THE GROWTH OF THE OVARIAN FOLLICLE OF THE GUINEA PIG UNDER NORMAL AND PATHOLOGICAL CONDITIONS.

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As the ovary seems to be a favorable organ for the quantitative estimation of cell growth, we undertook to analyze the growth energy of the granulosa cells in the ovaries of normal guinea pigs and also to study the growth energy of these cells under certain pathological conditions.

Method.

The growth energy was estimated by the determination of the percentage of mitoses in granulosa cells in the follicles of the ovaries of normal guinea pigs. A large number of cells was counted and the number of mitoses ascertained, thus making possible a comparison of the proliferative power of the various follicles by the relative percentage of mitoses.

The follicles were classified according to size into three groups, large, medium, and small, whose average measurements were: large, 788 by 611 μ; medium, 506 by 450 μ; small, 215 by 130 μ. These measurements are from the inner border of the theca interna on one side to the same point on the other side; *i.e.*, the space lined by the theca interna.

One other type of follicle was studied in normal ovaries; *viz.*, the mature type whose characteristics have been described in earlier papers by Loeb.[1] These follicles are on an average somewhat larger than the ordinary large follicle. There is relatively much more

[1] Loeb, L., *J. Morphol.*, 1911, xxii, 37; *Virchows Arch. path. Anat.*, 1911, ccvi, 278; *Zentr. Physiol.*, 1910–11, xxiv, 203.

cytoplasm in the cells which in hematoxylin- and eosin-stained sections is pink and gives the follicle a much pinker appearance than others in the same ovary.

Measurements of large, medium, and small follicles follow and are of the space lined by the theca interna.

Large Follicles.

Long diameter, between 1,076 and 550 μ.
Short " " 830 " 377 μ.
Average long diameter, 788 μ.
" short " 611 μ.

Diameter of Follicular Cavity.

Long diameter, between 973 and 434 μ.
Short " " 726 " 256 μ.
Average long diameter, 747 μ.
" short " 502 μ.

Medium Follicles.

Long diameter, between 650 and 408 μ.
Short " " 615 " 315 μ.
Average long diameter, 506 μ.
" short " 450 μ.

Diameter of Follicular Cavity.

Long diameter, between 575 and 169 μ.
Short " " 457 " 92 μ.
Average long diameter, 347 μ.
" short " 101 μ.

Small Follicles.

Long diameter, between 318 and 77 μ.
Short " " 227 " 77 μ.
Average long diameter, 215 μ.
" short " 130 μ.

Diameter of Follicular Cavity.

Long diameter, between 188 and 23 μ.
Short " " 108 " 29 μ.
Average long diameter, 80 μ.
" short " 69 μ.

Several of each of the preceding types of follicles, usually three, were studied in each ovary. In order to count the cells and mitoses we studied the follicle in serial sections with a $\frac{1}{12}$ oil immersion objective and a No. 8 ocular upon whose distal surface two parallel lines were ruled. This method presents some difficulties, one constant source of error being the confusion which results from focusing on the cells at different levels. Such errors are uniform throughout and although they depreciate the value of the estimation of the absolute number of cells in a follicle of a given size to some extent, their influence is practically nil from a comparative standpoint, the error being the same in all cases.

Growth of the Normal Follicle.

The protocol of Guinea Pig 1 gives the results obtained in the three sizes of follicles approximately the same as the average figures based on all the follicles studied (Table I). The two ovaries of the animal are numbered 1 and 2. It is shown here that there is a distinct difference in the percentage of mitoses of the different types of follicles. The medium follicles have the highest percentage of mitoses and therefore the greatest growth energy, the large ones the lowest, and the small follicles have a proliferative power which slightly exceeds that of the large type, but is considerably less than that of the medium follicle. This fact holds good in either ovary alone as well as the combined figure of both ovaries.

Table II shows the injurious effect of extirpation of corpora lutea by burning and the effect of slight postmortem change on the percentage of mitoses.

This difference in the growth energy of the various types of follicles is constant, whether we consider the follicle of one or two ovaries of the same animal, if the number of cells counted is sufficiently large, and furthermore, approximately the same relative difference in the percentage of mitoses was seen in all the normal ovaries examined.

Small follicles have relatively more variability in the percentage of mitoses than medium or large follicles. Various sized follicles and mature follicles studied in the different ovaries have been grouped and tabulated separately.

Table II gives a summary of the number of granulosa cells and mitoses counted with the percentage of mitoses in the large follicles of the ovaries of two normal guinea pigs, and also the ovaries of two guinea pigs in which the follicles were abnormal.

TABLE I.

Protocol of Guinea Pig 1.

Follicles in Ovary 1.				Follicles in Ovary 2.			
Follicle.	No. of cells.	No. of mitoses.	Percentage of mitoses.	Follicle.	No. of cells.	No. of mitoses.	Percentage of mitoses.
Large follicles.							
			per cent				*per cent*
No. 1	2,009	19	0.94	No. 1	2,604	8	0.30
" 2	3,550	14	0.39	" 2	3,125	21	0.67
" 3	2,390	25	1.0	" 3	2,349	23	0.97
" 4	2,122	28	1.3				
" 5	2,294	19	0.83				
Total.....	12,365	105	0.84	Total....	8,078	52	0.64
Medium follicles.							
No. 1	1,431	19	1.3	No. 1	2,617	36	1.3
" 2	2,685	20	0.74	" 2	2,076	25	1.2
" 3	2,437	27	1.1	" 3	2,173	15	0.68
Total.....	6,553	66	1.0	Total....	6,866	76	1.1
Small follicles.							
No. 1	749	5	0.66	No. 1	846	3	0.35
" 2	492	5	1.0	" 2	1,441	17	1.1
" 3	681	7	1.0	" 3	747	4	0.53
Total.....	1,922	17	0.88	Total....	3,034	24	0.78

Large Follicles.—In Table II the figures for four different guinea pigs are given. The figures given for Guinea Pigs 1 and 2 are compiled from a study of normal follicles and represent the true growth energy of large follicles, whereas the percentage of mitoses in the granulosa cells of Guinea Pigs 3 and 4 has been lowered in one case by burning out of the corpora lutea and in the other by postmortem change.

To summarize, the growth energy of eighteen large follicles has been studied. In normal ovaries 23,954 cells have been counted having a percentage of mitoses of 0.73. In abnormal ovaries 25,344 cells have been counted with a percentage of mitoses of 0.16.

TABLE II.

Percentage of Mitoses in Large Follicles.

Guinea pig No.	Ovary.	No. of cells.	No. of mitoses.	Percentage of mitoses.	Remarks.
					Normal follicles.
				per cent	
2		3,511	19	0.54	Heat 21 days before death.
1	1	12,365	105	0.84	7 days after ovulation.
	2	8,078	52	0.64	
Total.....		23,954	176	0.67*	
				0.73†	
					Pathological follicles.
3		8,417	12	0.14	Corpora lutea burned out of ovary.
4	1	8,813	0	0.0	Found dead. Ovaries taken out sev-
	2	8,114	29	0.35	eral hours after death.
Total.....		25,344	41	0.16*	
				0.16†	

* This figure represents the average obtained from the percentage of the respective ovaries.

† This figure represents the percentage of mitoses for the total of all the cells counted in that particular type of follicle, the total being compiled from the figures of all the follicles counted in the various animals.

Medium Follicles.—The figures of medium follicles are shown in Table III. The percentage of mitoses in all these follicles is 1 or more, with the exception of Guinea Pig 3 which is the animal from whose ovaries the corpora lutea had been burned out. Doubtless the low percentage of mitoses here is due to the heating of the ovary in the process of burning out the corpora lutea.

To summarize, in normal medium follicles (Guinea Pig 3 is excluded) 80,625 cells have been counted, having a percentage of mitoses of 1.2.

TABLE III.

Percentage of Mitoses in Medium Follicles.

Guinea pig No.	Ovary.	No. of cells.	No. of mitoses.	Percentage of mitoses.	Remarks.
				per cent	
5	1	13,924	147	1.0	10 days after birth of young.
	2	10,990	160	1.4	
6	1	5,823	76	1.3	Near the end of pregnancy.
	2	6,771	96	1.4	
7	1	4,828	55	1.1	Ovulation had just taken place.
	2	5,086	60	1.1	
2	1	9,428	128	1.3	Heat 21 days before removal of ovaries.
	2	10,356	131	1.2	
1	1	6,553	66	1.0	7 days after ovulation.
	2	6,866	76	1.1	
3		4,464	21	0.47	Corpora lutea burned out of ovary.
Total.....		80,625	995	1.1*	Total does not include Guinea Pig 3.
				1.2†	

* Average percentage of mitoses.

† Absolute percentage of mitoses.

Small Follicles.—Table IV shows that there is relatively greater variability in the percentage of mitoses of small, than either large or medium follicles. The growth energy of small follicles in various stages of cavity formation was compared, but no constant differences were found. Here again the ovaries of Guinea Pig 4, in which there has been slight postmortem change, showed a very low percentage of mitoses and their figures together with those of Guinea Pig 3, from whose ovaries the corpora lutea were burned out, are not included in the total.

To summarize, in normal small follicles 89,545 cells have been counted, having a percentage of mitoses of 0.66.

Mature Follicles.—The growth energy of six mature follicles in the ovaries of two guinea pigs was studied (Table V). In all, 24,445

TABLE IV.

Percentage of Mitoses in Small Follicles.

Guinea pig No.	Ovary.	No. of cells.	No. of mitoses.	Percentage of mitoses.	Remarks.
				per cent	
5	1	49,520	305	0.61	10 days after parturition.
	2	10,241	25	0.24	
6	1	6,693	84	1.20	Near the end of pregnancy.
	2	1,713	12	0.70	
2	1	6,084	22	0.36	Heat last observed 21 days before death.
	2	2,432	13	0.53	
7	1	3,831	60	1.56	Ovulation had just taken place.
	2	4,075	30	0.73	
1	1	1,922	17	0.88	7 days after ovulation.
	2	3,034	24	0.78	
3		3,929	28	0.71	Corpora lutea burned out of ovary.
4	1	3,754	3	0.0	Ovaries taken out several hours after death.
	2	6,473	17	0.26	
Total.....		89,545	592	0.75* 0.66†	Total does not include Guinea Pigs 3 and 4.
Total of Guinea Pigs 3 and 4.....		14,156	48	0.33	

* Average percentage of mitoses.
† Absolute percentage of mitoses.

TABLE V.

Percentage of Miloses in Mature Follicles.

Guinea pig No.	Ovary.	No. of cells.	No. of mitoses.	Percentage of mitoses.
				per cent
6		15,640	5	0.03
8	1	3,418	8	0.23
	2	5,387	4	0.07
Total.....		24,445	17	0.11* 0.06†

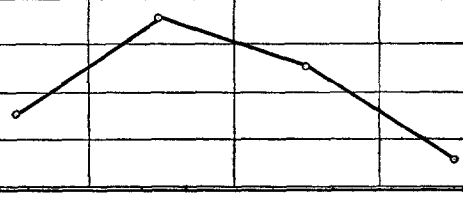
* Average percentage of mitoses.
† Absolute percentage of mitoses.

cells and 17 mitoses were counted with an average percentage of mitoses for the follicles of the respective ovaries of 0.11, whereas the absolute number of mitoses per hundred cells is 0.06.

It follows, therefore, that mitoses are almost absent in mature follicles, which agrees with the observation of Loeb[1] and others that mitoses are very infrequent in mature follicles.

Growth Curve.—If we represent the variation in the growth energy in accordance with the development of the different follicles, we obtain a curve such as is represented in Text-fig. 1. We see that the growth energy increases with the development of the follicle from small to medium size, and here it reaches its maximum, then it again

Type of follicle.	Percentage of mitoses.	Average size of small follicle 215 by 130 μ.	Average size of medium follicle 506 by 450 μ.	Average size of large follicle 788 by 611 μ	Average size of mature follicle 930 by 629 μ
Medium	1.2 per cent.				
Large.	0.73 per cent.				
Small.	0.66 per cent.				
Mature.	0.06 per cent.				



TEXT-FIG 1. Curve indicating the proliferative energy of follicles as a function of their size.

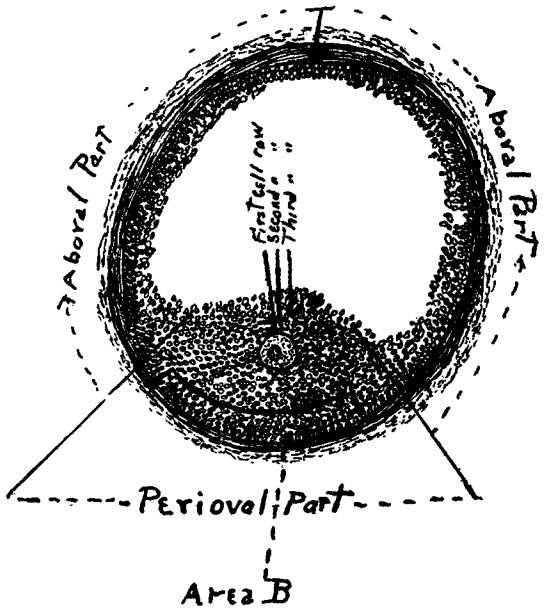
decreases, the growth energy of large follicles being at approximately the same level as that of the small follicles. A steep fall to mature follicles than takes place.

This curve bears some resemblance to that described by Robertson[2] and Ostwald[3] and some others for various growth processes. However, Robertson and Ostwald based their results not on percentage increases but on absolute increases. If the curves of Robertson and Ostwald were expressed in percentage increases they would differ markedly from ours. As Loeb has pointed out, it is probable that the decrease in growth energy of mature follicles is associated with greater cell differentiation in these follicles.

[2] Robertson, T. B., *Arch. Entwcklngsmechn. Organ.*, 1908, xxv, 581.

[3] Ostwald, W., in Roux, W., Vorträge über Entwickelungsmechanik der Organismen, Heft 5, Leipsic, 1908.

Quantitative Determination of the Location of Mitoses in the Granulosa Cells of Follicles of Various Sizes.—It has been observed by Loeb that the mitoses occurring in mature follicles are found in the discus proligerus. This observation suggested the possibility that the ovum stimulated the proliferation of the granulosa cells and made it desirable to investigate more closely the localization of mitoses in various kinds of follicles.



TEXT-FIG. 2. Areas in the ovarian follicle.

A number of follicles in the various ovaries having only a few granulosa cells surrounding the egg were selected. The number of mitoses occurring in the various cell rows around the egg was determined and, in addition, whenever a cavity had been formed the part of the granulosa in which the mitoses occurred was noted. Moreover, measured areas at various distances from the egg were compared as to the frequency of their mitoses.

In order to facilitate the description of our findings we found it necessary to divide the granulosa into several parts (Text-fig. 2). We divide the granulosa into two main parts: the perioval part which comprises the discus proligerus and the few cells distal to it which

are indicated on the diagram; the remaining part of the granulosa we call the aboval part. We also distinguish within the perioval part an area designated B on the diagram, of which the length is variable, but never exceeds the limitations of the perioval part, and the short diameter extends from the theca interna behind the egg towards it to the point where the cells begin to be more loosely arranged. We determined the relative frequency of mitoses in the peri- and aboval parts and in addition compared the number of mitoses per sq. μ in area B with the aboval part.[4]

26 small follicles in which the egg was surrounded by from five to ten rows of granulosa cells, were analyzed in the manner just described, with the following result. 8 of the 26 follicles (30 per cent) have 100 per cent of their total mitoses occurring in the first cell row. 17, including the above 8 (65 per cent), have 50 per cent or more of their total mitoses occurring in the first cell row. 4 (15 per cent) have less than 50 per cent of their total mitoses occurring in the first cell row, but more mitoses near the egg than near the theca interna. 3 (11 per cent) have their greatest number of mitoses midway between the egg and the theca. 2 (7 per cent) have more of their total mitoses near the theca than near the egg.

It has been shown here that 65 per cent of the total mitoses occur in the first two cell rows, 30 per cent of which are in the first cell row. By total mitoses we understand all the mitoses observed by study of the follicle in serial section. By first cell row we mean the row of cells encircling the egg (Text-fig. 2).

Four small follicles, in which the space lined by the theca interna had an average measurement of 253 by 170 μ and in which there was early cavity formation, were studied. The findings were as follows:

1st	cell row contains	16 per cent of the total mitoses of the follicles.
2nd	" " "	5 " " " " " " " " " "
3rd	" " "	10 " " " " " " " " " "
4th	" " "	8 " " " " " " " " " "
5th	" " "	6 " " " " " " " " " "
6th	" " "	6 " " " " " " " " " "
7th	" " "	0.8 " " " " " " " " " "
Remaining part of granulosa contains		44 " " " " " " " " " "

[4] Because of the variability of length of area B sometimes a few cells of the perioval part were included in the aboval part.

It is seen here that as the follicle increases in size the percentage of the total mitoses which occur in the first and second cell rows, decreases, yet 30 per cent of the mitoses still occur in the first three cell rows. The proliferative power of the cells near the theca is greater than in follicles of smaller size.

Next the results obtained in the study of nine small follicles, the cavities of which are of somewhat larger size than the preceding two kinds, are given. The average diameter of the space lined by the theca interna in these follicles was 215 by 132 μ; the average size of the cavity 72 by 71 μ.

1st	cell row contains	14 per cent of the total mitoses of the follicles.
2nd	" " "	9 " " " " " " " " " "
3rd	" " "	8 " " " " " " " " " "
4th	" " "	1 " " " " " " " " " "
5th	" " "	9 " " " " " " " " " "
6th	" " "	3 " " " " " " " " " "
9th	" " "	1 " " " " " " " " " "
Remaining part of granulosa	contains	52 " " " " " " " " " "

The results here are similar to those obtained in the preceding follicles. As the follicles increase in size there has been a gradual increase in the number of mitoses not in the immediate neighborhood of the egg.

The results of the analysis of the localization of mitoses in thirteen medium follicles, in which the average diameters of the space lined by the theca interna were 506 by 450 μ, are given below.

1st	cell row contains		4 per cent of the total mitoses of the follicles.
2nd	" " "		1 " " " " " " " " " "
3rd	" " "		3 " " " " " " " " " "
4th	" " "		2 " " " " " " " " " "
5th	" " "		4 " " " " " " " " " "
6th	" " "		2 " " " " " " " " " "
7th	" " "	less than	1 " " " " " " " " " "
Remaining part of granulosa	contains		80 " " " " " " " " " "

In medium follicles the remaining part of the granulosa includes a considerable number of cells in the perioval part of the follicle,

while in small follicles with a cavity the remaining part of the granulosa is made up almost entirely of cells in the aboval part.

In medium follicles the migration of the proliferating area from the first few cell rows encircling the egg to the cells near the theca behind the egg (see area B in Text-fig. 2), has been completed and now the greatest percentage of the mitoses of the follicle occurs in area B, as we shall see more specifically later on, and hence the majority of the 80 per cent of the mitoses in the remaining part of the granulosa occurs in this area.

The migration of the area of greatest mitotic activity reaches its maximum distance from the egg synchronously with the maximum growth energy of the follicle. Perhaps this is partly accounted for by the fact that the cells are farther apart and their number may be relatively smaller.

The analysis of the localization of mitoses in large follicles brought out the fact that the observation of Loeb that mitoses in mature follicles are limited to the discus proligerus, also to a certain extent holds good in large follicles which are not mature, as is shown by the following data.

Several large follicles were studied in the usual way and it was found that 43 per cent of their total mitoses occurred in the first two cell rows encircling the egg; 50 per cent occurred in the perioval (Text-fig. 2), and 7 per cent in the aboval part. The percentage of the total mitoses has increased in the first two cell rows coincidently with the decrease in growth energy of the follicle.

The difference in the growth energy of the perioval and aboval parts of large follicles is much greater than in medium sized ones, as in the case of the former the proliferative power of the aboval part has come almost to a standstill. This agrees with the observation of Loeb that degenerative processes usually attack the cells of the discus proligerus last.

It seems reasonable to assume on the basis of the preceding data that the egg may furnish a direct stimulus to the granulosa cells, especially in view of the fact, as will be brought out later, that the site of greatest mitotic activity is always near the egg.

We next compared the frequency of mitoses in the peri- and aboval parts of the follicles. We also compared the number of mitoses in the

aboval part reduced to the sq. μ equivalent of area B, with the latter, with the following results.

20 Small Follicles.

Perioval part contains 72 per cent of the total mitoses.
Aboval " " 26 " " " " " " "
Area B contains 80 per cent of the total mitoses.
Aboval part, reduced to sq. μ equivalent of area B, contains 19 per cent of the total mitoses.

6 Medium Follicles.

Perioval part contains 66 per cent of the total mitoses.
Aboval " " 33 " " " " " " "
Area B contains 71 per cent of the total mitoses.
Aboval part, reduced to sq. μ equivalent of area B, contains 25 per cent of the total mitoses.

2 Large Follicles.

Perioval part contains 93 per cent of the total mitoses.
Aboval " " 7 " " " " " " "
Area B contains 85 per cent of the total mitoses.
Aboval part, reduced to sq. μ equivalent of area B, contains 14 per cent of the total mitoses.

To compare area B with the aboval area, we determined the number of sq. μ in each and multiplied the number of mitoses counted in area B by the number of times the aboval part exceeded area B in sq. μ.

As a result of our study of the localization of mitoses in the granulosa cells we draw the following conclusions: (1) In all follicles the large majority of mitoses occurs in the perioval part. (2) In medium follicles where the percentage of mitoses is relatively highest, there are more mitoses in area B and in the aboval part than in large or small follicles. Moreover, in medium follicles there is a relative preponderance of cells some distance from the egg as compared with large and small, where they are more directly around the egg, showing that with increase in the percentage of mitoses in medium follicles, the granulosa cells not directly around the egg, gain relatively more in proliferative power than the cells around the egg.

Growth of the Follicle under Pathological Conditions.

We analyzed the proliferative power of follicles under two pathological conditions: (*a*) In follicles in which part of the granulosa cells had undergone degeneration by karyorrhexis, a condition which corresponds to early follicular degeneration; (*b*) secondly we investigated the condition in the follicles of hypotypical ovaries.

(*a*) *Growth Energy of Follicles in Beginning of Degeneration of Granulosa Cells.*—Only follicles which showed rather extensive degeneration by karyorrhexis were considered. In this form of atresia the degeneration is usually most evident in the cell rows nearest the cavity of the follicles. The growth energy in these follicles was determined in the same way as in normal ones and only those cells were counted in which there was no visible degeneration. The follicles and their cavities were usually somewhat larger than medium follicles. The results of the examination of twenty-seven follicles with partial granulosa degeneration are given in Table VI.

TABLE VI.

Percentage of Mitoses in Degenerating Follicles.

Guinea pig No.	Ovary.	No. of cells.	No. of mitoses.	Percentage of mitoses.	Remarks.
				per cent	
5	1	6,789	14	0.20	
	2	8,310	45	0.54	
6	1	7,247	10	0.13	
	2	2,304	0	0.0	
2	1	6,450	29	0.44	
	2	7,143	50	0.69	
3		2,604	0	0.0	Corpora lutea burned out.
4	1	4,870	0	0.0	Found dead.
	2	4,036	1	0.02	
Total.....		49,753	149	0.22*	
				0.29†	

* Average percentage of mitoses.

† Absolute percentage of mitoses.

It is shown here that both the absolute and average percentage of mitoses of the cells in these follicles which are not yet degenerating are much lower than in normal follicles of the same size.

It was observed during this study that the majority of the mitoses occurs in the cells of the discus proligerus and that the percentage of mitoses is proportionate to the amount of degeneration; the more extensive the degeneration the weaker is the proliferative power of the cells which have not yet degenerated.

(*b*) *Growth Energy of Follicles of Hypotypical Ovaries.*—Under this designation Loeb[5] has described ovaries which he has observed under several conditions, for instance, after the burning out of corpora lutea, etc. Hypotypical ovaries are smaller than normal; they are characterized by an early connective tissue atresia of follicles, taking place while the follicles are quite small, and hence there are no large, no mature follicles, and for the time being the ovary is sterile. It was our intention to determine if possible whether the failure of follicles in such ovaries to grow past small size was due to a diminished proliferative power of the granulosa or to an increased cell destruction. We may mention here that granulosa degeneration by karyorrhexis does not take place in the hypotypical ovaries except in isolated cells and not *en masse* as in normal follicles.

The results obtained in fifty-five follicles, in six hypotypical ovaries of three animals, are presented in Table VII. As has already been mentioned, the follicles in hypotypical ovaries become atretic at so early a stage of their development that only small follicles are seen well preserved. The average diameters of the space lined by the theca interna, of the follicles whose figures appear in Table VII, are as follows.

Long diameter of space lined by theca interna from 277 to 131 μ; average 209 μ.
Short " " " " " " " " 246 " 211 μ; " 178 μ.
Long " " cavity from 188 to 35 μ; average 91 μ.
Short " " " " 208 " 54 μ; " 135 μ.

Table VII shows that the average percentage of mitoses (0.57) and the absolute percentage (0.55) in the hypotypical follicles are nearly the same, but slightly lower than in normal follicles of the same size.

In the granulosa cells of the hypotypical follicles, those cells which remain preserved show almost the same proliferative power as the

[5] Loeb, *Zentr. Physiol.*, 1911–12, xxv, 342.

TABLE VII.

Percentage of Mitoses in Follicles of Hypotypical Ovaries.

Guinea pig No.	Ovary.	No. of cells.	No. of mitoses.	Percentage of mitoses.
				per cent
9	1	5,661	12	0.21
	2	5,668	24	0.42
10	1	9,491	51	0.53
	2	2,463	27	1.0
11	1	10,099	57	0.56
	2	8,703	61	0.70
Total.....		42,085	232	0.57*
				0.55†

* Average percentage of mitoses.

† Absolute percentage of mitoses.

granulosa cells of normal follicles. But it would be incorrect to state that the granulosa as such in hypotypical follicles shows the same proliferative power. Evidently a considerable number of cells which remain preserved in normal follicles undergo premature solution in hypotypical follicles and these cells no longer proliferate. Therefore the absolute number of mitoses in follicles of hypotypical ovaries is of course diminished. It is, however, of interest that the cells which remain show only slightly less proliferative power than the cells of normal follicles.

We also made comparative studies of normal and hypotypical follicles. (*a*) We compared the localization of mitoses in the two kinds of follicles and found that the localization phenomenon in hypotypical follicles parallels that of normal follicles of the same size. (*b*) We compared the size of the nuclei in normal and hypotypical follicles by measuring them at various phases in the granulosa in a number of follicles of each kind. It was found that on the whole the nuclei of normal follicles slightly exceeded in size the hypotypical. (*c*) The relative sizes of the cavities of normal and hypotypical follicles were compared and we found that the cavity of the hypotypical is relatively about twice as large as that of the normal follicle of the same size.

SUMMARY AND CONCLUSIONS.

1. The growth energy of the granulosa cells in the ovarian follicles of normal guinea pig ovaries varies with the size of the follicle, and follows a definite growth curve. The growth energy in small follicles is relatively low, then a gradual rise takes place with increase in size of the follicle up to a maximum which is reached when the follicle attains medium size. This ascending part of the curve is followed by a gradual fall in growth energy until in large follicles the proliferative power has fallen almost to the level of small follicles. Synchronously with maturity of the follicles there is an abrupt fall in growth energy to near the zero point.

2. There is a distinct localization of mitoses in the follicle. The large majority of mitoses is found in the perioval part. With increase in the growth energy which characterizes medium follicles, there is an increase in the proliferative power of the cells more distal to the egg, but still near the egg. We may therefore conclude on the basis of our observations and on the previous observations of Loeb, that the egg exerts a stimulus, which causes proliferation of the granulosa cells.

3. Under pathological conditions certain changes occur in the growth energy of the follicle: (*a*) Granulosa degeneration causes in the living cells a diminution in the proliferative power which is proportionate to the extent of the degeneration. (*b*) Hypotypical follicles have approximately the same or only slightly diminished proliferative power as normal ones, and thus their failure to grow is essentially due to disintegration of the granulosa cells.