Remarks

ON

ENDOMETRIOSIS AND ENDOMETRIOMATA *

BY

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ROYAL INFIRMARY

It is just ten years since J. A. Sampson read his epoch-making paper on perforating haemorrhagic cysts of the ovary,¹ and a sufficient interval has now elapsed to enable us to take stock of the position and assign these endometriomatous tumours to their proper place in gynaecological pathology and practice. This is easier to-day, because the novelty and glamour surrounding these tumours has largely disappeared, and the more adventurous spirits in gynaecology are turning their attention to other problems. I cannot pretend to discuss the subject adequately in the time at my disposal, but I will endeavour to place before you the principal etiological, pathological, and clinical features, reinforcing them as far as I can by statistics from a series of 137 cases operated on by myself during the past five years.

By endometriosis is meant the pathological state brought about when fragments of endometrium leave their proper situation in the uterus and implant themselves in neighbouring tissues, and by endometriomata the tumours which develop if conditions are favourable for the growth of these implants. In my opinion the vast majority of endometriomata arise in this way, but possibly a small number may be derived from Müllerian rests.

An endometrioma is therefore a tumour containing endometrial elements, or, at any rate, elements which look and behave like endometrium. Gland tubules in a richly cellular stroma are the histological criteria, but there may also be present a variable quantity of effused blood, cystic spaces lined by columnar or flattened epithelium and containing tarry blood, or hyperplasia of the muscular or fibrous tissue of the organs invaded. Physiologically these endometrial elements betray their origin by passing through the various phases of the menstrual cycle, including that of menstrual haemorrhage, and by undergoing a decidual change during pregnancy, though the latter, of course, is not specific to endometrium, but found constantly in the ovaries, and frequently in the peritoneal covering of the other pelvic organs.

ETIOLOGY OF ENDOMETRIOSIS

In 1908 Cullen² examined a number of specimens of diffuse endometrioma of the uterus, or diffuse adenomyoma as it was then called, and found as a result of his investigations that in places there was direct continuity between the endometrium proper and that contained within the tumour, and frequently an actual communication between the uterine cavity and several of the cystic spaces in the growth. This became known as the diverticular theory, and may be regarded as the simplest form of endometriosis. In certain other uterine endometriomata no such continuity can be demonstrated, and in these it must be assumed that the misplaced endometrium has reached its new situation by metastasis through the lymph vessels or venous channels of the uterine wall. Similar tumours not infrequently follow tuberculosis of the uterus or tubes, so it is possible that an inflammatory process may be a factor of some importance.

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Many theories were advanced to explain the occurrence of extrauterine endometriomata, different authorities suggesting that they were derived from Wolffian or Müllerian rests or by metaplasia from the peritoneal endothelium. In 1921, however, Sampson illuminated the whole problem with his theory of retrograde menstruation and cellular spill. According to this theory, some of the menstrual discharge with its normal content of endometrial fragments may pass backwards through the Fallopian tubes and so reach the pelvic cavity. The structures lying in closest relationship to the fimbriated ends of the tubes naturally receive most of the fragments, or implants as they are now called; but gravity and the normal movements of bowel and bladder render a much wider dissemination possible.

That retrograde menstruation is more than a mere theory, and does actually occur, is within the experience of every gynaecological surgeon; as when performing abdominal operations during the menstrual period he must have occasionally observed blood dripping from the fimbriated ends of the tubes or lying in the posterior cul-de-sac. Parity, retroversion of the uterus, enlargement or distortion of the uterine cavity by fibroids, or any obstruction to the flow of menstrual blood through the cervix, may all predispose to this retrograde flow. Direct endometriosis of the peritoneal cavity through the uterine wall may of course follow such operations as involve incision or puncture of the uterine wall—Caesarean section, or myomectomy, for instance. In my own series of cases, previous operations included 10 per cent. of curettings, 1 Caesarean section, 3 operations upon the appendages, and 7 appendicectomies.

However brought about, the result is a shower of implants which reaches the pelvic cavity and the various organs lying within it. The subsequent fate of these implants then depends on several factors—among others, their vitality and virulence, and the nature and resisting powers of the tissue invaded. The ovary and recto-vaginal septum appear to offer the best conditions for active proliferation, and it is therefore in these situations that extrauterine endometriomata are most commonly found. Three possible explanations in the case of the ovary may be the absence of a peritoneal covering, the breach of surface continuity which follows ovulation, and the greater concentration (possibly) in the ovary of the specific hormones controlling menstruation. There is always a definite reaction on the part of the invaded structures, and this leads to adhesions of great density and to hyperplasia of any fibrous or muscular tissue which may be present in the vicinity. The menstrual products of the tumour itself are also peculiarly irritating and still further intensify the local reaction.

From its very nature, endometriosis must result in a wide distribution of endometrial elements, and this is particularly so when it has followed retrograde menstruation and cellular spill. Even in the case of direct invasion of the uterine wall from the cavity it is quite possible that the resulting diffuse tumour really represents a number of different implants, each of which is surrounded by hyperplastic fibro-muscular tissue. The usual result of endometriosis, therefore, is the formation of multiple tumours in the pelvic organs, though not all of these become sufficiently prominent to form part of the clinical picture.

PATHOLOGY OF ENDOMETRIOSIS

The various elements composing endometrial tumours have already been referred to, and it is only necessary at this stage to describe the naked-eye appearances of pelvic endometriosis and the various fully developed tumours which may arise from that condition. Endo-

metriosis following direct invasion of the uterine wall from the endometrium usually results in a diffuse tumour, largely made up of hyperplastic fibro-muscular tissue, but also containing numerous islets of misplaced endometrium, some of which have become cystic and filled with blood. The external contour of the uterus is not usually altered, as the enlargement is uniform. The tumour differs from a fibroid in possessing no capsule, and in having its cut surface studded with the endometrial areas already referred to. Like a fibroid, however, it may occasionally grow outwards or inwards, and become pedunculated subserous, or submucous, as the case may be. In cornual tumours there is a localized swelling near the inner end of the tube, and on section this is frequently found to contain a cyst filled with tarry blood.

Endometriosis following retrograde menstruation and cellular spill produces naked-eye appearances which are unmistakable. The fimbriated extremities of the Fallopian tubes are usually patent. Dotted about the pelvic peritoneal cavity are numerous purplish blebs which microscopical examination will demonstrate to be endometrial implants. Some of these have irritated the peritoneal surfaces and led to dense adhesions, as evidenced by fixation of the ovaries and tucking up of the utero-vesical or utero-rectal peritoneum.

If conditions are favourable for further growth, definite endometriomata are produced; these differ in their naked-eye appearances according to the particular organ affected. In the ovary the physiological activity of the implants as judged by the amount of blood effused during menstruation is most marked, and the tumour therefore becomes cystic and filled with tarry blood. Sampson, indeed, regards the ovary as "a sort of intermediate host, hot-bed, or incubator, which may impart greater virulence to the tumour elements, and, if subsequent rupture occurs, lead to a wider distribution of the neoplasm." The tumour is usually about the size of a walnut, but sometimes much larger, and may even reach the dimensions of a large unilocular cyst. It is adherent at the original point of implantation, and, consequently, its contents always escape when the ovary is separated at operation. The firm walls of the cyst then prevent complete collapse, and the point of rupture remains open and ragged. In addition to the primary adhesion, others are usually present, and these firmly attach the ovary to adjacent structures, and, when separated, expose a raw granular surface. These adhesions probably result from leakage of the irritating cyst contents.

Next in importance comes the tumour of the recto-vaginal space, which develops presumably from an implant in the pouch of Douglas. The appearances are again characteristic, the rectum being tucked up and adherent to the posterior surface of the uterus and its wall much thickened and nodular, sometimes to such a degree that it closely simulates a malignant tumour. The growth may also involve the cervix and posterior vaginal wall, and even project as nodules or polypi into the posterior vaginal fornix.

The uterine wall itself may develop an endometrioma as the result of endometriosis of the pelvic cavity, the implants attaching themselves primarily to the peritoneal surface of the uterus or invading it from a tumour already established in the ovary, recto-vaginal space, or elsewhere. The direction of growth is towards the uterine cavity, however, and not away from it, as in the diffuse tumour already described.

Similar tumours are not infrequently found on the Fallopian tube, round or utero-sacral ligaments, pelvic colon, small intestine, and more rarely as pathological curiosities in the appendix, umbilicus, inguinal canal, or scar of a previous abdominal operation.

In my own series the distribution of the principal tumours was as follows:

Diffuse uterine	...	...	...	6 cases
Cornual	...	...	...	6 cases
Ovarian	...	...	...	44 cases
Recto-vaginal	...	...	...	44 cases
Ovarian and recto-vaginal	...	...	...	34 cases

The ovarian and recto-vaginal tumours, in addition to being frequently present together in the same case, were often associated with similar growths in the utero-sacral ligaments, uterus, or bowel; but separate classification of these is unnecessary, as all are essentially part of the same process.

The question of other lesions associated with endometrioma is important, and, of these, uterine fibroids must take first place. They were present in 40 per cent. of my own cases, and of sufficient size to be of clinical importance in 27 per cent. Looking at it from the opposite point of view, 10 per cent. of all fibroids operated on during the five years covered by the series were associated with endometrioma. Their influence as a possible factor in retrograde menstruation has already been mentioned, and would be expected to be more apparent in the case of single or nulliparous women. In single women the percentage of fibroids was actually about 50. Sampson has advanced a theory that fibroids may actually originate in endometriomata of the uterine wall, the endometrial elements disappearing at a later stage, and leaving only the fibromyomatous stroma.

True pelvic inflammation may be associated with endometriosis, but is unlikely to have advanced to the stage of tubal occlusion, as retrograde menstruation would then be impossible. Curtis³ believes that the two conditions are actually antagonistic, having noticed that, with improved prophylaxis in the management of gonorrhoeal infection and the resultant decrease in the incidence of salpingitis, there has been an enormous increase in the number of patients with misplaced endometrial tissue.

There appears to be no relationship between endometrioma and carcinoma of the uterus, but in two of my cases there was an associated malignant growth of the cervix. With ovarian carcinoma it is otherwise, however, and Sampson,⁴ after examining a number of specimens, has come to the conclusion that malignant ovarian disease may develop in misplaced endometrial tissue.

CLINICAL FEATURES OF ENDOMETRIOMA

Endometriosis is possible at any age between puberty and the menopause, but treatment of the resulting endometriomata is usually carried out during the period of sexual maturity. In my own cases 91 per cent. were operated on between the ages of 30 and 50 years. Twelve patients were under 30 years and nine over 50. The tumours are found most commonly in married women; there were only 17 single women among my 137 cases of endometrioma.

It is not possible to give statistics as to the frequency of endometriosis, but the number of endometriomata producing symptoms is considerable. I operate on between twenty-five and thirty of these cases each year, the laparotomies amounting to about 11 per cent. of the total abdominal operations. This figure is not very different from that given by Sampson, which is 12 per cent. of all abdominal operations carried out during sexual maturity.

In its early stages, endometriosis produces few symptoms for which it can be held responsible, and may only be discovered accidentally when the abdomen is opened for some other condition. As the implants mature and adhesions form, however, there will usually be increasing pelvic discomfort, dysmenorrhoea, and disturbances of the menstrual flow. Even then, certain associated lesions

such as fibroids or malignant disease may dominate the clinical picture and produce the symptoms for which the patient actually seeks advice. After consideration of my own cases, I came to the conclusion that endometrioma was entirely responsible for the symptoms in 65 per cent., and partly responsible in 8.7 per cent., while fibroids were entirely responsible in 21 per cent.

Coming to the question of symptoms it must be stated at the outset that there is not one which will definitely point to the existence of endometrioma. Lower abdominal pain is very common, and in my series was present in 40 per cent. of cases. Dysmenorrhoea, particularly of recent origin, is probably the most characteristic symptom, but it is by no means constant, and was complained of in only 31 per cent. of cases. When present, it is presumably due either to pre-menstrual congestion of the endometrial elements or to tension following accumulation of menstrual blood. Menorrhagia or epimenorrhagia is another common symptom, and was also found in 31 per cent. It has been suggested that this symptom is more likely to be due to associated fibroids than to endometrioma, but this is not borne out by my own figures, as the percentage of fibroids in patients complaining of this symptom was very little higher than that for the whole series—47 as against 40. Bearing down and rectal discomfort are frequently met with when the growths are in the recto-vaginal space, or when there are adhesions in the neighbourhood of the rectal wall. Back-ache is such a common complaint in women that its value in differential diagnosis is strictly limited, but this symptom is prominent when the ovaries are adherent in the pouch of Douglas or when the rectum or back of the cervix is involved. Dyspareunia is frequently complained of in similar circumstances, also shooting or "electric" pains extending down into the uterus and vagina. Occasionally there may be pain down one or other leg when an ovarian endometrioma is adherent to the pelvic wall. Marked constipation may be associated with extensive involvement of the rectum or other parts of the alimentary tract, and a blood-stained discharge present if a recto-vaginal growth has perforated the vaginal wall.

The physical signs naturally depend on the situation of the tumour. In the ordinary diffuse uterine tumour there will usually be moderate and uniform enlargement of the uterus, but with cornual tumours there may be definite irregularity. In either case the physical signs will closely resemble those of a uterine fibroid, and differential diagnosis will be impossible unless increasingly severe dysmenorrhoea has led one to suspect the true state of affairs.

In ovarian endometrioma there will be an enlargement and fixation of one or both ovaries, and as these are usually adherent to the back of the uterus, the latter will be retroposed and its mobility lessened. In the absence of evidence pointing to pelvic infection, such a finding should lead one to suspect an endometrial tumour.

When the growth is in the recto-vaginal space, the physical signs are most characteristic, the infiltrating character of the tumour and the presence of tender shotty nodules in the wall of the posterior fornix being sufficient evidence upon which to base a diagnosis. Recto-vaginal examination will prove helpful in these cases, as it may reveal fixation of the rectum to the back of the tumour.

To sum up, it may be stated that there are no pathognomonic symptoms of endometrioma, but that increasing dysmenorrhoea, menorrhagia, and dyspareunia should lead one to suspect the condition. The physical signs, however, are more characteristic, at any rate in the case of extrauterine growths, and fixation of the uterus and ovaries associated with a shotty nodular tumour behind the cervix affords conclusive evidence.

ENDOMETRIOMATA AND THE REPRODUCTIVE FUNCTION

That endometriomata seriously interfere with child-bearing is shown by the fact that patients with these tumours usually give a history of sterility or of no births having occurred for several years. In my series of 137 cases, after excluding 17 single women and 8 women who had been married less than three years, 41 per cent. were sterile. Of the parous women 75 per cent. had not been pregnant for at least five years and 50 per cent. for at least ten years. There was no special incidence of abortion, the abortion/full-term ratio being 1 to 5.8. Associated fibroids may be partly responsible for the absolute or relative sterility met with in those cases, but that their influence is not very great is shown by the fact that there is little difference in the incidence of these tumours in nulliparous and parous women, the percentages being 46 and 41 respectively. Endometrioma, at any rate in its early stages, is not an absolute bar to pregnancy, and I certainly know of one patient with a well-marked endometrioma of the recto-vaginal space who subsequently became pregnant, although no actual treatment was carried out for the tumour itself.

TREATMENT

As endometriomata are usually widely distributed and of an infiltrating character, it will be understood that conservative measures are only possible in the early stages, and that even then the chances of recurrence are considerable. A conservative policy is only justifiable, however, if one ovary alone is involved, or if there are isolated nodules in the recto-vaginal space causing dyspareunia.

In my own series I find that the uterus and all ovarian tissue were removed in 83 per cent. of cases, the operations on the remainder consisting of excision of one ovary or of nodules in the recto-vaginal space. I have no experience of radium in the treatment of endometrioma, but I would prefer local excision in early cases as being less likely to interfere with ovarian function. Owing to the dense adhesions present and the frequent involvement of bowel, radical operations may be among the most difficult in gynaecology, but the results both immediate and remote are extremely good. Total is preferable to subtotal hysterectomy, and it is quite unnecessary to excise infiltrating growths in the rectum or other parts of the alimentary tract, as atrophy will follow if both ovaries are removed.

There was only one death in the series, representing an operative mortality for the radical operations of 0.8 per cent. One of the patients treated by removal of the affected ovary has since been delivered of two full-term children. This is my only experience of pregnancy following conservative surgical treatment of endometrioma.

SUMMARY

1. Endometriosis is defined as the pathological state brought about when endometrial fragments invade the uterine wall or, passing through the Fallopian tubes in regurgitant menstrual blood, reach the pelvic cavity and the structures within it.

2. Cullen's diverticular and Sampson's retrograde menstruation and cellular spill theories are therefore accepted as providing the most reasonable explanation of uterine and extrauterine endometriosis respectively.

3. Endometrioma is defined as one of the tumours which develop when misplaced endometrial fragments or implants proliferate sufficiently to form clinico-pathological entities, and is accepted as the most suitable term to apply to all such tumours, whether uterine or extrauterine.

4. The clinico-pathological features of endometrioma are described, and stress is laid on the multiple character of the lesions resulting from endometriosis.

5. Surgical treatment is discussed, and radical measures are advocated for all but the earliest cases.

6. Statistics are quoted from a personal series of 137 cases operated on during the last five years, and individual cases referred to where necessary.

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JAUNDICE IN CHILDHOOD*

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Although, strictly speaking, the term "jaundice" implies staining of the skin, mucous membranes, or conjunctivae, such general staining by bile-pigments is always associated with an excess of bilirubin in the blood; and as such excess is the most constant finding, and precedes the staining of the tissues, it is convenient to regard excess of bilirubin in the blood as the measure of the condition under discussion. Before dealing with the various conditions, which in children are characterized by jaundice, it is useful briefly to review the mechanism of its production.

The modern view, well supported by experimental and clinical evidence, suggests that bilirubin is formed from haemoglobin by the cells of the reticulo-endothelial system, chiefly by those of the spleen, liver and bone-marrow. The bilirubin so formed is further changed by the polygonal cells of the liver and excreted through the bile-channels into the alimentary tract. The two forms of bilirubin are not physico-chemically identical, and can be distinguished by the test devised by Hijmans van den Bergh.¹ The bilirubin produced by the action of the endothelial cells gives an "indirect reaction" to the test, while that formed by the action of the polygonal cells gives a "direct" reaction. When the latter accumulates in the circulating blood, it is excreted as bile by the kidneys, but the former variety is rarely so excreted, the urine containing only an excess of urobilin. According to this conception, jaundice may be produced by (1) obstruction at any point in the biliary channels, the bile stagnant in the ducts being re-absorbed into the blood stream (van den Bergh's reaction "direct"); (2) disease of the polygonal cells, in which bilirubin, unchanged by and not excreted by these cells, passes into the general circulation (van den Bergh's reaction "indirect"); (3) disease of the liver, which may in one part involve the polygonal cells, and in another cause obstruction of the bile-channels (van den Bergh's reaction "biphasic"); and (4) excessive haemolysis, with the production of more bilirubin than the polygonal cells can change and excrete, the excess passing into the general circulation (van den Bergh's reaction "indirect").

Certain types of jaundice which will be discussed in this paper are undoubtedly due to toxins, and these types illustrate very well the important principle, perhaps even now not sufficiently realized in our attempts to understand and combat disease, that seldom if ever are morbid processes

due to one factor only: practically always it is necessary to consider what may be termed the "seed" and the "soil," and often, in addition, factors which we may liken to "fertilizers" in the parallel suggested. The liver is markedly prone to suffer from the presence of certain toxins in the circulating blood, but there is an equally marked tendency for some individuals to suffer more than others. As an example of this idiosyncrasy may be mentioned the well-known tendency of certain people to become jaundiced after comparatively small doses of atophan or novarsenobillon. But, in addition to this personal idiosyncrasy, the same individual may show a greater effect at one time than at another. During pregnancy, for example, the function of the liver appears to be more easily upset. Age, too, exerts an influence: other conditions being equal, the child's liver is more prone to suffer than that of the adult, though the effect may be counterbalanced by the greater tendency to repair in the former. Poisons which exert their toxic effects on the liver usually show a maximal effect in the infant.

The study of jaundice in childhood is therefore of considerable value, and deductions drawn therefrom may often with advantage be applied to corresponding conditions occurring in adults.

It follows from what was said in the opening paragraphs of this paper that jaundice is a symptom or sign found in a variety of conditions, and is in no sense to be regarded as a disease in itself. Some of the conditions which will be discussed are clinically quite distinct and comparatively easy of diagnosis: others, though fairly obvious in typical cases, show a tendency to merge into related conditions, of totally different prognosis: as an example of the latter class may be instanced the cases of acute or sub-acute necrosis of the liver which appear to have commenced as so-called "catarrhal jaundice."

JAUNDICE OF THE NEWLY BORN

Jaundice is such a common sign during the early days of life that it is convenient to discuss these cases as a group.

Icterus Neonatorum (Physiological Jaundice)

Obvious jaundice occurs in a considerable percentage of infants during the early days of extrauterine life. In a still larger percentage it is masked by the pink coloration of the skin, and in these it can be rendered apparent by carefully emptying the capillaries of blood. Probably all infants at birth show an excess of bilirubin in the blood: this was so in every case of a large series I personally investigated, the results being in agreement with those obtained by Bang² and Ylppo.³ The average concentration of bilirubin was 1:75,000, the normal in the adult being 1:400,000 to 1:1,000,000. Obvious jaundice does not appear before the second day, when it can usually be seen on the face, chest and back. It then makes its appearance on the upper parts of the limbs and on the abdomen. The sclerotics are the next to show the coloration, which appears last on the hands and feet. Mild cases may only show staining of the face and chest. The colour deepens for a few days and then gradually fades, fading taking place in the reverse order to the appearance, except that the sclerotics and the nails of the fingers and toes may retain the colour for a considerable time. The condition is more likely to be marked in premature babies. Except for a little drowsiness when the jaundice is deep, the health of the infant appears to be entirely unaffected, and the condition should be regarded as physiological. When an opportunity is obtained for post-mortem examination, as when death follows a birth-injury, it is of interest to note that staining of the tissues involves cartilage, cerebro-spinal

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