UNCOMMON OVARIAN TUMOURS.

A Short Description of the Granulosa Cell Tumour, Brenner's Tumour, Disgerminoma and Arrhenoblastoma.

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A RECENT re-examination of all the ovarian tumours sent to the Department of Obstetrics and Gynæcology in the University of Edinburgh during the last ten years has shown that specimens of eight granulosa cell tumours, eight Brenner's tumours, and three disgerminoma have been received for investigation. Further examination of this material has prompted the writer to present a short description of these tumours, and a description of the arrhenoblastoma has been added in order to complete a group of four uncommon ovarian neoplasms which have aroused much interest in recent years. Advances in female endocrinology have directed special attention to the granulosa cell tumours and the arrhenoblastoma on account of their functional endocrine activity, and the interest aroused by these two tumours has extended to the Brenner's tumour, as it is believed by some investigators to be related to the granulosa cell tumour, and also to the disgerminoma, which is often found in association with abnormalities of sex differentiation.

Granulosa Cell Tumours.—The granulosa cell tumours were first described by von Kahlden [1] in 1895, when he referred to one such tumour as an "adenoma" of the Graafian follicle on account of the granulosa-like appearance of the cells and their arrangement into follicles. In 1914 von Werdt [2] suggested the designation "granulosa cell" tumour, and this has now been widely adopted. There have been many contributions to the literature on this subject in recent years and foremost amongst these are the publications of Novak and Brawner,[3] Novak and Gray,[4] and Pratt.[5]

Over one thousand ovarian tumours have been examined in this laboratory in the last ten years and the incidence of

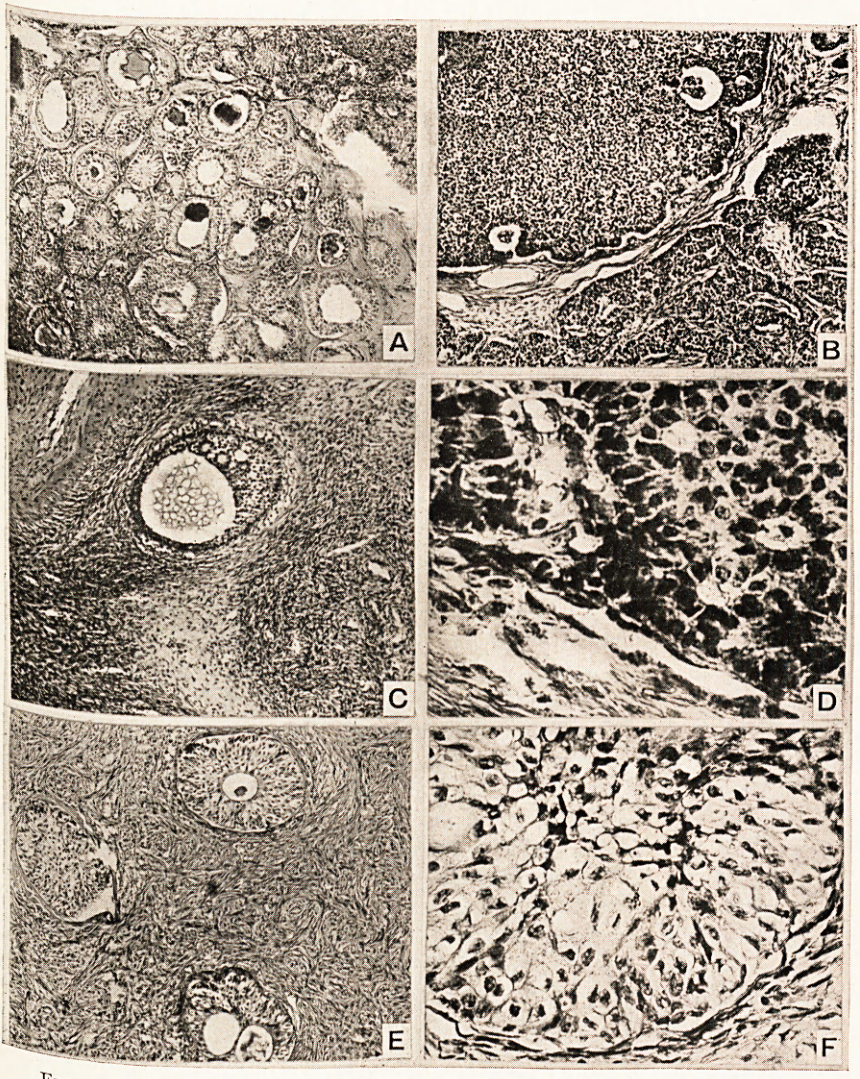

FIG. 1.—A, B, and D, Granulosa cell tumours. A, folliculoid type; B, solid alveolar and columnar type together. Note the compact margin and the hyalinised stroma. D, "Call-Exner" bodies. C, Graafian follicle showing "Call-Exner" bodies. E, Brenner's tumour showing typical islets of epithelial cells. F, Brenner's tumour, epithelial islet.

the granulosa cell tumour has been 0·7 per cent. The tumours may arise at any age from early infancy to old age, but they are most frequently encountered between the ages of forty and sixty years.

Pathology.—Granulosa cell tumours are, as a rule, unilateral; they grow slowly, rarely break the capsule, and do not tend to form metastases. The majority of tumours removed at operation are not much larger than an orange, because the symptoms cause early examination and diagnosis to be made. When small and solid the surface is smooth, but in the larger tumours lobulation and cystic degeneration produce irregularities. The smooth capsule is moderately thick, giving the tumour a bluish-white colour. In small tumours the capsule is thin and the growth may show a yellow tinge. The cut surface in small tumours is firm and pale with sometimes a yellowish or bright yellow colour. Large tumours generally show small and large cavities. Sometimes the tissue is soft and necrotic and much discoloured by interstitial hæmorrhage.

The histologic characters vary within very wide limits and it is rare to find a uniform microscopic picture. In typical growths the cells are small and polygonal and closely resemble the granulosa cells of a Graafian follicle. The nucleus is large and it stains well with basic stains. Segmentation figures are rarely seen. The cytoplasm of the cell body stains poorly and the cell membrane is rarely well defined. A considerable content of fatty granules in the cell can sometimes be demonstrated. This last feature characterises all those special ovarian tumours which are hormonally active. In atypical growths the cells are less well defined and they may bear little resemblance to granulosa cells.

A solid alveolar pattern characterises the arrangement of the cells, but this is greatly modified in different tumours. The cells may be arranged in a follicle-like pattern, in large and small masses or in long columns and cylinders. The separate masses of cells vary in size and shape and a notable feature of each cell mass is a uniform margin of short cubical cells placed radially in relation to the mass. An almost constant feature which greatly aids the diagnosis of the tissue is a small, rosette-like arrangement of the cells round a tiny eosin-staining hyaline mass which calls to mind the "Call-Exner" bodies found in the stratum granulosum of the rabbit's ovary and occasionally in the human ovary. The tumour may be roughly classified according to the predominant pattern assumed by the cells; this may be folliculoid, cylindromatous, or diffuse. These various patterns are frequently all represented in the one tumour. In the folliculoid type the cells are arranged round small and large cavities, thus forming "follicles" which resemble, somewhat remotely, the Graafian follicles of the ovary. In the cylindromatous type long

columns and cylinders of cells are separated from one another by dense trabeculæ of fibrous tissue which shows hyaline degeneration very frequently. Diffuse types occur in which neither "follicles" nor columns of cells are seen. In some of these the cells form large masses with a solid mosaic-structure or they may form into closely packed zig-zag cords. In other areas the cells appear to be mixed together at random, as in a sarcoma, and on this account it must be emphasised that in suspected tumours a thorough search will reveal, sooner or later, a transition from this atypical tissue to a tissue showing the characteristic features of the granulosa cell tumour. Although these tumours are sometimes classed with the ovarian carcinoma they rarely manifest themselves as malignant, clinically. Novak,[3] however, has stated that in one series which he examined he found 28 per cent. of the tumours malignant, but this figure is very high in the light of many other reports.

The granulosa cell tumours may give rise to symptoms related to their size and disposition in the pelvis, and also to such complications as degeneration, torsion of the pedicle, etc. In addition, the cells of this tumour apparently secrete an œstrogenic hormone which is responsible for a commonly associated endocrine syndrome. Overgrowth of the uterine muscle and hyperplasia of the endometrium take place and lead to irregular uterine hæmorrhage. Biological tests have shown that in the presence of a granulosa cell tumour there is a raised level of œstrogenic hormone in the blood and urine. This returns to normal after removal of the tumour. The endometrial hyperplasia, too, is proof of this abnormal œstrogenic activity.

In young children there is precocious appearance of the signs of puberty. Vaginal bleeding is intermittent and it often has the regularity of menstruation. Bodily growth is rapid and mental development is in advance of the years of the child affected. The breasts develop and pubic and axillary hair appears. These signs of maturity disappear almost completely after operation. In the sexually mature woman characteristic symptoms are masked by the normal physical development and functional activity. Menstrual disturbances such as amenorrhœa, menorrhagia and metrorrhagia are caused by the tumour, but such symptoms, at this age, have not the special significance they possess when present before puberty. With removal of the tumour the normal menstrual cycle is resumed, and in some cases pregnancy has

been known to occur. In the post-menopausal woman the tumour produces recurrent uterine bleeding and occasionally a somewhat significant enlargement of the breasts.

This description of the granulosa cell tumours would be incomplete without a reference to a small group of lipoid-containing ovarian tumours in which are found lutein-like cells, and which are classed apart from the granulosa cell tumours by some investigators, notably Loeffler and Priessel [6] and Melnick and Kanter.[7] However, Novak [3] and Schiller [8] include these in the granulosa cell group, basing their opinion on the work of Fischel [9] and Politzer [10] on the early development of the ovary. According to Fischel the granulosa cells and the theca cells of the ovary are developed, not from the germinal epithelium of the ovary, but from the primitive mesenchymal stroma of the ovary. If this theory of the dual potentiality of the mesenchyme is accepted then it can be readily understood that " rests " of this tissue, left over from the early developmental stage, may, at any time, give rise to tumours which will show one or more of the characters of the different tissues found in the mature ovary. According to the degree of differentiation which takes place in the tumour tissue the tumour may be composed of undifferentiated stroma or sarcoma-like tissue, or it may contain the more differentiated granulosa cells, or even lutein-like cells.

Brenner's Tumour.—In 1907 Brenner [11] described this tumour and incorrectly labelled it " oophoroma folliculare." Fothergill and Donald [12] had published a full report of such a tumour about four years previously, but it is by Brenner's name that it is universally known.

The incidence of the tumour in our series of ovarian tumours is about 0·7 per cent., which is the same as for the granulosa cell tumour. It is generally found in elderly women, but when it occurs in the wall of a pseudomucinous cyst, as occasionally happens, it may be found earlier.

Pathology.—As a rule the tumours are small; some are found as tiny nodules in the wall of an ovarian cystadenoma, while others form large fibromata. The cut surface is hard and white and feels very fibrous to the touch. The mass of the tumour is generally composed of dense cellular and avascular fibrous tissue. The stroma is somewhat similar to the ovarian stroma, but it shows a tendency to hyaline degeneration. Sprinkled throughout the stroma are small oval or round epithelial islets which, by a condensation of the stroma

cells into two or three concentrically arranged layers round their periphery, are thrown into strong relief. The cells of the epithelial masses are large and polygonal, except towards the edge of each mass where they are oval or even spindle-shaped. The longitudinal axis of the peripheral cells seems to be directed to the centre of each mass. The nucleus of the epithelial cells is small. The cell body stains poorly but the nucleus stains strongly with the basic dyes. Many of the epithelial islets acquire a superficial resemblance to the Graafian follicles through the formation of small central or eccentric cavities. These cavities contain a homogeneous colloid or mucoid-like substance which stains faintly pink with eosin. These central " droplets " were at one time thought to be ova, but it is now known that they arise from liquefaction of, or secretion from, the epithelial cells. The cells lining the central cavity are sometimes columnar with basal nuclei, and it appears that this differentiation is due to a pseudomucinous metaplasia. Areas of calcification are frequently found in the stroma.

The Brenner's tumour is not biologically active and therefore it does not give rise to any special symptoms from which a clinical diagnosis of the tumour type can be made.

Disgerminoma.—The disgerminoma of the ovary closely resembles the seminoma of the testicle, and some French writers actually refer to the ovarian tumour by this name. Other designations are sometimes used, such as embryonal carcinoma and big-celled solid carcinoma, but Robert Meyer's [13] original term, disgerminoma, has received the widest recognition.

This tumour is found less frequently than the granulosa cell tumour and, consequently, in any series of ovarian tumours it is a rarity. In our series of ovarian tumours it has only been found three times. Compared to the granulosa cell tumour it is found at an earlier age, occurring most frequently in the second and third decades. As a rule the tumours are unilateral, but exceptions to this rule are not unknown.

Pathology.—The size of the tumour is variable, but the majority are large and sometimes they may fill the pelvic cavity and even pass up into the abdominal cavity. Traces of the ovary may be found in small tumours, but in the large ones the ovarian tissue is completely lost. They are solid tumours and greyish white and are of a rubbery consistence. They may assume any shape, but frequently they are lobulated and not unlike the Krukenberg tumours. Local infiltration may occur when the tumour is of long standing. Degeneration is not common, but a certain amount of interstitial hæmorrhage

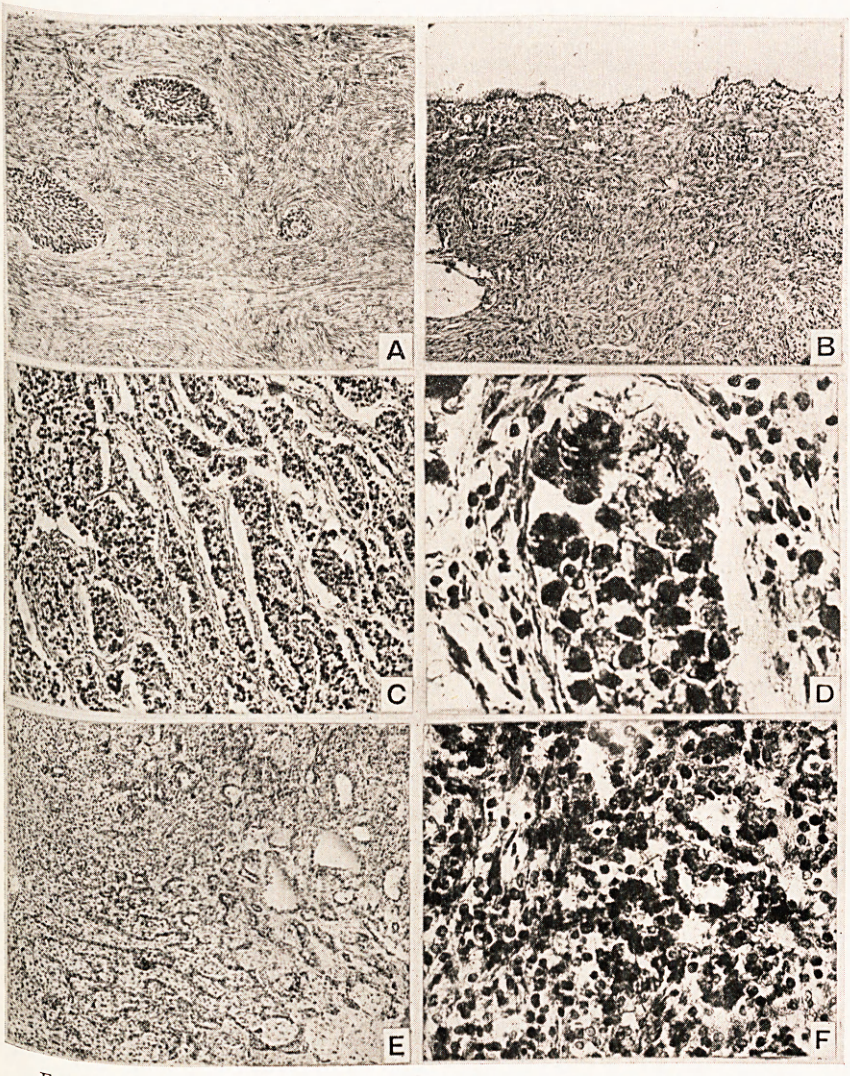

FIG. 2.—A, Brenner's tumour showing spindle-type epithelial cells composing islets. B, Brenner's tumour in wall of pseudomucinous cyst. C and D, Disgerminoma. D, showing the lymphocytes in the fibrous septæ. E and F, Arrhenoblastoma showing the solid epithelial cords and the ducts.

and some fatty degeneration are not uncommonly seen on the cut surface. Novak[14] holds that a streaky yellow discoloration is frequently present.

The cell type and architecture present unmistakable characteristics, and it is well to note that deviations from the typical structure are rarely seen. Large epithelial cells are arranged in large and small clusters, or, occasionally, in columns or strands. Between the clumps of cells wind thin and thick trabeculæ of fibrous tissue which is frequently seen to be undergoing hyaline degeneration. The fibrous septæ are always infiltrated with lymphocytes, as in the seminoma, and the presence of these lymphocytes in this distribution is a most important diagnostic feature. The large epithelial cells are about twice the size of a red blood cell, and with a thin cytoplasm, shrunken and broken cell membrane, and large dark-staining nucleus they present a very striking appearance. Mitotic figures are found fairly frequently. Throughout the tumour small areas of degeneration and interstitial hæmorrhage are seen, but large liquefaction-cavities are uncommon. In some of the areas where degeneration has commenced giant cells may be found, and their presence is sometimes explained by the presence of fatty changes in the degenerated area. Although the histologic picture suggests malignancy only 10 per cent. of the tumours ever manifest clinical signs of malignancy. Sometimes the epithelial cells are massed together, having lost their alveolar arrangement and much of the fibrous tissue stroma. In such tumours the cells are smaller than in the less malignant forms and numerous mitotic figures are seen. Here, too, the vessels are more numerous and interstitial hæmorrhages are common.

In hermaphrodites and in pseudohermaphrodites and also in certain types of women showing sexual infantilism, the disgerminoma is more frequently found than in women who are normally developed. At one time it was thought that the sexual anomalies which may accompany the tumour were due to the tumour, but that is not the case, as the sexual abnormalities must arise at a stage when the tumour has not even started to grow. The tumour may appear in apparently normal women who may at one time have borne children, or, as is reported, may even be pregnant when the tumour is diagnosed. The tumour has no capacity for hormone production and therefore it does not affect the menstrual cycle; it does not, in fact, produce any specific symptoms. It grows quickly and, by its increasing size, may cause all those symptoms associated with a large tumour. It is one of the few large tumours which appear in young women or adolescents, and as it is not

responsible for any disturbance in the endocrine glands, and as it does not produce the symptoms of a quickly growing malignant tumour, its particular nature may be fairly certainly diagnosed before operation.

Arrhenoblastoma. — This type of tumour was first recognised by Pick, who, in 1905, described such a tumour as a "testicular adenoma." Pick's [15] tumour was just one of a fairly large variety of ovarian growths which produce defeminisation and masculinisation. The arrhenoblastoma therefore stand out in great contrast to the granulosa tumours which, possessing œstrogenic activity, might be described as "feminising" tumours.

In a recent paper Novak [16] reported that he had been able to collect from his own records and from the world literature only fifty-one cases, so that it is apparent the tumour is a rare one. We have never encountered one of these tumours. Like the disgerminoma they occur most frequently in young women. Kleine,[17] however, has reported four cases all over the age of fifty years. On account of the striking symptoms which they produce the tumours are seldom allowed to grow very large.

Pathology.—The tumours form solid growths and they are almost invariably unilateral. If they attain a large size degenerative cystic cavities may develop, due to necroses and interstitial hæmorrhages. Meyer [18] divides all the arrhenoblastoma into three sub-groups according to their histologic structure, but in reality these groups form a continuous series of tumours varying from a well-differentiated glandular type which closely resembles testicular tissue to a solid, highly undifferentiated type which is sometimes difficult to distinguish from sarcoma. The pure tubular form, as described by Gnassi [19] is rare. The commoner types show a stroma of variable density in which are formed both complete and incomplete ducts and also solid columns of roughly spheroidal cells which are distributed at random throughout the stroma. Occasionally small collections of cells resembling the interstitial cells of the testicle are seen. It is possible that these are not representative of a specific element in the testicle but are merely macrophages. In view of the microscopic structure of the arrhenoblastoma it is surprising that very few of them are malignant.

Although cases are recorded in which no specific symptoms were produced, the tumour generally produces great disturbance of the sex characters. Defeminisation followed by positive masculinisation occurs. The more undifferentiated the tumour, the greater is its capacity for masculinisation. At first

amenorrhœa develops, the breasts decrease in size and subcutaneous fat disappears, so removing the typical female body contours. Later the voice loses its feminine character and becomes deep and even hoarse, the clitoris enlarges and hirsutism to a very marked degree develops. When the tumour is removed there is reversion to the original female type, except for the voice, which may remain low, and the overgrown clitoris, which seldom regresses. The abnormal hair on the face, body, and limbs may never quite disappear. The menstrual function assumes once more a normal rhythm and in some cases conception is known to have taken place. In a typical case the diagnosis is based on the presence of the tumour and the associated changes in the sex characters. Somewhat similar symptoms may be produced by an adrenal cortical tumour, and this must be kept in mind. At present, hormone analysis of the urine yields little information which would aid the differential diagnosis in either of these cases.

The **treatment** of all these tumours is, of course, surgical. The tumour is always removed and, generally, with it, the tube of the same side. When it is remembered, however, that a tumour may be not one of this relatively benign group but one of the primary ovarian carcinoma which are in all respects malignant, a more radical operation might be contemplated. If in a young woman the pre-operative diagnosis points to one of the four special tumours mentioned above, and if there are no accompanying signs or symptoms of malignant disease, the restricted operation should be performed. Subsequent pathological examination and diagnosis will be made, and if the clinical diagnosis is confirmed, no further treatment is necessary. If, however, the tumour is proved to be a primary carcinoma further surgical treatment is indicated. In an older woman a solid ovarian tumour may be one of this group or, more likely, a primary or secondary carcinoma, therefore it is neither necessary nor desirable to consider conservative measures, and radical removal of the tumour, uterus, and the opposite ovary should be carried out.

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