all of their uterine malignancies.

PATHOLOGY

The most frequent type of sarcoma is the type arising in a myoma; consequently, when one is performing a hysterectomy in women in the age group

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*Because of the rarity of these cases, an Albert Mathieu Chorionepithelioma Registry has been set up, and case reports should be sent to it; the present address is 26 East Preston Street, Baltimore 2, Maryland, this being the address of Dr. Emil Novak, the present Chairman of the Registry.

in which the ovaries are usually preserved, the uterus should be opened immediately and any myomas present should also be cut completely across for inspection. The findings which would indicate probable sarcomatous change are described by Novak as follows: "The sarcoma areas occur most frequently near the center of myomas, but may at times be noted only in the
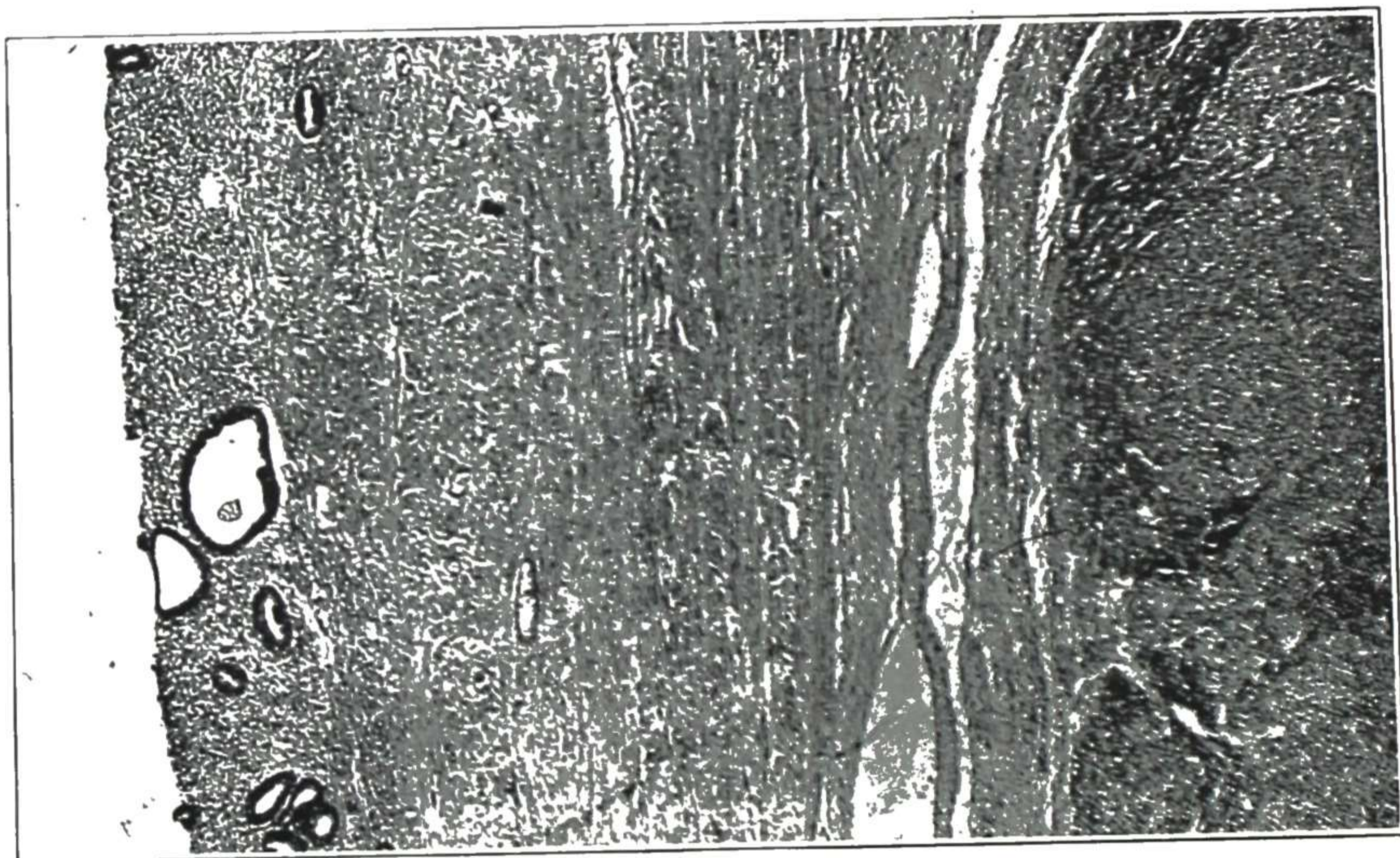

Fig. 736.—Sarcoma originating in an encapsulated intramural myoma about 8 cm. in diameter. At the left is the endometrium, in the center muscle tissue of the uterine wall and at the right the edge of the sarcomatous nodule. Gyn. Lab.
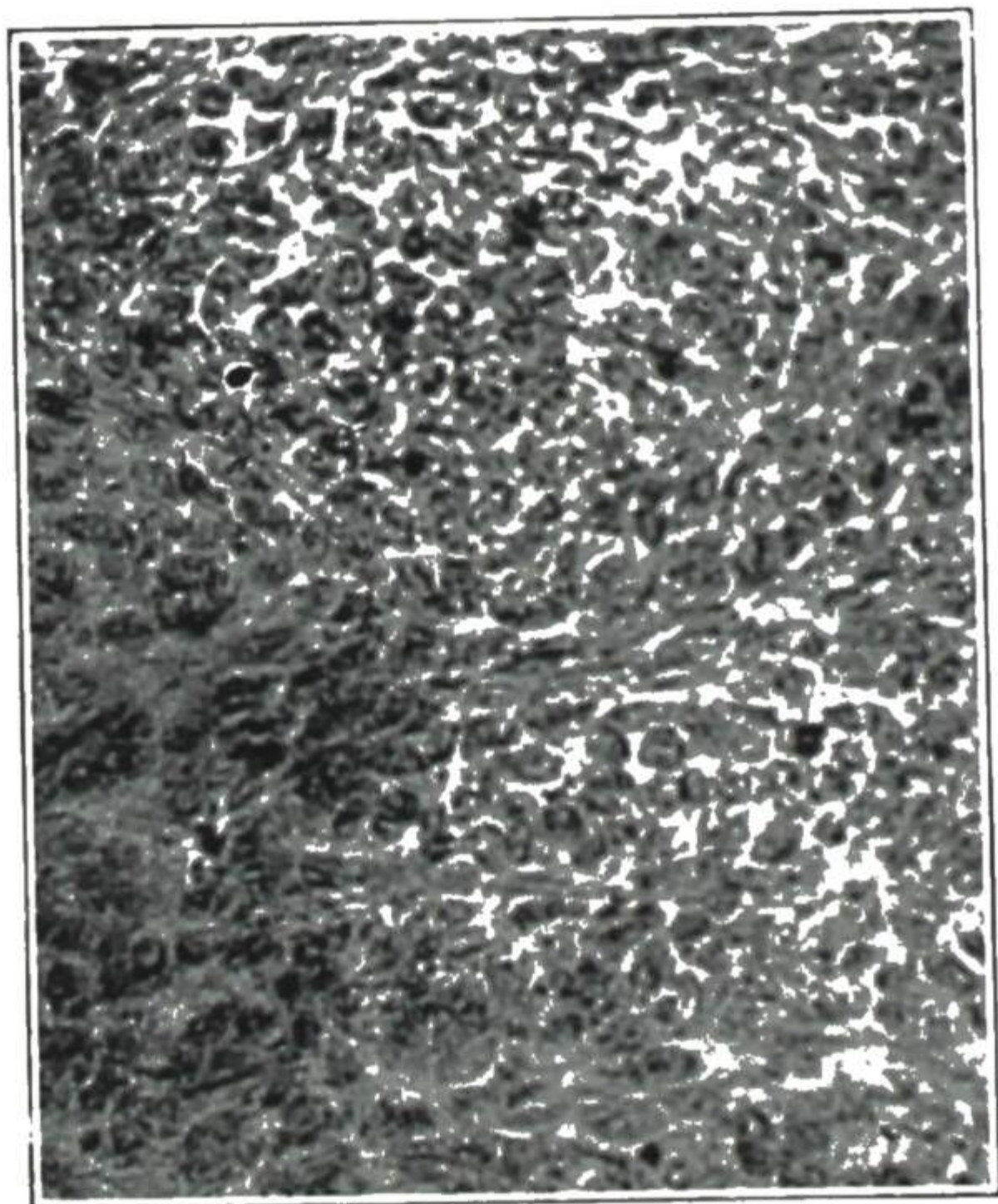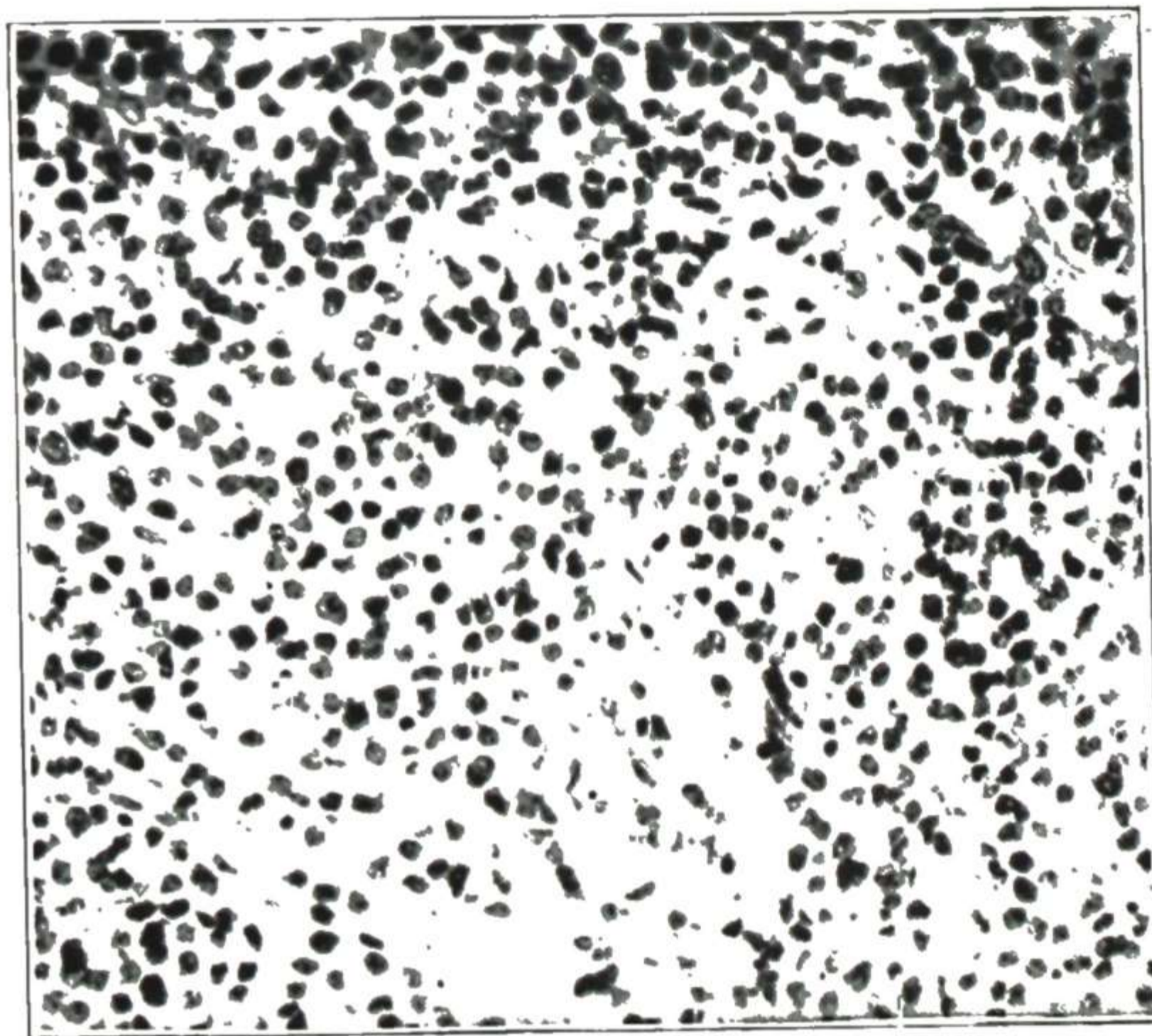

Fig. 737.

Fig. 738.

Fig. 737.—Sarcomatous change in submucous myoma. High power of Fig. 736. Large cells, chiefly spindle, occasional mitotic figure in field.

Fig. 738.—Photomicrograph of section from the tumor shown in Fig. 739. Gyn. Lab.

periphery. Instead of the hard rather glistening cut surface of a typical myoma, with its characteristic whorl-like appearance, the sarcoma areas present either the 'raw pork' appearance described by Cullen or, when necrotic changes are more marked, they present a brain-like pultaceous, broken down

area, with often a ragged cavity formation and perhaps hemorrhage." Though this can be confused with areas of simple hyaline degeneration, these latter areas are usually firmer than the sarcoma areas. When the endometrium is involved, it contains soft polypoid masses which, though they may resemble

Fig. 739.—Section through a sarcoma originating in a myoma of the uterus. This specimen is unusual in that the sarcomatous change is so uniform throughout the large tumor. A cross section of the uterus is seen at the lower right corner. Gyn. Lab.

benign polyps, are usually hemorrhagic and friable. Occasionally a sarcoma of the endometrium forms polyps which project from the cervix and may be mistaken for simple mucous polyps of the cervix. Such a case is shown in
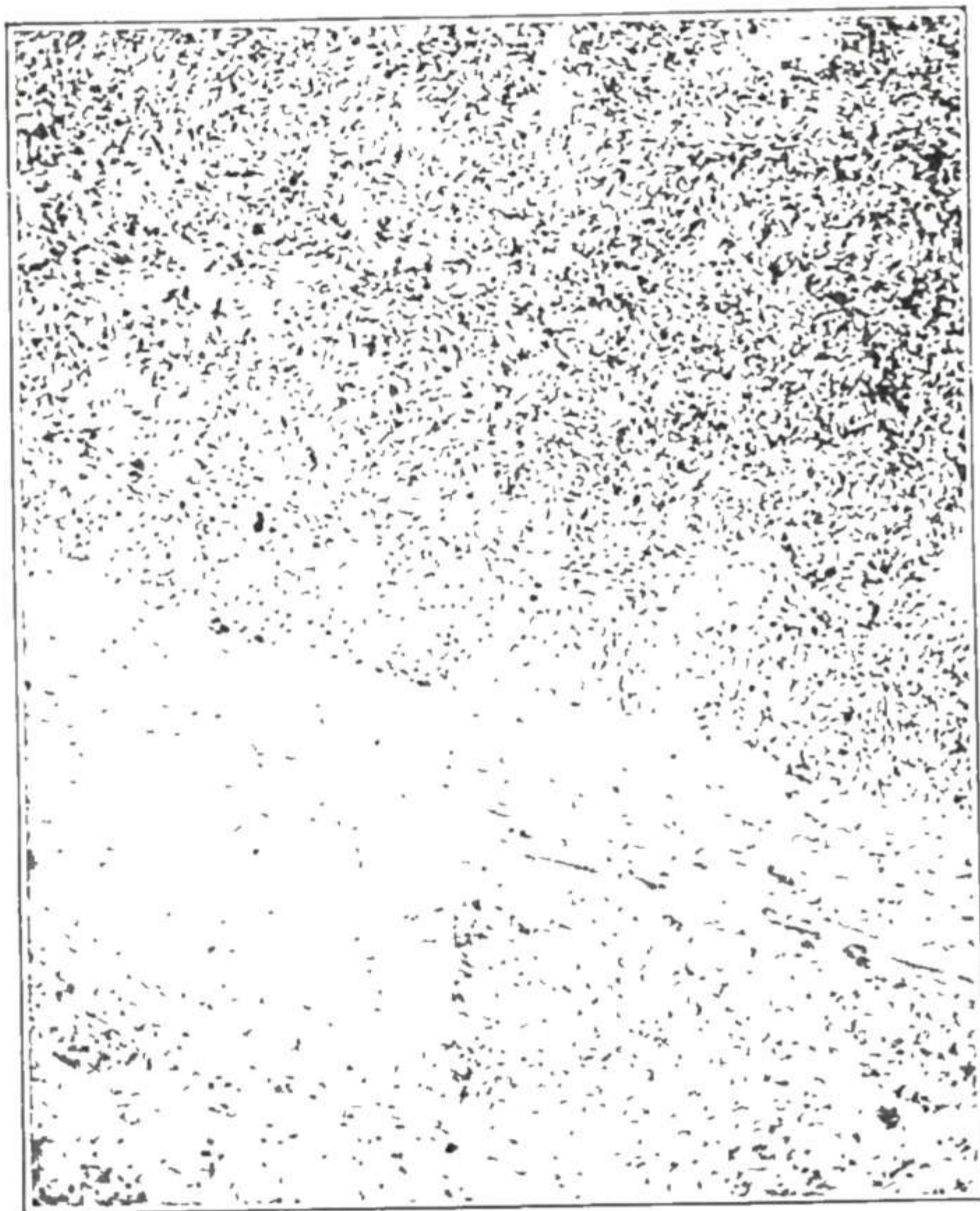
A.

B.

Fig. 740.—Sarcoma of the endometrium. Photomicrographs from the growing edge of the tumor. A, Low power, showing the line of junction of the sarcoma (above) with the normal wall. B, High power of the contact area. Gyn. Lab.
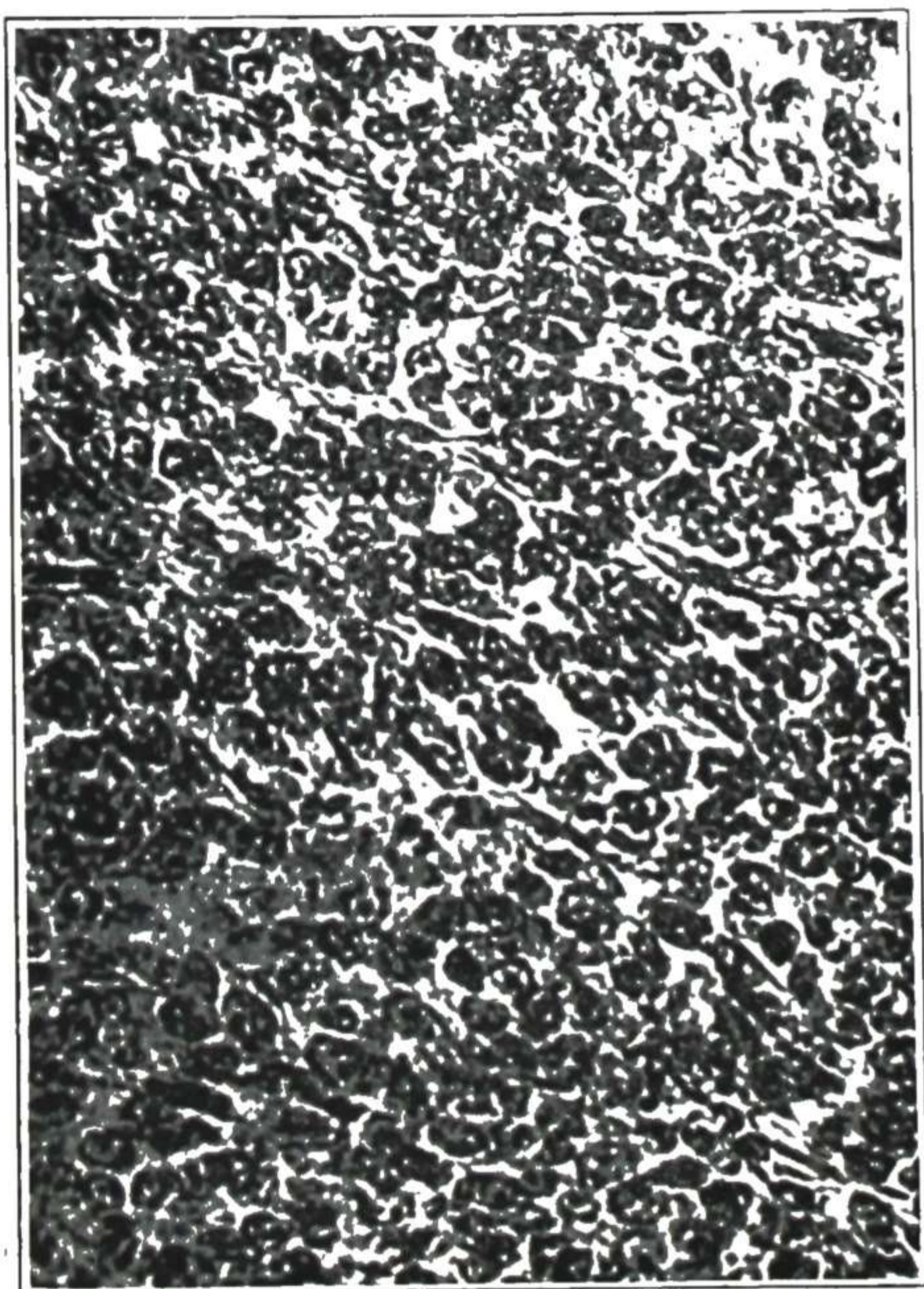

Fig. 741.

Fig. 742.

Fig. 741.—Sarcoma of the endometrium, high power. This is the round-celled type of sarcoma. The appearance in the spindle-celled type of sarcoma is shown in Fig. 742.
Fig. 742.—Curetting. Sarcoma of endometrium. Spindle-celled type. Gyn. Lab.
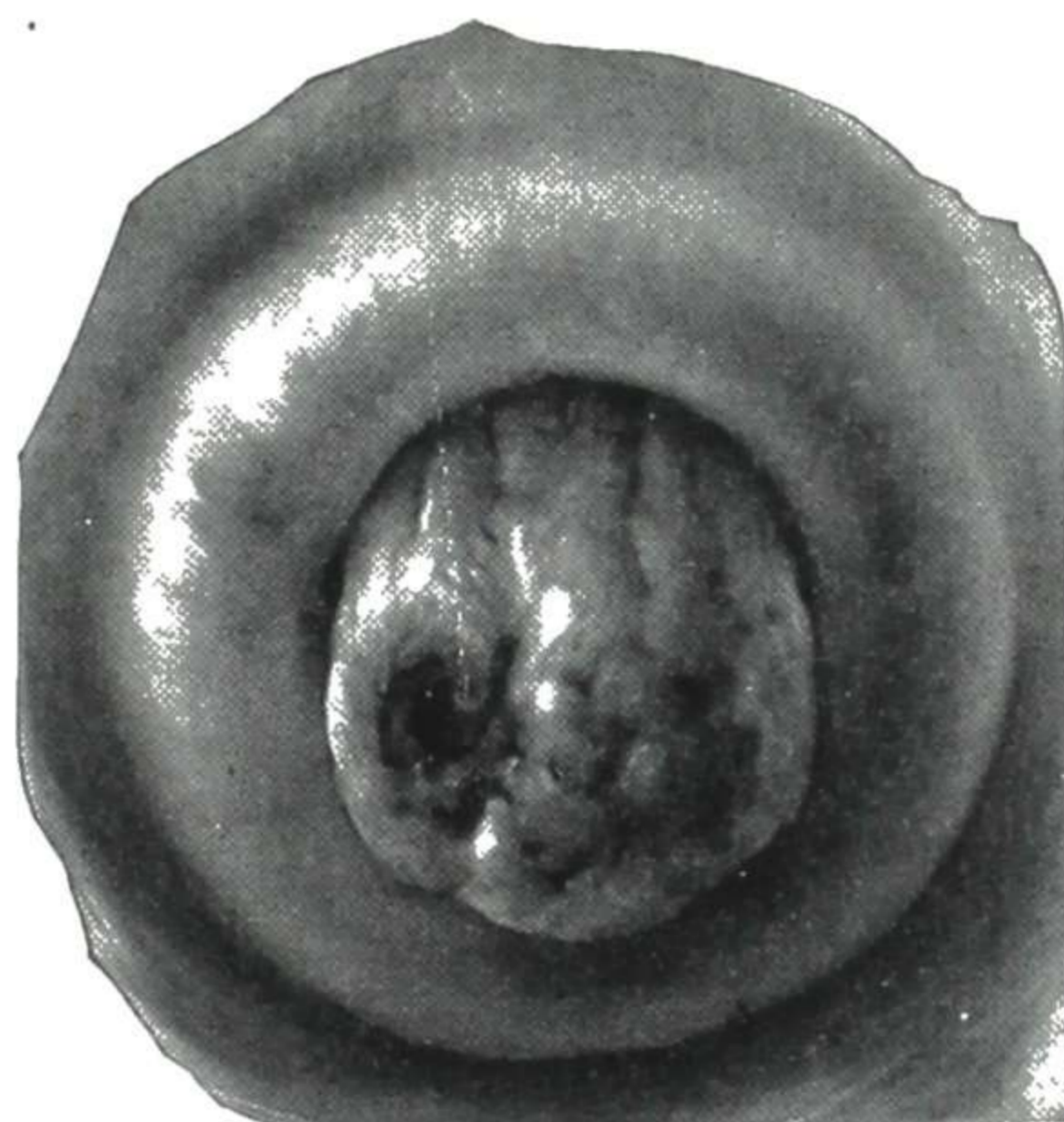
Fig. 743.—Polyp protruding from the cervix, which on removal and submission to routine microscopic examination proved to be sarcomatous. The uterus was then removed and when opened revealed the condition shown in Fig. 744. Gyn. Lab.

Fig. 744.—Extensive sarcoma of the corpus uteri originating in the endometrium. The exuberant growth formed polypoid masses which from time to time projected from the cervix (see Fig. 743) and were removed as simple cervical polypi. This happened several times before the patient came under the authors' care. Gyn. Lab.

Fig. 743, and it illustrates the importance of microscopic examination of all tissue removed from the cervix. The patient gave a history of having had a "simple" polyp removed from the cervix twice. There was no microscopic examination. As the polyp returned, she decided to go to another physician for a more thorough investigation. Examination showed a soft polyp projecting at the external os. This was removed and sent for routine microscopic examination, and it showed sarcoma. The uterus was then removed, and it showed extensive sarcoma of the endometrium (Fig. 744), which had been growing all this time.

The rare tumor, sarcoma botryoides, which usually occurs in children, has been discussed in Chapter 3. It presents as a pink grapelike mass usually filling the vagina. It is composed chiefly of mesodermal elements and in addition to the sarcoma cells one finds striped muscle and occasionally cartilage.
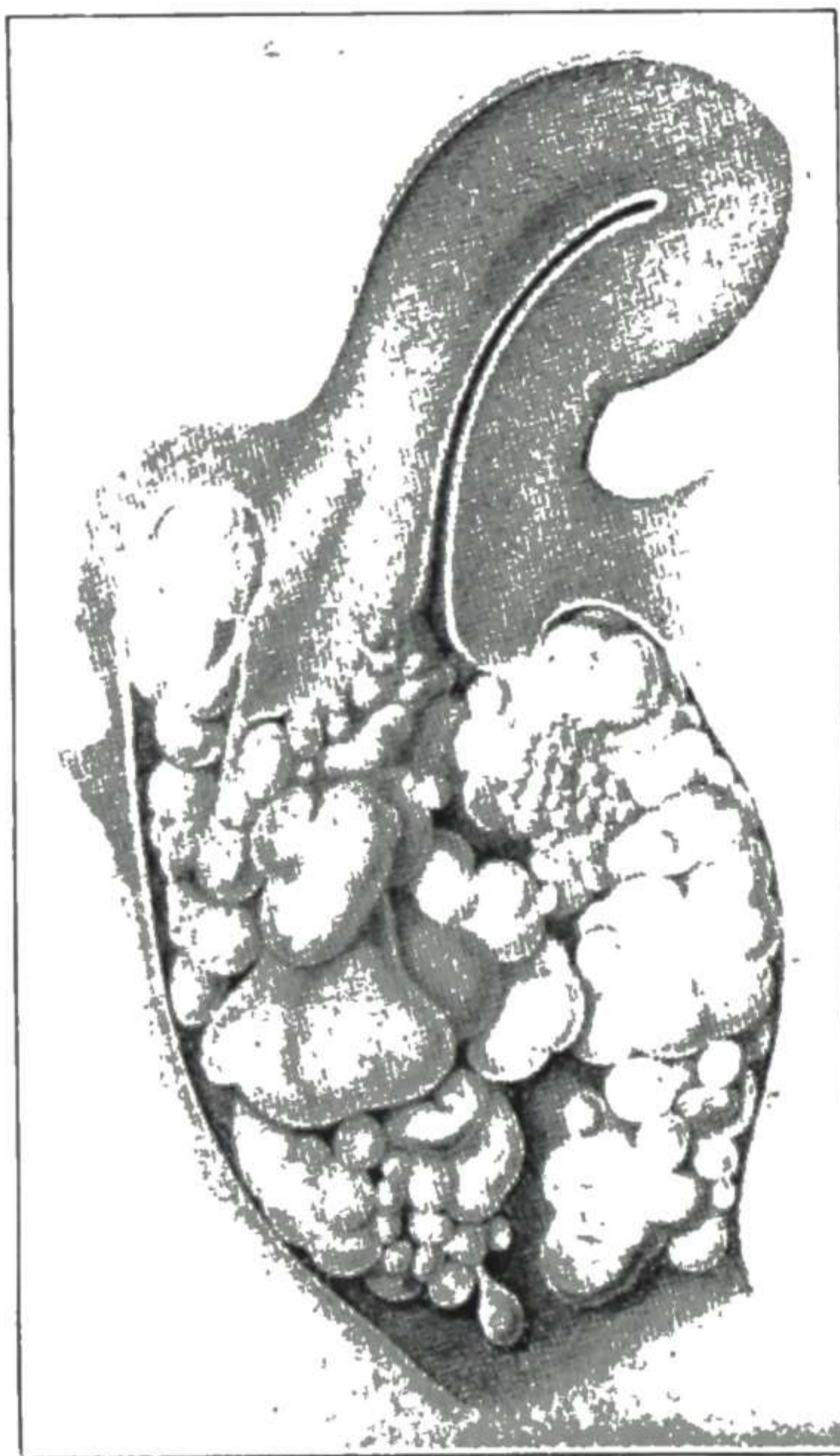

Fig. 745.—Grapelike sarcoma springing from the cervix uteri and forming a mass in the vagina. (From Kuestner: Kurzes Lehrbuch der Gynaekologie.)

Microscopically, the usual sarcomas may contain spindle cells or round cells or a mixture of the two; in addition to these, giant cells, formed by the congregation of degenerating sarcoma cell, are frequently present. A review of 94 mixed mesodermal tumors was reported by Glass and Goldsmith, and two recent cases were reported by McElin and Davis.

A sarcoma originating in a myoma is shown in Fig. 736, the point of contact with healthy uterine wall being shown. Higher magnification of the structure of this tumor is seen in Fig. 737. A very large sarcoma originating from a myoma is shown in the gross with uterus attached in Fig. 739, and the microscopic structure in Fig. 738. Sarcoma originating in the stroma of the endometrium is shown in Fig. 740. It has invaded the myometrium. Notice

the distinct line marking the limit of invasion. This line is shown also in Fig. 740. This is the round-cell type as shown in Fig. 741. The microscopic appearance of the spindle-cell sarcoma of the endometrium is shown in Fig. 742, which is from a curetting resulting in diagnosis. In Figs. 743 and 744 is shown a case of extensive sarcoma of the endometrium with a small mass protruding from the cervix. A grapelike sarcoma springing from the cervix, a rare type, is shown in Fig. 745.

TREATMENT

The treatment for sarcoma of the uterus is ordinarily prompt hysterectomy with removal of adnexa, followed by deep x-ray therapy. Special conditions may call for special modifications, and in inoperable cases radiation is the main reliance. The sarcoma which starts in a myoma gives the best rate of cure because it seems to be relatively low in malignancy. Of course this depends to a great extent upon the degree of extension; if early and surrounded by a good layer of myomatous tissue, the patient is frequently cured even with the incomplete operation of supravaginal hysterectomy. Novak states that though there have undoubtedly been some cases of sarcoma in the many cases of myoma which have been treated by radiation, sarcomatous recurrence in such cases is practically unknown. Schmitz found no sarcomas in cases irradiated for benign menopausal bleeding, though this procedure is the choice of treatment for this type of case in his clinic.

In contrast to the good results in the early cases, those not associated with myomas are more malignant, and in these, and in advanced cases of any type, there is no treatment that offers much hope. The five-year cure rate, of course, depends upon the number of early cases treated; in the eight series collected from the literature by Thornton and Carter there were 64 survivals in 253 cases, or approximately 25 per cent; the ten-year survivals in two of the series were about 6 per cent lower than that for five years.

Sarcoma botryoides, which is invariably fatal, is fortunately a rare lesion (Fig. 745).

Although there are a few substantiated cases reported of carcinoma and sarcoma occurring in the same uterus, Novak found that many of the cases so reported were in reality cases of very invasive adenocarcinoma of the endometrium. Another condition described variously as stromatous endometriosis, malignant stromatosis, and as stromatoid sarcoma (Mayeur) is probably a form of endometrial sarcoma. Corscaden has recently reported two such cases and found them peculiarly sensitive to radiation. One patient died of another disease eleven years after therapy, and the other, a seemingly hopeless case, was given palliative intensive deep x-ray therapy with excellent response, and she is alive eight years after treatment. Lash and Lash have recently reported a case and state that the mortality rate is 11 per cent and the recurrence rate 23 per cent in the 43 reported cases.

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Chapter 9
PELVIC INFLAMMATION

Since the discovery of the various antibiotics and their use in the prevention and treatment of infections, the incidence and severity of pelvic infections have been materially reduced so that the critically ill patients we formerly saw in the presulfonamide and preantibiotic era are seldom seen today. Likewise, the extensive chronic pelvic inflammations which formerly required surgery, often radical, for cure have been seen less frequently in the past five years. In spite of the improved results with new methods of prevention and treatment, there are still cases which do not respond; hence it is important that one should be conversant with all methods of managing these difficult cases. Another reason for retaining much of the material on former methods of treatment is that in many of the countries in which this text is used the antibiotics are not generally available.

Pelvic inflammation is the term applied to inflammation in the pelvis outside the uterus. The inflammatory process may be located in the fallopian tubes, in which case it is called "salpingitis," or it may be in the ovary, in which case it is called "oophoritis," or in the peritoneum, where it is known as "pelvic peritonitis," or it may be in the connective tissue, where it constitutes "pelvic cellulitis." The cause of these various forms of inflammation is the same—viz., infection—the symptoms are much the same, the treatment is in many respects the same, and two or three of the lesions are usually associated—in some cases so intimately associated that it is difficult to determine which is predominant. Consequently, it is convenient to group these lesions under the general term, pelvic inflammation, which at once identifies the type of process affecting the patient.

The continuous opening by which infection travels from outside the body into the peritoneal cavity is shown in Fig. 6. This continuous cavity is a large factor in the greater frequency of pelvic peritonitis in women than in men. There are narrowings which tend to check the upward progress of infection, for example, the external os and internal os and the uterine openings of the tubes. The mucus-filled cervical canal acts in the adult as an effective barrier to the upward extension of pathogenic bacteria, except the gonococcus, and even the gonococcus may be delayed and sometimes stopped by the protective qualities of the undisturbed canal contents. However, instrumentation in the canal interferes with this protective function and favors upward progress of any infection present. Hence, instrumentation within the uterus should be carried out only when indicated by conditions warranting the risk, and then under strict aseptic precautions.