

SELECT CLINICAL REPORTS.

(Under this heading are recorded, singly or in groups, cases to which a special interest attaches either from their unusual character or from being, in a special sense, typical examples of their class).

I.

A Case of Chorion-Epithelioma of the Uterus with Lutein Cysts in both Ovaries.*

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MRS. A. B., 46 years of age, was admitted into University College Hospital on January 28th, 1907. She had had five children and two miscarriages, the youngest child being seven years old. Twelve months ago she had a period of two months amenorrhœa followed by hæmorrhage lasting for three weeks and accompanied by the passage of some clots. This bleeding was assumed by the medical man she called in to be due to the onset of the menopause, but in view of the further history of the case no doubt she had an early miscarriage. After the bleeding ceased the periods returned and were regular until five weeks before her admission to the hospital. For this length of time there had been a slightly offensive blood stained discharge from the vagina. For the past two weeks there had been some throbbing pain in the vagina, and she said she had been losing flesh for a month or so past. Her bowels were moved regularly without pain, micturition was, however, attended with some difficulty, but her general health had been good until the onset of the present illness. She had suffered from a chronic winter cough for some years, and this was associated from time to time with the expectoration of a little blood. There was nothing of note in the family history. On admission the patient presented a sallow and somewhat cachetic appearance. In the lower part of the abdomen could be felt a smooth rounded not tender tumour which was taken to be the fundus uteri. On vaginal examination the anterior and left vaginal walls were seen to be occupied by a rounded swelling infiltrating the tissues around the urethra and extending on to the lateral wall. This latter portion of the tumour presented a friable and sloughing surface. The intact mucous membrane over the anterior part of the tumour was considerably congested and pressure on the area caused a good deal of pain. The urethral orifice was displaced somewhat to the left of the middle line but a No. 6 gum elastic catheter was readily passed. A similar smaller tumour occupied the right wall of the vagina, lying under

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the mucous membrane, and extending up into the right lateral fornix. The uterus was enlarged and there was a round swelling in the position of each ovary. A few days after admission the patient coughed up a small quantity of blood. An examination of the chest revealed some slight impairment of movement on the right side, weak breath sounds, and some coarse rhonchi. On February 6th the vaginal growths were excised very freely, together with the lower 2.75 cm. of the urethra, and practically the whole of the two lateral vaginal walls, the lower two-thirds of the anterior wall, and a part of the posterior wall. Besides the two main tumours already described three smaller nodules of growth were removed from the lateral and posterior vaginal walls. The raw surfaces left were closed as far as possible by stitching the remains of the posterior wall to the anterior, and the stump of the urethra was brought out through a button hole opening in a flap drawn over it from the anterior wall which, in its turn, was stitched to the cut edge of the mucous membrane below the clitoris. Considerable difficulty was experienced in getting beyond the limits of the growth in the right wall of the vagina as it extended high up into the right lateral fornix, and the raw surface left in this position could not be closed but was plugged with iodoform gauze. The patient made a good recovery from the operation and was able for the first week to retain her urine and to empty the bladder spontaneously.

On examination under the anæsthetic, the body of the uterus was found to be soft in consistence and considerably enlarged; the cervix was healthy; both ovaries were cystic.

Microscopic examination of the growths removed from the vagina showed them to be a chorion-epithelioma, and a week later, therefore, on February 13th, the uterus and appendages were removed by total abdominal hysterectomy. There were slight adhesions about the ovaries and some little difficulty was experienced in freeing the bladder from the uterus owing to the presence of a small nodule of growth projecting from the anterior surface of the uterus and adherent to the bladder. The latter organ had to be dissected free but this was done without any injury to its walls. An iodoform gauze plug was inserted between the cut edges of the vagina, the peritoneum sewn together over this, and the abdomen closed without drainage. No secondary growths were felt at the time of the operation in the abdomen.

Sixteen hours after the operation the patient had a sudden attack of abdominal pain, her pulse became small and feeble, she became markedly blanched and developed some dyspnœa.

An examination of the vagina revealed the fact that a good deal of hæmorrhage was taking place from the granulating surface in the right lateral fornix. The cavity was plugged firmly with iodo-



Fig. 1. Photograph of the uterus and ovaries. The anterior wall of the uterus has been removed showing the growth, almost filling the cavity. Both ovaries are enlarged and cystic.



Fig. 2. Photograph of the right ovary laid open showing the lutein cysts in its interior. Note the hæmorrhages into the interior of the cysts, into their walls, and into the stroma of the ovary.

form gauze under chloroform, and the patient was transfused with a pint and a half of saline solution. This treatment led to a rapid improvement in the symptoms and no further bleeding occurred. On the second and third day after the operation the patient had a slight rigor. On the fifth day the vaginal plug was extracted under nitrous oxide anæsthesia.

On the seventh day two more slight rigors occurred, the temperature only reaching 102° F. The patient has, up to the present date, made good progress, although her recovery has been retarded by a somewhat irregular temperature, an attack of diarrhœa, and a good deal of cough, with on two occasions, the expectoration of a little blood. Examination of the chest does not show definite signs of any growths in the lungs although over the scapular and axillary region on the right side there is some impaired resonance with weak breath sounds and in front there are some fine crepitations on taking a deep breath. The abdominal wound is soundly healed and the vagina is almost entirely healed. The signs in the chest taken together with the cough and the slight hæmoptysis are very suspicious of some secondary growths in the lungs, but if there are any possibly they may undergo atrophy as has happened in other cases where the primary growth has been completely removed. Unfortunately, no doubt in part as the result of the constant coughing the patient has lost the control over the bladder which she had for the first week after the second operation, and at the present time there is almost complete incontinence of urine.

The specimen consists of the uterus, Fallopian tubes, ovaries, and some secondary growths removed from the vagina.

The uterus (Fig. I.) is enlarged, measuring 10 cm. at its widest part by 11·5 cm. from fundus to external os. The uterine wall on section varies in thickness from 1 cm. in the left wall to 2·5 cm. in the middle of the right wall of the body where there is a small interstitial fibroid 1·5 cm. in diameter. A few small interstitial fibroids are situated in the right wall of the body and one in the left. The interior of the uterus is occupied by a growth which is invading the uterine wall above and on the right side, and to a lesser extent on the left side. The lower rounded margin of the growth descends to within 1·75 cm. of the internal os; the space left is occupied by blood clot. The growth itself on section has a friable surface and is reddish brown in colour, closely resembling in appearance a mass of blood clot except at its site of origin in the uterine wall where there is a layer of tissue yellow in colour, softish, and rather more granular in appearance than the uterine wall it is invading. The whole surface of the growth presents a homogeneous appearance and there is no evidence of the presence of cysts or of chorionic villi.

The cervical canal, which measures 3 cm. in length, is healthy. Both ovaries are enlarged, the right one measuring 5.5 cm. by 4 cm. (Fig. II.); the left 6 cm. by 5 cm. in its widest part. They both contain a number of cysts distributed throughout their substance, the largest of these being 2 cm. in diameter. The outer surfaces of the ovaries present a greyish red appearance, and the thin walled cysts cause well marked translucent projections on the surface. A section through the right ovary shows four cysts with well defined walls with a smooth surface, containing a clear mucinous fluid and showing a considerable degree of vascularity. Several of the cysts show hæmorrhages into their interior and into the cyst wall. In the stroma of this ovary there is a small quite distinct corpus luteum 6 mm. in diameter. A section through the left ovary presents a similar appearance although in this case the cysts (three in number) do not occupy so large an area of the section. The largest cyst in this ovary shows a definite inner lining which can be stripped away from the cyst wall. There is marked vascularity of the tissues and especially of the stroma. In some of the cysts the mucous contents have coagulated into a jelly like mass *in situ* whilst from others it has escaped.

Both Fallopian tubes are healthy.

The growths removed from the vagina comprise two large tumours and three smaller ones, the largest of these, measuring 6.5 cm. by 4 cm. was attached to the anterior vaginal wall involving the inferior wall of the urethra and extended into the left wall of the vagina. The latter part of the growth had destroyed the mucous membrane and formed an ulcerating and breaking down mass. Intimately united to the upper part of this tumour and removed with it is the lower 2.75 cm. of the urethra which has been laid open along the middle line superiorly. On section, portions of this tumour present a greyish white granular appearance, the tissue is soft and friable and breaks down readily. A smaller growth of similar character was removed from the left lateral wall of the vagina above the larger tumour. An oval mass, 4 cm. by 3 cm., of similar appearance on section, was removed from the right vaginal wall and extended high up into the right vaginal fornix, and two small tumours 1 cm. in diameter were excised from the upper part of the posterior wall of the vagina.

Microscopic examination of the tumour in the uterus (Fig. III.) shows the greater part of it to be composed of fibrin and blood clot. The growth itself is made up of branching columns of polyhedral cells with round or oval vesicular nuclei, arranged in an alveolar manner, while here and there are large cells containing several nuclei. There is an almost entire absence of any large syncytial masses in the uterine growth, although in places strands of syncytium are

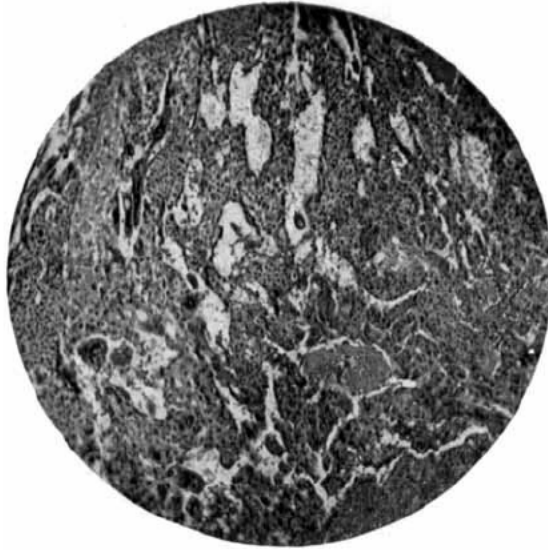


Fig. 3. Section of the tumour in the uterus showing columns of polyhedral cells with an alveolar arrangement with a number of large cells containing several nuclei in various parts of the section. No large syncytial masses are to be seen.

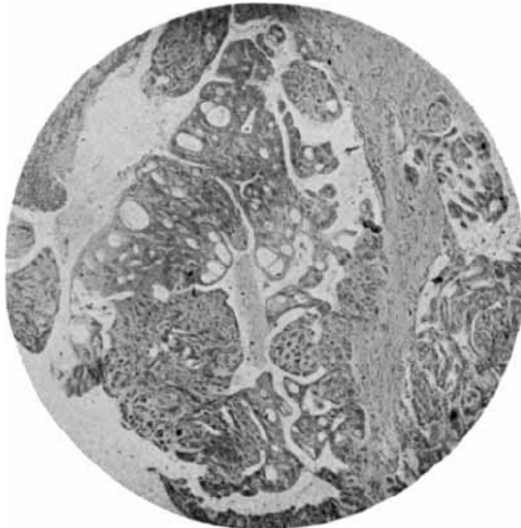


Fig. 4. Section of one of the growths in the vagina showing masses of protoplasm with numerous nuclei and vacuolar spaces, together with collections of cells derived from Langhans' layer.



Fig. 5. Section of the wall of one of the lutein cysts in the right ovary, showing: *a*, fibrous tissue of stroma; *b*, layer of lutein cells; *c*, coagulated contents of cyst.

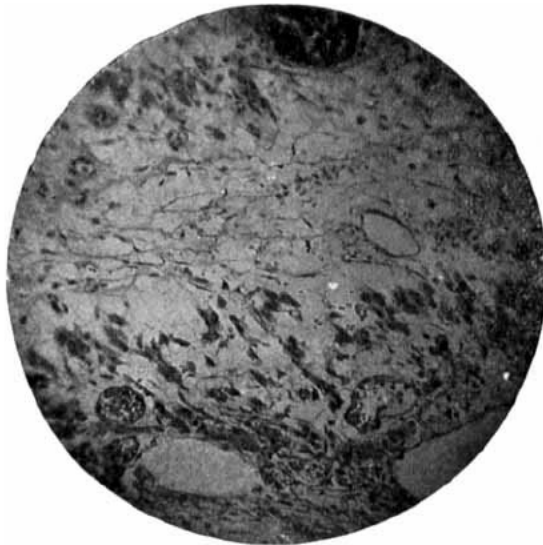


Fig. 6. Section of a portion of the right ovary showing lutein cells scattered throughout the stroma.

interspersed between the cell masses. The growth in the vagina (Fig. IV.), on the other hand, contains large masses of undifferentiated protoplasm containing numerous oval darkly staining nuclei and many vacuolar spaces as well as masses of smaller cells evidently derived from Langhans's layer of the chorionic epithelium which are mingled with the syncytial masses in an irregular manner. Everywhere blood clot and masses of fibrin are present with the tumour elements, even penetrating between individual cells, but there is no connective tissue stroma.

An examination of the ovaries shows that all the cysts (Fig. V. exposed on the cut section are derived from corpora lutea. The great majority of these cysts have no epithelial lining, but two small cysts in the right ovary had an internal lining of several layers of spherical cells. The cysts are limited externally by a layer of fibrous tissue derived from the stroma of the ovary, internal to this there is a well marked layer of lutein cells of varying thickness but present without exception in some portion of the wall of all the cysts examined, and in most of them exceedingly well marked. With the exception of the two small cysts already alluded to, in none is there any lining internal to the lutein layer, although in many places there is a well marked layer of fibrin covering the inner surface of the lutein cells. In both ovaries some lutein cells can be seen between the cells of the stroma (Fig. VI.) some little distance from the nearest cyst, but there is no general distribution of lutein cells such as has been described in other instances. Besides the cysts there is a well marked corpus luteum in the right ovary and a smaller one in the left ovary. In some of the cysts the innermost layer of the fibrous tissue immediately outside the lutein layer, namely the tunica vasculosa, is extremely vascular. If the amount of lutein tissue in the walls of the cysts be taken into account, there can be no doubt that there is an excess of this tissue present in both ovaries.

This case is a good example of the simultaneous occurrence of a chorion-epithelioma of the uterus with lutein cysts in both ovaries. These two conditions have now been found present at the same time in so many cases that such an association must be due to something more than mere coincidence. I am, however, I must confess, rather sceptical as to the truth of the hypothesis which assumes that they stand in a definite causal relationship to one another. That is to say that the development of a chorion-epithelioma in the uterus is due to an excess of lutein tissue in the ovary, and an over-production of the internal secretion of that organ. Such an excess of lutein tissue has now been met with in so many cases of hydatidiform mole and chorion-epithelioma as to constitute a most remarkable fact. If we consider for a moment, however, the changes which occur in

the uterus and in the ovaries in these cases we cannot but be struck by the very marked similarity between them. In the case of the uterus we have an excessive proliferation of the trophoblast or of the epithelium of the chorionic villi, together with the development of cystic spaces no doubt due to serous transudation into the tissues of the villi. In the ovary we have a marked proliferation of the cells of the corpora lutea with the development of cysts possibly of similar origin. In both instances the tissues chiefly affected are composed of young rapidly growing cells such as might be expected readily to respond to any undue stimulus. It seems probable that the cause of the development of a chorion-epithelioma, conforming as it does to the general law of carcinomatous growths in that it affects a tissue which, if we consider the total period of its life, is already old, will be found not to differ from the cause of a malignant growth in any other part of the body and that future researches will prove it to consist in some chemical change in the blood of the patient or in the fluids bathing the tissues of the part affected. Further evidence in favour of such an interpretation is I think to be found in the fact that some excess of lutein tissue has been demonstrated to occur in all cases of normal pregnancy, although not to such a marked extent as in cases of hydatidiform mole or chorion-epithelioma; nor is this surprising when we recollect that in cases of normal pregnancy there is no atypical proliferation of the trophoblast, and therefore we would not expect any undue development of the cells of the corpus luteum.

The experiments of Fraenkel and others, which have been brought forward to support the theory of the important part played by the corpus luteum in presiding over the development of the early ovum are far from conclusive, and although the development of the trophoblast and of the cells of the corpus luteum certainly appear to proceed *pari passu* in these cases of hydatidiform mole and chorion-epithelioma, yet the assumption that one depends upon the other seems to be far from warranted. Many more cases of this kind must be examined critically before we shall be able to come to any definite conclusion on this difficult subject. In this particular case whatever may be the true explanation as to the cause, the fact remains that in the ovaries there is marked excess of lutein tissue and in the uterus there is a typical chorion-epithelioma.

Postscript, April 25th, 1907. As the patient has died since the specimen was shown, it is now possible to complete the history of the case. The general weakness which was so marked a feature from the time of the second operation gradually became more and more evident and the patient wasted rapidly. On March 8th it was found that owing to the constant dribbling of urine, the capacity of the bladder had become greatly diminished. At this time very great weakness

of the leg and thigh muscles appeared, and subsequent examination showed a well-marked reaction of degeneration in the thigh muscles, although the electrical reaction of the leg muscles was normal. On March 17th a secondary growth was discovered on the inner side of the right thigh internal to the femoral vessels. On March 20th the growth which was situated just under the skin and superficial to the fascia was removed. There was practically no bleeding, nearly all the vessels entering the growth appearing to be thrombosed. A week later an examination of the chest showed definite signs (*viz.*, impaired resonance, weak bronchial breathing, and some fine crepitations) pointing to the existence of secondary growths, over the lower lobes of both lungs especially on the right side. On March 29th the patient had two convulsions with clonic and tonic spasms, the second convulsion being followed by a semicomatose condition which lasted for two hours. The fits were thought to be uræmic in origin. The urine was alkaline and offensive, had a specific gravity of 1012, and contained albumen and pus. On the next day the condition was very grave, but there was no paralysis of the arms or legs, the cranial nerves were unaffected and the pupils reacted well. On April 1st the woman gradually sank, and died in a comatose condition.

A post mortem examination showed the abdominal wound to be soundly healed, but in the remains of the vagina there were some small nodules of growth which showed signs of ulceration. There were no growths in the peritoneum. The right ureter and the pelvis of the right kidney contained pus. There were several small growths $\frac{1}{4}$ to 1 inch in diameter in each kidney. There were also a mass of breaking-down growth in the liver and spleen, and numerous growths scattered beneath the mucous membrane of the small intestine. There were no growths in the glands of the abdomen or in those of the chest. Both lungs, more especially the lower lobe of the right lung, were studded with small nodules of growth varying from $\frac{1}{12}$ th to 1 inch in diameter. In the brain there were two secondary deposits in the left parietal and occipital lobes. The spinal cord was healthy and there were no growths in the bones.