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Cancer of the Body of the Uterus.*

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Frequency of Malignant Disease of the Uterus.

The female sex is much more often affected by malignant disease than the male, and of all the organs of the body the uterus is most frequently attacked. In March, 1898, the Birmingham Branch of the British Medical Association appointed a Committee of which I was a member, to enquire into the influence of locality on the prevalence of malignant disease. The report of the Committee is published in the *Birmingham Medical Review* for May to July, 1900, and included in it is a table showing the sex and the organs affected in 4,972 persons who died of cancer in the course of ten years in a population of about 750,000. In 4,827 cases in which the sex was noted, 2,936, equal to 60·8 per cent. occurred in females. The excessive incidence in women is more than explained by the number of cancers affecting the generative organs, especially the uterus and breast. The stomach, including the pylorus, shares with the uterus the bad pre-eminence of being the organ most affected by malignant disease. The two furnish almost the same number of deaths, the uterus affording 724, all of which affect of course only one sex, whereas the stomach cases are spread over the two sexes. From the figures here given it is seen that in one out of every four women who die of malignant disease the uterus is the organ primarily affected. From the Registrar-General's report for 1901 it appears

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that there were 27,487 deaths from cancer, of which 16,596 were in females. If the rate just mentioned for the Midland Counties holds good generally there are each year in England and Wales about 4,000 deaths from uterine cancer; and as the duration of the disease probably averages two to three years there are at the present time approximately 10,000 women affected by uterine cancer in these countries alone.

Frequency of Malignant Disease of the Body of the Uterus.

The proportion of cases beginning in the body of the organ to the total number of uterine cancers has shown a tendency to rise in proportion to the increase in the number of exact observations. Thus Arnott, writing in 1870 on the results of 57 *post-mortem* examinations of patients dying from uterine cancer, mentions only one "remarkable case" in which the cervix was free. In 1876 Schatz had observed two affecting the body in a total of eight uterine cancers. In 1899 Gebhard states that about six per cent. of all uterine cancers are body cancers, a ratio which agrees with my own experience. In 1886 Gusserow had collected from literature 122 cases (including three unpublished cases of his own). Among these were some cases of sarcoma, while in the older literature, not rarely cases of sloughing fibroma were mistaken for cancer of the fundus. These latter cases are now, of course, easily and generally recognised, and do not lead to confusion, but it is still too much the rule to include cases of sarcoma when dealing with the question of cancer of the body. The two affections present so many differences and peculiarities that for the future separate consideration is to be desired for them.

Incidence of Cancer of the Body of the Uterus.

Cancer of the body of the uterus is not a disease of misery or destitution; none of my fifteen patients was very poor and the majority were in comfortable circumstances. The youngest patient was aged 47 and the oldest 76 years. Six of the women had attained the age of 60 years and upwards, and the average age of the 15 was 57 at the time the diagnosis was made. Three of the patients were widowed, apparently a large proportion, but in this connection the age must be taken into consideration. Four others were married; the remaining eight, more than half the total, were single women of whom at least five were undoubted virgins. The disease is the cancer par-excellence of adult virgins. Of the seven women who had been married and had thus been exposed to the chances of conception, the total was seven; of these one had had eight children and one miscarriage, and

three others had each borne one child 40, 50, and 14 years ago respectively; the other three were nulliparous. The seven married and widowed patients had had altogether eleven children and one miscarriage, an average of 1·57 children and 0·14 miscarriage to each patient. It therefore appears that the women who are affected by cancer of the body of the uterus are old women of whom a large proportion are single, and of whom the married ones have passed through considerably less than the average number of pregnancies.

Most of the patients had already passed the menopause; in one the history in reference to this point was not reliable; four patients were at or near the climacteric, and in the other ten menstruation had ceased, in three for more than twenty years, and in two others for more than ten years; thus in one-third of the cases the affection began more than ten years after the menopause. With regard to the climacteric age one patient ceased menstruation at 30, one at 40, and the others at various ages over 44. In four of the patients, a large proportion, the menopause did not come on till 50 or upwards. It therefore appears that carcinoma affects chiefly women who have passed the menopause, and that the age at which the menses cease often departs from the normal but not in any definite direction; occasionally menstruation ceases very early, but more frequently it is prolonged to a later age than usual.

The Origin and Development of Cancer of the Body of the Uterus.

Every organ appears to have its own particular form of cancer, and the body of the uterus is no exception to the rule. Here the typical form is a structure made up essentially of alveoli which in their simpler forms recall the glands normally found in the mucous membrane lining the cavity. It appears as if some of the glands have enormously increased in number and size, and have at the same time undergone a bizarre form of evolution which has carried them a greater or less distance towards a final stage of development into ordinary spheroidal celled carcinoma. Examination of my specimens appears to prove that at least in the great majority of cases cancer of the uterine body develops progressively through stages which begin with malignant adenoma at the one end and pass through adenocarcinoma, to form at the other end spheroidal celled carcinoma in which the evidence of glandular origin may have entirely disappeared. Any of these stages may be missed, or may persist for a considerable time; thus, for instance, a tumour of some standing may, as rarely happens, show the structure of a pure malignant adenoma; or more commonly the earliest stage observed is that of adeno-

carcinoma, which may persist for an indefinite time; but as a rule evidence of the evolution just mentioned may be discerned at different parts of the same tumour, and generally the most advanced stages appear to have been reached in the oldest and deepest parts of the growth, while at the growing portions the earlier stages are seen.

Squamous epithelioma. Cancer of the body of the uterus is usually described as beginning in two ways, either from the glands as just indicated, or from the surface epithelium. In the latter case it is stated that there is in the first instance an increase in the number of layers of surface epithelium, the upper layers undergoing a horny transformation. Then as in squamous epithelioma, processes starting from the deeper layers of the epithelium penetrate into the muscular wall of the organ and give rise to an ordinary squamous epithelioma such as is met with typically arising on the outer surface of the cervix or on the vulva. Occasionally only the first stage of this development occurs, the epithelium becoming stratified, squamous, and keratoid, and the surface appearing covered with a peculiar opaque whitish layer like the sugar icing on a cake. This is the condition known as uterine ichthyosis, and is analogous to the change which is frequently seen in patches on the tongue and on the innermost surfaces of the vulva. From a surface epithelium altered in this way the origin of a true squamous epithelium is easily intelligible, and at least nine cases in which the occurrence of this form of tumour has been described in the uterine body are referred to by Gebhard.

There is, however, another and a much more common way in which a tumour having some of the appearances of a squamous epithelioma may develop in the uterus. In the older portions of a carcinoma developing in the ordinary way from an adeno-carcinoma, groups of epithelial cells, especially in the central portions of the alveoli, undergo a hyaline change, the cell bodies becoming swollen and homogeneous, taking on a diffuse stain, and finally becoming fused together so that the distinction between the separate cells is lost. The nuclei at the same time undergo remarkable changes; they become swollen, stain less deeply and more diffusely than usual, and finally break up into irregular fragments and granules. In the cell bodies also, concentric lamellæ are often developed, and a group of cells which has undergone this degeneration frequently presents the appearances of a "cell nest" or "epithelial pearl," such as is typically found in squamous epithelioma. Typical changes of this kind were seen in three of my cases and all the intermediate stages could be followed from adeno-carcinoma through ordinary spheroidal-celled carcinoma to this imitation of squamous epithelioma.

In the *London Obstetric Transactions* there are several cases recorded in which a similar process appears to have occurred. Thus Targett (*Obst. Trans.*, 1900, p. 281) showed a specimen of carcinoma of the body of the uterus which was supposed to be squamous epithelioma, but on further investigation proved not to be so. Lewers (*Obst. Trans.*, March, 1903), showed a specimen of keratinising cancer of the body of the uterus, and Mrs. Boyd referred to a similar case. Doran (*Obst. Trans.*, 1903, p. 376) showed for Batchelor an important case of squamous epithelioma which was carefully examined by Lockyer, who found it to be typical; further examination showed, however, that the growth started in the columnar epithelium of the glands of the mucous membrane; in spite of this fact the last observer thinks it better to speak of the tumour as squamous epithelioma of the body of the uterus, a view with which I most emphatically disagree, since it can only lead to confusion of thought and expression. The term squamous epithelioma ought to be reserved for the form of growth that begins in a squamous epithelium and that is fully developed from the start. Where, on the other hand, the appearances described are due to a degeneration occurring in the later stages of a tumour which passes through a well-defined course of development, such as does the glandular cancer of the body of the uterus, it is better to speak of a tumour showing these changes as a keratoid or keratinising adeno-carcinoma (*vide* Fig. 4). Gebhard allows that this form of metaplasia of cells may occur in an adeno-carcinoma, and thinks such a change had taken place in at least four of the nine cases mentioned by him.

In the fifteen cases operated upon and investigated by me, in all but one the glandular nature of the swelling was apparent, and in the fifteenth the examination, which was not full enough to be conclusive, still afforded some indications that the cancer in this case also had a similar origin. In three of the cases there was marked keratoid degeneration, and in two of these, fairly typical cell nests were present in the older portions of the tumours. Before accepting the microscopic diagnosis of squamous epithelioma of the body of the uterus it is therefore necessary that the most careful and complete investigation of the specimen shall be made, including the examination of sections from different portions of the growth, and more especially from the growing edge.

In addition to my own fifteen cases I have been able to examine five other specimens in the museum of the university. Two of these appear microscopically to be alveolar carcinoma, but the specimens are too much macerated for detailed examination. A

third is a localised malignant adenoma of the everting type. The other two are examples of adeno-carcinoma of the body supervening on large submucous fibromyomata.

Glandular Cancer of the Body of the Uterus.

Cancer of the body of the uterus is often divided into diffuse and localised varieties. In thirteen cases of the present series which were treated by radical operations, the affection was diffuse in seven and localised in six. In the diffuse cases cancer symptoms had been present for a longer period than in the localised; in the former case the shortest duration of symptoms was nine months in one patient, in two others the evidence of cancer had been present for one year, and in the others for $1\frac{1}{2}$ to 2 years; the average duration of symptoms in six cases was $1\frac{1}{4}$ years. Of the patients with localised cancer, in one symptoms had been present for one year and in the other five for six months or less, the average for the whole six patients being six months. The symptoms in the diffuse cases were more severe at the time of operation, several of the patients showing marked cachexia, while in the localised cases as a rule the general health of the patient had suffered comparatively little. It is further to be noted that in the diffuse cases the growth was not only of greater superficial extension but had invaded the deeper layers of the uterine wall, so that in one case the whole organ including the cervix was involved, and in two peritoneal adhesions had formed to intestine and mesentery; in two other diffuse cases collections of pus had formed in the uterine cavity. There are therefore ample clinical and pathological reasons for considering that the localised and diffuse cases represent merely stages of the disease and not true varieties, a conclusion that is further strongly supported by the histological examination of the specimens.

Cancer of the body has also been classified according to the characters of the surface of the tumour which may be smooth and nodular, coarsely papular, or closely set with fine filiform or villous projections. The cases are accordingly divided into nodular, papillary, and villous, and of these the last variety is by far the most common. None of these classes corresponds to a distinct histological variety of tumour. To whichever variety a cancer belongs it forms in its early stages a localised tumour whose acquaintance has hitherto been made only after it has attained a certain definite size easily seen by the naked eye. The exact origin and especially the nature of the tumour germ or matrix which presumably gives rise to the disease is therefore entirely a matter of inference.

In the earlier stages of a malignant adenoma or adeno-carcinoma of the uterus the size, shape, and arrangement of the alveoli vary very greatly, but can for the most part be arranged in two varieties. In one of these the alveoli are large and the epithelial lining gives off buds or finger-like projections into the lumen; in the other the alveoli remain small and are arranged as if a tube more or less resembling a uterine gland had elongated and become tortuous, and at the same time had given off lateral processes which in their turn branch and branch again. In the latter kind of tumour the alveoli are often found in definite families or rounded collections, and according as they are cut transversely, obliquely, or longitudinally, appear as round, oval, or narrow elongated spaces lined with epithelium and separated from each other by a small quantity of connective tissue which is continuous with the rest of the stroma. This latter glandular type of cancer has been called *everting*, *extra-glandular*, or *axifugal*, while the first or papillary variety is described as *inverting*, *intra-glandular*, or *axipetal* (*vide* Figs. 1 and 2). As a rule both these varieties of structure are found co-existing in varying proportions in the same tumour, and portions showing a mixture of the peculiarities of both are frequent. It is therefore important to remember that they represent merely different arrangements and not distinct varieties of tumours; they are in fact chiefly important for purposes of description.

In the more advanced stages of development the alveoli become completely packed or filled with epithelial cells and the obvious glandular origin of the tumour may become lost (*vide* Fig. 3). Speaking generally the inverting type of tumour gives rise to large alveoli, while in the everting type the spaces tend to remain smaller.

Modes of Extension of Glandular Cancer of the Body of the Uterus.

At its very beginning cancer of the body of the uterus appears to be represented by a minute, possibly microscopic collection of cells, representing the tumour germ or matrix. Occasionally, as in two of my cases, two foci with a clear interval may be present, two matrices having begun to grow simultaneously. We are ignorant of the exact nature and relations of the matrix, which may have its seat among the surface epithelial cells or more probably in the subjacent mucous membrane. Whether it consists of one cell or a group of cells, and if the latter, whether it is made up merely of a collection of cells without definite arrangement, or of a group definitely arranged into a gland-like structure, we cannot tell. At the time when we first make its acquaintance a definite nodule visible

to the naked eye is already present and has a structure characteristic of one of the forms of cancer above described. This nodule grows in all directions, over the surface, outwards into the muscular wall of the organ, and inwards into the cavity. The growth takes place more easily in the direction of least resistance, and so we find in the early stage a nodule making a considerable prominence into the cavity. Superficial growth also appears to be easy in the cavity of the uterus and so the cancer tends to spread over the entire surface of the endometrium, its extension being bounded for a time, however, at the internal os. The growing margins of the tumour and its free surface, appear often to have a less dense structure and to represent an earlier stage in the development of the cancer, than the deeper parts invading the muscular coat, suggesting that pressure has something to do also with the development of adenocarcinoma into the spheroidal-celled variety in which the alveoli are filled with cells.

The statement is commonly made or implied that the local extension of the growth takes place at least in part by the conversion of the adjacent endometrium, the epithelium and glands becoming transformed into cancerous epithelium and alveoli owing to some sort of spermatic influence exerted by the tumour. If this were so the local extension of the growth would depend upon a process fundamentally different from the formation of glandular and remote metastases, the secondary tumours in the latter case being formed by the continued growth of groups of cells broken off and transplanted from the primary tumour. A careful examination of the growing edge, in those of my cases suitable for the purpose, affords no evidence of the conversion into cancer of the original glands and epithelium of the part. At or near the growing edge of the tumour the endometrium ceases abruptly. The new growth and the endometrium are sometimes closely contiguous, in which case the tumour may slightly overlap the margin of the endometrium. Sometimes at the margin of the growing tumour hæmorrhages are seen in the surface layers of the endometrium; at others there is an intervening band of connective tissue which may be of considerable breadth, or shows more or less marked infiltration with round cells, and is sometimes broken by hæmorrhage. The mucous membrane may be continued over the surface or upwards round the side of the cancerous tumour for some distance, as was well seen in one of my cases where the mucous membrane covering the tumour showed more marked signs of atrophy than the adjacent mucous membrane covering the unaffected portion of the uterine surface.

Growth at the periphery of the cancer thus appears to take place

at least in the great majority of instances by the continuous increase of its own constituent elements. Occasionally, however, it seems possible that the extension may take place by conversion of the epithelial cells of the endometrium in the neighbourhood, and there are appearances suggesting this process in sections taken from one of my cases.

For a considerable time the cancer forms a localised affection which invades the neighbouring portions of the uterine wall by growing into the tissue spaces of the fibro-muscular coat. After a time, however, it invades the larger lymphatic vessels as well as blood vessels of considerable size, and then rapidly spreads beyond the limits of the uterus. The last two avenues of extension are of the utmost practical importance in discussing the question of the time for operating, the method of operation, and the ways in which recurrence may be expected. By both lymphatics and blood vessels the spreading takes place by embolism, or less commonly by the direct invasion of the vessel wall.

Lymphatic Invasion.

The lymphatics of the uterus are arranged in three close networks situated in the mucous membrane, the muscular coat, and in the peritoneum with the subperitoneal layer of connective tissue. The lymphatic systems of the body and cervix of the uterus are continuous so that the cancer is able to spread in either direction from one to the other. The uterine lymphatics vary enormously at different ages; until puberty they are relatively few and small; during adult sexual life they are abundant and large, more especially during pregnancy; after the menopause the lymphatic supply becomes diminished progressively with advancing age. In this last change is found one of the chief reasons which explain the fact of cancer of the body of the uterus being, as a rule, slower in its growth and more favourable as regards treatment than cancer of the neck of the uterus.

In the muscular coat there are numerous large lymph vessels lying, along with large blood vessels, in the middle and outer muscular layers. These are the vessels through which the connection takes place between the lymphatics of the cervix and those of the body. The lymphatics of the uterine body are finally collected into three groups of collecting trunks:

(a) The principal or transverse group comprises 4 or 5 trunks which appear beneath the cornu of the uterus. These at first follow

the terminal segment of the uterine artery and then pass below the ovary where they are joined by the vessels from this gland. They then run with the ovarian vessels in the ovario-pelvic ligament and ascend towards the lumbar region, crossing with the vessels in front of the ureter. A little below the level of the hilum of the kidney the lymphatics curve sharply inwards and "descend in showers" upon the juxta-aortic glands of the same side, a few of them reaching the pre-aortic glands.

(b) One or two lymphatic vessels begin a little below the cornu of the uterus and run directly outwards to end in the middle chain of the external iliac glands, which also receives lymphatics from the cervix.

(c) A single lymphatic vessel runs along the round ligament to end in one of the upper and internal inguinal glands.

As in the case of the veins the uterine lymphatics communicate with those of the neighbouring organs, the vagina, rectum, broad ligament, tubes, ovaries and round ligaments.

The regional glands belonging to the body of the uterus are principally juxta-aortic glands, and secondarily certain of the external iliac and inguinal glands. The left juxta-aortic group forms an almost continuous vertical chain along the left side of the abdominal aorta; they lie on the vertical attachments of the psoas muscle and on the left pillar of the diaphragm, and are crossed in front by the left renal artery and vein. The right juxta-aortic glands lie some in front and some behind the vena cava. Three to six of the glands are pre-venous and are usually found below the junction of the renal vein with the inferior cava; the rest are retrovenous and lie like the left juxta-aortic glands on the origins of the psoas and on the external surface of the corresponding pillar of the diaphragm. Both sets of glands receive the efferent trunks of the common iliac glands, the parietal lymphatics, and the lymphatics of the kidneys and genital glands, including the adnexa and the corresponding half of the body of the uterus. From the juxta-aortic glands four groups of efferent vessels are given off and pass into the pre-aortic and retro-aortic glands, into the receptaculum chyli, and into the thoracic duct a little above its origin.

From the above description of the uterine lymphatics it appears that the first glands to be affected are those intimately connected with the large abdominal vessels, which have such relations as preclude their removal by operation. Fortunately it appears that

invasion of the lymphatics takes place relatively late in the course of the disease. The efforts of the practitioner must therefore be directed to diagnosing cases of uterine cancer at a stage before invasion of the lymphatics has taken place. By the lymphatics there is a kind of intermittent invasion of the body, a spread by stages or steps with definite halting places at which the invasion is temporarily arrested. For a time the cancerous emboli which are the carriers of infection from the uterine body are arrested in glands of the juxta-aortic group. After a time emboli are in turn given off from these glands and invade some of the mediastinal group, or they may be conveyed, by means of the efferents which join the thoracic duct, into the blood stream and thus to any of the remote places of the body. Lymphatic invasion differs in this way, and also in being more gradual, from the mode of spread that is due to invasion of the blood vessels, especially the veins, by emboli derived from the primary growth.

Invasion by the Blood-vessels.

The veins of the uterus are very thin walled so that on section they may appear as mere clefts or slits in the muscular wall of the body of the uterus, where there is a close plexus of large veins, the largest being found under the peritoneum on the posterior surface. From this plexus large vessels run outwards to the side of the uterus to enter into an extensive plexus placed along the lateral wall of the uterus and vagina on either side, the utero-vaginal plexus. At the level of the internal os arise from this latter plexus on either side, two uterine veins which accompany the uterine artery, one passing with the artery in front of the ureter and the other behind. The uterine veins join with the collecting trunks of the vesico-vaginal plexus to form a common stem, which also takes up the obturator vein and then joins the internal iliac. The uterine veins receive branches from between the layers of the broad ligaments and communicate with veins of the round ligaments and through these with veins of the abdominal walls and external genital organs; and further they communicate with the veins of the tube and ovary and also with the ovarian veins, and finally with the veins of the pelvic floor, rectum, and external genitals.

From the ovary, tube, and upper part of the broad ligament the blood is collected by a number of veins which form the large pampiniform plexus between the layers of the mesosalpinx. The vessels from this plexus terminate in the ovarian vein which runs upwards along with the ovarian artery into the lumbar region, where

the right ovarian empties itself into the vena cava, and the left into the left renal vein.

The invasion of the blood vessels by cancer appears to be more frequent than has been generally recognised. Where the veins are invaded the emboli pass immediately through the heart to the lungs. Schmidt (*Brit. Med. Journ.*, i., 1904, p. 851) has made observations on 41 cases of carcinoma with special reference to the dissemination by the blood stream. In 15 cases carcinomatous emboli were found in the small arteries of the lungs. It appears that in cancer of abdominal organs metastatic cell groups are frequently arrested in the pulmonary arteries, but that only a small proportion of these cell masses give rise to metastatic growths in the lungs, or break through the vessel wall into the perivascular lymph stream. The greater number are destroyed by the organisation of the thrombus surrounding them, or are encapsuled and rendered inert. A small minority grow forwards through the surrounding thrombus to the capillaries and small veins, and by getting into the general circulation may be carried to any remote part of the body. The method of invasion by the blood vessels may give rise in certain cases to a rapid and very widespread generalisation of the disease, leading to a rapidly fatal termination.

Resumé of Modes of Extension and Recurrence after Removal.

We can thus distinguish local and remote paths of extension of cancer. The local invasion takes place either (1) by simple continuity, alveoli spreading out along the lines of least resistance; in the case of the uterus in the interstices between the connective tissue and muscular fibres, and in the lymph spaces; or (2) by a more extensive form of local spreading which takes place along the blood and lymphatic vessels that remain in the uterus itself. Seelig has shown that cancer may spread along the lymphatic vessels from the cervix to the body, and a similar spread may undoubtedly also take place through the blood vessels. The remote paths are the lymphatic and blood vessels which drain the uterus, either of which may convey emboli from the original growth.

Recurrence after operation may be understood by a reference to the modes of spread just described; thus recurrence may be local:

1. At the site of the original growth, or
2. At a little distance from the former site but still within the limits of the organ.
3. Recurrence may take place at any part along the course of the lymphatics leading from the organ, or in the lymphatic glands.

4. Remote metastases may occur from emboli derived from the primary growth having been carried by the blood stream and lodged in some of the remote organs or tissues.

Relation to Fibromyoma.

In thirteen cancerous uteri removed by me fibroids were present in six of the cases, and in three of them (Cases 3, 8 and 12) the tumours were of notable size, so as to complicate the diagnosis and treatment. In three of the five other specimens present in the museum, there were also fibroids, and in two of them the tumour was as large as a fœtal head. It appears, therefore, that a very large proportion of cancers of the body occur in uteri which are already affected by fibroids, and this fact is in striking contrast to the relative rarity with which fibroids complicate cancer of the cervix. In every case the fibroids appear to have existed before the carcinoma began to develop; and the latter began in the endometrium, in some cases apparently over the fibroid, and in others certainly at a distance from it. In none of the cases is there any reason to think that the cancer began in the fibroid tumour itself, but in two of them the tumour was invaded by the cancer, the invasion being at the surface. The frequent concurrence of the two forms of disease seems to render probable the existence of some link in causation. It is well known that the presence of a fibroid frequently sets up a condition of chronic endometritis, glandular, interstitial, or mixed, and it is at least possible that the diminished physiological resistance of the endometrium brought about by this endometritis is the determining factor which sets free any matrix of cancer which may be present, and allows it to grow.

The co-existence of fibroids with cancer of the body is of great importance from the practical point of view. Any symptoms that may be present are only too likely to be set down to the presence of the fibroid, and in this way, as occurred in Cases 3 and 8 of my series, the growth of a cancer of the body of the uterus may be for a considerable time overlooked. When fibroids are present in a uterus, if the menses have ceased for a time and begun again, or if the bleeding increases, or if a profuse serous, mucous, or coloured discharge makes its appearance, especially at the climacteric, the cavity of the uterus should be explored without delay, and in case of doubt the uterus should be removed.

Symptoms.

Uterine cancer gives rise to certain symptoms sufficiently obvious to arouse the attention of the women affected, but no symptom or

group of symptoms is pathognomonic, especially in the early stage of the affection. Towards the end of the disease the well marked cachexia along with pelvic pain, irregular loss of blood, and stinking discharge from the vagina, together make up a picture seldom found in any other disease, but even when all these indications are present, it sometimes happens that they are caused by the sloughing of a simple submucous or polypoid fibromyoma. The diagnosis in every case must rest upon the objective examination of the patient, and in the earliest stages of the disease, when it affects the body of the organ, its recognition depends upon the microscopic examination of portions removed by the curette. It is necessary, therefore, that in every case of cancer or of suspected cancer, an objective examination shall be made, and it is further necessary that the examination shall be made at the earliest possible moment. Hence it is in the highest degree important that not only medical men but women themselves should be conversant with the symptoms that may indicate danger and call for immediate investigation. Twenty years ago the circumstances were different; a diagnosis of cancer of the uterus was equivalent to a sentence of death; the patients therefore put off consulting a medical man until the sufferings of the late stage of the disease compelled them, while the medical man on his part postponed examination in order that he might not deprive the patient of hope. At the present time at least one-third of the cases that are recognised sufficiently early can be cured by prompt operation. To wait until the symptoms become further developed is to run the risk of the disease in the meantime spreading beyond the reach of radical surgery. The responsibility for an immediate diagnosis in every case of suspected uterine cancer is therefore one of the most onerous burdens laid upon the medical practitioner.

In order that this responsibility may be met it is necessary to study carefully the earliest symptoms to which the presence of cancer may give rise; these are vaginal discharge of various kinds, bleeding, sometimes pain, and occasionally loss of flesh and strength. Among my 15 cases bleeding or bloody discharge was the first symptom complained of in 9, yellow or white discharge in 4, and pelvic pains in 2, in one accompanied by slight bloody mucous discharge and dysuria. The duration of the symptoms before my first examination varied from 3 months to 3 years; the average in the localised cases being 9 months, in the diffused cases 15 months, and in 2 cases which could only be curetted 2 years.

In the majority of cases the earliest symptom is a more or less constant discharge of thin serous fluid, often red stained. As the

cancer advances, and especially when it ulcerates, the discharge becomes thicker in consistence and opaque white or yellowish in colour, or becomes more or less brown or red by admixture with blood. Bleeding also occurs usually at irregular intervals, sometimes lasting for several days at a time and sometimes being absent for weeks together. With the progress of the disease bleeding usually becomes more profuse and may take the form of veritable floodings, but this usually happens only in the later stages of the affection. The occurrence of bleeding under circumstances involving active congestion or bodily exertion is a particularly suspicious symptom; thus bleeding during sexual intercourse, after active exertion, or during defæcation, always calls for prompt and thorough investigation. Increase in the amount, duration or frequency of bleeding near the expected menopause, and more especially the return of bleeding or the onset of a vaginal discharge of any kind at an interval after the menopause, is very suggestive, and should be presumed to be due to cancer until the contrary is proved.

I have examined the records of 762 women aged 50 and upwards who were seen by me for diseases peculiar to their sex during the eleven years with which this paper deals. Of this number there complained of bleeding 139, of whom 128 were married and 11 single. Of the married women 53, equal to 41·4 per cent., were suffering from cancer of the cervix or body of the uterus, or of the vagina. Of the 11 single women who complained of bleeding at the age of 50 and upwards, 7, equal to 63 per cent., were suffering from cancer of the uterus, and of these the cervix was affected in one, and the body of the uterus in six. It follows from these observations that bleeding at or after the menopause raises a strong presumption of uterine cancer, but it must not be forgotten that the disease is frequent also in women at much earlier ages. Uterine cancer is rare before 25, and uncommon before 30, but after this time becomes increasingly prevalent with increasing years.

It is a common fallacy that cancer invariably gives rise to pain. Observation proves that in the earlier stages notable pain is rare, while the disease not infrequently runs nearly its whole course without giving rise to notable suffering. This absence of pain is in a sense unfortunate, because its presence in the earlier stages would drive women to seek advice at a time when adequate relief is possible, but although no actual pain is present careful enquiry elicits the complaint of a feeling of heaviness or fulness in the lower abdomen, or a vague sense of pelvic discomfort. Sometimes when the cancer has formed a tumour of considerable size it projects into the uterine

cavity and causes severe bearing-down pains, due apparently to an attempt on the part of the uterus to expel the tumour. Severe pains of various descriptions, boring, burning, aching, shooting, in the lower abdomen, sacral region, vagina, rectum and thighs, come on at an advanced stage, but not usually before the cancer has extended beyond the limits of the uterus itself, and has invaded the connective tissue and pressed upon or irritated the large nerves in the pelvic cavity. Occasionally pain appears to be the first symptom, but careful enquiry will almost always elicit the fact that discharge of some kind has preceded its onset. Regularly recurring attacks of severe pain have been described by Simpson and by Ruge and Veit as occurring in cases of carcinoma of the body of the uterus and as being suggestive of the disease. Frommel has only seen this symptom in one case, and that not in an early stage, and in none of my cases were there pains answering to this description. The pains of cancer which come on in the late stage are not relieved by rest and are therefore usually described as being worse at night. When the disease approaches the peritoneum abdominal pain is usually complained of, and at this time widespread tenderness over the lower abdomen and some tympanites are common, the abdominal wall often feeling as hard as a board. Symptoms referred to the rectum and bladder are common, but only begin in the later stages of the disease. Piles and bleeding from the hæmorrhoidal veins are not uncommon, and frequently when cachexia has become marked, thrombosis of veins may occur as in Cases 3, 9 and 12. In the earlier stages of the disease the patients often complain of weakness and sometimes also of wasting, while at the same time they state that their appetite and digestion are good; such symptoms should always awaken the suspicion of serious organic mischief somewhere in the body. In the later stages of the disease the general symptoms of course become easy to recognise. There is marked emaciation, the complexion is of a dirty sallow hue, the mucous membranes are anæmic, there are marked lines of suffering on the face, the gait becomes stiff and awkward owing to the efforts of the patient not to increase her pain, the appetite becomes capricious, and finally bad, and late in the disease vomiting may occur, either uræmic in origin or due to carcinomatous peritonitis.

Metastatic growths are not very frequent and are therefore of minor importance. The growth much more commonly invades neighbouring organs, especially the bladder and intestines. Taking all cases of uterine cancer together, remote metastases occur in the liver in 9 per cent., the lungs in 7 per cent., and in the kidneys in 3·5 per cent. of the cases that have run their course.

Physical Examination.

It has already been said that the diagnosis of cancer of the body of the uterus depends on the results of physical examination, and the responsibility of the medical attendant for a prompt diagnosis of the affection cannot be too strongly emphasised. When a woman with suspicious symptoms consults him it is his imperative duty to employ every means to arrive at a correct opinion with the least possible delay. An immediate examination should be undertaken and should be complete and thorough. An error in diagnosis at the outset or the delay of a month in making the necessary examination, may destroy the patient's chance of a radical cure and cause her life to be sacrificed.

The physical investigation of a case of suspected malignant disease of the uterine body will now be described in the order in which it is usually carried out. The first step consists in the examination of the abdomen by the ordinary methods; by this means a tumour rising out of the pelvis may be discovered and its characters partly made out. In the case of a cancer of the fundus the presence of a lower-abdominal tumour usually imports that the disease is already far advanced or that it is associated with fibromyoma. In the majority of cases no tumour is present, and in the early stages of the disease there is not even lower-abdominal tenderness. In the later stages there is often marked lower-abdominal tenderness and rigidity, and these usually depend upon the existence of peritonitis, septic or malignant.

The next step consists in the examination of the vulva, vagina and cervix by the aid of vision and touch. These parts will be found to present no abnormal appearances but in the great majority of cases under consideration will show the usual signs of more or less advanced senile atrophy, and in a large proportion those also of virginity. Occasionally the cervix is found to be open, allowing a mass, friable and bleeding, to be felt inside the uterus, but this usually belongs to the later stages of the disease.

Bimanual examination in these patients is often difficult and unsatisfactory, and may have to be put off until an anæsthetic can be administered. The uterus frequently is found to be retroverted; in the early stages of the affection it is not enlarged, a statement which implies that it is in most of the cases smaller than that in the adult before the menopause. If now in a woman of 55 or more the uterus is found to be as large as that of a multipara of 40 it is obviously abnormal in size; it must therefore be constantly borne in mind that a size that is natural at one period of life may at another

signify abnormality of greater or less gravity. As cancer progresses the uterus increases in size, and in the later stages may become hard, irregular in form and in consistence at different parts of its surface, and finally fixed; but it is to be hoped that in the future these signs will rarely be allowed to develop. The important fact to be borne in mind is that cancer of the body in its early stages gives rise to little or no appreciable enlargement of the uterus.

During the examination there is generally more or less bleeding; as a rule the amount is slight and in gentle manipulations there is occasionally none; this bleeding during examination is suspicious but is by no means pathognomonic.

The use of the sound is the next step in the examination, and usually causes rather more profuse bleeding. The sound passes further than usual. In the senile virgin who is so frequently affected, a uterine cavity $2\frac{3}{4}$ inches in length is already greater than normal. The sound should be used as a probe and an attempt made to estimate the condition of the endometrium. Valuable information may sometimes be obtained about this, but the sensations received through the sound are very liable to misinterpretation. If the mucous membrane is smooth throughout there is probably no cancer; if the point of the sound passes over knobs and into depressions, and especially if it can be felt to sink into firm and friable or more commonly into soft and fleshy material the presumption of cancer is increased. In fungous endometritis, however, the sound also causes bleeding and is often felt to penetrate into fleshy prominences so that the information obtained by the use of the sound merely heightens the presumption of cancer and indicates the necessity for carrying the investigation further. During the examination by the bimanual method or by the uterine probe, rosy greyish, or reddish, soft, fleshy, friable material sometimes escapes from the external os and affords in women at or after the menopause very strong presumptive evidence of cancer.

The methods of examination thus far described will, in the great majority of instances, enable an opinion to be formed as to the absence or probable presence of uterine cancer; in the latter case or if doubt still remains arrangements should be made without delay for an examination under an anæsthetic, and in this connection we have carefully to consider what it should be proposed to do. Many of the patients with cancer of the fundus are nervous and frightened to a very unusual degree, and there is always increased risk to life and to reason in the administration of a second anæsthetic. Whenever, therefore, the probability is strong that cancer exists it should be arranged that if, under anæsthesia, the diagnosis is confirmed, a

radical operation should be immediately undertaken. In cases of doubt, however, where it is necessary to wait for a microscopic examination of curettings, two anæsthetics may sometimes be unavoidable.

Under anæsthesia the methods of examination so far described are in the first place repeated, and now generally yield much more definite and full information. The cervical canal is then dilated, and for this purpose I prefer Hegar's form of dilators to any of the two or three branched varieties. It is often an advantage to have introduced a laminaria tent the night before the operation. The degree of dilatation will depend upon the next step of the examination: if this is intended to be digital examination dilatation will have to be continued to No. 18 or 19 Hegar; if curetting is to be the next step No 12 Hegar will be sufficient. Even the degree of dilatation last mentioned will cause a certain amount of laceration, and the danger of implantation of cancer in a recent tear has to be borne in mind. Curetting properly carried out will provide the material for gaining information as to the structure of every part of the surface of the uterine cavity. Digital examination, on the other hand, may easily fail to give us information of a growth in the early stage while it is yet small. Curetting is therefore, in my opinion, more advantageous in all respects in these cases, and a preliminary dilatation to 12 Hegar is sufficient.

In using the curette there is in the later stages of the disease a definite danger of causing perforation of the uterus. In Case 12 this accident was narrowly escaped, and Spiegelberg tells of a case in which perforation caused in this way gave rise to a fatal septic peritonitis. The curetting should be systematic and thorough, the whole surface of the endometrium being carefully gone over in order. Long strokes should be made with the instrument so as to get as large portions as possible from the anterior wall, posterior wall, fundus, both tubal angles, and both sides of the uterus, and finally the cervical canal should also be carefully gone over because sometimes a cancer occurs in this situation and gives rise to the same difficulty in its recognition as cancer of the body. The curettings should be carefully collected for microscopic examination. After the curetting the uterus should be washed out with weak antiseptic lotion, followed by the application of strong solution of iodine, which is the most useful hæmostatic and antiseptic agent for the purpose.

Examination of Curettings.

The whole of the curettings are to be collected free from blood as

far as possible; they are then in a body embedded in paraffin, and while the paraffin is still fluid the vessel, preferably cylindrical like a test tube, is inverted on to a cork or wood block so that the curettings may gravitate to form a mass; sections taken from this paraffin block are then fixed on slides and stained by any reagent that may be preferred. In this way one section includes portions of the curettings from many parts of the body of the uterus, and any malignant structure that is present is with great probability included.

Alveoli. All degrees of structure between simple glandular endometritis and the most malignant cancer exist, and often some difficulty is found in deciding whether a particular portion of tissue shows a simple or malignant structure, but with increasing experience these instances become very much less common. In forming an opinion it is of great assistance to have as many portions of tissue for comparison as possible, and this is conveniently managed by the method above indicated. Attention has to be paid in the first place to the number of glandular acini, to the characters of the individual acini, and to their general arrangement. A great increase in the number of gland-like spaces is one of the most constant features in malignant adenoma and adeno-carcinoma, but it is at the same time one of the most uncertain, and is frequently well marked in simple endometritis. In the latter condition the superficial part of the mucous membrane nearest the surface epithelium is as a rule poor in glands and a large increase of glands lying close together in this part of the mucous membrane must be considered suspicious. In malignant disease the glandular acini frequently undergo repeated division and subdivision. In endometritis a gland is often seen to divide into two, but the process is hardly ever carried beyond this, and therefore marked subdivision of the glands is also suspicious. In well marked cases of malignant adenoma the gland-like acini often lie close together with only a fine dividing line in which is seen a row of spindle shaped nuclei. The epithelial cells lining the acini lie, as has been said, back to back instead of face to face, or, to put it differently—the space between two glands is narrower than the lumen of the gland.

The glandular acini in malignant disease are not only much divided and greatly increased in number so as to lie close together, but also show an extreme irregularity of course. A tortuosity so marked that acute angled bendings are seen sometimes to one and sometimes to the other side, strongly suggests malignant disease. In simple endometritis the course of the glands is chiefly vertical to the surface; in malignant disease they run in the most various directions, transverse and oblique.

In simple endometritis it is possible to make out the separate glands, but in malignant disease their increase in number and division gives rise often to an intricate network in which it is impossible to distinguish the individual glands.

Penetration of the glands into the muscular walls of the uterus is not a sign of malignant disease; frequently glands are found penetrating the muscular coat in a normal, or still more often in a chronically inflamed, endometrium.

Cells. Increase in the number of layers of epithelial cells lining the glandular cavities is one of the most important signs, but it is not available for malignant adenoma; in this form of cancer the acini are lined by a single layer of epithelium, often of beautiful high cylindrical shape; the epithelium frequently, however, has an irregular appearance on section due to the fact that the nuclei are placed in the cells at very varying levels. An increase in the number of layers of cells may be simulated where the section is thick or has passed obliquely across the alveolus. Sometimes the fundus of a gland is cut across and appears as a round or oval space filled with cells; in these cases a comparison with neighbouring acini usually quickly and easily solves any doubt that may arise. The regularity of the epithelium and the arrangement of the nuclei at the same height in the cells in simple cases, gives rise often in oblique sections to an appearance of zones of cells, some of the zones consisting of cells without nuclei; in the latter case the cells have been divided above or below the nuclei. In a malignant acinus there is no appearance of regular zones but the nuclei are scattered irregularly through the whole mass of cells. An increase in the number of cells causes the projection of bunches or faggots of cells into the lumen of an alveolus, and this is always to be regarded with suspicion. A similar appearance, however, is frequently met with during the early months of pregnancy in glands in the deeper layers of the decidua vera; here the presence of large collections of decidual cells would be an important indication of the nature of the specimen.

Differential Diagnosis of Curettings.

Diagnosis of cancer has to be made from other forms of malignant disease as well as from the various forms of endometritis and from the conditions which depend upon pregnancy. The stage of malignant adenoma is apt to be confused more especially with glandular endometritis, and in making a diagnosis it has to be borne in mind that in the latter affection the glands invade the muscular coat to some extent, and that they may be greatly increased in number. There is,

however, always a definite amount of inter-glandular tissue, either of the ordinary cellular type with numerous round and oval nuclei, or sometimes with streaks and patches of round-celled infiltration. The individual glands are increased in length and often corkscrew shaped or spiral, but they are always lined by a single layer of epithelial cells and as a rule the arrangement of these cells is regular, the nuclei standing at about the same level. Hesitation may arise in thick or oblique sections where the appearance of two or even more layers of cells may be given with the nuclei very irregularly placed, but in them a consideration of the specimen as a whole usually enables us to form a correct opinion. In a simple case the cells and their nuclei are fairly regular in size, and even where the cells are cut in different planes and directions, appearing here round and there oval, a correct estimate can still be formed.

In malignant adenoma there is only one layer of cells in the acini, but these are apt to be less regular in size, shape, and arrangement of nuclei, than in simple endometritis. The most characteristic appearance, however, is given by the great increase in size and number of the glands, which become greatly elongated and branched, and are so numerous in some parts that there appears to be hardly any inter-glandular tissue. This arrangement of acini is characteristic; where it can be made out that the cells are really arranged in more than one layer the evidence of malignancy is by so much the stronger. Fully developed spheroidal celled carcinoma in some of its appearances may be simulated by various other conditions. Where the alveoli are large with little inter-alveolar tissue, sarcoma may be suggested. In some cases endothelioma forms very close resemblances to true cancer, and in deciduoma malignum there is not infrequently an alveolar arrangement which at first sight may lead to confusion. In all cases, however, a careful examination of different parts of the growth, and especially of the youngest portions at the growing edges, will enable the microscopist to form a correct conclusion, and in many cases the clinical history will afford the strongest evidence in support of the correctness of his diagnosis.

To the careful observer the products of gestation can hardly ever cause serious difficulty in the diagnosis from cancer; the appearances of the chorionic villi, and the relations of collections of decidual cells to the structures in the endometrium, as well as the characters of the individual cells themselves, taken altogether, form a sufficiently characteristic picture.

Like every other mode of investigation the examination of curettings from the body of the uterus is open to fallacies and

difficulties. The evidence obtained from them is only a link in a chain, but it is one of the strongest links, and when suitable portions of tissue are skilfully collected and prepared, the evidence is conclusive as to the nature of the tissues available. It is necessary to bear in mind, however, that even the microscope will not enable us to prove a negative; in any suspected case it is most important that the curette should be carefully applied to every part of the surface of the cavity of the body and cervix of the uterus, and that the whole of the scrapings should be collected, embedded in paraffin, and cut in such a way as to give the greatest possible field for observation. If any piece of characteristic malignant tissue be present, no matter how small it may be, the diagnosis is then easily made. It is, however, possible that a malignant nodule in the wall of the uterus may be covered with normal or inflamed mucous membrane, or that the curetting may be imperfectly done or the pieces not fully collected. The microscopist can only pronounce an opinion on the portions of tissue supplied to him. With increasing experience he will be able to pronounce judgment with great confidence on the simple or malignant nature of any given curetted portion.

Diagnosis of Cancer of the Body of the Uterus.

When in a woman who is unmarried, or who has proved sterile or little fertile, serous or other discharge makes its appearance at or especially after the menopause, or where bleeding becomes excessive, prolonged, or irregular at the same epoch, a strong presumption of cancer is always aroused. A correct diagnosis must be made without delay and information is to be sought by vaginal and bimanual examination, which are, however, as a rule, of little value in the early stages of the affection; by the sound, which gives more important evidence by showing the length of the cavity, bleeding on gentle manipulation, and the presence frequently of soft friable, or firm nodular tissue in the uterine cavity; and by dilatation followed sometimes by digital examination, and always by curetting and microscopic examination of the removed fragments. In the early stage the last is infinitely the most important method of examination, and in any suspected case should be undertaken without delay. It is important to recognise that expert knowledge is necessary both in the use of the curette in these cases and in the examination of the curettings afterwards, and it is to be desired that suspected instances of the disease shall be investigated by competent observers at the earliest possible moment. In this way only can the best results of treatment be obtained.

Younger women than those described at the beginning of the last paragraph are, of course, frequently affected by malignant disease of the body of the uterus, and it is necessary, therefore, always to bear this possibility in mind. In them, however, the form of malignant disease of the body of the uterus is more commonly a rapidly fatal malignant deciduoma, and there is usually a connection with recent pregnancy, especially of hydatidiform mole, which should arouse suspicion. The occurrence of true cancer of the uterine body in women under 45 appears to be comparatively rare.

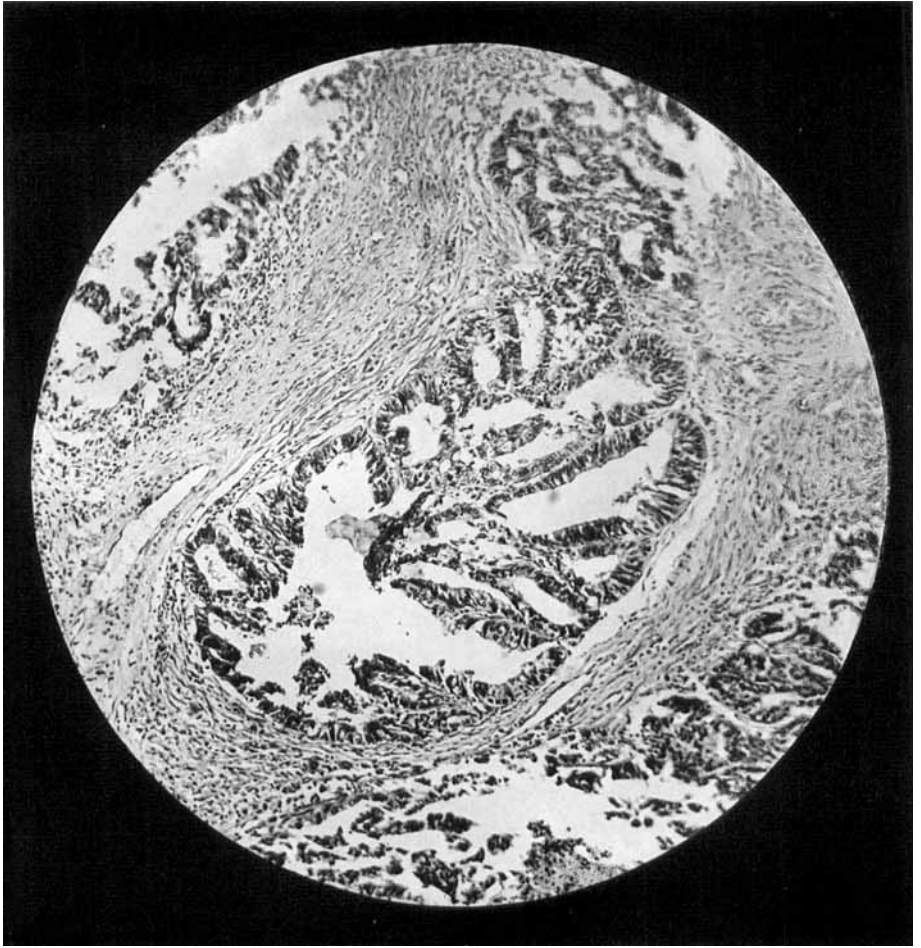


FIG. 1.—An alveolus of inverting adeno-carcinoma, showing numerous ingrowths of epithelium, many of them united by their apices.

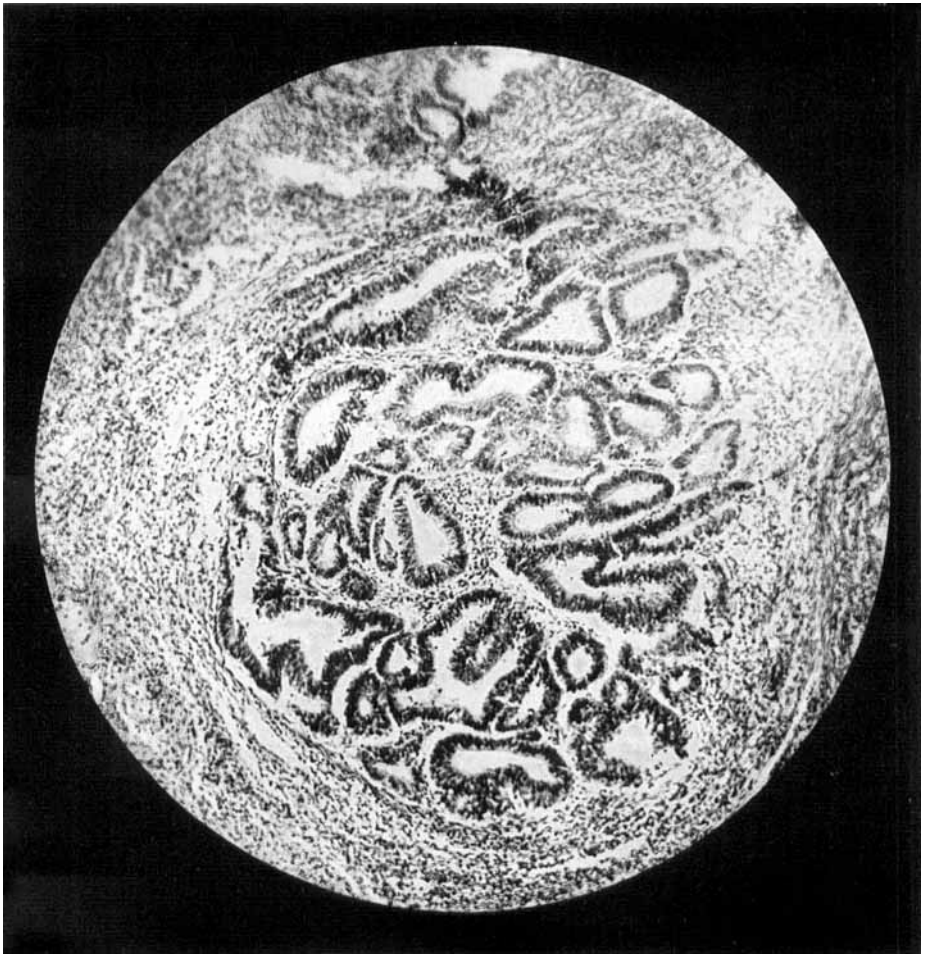


FIG. 2.—Lobule of adeno-carcinoma, everting form. Small acini lined mostly by one or two layers of epithelial cells. Small celled infiltration of stroma surrounding the lobule.

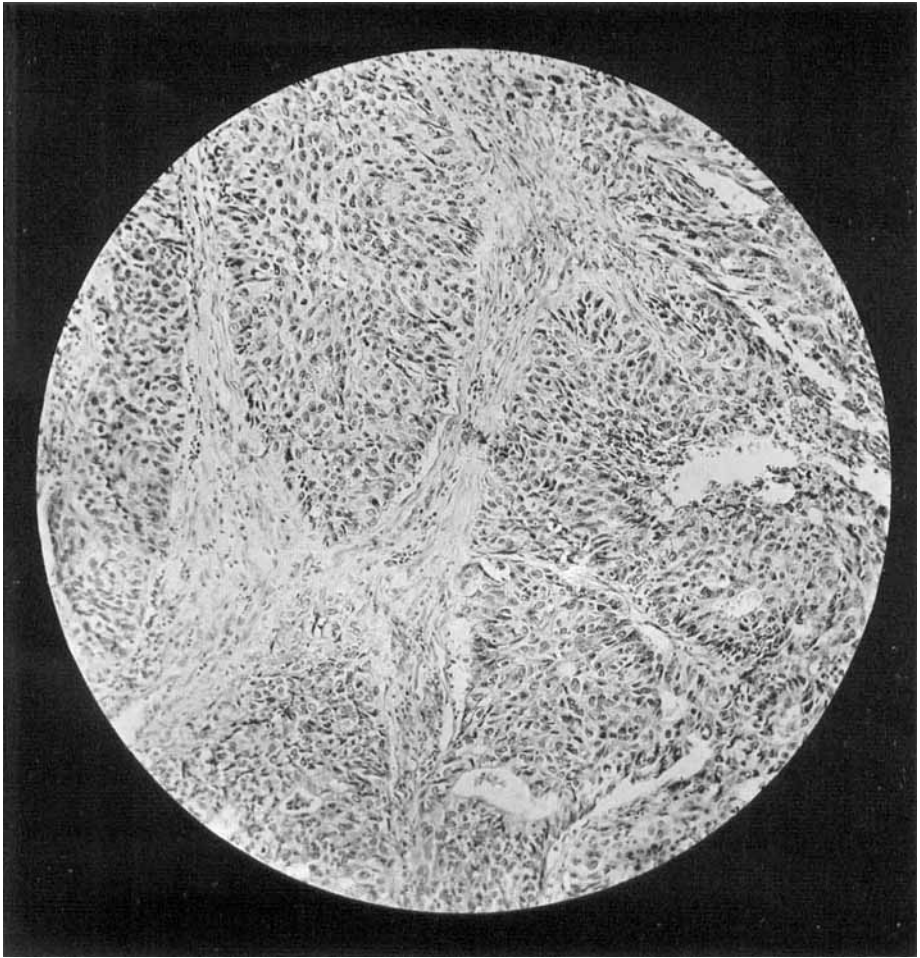


FIG. 3.—Carcinoma developed out of adeno-carcinoma. Large alveoli filled with epithelial cells, many of which are degenerated.

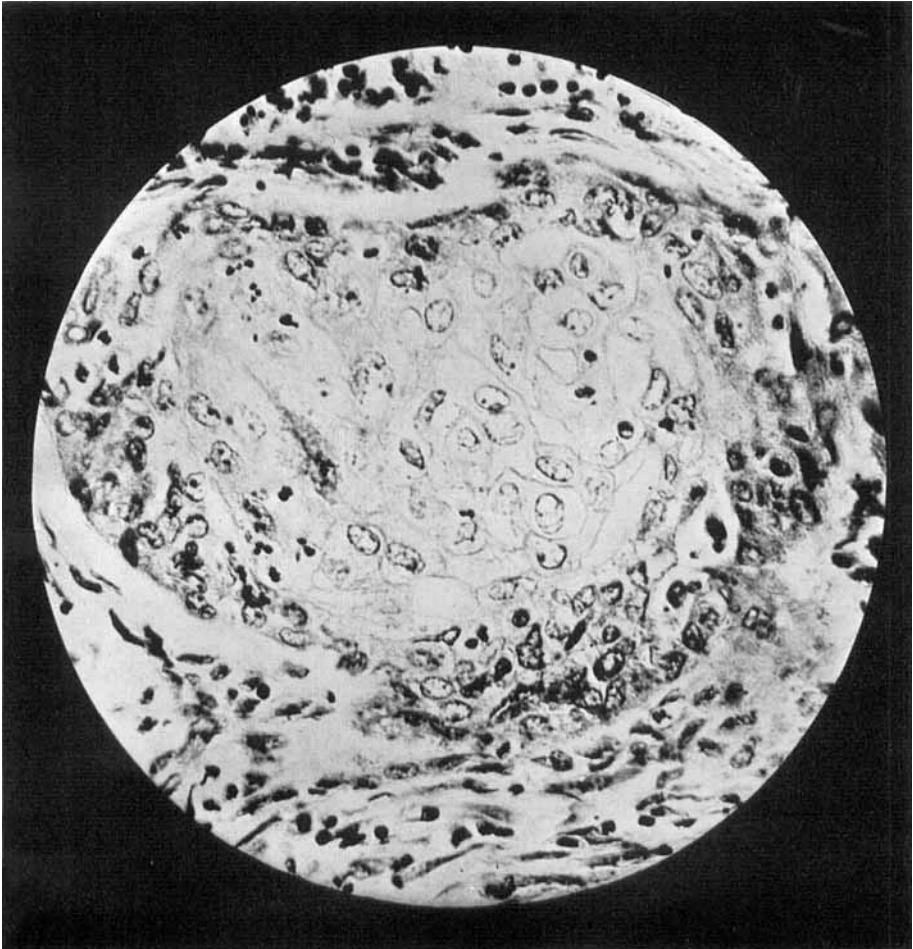


FIG. 4.—Small alveolus filled with cells that have undergone keratoid degeneration.

