THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Ernest J. Colberg final oral examination for the degree of

Master of Science

We recommend that the degree of

Master of Science

be conferred upon the candidate.

E. T. Bell.
Chairman

Fred L. Adair

H. E. Robertson

A. T. Henrici

Date _____

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THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Ernest J. Colberg for the degree of Master of Science. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science.

E. J. Bell
Chairman

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Date _____

THE DEVELOPMENT OF FOLLICULAR CYSTS IN THE PRE-PUBERTY PERIOD AND THEIR RELATION TO EPITHELIAL TUMORS OF THE OVARY

A Thesis submitted to the Faculty
of the
Graduate School
of the
University of Minnesota

by

Ernest J. Colberg

In partial fulfilment of the requirements
for the degree of Master of
Science
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The Development of Follicular Cysts in the Prepuberty Period and their Relation to Epithelial Tumors of the Ovary

The present study is an investigation of the development of cysts in the Graafian follicle during the prepubertal period with reference especially to the etiology of epithelial tumors of the ovary. Such a relationship is suggested by the well known tendency of both benign and malignant ovarian tumors to be cystic.

The great preponderance of the cystic over the solid type of tumor in the ovary appears from the following table:

Author	Tumors removed	Cystic	Solid
Gardner	804	752	52
Ulseko-Stroqonoff	202	192	10
Briggs	488	439	49

These were all tumors removed at operation.

Of especial interest in this discussion is the prevalence among the cystic ovarian tumors of the papillary cystadenoma, since it is this particular type of epithelial ovarian tumor that most strongly suggests the follicular cyst as its forbear.

A table is appended to show the relative frequency of these tumors.

Author	No. of ovarian cysts	No. of papillary cystadenomas	Percentage
Erdmann & Spaulding	200	36	18
Pfannenstiel	400	60	15
McCarty & Sistrunk	1000	163	16
Kelly	138	30	22
Martin & Libbert	200	55	27
Ulseko-Stroqonoff	202	10	10

This gives a percentage of 16.5 papillary cystadenomas in 2140 ovarian cysts. Papillary cystadenoma is the most important surgical disease of the ovary.

It is a condition that bears a very definite relationship to malignancy. Erdmann and Spaulding hold that two-thirds of all papillary cystadenomata give microscopic evidence of being cancerous or precancerous. Pfannenstiel places the proportion at 50%. Most such tumors, however, being encapsulated, are successfully removed. It is an established rule that all ovarian cysts requiring operative interference must be removed entire. Ravano states that 14% of all ovarian cystomata are malignant and Straute found the proportion to be 20% in 200 ovarian cysts. Bland-Sutton cites a case of death within 3 months from malignant metastases following the rupture of an ovarian cyst at operation. The relation of cystadenoma to carcinoma is further emphasized by the fact that McIlroy in a series of 15 primary cystic carcinomata of the ovary could demonstrate the coexistence of benign cystadenomata as well as of transitional or precancerous forms thruout the series.

Ulseko-Stroganoff states that proliferating cyst tumors are transitional forms between benign tumors and tumors undergoing carcinomatous degeneration, that the characteristic epithelial hyperplasia of the former shows this tendency toward malignant degeneration, and finally that in the cysts showing cancerous degeneration proofs are evident that they have developed from proliferating cysts. Ewing, McCarty have described the process of malignant transformation in the wall of ovarian cystadenoma. According to Erdmann and Spaulding the transition from the benign thru the various degrees to the malignant is imperceptible. The cells of the malig-

nant type are larger, pyknotic, show many mitoses, are atypical in arrangement and invade surrounding tissue. Often a small secondary cyst contains extremely malignant papillary elements.

Thus, while Ewing feels that there is some ground for the view that malignant ovarian epithelial tumors are carcinoma from the first, it is rather more than probable that they are frequently transformations of more typical adenomas. Gebhardt considers every papillary adenocarcinoma a degenerated adenoma. It is this probable relationship that inclines one to be critical of every cystic condition in the ovary. The etiology of cystadenoma of the ovary is as yet far from being fixed.

The ovarian cystadenomata are classified with the adenomas because of the columnar epithelium that lines such cysts. In the serous types it is ciliated, in the pseudomucinous cystadenoma it is a pseudomucin secreting epithelium with typical goblet cells. These tumors are frequently papillary. Due to the activity of the lining epithelium, warty excrescences and infoldings are formed in the wall and these processes may fill the entire cyst. Thus, while the simple cystadenomas are translucent, the more active papillary growths are opaque and papillary nodules appear on the surface. The proportion of papillary growth indicates the activity as well as the malignancy of the tumor. Simple serous cystadenomas are uniformly benign.

Various explanations are given for the serous as well as the pseudomucinous types of cystadenoma. The former are usually smaller but show a greater tendency to be bilateral and to produce metastases. Von Kahlden has described a small cystic ovary, usually found in patients past the menopause, where numerous small cysts of irregular size occur, lined with columnar epithelium. His theory

that these arise from infoldings of the surface epithelium (Keimepithel) will be discussed later, but Ewing considers that these small cysts represent the earliest stage of the serous cystadenoma. Schwartz states that serous papillary cystadenomata are derived doubtlessly from the germ epithelium and Goodall, Massabareau and Etienne consider this the source of ovarian epithelial neoplasms.

Ewing, however, believes that some of the serous cystadenomas probably begin as simple follicular cysts. Gebhardt declares that the pseudomucinous cystadenomata originate from the follicle of the ovum. That cystic tumors of the ovary, and especially papillary cystadenomata,have some association with the Graafian follicle has been suggested ever since the Graafian follicle was discovered. This idea gained all the more credence after Hodgkin in 1829 first pointed out the adenomatous character of papillary cystic ovarian tumors.

Fox, Klob, Mayweg, Spiegelberg and Boettcher accepted the Graafian follicle as the origin of most if not all cysts of the ovary. Fox and Mayweg considered the formation of papillomatous processes from the wall of the follicle the first step toward the formation of multilocular cystomata. The idea that the Graafian follicles develop a ciliated lining epithelium and thus give origin to papillary cystadenoma was advanced by Marchand, Frommel, and Koeberle. Von Velits (1889) described several papillary cystadenomata and claims in two cases in relatively intact portions of the ovary to have found small cysts, apparently dilated follicles, in one instance containing an ovum, these follicles being lined by a single layer of cylindrical epithelium which in rare cases was ciliated. In some of them he was able to demonstrate papillary growths. Steffeck (1890) and Williams (1891) credit the possibility of such a

development and Williams presented a microscopic section purporting to show a follicular cyst with papillary ingrowths, the cyst lined by epithelium of all possible forms, ranging from the typical cuboidal membrana granulosa cells in several layers to well marked cylindrical epithelium and low flattened single-layered epithelium. McCarty (1913) mentions the occurrence of small ovarian cysts with a lining varying from the many-layered epithelium of the Graafian follicle thru the columnar epithelium of the cystadenoma to the papillomatous projections of the intracystic papillary cystadenoma. Goodall (1920) however, scouts all these demonstrations as apochryphal and states that there is not one case in the literature of a Graafian follicle supposed to show developing papilloma that will stand the test of scientific criticism. Like most modern writers he fixes on the germinal epithelium as the source of the epithelial tumors of the ovary.

Other sources of origin have been given, such as the stroma of the ovary, the Wolffian bodies, etc. These will be taken up later for purposes of comparison and completeness. The purpose of the present study is to consider the development of the Graafian follicle in the prepubertal period and the possibility of proliferative or malignant change in such developing follicles. 400 sections have been studied, all prepared from prepubertal ovaries. All of the specimens are from cases under 14 years of age. They constitute material from routine autopsies. The total number of cases investigated is 24.

The ovary during the prepuberty period is the site of massive anatomical changes. These changes begin at birth or shortly before and contine thruout infancy and childhood. They are on such a large scale and seem to involve the normal structure to such a degree that

one is led to suspect the great possibility of real pathology. In fact, to draw the line between what is pathological and what is purely normal and physiological in the ovary is a difficult task.

These changes are due to a species of maturation or development of the follicles which occurs already in the prepubertal period. The course of this process never goes on to rupture of the follicle. Instead retrograde processes overtake the follicle, and the follicle cells and the ovum degenerate in situ. It resembles somewhat the sequence of events that occurs in Graafian follicles maturing during pregnancy. Atresia of the follicle and the ovum sets in and these decay without rupture of the follicle. In the developing Graafian follicle of the prepuberty period there are, however, no lutein cells formed as do occur, if to a limited extent, in these atretic follicles of pregnancy.

One of the most constant results of this prepubertal maturation is a follicular cyst. These cysts are frequently one and two millimeters in diameter. Macroscopic follicular cysts were found in 17 of the 24 cases examined. They are almost always multiple. The seven cases where follicular cysts were absent were all newborn and the inevitable deduction is that they had not yet had time to develop.

It has been a common mistake in the past to suppose that the growth and ripening of the ovarian follicles began only shortly before puberty. Henning, seeing follicles of advanced growth in a girl of 5 years, believed them an abnormal development due in his case to a disturbance of growth equilibrium by scarlet fever. Gohn saw follicles resembling those of the adult in 2 to 3 year old children. Bischoff, Franqué and Waldeyer found them in children from the first year but considered them pathological if earlier than

that. DeSinnty observed growing follicles in two full term fetuses. Our series includes 7 newborn, and in all but one Graafian follicles appear in various stages of development. Vallisnerius found the Graafian follicles constant after the second month. He found follicles that one month after birth measured 1 mm in diameter. In the later fetal monthshe found them present and of a size up to 180 micra in diameter. Delester says that Graafian follicles in process of evolution are constant in the ovaries of the newborn and that these follicles do not reach more than a certain volume before atresia sets in.

The epithelial downgrowths from the genital ridge begins to appear in the embryo already at the beginning of the second month. In the four months fetus the cells that are to become ova can be seen surrounded by a follicle layer. The follicles are prominent in the five months fetus. In the sixth fetal month Graafian follicles appear and at birth one finds a great number of both primary follicles and Graafian follicles (Winniwaerter).

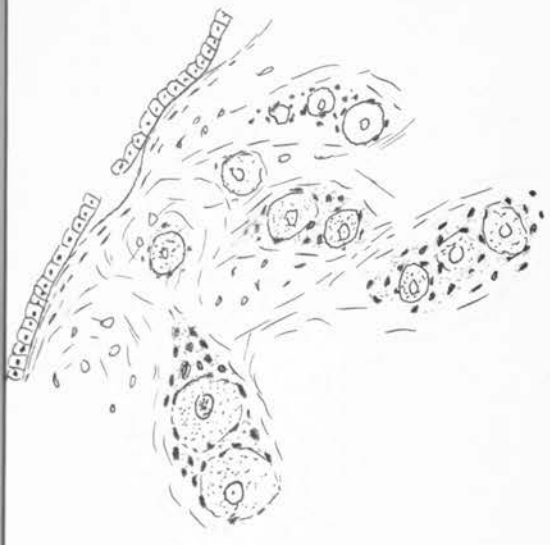
The formation of ova in the human ovary takes place exclusively in fetal life and in the first two years of postnatal life. It is virtually complete at birth. Winniwaerter found absence of mitoses in the parent cells of the ovum, the oögonia, already in the ninth fetal month. The number of follicles, Graafian and primary, has been estimated to be 70,000 at birth.

All observers are agreed that it is less at puberty. The present series of cases indicates that this number is greatest during the firstor second month after birth. In the 6 cases of newborn and infants of the first 10 days the medullary cords are still very prominent. They are readily distinguished from the surrounding ovarian stroma by their deeper stain and by their obvious epithelial char-

acter. This epithelial character is still very evident in the case (A-20-221) from the seventh month after birth and in children of one year (A-20-97, A-20-349). Plate I Fig 2 Plate I Fig 3 From the medullary cords are derived both the ova and the layer of cells surrounding the primordial ovum, the follicle cells. The epithelial origin and nature of these follicle cells becomes more and more obscured and they take on an appearance elongated and flattened and partially indistinguishable in the resting follicle from the appearance of the adjacent ovarian stroma. The development of primary follicles from the medullary cords seems still in process of development in our series of cases of the newborn. At the same time, the process of degeneration of ova has begun and is noticeable in all but one of our 6 cases of infants dying at birth or during the first week. After the first few weeks this degenerative process becomes the dominant one so that the number of ova must be greatest at birth. In ovaries from 10 to 12 years old children there is both a relative and an absolute decrease of the number of ova. It is with the fate of these ova and their follicles that we are directly concerned.

Waldeyer and Beigel indicated that a process of ripening of the ovarian follicle occurred already in the prepuberty period. This was followed by atrophy and a kind of corpus luteum. De Sinnty describes follicles in the ovaries of infants, which show all stages of maturation up to what may be called ripeness as far as premenstrual ovaries go, but, tho he mentions that retrogressive changes take place, he does not make it clear what these changes are. Schotlaender also describes a similar development of the follicle.

Runge studied 50 ~~pieces~~ pairs of ovaries in serial section. 10 of these were from fetuses of 4 to 9 months, 22 from full term fetuses and the rest from children up to 9 years of age.



A-20-221 Fig. 1

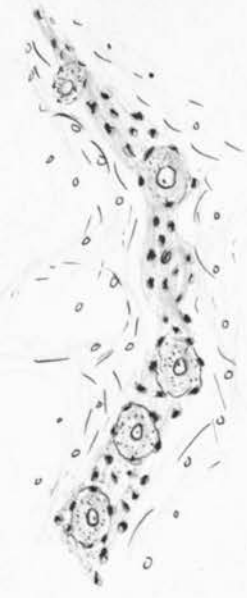


Fig. 2

A-20-97

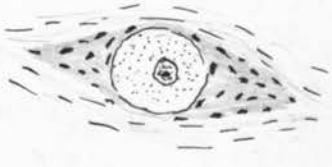


Fig. 3

A-20-349

30% of the fetal ovaries showed growing follicles. All occurred in the seventh month or after. In one 7 months fetus there was a follicle with an ovule 60 micra in diameter and with much liquor folliculi . In one 9 months fetus the follicles were in an advanced stage of development and there were two follicular cysts. Rurige concludes that ripening follicles, while not the rule in the fetal period, are nevertheless common enough to be considered physiological.

In 22 cases of the newborn he found 63.4% with growing follicles, these showing more advanced development than in the prenatal period. 18% of them showed follicular cysts and one contained a "typical lutein cyst". The follicular cysts varied from 1 to 3 mm in diameter. In our series of 6 cases from the same age there were no macroscopic cysts and the largest developing Graafian follicle measured .1 mm in diameter. Von Franque found follicular cysts in two specimens of ovaries of the newborn. In one the follicular epithelium was already in a state of degeneration. Nagel found in the newborn quite large ovaries with numerous cysts, 1 to 2 mm in size, showing normal follicles that had every appearance of maturity.

In 4 cases from the first year Rurige found growing follicles in all. Our series covers 7 cases from this period and developing Graafian follicles are very plentiful in every section. Rurige found follicular cysts in 25% of his group and corpora fibrosa in the same number. Our series of 7 cases (ages 6 weeks to 7 months) all showed either follicular cysts or corpora fibrosa, indicating by their size that definite follicular cysts had occurred. These cysts are practically always multiple and range in this series from .2 mm to 1 mm in diameter.

Rurige had 8 cases from the second year. All showed growing

Graafian follicles and 85.5% showed follicular cysts. 50% had corpora fibrosa. Our series contains 4 from this age. All show developing follicles and corpora fibrosa. 75% show macroscopic cysts and 50% show several follicular cysts up to 1 to 2 mm in diameter. See A-20-349 and A-20-449.

Our series contains 6 cases from the second to the twelfth year. Maturing Graafian follicles are present in all of them, tho not as many as in the first two years of life. All show corpora fibrosa and 66 2/3% contain follicular cysts. These cysts are multiple in occurrence and attain a maximum size of 3 to 4 mm in diameter.

Ripening Graafian follicles in all stages of development are thus present in all but 1 of the 24 cases examined. Macroscopic follicular cysts are present in 17 of the 24 cases. These cysts are due to the growth of the Graafian follicles and their subsequent dilation by fluid. To a very large extent they are a stage in the normal development of the Graafian follicle.

The nature of the development of the Graafian follicle in the prepuberty period. Runige and Stevens have discussed the nature of this process. The finding of a "typical corpus luteum" in a full time fetus indicates to Runige that the follicles may mature fully. Waldeyer also observed corpora lutea before puberty. This is, however, not the usual fate of the Graafian follicle in this period of life and even tho the corpora lutea in these instances showed the anatomical picture it is probable, as Runige states, that a whole series of developments that occur in the adult were lacking here. The corpus luteum of Runige's observation was smaller than this structure in the adult. Stevens in 70 pairs of ovaries from the prepuberty period found nothing in the least approaching a corpus

Fig. 1

A-20-349 (4X)

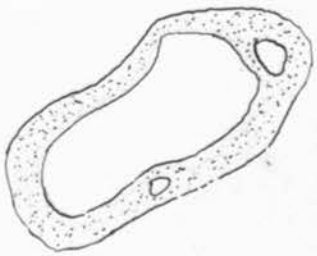


Fig. 2

A-20-449 (4X)

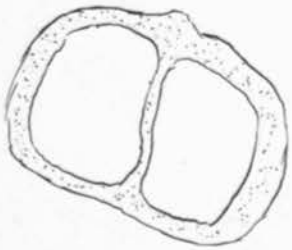


Fig. 3

A-20-449 (4X)

luteum. There is none in our series.

The ova in prepubertal premenstrual life are not expelled, altho reaching almost to the size and stage of maturity. Instead they are destroyed in situ in the same manner as most of the ova in the adult. Stevens, speculating as to the function of this process, says: "It is clear that the supply of sexual cells is unnecessary in infants and so the follicles do not burst, but it is not certain that the internal secretion is unnecessary. In all probability this plays an important part in the development of the female child."

These developing follicles uniformly involve the deeper lying ova, leaving the surface of the ovary and the peripheral zone of primordial follicles uninvolved. The younger follicles are found in all over the surface of the ovary and, according to Stevens, especially at the two ends. Even in the very large follicular cysts, reaching 2 mm or more, there is no tendency to move relatively nearer to the surface, altho they do cause more stretching and thinning of the cortex. There is in none of our series any suggestion of the imminent rupture of the follicle but instead the fluid is resorbed and the cyst contracts and is replaced by scar tissue. The development of new cysts causes these to impinge upon and compress the older cysts into crescentic or slitlike structures, thus leaving a much smaller space to be filled in with connective tissue.

All stages of this process can be seen in the prepubertal ovary. We failed to find them in only one case (that of newborn). The follicle and the contained ovum matures up to a certain point, then retrogressive changes set in. The follicle may be overtaken by this degenerative process, evidently, at any stage of its development.

Stevens studied 70 pair of ovaries from the age of 10 years

down. The resting or primordial follicle measures about .03 mm, which is practically the diameter of the ovum itself. The ovum is surrounded by a single layer of flattened cells, the follicle cells. These are closely applied to the ovum. These flattened cells look and stain like the connective tissue cells of the ovarian stroma. Stevens and Foulis made the mistake of supposing the follicle cells to be of stromal connective tissue origin. This mistake has probably come about because investigators have failed to study specimens of a sufficiently early stage. In sections from ovaries at the time of birth the epithelial derivation and character of the follicle cells is clearly manifest. Pl.III fig.2 A-21-139(full time fetus) is a beautiful demonstration of the medullary cords and it serves well in demonstrating the origin of the follicle cells. They are seen to be an entirely distinct layer from the stroma. Plate III fig.1 See A-21-131. This specimen is interesting as it shows the follicle cells to be a layer distinct from the stroma even before they have assumed the cubical epithelial arrangement of the zona radiata. The zona radiata is not present in the dormant follicle.

In the process of prepubertal ripening the first apparent change is that the flattened follicular cells surrounding the ovum proliferate until their nuclei are treble the number in the average dormant follicle. At the same time the cells are altered in shape and assume a cubical form, becoming more obviously epithelial in their appearance. The ovum itself increases slightly in size. A typical example is from Pl.III fig.3 A-21-47, tho similar ones can be found in practically any section.

Following this there is further proliferation of follicle cells from a single to a double layered structure. Pl.III fig.4 A-20-207. The cells are cubical with nuclei elongated radially, especially so in the

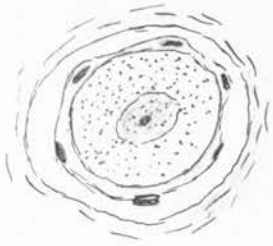
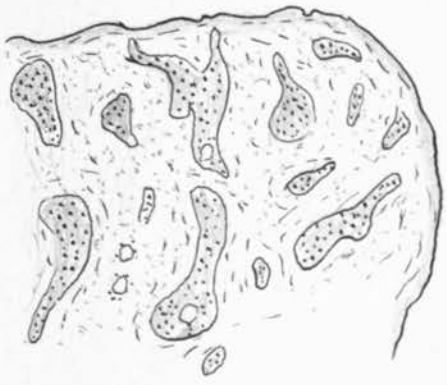
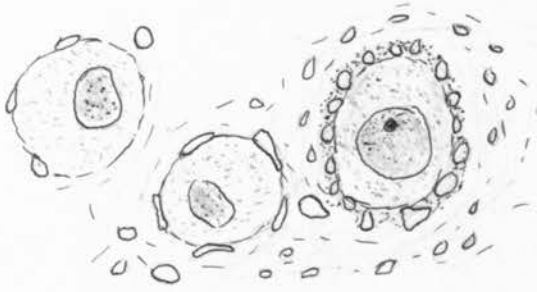


Fig. 1

A - 21 - 139



A - 21 - 139 Fig. 2



A - 21 - 47 Fig. 3

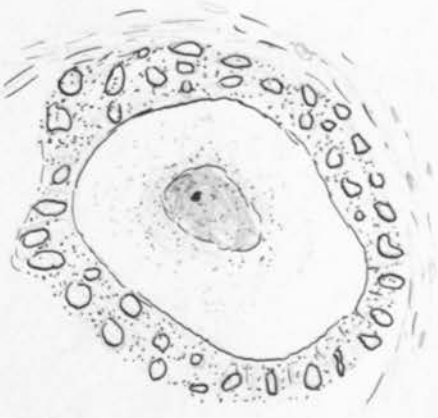


Fig. 4

A - 20 - 207

peripheral layer. Around the follicle is a definite delimiting clear zone. While a fibrous capsule can be demonstrated by means of the Van Gieson stain already in the dormant follicle, this tunic becomes more prominent as the follicle enlarges. There are at first no obvious blood vessels in this layer. Pl. IV 7:1

Further advance in the process is indicated by the proliferation of the follicle cells into a multilayered structure surrounding the slowly enlarging ovum. Spaces begin to appear between these cells representing the earliest accumulations of liquor folliculi. The proliferation and the accumulation of fluid go on apace, causing marked enlargement of the follicle. The liquor folliculi then collects in the center of the follicle. The cells of the membrana granulosa come to show more distinct cell bodies. A well marked cumulus oophoron is formed around the ovum while the membrana granulosa thins out away from the cumulus. The fibrous tunic around the follicle becomes well marked and becomes richer in vascular elements (A-20-207). This wreathlike arrangement of the blood vessels becomes more prominent in proportion as the follicle increases and serves to mark off the tunic of the follicle from the surrounding stroma. A-20-289 gives a perfectly typical example; also A-21-381, A-20-183. Pl. IV 7:2

In the average case the Graafian follicle will attain a size of .8 mm before retrogression sets in. Anything exceeding this can be definitely set down as a follicular cyst. In this process of ripening the ovum itself may, according to Stevens, attain a maximum diameter of .1 mm, as compared with 2 mm in mature adult ova.

The elements of the follicle degenerate in situ. The first change is a shrinking away of the membrana granulosa from the fibrous tissue wall of the follicle. In most cases there is a detachment of this membrane as a whole so that it can be seen floating

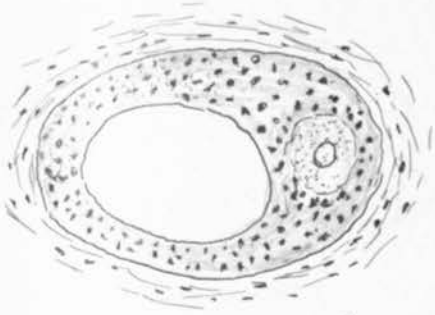


Fig. 1

A - 21 - 4

A - 20 - 193

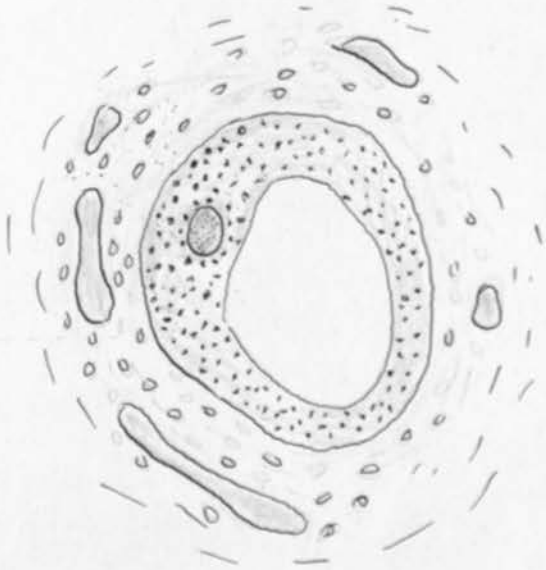


Fig. 2

A - 21 - 467

(A - 21 - 381) (A - 20 - 183)

free out in the lumen of the cyst. It then rapidly degenerates. This is the usual course and the largest cysts in the present series will show a membrana granulosa quite intact and floating free in the cavity of the cyst. See A-20-349. Pl.V 7:g.1 This specimen is interesting because this section shows the cumulus with the contained ovum. Also A-21-121, A-20-35. Occasionally the membrana granulosa does not come off as a whole but shreds remain attached to the wall of the cavity. See A-20-449, A-20-289. Pl.V 7:g.2 T hen, again, the sheath of the follicle cells may not come off as a membranous cast either complete or partial but may instead desquamate and flake off as individual cells. Examples A-20-155, A-20-183, A-20-221. Pl.V. 7:g.3 Pl.V. 7:g.4

Runge claims that the loss of the ovum from the cumulus oöphoron and from the follicle is the first token of degeneration in the follicle. Stevens and Von Kahlden, on the contrary, feel that the ovum is quite resistant. Stevens is correct in this, for the ovum can usually be found even in the larger Graafian follicles that are distinctly in the cystic stage. Surrounded by the follicle cells of the corona radiata it persists after the membrane granulosa has begun to show detachment and degeneration. A-20-349, A-20-289. Occasionally it is seen floating free without surrounding cells. The presence of the ovum, the cumulus oöphoron and the membrana granulosa indicate the undoubted follicular origin of all the cysts found in the present series. According to Stevens the ovum is eventually destroyed by a process of phagocytosis. He found sections that seemed to substantiate his view, sections that showed phagocytic cells invading the ovum thru a break in the corona radiata. He thot that these phagocytes were granulosa cells. This is probably a false view as the granulosa is of very specialized function and at this stage is already in process of degeneration.

Plate V

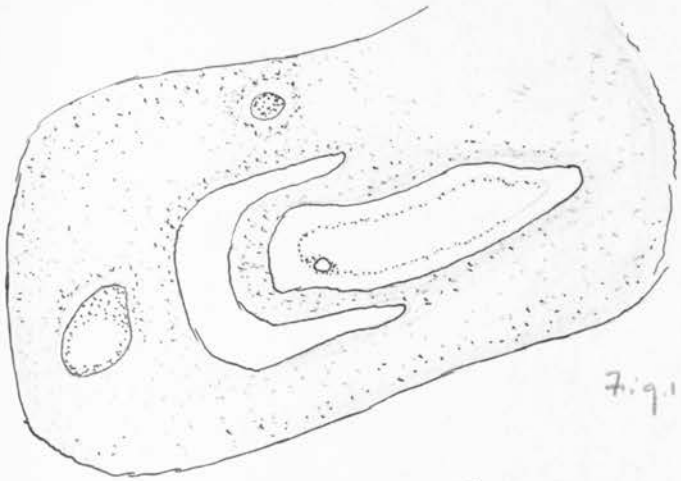


Fig. 1

A-20-349

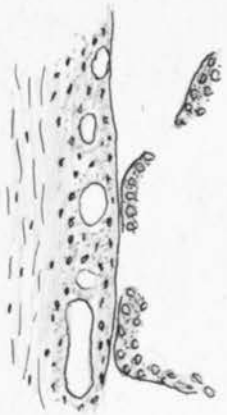
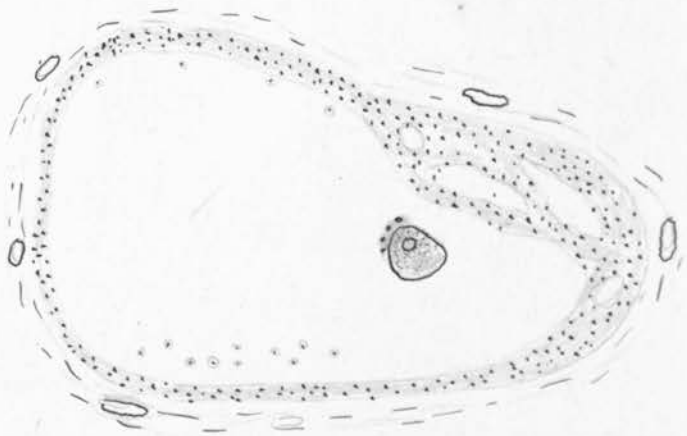


Fig. 2

A-20-449



A-20-155

Fig. 3

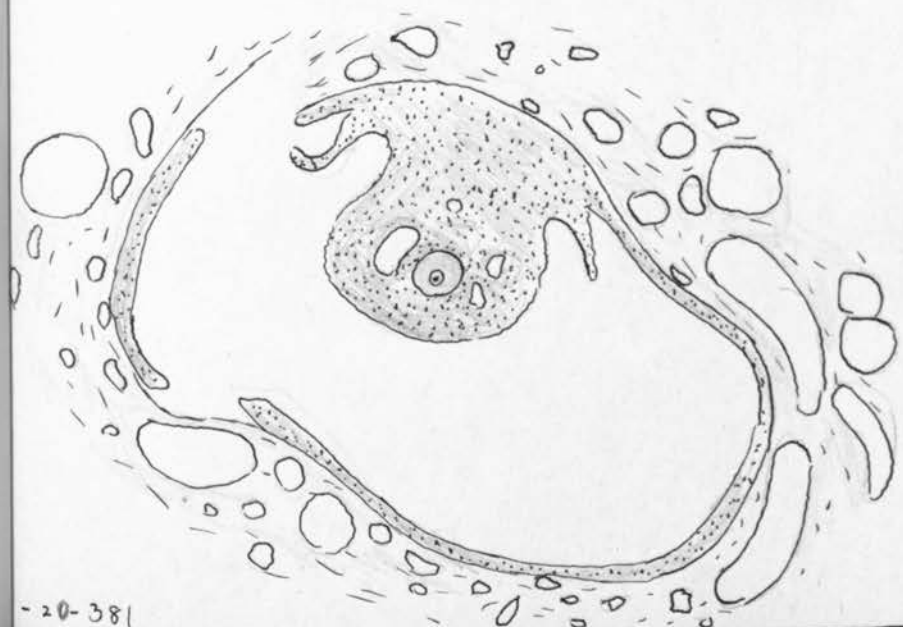
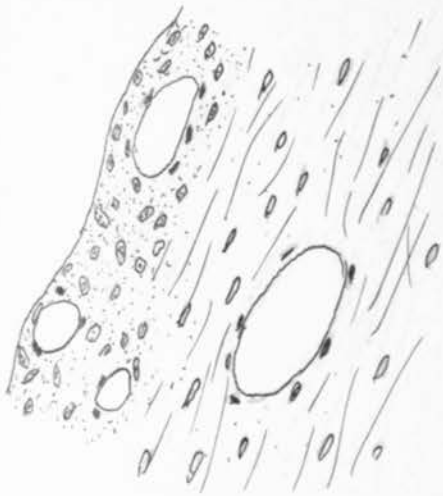


Fig. 4

-20-381

There has been some speculation as to the cause of the degeneration of the membrana granulosa. There is no absolutely definite stage at which it occurs. It may be a process of atrophy due to the increase and pressure of the liquor folliculi. Von Kahlden suggests disturbances in circulation as a factor. The epithelial cells nearest the center of the cyst lose their stain, become large and transparent and begin to show fatty and vacuolar degeneration. The cell wall fades and there is lysis of the nucleus. These large pale cells may desquamate and lie out in the lumen of the cyst. Cavities appear in the membrana granulosa. Nagel has called these spaces epithelial vacuoles. Eventually all the follicle cells degenerate and leave a cyst lined only by the connective tissue of the stroma.

This wall is very rich in its vascular supply with large arterioles in a wreathlike formation around the cyst. Small capillaries come to the very surface of the cyst. Plate XI A-20-449. This increase in capillary blood vessels in the fibrous coat is the first thing noticed in the process of organization of the cyst. Along with this increase in capillaries there is a proliferation of the connective tissue cells in the fibrous tunic. The result of this process is a zone of richly cellular and very vascular tissue extending equally all round the follicle. This layer is easily distinguished from the membrana granulosa by the presence of numerous blood vessels in the former while there are none in the latter. This layer rapidly increases in thickness and the blood vessels form definite capillary loops. There is thus a formation of granulation tissue and a process of organization. The coagulated material along the wall of the cyst furnishes the matrix for this process of thickening, young capillaries and fibroblasts pushing out into this material. The



A-20-449

A-20-344

fluid of the cyst is absorbed.

The absorption of the fluid is indicated by the contraction and collapse of the cyst. Some of these contracted cysts may be .5 to 1 mm in diameter, indicating an originally much larger cyst. See A-20-344, A-20-394, A-21-381. Most frequently the process of contraction is abetted by the formation of other cysts. Very good instances of this are frequent in our series. A-20-289, A-20-349, A-20-394. The margins of the cyst are thus drawn together and in the majority of cases brot into direct contact. Whatever cavity is left is filled in with young and very delicate connective tissue. The end result is a scar or corpus fibrosum. This scar is of variable size, possibly depending on the original size of the follicle. Often the scar is crescentic in shape, indicating its derivation from a compressed cyst. In general these scars leave no trace on the surface of the ovary and they gradually become indistinguishable from the rest of the stroma.

The follicular cyst differs in no way from the normal developing Graafian follicle except that it marks a heightening of the process. There is an excessive amount of liquor folliculi produced and the follicle may enlarge to a diameter of 5 mm.

The following table represents the findings in the 24 cases under consideration.

No.of the case	No. of cysts	Size of cysts
A-20-394	one	.3 x .7 mm
A-21-467	two	.5 x 1 mm
A-20-221	two	.5 x 1 mm
A-21-47	multiple, largest	1 x 1 mm
A-20-207	two	1 x 1 mm
A-21-206	multiple, largest	1 x 1.5 mm

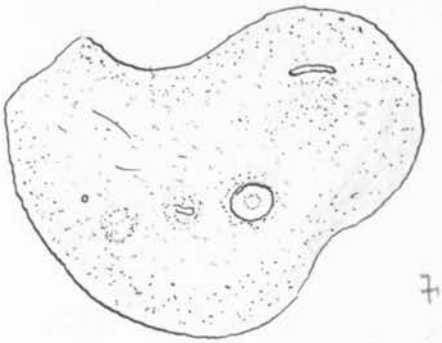


Fig. 1

A-20-344 (X10)

Ovary 5 X 6 m.m.

Cyst .5 m.m. containing memb. granulosa

Fig. 2

A-21-487 (X10)

Ovary 5 x 6 m.m.

3 contracting cysts, each 1 m.m. long

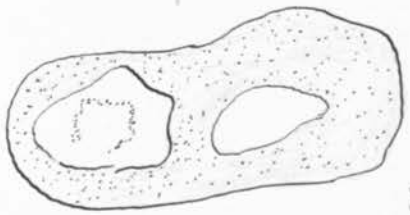


Fig. 3

A-20-221 (X10)

ovary 2 x 5 m.m.

2 cysts .5 x 1 m.m. - one with memb. granulosa

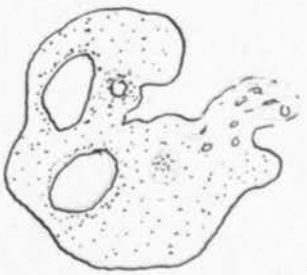


Fig. 4

A-21-47 (X10)

ovary 4 x 4 m.m.

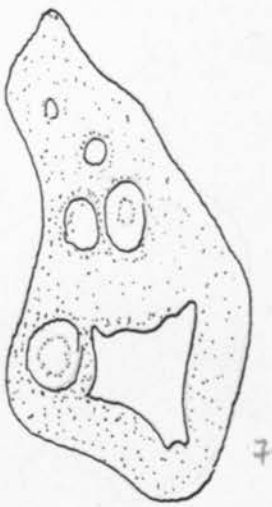


Fig. 5

A-20-207 X10

Ovary 4 x 6 m.m.

Contracting cyst 1 x 1 m.m.

Smaller cysts contain memb. gran.

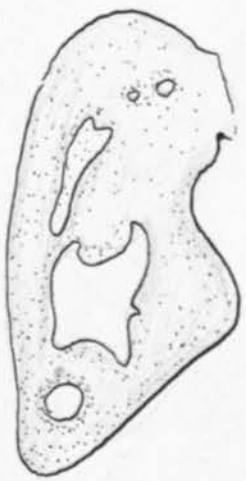


Fig. 6

A-21-204 X10

Ovary 3.5 x 7 m.m.

2 large contracting cysts

one 1 x 1.5 m.m., one .5 x 1 m.m.

latter filled with young c.l.

A-21-183	multiple, largest	1.5 x 2 mm	Pl. IX Fig. 1
A-20-155	multiple	1.5 x 2 mm	" " " 2
A-20-349	one	1 x 3 mm	" V " 1
A-21-4	two	2.5 x 3 mm	" IX " 3
A-20-289	several	2.5 x 3 mm	" " " 4
		2 x 2 mm	
		1.5 x 1.5 mm	
A-21-381	multiple	2 x 3 to 2.5 x 4 mm	Pl. X Fig. 1
A-20-499	two	2.5 x 4 mm	" " " 2
		2 x 5 mm	
A-20-449	three	2 x 5 mm	Plate II Fig. 2 and 3
		2 x 4 mm	
		1.5 x 4 mm	

In these larger follicles no further development of the ovum is found and the appearance of the ovum in the cumulus oophoron remains the same. The only change is a relative thinning of the membrana granulosa. The number of layers of follicle cells in the membrana granulosa is also reduced altho this structure to a very definite degree keeps pace with the growth of the cyst.

Is this condition pathological or is it physiological? Ewing holds that a moderate and variable development of cysts is physiological and occurs especially in infants and in gestation. According to Ewing they occur chiefly in early sexual life. But our series seems to indicate that they are at least as common in infancy. Nagel considers that they are due to a premature ripening of the follicles. Stevens, on the other hand, feels that they are purely physiological and Von Kahlden's opinion is the same. Goodall thinks that these cysts are unusually large and healthy Graafian follicles. That they must be considered normal seems the inevitable deduction

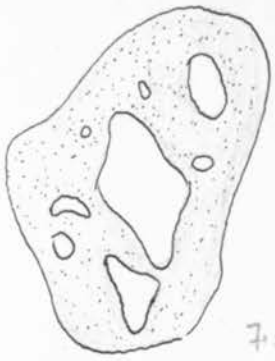


Fig 1

A-20-183 (X9)
Ovary 4×5 mm.
Cyst 1.5×2 mm.

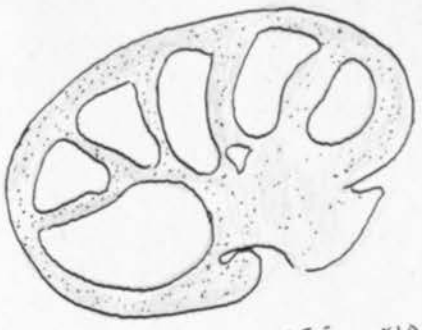


Fig 2

A-20-155 X10
Ovary 4×6 mm.
Multiple cysts 1.5×2 mm.

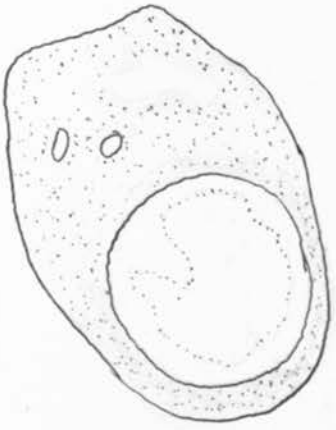


Fig 3

A-21-4 (X10)
Ovary 5×7 mm.
cyst 2.5×3 mm. with
memb. granulosa
also large Corpora fibrosum

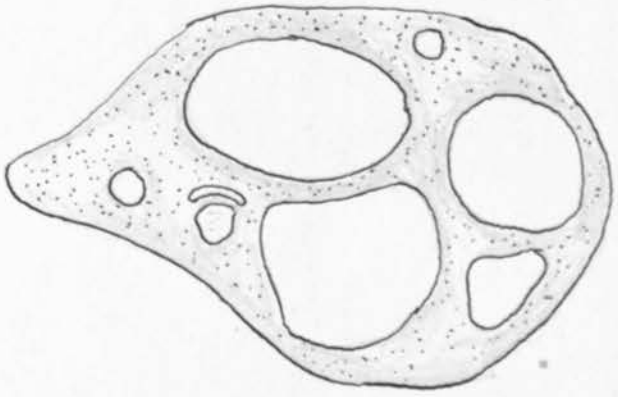


Fig 4

A-20-271 (X8)
Ovary 7×11 mm.
multiple cysts 2×3 mm. containing
memb. granulosa

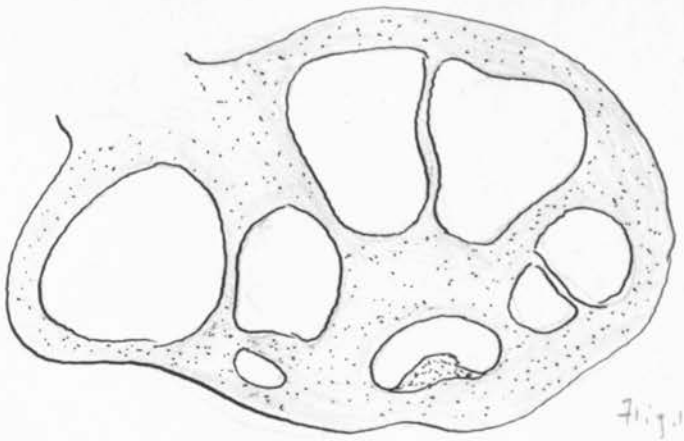


Fig. 1

A - 21 - 381 (X7)
Ovary 8 X 13 mm.
cysts 2 x 3 mm. & 2.5 x 4 mm.

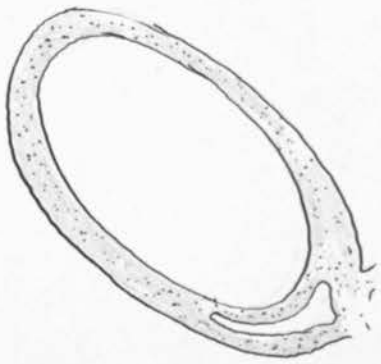


Fig. 2

A - 20 - 492 (X8)
Ovary 4 x 8 mm.
Cyst 2 x 5 mm. also
contracted cyst.

from our series, altho they are quite variable as to size and number.

A large proportion of the ovaries of children studied by Stevens contained follicular cysts of 2 and 3 mm diameter. These cysts are nearly always multiple. Stevens is of the opinion that the enlargement of the Graafian follicles to the dimensions of a follicular cyst is due to the fact that the regressive changes are postponed for some reason. Beyond the greater development of liquor folliculi both Goodall and Stevens feel that there is no abnormal change. The cause of the ordinary variations in these follicular cysts is undetermined.

Do these cysts furnish any basis for pathology?

Goodall and Ewing state that these cysts may enlarge sufficiently to become clinical. Cases of perhaps 1 cm or more in size are pathological and arise from distension of the Graafian follicle by inflammatory serous exudate. These cysts may be as large as one's fist and may be multilocular. This condition is perhaps best called Hydrops folliculi, altho this usage is not constant. The contents are serous, albuminous, fluid, without pseudomucin, but blood and fatty detritus may be added. The wall is distinctly ovarian tissue in a state of atrophy and fibrosis. Little ovarian stroma may be recognizable and the epithelial alveoli of the cystadenoma are winning. The follicular epithelium is usually destroyed. Low, warty, fibrous excrescences may appear on the inside wall. In some cases the process is an exaggerated cystic chronic ovaritis. The fairly constant presence of inflammation of pelvic organs indicates the inflammatory origin of such cysts. (Ewing)

In such a delicately constructed organ as the ovary it is reasonable to assume that impairment in vascular supply need not be

severe to bring about textural changes. Mild disturbances are sufficient if they last long enough. Torsion complete or partial of the mesovarium at its broad ligament attachment may embarrass the adequacy of the vascular supply and cause serous stasis (Reder). Ewing observed cystic degeneration with general edema of the ovary due to torsion. Von Franque describes in an infant dying 18 hours after birth a cyst in the left ovary 4 cm in diameter and reaching practically to the umbilicus. Winckel describes a fetus of 41 cm where both ovaries contained pale, transparent cysts 1.5 cm long. Gaifami in 50 autopsies on female infants found 3 cases of voluminous ovarian cysts (6%). In two of the cases these were unilateral, in one bilateral. In two of the cases the ovary was twisted on its pedicle. Examination showed that the altered ovary contained cavities of different sizes giving the organ a spongy appearance. The ovarian tissue was reduced to a thin layer in which some primordial and Graafian follicles were found. Gaifami states that this congenital condition might perhaps be the initial stage of a true ovarian tumor or at least throw some light on the genesis of ovarian tumors, especially the cystomata.

The above instances indicate that Hydrops folliculi occurs in early life as well as later, that it develops in maturing Graafian follicles or simple follicular cysts, and that inflammatory conditions are an important factor. Reder cites the influence of appendicitis. Altho cystic degeneration is frequently found to affect both ovaries in the cases operated upon for chronic appendicitis, the lesions are confined to the right ovary in 10 to 1 of all cases. Chronic inflammatory conditions of the appendix are the cause of an excessive vascular supply in which the ovary because of its proximity is compelled to share. In the etiology of true hemorrhagic

cysts of the adult ovary, Bauby and Caston feel that there is always a morbid condition of the ovary underlying it all. These may have been ovaritis from external or internal infection, syphilis, the exanthemata, etc. Added to these predisposing causes may be local congestions such as occur at puberty or with genital excesses.

Excluding Hydrops folliculi, Goodall does not believe that tumors ever arise from Graafian follicles in process of development and degeneration. Ewing considers that simple serous cystomata are related in structure and identical in origin with Hydrops folliculi, differing only in their greater size, in the preservation and overgrowth of lining epithelium and in the greater vitality of the connective tissue. They may be as large as a child's head or even as large as the larger cystadenomata. The walls of these cysts are cellular and actively growing and the lining cells multiply, even forming low papillary projections. The description given is that of an essentially neoplastic process. Ewing states that simple cystomata probably arise from ovarian follicles but the question is, from which form of these structures. He feels that they occasionally arise from fully formed Graafian follicles. Goodall found large and small cysts abundant in the 15,000 sections he examined but in none of them was there any evidence of a tumor arising from the Graafian follicle.

It is necessary to distinguish between the membrana granulosa of a developing Graafian follicle and the single layer of partially developed epithelium which surrounds a primordial ovum in the quiescent state. All epithelial structures in the ovary and therefore all epithelial tumors, also, are derived from a common source, the germinal epithelium. The question at issue is whether the very specialized derivatives of that germ epithelium which make up all the

epithelial elements in the already growing Graafian follicle are capable of carcinomatous degeneration.

That there are epithelial tumors of the ovary that are a neoplastic transformation of the cells of the primary follicle seems probable. Von Kahlden (1895), Lönnberg (1901), Gottschalk (1899), and Voigt (1903) have described such an adenocarcinoma of the ovarian follicle. This is a malignant tumor where the carcinoma cells appear in small folliclelike bodies, some solid and looking like giant cells, others cystic at the center.

The possibilities of developing malignancy in a follicular cyst are however very slight. The present study lends no support to such a belief. The ovum and the follicular epithelium are the only possibilities and the chance that any epithelial neoplasm should originate from them is remote. First, the follicular cyst constitutes merely an advanced stage in the normal process of the Graafian follicle, a process during which the ovum itself gives evidence rather of heightened function and of aging rather than of going back to an embryonic stage with embryonic possibilities of growth. In the follicular cyst the ovum is already in beginning dissolution and its growth possibilities are decreased, not increased.

That the unfertilized ovum may already in the ovary encounter special stimuli and special surroundings and thus undergo natural parthenogenesis is the theory of Waldeyer, Lecaillon and Goodall. Goodall bases this opinion on the important experimental work on parthenogenesis done by Loeb, Wolfsohn, Bischoff and others. Goodall explains the origin of dermoid and teratomatous tumors in this way.

While the majority of such neoplasms occur between the ages of 20 and 45 years, there are numerous examples in girls of 7 years and

less. They occur thus in the period before puberty as well as later. It is however impossible to establish any direct relation between them and the ovum of the developing Graafian follicle. Lukins holds that the entire parthenogenetic theory of dermoids is improbable.

Besides the ovum, the only other possible basis of an epithelial neoplasm present in the follicular cyst is the follicle cells or the so-called membrana granulosa. In the early stage of the Graafian follicle, the follicle cells appear as a single layer of low columnar epithelium. This epithelium suggests the columnar epithelium of the ovarian cystadenomata.

McCarty mentions that Graafian follicles may become simple cysts where the wall is composed of from 2 to 6 layers of small oval or round epithelial cells with clear fluid contents. "When a Graafian follicle ceases to be a follicle and becomes a simple cyst of this description is not known. That such cysts originate from Graafian follicles is to be strongly suspected because they have a similar lining and contain apparently the same clear fluid." He then mentions cysts with a lining that shows variations from the many layered epithelium of the Graafian follicle, thru the columnar epithelium of the cystadenoma to the papillomatous projections of the papillary cystadenoma.

That the membrana granulosa can contribute to the origin of tumors, that it can by virtue of some metaplastic tendency evolve into the ciliated or secretory epithelium of the ovarian cystadenomata is however gravely to be questioned. Goodall holds that transformation of the lining epithelium of the Graafian follicle to the usual lining of a new growth is an impossibility, that there is no creditable case of such a follicle showing developing papilloma

and that there is no evidence that cysts or new growths have arisen from Graafian follicles. After the death of the ovum the membrana granulosa, which is a membrane of highly specialized function, no longer has any raison d'être and slowly liquefies.

As the Graafian follicle develops a clear membrane or line of cleavage appears between the follicular cells and the surrounding stroma. This becomes visible early in the growth of the follicle and there is a tendency for the follicle cells to separate early from the wall at this point. The tendency of the membrane granulosa to separate as a complete membranous coat, the separation occurring along this line of cleavage, seems to indicate that it does not stand in very vital relationship to the stroma on which it rests but is rather a highly differentiated structure of transitory existence.

Occasionally a certain sector of the membrana granulosa can be seen still adherent to the wall of even fairly large follicular cysts but the line of cleavage is usually definite. At all events there are no signs in our series of any neoplastic change in this epithelium. The connective tissue wall around the typical follicular cyst is, however, very cellular in contrast to the surrounding stroma, and this densely cellular connective tissue does occasionally simulate epithelium. For the most part, however, it is quite characteristic and it contains young capillaries in all its levels.

Von Kahlden has studied the etiology of small cysts of the ovary with epithelial lining. These are an adenomatous development and are distinct from follicular cysts. These small cystadenoma are due to infoldings and overgrowths of the surface germ epithelium. They occur near the surface of the ovary while follicular or retention cysts are in the deeper layers. The former are not so regular and equal in size as the follicular cysts, they lack the absolutely

characteristic wreathlike vascular arrangement and the hyperemia that are both constant in follicular cysts. The former do not, as a rule, produce as large an ovary as the latter. The two types of cysts also show a different age incidence. The adenomatous type is on the whole a disease of advanced age, occurring after the menopause, while follicular degeneration is found chiefly in young subjects.

SUMMARY. While follicular cysts are frequent after birth thruout the prepubertal period and while they may attain a size of 5 mm or more in diameter they preserve in all cases in the present series always the appearance of degenerating Graafian follicles. That such cysts may under abnormal conditions enlarge to form simple cystomata seems most probable, but that they are able to assume the columnar epithelial lining of the cystadenoma and become epithelial neoplasms is not suggested by any observation made in the present study.

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