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SPECIAL ARTICLE

The Unusual in Tumour Pathology

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IT is no mere formality when I say that I feel a peculiar privilege—and a peculiar responsibility—in delivering a John Whittick Memorial Lecture. Not only was John my first assistant, and later my successor, as pathologist to the Royal Cancer Hospital in London, but he and his wife at once became, and ever after remained, close friends of my wife and myself.

When John and I were at the Cancer Hospital from 1947 to 1950, we collaborated closely, studying together all our necropsy and surgical material, discussing and sharing with each other our investigations of cases of special interest, and exchanging ideas arising out of our reading —a perfect partnership. I still have duplicate records of some hundreds of specimens that John and I studied together then; and, after I left the Cancer Hospital to go to Leeds, and again after John left London to come to Regina, he continued to send me material from unusual and problematical cases.

John Whittick's work in pathology, especially the histopathology of rare tumours, was to him a hobby as well as a profession, and it was carried out with quiet zest and meticulous thoroughness. To cases or problems that excited his interest—and these were many and diverse —he devoted endless patience in preparing and examining sections stained by many methods, and in reading relevant material. Because of his intellectual honesty, perfectionist standards and over-modesty, he was not a prolific writer. His few published papers give a very inadequate idea of the range and value of his research work. Besides the subjects of those papers, his unpublished researches, of many of which I have records, included the following: the histogenetic kinship of the various named tumours of lymphoid tissue; the simulation of Hodgkin's disease by torulosis of lymph glands; the association of this disease with lipo-melanic lymphadenopathy; hemangiosarcoma; so-called "lymphangiosarcoma" of the arm following post-mastectomy edema; embryonic rhabdomyosarcoma of the uterus; the rarer kinds of ovarian tumours; and the so-called "adamantinoma" of the tibia. I have purposely chosen as title for this lecture "The Unusual in Tumour Pathology", because it best embraces John Whittick's principal research interests. I shall discuss several groups of unusual tumours which I know were of particular interest to him; and several of the specimens which I shall describe were ones which he himself studied. All the specimens are filed in the Tumour Reference Collection of the Imperial Cancer Research Fund, London, England.

The John Whittick Memorial Lecture presented at the Twelfth Annual Cancer Symposium of the Allan Blair Memorial Clinic, Regina, Sask., May 1967.

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OVARIAN TUMOURS

A Composite Granulosa-theca-cell and Cystadenomatous Tumour

The first group of unusual tumours which I shall present are those of the ovary; and I introduce the subject by a specimen which John Whittick sent me from the Regina Grey Nuns Hospital in 1957.

CASE 1.—This was a 78-year-old woman, who had had a bloody uterine discharge on and off for four years, and from whom a huge cystic tumour weighing 19½ pounds was removed from the left ovary. Microscopically (Figs. 1 to 3), this shows a mixture of granulosa-cell, theca-cell and luteal-cell growth, along with many spaces lined by tall mucus-secreting epithelium, resembling that of a pseudomucinous tumour, and possibly ciliated in places. The widespread presence of this epithelium in nearly all parts of the very large tumour, and its relationships to the granulosa-theca-cell components, show that it is an intrinsic part of the tumour, a variant of the neoplastic parenchyma itself, and not just a coincidentally present cystadenomatous element. Thorough search of sections from many different parts of the tumour failed to find any other kinds of tissue; and this fact, along with the abundant granulosa-theca-cell tissue, discounts the idea that the growth might be teratomatous. Uterine curettings from this patient showed well-marked endometrial hyperplasia with early squamous metaplasia of the glands, indicating that the ovarian tumour had been secreting on excess of estrogens.

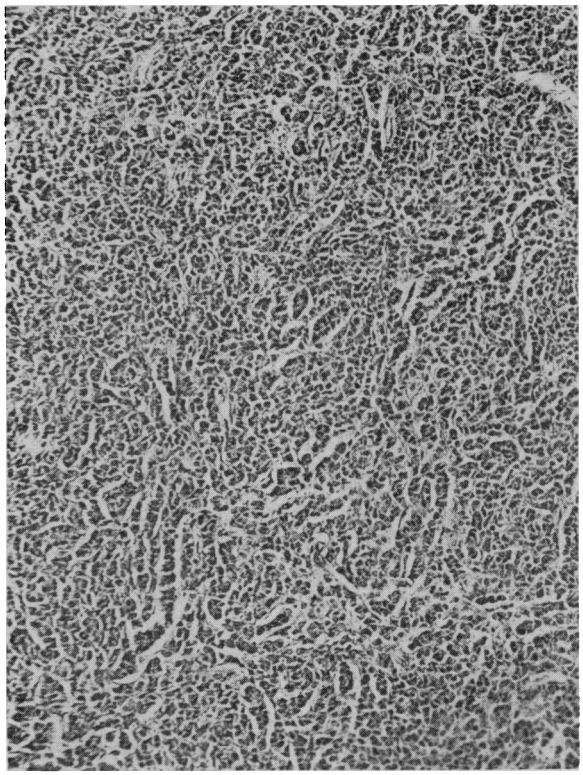

Fig. 1.—Case 1. Ovarian tumour; granulosa-cell area. (× 120.)

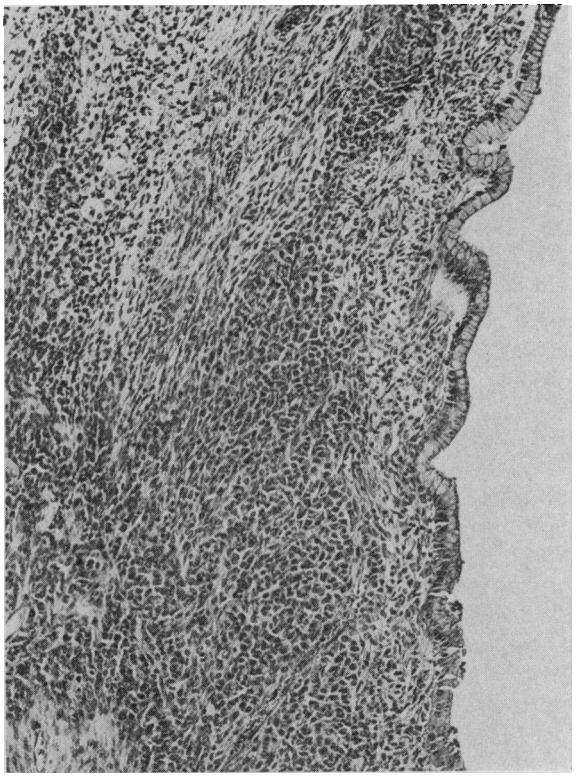

Fig. 2.—Case 1. Mucous columnar epithelium along with granulosa-theca-cell tissue. (× 120.)

Here, then, we have a tumour which consists of histologically typical, hormonally active granulosa-theca-cell tissue, along with well-differentiated mucous epithelium resembling that of a pseudomucinous tumour. This growth thus strikingly exemplifies an important general principle in ovarian pathology, namely, that tumours of ovarian parenchymal or follicular origin are capable of divergent differentiation in other and unexpected directions—a principle which is too often overlooked in our pigeon-holing taxonomy and nomenclature.

Masculinizing Tumours

I turn now to another class of ovarian tumours which illustrate the same principle, namely, the masculinizing tumours. From the time Meyer coined the name "arrhenoblastoma", understanding of this class has been bedevilled by the erroneous assumption, openly affirmed or implied, that androgen-producing tumours must contain male elements, an assumption embodied not only in Meyer's name "arrhenoblastoma", but also in a number of subsequently invented neologisms, e.g. "androblastoma", "gynandroblastoma" and "masculinovoblastoma". These confusing and histologically meaningless words, and the imaginative speculations accompanying

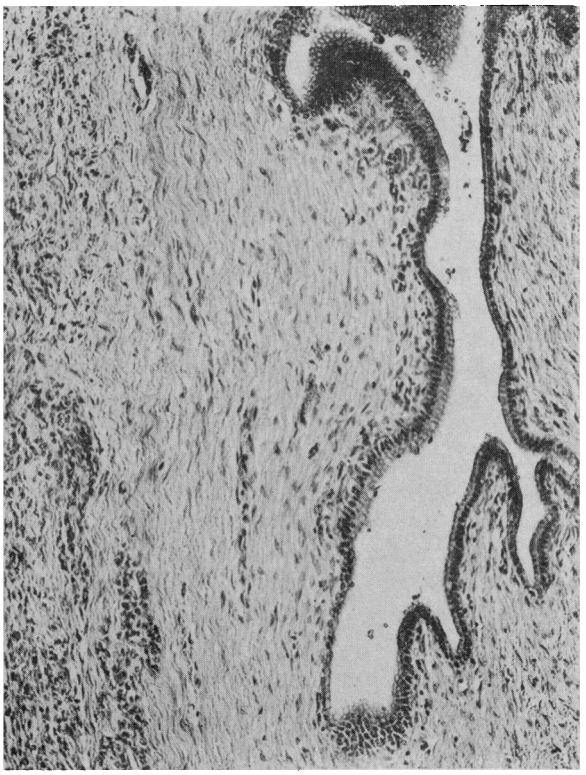

Fig. 3.—Case 1. Cavity lined by columnar epithelium. (× 120.)

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them, could have been avoided, for in 1943 Harold Burrows[6] (then on the research staff at the Royal Cancer Hospital, London) pointed out their fallacy. He said: "It is a gross mistake to suppose that because a tumour produces androgen it therefore should have an architecture like that of the testicle. In the male, androgens are derived from the interstitial glandular cells of the testicle, which have no tubular or strand-like arrangement. . . . Some ovarian tumours which induce hirsutes and other masculine phenomena are the colour of corpora lutea and are composed of cells which resemble those of luteal tissue, others might be described from their cytological appearance as thecomas, or as granulosa-cell tumours, and yet others look like tumours derived from adrenal tissue." I am sure that Burrows was right in insisting that the masculinizing tumours of the ovary do *not* contain any testicular or male tissues, and that the feminine tissues of the ovary itself are the source of the great majority of such tumours. To the list of the kinds of these tumours which Burrows indicated, we must now add the more recently identified hilar-cell tumours, a discovery which he would have greatly appreciated as a further vindication of his views. The following kinds of masculinizing ovarian tumours can now be distinguished:

(i) *Tumours of the granulosa-theca-cell class.*—John Whittick and I together examined many granulosa-cell tumours when we were at the Cancer Hospital, including several masculinizing tumours with a characteristic trabecular or retiform structure and in one case with pronounced luteinization of the granulosa cells. Several other specimens that I have since examined have also contained granulosa-theca-cell tissue; and a number of others who have described such tumours as "arrhenoblastomas" have commented on the presence of granulosa-like or theca-like areas in their tumours. My own experience and my reading lead me to believe that the majority of masculinizing tumours of the ovary, especially those of retiform, trabecular, pseudotubular or diffuse structure, belong to the granulosa-theca class. Estrogens and androgens are closely related chemically and easily interconvertible, and androgenic activity in tumours of this class may well be due to perverted chemistry in a primarily estrogenic tissue.

(ii) *Hilar-cell tumours.*—We now know that some masculinizing tumours consist entirely of hilar cells, like those of the ovarian hilum, the homologues of the Leydig cells of the testis. The tumours are usually small, benign, well-defined

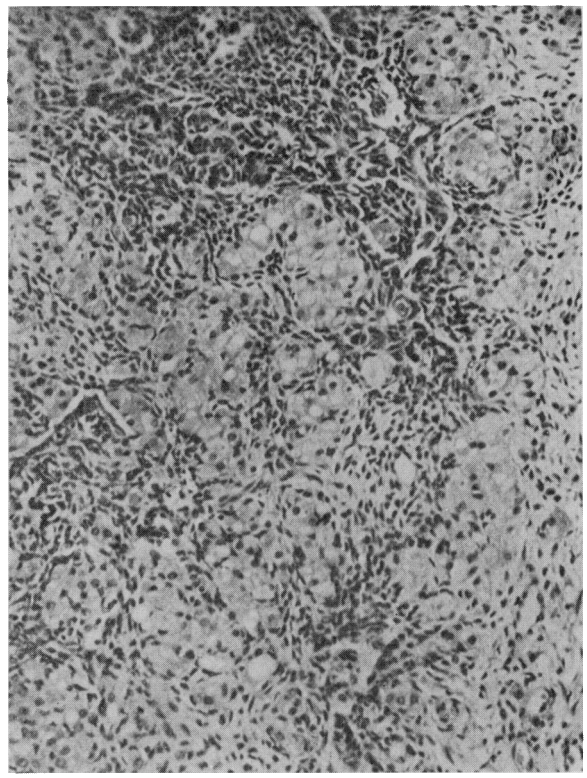

Fig. 4.—Case 2. Masculinizing tumour; plentiful granular and vacuolated cells, probably hilar cells, in a granulosa and theca-cell tumour. (× 150.)

growths, some of them situated in the ovarian hilum, brown or yellow in colour, and composed of solid or foamy polyhedral cells, resembling liver cells, containing lipoid material, brownish pigment, and sometimes eosinophilic droplets or spherules. Lipoid-laden hilar cells may be difficult to distinguish from luteal cells.

(iii) *Tumours containing both granulosa-theca and hilar cells.*—Tumours in this subgroup are not uncommon but are infrequently recognized. Several of the masculinizing tumours, and one non-masculinizing one, which I have examined contained both well-differentiated granulosa-like epithelium and interstitial groups of eosinophilic polyhedral liver-like cells resembling normal hilar cels. Two of these cases were as follows:

CASE 2.—(T.R.C. 2443.*) A 48-year-old woman, whose menses had ceased abruptly six years previously, complained that for six months she had lost hair from the temples, had had to shave her face daily, had noticed a change in her voice, and had had lower abdominal discomfort. Examination showed a pelvic tumour and normal external genitalia. No hormone estimations were carried out. A right-sided ovarian tumour was removed surgically.

*Refers to the number in the Tumour Reference Collection of the Imperial Cancer Research Fund, London, England.

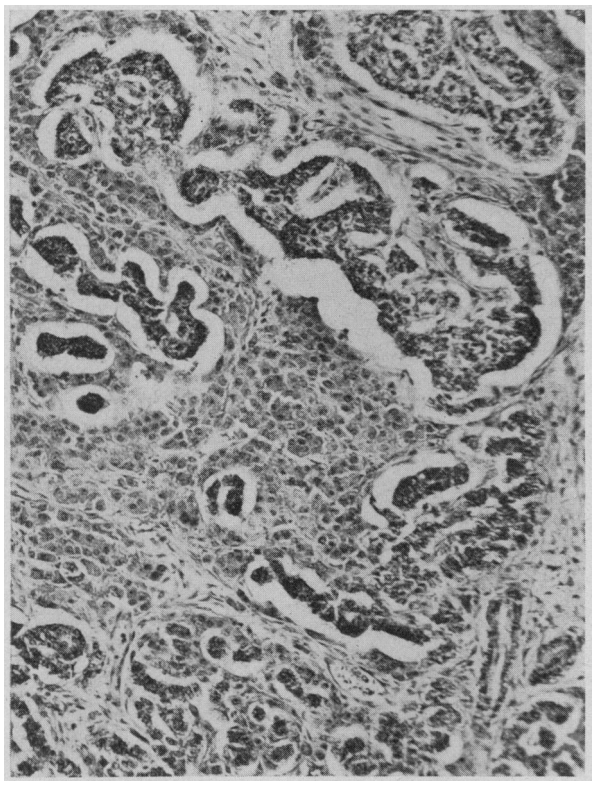

Fig. 5.—Case 3. Combined granulosa and hilar-cell tumour. (× 120.)

This was 9 cm. in diameter with an intact serous coat, its substance firm, yellow-orange and finely lobulated. Microscopically (Fig. 4), some areas show typical granulosa-like epithelium, others spindle-cell growth merging into fibrous areas, with transitions between the epithelial and thecomatous tissue in many parts. The epithelial component shows a distinct tubular structure in parts. A noteworthy feature is the presence of clusters of polyhedral liver-like cells, almost certainly hilar cells, some of them with foamy or granular cytoplasm. Sudan-staining shows plentiful fine fatty droplets in the spindle cells and coarser droplets in the presumed hilar cells. The tumour is thus very probably a combined one, containing both granulosa-theca cells and hilar cells. Even if we assume that the supposed hilar cells are really luteal cells, we still have a tumour of the granulosa-theca-cell class which has evidently secreted androgens and not estrogens.

CASE 3.—(T.R.C. 2442.) A 65-year-old woman complained of uterine bleeding of three months' duration. A cervical polypus had been removed 10 months previously. The patient was obese, but showed no other signs of any endocrine abnormality. The uterus was palpably enlarged, and hysterectomy along with removal of the enlarged ovaries was carried out, the right ovary containing a tumour 3 by 2 by 2 cm., the left measuring 2 by 2 cm. but not containing any tumour. The uterus (345 g.) contained multiple myomas and an irregular endometrial polypus 4 cm. in diameter attached to the fundus. Microscopically (Fig. 5), the ovarian tumour shows typical compact granulosa-epithelial clumps and trabeculae, interspersed between which are plentiful polyhedral liver-like cells identical in appearance with hilar cells. The left ovary shows marked theca-cell proliferation. The endometrial polypus is a benign but active one, and the rest of the endometrium, like the polypus, shows hyperplastic changes suggestive of hyperestrinism. The endometrio-myometrial zone is actively proliferating, as in a functional premenopausal uterus.

In this case, then, a relatively small ovarian tumour, composed of a mixture of well-differentiated granulosa and hilar cells, is accompanied by structural evidence that it had been secreting an excess of estrogens but not a significant amount of androgens. Needless to say, thorough hormonal studies of cases of this kind are desirable.

In tumours like those just described, containing both hilar and granulosa-theca cells, it is not necessary to suppose that their hilar-cell component has necessarily come from pre-existing hilar cells; as Hughesdon[16] has insisted, a tumour of the ovarian parenchyma may well be able to differentiate these cells as well as follicular cells. Salm[30] has made a valuable study of hilar-cell and combined hilar and granulosa-theca-cell tumours, including those of Cases 2 and 3.

(iv) *Tumours containing heterologous ("teratoid") tissues.*—Several reports[17] of masculinizing tumours have noted the presence of mucus-secreting epithelium, cartilage, or smooth or striated muscle, along with more usual components; and some have supposed these to denote that the tumours were of "teratoid" nature. As Case 1 indicates, however, mucous epithelium can differentiate in otherwise straightforward granulosa-theca-cell growths; and, since metaplastic ovarian tissues often produce endometrium, and since this endometrium is the source of some carcinomas and endometrial mixed tumours of the ovary and since endometrial mixed tumours can produce cartilage and smooth and striated muscle, we need not be surprised that some tumours of the ovarian parenchyma should differentiate similar heterologous tissues along with the more usual follicular derivatives.

(v) *Adrenal cortical tumours.*—These must be briefly mentioned here to complete the list of masculinizing tumours. It is well known that accessory nodules of adrenal cortex occur in the mesovarium, but rarely or never in the ovary itself. A few unequivocal cases of tumours arising

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from this tissue have been recorded. When such a tumour has attained a large size, its exact relationship to the ovary may be difficult to determine and it may readily be regarded as an ovarian tumour. Histologically also, it can be difficult to distinguish this tumour from a lipoid-rich hilar-cell tumour or from a luteoma—a highly luteinized ovarian-follicular tumour. The excessive secretion of 17-ketosteroids will help to make the distinction.

Conclusion

Except for the very rare ectopic adrenal tumour which we have just noted, all of the masculinizing tumours of the ovary arise from the ovarian tissues themselves and are histogenetically akin, despite their very variable structure. None of them arises from or contains any male tissues; and the histogenetically meaningless names "arrhenoblastoma", "gynandroblastoma", "androblastoma", "masculinovoblastoma" and "gonadoblastoma", perpetuating erroneous ideas of "maleness" of the tumours, should be discarded.

Endometrial Tumours of the Ovary

The frequent occurrence of endometriosis of the ovary prepares us for the now well-documented fact that endometrial tumours occur in this organ. A number of reports have been published[7, 8, 21, 32, 36] of adenocarcinomas and adenoacanthomas of endometrial type, some of which have had their origin in endometrial cysts in the ovary. In some of these cases, similar uterine tumours have accompanied the ovarian ones; and the question has arisen whether metastasis has occurred from one organ to the other, or whether both the ovarian and uterine growths were due to concomitant neoplasia in similar tissue in the two sites. While metastasis of uterine tumours to the ovaries and vice versa certainly occurs, multifocal tumour formation appears to be the more probable interpretation of some instances of coexisting uterine and ovarian carcinomas of endometrial type.

Since endometrial carcinomas occur in the ovary, the occasional endometrial mixed tumour might be expected to occur in this location. I am sure that such tumours do indeed occur. I have studied several ovarian tumours in which both epithelial and rhabdomyoblastic or chondrosarcomatous components, exactly like those of the uterine mixed tumours, have been present (T.R.C. 347 and 2171). Katsunuma, Hirsch and Veenbaas[20] have also reported a case.

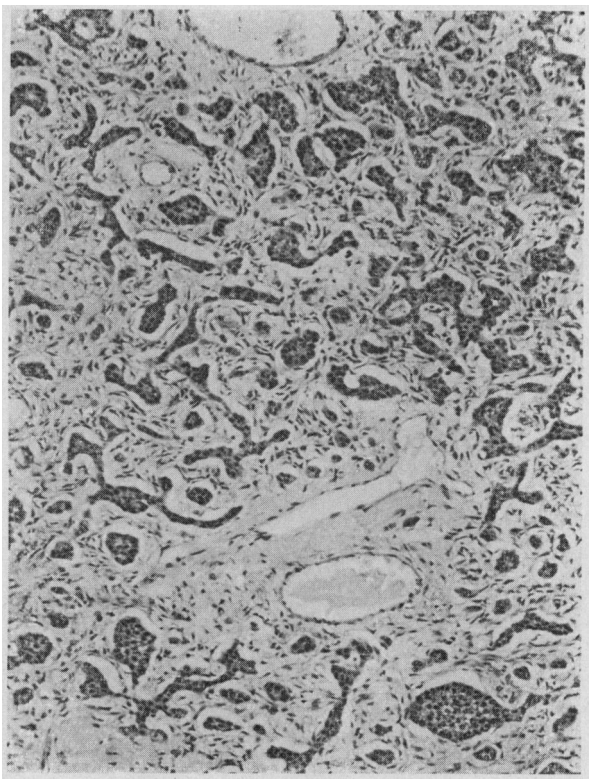

Fig. 6.—Case 4. Secondary argentaffin carcinoma of ovary. (× 120.)

Argentaffin Carcinoma of the Ovary

This rare tumour occurs in two forms, primary and secondary.

(i) The *primary* form arises in an ovarian teratoma.[3, 11, 12, 14, 23, 33] Sometimes the growth demonstrably originates from the epithelium lining a cyst in the teratoma, as in the second case of Stewart, Willis and de Saram,[33] depicted also in my "Pathology of Tumours".[38]

(ii) A *secondary* growth, metastatic from a primary argentaffin carcinoma in the alimentary tract, is occasionally seen, as in the following remarkable instance reported by Quinn.[27]

CASE 4.—(T.R.C. 2394.) A large right ovarian tumour, along with the uterus, tubes and left ovary, was removed from a 61-year-old woman. The right ovary was replaced by a solid yellow mass 9 cm. in diameter; the right tube and parts of the myometrium were infiltrated by similar growth; and the left ovary contained a small nodule of yellow growth. The left tube was normal. Microscopically (Fig. 6), the entire tumour was an argentaffin carcinoma, with no sign of teratoma in the many blocks that were examined. Three months later, a mass was palpable in the right iliac fossa. At operation the terminal ileum, cecum and ascending colon were removed. The cecum contained a mass of argentaffin carcinoma with large metastases in the ileocecal lymph glands. There was no clinical or biochemical evidence of "carcinoid syndrome".

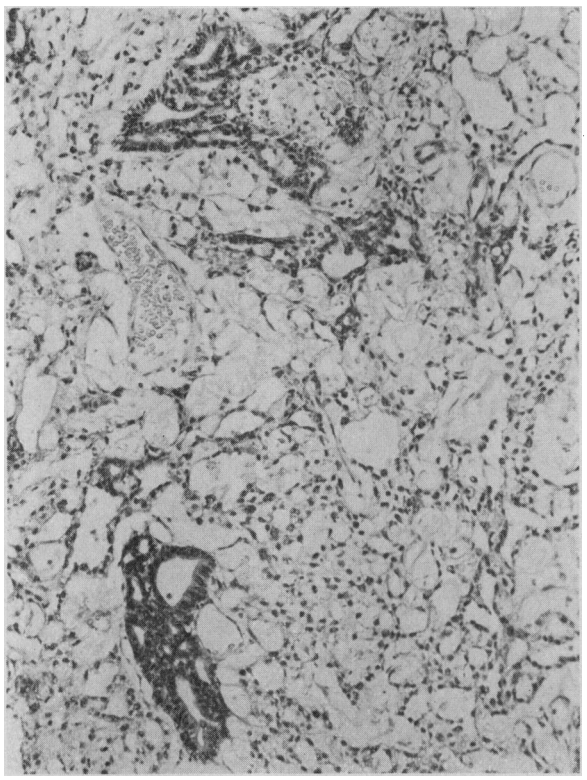

Fig. 7.—Ovarian tumour, weighing 365 g., removed surgically from a 12-year-old girl; fatal abdominal recurrence seven months later. (× 120.)

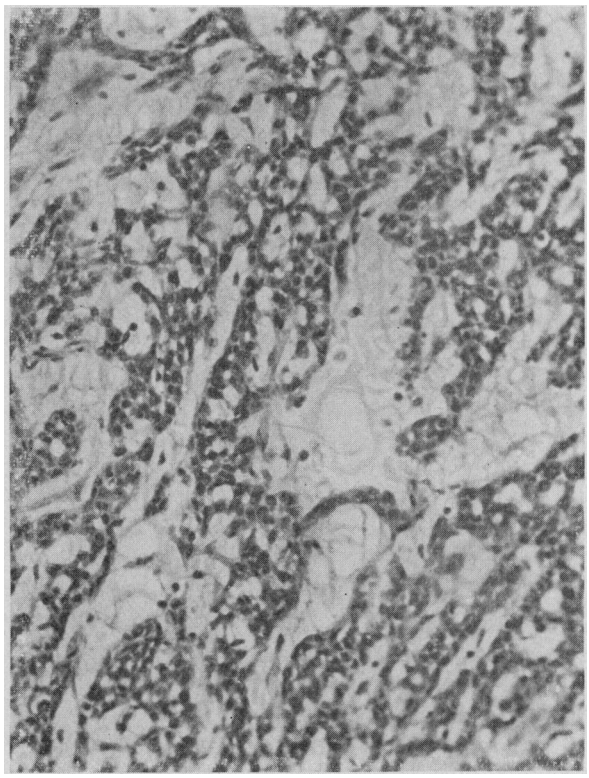

Fig. 8.—Case 5. Parovarian granulosa-cell tumour. (× 200.)

A Distinctive Ovarian Tumour of Young Subjects

An unusual kind of ovarian tumour occurs in children and young adults, mainly in the second decade. It is a bulky, soft, solid growth, unaccompanied by endocrine disturbances. Microscopically it shows diffuse sheets, networks, papillary and tubular formations of vacuolated glycogen-rich cells (Fig. 7). At first included by Schiller with his "mesonephromas", this kind of tumour was later separated as "embryonal carcinoma" by Neubecker and Breen[25] and as a "germinal tumor" by Huntington *et al.*,[18] who thought that it was identical with the histologically somewhat similar-looking tumours of the infant's testis. I have examined five of these tumours and have failed to find any evidence that they are teratomatous, and I doubt their supposed homology with the infant testicular tumours, from which they not only differ structurally in some respects but also in their age incidence—the testicular tumours occurring in very young infants, and the ovarian ones in older children or adolescents. Further careful studies of these ovarian tumours are needed, unprejudiced by previous speculations about them.

Ovarian Tumours in Extraovarian Situations

Primary granulosa-cell tumours of the broad ligament or other pelvic sites unconnected with the ovary are not rare. In "Pathology of Tumours"[38] I have depicted a typical example from the broad ligament of a 56-year-old woman and have referred to other reported cases. The following is another instance:

CASE 5.—(T.R.C. 420.) A 39-year-old woman had had pelvic discomfort for several months. At operation a large left-sided cystic parovarian tumour, unattached to the ovary, was removed. This was 8 cm. in diameter, with shaggy solid areas of growth in the wall of a single cystic cavity. Microscopically (Fig. 8), this is a typical granulosa-cell tumour of retiform pattern. The patient had had no menstrual disturbances.

Most extraovarian granulosa-cell tumours are in the broad ligament, but in rare cases they occupy other sites. I have seen one tumour which extensively involved the uterine wall (T.R.C. 2186), and another which was attached to the posterior pelvic peritoneum just below the aortic bifurcation. The precise histogenesis of such tumours is uncertain; as far as I know, accessory ovarian tissue has not been seen in the broad ligament or retroperitoneal area, and

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it is possible that the tumours may arise, not from pre-existing already differentiated ovarian tissue, but from plastic juxta-genital mesoderm with ovary-formative potentialities—analogous to the metaplastic formation of extrauterine endometrium from the ovary or peritoneum.

The occurrence of granulosa-cell tumours in extra-ovarian sites raises the possibility that other kinds of ovarian tumours may sometimes also occur in these sites. I do not know of any reports of extra-ovarian thecomas, hilar-cell tumours, Brenner tumours or dysgerminomas; but the possibility should certainly be borne in mind.

UTERINE AND TUBAL TUMOURS

Embryonic Tumours of the Uterus

The embryonic botryoid sarcomas of the urogenital organs in young children greatly interested John Whittick; and at the Royal Cancer Hospital in 1949 he made a particularly thorough necropsy study of the following unusual example (which I have briefly recorded in my book on the tumours of children,[39] p. 68):

CASE 6.—(T.R.C. 553.) Vaginal bleeding occurring when the child was 3 years old was found to be due to a bulky, smoothly polypoidal tumour filling the vagina. She was given a full course of deep x-ray treatment; but this had little effect on the tumour, and she died just over a year later. The necropsy report was as follows (I quote from John Whittick's original report): "The growth, which is uniformly soft and white, except for much superficial necrosis and greenish-brown discolouration, is attached to the posterior vaginal and lower uterine wall (attachment 8.0 cm. long) and projects forward (4.8 cm. thick; 5.0 cm. transversely). The cervix has been destroyed; so that the junction of vagina and uterus is not recognizable. The upper margin of the tumour is more obviously polypoid and almost completely fills the cavity of the body of the uterus, but it has no attachment here. From the tumour base there is no infiltration of the rectal wall nor of the pelvic connective tissue. . . . The peritoneal cavity contains about 1 oz. of clear straw-coloured fluid. There are no peritoneal secondary growths; but attached to the diaphragm on the right side anteriorly is a smooth-surfaced disc (4.0 x 3.4 x 1.0 cm. thick) of firm greyish-white tissue attached by a short fine pedicle (0.4 cm. long)." Apart from displacement of the bladder upwards and bilateral hydronephrosis and hydroureter, all other organs were normal, and there were no metastatic tumours. Microscopically (Fig. 9), many sections of the uterovaginal tumour showed typical rhabdomyosarcoma with plentiful well-formed cross-striated fibres; and the diaphragmatic tumour also is a rhabdomyosarcoma of similar structure.

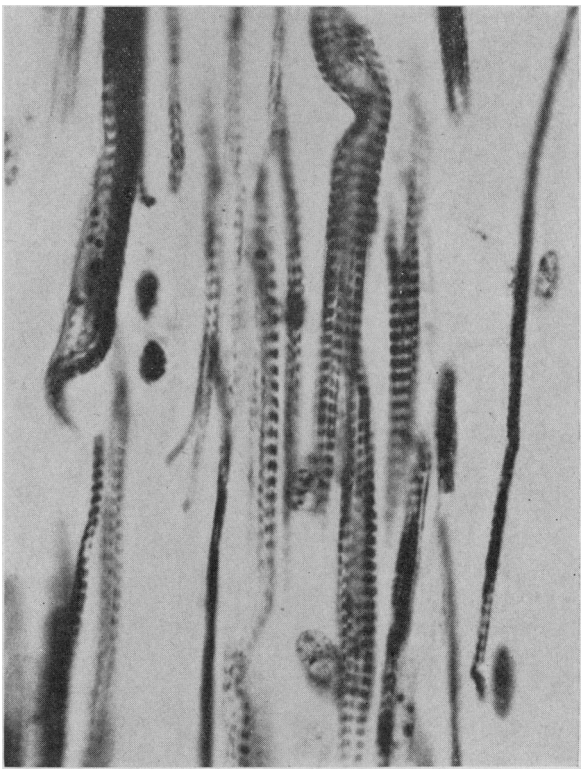

Fig. 9.—Case 6. Uterovaginal rhabdomyosarcoma. (× 1000.)

This case showed two unusual features: (a) the tumour involved the uterus as well as the vagina, a finding which has only rarely been reported in this class of tumour;[15] and (b) the nature of the diaphragmatic growth was debatable. It was uncertain whether this was a peculiarly situated solitary metastasis of the uterovaginal tumour, or an independent primary tumour. Either interpretation makes the case an extraordinary one.

In my book on children's tumours[39] (p. 63) I have recorded another very rare embryonic uterine tumour in a child, in this case of the endometrium. The specimen was given to me by Dr. Barbara Ockenden, who had worked with John Whittick and me at the Royal Cancer Hospital in 1948-49.

CASE 7.—(T.R.C. 552.) When the child was 4 months old, she had a vaginal hemorrhage, which ceased without treatment. At the age of 18 months, however, she was admitted to hospital with anemia and a large pelvic tumour. Operation showed this to be an enlarged uterus, accompanied by large deposits of growth in the pelvic and para-aortic lymph glands. The excised uterus was distended by a mass of soft growth enclosed in a thin shell of myometrium, and the left tube also was distended by tumour. Microscopically (Willis[39]; Fig. 35), all parts of the tumour show two distinct but closely

intermingled components, (a) an epithelial component, consisting of irregular trabeculae and tubules of small compactly grouped cells, and (b) a diffusely cellular, small-spindle-cell component, with a whorled arrangement in places, but no signs of differentiation into muscle, cartilage or other tissues.

I have been unable to find any report of a uterine tumour in a child similar to this one; and, until other specimens of the same kind are studied, it would be premature to say more than that it is clearly a malignant one with the histological characteristics of a truly embryonic tumour, comparable with such well-known tumours of some other organs as nephroblastoma and hepatoblastoma.

Endometrial Stromal Sarcoma

This relatively rare tumour merits special attention. Typically it consists of rather uniform diffusely cellular tissue, composed of small undifferentiated cells resembling those of hyperplastic endometrial stroma, devoid of glands and other epithelial structures (Fig. 10). Some of the tumours form bulky localized masses, but others are ill-defined and ramify through the myometrium, where they often show characteristic polypoidal or worm-like extensions within small or large veins. The tumours are slow-growing and usually of low malignancy. Many are cured by hysterectomy, but recurrence and metastasis take place in some cases.

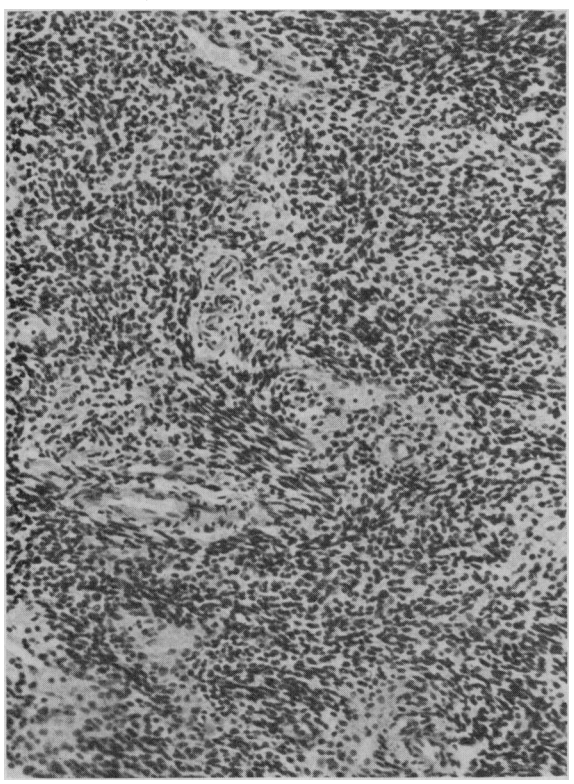

Fig. 10.—Endometrial stromal sarcoma, from a 41-year-old woman. (× 120.)

While most stromal sarcomas are fairly uniform and stroma-like in their cytology, some interesting variations occur. Symmonds, Dockerty and Pratt[35] reported the presence of osteoid; Bird and I[4] saw the differentiation of smooth muscle, a feature which I have seen plainly in several other specimens; and Norris and Taylor[26] reported epithelial differentiation (also in T.R.C. 2466). These variant characters, I believe, show that, though the stromal sarcomas form a fairly distinct class, they are histogenetically akin to the more malignant and less rare "mixed mesodermal" tumours of the endometrium. Indeed, I believe that all tumours of the endometrium can be regarded as one large family with a wide spectrum of structure and behaviour, the adenomyomas and stromal sarcomas occupying the less malignant end of the spectrum and the common adenocarcinomas, carcinosarcomas and mixed tumours ranging over its more malignant end.

Unusual Kinds of Carcinoma of the Cervix Uteri

(a) *Highly differentiated papillary squamous carcinomas*, growing out as cauliflower-like masses but long remaining superficial and non-invasive, are rare. They are relatively benign and curable, but they may eventually become invasive.[13, 22]

(b) *Combined squamous-cell and adenocarcinomatous tumours*, not due to confluence of two separate growths but to divergent differentiation of the one growth in two different directions, are very unusual[9, 31]—see Fig. 11 (from T.R.C. 2461). Moss and Collins[24] (T.R.C. 1191) reported a combined squamous-cell and adenocystic carcinoma.

(c) *Papillary adenocarcinomas of the cervix* arising from remains of Gartner's ducts form a distinctive group, of which the following is a probable example:

CASE 8.—(T.R.C. 1051.) A 30-year-old woman had had an indolent friable bleeding lesion of the cervix for several months, and hysterectomy was performed. Microscopically, the growth formed a layer of nearly uniform thickness of about 1 cm. involving the external os and extending up into the cervical canal. Microscopically (Fig. 12), it is a highly differentiated papillary adenocarcinoma with little or no mucin secretion.

Because of its distinctive histological appearance and the youth of the patient, this tumour

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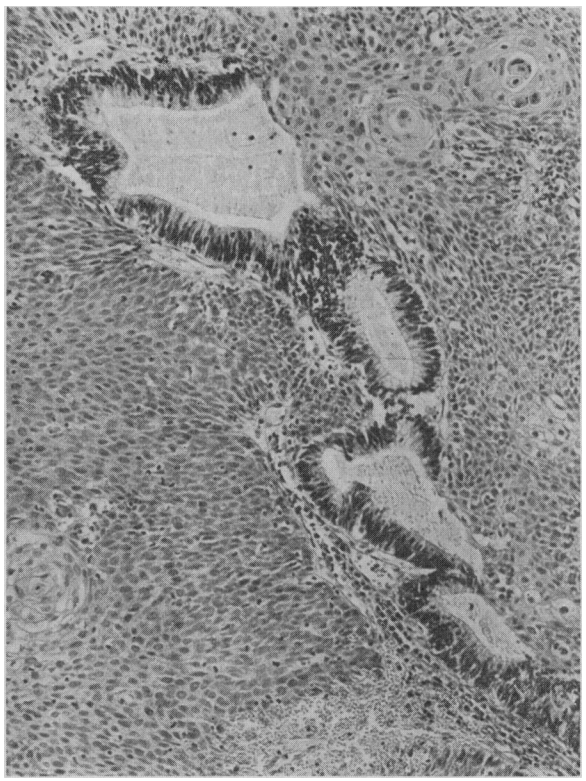

Fig. 11.—Combined squamous and glandular differentiation in a carcinoma of uterine cervix. (× 120.)

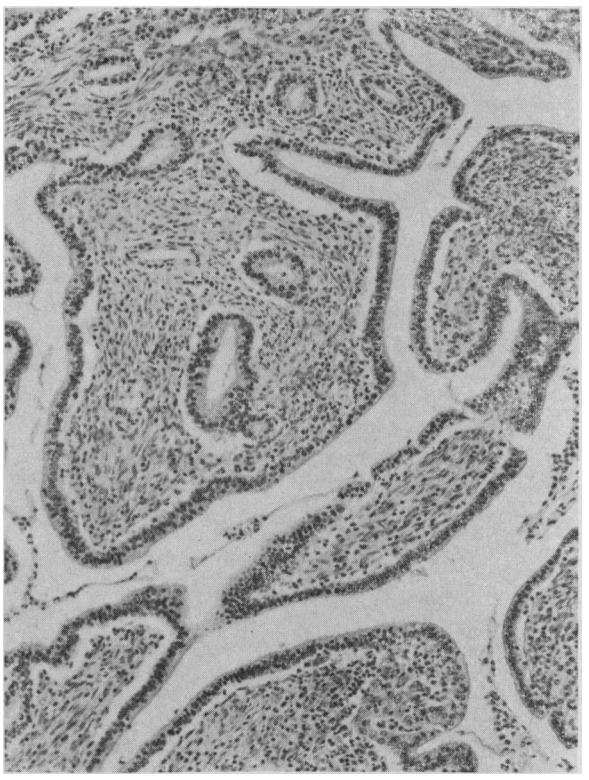

Fig. 12.—Case 8. Papillary adenocarcinoma of cervix. (× 120.)

was presumed to have arisen from the cervical part of Gartner's duct, though this is not certain. However, indubitable cases of similar papillary growths of mesonephric-duct origin have been reported; for example, Beck and Scott[2] saw such a growth in the vaginal fornix of a 40-year-old woman which demonstrably arose in a cyst-adenoma of the mesonephric duct. Papillary adenocarcinomas of the vagina in infants and young children are well known,[39] and it is probable that they too arise from Gartner's ducts.

Adenomatoid Tumours of Tube and Uterus

These relatively rare benign tumours, identical in structure to the less uncommon paratesticular tumours in men, have been well described by Ragins and Crane,[28] Efskind[10] and Bolton and Hunter.[5] The following is a typical example:

CASE 9.—(T.R.C. 2456.) A 42-year-old woman, who had had irregular painful menses, had a hysterectomy. Multiple uterine myomas, cervical polypi, ovarian endometriosis and a well-defined rounded tumour 1 cm. in diameter in the wall of one tube unattached to either serosa or mucosa were found. Microscopically (Fig. 13), this had the characteristic structure of an adenomatoid tumour, namely, tubular spaces most of which were lined by flat cells, but some of which had plump lining cells, often vacuolated.

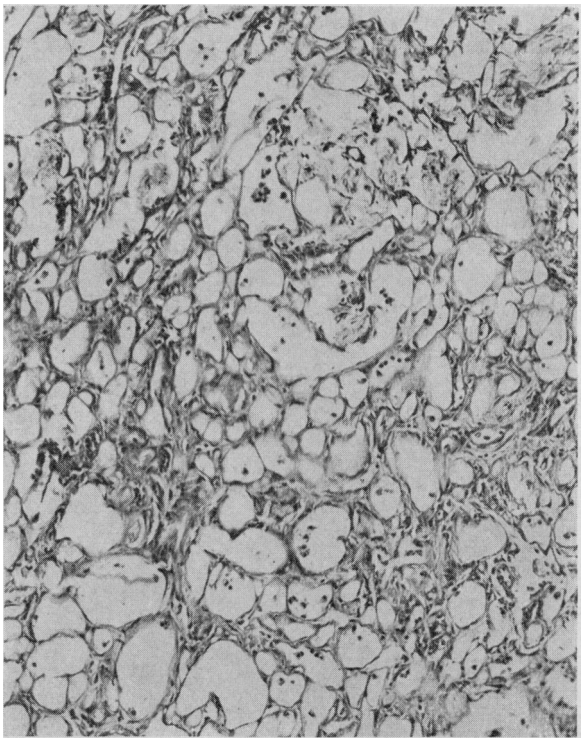

Fig. 13.—Case 9. Adenomatoid tumour of Fallopian tube. (× 120.)

There is no doubt that these tumours are epithelial in nature, and I am convinced that the tubal and uterine ones, like their male counterparts, arise from Müllerian epithelium. The uterine wall is a much less frequent site than the tubes.[5]

TUMOURS OF THE PARATESTICULAR MÜLLERIAN VESTIGES

In 1955, Bailey, Wilson and I[1] reported a papillary tumour of the appendix testis, which had been removed along with the testis and hydrocele sac from a 21-year-old man, who had been aware of a lump for five years. The tumour occupied the exact site of the appendix testis, and had produced multiple small implants in the hydrocele sac. Microscopically, the main growth and the implants all showed a highly differentiated papillary adenocarcinoma with tall and cuboidal epithelial cells clothing the papillae. The patient was still well several years later.

Since then, I have seen several similar tumours, including the following two:

CASE 10.—(T.R.C. 2490.) (This specimen was given me by Dr. J. H. O. Earle, a former colleague of John Whittick and myself in London.) A 64-year-old man had noticed recent scrotal enlargement; and the testis and a large hydrocele sac were removed. At the site of the appendix testis there was a cluster of small tumours, the largest 1.8 cm. in diameter, and there were some separate small nodules elsewhere in the sac. Microscopically (Fig. 14), the tumour is a highly differentiated papillary one with a structure very similar to that reported by Bailey, Wilson and myself.[1]

CASE 11.—(T.R.C. 2491.) A 51-year-old man had recently noticed scrotal enlargement, and the testis and a hydrocele sac were removed. Attached to the upper pole of a normal testis, at the exact site of the appendix testis and separate from the epididymis and its appendix, there was a rounded papillary growth 1.8 cm. in diameter. Microscopically (Fig. 15), this shows a well-differentiated papillary structure, clothed by a thick cellular layer of epithelium in which numerous acinar structures are developing.

Those who, like Sundarasivarao and me, have studied the structure of the normal appendix testis will have no doubt whatever that the foregoing tumours were indeed papillomas or low-grade papillary carcinomas of that organ, and homologous with the better differentiated papillary carcinomas of the fimbriae and outer end of the Fallopian tube—of which the appendix testis is the male homologue.

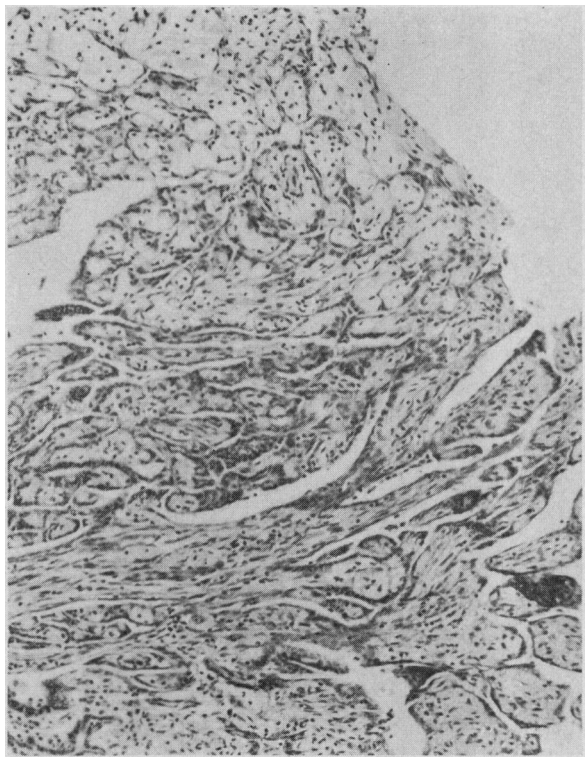

Fig. 14.—Case 10. Papillary tumour of appendix testis. (× 120.)

The paratesticular *adenomatoid tumours*, structurally similar to, but commoner than, their

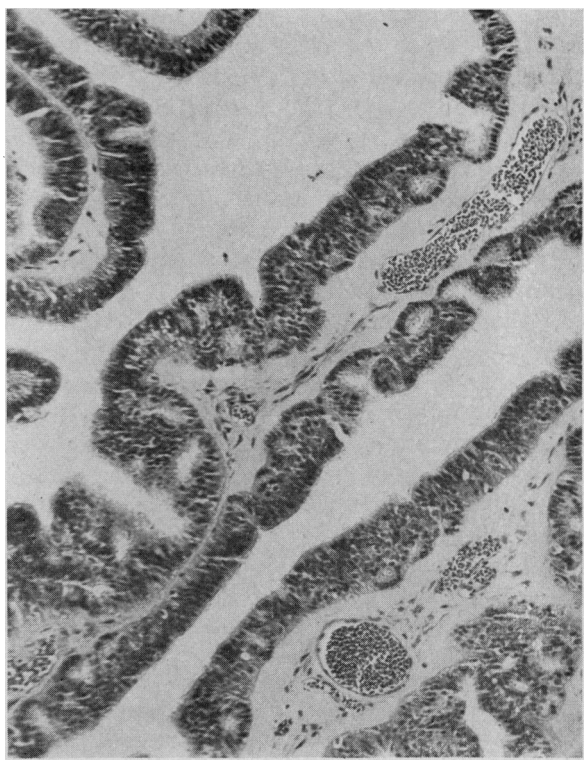

Fig. 15.—Case 11. Papillary tumour of appendix testis. (× 120.)

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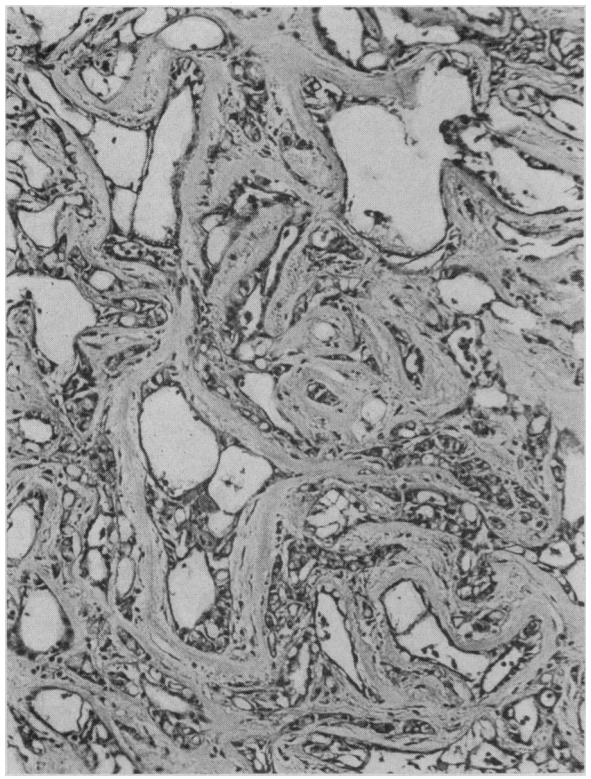

Fig. 16.—Case 12. Adenomatoid tumour of epididymis. (× 120.)

counterparts in the tube and uterus (noted in the previous section), must be mentioned here. Sundarasivarao,[34] while working in my department in Leeds, carefully studied a number of these and advanced strong evidence that they too arise from the Müllerian residues. In particular he noted one which occupied the position of the appendix testis, and which in most parts showed the usual empty-looking tubular structure of the adenomatoid tumours, but which in other parts showed papillary structure with tall columnar and cuboidal epithelium exactly resembling that seen in the unquestionable tumours of the appendix testis just described. Most of the adenomatoid tumours, however, show only the tubular arrangement, the tubules usually being lined by flat cells, but sometimes by plump or vacuolated cells of undoubtedly epithelial nature, as in the following case:

CASE 12.—(T.R.C. 54.) A 50-year-old man had noticed a painless lump in his scrotum for 17 months. At operation a well-defined rounded tumour 3 cm. in diameter was removed from the lower pole of the epididymis. Microscopically (Fig. 16), it shows plentiful tubules lined by plump solid or vacuolated epithelial cells, which show all degrees of vacuolation and flattening, to produce the characteristic flat-celled adenomatoid structure.

It only remains to add here that the not infrequent situation of adenomatoid tumours at the lower pole of the epididymis is no reason for rejecting their Müllerian origin; for, as Sundarasivarao found, vestiges of the Müllerian duct are not confined to the appendix testis and its neigbourhood but occur at all levels of the epididymis.

UNUSUAL MAMMARY TUMOURS

John Whittick and I studied several mammary sarcomas, some of which showed bony or osteoclastic differentiation, and one specimen of carcinosarcoma. A summary of this work is presented elsewhere.[37] John would have enjoyed studying the following two unusual tumours, which I have since seen:

CASE 13.—(T.R.C. 2268.) A well-circumscribed tumour, which had been noticed for six months, was removed locally from the breast of a 48-year-old woman; she was well four years later. Microscopically (Fig. 17), the tumour has the pattern of an intracanalicular fibroadenoma, but the non-epithelial component, instead of being fibromatous, consists of young proliferating adipose tissue: it is a lipofibroadenoma.

This tumour, like another similar one which I reported briefly in 1959,[37] was regarded as

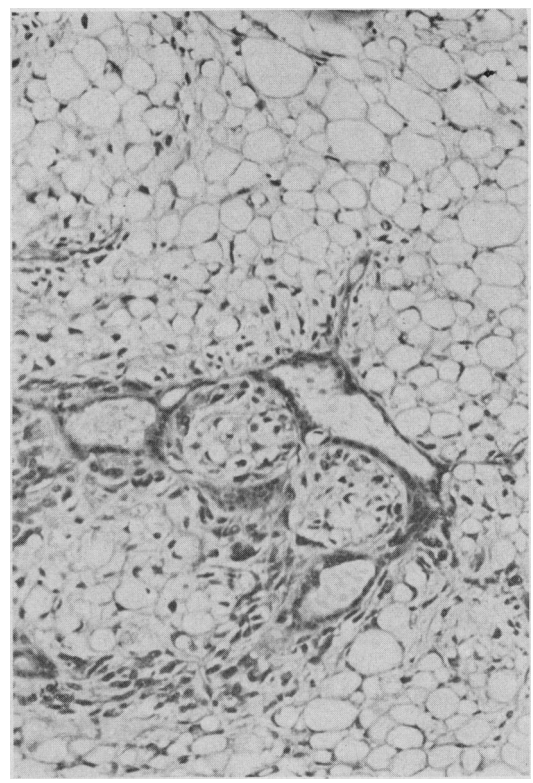

Fig. 17.—Case 13. Mammary lipofibroadenoma. (× 150.)

benign. Jackson,[19] however, reported a similar but more actively growing tumour which produced blood-borne liposarcomatous metastases.

CASE 14.—(T.R.C. 2291.) An 83-year-old woman had been aware of a lump in her breast for five months. When excised, this was a well-circumscribed mass 6 cm. in diameter, containing bony-hard areas. Microscopically (Fig. 18), it showed a mixture of keratinizing squamous-cell carcinoma and cellular sarcoma with much osteoid, bony and cartilaginous differentiation—a very unusual combination.

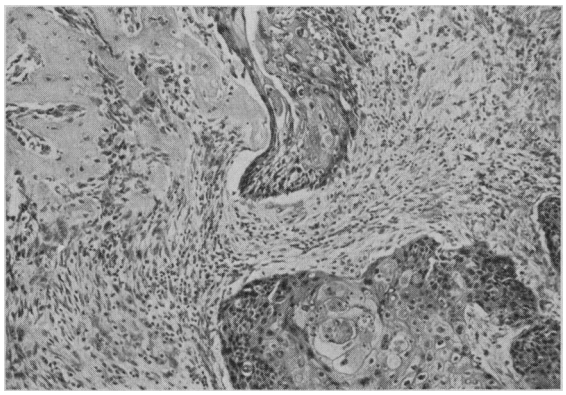

Fig. 18.—Case 14. Combined squamous carcinoma and osteosarcoma of breast. (× 75.)

While on the subject of mammary tumours, I must discuss briefly the nature of the tumours which sometimes arise in the edematous arm following radical mastectomy and which have been widely accepted as "angiosarcomas". One very instructive example, which John Whittick and I studied together at the Royal Cancer Hospital in 1949,[29] was as follows:

CASE 15.—In 1940, when the woman was 58 years old, left radical mastectomy was performed to remove an active carcinoma. The left arm later became and remained edematous; and in 1948 a local painful swelling developed on the lateral aspect of the upper arm. In 1949 a reddish-black tumour mass was excised. Microscopically both John and I, influenced by recent reports of so-called "lymphangiosarcomas" in such cases, reported our case as one of "angiosarcoma"—noting, however, that blood vessels rather than lymph vessels appeared to be involved. The tumour soon recurred, and the limb was amputated. Following a further recurrence in the stump, an interscapulothoracic amputation was performed. The woman died in 1951 at the age of 68. Incomplete necropsy (by John Whittick) showed extensive nodules of hemorrhagic growth spreading from the left shoulder region down over the lateral thoracic and abdominal walls, and multiple small metastases in the lungs. I quote from a letter which I received from John in June 1951, in answer to an enquiry of mine about the progress of the case: "She died recently, but a necropsy was refused. However, I stole her lungs and a few early metastases are present. These suggest only carcinoma, and in looking back through all the earlier sections I wonder if it is not just haemorrhagic secondary carcinoma of the breast which she has had all along. The angiosarcomatous appearance is present in growth occurring in the oedematous left arm, but the last recurrence in the shoulder region and the lung metastases are very like carcinoma."

On reviewing all the material, I agreed with John that this was not a case of true angiosarcoma, but of recurrent mammary carcinoma with a peculiar habit of growth in the edematous tissues. Twelve years later, Salm[29] came independently to the same conclusion for this case and for two others; and he advanced evidence that many other reported cases of supposed "angiosarcoma" of the postmastectomy edematous limb were in fact recurrent carcinomas—an opinion which I share. But it was John Whittick who, on the strength of our Cancer Hospital case, was the first to suspect that the diagnosis of "angiosarcoma" in such cases was fallacious.

EPITHELIAL TUMOURS OF THE TIBIA

The histogenesis of the now well-known epithelial tumours of the tibia—often called by the unfortunate name "adamantinoma"—was a problem which greatly interested John Whittick. In 1953, a quartet correspondence concerning three tumours of this class took place between John, the late Dr. Leila Hawksley (also one-time pathologist to the Royal Cancer Hospital), the late Sir Thomas Fairbank and myself. One of these cases, first examined by Dr. Hawksley in 1939, was of special interest; it was briefly as follows:

CASE 16.—A woman aged 32 in 1938 had had markedly bowed tibias since infancy. Radiographs from 1934 onwards showed the appearances of cystic change in both bones and the gradual destruction and disappearance of the left tibia. Amputation was performed after this leg had fractured. The tibia was almost wholly destroyed, and John Whittick's report on it (with which I agreed) was as follows: "A squamous-cell carcinoma consisting partly of keratinizing compact cell groups and finely scattered carcinoma cells which in part have a pseudosarcomatous appearance. In addition there are inflammatory changes, bone destruction and callus formation." It must be added here that, because a biopsy had been done at another hospital (and the specimen lost) two years before the amputation, Dr. Hawksley had hesitated to diagnose a primary tibial growth, since it was just possible

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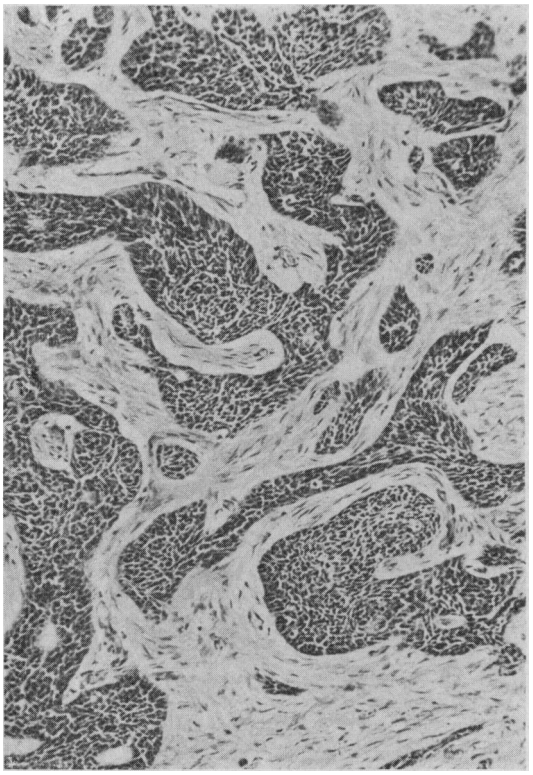

Fig. 19.—Basal-cell structure in epithelial tumour of tibia of a 34-year-old woman. (× 120.)

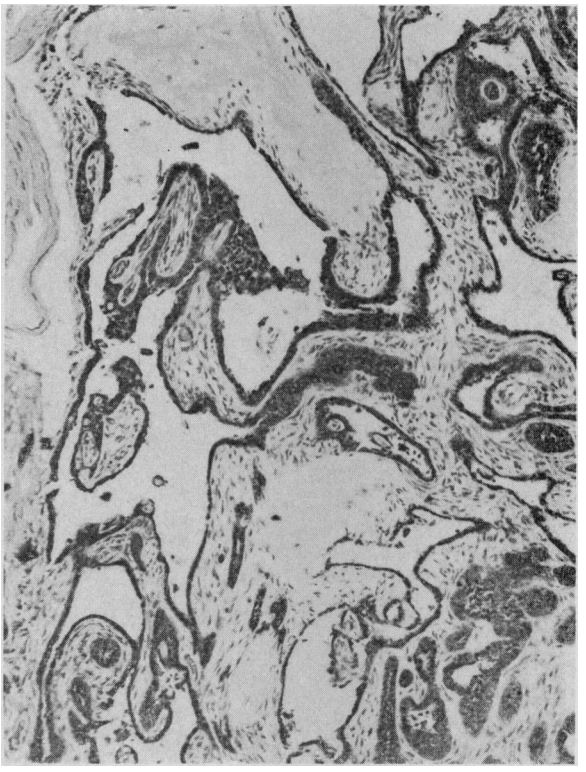

Fig. 20.—Glandular structure in an epithelial tumour of tibia of a 40-year-old man. (× 120.)

that the tumour had arisen from epidermal cells implanted when the biopsy was done. However, we finally concluded that the progressive destruction of the tibia before the biopsy and the extent of the growth in the amputated limb made it almost certain that we were dealing with a primarily intratibial squamous-cell carcinoma. Dr. Hawksley had asked for a biopsy on the other tibia, but this was refused. Contact with the patient was subsequently lost.

At the same time that we were re-examining the material from the Cancer Hospital case, Sir Thomas Fairbank showed us sections of a tibial tumour from another patient, a 42-year-old man who had had a deformity of one tibia since childhood. There was also extensive bone destruction in this tibia. Amputation was eventually performed, and the sections showed a well-differentiated squamous-cell carcinoma. Our experience with this case confirmed our belief that the earlier case was indeed one of primary intratibial carcinoma. The two cases together afford strong evidence for the origin of epithelial tumours of the tibia from developmentally displaced epithelium.

It remains only to add that the supposed synovial origin of tumours of this class is quite unacceptable; their histology is plainly that of cutaneous carcinomas. Some, like the two just described, are squamous-celled and keratinizing; some show in part a structure resembling that of "adamantinoma;" still others resemble basal-cell carcinomas of the skin (Fig. 19); and rarely the tumour shows glandular or tubular differentiation recalling that of a sweat-gland tumour (Fig. 20).

CONCLUSION

I could go on and describe many other unusual kinds of tumours which engaged John Whittick's attention, including many more examples from his own records. But my time has sped: and I think I have presented sufficient evidence of his versatility, spirit of enquiry, and thoroughness as a histopathologist. I hope I have also conveyed something of the stimulus and pleasure which it gave me to work with such a man; and how privileged I feel to be able to put on record a few of the striking cases which he studied, but which, because of his innate and excessive modesty, he never published. He was one of those experienced histopathologists whose work gives the lie to a prevalent idea that the pathological anatomy of tumours is an exhausted subject. The truth is otherwise; we are constantly extending our knowledge of tumour histogenesis, appreciating more the great variety of tumour

types and the range of their structure and behaviour, and so we are steadily improving our taxonomy and nomenclature. John Whittick's work contributed very substantially to these advances.

For permission to report the cases described I am indebted to the following pathologists: Dr. A. F. Burry of Brisbane for Case 2; Dr. R. Salm of Truro for Case 3; Dr. Dermer E. Smith of Sydney for Case 4; Dr. R. E. Rewell of Liverpool for Case 5; Dr. D. Evans of Cardiff for Case 8; Dr. P. J. Mullaney of Dublin for Case 9; Dr. J. H. O. Earle of London for Case 10; Dr. H. J. R. Kirkpatrick of Fife for Case 11; Dr. H. S. Kellett of Bradford for Case 12; Dr. C. H. R. Knowles of Chichester for Case 13; Dr. G. R. Osborn of Derby for Case 14 and for the specimen shown in Fig. 10; Dr. Ruth Osmond of Adelaide for that shown in Fig. 11; and to the Manchester Children's Tumour Registry for that shown in Fig. 7 (CTR 21/62). All of these specimens are filed in the Tumour Reference Collection of the Imperial Cancer Research Fund, London, and are denoted in the text by their T.R.C. numbers. I am very grateful for the help of Dr. Stretton Young, head of the Fund's Division of Pathology, and to Mr. E. V. Willmott and his staff in the photographic department of the Fund for their excellent photomicrographs.

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