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Post-menopausal bleeding with particular reference to granulosa cell tumor of the ovary

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POST-MENOPAUSAL BLEEDING WITH

PARTICULAR REFERENCE TO GRANULOSA

CELL TUMOR OF THE OVARY

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TABLE OF CONTENTS

POST-MENOPAUSAL BLEEDING WITH
PARTICULAR REFERENCE TO GRANULOSA
CELL TUMOR OF THE OVARY

The menopause, climacteric, is that period in the woman's life when the reproductive function ceases, menstruation either gradually or suddenly becomes a thing of the past. Not infrequently this is a stormy period in the woman's life and many pathological degenerative changes begin now along with the normal physiological involution of the reproductive organs. These pathological degenerative changes are either benign or malignant, too frequently the latter.

Normally after the menses cease, there is no flow of blood whatsoever from the vagina and any spotting or bleeding, however slight, must be considered as pathological. The importance of post-menopausal bleeding can not be emphasized too strongly because too often through careless handling, the woman's life is laid forfeit. Too often the source of the trouble is laid to "the change of life" when in reality pathology exists in the generative tract. This subject has a very important place in the practice of medicine because it is not an infrequent happening and too often it is due to a malignant degeneration. If any hope of cure exists, it lies in the immediate approach to the problem, an

early diagnoses and institution of treatment.

Bleeding from the vagina is an indication for a thorough examination of the entire generative tract, because pathological lesions benign and malignant extend from the vulva to the ovaries. In many instances, the source becomes immediately evident and treatment may be started at once. Both benign and malignant lesions may coexist and it is dangerous to allow an apparent benign cause to be the entire explanation of post-menopausal bleeding without first ruling out all possible malignancies. (Anspach 2)

Many types of classification of post-menopausal hemorrhage are found in the literature. A composit of many of these by Payne (58) follows:

Author	Cases	Malignant	Benign
Brown (8)	164	66.8%	33.2%
Taylor (82)	298	63.0%	37.0%
Keene (31)	602	61.4%	38.6%
Geist and Matus (23)	190	58.0%	42.0%
Norris (51)	189	60.7%	39.3%
Pemberton & Lockwood (59)	195	58.9%	41.1%
Kanter & Klawaiss (30)	98	67.1%	32.9%
Green-Armytage (25)	304	38. %	62. %

These all agree roughly that about 60% of post-

menopausal hemorrhages are of malignant origin and 40%
are benign. This emphasizes the importance of this
symptom.

Payne (58) and Keene (31) then differentiate the
organs involved in these benign and malignant lesions:

Organs Involved	Benign	Malignant
Vulva and Vagina	20.1%	4.%
Cervix	58.5%	53.%
Tubes and Ovaries	2.1%	2.%
Uterus	16.2%	39.6%
Unexplained	2.6%	0.0%

This reveals the cervix as being the offender in
most of the cases both benign and malignant and also
shows a marked increase in percentage in cases of
uterine malignancies.

These two authors then group the types of benign
lesions:

Unexplained	2.6%
Trauma	27.5%
Inflammatory	29.6%
Tumors	40.3%

The importance of neoplastic activity is readily
seen because even in the benign lesions almost one-half
are on a neoplastic basis. Of these benign tumors,
ovarian cysts accounted for five cases, polypi, 53 and
myomas, 36. The polypi are both endometrial and cervical —

and are the most frequent single cause of post-meno-
pausal uterine bleeding. The myomata are a heritage
from days of uterine activity and degeneration in these
is an important factor in their bleeding. The ovarian
cysts are more rare and among these are granulosa cell
tumors which will be dealt with in fuller detail later
on in this paper.

Atrophy of the genital tract is responsible for the
most of the rest of the cases. The ischemic, thin,
senile vaginal mucosa is especially susceptable to non-
specific infections and trauma. In this category are
such conditions as senile vaginitis, urethral mucosa
prolapsus, atrophic cervical erosion and ulcers of
uterine prolapsus. These conditions produce more of a
spotting and frequently hides a carcinoma of some other
portion of the genital tract. Trauma is an important
factor in these lesions because with the atrophic
senile mucosa only slight injury tears the mucosa, this
is demonstrated in uterine and urethral prolapsus.
These are among the most frequent benign lesions seen
causing post-menopausal hemorrhage:

Kantar and Klawaiss (30) list 98 cases:

Carcinoma Cervix uteri	51	52.08
Carcinoma Corpus uteri	11	11.02
Carcinoma Vagina	1	1.02
Carcinoma Ovary	1	1.02

Carcinoma Vulva	2	2.04
Zona Granulosa Tumor	1	1.02
Senile Vaginitis	3	3.06
Urethral Caruncle	2	2.04
Fibromyomata	7	7.14
Erosions of Cervix	3	3.06
Prolapse of Uterus	5	5.10
Polyps of Cervix	8	8.16
Ulcer of Vagina	1	1.02
Fibrosis of Uterus	2	2.04
	98	

Green-Armytage (25) in a series of 304 cases divides them into visible and invisible causes.

Visible Causes

Urethral Caruncle	7
Urethral Carcinoma	4
Vulvar Carcinoma	10
Decubitus Ulceration with Prolapse	30
Traumatic pessaries etc.	18
Granuloma pudendum	8
Tuberculous ulcer of vagina	2
Syphilomata	5
Vaginal Carcinoma	5
Vaginal Polyposis	1
Polypi of Cervix	23
Infl. Granulomata of Cervix	1

Carcinoma Cervix	25
Tuberculosis Cervix	1
	140

Invisible Causes

Carcinoma Corpus uteri	21
Sarcoma Corpus uteri	7
Fibroid uterus	25
Polyps	37
Senile Metropathia	7
Metropathica Hemorrhagica	17
Ovarian Tumors	
Benign	6
Malignant	36
Granulosa Cell Tumors	5
Arterio-sclerosis	2
Tuberculosis of uterus and adenexia	1
	164

Then again Pemberton and Lockwood (59) list the benign causes of post-menopausal bleeding from their series of 195 cases.

Polypi		62
Cervical	25	
Endometrial	21	
Myomatous	4	
Mixed	2	

Polypi and Fibroids	4
Fibroids Only	2
Cervicitis	72
Endometrial dysplasia	1
Ovarian Tumor	7
Pelvic Inflammation	2
Cirsoid Aneurysm of Uterus	1
No lesion accountable	43
	195

These give idea of variety of local lesions which may be cause of vaginal bleeding. The polypi, myomata and senile inflammations are the most important and frequent causative facotrs except malignancies.

von Graff (86) says the cause of uterine bleeding at this time is due to the fibrosis which the uterus undergoes, the reduction of muscular elements and increase in fibrous connective tissue elements, resulting in a dimminished contractility of uterus. This uterine sclerosis is an important factor in hemorrhage.

Brown (8) says this bleeding is rarely functional and Hartman, Frior and Beiling (28) offer an explanation of this by their experimental work on animals. They found that menstruation will procede for a time without ovulation or formation of corpora lutea and that from their experimental evidence the hormone of the anterior lobe of the hypophysis is responsible. In yearlings

with hypophysis removed, injection of ovarian extract produced no hemorrhage while in normal ones it did. Then injections of anterior lobe extract produced bleeding in both normal and hypophysectomized animals.

Hawkins (29) lists some of the systemic diseases which might be responsible for uterine bleeding such as scarlet fever, diphtheria, typhoid, scurvy, malaria, lead poisoning, blood dyscracias with a deficiency in thrombin and calcium, chronic depression, hysteria and sedentary habits, chronic renal, cardiac and hepatic disease. The probability of the former being the cause in post-menopausal women is slight.

Anspach (2) describes in good detail the procedure to be followed when such a patient presents herself. First, the prime requisite of the examiner is that he be familiar with and able to recognize any and all causes of post-menopausal bleeding of local origin.

In examining external genitalia look for evidences of senile vaginitis in the atrophic mucosa. It frequently is the cause. Fissures especially at the fourchette are lesions also frequently seen. Prolapse of the urethral mucosa with ulceration is easily identified. Decubitus ulcers of cervix with prolapsus are visualized. Rarer, ulcerations of tuberculosis and syphilis will bleed as will venereal warts. Herpes eruptions have been the source.

Malignancies of the vulva and vagina bleed freely but usually start with a thin irritating discharge. Malignancies about or of the clitoris produce a hopeless picture unless seen very early.

The inflammatory lesions usually predominate in the lower genital tract.

The first examination should reveal whether the blood is coming from uterus or cervix. Inspection of cervix leads to carcinoma, sarcoma, polyps or erosion. A biopsy may be required for differentiation. If the cervix is not diseased and the blood is coming from the uterus, the body and adenexa must be examined closely. If the uterus is enlarged it is probably the source of the bleeding; if not, it doesn't rule the fundus out, however. Vigorous palpation may disclose sight of hemorrhage. If unsuccessful, try again in a few days or use the Clark Test.

During the interim apply silver nitrate in a 1-2% solution to abrasions of the mucosa and cervix and douches of .5% lactic acid to heal lesions of lower genital tract which may accompany lesions above.

As for the tubes and ovaries, if the uterus is not large and bleeding from above, think of Carcinoma of the tubes and if an adenexa mass is present a section is warranted. Carcinoma of ovaries does not always produce bleeding but a granulosa cell tumor in senile women

gives the characteristic picture of pseudo-menstruation with or without palpable ovarian tumor.

The blood may come from the rectum or bladder or in an apprehensive woman highly colored urine or feces may be thought of as blood. At any rate, examine these sources and even if they turn out positive examine the rest of the urogenital tract.

Witherspoon (89) tells of the advantages of a diagnostic curettage when vaginal examination reveals nothing remarkable. The procedure should be done to rule out malignancies. The curettage aids in diagnosis of pyometria, cervical polyps, fibroids, senile endometritus, frank hyperplasia, and carcinoma. Pyometria, senile endometritus show tissue possessing inflammatory reactions with no malignancy. Polyps and fibroids show up with microscopic examination. In hyperplasia as seen in granulosa cell tumor the endometrium is thickened, smooth glistening, comes away in abundant strips. In carcinoma there is brought out whitish firm blocks of necrotic tissue. Normally at this age the endometrium is thin, scanty, and the uterus is hard and sclerotic. Curettment saves unnecessary operations on benign lesions and prevents incomplete operations when extensive malignancies are present. The procedure is a safe and simple one to do.

All things considered then, it appears that postmenopausal vaginal bleeding is a fairly complicated

picture and every effort must be made to determine its source because of the high percentage of cases in which the cause is a malignancy which demands an early start in treatment to give patient any hope. Every effort possible should be advanced to educate these post-menopausal women to seek competent medical advice at the very onset of any spotting or bleeding however slight.

Now, in the following pages, one or the rarer causes of vaginal bleeding will be considered in detail.

GRANULOSA CELL TUMOR OF THE OVARY

AS A CAUSE OF VAGINAL

BLEEDING

DEFINITION

Granulosa Cell Tumor of the ovary is that condition which is characterized in young girls by sexual precocity, in sexually active women by menstrual irregularity, in post-menopausal women by rejuvenation and pseudo-menstruation, which pathologically is made up of structures resembling normal follicles, which originated from embryonal mesenchymal "rests", which secretes folliculin causing secondary endometrial Hyperplasia, which is of low malignancy and which is usually readily amenable to treatment by exterpation of tumor.

GRANULOSA CELL TUMORS

OF THE OVARY

INTRODUCTION

While this paper deals primarily with post-menopausal conditions, the scope of the granulosa cell tumor is wider than that: so for completeness the granulosa cell tumor in it's entirety will be considered.

This tumor of the ovary, which as its name indicates, is related to the granulosa cells of the Graafian follicle morphologically more than as a direct descendant, has stirred up special interest in the profession at this time when everything seems to be connected in some manner or form to the endocrine glands. It is a tumor of the ovary which does produce hormonal effects, as proved by many investigators. The hormone folliculin with its characteristic effects, has been demonstrated in the urine and tumors of women who have a granulosa cell tumor.

This tumor has long been seeking to invade the knowledge of the profession, being described first in 1895 by v. Kahlden (87) but from then up until only four or five years ago there have been but few attempts to say much about it in the literature. The ordinary texts as yet devote a very brief description to what in the past few years has turned out to be one of the most interesting problems with which we have to deal. To

quote Novak and Brawner (55) on this:

"The present day interest in tumors of this variety
is due, first, to a realization of the fact that they are
not nearly as rare as was once believed; and second, to
the fact that they possess interesting biological pro-
perties not possessed by most other ovarian tumors. It
is this last characteristic expecially which, in this
day of feverish interest in gynecologic endocrinology,
has stimulated the study of granulosa cell tumors of the
ovary".

Lissowetzky (43) says that growths of the germinal
epi. are important clinically because they are always
strong enough to exert secretory influences bringing
about marked changes in entire organism.

HISTORY

Most authors attribute (TeLinde (83), Novak (54), Brawner (55), Long (53), and others) the description of the first granulosa cell tumor to v. Kahlden (87) when he described his "adenoma of the Graafian follicle" in a nine year old girl in 1895. In this case he was concerned more with the pathological than the clinical side of the story and he believed the tumor to be a result of proliferation of the Graafian follicle. He described it as "a peculiar form of ovarian carcinoma". Robinson, however, quotes Rokitansky (65) and says that in 1855 he described an ovarian tumor composed of epithelial cells closely resembling the granulosa of the follicles and containing ovoid and folliculoid bodies. Aconni (1) in 1890 observed in a papillary cystadenoma of the ovary structures similar to primordial ova and interpreted these as products of neoplastic activity, not as a cystic degeneration as Rokitansky did. Emanuel in 1893 described a bilateral tumor in ovaries as a transformation of follicular cells. Later writers now are inclined to doubt whether the tumors described by Rokitansky, Aconni and Emanuel were really granulosa cell tumors.

Schroder (68) in 1901 described a tumor of the ovary in a woman, 36, which resembled follicular epithelium and

and he believed it to be derived from granulosa cells and like v. Kahlden believed ova were present. To this tumor he gave the name folliculoma.

Liepman (42) in 1904 advanced the idea that these cells were not true ova but rather products of regressive metamorphosis. To Werdt (88) in 1914 goes the honor of giving the present name to the tumor when he described six cases although two were obviously not granulosa cell tumors (Novak and Brawner (55)). He gave them the name of granulosa cell tumors because of their resemblance to granulosa cells, and because the theca interna and ova were missing.

To Meyer in 1915 goes the first description of the most favored concept of histeogenesis namely from embryological rests in development of the follicle and also the refuting of the idea origin from adult granulosa cells.

TeLinde (84) when he wrote his article in 1930 said only three cases had been reported in the American Literature; Robinson (63) in 1923, and King (33) in 1929, the rest of those reported were in foreign literature and were under the names of adenoma of Graafian follicle, folliculoma ovarii malignum, carcinoma folliculoides, oophoroma folliculare and granulosa cell tumor.

Since then the number of cases reported has been steadily increasing and now it has been estimated over 200 cases have been reported. Novak (55) says it would

be difficult and of no great value to attempt to review
all of the cases reported because of the difficulty of
appraising properly many of the cases reported in the
older literature, especially where good illustrations
were lacking.

INCIDENCE

The earlier writers were all inclined to believe this to be one of the very rare ovarian neoplasms. At the present, it is being realized more and more that the condition is not as rare as was formerly thought. Knowledge concerning this tumor is appearing with new cases all the time.

While most authors are agreed that most cases occur beyong the menopause, the tumor is not restricted to those years. To quote a few specific facts:

M. Schultz (69) in 1933 says the tumor is relatively rare and benign, there having been 4 cases in 43 ovarian carcinomata in 7,500 gynecological cases in 19 yrs.

Szathmary (78) in 1932 says there had only been four cases in the entire Hungarian literature reported at that time. He reviewed the world's literature and there were only 110 cases, 50 % of which were in women over 50 years old and 2 cases in five year olds.

Eerland and Vos (14) in 1935 say that in Java in 8 years there has been 451 ovarian tumors, 8 of which were granulosa cell tumors.

Fauvet (17) in 1933 says the condition is not so rare as was formerly thought as 8 cases in 76 ovarian carcinoma at the University clinic of Leipzig shows.

As regards age incidence most writers report on cases beyond puberty. (Kelley and Guassie (32), Lepper,

Baker and Vaux (41), Novak in 1933. (52). The age
distribution varies from 14 months to over 70 years
old. Eerland (13) in 1932 reported a case in Javanese
child of 14 months which was proved by autopsy to be a
typical granulosa cell tumor with typical cells and
follicle like cysts. Best (3) in 1935 reported case
in a 6 year old with sexual precocity; Bland and Gold-
stein (4) in 1934 reported one in a girl 7 years old.

Bland and Goldstein (5) 1935 listed 150 cases.

10 yrs. & under	8 cases
10-19 yrs.	7 cases
20-49 yrs.	65 cases
50 yrs.	70 cases

This bears out the above contention while in a
smaller series Novak and Browner (55) in 1934 had only
6 cases definitely beyond the menopause in a series of
33 patients and Kleine (38) had only 3 in a series of
12 cases.

Novak and Brawner:

	Cases	Percent
10 yrs. & under	5	15.15
10-19	1	3.03
20-29	4	12.12
30-39	7	21.21
40-49	12	36.36
50-59	3	9.10
60-69	1	3.03

They all seem agreed that the cases before puberty
are very rare and from summary of all, the rest are al-
most evenly divided before and after the menopause.

Louros (45) in 1935 presented two cases in sisters,
one nineteen and unmarried who died with pulmonary
metastatic lesions which was diagnosed by R. Meyer,
and the other , twenty-two married and who after removal
of tumor recovered completely. This makes one think of
possibility of heredity.

The tumor seems world wide being reported from many
sources in the literature.

ETIOLOGY AND HISTEOGENESIS

The etiology of this neoplasm is no different from the etiology of any other neoplastic growth, there seems to be an inherent factor stimulated by an exciting agent which leads to the proliferative growth. Goodall (24) in 1912 says the local origin is explainable but wonders why at certain time these cells proliferate. He attributes it to one of the following:

1. Inhibitory substance which disappears.

2. Stimulating substance which appears.

Before airing the theories as to histeogenesis, it would be well at this point to review briefly the ovarian development and origin because herein lies the explanation. Felix (18) says the sex cells and surrounding cords arise from the germinal epithelium which arises from the peritoneum of the body coelom and which is formed directly from embryonic connective tissue. The granulosa cells are formed by proliferation of cells about the sex cells. Fischel (19) says the germinal epithelium does not form the sex cells but that these are formed in thickenings of the embryonic connective tissue just beneath the germinal epithelium but which is entirely distinct from it. He denies absolutely any projections of the germinal epithelium down into the ovarian stroma. He wonders how the omnipotent sex cell can be considered to arise from a tissue (the germinal

epithelium) which has already undergone some special-
ization. Fischel's view whether correct or not gives
a better explanation of the varied picture seen in
granulosa cell tumors as will be shown below. The
granulosa cells arise from the cells immediately surround-
ing the sex cells and cords. The common view is that the
germinal epithelium makes a second down-growth into the
ovarian stroma about the 3rd month of intra uterine life
and forms what is known as Pfl ugers egg tubules or
cords and from these arise the primordial follicle with
their enclosed sex cells. These tubules then disappear
leaving the primordial follicles in the ovarian stroma
(the medullary portion).

There are two main sides in the histeogenesis of
these tumors. On one side are those who believe the
tumor arises from embryological "rests" and that no ova
are present in the tumors and in the other are those who
claim that the tumor arises by a proliferation of adult
granulosa cells and that ova are present. The first
viewpoint was first put forth by Meyer and since then
has found support by Novak (53), Brawner (55), Te Linde
(83,84), Geist and Matus (22,23), Taussig (81), Eerland
and Vos (14). The latter viewpoint is supported by
Schroder (68), Robinson (63,64), Eiss (15), Ewing (16),
Show (72), Holmer (27), Lissowetzky (43,44), Blau (6),
Eerland (13), and Krompecher (39).

Rokitansky (65) in 1855 believed the condition resulted from a cystic degeneration of the ovary. Then v. Kahlden (87) in 1895 said the tumor was the result of segmentation of primordial follicle and ova. Schroder (68) in 1901 first said the tumor origin was from granulosa cells of follicle with ova present. Liepman (42) in 1904 believed origin to be from a retrogressive metamorphosis of the follicular epithelium.

Goodall (24) in 1912 wrote a massive article on the origin of epithelial new-growths in the ovary in which he put forth six views as to origin:

1. Germinal Epithelium.

2. Paraovarium which has invaded ovary.

3. Ingrowths of fimbrica ovary.

4. Graafian follicle

5. Corpus luteum.

6. Any of above.

In this article, Goodall compares human vestigial structures with lower forms in an extensive comparative anatomical research. He observed fetal structures persisting in the human ovary and could identify them through his anatomical studies. He found a variable amount of glandular tissue which was not connected with Graafian follicles or any other functioning tissue. This arrest of development in functioning material is always a bilateral phenomenon. In this work, Goodall showed

the rete ovarii to be present in one out of eleven cases
in the 120 cases studied and it was always bilateral in
position and because of its location near the hilum, it
had been thought of as of paraovarium origin. Goodall
however, showed that in fetus it extends from core of
the ovary to the infundibulo-pelvic ligament and be-
cause the cells stained with Sudan III like stroma cells
of the ovary. This relation to hilum is no criterion
as to origin then. He puts forth a new view as to origin
of tumors of ovary by saying the ovary is vulnerable to
neoplastic growths because it contains so much tissue
superfluous to its general economy that each bit of this
tissue is a menace to the ovary. Goodall was at a loss
to explain why one person would have abundant "rests"
and another none or few. He believed it to be an idio-
syncracy, atavistic in character, from his study of
ovarian tumors in families. The bilateral character of
these "rests" is seen from Royal Victoria Hospital
records from 1902-1912 in which there were 37 double
and 9 single ovarian tumors. From this he concluded
ovarian malignancies started simultaneously in both
ovaries independant of each other. Because the growths
in granulosa cell tumors are so varied, and because he
has seen invasion of ovary by germinal epithelium, he
believed this to be the source of these. He said the
presence of cilia did not rule out the germinal epithel-

ium as the source because in lower forms, ciliated germinal epithelium is normal and this would be a developmental arrest at that point. Goodall goes on to say that embryological arrests are not responsible for all tumors in women beyond thirty because he has seen corpora lutea in shrinking down, pull down the germinal epithelium into folds which caused many changes in cellular structure. Some men say chronic inflammation will do the same thing as well as the lobulated ovaries seen in some children and feti. Goodall refutes earlier ideas of origin of granulosa cell tumors by saying he has seen no indication for saying follicular epithelium is responsible for their growth and that all that can happen to these is formation of follicular cysts, which is a degenerative process, not a vegetative one. The corpora lutea give rise to retention cysts but no neoplasms.

Meyer (47) in 1915 advanced his theory which is accepted by most authors now. He states there is no proliferation of follicular epithelium even in inflammatory condit ions and these tumors usually begin in women beyond menopause in whom there are no follicles nor ova present. This eliminates follicles as a source of the neoplastic activity. His idea is more against formation from follicular epithelium than for origin from embryological rests.

Geist (22) in 1922 stated that no normal follicles are present as one would expect if origin of granulosa

cell tumor was from proliferation of adult follicles
and also there are no ova present. He supports Goodall's
idea that the origin is from medullary "rests" which are
known in the fetus to produce normal follicles.

He claims the fact that the tumor has so many vari-
ations (which all writers agree) precludes orgin from
an adult mature cell such as the granulosa cell of the
adult follicle and that only a cell of primitive poten-
tialities is capable of producing such a varied picture
in the same tumor.

Roninson (63) in 1923 reduced the assumption of
v. Kahlden's in 1895 to an absurdity by asking how a
whole follicle could become adenomatous if as v.
Kahlden says each cell is a finished product incapable of
further activity. At this time, he agreed with Meyer's
and believed Meyer's work to be the best done yet on the
subject. He agreed that normal follicular epithelium was
dependant upon presence of an ovum. He explained the
theca interna, described by some authors in their
pathological reports, as due to the antipodal position
of the nuclei of the epithelium surrounding the cysts
and not as a real theca interna.

Krompecher (39) in 1924 described origin from nor-
mal stratum granulosum and included such tumors as
follicular adenoma and medullary carcinoma with the gran-
ulosa cell tumors.

Ewing (16) in 1928 in his book on neoplastic diseases, speaks of origin from follicles because of diffuse neoplastic overgrowth which he saw of the lining cells of small cortical follicles.

Fleming (20) in 1929 writing on origin or three ovarian cylindromata, lists the possible sources of growth.

I. Extrinsic

II. Intrinsic

    A. Granulosa Cells.

    B. Medullary Cords.

    C. Superficial ovarian epithelium.

    D. Rete Ovarii.

    E. Theca interna.

As regards extrinsic origin, he said it might be possible but very unlikely because no cells seen in surrounding ovarian tissue and no presence of carcinoma elsewhere in the body. He also puts weight on the fact that most patients are well many months and years after removal of ovarian tumors which is inconsistant with the idea that they are metastatic growths.

He says while cells resemble granulosa cells, he doubts this as origin because cells are more distinct, nuclei are not peripheral where cysts lie next to connective tissue, and the masses in the center of cysts are degenerative products and not ova.

He believed tumors arose from the medullary cord rests which as said before are capable of forming follicles in the fetus.

He rules out superficial epithelium by saying in his series of three cases that there were no ingrowths of this epithelium seen and that the tumor cells in no way resemble this epithelium.

The rete ovarii he ruled out by saying that in two of his cases, the hilus of the ovary was not involved at all and cells do not resemble rete cells either.

The theca interna is also ruled out because while cells may resemble the theca interna, there is present no meshwork between the cells.

Robinson (64) in 1930 makes more hypotheses absurd by disagreeing with Goodall's explanation of "rests" being found in fetal and children's ovaries is not consistant with presence of granulosa cell tumors in old women. He then goes back to his original idea of 1923 when he said the follicle as a whole was incapable of adenomatous growth but adds there is a difference between the follicle as a whole and the follicular epithelium. He agrees that the number of follicles (about 200,000) never increases but does believe the follicular epithelium possesses unequaled metaplastic properties. He claims the morphological resemblance of the tumor cysts to normal follicles with ova is not a degenerative process nor the result of

liquification but a reversion to type of the epithelium
(follicular) and the granulosa cell tumor starts in the
follicle itself by proliferation of the follicular epi-
thelium and the so-called folliculoid and ovoid bodies
described are remains of follicles. He says in one of
his cases he observed a typical Graafian follicle with
the granulosa cells invading the ovarian stroma. He
states this proliferation first forms in strands or
clumps, then invades the stroma and becomes solid. He
also observed some granulosa cells invading corpora lutea.

TeLinde (83) in 1930 considered the possibility of
origin of granulosa cell tumors from adult granulosa
cells of a Graafian follicle and from embryological
"rests". He favored the latter because in one of his
cases which portrayed a microscopic tumor, the tumor
was located in the medulla of the ovary. This is the
site of development of the follicles before they mi-
grate to the cortex which some place is the only place
follicles are found in the adult.

Lissowetzky (43) in 1930 believed morphological re-
semblance of tumor to normal follicular arrangement of
intrinsic connection because of the secretory capacity
of the tumor cells and the presence of lipids in them
as in normal follicular epithelium.

Meyer (47) in 1931 said it had never been demon-
strated that the granulosa cell tumor could arise from
follicular cells and it was highly unlikely because of

the slavish dependance of the same for their existance
upon the presence of ova which were not present in a
granulosa cell tumor. He admits proliferation of gran-
ulosa cells in case of a chorioepithelioma or a hydati-
form male but in these cases, they always disappear upon
removal. He denies this could be responsible for a gran-
ulosa cell tumor. He states majority of cases found in
women beyond menopause when no follicles are present..
He further states that there are present in the medul-
lary portion of the ovaries of every fetus, child and
some older women, unused cells which form normal granu-
losa cells and these remain in an undifferentiated state
until later in life when some exciting mechanism causes
proliferati on with formation of granulosa cell tumors.
Meyer also said many of the smaller tumors arose from
medulla and contained no ova in the follicles and no
theca lining them. This agreed with TeLinde's view.
He had two cases of granulosa cell tumors in tissue at-
tached to the ovary proving some embryological abnormal-
ity. He had a case in a child with normal follicles
in a portion of the ovary which he considered inconsis-
tant with view that the origin was from follicular epi-
thelium.

Taussig (81) in 1931 supported the view of Meyer
and TeLinde. Syathmary (78) and Blau (6) in 1932 sup-
ported the view of origin from normal follicular epi-

thelium while Eerland (13) supported the view of from embryological "rests" by saying these tumors arose from germinal epithelium which did not form primordial follicles.

Eiss (15) in 1933 supports Robinson's view by citing a case in which he observed origin of tumor by proliferation of granulosa cells about a Graafian follicle. He also stated that all these ovarian epithelial tumors are different phases of the same tumor.

Show (72) in 1933 gives a critical analysis of present work done and says every article on the histeogenesis of ovarian tumors is cluttered up with inaccuracies but he makes no definite statements himself. He disagrees with Goodall and denies presence of embryological "rests" and says if present at all, they are extremely rare and that the medullary cords which are the site of these "rests" all disappear. He further states that during the third month of intra-uterine life, there appears a second downgrowth from the germinal epithelium and from this system the primordial follicles arise and some follicles arise in medulla independent of this second growth. (Consistant with Fischel's view.) He claims it is pure hypothesis to say neoplasms arise from either medullary cords or these secondary downgrowths. He says if these secondary cords were tubules and as such have never been described, he could visualize their being sources of neo-

plasms. In view of these inaccuracies, he rejects these theories as harkening back to the unscientific days of the 19th century.

In 1933 Brewer and Jones (7) came out with assumption that these conditions are not neoplasms at all but rather a hyperplasia of the granulosa cells in spite of the bizarre patterns seen. They say the groupings are discrete and there is very little invasion of the ovarian stroma. They believed the site of this hyperplasia to be in the medulla and in these cases, the cortical follicles were not abnormal.

Holmer (27) also, in 1933 in describing a case with metastasis, says origin from granulosa strands. He believed the condition to be a systemic disease and when primary source was removed, metastatic lesions would disappear. He linked this systemic disease up with periods of greatest ovarian change, at beginning and ending of sexual activity. His patient, later on, had a recurrence of mass in pelvis.

Novak himself (52, 54, 56), Novak and Brawner (55) and Novak and Long (53) in 1933 and '34 interpreting the origin of the granulosa cell tumors in light of Fischel's view of ovarian development decided the origin of these tumors was from embryological "rests". They said all pathological variations of this tumor were explained by this view. The origin of the tumor was from

a cell of embryonal mesenchyme which retained potential-
ities of forming either sarcomatous structures or carcin-
omatous structures, thus explaining the ovarian sar-
comata with hormonal disturbances as being another type
of granulosa cell tumor. They also say these "rests"
have been observed in close connection with granulosa
cell tumors.

Eerland and Vos (14) in 1935 also support this view
of origin from mesenchymal rests with multipotentialities.

This then, gives the whole confusing picture as to
the histeogenesis. Each view seems to possess some truth
as to being the real thing and seems based on some evi-
dence, yet no one seems to explain all cases with ex-
ception of those interpreted in light of Fischel's view
on ovarian development but even Fischel's view is not
undisputed. It seems, however, the weight of evidence
and the present day trend to explain neoplasms in gen-
eral to proliferation of embryological rests favors this
type of origin as regards granulosa cell tumors of the
ovary. The biggest objection to the view of origin from
normal follicular epithelium is that it is totally lack-
ing as an explanation to the majority of cases, that is,
those which occur even years beyond the menopause when
no more follicles are present. Those writers who describe
these tumors as arising from the medulla of the ovary and

other places where follicles are not present have a convincing argument also. So until a better explanation is offerred, this serves the purpose very well.

PATHOLOGY

The pathological picture, expecially the microscopic picture is highly varied but modern theory of histeogenesis of the granulosa cell tumor has explained this varied multi-colored picture. The pathology in these conditions is divided into two groups.

    1. Pathology of the Ovarian Tumor.

    2. Pathology in Associated Structures.

        A. Metastatic lesions.

        B. From hormonal influence.

1. Pathology of the Ovarian Tumor.

Gross - These tumors usually occur unilaterally, although they may be bilateral. They vary in size from being almost microscopic to the one of TeLinde's (83) which was 30 cm. in diameter and weighed 9.2 kilograms. They usually, however, are relatively small because they are removed before becoming large. All authors agree on the gross description of the tumor. It is well encapsulated, being covered by a thick fibrous capsule, even the large one TeLinde described which was of four years duration. There are some few of the malignant ones which are not well encapsulated, being fixed more or less in the pelvis. There may be ascites present in the abdominal cavity upon opening abdomen but this is usually not the case. These tumors show a marked vascularity, glisten

on exposure, are whitish to pinkish in color depending
upon thickness of capsule. Usually the entire ovary is
involved. No normal ovarian tissue can be seen. They
may be firm or spongy depending on the predominant type
of pathology present. The small ones tend to be firm
and the larger ones softer and spongy due to the cystic
formations in the tumor. On cut section, there are seen
a variable number of different sized cysts varying from
pea sized to egg sized and which are filled with a straw
colored clear fluid which may at times be hemorrhagic.
Kelley and Guassie (32) described a case in which the
surface of the tumor was marked-ly lobulated and on the
cut surface showed numerous rough nodular areas separ-
ated by thick fibrous septa. These nodules vary from 3
to 5 cm. in diameter and were gray and yellow in color
and appeared very coarse. This was of the cylindromatous
variety to be described below. These tumors may have a
twisted pedicle. Plate (61) described one in a young
girl 14 years old in which the tumor pedicle was twisted
to an angle of 270°.

Microscopic:

All authors agree there is a varied picture pre-
sented by this tumor and must abide by the classifica-
tion set forth by Meyer (47). The same authors follow
his classification as to type of tumor as were siding
with him in the question of histeogenesis.

The extreme variability of the microscopic picture accounts for the confusion which has existed in the nomenclature and classification of these tumors. Not only do different granulosa cell tumors vary, but different parts of the same tumor vary. This means many sections of the tumor must be studied to get a clear picture.

Meyer's classification of types of pathology seen divides granulosa cell tumors into four types:

1. Folliculoid or ovoid.
2. Cylindromatous.
3. Diffuse.
4. Sarcomatous.

All four of these types can be found in any one tumor but usually one predominated and the tumor is named from the type that predominates.

Regardless of pathological type, the cells in these tumors remain about the same. Morphologically, they resemble normal granulosa cells of the follicles in the ovary; hence the name of the tumor. The cells are very uniform in size, shape and staining characteristics. The tumors cansist of a fibrous or fibromyxomatous stroma invaded by masses of polyhedral cells, which possess no definite cell membrane. The cytoplasm in different tumors varies from clear to a clear granular foamy substance, but in all instances, is scanty, the nuclei being the prominent part of the cell. The cytoplasm

takes an eosin stain. The nuclei are round or oval and
contain chromatin and evident nucleoli. The chromatin
is arranged in five granules and threads. The nuclei
take a deep hematoxylin stain. There is a paucity of
mitotic figures except as noted in very young tumors.
The bulk of the tumor is made up of these masses of gran-
ulos like cells. There is more or less hyaline stroma
and the older the tumor, the more stroma and hyaline de-
generation present suggesting along with disappearance of
mitotic figures that as these tumors become older, activ-
ity decreases and fibrosis and degeneration set in. The
blood vessels are immature and in some cases (Kelley and
Guassie 32) showed proliferation of the intima with
occlusion of the lumen. Some of these tumors (Novak 52,
Eerland 14) show variable amounts of nodules composed
of cells resembling corpus luteum cells. Novak suggests
that a metamorphosis had taken place in his case and
Eerland says the presence of these lutein like cells is
evidence of maturity. He says maturity increases as the
arrangement of cells in the tumor passes from structures
resembling primordial follicles, to Graafian follicles
to corpus luteum. These tumor cells contain lipoid
substance as is shown by Sudan III and this is evidence
that these cells also possess a secretory function which
is also borne out by presence of decidua reactions and
secreting epithelium present in the endometrium. Plate

(62) describes one of these fat containing tumors as resembling the "lipoid folliculoma of Lecene."

The histological criteria of malignancy in these tumors are much in discord with the clinical. There may in some instances, be much histological evidence of malignancy such as hyperchromatosis, disparity of nuclei and cells, and mitotic figures expecially in the young tumors with no evidence of malignancy clinically years after removal (Novak and Brawner 55).

To return to Meyer's classification, the first type to be considered, is the folliculoid variety. It is to be remembered that follicles are present in some sections of all of these tumors but that this is just a convenient term to apply when these structures predominate. The folliculoid type is that one which, on cut section shows a myriad of small to large cystic cavities. In this form, the tumor cells arrange themselves in rosettes a-bout a central lumen to resemble primordial follicles. Krompecher (39), made an interesting observation con-cerning these in 1924. He said these same rosette features are seen in basal cell tumors of the salivary glands and are not characteristically peculiar to the granulosa cell tumor as primordial follicles. Often in these rosettes are seen areas of cystic liquification (Meyer 47) and surrounding tumor cells are theca like structures. In these larger follicle like cysts, this

theca like capsule is apparently due to the antipodal arrangement of the nuclei of the cells surrounding the cyst. The cells of the inner layer have their nuclei towards the lumen and the cells of the outer layer have their nuclei peripherally. This liquification as stressed by Meyer has been opposed strongly by Robinson (64) and his followers who say this structure is really a remains of a true follicle. In the center are found homogenous masses which earlier writers confused and thought to be atypical ova, but Meyer said these were just products of cystic degeneration and this still meets with disapproval of some (Robinson and followers). In many instances, these cystic cavities are large and resemble Graafian follicles more than maturing and primordial follicles. These cysts then, are called either "microfolliculoid" or "macrofolliculoid" by Novak and Brawner (55). Te-Linde (83) observed, also, in some of these larger cysts, not only an outer hyalinized membrane, but also an inner one which separated the granulosa cells of the tumor from the cystic cavity. This is further evidence of origin of cystic cavities as a degenerative phenomenon.

Brewer and Jones (7) reconstructed these follicle like structures. The cells lining them were cuboidal and in many instances, contained central cells similar to and the same size as ova. Each of these had an

eccentric nucleus and lots of yolk. They are the ones who said this condition was not a neoplasm but a granulosa cell hyperplasia, saying in spite of bizarre groupings of cells, they were discrete and not unlike the fetal picture in the formation of primordial follicles.

Geist (22) in 1922 in describing case in woman 52 years old, post-menopausal, said tumor was polycystic. There were small white nodules of epithelial cells in unchanged stroma and these varied from few strands to large aggregates and branching strands. He says the cysts form by fusion of small patches of degenerative necrosis in the centers of these aggregates. The cysts were eccentrically placed in these cell masses, and in enlarging, they grow by extension and fusion of smaller cysts. He showed photomicrographs illustrating this feature. He says in the center of these cavities is a homogenous mass which, on first appearance, seems to be an ovum but on closer examination, it proves to be a secretion product or a disintegrating product of degeneration. This process is a pseudo-oogenic process. In many of these cavities, there are multiple pseudo-oogenic attempts.

Holmer (27) in 1933, brought in a new idea on these cystic cavities, instead of interpreting them as being degenerative or liquification attempts, he says the size of these cavities tended to be reduced by inward

growths of radially arranged cells.

In this same tumor described by Holmer, the cells were very active and many atypical mitotic figures were present, explaining the reason for metastasis. Holmer said there was very little stroma present in this tumor about the follicles and that present gave him the impression of being there before the tumor was found. This same tumor showed cells rich in lipoid substance as seen with Sudan III and cells resembled corpora lutea cells very closely, even under high power. He said there were some degenerative ova in some of the follicular cavities. Some portions of the tumor had a wild appearance with irregular cavities and shoots of epithelial cells suggesting malignancy. Some parts of the tumor, he thought, resembled hypernephroma tissue but absence of hemorrhage ruled this out according to Holmer.

Plate (62), in describing 600 gram tumor, in a woman 61 years old, of the left ovary, said the tumor composed of two parts: one of which possessed typical granulosa cell tumor appearance with follicles and cylinders both, and the other part was a teratoma containing glands, bone and myxomatous tissue.

Meyer (47) also described folliculoid tumors in association with a fibroid of the ovary and another with a papillary cystoma.

Frankl (21) describes a case in a woman 62 years

old, nine years post-menopausal in which there was a typical follicular granulosa cell tumor of the left ovary and the right ovary had a pea sized tumor of typical thyroid tissue. Frankl believed there was no relation between the two. This resembles the tumor described by Lissowetzky in which there was structure resembling thyroid tissue in the same ovary of the tumor in which he believed there was a relation.

To return, then, to the second group in Meyer's classification, the cylindromatous predominating type, the main grouping here consists of branching and anastamosing cords and strands of typical tumor cells. These cords are separated by bands of fibrous connective tissue in variable amounts. These septa split the epithelial cells into typical cylinders. Grossly, these tumors are predominantly hard and firm. They resemble closely medullary carcinoma of the ovary. The connective tissue septa usually show evidences of overgrowth and hyaline degeneration. All sorts of bizarre pictures are seen due to the different arrangements of connective tissue and epithelial cell strands. This type and the follicular type are the two most frequent types seen, the rest being very rare.

The third type, or the diffuse type, shows many masses of epithelial cells but not many follicles or cylinders.

The last type or the sarcomatous type is explained by the theory of histeogenesis which claims these tumors arise from mesenchymal embryological "rests" and these tumors when only one section is studied, presents a pathological picture not at all different from other ovarian sarcoma with malignant connective tissue cells. The distinguishing features in this type of granulosa cell tumor lies in the presence of symptoms arising from overproduction of folliculin and from study of many sections, some of which will show features of other types of granulosa cell tumor.

Novak and Brawner (55) observed transitions in a sarcomatous granulosa cell tumor from the usual epithelial cells seen to the sarcoma cells. Only origin from a highly undifferentiated multi-potential cell could produce such a varied picture.

2. Pathology of Associated Structures.

A. Pathology from Metastatic Lesions.

In all cases recorded with metastasis elsewhere in the body, the typical pathological picture is presented, Klaften (36), a typical granulosa cell pathology in a metastatic lesion in the leptomeninges at the base of the brain in a 10 year old girl. Saltman (67) reports a case in a woman aged 43 with typical pathology in metastatic lesions in the first and second sacral vertebrae. This woman died in the 10th post-operative day from a

paralytic illeus. This was the first recorded case
with metastatic bone lesions. Holmer (27) in his
description of a case with metastasis to cervix and body
of uterus, showed along with typical granulosa cell
tumor pathology, a picture resembling corpora lutea
cells which were also seen in primary lesion. These
cells possessed staining reactions of corpora lutea cells
also.

B. Pathology from Hormonal Influence.

The associated changes are those due to the presence
of an overproduction of folliculin which affects the
primary and secondary sex organs.

In young girls, before puberty when this tumor
occurs, there is hyperplasia of the endometrium, men-
strual flow and hypertrophy of the uterine muscula-
ture. The enlargement which makes the uterus the size
it would have become with normal onset of active sex
life. The vulva assumes a mature appearance, enlarges
and pubic hair appears. The mammary glands undergo
hypertrophy and proliferation of tubules and stroma tis-
sue but no secretion (Novak and Brawner 55) and instead
of normal flat chests, these girls have the appearance
of mature women. Axillary hair also appears. Also in
young girls, as has been mentioned before, there is
early union of epiphyses and ossification of the skele-
ton.

In sexually active women, there is hyperplasia of the endometrium of the swiss cheese variety due to the overstimulation by folliculin. This pathology is the same as when seen in any other case of hyperfolliculin influence. The other changes, as seen in the young girls, would not be evident in these sexually mature women.

In post-menopausal women, the uterus is normally atrophic and the endometrium is thin, but under the influence of the folliculin, again, these uteri enlarge and become like they were before the menopause and instead of the thin, atrophic, senile endometrium, there is a thick hyperplasia of the glandular elements. This condition of hyperplasia in post-menopausal women is seen only in granulosa cell tumors.

Novak (53) cites a case in which there was marked secretory changes in the epithelium of the endometrium which further substantiates the view that the cells found in the ovarian tumors were lutein cells. The presence of secretory changes in the endometrium presupposes presence of progestion which, so far as is known, comes only from corpora lutea. Some observers have even seen decidua changes in the endometrium. Klaften (37) found evidences of endometrial activity by demonstration of glycogen in the cells.

The extent of uterine enlargement in these cases is

shown by Szathmary (80) in description of a case in a
woman 63 years old; the uterus was 21 x 13 x 10 cm., and
weighed 780 grams or 13 times the normal size.   There
were no myomata present just, hypertrophy.

The one constant finding which has been observed
in every case available for study is hyperplasia of the
endometrium and this, in post-menopausal women, is of
daignostic significance.

C.   Pathological Physiology.

The pathological physiology seen in these tumors
is the abnormal menstruation seen in the post-meno-
pausal women, and the young girls due to presence of
folliculin.   The endocrine influence of these tumors is
what has stimulated all the interest recently in them.
That folliculin is present has been demonstrated, as
described above, by Schuschiana (70) and Neuman (50).
The tumor cells retain capacity to secrete folliculin.

The presence of menstruation without ovulation
proves the hormonal influence of folliculin is the im-
portant factor.   The menstrual flow is not unlike that
normally seen.   Dworzak (11) describes menstruation in
a woman 52 years old with a granulosa cell tumor, post-
menopausal, which occured every two or three months
for two years and lasted for two or three days.   Novak
and Brawner (53-55) remark about the periodicity of this
pseudomenstruation.   Fluctuations in the blood level of

folliculin bring about the onset of blood flow. There is a periodic drop in the blood level of the folliculin. The cause for this drop is a reciprocal relationship existing between the tumor mass and the anterior pituitary through which the ovary normally works. When the blood folliculin reaches a certain level, an inhibition of the anterior pituitary develops and there is a resultant drop in ovarian activity because of action of ovary through the anterior pituitary and bleeding follows. (Novak 56).

The importance previously attached to withdrawal of either ovum or corpus luteum hormone as cause of menstrual flow, has been negated by the granulosa cell tumor because no ova are present and only in a few have corpora lutea like bodies been seen. In all there is the menstrual flow or irregularity of the menses.

The presence of progestion has been suggested in some few of the tumors by the secretory changes in the epithelium of the endometrium and by the presence of decidua reactions seen. (Novak 56).

There can be no development of pregnancy in those cases where pseudo-menstruation exists because there is no ovulation.

SYMPTOMS

Neumann (50) sums up symptoms by saying the tumor produces:

1. Maturity in children.

2. Menstrual disorders in sexually active women.

3. Youthfullness in post-menpausal women.

The symptoms seen in granulosa cell tumors vary with the age of the patient and they are conveniently grouped into three classes:

1. Those occuring in girls before puberty.

2. Those occuring during active sexual life.

3. Those occuring post-menopausal.

In those tumors occuring in young girls before puberty, the symptoms are those of sexual precocity, associated with or without an abdominal tumor. The sexual precocity includes development of secondary sexual characteristics with the onset of production of folliculin in the tumor. These characteristics are appearance of axillary and pubic hair, enlargement of the mammary glands, onset of menses. It is to be remembered, however, there is no ovulation associated with this, so pregnancy can not occur. (Novak 53) These symptoms all subside and disappear with removal of the tumor and withdrawal of the folliculin although Pahl (57) describes a case in a girl of seven with persistance of precocity after removal

of the tumor but there was an inability to find the hor-
mone in the urine. The breats, in this case, did, how-
ever, shrink a little. Rummeld (66) describes a case in
a girl of five years with removal of tumor and relief
from symptoms again with recurrence of tumor followed by
relief for 10 years following removal of recurrent tumor.
Klaften (36) reports symptoms of an interesting case in
a girl seven years old who developed severe nose bleeds
and at eight years, menstruation commenced. When the
child was nine years old, the pelvic tumor was removed.
This child improved, then, for 6 months and then head-
aches commenced. She began vomiting and showed signs
and symptoms of increased intra-cranial pressure. She
died in six more months and autopsy revealed a granulosa
cell tumor of the ovary with metastasis to leptomeninges
at the base of the brain.

The symptoms referable to the abdominal tumor are
those of any abdominal tumor, increasing in size with or
without pressure manifestations, torsion of the pedicle,
pain and ascites.

In the second group are those women during the active
reproductive era and in these, the symptoms are hard to
evaluate. There is a menstrual disturbance, which usually
is first associated with long periods of amenorrhea fol-
lowed by irregular menorrhagica. Holmer (27) describes
a case in a woman of 49 with metastasis to the cervix

and body of the uterus who had had almost continual
bleeding at admission with menstrual periods coming
closer together for a year. Smit (73) describes a case
in which uterine bleeding was the only symptom. Placeo
(60) describes a case in a girl 20 years old with metro-
rrhagia for four years. Szathmary (79) says tumors are
unilateral, so amenorrhea must be on a cachectic basis,
but apparently he forgets hormonal influence which
brings this about. The symptoms referable to the abdom-
inal tumor are not unlike those of the child.

The most interesting group is that one in which the
tumor occurs in women beyond the menopause. The onset
of symptoms may be any place from a continuance of nor-
mal periods to as far beyond the menopause as 22 years.
(TeLinde 83) In this last case, a woman bled for a few
days approximately every month for 6 months. These wo-
men almost invariably have a recurrence or return of the
menses, "pseudo-menses", during which the bleeding is
more or less cyclic and regular. Novak (54) says bleed-
ing of granulosa cell tumor is almost characteristic in
these post-menopausal women because of its periodicity
which distinguishes it from bleeding from other ovarian
tumors which usually is due to a metastasic lesion in the
uterus. Schultz (69) describes a case in a woman 2 years
post-menopausal where there was disappearance of vaso-
motor symptoms and upon removal of tumor, there was re-

currence all because of restoration of folliculin and
then subsequent withdrawal again. These women seem to
be rejuvenated and feel like younger women again. There
is usually some enlargement of the atrophic breasts and
colostrum may be expressed. Many times removal of tumor
causes these woman to suffer another climacteric set of
symptoms requiring ovarian extract for relief. There is
also an abdominal tumor here which may or may not pro-
duce symptoms as in younger women.

Bland and Goldstein (5) list analysis of symptoms
in 117 patients from all age groups:

Uterine bleeding	70 Cases
Abdominal tumor	16
Abdominal pain	13
Amenorrhea	5
Urinary symptoms	0
Breast enlargement	10
Sexual precocity	8
Ascites	1
Hypertrichosis	2
Accidental finding	1
Loss of weight	0
Masculinity	1
Recurrent in Vagina	1

These above are all to be expected but the mas-
culinity in one case. The granulosa cell tumor is the

"feminizing tumor" and masculinity is definitely out of line. This may have been a case of ahrenoblastoma, some-times confused with granulosa cell tumors and which is a masculinizing tumor.

It is seen the majority of symptoms are referable to the presence of the hormone folliculin and it shows its various manifestations in the different age groups. The symptoms referable to the abdominal mass are alike at all ages.

The duration of symptoms before consulting the doc-tor, varies from first menstrual irregularity to as long as four years as in a case of TeLinde (83) in which tumor was 30 cm. in diameter.

SIGNS

Examination of these patients doesn't always reveal much. Externally there are the signs of sexual precocity mentioned above in the pre-puberty cases. In those cases occuring during active sexual life, there is usually not much to be seen from external examination. In the post-menopausal woman, there are the signs of renewed sexual activity similar to those of the young girls, return of menses, enlargement of breats and appearance of rejuvenation. In some cases, an abdominal tumor is evident and palpable, but this is not always the case.

Pelvic examination shows an enlarged uterus with or without a palpable ovarian tumor which usually is palpable and unilateral. The uterus in the senile cases, instead of being atrophic and small as one normally finds, is the size of a uterus in active sex life. TeLinde (83) and Holmer (27) in a case with metastasis to the cervix and body of the uterus found the uterus to be three times the normal size with an ulcerative mass on the portio-vaginalis of the cervix. Szathmary (80) described a case in a woman 63 years old with a left ovary tumor having a uterus thirteen times normal size (21 x 13 x 10 cm.) and weighing 780 grams and no myomata were present, just hypertrophy. The palpable ovarian tumors vary from

those just perceptable to the size of a man's head as
in the case of TeLinde (83) in which tumor reached um-
bilicus and weighed 9.2 Kilograms.

Diagnostic curettage of the uterus in cases of
granulosa cell tumor yielded only a frank hyperplasia
of the Swiss cheese variety of the endometrium in all
cases observed.

Laboratory Work

Examination of the blood shows some slight second-
ary anemia in all patients, the extent of which is dir-
ectly proportional to the degree of menorrhagica and
bleeding. There is also a slight leukocytosis 10 to
12,000.

Tests for the presence of folliculin in the urine
and blood of these patients are positive. Schuschiana
(70) in quantitative estimations of folliculin in the
urine of a woman, nine years after the menopause with a
granulosa cell tumor found in five days before operation
for removal, 326 mouse units of folliculin and in the
feces, 619 mouse units. In the first eight days post-
operative, 158 mouse units were recovered from the
urine, and on the 66th day post-operative, there was
none. Neumann (50) demonstrated folliculin in 40 cc.
and 20 cc. of blood pre-operatively and was unable to
demonstrate any in 80 cc. post-operatively. In another
case, in a 61 year old woman, he demonstrated folliculin

in 60 cc. of blood pre-operatively and was unable to demonstrate any in 60 cc. of blood eighteen weeks post-operatively. He also produced oestrus in castrated animals with implantations of the tumor removed.

Szathmary (79), in his review of worlds literature in 1933, found positive Ascheim-Zondeck reaction in the urine in two out of 127 cases with several negative results following attempts by defferent observers.

X-ray studies show in children that the epiphysis are united 7-10 years earlier than normal (Bland and Goldstein 4). Klaften (36) showed early ossification of skeleton expecially in the bones of the hand in the case of a four year old girl.

Klaften (37) showed in two cases elevated B.M.R., one 18 plus and the other 24 plus which returned to normal following operation.

DIAGNOSIS

If curettement in a periodically bleeding enlarged uterus, in a post-menopausal woman yields a frank hyperplasia instead of a carcinoma, then suspect a granulosa cell tumor of the ovary; especially if there is an associated ovarian enlargment. Novak (54). These findings justify a laparotomy. The significance of this periodic bleeding and hyperplasia becomes greater the longer after the menopause they occur. Kleine (38) goes even farther and says while bleeding may occur with other ovarian tumors, a distinct glandular hyperplasia of endometrium is peculiar to granulosa cell tumors of the ovary post-menopausal because the hyperplasia is due to hyperfolliculin secretion and in post-menopausal women, this is synonymous with a granulosa cell tumor.

In children, presence of precocious puberty, uterine enlargement and an ovarian tumor and in sexually active women, menstrual irregularity with hyperplasia and an ovarian tumor varrant an exploratory laparotomy.

The possibility of a physiological diagnosis is recognized by Novak (54) by the demonstration of folliculin in urine of post-menopausal women.

The most important criteria for microscopic diagnosis, are the morphological resemblances of the tumor

cells to normal granulosa cells and evidences of growth characteristics identical with them also, that is, radial arrangement about central mass and cystic formation.

Cabot (9) in his discussion on cases in the New England Medical Journal, lists several confusing conditions to be differentiated from granulosa cell tumors as causes of vaginal bleeding:

1. Thrombopenic purpura - ruled out by tests for same, mainly by decreased platelet count and bleeding from all mucous membranes, not only vaginal mucosa.

2. Tuberculoses of the endometrium - usually associated with tuberculosis of the tubes and amenorrhea.

3. Pedunculated fibroid - This is differentiated by relation of mass to the uterus, and there are more varied symptoms such as bladder pressure and backache.

4. Inflammatory mass - Temperature and high white blood count rule this out.

5. Endometriosis - ruled our by absence of fixation in the pelvis.

6. Ovarian tumors - Usually the granulosa cell tumor is the only one with menstruation unless there is a metastatic lesion in the uterus.

   A. Fibroid - ruled out with difficulty, usual-

ly pressure pain is present but may need histological differentiation.

    B.   Sarcomas - These are rapid and progressive and usually diagnosed after death and from lung metastasis.

    C.   Carcinoma - Pelvis usually firmly fixed in this condition.

    D.   Dermoid - More pain here and also usually has twisted pedicle and pits on pressure.

Differential Diagnosis

The reader is referred to beginning of this paper for differentiation of granulosa cell tumor from other causes of post-menopausal bleeding and to review and classify again the things granulosa cell tumors might be confused with as regards post-menopausal bleeding. The importance of thorough examination to reveal site of bleeding and the tremendous aid of a diagnostic curettage are again emphasized.

Other ovarian tumors may be confused with granulosa cell tumors. Novak and Long (53) make a gross differentiation:

    1.   Granulosa cell tumor is a feminizing tumor (the only one).

    2.   Ahrenoblastoma is a masculinizing tumor.

    3.   Brenner tumor possesses no hormonal influences.

Dworzak and Podleschak (12) also stress the impor-

tance of the granulosa cell tumor in being a feminizing tumor.

The tumors of the ovary with which granulosa cell tumors are usually confused are the adenocarcinoma, medullary carcinoma and sarcoma and in all probability, many granulosa cell tumors have been so classified. Workers, now, when going through old case records of ovarian carcinoma, where pathological material has been saved, are continually running across typical granulosa cell tumors which have been so classified.

Lyday (46) lists the chief morphological differences between granulosa cell tumors and other ovarian carcinoma.

1. Uniformity of proliferating epithelium, especially during the early stages of neoplastic activity.

2. Absence of mitoses with rare exceptions. (TeLinde's (83) case of an early tumor with abundant mitotic figures.

3. Absence of infiltrative and destructive tendencies.

4. Spreading by extension, not by lymph and blood stream.

The various pathological types of granulosa cell tumor have their own special confusing problems as:

1. Folliculoid type is confused with adenoma.

2. Cylindromatous type is confused with endothel-

ioma, medullary and alveolar carcinoma.

3. Diffuse type is confused with medullary car-
    cinoma.

4. Sarcomatous type is confused with sarcoma.

If only one section of granulosa tumor is saved
for sectioning, microscopic differentiation may be im-
possible. It is only through using many sections and
studying the varied picture which always is presented
that it is possible to rule out these above confusing
elements. In a single section, especially of the sar-
comatous type, it is impossible to differentiate it from
any other ovarian sarcoma.

Lissowetzky (44) described a tumor in which there
was a resemblance to thyroid tissue and he emphasized
the possibility of confusing these with teratoid growths
in the ovary which actually possessed real thyroid tissue.

PROGNOSIS

This tumor is of relatively low malignancy but not
as low as was previously thought as clinical analysis of
a series of cases show. The proof that these are rel-
atively benign, is well illustrated in TeLinde's case
with duration of symptoms for four years and then com-
plete recovery following removal.

Szathmary (78) says it is a good thing these tumors
do produce a menstrual disorder because patients are
forced to seek medical aid early in the course of the
tumor.

Removal of the tumor in most cases is followed by
prompt relief from symptoms. There is cessation of the
menses in young girls and post-menopausal women and re-
turn to normal cycle in sexually active women in whom
the tumor only was removed. There also follows invol-
ution of uterus and breasts.

In those cases which are malignant, metastasis oc-
curs both by direct extension as illustrated above with
a tumor in which metastases were found in the cervix and
the uterus and by the blood stream as seen in cases with
pulmonary metastasis (Louros 45), leptmeninges metastas-
is (Klaften 36), and skeletal metastasis (Saltman 67).

Recurrent tumors are not necessarily disastrous
either as shown by the case of Klaften (34) in which a

recurrent tumor was removed after a primary removal of the tumor 11 years previously with complete recovery.

It is not disastrous either to spill cystic fluid in the abdominal cavity (Schultz 69).

Taussig (81) says one important source of danger in these tumors lies in their fine blood supply which might lead to a fatal hemorrhage in case of a rupture of the capsule. He also says the endometrial hyperplasia may be a precursor to adenocarcinoma of the uterus.

To quote a few statistics as to mortality and malignancy:

Klaften on 80 cases.

6 inoperable when first seen	7.5 %
4 recurrences	5.0 %
70 favorable results	87.5 %

Bland and Goldstein on 160 cases.

Unknown	64
Recovery from operation	32
Well one year post-operative	36
Well ten years " "	6
Died within year "	9
Died post-operative	7
Died after 4 years	2
Found at autopsy	2
Died with Metastasis and no operation	2

Novak and Brawner on 32 cases found 9 or 28.1 % malignant.

Meyer on 33 cases:

> 17 followed
>
> 13 well one to eleven years post-operative.
>
> 4 recurrances.

Murphy on 7 cases.

> 3 alive   3 years,   1½ years,   1½ years.
>
> 4 dead.
>
> 1. 9 years from cerebral hemorrhage. Had had surgery and x-ray for three years.
>
> 2. Four months. No response to irradiation. 1152 r in 4 treatments in 8 days.
>
> 3. Thirteen months. 2576 r. Two courses. seven months apart. x-ray was only palliative here. Had a diagnostic operation.
>
> 4. Six days. Admitted moribund with mass to umbilicus. 565 r.

These figures show malignancy varies from about ten to twenty-five percent.

TREATMENT

It is essential to have a diagnostic curettage in
all irregular bleeding and then, if hyperplasia is pre-
sent, laparotomy is indicated.

In cases of granulosa cell tumor, the treatment
depends upon the age of the patient somewhat. The op-
timum treatment is removal, not only of the tumor mass,
but of all generative organs, the uterus and adenexa
and this is what is done is those women beyond menopause
and most of the cases occurring in sexually mature women.
If, however, a woman wants more children, or the case is
in a child, unilateral salpingo-oophorectomy may be ad-
visable and frequently is done with complete success.

Stewart (76) is writing on sensitivity of ovarian
tumors to x-ray, says the malignant granulosa cell tu-
mors are very radiosensitive. There is an initial marked
regression following irradiation which clinically is
interpreted as a complete regression or a decided partial
regression which is followed by a fairly prompt recur-
rence and death. The irradiations administered to arrive
at these results were all patients could tolerate, so re-
sults can not be attributed to in adequate therapy. At
present, x-ray should only be used as a palliative meas-
ure or in conjunction with surgery. Stefansik (75) says
all granulosa cell tumors should be considered malignant

and treated by radical operation with subsequent irradiation.

It seems then, that Stefancsik's idea would be the surest one to follow except in those few favorable cases in children where dissection of the tumor could be made. This plan would promise most favorable outcome.

With metastatic lesions evident in general, any measure is purely palliative and nothing would be of any use.

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CONCLUSION

Post-menopausal hemorrhages have been classified and all available literature concerning the granulosa cell tumor of the ovary has been reviewed.

Emphasis is again stressed on the importance of searching for the source of post-menopausal bleeding and early beginning of treatment if the source proves to be malignant.

Granulosa cell tumors, while being a rare cause of post-menopausal hemorrhage, are one of the most interesting because of their endocrine influences on the organism.

The confusion still remaining as regards the etiology and histeogenesis of these tumors and the confusing picture of pathological types, show there is still much work to be done on these tumors to clear up the picture.

The clinical features as regards symptoms, findings, prognosis and treatment, are fairly well worked out.

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