TITLE: REVIEW AND DIAGNOSIS OF NORMAL OVARIES, THEIR VARIANCES AND NEOPLASTIC LESIONS. EVALUATION OF THE TECHNICAL QUALITY OF THE SLIDES AND INTEROBSERVER DIAGNOSTIC CONCURRENCES.

A DISSERTATION SUBMITTED IN PART-FULFILMENT FOR THE DEGREE OF MASTERS OF MEDICINE (PATHOLOGY).
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DECLARATION

This work is original and has not to my knowledge been submitted for a degree in any other university.

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DEDICATION.

To my dear mother and the memory of my dad.

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SUMMARY

A total of 407 cases were recorded under "ovarian lesions" in the department of histopathology KNH over a 5 year period, extending from 1st January 1986 to December 1990. These 407 case excluded all the lesions recorded as inflammatory .
Out of 407 recorded cases, 368 cases had either the previous histology slides retrieved or had the paraffin embedded tissue blocks retrieved and processed.

Following a microscopic review of the 368 cases, 70 of these were omitted because they did not show any ovarian tissue or the required diagnosis as outlined.

Two hundred and ninety eight cases were therefore recruited into the study . Sixty percent of these were diagnosed as normal ovaries or their variances, that is corpora lutea and graafian follicles that were apparently considered abnormal ovaries and hence removed. Eight of this had no epithelial lining and were diagnosed as simple ovarian cysts.
Forty percent of the cases were microscopically identified as neoplasm that are listed in the World Health Organization (WHO) classification namely epithelial tumours , germ cell tumours , sex cord-stromal tumours and lymphoma .

Three of these neoplastic cases had two types of tumours identified , this included two cases with diagnoses of Brenner

tumour with mucinous cystadenoma and another case with a diagnosis of benign cystic teratoma and serous cystadenoma. In two of the above cases, the tissues demonstrating the two types of tumour, were submitted in separate bottles.

The diagnoses of all the cases were independently made without prior knowledge of the original diagnoses. The second diagnoses were first made by the investigator and then reviewed by the supervisor before the final diagnoses were made. The second diagnoses were then compared with the original ones made by various pathologists within the department of human pathology on staff at the time when the tissues were submitted to the laboratory.

Out of the slides examined 66% were found to be of reasonable technical quality, adequate for a definitive diagnosis. The remaining 34% were of a less than the desired quality and required an increased amount of time to achieve a diagnosis. There was an overall diagnostic interobserver variation of 21%

.

INTRODUCTION.

The ovary is a complex organ from an embryonic, anatomic and functional standpoint. Therefore it is not surprising that its tumours are diverse, complicated and often histogenetically poorly understood (1).The gonad develops primarily from the mesoderm except for the germ cells which arise from the endoderm.

In the sexually mature females, the ovary undergoes marked cyclic changes that result in structural changes that may be grossly and microscopically mistaken for neoplasm.

Ovarian tumours account for a considerable proportion of clinically important tumours of the female with 2/3 of the cases being encountered in the reproductive age groups.

Most of these tumours are frequently large with relatively minimal symptoms and 2/3 of the malignant tumours have spread beyond the ovary at the time of the diagnosis. This late presentation and diagnosis results in a poor outcome for malignant tumours (2).

Microscopic interpretation of tissue sections on glass slides, is a subjective value judgement as are most professional decisions based on value judgements.

The quality and accuracy of this diagnostic process depends on the training and experience of the pathologist and the technical quality of the tissue preparation on the glass slide.

The technical quality of the glass slide tissue preparations, previously prepared and diagnosed were evaluated, where the original slides were not available or the staining was pale, newly prepared slides were evaluated.

BACKGROUND INFORMATION.

The ovaries are paired pelvic organs that lie on either side of the uterus close to the pelvic wall, behind the broad ligaments and anterior to the rectum.

In the adult female, the ovaries have an ovoid shape; measure approximately 3-5 cm by 1.5-3 cm by 0.6-1.5 cm and weigh an average of 5-8 g. The weight and size varies depending on the follicular status and therefore the size and weight may considerably exceed the above dimensions.

Embryologic development of the ovary starts towards the end of the fourth week when primordial germ cell, identifiable in the yolk sac, migrate into the medial portion of the urogenital ridge. Following the arrival of the germ cells, the mesodermal epithelium proliferates and forms the epithelium of the final gonad. In the presence of 46XX genetic constitution, the dividing germ cells become incorporated into a proliferating mass of surface epithelial cells. This result in a thickened cortex which precedes the organization of the adult ovary.

From the 2nd trimester to early 3rd trimester the thickened cortical mass of proliferating epithelial and germ cells are divided into small groups by strands of stromal tissue, extending from the medulla to the cortex.

The small groups of germ cells and epithelial cells are

further subdivided into primordial follicles composed of a single germ cell surrounded by a layer of epithelial cells which constitute the primitive granulosa.
In normal development each germ cell is characteristically encapsulated in its own follicle, this is associated with entry into meiosis and no further proliferation.

Some of the early proliferations that do not degenerate, remain as tubular structure called rete ovarii. Interstitial (leydig) cells develop extensively in the stroma of 2nd trimester female gonad but degenerate in most cases by term. A few cells may be found in the hilum of the adult ovary, where they may be associated with the rete ovarii and are called hilus cells.

The ovary is covered by a single focally pseudostratified layer of modified peritoneal cells that constitute the surface epithelium. These cells vary from flat, through cuboidal to columnar and several types may be seen in different areas of the same ovary.
The surface cells are separated from the underlying stroma by a distinct basement membrane.

The stroma of the ovarian cortex and medulla is composed of densely cellular whorls of spindle shaped fibroblastic cells with scant cytoplasm. The amount of stroma in the cortex and the medulla varies considerable from one person to another,

decreasing considerably in the menopause. The fibroblastic ovarian stromal cells differentiate into a variety of cells which include follicular theca interna cells, enzymatically active stromal cells, smooth muscle cells, decidua cells, endometrial stromal type cells, fat cells, stromal leydig cells and rare cells of neuroendocrine or APUD type.

At birth approximately 400,000 primordial follicle are present in the ovary and progressively decrease until they disappear at the time of menopause.

The primordial follicle consists of a primary oocyte surrounded by a layer of flattened granulosa cells resting on a thin basal lamina. Rare primordial and maturing follicles may contain multiple oocyte. The oocyte is at the interphase period and remains as such until it degenerates or undergoes follicular maturation before ovulation. Follicular maturation begins during the luteal phase of the preceding menstrual cycle and continues throughout the follicular phase with resultant ovulation.

Following ovulation of one or occasionally multiple follicles, a corpus luteum is formed. The corpus luteum is composed of an inner layer of luteinized granulosa cells and an outer layer of the theca interna lutein cells.

In the absence of fertilization, involution takes place and a fibrotic structure called corpus albicans is formed.

Early follicles degenerate and disappear without a trace. Antral follicles result in the formation of corpus fibrosum (3,4). Following the usual physiological process in the ovary, cystic follicles and cystic corpus luteum may develop. These resemble the usual structure but are larger. They measure 3-8cm whereas the normal follicles and corpus luteum are less than 2.5 cm in diameter.The enlarged cystic corpus luteum usually regress after varying amounts of time. Occasionally the may rupture with haemorrhage.

Cystic follicles are common during fetal life, throughout the reproductive period and rarely in the menopausal period. Cystic corpus luteum occur during the reproductive period and exceptionally may follow sporadic ovulations in a post menopausal woman.

Simple ovarian cysts are of unknown origin in which the lining has been destroyed and cannot be identified. Most are thought to be follicular in origin.

Ovarian tumours account for a significant proportion of clinically important tumours of the female. Ovarian cancer remains as an important cause of death in gynaecological oncology, and has been reported in new York city to be a leading cause of death among women with genital cancer.(5,6)

About two thirds of ovarian tumours are encountered in the reproductive age group and over 90% between the ages 20-65

years, less than 2% are found in children, 80-85% are benign tumours. It has been reported that the chances that a primary ovarian tumour is malignant in a patient under the age of 45 years is less than 1 in 5, but beyond the age of 45 years is almost 1 in 3.

Ovarian cancer is the 5th most common cancer in females in the United States, accounting for 5% of the total number of cancers and 25% of all the cancers of the female genital tract. It accounts for 47% of all deaths due to cancers of female genital organs. The risk at birth of a female developing an ovarian cancer sometimes in her life is almost 1.5%, and of her dying from it, almost 1% (2).

Ovarian cancer is the most lethal gynaecological malignancy in the western world with Sweden reporting the highest rates in the world, followed by Denmark (7). African data is not available but in Kenya cancer of the ovary is over shadowed by cancer of the cervix which ranks first among the genital cancers.

Japan reports rates that are 3-7 times lower than the Western countries but it has been noted that Japanese migrants to the United States have incidence rate approaching those of the American natives indicating that factors other than genetics play a role in the lower frequencies in the Japanese. Blacks in United States have a lower incidence rate of ovarian cancer

than Whites but the difference is not as great as that between the Japanese and the Americans. Incidence rates in Africa are said to be lower than those in western countries.

The aetiology of ovarian cancer is not known, epidemiology and animal investigations have not provided clues to the aetiology of ovarian cancer. There are two speculations on the pathogenesis of human ovarian cancer, the first is by Fathalla who proposed that the aetiology is due to repeated trauma on the surface epithelium following monthly ovulation . This is supported by the evidence of rarity of ovarian cancer in mammals with oestrus cycles and infrequent ovulation, the rarity of common epithelial tumours in children and women with gonadal dysgenesis and their increase incidence in nuns and single women .

Pregnancy appears to protect a woman against ovarian cancer but it is not clear whether this is due to suppression of the ovary or due to other factors.

The second speculation put forward by Woodruff and Julian proposes that carcinogenic agents enter the peritoneal cavity via the genital tract and act upon the surface epithelium and its inclusion cysts in which these agents get trapped. The nature of these substances and whether they are actually there is not known (2).

The relative frequency of ovarian neoplasm varies according to information source in different texts. In a previous United States study (8), benign cystic teratoma was found to be the single most common ovarian neoplasm accounting for 44% of all neoplasm, and was 57% more common than benign serous tumours.

Germ cell neoplasms were the most common group of benign ovarian neoplasms, whereas epithelial tumours were the most common of the malignant neoplasm. Stromal neoplasm and tumours of borderline malignancy were uncommon at all ages.
The symptoms frequently encountered in ovarian neoplasms include abdominal pain and swelling, ascites and features of widespread metastasis. Rare features include pyrexia of unknown origin and Zollinger-Ellison syndrome (9,10,11,12).

Most ovarian tumours are diagnosed late and thus have a poor prognosis. Many factors have been found to correlate with prognosis in patient with ovarian neoplasms. These include tumours stage, histologic type, tumour grade, residual disease, ascites, psammoma bodies, site of metastases, age, race, ploidy, and presenting symptoms. A multivariate analysis of these factors has shown that tumour grade and presence of residual disease are stage specific independent prognostic factors (13).

There has been an increasing body of evidence in the literature in support of a hereditary aetiology for a variety of cancers including those involving the ovary. This implies that the prognosis of ovarian cancer could be improved in patients whose aetiology is attributed to prominent genetic susceptibility if biomarkers could be identified (14). In ovarian cancers, environmental factors are thought to play an important role in the aetiology (15).

Ovarian tumour classification is controversial largely due to the incomplete understanding of the gonadal embryology and morphology.

The classification has been based on the recognition of identifiable cell type and patterns of growth. Classification of the common epithelial tumours, the statistically most important category of ovarian neoplasms follows closely the recommendations of FIGO - International Federation of Gynaecology and Obstetrics.

Following the classification by Scully (2), which is a slight modification of the WHO classification (16), ovarian neoplasm can be grouped as follows:

Table II

HISTOLOGIC CLASSIFICATION OF OVARIAN TUMORS

COMMON "EPITHELIAL" TUMORS

SEROUS TUMORS
- Benign
  - Cystadenoma and papillary cystadenoma
  - Surface papilloma
  - Adenofibroma and cystadenofibroma
- Of borderline malignancy (carcinomas of low malignant potential)
  - Cystadenoma and papillary cystadenoma
  - Surface papilloma
  - Adenofibroma and cystadenofibroma
- Malignant
  - Adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma
  - Surface papillary carcinoma
  - Malignant adenofibroma and cystadenofibroma

MUCINOUS TUMORS
- Benign
  - Cystadenoma
  - Adenofibroma and cystadenofibroma
- Of borderline malignancy (carcinomas of low malignant potential)
  - Cystadenoma
  - Adenofibroma and cystadenofibroma
- Malignant
  - Adenocarcinoma and cystadenocarcinoma
  - Malignant adenofibroma and cystadenofibroma

ENDOMETRIOID TUMORS
- Benign
  - Adenoma and cystadenoma
  - Adenofibroma and cystadenofibroma
- Of borderline malignancy (carcinomas of low malignant potential)
  - Adenoma and cystadenoma
  - Adenofibroma and cystadenofibroma
- Malignant
  - Carcinoma
    - Adenocarcinoma
    - Adenoacanthoma
    - Adenosquamous carcinoma
  - Malignant adenofibroma and cystadenofibroma
  - Endometrioid stromal sarcomas
  - Mesodermal (müllerian) adenosarcoma
  - Mesodermal (müllerian) mixed tumors, homologous and heterologous

CLEAR CELL (MESONEPHROID) TUMORS
- Benign
  - Adenofibroma
- Of borderline malignancy (carcinomas of low malignant potential)
- Malignant
  - Carcinoma and adenocarcinoma

BRENNER TUMORS
- Benign
- Of borderline malignancy (proliferating)
- Malignant

MIXED EPITHELIAL TUMORS
- Benign
- Of borderline malignancy
- Malignant

UNDIFFERENTIATED CARCINOMA

UNCLASSIFIED EPITHELIAL TUMORS

SEX CORD-STROMAL TUMORS

GRANULOSA-STROMAL CELL TUMORS
- Granulosa cell tumor
- Tumors in the thecoma-fibroma group
  - Thecoma
  - Fibroma
  - Unclassified
    - Sclerosing stromal tumor
    - Others

SERTOLI-LEYDIG CELL TUMORS; ANDROBLASTOMAS
- Well differentiated
  - Sertoli cell tumor; tubular androblastoma (tubular adenoma of Pick)
  - Sertoli cell tumor with lipid storage; tubular androblastoma with lipid storage (folliculome lipidique of Lecène)
  - Sertoli-Leydig cell tumor (tubular adenoma with Leydig cells)
  - Leydig cell tumor; hilus cell tumor
  - Stromal Leydig cell tumor
- Of intermediate differentiation
- Poorly differentiated (sarcomatoid)
- With heterologous elements

GYNANDROBLASTOMA

UNCLASSIFIED
- Sex cord tumor with annular tubules
- Others

LIPID (LIPOID) CELL TUMOR

GERM CELL TUMORS

DYSGERMINOMA

ENDODERMAL SINUS TUMOR

EMBRYONAL CARCINOMA

POLYEMBRYOMA

CHORIOCARCINOMA

TERATOMAS
- Immature
- Mature
  - Solid
  - Cystic
    - Dermoid cyst (mature cystic teratoma)
    - Dermoid cyst with malignant transformation
- Monodermal and highly specialized
  - Struma ovarii
  - Carcinoid
  - Strumal carcinoid
  - Others

MIXED FORMS

MIXED GERM CELL AND SEX CORD–STROMAL TUMORS

GONADOBLASTOMA
- Pure
- Mixed with dysgerminoma or other form of germ cell tumor

OTHERS

SOFT TISSUE TUMORS NOT SPECIFIC TO OVARY

UNCLASSIFIED TUMORS

SECONDARY (METASTATIC) TUMORS

TUMOR-LIKE CONDITIONS

PREGNANCY LUTEOMA

HYPERPLASIA OF OVARIAN STROMA AND STROMAL HYPERTHECOSIS

MASSIVE EDEMA

SOLITARY FOLLICLE CYST AND CORPUS LUTEUM CYST

MULTIPLE FOLLICLE CYSTS (POLYCYSTIC OVARIES)

MULTIPLE LUTEINIZED FOLLICLE CYSTS AND/OR CORPORA LUTEA (HYPERREACTIO LUTEINALIS)

ENDOMETRIOSIS

SURFACE-EPITHELIAL INCLUSION CYSTS (GERMINAL INCLUSION CYSTS)

SIMPLE CYSTS

INFLAMMATORY LESIONS

PAROVARIAN CYSTS

Common epithelial tumours are considered to be derived from the surface epithelium (coelomic epithelium-mesothelium) and adjacent ovarian stroma. They constitute over two third of all the primary neoplasms and almost 90% of all malignant ovarian neoplasms. The cause of the high neoplastic potential of the ovarian surface epithelium is not known. Although the epithelial tumours show a wide histologic variation, they are thought to have a common ancestry which is supported by the occurrence of a combination of the various histological types of epithelial tumours.

The difficulty of differentiating a borderline from malignant tumour significant and also varies from one subtype of common epithelial tumour to another being greatest in tumours characterized by the presence of small locules, glands or nests.

Patients presenting with ovarian cancers while still young have a better prognosis. This is possibly due to the fact that younger patients are otherwise more fit to withstand aggressive surgery and cytotoxic therapy not normally employed in older patients (5).

The clinical implications of lymphocytic infiltration has been shown to be a good prognostic indicator in cervical carcinoma. A similar response has been suggested in trophoblastic disease and breast cancer.

An association between the prognosis and intensity of lymphocytic infiltration seen in histologic section of ovarian adenocarcinoma has been demonstrated. The lymphocytic infiltration is presumed to be an expression of the local host response and this has been suggested as a possible morphologic indication of tumour behaviour and response to therapy (17).

Sex cord- stroma cells tumour include all the neoplasm derived from the sex cord or primitive cortical lobules and the specialized stroma (mesenchyme) of the developing gonad. The generic term reflects differing views of gonadal embryology.

These tumour accounts for approximately 6%-8% of all ovarian tumours and include the majority of functioning tumours with clinical manifestation. Fibromas which are almost never associated with endocrine manifestations account for approximately half of all such tumours (2,3).
The clinical symptoms associated with these tumour are of endocrine origin. The tumours may produce either oestrogen and/ or androgens. The effect of the hormones produced will depend on the age of the patient .

Virilizing tumours are uncommon being less than 1% of all ovarian tumour. Some hilar cell tumour have been associated with endometrial abnormalities and carcinoma. It has been suggested that premenopausal women tend to show virilization

whereas postmenopausal women present with bleeding and signs of oestrogen activity (18).
Sclerosing stromal tumours are said to occur more commonly in the under 30 year old patients differing from other sex cord-stromal tumours which have a peak incidence in the 5th and 6th decade. Over 70% of the reported cases are under 30 year of age (19).

Germ cell tumours of the ovary are composed of a number of histologically different tumour types that are believed to be derived from the primitive germ cell of embryonic gonad. The concept of germ cell tumour as a specific group of gonadal neoplasm is based on :- i. the common histogenesis of these neoplasm ii. the relative frequent presence of histologically different neoplastic elements within the same tumour mass iii. the presence of histogenetically similar neoplasm in extra gonadal locations along the line of migration of the primitive germ from the wall of the yolk sac to the gonadal ridge iv. the remarkable homology between the various tumours in the male and the female (2,3).

The germ cell tumours constitute the second largest group of ovarian neoplasms after the common epithelial tumours. In Europe and North America, they comprise approximately 20% of all ovarian neoplasms but in Asia and Africa they constitute a much larger percentage of the ovarian tumours.

Germ cell tumours are encountered most frequently in the first to the sixth decade though they have been observed during fetal life. In children and adolescents, more than 60% of ovarian neoplasms are of germ cell origin and a third of them are malignant. In the adults the great majority of germ cell tumours (95%) are benign and consist of mature cystic teratomas (dermoid cysts).

Dysgerminoma is a rare germ cell tumour that has a high cure rate which is markedly in contrast with the low rates associated with other malignant ovarian tumour (20). It occurs principally in young females with 80% of the cases seen in patients less than 25 years of age. The tumour just like the seminoma is highly radiosensitive. The majority of metastatic germ cell tumours of the ovary appear to be curable provided that effective treatment is provided early. This has been shown in studies involving the treatment of malignant teratomas and dysgerminomas (21).

Malignant components arising in benign cystic teratoma of the ovary are rare. It occurs in 1 to 2% of dermoid cysts and the commonest histologic type is the infiltrating squamous cell carcinoma. Other malignant types include adenocarcinoma, the second commonest type, carcinoid, malignant melanoma and a variety of sarcomas (2,3,22). Epidemiologic data showing that ovarian teratomas occur at an early age and often are

bilateral, supporting a genetic theory, as these characteristics are common to hereditary tumours. A few familial occurrences of benign cystic teratomas have been reported thus emphasizing the possible familial factor involved in the development of these tumours (23). It is suggested that careful gynaecologic examination and follow up of relatives of such patients may better disclose the true incidence of the familial occurrences of these ovarian neoplasms.

A few cases of spontaneous rupture of benign cystic teratomas has been reported. This is in keeping with the low rates of spontaneous ruptures of ovarian cysts at approximately 2% . Benign cystic teratoma have a thickened capsule hence they do not rupture easily (24).

The other types of germ cell tumours are rare and often occur in association with other germ cell tumours. Primary choriocarcinoma of the ovary, may be gestational or non gestational. Pure non-gestational choriocarcinoma of the ovary is extremely rare though it has been reported (25).

The ovary is also capable of developing a heterogenous group of tumours that are not unique to it. These tumours are thought to arise from the supporting tissues and pose difficult problems in diagnosis, histogenesis, and therapy. They have to be differentiated from primary ovarian tumours containing

mesenchymal tissue, as well as from metastatic neoplasms affecting the ovary (2,3).

Primary malignant lymphomas of the ovary are extremely rare. Lack of lymphocytic aggregates in the ovary has raised doubts as to the actual existence of primary ovarian lymphomas (26). Burkitt's lymphoma is the most common malignant lymphoma in which involvement of the ovary manifest itself clinically.

Metastatic ovarian tumours may originate from a variety of organs and tissues outside the female genital tract, but the most common tumours to metastasize to the ovary originate from the intestines, stomach, breast, and haemopoietic tissue (27). The incidence of metastatic tumours varies due to the differences in types of studies done whether autopsy findings and/or surgical specimen.

Quality control and quality assurance programmes are designed to improve the accuracy of diagnosis. It has been demonstrated that if there is consistency of intraobserver diagnosis and if there is interobserver agreement with a group of pathologist, the diagnosis is more likely to be correct than if there is poor interobserver agreement or interobserver variation (28).
Accepted standards for a 'correct diagnosis' can be that made by recognized experts, a high concensus dignosis by a group of

ten to twenty pathologist or based on biologic behaviour of the lesion (outcome). Factors that enhance accurate diagnosis are;- i. a well chosen biopsy to represent the lesion, properly fixed and with adequate clinical data provided. ii. proper examination of the gross by the pathologist with appropriate samples taken. iii. Good technical processing by adequately trained and experienced technologists who have available appropriate and other necessary resources needed for sectioning, staining and mounting. The above activities are objective and can therefore be controlled. These are referred to as the quality control aspect of the diagnostic process.

Quality assurance is the estimation of the accuracy and consistency (precision) of results. Interpretation of sections on the glass slides is a subjective value judgement, as are most professional decisions based on value judgements. The quality and accuracy of this diagnostic process depends on the training and experience of the reporting pathologist and the technical quality of the tissue preparation on the glass slide.

A quality assurance programme has both an internal and external component which are basically aimed at improving the diagnostic performance and hence quality patient care (28,29). The internal components of quality assurance in anatomic pathology includes well trained personnel of all cadres, surgical and autopsy specimens of good technical quality, pathologists

reports that meet the defined needs and performance evaluation using whatever means that are appropriate for the given setup.

The external component of a quality assurance programme is used to evaluate and compare the overall performance of several institutions. These provides assurance not only to the professionals and institutions but also to the public at large, that performance is being evaluated by independent bodies and identified deficiencies are corrected (28).

GENERAL OBJECTIVES.

The general objective of this study was to determine the normal ovarian variants and neoplastic lesions received and processed in the laboratory of histopathology KNH, and to also determine the technical quality of diagnostic material and the consistency of diagnoses. .

SPECIFIC OBJECTIVES.

1. To retrieve from histopathology records, the reports of all those cases reported as normal ovaries or their variances and neoplastic lesions of the ovaries within the period 1st January 1986 to 31st December 1990.
2. To review the histology of all such cases and classify them using the WHO classification.
3. To determine the number of the various ovarian neoplasm and the number of normal ovaries and their variances processed within the study period.
4. To determine the age distribution of the ovarian neoplasm.
5. To determine the technical quality of the sectioning and staining of the diagnostic glass slides.
6. To determine the interobserver variation of the diagnoses made.

MATERIALS AND METHODS

The laboratory files bearing duplicate histology records of all the ovarian tissue processed in the department of histopathology within the period 1st january 1986 to 31st december 1990 were identified and retrieved. The laboratory numbers of all cases recorded as normal ovarian tissue, their variances and neoplastic conditions were listed down. Corresponding histology slides were retrieved and assessed for suitability for microscopy. The tissue blocks of the cases with missing or unsuitable slides were retrieved and new slides made. Those cases with both slides and tissue blocks missing or with inadequate material were omitted from the study.

The gross description of those included into the study was noted. All the slides reviewed were stained with haematoxylin and eosin. Following the review of the recruited cases, a diagnosis was made without knowledge of the original diagnosis and compared with the original report. Where there was a discrepancy, the slides was reviewed a second time and a final diagnosis made.

The technical quality of each slide was assessed and graded as excellent, average quality, poor but diagnosable and very poor. The grading took into account the tissue fixation, sampling, dehydration, quality of mounting media, cutting, stain and the evaluationof the overall quality.

RESULTS

Two hundred and ninety eight (298) cases were included in the study. Of these 178 (60%) were grouped under normal ovaries and their variances and 120 (40%) were grouped under neoplastic lesions

The breakdown of the two groups was as follows:

Table 1: Normal ovaries and their variances.

Diagnosis	No of Cases
Corpus luteum	102 (57%)
Graafian follicles	16 (9%)
Simple cysts	8 (5%)
Normal ovary	52 (29%)
Total	178 (100%)

Cases recorded under normal ovary showed normal ovarian stroma with unremarkable follicles and corpora lutea.

Those grouped under corpus luteum and graafian follicles had the bulk of tissue showing the corresponding structure with minimal ovarian stroma. Cases recorded under simple ovarian cysts had benign features and had no identifiable epithelial lining.

Cystic corpus luteum represented 57% of all the normal variants, followed by normal ovaries 29% , cystic follicles 9% and simple cysts 5% .

Table 2: Tumours.

Diagnosis	No of Cases
Epithelial tumours	57 (47%)
Germ cell tumour	45 (38%)
Sex cord - Stromal cell tumour	16 (13%)
Lymphoma	2 (2%)
Total	120 (100%)

A total of 120 neoplasm were analyzed. Epithelial tumours comprised the largest group 47% followed by the germ cell tumours 38% , sex cord-stromal tumours 13% and the lymphomas 2%

The 4 categories of tumours were analyzed for the specific tumour types and the results were as follows;

Table 3: Epithelial tumours

Type of tumour	No of Cases
Serous	
Cystadenoma	7
Papillary cystadenoma	4
Adenofibroma	5
Cystadenoma borderline	4
Cystadenocarcinoma	8 (49%)
Mucinous	
Cystadenoma	8
Cystadenoma borderline	1
Cystadenocarcinoma	2 (19%)
Endometrioid adenocarcinoma	2 (4%)
Brenner tumours	3 (5%)
Anaplastic carcinoma	8 (14%)
Infiltrating adenocarcinoma	5 (9%)
TOTAL	57 (100%)

Serous tumours were the commonest of the epithelial tumours comprising 49% , followed by the mucinous tumours 19%, endometrioid tumours 4% were the least commonest. Anaplastic tumours together with infiltrating adenocarcinomas comprised 23% of these tumours.

Table 4 : Germ cell tumours

Type of tumour	No of Cases
Dysgerminoma	3 (7%)
Endodermal sinus tumour	1 (2%)
Benign cystic teratoma	39 (89%)
Struma Ovarii	1 (2%)
Total	44 (100%)

Out of the 44 germ cell tumours seen, benign cystic teratomas formed the largest group (89%), followed by the dysgerminomas (7%) with one each of endodermal sinus tumour and struma ovarii.

Table 5: Sex Cord- Stromal cell tumours

Type of tumour	No of Cases
Granulosa cell	7 (44%)
Thecoma	3 (19%)
Fibroma	2 (12%)
Leydig cell (hilar cell)	3 (19%)
Sertoli - Leydig cell tumour	1 (6%)
TOTAL	16 (100%)

These were a total of 16 sex cord-stromal cell tumours. Granulosa cell tumours were the commonest 44% .

Table 6: Mixed Germ cell and Sex cord-Stromal tumours

Type of tumour	No of Cases
Gonadoblastoma	1

Table 7:Lymphoma

Type	No of cases
Burkitts	1
Lymphoma(unclassified)	1
TOTAL	2

The age distribution of the tumour types was as follows:

Table 8: Epithelial tumours

Age in yrs	0-10	11-20	21-30	31-40	41-50	51-60	>60	U^
Serous Cystadenoma & papillary cystadenoma	-	1	3	1	-	2	-	4
Serous Cystadeno-fibroma	-	1	2	2	-	-	-	-
Serous border line & cyst adenoca.@	-	-	1	5	2	2	1	1
Mucinous Cystadenoma	-	-	5	-	1	1	-	1
Mucinous B/L* &adenoca. @	-	-	-	-	1	1	1	-
Endometrioid Carcinoma	-	-	1	-	-	-	-	1
Brenner Tumour	-	-	-	-	-	-	2	1
Anaplastic Carcinoma	1	-	1	-	2	-	2	2
Infiltrating adenoca. @	-	-	2	-	2	-	-	1
TOTAL	1	2	15	8	8	6	6	11

* B/L stands for border line.
@ Adenoca stands for adenocarcinoma.
U^ Stands for unknown

A total of 57 epithelial tumours were analyzed for age, the 21-30 year group had the largest number of cases 15 (26%),

followed by the unknown 11 (19%) The unknown included all the cases recorded as adults and those without any age given.

Table 9:Germ cell tumours and mixed Germ cell sex cord - stroma tumour

Age in years

Tumour type	0-10	11-20	21-30	31-40	41-50	51-06	>60	U^
Dysgerminoma	-	-	-	-	-	-	-	3
Endodermal Sinus tumour	-	1	-	-	-	-	-	-
B/cystic * teratoma	1	7	16	4	-	2	-	9
Struma ovarii	-	-	-	-	1	-	-	-
Gonadoblasto	1	-	-	-	-	-	-	-
TOTAL	2	8	16	4	1	2	-	12

* B/cystic stands for benign cystic.
U^ stands for unknown.

The 21-30 age group had the largest number of cases 16(36%), followed by the unknown 12(27%).

Table 10: Sex Cord - Stromal cell tumour.

age in years.

Tumour type	0-10	11-20	21-30	31-40	41-50	51-60	>60	U^
Granulosa	-	-	3	-	-	2	-	2
Thecoma	-	-	2	-	-	-	-	1
Fibroma	-	-	1	-	-	-	-	1
Sertoli/L *	-	-	1	-	-	-		-
Leydig(Hilus)	1	2	-	-	-	-	-	-
TOTAL	1	2	7	0	0	2	0	4

* Sertoli/L represents sertoli/Leydig
U^ stands for unkown.

The 21-30 year group had the largest number of cases 7(44%), the unknown followed with 4(25%).

The two lymphoma cases had no ages indicated in the histology request forms.

Table 11:Quality of technical preparation.

Grading	No of Cases
Very poor	8 (3%)
Poor/diagnosable*	93 (31%)
Average quality	191 (64%)
Excellent	6 (2%)
Total	298(100%)

* Should read 'poor but diagnosable'.

In the above grading, the grade very poor refers to slides in which interpretation was made with a lot of difficulties due to a number of technical defects. Excellent implied that the preparation was close to ideal. Poor but diagnosable implied that the slide could be diagnosed but often required a great deal of time. Average quality refers to slides that were better than "diagnosable " often there were multiple slides which varied considerably in quality but examination of a number of the slides provided a reasonable quality for diagnosis.

Table 12:Interobserver variation.
Original diagnosis versus second diagnosis.*

Diagnosis	cases
Benign lesion-normal ovary/variances	28(42%)
Benign tumours-benign mainly tumours	11(16%)
Malignant tumours-malignant tumours	8(12%)
Malignant tumours-borderline tumours	2(3%)
Malignant tumours-benign tumours	6(9%)
Benign lesion-malignant tumour	1(2%)
Malignant tumours-normal ovaries	2(3%)
Sex cord stromal tumours **	9(13%)
Total	67(100)

*See appendix 2 for further details.

**There were nine tumours in this group with different diagnoses. Seven of these had an original diagnosis of granulosa theca cell tumours with five having a second diagnosis of granulosa cell tumour and two having a second diagnosis of thecoma. The final two, one had an original diagnosis of sex cord tumour with annular tubules whereas the second diagnosis was gonadoblastoma, and the last one was originally diagnosed as fibroma with a second diagnosis of thecoma.

The benign - normal category comprising 42% was the largest group with differing diagnoses

DISCUSSION.

The ovary under the influence of gonadotrophins under goes cyclic changes that result in phenomena that can be mistaken clinically for neoplasms. Pelvic ultra sound of sexually mature females commonly shows unilocular cystic ovarian structures usually less than 8cm in diameter that are follicular in origin, these cystic structures regress with time (30). At laparotomy, other cystic structures that are of corpus luteum origin may be encountered. These types of cystic structures should almost always be macroscopically recognisable because of their characteristic yellow colour and occasional haemorrhagic contents. The ability to differentiate normal variations of ovaries from tumours will depend on the training and experience of the gynaecologist.

In this study, 60% of the cases were reported as variations of normal ovaries. Nineteen of the fifty two normal ovaries processed, were submitted together with hysterectomy specimens most of which were removed for leiomyomata. In a number of cases where laparotomy was done for an ectopic pregnancy, the surgeon presumably considered corpus luteum of pregnancy in the opposite ovary as a tumour or neoplastic cysts and removed it. Haemorrhagic corpus luteum may clinically be mistaken for an endometriotic cysts though none was encountered in this study. The majority of the cases with normal ovaries or their variants were in the reproductive age group.

Cystic corpora lutea were the most commonly encountered normal ovarian variants which is consistent with the majority of the patients being in their reproductive age group.

Two previous studies done by Ojwang and Machira on patients admitted to Kenyatta national hospital (31,32), also found common epithelial tumours to be the commonest types.
Of the epithelial tumours, the serous tumours (49%) were the commonest which is similar to that reported in the two previous studies mentioned above. The anaplastic and infiltrating adenocarcinoma of unidentifiable pattern together formed the second largest group (23%). Due to incomplete data recorded in the laboratory files, it was not possible to determine the proportion of these tumours that were metastatic. Endometrioid tumours were the least common. The data available did not provide evidence suggestive of a concomitant tumour in the endometrium.

Germ cell tumours comprised 38% of the cases. These were the second commonest and similar to that reported in the literature. Of the germ cell tumours in this study, Benign cystic teratomas were the majority (89%), which is in contrast to Machira's study which reported dysgerminoma as the commonest germ cell tumours (32). These tumours in the current study were also the commonest neoplasm which is in agreement with other studies (22).

There was no single case of malignant teratoma reported within the study period. Germ cell tumours were reported in all the age groups with the exception of those over 60 years. The youngest case of a benign cystic teratoma is reported in literature to have occurred in a three month old baby (33).

Sex cord-stromal tumours comprised 13% of all the tumours. The commonest type was the granulosa cell tumour (44%) and all the cases had varying amounts of theca cells. The majority of these tumours showed a diffuse histologic pattern with poorly formed or no Call-Exner bodies. These tumours are said to occur at any age including stillborn though the majority occur in the post menopausal women (34). Three of the cases were in the 21-30 age group, two were in the 51-60 age group and the age of two cases were unknown . Granulosa cell tumours may also be found in clinically normal ovaries (35). There were three cases that had only theca cell and were reported as thecoma.
Leydig cell tumours were 19% of all the sex cord-stromal tumours and were seen in patients under 20 years of age.
The majority of the sex cord-stromal tumours were seen in the 21-30 age group.

Out of the 120 tumours reviewed, the largest number of patients (32%) were in the 21-30 year group followed by patients unknown age (21%). The under 10 year group had the least number of patients (3%).

Out of the 278 cases analyzed 67 had different diagnoses resulting in an interobserver variation of 24% . The majority of these cases (45%), had a diagnosis of a benign lesion in the original report and a second diagnosis of normal ovary. The main problems relating to consistency of pathologist diagnosis appears to due to 'is a cystic corpus luteum normal or is it a pathologic corpus luteum cyst', the use of a standard terminology (classification), and recognizing the differences between graafian follicle and corpus luteum. When pathologist persist in calling normal cystic structures cysts, it perpetuates the belief at the clinical level that removing all cystic lesions is the proper treatment.

Eighteen percent of the cases with differing diagnoses had both diagnoses reported as benign but of different types. There did not appear to be any pattern or reason for the interobserver variation. In a few of the cases the original diagnosis may have been made on a slide not available for the second diagnosis.

Ten percent of the cases had both the diagnoses reported as malignant but differed in the tumour types. This group reflects the fact that the best interobserver agreement is achieved in common lesions and in the case of neoplasms between benign and malignant. In a large series of breast lesions, there was 98% agreement in the diagnostic placing of lesions into the two

categories of benign and malignant. There was considerable disagreement on the definitive classification in each group (28).

Two of the cases were originally reported to be malignant but the second diagnosis was borderline.

Six (9%) of the cases were diagnosed initially as malignant. The second diagnosis was benign. Four of the above cases with initial diagnosis of malignant tumour were called the benign counterpart. The other two cases were called benign of a different tumour type.

Only one case was initially reported as benign with the second diagnosis being a malignant tumour, a case of endometrioid carcinoma.

Two cases originally reported as malignant had a second diagnosis of normal ovary.

The technical quality of the majority of the slides examined (64%) were graded as average technical quality and only 2% were graded as excellent. This was attributed to the low quality of the reagent used. Of the remaining 34% , diagnosis was only possible after a considerable amount of time was spent on the slides.

The majority of the slides examined were newly prepared by one individual but the original slides had been prepared by various members of the technical staff in the histopathology laboratory within the study period.

CONSTRAINTS.

1. Poor filing and storage facilities of both the histology slides and paraffin embedded tissue blocks resulted in undue delay in their retrieval with misplacement of some and hence 109 (27%) of the total recorded cases had to be omitted from the study.This almost certainly created a bias of the data compiled.
2. Use of poor quality reagents resulted in histology slides whose use was limited in terms of time and cannot be used for comparative study in the future.
3. Illegible and incomplete clinical data on the patients request forms limited the usefulness of the results generated and created a bias. Based on this study and the day to day evaluation, the gross description of the tissues submitted were generally very brief and inadequate to be of value in coming to a definitive diagnosis.
4. Inadequately sampled and bad fixation of tissue created difficulties in diagnosis in some of the cases.

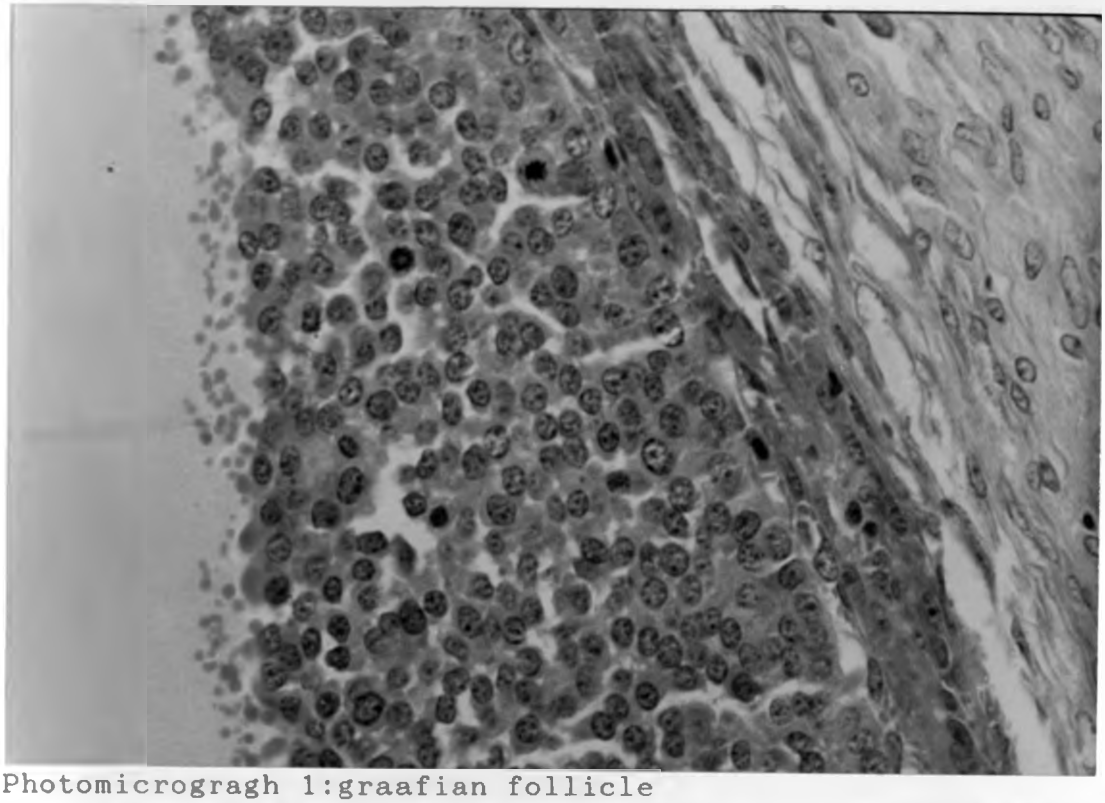
CONCLUSIONS.

1. Too many normal ovaries are being removed.
2. There is a high degree of interobserver variation within the department.
3. There is need for a technical quality control program and a quality assurance program within the department of human pathology including the use of a standard nomenclature in order to achieve a greater degree of consistency of diagnosis.

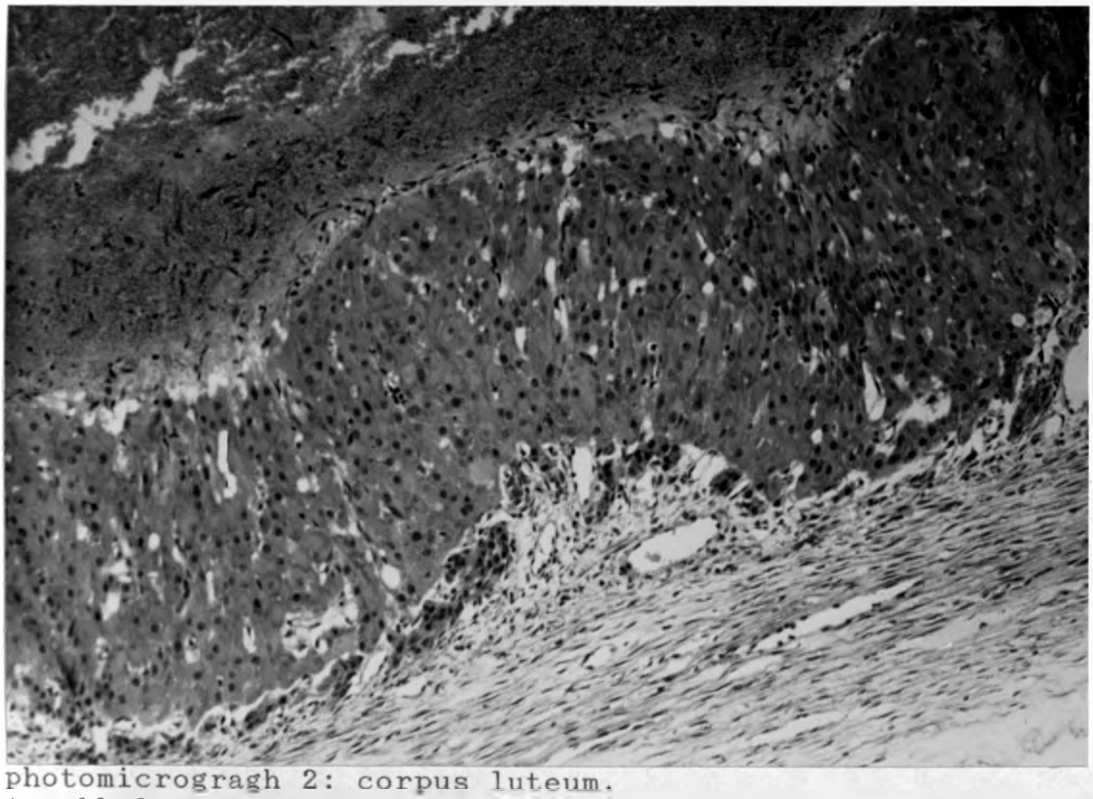
RECOMMENDATIONS:

1. Improvement of the filing and storage facilities, with the slides and tissue blocks preferable stored in a separate room from the main laboratory. This would ensure easy and complete retrieval not only for case studies but also for day to day diagnoses.
2. Use of adequate quality reagents would in the long run be more economical. This would eliminate the need to reprocess tissue blocks except in breakages.
3. Collaboration with the department of obstetric and gynaecology on means of minimizing the number of normal ovaries removed at laparotomy. If necessary a collaborative study relating clinical, intra operative and microscopic finding could be carried out, especially for clinical identification of normal variances of cystic ovarian structures which created the largest number of problems.
4. Introduce a consistency of nomenclature and the reporting language within the Department of human pathology.
5. Feedback to and encouragement of the technical staff to maintain a high standard of technical quality slide preparation.

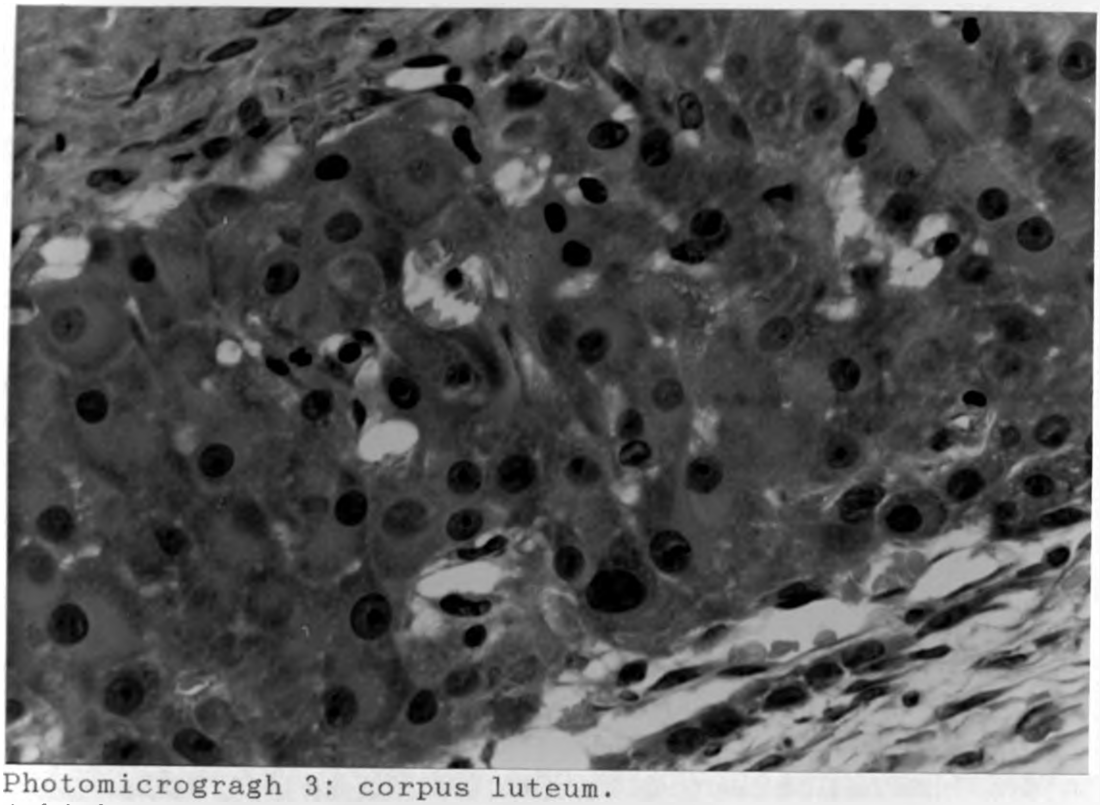
6. Introduction of an internal quality assurance programme in surgical pathology and cytology. Introduction of a national quality assurance program that would involve all the laboratories and practising pathologist within Kenya. Ideally the initiation of an external quality assurance program involving East, Central and Southern Africa would enhance the quality of patient care.



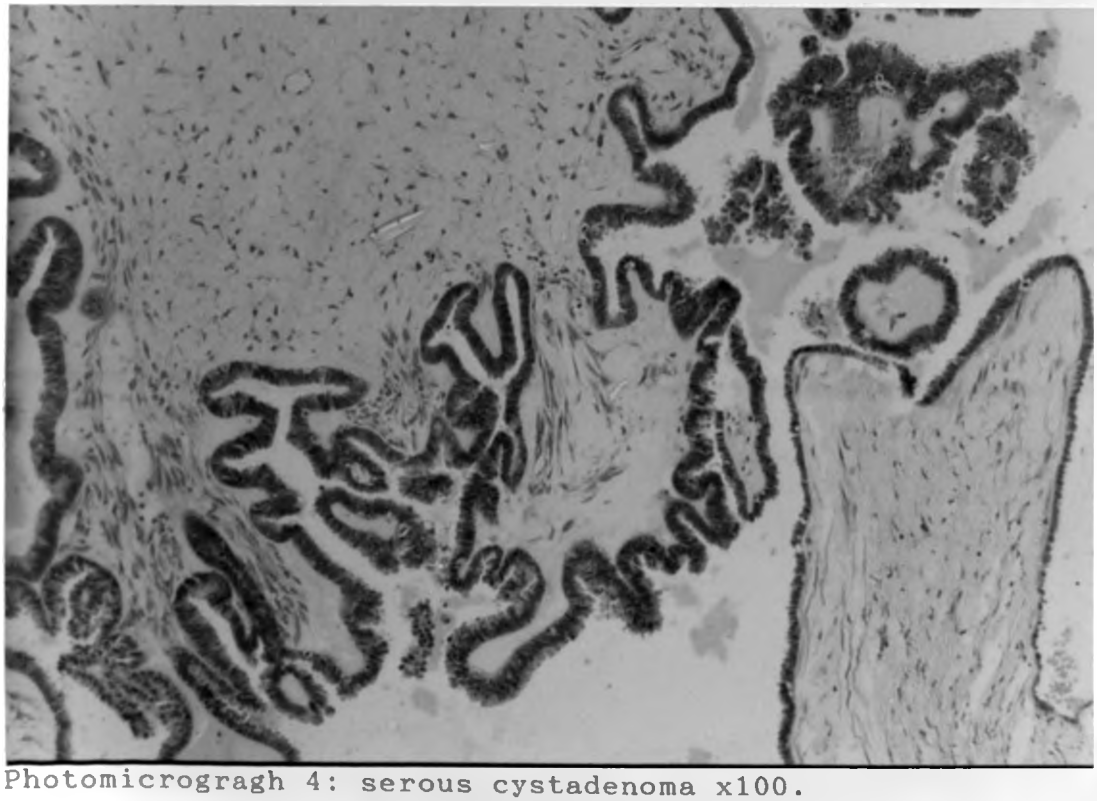
Photomicrogragh 1:graafian follicle
granulosa cell occupy the upper three quarters with mitoses near the top x400.



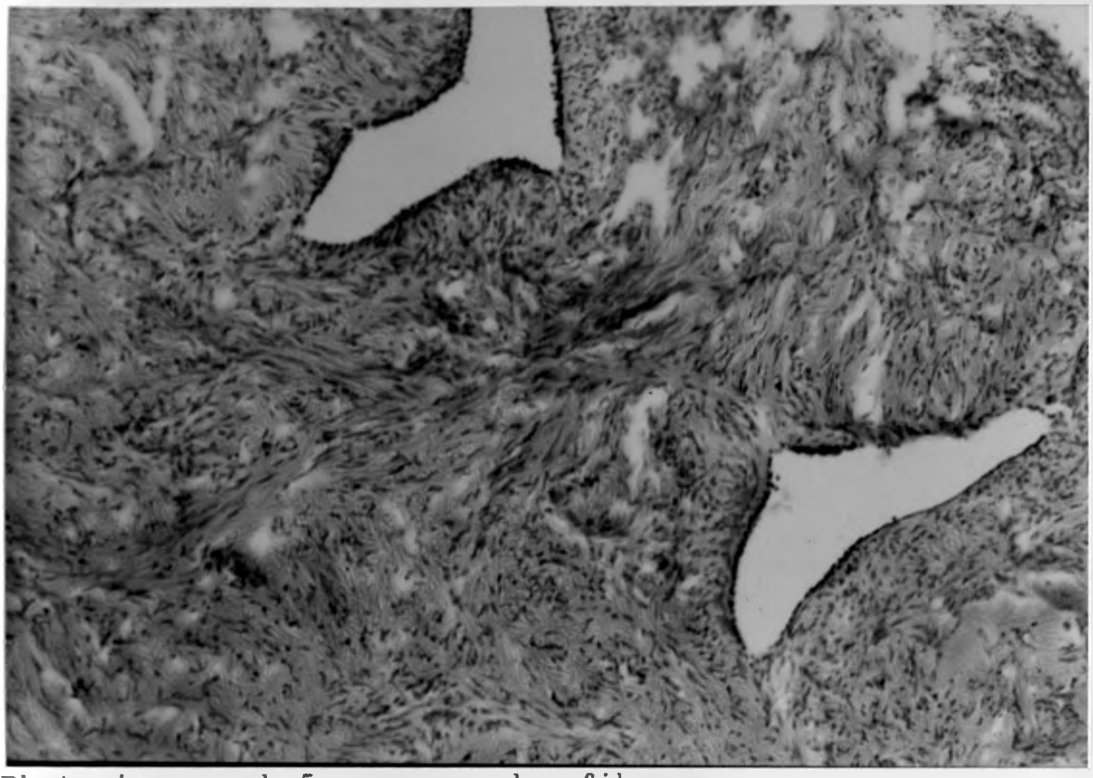
photomicrogragh 2: corpus luteum.
A well formed layer of granulosa lutein cells and theca lutein cells. There is haemorrhage in the center of the corpus luteum (top left) x100.



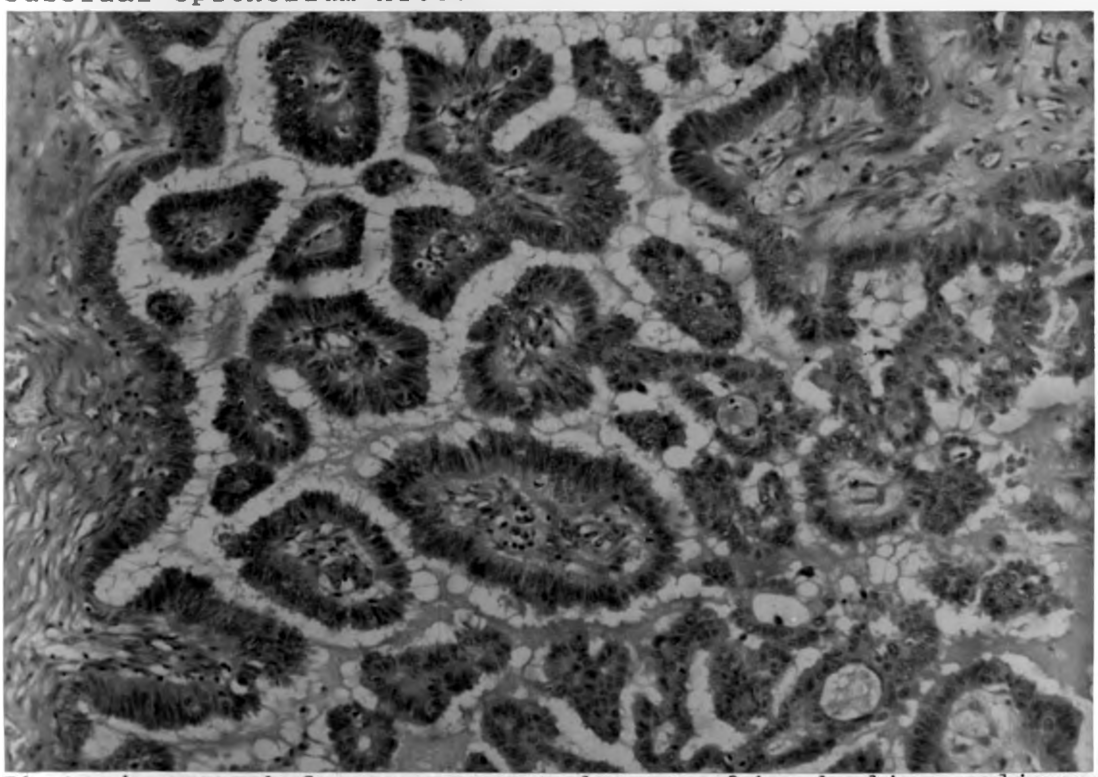
Photomicrogragh 3: corpus luteum.
A higher magnification of the granulosa lutein cells x400.



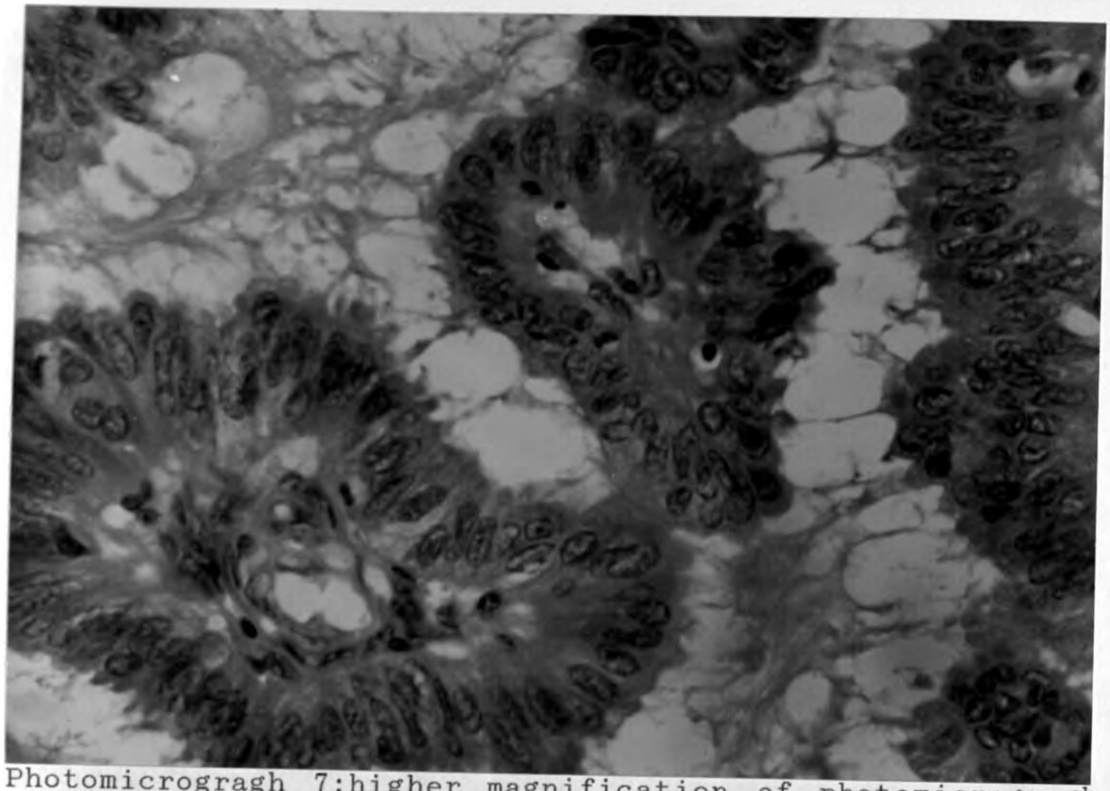
Photomicrogragh 4: serous cystadenoma x100.



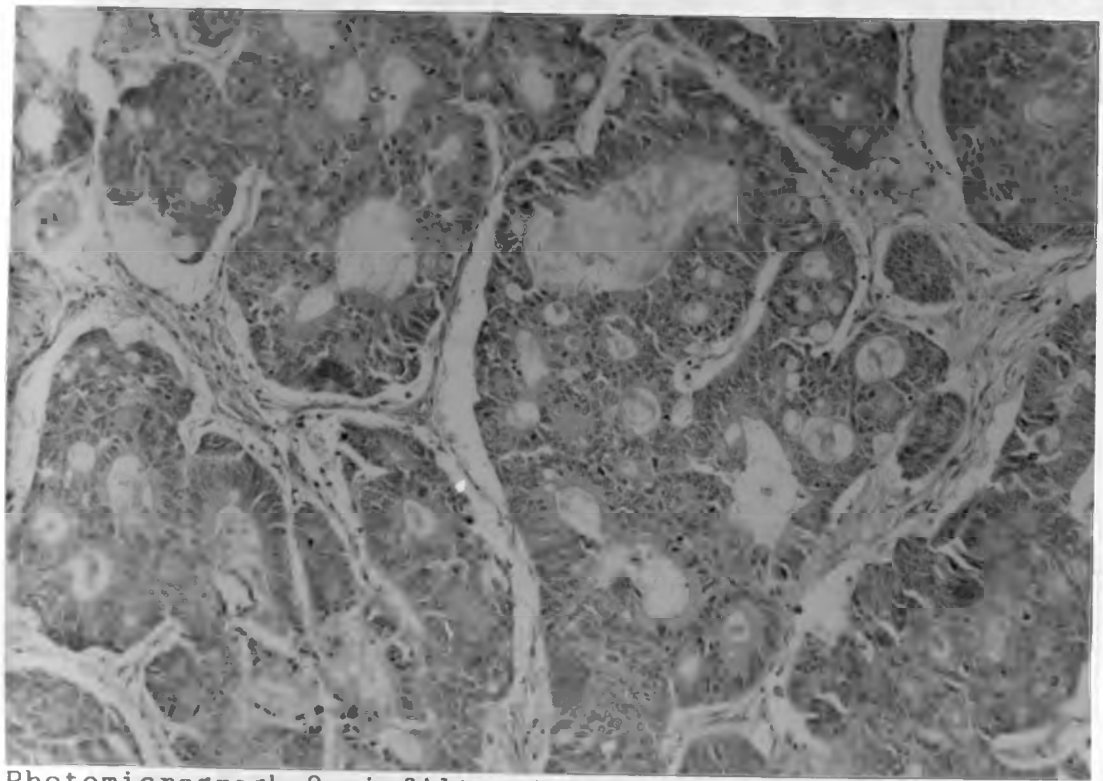
Photomicrogragh 5: serous adenofibroma.
Fibrous stroma with cystic glands lined by a single layer of cuboidal epithelium x100.



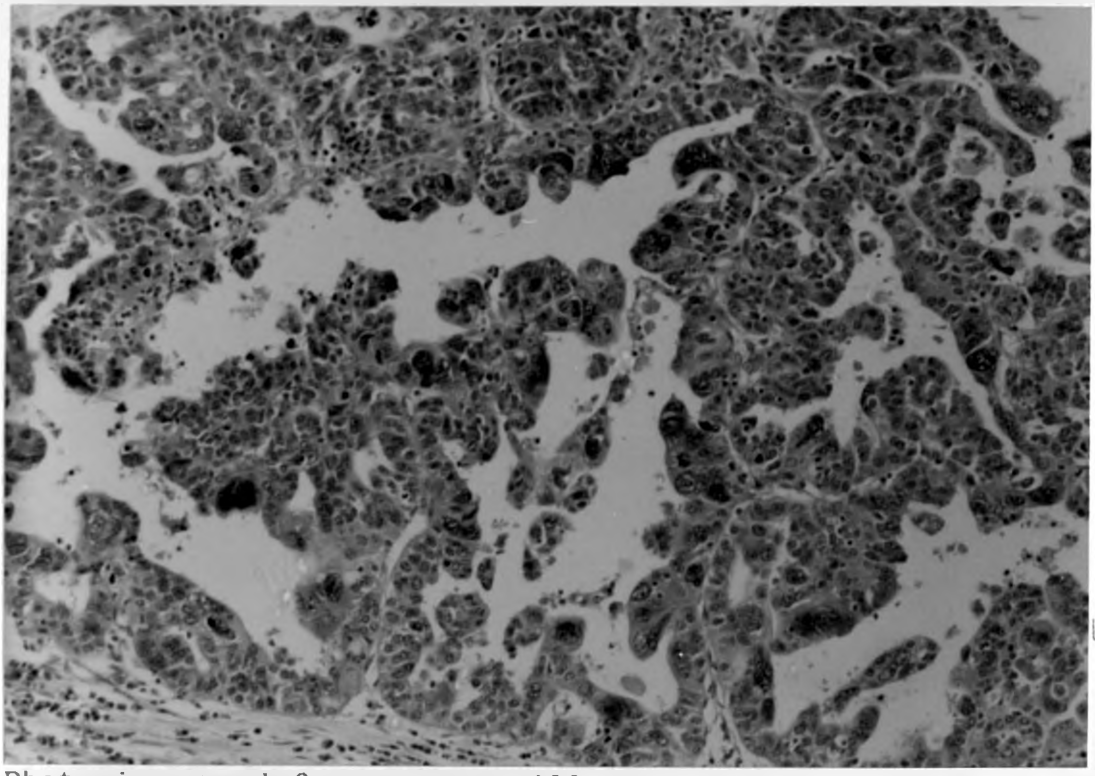
Photomicrogragh 6: serous cystadenoma of borderline malignancy x100



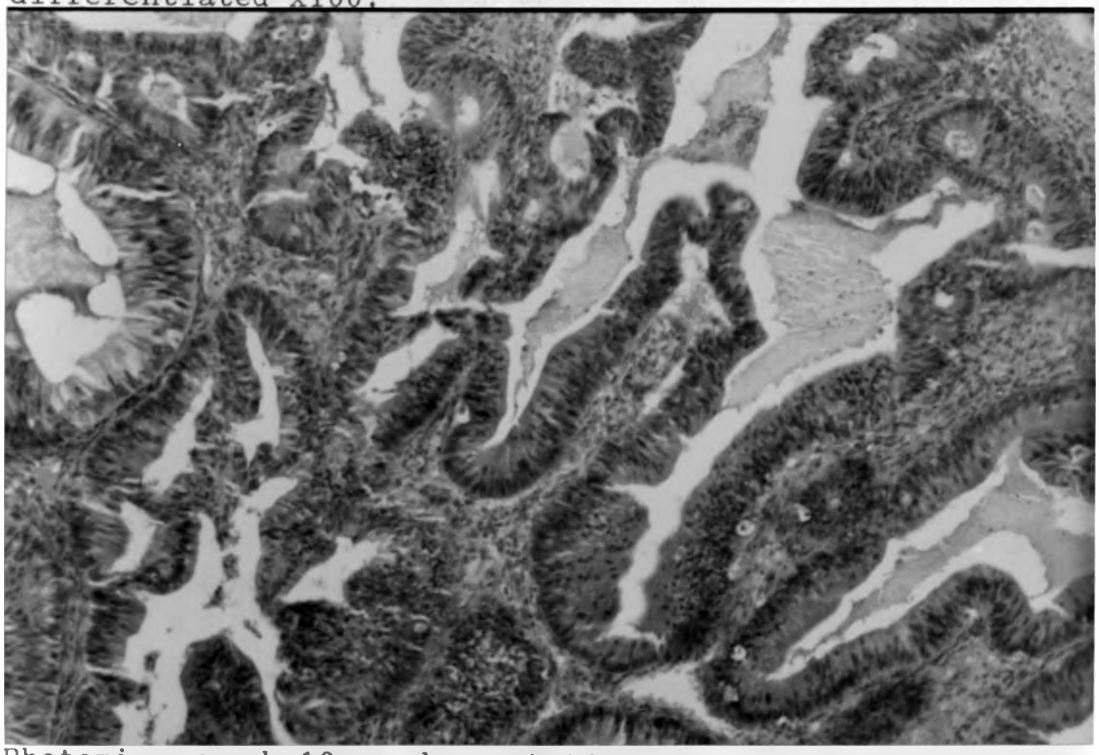
Photomicrogragh 7:higher magnification of photomicrogragh 6 x400



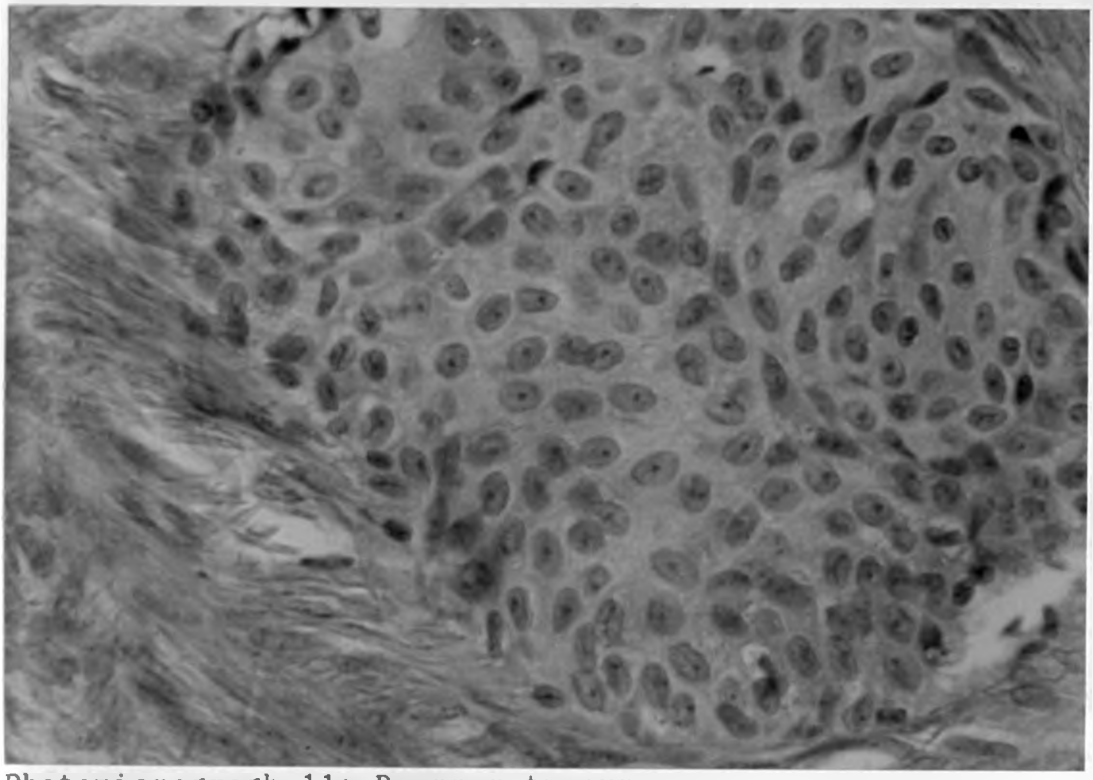
Photomicrogragh 8: infiltrating serous adenocarcinoma x100.



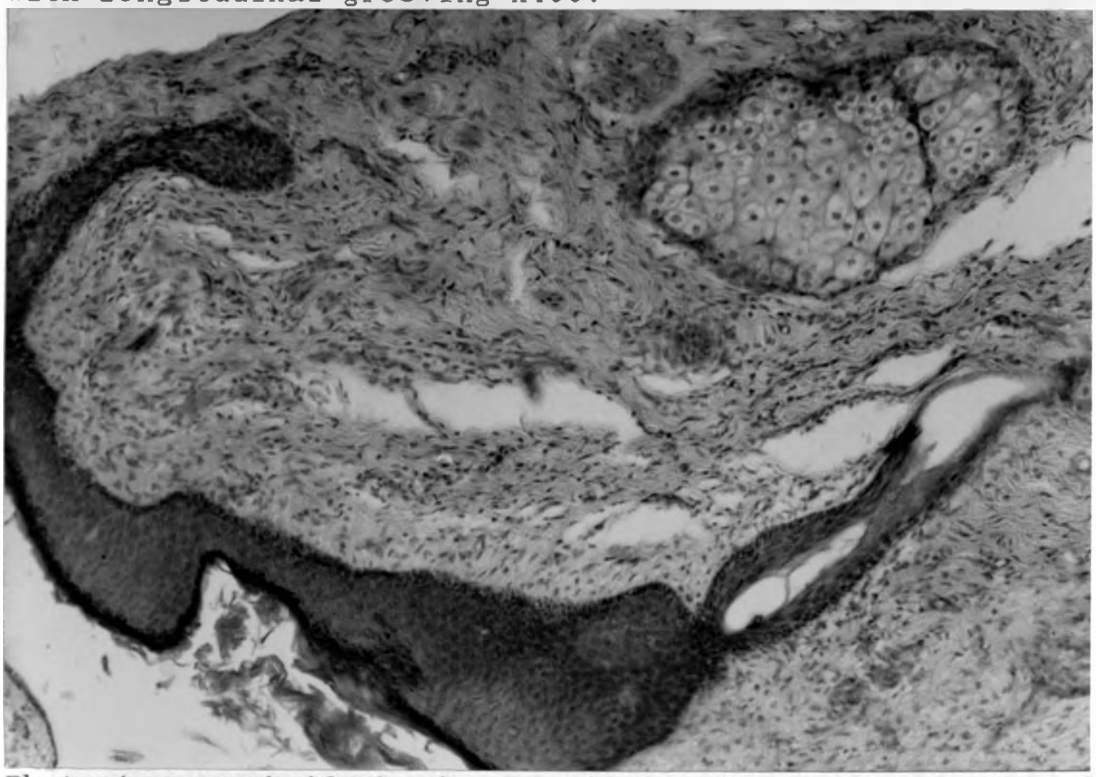
Photomicrograph 9: serous papillary cystadenocarcinoma, poorly differentiated x100.



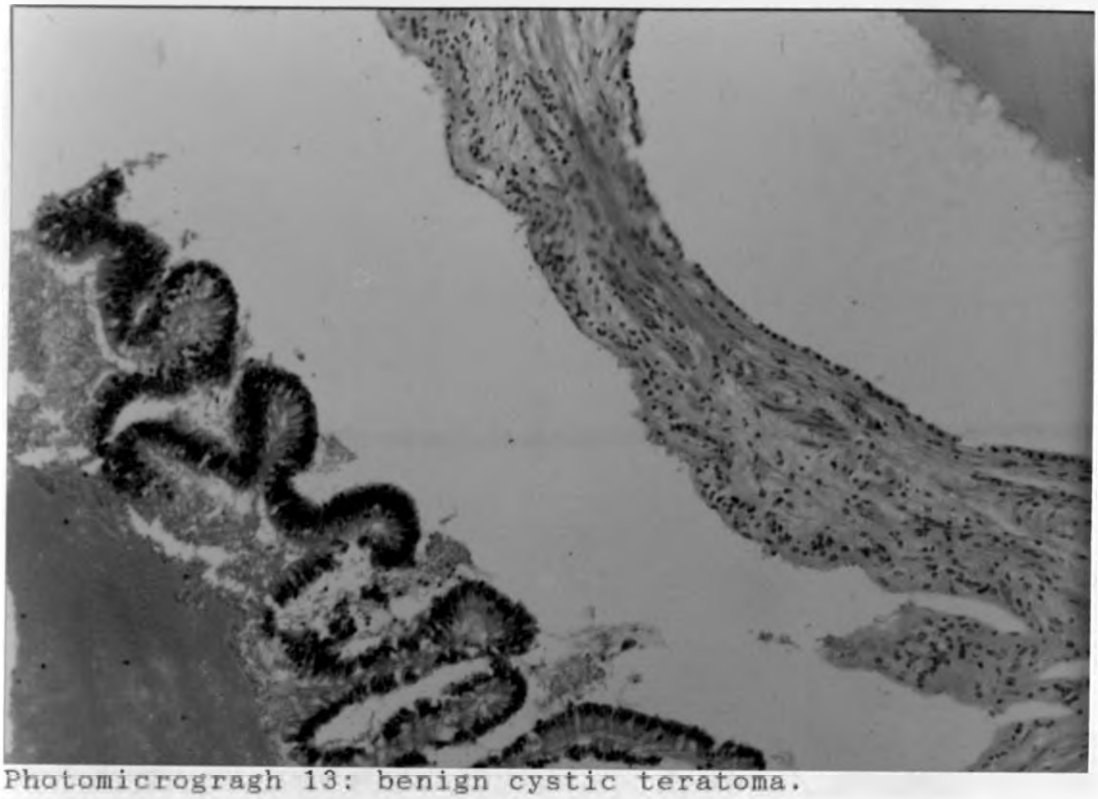
Photomicrograph 10: endometrioid carcinoma.
Glands lined by pseudostratified epithelium resembling that of carcinoma of the endometrium x100.



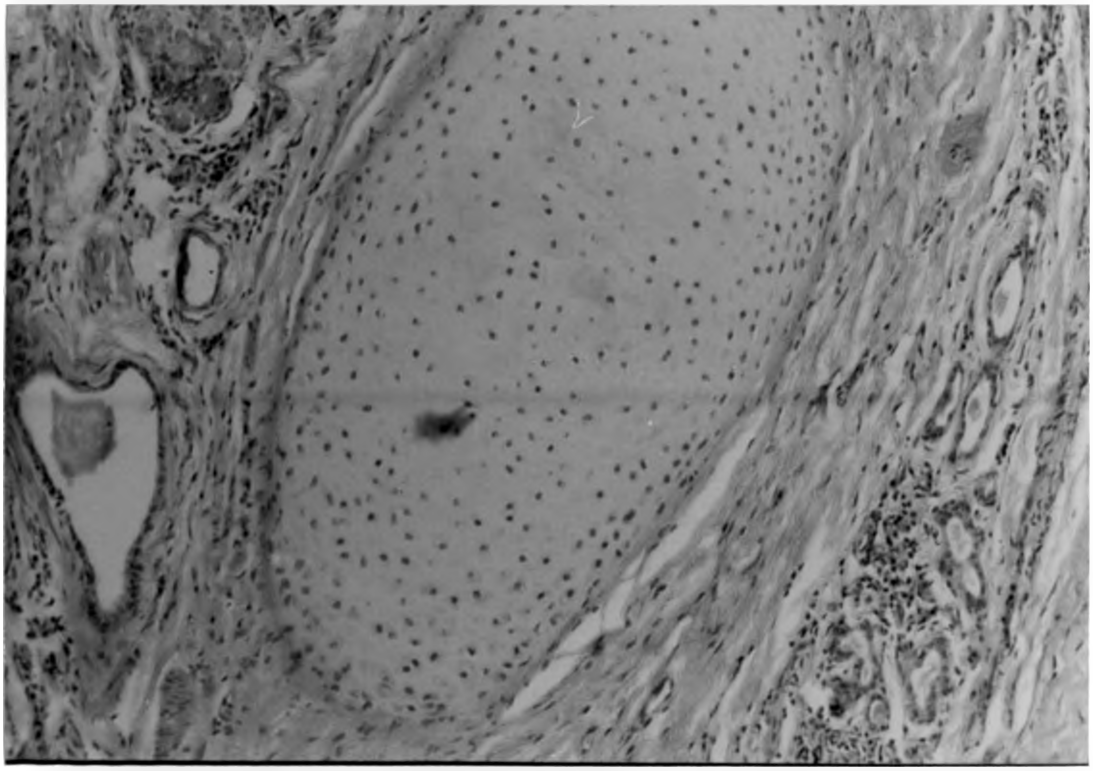
Photomicrograph 11: Brenner tumour.
Epithelial cell with ovoid nuclei, prominent nucleoli and a few with longitudinal grooving x400.



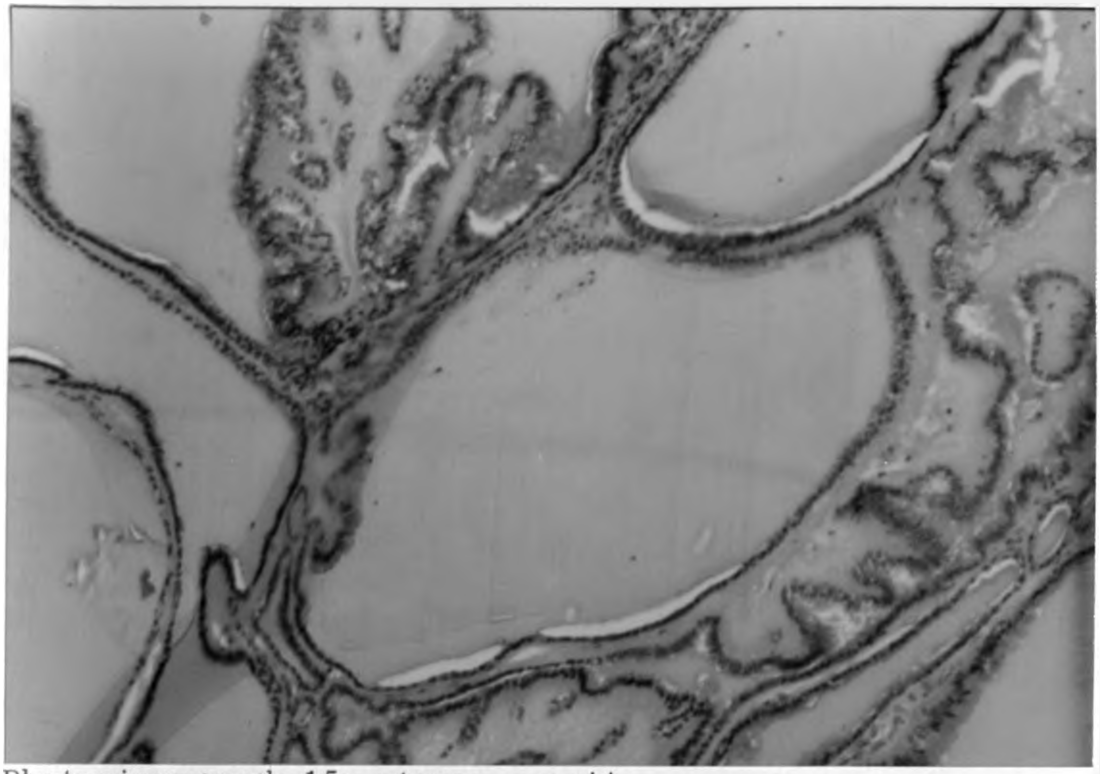
Photomicrograph 12: benign cystic teratoma.
Epidermis with a sebacious gland x100.



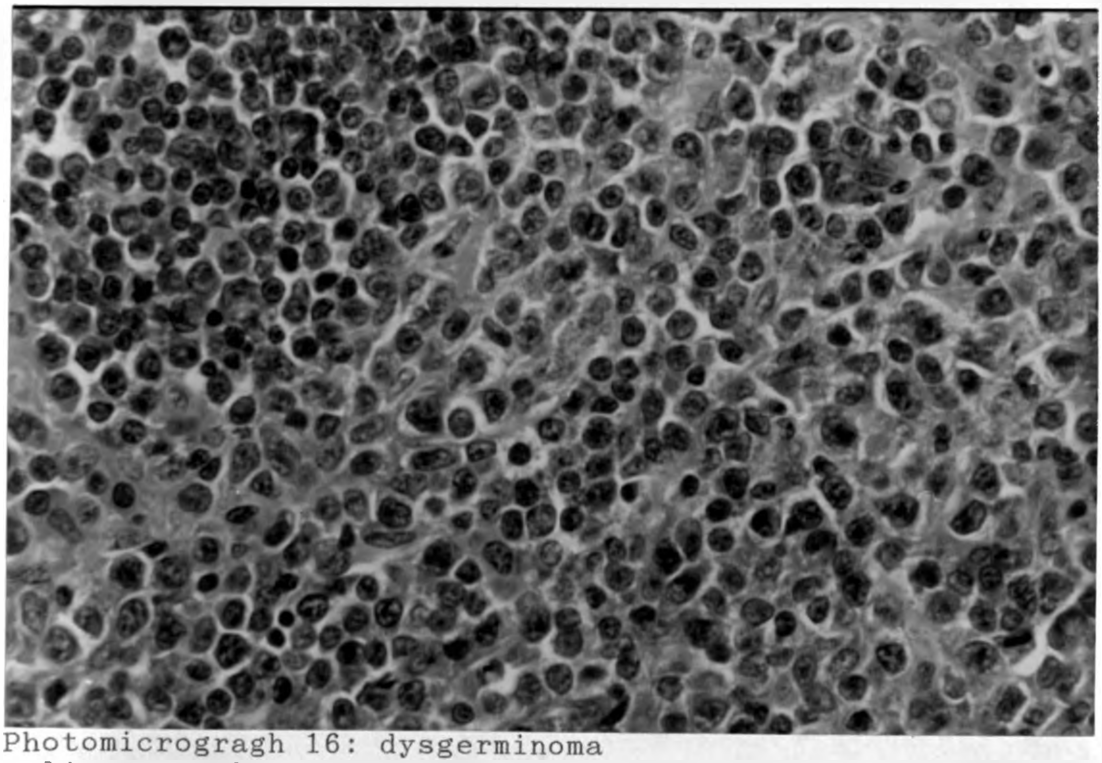
Photomicrogragh 13: benign cystic teratoma.
Respiratory epithelium and the wall of a cystic space lined by cuboidal epithelium x100.



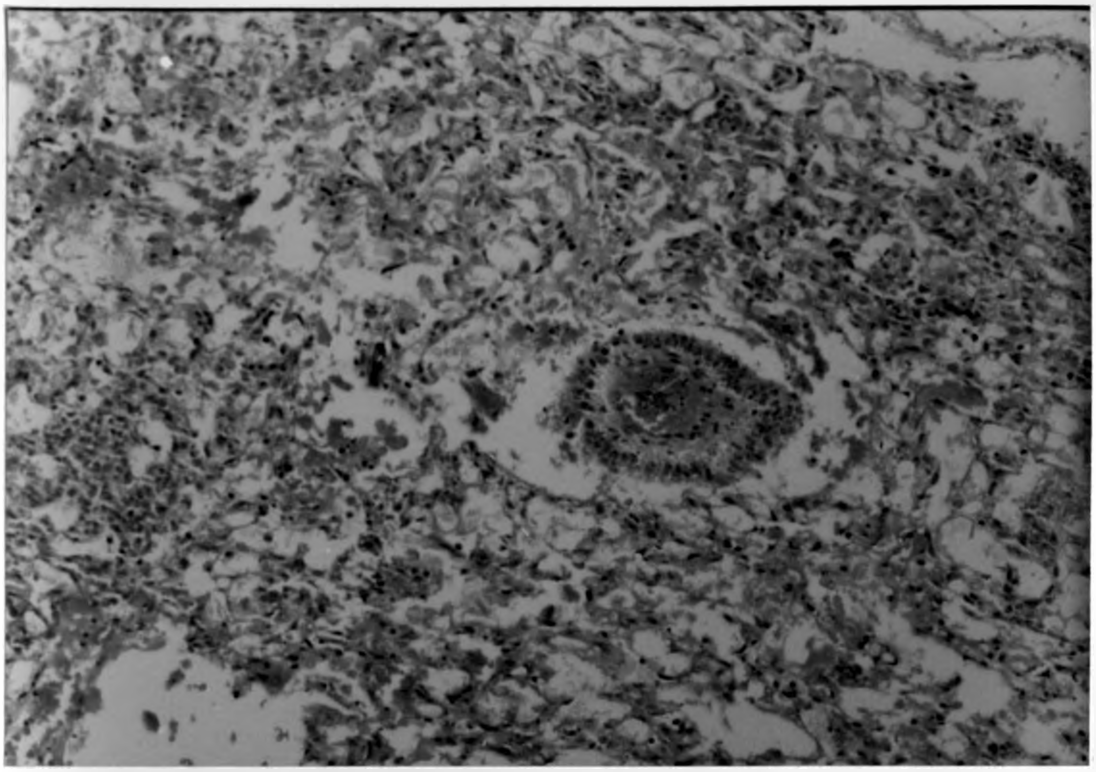
Photomicrogragh 14: benign cystic teratoma.
Mature cartilage with glandular spaces on both sides lined by epithelium, note a focus of salivary glands (top left) x100.



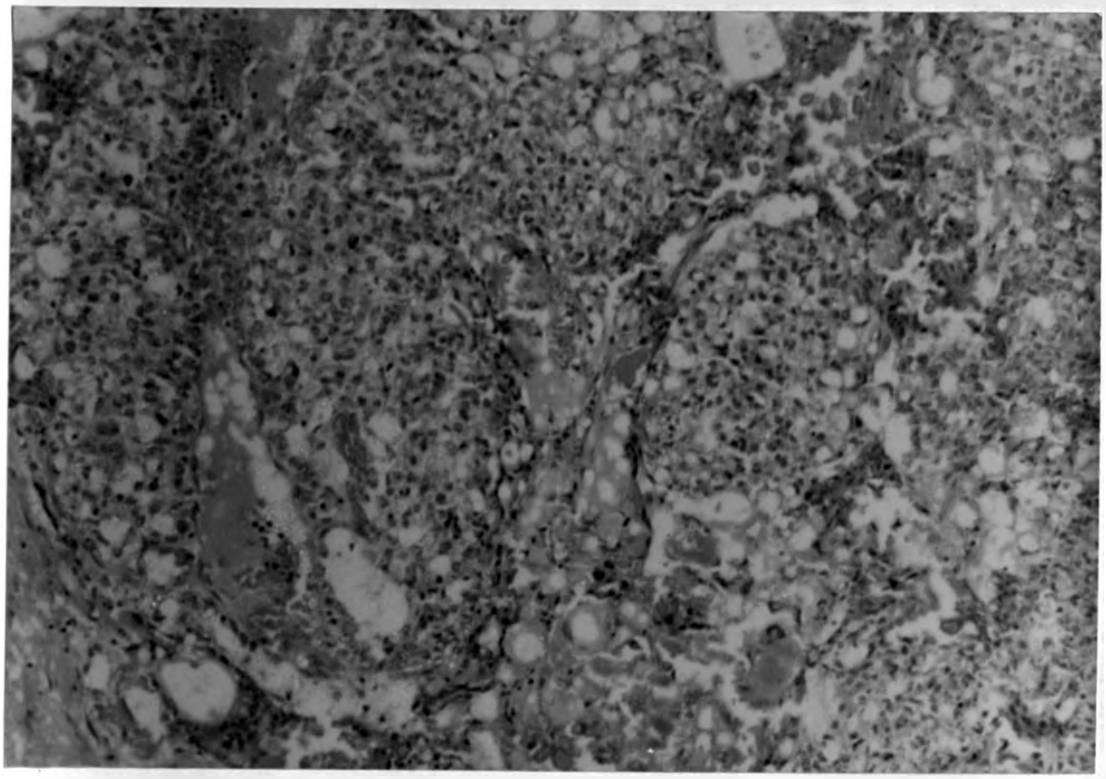
Photomicrogragh 15: struma ovarii
Note papillary pattern and glandular space filled with colloid material x100.



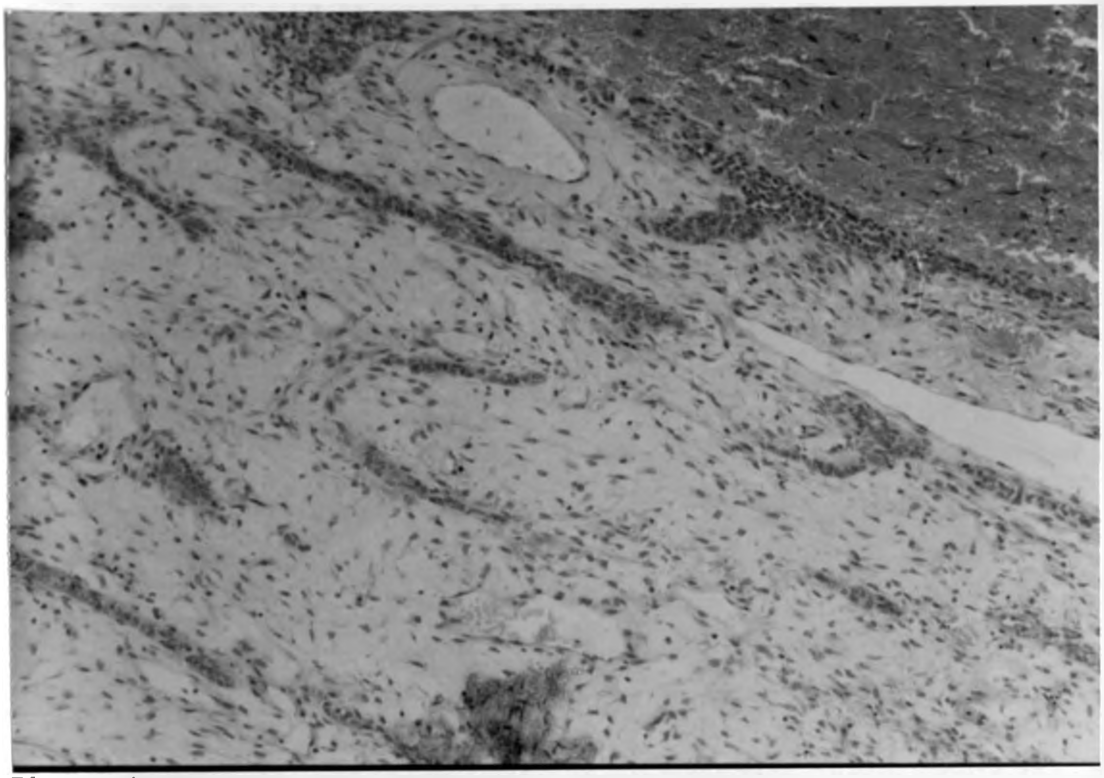
Photomicrogragh 16: dysgerminoma
Malignant cells with round nuclei and a prominent nucleoli. A few lymphocytes are scattered among the tumour cells, best seen in the top left corner x400.



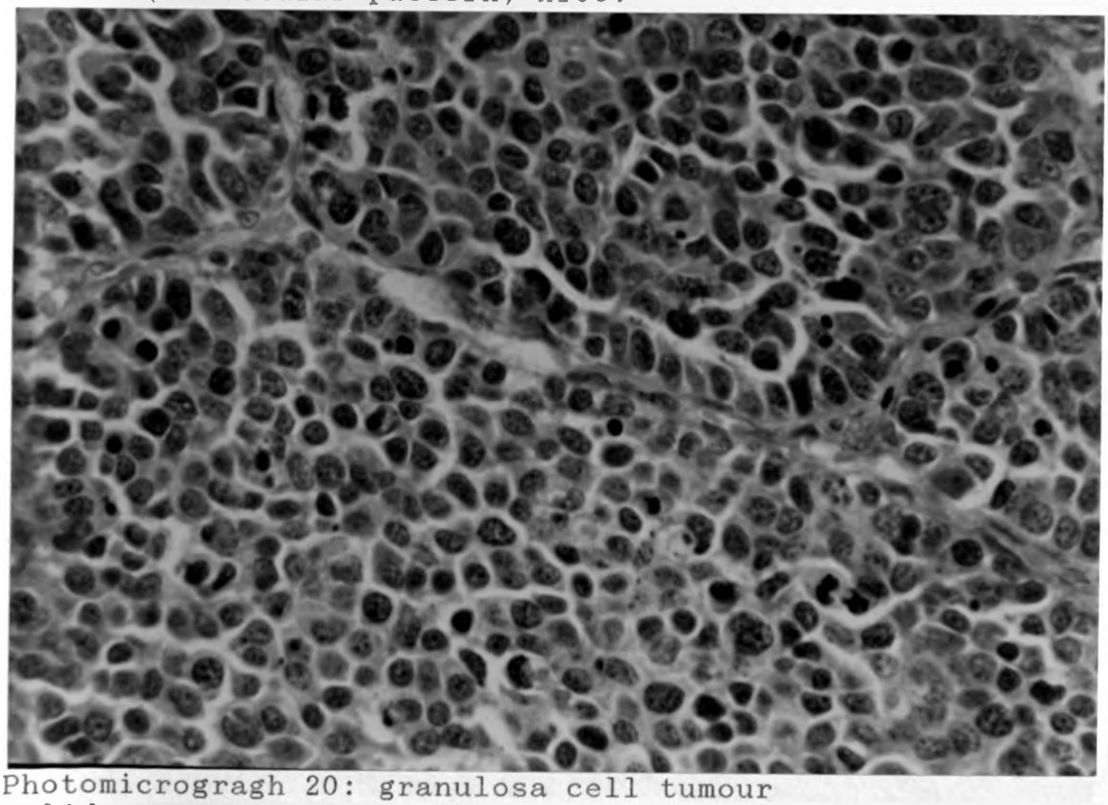
Photomicrogragh 17: endodermal sinus tumour
Reticular pattern with a Schiller-Duvall body x100.



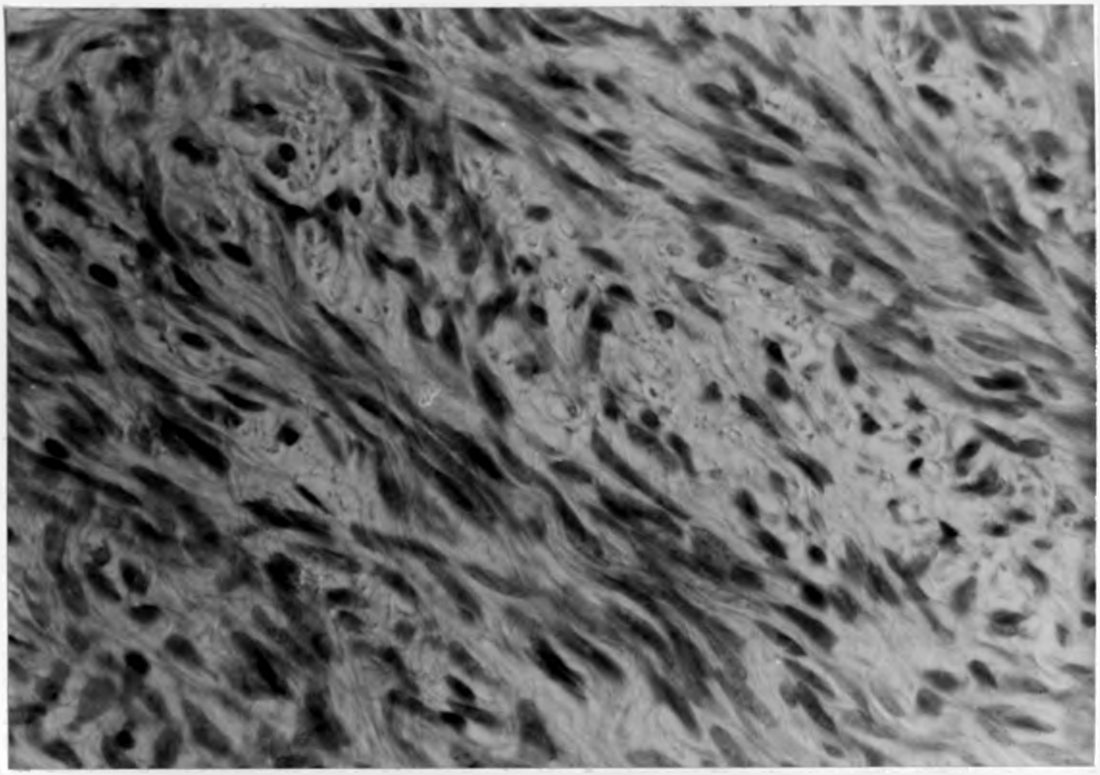
Photomicrogragh 18: endodermal sinus tumour
Note the pale red solid homogeneous hyaline bodies x100.



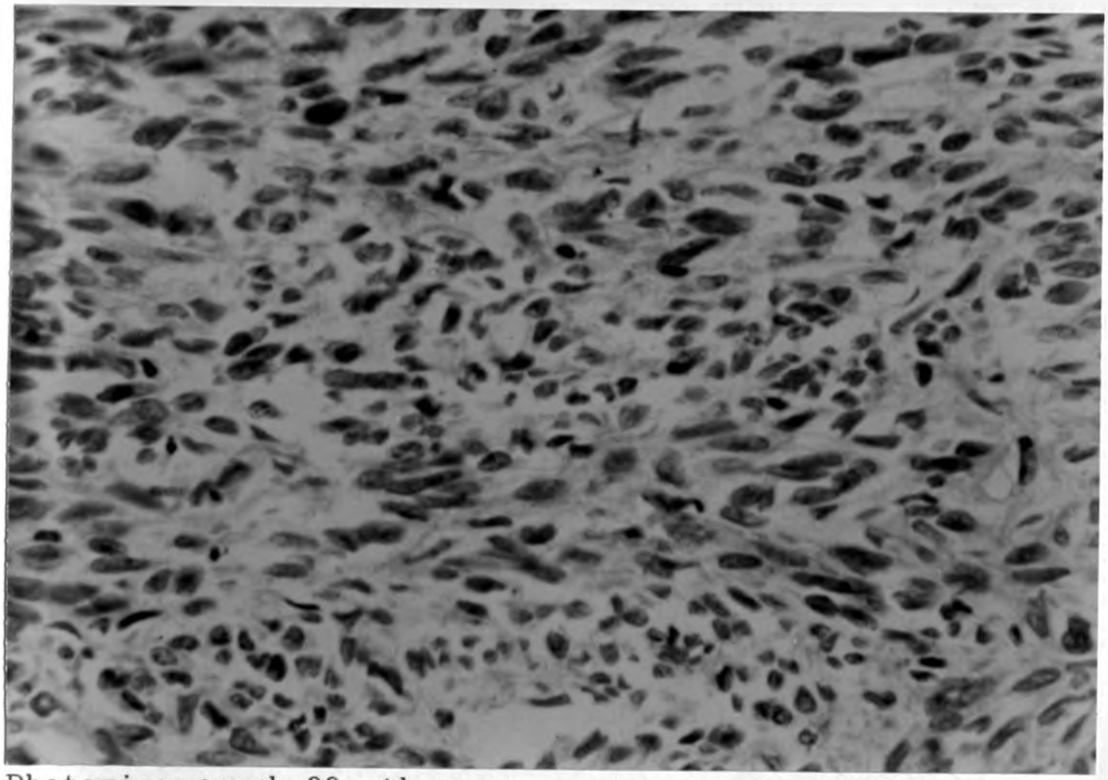
Photomicrogragh 19: granulosa cell tumour
Trabeculae of granulosa cells are separated by thecofibromatous stroma (trabecular pattern) x100.



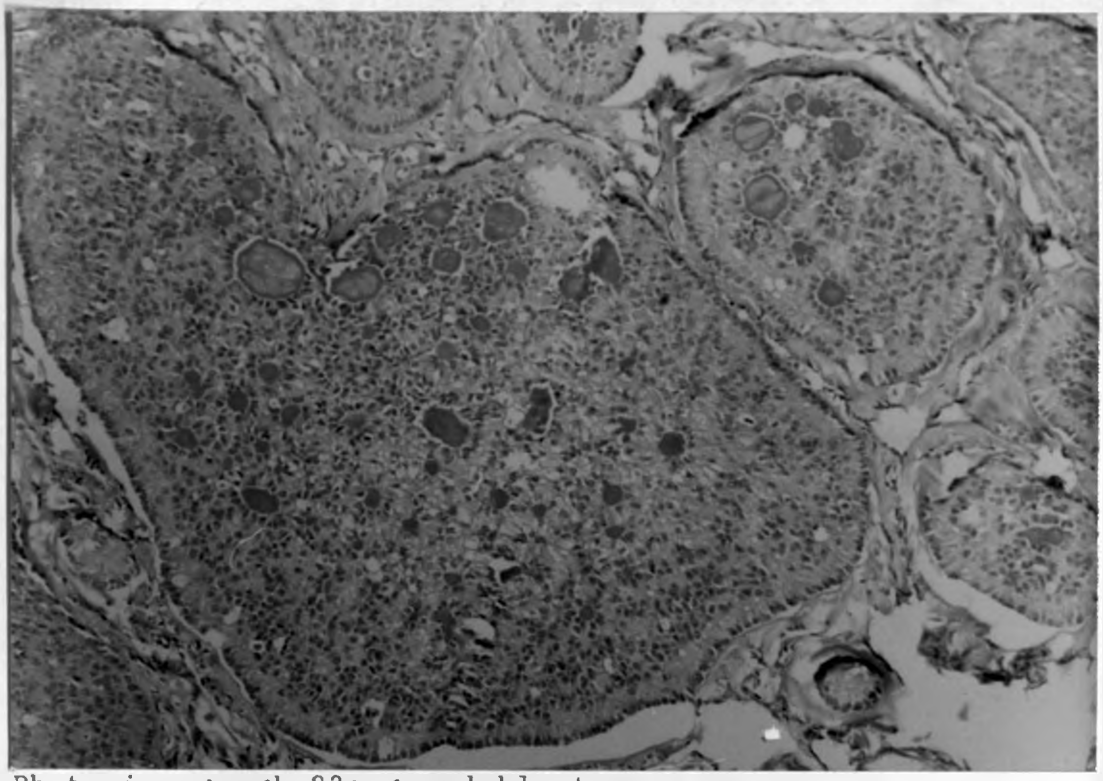
Photomicrogragh 20: granulosa cell tumour
Solid pattern - large round and polyhedral nuclei with varying amount of cytoplasm x400.



Photomicrogragh 21: fibroma.
Bundles of uniform spindle cells x400.



Photomicrogragh 22: thecoma.
Ovall and spindle cells.



Photomicrogragh 23: gonadoblastoma.
Nests of germ cells containing round pink staining hyaline bodies x100.

Photomicrogragh 23: gonadoblastoma.
Higher magnification of the nests of cells with hyaline bodies. The germ cells are similar to those of a dysgerminoma with round nuclei and prominent nucleoli x400.

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APPENDIX - 1

Haematoxylin and Eosin method.

1. Bring section to water.
2. Stain in Mayer's haematoxylin.
3. Wash in water.
4. Differentiate in 1% acid alcohol.
5. Wash in water.
6. Blue in Scotts' tap water for 30 seconds.
7. Rinse in water.
8. Counterstain in 1% eosin for 5 minutes.
9. Rinse in water.
10. Dehydrate in alcohol.
11. Clear in xylene.
12. mount in DPX.

APPENDIX 2

BENIGN LESIONS - NORMAL OVARY OR NORMAL VARIANCES.

-Cystic corpus luteum - normal ovary, remnants of cystic follicle

-Simple ovarian cyst - normal ovarian tissue

-Fibroma and follicular cyst - normal ovary

-Simple ovarian cyst - normal ovary

-Haemorrhagic ovarian cyst with no definite lining - normal ovary.

-Corpus luteum cyst - graafian follicle

-Haemorrhagic necrosis probably secondary to infarction - cystic follicles.

-Fallopian tube and endometriotic cyst - corpus luteum.

-Follicular cyst - corpus luteum.

-Follicular cyst - corpus luteum.

-Polycystic ovarian disease - normal ovary.

-Infarcted haemorrhagic ovary - corpus luteum.

-Fibroma - normal ovary.

-Granulosa theca cell tumour - Normal ovary granulosa cell like proliferation.

-Polycystic ovary - normal ovarian tissue with several cystic follicles

-Benign teratoma - corpus luteum.

-Polycystic ovary - numerous small cystic follicles.

-Simple cyst of ovary - normal ovary.

-Serous cystadenoma - normal ovary with regressing c/luteum

-Ovary and serous cyst - cystic corpus luteum.

-Serous cyst with tuboovarian adhesions - normal ovary with normal surface epithelium.

-Simple cystic teratoma - normal ovary.

-Follicular cyst with haemorrhage - cystic corpus luteum.

-Simple serous cyst - corpus luteum.

-Ovary containing a follicular cyst - normal ovary.

-Follicular cyst with haemorrhage - corpus luteum.

-Corpus luteum cyst - cystic follicle.

-Follicular cysts - corpus luteum.

BENIGN TUMOUR - BENIGN MAINLY TUMOUR

-Dermoid cyst - simple cyst.

-Serous cystadenoma - mucinous cystadenoma.

-Inclusion cysts - serous adenofibroma.

-Dilated follicular cyst and endometriotic cysts - polycystic ovary.

-Sex cord tumour with annular tubules - gonadoblastoma.

-Intermediate differentiated sertoli leydig cell tumour - hilus cell tumour.

-Simple cyst of ovary - serous cystadenoma.

-Mucinous cyst benign - simple cyst .

-Benign juvenile granulosa cell tumour - Leydig cell tumour.

-Serous cystadenoma - simple cyst .

-Benign serous papillary cystadenoma - serous cystadenofibroma.

-Follicular cysts - corpus luteum.

MALIGNANT TUMOURS - MALIGNANT TUMOURS

-Papillary adenocarcinoma with some clear cell areas - endodermal sinus tumour.

-Burkitts lymphoma - Lymphoma not classified due to poor technical quality

-Well differentiated serous cystadenocarcinoma metastasized - anaplastic carcinoma.

-Endometrioid adenocarcinoma - papillary serous cystadenocarcinoma.

-Serous cystadenocarcinoma - dysgerminoma.

-Serous cystadenocarcinoma - dysgerminoma.

-Papillary cystadenocarcinoma mucous producing - serous cystadenocarcinoma.

-Infiltrating large cell anaplastic carcinoma consistent with a primary ductal carcinoma from the breast - poorly differentiated carcinoma with many mitosis some cell show intracytoplasmic mucin not suggestive of ductal carcinoma of breast.

MALIGNANT TUMOURS - BORDERLINE TUMOURS

-Serous cystadenocarcinoma - Serous cystadenoma of borderline malignancy.

-Serous papillary cystadenocarcinoma - papillary serous cystadenoma of borderline malignancy.

MALIGNANT TUMOURS - BENIGN TUMOURS

-Serous cystadenocarcinoma - papillary serous cystadenoma.

-Papillary cystadenocarcinoma - serous adenofibroma.

-Malignant papillary cystoma - Serous cystadenoma.

-Bilateral serous carcinoma of borderline type - papillary serous cystadenoma.

-Serous cystadenocarcinoma - serous cystadenofibroma.

-Mucinous cystadenocarcinoma - serous cystadenoma.

BENIGN - MALIGNANT

-Haemorrhagic congested infarcted ovarian torsion - endometrioid carcinoma

MALIGNANT TUMOURS - NORMAL OVARY

-Sclerosing stromal tumour - normal ovary.

-Necrotic cystadenocarcinoma - corpus luteum.