

A CASE OF CHORIO-EPITHELIOMA WITH  
PULMONARY METASTASES.

By CUTHBERT LOCKYER, M.D., F.R.C.S.

(Received December 9th, 1901.)

(*Abstract.*)

IN this case the evidence of an abortion lay in the fact that the patient lost blood freely four months before admission, the loss continuing until the case was sent to hospital.

The patient was forty-two years of age. She had given birth to seven children. The last confinement took place three and a half years before admission into the Samaritan Hospital. Three abortions are recorded, the last being thirteen years before the patient was sent to the above hospital.

The patient was admitted with evident uterine enlargement, and in a condition which prohibited operative interference. The uterus was perforated by a new growth in its walls, and secondary deposits were found in the lungs.

The pathological characters of the primary and secondary growths are described at length in the paper.

Pathological proof of the occurrence of chorio-epithelioma immediately following on the removal of hydatidiform mole is also added.

I AM indebted to my senior colleague, our late President, for allowing me to bring this case before the notice of the Obstetrical Society. Mr. Doran has further given me free access to his clinical notes of the case.

The following is an extract of these notes :

A. D—, aged 42, was admitted into the Samaritan Free

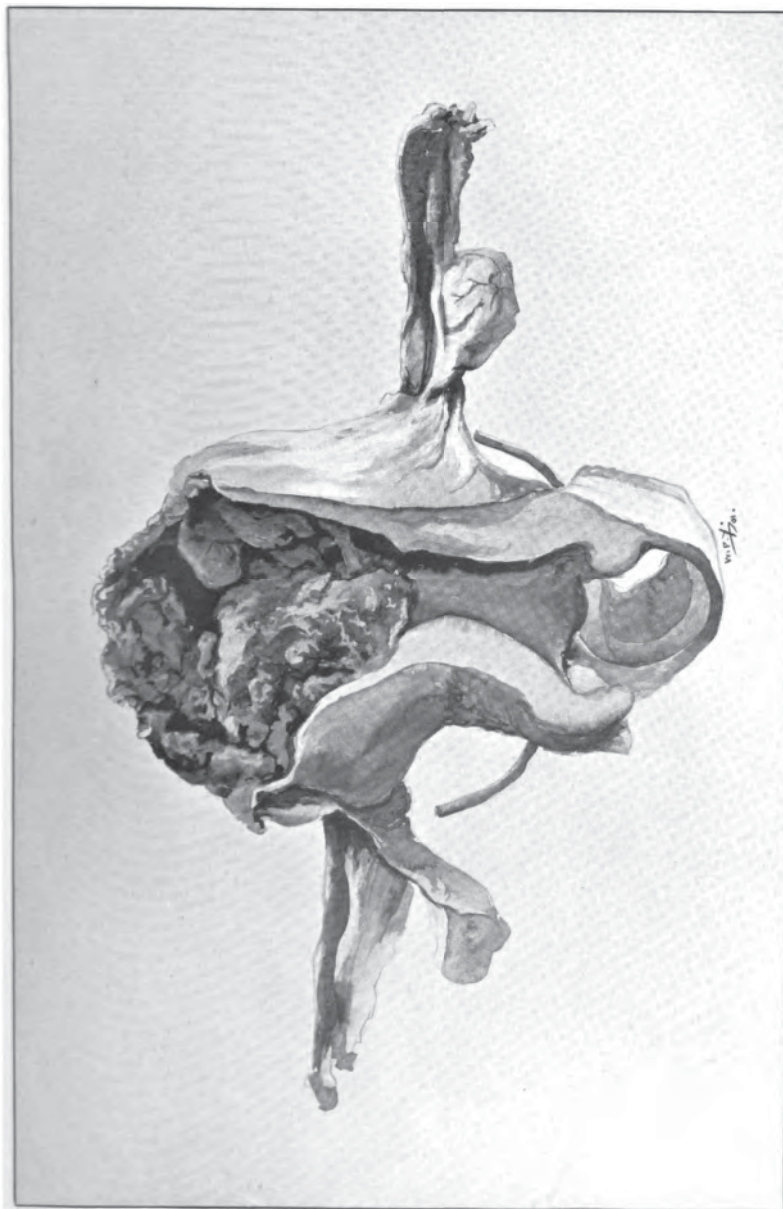
Hospital on November 20th, 1900, complaining of an abdominal tumour and of having lost blood freely since June 4th of the same year. The patient had been married for twenty years, was the mother of seven children; the last confinement took place three and a half years before admission, when she gave birth to "pigeon twins." Three premature labours had previously occurred, before one of which she bled all through the pregnancy (*i.e.* for six and a half months), and at the end of this long period of bleeding "a false conception" came away. This happened thirteen years prior to admission. Details of the other two premature confinements are not given. All labours were instrumental. Until June, 1900, her periods used to occur every three weeks, the show lasting four days, and eight to ten towels were used.

The patient had typhoid fever when nineteen years of age; she married at the age of twenty-two, and during her married life suffered from ulcers of the left leg and "swollen veins"—a point of interest, as will be presently explained. The case was sent to Mr. Doran by Dr. Auty, of Willesden, who wrote on November 13th saying that he was sending a woman suffering from a uterine tumour which had been diagnosed on October 10th by an obstetric physician as pregnancy at four and a half months. He himself rightly suspected malignancy. Two days later (October 12th) she was taken much worse, and flooded so severely that she was confined to her bed for a time, but at the date of writing (November 13th) she was able to get about. No definite history of a recent abortion could be obtained from the patient nor from her doctor. Examination on admission revealed an irregular elastic mass occupying the hypogastrium and rising into the umbilical region, ascending higher on the left than on the right side of the mid-line. The os uteri was patulous, and the uterine cavity measured 5 inches; nothing could be felt in the fornices. On consultation it was agreed that the patient was not in a fit state for any operation.

On December 19th much tympanites and tenderness were first noted ; this subsided by the next day, when the uterus was felt to be freely movable on bimanual palpation. She had lost much flesh since admission, and there had been much blood and foul discharge *per vaginam*. The nocturnal temperature was always high, especially since December 1st, from which date it varied from 100·8° F. to 102·8° F. She had several rigors and frequent attacks of pelvic and abdominal pain. The urine was always loaded with urates, and contained a large trace of albumen, but no sugar. On January 24th the patient had a rigor and a pulse rate of 160 ; this fell to 96 in a few hours, and death occurred on January 25th at 9.25 a.m. A post-mortem examination was made by Dr. Cecil Bosanquet, the pathologist to the Samaritan Hospital, who reported as follows :—The body was considerably emaciated ; rigor mortis was feeble, but present twenty-four hours after death. There was no general peritonitis. The coils of small intestine were adherent to the top of the uterus and to one another, forming to some extent a roof to the pelvis. Here there was much old and recent peritonitis, chiefly recent, with effusion of lymph and of some blackish fluid, the latter being derived from a sloughy-looking ragged aperture situated upon the posterior wall close to the fundus of the uterus, with the cavity of which it communicated. Most of the adhesions were easily broken down, so that the uterus was practically free. The liver weighed 4 lbs. 12 oz., was “nutmeg” in appearance, but otherwise normal. No secondary deposits were discovered in the abdomen. The spleen was normal, and weighed 6½ oz., the left kidney weighed 6½ oz., the right 5½ oz. ; their capsules were somewhat adherent, and there was cloudy swelling of the tubules. The adrenals and pancreas were normal, as were the stomach and intestines, except for the adhesions in the pelvic region already mentioned.

The uterus was large—nearly 6 inches in length,—not adherent to neighbouring structures (except to the

Plate I.



Illustrating Dr. Lockyer's Paper on Chorio-Epithelioma with Pulmonary Metastases.

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DESCRIPTION OF PLATE I.

Illustrating Dr. Cuthbert Lockyer's specimen of Chorio-epithelioma.

Uterus opened from behind, showing the growth invading the body as far as the internal os.



omentum and some coils of intestine roofing over the pelvis). At the upper portion of the body of the organ on its posterior aspect was an aperture with blackish, ragged, sloughy walls, communicating with the cavity of the uterus. The organ was preserved for further examination. The appendages were not diseased, the pleural and pericardial cavities were free. Both lungs were studded throughout with nodules of new growth, very vascular in appearance, varying in size from that of a large walnut to that of a cherry-stone; the lower lobes were deeply congested. The heart weighed  $11\frac{1}{2}$  oz., and appeared normal; its cavities were full of blood-clot, and the right side was somewhat dilated. The brain and spinal cord were not examined. Dr. Bosanquet sent me the uterus and appendages, with portions of the lungs. The specimen, as I received it forty-eight hours after death and twenty-four hours after removal from the body, was in a decomposing condition, and consisted of the uterus, vagina, rectum, bladder, and ureters, and the external and internal iliac arteries, to the latter of which were attached, on the left side, some enlarged iliac glands. The lung was better preserved, having been at once put into Kaiserling's solution. The broad ligaments were quite free of exudate, and showed no sign of adhesions, old or recent. The vessels, both arterial and venous, were enlarged, the veins of the left broad ligament especially so, being tortuous and varicose; an attempt to inject these veins with coloured size failed, as they were "button-holed" in many places in their removal from the body. Two small glands the size of cherry-stones were found in the left broad ligament; these shelled out with ease from the surrounding connective tissue. The enlarged iliac glands were very different, being adherent to the left external iliac vessels; the largest measured 2 cm. by 1 cm. On section they presented no necrotic areas nor hæmorrhages to the naked eye, having only the appearance of chronic inflammation. The enlargement seemed clearly due to the old ulcers on the corresponding

lower extremity. The round ligaments of the uterus were thickened. The right Fallopian tube measured 10 cm., was pervious throughout, and was not thickened. The right ovary was normal, measuring 2 by 2 cm.; its ligament was thickened and short.

The left tube measured 8 cm.; its lumen was patent, and its walls somewhat thickened. The right ovary measured 5 cm. in its long diameter; it was enlarged owing to a thin-walled cyst in its outer part, which measured 2.6 cm. in long diameter and contained clear golden fluid. The ligament of the right ovary was reduced to a mere stump, so that the ovary was close to the uterus. The bladder was normal in size, was quite free from the surrounding structures, the vesico-uterine pouch being quite empty. The walls were healthy and of normal thickness, and the mucosa was not injected. The vaginal mucous membrane was healthy. The rectum, urethra, and ureters were all normal. The enlarged uterus had a lateral deflection to the right side, and was somewhat club-shaped. Its vertical measurement was 13.5 cm.; its fundus rose 5.5 cm. above the level of the attachments of the Fallopian tubes, the latter being 10.5 cm. apart. The vaginal cervix was œdematous, and the lips eroded; the os was very patulous, and from it a fœtid dark discharge escaped. The posterior lip was elongated, and the cervical canal measured 6 cm. in length; its mucous membrane was florid in colour and spongy in consistence. The cervical wall measured 1.5 cm. in transverse section. There was no growth in any part of the cervix. The corpus uteri measured 7 cm. vertically. It was occupied in its entire extent by a growth, the characters of which are given below. The posterior surface of the body had been perforated close to its upper extremity by ulceration of the growth. The edges of the perforation are extremely thin (2 mm.), ragged, irregular, deeply pigmented, and sloughy. The perforation ran across the transverse diameter of the organ and measured 6 cm. The growth consisted of a



Fig. 1.



Fig. 2.

Illustrating Dr. LOCKYER'S Paper on Chorio-Epithelioma with  
Pulmonary Metastases.

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DESCRIPTION OF PLATE II.

Illustrating Dr. Cuthbert Lockyer's specimen of Chorio-epithelioma.

FIG. 1.—Surface of lung, showing the secondary growths in their natural colour and size.

FIG. 2.—Transverse section of lung, showing invasion by two secondary nodules.

congeries of rounded and oval bosses fused together, and of a deep sepia colour. It formed the entire lining of the body of the uterus, but ended abruptly at the os internum. The largest bosses of growth occupy the uterine cornua on either side, that on the left being spherical in shape with a diameter of 2 cm., that on the right side oblong with a long diameter of 2.5 cm.; the rest of the growth, though tuberos, was more sessile. The thickest part of the uterine wall—that just above the internal os—measured .75 cm. in section; proceeding upwards the wall gradually thinned away towards the perforation. The uterine cavity was distended into a large sphere by the growth, its dimensions being 6.5 by 5 cm.

The lungs were studded throughout with rounded nodules, most numerous immediately beneath the visceral pleura; these nodules varied in size from one measuring 5 by 4 cm. to others the size of a pea; they were flattened and discoid as seen from the surface, but oval on section. The surface of the growths was of a deep maroon colour, and on section this hæmorrhagic area formed a peripheral ring around a pale grey centre which cut like a soft sarcoma, and presented a smooth homogeneous surface. Where the lung was thinnest the nodules extended nearly through its entire thickness. Some nodules were hæmorrhagic throughout. The bronchial mucous membrane appeared healthy. The bronchial glands were small and filled with particles of carbon.

Microscopic sections of the primary uterine growth were taken from six different levels, beginning above at the margin of the perforation and extending down to the thickest muscular part at the margin of the internal os.

Sections were also made of the two small glands found in the left broad ligament, of the larger iliac glands adherent to the left iliac vessels, and of several pulmonary growths. The main features revealed in sections of the primary growth may be summed up as follows:

1. The uterine mucosa ceases to be distinctly recognizable where the growth begins, that covering the muscle in

the neighbourhood of the growth (*i. e.* at the internal os) being infiltrated and degenerate.

2. The muscularis is deeply invaded by a small-celled infiltration, and the venous channels contain cellular emboli at a considerable distance from the growth.

3. The muscularis is invaded by protoplasmic masses in which no differentiation of individual cells is possible, and also by large cells of various shapes and sizes containing either a single large granular nucleus or two or more smaller nuclei.

4. The individual muscular bundles are widely separated, the intervals being sometimes filled by the above cellular elements or by leucocytes, but in other cases being empty, having been probably filled originally by œdematous fluid.

5. Large hæmorrhagic areas occur in the muscularis; these areas have no endothelial lining and lie apparently free between the widely separated muscle-fibres.

6. The muscle-cells are in every stage of atrophy and degeneration; their nuclei are swollen and granular, but for the most part maintaining their spindle shape; their protoplasm in some cases stains badly or refuses to stain at all.

7. The walls of the uterine arteries are thickened, and the lumina (as also those of the veins) are filled with thrombi, in which an undue proportion of white cells are seen deeply stained with hæmatoxylin, appearances suggesting the presence of acute inflammation of the muscle tissue coupled with degeneration.

The sections of the growth itself show that it is largely made up of necrotic tissue and remains of hæmorrhage, the latter consisting of strands of fibrin arranged in alveolar spaces, which have no endothelial lining or wall of any kind, but around which are often grouped large uni- and multinuclear cells and masses of multinuclear protoplasm. No red discs are seen in this fibrinous meshwork, but they are invaded by an abundance of leucocytes sufficient in number to obscure in

parts the fibrinous matrix in which they lie embedded. Where the leucocytes are absent the meshes of fibrin are filled up with granular *débris*. A section of the most prominent nodule presents nothing but a mass of fibrin, with here and there a large necrotic cell devoid of a nucleus, and which stains with eosin only. These cells, when present, are arranged along the thicker strands of fibrin which divide the area into more or less complete compartments. No leucocytes are seen invading this nodule, and the entire section of 2 cm. in extent stains with eosin only. In a section made to include the superficial layers of the muscular wall and the deeper portions of the growth, large fibrinous areas are still seen, but the growth becomes more cellular and protoplasmic. The larger cellular areas present an alveolar structure with clear empty spaces like those seen in connective tissue distended with fat. These empty spaces have walls of varying thickness; between some of them the walls have given way and two spaces become fused into one. This condition seems akin to that figured in Cullen's work, 'Cancer of the Uterus,' p. 607, as a feature of the growing neoplasm. It is, however, the result of degeneration, and perhaps the work of some gas-producing organism. Adjacent to such areas are seen columns of protoplasm spreading out amongst hæmorrhages as solid bands; in them are seen polymorphic nuclei, which, in some instances, are undergoing karyokinesis. In other areas the protoplasm occurs in extensive plates from which proceed columns of various shapes and sizes which join up to form other smaller masses, and also to include other hæmorrhagic areas. The protoplasmic plates are vacuolated, as also are the larger bands, whilst in the protoplasmic plates the nuclei are arranged without any definite order, being in some places close together and in others more widely separate; in the columns they are seen arranged in single or in double rows. There are outlying cells adjacent to the columns which appear as buds of the same; these are

epithelioid in character, containing large nuclei which occupy the greater part of the cell, and which stain deeply with logwood; the nuclear protoplasm is for the most part granular, and shows a chromatin network; now and then a distinct nucleolus is visible. Such tissue as that just described occurs only in the deeper parts of the growth, lying between the more superficial necrotic tissue and the large hæmorrhagic areas on the one hand, and the muscularis on the other; in other words, at what might be called the attached portion of the growth, which is the most recent in origin. Here the growth is better nourished, as lying nearer the uterine circulation, and is consequently more typical.

There is, however, between this area and the muscularis no marked line of demarcation, for the columns previously described run in between the muscle-fibres, as do also the free isolated epithelioid cells and the fibrinous masses, so that the more superficial muscular strands present muscle-cells which are atrophied by pressure and degenerated, and which intermingle with the cells of the growth now as narrow spindles and now as granular oval cells, whose protoplasm stains but feebly if at all with hæmatoxylin. Deeper in the substance of the muscular wall the cells of the latter gradually assume a more normal appearance; the bands of new growth disappear, the discrete polymorphonuclear cells are less numerous, and instead of single muscle-cells muscular bundles are met with. Here, too, another phenomenon appears in the shape of an extensive infiltration of small round-cells, which is so dense in parts as to obscure all other structures from view. If a hæmorrhage occurs in this neighbourhood it is also densely invaded by leucocytes. Still deeper in the uterine wall large venous spaces, with distinct but perhaps imperfect walls, are seen; these are filled with red discs in a good state of preservation for the most part, and amongst the blood-cells appear the epithelioid cells with their large deeply stained nuclei, doubtless on their way to form metastases in the selective



viscera. The arrangement of the plasmodial cells in the neighbourhood of hæmorrhages is sometimes suggestive of the formation of a villus (*vide* drawing A),—that is to say, one finds now and again a circular or oval clear space, walled in more or less completely by syncytium, from which uninuclear cells proceed; there are, however, no vessels or stroma within such spaces, and the resemblance to a villus lies wholly in the shape and in the limiting plasmodial band. But cells within hæmorrhages are so modified in shape and size by imbibition of fluids that it is not an easy matter to settle clearly their histogenesis. I am therefore inclined to regard such a structure as accidental, and I should like to add, in passing, that the discovery of a typical villus within the elements of the uterine growth now under discussion is not at all essential to the acceptance of the view that it has its origin in the fœtal or chorionic portion of a previously shed placenta. To expect a morbid growth to reproduce the minute anatomy of the structure from which it arose in every detail is unreasonable. If, in examining a tumour of the breast, we find alveolar spaces full of glandular spheroidal cells, confined within the limiting basement membrane, we accept this as an imperfect mimicry of glandular tissue, and make the diagnosis of adenoma—a diagnosis at which we should never be able to arrive if we waited until we found perfect acini reproduced.

To return to the microscope. The pulmonary metastases will now be considered. Here one finds at the outset that the part which promised macroscopically to yield the best results, namely, the pale homogeneous centre of a button of growth, is, in fact, made up of degenerate hæmorrhagic and cellular *débris*. Coming, however, to the periphery of the growth, columns of large cells and vacuolated protoplasm are found, the cells resembling the large clear cells of the second layer of a villus wall (Langhan'sche Zellschicht). In my sections these cells are far better seen in the pulmonary growths than in the primary focus. Intermingled with these cells are particles

of carbon, often in large amount. The enlarged lymphatic glands show signs of chronic and recent inflammation, but they contain no evidences of new growth.

*Nomenclature.*

I have called this specimen a chorio-epithelioma for the following reasons :

The multinucleated protoplasm, arranged now in bands and now in masses, is similar in microscopic structure to the elements found in the walls of a chorionic villus. A villus wall, it will be remembered, is composed of a superficial layer of undifferentiated nucleated protoplasm and of a deeper layer of large epithelial cells called Langhans' layer. Of the histogenesis of the latter no doubt is expressed—it is of foetal origin. As to whether the outer layer is maternal or foetal authorities differ. For my purpose it is sufficient to accept the latest theory—an acceptance shared by Dr. Eden, van der Hoeven, Cullen, and others,—to regard it as foetal epiblast, and to use for it the term syncytium (since it bounds a hollow space). Now the plasmodial tissue seen in the growth, being identical in character with the syncytium of a villus, may be termed syncytial masses, and in order to afford proof of this identity sections have been made of three placentæ which have undergone hydatidiform degeneration. In these one sees what may be regarded as the starting-point of epithelial new growth from the syncytium of the villi. Under the microscopes on the table are to be seen the vesicular villi, with buds and masses of protoplasm proceeding from the syncytium, pushing in a malignant manner through that loose fibrinous layer which intervenes between the syncytium and the decidual cells of the mother (Nitabuch's layer) towards the maternal tissues. How far this trespassing has taken place into the placenta may be seen in the sections—quite far enough to pronounce the process as incipient malignancy, and to justify the belief that under given conditions it may proceed

beyond the placenta into the uterine wall, and from thence by the blood-stream to other organs.\*

There is, moreover, a proliferation of the cells of Langhans' layer seen better in some of the villi than in others. Now the only point of distinction between the overgrowth which one finds in a vesicular mole and a typical bit of a chorio-epithelioma is that in the former the villi from which the overgrowth proceeded are unmistakably present, whereas in the chorio-epithelioma, at least in my case, they are not. Although the *fons et origo* lacks demonstration in the latter, the new growth is identical in microscopical characters in each case. Since, then, we have a new growth, the elements of which are so identical with the two layers of a chorionic villus as to form an exact reproduction of it, it seems quite logical to regard the growth as arising in such a situation; the villus may never itself trespass beyond the placental domain, but its syncytial outgrowths do.

Before Mr. Doran sent me this specimen to examine I had seen two other cases of deciduoma malignum at the Samaritan Hospital. The clinical features in all three were similar. As Mr. Corrie Keep intends to bring forward these cases, I will not forestall what he has to say, but a point of importance is brought out by comparing the sections of Mr. Keep's two cases with the one I have had the pleasure of working at. In the former two cases the new growths are very similar; they are both made up of large modified connective-tissue cells like those found in a normal decidual membrane or in the maternal part of the placenta. No syncytium can be found on most careful examination, and both cases appear to me to be examples of a condition first described by Sanger as *sarcoma*

\* Since writing this paper I have had an opportunity of demonstrating the fact that syncytial masses are capable of proceeding from a vesicular mole, not only through the placenta but into the substance of the uterine muscle. The sections proving this point are taken from a uterus removed within a few weeks of the delivery of a hydatidiform mole. I refrain from saying more about this case, as it will shortly be brought before the notice of this Society by one of my colleagues.

*deciduo-cellulare*, the origin of which is considered to be the maternal decidual cells.

This marked difference in the microscopic features may be in great part the cause of the prevalent diversity of views as to the real nature of these extremely malignant uterine growths. Those observers who claim for the growth a mesoblastic origin may have worked solely with growths like Mr. Keep's two cases. The supporters of the theory of an epiblastic origin may have studied only growths like the one before us to-night. However that may be, I would point out that two varieties of tumour, histologically very distinct, are passing under the collective designation of deciduoma malignum, and that whilst this nomenclature may be convenient for compilers of indices, pathologists should draw a sharp distinction between the chorio-epithelioma or syncytial carcinoma on the one hand, and the mesoblastic sarcoma of the decidua on the other, although no clinical distinctions such as a history of a previous hydatidiform degeneration is obtainable. The malignant sequela of the vesicular mole is invariably a syncytioma.

The PRESIDENT remarked that at the present time it was quite impossible to prove definitely whether these malignant growths were of maternal or of foetal origin. Even if it could be shown that they were developed from the outer epithelial layer of the villi of the chorion, that would not settle the question, simply because it was still disputed whether that layer was maternal or foetal. It was for this reason that he had named his own specimen, shown at this Society some months ago, deciduoma malignum, the name given by Sanger, who first described it. Of course Dr. Lockyer had as much right to call it chorio-epithelioma, but at the same time it might be more convenient to continue the original name until more was known. He could not help leaning to the view that it was foetal in origin, and he did not see how those who believed in its maternal origin could get over the fact that it so often followed upon hydatidiform mole. The point raised by Dr. Lockyer that there were two sorts, one without syncytial elements, probably maternal in origin, and to which the term deciduoma malignum would be appropriate, and one with syncytial elements of foetal origin, for which the term chorio-epithelioma would be better applied,

ANNUAL MEETING.

FEBRUARY 5TH, 1902.

PETER HORROCKS, M.D., President, in the Chair.

Present—45 Fellows and 2 visitors.

Books were presented by the Radcliffe Librarian and the Medical Society.

Edward James Ambrose Haynes, F.R.C.S.I. (Perth, Western Australia), was declared admitted.

The following gentlemen were proposed for election :—  
Henry J. F. Simson, M.B., F.R.C.S.Ed. ; Evan James Trevor Jones, M.D.Brux., L.R.C.P.Lond. ; John Tennant, M.A., M.B., C.M.Edin. ; H. Simpson Newland, M.B.Adel-  
laide, F.R.C.S.Eng.

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DERMOID CYST OF OVARY REMOVED BY POS-  
TERIOR COLPOTOMY.

Shown by AMAND ROUTH, M.D.

THE patient was a multipara aged 53, who had been treated by Dr. Booth, of New Cleethorpes, Grimsby, for metrorrhagia of eight months' standing. Dr. Booth sent