THE GRANULOSA CELL TUMOUR.

T H E S I S

for the degree of

MASTER OF SURGERY

in the

UNIVERSITY OF CAPE TOWN

by

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INTRODUCTION :

The granulosa cell tumour is a rare but interesting ovarian neoplasm. As gynaecologists and pathologists have gradually acquired a clearer conception regarding its symptoms, signs and histology, it is, although still uncommon, more frequently diagnosed.

In attacking the problem of granulosa cell tumours a fundamental difficulty soon crops up. This major obstacle is that the tumour, a neoplasm of epithelial cells, veers towards the Sarcomatous picture histologically and not towards the Carcinomatous one, as might be expected. This behaviour requires explanation.

In this thesis an attempt will be made to demonstrate this seemingly peculiar behaviour and also to show that this behaviour is understandable as the granulosa cell takes its origin from the ovarian stromal cell - a cell undistinguishable from a fibroblast.

A review of the literature will be given in conjunction with 10 cases, 7 of which are definite granulosa cell tumours. The remaining 3 cases are used for purposes of demonstration.

Historical:

A review of the literature shows that the earlier work on the granulosa cell tumour was done by German pathologists.

The story of the tumour, briefly, starts in 1859, when Rokitansky (95) described a lobulated left ovarian tumour the size of a child's head in a woman aged 65. The histology of the tumour revealed Lutein cells and much lipoid.

In 1882 Maffucci (68) described a similar pathology barring that a mixture of both Lutein and granulosa cells were found in the tumour.

Acconci (1) in 1888 contributed a further description.

In 1895 von Kahlden (108) gave the first unmistakable description and called the tumour a "Graafian Follicle Adenoma".

It was as late as 1914 that von Werdt (109) attached the name of granulosa cell to the tumour.

Robert Meyer in 1915 (75) and 1931 (76) has done much to clarify the pathology of the tumour.

Since 1930 the Americans have entered the field of discussion and have made many contributions to the literature of this subject.

Definition:

Novak's (79) definition of the granulosa cell tumour, i.e., "a tumour made up of cells whose individual characteristics as well as their physiologic function are similar to those of the normal follicular epithelium" is most apt, as it indicates that the tumour cells resemble the cells of the follicle in every way, except in arrangement.

Clinical Criteria for Diagnosis:

The symptoms largely depend upon the age or the "phase" of the patient, i.e., whether she is in the stage of active sex life, before the onset of puberty or has reached the menopause.

Pubertal Age:

The patient usually shows the symptoms and signs of puberty at a young age, e.g., 4 years, i.e., pubertal hairs start growing, breasts enlarge, there may be vaginal bleeding at odd intervals.

An ovarian tumour is felt, i.e., the patient presents with signs and symptoms of Precocious Puberty and has an ovarian tumour.

Phase of Active Sex:

In this age group the condition may be most

difficult to recognise clinically. The patient may complain of menorrhagia, amenorrhoea followed by menorrhagia; or there may be no menorrhagia whatsoever.

If an ovarian tumour is detected the diagnosis may be easy.

Post-menopausal Age:

The main symptom in this age group usually is vaginal bleeding which may or may not be periodic. The detection of an ovarian tumour together with a hyperplastic endometrium usually clinches the diagnosis.

The uterus is not atrophic as would be expected but may be the size of a uterus of a woman in active sex life, or even larger. Therefore, there are signs and symptoms of sexual rejuvenation.

From these criteria it will be noticed that the common signs and symptoms of the tumour are not produced by virtue of its anatomy but because it secretes a hormone.

The hormone it secretes is a feminising one, as is proved clinically by the fact that it produces an early puberty in young girls and rejuvenates the post-menopausal uterus.

Biochemically, high concentrations of oestrin

are found in the blood, urine and faeces of these patients (79, 84, 37). The tumour itself is rich in oestrin (37).

This brings the granulosa cell tumour into line with functioning tumours in general.

Functioning Tumours:

Functioning neoplasms are of great interest because not only do they behave as neoplasms morphologically but, in addition, they secrete their respective hormones, which act on the body in an uncontrolled way, i.e., the secretion of the neoplasm is put out in quantities totally unrelated to bodily requirements.

They are, consequently, diagnosed clinically because of their function and not so much because of their topography, e.g.,

Thyroid:

A secreting adenoma of this gland leads to signs and symptoms of hyperthyroidism, n.l., loss of weight, excitability and dislike of hot weather, sweating of the palms.

A localised swelling of the thyroid is found. The important finding, however, is a raised Basal metabolic rate.

The symptoms and increased basal metabolic rate are due to a hypersecretion of Thyroxin by the adenoma.

If the adenoma is removed the patient returns to normal.

Parathyroid:

Functioning neoplasms of this gland may be either malignant (2) or benign (2. 34. 60. 83. 98. 107).

Parathyroid extract produces the same chemical changes found in the body (2. 88), as do the neoplasms, i.e., the calcium and phosphorus metabolism is upset producing:

(I) a high blood calcium (2. 34. 60. 98);

(II) low blood phosphate (2. 34. 60. 98);

(III) increased urinary excretion of both calcium and phosphorus (2). This often leads to the formation of renal calculi (2. 34);

(IV) general osteoporosis and the development of bone cysts (2. 34. 60. 98. 107).

These changes produce the following symptoms:

(I) Muscular and joint pains (60),

(II) Muscular weakness (34. 83. 107).

(III) Pathological fractures (2. 60. 107),

(IV) Localised swelling of bone (2. 60),

(V) Polyuria and Polydipsia (83. 107).

(VI) Symptoms of renal calculi (2. 34),

(VII) Gastro-intestinal upsets (60. 83).

Removal of the tumour leads to gross improvement in the symptoms and to recalcification of bones - cysts included (83).

Pheochromocytoma.

This secretory pheochrome medullary adrenal tumour (17. 53) usually is benign (17) but may be malignant (65).

The tumour liberates a pressor, adrenalin-like substance (30. 53. 54. 59. 73). This hormone may be liberated at intervals (30. 73).

The symptoms (17. 30. 53. 54. 59. 64. 73) are paroxysmal attacks of severe headaches, dizziness, pallor, choking sensations, abdominal cramps, nausea and vomiting.

During these attacks the patient has hypertension, i.e., the attacks of hypertension are paroxysmal (30. 53. 54. 59. 64. 73).

The symptoms are those of a generalised vasoconstriction (17. 53).

Attacks can be produced by anger, fear, excitement and sexual intercourse (30).

Similar attacks are produced in dogs by giving them an epinephrine shock (30).

In some cases the hypertension is a permanent feature (64).

Successful removal of the tumour cures the condition (17. 30. 53. 73.)

Supra-renal Cortex:

The cortex of the supra-renal gland secretes androgens (22). This is a masculine hormone. Therefore, a neoplasm of the supra-renal cortex will lead to virilism (54).

In the female infant the result will be pseudo-hermaphroditism (22).

If the tumour occurs in an adult female she will lose her feminine characteristics and gradually will assume both the masculine form and desires (16. 22).

The gentle feminine contour becomes rough and masculine. Beard and male distribution of hair appear. The voice becomes coarse. Fat is deposited around the neck.

The abdomen becomes fat and crossed with striae. The latter occurs in the male as well (112).

Androgens are excreted in the urine in excessive quantities (22).

Removal of the tumour leads not only to an arrest of (24) but also to a cure of the symptoms (22).

Islet of Langerhans.

Islet tumours - Nesidioblastomas (99) can be either benign (43. 89. 92. 99) or malignant (18. 43.) and are secretory.

Benign and malignant tumours (and secondary deposits) have been found rich in insulin (43).

The effects (18. 43. 89. 92. 99. 111) of a hyper-secretion of insulin are:

Attacks of abdominal pain, pallor, sweating, tremor and emotional symptoms, with disorientation.

"Vacant" states, i.e., periods of amnesia, are a frequent complaint. Epileptiform attacks are not infrequent.

The blood sugar is low (43. 89. 92).

Complete removal of the tumour cures the condition (89. 92. 111).

Thymus.

Little is known about the secretion of this gland. It is known, however, that a high proportion of patients suffering from Myasthenia gravis have thymic tumours (23).

Patients with thymic tumours often show great improvement following removal of the tumour (11. 23. 25. 26. 44. 52. 104).

Adler (quoted by Homburger (52)) produced typical myasthenia gravis in dogs by repeatedly implanting infantile thymus into the animals.

Pituitary:

The anterior lobe presents the neoplasms which are of particular interest. No neoplasm of the posterior lobe has been found up to date (24).

Three main types of cells are found in the anterior lobe of the pituitary gland, n.l., chromophobe, eosinophile and basophile.

Neoplasms of the latter two types of cells are secretory and, therefore, they fall into the scope of this subject.

(a) Eosinophile adenoma.

The secretion of the eosinophile cells are intimately associated with skeletal growth (24. 54); hence a hypersecretion from a neoplasm of these cells will lead to gigantism (24. 54. 13) in young individuals, i.e., occurring before the union of the epiphyses.

In older people the result will be acromegaly - the hands, feet and lower jaw bear the brunt and enlarge. The jaws may match so badly as to make mastication a most difficult problem (24).

(b) Basophile Adenoma:

Cushing's syndrome is produced by the neoplasia of pituitary basophil cells (24. 54. 13).

An increase inweight with painful deposits of fat, especially in the regions of the face, neck and trunk occurs. Striae of purplish discolouration appear in the skin. A change of voice to the male type and hirsutism follows.

These tumours hardly ever reach the size to produce any changes in the pituitary fossa due to pressure (24).

Therefore, they are diagnosed purely by their abnormal functions.

OTHER OVARIAN SECRETORY TUMOURS.

(a) Arrhenoblastoma.

This is a rare variety of ovarian tumour. Up to date not one specimen of this type of tumour has come through the Department of Pathology of the University of Cape Town.

The tumour is of special interest in that it secretes a masculinising hormone. The woman suffering from it gradually loses her feminine characteristics and takes on the male form. (6. 13. 54. 57. 66. 74. 110).

There is a cessation of menstruation. The patient becomes sterile. The voice becomes deeper and hair grows

in masculine distribution.

The uterus becomes atrophic and the other ovary atrophies (6).

Histologically, practically all the stages of testicular development can be made out (6. 74).

Removal of the tumour is followed by practically return to the normal. The superfluous hair falls out. The other ovary enlarges and normal function is restored (6).

(b). Theca Cell Tumour.

This feminising tumour is extremely rare. The cells in its make-up correspond to the Theca cells normally found surrounding the follicle (7).

The hormonal effects are similar to those of the granulosa cell tumour. The only difference between a Theca and granulosa cell tumour is a histological one.

Most authors, prominent amongst them Greenhill and Greenblatt (41), Novak (in discussion) (51), Novak & Brawner (81) state that these tumours should be classified as granulosa cell tumours as clusters of Theca cells are found in granulosa cell tumours, and vice versa.

Greenhill and Greenblatt state that the pro-granulosa cell is the parent cell of Thecomas and granulosa cell tumours (41).

GRANULOSA CELL TUMOURS.

In searching the records for granulosa cell tumours records of 7 cases were found in the Department of Pathology of the University of Cape Town. Three cases have been added for purposes of demonstration.

Case 1 - Mrs. Kotze (page14) - was added in order to show the massive layers of granulosa cells lining a cyst. These cells are surrounded by Theca interna cells, also in abnormal numbers. The cells surrounding the Theca cells are fibrobatoid in character.

These three types of cells, n.l., granulosa, Theca and fibromatoid, are found in close relation in most instances of granulosa cell tumour. The relations, just off normal, are shown (Figs. 1. & 2.).

This case is also used to point out the fact that the over-abundance of granulosa and Theca cells was, in all probability, the cause of her symptoms, as the endometrium (Fig.3) is in the proliferative stage and, therefore, due to a secretion of oestrin.

Case 9 - Mrs. Johnson (page 67) - is used to demonstrate the close morphological relationship between a granulosa cell tumour and a myosarcoma of the uterus. She had an associated adeno carcinoma of the body of the uterus.

Case 10 - Mrs. van Eeden (page 72) - demonstrates the further morphological step, n.l., a mixed cell sarcoma of the ovary.

CASE No.1.

Name:	KOTZE, Maria.
Age:	45.
Married.	
Occupation:	Housewife.
Race:	European.
Hospital:	Groote Schuur.
Index No:	71100.
Admitted:	1.8.45.
Complaint:	Increasing Menorrhagia.
Duration:	3 years.
Pregnancies:	8 . Eldest 24. Youngest 16.

Labours and puerperia were normal, barring for puerperal sepsis following the birth of the 8th child.

Abortions:	4. Uncomplicated, all before the birth of the last child.	
Menstruation:	Menarche:	10.
	Cycle:	3-4/28-day type until 3 years ago. Completely irregular since.
	Flow:	Moderate up to 3 years ago. Increasingly profuse since.

L.M.P. 10.7.45 - still bleeding.

Intermenstrual: Clear.

Micturition: Normal.

Bowels: Regular.

History:

The patient states that she was quite fit until 3 years ago. Her periods were regular. Subsequently, however, her periods have come on irregularly. They last up to 10 days. She has not missed a period. The clear period lasts from 7 to 20 days.

Instead of having to wear about 2 pads during menstruation, she how has to wear 4.

This last period started on 10.7.45. She is still bleeding.

At no time has she suffered from flushes or flatulence.

On Examination:

General Condition: Good.

Local: Abdomen: No abnormality detected.

C.V.S. B/P 130/80.

No abnormal sounds heard.

Respiratory: No abnormality detected.

Vaginal: Cervix: Healthy.

Uterus: Anteverted. Slightly enlarged. Mobile.

Adnexa: Not felt.

Urine: Clear.

2.8.45. OPERATION.

Lower midline incision.

The uterus was found to be slightly enlarged. It harboured a small subserous fibroid seedling.

The right ovary was cystic. It was surrounded by flimsy adhesions.

The right tube appeared normal.

The left ovary was bound down by firm adhesions, as was the tube.

The right ovary, right tube, left tube and a portion of the left ovary were removed and a subtotal hysterectomy was done.

Pathology Report No.1216.

"Subserous fibroid shows the structure of a simple fibromyoma.

Endometrium is thick and fleshy and shows the features of a prominent proliferative phase, with occasional cystic glands.

Ovary includes a cystic structure which appears to be of follicular origin and is lined by massive granulosa tissue."

The interesting feature of this case is that the picture it produced clinically was produced by an oversecretion of oestrin, i.e., an overgrowth of endometrium in the proliferative phase with cystic formation.

The pathology detected was an overgrowth of granulosa cells, in the wall of a cyst. The granulosa cells are more massive than usually found in a simple follicular cyst.

Fig. 1.

Follicular Cyst
X 30.

1. Granulosa cells;
2. Theca cells,
3. Fibromatoid cells, i.e., stromal cells.

Note that there is no clear line of differentiation between the Theca and fibrmmatoid cells. The one type of cell gradually veers into the other.

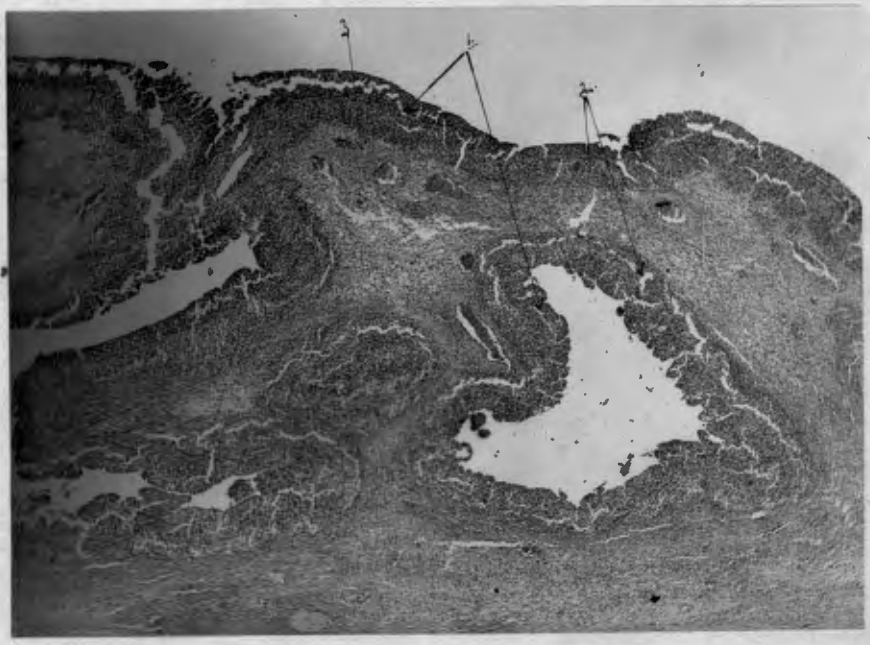
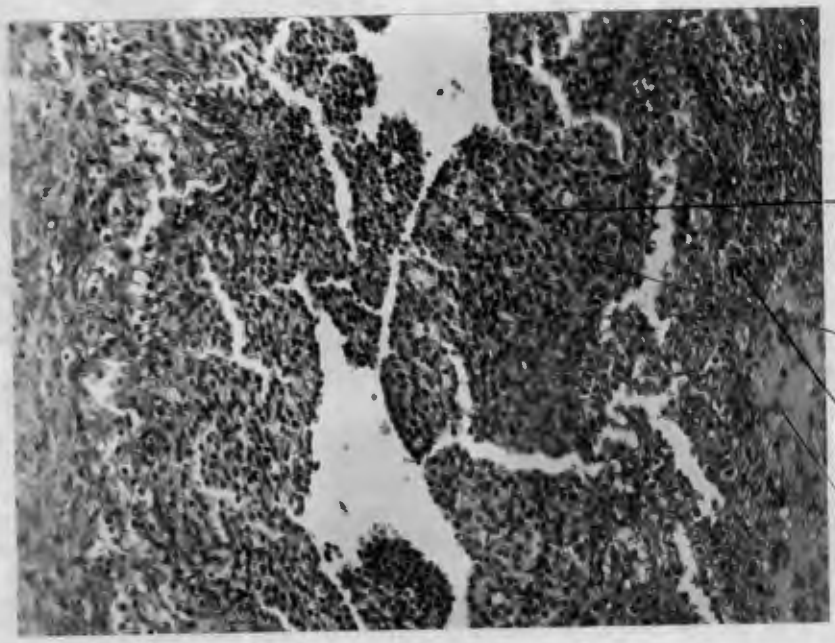


Fig. 2.



Follicular cyst

X 150.

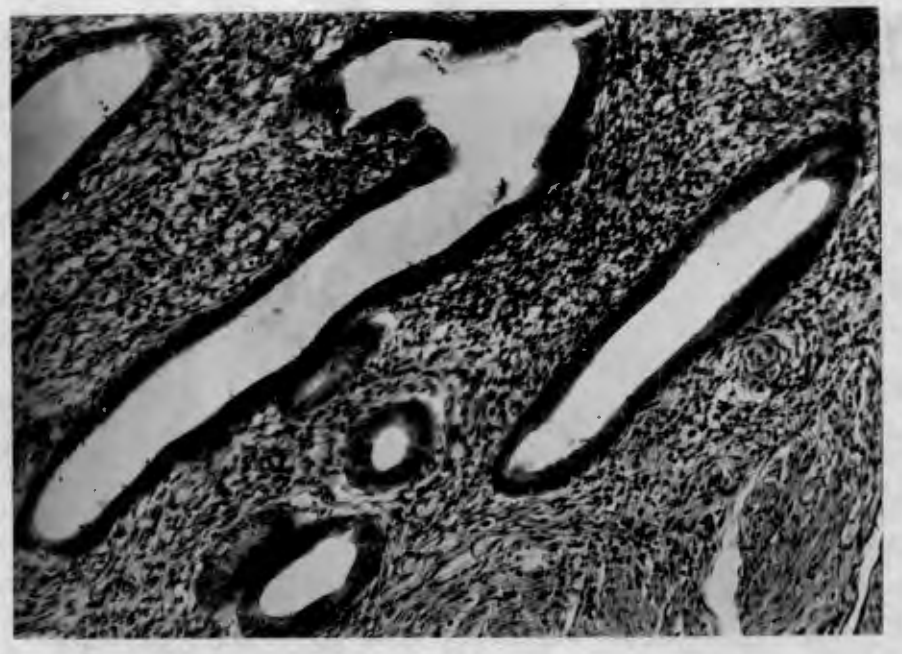
1. Massive layer of granulosa cells.
2. Note trabeculation
3. Theca cells.
4. Fibromatoid cells.

Fig. 3.

Endometrium

X 150.

Proliferative stage.



CASE No.2.

Name:	DAVIDS, Salome.
Age:	55 years.
Race:	Coloured.
Widow.	
Occupation:	Domestic.
Hospital:	Groote Schuur.
Index No.:	12761.
Admitted:	13.3.39.

Complaint: Vaginal bleeding and abdominal swelling.

Duration: 12 months.

Pregnancies: 7. Eldest 37.
Youngest 18.
No labour or puerperal complications.

Abortions: Nil.

Menstruation: Menarche: 14 years.
Cycle: 6/28-day type. Regular. Profuse.
Menopause: 50.

Postmenopausal: Slight continuous bleeding for the past 12 months.

Micturition: She has detected no abnormality.

Bowels: Regular.

Previous illnesses:

She had rheumatic fever 8 years ago.

Present Condition:

The patient states that she was quite well until 12 months ago. Ever since she has been bleeding daily. The amount lost is very slight, and there is no need for wearing any pads. Rarely, however, the bleeding is brisk. For the past few months the bleeding has been very slight indeed.

Since the onset of the bleeding she has noticed that her abdomen has become increasingly swollen.

She does not suffer from breathlessness or swelling of the feet.

On Examination:

General condition: Pallor of mucous membranes.

Local. Abdomen: Gross distension. Tumour from pelvis to left subcostal margin. The tumour was cystic.

C.V.S. B/P. 220/120.
Presystolic murmur at apex.

Resp. N.A.D.

Vaginal: Introitus admits 2 fingers.
Cervix in axis of vagina.
Os Patulous.

Large Polypoid mass protruding through OS.

Uterus in axis of vagina.

Fornices: Slightly enlarged cystic mass could be felt high up in both fornices.

Speculum: Large polypoid mass can be seen protruding through OS. It bleeds readily.

Haemoglobin: 30%.

15.3.39. Diagnostic curettage done.

OPERATION SHEET reads:-

"The polypi protruding through the OS were removed by forceps - a good quantity of tissue was removed. Bleeding was profuse and so a curettage was done. Much tissue was removed."

24.3.39. Pathology Report :-

"A very markedly hyperplastic endometrium with many large cystic glands. There is no tumour. Tissue sent is all of the same structure. There is no cervical polyp included."

The reason for the inability to find the cervical polyp in the Department of Pathology can most likely be explained on the grounds that the polypi projected through the OS and actually were uterine endometrial polypi.

8.4.39. ABDOMINAL OPERATION.

Midline incision extending from 3 inches above the umbilicus to symphysis pubis.

As the abdomen was opened a large cyst was displayed.

A trocar and canula was inserted and 10 pints of blood-stained fluid were drawn off.

The tumour was found to come from the left ovary. It was removed.

The rest of the genitalia were normal and were left in situ.

The tumour weighed 17 lbs., i.e., after the 10 pints of fluid were withdrawn.

The patient made an uninterrupted recovery and was discharged from hospital on 2.5.1939.

The tumour is on the shelves of the Department of Pathology at present. The photograph is attached.
It measures 13 inches x 5½ inches x 7 inches.

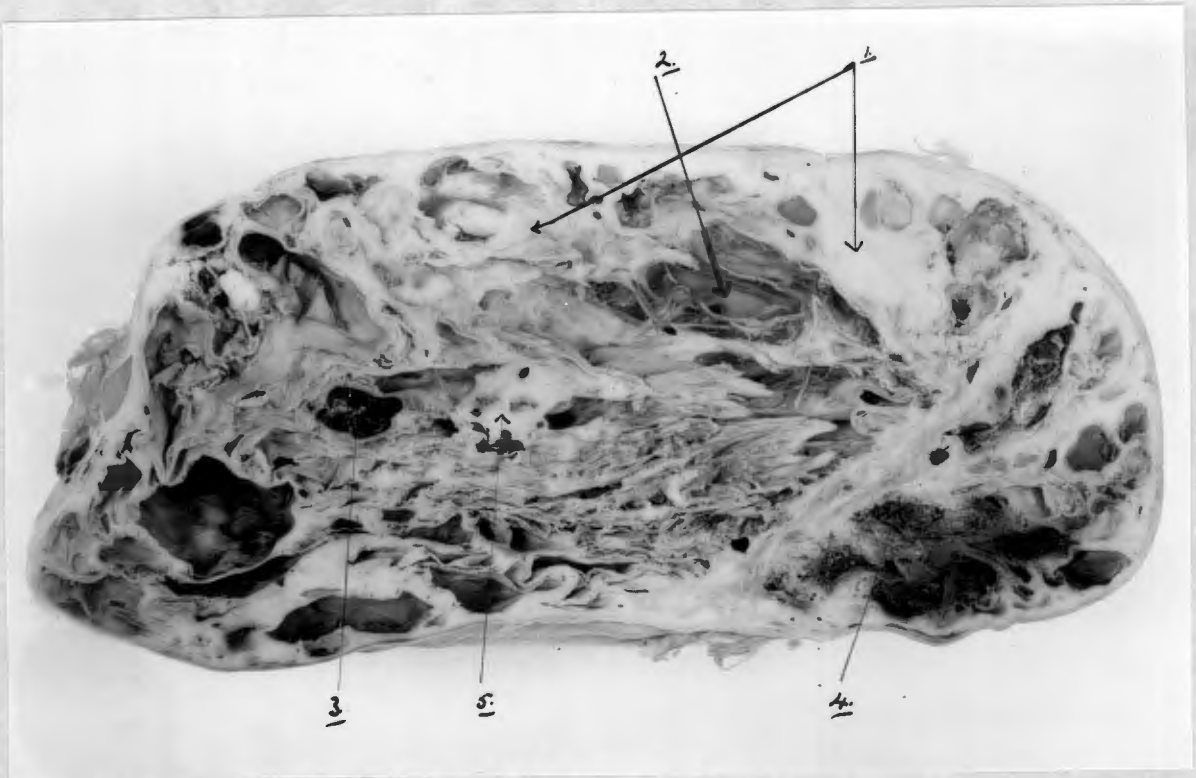
On cut section there are many cystic areas in the cellular neoplasm. The sizes of the cysts vary greatly. The tumour has a whitish-grey colour, barring centrally, where there is a yellowish tinge. In some areas there are evidences of haemorrhages into the tumour.

2.5.39. Pathology Report:

"The structure is that of a granulosa cell tumour.

Salome Davids. (a)

Fig. 4. Cut section of tumour.



1. Solid cellular areas.

2. Cystic spaces

3. Haemorrhage into cyst.

4. Necrotic area.

5. This area has a yellowish tinge.

Salome Davids. (b).

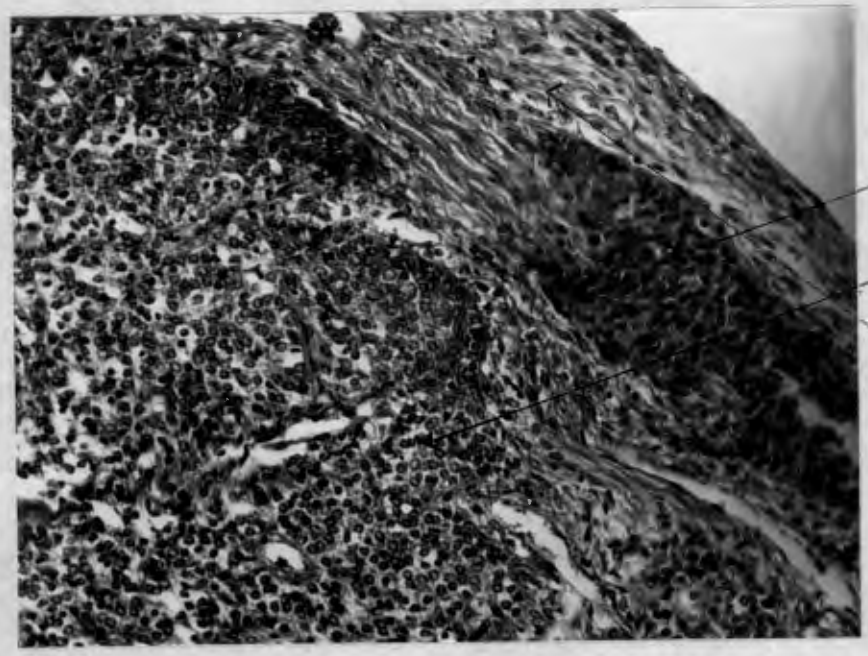


Fig. 5.

X 225.

1. Granulosa cells.
2. Theca cells.
3. Fibromatoid cells.

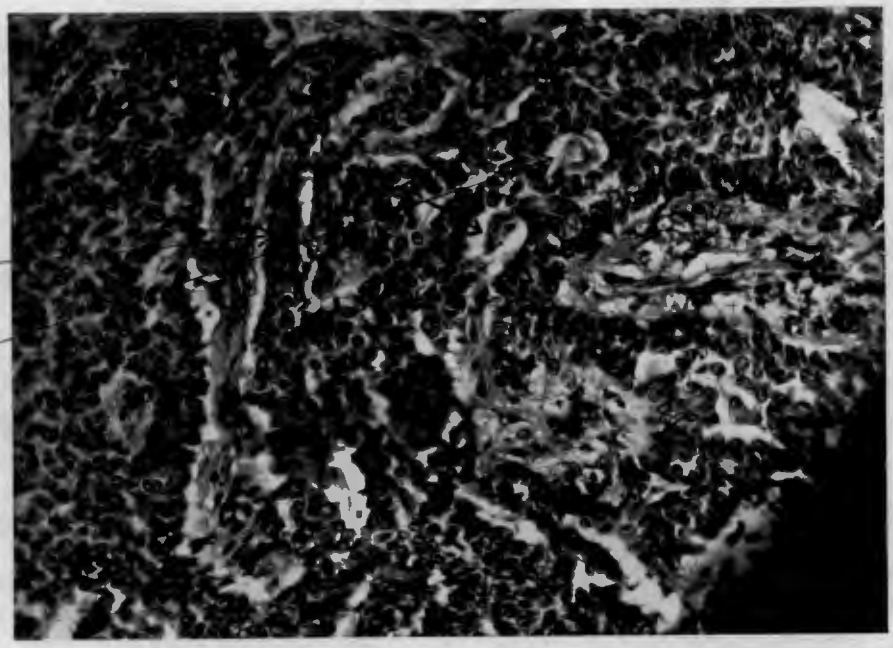


Fig. 6.

X 225.

1. Trabecular variety.
2. "Call-Exner" bodies.

Note:- The granulosa cells in rosettes around these bodies.

Salome Davids. (c)

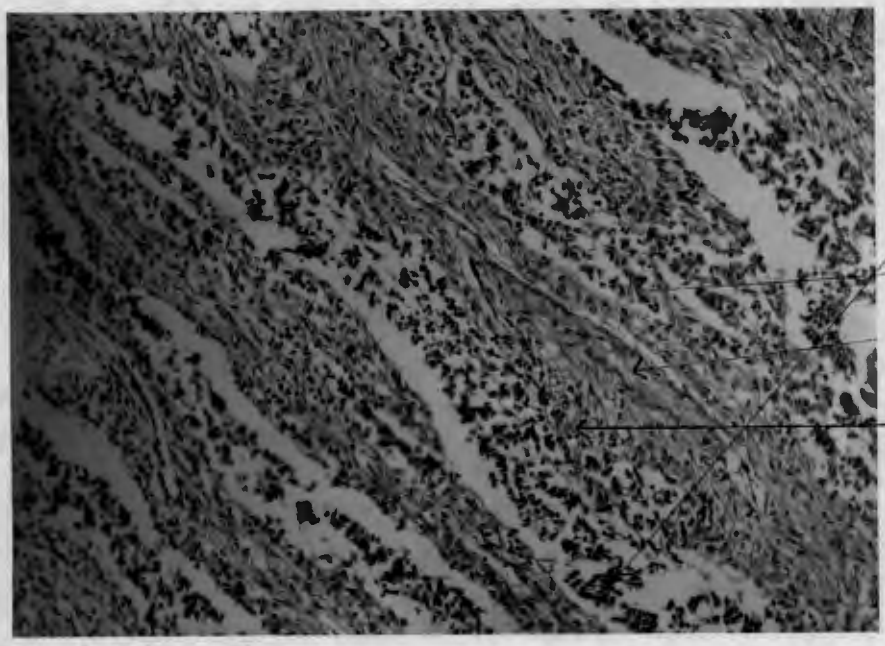


Fig. 7. X 150

Trabeculations of

(1) granulosa cells;

(2) Theca cells;

(3) Fibromatoid cells

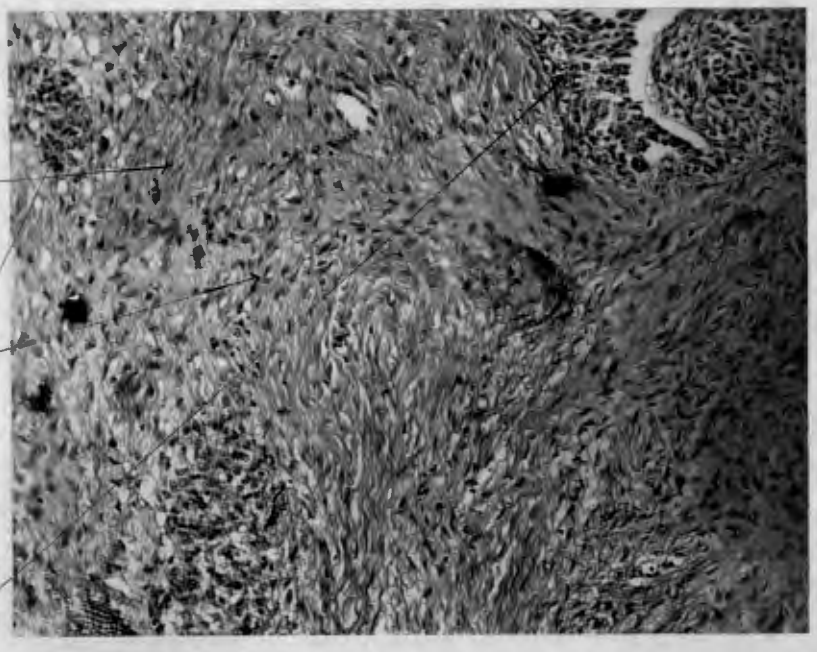
Note: The differentiation in this area. It is as if Theca and then granulosa cells are budding off the fibromatoid cells

Fig. 8. X 150.

1. Fibromatoid cell nuclei - like fibroblasts, i.e., nuclei are thin and elongated - they vary in size, becoming more and more swollen.

2. Granulosa cells.

3. ? Theca ? Granulosa Cells.



Salome Davids. (d).

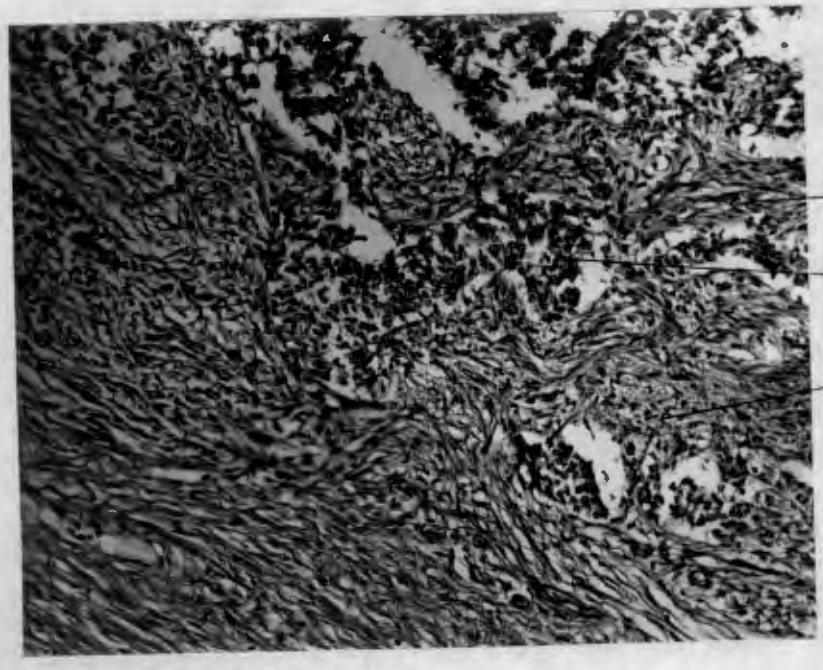


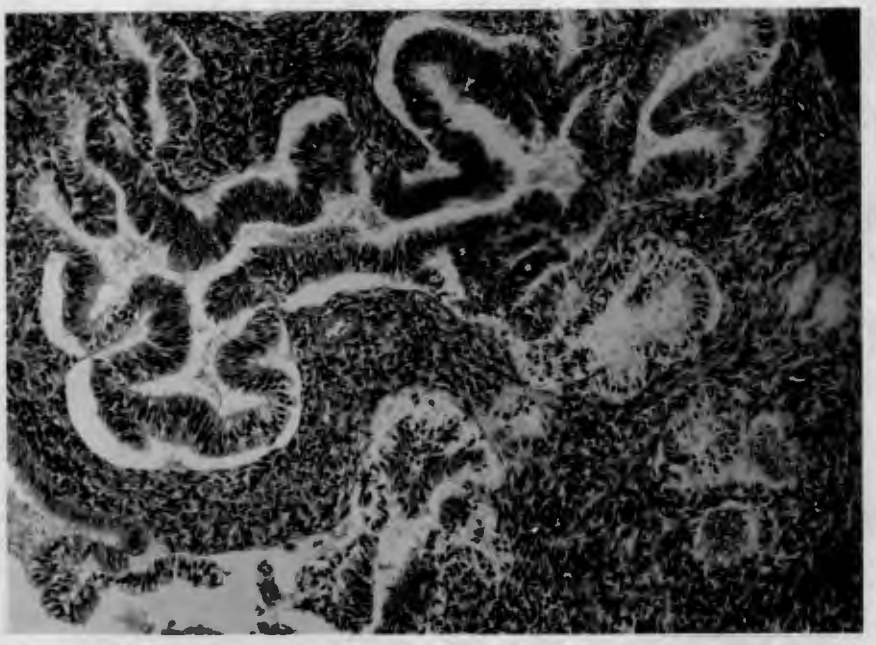
Fig. 9. X 150.

Intermingling of:

1. Fibromatoid cells;
2. Granulosa cells;
3. ? Granulosa
   ? Fibromatoid
   ? Theca cells.

Fig. 10. X 225.

Endometrium in Proliferative Stage.



CASE No.3.

Name: BONANI, Rachel. Groote Schuur Hospital.

Age: 50 years. Admitted 5/7/45.

Race: Native.

Complaint:
1. Post-menopausal bleeding which started 8 weeks ago and lasted for 14 days.
2. Abdominal swelling, swelling of the ankles at night and dyspnoea on exertion for the past 4 weeks.

Pregnancies: Full-term. Eldest 24.
Youngest 14.
There were no labour or puerperal complications. Although no contraception was practised she has not been able to become pregnant since the birth of her last child.

Abortions: Nil.

Menstruation: Menarche 13.
Menopause 47½.
She suffered from neither menstrual or inter-menstrual disorders.

Post-menopausal: 8 weeks ago she began bleeding vaginally.
The amount lost was slight.
The bleeding was continuous and lasted 14 days.

It ceased spontaneously.

It was completely painless.

For the past month she has noticed a slight yellowish-white vaginal discharge.

Micturition: Slight nocturnal frequency for the past 6 months.

No dysuria.

Bowels: Regular daily action.

Previous: She has never been seriously ill.

Present: The patient states that she was quite fit until 13/5/45. On that day she began to bleed steadily vaginally. The blood lost was very slight and lasted continuously for 2 weeks. During the past month she has become increasingly dyspnoeic, she has noticed that her abdomen has become larger and that her ankles are swollen at night. She has been taking matters easily during the past week, with the result that there has been an improvement in the dyspnoea and swelling of the ankles.

She did not suffer from any subjective menopausal phenomena.

On Examination:

General condition: Good.

Well-covered.

No evidence of oedema.

Local : Abdomen : Lump the size of a cocoanut in the right iliac fossa.

Consistency: Soft rubber.

Surface: Smooth.

Edges: Well-defined.

Relations: Freely mobile in the abdominal cavity.

C.V.S. No abnormality was detected, i.e., no enlargement or murmurs.
B/P: 170/100.

Resp. No abnormality detected.

Vaginally: Normal parous introitus.

Cervix points downwards and outwards. There is a healed left lateral tear. The cervix is mobile.

Uterus is enlarged to the size of a tennis ball. It is anteverted, mobile and completely distinct from the mass in the right iliac fossa.

Adnexae: The mass in the right iliac fossa could be palpated in the right fornix. The consistency was that of soft rubber.

Speculum: There was a slight whitish vaginal discharge. There were a few Nabothian follicles.

(This patient was seen by me in the Out-patient Department on 29/6/45 and a diagnosis of Granulosa Cell Tumour was made. She was not admitted immediately as no beds were available).

6/7/45. X-ray of the chest revealed clear lungfields and no cardiac enlargement.

9/7/45. OPERATION.

The abdomen was opened by means of the lower midline incision.

There was about 1 pint of straw-coloured free fluid within the abdominal cavity.

The left ovary was enlarged to the size of a cocoanut and was lying in the right iliac fossa. It had a long pedicle. The left tube was slightly elongated.

The right tube and ovary were normal in size.

The uterus was enlarged to the size of a tennis ball and harboured an intra-mural fibroid in its left cornual region.

A pan hysterectomy was done in the usual way. There were no technical difficulties.

The abdomen was closed by stitching consecutive layers.

On section the ovarian tumour was very soft and fleshy. It had a reddish-grey discolouration. There were a few cysts along the peripheri of the tumour.

The uterus harboured an intramural fibroid the size of a golf ball in the region described above. In addition, there was a fibroid the size of a pigeon's egg in the broad ligament attachment area of the uterus on the left side.

The cavity of the uterus harboured an endometrial polyp in the fundal region.

17/7/45: Stitches removed. Wound well healed.

19/7/45: Pathology report (1055/45) states that the ovarian tumour is a granulosa cell tumour. The fibroids are simple. The polyp is endometrial.

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Rachel Bobani (a)

Fig.11. Posterior view of specimen.

1. Cut section of granulosa cell tumour.
   (a) Solid, cellular, "liver sausage" appearance;
   (b) Cystic spaces.
2. Fibromyoma in broad ligament.

Rachel Bobani. (b).

Fig.12.

Anterior view of Specimen:

1. Granulosa cell tumour - well encapsulated.

2. Endometrial polyp.

3. Intramural fibromyoma.

4. Normal right ovary.

Rachel Bobani. (c).

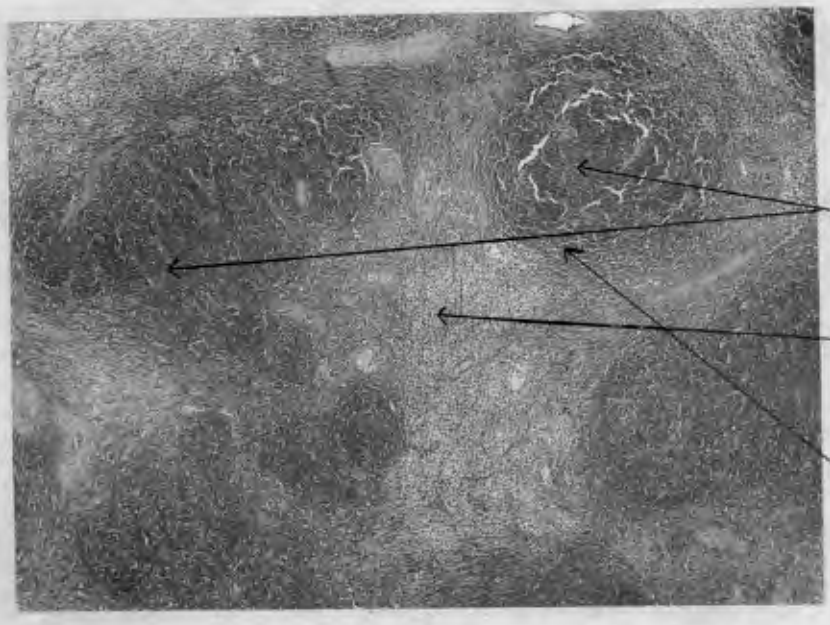


Fig.13. X 30.

1. Areas of granulosa cells;
2. Areas of "luteinised" cells; i.e.,
3. Area A.

Fig.14. X 150.

Area A. of Fig. 13.

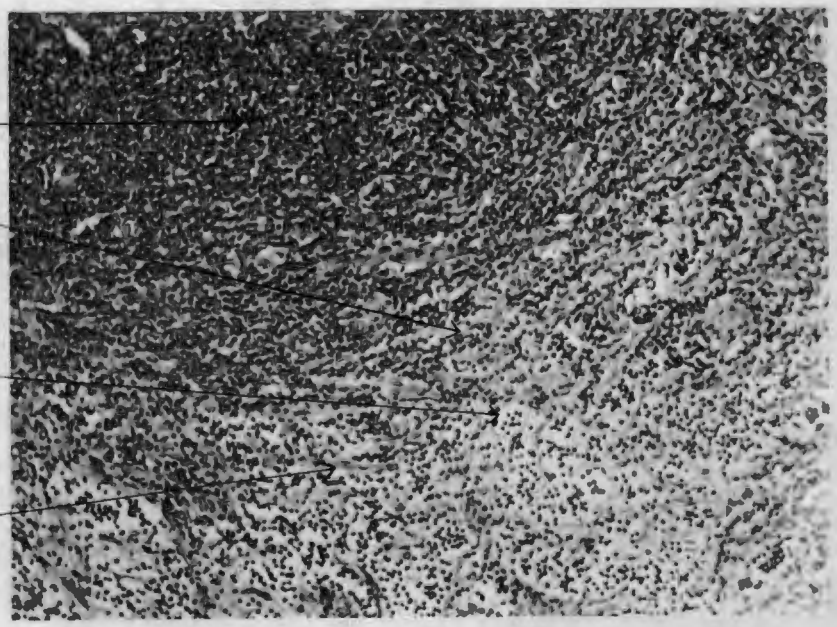
1. Granuloma cells.

   Note the trabecular formation at the junction between the 2 types of cells.

2. Luteinised cells.

   Note the clarity of these cells.

3. Fibromatoid Cells interspersed with the other cells.



Rachel Bobani.

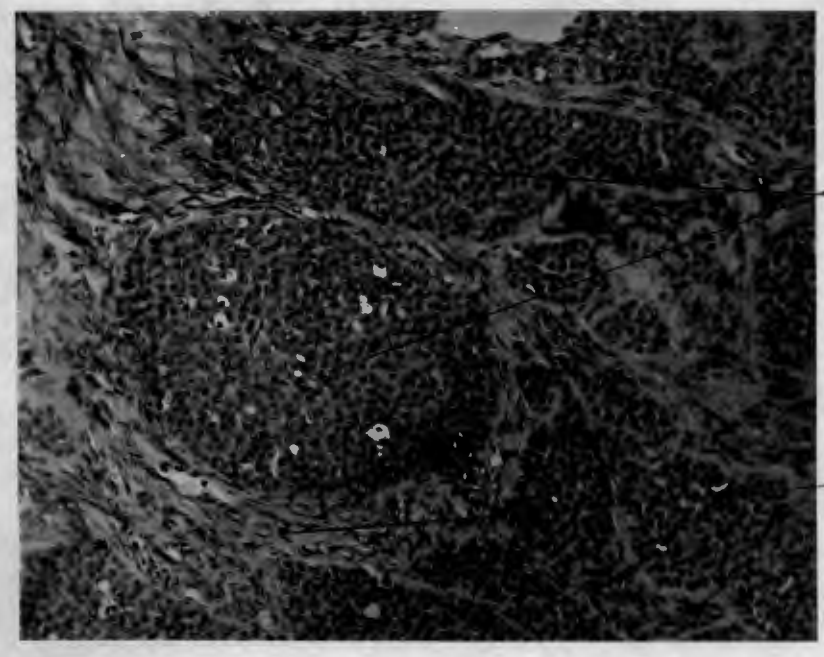


Fig. 15. X 150.

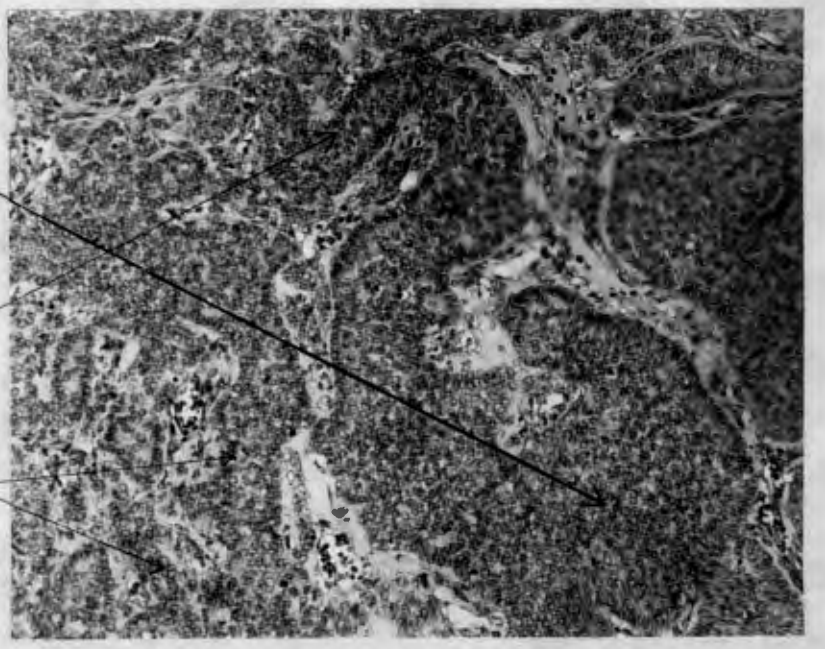
Areas of granulosa cells diffusely arranged surrounded by fibromatoid cells.

Fig.16. X 150.

(a) Diffusely-arranged granulosa cells branching off into

(b) a Trabecular form.

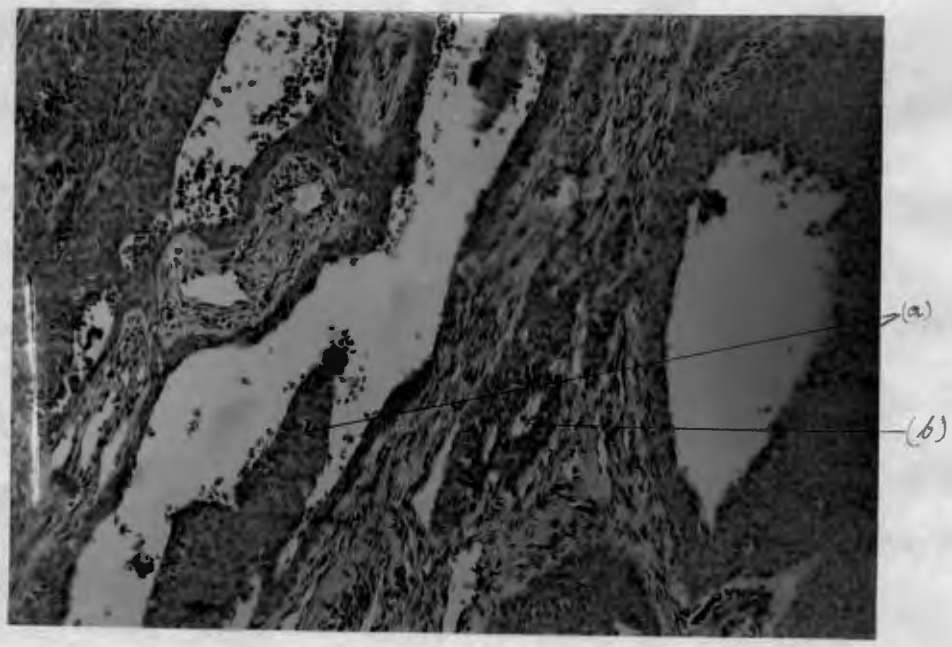
(c) Other trabecular forms.



Rachel Bobani. (e).

Fig. 17.

X 150.



(a) Massive gramulosa cells lining spaces, i.e., cystic variety.

(b) *Call-Exner body.

Fig. 18.

X 30.

Endometrium in Proliferative phase.

CASE No.4.

Name: SMIT, Barbara Magdalena.

Age: 54.

Race: European.

Hospital: Groote Schuur.

Index No.: 38896.

Married.

Admitted: 19. 1. 42.

The history of this patient was either lost or not written up in the first place.

The history given here is the result of piecing together bits of information gathered after consulting her private doctor's letter, notes made in the X-ray Department when she was receiving deep X-ray therapy and odd bits written on X-ray forms. A few threads were also gathered from a history she gave two years later when she had a thyrotoxicosis.

I have written to this patient but, as yet, I have received no reply.

History:

The patient was sent in as an urgent case suffering from a large pelvic growth causing retention of urine and obstruction of the large bowel.

Her menopause was in 1939.

On Examination:

Recto coele + +

Lump in abdomen continuous with lump in the Pouch of Douglas.

Cervix pushed downwards and forwards.

30.1. 42.

Lower midline abdominal incision.

In the lower part of the abdomen was a large, dirty black area of debris and clot. A malignant growth appeared to have spread from the sigmoid colon to the back of the uterus, to adnexa and ovary on the right side.

The peritoneum was also involved.

The whole mass was very friable and bled very easily, and this bleeding was very difficult to check.

A small piece of growth was sent to the Pathology Department.

12. 2. 42.

Pathology Report: "The tumour does not have the structure of a primary gut tumour. The structure indicates an ovarian primary origin and I think this is an example of a diffuse type of granulosa cell tumour."

19. 2. 42. X-ray of chest:

No evidence of secondary deposits.

21. 2. 42.

Deep X-ray therapy commenced. An extensive course of treatment was given, i.e., a total of:

Anterior 3,800 Roentgens.

Posterior 3,350 "

The treatment was stopped on 23. 3. 42.

The patient was discharged in April, 1942.

18. 5. 42.

She returned for a check-up.

On Examination:

Abdomen: No mass detected.

Vaginal: Uterus - anteverted. Normal in size.

Fornices - clear.

As far as can be detected, the pathology has disappeared completely.

July, 1942.

The patient returned. She feels well and is symptomless.

P.V: No abnormality detected.

November, 1942.

No complaints except occasional attacks of flushing.

May, 1943.

She has put on 40 lbs. in weight since leaving hospital.

She feels very well.

Abdominally and vaginally: No abnormalities could be detected.

5. 4.44.

The patient was admitted to hospital for thyrotoxicosis (B.M.R. 86).

Abdominal examination revealed a tender lower midline scar. No other abnormality was detected.

Fig. 19. X 150.

Sarcomatoid variety.

Evidence of trabeculation can be seen.

The general appearance, however, suggests a round and spindle-celled Sarcoma.

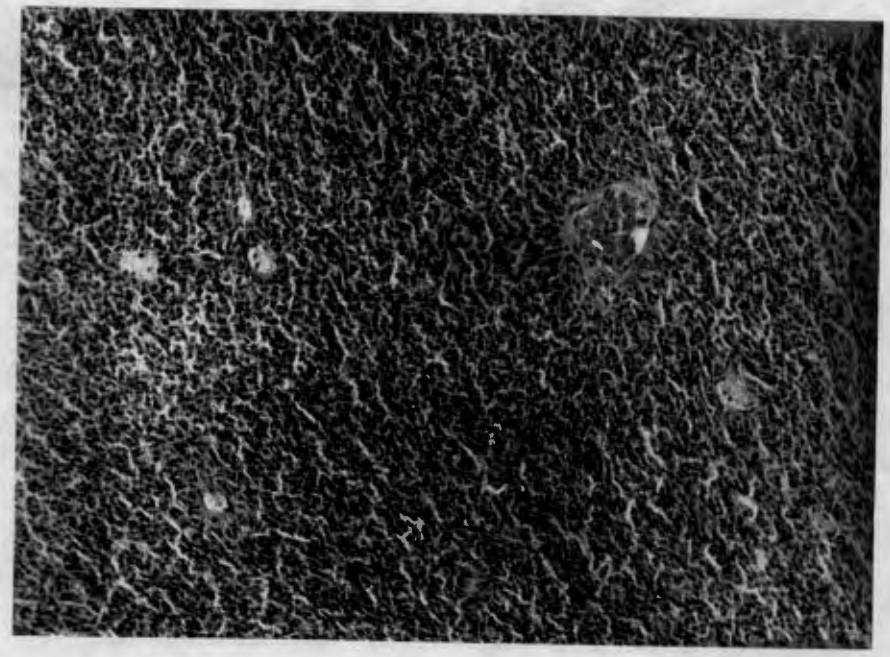
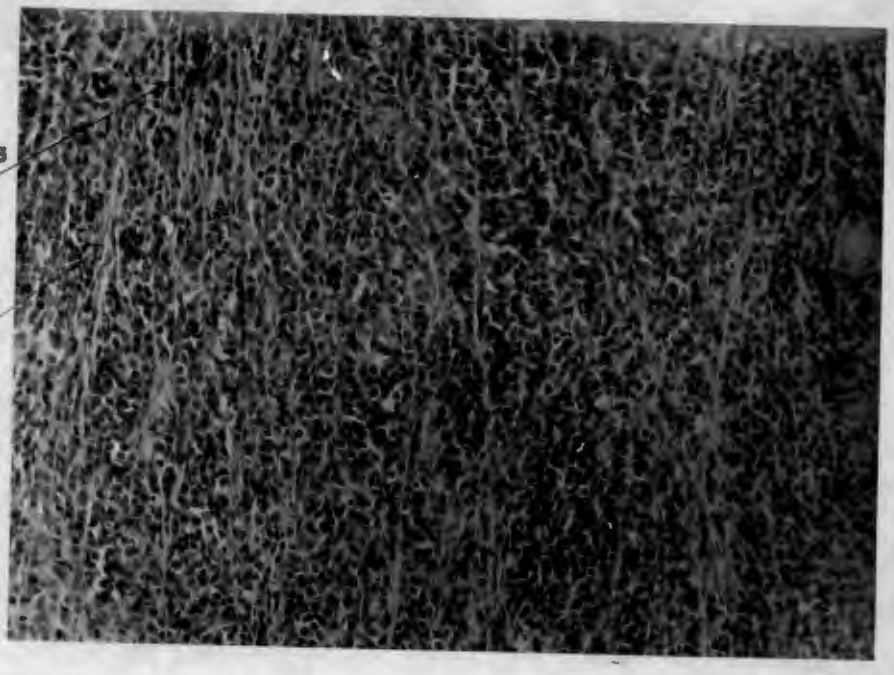


Fig. 20 X 150.

(a) Granulosa Cells arranged in Trabeculae.

(b) Fibromatoid cells.



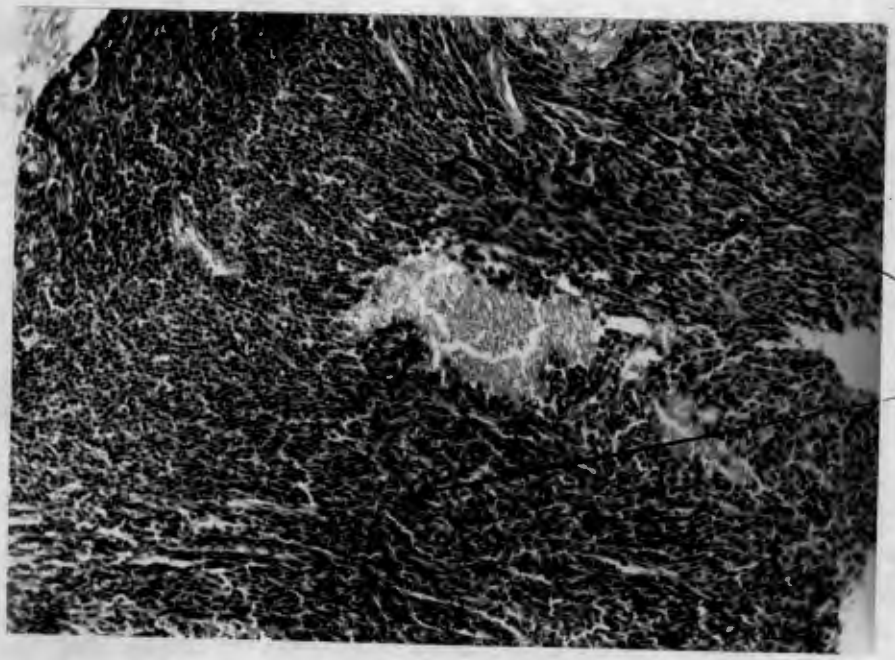


Fig. 21. X 150.

Transition between

(a) Trabeculae,

(b) Diffuse

or

Sarcomatoid types.

CASE No.5.

Name: ISSIE ANDREAS.

Age: 47 years.

Married: 21 years.

Race: Coloured.

Hospital: Groote Schuur.

Index No: 46427.

Admitted: 1/11/41.

Complaints:

1. Sterility. 21 years.
2. Abdominal lump 7 years.
3. Backache 7 years.
4. Amenorrhoea. 7 years.

Pregnancies: Nil.

Abortions: Nil.

Menstruation: Menarche: 17 years.

Cycle: 4/30-day type. Regular.

Flow: Increased after marriage.

Last menstrual period: 7 years ago, i.e., in 1934.

Discharge: Slight, continuous whitish discharge since onset of amenorrhoea.

Micturition: Slight nocturnal frequency - once to twice nightly - for the past few years.

No dysuria.

Bowels: Regular.

Present History:

The patient states that her periods ceased 7 years ago. She did not suffer from any of the usual menopausal phenomena, e.g., flushes, flatulence, etc.

Seven years ago she also noticed an abdominal lump. It was small and soft. It lasted for two years and then disappeared for a while. It soon reappeared but now was hard. It has grown in size steadily since.

During this interval she has also suffered from occasional attacks of pain in the back. This pain radiated down the right leg.

On Examination:

General condition: Good.

Local: **Abdomen:** Mobile lump size of a cocoa-nut was felt in the right iliac fossa.

Vaginal: Uterus retroverted; hard tumours - one on either side of the uterus - were felt.

6.11.41. ABDOMINAL OPERATION.

Lower midline incision made.

The uterus was found to harbour many fibroids.

The right ovary was neoplastic and enlarged to the size of an orange.

A high subtotal hysterectomy and double salpingo-oopherectomy was done.

The patient was discharged fit on 25/11/41.

Pathology Report 25.11.41 :

"Histology of the ovarian tumour is that of a granulosa-cell tumour. Mitotic figures are very very scanty and the tumour is well encapsulated."

Fig. 22. X 150.

(a) Capsule.

(b) Fibromatoid cells predominating.

(c) Granulosa cells - they appear to be fibromatoid cells with swollen nuclei.

The cells are arranged in Trabeculae.

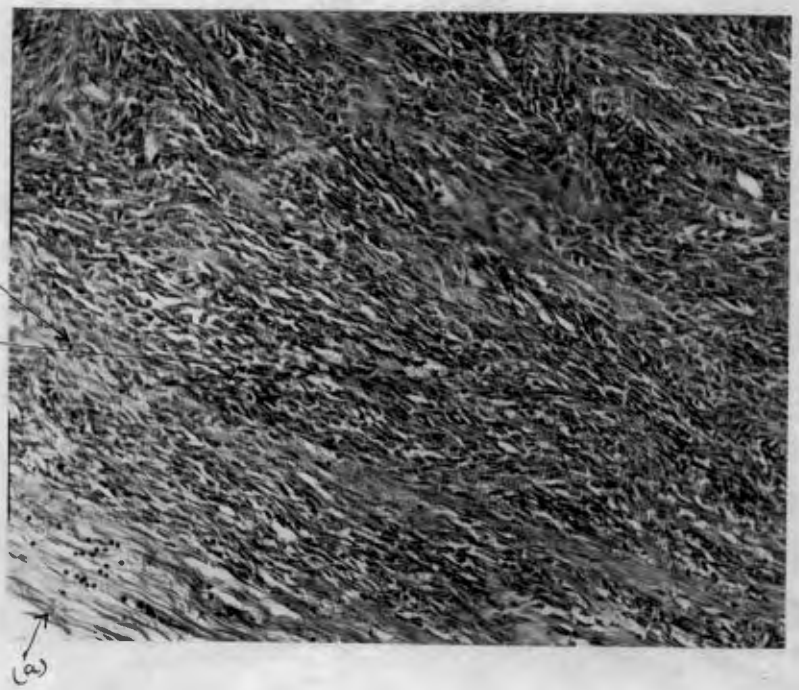


Fig. 23. X 150.

(a) Fibromatoid cells predominating.

(b) Difficulty to determine whether these cells are granulosa or Theca cells.

The nuclei of many of fibromatoid cells are "swollen". This makes the cell almost indistinguishable from the granulosa cells.

Fig. 24. X 150.

This demonstrates the last-mentioned feature well.

CASE No.6.

Name: Dolly Salmon.

Age: 35.

Race: European.

Occupation: Bookkeeper.

Hospital: St. Joseph's and Groote Schuur.

G.H.S.Index No. 37859.

Single.

Admitted: St. Joseph's 19/8/41.
Groote Schuur 8/10/41.

Dr. Ruby Sharpe's private patient at St. Josephs.

Pregnancies: Nil.

Abortions: Nil.

Menstruation: Menarche: 13.

Cycle: 6-7/28 day type.
Regular.

About two years ago for about 4-5 months her periods came twice monthly. The amount lost was normal.

Flow: Moderate until May, 1941; ever since the flow has been profuse.

Intermenstrual: Clear.

Micturition: Since February, 1941, she has been troubled by both diurnal and nocturnal frequency. She has to pass water about 3 to 4 times nightly.

Bowels: She has become very constipated and has to take aperients to make her bowels act.

Past History:

For the past three years she has been suffering from a continual feeling of tiredness and irritability. During this period she has had frequent bilious attacks - vomiting 2 to 3 times weekly during these spells. These attacks were not accompanied by any abdominal pain.

Two years ago she had an attack of vomiting and diarrhoea which lasted for about 10 days. She was the only one in her family or amongst her friends who had this attack.

A year later she had a similar attack but of 7 days' duration. During this attack she had a severe lower abdominal pain one morning and this was accompanied by 3 hours of continuous vomiting - and no diarrhoea.

Especially since this last attack has she suffered from severe lassitude but no shortness of breath.

Present Condition:

(Menstrual history has already been referred to).

Six months ago she wanted to join the Services. She was examined and a lump was detected in her lower abdomen. She was referred to a gynaecologist.

On Examination:

General condition: Fair.

Local: Abdomen - Mobile mass the size of a cocoanut was felt in the right iliac fossa.

P.V. Uterus - normal in size, shape and position.

Adnexa - Ovarian tumour of right ovary - as described by abdominal palpation.

20. 8. 41. OPERATION.

Lower midline abdominal incision made.

The omentum was oedematous.

Bilateral solid ovarian tumours found. The right was the size of a cocoanut.

A total hysterectomy and bilateral salpingo-oöpherectomy was done.

Pathology Report 996/41.

"The structure is that of a diffuse small round-celled tumour. The cells somewhat resemble lymphocytes, but it is possible to trace forms which show their probable epithelial nature and granulosa cell type.

Although there are not cytological evidences of active growth, nevertheless there is invasion of the uterine muscle."

Post-operatively the patient made a slow recovery and became increasingly breathless. When she sat up in bed her breathing was much easier. This shortness of breath increased until she could hardly breathe.

On examination it was found that she had a pleural effusion on the left side. The fluid was aspirated - it was chylous. She had to be aspirated every 2 or 3 days.

She was then transferred to the Groote Schuur Hospital, where her chest was aspirated on alternate days. Both pleural cavities were aspirated.

12. 10. 41.

Portable X-ray of chest taken.

Report by Dr. Oosthuizen (S.F.):-

"There is evidence of bilateral pleural effusion. On the left side there is a fluid level, the result of air in the pleural cavity.

In addition to the pleural changes, there is a rounded (or semi-rounded) opacity in the region of the right cardiophrenic angle. The true nature of this could not be determined. It is compatible with a secondary deposit. One would, however, like to see more views after an interval before making a definite diagnosis."

A course of deep X-ray therapy was started on 14.10.41. and stopped on 10.11.41.

A.P. 4,000 Roentgens were given.

P.A. 3,950 " " "

The treatment had the effect of reducing the size of the secondary.

11.11.41. X-ray Report :-

(a). "There is still evidence of fluid at both bases. The amount of fluid at the right base is less, but on the left side there is probably a little more than before.

(b). Adhesion running obliquely upwards from left hilum is now clearly visible.

(c). The semi-rounded opacity at the right base, the nature of which is not yet determined with absolute certainty (? secondary), is now slightly smaller."

She went home on 25. 2. 42. with a presumptive diagnosis of secondary malignant deposit pressing on the thoracic duct.

Between 8/10/41 and 25/2/42 a total of 19 gallons 6½ pints of chyleus fluid was withdrawn from the patient's chest.

This patient died a few months after leaving hospital. No postmortem was done.

The X-ray pictures have vanished and hence cannot be reproduced.

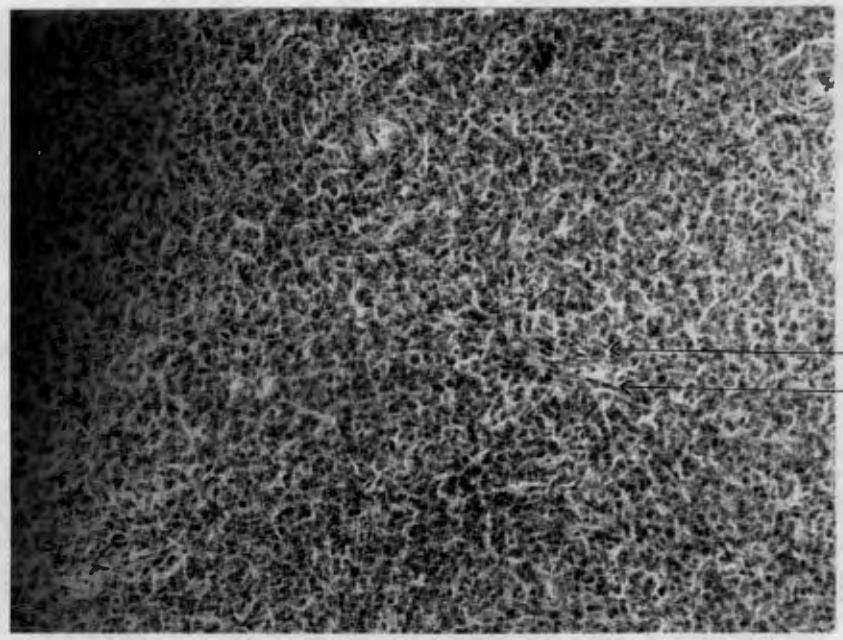


Fig. 25. X 150.

Sarcomatoid variety.

(a) Granulosa cells intermingled with

(b) Fibromatoid cells.

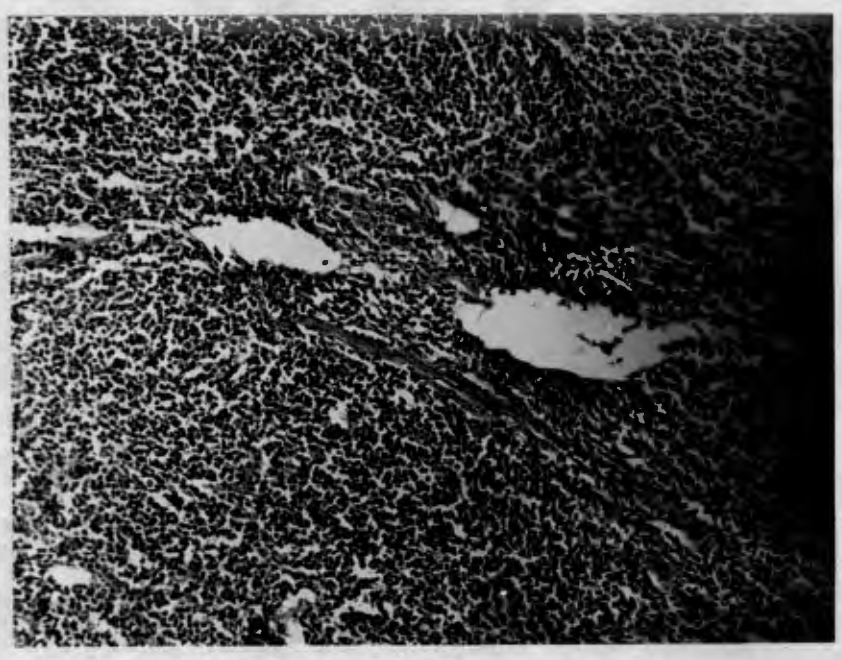


Fig.26. X 150;

Mixture of Sarcomatoid and Trabecular varieties.

Fig. 27. X 150.

(a) Granulosa cells surrounding clear spaces.
An attempt at producing Follicles, i.e., Follicular variety.

(b) Mixture of Fibromatoid and Granulosa cells.

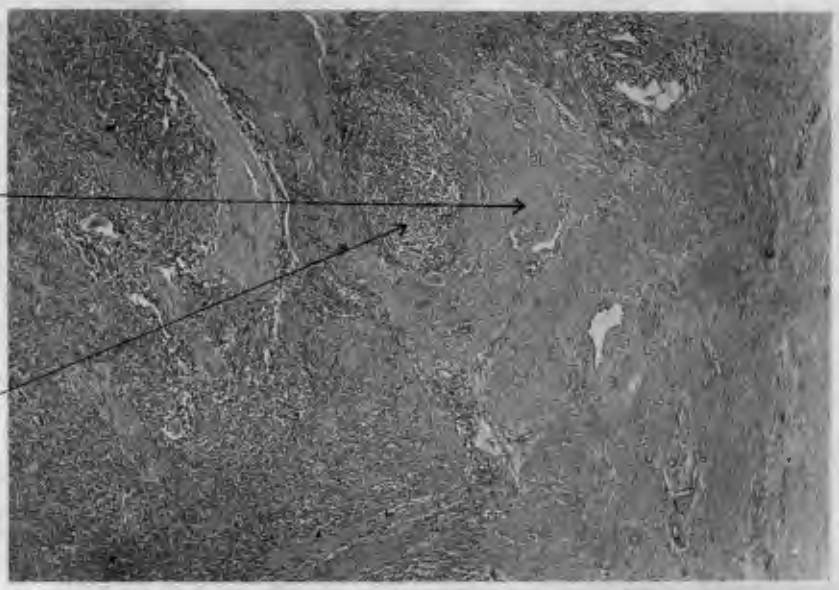


Fig. 28. X 30.

(a) Uterine Muscle being invaded by

(b) granulosa cells.

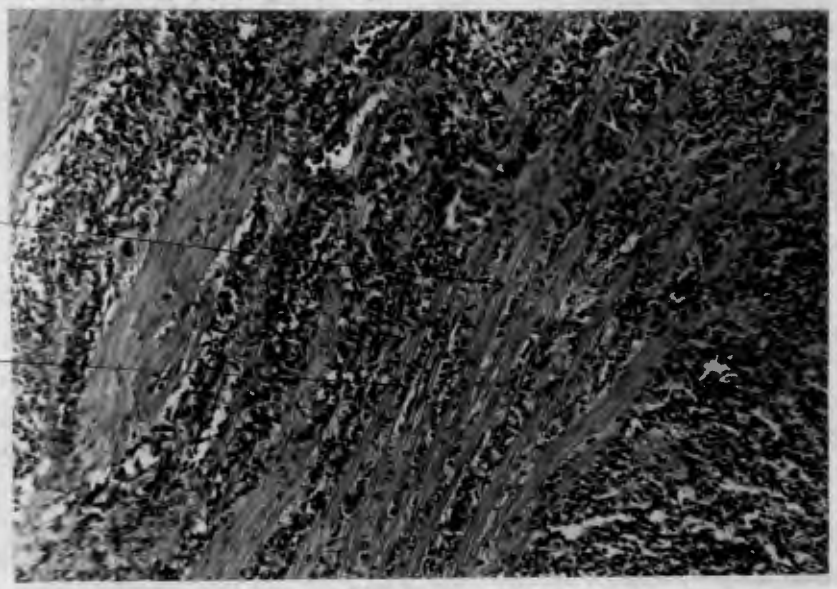


Fig. 29. X 150.

Uterine muscle invaded by granulosa cells.

Trabeculations can be made out.

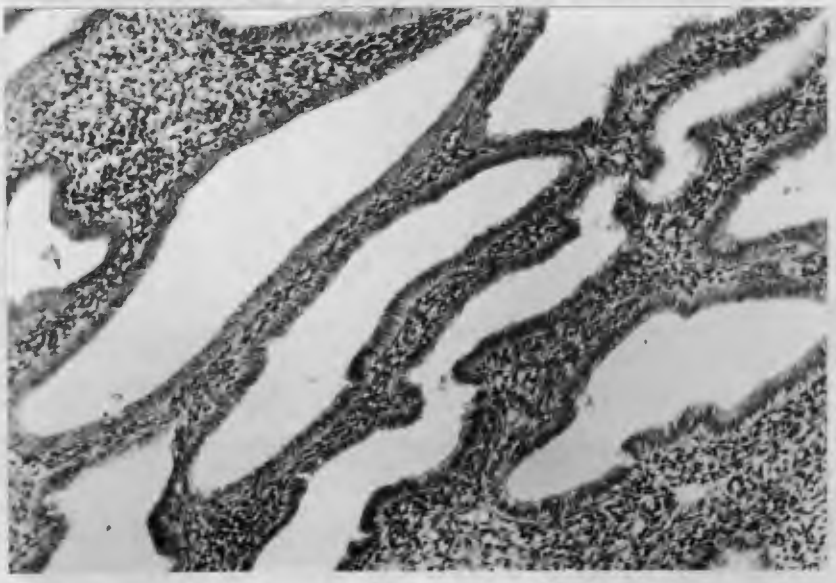


Fig. 30. X 150.

Endometrium in Proliferative phase.

Name: VERSTER (Mrs).

Age: 36.

Race: European.

Occupation: Housewife.

Address: South West Africa.

Hospital: Volks.

Date: 11.11.42.

Dr. Knoblauch's private patient.

Complaint: Abdominal lump.

Duration: 1 month.

History:

The patient states that her menstrual cycle always was 8-10/28-day type and that her flow has always been copious. She has not suffered from any inter-menstrual discharge, urinary troubles or bowel complaints.

She was quite well until a month ago when she noticed a lump in her lower abdomen. This lump has increased in size.

On Examination:

General condition: Good.

Local: Abdomen: A large tumour the size of an orange, freely mobile in all directions, was palpated within the abdominal cavity - below the umbilicus.

S.V.C. and Resp.: N.A.D.

Vaginal: Cervix: Normal.

Uterus was the size of a grape fruit and harboured multiple fibroids.

Adnexa: No abnormality was detected.

13.11.42. OPERATION.

Uterus was the size of a grape fruit and harboured 3 fibroids.

The right ovary was enlarged to the size of an orange and was neoplastic. The tumour had a brain-like appearance and consistency. It had a long pedicle. The omentum was attached to it.

Total hysterectomy and bilateral salpingo-oopherectomy was done.

Pathology Report:

"The structure is that of a very cellular and actively-growing tumour. The structure is, in parts, almost sarcomatous but the evidence is that this is a diffuse granulosa cell tumour and mitosis are frequent and the tumour is rapidly growing but appears circumscribed."

This patient died in South West Africa towards the end of 1943. Cause of death is unknown.

Fig. 31. X150.

Mixture of granulosa (a) and fibromatoid (b) cells.

Clear differentiation between the intermediate forms is difficult.

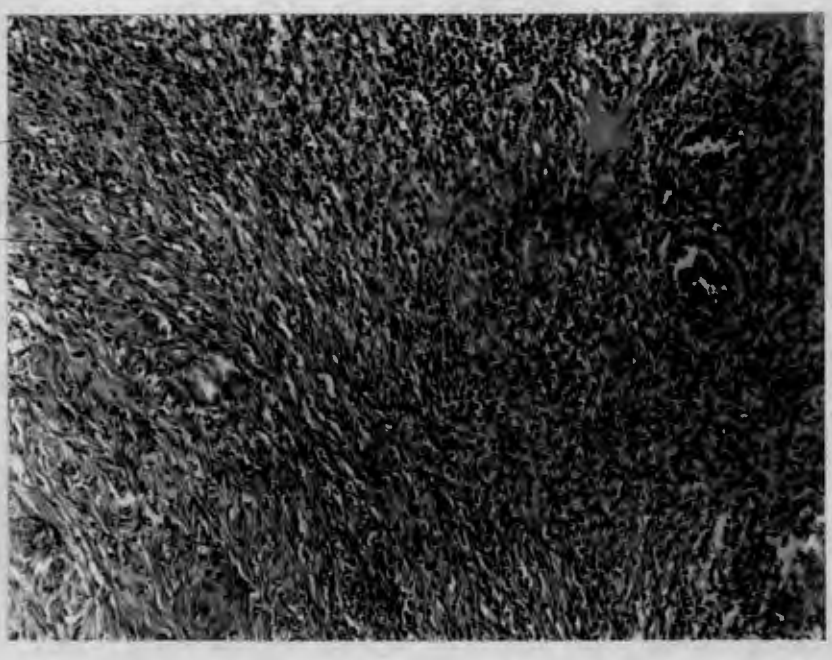


Fig. 32. X 150.

Sarcomatoid (a) and Trabecular (b) varieties.

CASE No.8.

Name of Patient:	KOLITA STRUIS.
Race:	Coloured.
Sex:	Female.
Age:	4 years (born 16.6.41).
Hospital:	Government Native, Windhoek.
Admitted:	August, 1945.
Index No.	A-640-45.

1. Pain in both legs - about 12 months.
2. Breasts enlarging - noticed 6 months ago.
3. Growth of axillary and pubic hair - noticed 6 months.
4. Swelling of and pain in the abdomen - since middle of May.
5. Swelling in the groin - noticed 20. 5. 45.
6. Vaginal bleeding - June and July.
7. Cough - 3 days.

History:

Personal and family history:-

Born in Keetmanshoop district. Adopted by present parents when 16 days old. Still lives in the same district. Diet for the first year consisted of goat's and cow's milk and occasionally Klim. After that mostly brown bread, meat and mealies. Practically no fruit or vegetables.

Walked at 9 months. Could speak words at 11 months and sentences at 12 months. Visitors remarked on the

fact that the child was so intelligent. (This information volunteered).

About the family, very little is known. There are about seven older sisters. They are all normal, but one of them is supposed to have started menstruating regularly at the age of seven. This her people believed to have been caused by a fall she had had shortly before.

Previous illnesses:

Often troublesome as a baby. At about one year of age she started crying every time she passed urine or had a motion. This gradually improved and disappeared over a few months. During this time she also frequently complained of pains in the legs but never in bed with it. No other illness of note.

Present History:

(1) Pains in the legs: This became worse about 12 months ago. The pains were mostly in the upper parts of both legs and not limited to the joints. Came on mostly while she was playing. She often cried with the pains. With rest they usually slowly disppeared over an hour or two. These pains have become much more frequent during the past year.

(2) Breasts enlarging: The mother noticed this first

about 6 months ago. Since then have gradually developed to the present stage. Never any pain.

(3) Axillary and Pubic Hair: Also noticed first about 6 months ago. It has grown considerably thicker during this time.

(4) Swelling in the Groins: On the 20th of May, 1945, the child was playing outside and came in crying with pain. The mother then saw the swellings in the groins for the first time. Then swellings have always been soft and disappeared, on lying down. They re-appeared on coughing or standing up. Sometimes reached size of oranges. With straining then always painful.

(5) Swelling of and pain in Abdomen: Since about the middle of May this year complained of pain in abdomen, especially on walking. Abdomen tender to touch. Always more on right side. Mother saw that abdomen was swollen.

On 20th July had more severe attacks of pain in abdomen which did not pass off with rest as before. Pain persisted till next day. She vomited a few times.

Since this attack stayed in bed. An attack like this every 3 - 5 days and often vomited with it.

Lost much weight since this time.

(6) Vaginal Bleeding: Slight painless vaginal bleeding lasting 16 days during first half of June. Blood not bright red but pale.

A second vaginal bleeding from the 15th to 20th July.

(8) Cough: 3 days. Troublesome and caused lot of abdominal discomfort. Sputum - yellowish white.

EXAMINATION:-

General Examination: T. 102. P.134. R.34.

Child in poor state of nutrition. Skin very lax and dry. Tongue dry and furred. Cried with every movement of the body and legs. Well marked growth of axillary and pubic hair. Breasts about size of half oranges and soft.

Local Examination - Abdominal:

Abdomen definitely distended but no localised swelling seen. Liver edge palpable medial to the ninth costal cartilage. Spleen not felt. Large lump rising out of the pelvis more on the right side of the abdomen and extending to a little below the right costal margin. Estimated size about 6 by 8 inches. Edges well-defined on sides. Slightly mobile from side to side. Surface smooth. Tender, especially at the upper end. Dull over the whole tumour.

Groins: Bilateral easily reducible oblique inguinal hernias.

Respiratory System: Numerous rhonchi over both lungs.

Other Systems: N.A.D.

Blood Count: White Cells 14600. Reds 4840000.

Diagnosis: Ovarian tumour producing active hormone.

TREATMENT.

Decided to treat cough and then operate.

Put on Vit. C 200 m.g. per day and diet with high vitamin content. Also Sulphadiazine and cough mixture.

Progress: Cough improved but temperature remained high. Complained of very severe abdominal pain and very tender over upper part of tumour.

Complication in tumour suspected and operation without further delay decided upon.

OPERATION.

Anaesthetic: Ethyl Chloride following by open ether.

Right paramedian incision made from level umbilicus to just above pubes. Fair amount of colourless free fluid in peritoneal cavity. Right ovary replaced by tumour with mesovarium as well-defined pedicle.

Upper pole adherent to omentum with many large veins running with adhesions.

LEFT
Right ovary normal. Uterus definitely enlarged to about the size of puberty uterus.

Ovarian pedicle ligatured and cut, leaving tube intact.

Omental adhesions ligatured and cut through normal

omentum, this leaving piece of omentum on tumour.

Tumour removed and wound closed in normal way.

Post-operative: Glucose saline drip first day. Temperature gradually came down to normal.

(Hernias left for later date because her general condition was poor).

Made very good recovery and left hospital after three weeks. Free of pain. Will return after three months.

Struis.

Pathology report :-

The structure is that of a granulosa cell tumour.

Fig. 33.

Child aged 4 years with enlarged breasts and swollen abdomen.

(These photographs were taken in Windhoek. Unfortunately, the pubic and axillary hair is not demonstrated).

Fig. 34.

Cross section of ovarian tumour.

(a) "Brain-like" cellular appearance.

(b) Fibrous septa.

(c) Area of infarction.

(d) Cystic spaces.

Fig. 35. X 150.

(a) Trabecular variety.

(b) Follicular variety.

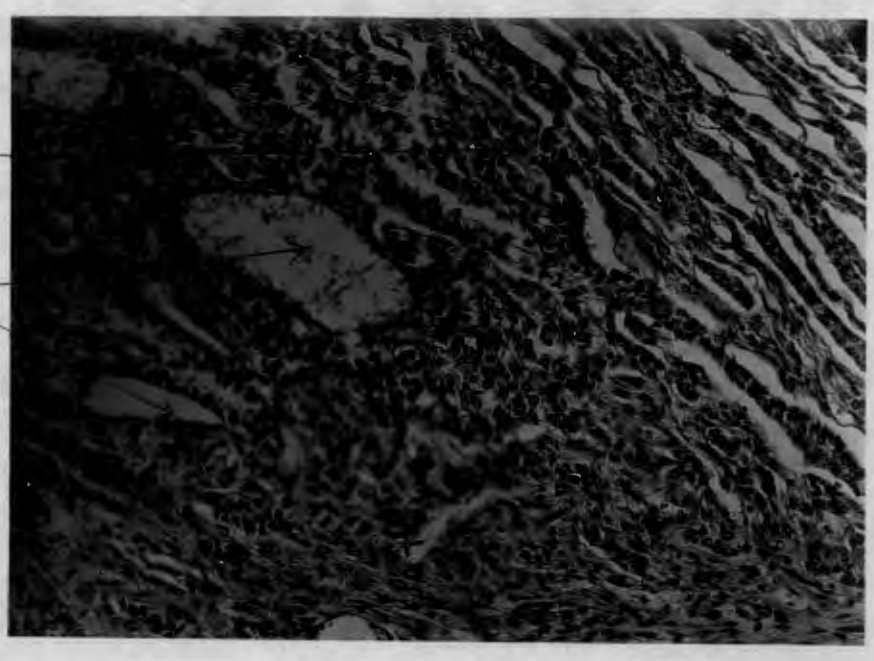


Fig. 36. X 150.

(a) Follicular variety.

(b) Call-Exner body.

(c) Cyst.

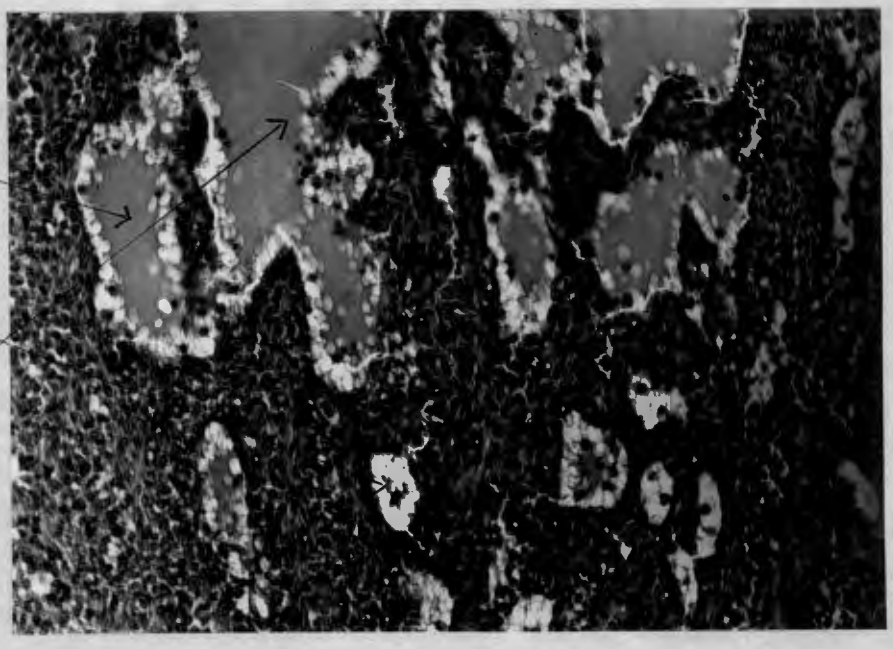


Fig.37. X 150.

Diffuse variety.

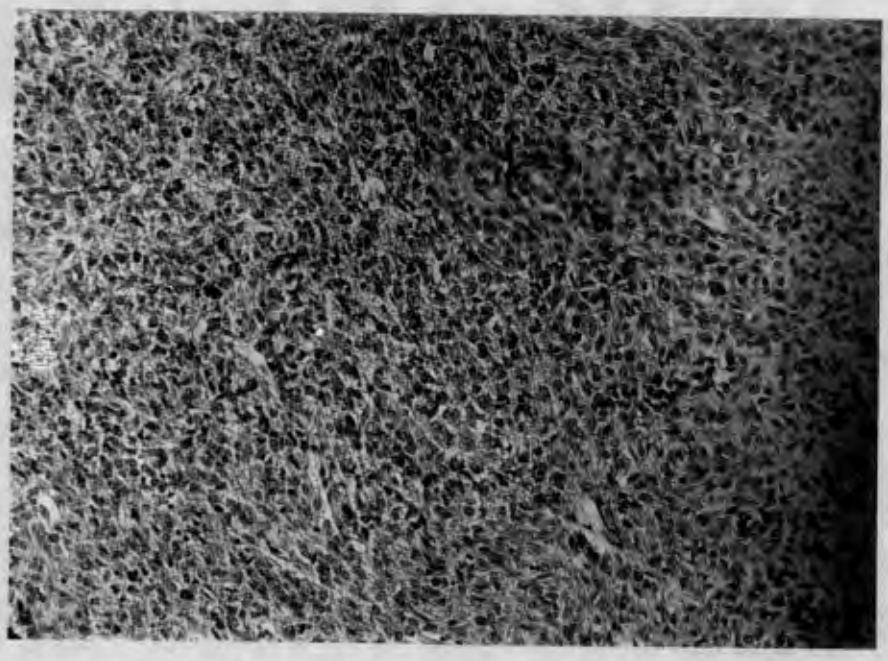


Fig. 38. X 150.

Mixture of fibro-
matoid and
? granulosa
? Theca cells.

Great similarity
in appearance.

Name: JOHNSON, Catherine.

Age: 53.

Hospital: Groote Schuur.

Index No.: 72252.

Admitted: 7. 9. 45.

Widow.

Complaint: (1) Vaginal bleeding 9 months.
(2) Hypogastric pain 2 months.

Pregnancies: 2. Eldest 22.
Youngest 18.
No labour or puerperal complications.

Abortions: Nil.

Menstruation: Menarche: 14.
Cycle: Regular 4/30. Moderate flow.
Menopause: 46.

Postmenopausal: Slight intermittent attacks of vaginal bleeding for the past 9 months.

Micturition: No frequency, dysuria or change in colour of the urine.

Bowels: Regular.

Present Condition:

The patient states that she was quite fit until 9 months ago, when she started noticing slight vaginal bleeding on exertion. The bleeding was painless and slight in amount, it was bright red in colour with no associated discharge. The bleeding has increased in quantity and frequency during the past two months.

For the past two months she has been suffering from a slight, more or less continuous dull aching hypogastric pain. This pain radiates to the small of her back.

She has lost about 6 lbs. in weight during the past two months.

She does not suffer from any lassitude or feeling of lack of energy.

On Examination:

General condition: Good.

Local: Abdomen: Nil abnormal detected.

C.V.S. " " " B.P. 120/80.

Resp. " "

Per Vagina: Uterus: Enlarged to the size of a tennis ball.
Mobility impaired - seems to be held down on the left side.

Adnexa: Slight thickening on left side.

Speculum: No signs of cervical disease seen.

7.9.45. Diagnostic curettage performed.

Ca. of the body diagnosed histologically.

10.9.45. OPERATION.

Abdomen opened by using the lower midline incision.

The right tube and ovary appeared normal.

The left tube and ovary " "

The uterus was enlarged. There was a knob, the size of a nmartje, on the left side of the uterus, involving the parametrium.

Tubes and ovaries were freed from their pelvic wall attachment.

The anterior layer of uterine peritoneum was stripped and stretched to the anterior abdominal wall - thus leaving a clear field.

The uterine arteries were exposed and clamped close to their origins.

As the parametrium on the left side was involved, the left ureter was exposed. It was surrounded by new growth. The new growth was now freed from the lateral pelvic wall.

There were a few secondaries in the posterior

on the anterior layer of the peritoneum of the Pouch of Douglas. These were removed together with stripping the posterior uterine wall.

Amputation was effected very low down. 1/3rd of the vagina was removed.

The haemostasis throughout the operation was complete.

The raw area was now peritonealised after the stitches holding the anterior layer of uterine peritoneum were freed.

Steraps inserted into pelvis.

Abdomen closed.

11.9.45. Pulse and temperature normal.
Patient is comfortable.

20.9.45. Stitches removed.
Wound well healed.
Patient is bright.

Patient's Identification C.W. JOHNSON Path. No. 1364

Uterus. There is a carcinoma in the fundus uteri. It grows into the lumen as a papillary structure and invades the myometrium as adeno-carcinoma. Independent of the adeno-carcinoma there is a large rounded cellular tumour attached to and partly embedded in the lateral wall of the uterus. This tumour has the structure of a cellular myosarcoma.

There is a small nodule of cellular tissue implanted on the peritoneal surface of the fatty tissue sent for examination. It is somewhat distorted by inflammation, but is almost certainly secondary to the myosarcoma.

Fig. 39.

Uterus opened from the left side transversely.

(a) Uterine cavity.

(b) Cervix.

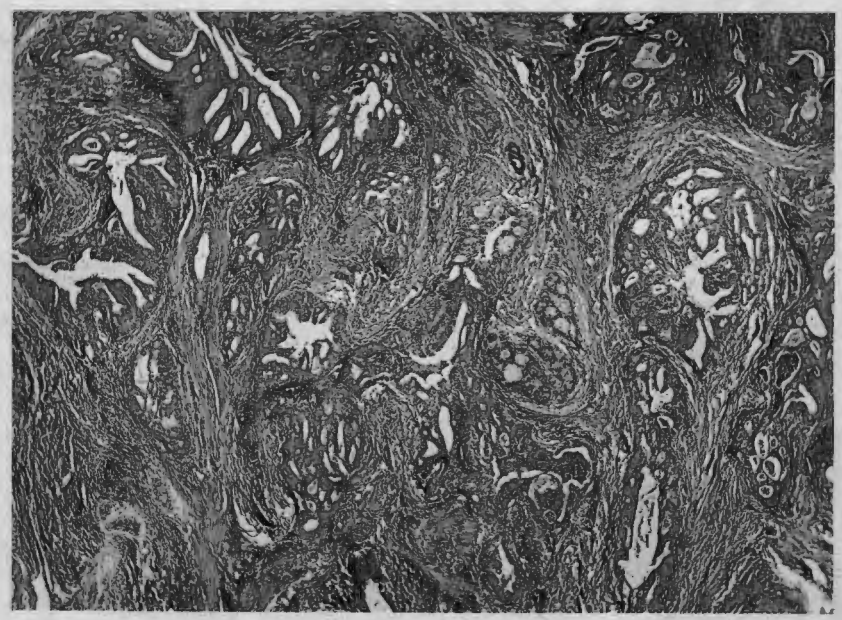
(c) Carcinoma of the body.

(d) Endometrial polyp.

(e) Myosarcoma.

Fig. 40. X 30.

Adeno Carcinoma of the body of the uterus.



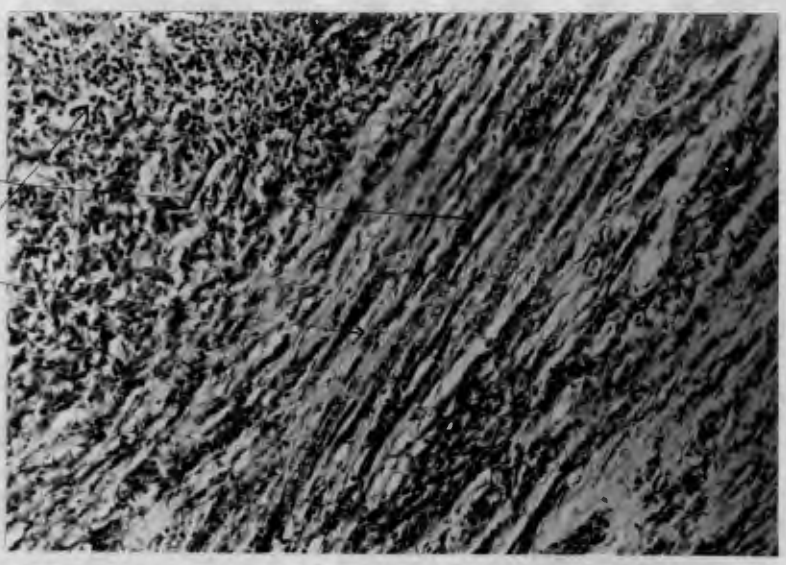


Fig. 41. X 150.

(a) Cells arranged in Trabeculae.

(b) Fibromatoid strands.

(c) Cells with clear protoplasm.

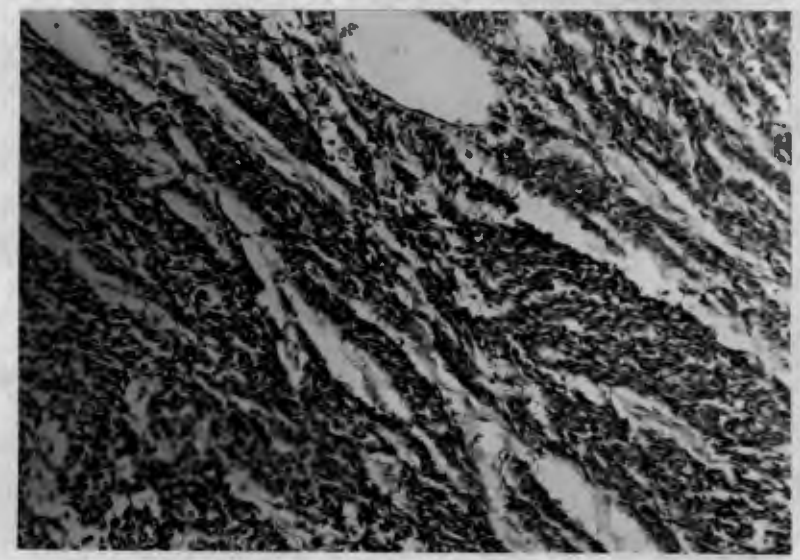


Fig. 42. X 150.

Sarcoma.

Note Trabeculations.

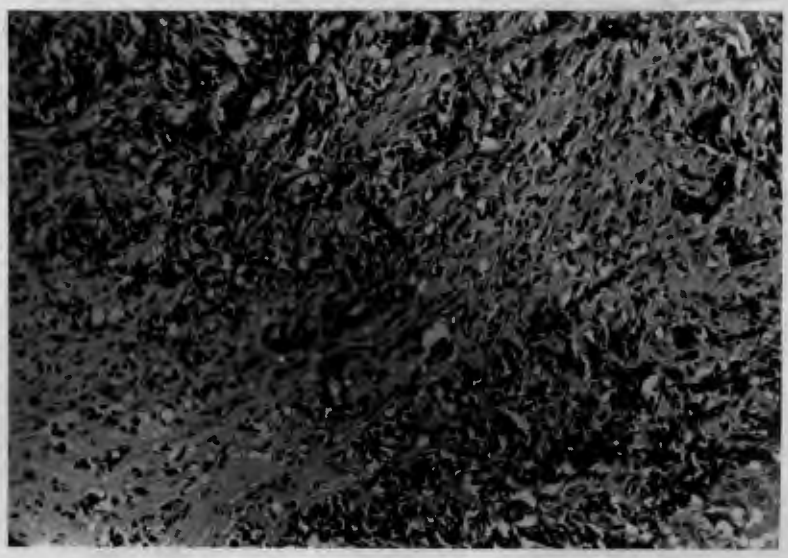


Fig. 43. X 150.

Dense areas of cells actively proliferative.

Fig. 44. X 150.

Mostly round cells with few spindle cells.

Not unlike 'Luteinised' cells.

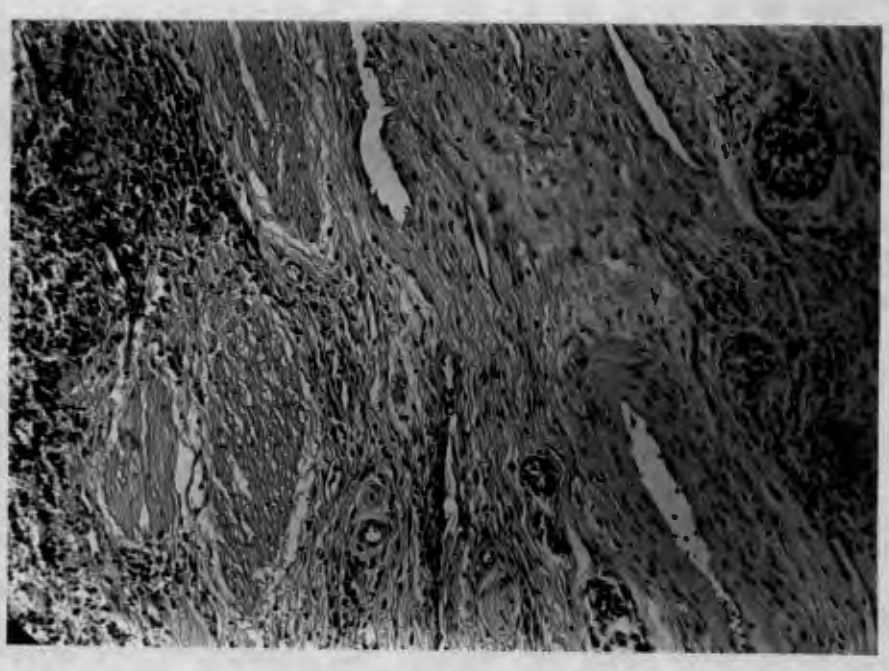


Fig. 45. X 150.

Infiltration of muscle.

Name: VAN EEDEN, Maria E.

Age: 48.

Race: European.

Married.

Hospital: New Somerset (Thomas Ball).

Index No.: 3304.

Admitted: 20.8.31.

Complaints: Heavy feeling in lower abdomen. Tumour felt in lower abdomen.

Duration: 3½ years.

Pregnancies: 1. 7 years ago.

The patient thinks a lump was present at the time of the pregnancy as the uterus was said to be unduly large at the third month. After labour the doctor in attendance thought she had a second child - the uterus was so large.

Abortions: Nil.

Menstruation: Menarche: 12.

Cycle: 6/28-day type.

Regular until about 1 year ago. Ever since she has bled only every 2 - 3 months.

Flow: Moderate.

Pain: Nil.

L.M.P. 3rd May, 1931.

Intermenstrual: Clear.

Micturition: Frequency for the past 3 years. This frequency is not a constant feature. At times she has to pass urine every half-hour. She has to get up once nightly.

Bowels: For the past few years her bowels have been loose; she has about 3 motions daily.

Present Illness:

Four years ago she missed a period. She saw a doctor, who told her that her uterus was the size of a 3 months' pregnancy. This was followed by a normal period.

About 3 years ago the patient began suffering from a heavy feeling in her lower abdomen and discovered that there was a lump about the size of an orange towards her left side. During this time she has also suffered from frequency.

For the past year the lump has definitely increased in size.

Since January, 1931, it has not varied in size.

Since January, 1931, she has had 3 attacks of colicky pain, the last was on August 13th. This attack has not entirely passed off - the previous attacks lasted about 24

hours only.

The pain was not associated with diarrhoea, constipation, vomiting or haematuria.

She was operated upon in August. A large growth - Fig. 2.- was removed from the pelvis.

The notes read as follows:-

"Several small glands on right side of neck appeared before discharge."

Pathology Report 3.9.31. (Serial No.568).

"Tumour is a mixed-celled sarcoma. There are numerous mitotic figures. There are large areas of degeneration and much haemorrhage in parts of the tumour."

This patient died on the 9th May, 1932, at Swellendam.

Fig. 46.

Sarcoma of Ovary - Cross-section.

(a) Cellular appearance.

(b) Haemorrhage into the tumour.

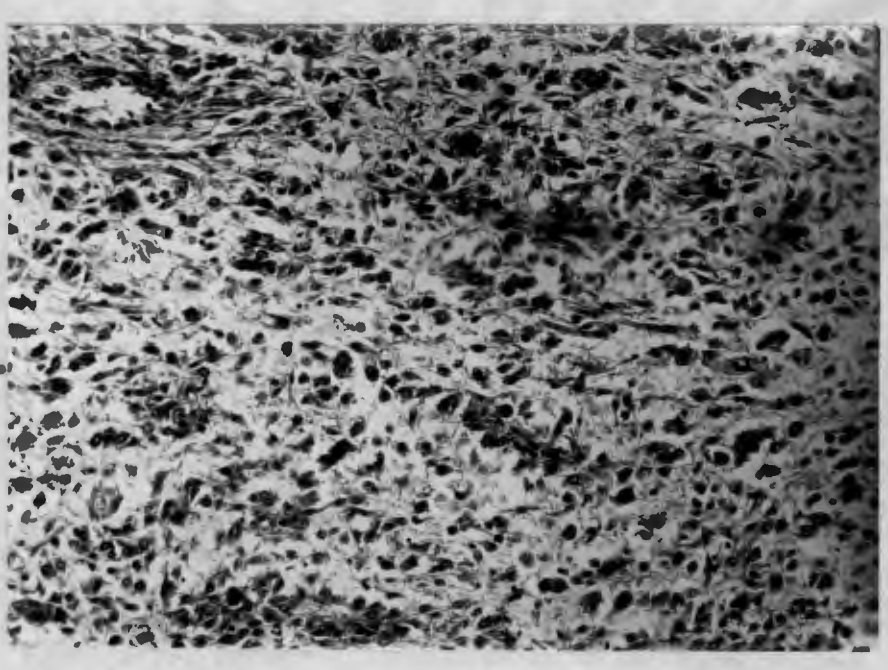


Fig.47. X 250.

Round and spindle cell Sarcoma.

Few trabeculations.

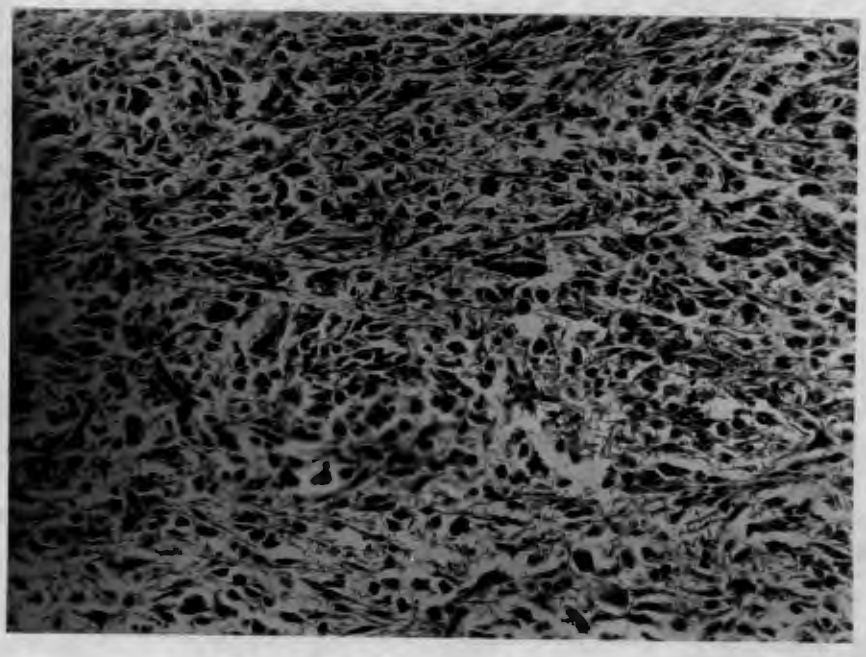


Fig. 48. X 250.

Round and spindle cell Sarcoma.

NAME:	Age:	Race:	Presenting symptoms:	Treatment	Result.
(1) Mrs. Kotze	45	European	Menorrhagia for 3 years	Subtotal Hysterectomy: Bilateral Salpingo-oopherectomy Partial left oopherectomy	Immediate good.
(2) Salome Davids	55	Coloured	Post-menopausal bleeding	Oopherectomy	?
(3) Rachel Bobani	51	Native	Post-menopausal bleeding	Panhysterectomy	Immediate good.
(4) Barbara Smit	54	European	Abdominal lump causing intestinal and urinary obstructive symptoms	Inoperable Deep Xray Therapy	good 2 years afterwards.
(5) Issie Andreas	47	Coloured	Abdominal lump (amenorrhoea 7 years).	Subtotal hysteredomy: Bilateral salpingo-oopherectomy	
(6) Dolly Salmon	35	European	Vomiting & diarrhoea 3 years. Menorrhagia 3 months	Total hysterectomy Bilateral salpingo-oopherectomy	Died 1 year later. Developed a s ary in the ch soon after th operation.
(7) Mrs. Verster	36	European	Menses always copious Abdominal lump - 1 month	Total hysterectomy Bilateral salpingo-oopherectomy.	Died 1 year a the operation
(8) Kolita Struis	4	Coloured	Precocious puberty	Oopherectomy	Immediate go
(9) Mrs. Johnson		European			

DISCUSSION.

Incidence.

In order to gain the correct perspective of the granulosa cell tumour, its incidence is well worth studying.

Ewing (31) states that it forms between 1 and 10% of all ovarian tumours.

Scathmary (quoted by Harris (50) gives the incidence as 0.9% in a series of 1114 ovarian tumours.

Von Szathmary (quoted by Traut & Butterworth (103) gives the figure as 4.4% of all solid ovarian tumours).

Klaften and Fauvets (both quoted by Harris (50) give their figures as 4.04 and 1.4% respectively of all ovarian tumours.

Schroeder (quoted by Traut & Butterworth (103)) states that the granulosa cell tumour forms 2.3% of all solid ovarian tumours.

Zemke & Herrell (113) state that 20% of all ovarian tumours are solid and that, of these, 10% are granulosa cell tumours.

From these figures it will be noticed that the tumour is rare but not so uncommon as to be diagnosed with grave misgivings.

Age Incidence.

Granulosa cell tumours occur at any age.

The case described by Zemke and Herrell (113) is the youngest on record. Their patient was 14 weeks old and would not put on weight. She had an abdominal lump.

Bilateral ovarian tumours were found at operation. Histologically these turned out to be granulosa cell tumours.

The eldest patient, with this type of tumour, on record, was 76 years (88).

Ewing (31) states that it occurs most frequently in women between the ages of 30 and 60.

Docherty and McCarty (29) give the age incidence as 5-10% occurring before puberty; 30% occurring during reproductive life and 60% occurring post-menopausally.

Novak & Brawner (81) find the incidence between

1 and 10	years:	15%
11 and 40	"	36%
40 and 70	"	48%.

The commonest age for the tumour to occur is about the menopause and soon after it (29. 76. 81. 88).

Symptoms.

It has been stated earlier that the symptoms depend upon the age of the patient. In most cases the symptoms are due to a continuous oversecretion of oestrin.

(a) Prepuberty:-

The essential train of symptoms will be along the lines of puberty (110). Kolita Struis (page 57) is a case in this series.

There is a marked acceleration of skeletal growth (35. 80. 86). The union of the epiphyses is hastened (31).

Pubic and axillary hair start growing (79. 82. 86. 88) - vide Fig. 33. (page 63).

The contour of the body becomes more rounded and adult in form (82).

According to Parks (86) the mental age of the patient is not affected. Ewing (31) and Pratt (88) state that they are usually overmature mentally. The history of Kolita Struis (page 57) states that she was well-advanced for her age.

Uterine bleeding may occur at regular or irregular intervals (31. 86. 88). The case cited in this series had two vaginal bleeds and hence no firsthand comment can be made.

The uterine bleeding is due to a hyperplastic endometrium (31).

The uterus is usually enlarged (31), although Zemke and Herrell (113) found a normally-sized uterus in the patient on which they operated. It must be taken into account that their patient was only 14 weeks old. The uterus in the case quoted in this series was enlarged to the size of a uterus of that found at normal puberty.

The signs and symptoms, therefore, are those of a precocious puberty (29. 81. 86).

Removal of the tumour leads to a regression of the symptoms (88. 86).

In Parks'(86) patient, a girl aged 5 years, there was profuse vaginal haemorrhage lasting 48 hours following the operation. This, in all probability, was due to the drop in circulating oestrin, as normal menstruation is due to periodic drops in blood folliculin (80).

On the 24th day her breasts were smaller and 16 months afterwards her pubic hair had fallen out.

Boyd (13) states that a precocious pregnancy might have followed in a young girl with a granulosa cell tumour. This statement probably is incorrect as Novak (80) has pointed out that there is no ovulation when a granulosa cell tumour is present. There is just an over-secretion of oestrin.

The ovarian tumour in a young girl with precocious puberty is, in all likelihood, (but not necessarily) a granulosa cell tumour.

Frank (35) states that precocious sexual development may be found in young girls with ovarian carcinomata or teratomata. Removal of these tumours leads to a regression of the puberty.

To confuse the issue a bit more, Frank also quotes a

child with a malignant ovarian tumour, a high oestrin content of the urine and no precocity.

However, removal of a granulosa cell tumour which contains (103) and secretes (19. 50. 82. 84. 88) oestrin, leads to a retrogression of precocity and hence it may be assumed that the precocity is due to an over-secretion of oestrin (88).

The symptoms and signs in Struis were those of a precocious puberty plus an ovarian tumour. The tumour has been removed and it is yet too early to comment on the changes in the patient.

The interesting feature of the histology is the mixture of granulosa, Theca and fibromatoid cell. This phenomenon will be dealt with when the histology of granulosa cell tumours is discussed.

(b) Active reproductive period.

During this phase of life it is most difficult to diagnose the condition. As the symptoms usually will be due to an over-secretion of oestrin (84)the brunt of the symptoms will, therefore, fall on the mentrual cycle.

The presenting symptoms are, in most cases, due to this over-secretion of oestrin. Rarely are they due to an abdominal lump and secondary deposits.

SYMPTOMS DUE TO HYPEROESTRINISM.

(1) Amenorrhoea. (12. 27. 29. 51. 57. 81. 88). This phenomenon is due to a continuous high concentration of oestrin in the blood. The amenorrhoea may last for variable long intervals. The patient may be under the impression that her manopause set in at an early age, whereas the correct interpretation may be that her amenorrhoea was due to the granulosa cell tumour. This may be the explanation of the early menopause of Issie Andreas (page 43). Her periods ceased at the age of 40. At no time did she suffer from any subjective menopausal symptoms.

(11) There may, however, be periods of amenorrhoea lasting from 2 to 3 to 4 months followed by uterine bleeding. This state of affairs is also found in Metropathia Haemorrhagica (33. 38). Menstrual bleeding only follows when there is a drop in the circulating oestrin (79 & 88).

Allen (quoted by Pratt (88)), working on monkeys, found that no uterine bleeding was produced on continuous injections of oestrin. As soon as the injections were stopped uterine bleeding followed.

In Metropathia Haemorrhagica a follicular ovarian cyst is usually found (38. 42) and there is an absence of the corpus luteum (33). The absence of corpus luteum is also found in granulosa cell tumours (79. 88).

The endometrial pictures found in both conditions are identical - i.e., endometrial overgrowth in the proliferative stage. (12. 29. 31. 37. 38. 50. 62. 67. 76. 81. 88. 102. 103).

i.e., the endometrium found in hyperoestrinism.

The palpation of an ovarian tumour will exclude Metropathia Haemorrhagica.

(III) Menorrhagia.

On the other hand the periods may be frequently irregular and the flow excessive (31.50.57.81.88). Menstruation becomes normal when the tumour is removed. (88).

The first case quoted - Mrs. Kotze - (page 14.) complained of irregular periods with an excessive flow. The uncommon features of the follicular cyst found in her ovary, n.l, the massive granulosa and Theca cells are most likely the cause of her symptoms

The cases of granulosa cell tumour in this series with these symptoms are Mrs. Verster (page 54) and Dolly Salmon (page 47).

Incidentally, they were 36 and 35 years old respectively. They had highly malignant tumours, both histologically, and, as was borne out by the fact that both of them died about one year post-operatively.

(IV). Sterility.

Patients suffering from this tumour will, naturally, be sterile (79.88). as their periods are anovulatory (79.88). and, therefore, no corpus luteum is present (79.88).

(V) Vomiting and Diarrhoea.

Crichton (28) states that vomiting and diarrhoea are often caused by large doses of oestrogenic preparations. Dolly Salmon (page 47) complained of causeless biliousness for 3 years and attacks of vomiting and diarrhoea, unassociated with any pain, for two years. It can be assumed that these attacks were due to an abundant liberation of oestrin by the tumour.

Vogts (105) patient complained of "dysentery", nausea and anorexia. No comment was made on these symptoms. The same explanation may hold for these symptoms of his patient.

(VI). Breast Changes.

The breasts may enlarge and become tender (12.50.67.81). The explanation given for this phenomenon is hyperoestrinism.

SYMPTOMS DUE TO THE ABDOMINAL LUMP OR SECONDARIES.

(1) The abdominal lump may be the presenting feature (8.88.106).

Mrs. Verster (page 54) is a case in point. She was not worried about her menorrhagia at all. What brought her seeking medical advice was that she had noticed an abdominal lump.

(II) The ovarian tumour may twist on its pedicle (88) and give rise to acute abdominal pain.

(III) Spread, from the original site, involving adjacent structures may produce effects on the latter. Mrs. Smit (page 38) - although a post-menopausal patient, is used here to demonstrate a symptom - came into hospital because of signs and symptoms of a chronic bowel obstruction. A laparotomy was done and an ovarian tumour involving the pelvic organs was found. The histology is on pages 41 & 42.

SYMPTOMS DUE TO ASSOCIATED PHENOMENA.

Vogt (105) reports a case of granulosa cell tumour with haemoperitoneum and haemothorax. Removal of the tumour led leads to a complete recovery, i.e., following the removal of the tumour the haemothorax and haemoperitoneum cleared.

The patient, therefore, presented with the syndrome first described by Meigs (71. 72) Perlmutter's case (87) - a Thecoma - had a similar syndrome.

The mechanical and associated symptoms can be found in any age and they are in no way due to the granulosa cells.

POST-MENOPAUSAL SYMPTOMS.

The usual symptom bringing patients of this age group to seek medical attention is uterine bleeding (29.31. 32.50.62.79.81.82.88.101.102.103).

In this series 2 cases are recorded, Salome Davids (page 19) and Rachel Bobani (page 27).

The bleeding may be at regular or irregular intervals and usually is excessive. Salome Davids had a more or less slight continuous loss. Rachel Bobani's loss was also very slight. She had 14 days bleeding.

In both cases a hyperplastic endometrium was found.

Fahmy (32) and Te Linde (102) point out that post-menopausal bleeding occurs with ovarian neoplasms other than granulosa cell tumours.

Dockerty and McCarty (29) go so far as to say that if a patient suffers from post-menopausal bleeding and a diagnostic curettage reveals a hyperplastic endometrium, an exploratory laparotomy is indicated, even in the absence of a palpable pelvic tumour.

Novak & Long (82) state that German workers are in full agreement with the above statement.

However, Howard Taylor (100) has found a hyper plastic endometrium in a patient suffering from a pseudomuninous cystadenoma.

The uterus in a patient suffering from a granulosa cell tumour is usually larger than normal (31.88.103). This is said to be due to the rejuvenating effect of the oestrin.

Mechanical symptoms, i.e., symptoms due to the lump or secondaries are not so frequent.

Mrs. Smit (page 38) is a case showing mechanical symptoms in this series.

Voigt (106) reports a case whose presenting symptom was an abdominal swelling.

Breasts:

The breasts usually enlarge and become tender. (12.50.57.67.74.81).

Meyer (76) reports 2 cases of actual galactorrhoea with granulosa cell tumours. This phenomenon is difficult to explain as therapeutically oestrogenic preparations are given to stop lactation.

The breast and uterine changes are apparently due to oestrin as injections of oestrin produce similar changes in the experimental animal (103).

Psychical:

There may be increased sexual desire (103).

However, it must be stressed once more that the granulosa cell tumour is a rare neoplasm.

Howard Taylor (100) states that out of 405 cases of post-menopausal bleeding 23 were due to ovarian neoplasms. Of the latter 4 were granulosa cell tumours.

Therefore, if a patient complains of post-menopausal bleeding and an ovarian neoplasm is detected the odds are

5 to 1 against its being a granulosa cell tumour.

Hormonal:

No hormonal studies were made in the cases in the series quoted; hence purely a review of the literature will be given.

The tumour itself has been found to contain large quantities of oestrin (10.84). Zondek (quoted by Geist (37) has shown that the granulosa cells per se contain oestrin and, incidentally, that they contain less oestrin than the Theca cells.

The tumour secretes oestrin (12.21.50.79.82). Extracts of the tumour produce oestrous effects when injected into mice (81).

The blood (29.31.67.81.88), urine (29.31.103) and faeces (29) of patients suffering from granulosa cell tumours contain high concentrations of oestrins.

Novak & Brawner (81) and Pratt (88)have suggested that urinary examinations for excessive oestrin is a valuable diagnostic aid. This is a reasonable but not a foolproof suggestion, as Frank (35) has pointed out that other malignant ovarian tumours can secrete oestrin.

Harris (50) states that Progestin is secreted by some of these tumours. Greenhill and Greenblatt (41) state

that the term "Luteinisation" should be reserved for these progestin-secreting tumours. The latter is a reasonable suggestion as Novak & Brawner (81) state that the Lutein cell is a modified granulosa cell and progestin but a modification of oestrin.

Butterworth (21) found that if mice with artificially-produced granulosa cell tumours were given injections of Antuitrin S the tumour became luteinised.

The urine in a few cases have shown a positive Zondek-Ascheim reaction (13).

Pratt (88) states that Prolan A is only of value if found pre-menopausally as it may be a normal finding after the menopause.

ASSOCIATED PHENOMENA.

(1) Endometrium.

(a) The more or less constant finding in a patient with a granulosa cell tumour is a thickened, boggy endometrium in the proliferative stage (12.29.31.37.50.62.67. 76.81.102.103)/ vide Figs. 10, 18.30. This type of endometrium is also found in mice with artificially-pfoduced granulosa cell tumours (21). The same endometrial picture is also produced by injecting oestrin into experimental animals (103).

The endometrial picture, therefore, can be said to be due to hyperoestrinism.

(b) Rarely the endometrium will be found to be in the secretory or premenstrual stage (41.81.88). Meyer (76) states that a decidua can be found in these patients. This secretory endometrium is due to a secretion of progestin. Greenhill and Greenblatt (41), therefore state that the premenstrual or progravid stage only occurs when the granulosa cells become luteinised.

Novak & Brawner (81) agree with the above statement.

(c) Endometrial polyps are common findings (37.50.88), vide, Cases Nos. 2 and 3.

CARCINOMA OF THE BODY OF THE UTERUS.

Not very uncommonly a carcinoma of the body is associated with a granulosa cell tumour.

Two of Henderson's (51) 21 cases had carcinoma.

Two of Dockerty and McCarty's (29) 30 cases had carcinoma.

Te Linde (102) quotes a case with a carcinoma. In the histology he found all the variations from hyperplasia of the endometrium to carcinomatous change.

Kirshbaum (58) cites a case with Theca cell tumour plus a carcinoma of the body.

Not much is known about the carcinogenic action

of oestrin. This association between carcinoma of the body and granulosa cell tumours is a subject left severely alone by practically all the authors.

ENDOMETRIOSIS.

Pratt (88) states that Endometriosis is found in association with granulosa cell tumours in some cases.

Traut & Butterworth (103) found one true case of adenomyosis amongst their mice with granulosa cell tumours.

In my series no Endometriosis was found.

Conceivably Endometriosis may be due to an oestrin endocrine imbalance. However, it is very rarely found in association with granulosa cell tumours.

FIBROIDS.

These benign neoplasms are found in a relatively high proportion of cases.

Five of Henderson's '51) 21 cases had fibroids,

Eight of Dockerty & McCarty's (29) 30 cases had fibroids.

Three of the series of cases reported, n.l., Andreas, Bobani and Verster, had fibroids.

Krishbaum's (58) case had fibroids.

Oestrin has been blamed as an etiological factor of fibroids.

Traut & Butterworth (103) state that, curiously enough, fibromyomas are rarely seen with hyperoestrinism induced by granulosa cell tumours. Yet Butterworth (21) gives fibroids as an associated finding in mice with artificially-produced granulosa cell tumours.

The association of uterine neoplasms, e.g., fibroids, carcinoma, polypi and endometriosis with oestrin secreting neoplasms is most interesting and is more common than mere coincidence. Future work will no doubt throw much light on this problem.

BREAST CHANGES.

These changes have been described inthe symptoms of the different age groups.

It is of interest to note that Furth and Butterworth (36) found the incidence of breast neoplasms to be much greater in mice with granulosa cell tumours than in exact controls.

Occasionally granulosa cell tumours may be found in association with ovarian dermoids (88).

Murray, Dockerty and Pemberton (78) report a case in which an associated Struma Ovarii was found.

The tumour has been found responsible for a Meigs' syndrome, i.e., hydrothorax and ascites (58. 105.)

SITUATIONS OTHER THAN IN THE OVARY.

Ragins & Fraenkel's (90) case was of a woman aged 37 years. Her complaint was abdominal enlargement for a year, amenorrhoea a year ago and menorrhagia since.

At operation they found a mass in the right broad ligament. It was cystic and the ovary was spread over it. Histologically it proved to be a granulosa cell tumour.

This by no means proves that the granulosa cell tumour originated in the broad ligament. It could have originated in the ovary and enlarged into the broad ligament.

Voigt (106) quotes a case of a 51-year old woman who had a hysterectomy performed 3 years previously for fibroids. Nine months before her second operation she noticed an abdominal lump. On examination the lump corresponded practically to the size of a full-term pregnancy.

Laparotomy was performed and a huge growth was removed from the mesosigmoid. It turned out to be a granulosa cell tumour.

Voigt states that the tumour might have arisen from a rest along the embryological ovarian tract. His data are insufficient. The correct explanation may be that whilst stitching the peritoneum of the broad ligaments and uterine stump after the hysterectomy, the left ovary was tucked into the upper part of the cut infundibulo-pelvic ligament. Growth of the

ovary in this site might easily extend into the meso-sigmoid.

PATHOLOGY.

Gross.

These tumours vary greatly in size. The smallest reported tumour was the size of a pin's head (29. 50) and the largest weighed 34 lbs. (29.50).

Salome Davids (page 19) tumour weighed 17 lbs. after 10 pints of fluid were withdrawn. The tumour usually is well encapsulated (29.30) (vide, Figs.11 and 12) and unilateral (29.81.99).

Rarely are they bilateral (31.88.113.).

The surface is usually smooth (81.88). Infrequently it is knobbly (88).

In Rachel Bobani (Figs.11 & 12) and Salome Davids (Fig.4) the surfaces were smooth. In Struis (Fig.34) it was knobbly.

It may be soft and solid (29.50.81.88). This was also the finding in the tumour (Figs.11. & 12).

It may be partly solid and partly cystic (31.81.) - vide, Fig.4.

The whole tumour may be cystic with the granulosa cells in the wall of the cyst (31.81.)

According to Dockerty & McCarty (29) 90% of these tumours are unilateral and 90% are solid.

Occasionally these tumours have spread beyond their confines and practically choke the pelvis, e.g., Mrs. Smit (page 38).

The tumour may, therefore, be of any size, shape or consistency. The only important finding is the presence of an ovarian tumour clinically.

CUT SURFACE.

The solid, partly solid, partly cystic, or cystic appearance is seen. The cysts may contain yellow, clear or bloodstained fluid (88.) vide, Fig. 4., page 23.

The colour of the tumour varies considerably. It may be yellow (88) or have a yellowish tinge in one area (Fig.4). Frequently the colour is that of a liver sausage (29) - vide, Fig.12.

On the other hand, the tumour may have a cellular brain-like appearance not unlike a Sarcoma (50), vide, Fig.34.

Many fibrous septa are often seen permeating the tumour (Fig.34).

Necrotic changes in the tumour is not an uncommon finding (88). Fig. 4. demonstrates this finding. The description of the operation on Mrs. Smit (page 38) is also illustrative.

MALIGNANCY.

The malignancy cannot be judged by the histologist but lies purely in the field of the clinician (88).

Dockerty and McCarty (29) state that 90% of the tumours are of a low-grade malignancy.

Novak & Brawner (81) had 9 recurrences in 32 cases, i.e., a 28.1% malignant rate. They state that once the tumour recurs death soon follows.

Varangot (quoted by Henderson (51)) finds that 25% are malignant.

Te Linde (102) states that the malignant rate is low and places it between 5 and 10%.

In this series 2 out of the 7 cases are known to be dead - and presumably died of secondaries. The figures are too small and too inaccurate to even make an attempt at a percentage.

Arnold, Koerner and Mathias (quoted by MacCartney (62) report a case who had her first operation in 1908. Secondaries were removed in 1924. She died of secondaries in 1928, i.e., 20 years after the removal of the primary.

MacCartney's (62) case developed secondaries after 5 years.

Harris (50) and Pratt (88) state that secondaries may present 3 to 21 years after the removal of the primary neoplasm.

From these data it will be observed that the malignant rate is much higher than is generally known and that secondaries may appear at any time.

It will also be noticed that in no way is there a benign or a malignant granulosa cell tumour. They should all be treated as malignant.

Therefore, the prognosis, although in most instances, bright, should always be guarded.

SPREAD.

The tumour disseminates in the four ways in which any infection or neoplasm spreads, as is taught in Morison and Saint's (77) Surgical Principles.

(i) By continuity of tissue to the broad ligament (50), uterus (10.50) - vide Figs: 28 and 29 - and Peritoneum (31.50.62).

(ii) By contiguity of tissue to the omentum (10.50) and gut (Mrs. Smit).

(iii) Lymphatic spread has been reported (62) and is demonstrated in the history of Dolly Salmon. The cisterna chyle was compressed. (This might have been due to a secondary within it - or a blood-spread secondary deposited near it).

(iv) Blood Spread.

Secondaries have been found in bone (37.50), brain (50.62), meninges (31), pleura (31), liver (31).

Novak & Brawner (81) and Geist (37) state that secondaries can occur anywhere in the body.

COMPLICATIONS.

(i) The most important complication, naturally, is extension of the tumour. This has been fully discussed in the previous chapter.

(ii) As with other ovarian neoplasms the tumour may twist on its pedicle and hence the patient will present as an acute abdomen.

(iii) Haemorrhage may occur into a cyst.

(iv) Ascites, although uncommon, is occasionally found, e.g., Rachel Bobani and Kolita Struis.

(v) Meig's syndrome, i.e., Ascitis plus hydrothorax has been described by Vogt (105) and Perlmutter (8).

(vi) Sterility has been stated to be a complication. This is an "associated phenomenon" rather than a complication. The sterility is inevitable as the bleeding - if any - is anovulatory. (27.81).

TREATMENT.

The treatment of choice is surgical removal of the tumour. How much of the genitalia should be removed with the ovarian tumour depends upon the age of the patient and whether it has spread into the genitalia or not.

AGE FACTOR.

If a young girl suffers from a granulosa cell tumour and only one ovary is affected, there is no need for removing more than the affected organ (88. 29.)

This was the treatment used in Kolita Struis (page 57.).

Zemke & Herrel (113) removed both ovaries from a 14-weeks old infant. She was fit 3 years afterwards.

In a woman in the reproductive stage, if the tumour is confined to one ovary there is no need for more than removal of that ovary. Dockerty & McCarty (29) state that surgery should be conservative.

Countiss (27) reports pregnancy following a few months after removal of a unilateral granulosa cell tumour. This case, incidentally, also proves that the patient returned to absolute normal and full function after the removal of her secretory tumour.

In the post-menopausal group there is no need for conservatism; the operation should be radical. Both tubes and ovaries and the whole uterus should be removed. This was the treatment given to Rachel Bobani (page 27).

DEEP XRAY THERAPY.

This method of treatment should be confined to inoperable cases only.

In reviewing the literature this method is stated not to be very successful.

Gnassi, Faison & Fellman (39) state that the granulosa cell tumour is usually considered to be radiosensitive. They state that the regression is temporary. The tumour recurs and soon kills its host.

Mrs. Smit (page 38) is of interest. - She had a laparotomy done in January, 1942, and an imoperable growth was found. A snip was taken and a granulosa cell tumour diagnosed. This was followed by deep Xray therapy, with good immediate effect. She then complained of subjective menopausal phenomena. In 1944 she returned to the Groote Schuur Hospital and had a thyroidectomy performed for hyperthyroidism. At that time there was no evidence of a recurrence of the ovarian tumour.

OPERATION FOLLOWED BY DEEP XRAYS.

Authors are not yet agreed as to whether surgical removal of the tumour should or should not be followed by deep Xray therapy. Kleine & Schiller are quoted by Pratt (88) on this subject. Ewing (31) is doubtful.

Each case should be judged by its own merits. Where there is evidence of local spread deep Xrays should follow the operation.

Mrs. Verster (page 54) and Dolly Salmon (page 47) should have had deep Xray therapy. The latter patient

had her Xray treatment confined to a secondary detected three weeks post-operatively.

Deep Xrays would have been harmful in Countiss' (27) patient as the treatment would have destroyed the other ovary and, hence, would have destroyed her chances of becoming pregnant.

HISTOLOGY.

Histologically different types of pictures are described. These patterns vary from the most differentiated follicular type to the cylindroid (representing the growth of granulosa cells following the rupture of the follicle), to the undifferentiated diffuse or sarcomatoid type.

Cysts are also found. Examples of these types have been shown in the appropriate microphotographs.

It must be emphasized that these "types" are used for purposes of description and recognition only and that they are of no other practical importance whatsoever.

In studying the slides the different patterns are striking. All the above types are often found in a single section. Usually one pattern dominates the picture. In all the slides in this series the predominating pattern was the trabecular or cylindroid one.

In describing these different types the literature will not be quoted as practically every article written on granulosa cell tumours has these types described in a

variety of ways and lengths.

FOLLICULAR VARIETY.

The cells are seen arranged radially around a clear space - as, roughly, they are found in normal follicles - Figs. 27 and 35 are good examples.

Rosette-like areas, "Call-Exner" bodies may be found where the cells surround smaller clear spaces. These clear spaces may have a pigment in them and then resemble ova. (Figs. 17.36). They are said to be collections of oestrin surrounded by granulosa cells.

CYLINDROID OR TRABECULAR VARIETY.

The cells are arranged in rods or cylinders, as is demonstrated in Figs. 6,7,16.20.35, etc.). This was the predominant type on all the sections of this series. The long epithelial strands may give the appearance of being cut into sections, by ingrowths of connective tissue.

CYSTS.

These are lined by many layers of granulosa cells and resemble follicular cysts excepting that the granulosa cells are more massively arranged around them, e.g., Figs. 17 and 36).

DIFFUSE TYPE.

In this variety there is no pattern to the cells

at all. They are arranged diffusely and are indistinguishable from other malignant tumours (31.88) - especially sarcomata and, hence, the term SARCOMATOID variety.

In the diffuse type, per se, it is practically impossible to diagnose a granulosa cell tumour. Many sections may have to be taken and searched in order to detect trabecular follicular types and Call-Exner bodies. The trabecular type may give rise to grave difficulties, e.g., Mrs. Johnson's slides, vide, Figs. 41, 42, 43.

The histological diagnosis may be so difficult that Ewing (31) states that the pathologist may have to lean heavily on the endometrium and symptoms and signs for support.

The granulosa cells may be in clusters and intermingled with Theca cells (Figs. 5, 7, 9, 23.)

In some sections it is impossible to state whether Theca or granulosa cells are being dealt with. This was particularly the case in the slides of Struis.

In the latest edition in this country of Surgery, Gynaecology & Obstetrics, i.e., Sept. '45 (Banner & Dockerty) correlates the findings in a series of Theca cell tumours. Yet the conclusion come to is that in practically all instances granulosa cells were present in fair numbers.

There is hence no need to differentiate between these tumours - especially as there are no differences in signs, symptoms and hormonal secretions as well.

For exactly the same reason is there no need for a different classification if the histology reveals an emphasis on corpus luteum cells. These tumours are then referred to as Luteomas.

Butterworth (21) has found that if mice in which granulosa cell tumours were produced experimentally were given injections of Antuitrin S, the granulosa cells changed into corpus luteum cells.

Novak & Brawner (81) state that the Lutein cell is but a modified granulosa cell.

Frequently luteum cells are found in granulosa cell tumour section, i.e., Fig.14.

In studying these sections it will be noted that right from the caricature of normal cell relation (Figs. 1 and 2) to the wicked-looking diffuse type, Figs. 23., 24, 32, 33, the fibromatoid cells are in close relationship to the granulosa and Theca cells.

PATHOGENESIS.

The main theories in regard to the pathogenesis of the granulosa cell tumour are that it originates from

(i) A cell rest (Meyer) - following Cohnheim's theory as to the origin of tumours.

(ii) Germinal epithelial tubular down-growths (Walthard). This theory really boils down to a cell rest as well, i.e., Embryological cell complexes.

(iii) Cells surrounding the follicle normally (von Kahlden).

(iv) That it is a reaction on the part of the ovarian stromal cells to a particular chemical or physical stimulus (my own view).

In order to understand these views fully it is essential that the origin of the granulosa cell itself should first be considered.

ORIGIN OF THE GRANULOSA CELL.

The granulosa cell is intimately linked with the ovum both functionally and anatomically.

The theories regarding its origin correspond closely to those linked with the origin of the ovum..

There are two main schools of thought concerning the origin of the ovum.

They are:- 1. That it originates from the germinal epithelium,

2. That it is formed within the ovary.

Evidence that it originates from the germinal epithelium.

McCosh (63) found that in the Amblystoma Maculatum the germinal epithelium gives rise to germ cells.

Allen (4) quoting Ludwig, Gatenby and Braun respectively, states that those workers found that the whole ovary in selachians, amphibians and reptiles regenerates seasonally from the germinal epithelium. Robinson (quoted by Allen) working on ferrets found that new groups of ova and follicle cells are formed from the germinal epithelium throughout life.

Allen found the same phenomena in mice.

Hargitt (45.46.47.48.49.) found that the entire ovary - including its germinal epithelium - is formed by a local proliferation of peritoneal cells - in the albino rat. New ova were formed from the germinal epithelium throughout life. There is a relation between the activity of the germinal epithelium and the number of oocytes in the ovary.

He states further that the germinal epithelium forms ova, follicle cells and interstitialcells.

Butcher's (20) findings correspond to those of Hargitt.

Papanicalcau (85),studying the guinea-pig ovary, states that ovogenesis is a continuous process occurring from the time of sexual differentiation to the cessation of sexual activity. The ova come from the germinal epithelium.

The view that ova and granulosa cells are formed by the germinal epithelium is also supported by Keith (56) and Ramsay & McCarty (91).

League and Hartmann (61) state that anovular follicles - complete with granulosa cells, basement membrane and Theca interna cells - are common in the ovaries of the opossum, monkey and armadillo.

In the opossum there may be nests of loosely-arranged granulosa cells within a basement membrane. These cells are said to arise from Pflueger's tubules and have failed to link up with ova - which are formed within the ovary.

ROA (93) working on LORIS - a South Indian animal - found that ova are formed both from germinal epithelial "dips" and from transformed interstitial cells.

Goodall (40) found that in the cow embryo, immature ova are formed in germinal epithelium downgrowths, i.e., in Pflueger's tubules. He states that the germinal epithelium forms the ova and secretory cells of the ovary and that the supporting cells come from the connective tissue of the Wolffian body.

According to Goodall, the interstitial cells of the ovary possess potentialities of ovogenesis and hormonal secretion.

OVA AND GRANULOSA CELLS FORMED IN OVARY.

Fischel, supported by Schiller (quoted by Harris (50) Pratt (88)) states that the ova, granulosa and connective tissue cells originate in the mesenchyme of the ovary - and NOT from the germinal epithelium.

Keibel and Mall (55) state that once the tunica-albuginea forms no more ova enter the ovary. The ova in the ovary, within the tunica albuginea, then become surrounded by cells which differ in no way from connective tissue cells. These cells become the follicular cells.

Arey (5) agrees with this concept.

Martinovitch's work is of great interest. He explanted an embryonic ovary and found that new ova were formed by division of previous oogania only. No new ova were formed from the germinal epithelium. (69).

Simkins (97) found that all the cells of the gonad are derived from the germinal epithelium.
In the human ovary he states (96) that the genitaloid cells come from the germinal epithelium until the tunica albuginea appears. From then onwards they form both in the germinal epithelium and within the ovary. Within the ovary they form from indifferent medullary cells. Those formed in the germinal epithelium do not migrate into the ovary.

Large and small cells cluster around the ova. They are the Theca interna and follicular cells.

From these data the following conclusions may reasonably be drawn:-

(i) Essentially the whole ovary is formed by a proliferation of an area of cells lining the coelomic cavity, i.e., from peritoneum.

(ii) That ova and granulosa cells are formed from the germinal epithelium in lower animals - and are formed in this manner until the cessation of the reproductive period, e.g., worms, amphibians, reptiles and lower mammals.

(iii) Higher in the scale of animals ova are formed both in the germinal epithelium and within the ovary, e.g., Loris.

(iv) Still higher in the animal scale the germinal epithelium is responsible for the initial formation of ova and also for the formation of cells which become embedded within the ovary and have potentialities of becoming ova or granulosa cells, e.g., cow - as shown by Goodall;

man - as shown by Simkins and Keibal & Mall.

Keibel & Mall (55) find that the granulosa cells appear as cells indistinguishable from fibroblasts.

It is, therefore, reasonable to assume that in humans the granulosa cell takes origin from a fibromatoid ovarian stromal cell, i.e., that given a certain stimulus, e.g., the immediate presence of an ovum. This stromal cell will react and change its morphology, becoming a secretory granulosa cell.

Change in morphology and secretion occurs regularly in the ovary, e.g., after the rupture of a follicle granulosa cells proliferate and become Lutein cells (Bullough (19) granulosa cells secrete oestrin and the corpus luteum secretes both oestrin and progesterone.

A growth of this follicle is accompanied by the formation of Theca cells.

Maximow & Bloom (70) state that the ovarian stromal cell should not be regarded as an ordinary fibroblast.

THEORIES.

1. Cell Rest.

Cohnheim was the first to apply the cell rest theory to the origin of tumours. Meyer (75. 76) has applied this theory to the origin of granulosa cell tumours.

He states that the tumour originates from unused granulosa cells,i.e., granulosa cells that have not been called upon to form follicles. These unused granulosa cells are stored in the ovary as undifferentiated cells.

Masses of granulosa cells are found in the ovary of every full-term pregnancy. Sometimes they are found in numbers in the normal adult ovary. They may, however, be present in primitive form.

This theory is supported by many authors. Amongst them are Novak & Brawner (81).

Te Linde (102) found an early granulosa cell tumour in the medulla of the ovary. Normal granulosa cells are found with the follicles, i.e., in the ovarian cortex. By this finding he supports the cell rest theory and condemns the suggestion that the tumour takes origin from the granulosa cells of the follicle.

Against the cell rest theory is Traut & Butterworth's (103) argument. They state that cell rests are very rarely seen in the ovaries of the age group in which these tumours must commonly occur, and that the "rests" are frequently found in the ovaries of young girls - in which age group the tumours are rarely found.

2. Germinal Epithelial Downgrowth Rests.

Walthard (quoted by Harris (50), Pratt (88), etc.) was the first to expound this theory. These "rests" are remnants of Phlueger's Tubules.

He is supported by Blair Bell (9). These "cell-complexes" are rarely seen in ovaries.

Goodall (40) states that an invasion of germinal epithelium into the ovary may give rise to the granulosa cell tumour. Voigt's (106) argument against this theory is adequate. He states that in the age in which the tumour is most commonly found - i.e., in the post-menopausal age - there is no germinal epithelium.

3. From Cells surrounding the Normal Follicle.

Von Kahlden described the tumour as a graafian follicle adenoma. His concept was that the neoplasm originated from the cells surrounding the follicle.

This view is expressed by Robinson (94), Dockerty & McCarty (29), Traut & Butterworth (103).

Against this view is the argument put forward by Te Linde - quoted in support of the cell rest theory.

Schiller (quoted by Harris (50), Pratt (88), etc.) states that most granulosa cell tumours occur after the menopause, i.e., when no more follicles form. Therefore, there can be no follicular cell origin for the tumour of patients in that age group.

Butterworth (21), Furth & Butterworth (36), following on the work of Brambell, Parkes & Fielding (14) and Brambell & Parkes (15), found that when the ovaries of mice were irradiated, nests of granulosa cells could be seen in the peripheri of the ovary soon afterwards. These cells, in all

probability, originate from undifferentiated ovarian cells.

They multiply and form anovular follicles.

Simultaneously, a proliferation and downgrowth of the germinal epithelium occurred.

No connection between these downgrowths and the anovular follicles was found.

The multiplication of the follicular cells continued and the cells then started infiltrating the ovary in this way, forming granulosa cell tumours.

4. Origin from Stromal Cells.

The study of the reaction to stimuli is interesting.

According to Eugene Marais (in his book, "The Soul of the White Ant"), a stick stuck into an ant heap in a certain direction, and withdrawn, will cause a peculiar reaction on the part of the ants. Instead of sealing off the hole left in their heap, they will start building a spire. Architecturally, this spire is all wrong; it breaks off time and again - yet they continue building it in that fashion. Is this an example of neoplasia ?

In the body there are certain normal responses to stimuli, e.g.,

If pyogenic organisms invade the body the chemical and physical stimuli they produce sets up a reaction. This reaction is termed inflammation.

The stimulus of an ovum in the ovary leads to the collection of fibromatoid cells around it which change their morphology and become granulosa cells. The stromal cells surrounding these cells change to theca interna cells.

If an ovum becomes impregnated within the ovary the stromal cells change their morphology and become decidual cells (70).

If the ovary, on the other hand, is stimulated by irridiation (21.36.) the reaction will be abnormal granulosa cell formation. These granulosa cells, as stated before, multiply and eventually invade the rest of the ovary.

The conclusionthat is reasonable is that there are fibromatoid cells in the ovary that have toti potential qualities; they react differently to different stimuli.

What the exact stimulus is for the production of granulosa cell tumours is unknown.

From the histological pictures shown the close relationship between the fibromatoid, granulosa and theca cells is evident.

It is as if the mild reaction to the stimulus would be purely a fibromatoid one - as is found in the Fibroma of the ovary.

If the reaction is more severe - localised collections

of arranged granulosa-like cells will be found in a fibromatous background. This would be the BRENNER tumour.

A still more uncontrolled reaction would result in a granulosa cell tumour or a Thecoma.

The completely uncontrolled reaction - according to this view - would be a total undifferentiated fibromatoid reaction, i.e., a SARCOMA.

This theory has been hinted at in the literature. Fischel (quoted by Harris (50)) states that "the tumours, where unripe, have the character of connective tissue and, when ripe, show epithelial structure."

Morphological resemblance proves very little indeed.

The pathologist, however, may find himself in difficulties in deciding whether a tumour is a Sarcoma or a granulosa cell tumour.

This statement is well borne out by considering the microphotograph of Mrs. Johnson (pages 71 A. & B - Figs. 41, 42, 43, 44 and 45.

If Figs. 41 and 42 be compared with Fig. 29, a striking resemblance will be noted.

Fig. 44, on the other hand, has practically the exact appearance of Fig. 14.

A slight difference can be noted when Figures 27 (excluding the two attempts at follicular formation) and 47 are compared.

Fig. 48 appears to be a gross enlargement of a section of Fig. 37.

This morphological difficulty can be so great that Ewing (31) states that the pathologist has to lean heavily on the endocrinal changes and the endometrium for support before a diagnosis can be ventured.

Glancing at Fig. 39 will show that Mrs. Johnson had an endometrial polyp and a carcinoma of the body of the uterus - two not uncommon findings with a granulosa cell tumour.

Novak & Brawner (81) state that some ovarian sarcomas have the same biological effects as the granulosa cell tumour.

Therefore, it can be stated that the undifferentiated forms of granulosa cell tumours have a sarcomatous appearance.

Turning to Figs. 5, 9, 15, 22, 23, 24, 31, 35 and 38, the striking feature is the relationship between the

fibromatoid and the granulosa cells.

In some areas of these sections there are cells which are neither fibromatoid nor granulosa in type. It is as if they were intermediate forms, i.e., fibromatoid cells with swollen nuclei.

This inter-relationship is so constant that the explanation is either different cellular reactions to the same stimulus or that the stimulus calls upon the reaction of the fibromatoid cell, which, in its response, gives origin to the granulosa cell.

CONCLUSION.

The view that the granulosa cell tumour is the fibromatoid cell reaction to a stimulus is reasonable, as it has been shown that:

1. The normal granulosa cell takes origin from a fibromatoid cell.
2. The tumour of the granulosa cell, when undifferentiated, has the appearance of a Sarcoma.
3. From the microphotographs shown, the appearance of the fibromatoid cells suggest that there is a morphological change from fibromatoid to granulosa cell.

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