# Ovarian Cancer

Edited by Norman M. Bleehen

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With 48 Figures and 46 Tables

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# *Preface*

The subject of the Sixth Symposium on Clinical Oncology of the Royal College of Radiologists held in February 1984 was ovarian cancer. This publication presents the collected papers delivered at that meeting, but excludes much useful discussion which also took place.


The annual clinical oncology symposia have been designed to review topics of current interest in cancer therapy from a multidisciplinary point if view. It was gratifying to the organisers and all who took part that the aims were so well met by both the contributors and discussants. We believe that this can only be to the advantage of future research and our present and future patients.

Ovarian cancer is a common gynaecological cancer which freqently presents late. Its clinical management is bedevilled by the variable referral routes through which patients present for treatment. Thus, many are first seen by general abdominal surgeons who may not be expert in their treatment, rather than gynaecologists or gynaecological oncologists. There are many interesting features about it which have been discussed by the various speakers. Early spread within the abdomen is common, spread outside the abdomen less common. There is a variety of histopathological types, each with distinct aetiological, prognos-

tic and therapeutic assocations. In contrast to most cancers, surgical debulking of tumour is considered valuable even when there is no possibility of removing all tumour by the knife.

Radiotherapy has an important role in the management of both early and late disease whilst chemotherapy is rapidly finding a useful place. The questions of how best either modality should be given, whether alone or in combination, have been reviewed. Considerable excitement has been generated by the possibility of predictive testing of tumours for chemotherapy responsiveness, but a note of sensible caution was sounded at the meeting.

As with all tumours, diagnostic imaging methods are of importance. Ovarian cancer is a happy hunting ground for the exciting new imaging techniques such as computerised axial tomography and nuclear magnetic resonance that are currently becoming available. Tumour markers are available which may not only be used as an immunohistopathological guide to tumour type, or serum marker for estimation of residual or recurrent tumour mass, but now can be seen to be of value in immunoscintigraphic localisation by external radionuclide scanning. Many such exciting developments were discussed. It is hoped that this volume will therefore be of assistance and guidance to those interested in the problem of cancer of the ovary.

I wish to express my gratitude to all the speakers and discussants from the audience who enabled the symposium to proeed with vigour and interest. Finally I wish to acknowledge and thank my secretaries, Miss Lesley Sargeant and Miss Frances Rankine, for their help; Mr Michael Jackson of Springer-Verlag for his tact in understanding the problems of an editor; and Mr. A.J. Cowles and his staff at the Royal College of Radiologists for providing their excellent administrative support.

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# *Pathology*

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## Classification

No other organ in the human body gives rise to as many tumours as does the ovary. Because there are so many different tumours, it is essential to empoly a sensible method of classification. In these circumstances the classification is not merely a way for pathologists to make things look more complicated than they really are; it also serves the important purpose of bringing the tumours together into similar groups, outlining differences and similarities in origin, structure and, above all, behaviour.

The classification of ovarian tumours which is in use today was initiated by the International Federation of Gynecology and Obstetrics (FIGO) and further developed by the World Health Organisation (WHO) in the mid 1960s (Serov et al. 1973). It is ostensibly a classification based on histogenesis but it is, in practice, a morphological classification, with the histogenetic background being deduced from the morphological appearances. The main structures of the normal ovary from which it is believed tumours develop are: the serosa, which gives rise to the epithelial tumours; the mesenchyme, which gives rise to the sex-cord stromal tumours; and the germ cells, which give rise to the germ cell tumours. At its simplest level, therefore, the classification of ovarian tumours consists of these three groups - the epithelial tumours, the sex-cord stromal (or gonadal stromal) tumours and the germ cell tumours - each of which has many subdivisions. There are, unfortunately, some tumours which do not fit into any of these groups, mainly because their origins are not so obvious from their appearances, and these are therefore listed separately. The full classification of primary ovarian neoplasms is as shown in Table 1.

More than 90% of ovarian cancers fall into the epithelial group (Fox and Langley 1976) and these will be examined more closely, first from the point of view of tumour development. As a woman ages, the surface of the ovary becomes more corrugated, perhaps

**Table 1.** Primary ovarian tumours

| |
|---|
| Epithelial |
| Sex-cord mesenchymal |
| Germ cell |
| Lipid (lipoid) cell |
| Gonadoblastoma |
| Soft tissue tumours not specific to the ovary |
| Unclassified tumours |
| Tumour-like conditions |

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as a result of ovulation, with clefts of serosa being formed, some of which may be nipped off completely, to form tiny cysts in the outer cortex. These are the very common serosal inclusion cysts and they are assumed to be the starting point for the development of most epithelial tumours of the ovary. Having stated that epithelial tumours originate from the surface epithelium, it may appear rather convoluted to take this serosa through the process of cyst formation, but these acrobatics are necessary to explain why the great majority of epithelial tumours are cystic. To appreciate the different histological types of epithelial tumour which may arise from the serosal inclusion cyst, we have to remember the embryology of the ducts of the female genital tract. The paramesonephric (Müllerian) duct is formed by direct invagination and multiplication of the coelomic lining cells. These cells will eventually form the epithelial elements of the fallopian tube, endometrium and endocervix, as well as the ectocervix and perhaps part of the upper vagina. At this very early stage of development, it is therefore apparent that these Müllerian duct cells have the ability to differentiate into all of these epithelial types. It can be argued that, if the coelomic lining cells which eventually give rise to the Müllerian duct system have these developmental competences, then adjacent coelomic lining cells on the surface of the developing ovary, and indeed the mature ovary, may be able to express the same developmental competences and differentiate along the same lines if suitably stimulated. If the epithelial lining of a serosal inclusion cyst becomes neoplastic and, as a consequence of the processes described above, differentiates along one or other cell line, then the type of epithelial tumour that results is shown in Table 2.

Although the epithelial types seen in the clear cell carcinoma and the Brenner tumour are not of Müllerian appearance, these tumours are included in the epithelial category and are usually considered to be of Müllerian origin, in that they derive from the ovarian serosa, which has been referred to as forming part of the 'secondary Müllerian system' (Lauchlan 1972). The complete list of epithelial tumours is shown in Table 3.

Of the other main groups of primary ovarian tumours, those of sex-cord stromal origin and germ cell origin are also subdivided and for the sake of completeness will be ex-

**Table 2.** Epithelial tumours

| | |
|---|---|
| Fallopian tube | = Serous |
| Endocervix | = Mucinous |
| Endometrium | = Endometrioid |
| Mesonephric | = Clear cell |
| Transitional | = Brenner |

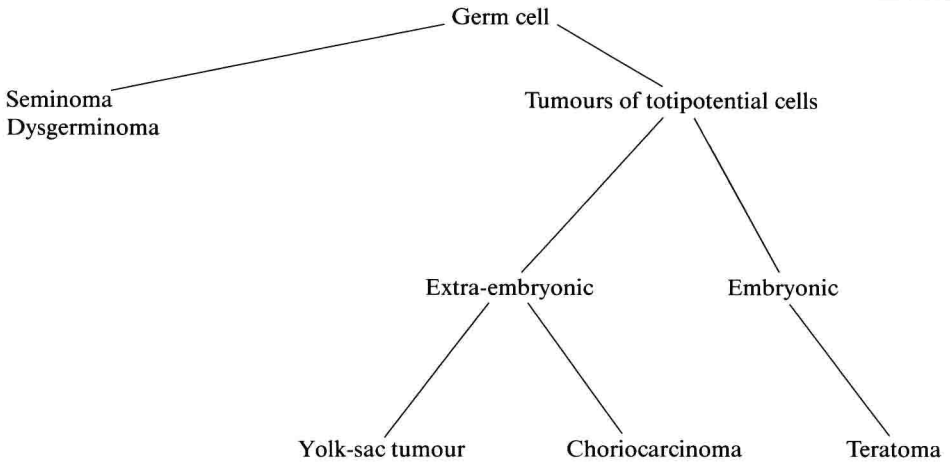
**Table 3.** Epithelial tumours

| |
|---|
| Serous |
| Mucinous |
| Endometrioid |
| Clear cell |
| Brenner |
| Mixed |
| Undifferentiated |
| Unclassified |

**Table 4.** Sex-cord stromal tumours

| |
|---|
| Ovarian differentiation (granulosa-stromal) |
| Granulosa cell tumour |
| Thecoma-fibroma |
| Testicular differentiation (androblastoma) |
| Sertoli-Leydig cell tumour (arrhenoblastoma) |
| Leydig cell tumour |
| Sertoli cell tumour |

**Table 5.** Germ cell tumours




amined briefly. Table 4 shows the two major subdivisions of the sex-cord stromal tumours: those with the morphological appearance of ovarian tissue, which are usually, but not always, feminising, and those with the morphological appearance of testicular tissue, which are much rarer and are usually, but again not always, virilising. The only member of this group which is consistently malignant and therefore concerns us here is the granulosa cell tumour.

Germ cell tumours are rather more complicated and the constituent members of the group are shown in Table 5.

## Surface Serous Tumours of the Ovary

As stated above, the great majority of epithelial tumours of the ovary are cystic and may develop from serosal inclusion cysts. A few tumours, however, undoubtedly do arise directly from the surface covering of the ovary and develop as exophytic, papillary growths. Tumours of this type are particularly likely to be associated with multiple pelvic and peritoneal seedlings of carcinoma. This may be expected because of the ease with which cells may break off and are then already in the peritoneal cavity without having to rupture the

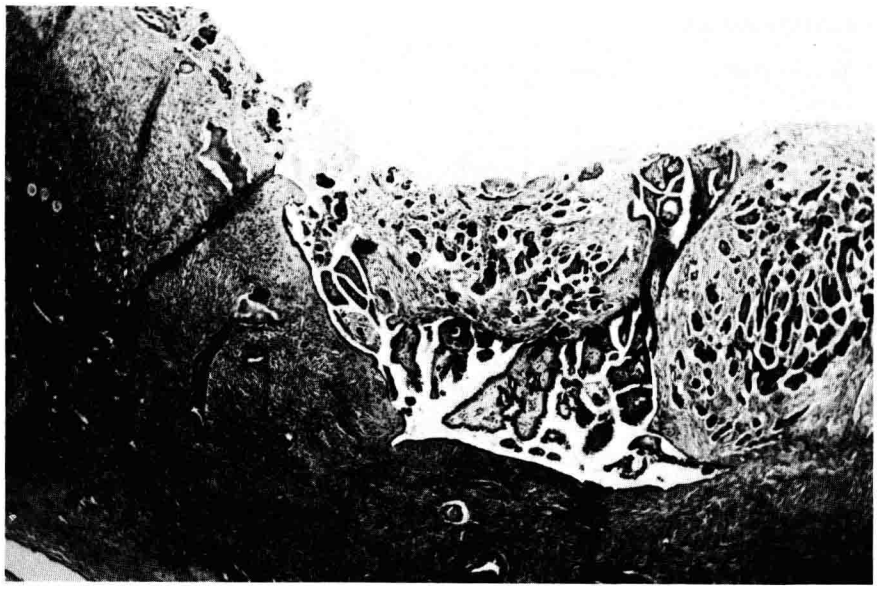


**Fig. 1.** Surface papillary carcinoma of the ovary (primary papillary peritoneal neoplasia). One of the numerous bilateral surface deposits of serous tumour. The omentum was also extensively involved but there was no identifiable ovarian primary tumour. H and E, × 76

capsule of the tumour. The ovarian involvement is very often bilateral. In many cases it is possible to identify one or other ovary as the site of the primary tumour, but occasionally this is not possible and the ovaries seem to be involved only by small surface deposits, indistinguishable from secondary implants (Fig. 1). These women often have quite widely disseminated intrapelvic and intraperitoneal tumour deposits, with extensive omental involvement. Although these tumours are morphologically identical to serous carcinomas it is questionable whether they should be considered as true ovarian primary tumours, and the term primary papillary peritoneal neoplasia has been coined to describe them (Foyle et al. 1981). It is argued that they probably represent a multifocal in situ neoplastic change taking place in the peritoneum generally but mainly in the pelvis, perhaps including the ovaries as part of the wider serosal change. The mechanism of histogenesis is probably the same as has been described for epithelial tumours generally. It is interesting to note that tumours of this type have been reported in women who have had prophylactic bilateral oophorectomies because of a strong familial tendency for ovarian cancer (Tobacman et al. 1982). These surface papillary tumours may be of any grade, from borderline to grade 3, but are usually stage III or IV when diagnosed. The survival of patients is shorter than that of patients with ovarian serous papillary carcinoma of the same grade without predominant surface involvement (Gooneratne et al. 1982). The recognition of this rather uncommon phenomenon explains some very puzzling histological and clinical findings in patients with serous tumours.

## Endometrioid Tumours

Endometrioid tumours are so called because their structure resembles that of the primary endometrial tumours which arise in the body of the uterus. The tumour types that come under the heading of endometrioid tumour of the ovary therefore consist not only of the fairly common carcinoma but also the mesenchymal and mixed tumours. Table 6 shows a complete list of endometrioid tumours of the ovary.

Although the adenocarcinoma is the commonest member of the group, the epithelial tumours may show any of the less common epithelial patterns seen in the endometrium. Exactly what morphological features are required to enable an adenocarcinoma to be put into the endometrioid category have not been fully defined; it is not quite enough to state that any carcinoma looking like an endometrial carcinoma is an endometrioid carcinoma when found in the ovary, because an endometrial carcinoma itself may have several patterns. The basic feature of an endometrioid carcinoma is the glandular pattern, resembling the characteristic endometrial tumour, with elongated, oval or tubular glands lined by multilayered epithelium (Fig. 2). The cells do not usually contain abundant mucin but nevertheless the distinction from a mucinous carcinoma or a secondary large bowel carcinoma may not be as easy as it might seem. Many endometrioid carcinomas have papillary areas, rather more so than the endometrium, which may make their distinction from papillary serous carcinoma difficult. While on the subject of papillary carcinoma it should be stressed that papillary carcinoma of the ovary is not a precise diagnosis as papillary areas are nearly always found in serous and clear cell carcinomas, are often found in endometrioid carcinomas, and may be present in mucinous carcinomas. If the degree of differentiation allows it, which it should if the papillary pattern is well developed, the histopathologist should attempt to assign the tumour into one of these four epithelial types.

As in the endometrium, endometrioid carcinomas of the ovary may show areas of squamous metaplasia, the resultant tumour sometimes going by the name of endometrioid adenoacanthoma. The presence of malignant squamous elements in an adenosquamous carcinoma imparts a more aggressive nature to the tumour. Fu et al. (1979) reported a 5-year survival rate of only 21% in patients with adenosquamous carcinoma, compared with 90% in those with endometrioid adenoacanthoma.

The relationship of endometrioid carcinoma of the ovary to endometrial carcinoma in the body of the uterus is interesting. Up to 30% of women with endometrioid carcinomas

**Table 6.** Endometrioid tumours

| |
|---|
| Benign |
| Adenofibroma |
| Cystadenoma |
| Borderline |
| Malignant |
| Carcinoma |
| Adenocarcinoma |
| Adenoacanthoma |
| Adenosquamous |
| Endometrial stromal sarcoma |
| Mixed Müllerian tumours |

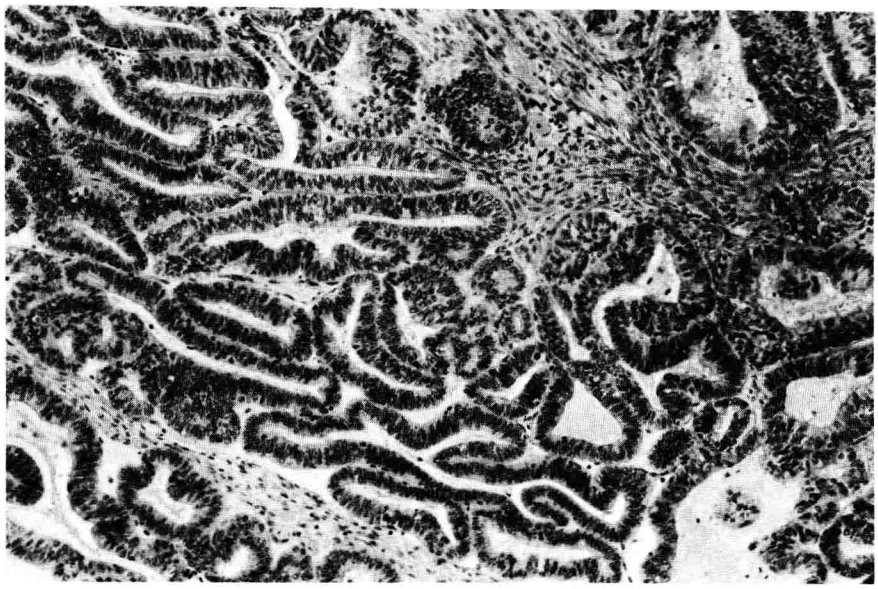


**Fig. 2.** Endometrioid carcinoma. The glandular pattern is similar to that seen in the commonest type of endometrial carcinoma. H and E, × 176

of the ovary are found also to have endometrial carcinomas in the uterus (Fox and Langley 1976). In a few of these cases it may be that one tumour is primary and the other is secondary, but in the majority it is believed that they represent two synchronous primary tumours. Often the ovarian tumour is large, whereas the uterine tumour is small and may be confined to the endometrium, perhaps surrounded by an area of atypical hyperplasia. Furthermore, some 10%–20% of women with endometrioid carcinomas of the ovary can be shown to have coexistent endometriosis (Czernobilsky et al. 1970). The true figure may in fact be higher, but the expansion of the tumour destroys the pre-existing endometriosis. This synchronous development of endometrioid carcinoma of the ovary and endometrial carcinoma of the uterine body may thus be regarded as a field change. The carcinogenic stimulus or stimuli is thought to have a similar effect on the endometrium in the uterus and on the ectopic endometrium in endometriosis or even upon ovarian tissue which is capable of endometrial differentiation. Finally, it should be remembered that endometrioid tumours have been found at other sites of endometriosis, away from the body of the uterus and the ovaries.

This association between an endometrioid carcinoma in the ovary and an endometrial carcinoma of the uterine body is of great importance as it means that the status of the endometrium must be assessed in all women with ovarian tumours. Although most women who are found to have malignant ovarian tumours at laparotomy will have a hysterectomy as part of the initial treatment, this is not always the case, particularly if the woman is young and the cyst is not overtly malignant at operation. In the latter circumstances, if the tumour turns out to be an endometrioid carcinoma, it is vital that the endometrium is investigated at a further operation, either by curettage or hysterectomy. An additional, perhaps rather theoretical, significance of making a correct diagnosis of endometrioid carcinoma is the possibility of progestogen sensitivity. Some endometrial carcinomas have been shown to have oestrogen and progesterone receptors, although only a minority show

**Table 7.** Mixed Müllerian tumours

| |
|---|
| Müllerian adenofibroma |
| Epithelium benign; stroma benign |
| Müllerian adenosarcoma |
| Epithelium benign; stroma malignant |
| Malignant mixed Müllerian tumour |
| Epithelium malignant; stroma malignant |
| Homologous |
| Heterologous |

**Table 8.** Differences between ovarian malignant mixed Müllerian tumour (MMMT) and immature teratoma

| MMMT | Teratoma |
|---|---|
| Older age of patient | Younger age of patient |
| Malignant epithelial and mesenchymal elements | Malignant epithelial elements rare |
| Neuroectodermal elements not seen | Neuroectodermal elements common |

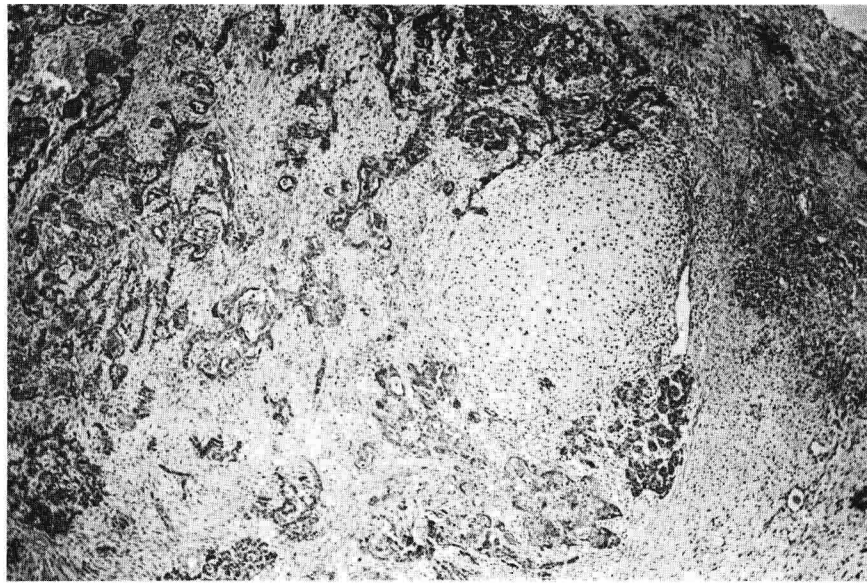


**Fig. 3.** Malignant mixed Müllerian tumour. Carcinomatous glands with sarcomatous stroma; a focus of chondrosarcoma is seen to the right of the centre. H and E, × 58

any clinical response to progestogen therapy. It would be expected that the morphologically identical endometrioid carcinoma of the ovary might also have progesterone receptors and so also respond to added progestogen therapy. To date, there is very little reliable information available about progesterone receptors in ovarian cancers generally, and nothing about endometrioid tumours in particular. Nevertheless, it might seem reasonable

to suggest that progestogens could be added with benefit to the total treatment regimes for women with endometrioid carcinomas.

Let us now look briefly at some of the rarer variants of the endometrioid tumour - the mixed Müllerian tumours of the ovary (Table 7). These again mimic the tumours of the same name in the uterine body and are found in three degrees of malignancy. The very rare Müllerian adenofibroma is a mixture of benign mesenchymal elements and benign epithelium; the Müllerian adenosarcoma has malignant mesenchyme and benign epithelium; and the least rare malignant mixed Müllerian tumour is composed of malignant mesenchyme and malignant epithelium. The last two categories may have sarcomatous elements of homologous type, i.e. of a tissue type that would normally be found in the uterus, or they may be of heterologous type, containing tissue that would not normally be found in the uterus, such as bone, cartilage and striated muscle. Malignant mixed Müllerian tumours of heterologous type used to be called mixed mesodermal tumours; the appearance of one example is show in Fig. 3. The glandular elements are of moderately differentiated carcinoma and the mesenchymal elements contain areas of endometrial stromal sarcoma, cartilage and striated muscle. These are highly malignant tumours. The most difficult and important histological problem is to distinguish them from immature teratomas, as the malignant mixed Müllerian tumour also contains several tissue types. Sometimes this distinction can be very difficult, but the diagnosis is aided by the features listed in Table 8. The ages of women with these two tumours is different, germ cell tumours generally affecting females in the first three or four decades of life whereas malignant mixed Müllerian tumours more usually occur in women over 50. While the malignant mixed Müllerian tumour is composed of tissue which is sarcomatous and carcinomatous, the teratoma is composed of immature, embryonic, not-yet-differentiated elements. The distinction between these two types of tissue may sound straigthforward enough in theory, but in practical terms it can be very difficult to tell embryonic from sarcomatous mesenchyme. More useful in practice, perhaps, is the fact that the hallmark of the immature teratoma is presence of immature neuroepithelial elements. These are often very distinctive, but are never seen in malignant mixed Müllerian tumours.

## Borderline Tumours

A few words about borderline tumours of the ovary would be appropriate, despite the fact that many would not consider them to be genuine cancers. The term borderline itself is not an altogether satisfactory one; although it is acceptable among pathologists, many gynaecologists interpret it as meaning that the pathologist is sitting on the fence and is not able to say whether the tumour is benign or malignant. The WHO classification of ovarian tumours (Serov et al. 1973) defines a borderline tumour of the ovary as one 'that has some, but not all, of the features of malignancy: those present include, in varying combinations, stratification of epithelial cells, apparent detachment of cellular clusters from their sites of origin and mitotic figures and nuclear abnormalities intermediate between those of clearly benign and unquestionably malignant tumours of a similar cell type: on the other hand, obvious invasion of the stroma is lacking'. This last feature is of the utmost importance in defining a tumour as borderline. The exclusion of invasion in the presence of epithelial atypia demands extensive and thorough sampling of the tumour, some of which, particularly those of the mucinous variety, can be very large.

Borderline tumours comprise between 8% and 15% of serous tumours of the ovary and about 20% of mucinous tumours (Ovarian Tumour Panel 1983). Examples of serous

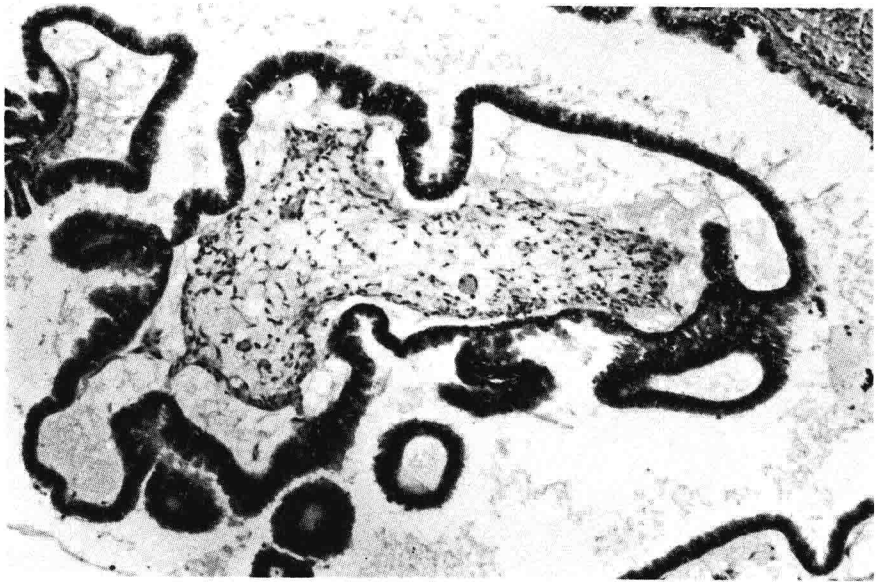


**Fig. 4.** Borderline serous tumour. The epithelium covering the papillae is thickened with multilayering, tufting and nuclear atypia. H and E, × 160

and mucinous borderline tumours are shown in Fig. 4 and 5. The situation is complicated by the fact that some of the tumours have extra-ovarian spread, with peritoneal deposits throughout the abdominal cavity. The deposits are usually superficial and may show the same borderline, non-invasive features as the ovarian primary tumour. In some examples, however, the extra-ovarian tumour may be of a worse histological grade than that found in the ovary. Borderline tumours of serous and mucinous types have been fairly fully described and extensively studies. However, borderline tumours of endometrioid and clear cell (mesonephroid) type and borderline Brenner tumours are sufficiently rare to remain rather obscure at present.

The reason for defining this intermediate group of ovarian epithelial tumours is that it does appear to represent a genuine subdivision which has a prognosis between that of the benign tumours and the frank carcinomas. Patients with serous borderline tumours have been reported to have a 5-year survival rate of 90%–95% (Tang et al. 1980) and a 10-year survival rate of 75%–90% (Nikrui 1981). Survival rates after 15 years have now been reported and these are in the 65%–75% range (Nikrui 1981). It is interesting to note that the mucinous borderline tumours have, on the whole, a rather poorer prognosis than the corresponding serous tumours. This is in contrast to the relative prognoses of the respective carcinomas, perhaps suggesting that some mucinous carcinomas may be erroneously diagnosed as borderline.

These results indicate that, even if energetic treatment is not justified immediately for borderline tumours, long-term follow-up must be maintained. Some would advocate that the therapy should be no less radical than for an unquestionably malignant tumour of the same stage (Ovarian Tumour Panel 1983). Nevertheless, borderline tumours present a number of dilemmas. Tumours of identical histological appearance and stage can behave in strikingly different ways, some apparently advancing very indolently, if at all, over many years, while others lead to the death of the patient in a short time. It may be that