DYNAMICS OF OVARIAN HYPERTROPHY UNDER EXPERIMENTAL CONDITIONS.*

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WITH TWO PLATES.

In experiments performed on guinea-pigs and mice, we have demonstrated that small testicular fragments remaining in the body after removal of the greater part of testicular mass, do not hypertrophy though they are sufficient for the normal masculinisation of the animal; this is in full accordance with what has been demonstrated formerly by Pézard in the fowl. The lack of hypertrophy of the fragment as a whole is not an apparent one caused by the backward development of the seminiferous tubules and by decrease of their diameter; the fragments remain very small even when the tubules are in full spermatogenesis. It has been further shown that the hypertrophy of the interstitial cells as occurring in testicular fragments is most likely caused by some local conditions; this hypertrophy seems to be due not to increased endocrine requirements of the body to the interstitial cells, but due to processes going on in the seminal tubules; the hypertrophy of the interstitial cells is by no means a constant phenomenon in testicular fragments.

These statements are in full contradiction to what is known about the behaviour of an ovarian fragment. Carmichael and Marshall showed that ovarian fragments can undergo a very pronounced hypertrophy. These findings were fully confirmed in rabbits. Ovarian fragments in rabbits even when originally very small can attain the weight of a normal ovary.

It was tried to explain this contradictory behaviour of testicular and ovarian fragments in the following manner. I assumed that the hypertrophy of the testicle after unilateral castration is really to be considered not as such. I suggested that the increase in weight in this case is caused by a quicker development of the remaining testicle, the climax

* Preliminary communications in the C.R. de la Soc. de Biol.; see References (No. 7). The experiments have been performed in 1920 to 1922.
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being sooner attained than normally. It was shown by experiment⁸ that this conception is true. Now, if there is
only a quicker development of the diminished quantity of testicle after partial castration, all that happens in a testicular
fragment is that the seminal tubules will quickly attain their climax; every mm.³ of testicle has its definite or limited
maximal potential mass which can be attained by means of spermatogenesis.⁹ The situation is a wholly different one in
an ovarian fragment which has no limited potential mass, the
latter depending upon the number of ova developing to Graafian
follicles. An ovarian fragment, however small it may be,
contains a quantity of young ova which under given general
conditions can develop to follicles and transform the fragment
into a body which has the weight of a normal ovary or even
more. Possibly some substances which are necessary for the
development of the gonads, and which are present in the
body in a definite quantity, are responsible for this, as it was
suggested by Sand¹⁸ and by Hammond.⁴ If the necessary
number of young ova is present in the ovarian fragment, the
number of ova entering into follicular development will be
limited only by the amount of these hypothetical X-substances.

If our theory as to the cause of the hypertrophy of an
ovarian fragment is right, there must be in small ovarian
fragments a gradual but very pronounced diminution of young
ova, a relative greater number of ova developing into follicles
than under normal conditions. If for instance the normal
number of young ova in two ovaries of the rabbit at birth
is 200,000, and 20,000 atretic follicles and follicles of other
kinds are formed during the first months after birth, there
will be a decrease of the total number of young ova of 10 per
cent. But if the total number is reduced to only 40,000 young
ova as present in an ovarian fragment, the total number of
young ova will be reduced in the first months to about 50 per
cent., when the absolute number of ova developing into follicles
remains normal. Ovarian fragments should reveal, according
to this theory, after a certain delay a highly reduced number of
young ova. By the following experiments we will demonstrate
that this is most likely so.

When these experiments had already been performed the
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paper of Pearl and Schoppe came to my knowledge. They have shown that in the fowl after partial removal of the ovary the relative number of young ova which in the regenerating ovary develop to visible size, is significantly increased so that the total number of visible oocytes remains normal. So it must be said that the data as given in my paper are really only a confirmation for mammals of what had been shown, in a more exact manner, by Pearl and Schoppe for the fowl.

SERIES A.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>I.*</td>
<td>130</td>
<td>Gms. 1100</td>
<td>Gms. 1750</td>
<td>Days. 147</td>
<td>Normal control.</td>
</tr>
<tr>
<td>II.*</td>
<td>131</td>
<td>Gms. 980</td>
<td>Gms. 1580</td>
<td>Days. 147</td>
<td>Right ovary and upper half of left ovary removed.</td>
</tr>
<tr>
<td>III.+</td>
<td>136</td>
<td>(1 m. old)</td>
<td>1420</td>
<td>177</td>
<td>Normal control†</td>
</tr>
<tr>
<td>IV.+</td>
<td>134</td>
<td>(1 m. old)</td>
<td>1200</td>
<td>177</td>
<td>Right ovary and upper ½ or ⅔ of left ovary removed.</td>
</tr>
</tbody>
</table>

* I. and II. of same litter.
† This normal animal was engrafted (for other experimental purposes) with the ovaries from 134, but the grafts did not take.
‡ Of different litters but difference in age only of one day.

In series A one whole ovary and a large part of the second ovary were removed, only a part of the under pole of the ovary remaining in the body. The operation was performed aseptically; the incision was made in the linea alba. No ligature of ovarian vessels was made on the side where the ovarian fragment was left. The experiment lasted about five months. In case II. the ovarian fragment became as big as a normal ovary and showed almost no difference in ovarian structure from the normal, but the number of young ova was undoubtedly reduced (figs. 1 and 2). In case IV. the ovarian fragment originally was a smaller one and nevertheless attained
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almost the weight of a normal ovary. The increased fragment revealed a great number of follicles separated from one another by connective tissue of the stroma. The fragment was cut into an uninterrupted series and every section has been examined. To show the difference between the number of young ova in a normal ovary and in the ovarian fragment of case iv., we have photographed a place where the greatest number of young ova was crowded together in the fragment (figs. 3 and 4).

SERIES B.

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Weight At Operation.</th>
<th>Duration of Experiment.</th>
<th>Operation Performed.</th>
<th>General Condition of Ovary or Fragment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. 48</td>
<td>Gms. 570 (2m. old)</td>
<td>Gms. 1950 Months. 16</td>
<td>Normal control</td>
<td>R. ovary— Weight, 335 mgms. L. ovary— Weight, 346 mgms. Both ovaries contained big corpora lutea.</td>
</tr>
<tr>
<td>II. 50</td>
<td>610 (2m. old)</td>
<td>1960 16</td>
<td>Normal control</td>
<td>R. ovary— Weight, 190 mgms. L. ovary— Weight, 169 mgms. No corpora lutea.</td>
</tr>
<tr>
<td>III. 52</td>
<td>610 (2m. old)</td>
<td>1940 16</td>
<td>It was intended to be castrated, but two ovarian fragments found when killed.</td>
<td>1. Fragment— Weight, 94 mgms. 2. Fragment— Weight, 60 mgms. In both fragments young ova almost completely absent.</td>
</tr>
</tbody>
</table>

All animals of same litter.

The experimental animal of series B was really a casual observation. It was originally intended to castrate this animal and it was kept for sixteen months as a castrate. When opening then the abdominal cavity it was found that the uterus was even better developed than in one of two normal controls (fig. 12). When search was made in the abdominal cavity two ovarian fragments at a certain distance from one another were found. The fragments were of the typical yellowish colour of the ovary or the adrenal; no follicles were visible to the naked eye. The weight of both fragments together was about
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the weight of a normal ovary of one of the control animals. The histological examination revealed that both bodies consisted really of ovarian tissue (fig. 5). There were more or less centrally located follicles, the number of which in both fragments together was scarcely smaller than in a normal ovary. There was typical ovarian interstitial tissue (figs. 13, 14, 15) but a minimal number of young ova; there was almost complete disappearance of the latter as it could be ascertained when comparing with the ovaries of the normal controls (fig. 6). Both fragments were surrounded by a relatively thick capsule of connective tissue. Most probably two very small ovarian fragments were left behind on the left side when the ovary was removed and had undergone a very considerable hypertrophy by follicular development. The great quantity of highly developed interstitial tissue in both these fragments (fig. 14) is probably the result both of follicular atresia and of epitheloid transformation of stroma cells (see below). We must suppose that the number of young ova in the fragments was originally great enough to give rise to follicular development as in a normal ovary, and that the number of young ova was precociously exhausted as the original number of young ova was considerably smaller than in a normal ovary.

In series C four rabbits weighing less than 1 kg. were used. The incision was made on the left and right side beneath the last rib the animal being fixed the back upwards. This operation is a much simpler one and harms the animal less than when the incision is made in the linea alba. The disadvantage is that orientation is more difficult in very fat animals. No ligature was made. One whole ovary and the greater part of the second ovary were removed; an upper fragment remained representing about $\frac{1}{4}$ or $\frac{1}{3}$ of an ovary. In case ii. the removed part of the ovary was weighed and by comparing with the weight of the removed whole ovary it was calculated that the fragment had an original weight of 3 mgms. These animals were kept under observation for 5½ months; the experiment was interrupted by death of all the experimental animals and necropsy was made only three days after death. Then the control animal was killed and it was found to have pneumonia. In case iii. an ovarian fragment was not
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found, whereas in cases ii., iv., and v. the fragment was detected. The fragments weighed 41 and 51 mgms.; in case iv. the fragment was detected only after microscopical examination. The ovaries of the normal controls weighed only 22 to 23 mgms.

SERIES C.

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Weight At Operation</th>
<th>Duration of Experiment</th>
<th>Operation performed</th>
<th>General Condition of Ovaries or Ovarian Fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>700</td>
<td>2 m. 3 w. old</td>
<td>171</td>
<td>Left ovary and greater part of right ovary removed, only an upper fragment remaining. Weight of l. ovary, 12 mgms. Weight of r., removed part, 9 mgms.</td>
</tr>
<tr>
<td></td>
<td>880</td>
<td>2 m. 3 w. old</td>
<td>168</td>
<td>Died of disease (6 weeks before death = 1880 gms.).</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Died of disease (6 weeks before death = 1370 gms.).</td>
</tr>
<tr>
<td>III.*</td>
<td>219</td>
<td>750</td>
<td>168</td>
<td>Left ovary and under part of right ovary removed. Weight of l. ovary, 11 mgms. Weight of r., removed part, 6 mgms.</td>
</tr>
<tr>
<td></td>
<td>(2 m. 3 w. old)</td>
<td></td>
<td></td>
<td>Died of disease (6 weeks before death = 2080 gms.).</td>
</tr>
<tr>
<td>IV.</td>
<td>222</td>
<td>700</td>
<td>168</td>
<td>Right ovary and greater part of left ovary removed, only an upper fragment remaining.</td>
</tr>
<tr>
<td></td>
<td>(2 m. 1 w. old)</td>
<td></td>
<td></td>
<td>Died of disease (6 weeks before death = 2080 gms.).</td>
</tr>
<tr>
<td>V.</td>
<td>223</td>
<td>880</td>
<td>164</td>
<td>Left ovary and about ³ of right ovary removed, only an upper fragment remaining.</td>
</tr>
<tr>
<td></td>
<td>(2 m. old)</td>
<td></td>
<td></td>
<td>Died of disease (6 weeks before death = 1240 gms.).</td>
</tr>
</tbody>
</table>

* I., II., and III. same litter.

We see that the weight of the ovarian fragments was 2½ times greater than that of these ovaries; but the ovaries of the control (fig. 7), which grew noticeably slower than some of the experimental animals, were found to be less developed than generally at this age. Of most interest is case ii., where the fragment finally weighed about 17 times more than the original fragment. The weight of a normal ovary, at an age of about eight months, would have been of about 50 mgms. As the weight of the normal ovary in case ii. was originally 12 mgms., there must have been normally an increase in weight
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of about 4 times as compared with 17 times calculated for the ovarian fragment. In case II. (fig. 8) a few young ova were detected, whereas no young ova at all were found in case IV. (fig. 9). A restricted number of young ova was present in case V. (fig. 10), where the hypertrophied ovarian fragment resembled histologically very much a normal ovary, differing from the latter only by absence of nests of young ova as normally present in the periphery. We see that in all these cases of series C there was a more or less complete disappearance of young ova, which most likely have transformed themselves into follicles and interstitial tissue. Originally it was supposed\(^7\) that the very small number of young ova in ovarian fragments is partly due to the fact that the number of young ova is not equal throughout the whole ovary being very small nearer to the hilus; it was thought that the fragment possibly came from near that place of the ovary. But this argument was an erroneous one. When an upper or an under fragment of an infantile ovary is formed it contains always young ova more or less corresponding to the respective fraction of the total number of young ova in the whole ovary. A glance on a microscopical section of an upper fragment taken from a young rabbit suffices to demonstrate this (fig. 11). Now, in all the animals of series C an upper fragment remained in the body, and there was nevertheless five months afterwards only a very small number of young ova in the hypertrophied fragment.

Against our conclusions two objections may be made. One might object that the extraordinary diminution of the number of young ova is only an apparent one due to the fact that in the hypertrophied ovarian fragment the young ova are disseminated in a greater volume. But in one case (series B III.) we have counted the total number of young ova present in both fragments, which was about 1200. Now, on one section of 7.5\(\mu\) of the ovary of the control (B II.), about 130 young ova were counted. Though our counting was by no means exact, it is clear that the total number of young ova in the ovarian fragments was an extraordinary small one, representing only a minimal per cent. of the normal number. But as we do not know how big the fragments in this case originally were, it is not possible to say whether the very small number of young ova was really caused by diminution of the

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original total number; it may be possible that in these two fragments the total number of young ova was from the beginning an extremely small one. In another case (series A iv.) the total number of young ova was about 12,000, the fragment having been originally about one-third or one-fourth of a normal ovary. We have made no exact counting of the total number in a normal ovary of the rabbit in different ages. But a rough calculation from single sections shows that the total number of young ova in the ovary of a rabbit about six months old will be about 60,000. Then the diminution of the number of young ova in this case seems to be not a very marked one. The ovarian fragments of series C were not cut into complete series of sections; so it was not possible to calculate the total number of young ova in these increased ovarian fragments. But there can be scarcely any doubt that the total number of young ova in the case C ii. and C iv. was an extremely small one. I shall return to this question in the next paper, where an exact count of the total number of young ova has been made, and where it will be shown that an almost complete disappearance of young ova in an ovarian fragment is surely possible.

One might further object that the changes as occurring in an ovarian fragment and leading to considerable reduction or disappearance of young ova might be caused by local conditions or by operative interference. I have examined this question in experiments on cats with which we shall deal in the following paper. These experiments showed that it is not very probable that the operative interference itself is sufficient to explain the exhaustion of young ova in an ovarian fragment.

Arai, working under Donaldson, has shown that the number of follicles in the remaining ovary is, after unilateral castration, greater than in a normal ovary in such a manner that the number of follicles developed after unilateral castration is equal to the total number of follicles in a normal animal. The same has been stated by Pearl and Schoppe. These statements of Arai, based on a very careful counting, fully correspond to our conception and to what is shown by our experiments with ovarian fragments. In experiments with unilateral castration which we have already communicated elsewhere, we also had the impression in accordance with Arai.
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that the number of follicles is a very great one, though we have not especially counted the follicles.

SERIES D.

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Weight At Operation</th>
<th>Weight When Killed</th>
<th>Duration of Experiment</th>
<th>Operation Performed: . . . Additional Ovaries Engrafted</th>
<th>General Condition of Ovaries or Ovarian Fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. 136</td>
<td>Gms. (1 m. old)</td>
<td>1420</td>
<td>177</td>
<td>3/2 additional ovaries</td>
<td>Weight of ovaries, 34 and 40 mgms.</td>
</tr>
<tr>
<td>II. 118</td>
<td>240</td>
<td>1500</td>
<td>179</td>
<td>Normal control</td>
<td>Weight of ovaries, 37 and 47 mgms.</td>
</tr>
<tr>
<td>III. 119</td>
<td>150</td>
<td>1360</td>
<td>179</td>
<td>2 additional ovaries</td>
<td>Weight of ovaries, 45 and 53 mgms.</td>
</tr>
<tr>
<td>IV. 121</td>
<td>240</td>
<td>1420</td>
<td>179</td>
<td>Normal control</td>
<td>Weight of ovaries, 46 and 44 mgms.</td>
</tr>
<tr>
<td>V. 124</td>
<td>250</td>
<td>1520</td>
<td>179</td>
<td>3 additional ovaries</td>
<td>Weight of ovaries, 47 and 54 mgms.</td>
</tr>
<tr>
<td>VI. 132</td>
<td>1000</td>
<td>1630</td>
<td>147</td>
<td>3 additional ovaries</td>
<td>Normal appearance of ovaries (not weighed).</td>
</tr>
<tr>
<td>VII. 129</td>
<td>780 (2½ m. old)</td>
<td>1770</td>
<td>182</td>
<td>Normal control</td>
<td>Weight of ovaries, 73 and 79 mgms.</td>
</tr>
<tr>
<td>VIII. 125</td>
<td>720 (2½ m. old)</td>
<td>1550</td>
<td>182</td>
<td>5 additional ovaries</td>
<td>Weight of ovaries, 80 and 89 mgms.</td>
</tr>
</tbody>
</table>

* II. and III. same litter. † IV. and V. same litter. ‡ VII. and VIII. same litter.

If the conception is true that the number of young ova entering into follicular development depends upon some general factor, it should be possible to suppress follicular development in the ovaries in situ by engrafting ovaries into a not castrated animal; it is well known that follicular development is accelerated in the ovarian graft. Haberlandt 8 seems to have shown that sterility can be caused in rabbits and guinea-pigs by ovarian implantation. It is very likely that the exaggerated process of follicular development in the graft inhibited the follicular development in the ovaries in situ.

To examine this question I made a series of experiments in which a great quantity of ovarian mass was engrafted into not castrated animals. The experiments (series D) were performed on rabbits about one to three months old. Ovaries of animals of the same age and mostly of the same litter have been engrafted subcutaneously. The number of ovaries engrafted was from almost two to five. The result of these experiments was a negative one in all the five animals which had received about fifteen ovarian grafts. The first examina-
tion of the animals was made about two months after the operation, and in most of the cases nothing was felt by palpating; only in one case (v.) a formation of about the size of a pea was found in the place of the graft and it was thought to be a degenerated cystical ovary. Later on this body wholly disappeared. The animals were kept for about six months after the operation, and the ovaries *in situ*, as to weight and follicular development, were found fully normal. In those experiments where normal control animals of the same litter were available (III., v., VIII.), the weight of the ovaries was even a little greater in the experimental animals than in the controls.

How is one to explain these results in view of the great facility of ovarian transplantation in female castrates and even in male castrated or normal individuals? The original hope to inhibit follicular development in the ovaries *in situ* by the ovarian graft was evidently checked by the fact that the ovaries *in situ* were better fitted by vascularisation than the ovarian grafts. The survival of the graft depends evidently upon some available substances as present in the body fluids, as Sand and Hammond have supposed, and as I rendered probable by experiments with unilateral castration of male rabbits. Evidently the ovarian graft made in presence of the ovaries *in situ* has less chance of survival and of follicular development than the graft made in a castrated animal. Had we used ovaries of adult animals possibly the result would have been a positive one, *i.e.* possibly the development of the ovaries *in situ* would have been somewhat inhibited as in the experiments of Haberlandt, quoted above. In the latter case the influence might have been an hormonic one, an influence by substances entering gradually into the blood from the graft even if undergoing resorption. Surely it is very difficult to say whether this explanation is right or not. A greater number of comparative experiments with ovarian grafts in normal and castrated females, and with ovarian grafts from animals of different ages only could decide the question. Sand has performed similar experiments in the guinea pig, but as yet he has not given the full details*

* During 1924 I have made a new series of experiments in which a third ovary has been engrafted into not castrated female guinea pigs. The intrarenal method of ovarian transplantation was used which guarantees success in every case when the glands *in situ* are absent. So comparison is easy. The results will be given elsewhere.
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We shall now discuss the experiments of series A, B, and C from another point of view. It is of great interest to examine the question, how far the small ovarian fragments have proved to be able to perform the endocrine function of the ovary. The uterus of the rabbit can serve as a very good index of the ovarian hormonal activity, as castration causes a very far-going atrophy or underdevelopment of the uterus.

In out of seven experiments there was only one (C III.) in which the uterus of an animal of about eight months was like that of a castrate. In this animal which lived five months after the operation, the fragment was not found. Three of the remaining six animals had a normal uterus or, as in B III., the uterus was even better developed than in one of the normal controls (fig. 12). The highly hypertrophied ovarian fragments were in these three cases very poor in young ova, especially B III. and C II. (figs. 5 and 8). There was in these three cases a seemingly normal quantity of follicles in different stages of development. No corpus luteum was present. In C II. there was a tendency to cystical degeneration which we shall meet again in another case in a more pronounced manner (C IV.). In B III. where the uterus was highly developed the quantity of interstitial tissue was like that in a normal ovary and the interstitial cells were highly developed (figs. 13 and 14). There were highly developed interstitial cells like in an adult animal also in case C II. (fig. 16). In the third case (A II.) the quantity of interstitial tissue outside the follicles was poor, interstitial tissue consisting mostly of nests separated from one another by connective tissue.

If we go through these three cases with a well-developed uterus we must conclude that the normal hormonal activity of the ovarian fragment depends upon an increased relative number of ova which enter into follicular development, and by this furnish the necessary amount of endocrine cells originating from the granulosa or from the theca interna, and probably conditioning also a transformation of stroma cells into what are called interstitial cells (fig. 15).

We shall discuss now the remaining three cases where the uterus was less developed than in a normal animal of that age. It must be insisted on that in all these three experiments the uterus, though less developed than in a normal, was by no
<table>
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<th>Weight or Age.</th>
<th>Duration of Experiment.</th>
<th>Condition of the Uterus.</th>
<th>Condition of the Fragment.</th>
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<tbody>
<tr>
<td></td>
<td>At Operation.</td>
<td>At end of Experiment.</td>
<td>Gms.</td>
</tr>
<tr>
<td>C III. 219 A II. 131</td>
<td>Gms. 750 (2 m. 3 w.)</td>
<td>Gms. (1370)</td>
<td>1580</td>
</tr>
<tr>
<td>B III. 52</td>
<td>Gms. 610 (2 m.)</td>
<td>Gms. (1940)</td>
<td>1580</td>
</tr>
<tr>
<td>C II. 218</td>
<td>Gms. 880 (2 m. 3 w.)</td>
<td>Gms. (1880)</td>
<td>1580</td>
</tr>
<tr>
<td>A IV. 137</td>
<td>Gms. 1 m.</td>
<td>Gms. (1200)</td>
<td>1580</td>
</tr>
<tr>
<td>C IV. 222</td>
<td>Gms. 700 (2 m. 3 w.)</td>
<td>Gms. (2080)</td>
<td>1580</td>
</tr>
<tr>
<td>C V. 223</td>
<td>Gms. 880 (2 m.)</td>
<td>Gms. (1240)</td>
<td>1580</td>
</tr>
</tbody>
</table>

(Complete series of sections.) Almost complete lack of young ova. Follicles in different stages of development, from smallest to big. Total number of Graafian follicles in both fragments together seemingly no smaller than in a normal ovary. Follicles mostly in centre. Many traces of atretic follicles, but interstitial tissue mostly compact like in the control. Highly developed interstitial cells. No corpus luteum (?) as present in one of both controls.

Only a few young ova. Many big Graafian follicles and younger follicles. As much interstitial tissue as in a normal ovary. Well-developed interstitial cells, at many places highly developed like in adult animal. Tendency to cystic degeneration. No corpus luteum.

(Complete series of sections.) Number of young ova reduced. Number of big Graafian follicles about half of that in the ovary of the control, but great number of atretic follicles. Very few interstitial tissue outside follicles undergoing atresia and transforming into nests of epitheloid cells. Interstitial cells of type intermediate between infantile and adult. No corpus luteum; none in the control.

Fragment consisting mostly of a few cystically enlarged Graafian follicles. Almost no young ova to be found. Very small quantity of interstitial tissue, but well-developed interstitial cells, sometimes highly developed.

Very few young ova. Otherwise picture of a quite normal ovary. Interstitial cells mostly of the infantile type or of type intermediate between infantile and adult; places with well or highly developed interstitial cells also present.
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means like the uterus of a castrated animal. This statement
is of importance as by this it is shown that the ovarian
fragment was in a state of hormone activity. The number of
young ova was sometimes highly reduced (figs. 4, 9, and 10) and
a great many follicles in different stages of development were
present; in C iv. (fig. 9) the fragment consisted mostly of a
small number of cystically enlarged Graafian follicles. As to
the interstitial tissue it was present in all the three cases
though in a very small quantity in C iv. It is of great interest
to notice that in A iv. (fig. 17), the interstitial cells belonged to
the type intermediate between infantile and adult. It is easy
to show that in the normal rabbit's ovary the development of
the interstitial cell is concomitant with the development of
the uterus. By and by the interstitial cell enlarges to become
finally, in the adult ovary, the characteristic big epitheloid cell
in which a great clear spheric nucleus is surrounded by a wide
area of vacuolated protoplasm.* In C v. the interstitial cells
were also mostly not of the adult type, though good and even
highly developed interstitial cells were also present. The same
is true for C iv. There is no reason to assume that in these
cases the condition of the interstitial tissue is directly respon-
sible for the incomplete uterine development. One might be
rather inclined to explain the uterine underdevelopment, in
accordance with the point of view of Pézard,14 in the following
manner. In experiments with partial castration in young male
animals, it can be shown9 that the incomplete musculinisation,
as sometimes observed after removal of more than one
testicle, is nothing else than a retardation of development of
the sex characters as caused by a retardation of the develop-
ment of the testicular fragment. This latter retardation is
evidently caused by the operative interference with the young
testicle. The incomplete development of the uterus as present
in the last three mentioned experiments might also be explained
as caused by retardation; the uterus was in these cases rather
not yet fully developed than underdeveloped. Then we should
assume that there was a retardation in attaining full quantitative
hormonie standard in the ovarian fragment in these cases.
There was evidently a certain latent period as necessary for

* See fig. 99 A, B, and C in Lipschütz, The Internal Secretions of the Sex
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the formation of a certain number of endocrine interstitial cells by the means of follicular development, till, to speak with Pédard, the minimal quantity of endocrine cells and the threshold quantity of hormones was attained. There is indeed no full certainty that this explanation is really the right one.

It is of great interest to compare these results with those in experiments with experimental hermaphroditism. The period of latency, i.e. the time between ovarian implantation and the appearance of the hypertrophy of the teats was a very long one when only an extremely small ovarian fragment instead of one or two ovaries was engrafted. It seems very probable that in these experiments with hermaphroditism we have the same phenomenon as in the experiments related above. It takes a longer time till an ovarian fragment has produced as many endocrine cells as necessary for producing the threshold quantity of hormones.

Summary.

The number of young ova in hypertrophied or increased ovarian fragments is reduced, sometimes highly reduced. This phenomenon has been seen in five experiments on young rabbits.

It is not very likely that the diminution is an apparent one due to the increased volume of the ovarian fragment.

Ovarian hypertrophy is not due to new formation of young ova but to follicular development.

The diminution of the number of young ova is explained by the fact that in an ovarian fragment a relatively increased number of young ova are used for follicular development.

It is very probable that the increase of follicular development, as taking place in an ovarian fragment and causing hypertrophy of the latter, is due to some general factor possibly to some substance available in the body in a given amount.

The ovarian fragment which alone remains in the body, reveals a tendency to cystic degeneration; hypertrophy is in some cases nothing else than increase in volume by formation of big follicular cysts.

In five young rabbits fifteen ovaries from animals mostly of the same litters were subcutaneously engrafted. The grafts disappeared without any exception, in any case two months after the operation. In view of the great facility with which ovarian grafts generally take in homoiotransplantation, these
Dynamics of Ovarian Hypertrophy

_negative results though not proving make it probable that the taking of the ovarian graft is rendered difficult when the ovaries _in situ_ are present and use the substances as necessary for follicular development.

In three out of six cases of rabbits containing hypertrophied ovarian fragments the uterus was normal; the fact that the uterus was less developed in the remaining cases might be explained by the long latent period as necessary till the threshold quantity of hormones can be produced by the ovarian fragment.

I am much indebted to my former co-worker Dr Karl Wagner, now Professor of Histology at the University of Kowno, for the sections for figs. 1 to 10 and 13 to 17; to Dr H. E. V. Voss for the sections for fig. 11; and to my friend Sergej Vešnjakov for the photographs.

References.

1 Arai (1920), _Amer. Journ. of Anat._, 26, 59.
2 Carmichael and Marshall (1908), _Journ. of Physiol._, 36, 431.
10 Lipschütz et Voss (1924), _C.R. de la Soc. de Biol._, 90, 1710.
12 Péizard (1918) _Bull. biolog. de la France et de la Belgique._, 63, 1, 1923, _Journ. de Physiol. et de Path. Génér._, 90, 200; 1923, 495.
13 Sand (1922), _Journ. de Physiol. et de Path. Génér._, 90, 422.

Description of Plates.

All figures have been reduced to 3/5. The OO x indicates the augmentation at which the photos were made.

<table>
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<td>1</td>
<td>Section through ovary of A 1. (Prot No. 130). Normal control. 100 x. Helly, Heidenhain.</td>
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<tr>
<td>2</td>
<td>Section through hypertrophied ovarian fragment of A 11. (Prot No. 131). x. Flemming, Heidenhain. Place rich in young ova. Note that the number of young ova is reduced as compared with fig. 1.</td>
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FIG. 3.—Section through ovary of A III. (Prot. No. 136). 100 x. Helly, Häm.-Eos.

FIG. 4.—Section through hypertrophied ovarian fragment of A IV. (Prot. No. 134). 100 x. Helly, Häm.-Eos.—Place rich in young ova. Note that the number of young ova is markedly smaller than in a usual place of the normal ovary in fig. 3.

FIG. 5.—Section through highly hypertrophied ovarian fragment of B III. (Prot No. 52). 23 x. Helly, Häm.-Eos.—Almost complete absence of young ova, only a few being present. Follicles in different stages of development. An atretic follicle very similar to a degenerating corp. lut. is to be seen to the left from the centre (extravasation of blood in the middle of fibrous tissue and surrounded by epitheloid cells with a clear protoplasm); the same near the under limit. The greater part of the fragment is occupied by big epitheloid interstitial cells (see fig. 14). Note the thick capsule of connective tissue.

FIG. 6.—Section through ovary of B II. (Prot. No. 50). Normal control. 23 x. Helly, Häm.-Eos.—Note the great number of young ova (to be seen as white disks between the follicles).

FIG. 7.—Section through ovary of C I. (Prot. No. 217). Normal control. 23 x. Helly, Heidenhain.—Note the great number of young ova which are to be seen as white disks on the periphery between the follicles.

FIG. 8.—Section through hypertrophied ovarian fragment of C II. (Prot. No. 218). 23 x. Helly, Heidenhain.—Very few young ova present (to be compared with fig. 7). Tendency to cystic degeneration. Well-developed interstitial cells.

FIG. 9.—Section through increased ovarian fragment of C IV. (Prot. No. 222). 26 x. Helly, Heidenhain.—Almost no young ova found; cystic degeneration. Well-developed interstitial cells.

FIG. 10.—Section through hypertrophied ovarian fragment of C V. (Prot. No. 223). 22 x. The picture comprises about one half of the ovarian fragment, Helly, Heidenhain.—A few young ova and a great number of degenerated ova (the latter are to be seen as shrunken hyaline disks, surrounded by a white circle). Tendency to cystic degeneration. Well-developed interstitial cells.

FIG. 11.—Section through the upper pole of the ovary of a young rabbit of 500 grams (Prot. No. 223a). 100 x. Bouin. Häm.-Eos.—Great number of young ova.

FIG. 12.—Uteri of three animals of the same litter (Series B). Photographed from preparations preserved in formaline.—For particulars see table, Series B. The uterus is the biggest in B I. where there were several corpora lutea. The animal with an ovarian fragment had a uterus bigger than one of the normal controls which had no corpora lutea.

FIG. 13.—Section through the normal ovary of B I. (Prot. No. 48). 350 x. Helly, Häm.-Eos.—Big epitheloid cells surrounded by connective tissue cells or capillaries.

FIG. 14.—Section through ovarian fragment of B III. (Prot. No. 52). 350 x. Helly, Häm.-Eos.—Interstitial cells like in a normal animal. The connective tissue cells are well visible. Uterus normal.

FIG. 15.—Section of the second ovarian fragment of B III. (Prot. No. 52). 350 x. Helly, Häm.-Eos.—The capsule of this fragment was a thinner one and at one place it was absent, interstitial cells being directly in touch with fat.

FIG. 16.—Section through ovarian fragment of C II. (Prot. No. 218). 350 x. Helly, Heidenhain.—Big interstitial cells like in a normal ovary. Uterus normal.

FIG. 17.—Section through hypertrophied ovarian fragment of A IV. (Prot. No. 134) 350 x. Helly, Häm.-Eos.—Interstitial cells less developed.Threads of interstitial cells are separated by great quantity of fibrous connective tissue. Uterus less developed than in a normal animal of that age.
DYNAMICS OF OVARIAN HYPERTROPHY UNDER EXPERIMENTAL CONDITIONS.—ALEXANDER LIPSCHÜTZ.

PLATE II.