OVARIAN TUMORS

Tumors and Tumor-like Conditions of the Ovaries, Fallopian Tubes and Ligaments of the Uterus

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FOREWORD

The treacherous nature of ovarian tumors has long been well known. The overall picture with regard to prognosis of malignant neoplasms arising in this organ is dismal at best. They are unique in this respect among gynecological tumors, paradoxically being less prevalent than cancers of the cervix or corpus uteri, yet resulting in many more deaths annually. Essentially no meaningful advances have been made in recent decades insofar as improvement of the overall poor salvage reates are concerned. It is this ominous outlook that emphasizes the importance of adnexal tumors as a major unsolved problem in our discipline. This book, the fourth in the series Major Problems in Obstetrics and Gynecology, addresses itself to a vital area of paramount concern to all practitioners.

Compounding the silent nature of such tumors, which are almost invariably characterized by a total absence of symptoms until dissemination has taken place, is the factor of their inaccessibility for early detection. Furthermore, therapy heretofore has been based largely on somewhat unreliable data, particularly with regard to classifications of homogeneous groups of patients for purposes of analyzing the efficacy of various treatment modalities. It is perhaps true that there is no other form of cancer, certainly no other gynecological tumor group, where variations from clinic to clinic are as great as in cancer of the ovary with reference to such very important matters as interpretation of histogenetic origin, morphologic type, histologic degree of anaplasia, and clinical extent of disease. As a result, accumulated data concerning that treatment tend to be a source of unending frustration to gynecological oncologists.

This book is one of the most comprehensive surveys of the histopathology of ovarian tumors. Moreover, it is one of the very few extant dealing in any depth at all with other adnexal tumors, including those of the fallopian tubes and the supporting uterine ligaments. In this regard, it can be considered a source book. It attacks a most complicated area. Diverse opinions and scattered reports are collated and digested for study and easy assimilation. The book meets a practical need effectively by covering in great detail aspects of morphology, theories of origin, and conflicting classifications, and by providing specific information on malignant potential and prognosis of the entire spectrum of tumors likely to be encountered in the course of pelvic surgery. In addition, it provides a wealth of reference material, and is both authoritative and thoroughly encyclopedic, while at the same time offering very practical material on diagnosis, evaluation, and treatment.

This important addition to the Series can be expected to serve as a manual for gross and microscopic recognition of adnexal tumors, concentrating on descriptions of hallmark characteristics, incidence data, surveys of relevant historical interest, concepts of origin, and ancillary diagnostic aids. It deals secondarily with modalities of available therapy, as well as potential for cure and prognosis for survival. Nomenclatural conflicts are clarified. Pathways of spread are defined and the clinical accidents attendant upon the growth of such lesions are reviewed. Illuminating cases are cited throughout. Examination of the opposite ovary is repeatedly stressed in all pertinent instances where bilaterality may be suspected.

The authors are particularly well equipped to deal with this subject, especially from the pathological point of view, providing the clinician with keen and unclouded insights into important clinicopathological relationships. These latter will prove very useful indeed to the physician who must make those most important decisions on how to deal with a given lesion encountered at the operating table, where gross characteristics and at most only a cursory frozen-section examination will dictate his immediate course of action. Under such circumstances, not all uncommonly encountered, the type of information available herein will be invaluable. Without such a firm grasp on the pathology of adnexal neoplasms, the pelvic surgeon may do irreparable harm in terms of either excessive surgery for patently benign lesions or, worse still, inadequate or inappropriate extirpative procedures for malignant varieties. The value of this book from that point of view cannot be overstated.

Boston

EMANUEL A. FRIEDMAN, M. D., MED. SC. D.

PREFACE

There is no dearth of textbooks on gynecological pathology and only a few deal exclusively with the ovary or fallopian tube. However, we have found that the majority of these do not really present many of the facts which have been recorded in the last century and the early twentieth century. It can be said that in the older medical literature, "Full many a gem of purest ray serene the dark unfathomed shelves of libraries bear."

We do not claim to have unearthed all these "gems" but we would like to draw attention to the existence of these works.

In recent years, the general principles of oncology have undergone significant change in response to ongoing basic and clinical investigations. These changes in principle we have attempted, in so far as we were able to do this, to incorporate into the more specific presentation of the biology, the effective diagnosis and the rational management of ovarian neoplastic disease.

The subject of ovarian tumors is one where considerable confusion and ignorance exists. We have attempted to present what is known, hopefully in a manner which can be readily understood. If we have failed we hope our critics will bear with us and at least give us credit for trying.

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N. A. Janovski

T. L. Paramanandhan

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Part One

TUMORS OF THE OVARY

Chapter One

INTRODUCTION AND CLASSIFICATION OF OVARIAN TUMORS

The most difficult and challenging chapter in the field of gynecological pathology is the classification and understanding of the histogenesis of ovarian tumors. Willis states, "The ovary remains the most perplexing region as regards the derivation of many of its tumors, partly because of the great variety of tumors observed in this organ, not a few of which consist of tissues not recognizably like any of the normal constituents of the ovary, and partly because of uncertainty regarding the histogenetic relationship of normal tissues in the ovary, in which, it now appears probable, stromal and epithelial elements may be intermutable. The teratomas comprise another group of undetermined histogenesis."

In the ovary, we encounter a situation in which there is no host-tumor resemblance. This in itself constitutes a problem, because it is usual to expect a tumor to resemble the parent tissue histologically, allowing for alterations due to anaplasia, embryonic reversion, vascular insufficiency and mechanical factors. In the interpretation of each tumor entity, the histopathologist has to identify its pattern and also to try to identify which particular derivative of the ovarian mesoderm the tissue arose from and what elicited it.

In the ovary, the problem is further complicated by the endocrine activity of the tumor. In the ovarian tumors, any specific cellular type does not always produce the same hormonal substance but can secrete several hormones, and one and the same hormone can be secreted by different varieties of cells. This is particularly true of tumors rich in lipid cells. This feature, although it may sound perplexing, is readily explained, since the cellular synthesis of both androgens and estrogens commences with progesterone. It must be borne in mind that this substance is also the precursor of corticoids. Hence, these cells are the potential producers of steroid hormones as well, and it is their enzyme complement which determines which synthetic pathway will dominate, thereby producing the difference in endocrine activity.

Tumors histologically of the feminizing mesenchymoma type have occasionally showed virilizing effects. It is a remarkable feature that most of these cases have been in association with pregnancy. The virilizing manifestations are mainly related to the progesterone metabolism. In the recent literature, the virilizing propensities of most progestogens, in relation to the fetus in utero, has received prominent attention. Some authorities feel that progesterone may in some circumstances exert a similar influence in the adult female. Androgenic activity has been most frequently documented as occurring in pregnancy, and estrogenic activity as occurring in the postmeno-

pausal female. It must be borne in mind that these are the types of activity which would be readily detected in these phases of life. For example, it would be difficult to detect a tumor with feminizing properties during pregnancy. In the literature a case is recorded of a patient showing signs of virilization during pregnancy. Postpartum there was no progression of the virilizing symptoms, and two months later a Brenner tumor was removed.

These hormonal effects are particularly important since in the literature there are an increasing number of reports of the association of feminizing ovarian tumors and endometrial carcinomas, particularly with the thecomas and granulosa cell tumors. Schröder, in 1922, was the first to report the association of a granulosa cell tumor with a carcinoma of the endometrium. Many authorities believe that when these estrogenizing tumors occur just before or after the menopause, there is an increased risk of endometrial cancer. The incidence of feminizing mesenchymomas associated with carcinoma of the endometrium have been cited as ranging from 3 to 27 per cent by Hertig and Gore (1961). Fathalla, (1967 ii) even advocates a careful search for a small functioning unsuspected tumor of the ovary in all cases of endometrial carcinoma.

In addition recent histochemical studies have indicated that many of the common ovarian tumors, both primary and secondary, which are not normally hormonally active, are for some reason endocrinologically active, confusing the picture further. Some workers postulate that the tumor itself in these cases produces the steroids. It must be borne in mind that the "epithelial" tumors are mesodermal in origin. It has been postulated that all mesodermal tissues may, under suitable circumstances, produce steroidogenic hormones. However, there are recorded cases where resection of the ovaries was not followed by continued steroid production, in spite of the fact that metastases were present in other sites as well.

Some tumors are capable of producing gonadotrophic substances; for example, carcinomas of the bronchus have been shown to produce substances with effects similar to pituitary trophic hormones. In these cases regression of the Cushing's syndrome occurred with removal of the tumor. This is unlikely in the case where only the metastases to the ovary show a hormonal effect.

It is possible that the mechanical stimulation of the proliferating tumors may be a factor in the activation of mesenchyme to produce steroid hormones. In many of these cases a theca or lutein cell reaction in the stroma surrounding these tumors has been demonstrated. Lipid stains have revealed marked fat deposition in the cells immediately surrounding the tumor.

The tumors which become unexpectedly active most often are usually ones in which multiple, small islets of epithelial cells are set in an ovarian stroma, possibly due to the increased surface area, and hence result in stimulation of the ovarian stroma, i. e. Brenner tumors. Wagner (1950) postulated that in cases of virilization it was due to the unopposed activity of the adrenals following destruction or compression of the ovarian mesenchymal tissue. Hyperplasia of the hilus cells has also been reported as a source of steroid synthesis.

Further work has to be done before this problem is solved, and it has been proposed that, in all ovarian tumors, a 24-hour specimen of urine be collected preoperatively and stored. If the histology of the tumor in any way indicates that the neoplasm may have been hormone producing, hormone studies could be done on the urine. In addition hormone studies could be done on a sample of blood from the ovarian vein at the time of surgery, comparing it with hormone studies from peripheral venous blood obtained at the same time.

The picture is made more complex by the continued appearance of a number of partially or completely synonymous names in the literature. Considerable difficulty may also be encountered in the histological interpretation of an ovarian tumor because of its large size, rendering adequate sampling a tedious process. The interpretation of many tumors depends on the careful study of sections from multiple sites; in some cases the greater the number of sections, the more confusing the histological picture.

Different classifications have been proposed throughout the years by different authorities, some of which are enumerated here. Some have suggested dividing ovarian tumors into benign

and malignant categories; others have classified them according to consistency (cystic and solid). Some authorities, in their classifications, have taken into consideration the embryological and histogenetical properties of ovarian neoplasms, and others have attempted a classification according to certain biochemical and clinical features such as feminization or masculinization. A classification of ovarian tumors on a histochemical basis has also been proposed.

In spite of these numerous attempts, a generally acceptable classification of ovarian tumors has yet to be proposed and the oncogenesis of many of the known tumors remains an enigma. Considerable additional investigation is necessary in order to establish a proper and workable classification of ovarian tumors. With the introduction of the newer techniques in histochemistry, enzyme studies, electron microscopy, cytogenetics, tissue culture and so forth, it is hoped that in the next decade a more profound understanding of the histogenesis, embryogenesis and pathogenesis of the ovarian tumor will be established.

Numerous workers in the field have made attempts based on one or several principles as mentioned earlier, and in chronological order the more recent classifications are those of Schiller (1940), Taylor (1940), Geist (1942), Barzilai (1943), Selye (1946), Novak (1952), Teilum (1952), Willis (1953), Bassis (1960), Hertig and Mansell (1961), Santesson (1961), Godefroy–Vandeville (1965), Dubrauszky (1966), Abell (1966), De Brux and Ancla (1967), Scully (1968), and Motlik (1970). The Expert Committee of the International Federation of Gynecology and Obstetrics at a meeting in Stockholm in 1961 attempted to classify ovarian tumors with an emphasis on neoplasms of paramesonephric celomic (Müllerian) epithelial origin. The World Health Organization team of experts at a meeting in Leningrad in 1967 discussed the classification of ovarian tumors and came up with some interesting ideas and proposals. In spite of these numerous classifications, no one classification, satisfactory and acceptable to both gynecologists and pathologists, has yet been presented.

Ovarian tumors may be encountered in females of all ages—the youngest being a 30-week-old fetus with a bilateral, unclassifiable ovarian tumor and the oldest being a 92-year-old woman. Although genital neoplasms are uncommon in childhood and adolescence, ovarian tumors are the most frequent of all genital neoplasms in this age group and are often overlooked until they create a special problem.

In childhood, ovarian tumors account for 1 per cent of all tumors and have been recorded since the last century. Giraldes (1867) is credited with performing the first oophorectomy in a child for tumor. In children, teratomas and follicle cysts are the most frequent types of ovarian tumor, but almost every type of ovarian neoplasm seen in adult life has been encountered in girls under 16 years of age.

Approximately 20 per cent of all ovarian tumors in the first decade of life are malignant. Abell et al (1965) feel that neoplasms of germ cell origin are more frequent in the first two decades of life and that in adult life neoplasms of nongerm cell origin were more common. Metastatic tumors have also been recorded in the ovaries of children; lymphomas and even metastatic mucin-producing adenocarcinomas from a primary site in the stomach and colon have been noted.

The peak incidence of benign tumors of the ovary is in the age group between 20 and 44 years, whereas in malignant ovarian tumors the peak is in the 45 to 64 years age group, with a mean of 53 years. Buka and McFarlane (1964) found that 30 per cent of their cases of primary ovarian carcinoma occurred in nulliparous women and that 78 per cent of the patients had not borne more than two children. Sixteen of their cases had a family history of cancer. Humphries et al (1966) claimed that in a series of 180 cases 5 per cent of all females affected by Peutz-Jeghers syndrome had papillary cystadenomas of the ovary, indicating the possibility that the same mutant gene was involved. Scully (1970) also described an increased incidence of the "sex cord tumor" in association with Peutz-Jeghers syndrome. A number of cases have been reported in the recent literature of ovarian tumors occurring in siblings and in successive generations. However, there does not appear to be any conclusive evidence of an inherited tendency for ovarian tumors.

Recent statistics indicate that the number of women dying of cancer of the ovary in the USA is increasing, having doubled in the last 30 years. The annual incidence per 100,000 women, according to Segi and Kurihara (1966) is 13.2 in the USA and 13.4 in Sweden. Chile has the lowest figure of 2.5 and Japan is a close second with 2.6. Segi and Kurihara's figures indicated an incidence which was 3 times higher in white women of European and North American origin as compared to women of Asian and African origin. These findings were confirmed in a report from Israel by Schenker et al (1968).

No predilection for either ovary has been found, with the exception of dysgerminomas and Brenner tumors which appear to be more common on the right side.

Approximately 75 per cent of all ovarian tumors represent benign tumors; only 25 per cent are malignant. Malignant tumors of the ovary constitute 15 per cent of all malignant gynecological neoplasms, but since they are usually detected in an advanced stage their prognosis is on the whole poor. It is anticipated that in the USA alone, approximately 10,000 women will die annually of a malignant neoplasm of the ovary (Table 1).

In spite of the vast improvements in the fields of surgery and radiotherapy and the introduction of chemotherapy in the treatment of cancer, the mortality rate from malignant neoplasms of the ovary has not been appreciably altered in the last 30 years (Table 2). Maus et al (1968), in Ontario, reported a 5-year survival rate of 25 per cent in a series of 1722 cases. Sixty-five per cent of all cases of carcinoma of the ovary are first diagnosed when the tumor is inoperable and only 11 per cent are diagnosed when the tumor is restricted to one ovary and is completely removable. The three factors affecting prognosis are: (1) the clinical stage of malignancy, (2) the histological type of tumor, and (3) the type of treatment.

Table 1

Estimated Cancer Deaths in Women in the USA (1970)

Site	Number
Breast	30,100
Cervix uteri	9,400
Corpus uteri	3,500
Ovary	9,900
Other and unspecified genital areas	850
Total — Genital organs (excluding breast)	23,650
All sites (females only)	150,000

Clinical Stage of Malignancy

An international agreement on a uniform staging of all cases of ovarian cancer is of vital importance. Although this implies only an estimate of the anatomical extent of the growth, it facilitates an accurate, concise description of the apparent extent of invasion, especially

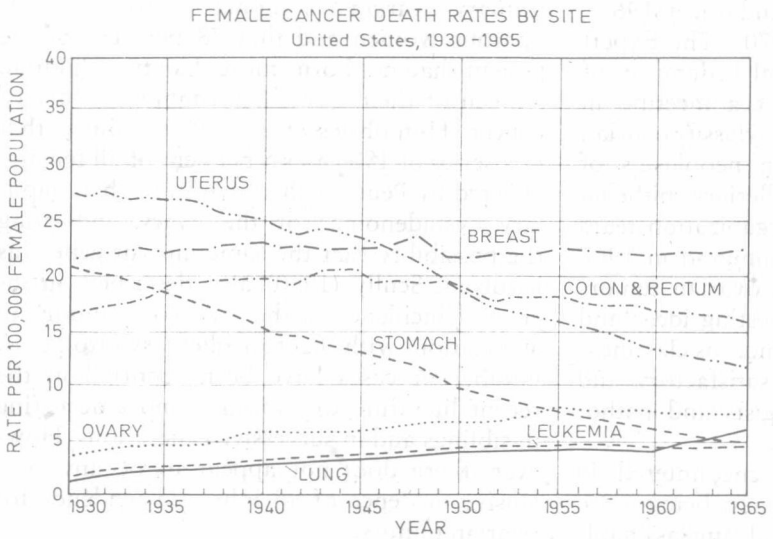

Table 2

National Vital Statistics Division and Bureau of the Census; Epidemiology and Statistics Departments, American Cancer Society.

in cases which are inoperable or in which portions have to be left behind due to technical difficulties of surgery. Several methods of clinical staging have been proposed in the past and have been adopted by various groups. We hope that the following staging as proposed by the International Federation of Gynecology and Obstetrics in 1965 will be universally adopted, thereby minimizing confusion.

I. Growth limited to the ovaries
   - Ia. Growth limited to one ovary—no ascites
   - Ib. Growth limited to both ovaries—no ascites
   - Ic. Growth limited to one or both ovaries —ascites present with malignant cells in the fluid

II. Growth involving one or both ovaries with pelvic extension
   - IIa. Extension or metastases to the uterus or tubes only
   - IIb. Extension to other pelvic tissues

III. Growth involving one or both ovaries with widespread intraperitoneal metastases to the abdomen (omentum, small intestines and mesentery)

IV. Growth involving one or both ovaries with widespread distant metastases outside the peritoneal cavity

Special category: Unexplored cases which are clinically diagnosed as ovarian carcinoma (surgical, therapeutic or exploratory procedures not having been performed)

Note: The presence of ascites will not influence the classification of stages II, III and IV.

Histological Type of Tumor

In any given tumor in general, the more anaplastic the tumor the worse the prognosis. In addition, certain histological types of tumor carry a better prognosis. The prognosis of the different types of tumors will be mentioned when each is discussed specifically. It must be emphasized, however, that frequently one encounters a tumor which histologically is highly malignant, yet the patient survives very much longer than another patient with a tumor which appears less malignant histologically but biologically progresses extremely rapidly.

Treatment

The recommended treatment for ovarian malignancy is total abdominal hysterectomy with bilateral salpingo-oophorectomy, together with removal of as much tumor tissue as is technically possible without endangering the safety of the patient. Surgery should be followed by external abdominopelvic irradiation and protracted chemotherapy. In the management of ovarian tumors both benign and malignant, whether in children or in adults, important principles are applicable.

1. The abdominal incision should be large enough to remove the tumor without aspirating or rupturing it.
2. All ovarian tumors should be opened or sectioned by a pathologist in the operating room before the abdomen is closed.

Modifications of the previously mentioned radical approach may be considered if the malignancy is a very low-grade serous type, a dysgerminoma or a granulosa cell tumor, if the lesion is confined to a cyst or the ovary alone, or if ovarian conservation is preferable because of the patient's youth. In these cases, however, the contralateral ovary should be bisected and diligently searched for a histologically similar bilateral tumor and then the ovary or what is left of it reconstructed in such a manner that a hematoma will not develop in the depths of the ovary. It must be borne in mind, however, that conservation of the other ovary is accompanied by an increased risk that an independent neoplasm may arise in the contralateral ovary. It is a remarkable feature that cases considered inoperable at the time of laparotomy have a mortality of 13 per cent in the first month following surgery.

In the event of a clinical diagnosis of malignant ovarian tumor there are some gynecologists who advocate external irradiation a day or two prior to surgery, hoping that any tumor cells which may be disseminated during the operative procedure will not be viable, reducing the chances of iatrogenic metastases.

Postoperative irradiation is recommended for incompletely removed carcinoma. Maus et al (1968) claim that radiotherapy following surgery has not appreciably altered the survival rate in stage I carcinomas over that obtained by surgery alone. The radiosensitivity of the

ovarian tumor depends on the size of the tumor. A large tumor requires a larger dose of radiation. Usually, the larger the tumor the more difficult it is to achieve suppression of the growth of the tumor. The histological type affects the radiocurability of ovarian tumors. Although the more anaplastic tumors are radiosensitive it is difficult to achieve a cure because of their rapid rate of growth and faster turnover time and the fact that they contain more viable cells per unit volume.

Most authorities (clinicians and pathologists) advocate the salvage of ovaries in cases of hysterectomy for other benign conditions. These residual ovaries continue to function in the absence of the uterus and later may be the seat of a benign or malignant tumor. Grogan (1967), in a series of 122 cases of residual ovaries removed later, found 17 benign tumors (14 per cent) and 10 malignant ones (8.2 per cent). This is an important fact that must be borne in mind by the gynecologists.

In children, however, where the tumor is benign but bilateral, every effort must be made to try to dissect out the tumor, conserving as much ovarian tissue as possible, since serious growth disturbances may follow bilateral oophorectomy. Even a small tag of ovarian tissue left may become invaluable when the girl is pubescent since enough ovarian hormone may be produced by the fragment to give her a feminine habitus, induce normal growth and cause the menarche. Similarly, in children, even though the ovary is removed, the fallopian tube should be saved in all benign conditions since the patient may need it, if later something happens to the contralateral tube.

Table 3

Treatment of Ovarian Carcinoma

Stage	Extent of Surgery	Postoperative radiotherapy	Postoperative chemotherapy
IA	Hysterectomy and bilateral salpingo-oophorectomy	No	No
IB	Hysterectomy and bilateral salpingo-oophorectomy	No	No
IC	Hysterectomy, bilateral salpingo-oophorectomy and greater omentectomy	Yes	Yes
N. B. in Stages IA and IB	In young women with unilateral ovarian involvement, ipsilateral salpingo-oophorectomy with examination of the contralateral ovary and frozen section is indicated	No	No
IIA	Hysterectomy, bilateral salpingo-oophorectomy, and greater omentectomy with removal of as much tumor as possible	Yes	Yes
IIB	Extensive surgical removal of involved organs and tissues with preservation of natural function of remaining organs	Yes	Yes—Consider re-exploration with excision of residual tumor mass following reduction
III	Extensive radical surgery as complete as possible with maximal surgical effort. Removal of as much of the primary tumor and metastases as possible without endangering the life of the patient	Yes	Yes—Consider re-exploration with excision of residual tumor mass following reduction
IV	Extensive radical surgery if possible	Only after the completion of a chemotherapy course	Yes—Consider re-exploration with excision of residual tumor mass following reduction
X Special category	A priori—no. Peritoneoscopy or exploratory laparotomy	Only if there are no metastases	Yes

* The above table is based on the work of Jamain et al (1971).

Chemotherapy has not substantially altered the five-year survival rate, and cancer of the ovary remains a powerful but insidious killer. Table 3 summarizes treatment in the different stages of ovarian cancer as generally advocated today.

Considering the fact that carcinoma of the uterine cervix was a potent killer two to three decades ago but that early diagnosis has altered the gloomy picture, we join others in advocating regular biannual examination of all women over the age of 30 years with the prospect that early detection of ovarian neoplasms will carry a more favorable prognosis.

In cases where an ovarian carcinoma in stages I or IIa is treated by surgery, regular cytological examination of washings after a peritoneal lavage, aspirated from the cul-de-sac, is advocated in the hope of early detection of recurrence or metastases.

Ultrasonic echograms are becoming increasingly popular as an aid in the diagnosis of pelvic tumors (Fig. 1 *A* and *B*). These echograms consist basically of two stages:

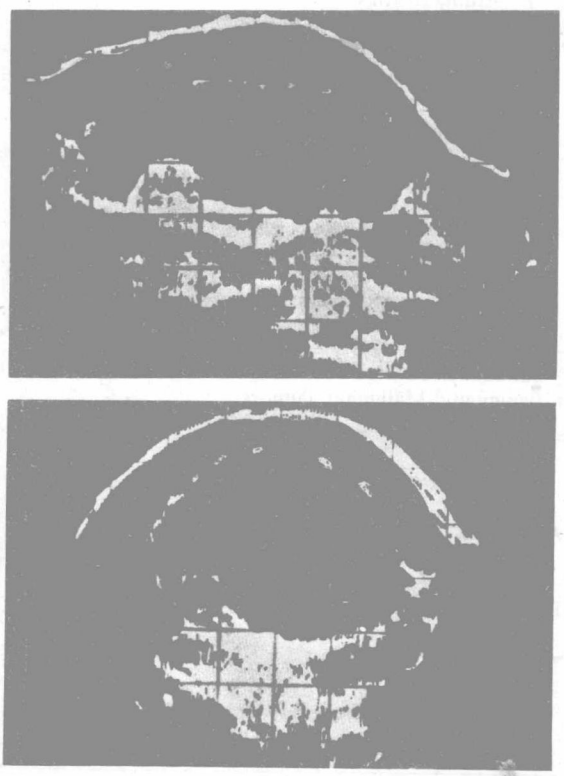

Figure 1. Echogram of a serous cystadenoma. *Top*, lateral view; *Bottom*, transverse view.

1. A differential study using different frequencies.
2. A careful study of the echograms using different volumes of sound.

In the hands of experts in the field, these ultrasounds yield information regarding the number, shape, size and even the consistency (cystic or solid) of the pathological lesions. It is hoped that with frequent use, better interpretation of these echograms will yield more information in the future. An unequivocal diagnosis of malignancy by ultrasonic examination is not possible at this time.

No new concepts as to the etiology of ovarian neoplasia are presented herewith. The concepts regarding the specific tissues of origin of some ovarian tumors are clarified to a degree in the proposed classification in Table 4 (General) and Table 5 (Special).

Table 4

Histogenetic Classification of Ovarian Tumors

A. Ovarian tumors of paramesonephric, celomic (germinal, Müllerian) epithelium
B. Ovarian tumors of nonspecialized, sex-undifferentiated mesenchyme or gonadal stroma
C. Ovarian tumors of specialized, sex-differentiated mesenchyme or sex cords (potentially steroid-producing ovarian tumors)
D. Ovarian tumors of germ cell origin
E. Ovarian tumors of mesonephric rests
F. Ovarian tumors arising from heterotopic (accessory) tissue in the ovary
G. Secondary or metastatic tumors of the ovary

Table 5

I. Ovarian Tumors of Paramesonephric Celomic (Germinal, Müllerian) Epithelial Origin

A. *Benign Tumors*
   1. Serous papillary cystadenoma
   1a. Serous surface papilloma
   2. Mucinous cystadenoma*
   3. Endometrioid cyst (Santesson)
   4. Mixed seromucinous cystadenoma (Glazunov)
   5. Cystadenofibroma (serous, mucinous and endometrioid)*
   6. Brenner tumor*
   7. Adenomatoid tumor
B. *Facultative (Potentially) Malignant Tumors*
   1. Proliferating serous cystadenoma without stromal invasion
   2. Proliferating mucinous cystadenoma without stromal invasion*
   3. Proliferating endometrioid cystadenoma without stromal invasion (Horalek-Santesson)

4. Proliferating mixed seromucinous cystadenoma without stromal invasion (Glazunov)
5. Proliferating cystadenofibroma (serous, mucinous, endometrioid)
6. Proliferating Brenner tumor without stromal invasion

C. *Malignant Tumors*
1. Serous cystadenocarcinoma*
1a. Serous papillary surface carcinoma
2. Mucinous cystadenocarcinoma*
3. Endometrioid adenocarcinoma* (Horalek-Santesson)
4. Mixed seromucinous cystadenocarcinoma (Glazunov)
5. Malignant cystadenofibroma or fibroadenocarcinoma (serous, mucinous and endometrioid)*
6. Malignant Brenner tumor
7. Paramesonephric clear cell carcinoma*
8. Undifferentiated (anaplastic) carcinoma*
9. Unclassifiable carcinoma

* Stromal luteinization has been described in these cases

II. Ovarian Tumors of Sex-Undifferentiated Mesenchymal Origin

A. *Benign Tumors*
1. Fibroma
2. Myxoma
3. Leiomyoma
4. Neurofibroma
5. Neurilemmoma
6. Ganglioneuroma
7. Hemangioma
8. Lymphangioma
9. Osteoma
10. Lipoma
11. Benign mixed mesodermal tumor

B. *Malignant Tumors*
1. Fibrosarcoma
2. Myxofibrosarcoma
3. Leiomyosarcoma
4. Neurofibrosarcoma
5. Hemangioendotheliosarcoma
6. Lymphangiosarcoma
7. Hemangiopericytoma
8. Rhabdomyosarcoma
9. Pleomorphic (undifferentiated) sarcoma
10. Carcinosarcoma
11. Malignant mixed mesodermal tumor
12. Primary malignant lymphoma (reticulum cell, lymphoblastic, lymphocytic and Hodgkin's disease)

*III. Ovarian Tumors of Sex-Differentiated Mesenchymal Origin***

(Potentially steroid-producing ovarian tumors)

A. *Benign Tumors*
1. Luteoma gravidarum
2. Stromal luteoma

B. *Facultative (Potentially Malignant) Tumors*
1. Granulosa cell tumor
   a) Follicular type—Macrofollicular
      Microfollicular
   b) Alveolar type
   c) Trabecular type
   d) Diffuse (sarcomatoid) type
2. Theca cell tumor (Thecoma)
3. Granulosa-theca cell tumor
4. Androblastoma (Sertoli-Leydig cell tumor)
   a) Tubular adenoma of Pick
   b) Tubular adenoma with or without lipoid storage
   c) Trabecular type
   d) Diffuse (sarcomatoid) type
5. Sex cord tumor with annular tubules (Scully)
6. Hilus cell tumor—Berger tumor
7. Gynandroblastoma
8. Unclassified sex mesenchymal tumors

** *Any* of the above tumors may be associated with paradox hormonal action

IV. Ovarian Tumors of Germ Cell Origin

A. *Benign Tumors*
1. Teratoma, cystic, benign
2. Teratoma, solid, adult, benign
3. Fetiform teratoma
4. Struma ovarii*

B. *Secondary Tumefaction in Benign Tumors of Germ Cell Origin*
1. Tumors arising in cystic or solid teratomas*†
2. Tumors arising in Struma Ovarii*†
3. Carcinoid Tumor*†

C. *Malignant Tumors*
1. Dysgerminoma*
2. Teilum tumor (mesoblastoma vitellinum)
2a. Polyvesicular vitelline tumor (Teilum)
3. Choriocarcinoma*
4. Polyembryoma
5. Malignant teratoma (teratocarcinoma)*
6. Gonadoblastoma (dysgenetic gonadoma)*

* Functional Tumors
† Benign and Malignant Tumors

V. Ovarian Tumors from Mesonephric Rests

A. *Benign Tumors*
1. Mesonephric adenoma
2. Mesonephric cystadenofibroma

B. *Malignant Tumors*
1. Mesonephric carcinoma (mesonephroma)

VI. Tumors Arising from Heterotopic (Accessory) Tissue in the Ovary

A. *Benign Tumors*
1. Adrenal cell rest tumors*

2. Benign tumors developing in pre-existent endosalpingiosis
3. Pheochromocytoma*

B. *Malignant Tumors*

1. Malignant adrenal cell rest tumor*
2. Malignant tumors arising in pre-existent endometriosis
3. Stromatosis ovarii

* May be functional

VII. Metastatic Tumors of the Ovary

1. Metastatic tumor from breast
2. Metastatic carcinoma from uterus, oviduct and rest of the reproductive tract
3. Metastatic carcinoma from stomach (Krukenberg tumor)*
4. Metastatic carcinoma from large intestine
5. Metastatic carcinoid*
6. Metastatic carcinoma from miscellaneous organs
7. Metastatic carcinoma with stromal luteinization (thecomatosis)*
8. Metastatic malignant melanoma
9. Leukemic infiltration of ovary
10. Malignant lymphoma (secondary)
11. African lymphoma syndrome (Burkitt's tumor)
12. Metastatic sarcoma
13. Metastatic tumors of undetermined origin
14. Metastatic tumors in pre-existing ovarian tumors

* May be functional