

THESIS for the Degree of M.D. of GLASGOW UNIVERSITY

FUNCTIONING OVARIAN TUMOURS

A Clinical and Pathological Study

with

Special Reference to the Occurrence of
Male-directed cells in Granulosa Cell Tumours

by

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PREFACE

This thesis is the report of a study of the pathology and clinical features of a series of hormonally active ovarian tumours. The study forms the basis for a discussion on the origin and significance of the cellular elements of these tumours and on the relationship of the histological structure to the clinical effect.

The functioning tumours are not an entirely self-contained group. A transition can be traced to the fibroma on the one hand and carcinoma on the other. In order therefore to put the functioning tumours in their proper perspective the results of the examination of a series of ovarian fibromas and of ovarian carcinomas is included and a comparison is made.

As there appears to be a distinct parallel between the cellular changes in the developing gonad and in the functioning tumours, it was necessary also to examine a series of foetal and neonatal ovaries and testes. A report on the findings in this series is also given.

The thesis thus consists of:-

First: A review of the relevant features of gonadal development.

Second: A description of the pathology and clinical effect of the series of tumours which has been divided

arbitrarily on histological grounds into 5 groups thus:-

thus:-

- (1) Fibromas.
- (2) Thecomas and stromal hyperplasia.
- (3) Diffuse granulosa cell tumours.
- (4) Differentiated granulosa cell tumours.
- (5) Carcinomas.

Third: A discussion on the clinical features associated with the tumours and, more particularly, a discussion on the significance of male directed cells in the functioning tumours.

MATERIAL

It is the practice in the Royal Samaritan Hospital, Glasgow, for some members of the clinical staff to be appointed pathologist and assistant pathologist in addition to their normal clinical duties. Each appointment lasts for about 3 years and during his tenure of office the pathologist is responsible for reporting all the histological specimens which number over 3,000 a year. In cases of doubt the advice of the consultant pathologist for the Maternity Group of Hospitals (Dr. A.D.T.Govan) is sought. The clinician therefore has the opportunity of developing an interest in and a knowledge of gynaecological pathology.

All the pathological material for this paper was available in the Royal Samaritan Hospital. The commoner tumours, fibromas and carcinomas occurred in the years 1948-1954 during which time the author was assistant pathologist and later pathologist to the hospital. The less common tumours occurred over a longer period and all the tumours which could be traced were examined.

All the patients, except one, were operated upon in the Royal Samaritan Hospital, some by the author himself but the majority by other members of the staff. A follow-up was carried out on all the patients with hormonally active tumours and with carcinomas. Recent information was obtained on all

all but 4 of the former and all but 1 of the latter.

The series consisted of:-

28 patients with fibroma of the ovary.

36 patients with hormonally active tumours.

47 patients with primary carcinoma of the ovary.

12 patients with secondary carcinoma of the ovary.

The embryological material was obtained from various sources. Foetal and infant gonads were obtained from the Royal Maternity Hospital; foetal, infant, adult and senile testes from the Anatomy department of Glasgow University and from the Royal Infirmary. Testicular biopsies were given by Mr. W. Mack, Consultant Urologist to the Western Infirmary.

The histological work was done in the Royal Samaritan Hospital where the author received unfailing help from the chief technician, Mr. Thomas Pearston in cutting and staining the sections, experimenting with various staining methods and in taking the photographs.

INTRODUCTION

In the generally accepted classification of functioning ovarian tumours, thecomas and granulosa cell tumours are considered to be feminizing and arrhenoblastomas and adrenal-like tumours are considered to be masculinizing.

The granulosa cell tumour is thought to reproduce the cellular structure of the mature granulosa of the Graafian follicle, the thecoma to reproduce the cells of the theca interna and the arrhenoblastoma to reproduce male elements which have lain dormant while the ovary was developing. There is less agreement about the nature of the adrenal-like tumour which is thought by some to consist of adrenal tissue, ~~by some to consist of adrenal tissue~~, by some to be luteal and by others to be hypernephric in origin.

Few readers of gynaecological textbooks can fail to have been confused by the descriptions given of granulosa cell tumours and of arrhenoblastomas. The illustrations provided as a guide to the differentiation of the two groups serve to emphasise their similarity. If the pathology of the arrhenoblastoma is at last understood then a more formidable obstacle has to be surmounted in understanding the adrenal group of tumours. Such, at least, was the author's experience.

The results of this study suggest that granulosa cell tumours and arrhenoblastomas belong to the same group

group histologically and histogenetically and they cannot be divided morphologically.

Much of the confusion has arisen because the original "typical" arrhenoblastoma described and named by Meyer (1930) was not in fact a masculinizing tumour although, according to the interpretation of the histology given by Meyer, it should have been. As will be shown later the majority of "typical" arrhenoblastomas which have been described had either no endocrine effect or were feminizing tumours.

In this series the diffuse granulosa cell tumours alone had a reasonably homogeneous structure and a reasonably predictable clinical effect. The tumours of the group which has been called differentiated granulosa cell tumours showed a constant tendency to revert to more primitive or male directed structures and yet their effect was generally speaking feminizing. It was for this reason that the study of the embryology of the gonad was thought to be necessary. It will be shown that the male-directed elements are similar to the Sertoli cells of the testis and that granulosa in tumours may be regarded as a transitional stage between Sertoli and luteal cells.

The study has not been very successful in elucidating the true nature of the adrenal-like group of tumours since none of the 3 tumours which were histologically identical with those described in the literature, was masculinizing and all were considered to be primary carcinomas of the ovary.

In addition to these pathological considerations the report shows the relative infertility of patients who suffer from ovarian tumours, the comparative benignity of the functioning tumours and confirms the lethal effect of carcinoma of the ovary.



The Embryology of The Gonad

The following description of the early stages of development of the gonad is not the result of observations by the author himself but is based on the published work of such embryologists as Gruenwald (1942), Gillman (1948), Boyd and Hamilton (1950), and Schiller (1950). The observations regarding the histology of the foetal, neonatal and adult gonads are however at first hand and are the result of the examination of serial sections of foetal ovaries at 32 weeks, 40 weeks (5) and infant ovaries at 16 hours, 16 days, 4 weeks, 28 weeks, one year and 15 months after birth and of foetal testes at 28 weeks, 38 weeks, 40 weeks and adult and senile testes.

The object of this study was to determine if possible the origin and fate of the sex cords, the interstitial cells and Sertoli cells since it was thought that these structures might be reproduced in the functioning ovarian tumours.

Early Stages.

The coelomic cavities are clefts in the lateral mesoderm and at first have no lining; but very soon the mesoderm which bounds the cavity differentiates from the deeper layers in the nature and arrangement of its cells and assumes an epithelial appearance. The genital ridge forms when the embryo is

is about 6 mm. in length and by this time the coelomic epithelium has already differentiated. It is stressed by both Gruenwald (1942) and Gillman (1948) that there is no borderline between the lining and the underlying tissue but there is a gradual transition from the superficial to the deeper layers. This is particularly well illustrated in Gillman's plate 1 no. 2., and emphasises the fact that the gonad is a common unit developed from the primitive mesenchyme.

It is generally agreed and appears to be amply proved by Witschi (1948) and others that the primordial germ cells do not arise within the gonad but migrate into that organ from the region of the hind gut as early as 7 mm.

The sex cords develop when the embryo reaches about 15 mm. in length. They maintain the histological characteristics of the coelomic epithelium and are arranged in a radial fashion through the mesenchyme.

There is some disagreement as to the origin of these cords. Gillman is quite emphatic that they arise from the coelomic epithelium and are the result of the penetration of the mesenchyme by epithelial processes. Gruenwald favours the theory of Fischel (1930) that they arise by a differentiation of the mesenchyme in situ, and that they grow outwards to link up with the coelomic epithelium. Boyd and Hamilton tend to support Gillman's view.

Gillman points out that it is extremely important to

to accept the fact that the cords arise from the coelomic epithelium because the cords will produce the granulosa and the mesenchyme the stroma and the theca. He insists therefore that the granulosa and the theca have a different nature and that there can be no metaplasia from one to the other. In applying his theory to ovarian tumours he supposes that the granulosa cell tumour has a different origin from the thecoma, the latter being a cellular reaction to the former. In this he vitiates his argument since in ovarian tumours a transition from granulosa to thecoma is frequently seen.

It does not seem necessary to be so dogmatic because even Gillman admits that both mesenchyme and coelomic epithelium have a common origin in the primitive mesenchyme.

The fate of the sex cords is probably of more importance. It is agreed that in the testis they form the seminiferous tubules and ensheath the primordial germ cells and become the Sertoli cells. In the ovary the sex cords form the pregranulosa which also encircles the germ cells but whether or not the pregranulosa forms the granulosa is a matter for debate. Gillman says it does; Fischel says it does not. This problem is discussed later.

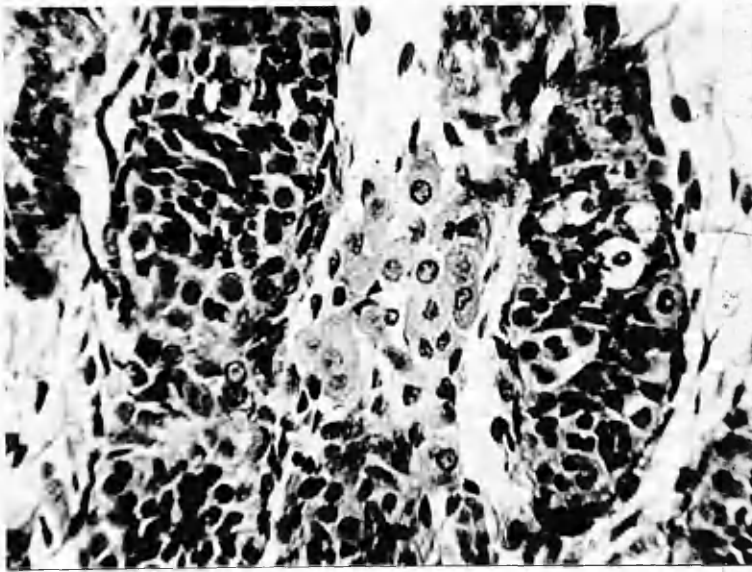


Figure 1.

Testis at 40 weeks showing sex cords differentiated into Sertoli cells. Large Leydig cells are present. The spermatozoa can be seen clearly. x 475.

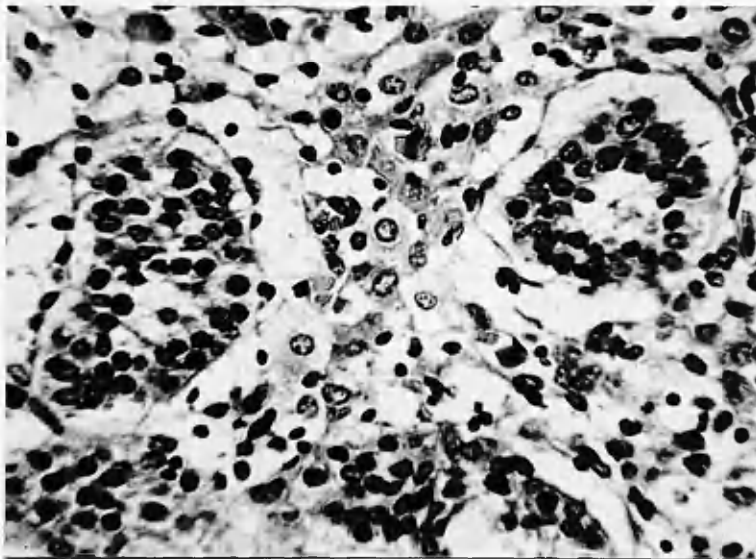


Figure 2.

Testis at 28 weeks. Canalization of the cord has begun. An antipodal arrangement of nuclei is seen in the right hand cord. x 475.

The Developing Testes.

(a) The Sertoli Cells.

By 28 weeks the testis contains all the elements which make up the adult testis with the exception of spermatozoa. The cords are well defined. As a rule they are bounded by a fine layer of endotheloid cells and they are arranged in a radial fashion from the hilus. The cords are made up of Sertoli cells which are arranged irregularly and without a definite pattern (fig.1.). The Sertoli cells have deep staining nuclei and are oval or elongated. The nuclei tend to be crowded together and the cytoplasm which stains pink with eosin, is scarce. The cell margins are poorly defined. The spermatogonia can be easily recognised in the cords. They are relatively few in number and they are usually found at the periphery. They have spherical nuclei which stain deeply, the cytoplasm is abundant and the cell margin is distinct. The cytoplasm stains faint pink with eosin and a deeper pink with pyronin, the latter reaction being probably due to the content of ribonucleic acid as cells treated with ribonuclease take no stain with pyronin. The beginnings of canalization may be seen as early as 28 weeks (fig.2.)

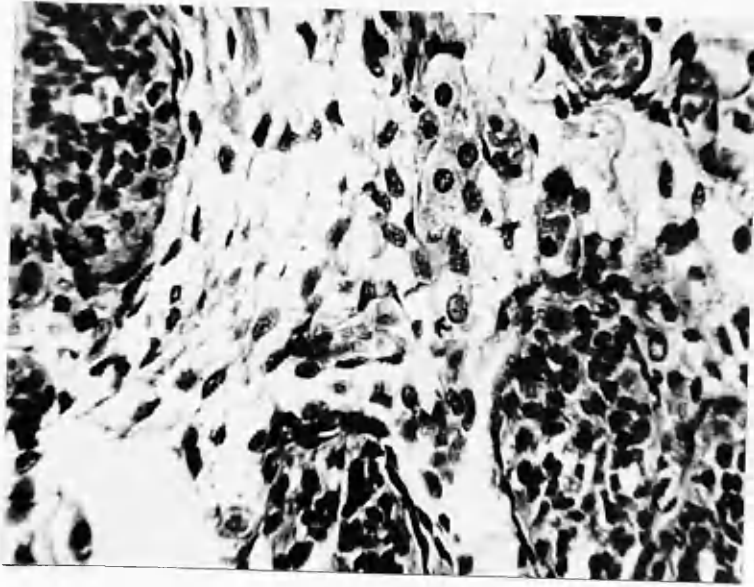


Figure 3.

Testis at 40 weeks showing Leydig cells in close apposition to the seminiferous tubule. x 475.

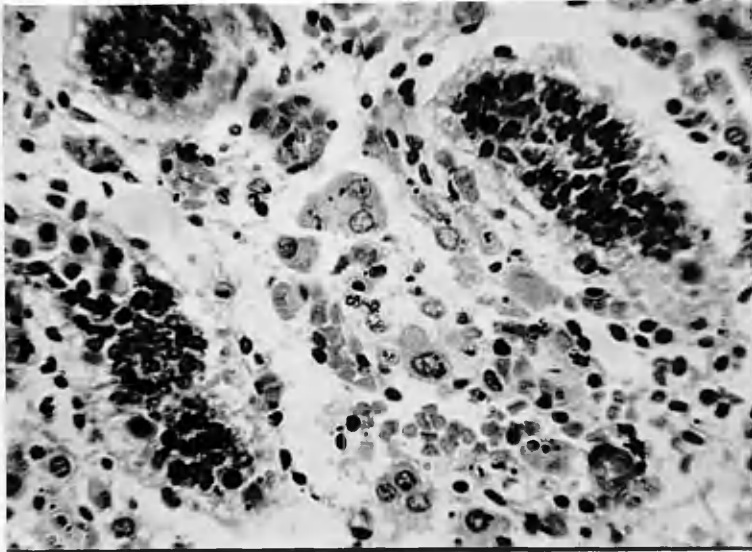


Figure 4.

Testis at 28 weeks showing very large Leydig cells. x 475.

There is a gradual diminution in the number of Sertoli cells as the testis grows older and in the adult the seminiferous tubules consist almost entirely of spermatogonia and their products with a few Sertoli cells round the periphery. It is uncommon to find a complete ring of Sertoli cells in the active testis and in the senile testis they are either difficult to recognise or they have almost entirely disappeared.

(b) The Interstitial or Leydig Cells.

The Leydig cells can be recognised in the 17 mm. embryo and by 54 mm. they are very numerous and form the bulk of the testis. As the embryo increases in size they gradually diminish in numbers. Gruenwald believes that they may develop from the sex cords and Gillman that they develop from the mesenchyme. They certainly can be seen in very close apposition to the sex cords as shown in figures 1 and 3 in which the endothelial covering of the cord has opened giving a direct continuity between the Sertoli and Leydig cells. It would appear that the formation of Leydig cells is a reaction to the presence of Sertoli cells just as the theca lutein cells are a reaction to the granulosa. Whether the reaction takes place within the cord or in the

the interstitial tissue is immaterial. Even in ovarian tumours the one type of cell is rarely to be found without the other although the proportion of each varies greatly.

The Leydig cells are very large and have much granular cytoplasm (figs. 1-4). The cell margin is well defined and long attenuated processes of cytoplasm link up the cells with their neighbours. The nuclei are big, they are round or oval and have a smooth surface. Within the nucleus there is a delicate tracery and many dark-staining granules are present. The staining reactions of the cells are not constant. With haemotoxylin and eosin some stain a very deep pink in the cytoplasm while adjacent cells take little colour. The staining of the nuclei is also variable. The cells appear to contain ribonucleic acid but not in constant amounts.

Leydig cells were found in all the specimens examined and were as numerous at 28 weeks as they were at 38 and 40 weeks. In the testis of the foetus of a diabetic mother they were crowded in the interstitial tissue.

Many attempts have been made to find some specific property of Leydig cells which would enable them to be recognized in unusual situations. Reinke (1896) described

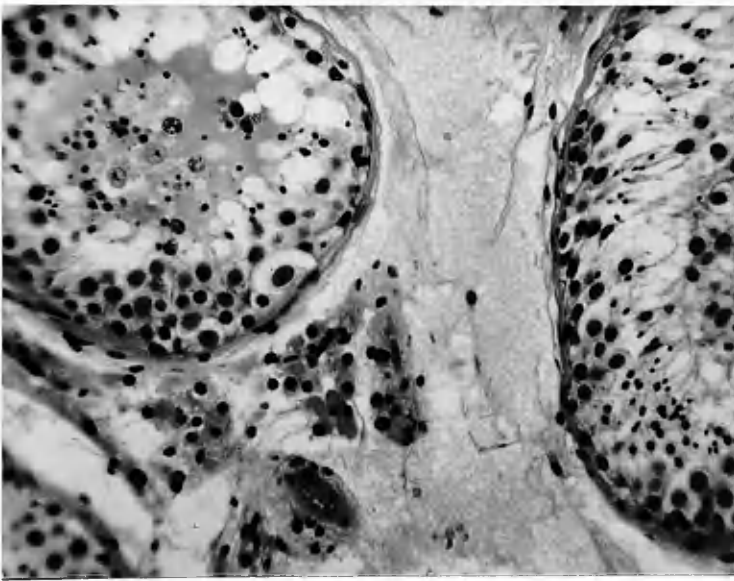


Figure 5.

Active adult testis showing few Sertoli and Leydig cells. A Reinke crystalloid is thought to be present in the centre of the field.
x 250.

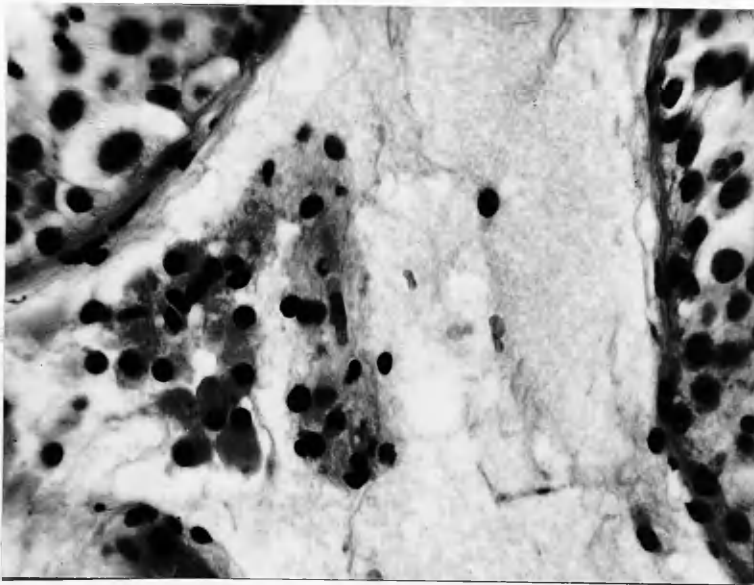


Figure 6.

High power field of Figure 5 showing Leydig cell with Reinke crystalloid.
x 525.

described the presence of very large bodies, rod-shaped with rounded ends which may be as long as the cell itself and may protrude through the cell wall to lie in the intercellular space. He found these crystalloids, as they came to be called, in the Leydig cells of the testis of a man of 25 years, and in several other testes which were actively producing spermatozoa. They were not found in the prepubertal or senile testis.

These crystalloids were not seen in the Leydig cells of any of the foetal or senile testes examined by the author, nor were they found in any of the cells thought to be Leydig cells in the ovarian tumours. A few were seen in an active adult testis in which the Leydig cells were relatively scarce (figs.5 & 6). The only tumours in which they have been found are in the hilus cell tumours reported by Sternberg (1949) and in the Leydig cells of a masculinizing tumour reported by Langley (1954). Teilum (1950) also reports having found them in hilus cells. Reinke himself thought that the presence of crystalloids indicated active spermatogenesis, some authors consider them to be associated with the production of androgens by the cells and others consider them to be an artefact. The presence or absence of the crystalloids is thus of doubtful value

value in the identification of Leydig cells.

Whitehead (1912) described the staining reactions of the granules in the cytoplasm of Leydig cells. These staining reactions can be recognized quite easily but they are not specific. Several staining reactions were investigated by the author including staining for ribonucleic acid, but as described above the intensity and character of the stain was variable even in similar cells adjacent to one another.

It is therefore on the morphology alone that the cells can be recognized. This is unfortunate because they have much in common with the theca-lutein cells, the luteal cells, the hilus cells and the adrenal-like cells which occur in the ovary.

The Developing Ovary.

(a) Sex Cords and Granulosa.

The sex cords of the ovary surround the ova and become the pregranulosa. The cells of the sex cord are very similar to Sertoli cells; they have deep-staining irregularly shaped nuclei and little cytoplasm. They are arranged in clusters, cords or vague alveoli (fig.7). Some of these cells surround the ova unchanged but others become larger and better

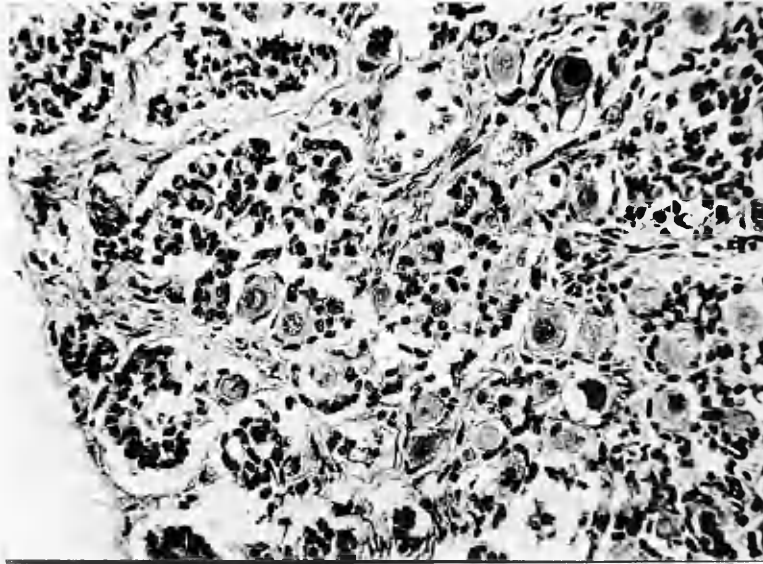


Figure 7.

Ovary at 39 weeks showing the dark staining sex cord encircling
some ova. x 275.

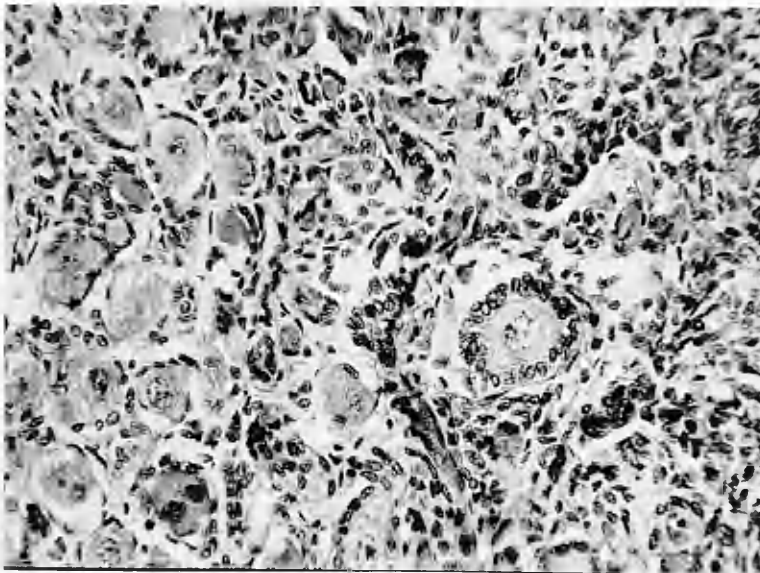


Figure 8.

Ovary at 39 weeks showing variability of cells surrounding
ova. x 275.

defined with smooth pale nuclei and more defined cytoplasm (fig.8). These latter cells appear to be true granulosa cells and as the single layer multiplies into a deep stratum, the transition to granulosa is complete.

There are, however, many ova which are surrounded only by thin, attenuated, endothelioid cells which seem to bear little resemblance to pregranulosa or sex cords (fig.8). These cells may also be seen in the adult ovary surrounding the primordial follicle. A study of the foetal ovary suggests that these cells represent a resting phase of the pregranulosa, a phase which tends to become more complete as the ovary becomes older, and when suitable conditions occur the cells develop once more into granulosa cells.

Gillman explains this phenomenon as the result of pressure of the invading stroma cells on the pregranulosa which seems a little unlikely. Fischel and his adherents consider these endothelial cells to be stromal cells which later develop into granulosa.

There is no doubt from personal observation that some pregranulosa does become granulosa. It would seem reasonable to assume that these endothelioid cells are merely a resting phase of the pregranulosa which may later be stimulated as in the adult to form granulosa.

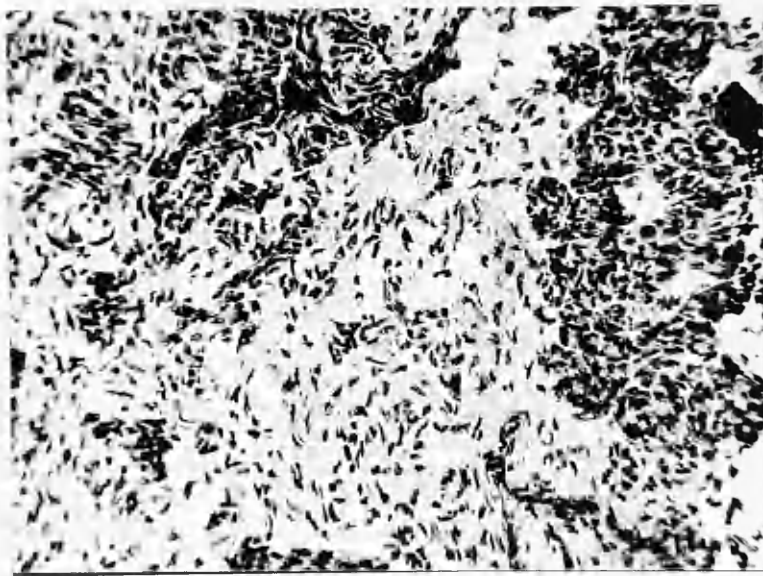


Figure 9.

Ovary at 16 days showing the remains of the sex cord or pregranulosa scattered through the stroma. x 258.

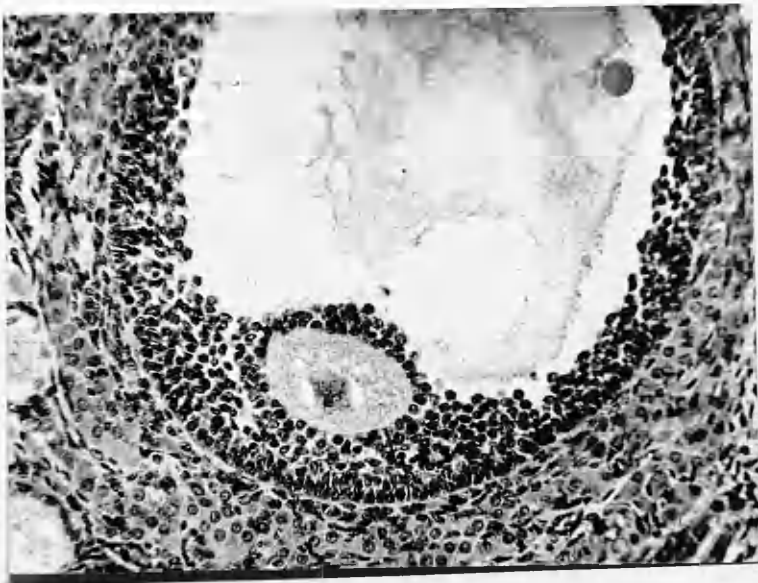


Figure 10.

Foetal ovary at 32 weeks showing well developed Graafian follicle with a remarkable reaction in the theca interna. x 275.

granulosa.

At birth there is still much redundant pregranulosa irregularly distributed through the ovary. It is usually in contact with the superficial epithelium (fig.9). The cells lose much of their cytoplasm, become smaller and gradually retreat to the periphery leaving only a few islands of cells in the stroma.

(b) Theca Cells.

The character of the stroma is inconstant. In the younger ovaries there is very little but such as there is may be well differentiated and adult in appearance. In the older ovaries where the cortex is well defined the stroma resembles a rather loose undifferentiated fibrous tissue.

The thecal reaction in the stroma round the developing follicles is intense. Even in a 32 weeks ovary the theca-lutein cells are well defined. The similarity between this and the Leydig reaction in the testis is remarkable; (fig.10).

Summary.

In relation to ovarian tumours, the significant features of this brief review of gonadal development are as follows:-

First.

First.

The sex cord is developed either directly or indirectly from the primitive mesenchyme.

Second.

Both Sertoli cells and pregranulosa are developements of the sex cord and are thus closely related to one another.

Third.

The stroma reacts in a similar way to the granulosa as the interstitial tissue does to the seminiferous tubule.

The Pathology and Clinical Effect of the Ovarian Tumours.

As mentioned in the preface the series of tumours has been divided into 5 groups: fibromas, thecomas, diffuse and differentiated granulosa cell tumours and carcinomas. Since there is no sharp dividing line between these groups, the classification of the doubtful tumours is a matter of personal opinion. In this series the classification has been done on a histological basis and the clinical effects have been compared afterwards. The result is that at least two tumours classified as fibromas had the clinical effect of thecomas, several histological thecomas and granulosa cell tumours had no obvious endocrine influence and one masculinizing and one defeminizing tumour have been included in the granulosa series because they were histologically indistinguishable from granulosa cell tumours. To bridge the gap between the normal and the neoplastic 2 cases of stromal hyperplasia have been included.

Full details of the clinical findings and treatment of each patient and of the pathology of each tumour are given in the appendix. Only the main features are considered in the following description.

FIBROMAS.(28 Cases).

A series of 33 tumours had originally been diagnosed by myself or another as fibromas. From this series 2 tumours were rejected as being thecomas, 2 as adenofibromas and 1 as a fibromyoma. This left 28 "true" fibromas. These tumours varied in size from 25 to 2.5 cms. in diameter. Most of the larger tumours were necrotic in the centre and were often mistaken clinically for cysts.

There was a gradual transition in the histological structure from fibroma to thecoma and it was not easy to distinguish between them. Staining reactions were inconstant and the appearance of the cells was not a certain guide. The most useful stain was Van Gieson's connective tissue stain. It had been noticed when examining normal ovaries that the capsule and fibrous framework of the ovary absorbed a deep pink and contrasted strongly with the active stroma which took no pink at all. This reaction was constant even in senile ovaries. When the stain was applied to the fibroma-thecoma group it was found that fibromas stained deep pink while tumours thought to be thecomas usually took little stain. The staining reaction was by no

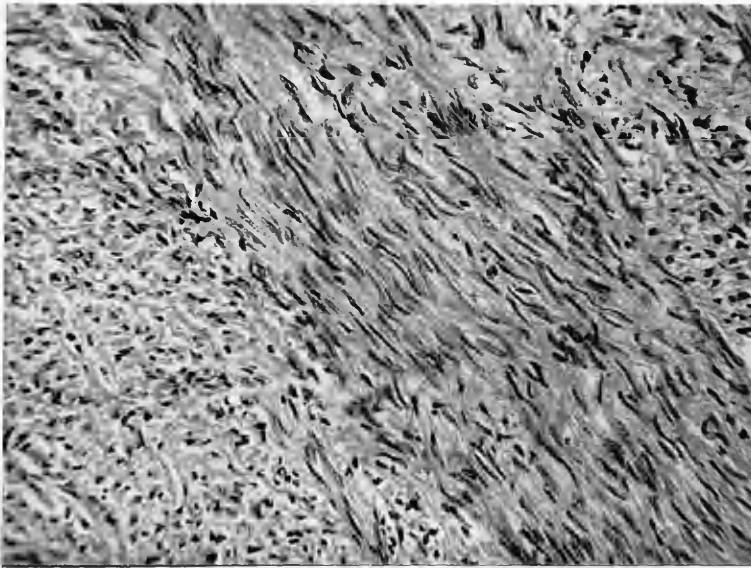


Figure 11.

Case 3. Fibroma showing abundant fibrous tissue and elongated nuclei.
x 275.

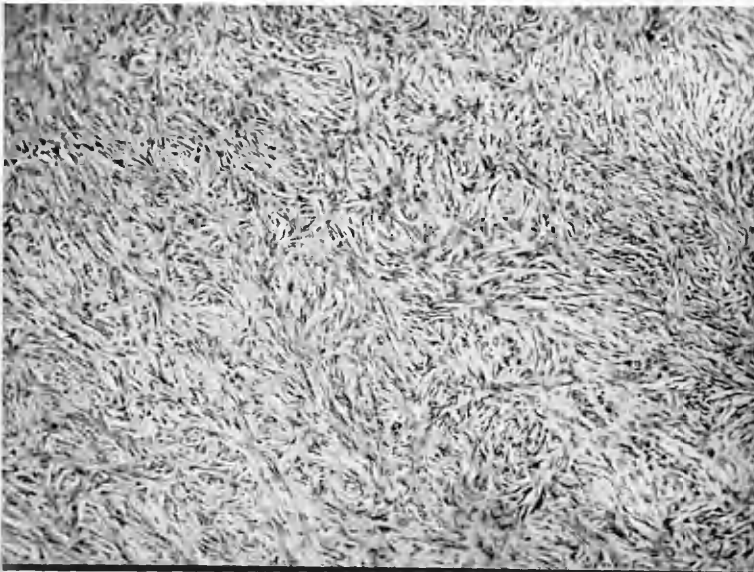


Figure 12.

Case 26. Dense fibroma showing interlacing bundles of fibres.
x 140.

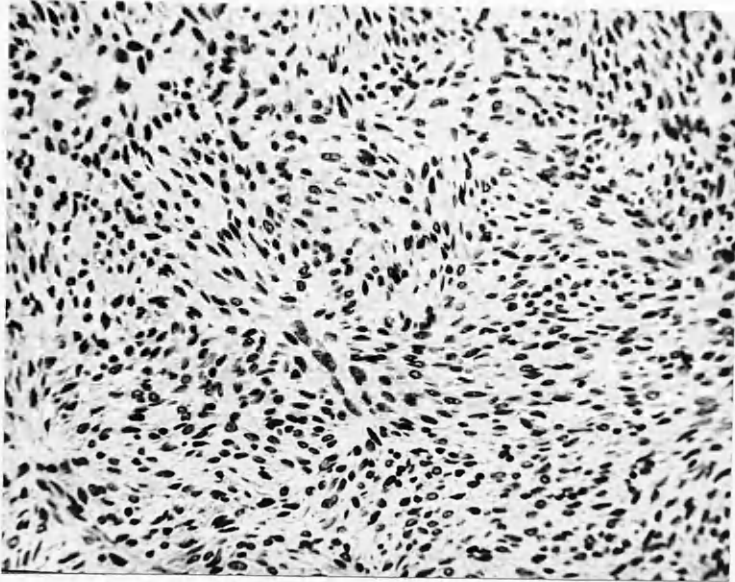


Figure 13.

Case 2. Fibroma showing oval and rounded nuclei.

x 275.

no means conclusive but it was found to be a useful aid to diagnosis.

The histological pattern varied. The most mature tumours contained a high proportion of fibrous cytoplasm in interlacing bundles. The nuclei were long, thin and tortuous and as cross-section they were kite-shaped, star-shaped or tufted. (Fig.11). A whorled pattern was evident in some specimens. (Fig.12). In the more cellular fibromas the nuclei were shorter and thicker, some were polygonal or oval. (Fig.13)

Clinical Features.

Age: The youngest patient was 21 and the oldest 81. The average age was 50. Only 3 patients were under 40.

Parity: 3 patients were unmarried. 11 patients were married and nulliparous, thus 50% of the patients were nulliparous.

Symptoms: The majority of patients complained of abdominal pain or abdominal distension. In 3 patients the discovery was accidental.

8 patients complained of uterine bleeding. This requires further analysis.

2 patients had adenocarcinoma of the uterus. (cases 10 and 11).

1 patient had a simple endometrial polyp.

2 patients had endometrial hyperplasia.

Case 15 had a relatively acellular fibroma with a luteal cyst in the same ovary.

Case 18 had fibroids and a cellular fibroma in association with a corpus luteum. This tumour may have been thecomatous.

1 patient had severe menorrhagia at the age of 42. The tumour was small and had probably no connection with the bleeding. The endometrium was in the secretory phase. (case 20).

1 patient had severe menorrhagia with normal endometrium.

It was noted in this case that the second ovary showed active stroma. (case 6).

1 patient had vaginal bleeding for 8 weeks at the age of 36. The second ovary was thought to contain thecomatous areas. (case 8).

The high incidence of bleeding in these cases is remarkable. It may have been coincidental or it may have been due to abnormal ovarian function. In none of these cases except perhaps No.18 was there much doubt about the histological diagnosis.

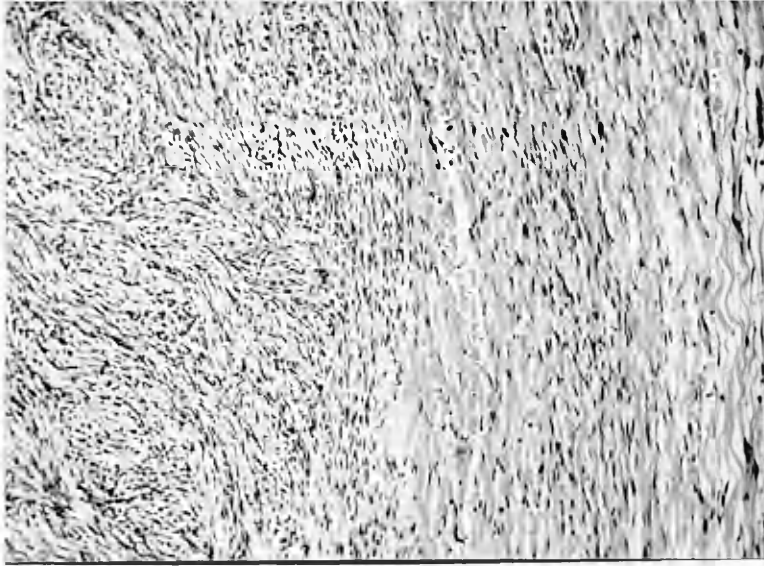


Figure 14.

Case 34. Thecoma histologically like a fibroma except that the parenchyma (left) took no Van Gieson stain whereas the capsule (right) stained pink. x 275.

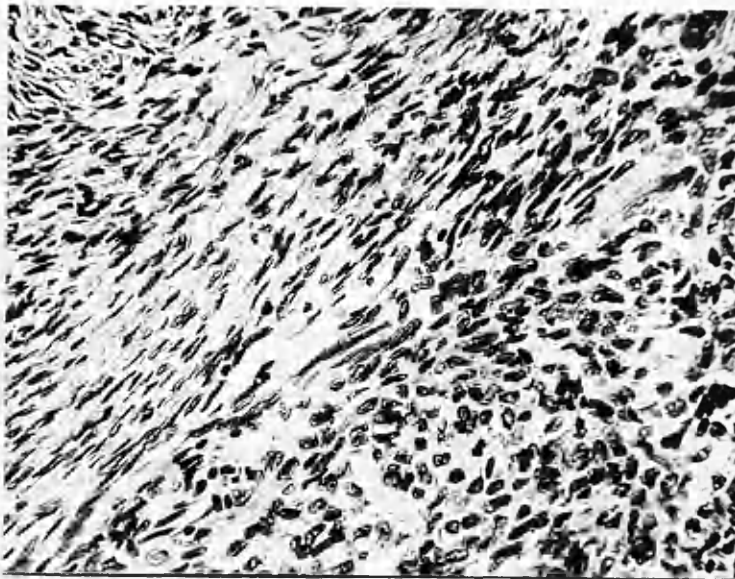


Figure 15.

Case 29. Histologically a typical thecoma. No post-menopausal bleeding. x 315.

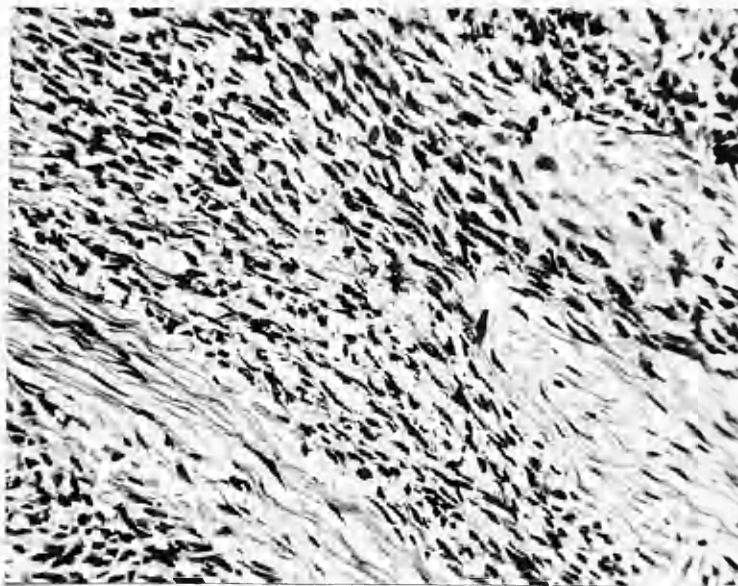


Figure 16.

Case 31. Probably a thecoma showing hyaline degeneration of the connective tissue. There was much lipoid in this tumour. x 275.

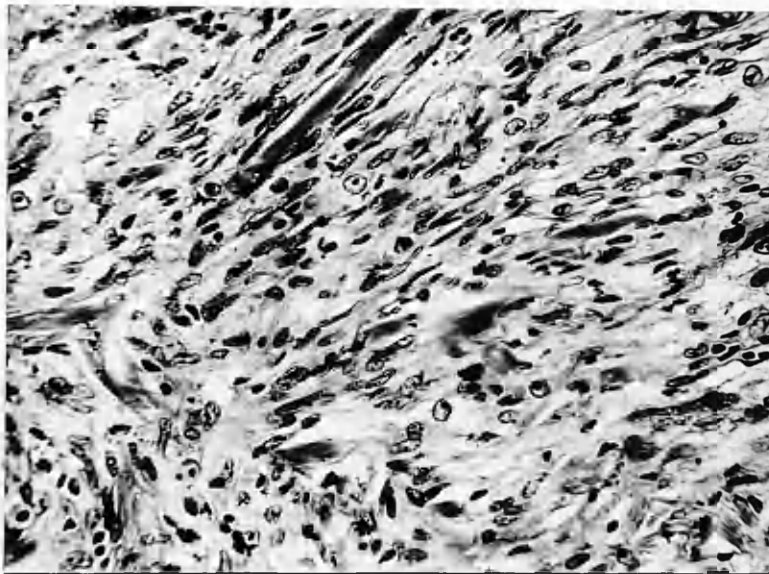


Figure 17.

Case 33. Thecoma with sarcoma-like appearance due to necrosis of the tumour. x 275.

THECOMAS and STROMAL HYPERPLASIA.

(8 cases).

6 tumours were classified as thecomas and 2 as stromal hyperplasia not quite established as neoplastic. The histology of these tumours illustrated the difficulty in diagnosis.

Case 34 gave a history of post-menopausal bleeding but the tumour except for the fact that it took no Van Giesons stain had the histological appearance of a fibroma (Fig.14). Case 29 showed the typical appearance of a thecoma with oval or elongated nuclei and a fibromatous arrangement of the cells (Fig.15). Case 31 showed a histological transition between cases 34 and 29. This tumour contained much lipoid and produced no endocrine effect (Fig.16).

A somewhat bizarre histology was seen in case 33. The tumour was taken from a girl of 21 who had excessive vaginal bleeding. She has since become pregnant. The extensive necrosis of the tumour was probably responsible for the sarcoma-like appearance (Fig.17). A transition to granulosa cell tumour was seen in case 30. ^(Fig.18) This tumour produced no obvious endocrine effect.

The two cases of stromal hyperplasia were remarkably

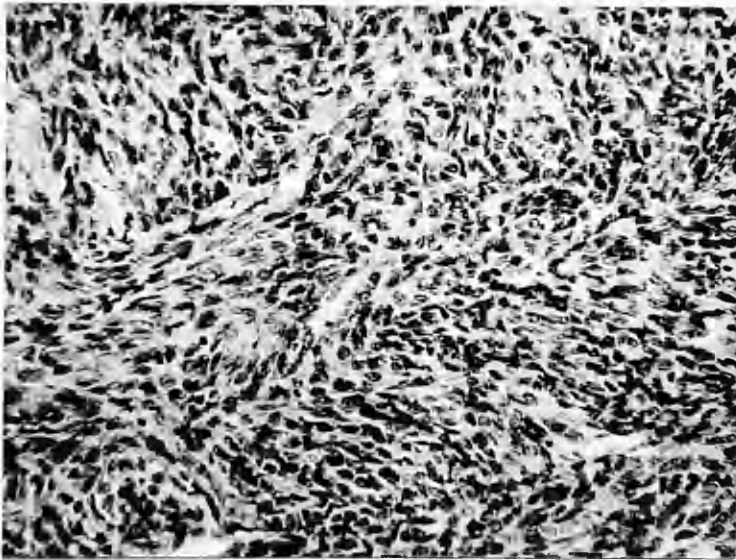


Figure 18.

Case 30. Histologically a transitional stage between thecoma and granulosa cell tumour. This tumour produced no obvious endocrine effect. x 315.

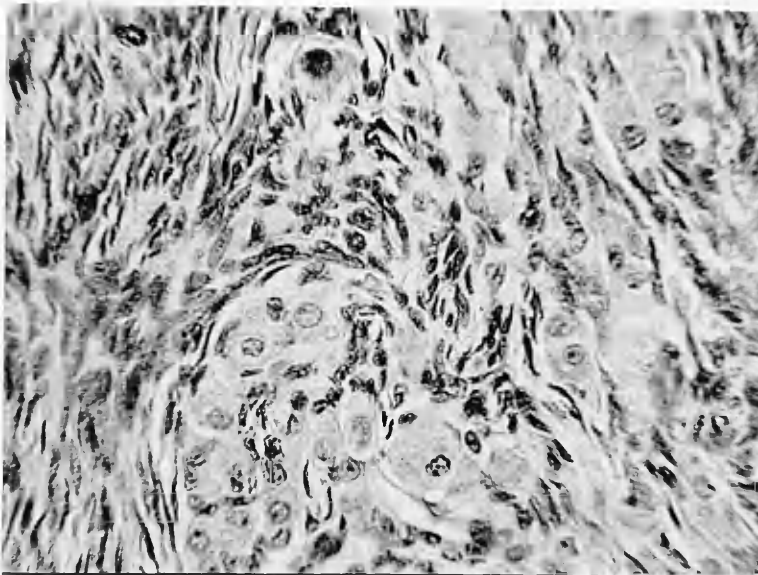


Figure 19.

Case 35. Very large Leydig-like cells in an ovary showing stromal hyperplasia, associated with post-menopausal haemorrhage. x 315.

alike (cases 35 and 36). Both patients were 66 years of age and both had 3 children. One complained of red vaginal discharge, the other of irregular vaginal bleeding. Both patients showed a high degree of endometrial hyperplasia. One patient had a menopausal course of deep X-ray but the bleeding had returned. All the ovaries had a similar atrophic appearance to the naked eye but on histological examination the stroma was seen to be unusually active and deep-stained. Case 35 was of particular interest. In addition to the diffuse overgrowth of the stroma one area showed a number of large cells with large nuclei and abundant clear cytoplasm. (Fig.19). The cells were found in association with a structureless corpus albicans. The cells may have been luteal but they bear a striking resemblance to Leydig cells.

Clinical Features.

Age. The youngest patient was 21 and the oldest 73.

The average age was 58.

Parity. 4 of the eight patients were unmarried, one was married and nulliparous. 7 children were born of 3 patients.

Symptoms. 3 patients complained of abdominal swelling. Two of these patients had uterine

uterine fibroids and small thecomas.

5 patients had abnormal uterine bleeding.

Endometrial hyperplasia was confirmed in 3 cases.

Treatment. 2 patients had a total hysterectomy and 1 a sub-total hysterectomy, with bilateral salpingo-oophorectomy in all 3 cases. 1 patient had bilateral salpingo-ooperectomy. The remaining 4 patients had the affected ovary removed, in one case supplemented by a menopausal course of deep X-ray.

Prognosis. One patient was not traced.

7 patients were alive, 7, 7, 7, 6, 5, 4 and 1 year after operation. None of these patients had further vaginal bleeding and all except one enjoyed reasonably good health.

The type of operation performed appeared to have little effect on the result provided the tumour was removed.

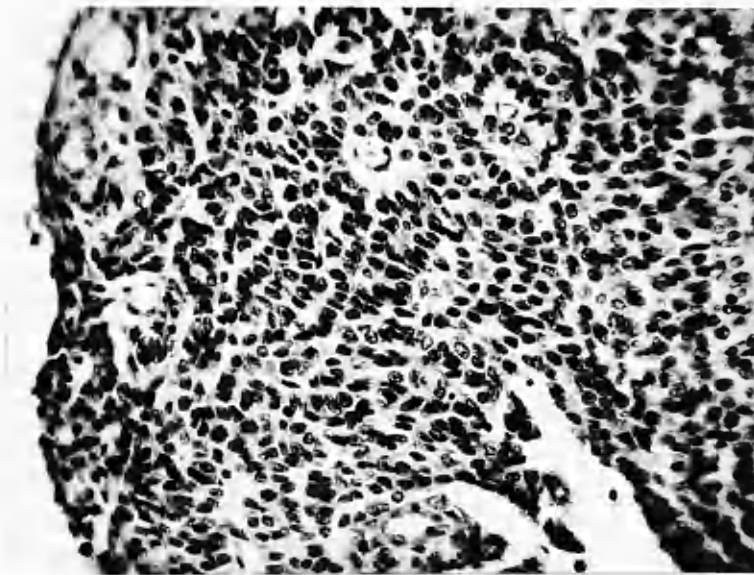


Figure 20.

Case 50. Diffuse granulosa cell tumour showing large deeply staining nuclei. Even in this tumour the cells tend to arrange themselves in cords. x 300.

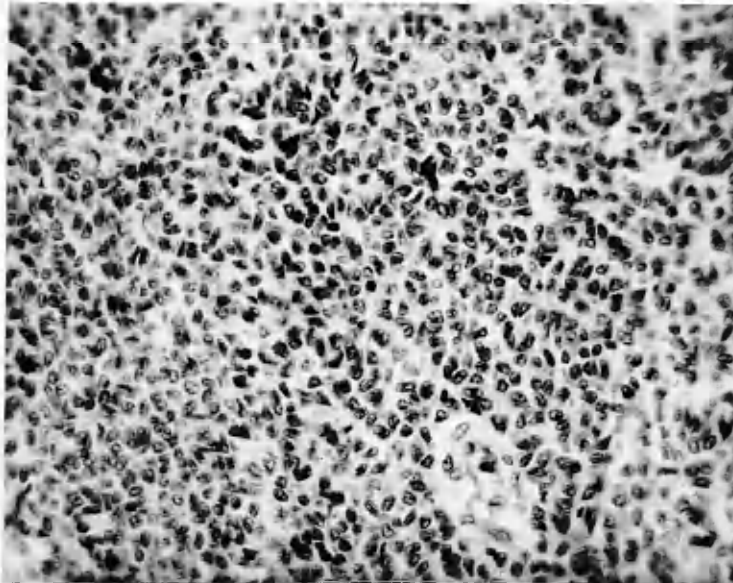


Figure 21.

Case 40. Diffuse granulosa cell tumour showing grooving of the nuclei. x 290.

DIFFUSE GRANULOSA CELL TUMOURS.

(16 cases.)

The tumours of this group consisted of typical granulosa cells with a varying amount of connective tissue. The granulosa cells formed little or no pattern but the sheets of cells were split up by connective tissue which made intricate designs.

The granulosa cells were closely packed. They had oval or polygonal nuclei, rather large and similar to one another. The nuclei stained deeply and nucleoli were usually seen. The cytoplasm was minimal and the cell margins were poorly defined (fig.20). Some nuclei showed grooving of the nuclei such as is seen in Brenner tumours (Fig.21).

2 tumours showed a departure from the usual pattern. In case 39 many of the cells were enlarged and had clear abundant cytoplasm with small nuclei. The changes were thought to be luteinization. This tumour had no obvious endocrine effect (Fig.22). Case No.43 had vaginal bleeding from a very hyperplastic endometrium at the age of 60. The tumour was very small and contained large pale cells with large spherical nuclei scattered irregularly through the granulosa. The cells

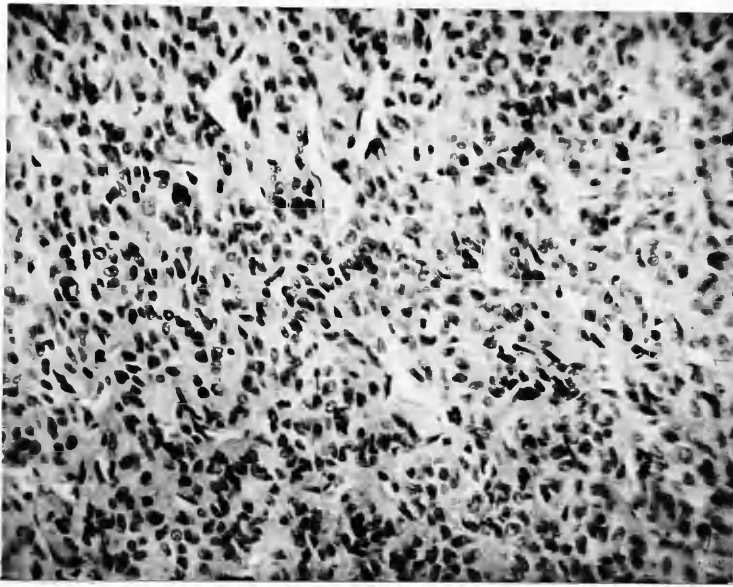


Figure 22.

Case 39. Diffuse granulosa cell tumour showing changes suggestive of luteinization.

x 290

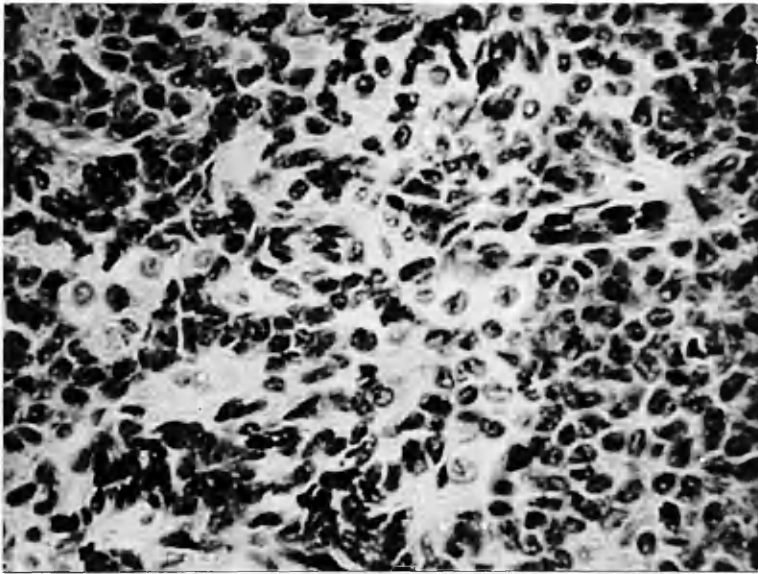


Figure 23.

Case 43. Diffuse granulosa cell tumour showing large pale Leydig-like cells.

x 550.

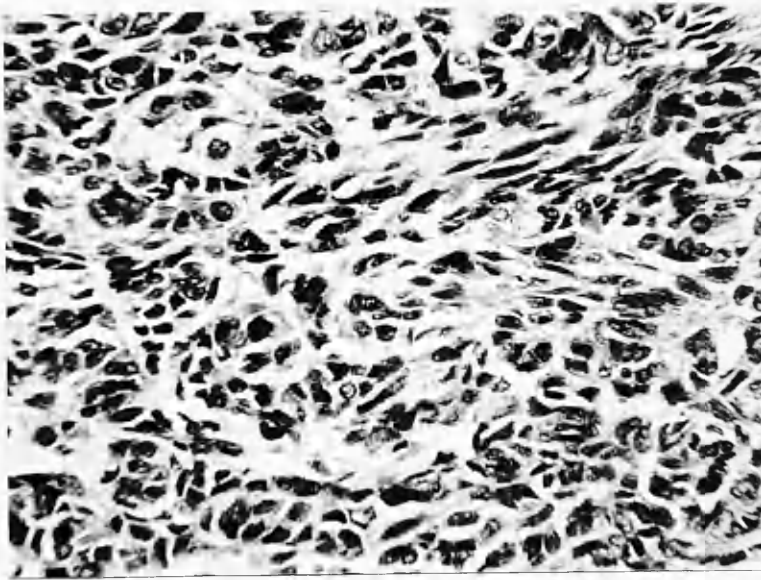


Figure 24.

Case 52. Masculinizing tumour of the diffuse granulosa type.
x 550.

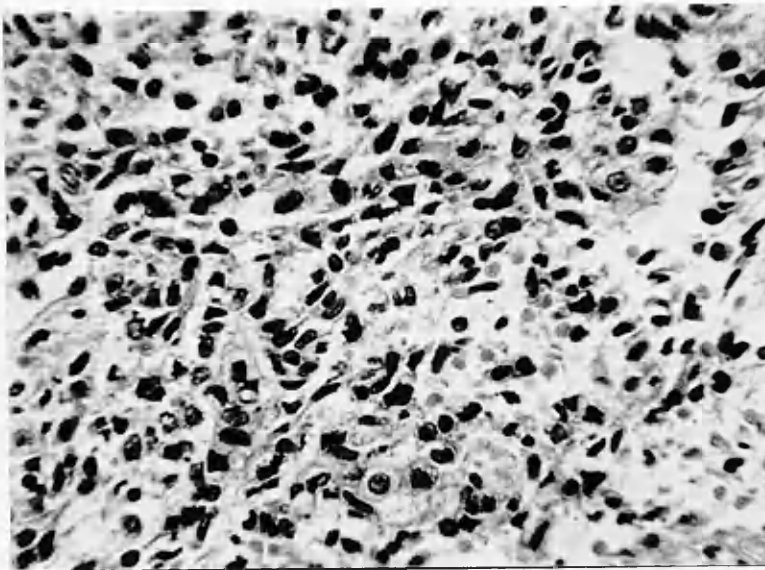


Figure 25.

Case 52. Another part of the same tumour showing several
Leydig-like cells.
x 550.

cells were more clearly defined than in case 39 and resembled Leydig cells (Fig.23).

An interesting contrast in clinical effect was seen in case No.52. This tumour occurred in an unmarried girl of 21 who at the age of 19 began to have irregular vaginal bleeding. This persisted for 8 months and was succeeded by amenorrhoea. Coincident with the onset of amenorrhoea she noticed a growth of hair on her face and limbs and her voice became deep. After a year these signs were well established and shaving had become necessary. A tumour 11 cms. in diameter was removed from the right side. Within a month of the oophorectomy menstruation was re-established and the cycle has been regular ever since. The hair gradually disappeared but the voice remained deeper than usual. The patient married during the war, she has had no children, the voice is still deep but she is well 17 years after operation.

The tumour was histologically a diffuse granulosa cell tumour with no cording or tubule formation but Leydig like cells could be seen in some areas (Figs. 24 and 25).

Clinical Features.

Age. The youngest patient was 21 and the oldest

oldest 68. The average age was 55.

Parity. 9 patients were nulliparous of whom 4 were unmarried. 7 patients gave birth to 27 children between them. This was a high infertility rate.

Symptoms. In 12 patients the effect of the tumour was feminizing, indicated by abnormal uterine bleeding.

In 1 patient the effect was strongly masculinizing. 3 patients complained of abdominal pain or swelling.

Endometrium. The endometrium was examined in 13 cases.

Adenocarcinoma was found in one case, endometrial hyperplasia in 9 cases, proliferative endometrium in 2 cases and senile endometrial polyps in 1 case.

Treatment. Total hysterectomy was done in 5 cases, subtotal in 6. In each case accompanied by bilateral salpingo-oophorectomy. Bilateral salpingo-oophorectomy was performed in 1 case, uni-lateral in 2 cases and exploratory laparotomy in 1 case.

Prognosis. 13 patients were alive and well from 2 to 17 years after operation.

1 patient with inoperable carcinoma died within 6 months.

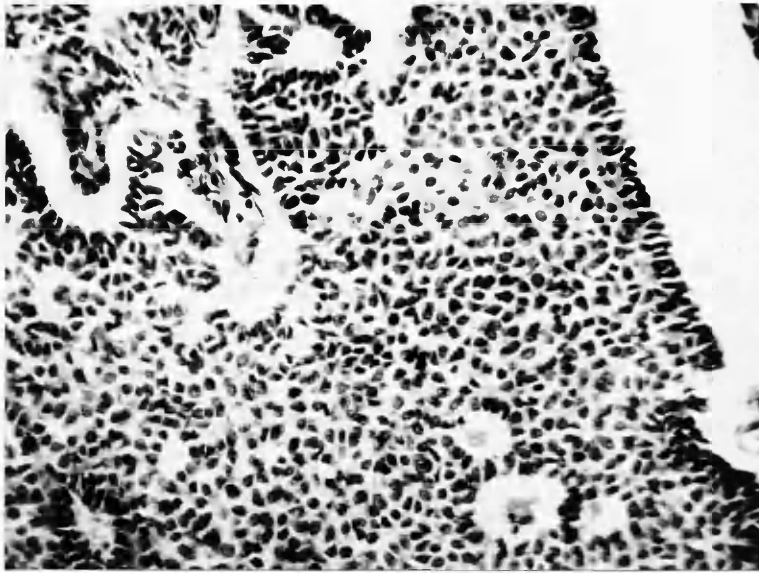


Figure 26.

Case 61. Area of typical granulosa showing rosettes and columnar arrangement of cells at the margin. x 290.

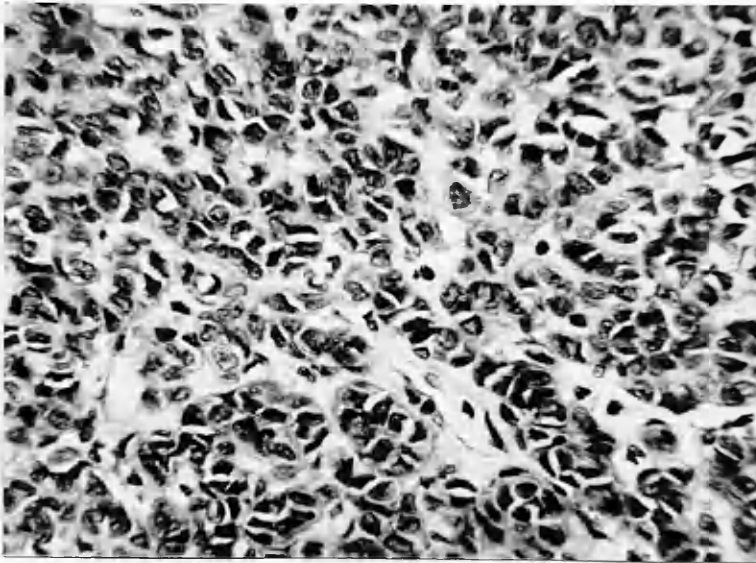


Figure 27.

Case 59. The cells form rows or cords without differing in nature from those around them. x 550.

1 patient died 7 days post-operatively and 1 is presumed to have died within the 20 years after operation.

DIFFERENTIATED GRANULOSA CELL TUMOURS.

(12 cases).

This group consisted of tumours in which the granulosa cells had assumed a definite pattern. The basic pattern was considered to be that which reproduced the characters of the granulosa of the Graafian follicle. In such tumours the granulosa consisted of cells with large smooth oval or rounded granular nuclei, evenly stained, with little cytoplasm and ill defined cell margins. Rosette formation was frequent and the cells at the periphery of the granulosa masses were arranged in a columnar fashion at right angles to the margin (Fig.26). The granulosa tended to be split up into columns by hyalinized connective tissue.

These tumours might be called "typical" granulosa cell tumours but there was no tumour in the group which showed this typical arrangement without some further differentiation being observed.

This further differentiation was a tendency on the part of the cells to arrange themselves in rows or cords,

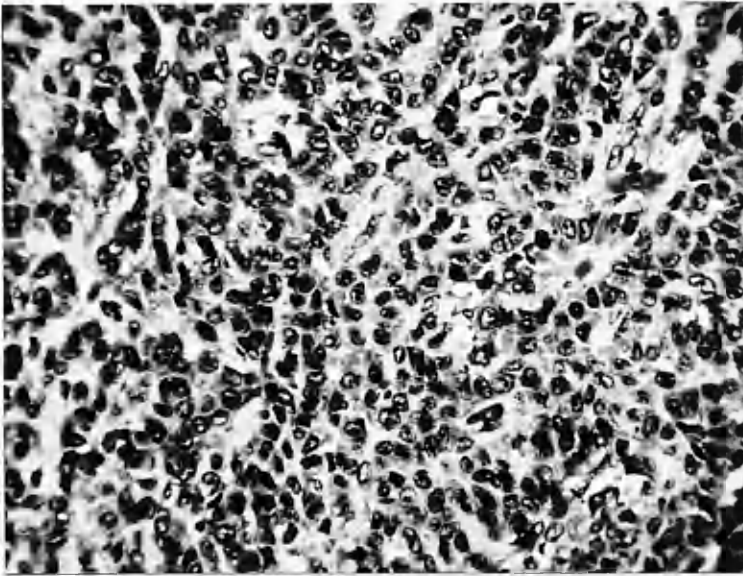


Figure 28.

Case 63. The granulosa tends to be arranged in parallel columns of cells. x 300.

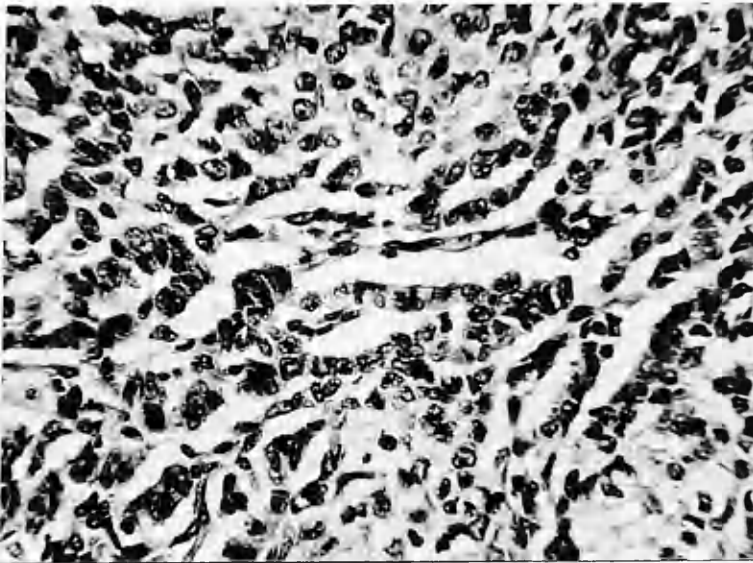


Figure 29.

Case 54. Primitive tubule formation without differentiation of the cells. x 300.

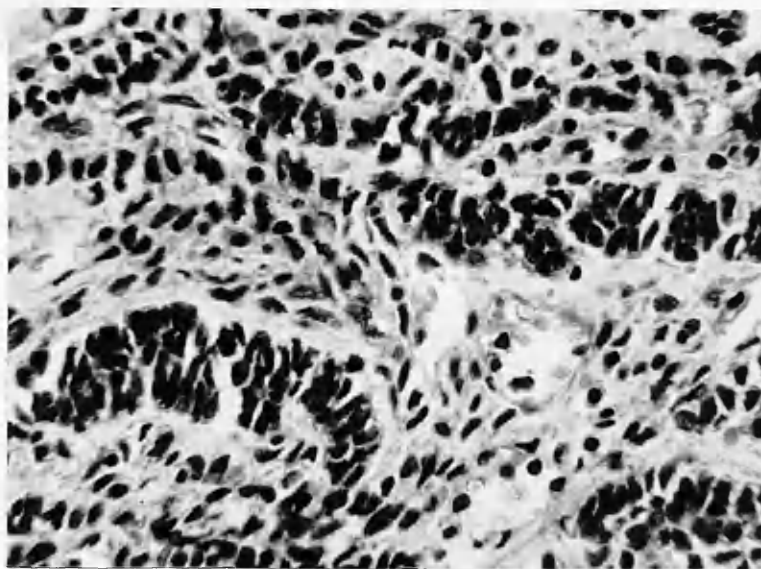


Figure 30.

Case 57. Cords of cells sharply distinguished from the surrounding tissue. The likeness of these cells to Sertoli cells is remarkable. Compare Fig. 31. x 475.

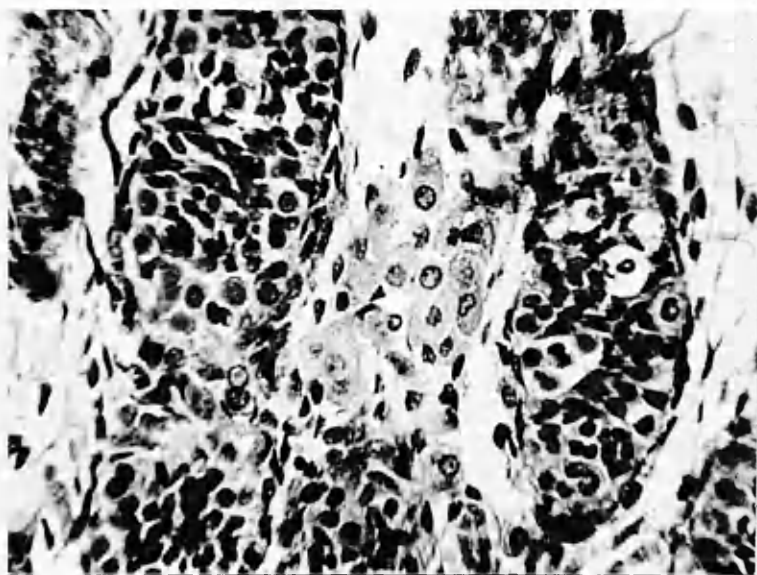


Figure 31.

Testis at 40 weeks. Shows Sertoli and Leydig cells. x 475.

cords, or to form tubules or glands. It was the cording and tubule formation in these tumours which particularly aroused the author's interest because it was interpreted as being a reversion of the tumour to a male type of cell. The significance of the cording and tubule formation is discussed later but in the following description it will be noticed that there appears to be a distinct parallel between the histological changes in the growing tumour and in the developing gonad.

In its least obvious form the cording was manifest by the tumour cells tending to arrange themselves in rows, the cells in the rows being similar to those around them (Figs.27 and 28), or to form tubules without much differentiation of the cells themselves (Fig.29). In a further stage of differentiation the rows became more obvious and the cells assumed a different character (Fig.30). These cords of cells showed a sharp contrast to the tissue surrounding them and a likeness could be seen between these cells and the Sertoli cells of the developing testis. (Fig.31).

The male directed character of the tumour cells was emphasised by the appearance of a tubular pattern. In 5 cases this was particularly marked but all these 5 cases also contained granulosa cells and a transition could be

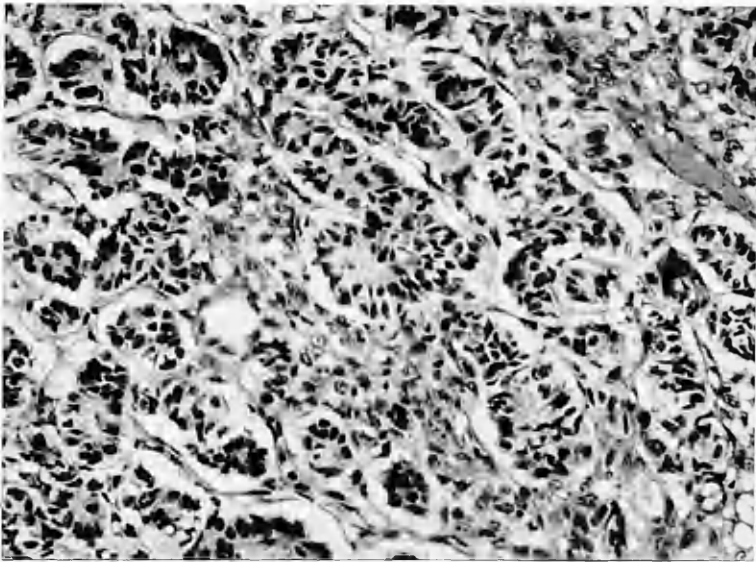


Figure 32.

Case 64. Tubular area in an otherwise typical granulosa cell tumour showing a Leydig-like reaction in the interstitial tissue.

x 275.

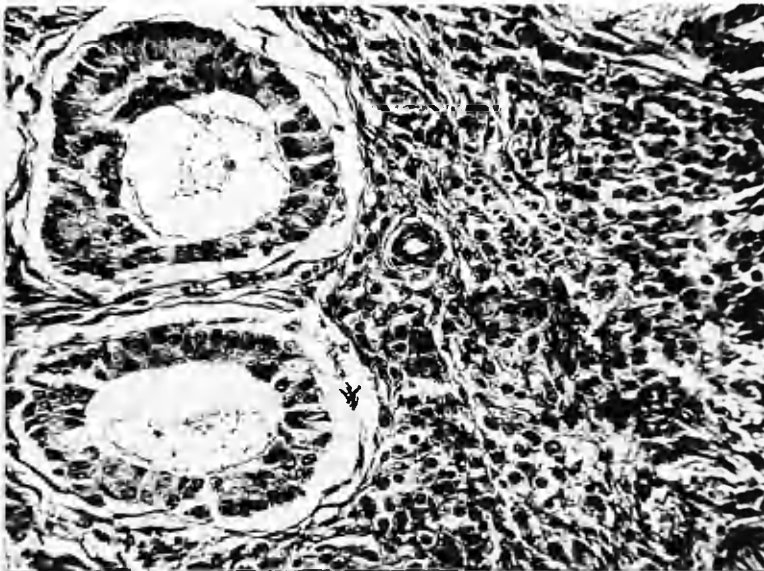


Figure 33.

Case 55. Tubules in granulosa cell tumour showing antipodal arrangement of nuclei and swelling of cells in the interstitial tissue.

x 275.

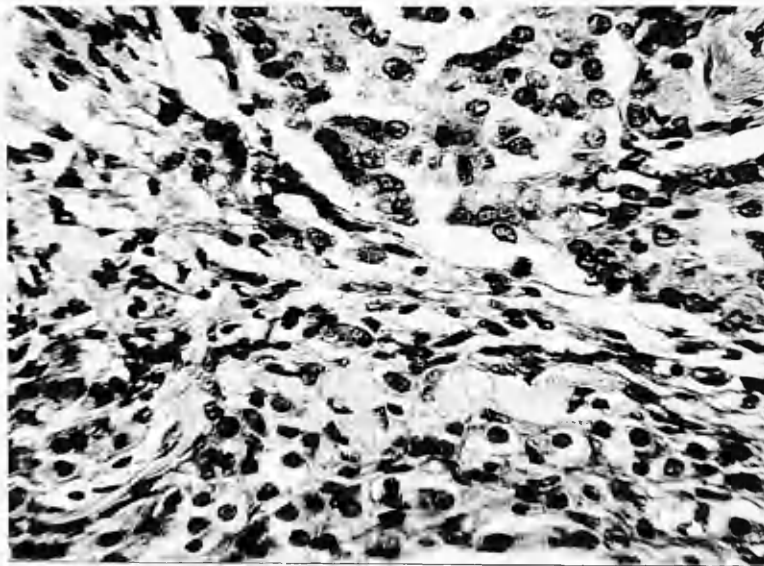


Figure 34.

Case 55. High power field of Fig. 33 showing large bloated
Leydig-like cells x 550.

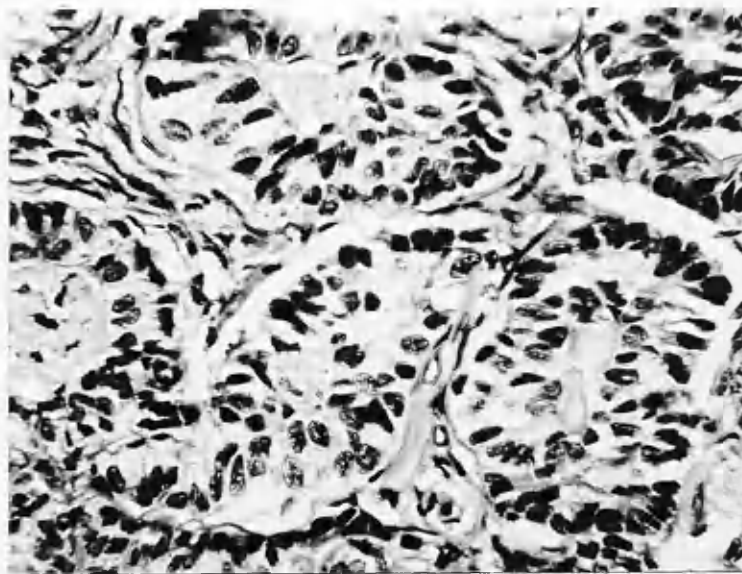


Figure 35.

Case 53. Tubular portion of granulosa cell tumour. x 550.

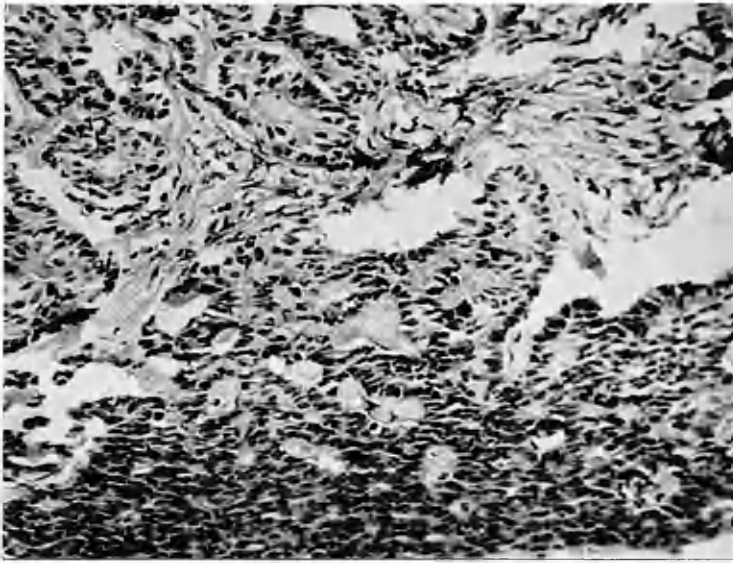


Figure 36.

Case 53. Shows transition from granulosa to adenomatous tissue.
x 275.

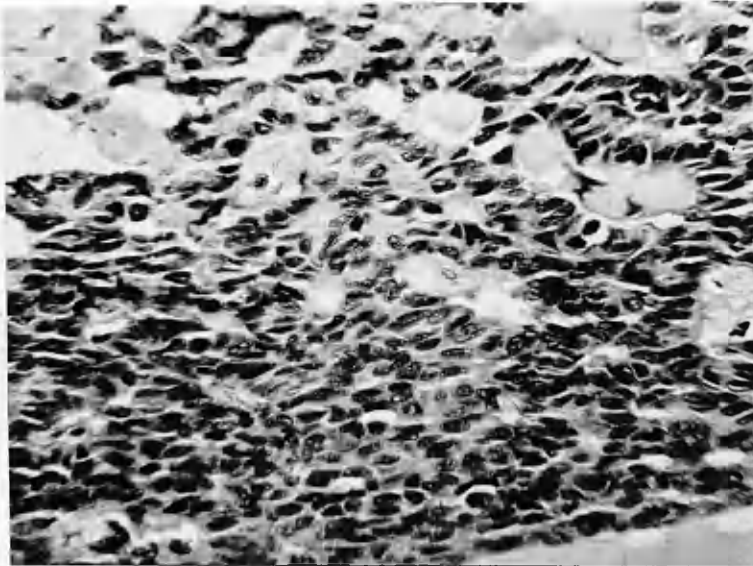


Figure 37.

Case 53. Shows Leydig or luteal reaction in cells near the
centre of the figure.
x 550.

be traced from the granulosa to the tubular pattern. It was also evident that these Sertoli-like tubules were associated with a Leydig reaction as in the developing testis.

Case No.64 was for the most part a typical granulosa cell tumour but one area showed tubule formation with Leydig like cells in the interstitial tissue. This tumour was associated with marked cystic glandular hyperplasia of the endometrium with a decidual change in the superficial layers of the stroma without secretory activity of the glands (Fig.32). Case No.55 had an adeno-carcinoma of the uterus and in one ovary a tiny tumour showing all transitions from thecoma to tubular adenoma was found. In this case too the cells surrounding the tubules were large and clear resembling theca-lutein or Leydig cells (Figs.33 and 34). Case No.53 had large uterine fibroids and menorrhagia. The ovarian tumour was small and for the most part tubular but in one area a transition to granulosa could be clearly traced (Fig.36). The Leydig reaction in this tumour was not marked but some cells of this nature were seen (Fig.37). Case No.58 had cystic glandular hyperplasia of the endometrium which persisted after a menopausal course of X-ray. The ovaries had an atrophic

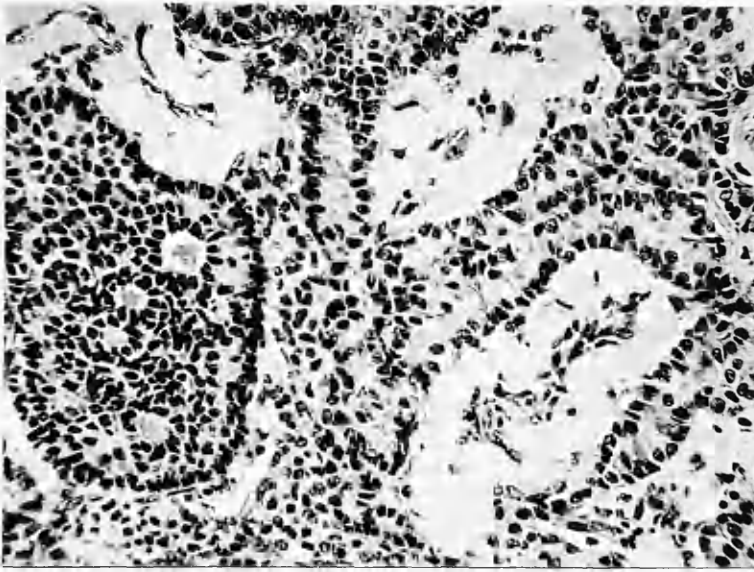


Figure 38.

Case 58. Showing granulosa and tubule formation.

x 275.

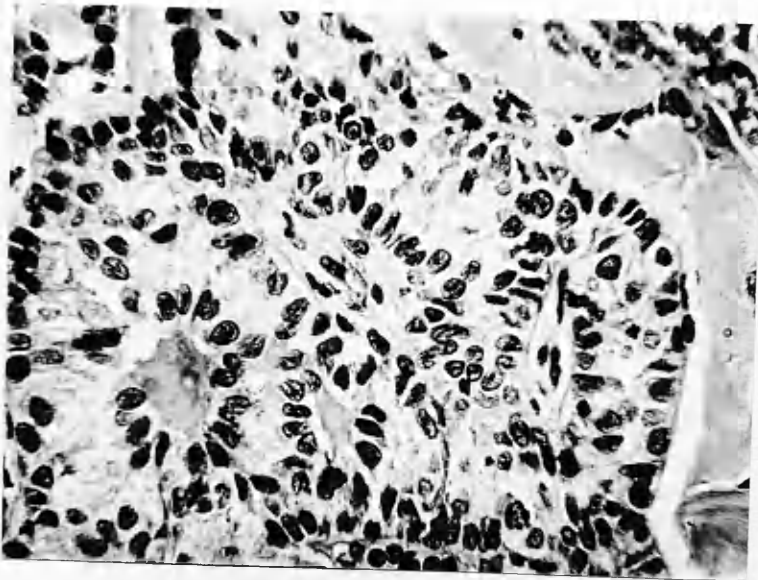


Figure 39.

Case 58. Higher power view of tubules showing antipodal arrangement, vacuolation and grooving of nuclei.

x 550.

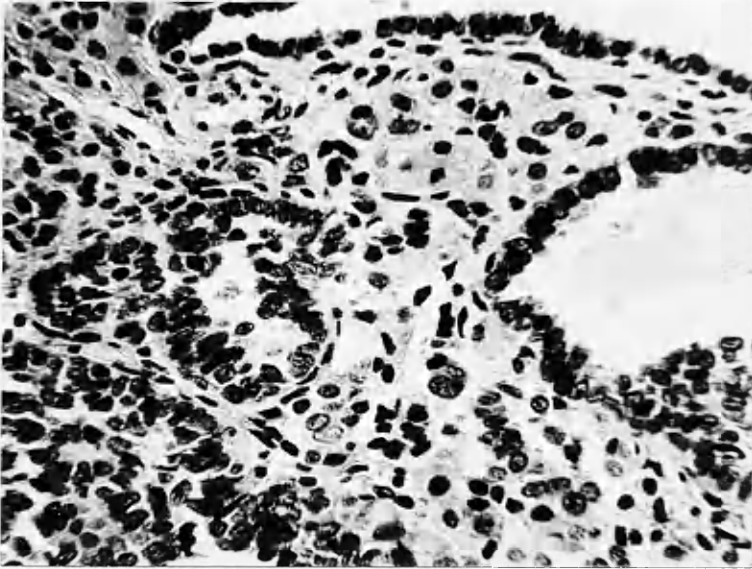


Figure 40.

Case 60. Shows Sertoli-like tubule with Leydig cells in the interstitial tissue. The tumour consisted otherwise of diffuse granulosa. x 475.

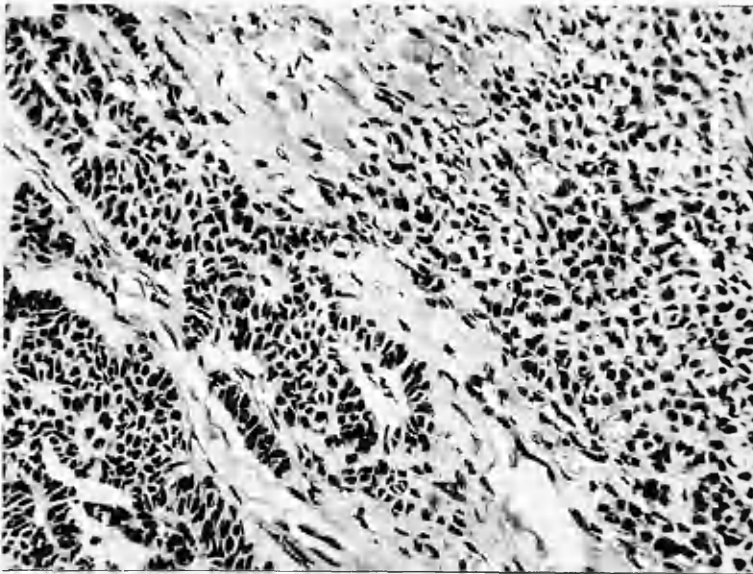


Figure 41.

Case 62. Defeminizing tumour showing right, diffuse granulosa and left, differentiated cells forming a tubular pattern.

x 255.

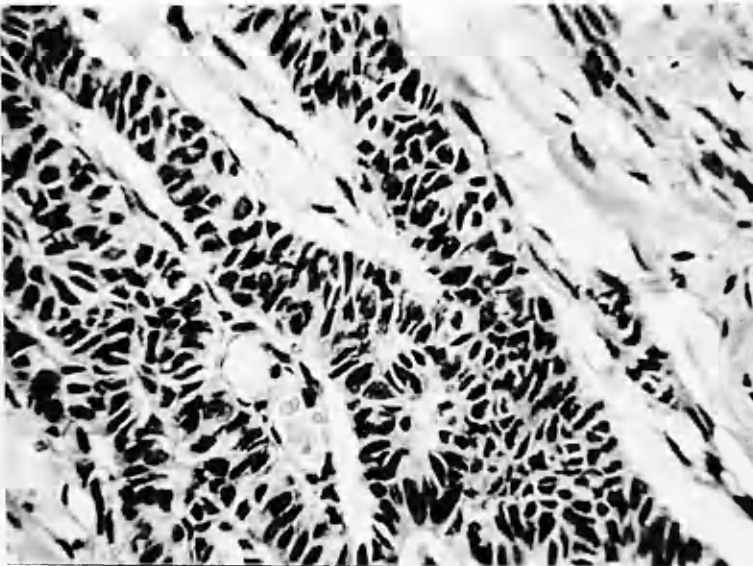


Figure 42.

Case 62. Detail from Fig. 41 showing Sertoli-like nature of cells. No Leydig cells are seen.

x 550.

atrophic appearance but in the centre of one was a tumour 10.5 x 4.5 mm. in section. The tumour showed highly differentiated tubules made up of cells arranged in an antipodal fashion and showing vacuolation. The nuclei were oval and many showed grooving. Typical granulosa was also present. The interstitial cells showed little reaction (Figs.38 and 39). Case No.60 developed severe menorrhagia at the age of 28. A tumour 10 cms. in diameter was removed. This tumour was for the most part a diffuse granulosa cell tumour with an irregular and rather vague pattern of cords. At one point the cells changed their pattern and were arranged in tubules of Sertoli-like cells. There was a marked Leydig reaction in the cells of the interstitial tissue (Fig.40).

A defeminizing effect was produced by the tumour in case No.62. The patient aged 29 had one child, menstruation was never regular occurring every 3-4 months with a normal flow. She had amenorrhoea for 10 months prior to examination. After the tumour was removed the periods became normal. The tumour was of the diffuse granulosa-thecoma type except for the presence of well differentiated cells in parallel columns forming a tubular pattern.(Figs.41 and 42). No Leydig-like cells were found in this tumour.

Clinical Features.

Age. Two of the patients were aged 29, the next youngest was 45 and the oldest 64. The average age was 49.

Parity. 3 patients were unmarried and nulliparous. 3 patients were married and nulliparous.

6 patients had 37 children between them.

Half the patients were therefore nulliparous.

Symptoms. In 10 patients the effect of the tumour was feminizing producing abnormal uterine bleeding. In 1 case the effect was defeminizing - amenorrhoea. 1 patient complained of pelvic pain only.

Endometrium. 4 patients had cystic glandular hyperplasia.

1 patient had adenocarcinoma of the uterus.

2 patients had little or no endometrium in the uterus.

5 patients had no endometrial specimen available.

Treatment. 1 patient had a total hysterectomy and bilateral salpingo-oophorectomy performed (adenocarcinoma).

3 patients had subtotal hysterectomy and bilateral or unilateral salpingo-oophorectomy.

8 patients had only the affected ovary removed.

Prognosis. 1 patient died of metastases.

8 patients were well up to 16 years after operation.

3 patients operated on up to 20 years ago could not be traced.

The type of operative procedure carried out seemed to have little effect on the prognosis.

Carcinoma of the Ovary.

(59 Cases).

This group of tumours has been included for two reasons. First in order to give material for a comparison of the clinical features with fibromas and the functioning tumours, and second because several tumours were found in the series which were identical with tumours described in the literature as masculinizing adrenal-like tumours or luteomas. None of the tumours in this series appeared to have an endocrine effect.

59 malignant tumours of the ovary were included in the series, all except one occurred in the period 1948-54, the exception being a particularly good example of "luteoma" (No.121). From the 59 cases 7 have been considered in a subgroup as "ovarian carcinoma with clear cells".

The carcinomas were divided histologically in three main groups.

First. Primary adenocarcinoma. These tumours were made up of rather large cells with a considerable amount of cytoplasm and large pale or oval nuclei. The pattern was adenomatous, often well defined but frequently showing dedifferentiation into solid masses of cells. 21 tumours fell into this group, most of which appeared to be highly malignant.

Second. Cystic tumours showing malignant change.

There were 17 tumours in this group, 13 being papillary, serous adenocarcinomas and 4 only being pseudomucinous cystadenocarcinomas. These figures are rather striking when compared with the simple cysts which occurred during the same period of which 108 were pseudomucinous cysts and only 17 papillary serous cysts. The reason why there should be this reversal in proportion is not obvious.

Third. Secondary carcinoma. 12 tumours were secondary to carcinoma elsewhere. All these tumours were remarkable for the faithful way in which they reproduced the histological characteristics of the primary growth.

The only surviving patients in this group had tumours secondary to adeno-acanthoma of the uterus. Six tumours could not be included in any group, details are given in the appendix.

Clinical Features.

(1) Primary carcinoma. (21 cases)

Age:- The youngest patient was 30, the oldest 63.
The average age was 53.

Parity:- Four patients were unmarried and 10 were nulliparous.

11 patients bore 34 children between them.

Symptoms:- 4 complained of vaginal bleeding.

Case 65 No obvious reason. Endometrium not examined. Age 61.

Case 70 Uterus riddled with cancer.

Case 80 Invasion of uterine wall.

Case 82 Cystic glandular hyperplasia. Age 55.

The remainder complained of abdominal symptoms.

Prognosis:- 14 of the patients are now dead.

(1 presumed dead - Case 82).

7 are still alive as follows.

Case 65 deep X-ray alive at 3 years.

Case 71 deep X-ray alive at 2 years.

Case 74 very malignant looking tumour. X-ray.
Alive at 8 years.

Case 76 Salpingo-oophorectomy. Alive at 7 years.

Case 77 Salpingo-oophorectomy. Alive at 7 years.

Case 79 Fibro-adenocarcinoma, salpingo-oophorectomy.
Alive at 6 years.

Case 83 Subtotal hysterectomy, bilateral salpingo-oophorectomy. Alive at 5 years.

(2a) Papillary cystadenocarcinoma (13 cases).

Age:- Youngest patient was 35, oldest was 69.

Average age 50 years.

Parity:- 2 patients were unmarried, 7 were nulliparous.

6 patients bore 11 children. (one patient had 5).

Symptoms:- One patient only complained of post menopausal bleeding. She had a coincident endocervical carcinoma.

Prognosis:- 9 patients are dead.

4 patients are still alive.

Case 88 Histologically on the border-line of malignancy. Salpingo-oophorectomy. Well at 5 years.

Case 94 Border-line malignancy. Salpingo-oophorectomy. Well at 5 years.

Case 95 Border-line malignancy. Bilateral salpingo-oophorectomy. Well at 8 years.

Case 98 Age 69. A highly malignant tumour. X-ray. Well at 3 years.

(2b) Pseudomucinous cystadenocarcinoma (4 cases).

Age:- Youngest 26, oldest 51, average age 44 years.

Parity:- 2 unmarried, 3 nulliparous, 1 patient had 4 children.

Symptoms:- 3 complained of irregular bleeding.

Case 99 very hyperplastic endometrium.

Case 100 adenocarcinoma of uterus.

Case 101 no obvious reason.

Prognosis:- 1 patient died. This was an unusual case. The patient (case 102) was a nurse who complained of abdominal swelling. The abdomen was full of pseudomucinous growth much of which was removed. A full course of deep X-ray was given. The growth infiltrated the wound and the patient eventually died. Histologically although many biopsy specimens were examined it was difficult to persuade oneself that the growth was malignant.

3 patients are well, as follows:-

Case 99 Subtotal hysterectomy, bilateral salpingo-oophorectomy. Deep X-ray. Well at 7 years.

Case 100 Primary carcinoma of uterus and primary carcinoma of ovary. Total hysterectomy and bilateral salpingo-oophorectomy. Deep X-ray. Very well at 7 years.

Case 101 Invasive tumour. Salpingo-oophorectomy,
and X-ray. Well at 6 years.

(3) Secondary Carcinoma. (12 cases).

Age:- The youngest patient was 13, the oldest 67.

Average 49 years.

Parity:- 4 unmarried, 8 nulliparous. 4 patients
bore 12 children; (one patient had 6).

Symptoms:- Only patients suffering from uterine
cancer complained of bleeding.

Pathology:- Ovarian tumours were secondary to -

Sigmoid 2 cases. Nos. 109, 105.

Bowel and Stomach. 1 case. (Krukenberg tumour) No.114.

Sarcoma of nasopharynx. 1 case. No.107.

Uterus 8 cases. Nos.103, 104, 106, 110, 111, 108, 112, 113.

Prognosis:-

6 patients are alive all of whom had tumours
secondary to adenocarcinoma or adenoacanthoma of
uterus. They have survived for 8, 6, 6, 5, 4, and
3 years. 6 patients have died.

(4) Miscellaneous. (9 cases).

3 cases diagnosed as sarcoma are all dead. Nos.115,116,117.

1 case of malignant endometriosis is well 8 years later.119.

1 case of squamous epithelioma in a dermoid is dead. 118.

1 case of fibroadenocarcinoma is dead. 120.

3 cases of carcinoma with clear cells. 1 is presumed
dead, 121, two are alive 3 and 1½ years after

after operation. 122, 123.

OVARIAN CARCINOMA WITH CLEAR CELLS.

The title given to this group of tumours was suggested by Saphir and Lackner (1944) and it appears to be a good one because it does not presuppose the histogenesis of the group in the way that "luteoma", "adrenal" or "hypernephric" tumour does. There is so much confusion in the pathology of this group of tumours that it is not the author's intention to complicate it further. The point he wants to make is that there are tumours histologically identical with the "luteoma" group which appear to be straightforward adenocarcinomas without any endocrine effect.

There were 7 tumours in this group. 4 of these tumours were in the series of primary adenocarcinomas, 2 had been discarded from the carcinoma series as belonging to the dysgerminoma group and one was a specimen which had been preserved in the museum.

Tumour No.121 was taken from a woman of 58 who had had 10 children. She complained of abdominal swelling. The tumour had a well defined capsule and was supported by a network of connective tissue which divided the

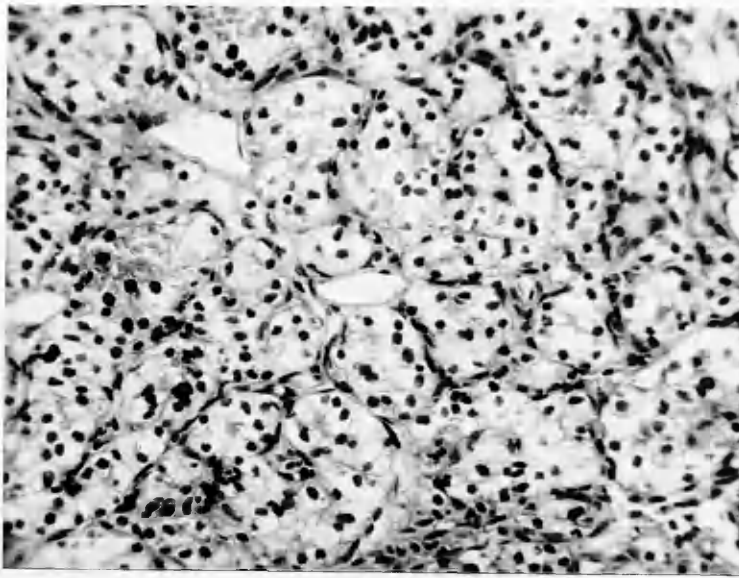


Figure 43.

Case 121. Carcinoma with clear cells resembling luteoma. The tumour contained much lipid. x 290.

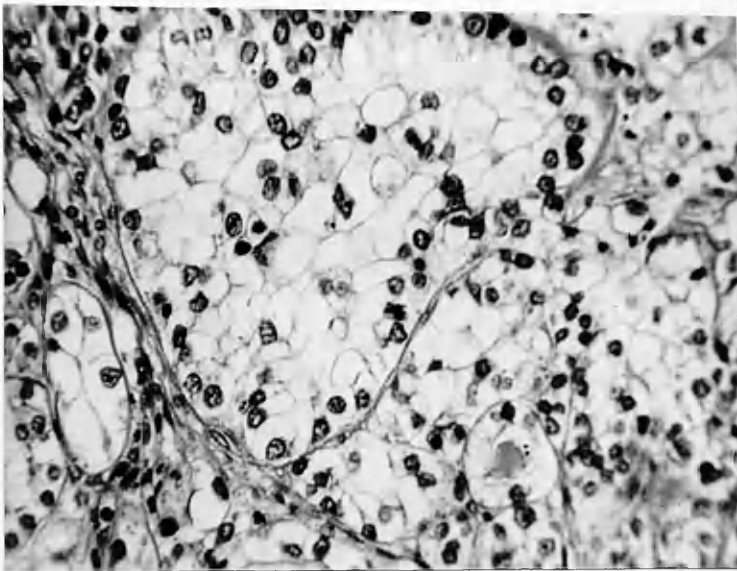


Figure 44.

Case 70. Cells resembling luteal cells in a carcinoma of the ovary. x 290.

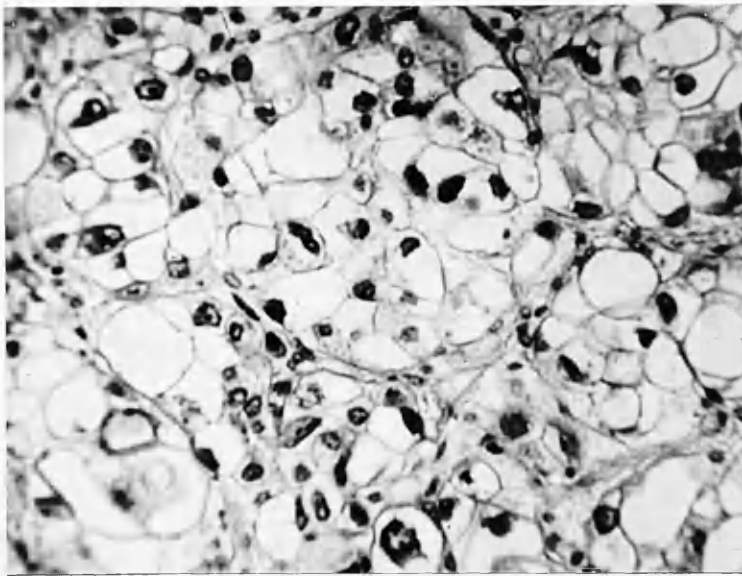


Figure 45.

Case 122. The cells appear more malignant in this tumour. The endometrium was hyperplastic. x 290.

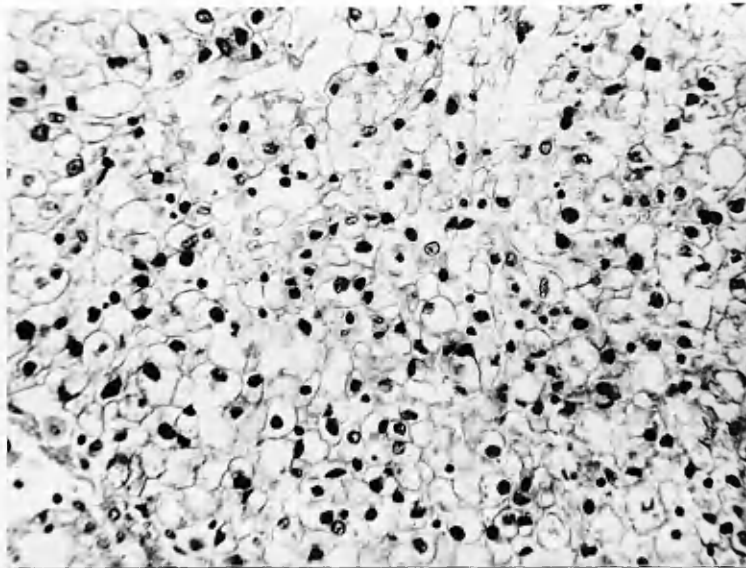


Figure 46.

Case 123. Tumour similar to above but note the discrepancy in the size of the cells. x 290.

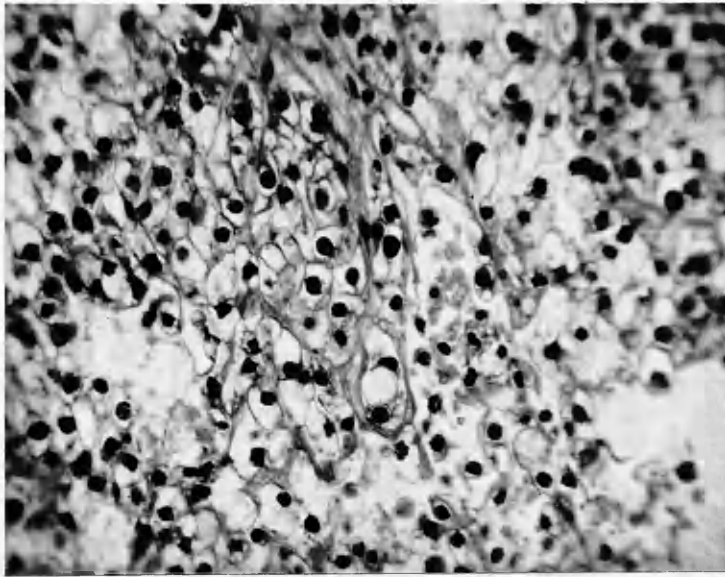


Figure 47.

Case 76. The tumour has a similar structure to that shown in
Fig. 46. x 290.

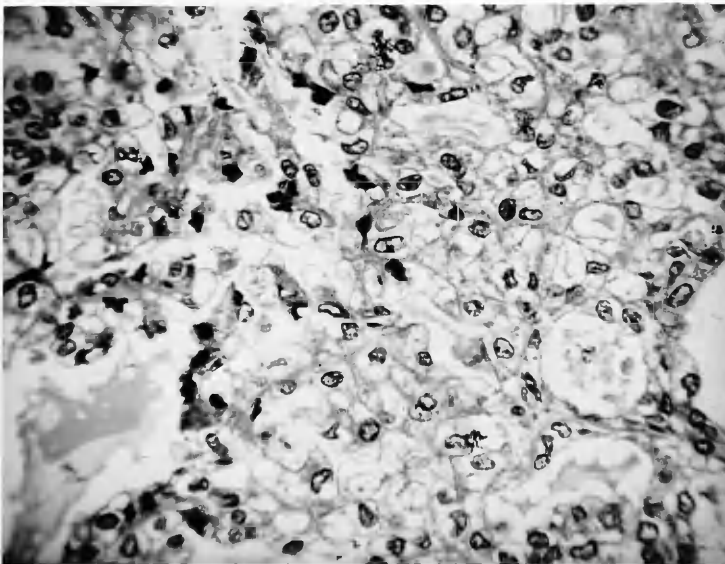


Figure 48.

Case 78. A similar type of tumour with less definite pattern.
x 290.

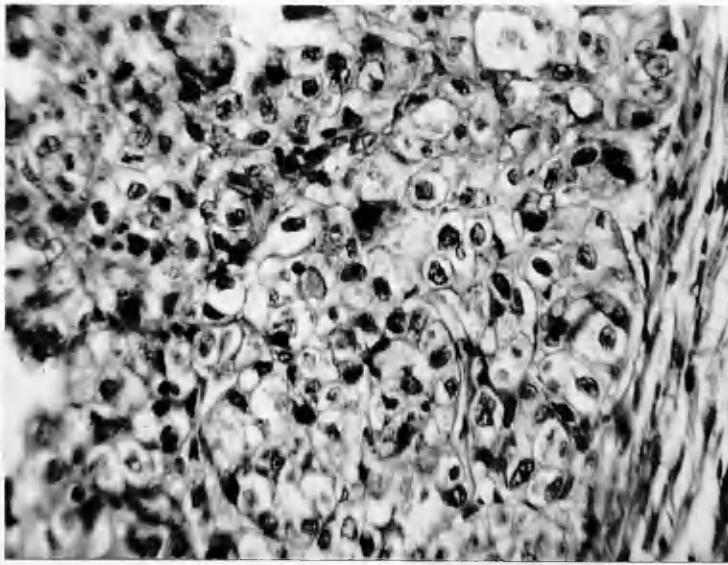


Figure 49.

Case 77. Carcinoma of the ovary containing some clear cells.
x 290.

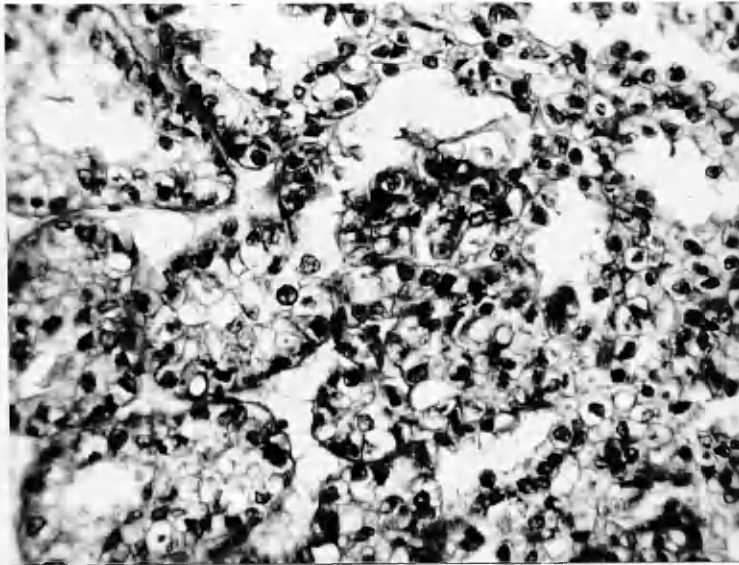


Figure 50.

Case 77. Another part of the same tumour showing adenocarcinomatous structure.
x 290.

the tumour cells into small groups. The tumour cells had abundant cytoplasm loaded with lipoid and were roughly quadrilateral in shape. The nuclei were small and round. There was a close resemblance to lutein cells (Fig.43). In other parts of the tumour there was a frankly adenocarcinomatous appearance. Tumour No.70 was very similar but the groups of cells were larger and the nuclei tended to be arranged peripherally. In this case the pelvic contents were riddled with the growth and the patient died shortly after the operation. There were no masculinizing features (Fig.44). Tumour No.122 combined the features of the two previous cases but the connective tissue was minimal and histologically the tumour appeared to be more malignant. (Fig.45). In this case the tumour was associated with post-menopausal haemorrhage from a markedly hyperplastic endometrium.

Case 123 showed cells similar to those already described with a resemblance to luteal cells. There was no endocrine effect and clinically the tumour was an adenocarcinoma. (Fig.46). Case 76 retained some similarity to the luteal-like tumours but was more frankly adenomatous (Fig.47). Case 78 was much the same (Fig.48) while case 77 showed a further transition towards adenocarcinoma (Figs.49, 50).

Only one of these tumours appeared to exercise an endocrine effect and the effect was feminizing. This is rather interesting because case No.121 is identical to the masculinizing tumour reported by Burkett and Abell (1944) and the resemblance of cases No.121 and 70 to the hypernephric tumours published by Saphir and Lackner (1944) is very striking.

Clinical Features.

Age: The youngest patient was 39, the oldest 58.

The average age was 49.

Parity: Two patients were unmarried, 3 were married, but nulliparous, one patient had 10 children and 1 one child.

Symptoms: Two patients complained of post-menopausal haemorrhage. One had adenocarcinoma of the uterine body, one had hyperplastic endometrium.

Prognosis: One patient was untraced.

Two patients are dead.

Four patients are well 7, 7, 3 and 1 year after operation.

TABLE I	
<u>AVERAGE</u>	<u>AGE</u>
Fibromas - - - - -	50 years
Thecomas - - - - -	58 "
Granulosa Cell Tumours:	
Diffuse - - - - -	55 "
Differentiated - - - - -	49 "
Carcinoma:	
Primary adenocarcinoma - - - - -	53 "
Papillary cystadenocarcinoma - - - - -	50 "
Pseudomucinous cystadenocarcinoma - - - - -	44 "
Secondary - - - - -	49 "
Clear cells - - - - -	49 "

Discussion.

(1) The Clinical Features.

The classification of the tumours in this series has been done on a histological basis in order that the clinical features of the groups might be compared. The groups show many similarities and some discrepancies.

(a) Age. All the groups had an age of incidence which fell in the duodecade 44 - 55 the thecoma growth being the oldest at 55 and the pseudomucinous adenocarcinoma group (which only consisted of 4 patients) the youngest at 44. This is the age of incidence of most ovarian tumours simple and malignant. (Mackinlay 1956). It is also the age of the menopause. Whether there is any connection between the two cannot be confirmed but it may well be that the functional changes in the ovary at this epoch and the changes in the influences upon the ovary predispose to tumour formation.

Table 1.

(b) Parity. The high incidence of nulliparity in the patients is striking. Not only were many of the patients unmarried but many of those who had been married for long periods had no pregnancy. The infertility rate was highest in the carcinoma group, particularly in the

Table II

PARITY

	Unmarried	Married and nulliparous	Total nulli- parous	Total Cases
Fibromas - - - - -	3	11	14	28
Thecomas - - - - -	4	1	5	8
Granulosa Cell Tumours:				
Diffuse - - - - -	4	5	9	16
Differentiated - - - - -	3	3	6	12
Carcinoma:				
Primary adenocarcinoma - - - -	4	6	10	21
Papillary cystadeno- carcinoma - - - - -	2	5	7	13
Pseudomucinous cystadeno- carcinoma - - - - -	2	1	3	4
Secondary - - - - -	3	4	7	11
Clear cells - - - - -	2	3	5	7
Total carcinoma - - - - -	14	16	30	58
Miscellaneous - - - - -	3	1	4	9

the subgroup 'carcinoma with clear cells' in which only 2 patients out of 7 had any children. 50% of the fibroma group had no family or were unmarried, and over 40% of the granulosa cell group were nulliparous. It is generally accepted by those who have studied infertility that 9 out of 10 couples conceive within 3 years of marriage provided contraception is not practised (Sharman 1956). The fact that 28 patients out of 122 who were of age to be married were not, may be significant, a desire for marriage is surely the result of endocrine influence. 37 patients out of 94 married women in the whole series were nulliparous. This appears to be a high enough infertility rate to conclude that the ovarian function had been disturbed for a long time before the tumour was diagnosed.

Table 11.

(c) Symptoms. The great majority of patients complained either of abnormal uterine bleeding or of abdominal pain or swelling. Bleeding was not however confined to the thecoma-granulosa group. 6 patients in the fibroma group had bleeding of uncertain origin and 2 of these had hyperplastic endometrium. 15 patients in the carcinoma group had bleeding but in 11 of these the bleeding was due to uterine carcinoma. One patient with carcinoma with clear cells had hyperplastic

TABLE III

SYMPTOMS.

	Total Cases	Abnormal Uterine Bleeding	Due to Carcinoma	Masculin- izing
Fibroma -----	28	8	2	-
Thecoma -----	8	5	-	-
Granulosa Cell Tumours				
Diffuse -----	16	12	1	1
Differentiated -----	12	10	1	1
Carcinoma -----	59	15	11	-
Clear Cells -----	7	2	1	-

TABLE IV

PROGNOSIS

	Total Cases	Alive	Dead	Untraced
Thecoma -----	8	7	-	1
Granulosa Cell Tumour:				
Diffuse -----	16	13	3	-
Differentiated -----	12	8	1	3
Carcinoma:				
Primary adenocarcinoma -----	21	7	14	-
Papillary cystadenocarcinoma -	13	4	9	-
Pseudomucinous " " -	4	3	1	-
Secondary -----	12	6	6	-
Clear Cells -----	7	4	3	-
Miscellaneous -----	9	3	6	-

hyperplastic endometrium. In the thecoma-granulosa group 75% of the patients had abnormal uterine bleeding, but two of the tumours were associated with masculinizing or defeminizing.

Table 111.

(d). Prognosis. Only 2 cases in the thecoma-granulosa group were clinically malignant and inoperable, both of these patients died. 2 more patients who died are not thought to have died as a result of the tumour growth. Of the 32 patients traced 28 are alive and well and 4 are dead. This gives a mortality of 12.5% This figure is about halfway between the figures of Novak E (1953) 27%, Burslem Langley and Woodcock (1951) 30%, and Henderson (1942) who found only one malignancy in 30 tumours. The prognosis in carcinoma of the ovary is extremely bad. Almost two thirds of the patients in this group are already dead despite the fact that no patient has been under observation for more than 8 years. Two interesting points arise in this connection. First the surprising success of deep x-ray therapy in the most unlikely cases (74 and 98) and second the fact that 6 patients with carcinoma of the ovary secondary to adenocarcinoma or adeno-acanthoma of the uterus are still alive. It would seem that X-ray therapy is always worth while even in apparently hopeless cases.

Table IV.

(2) The Significance of male-directed cells in Ovarian Tumours.

In the thecomas and diffuse granulosa cell tumours, the tumour cells resemble cells which normally occur in the ovary but in the differentiated group, cells appear which have no counterpart in the normal adult ovary. The occurrence of these cells has led to much confusion in interpretation and a brief historical review is necessary in order that factors which led to the confusion may be appreciated.

(a) The Establishing of the Arrhenoblastoma group of Tumours.

The work of Robert Meyer is the foundation of our present knowledge of feminizing and masculinizing tumours and it is worth while to consider his papers on male elements in ovarian tumours fully. In 1930 he published at least 5 papers on the subject.

In his first paper (Meyer 1930a) entitled "Tubulare testiculare and solid forms of andreiblastoma ovarii and their influence on masculinization" he described a case similar to Pick's (1905) adenoma. The illustrations suggest that this was a malignant granulosa cell tumour with some tubule formation. It was not masculinizing. He referred to two similar cases he had already described

described and then reported 6 cases of "atypical tubular ovarian tumours".

Case 1 had a manly stride and deep voice with irregular vaginal bleeding. The tumour looked sarcomatous with well marked cording similar to case 57 in this series.

Masculinizing \pm

Case 2 had menorrhagia followed by 9 months amenorrhoea. The illustrations suggest that this may have been a secondary tumour. Some endometrial type glands are seen.

Masculinizing \pm

Case 3 was 14 years postmenopausal and had developed a deep voice which recovered after operation. There were some glandular elements in this tumour and Leydig-like cells at the periphery.

Masculinizing \pm

Case 4 was strongly masculinizing and histologically resembled case 2 above.

Masculinizing ++

Case 5 was strongly masculinizing and looked like a granulosa cell tumour with degeneration.

Masculinizing ++

Case 6 had menorrhagia, a deep voice and coarse hair on face and limbs, histologically a typical granulosa cell tumour.

Masculinizing \pm

He grouped these cases together as andreiblastomas and suggested that the first group was typical and the

the second atypical. It will be noted that none of the first group was reported as being masculinizing and only 2 of the second group were undoubtedly masculinizing. It is also interesting to note that 3 of the tumours contained recognizable granulosa elements.

The second paper (Meyer 1930b) was read at a meeting of the Berlin Pathological Society in February. In it he described the collection of 8 cases of testicular adenoma of the ovary only one of which was masculinizing (Neumann 1927), and 8 cases of the atypical group. He had found it necessary to describe a middle group, histologically closing the gap between the typical and atypical tumours and reported the collection of 6 such tumours 4 of which he described fully. The article was not illustrated. None of the 4 he described was definitely masculinizing and two of the patients complained of menorrhagia. In the discussion on the paper Dr.C.Benda suggested the name 'arrhenos' would be a better designation for such tumours.

In the paper to the German Pathological Society (Meyer 1930c) he once again described the middle group and adopted the name 'arrhenoblastoma'. In July (Meyer 1930d) he amplified cases 5 and 6 of his middle group and in September (Meyer 1930e) he gave a similar report. Case 5 had irregular periods followed by

by 6 years amenorrhoea at the age of 51 and the tumour looked like a typical granulosa cell tumour. Case 6 had much vaginal bleeding for 6 months and had a deep voice. The tumour appeared to be an indefinite type of adenocarcinoma.

This summary of Meyer's work has been given because after these articles were published it was accepted that the arrhenoblastomas were masculinizing tumours, that the typical arrhenoblastoma was a tubular tumour similar to the adenoma of Pick, that the atypical tumours were more common and usually had traces of male elements and that the granulosa cell tumour was quite a separate entity. This is still widely accepted today.

In Meyers series none of his typical arrhenoblastomas was masculinizing, only 2 of his atypical arrhenoblastoms were positively masculinizing and one of these resembled a granulosa cell tumour and at least 2 of his intermediate group were more feminizing than masculinizing. It is scarcely surprizing that the pathology of this supposedly masculinizing group of tumours is confused.

(b) Pick's "adenoma testiculare ovarii".

This tumour was originally described by Pick (1905). It was a tubular tumour very similar to Cases 53, 58 and 64 in this series, and it came to be regarded as the typical

typical arrhenoblastoma. Most of the cases of Pick's tumour which have been described have, despite their male appearance, been either feminizing or had no obvious endocrine influence.

Pick's own tumour was feminizing, Dougal's (1945) case and one of Henderson's (1942) cases were feminizing and cases 58 and 64 in this series were strongly feminizing.

Several tumours described have had an anomalous effect. Salen (1899) reported a tumour in a woman whose only abnormality was a clitoris 5 cm. long, Simon (1903) reported a very similar case. Novak J (1943) reported an interesting case in which two sisters who appeared to be normally female both had Pick's adenomas associated with the absence of the uterus.

Amongst those tumours which appeared to have no effect are those of Blacker and Lawrence (1896) in an 8½ months foetus, Neumann (1925) in an infant which died 14 days after birth and Novak E (1938) case 5.

Only 3 masculinizing tumours of this nature have been traced in the literature. The beautifully illustrated case of Blair Bell (1915) which was strongly masculinizing. The tumour in this case contained many Leydig cells, and the case of Neumann (1927) which was also masculinizing. Popoff's (1930) case had 5 months amenorrhoea.

In view of the variety of clinical effect associated with this tumour it is unfortunate that it should have been regarded as the typical arrhenoblastoma.

(c) Androblastoma.

Teilum (1950) has pointed out that there was a similarity between tumours of the ovary and tumours of the testis and stated that practically any tumour of the testis might arise in the ovary. He described (Teilum 1946) a feminizing testicular tumour similar to an ovarian arrhenoblastoma which, in addition to Sertoli cells contained many lipoid cells too. He suggested that all tumour of both testis and ovary which contained male directed cells should be called androblastomas and that the term arrhenoblastoma should be reserved for such tumours as are characterized clinically by virilizing. This would undoubtedly be a way out of the difficulty of nomenclature but in his articles he has made some assertions which are hard to understand.

He (Teilum 1949) likened the testicular tumour to the Folliculome Lipidique of Lecène, a feminizing tubular tumour with many lipoid cells and disagreed with authors who had published similar cases and had placed them in the granulosa group. 'These authors' he said (which included Plate (1933) Dougal (1945) and Henderson (1942)" interpret the tumour as belonging to the granulosa

granulosa cell tumour group as apparently they have attributed a greater importance to the function of the tumour than to the morphological conditions". He insisted that the tumours originated from a testicular blastoma in which differentiation tending towards Sertoli and/or Leydig cells might take place.

It is understood from these remarks that Teilum considered the granulosa cell tumour group and the androblastoma group to be mutually exclusive and that there was no transition between the groups. The author has not^x been able to obtain the original articles of Lecène (Moulonguet 1932) but Plate's (1933) article described Lecène's tumours and noted the similarity of the tumour he described. Plate's tumour was feminizing and the greater part was composed of cells of the 'luteoma' type but his figure 5 showed typical granulosa. It would be reasonable to suppose that this tumour was related to the granulosa group. Teilum excluded the tumours of Dougal and of Henderson from the granulosa group. While granulosa was not noted in these authors' illustrations the tumours were identical to cases 53, 58 and 64 of this series all of which contained granulosa elements.

The term androblastoma as defined by Teilum would

^x This article has since been obtained.

would therefore appear to be just as confusing as the term arrhenoblastoma as defined by Meyer. It is noteworthy that both the authors insisted that the tumours arose from testicular anlage.

(d) The Gynandroblastoma.

Meyer (1930a) recognised that female elements occurred in the atypical growth of arrhenoblastomas and suggested (p.519) that the name gynandroblastoma could be used for the cases 5 and 6 which he had described. Plate (1938) applied this name only to tumours which showed a feminizing and later a masculinizing effect, for instance menorrhagia followed by amenorrhoea and masculinization, and which contained both male and female elements. He described such a case and collected 9 cases in the literature. Meckler and Black (1943) described a case of coincident vaginal bleeding and masculinization and concluded that gynandroblastoma was a clinico pathological syndrome with no constant accompanying histology.

When so many granulosa cell tumours appear to contain male elements and so many masculinizing tumours contain female elements the introduction of this group appears to complicate the pathology unnecessarily.

(e) What is the typical masculinizing Ovarian Tumour?

It has been shown that the typical arrhenoblastoma is only rarely a masculinizing tumour. What, then, is the usual histological character of the masculinizing tumours? They appear to be fall into 3 groups, the atypical arrhenoblastomas, the luteal or adrenal group of tumours and the hilus cell tumours.

(1) The atypical arrhenoblastomas.

In this series there was only one masculinizing tumour (case 63). In this case the tumour had the appearance of a diffuse granulosa cell tumour with no pattern. Throughout the tumour large clear cells resembling lutein or Leydig cells were seen in small numbers. No particular feature was recognised which distinguished this tumour from similar tumours which had a feminizing influence, case 43 for example.

Many tumours have been described in the literature which were masculinizing and were therefore called atypical arrhenoblastomas and yet had the histological characteristics of granulosa cell tumours. Meyer's (1930a) case 5, one of the most strongly masculinizing he described looked like a typical granulosa cell tumour and so did his case 5 of the intermediate group (Meyer 1930e). Novak and Long's (1933) case resembled a diffuse granulosa

granulosa cell tumour with some cording, Taylor, Wolfermann and Krock's case (1933) was a thecomatous granulosa cell tumour with cording, Baldwin and Gafford's (1936) showed cording and Novak E's (1938) cases 3 and 4 were similar. In this latter group Leydig-like cells were seen in 3 out of the 6 cases described.

The typical masculinizing tumour of this group may therefore be said to resemble some form of granulosa cell tumour with or without Leydig-like cells.

(2) The luteal group of Tumours.

There is no doubt that some of the tumours of this group are associated with masculinization but there is a great deal of dispute as to the nature of the cells which comprise the tumour. Strongly masculinizing tumours histologically identical with cases 70 or 121 of this series have been reported by Burkett and Abell (1944), Williams and Mendenhall (1947) Douglas (1947) Twombly (1946), Searle, Haines and Baker (1948) and Novak E (1938) (3 cases).

(3) Hilus Cell Tumours.

Sternberg (1949) drew attention to groups of large lipoid containing cells similar to Leydig cells which are found in the hilus of the ovary. He found them in 80% of ovaries and many of them contained Reinke's

Reinke's crystalloids. (The author has only been able to find them very occasionally) and reported 2 tumours of these cells which produced masculinization and 2 cases of hyperplasia which produced a similar effect. Berger (1942) also reported an adenoma of the hilus cells associated with masculinization. The descriptions suggest a likeness to case 35 in this series (Fig.19) which was associated with post-menopausal bleeding.

This analysis suggests that the typical masculinizing tumour either resembles a granulosa cell tumour which may or may not contain Leydig-like cells, or tumour of large fat-laden cells.

(f) What is the typical feminizing ovarian tumour?

The present series of feminizing tumours agrees in the main with the many series of feminizing tumours which have been published (Burslem, Langly and Woodcock's publication (1951) is probably the most useful recent article), except that the occurrence of cording and tubules has been emphasised in the present series. A feminizing influence may be expected with cases of stromal hyperplasia without tumour formation, with thecomatous tumours which may resemble ovarian stroma or fibroma, with diffuse granulosa cell tumours or with granulosa cell tumours which may be almost entirely tubular or adenomatous. Granulosa-like tissue was

was found in all the tumours of the 2 latter groups no matter how tubular the tumour was. The present series may be said to represent a complete transition from the hyperplastic stroma to the tubular adenoma and any degree of histological differentiation between these limits may be associated with feminization.

It seems therefore that there is very little difference in histology between the feminizing and the masculinizing tumours except perhaps for the 'luteal' group of tumours which have been shown to be histologically identical with carcinomas which had no endocrine influence at all.

(g) The Potentiality of normal cells.

Before considering the potentialities of ovarian tumour cells the potentiality of the cells of the normal gonad must be discussed.

(1) The Stroma and Theca.

The ovarian stroma is a complex mixture of spindle cells, muscle cells and fibrous tissue. This may describe the morphology of the cells but not their extraordinary capacity for differentiation. Even in the most atrophic ovaries the stroma is well defined and has different staining reactions from the capsule of the ovary surrounding it and the fibrous tissue which divides it into segments.

Stromal hyperplasia may be associated with endocrine abnormalities, usually feminizing as in cases 35 and 36 of this series. The theca is a modification of the stroma associated with the growth of granulosa, and tumours of the theca cause an overproduction of oestrogens. The theca has the capability of differentiating into large lipid cells which according to Shippel (1950) are a potent source of androgens. In abnormal conditions the stroma also appears to be able to differentiate into lipid cells as in case 36.

Lipoid cells arise under very similar conditions in the interstitial tissue of the testis and in both ovary and testis they arise in association with a developmental product of the ~~sex cord~~ - the granulosa and the seminiferous tubule.

(2) The granulosa and the Sertoli cells.

It is debatable whether the granulosa arises from the stroma or from the sex cords. Its capacity for forming luteal cells is in keeping with a stromal origin but the granulosa of the Graafian follicle is so sharply defined from the theca that it seems likely that the stroma and the granulosa ~~and the theca~~ arise from different sources. In the embryological discussion at the beginning of this paper it was shown that in at

at least some cases the pregranulosa could be seen developing into mature granulosa. There seems little doubt that the granulosa produces oestrogens and no doubt that tumours of the granulosa are associated with excessive oestrogen production.

The Sertoli cells of the testis arise from the sex cords and there is much evidence to show that these cells are oestrogen producers. Berthrong, Goodwin and Scott (1949) have shown that the feminizing testicular tumours of male dogs are composed of Sertoli cells and the human feminizing testicular tumour described by Teilum (1946) was principally a Sertoli cell tumour. If the granulosa does arise from the sex cords as it would appear to do then the parallel between Sertoli cells and granulosa is almost complete.

There is however an important difference between them, that is the ability of the granulosa to form luteal cells. Luteinization is the normal fate of the granulosa but luteinization of the Sertoli cells has not, to the author's knowledge, been described unless as Gruenwald (1942) suggested they give rise to the Leydig cells.

(3) Luteinization and Leydig cells.

The corpus luteum is formed from the granulosa under the influence of the luteinizing hormone of the

anterior pituitary. The secretory product of the corpus luteum, progesterone, is more closely allied to the androgens than to the oestrogens. (Cameron (1940). Biochemically luteinization may be regarded as a form of masculinization. Leydig cells are producers of androgens and are thought to be largely responsible for the maleness of man. Testicular Leydig cell tumours produce androgens (Teilum 1950). Theca lutein cells are thought to be a source of androgens in the ovary (Shippel 1950). Tumour cells of a similar nature may produce masculinization. Thus we have cells of a similar nature, luteal cells, theca lutein cells, hilus cells, Leydig cells and 'luteoma' cells all of which produce androgens or similar substances and all of which are so alike that they cannot, with certainty be distinguished from one another.

(h) Lipoid cells in Ovarian Tumours.

The similarity of the cells mentioned in the previous paragraph is well illustrated by the case reported by Rottino and McGrath (1943). The authors described a case of masculinization with hyperplasia and luteinization of the ovarian stroma. They asked 4 eminent gynaecological pathologists to examine the slides and give their opinion of the nature of the luteal cells. Traut

said the condition was partial luteinization of a theca cell tumour, Schiller said the clear cells were of adreno-cortical origin, Novak said they were luteinized granulosa cells and Plaut remarked on the similarity of the cells to those of the interstitial gland of the rabbit! It seems pointless to say as Langley (1954) and Marchetti and Lewis (1952) did that the groups should be distinguished when differentiation appears to be a practical impossibility.

(i) Sertoli cells in Ovarian Tumours.

The resemblance in pattern and morphology between the cells of the seminiferous tubules in the foetal testis and the cells in the early cording in granulosa cell tumours has already been indicated. As the cording becomes more pronounced the likeness to Sertoli cells increases. When the cording assumes a tubular pattern the Sertoli cells become larger with abundant vacuolated cytoplasm and the nuclei become larger and more rounded and are arranged in an antipodal fashion. There is no true parallel to this in the foetal or adult testis. When the seminiferous tubules first become canalized the majority of the cells are Sertoli cells, but when active spermatogenesis is taking place, the Sertoli_{cells} form a minor fraction of the tubular structure. They are peripheral, their nuclei are larger and rounder

and they appear to have a considerable amount of cytoplasm. The tubules in ovarian tumours are thought to represent the seminiferous tubules without spermatogonia. It is not easy to visualise such a structure for even in the senile testis in which spermatogenesis is finished, the tubules are relatively acellular but the majority of cells are spermatogonia. However as a gradual transition can be traced from cords of Sertoli cells to tubules, it is reasonable to suppose that the ovarian tubules represent the supporting structures of mature seminiferous tubules and that the cells which compose them are Sertoli cells. This supposition is rendered more likely by the appearance of Leydig-like cells in the interstitial tissue of the adenoma.

(j) *Résumé.*

It has been suggested that granulosa cells, theca cells stromal cells and Sertoli cells may produce oestrogens and feminizing effects and that lutein cells, theca-lutein cells hilus cells and 'luteoma' cells may produce androgens and masculinizing effects. It has also been suggested that granulosa cells, theca cells and occasionally stromal cells may under certain conditions change their nature entirely and become lipid containing producers of androgens or androgen-like substances. There

There is a constant state of flux in these cells between oestrogen and androgen production controlled by some guiding hormone probably from the pituitary. The only consistent producer of oestrogen is the Sertoli cell.

Conclusion.

(1) Granulosa and Sertoli cells.

This discussion appears to lead to one conclusion: that, in tumours, the granulosa must be regarded as a half-way stage between Sertoli cells and luteal cells.

Histologically this has been demonstrated in most of the differentiated granulosa cell tumours of this series and it is especially clear in cases 53 (Fig.36) 55 (Fig 33 and 58 (Fig.28). On a histogenetical basis the hypothesis is probable. If both granulosa and Sertoli cells arise from the sex cord the cells are very closely related. If Fischel's theory is proved correct one has only to go back one stage in development, to the primitive mesenchyme, to find a common ancestor.

If this is accepted a number of difficulties in the pathology are solved.

- (1) The status of the granulosa cell tumour is unchanged.
- (2) The androblastoma is a granulosa cell tumour in which the granulosa cells have differentiated into Sertoli cells.
- (3) The gynandroblastoma is a tumour in which the

the transition from granulosa to Sertoli cells is not completed.

(4) The folliculome lipidique of Lecène is either a luteinized granulosa cell tumour or an androblastoma in which the Sertoli cells have produced an excessive Leydig reaction in the interstitial tissue similar to that which occurs in the testis of the child of the diabetic mother.

(5) The atypical arrhenoblastoma of Meyer is a granulosa cell tumour in which luteinization has taken place and the lutein cells are producing effective androgens.

(2) Lipoid Cells.

The problem of the lipoid cells remains unsolved. It seems certain that they may produce androgens but they do not always appear to do so.

Teilum (1949) has said that the virilizing effect depends on hormonally active Leydig cells or their precursory types. Perhaps we do not recognise the precursory types and granulosa-like cells may begin to secrete androgens before a morphological change can be detected. This would explain the effectiveness of the small number of Leydig cells in the masculinizing tumour No.52 and the apparent lack of Leydig cells in the

the defeminizing case No.62. The appearance of lipid cells in feminizing tumours may be an attempt on the part of the tissues to maintain the oestrogen-androgen balance. The lack of endocrine effect in the large lipid tumours may be because the neoplastic cells lose the power of elaborating an internal secretion.

There can be no certain answer to these problems until some means, possibly histochemical, is devised which will indicate the hormonal activity of the individual cells.

(3) Nomenclature.

The acceptance of the hypothesis that granulosa is a transition between Sertoli cells and lutein cells does not necessitate a change in nomenclature except in so far as the terms arrhenoblastoma, androblastoma and gynandroblastoma may be discarded.

All these tumours are granulosa cell tumours in varying degrees of differentiation and such descriptive terms as feminizing tubular granulosa cell tumour or masculinizing luteinized granulosa cell tumour would be more accurate clinically and histologically.

S U M M A R Y.

- (1) A series of 123 ovarian tumours is reported of which 36 were hormonally active.
- (2) The comparative infertility of women who suffer from ovarian tumours is noted.
- (3) The prognosis in cases of granulosa cell tumour was found to be good, in cases of carcinoma of the ovary extremely bad.
- (4) The significance of male directed elements in functioning ovarian tumour is discussed.
- (5) Evidence is produced that granulosa in tumours should be regarded as a transition between Sertoli and luteal cells.
- (6) The discarding of such anomalous terms as arrhenoblastoma, androblastoma and gynandroblastoma is recommended as these tumours are shown to be granulosa cell tumours in varying stages of differentiation.

A P P E N D I X

FIBROMAS

1. (27532) Age 50. Married 32 years. 4 children. Menopause at 46.
 Complaint:- Post-menopausal bleeding every 3 weeks lasting for one week for past 8 months. Abdominal swelling. Massive kidney-shaped tumour of right ovary. Large endometrial polyp. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Tumour measures 25 x 12.5 x 17 cms. Weight with uterus 2080 gms. Polyp 5 cms. long.
 Histology:- A typical fibroma with widely spaced attenuated nuclei. A few areas of necrosis. Endometrium shows proliferative activity. Polyp has fibrous stroma with dilated glands.

2. (18543) Age 21. Unmarried. No children. Periods normal.
 Complaint:- Abdominal swelling. Persistent vomiting for 3 months.
 Left salpingo-oophorectomy.
 Pathology:- Tumour measures 12 x 7 x 7 cms.
 Histology:- A typical fibroma. In one area the tumour is cellular with round and oval nuclei. This passes into relatively acellular area without margin.

3. (18255) Age 63. Married 37 years. 2 children. Menopause at 51.
 Complaint:- Severe right-sided abdominal pain for 6 months.
 Solid tumour of right ovary with torsion. Some free fluid. Uterus normal. Bi-lateral salpingo-oophorectomy.
 Pathology:- Solid tumour 8 cms. in diameter.
 Histology:- A typical fibroma. Left ovary atrophic.

4. (18591) Age 59. Unmarried. No children. Menopause at 45 years.
 Complaint:- Sudden pain in right iliac fossa. Right-sided solid ovarian tumour. Uterus and left adnexa normal. Total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Solid ovarian tumour 12 cms. in diameter. Tumour is blood-stained and congested. Uterus normal. Left ovary and tubes atrophic.
 Histology:-

4. Histology:- Fibroma. The nuclei are long and cigar-shaped with little twisting. They are spaced far apart in interlacing fibrous bundles. Left ovary shows well stained and highly cellular cortex. Endometrium senile with dilated glands.
5. (18662) Age 53. Married 29 years. One premature child. Menopause at 46.
Complaint:- Left-sided abdominal pain for 5 years. Increase of weight.
Right-sided ovarian tumour with a few light adhesions. A little ascites. Uterus small, left tube and ovary normal. Right oophorectomy.
Pathology:- A solid tumour 6 cm. x 4 cm. x 4 cm. The ovary protrudes from one pole of the tumour.
Histology:- A cellular fibroma continuous with the rather fibrous ovarian stroma.
6. (9727c) Age 44. Married. No children.
Complaint:- Profuse menorrhagia and epimenorrhoea. Admitted as ? carcinoma of cervix. Biopsy negative. Small right-sided ovarian tumour. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
Pathology:- Right ovary has tumour 7 cms. in diameter growing from hilus. Weight with ovary 60 gms. Uterus thick walled; left ovary small.
Histology:- Typical fibroma with much hyaline degeneration. Right ovarian cortex normal. Stroma of left ovary active. Endometrium proliferative but no hyperplasia.
7. (5672c) Age 69. Married 42 years. 4 children. Menopause at about 45. (diabetic)
Complaint:- Sudden attack of abdominal pain. Torsion of left-sided ovarian tumour. Bi-lateral salpingo-oophorectomy.
Pathology:- A solid tumour measuring 17 x 12 x 10 cms. Almost completely necrotic except at one pole.
Histology:- Fibroma with extensive necrosis. Right ovary contains follicular cysts.
8. (20741) Age 36. Married. One child.
Complaint:- Vaginal bleeding for 8 weeks. Periods previously normal. Uterus normal. One ovary contains solid tumour 5 cms. in diameter, the other ovary is cystic. Resection of both ovaries.
Pathology:-

8. Pathology:- Tumour is partially enclosed by ovarian tissue which forms a capsule to it. Fibroma showing much hyaline degeneration but not a complete destruction of nuclei. Thecomatous areas are observed in the stroma of the other ovary.
9. (5585c) Age 58. Unmarried. No children. Menopause at 46. Complaint:- Felt "a lump in the front passage". No other complaint.
Ovarian tumour 23 cms. in diameter on the left side. Moderate amount of ascites. Total hysterectomy, bi-lateral salpingo-oophorectomy.
Pathology:- Uterus contains small endometrial polyp. Right ovary normal. A lobulated smooth tumour 23 x 23 x 20 cms. growing from the distal end of the ovary which is still recognizable.
Histology:- Fibroma with rather large nuclei some spindle shaped, others polygonal or rounded. Ovarian cortex stains well. Many corpora albicantia. Endometrium not completely atrophic, deep in places but glands show little activity. Polyp is similar.
10. (12559) Age 41. Married 9 years. No children. Complaint:- Irregular vaginal bleeding for about a year. Uterus normal. Both ovaries slightly enlarged. Total hysterectomy. Bi-lateral salpingo-oophorectomy.
Pathology:- Adenocarcinoma of the body of the uterus. (Radium had been inserted prior to hysterectomy.)
Left ovary contained a hard tumour 2.5 cms. in diameter. Right ovary contained a follicular cyst of similar size.
Histology:- No evidence of carcinoma after radiation. A relatively acellular fibroma which appears to grow from the stroma of the left ovary. Cyst of right ovary lined by cuboidal epithelium.
11. (Annexe B381) Age 52. Married. No children. Menopause at 50.
Red vaginal discharge after one year's amenorrhoea. No actual bleeding.
On curettage adenocarcinoma of the uterus was found. Total hysterectomy, bi-lateral salpingo-oophorectomy.
Left ovary enlarged by a tumour 5 cms. in diameter, thought to be a secondary.
Histology:- Uterus contains a poorly differentiated adenocarcinoma. Right ovary atrophic and covered with a layer of degenerated cells. Left ovary contains a typical

11. typical lobulated fibroma growing out of the ovarian tissue. Over the surface of the tumour and the ovary is a layer of degenerated cells suggestive of malignant spread from the endometrium.
12. (3079c) Age 51. Married 28 years. 4 children. Menopause at 47.
 Complaint:- Dragging vaginal pain. Had slight vaginal bleeding one year ago.
 Left ovary contains a tumour 12 cms. in diameter. Other pelvic organs normal. Small amount of free fluid in the abdominal cavity. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Uterus normal. Left ovary replaced by a white tumour 12 cms. in diameter which has small cystic spaces filled with gelatinous material. Right ovary appears normal.
 Histology:- A fibroma which shows a great variation in affinity for stain due to degrees of degeneration. Right ovary has active cortex. Endometrium senile.
13. (13910) Age 52. Married 19 years. No children. Menopause at 40.
 Complaint:- Progressive abdominal swelling for the past year.
 Large right-sided ovarian tumour. Other pelvic organs normal. Some ascites. Right oophorectomy.
 Pathology:- A colourless kidney-shaped tumour measuring 15 x 10 x 7 cms. Rubbery consistency.
 Histology:- A typical homogeneous fibroma.
14. (14164) Age 56. Married 29 years. 3 children. Menopause at 45.
 Complaint:- Attacks of lower abdominal pain.
 Ovarian tumour found on examination under anaesthesia. Cervical polyp removed, no endometrium obtained. Oophorectomy.
 Pathology:- Tumour measures 12 x 10 x 7 cms. and is partly cystic and partly solid.
 Histology:- Fibroma with areas of complete necrosis and liquefaction causing cystic appearance.
15. (Annexe B209) Age 40. Married 17 years. One child. Irregular vaginal bleeding for 2½ years lasting from 4 days to six weeks at intervals of 3 to 11 weeks. Uterus

15. Uterus retroverted and adherent to bowel. Left ovarian tumour. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
Pathology:- Uterus, right ovary and tube normal. Left ovary contains a thin-walled cyst and a hard white tumour both 2.5 cms. in diameter.
Histology:- A fibroma, relatively acellular. The wall of the cyst resembles lutein tissue. Endometrium shows mild cystic glandular hyperplasia.
16. (Annexe B446) Age 59. Married 37 years. 3 children. Menopause at 43 years.
Complaint:- Abdominal pain since a repair operation one year ago. Very severe during the past 10 days. A semi-solid tumour of the left ovary the size of a rugby football, adherent to bowel. Right ovary atrophic. Uterus contained two small fibroids. Left salpingo-oophorectomy.
Pathology:- No gross description available.
Histology:- A fibroma showing areas of hyaline degeneration and necrosis.
17. (Annexe B22) Age 44. Married 16 years. No children. Menopause at 42.
Complaint:- Swelling of the abdomen for 5 months. Abdominal pain for 2 weeks, very severe on day of admission. Large pelvic mass on the right side of the uterus adherent to bowel and rectum. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
Pathology:- A small uterus with a fibroid 5 cms. in diameter in the left broad ligament. A solid tumour 6 cms. in diameter with a cystic appendage 12 cms. in diameter replaces the left ovary. The tumour was yellow in colour and the cyst contained blood-stained fluid.
Histology:- A cellular fibroma with varied staining reactions. The cyst is lined a single layer of cuboidal and columnar epithelium which shows some secretory activity. The endometrium shows proliferative activity.
18. (15745) Age 55. Married 20 years. One child. Still menstruating.
Complaint:- Very heavy but regular periods. The endometrium on curettage showed cystic glandular hyperplasia on histological examination. A total hysterectomy and bi-lateral salpingo-oophorectomy was done a week later.
Pathology:-

18. Pathology:- The uterus is 10 cms. long and contains a number of small fibroids up to 2.5 cms. in diameter. Right ovary measures 8 x 5 x 6 cms. with a bright orange area at one pole.
 Histology:- A cellular fibroma of the right ovary which contained also a corpus luteum. (Very unusual at this age) The left ovary had 2 degenerating corpora lutea and the stroma had an active appearance.
19. (16144) Age 64. Married 42 years. 3 children. Menopause at 50.
 Complaint:- Severe left-sided abdominal pain for 7 days. Uterus senile, large left-sided ovarian tumour. Right ovary had been removed 26 years previously. Left salpingo-oophorectomy.
 Pathology:- Tumour measures 17 x 12 x 10 cms. nodular and encapsulated with an area of inflammation at one pole. Cut surface white and whorled with many small haemorrhages. It contains a cyst 4 cms. in diameter.
 Histology:- A fibroma with very variable staining due to degeneration and in some places liquefaction.
20. (16181) Age 42. Married. One child.
 Complaint:- Frequent and profuse periods for 4 months. Previously normal.
 Retroverted uterus with nodular growth in right ovary. Total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Uterus 9 cms. long. Cervix patulous. Left ovary normal. Right ovary twice normal size.
 Histology:- Right ovary contains a corpus luteum and an acellular fibroma 1 cm. in diameter growing from the hilus. Left ovary has deeply staining stroma. Endometrium in the early secretory phase.
21. (15862) Age 46. Married 12 years. No children. Normal menstruation.
 Complaint:- Vaginal discharge.
 Tumour of left ovary found at operation for discharge. Bi-lateral salpingo-oophorectomy.
 Pathology:- Left ovary 8 cms. in diameter, enlarged by a solid tumour, hard and white. The tumour is growing from ovarian tissue which contains a small cyst and several little blood-filled cysts.
 The right ovary is slightly enlarged and contains blood-filled cysts.
 Histology:-

21. Histology:- Much of the fibroma is structureless but it can be seen to grow without margin from the ovarian tissue. Endometriosis is present in other parts of the ovary. The appearances suggest neoplasm and not a fibrous reaction to the endometriosis. The right ovary contained endometrial and follicular cysts.
22. (25540) Age 50. Married. No children. Menopause at 46.
 Complaint:- Prolapse. No other symptoms.
 A large smooth solid ovarian tumour on the left side. Right ovary and uterus normal. Bi-lateral salpingo-oophorectomy. A repair operation was carried out 6 months later.
 Pathology:- A smooth white globular tumour measuring 18 x 15 x 12 cms. On section pink in colour and whorled.
 Histology:- A fairly cellular tumour homogeneously stained. Fibroma. Right ovary senile.
23. (17322) Age 24. Married 3 years. No children. Periods last 6 days every one to two months.
 Complaint:- Increasing abdominal swelling for six months. A cyst the size of a melon adherent to the back of the uterus and the posterior vaginal wall. Left ovary enlarged but normal. Right oophorectomy. The patient became pregnant 3 months later.
 Pathology:- A unilocular ovarian cyst 18 cms. in diameter. Extremely heavy and walls up to 2 cms. thick. Probably central necrosis of a solid tumour.
 Histology:- A fibroma with very thin elongated nuclei. Much necrosis.
24. (9285c) Age 23. Married 4 years. No children. Periods irregular lasting 4 days every 4-6 weeks. Amenorrhoea for past 5 months.
 Complaint:- Was thought to be pregnant; seen at ante-natal clinic and referred to Samaritan Hospital. She began to menstruate 3 days before admission.
 Right-sided solid ovarian tumour size of melon. Uterus small and ante-flexed. A quantity of straw-coloured fluid in the abdomen. Left ovary slightly enlarged. Right oophorectomy.
 Pathology:- A solid ovarian tumour 18 x 12 x 12 cms. with a necrotic haemorrhagic area in the centre 6 cms. in diameter.
 Histology:-

24. Histology:- A fibroma in which some areas stain more heavily than others. The deeper stained areas are more cellular and the nuclei are larger. It was thought that this might be a myoma but Van Gieson's stain showed it to be of fibrous tissue.
25. (17650) Age 81 Married 55 years. No children. Menopause at 50.
 Complaint:- Left-sided abdominal pain. Abdominal swelling. A cyst the size of a melon with a very twisted pedicle. Adherent to small bowel and causing a two turn volvulus of small bowel mesentery. Uterus senile. Volvulus undone, oophorectomy. Uninterrupted recovery.
 Pathology: A white waxy tumour shaped like a huge kidney and measuring 20 x 15 x 10 cms. Central necrosis leaving walls about 2 cms. thick.
 Histology:- Only the outer surface of the tumour had recognizable cells; these had the pattern and character of a relatively acellular fibroma.
26. (26805) Age 68. Married 37 years. No children. Menopause at 50.
 Complaint:- A lump in the lower abdomen which causes pain when she bends.
 Bi-lateral ovarian tumours. Atrophic uterus with sub-serous fibroid. Sub-total hysterectomy. Bi-lateral salpingo-oophorectomy. Some ascites was present.
 Pathology:- Uterus tiny. Fibroid 2.5 cms. in diameter. Both tumours have a similar appearance and both appear to grow out of the pole of an otherwise normal ovary. One tumour is 12 cms. in diameter, the other 6 cms. Both are white and whorled. The endometrium shows senile cystic dilatation of the glands.
 Histology:- Fairly cellular fibromas with oval nuclei predominating.
27. (7609) Age 45. Married 8 years. One child. Periods scanty.
 Complaint:- Left-sided abdominal pain worse on stooping. This patient had 4 admissions for various complaints including hernia of abdominal wound.
 Retroverted uterus with small tumour of right ovary. Left ovary atrophic. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:-

27. Pathology:- Uterine body 3 cms. long. Endometrium congested. Right ovary 5 cms. in diameter with a warty out-growth at one pole.
Histology:- A small fibroma with several cystic spaces lined by cuboidal epithelium.
28. (Annexe B225) Age 54. Married 29 years. One child.
Menopause at 48.
Complaint:- Abdominal pain and swelling.
Left ovary size of small melon with complete torsion of the pedicle. Right ovary normal. 2 pints of free fluid in the abdomen. Bi-lateral salpingo-oophorectomy.
Pathology:- Tumour measures 15 x 12 x 10 cms. and appears to be growing on a pedicle from the distal pole of the left ovary. Right ovary appears normal.
Histology:- Tumour is a fibroma with widely spaced oval nuclei. There is much hyaline degeneration. The ovarian tissue is normal. The stroma of the right ovary stains deeply.

THECOMAS

29. (Annexe B197) Age 66. Unmarried. Menopause at 45.
 Complaint:- Abdominal swelling. No bleeding.
 A large solid tumour of left ovary. Right ovary small with a warty growth on it. Uterus small. Some free fluid in the abdomen. Bi-lateral salpingo-oophorectomy.
 Pathology:- A hard white tumour measuring 18 x 12 x 11 cms. Right ovary contains a very hard tumour 1.5 cms. in diameter.
 Histology:- The left ovarian tumour is a fibroma with little degener^{er}ative change. The smaller tumour is contained within the cortex of the ovary. The tumour is cellular, nuclei oval or rod shaped with rounded ends. It is not completely defined from the stroma but sometimes merges with it. The tumour takes no pink stain with Van Gieson.
 Diagnosed as thecoma.
 Patient is well 4 years after the operation.
30. (7349c) Age 56. Unmarried. No children. Menopause at 40.
 Complaint:- Vaginal discharge and shortness of breath.
 Diagnosed as large multiple fibroids. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Uterus distorted by a large number of fibroids the largest being 8 cms. in diameter. Right ovary cystic 5 cms. in diameter. Left ovary contains a hard yellow tumour 2 cms. in diameter.
 Histology:- Right ovary has a narrow cortex. The medulla is hyaline. Left ovary shows a sharply defined tumour with a vague whorled arrangement split up by fibrous septa. Cells have little cytoplasm and well stained oval nuclei. This tumour represents a transition between thecoma and diffuse granulosa cell tumour. Endometrium thick with fibrous stroma and greatly dilated inactive glands.
 The patient was fairly well 5 years after operation but still had shortness of breath. No bleeding.
31. (13049) Age 52. Unmarried. No children. Menopause at 51.
 Complaint:- Lower abdominal pain and swelling. No bleeding.
 A right-sided ovarian cyst. Right salpingo-oophorectomy.
 Pathology:-

31. Pathology:- The tumour is half solid, firm and white, and half cystic, the spaces being filled with colourless liquid. It is 12 cms. in diameter.
 Histology:- The tumour is fairly cellular and the cells have a long spindle-shaped appearance or are oval. Some of the oval nuclei have a longitudinal groove. The tumour takes no pink stain with Van Gieson and contains a considerable amount of lipoid shown by Sudan 3. This tumour was diagnosed as a thecoma tending towards fibroma. Patient is very well 7 years after the operation. She had fairly severe flushings during the month after the operation.
32. (743c) Age 73. Unmarried. No children. Menopause at 50.
 Complaint:- Vaginal bleeding for 8 months. Abdominal swelling.
 A large ovarian tumour on the left side. Uterus and right ovary normal. Right salpingo-oophorectomy.
 Pathology:- Tumour measures 25 x 17 x 12 cms. Mainly solid but some parts are soft and cystic.
 Histology:- No specific pattern but cells tend to be spindle-shaped and grouped in whorls. The farther from the capsule the shorter and more oval are the nuclei.
 Thecoma with areas of necrosis. No specimen of endometrium was available.
 No follow-up information was obtained about this patient who was 73 when operated on in 1942.
33. (28158) Age 21. Unmarried. No children.
 Complaint:- Excessive vaginal bleeding for a year.
 A solid tumour of the right ovary, otherwise the pelvic contents normal. Right salpingo-oophorectomy.
 Pathology:- Tumour solid and rubbery with cystic spaces. Measures 11 x 10 x 7 cms.
 Histology:- A cellular tumour with cells not arranged in fibrous pattern but irregularly dispersed. Nuclei vary in affinity for stain. Mostly oval. Much of the tumour has lost its structure. Thecomatous type of tumour.
 Patient married and became pregnant within a year of the operation.
34. (13050) Age 62. Married 23 years. One child. Menopause at 45.
 Complaint:- Irregular vaginal bleeding for 6 months. This consisted of 5 attacks at intervals of about 4 weeks and lasting for about 14 days.
 Solid tumour of right ovary. Uterus enlarged and soft. Right oophorectomy. She had further vaginal bleeding and

STROMAL HYPERPLASIA

35. (6967c) Age 66. Married 44 years. 3 children. Menopause at 52.
 Complaint:- Irregular vaginal bleeding for 2 months (diabetic).
 Curettage produced hyperplastic endometrium. Total hysterectomy and bi-lateral salpingo-oophorectomy a fortnight later.
 Pathology:- Bulky uterus with several small fibroids, largest 3.5 cms. in diameter. Ovaries appear normal.
 Histology:- Both ovaries show diffuse overgrowth of stroma not quite established as neoplastic. Many corpora albicantia. In an area of one ovary there are numerous cubical cells with much cytoplasm. Nuclei are larger than usual in lutein cells. The cells appear to arise in association with a corpus albicans. Endometrium shows a very high degree of hyperplasia on the border-line of malignancy. Patient is very well 6 years later. No menopausal symptoms.
36. (3551) Age 66. Married 43 years. 3 children. Menopause at 48.
 Complaint:- Red vaginal discharge at irregular intervals for 9 months.
 Curettage produced endometrium which showed marked cystic glandular hyperplasia. Menopausal course of deep X-ray. 3 years later she had profuse bleeding lasting several weeks. No palpable abnormality. Total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- A thick walled uterus 10 cms. long. Endometrium shows evidence of recent haemorrhage. One ovary replaced by a calcified tumour 2 cms. in diameter, the other contains yellow areas.
 Histology:- Both ovaries present a similar appearance in that the whole ovary apart from the capsule and corpora albicantia is apparently active stroma with no tumour formation. There is little connective tissue. In one ovary around sinus-like blood-vessels are small groups of granulosa cells which have large clear fatty cells in the centre. Round these groups the stroma is less well stained. The other ovary is all thecomatous and does not show these cells. The endometrium shows well marked cystic glandular hyperplasia.
 The patient is enjoying only moderate health 7 years after

36. after the second operation. No menopausal symptoms or bleeding.

DIFFUSE GRANULOSA CELL TUMOURS

37. (1733/50) Age 58. Married 17 years. No children. Menopause at 40.
 Complaint:- Abdominal swelling. No vaginal bleeding or discharge.
 Friable brain-like tumour of right ovary. Free in abdomen. No free fluid. Total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Uterus normal in size, endometrium thickened. Left tube and ovary normal. Right ovary replaced by a lobulated tumour 15 x 10 x 5 cms. The tumour is a shell 1 to 2.5 cms. thick surrounding a mass of pultaceous material.
 Histology:- Some normal ovarian stroma is left and the tumour grows out from it. Tumour highly cellular with pale oval nuclei and poorly defined cytoplasm. Cells are in solid sheets with little pattern. Near the cortex a thecomatous arrangement is seen. Centre of tumour is necrotic. Endometrium shows active proliferation with some cystic dilation of glands.
 Left ovary has well stained cortex.
 Patient went to America and a letter was received from her doctor (Louis Phaneuf) to say that the pelvis was normal 2½ years later. Dr. Phaneuf has died and no further information about the patient could be obtained.
38. (27130) Age 53. Unmarried. No children. Menopause at 41.
 Complaint:- Slight baginal bleeding 3 weeks before admission.
 Patient had a well differentiated adenocarcinoma of the uterus. Uterus and adnexa normal in appearance. Total hysterectomy, bi-lateral salpingo-oophorectomy.
 Pathology:- Uterine cavity filled by a polypoidal growth. In the centre of one ovary is a tiny tumour.
 Histology:- Endometrial polyp shows adenocarcinoma with solid areas. The remainder of the endometrium shows cystic dilatation of senile glands. The ovarian tumour measures 6.9 x 4.8 mm. It is a highly cellular granulosa cell tumour with deep staining oval nuclei and little cytoplasm. Nuclei are all about the same size. There is no definite pattern. Normal stroma surrounds the tumour; there is no evidence of infiltration. The second ovary was normal.
 Patient was given a course of deep X-ray therapy. She moved to Aberdeen. The radio-therapist reports that there is no evidence of recurrence 2½ years after operation.

39. (16065) Age 50. Married 22 years. No children. Menopause at 45.

Complaint:- Abdominal pain for 2 months. No vaginal bleeding.

Left-sided ovarian cyst size of melon. Right ovary normal. Uterus contains 2 small fibroids. Right salpingo-oophorectomy.

Pathology:- A ruptured cyst 18 cms. in diameter. The walls are up to 5 cms. thick suggestive of central necrosis of a solid ovarian tumour.

Histology:- The tumour tissue is split up by many bands of hyaline fibrous tissue. The nuclei are closely packed together forming a dense sheet. They stain deeply and are oval with well stained nucleoli. Cell margins are not defined and the amount of cytoplasm varies. In some areas there is a very vague trabecular pattern, and in others a change suggestive of luteinization is seen. There is no evidence of invasion. In some areas the pattern is thecomatous.

The patient did not enjoy good health but 2½ years after the operation was relatively well. There had been no vaginal bleeding.

40. (22492) Age 54. Married 22 years. No children. Menopause at 50.

Complaint:- Vaginal bleeding after 4 years amenorrhoea. Left-sided ovarian cyst with haemorrhage into the cavity.

Adhesions to parietal peritoneum. Multiple fibroids. Right ovary normal. Sub-total hysterectomy. Bi-lateral salpingo-oophorectomy.

Pathology:- Uterus contains numerous small fibroids. Tumour measures 15 x 12 x 10 cms. White in colour with central necrosis.

Histology:- Typical granulosa cell tumour plump oval, polygonal or cuboidal nuclei. Many show grooving. Minimal cytoplasm. No malignant forms seen. Connective tissue bands frequent and almost completely hyalinized. The granulosa cells form no pattern. The right ovary shows a remarkable growth of deep staining ovarian stroma almost thecomatous in appearance.

The patient is very well 6 years after the operation. She still occasionally has hot flushes and sweating.

41. (26103) Age 49. Married 26 years. 4 children. Menopause at 43.

Complaint:- Vaginal bleeding after 6 years amenorrhoea. The bleeding lasts 7 days at 2 monthly intervals and was not relieved by curettage 6 months previously.

41. previously.

Both ovaries slightly enlarged, uterus normal. Sub-total hysterectomy, bi-lateral salpingo-oophorectomy, appendicectomy.

Pathology:- Uterine cavity contains 2 endometrial polyps. A tumour 4 cms. in diameter is growing out of the distal pole of the right ovary. The left ovary is cystic.

Histology:- The polyps show a little proliferative activity with a few dilated glands. The cells of the tumour stain poorly. They have oval or rounded nuclei and are divided up by bands of fibrous tissue. There is no pattern.

Appears to be a poorly differentiated granulosa cell tumour. The patient is very well $3\frac{1}{2}$ years after the operation.

42. (24061) Age 59. Married 35 years. No children. Menopause at 53.

Complaint:- Two incidents of slight vaginal bleeding after 6 years amenorrhoea.

Small right-sided ovarian tumour. Curettage, right oophorectomy.

Pathology:- The tumour measures 6 x 3 x 3 cms. Lobulated and solid. Half is white and fibrous and half buff-coloured.

Histology:- Part of the tumour consists of cells with pale rounded oval or spherical nuclei, a fair amount of cytoplasm but no pattern. Much of this is split up by hyaline bands of connective tissue. Other parts have cells with deeper staining nuclei, attenuated and forming a vague whorled pattern. The margin between tumour and ovarian hilar tissue is not clearly defined. This was considered to be rather a malignant granulosa cell tumour. The endometrium showed a very considerable degree of cystic glandular hyperplasia. The patient was well until 4 years after the operation when she reported with vaginal bleeding of 5 days duration. She had an extensive cervical erosion which bled to the touch. On curettage the endometrium was very scanty but showed on histological examination a high degree of hyperplasia. The patient is being kept under observation and has had no bleeding since the curettage a year ago.

43. (22323) Age 60. Married 10 years. No children. Menopause at 52.

Complaint:- Vaginal bleeding after 8 years amenorrhoea. Uterus contained many small fibroids. Curettage. Endometrium showed active proliferation. Had no bleeding for 6 months after operation but bleeding recurred at intervals of 1-4 months. A second curettage 18 months later showed

showed very active endometrium, sub-total hysterectomy, bi-lateral salpingo-oophorectomy.

Pathology:- Uterus enlarged and distorted by many small fibroids. Left ovary atrophic. Right ovary looks active and contains a white tumour 1.5 cms. in diameter with central necrosis.

Histology:- Endometrium shows an extreme degree of hyperplasia in most areas. A few areas show little activity. Left ovary senile. Tumour consists of rather fibrous spindle-shaped cells among which are groups of more active cells arranged in islands or in columns. Tumour merges with ovarian stroma and has no definite pattern. Within the tumour were large pale cells with abundant cytoplasm and round nuclei. These cells were similar to Leydig or lutein cells and were scattered irregularly through the granulosa. The patient had flushings and palpitations after the operation but was very well 4½ years later.

44. (19075) Age 51. Married 27 years. 6 children.
Complaint:- Menorrhagia. Periods last for 14 days. Bulky retroverted uterus with some adhesions. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Appendicectomy.
Pathology:- Uterus 9 cms. long. Endometrium congested. Left ovary slightly enlarged contains a small tumour surrounded by ovarian tissue.
Histology:- Tumour consists of solid masses of cells with deep staining round and oval nuclei closely packed together. Little cytoplasm. Some areas show a vague pattern of cords. Tumour is well defined from stroma. Right ovary senile. Endometrium shows a mild degree of hyperplasia. Patient very well 9 years after operation. No menopausal symptoms. No bleeding.
45. (5933) Age 52. Married 16 years. 5 children.
? Menopause at 48.
Complaint:- For 4 years patient had very scanty periods but during past 6 months has had daily bleeding. Abdominal swelling. (diabetic). Solid tumour of left ovary adherent to omentum. Uterus and right ovary normal. Subtotal hysterectomy, bilateral salpingo-oophorectomy.
Pathology:- Normal uterus. Tumour 14 x 13 x 7 cms. Half solid, half cystic.
Histology:- The greater part of the tumour is

is necrotic and structureless. Granulosa cells have polygonal or spindle-shaped nuclei and are separated into oval groups by a reticulum of hyaline connective tissue. Capsule intact. Endometrium shows active proliferation within normal limits for a younger woman. Patient during the 20 years since operation but no information was obtained as to when and from what cause.

46. (3218c) Age 59. Married 33 years. 5 children. Menopause at 40. Complaint: Vaginal bleeding. 4 incidents since the menopause. Bulky uterus, retroverted. Curettage. Endometrium showed a considerable degree of hyperplasia with many greatly distended glands. Menopausal course of deep X-ray. 6 months later bleeding for 3 weeks. Total hysterectomy, bilateral salpingo-oophorectomy. Pathology:- Uterus 12 cms. long, symmetrically enlarged. Endometrium polypoidal. Right ovary atrophic; hydrosalpinx of right tube. Left ovary 3 cms. long filled with caseous material. Histology:- Endometrium shows well marked metropathia haemorrhagica (more hyperplastic than previous specimen). Left ovary contains a granulosa cell tumour 2 cms. in diameter. Nuclei oval or spindle shaped. No pattern, no infiltration, surrounded by normal ovarian tissue. Granulosa cell tumour tending towards thecoma. Right ovary senile. Patient very well 9 years later.
47. (14983) Age 56. Married 31 years. 2 children. Menopause at 48. Complaint:- Vaginal bleeding for 3 months. Right ovary enlarged and bound down by strong adhesions. Uterus and left ovary normal. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Pathology: Uterus normal, right ovary 5 cms. in diameter, hard and solid. Left ovary normal, left hydrosalpinx. Histology:- Cystic glandular hyperplasia of endometrium. Right ovary contains a patternless granulosa cell tumour much split up by hyaline connective tissue. Patient had menopausal symptoms after operation but was well 12 years later.

48. (14594) Age 59. Married 32 years. 3 children.
Menopause at 49.
Complaint:- Weakness. No bleeding.
Large solid ovarian tumour. Uterus normal. Second ovary normal. Bilateral oophorectomy.
Pathology:- Tumour measures 19 x 12 x 11 cms.
Partly cystic partly solid. Solid portion cuts like fibroma, cystic portion contains serous fluid.
Histology:- Originally diagnosed as fibroma undergoing sarcomatous change, but areas of typical patternless granulosa cell tumour are seen undergoing much myxomatous degeneration. Diffuse granulosa cell tumour-thecoma-fibroma. No endometrial specimen taken.
Patient died on the 8th day after operation.
Cause of death not established.
49. (Annexe B.333) Age 58. Unmarried. No children.
Menopause at 49.
Complaint:- Vaginal bleeding at 2 monthly intervals for 2 years.
Right sided ovarian tumour size of 5 months pregnancy. Uterus and left adnexa normal. Subtotal hysterectomy. bi-lateral salpingo-oophorectomy.
Pathology:- Uterus 8 cms. long. Left tube and ovary normal. Tumour measures 15 x 10 x 6 cms. Solid with central necrosis.
Histology:- A typical patternless granulosa cell tumour with deep staining oval nuclei. Some areas thecomatous. Connective tissue tends to split up the more typical granulosa into groups. Endometrium shows cystic glandular hyperplasia.
Patient very well 8 years later. No menopausal symptoms. No bleeding.
50. (23310) Age 67. Unmarried. No children. Menopause at 50.
Complaint:- Sudden profuse vaginal bleeding 5 days ago. Malignant tumour of ovary with extensive adhesions to bowel, uterus and pelvic peritoneum. Operation impossible. Curettage, biopsy of tumour.
Histology:- Large masses of cells with oval and round nuclei. Little cytoplasm. An occasional gyriform appearance. Much necrosis of connective tissue. Endometrium shows a high degree of cystic glandular hyperplasia.
Patient could not be traced but is assumed to have died.

51. (P7/54) (Private case). Age 68. Married. 2 children.
 Complaint:- Slight vaginal bleeding on one occasion. Uterus slightly enlarged. No adnexal lesion. Curettage. Endometrium shows marked metropathia haemorrhagica. Total hysterectomy, bilateral salpingo-oophorectomy one week later.
 Pathology:- Uterus 9 cms. long. Tumour 2.5 cms. in diameter in right ovary, welldefined capsule.
 Histology:- Much the greater part of the tumour is converted into hyaline connective tissue very similar in structure to a corpus albicans. On the periphery are granulosa cells with pale rounded nuclei and a fair amount of ill defined cytoplasm. This tumour is interesting because it seems to show the probable fate of some untreated granulosa cell tumours, that is the conversion into hyaline connective tissue similar to the fate of the follicular granulosa without an intervening luteal phase.
 The patient is well 2 years later.
52. (10055) Age 21. Unmarried. No children.
 Complaint:- Amenorrhoea for 1 year after bleeding at irregular intervals for 8 months. Periods previously normal. Growth of hair on face and limbs and deepening of voice.
 Solid right sided ovarian tumour. Uterus and left adnexa normal. No endometrium on curettage. Right oophorectomy.
 Pathology: Tumour is mostly solid but there are a few small cysts at one pole. It is yellow and measures 11 x 8 x 6 cms.
 Histology:- A diffuse granulosa cell tumour with some cording of the cells. Nuclei variable in shape and size but mostly oval or polygonal. The amount of cytoplasm varied too. A number of large clear cells with abundant cytoplasm and large round nuclei, ? Leydig cells are seen throughout the parenchyma of the tumour. There is nothing to differentiate this from a granulosa cell tumour.
 The patient's periods became normal within a month of operation and the abnormal hair gradually disappeared but the voice remained deeper than usual.

DIFFERENTIATED GRANULOSA CELL TUMOURS

53. (13704) Age 45. Unmarried. No children.
 Complaint:- Increasing abdominal swelling.
 Menorrhagia for past 8 months. Periods have also become irregular. Midline swelling equal to 5 months pregnancy. Multiple fibroids. Right adnexa converted to cystic swelling size of cricket ball. Subtotal hysterectomy, right salpingo-oophorectomy.
 Pathology:- Uterus contains fibroid 14 cms. in diameter. Right-sided broad ligament cyst, right ovary appears normal.
 Histology:- The endometrium is replaced by a narrow band of pus and granulation tissue with a few ghost glands. The ovary shows normal stroma with no follicles but several epithelial inclusions. In the centre of this ovary is a tubular adenomatous tumour sharply defined from the rest of the ovary. The tumour has a glandular pattern and consists of epithelial cells with large pale ovoid or broad polygonal nuclei varying in size. The cytoplasm is vacuolated and cell margins are poorly defined. Secretion is present in the lumen of many glands. At one point only there is a cystic space surrounded by typical granulosa with rosette formation. The adenomatous tumour tissue merges gradually with this granulosa. The whole tumour measures 13.3 x 5.1mm. The secretion does not stain with mucicarmine. The arrangement and character of the adenomatous cells suggests that they are Sertoli cells differentiating from granulosa cells.
 The patient is now married and has been "exceptionally well" since the operation 7 years previously. She had slight flushings after the operation.
54. (23618) Age 50. Married 27 years. 5 children.
 Menopause at 40.
 Complaint:- Almost continuous vaginal bleeding for a year after 6 years amenorrhoea.
 Curettings showed metropathia haemorrhagica. No palpable lesion. Menopausal course of deep X-ray.
 Readmitted 2 years later with vaginal bleeding. Left ovary cystic and size of a tomato. Right ovary and uterus normal. Left salpingo-oophorectomy.
 Pathology:- A solid tumour 7 cms. in diameter with central necrosis and haemorrhage.
 Histology: The tumour has a capsule of ovarian tissue and is defined from the capsule except in one area where the tumour assumes a thecomatous appearance and merges with the ovarian stroma without

without margin. The following features were recognized. (1) In the better defined areas there is a narrow tubule formation, long parallel strings of cells with a channel between. Cells have large cubical, oval or polygonal nuclei with indistinct cell margins. Nucleus takes about half the cell volume. (2) Solid areas of granulosa with rosette formation. (3) Thecomatous areas with long attenuated nuclei and fibrous appearance. (4) Groups of large vacuolated cells with abundant cytoplasm and round nuclei centrally placed. This tumour shows all transitions from Sertoli-like cells to thecoma.

Patient is well $3\frac{1}{2}$ years after the major operation.

55. (7248c) Age 51. Unmarried. No children.

Menopause at 49.

Complaint:- Vaginal bleeding. After 23 months amenorrhoea had 2 apparently normal periods followed by 3 months continuous bleeding.

Adenocarcinoma of uterus. Total hysterectomy, bilateral salpingo-oophorectomy. Full course of deep X-ray therapy.

Pathology:- Uterus 9 cms. long. Endometrium thickened and haemorrhagic. No evidence of invasion of muscle. Tubes and ovaries normal.

Histology:- Endometrium shows a well differentiated adeno-carcinoma with squamous metaplasia. One ovary shows deeply staining active stroma. In the centre of the second ovary is a granulosa cell-tumour measuring 8.0 x 4.3 mm. The tumour shows variations in structure. (1) Tubular processes lined by large vacuolated cells with large round nuclei. Cells are almost cubical or columnar and groups are split up by connective tissue. In the tissue surrounding the tubules Leydig-like cells are seen. (2) Tubules formed by lacunae in solid areas, the tubules being lined by cells similar to (1). (3) Solid areas with rosette formation. (4) Areas in which small cells with deeply staining crowded nuclei form long parallel cords. (5) Solid areas with no pattern. (6) Thecomatous areas. This tumour shows all transitions from "adenoma testiculare" to thecoma. Patient reported regularly and is well $5\frac{1}{2}$ years after operation.

56. (22574) Age 57. Married 30 years. 2 children.

Menopause at 50.

complaint:- Blood stained vaginal discharge. Chronic cervicitis (cauterization). Solid tumour of left ovary. Uterus and right adnexa normal. Left oophorectomy.

Pathology:- A spherical tumour 6 cms. in diameter, yellow in colour with necrotic centre.

Histology:- No endometrial specimen. Tumour is not altogether defined from ovarian stroma. The cells have pale oval or long nuclei and are arranged in vague rosettes and cords. There is some attempt at tubule formation. Several areas thecomatous. Patient is very well 5 years later. No further bleeding.

57. (2033/49) Age 62. Married 29 years. 4 children. Menopause at 50.

Complaint:- Slight vaginal bleeding at intervals for one year. Ovarian cyst on left side size of rugby football. Uterus symmetrically enlarged. Right ovary atrophic. Left salpingo-oophorectomy.

Pathology:- An ovarian tumour 19 cms. in diameter grey white in colour. Extensive central necrosis.

Histology:- Tumour consists of masses of granulosa cells with rounded, cuboidal or polygenal nuclei. A striking feature is the presence of columns and incomplete tubules of much darker staining cells within the tumour. The columns usually consist of two parallel rows of cells with polygenal nuclei and sometimes columnar in shape.

The patient was fairly well but frail 6½ years later. No further bleeding.

58. (20019) Age 59. Married 28 years. 7 children. Menopause at 51.

Complaint:- Irregular vaginal haemorrhage at long intervals for two years.

No palpable pelvic abnormality. Curettage.

Cystic glandular hyperplasia. Menopausal course of deep X-ray. Bleeding recurred after 6 months.

Readmission. Sub-total hysterectomy, bilateral salpingo-oophorectomy.

Pathology:- Uterus 7 cms. long, thick walled.

Ovaries look senile.

Histology:- Endometrium shows more active cystic glandular hyperplasia than specimen of previous year.

The smaller ovary measures 12.5 x 7.9 mm. Stroma is well stained. Larger ovary measures 20.8 x 8.8 mm.

Stroma well stained and surrounds a lobulated granulosa cell tumour increasing 10.5 x 4.5 mm. The tumour varies as follows.

(1) Masses of cells with well stained often grooved nuclei forming rosettes.

(2) Columns of cells with an adenomatous arrangement. Cells are cuboidal with abundant vacuolated cytoplasm and secretion in the central lumen.

(3) Hyaline connective tissue splits up the columns of cells.

The tumour shows transition from typical granulosa to primitive tubules of Sertoli-like cells.

The patient 'enjoys perfect health', 7 years after operation.

59. (21096) Age 64. Married. No children. Menopause at 45.
 Complaint:- Pelvic pain. No bleeding.
 Ovarian cyst size of melon on right side. Uterus normal, left adnexa normal. Bilateral salpingo-oophorectomy.
 Pathology:- A tumour of brain-like consistency white in colour with many haemorrhages, measuring 19 x 15 x 11 cms. Left ovary normal.
 Histology:- A solid mass of deep staining cells with rounded or polygenal nuclei varying in size. A vague adenomatous arrangement and cording is noticed. The capsule appears to be intact. The appearances suggest granulosa cell tumour with ? sarcomatous degeneration. Left ovary senile.
 The patient was admitted to another hospital 3 years later. Massive abdominal secondaries were found on laparotomy. She died 6 months later.
60. (23567) Age 29. Married 9 years. No children.
 Complaint:- Periods regular until 8 months ago when she began to menstruate every fortnight, the period lasting for 7 days.
 Left ovarian cyst lying in front of uterus. Right adnexa and uterus normal. Left oophorectomy.
 Pathology:- A solid tumour with central necrosis measuring 10 cms. in diameter.
 Histology:- A diffuse granulosa cell tumour with an irregular pattern in some areas. Parallel rows of cells with polygonal or oval nuclei. In one area the cords form a pattern of tubules and Leydig like cells are seen in the interstitial tissue.
 No endometrial specimen was taken.
 5 years after the operation the patient's health is good. She has had no family and periods have been irregular for the past year.
61. (6782) Age 29. Unmarried. No children.
 Complaint:- Frequent irregular vaginal haemorrhage. Periods were regular until a year ago.
 Tumour size of grapefruit on left side. Uterus and right adnexa normal. Left Salpingo-oophorectomy.
 Pathology:- A solid tumour with central necrosis, white in colour, measuring 13 x 9 x 6 cms.
 Histology: Columns of granulosa cells divided by connective tissue. Columns have a central cavity with distinct lining. At the periphery of the columns the cells are arranged in columnar fashion. Rosettes frequent and well formed. Areas of "cording" present. One area is quite different

different where the granulosa more thecomatous in nature seems to be growing without margin from the ovarian stroma. The groups of cells are roughly oval and merge with the stroma. The operation was 16 years ago and the patient could not be traced.

62. (10602) Age 29. Married 7 years. 1 child.
 Complaint: 11 months amenorrhoea. Abdominal pain for two weeks. Menstruation was always irregular occurring every 3-4 months with normal flow. Right ovary size of tangerine. Uterus normal, left adnexa normal. Right oophorectomy.
 Pathology:- A thin layer of ovarian tissue surrounds a soft yellow tumour which measures 8 x 7 x 6 cms.
 Histology:- Most of the tumour is thecomatous but there are areas where columnar and cubical cells form long parallel rows and giving a tubular appearance. Patient's general health was never good. The periods became normal after the operation and she had a miscarriage at 4 months 18 months later. 17 years later periods are still normal but she suffers from dyspepsia and haemorrhoids.
63. (11403) Age 54. Married 32 years. 4 children.
 Complaint:- Abdominal swelling. Severe menorrhagia. Periods last from 14 - 21 days.
 Left sided ovarian cyst. Uterus and right adnexa normal. Left oophorectomy.
 Pathology:- A solid ovarian tumour with central necrosis measuring 25 x 22 x 12 cms.
 Histology:- Columns of granulosa cells split up by connective tissue. Nuclei round or oval and cell margins indistinct except at periphery of columns. Rosettes frequent and a tendency to cording of the cells. Much degeneration. No endometrial specimen.
 No information could be obtained about the patient who was operated on 16 years previously.
64. (14417) Age 61. Unmarried. No children.
 Menopause at 37.
 Complaint:- Vaginal bleeding for seven days.
 A cervical polyp was removed, left ovary noted to be cystic. Patient dismissed. Readmitted with vaginal haemorrhage one year later. Large multilocular cyst of left ovary. Small cyst of right ovary. Uterus normal. Subtotal hysterectomy, bilateral salpingo-oophorectomy.
 Pathology:- An ovarian cyst 13 cms. in diameter with

with a solid portion 2.5 cms. in diameter.

Histology:- Tumour shows large masses of cells but in one area there is attempted gland formation with cords and rosettes. Leydig-like cells are seen in the interstitial tissue. The endometrium shows marked cystic glandular hyperplasia, no evidence of secretion but a decidual change has taken place in the stroma in the superficial levels. No information was obtained about the patient who was operated on 20 years ago.

Primary Adenocarcinoma of Ovary.

65. (15927) Age 61. Married. No children.
Complaint:- Vaginal bleeding for 1 week.
Enucleation of tumour. Deep X-ray.
Dedifferentiating adenocarcinoma.
Well 3 years later.
66. (24582) Age 34. Married. 1 child.
Complaint:- Abdominal swelling.
Inoperable carcinoma.
Dedifferentiating adenocarcinoma.
Died in 1 year.
67. (24889) Age 50. Married. 4 children.
Complaint:- Lower abdominal pain.
Bilateral salpingo-oophorectomy. Deep X-ray.
Bilateral adenocarcinoma.
Died in 3 years.
68. (15616) Age 62. Married. 7 children.
Complaint:- Abdominal swelling:
Salpingo-oophorectomy. Deep X-ray.
Adenocarcinoma becoming solid.
Died in 2 years.
69. (2246/52) Age 30. Married. 2 children.
Complaint:- Abdominal swelling.
Inoperable carcinoma. Deep X-ray.
Dedifferentiating adenocarcinoma.
Died within a year.
70. (9612) Age 58. Married. No children.
Complaint:- Postmenopausal bleeding.
Uterus riddled with growth. Bilateral adenocarcinoma.
Adenocarcinoma with clear cells.
Died 2 days after operation.
71. (9683) Age 63. Married. 6 children.
Complaint:- Abdominal swelling.
Removal of tumour piecemeal. Deep X-ray.
There is a vague granulosa cell appearance in this
tumour.
Well 2 years later.
72. (27029) Age 53. Unmarried.
Complaint:- Abdominal swelling.
Ovarian cystectomy. Deep X-ray.
Adenocarcinoma with clear cells.
Died in 18 months.

73. (1730/48) Age 62. Married. 6 children.
Complaint:- Prolapse.
Inoperable carcinoma.
Solid carcinoma from adenocarcinoma.
Died in 2 years.
74. (54280) Age 58. Married twice. No children.
Complaint:- Abdominal swelling.
Subtotal hysterectomy, bilateral salpingo-oophorectomy.
Deep X-ray.
A very malignant-looking solid-adenocarcinoma.
Very well 8 years later.
75. (5540c) Age 56. Married. 2 children.
Complaint:- Abdominal pain and swelling.
Inoperable carcinoma. Deep X-ray.
Dedifferentiated adenocarcinoma.
Died within 2 years.
76. (269/49) Age 47. Married. No children.
Complaint:- Abdominal discomfort.
Bilateral salpingo-oophorectomy.
Adenocarcinoma with clear cells.
Well 7 years later.
77. (21523) Age 39. Unmarried.
Complaint:- Abdominal swelling.
Very large ovarian tumour. Salpingo-oophorectomy.
Carcinoma with many solid areas and areas of
clear cells.
With large nuclei.
Very well and working 7 years later.
78. (6405c) Age 47. Married. No children.
Complaint:- Abdominal swelling.
Huge cyst. Bilateral salpingo-oophorectomy, sub-
total hysterectomy.
Deep X-ray.
Histology very similar to No.77.
Died in 6 months.
79. (21998) Age 63. Unmarried.
Complaint:- Abdominal swelling.
Bilateral tumours removed.
Primary carcinoma of the fibrocystadenocarcinoma
type.
Very well 6 years later.
80. (13899) Age 61. Married. 2 children.
Complaint:- Post menopausal haemorrhage.
Bilateral carcinoma invading uterus. Pan
hysterectomy.
Dedifferentiated adenocarcinoma.
Died in 3 weeks. Cerebral haemorrhage.

81. (742/50) Age 61. Married. No children.
Complaint:- Abdominal swelling.
Ovarian cyst:- Subtotal hysterectomy, bilateral salpingo-oophorectomy.
Primary adenocarcinoma becoming anaplastic.
Died within 2 years.
82. (405/51) Age 55. Married. 1 child.
Complaint:- Post-menopausal bleeding.
Bilateral carcinoma.
Dedifferentiating adenocarcinoma. Endometrium showed cystic glandular hyperplasia.
This patient could not be traced.
83. (23758) Age 47. Married. 2 children.
Complaint:- Abdominal swelling.
Ovarian cyst. Subtotal hysterectomy, salpingo-oophorectomy.
Dedifferentiating adenocarcinoma.
Very well 5 years later.
84. (23975) Age 61. Unmarried.
Complaint:- Abdominal swelling.
Solid tumour with adhesions.
Adenocarcinoma with simple cyst adenofibroma.
Died postoperatively.
85. (7983c) Age 44. Married. 1 child.
Complaint: Abdominal swelling.
Massive ascites, many secondaries. Removal of primary growth, deep X-ray.
Anaplastic carcinoma.
Died within a year.

86.

Papillary Cystadenocarcinoma.

86. (8725) Age 43. Married. No children.
Complaint:- Abdominal swelling.
Papillary cyst undergoing malignant degeneration.
Cyst removed. Deep X-ray.
Died in 2 years.
87. (24694) Age 48. Married. One child.
Complaint:- Vomiting.
Inoperable carcinoma.
Papilliferous carcinoma.
Died within 6 months.
88. (1575) Age 47. Married. 1 child.
Complaint:- Abdominal swelling. Previously had
X-ray.
Menopause for metropathia.
Large ovarian cyst removed. Papillary serous cyst
showing great hyperplasia. On borderline of
malignancy.
Well 5 years later.
89. (16421) Age 47. Married. No children.
Complaint:- Abdominal pain.
Inoperable carcinoma. Deep X-ray.
Papilliferous adenocarcinoma.
Died in 8 months.
90. (26069) Age 58. Married. 2 children.
Complaint:- Abdominal swelling.
Bilateral cysts, extensively adherent, removed.
Deep X-ray.
Dedifferentiated papillary carcinoma.
Died in 15 months.
91. (Annexe 267B) Age 49. Married. 1 child.
Complaint:- Abdominal pain.
Abdominal carcinomatosis.
Papillary carcinoma.
Died postoperatively.
92. (5201c) Age 60. Unmarried.
Complaint:- Post-menopausal bleeding.
Endocervical carcinoma, bilateral serous
cystadenocarcinoma. Deep X-ray.
Died in 18 months.
93. (20175) Age 52. Married. No children.
Complaint:- Abdominal pain.
Hysterectomy for fibroids at 40 years. Inoperable

Inoperable carcinoma.
Papilliferous carcinoma.
Died in 2 months.

94. (12515) Age 48. Married. 5 children.
Complaint:- Abdominal swelling.
Bilateral adherent cysts removed. Deep X-ray.
Borderline of malignancy - papilliferous cysts.
Well 8 years later.
95. (20284) Age 35. Unmarried.
Complaint:- Abdominal pain.
Bilateral multilocular cysts removed.
Probably malignant but show no infiltration.
Very well 8 years later.
96. (12563) Age 47. Married. 1 child.
Complaint:- Abdominal swelling.
Bilateral cysts removed. Deep X-ray.
Papillary carcinoma becoming dedifferentiated.
Died within 2 years.
97. (Annexe B.258) Age 46. Married. No children.
Complaint:- Abdominal swelling.
Ovarian cyst and bowel tumour. No obvious
connection.
Cyst removed, colostomy.
Serous papillary adenocarcinoma.
Died in a few months.
98. (9573c) Age 69. Married. No children.
Complaint:- Abdominal swelling.
Partial removal of adherent cyst. Deep X-ray.
Papillary carcinoma. Highly malignant.
2 years later showed two old fractures femora.
? post-radiation. No evidence of recurrence
3 years.

Pseudomucinous Adenocarcinoma.

99. (5726c) Age 49. Married. No children.
Complaint:- Post-menopausal bleeding.
Adherent cyst, subtotal hysterectomy, bilateral salpingo-oophorectomy. Deep X-ray.
Pseudomucinous adenocarcinoma. Hyperplastic endometrium.
Very well 6 years later. No bleeding.
100. (1012/49) Age 51. Married. No children.
Complaint:- Irregular vaginal bleeding.
Adenocarcinoma of uterus. Bilateral pseudomucinous cystadenocarcinoma. Appearances suggest two separate malignancies.
Pan hysterectomy.
Very well and working 7 years later.
101. (14534) Age 49. Married. 4 children.
Complaint:- Irregular bleeding.
Left ovarian cyst removed.
Pseudomucinous cystadenoma with malignant change and invasion. Deep X-ray.
Well 5 years later.
102. (9104c) Age 26. Unmarried.
Complaint:- Abdominal swelling.
Partial removal of ovarian cyst. Deep X-ray.
Secondaries in abdominal wound.
Hyperplastic but not obviously malignant pseudomucinous cyst adenoma.
Died within a year.

Secondary Carcinoma of Ovary.

- 103. (15876) Age 54. Married. 2 children.
Complaint:- Irregular bleeding.
Adenocarcinoma of uterus with ovarian secondaries.
Subtotal hysterectomy, bilateral salpingo-
oophorectomy.
Deep X-ray.
Well 4 years later.
- 104. (15687) Age 57. Married. No children.
Complaint:- Abdominal pain.
Adenocarcinoma of uterus with secondary deposits
in both ovaries. Pan hysterectomy. Deep X-ray.
Well 3½ years later.
- 105. (25406) Age 51. Married. No children.
Complaint:- Abdominal discomfort.
Carcinoma of sigmoid with bilateral ovarian
secondaries.
Pan hysterectomy.
Died within 6 months.
- 106. (26969) Age 60. Married. No children.
Complaint:- Post-menopausal haemorrhage.
Adenoacanthoma of uterus with secondary deposits
in one ovary. Pan hysterectomy, deep X-ray.
Very well 2 years later.
- 107. (12328) Age 13.
Complaint:- Abdominal pain and swelling.
Round cell sarcoma of nasopharynx with bilateral
ovarian secondaries. Ovaries removed. Deep
X-ray.
Died within 6 months.
- 108. (20488) Age 46. Married. 2 children.
Complaint:- Irregular haemorrhage.
Adenocarcinoma of uterus with secondary deposits
in one ovary. Pan hysterectomy.
Died in about 3 years.
- 109. (13291) Age 45. Married. No children.
Complaint:- Vaginal bleeding.
Carcinoma of sigmoid with small secondary deposits
in one ovary. Normal endometrium.
Died 5 years later.

110. (6650c) Age 67. Married. 6 children.
Complaint:- Post-menopausal bleeding.
Advanced adenocarcinoma of uterus with
secondaries on one ovary. Pan hysterectomy,
deep X-ray.
Died in 5 years.
111. (6718c) Age 57. Unmarried. No children.
Complaint:- Post-menopausal bleeding.
Adenocarcinoma of uterus with secondary deposit
in one ovary. Subtotal hysterectomy, bilateral
salpingo-oophorectomy. Deep X-ray.
Well 6 years later.
112. (6957c) Age 43. Unmarried. No children.
Complaint:- Abdominal swelling.
Primary adenoacanthoma of uterus with
secondary adenoacanthoma in one ovary and well
differentiated adenocarcinoma in the other.
Pan hysterectomy. Deep X-ray.
Well 4 years later.
113. (Annexe 373B) Age 52. Married. No children.
Complaint:- Abdominal swelling.
Primary adenoacanthoma of uterus faithfully
reproduced in one ovary. Subtotal hysterectomy,
bilateral salpingo-oophorectomy.
Very well 5 years later.
114. (16518) Age 46. Married. 1 child.
Complaint:- Abdominal pain.
Primary carcinoma of descending colon. Secondary
in one ovary of Krukenberg type. Deep X-ray.
Died in 6 months.

Miscellaneous.

115. (1373/48) Age 50. Unmarried.
Complaint:- Abdominal swelling.
Inoperable carcinomatosis. Laparotomy.
Died post-operatively.
Histologically a fibrosarcoma.
116. (6091c) Age 24. Married. 2 children.
Complaint:- Abdominal pain.
Bilateral ovarian tumour removed.
Deep X-ray.
Histologically a fibrosarcoma.
Died within a year.
117. (22033) Age 39. Married. No children.
Complaint:- Swelling of legs and irregular periods.
Bilateral tumour removed.
Round cell sarcoma.
Died in 14 days.
118. (12544) Age 52. Unmarried. No children.
Complaint:- Abdominal swelling.
Incomplete removal of ovarian tumour.
Dermoid cyst with malignant degeneration of squamous epithelium.
Died in 6 months.
119. (19944) Age 46. Married. 1 child.
Complaint:- Anorexia and vomiting.
Ovarian cyst adherent, removed.
Low grade malignant change in ovarian endometriosis.
Patient now in America and is very well 8 years later.
120. (21013) Age 38. Married. 2 children.
Complaint:- Abdominal swelling and vaginal bleeding.
Adherent bilateral ovarian tumour removed.
Histology uncertain. ? fibroadenocarcinoma, ? endometriosis.
Died in one year.
121. (2679) Age 58. Married. 10 children.
Complaint:- Abdominal swelling.
Ovarian tumour removed.
Lipoid laden tumour of the clear cell type.
No information available.

122. (25031) Age 55. Unmarried. No children.
Complaint:- Bleeding after 6 years amenorrhoea.
Multiple fibroids with bilateral ovarian
tumours. Pan hysterectomy.
Endometrium hyperplastic. Bilateral clear
cell tumours.
Well at 3 years.
123. (18726) Age 44. Married. 1 child.
Complaint:- Progressive abdominal swelling.
Large adherent ovarian tumour removed.
Deep X-ray.
Adenocarcinoma with clear cells.
Well at 18 months.

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