The Postnatal Growth and Development of the Reproductive Tract in the Female Albino Rat.

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Introduction.

This study aims to be a preliminary survey of the essential features of the postnatal growth and differentiation of the reproductive tract of the female albino rat, confined primarily to the period up to establishment of sexual maturity. The normal growth and variability of the body and of the various systems and organs in the albino rat have been carefully investigated by Donaldson ('06, '08, '09), by Jackson and Lowrey ('12), by Jackson ('13), and by Hatai ('13). In Jackson's and Hatai's work the ovary has been included, but as far as the writer is aware, no study of the growth of the tract as a whole, including the uterine tubes, uterus and vagina, has been made. Numerous researches deal with the reproductive organs of the rat in other ways. Among such are those of Coe ('08), Kirkham ('10), Kirkham and Burr ('13), Sobotta and Burckhard ('11) on the maturation, ovulation and fertilization of the ovum; Lane-Claypon ('07) on oögenesis and the interstitial cells; Belloy ('99) on the corpus luteum; Hatai ('13, '15) on results of gonadectomy; Frank ('11) and Corner and Warren ('17) on the corpora lutea and the formation of deciduomata; Arei ('20) on the number of ova; and the extensive series of studies by Long and Evans ('16-'21) on the oestrus cycle and allied problems.

It is hoped that such a preliminary survey of the growth and development of the entire tract will serve to give a sufficiently useful acquaintance with the general trend of postantal processes to permit a more intelligent formulation of investigations directed toward more specific ends. It was therefore considered desirable to combine a quantitative study of the weight changes in the various parts of the tract with a study of the general structural changes and to attempt to determine the correlations between these phenomena. The structural changes studied involve only the more general phases of histology. No special effort has been made to deal here with special cytologic questions, interesting though these may be. Such questions belong rather to the more specific and restricted problems growing out of this general survey. Furthermore, the complexity of the postpubertal period makes necessary the employment of different methods for the analysis of the later growth. This period is therefore dealt with only incidently in the present study.

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Material and Methods.

This study is based on a series of 150 female albino rats (Mus norvegicus albinus) supplied from the colony of the Department of Anatomy, University of Minnesota. In 125 of these, organ weights as well as body weights were available. These animals (Table 1) range from birth to approximately 300 days of age and from 2.7 grams to 294 grams in body weight. Thirty of these had given birth to one litter each and were sacrificed at different periods after parturition, varying from 12 hours to 3 months. The remaining 95 were all virgins which had been isolated during prepubertal life in separate cages away from males. The last two animals of the series (Nos. 124 and 125) were put back with males for several weeks before they were finally sacrificed, failing, however, to become pregnant. In nearly all cases the ages were known. Most of the animals were in healthy condition and well nourished. A few distinctly undernourished animals were taken in order to get some idea as to the effect of poor nutrition, but this phase will be made the subject of special study. The rats were fed

Graham bread and whole milk, corn and water being kept in the cages at all times. Green vegetables, usually cabbage, were also supplied occasionally.

The animals were sacrificed at random when they reached a body weight which fitted into the series without too much duplication. Such random selection, of course, makes for great variability, especially after the age of puberty, but since this variability was one of the features to be noted, it was considered desirable, and chance was relied upon to furnish examples of the various stages of the sexual cycle.

The rats were chosen with reference to their body weights for it was soon apparent that variation in the reproductive organs was even greater in animals of the same age than in animals of the same weight. Again, body weight has been chosen as base reference in preference to body length because the state of nutrition so profoundly affects the reproductive organs. Older animals, especially those under weight, may display very small reproductive organs in spite of their elongated bodies. However, in uniformly well nourished animals, especially prior to sexual maturity, body length may be even a better criterion of sexual development than is body weight. On the other hand, body weight is much the more accurately determined. The rats were not taken in the order given in Table 1. For the sake of convenience and ready reference they have been arranged in a series from the lightest to the heaviest. In the column of individual rat numbers, the letter indicates the series, the number preceding the decimal point designates the litter, and the number following is for the individual.

The animals were killed with ether or chloroform. As soon as dead they were weighed and measured for body (nose-anus) and tail length. The entire reproductive tract was then removed, note being made of the open or closed condition of the vagina (if the animals were approaching maturity) and of such features as congestion of the organs or distention of the uterus. The tubes and ovaries were isolated by severing the tube close to the tip of the uterine horn. They were then carefully dissected apart and (so far as possible) ~~of~~ the extraneous fat and connective tissue removed without injuring the organs desired. The uterus and vagina were then similarly isolated. While this was being done as much of the tract as possible was kept covered with masses of body fat in order to prevent drying. As quickly as they were isolated and cleaned the organs were placed in a small glass-stoppered moist chamber (weighing bottle). The uterus and vagina were separated by transection of the latter in a plane just missing the tip of the cervix uteri. Posteriorly the vagina was freed by similar transection immediately anterior to the vaginal orifice. In the cases of the smallest animals some of the dissection was necessary under the binocular microscope. The separate organs were then weighed to tenths of a milligram in the glass-stoppered moist chamber. Each set of organs in turn was removed from the weighing bottle and put immediately into the fixing solutions, the weight of the part being obtained by subtraction. A very slight error was unavoidably due to such slight evaporation of the moist chamber as occurred during the momentary lifting of the stopper for removal of the organs. Such error was, however, quite negligible when considered in comparison with the difficulties of uniform technique in dissection. In 50 animals the hypophysis, epiphysis, thyroid (and parathyroid), thymus, and suprarenals were also taken and similarly weighed and preserved. These organs are not considered in the present study.

The fixative~~s~~ most commonly employed was Zenker's fluid, although Flemming's and Bouin's fluids and formalin were also used. Embedding was uniformly in paraffin at 58°C and sections 5 to 7 micra thick were stained with haematoxylin and eosin or with iron-haematoxylin. The entire ovaries and tubes were sectioned serially. Of the uterine horns and vagina, only a hundred or more sections of a representative portion (about the middle) of each were made.

A volumetric study was also made of 25 selected ovaries using Jackson's paper method. This consisted of projecting with the aid of an Edinger projection apparatus every 5th, 8th, 10th or 12th section of the organ, as the case might require, upon a special paper of uniform weight, outlining the elements desired under uniform magnification, and then cutting out, segregating, and weighing the total amounts of paper representing each of the elements. Thus the percentage volumes of follicular tissue, liquor folliculi, interstitial tissue, corpora lutea, and ovarian stroma can be quite accurately determined.

The organs were all weighed to tenths of a milligram; the body weights of the smallest rats also to four decimal places, the largest rats, however, only to grams or halves of a gram. Calculations of percentage weights were made on basis of the numbers to the fourth decimal place, but in the table, these are expressed only to the third decimal place. From the field graph of each organ an approximate curve has been constructed through points corresponding to averages of the data conveniently grouped. Beyond 160 grams body weight the data are too heterogeneous to permit such treatment. With the number of cases available no pretense of accuracy can be made for these curves and mathematical formulas for them are hardly justified.

Using the curves of the absolute weights as a basis, the percentage curves of chart 5 have been constructed.

In the calculation of percentage weights, a Keuffel and Esser "Peerless" Rechenmachine was used. In Table 1 are arranged, in serial order according to the body weights of the rats, the absolute and percentage weights of the ovaries, uterine tubes, uterus and vagina.

In addition to these 125 cases of known weights there were also available for microscopic study the preparations of 25 other sets of organs from rats of known age, weight, etc., but in whom the organs were fixed for the most part in situ and in which therefore the weights of the organs were not determined.

1. Growth in Weight of the Ovaries.

The growth in weight of the ovaries in the albino rat throughout postnatal life has been previously described by Jackson ('13) and by Hatai ('13). These data are also compiled by Donaldson ('15). With their results the present study is in general agreement. It has been repeated chiefly for the sake of correlation with the growth of the other portions of the reproductive tract. Both ovaries are considered together, since the work of others has shown nothing of significance in the usually slight differences of the two. The ovaries of the newborn rat have been found to weigh from .0006 to .0009 of a gram. The higher figure is perhaps more nearly correct. During the manipulations of dissection and weighing some chance for evaporation must occur, and in such small masses of tissue this may result in errors disproportionately large. In the younger stages the variability due to technique may further augment such errors, due, for instance, to the variable amount of stroma retained at the hilus of the ovary.

Inspection of the field graph in Chart 1 reveals that there are three points in the life of the rat when the growth of the ovaries makes a decided change in rate. These occur at approximately 30 g., 60 g. and 120 g. body weight. The interval from birth to the 30 gram stage, which corresponds to a period of 25 to 30 days, may be designated as the first period or phase of ovarian growth. During this period there is (after a brief initial period of relative retardation) an increase in the weight of the ovaries at a rate greater than that of the general body growth. The field graph and the curve of relative (percentage) growth (Chart 5) would seem to indicate that the growth during this initial phase is slowest just after birth and increases in rate later in the period, slowing up again rather suddenly toward the end. The growth just after birth appears to be so much slower than that of the body that the percentage growth curve takes an actual dip during the first week. The growth curve of absolute weights, as well as that of percentage weights, therefore presents a convexity toward the abscissa.

Jackson's and Hatai's data show quite the reverse, indicating that growth is most rapid just after birth (as though it were directly continuous with a rapid growth process in the foetal ovaries), and that there is a gradual retardation toward the end of this initial period. In the present field graph, therefore, my early cases fall below Hatai's curve, but the later cases are considerably above his curve. Whatever may be the cause of this discrepancy, it can scarcely be ascribed to technique, for reference to Charts 2, 3 and 4 on the absolute weights of the tubes, uterus and vagina, reveals a consistent correspondence with this behavior of the ovary. The abruptness with which the growth rate of the ovary here appears to change is no doubt exaggerated and would perhaps be diminished in a larger series of cases.

At birth the percentage weights of the ovaries agrees well with Jackson's ('13) data and equals about .017 per cent of the body weight. Variability is great, however. In the succeeding three weeks the relative weight generally falls below that at birth, individual cases reaching a low level of .057 per cent of the body weight. During the fourth week the relative weight rises rapidly reaching the high point in rats weighing 28 to 30 grams and 25 to 30 days old. The average percentage weight for the group about 30 grams in body weight is about .037 per cent. The percentage weight curve (Chart 5) does not indicate so high a value. Even when grouped it is found that here and there the average weights will fall above or below the average curve. In order to fit the figures, a curve would have to be constructed displaying much more abrupt change than does that of Chart 1. Only a very large number of cases could furnish the proper evaluation of the true curve at this point.

Arai ('20) has recently shown that the greatest decrease in the number of ova in the rat's ovary occurs in the first 23 days of life, after which time the rate of decrease becomes markedly less. There is a correlation between this disappearance of ova and the growth of the ovary. This will be considered in connection with the structural changes occurring at this time. It may further be interesting to speculate whether the fair agreement in time between this early spurt of growth and the usual period of lactation is anything more than coincidence. Roughly speaking, by the end of this initial growth period the ovaries have grown relatively twice as much as the body.

Now follows a second period, from about 30 grams to 60 grams body weight during which the rate of growth is much diminished. Jackson described this actual decrease in relative weight of the ovaries, his data indicating a drop from .030 per cent to .015 per cent.

The slightly higher value (.017) from my data can probably be explained as due to chance variation in a small series of data. Because of this retardation, the body generally has outgrown the ovaries, which at 60 grams body weight are of a relative size about equal to that at birth. The values obtained for the absolute weights of the ovaries during this second period are somewhat higher than those of Jackson's records, consequently the cases distribute themselves generally above Hatai's curve (based upon these data), as shown in Chart 1.

When the animals reach a body weight of about 60 grams a third period sets in--a second period of acceleration--marking the prepubertal and pubertal growth and extending through the establishment of sexual maturity or until a body weight of 120 or 130 grams is attained. This also corresponds fairly well with Jackson's and Hatai's findings, although here also the values obtained average a little higher than theirs. Sexual maturity, as expressed by ovulation, appears to fall usually about the middle of this period, in rats of 90 to 100 grams in body weight. The variation in the ovarian weights now increases markedly so that the field graph (Chart 1) presents a conspicuous scatter. In the early part of the period the increase is slow, gathering impetus through the middle three-fifths of the period and decreasing again toward the end of the period. A curve to fit this graph must therefore be double; one of acceleration in the early part of the period and one of retardation in the latter part. At the end of the period the relative weight of the ovary has reached an approximate mean value of .035 per cent. Beyond this point of 120 grams body weight, the absolute weight of the ovaries continues to increase (variably) but reference to the relative weights (Chart 5) indicates that this fourth period is again one of retardation. The scatter in the field graph becomes still more marked, due, of course, to the great variability induced by the structural and functional changes of the ovaries during the oestrus cycles. A larger number of cases would be very desirable, especially additional cases at the end of the series. But even with the present limited data it is clear that the percentage weight is rapidly falling, reaching in the last animal of the series a value .0176 per cent.

2. Growth in Weight of the Uterine Tubes.

At birth the ovary is partially enclosed in a peritoneal fold, an extension of the mesovarium and mesosalpinx (Figs. 1, 2, 3). During further growth this fold still more completely covers the ovary until finally a thin peri-ovarian capsule is developed, isolating the ovary from the body cavity. It is in this capsular fold that the uterine tube develops. The complex coiled up form of the adult tube is not so apparent at birth, the tube presenting more the simple form of a letter C. The lower end of this tube joins the upper extremity of the uterine horn, the upper end of the tube opening within the capsule of the ovary close to the hilus. The early growth of the tube in length is very marked and out of proportion to the distance between its extremities. Consequently a greatly convoluted tube is eventually developed, reaching approximately its complete form in a week or ten days. By the time the animal reaches maturity the tube, instead of partially encircling the ovary, has become a compact, coiled mass, only a fraction of the size of the ovary, and lying at the side of the hilus. In the mouse Sobotta ('95) found that the periovarian capsule became distended with fluid during oestrus, an observation Evans and Long have verified on the rat. In the present series it seems to be demonstrable that the closure of the capsule may at least be considerably delayed and perhaps in some instances there may be some doubt as to an absolute closure.

Accurate weights of the tubes are difficult to obtain by direct means, especially in the early stages. The minute size, fragile structure and the relation to the capsule and mesentery make it extremely difficult to isolate the tubes satisfactorily. A large amount of the mesosalpinx is unavoidably included, making the weights actually too high and in the youngest stages disproportionately so. Nevertheless the graphs of the weights of the tubes (Chart 2) reveal a general correspondence with the type of growth observed in the ovary. The same four periods are readily distinguished and the 30 g., 60 g. and 120 g. points in the series correspond to points in its growth curve homologous with those of the ovary. Moreover, if one looks for correspondence in variability (especially in grouped cases) it is frequently seen that a decided rise or fall in the values for the tubes agrees with a similar rise or fall in the values for the ovaries. Exceptions, which occur, are probably due chiefly to technical error.

For the relative (percentage) growth of the tubes (Chart 5) the following values are obtained as averages of groups at or near the corresponding periods:

Percentage of body weight formed by the uterine tubes.

In the newborn,-	.0166 per cent
At body weight of 30 g.,-	.0152 " "
" " " " 60 g.,-	.0088 " "
" " " " 120 g.,-	.0139 " "
" " " " 280-294 g.,-	.0070 " "

The value for the newborn is certainly much (perhaps twice) too large; .0080 per cent is probably nearer the correct figure. If such a correction be admitted it is seen that the alternate periods of acceleration and retardation characterize the growth of the tubes quite as well as they do that of the ovary. Again making general comparison with the graphs for the ovaries it may be noted that the sag in the curve of absolute weights during the first period is also seen in the tubes, although less marked. The great increase in variability after puberty emphasizes the fluctuation of the weight of the tubes in the sexual (oestrus) cycle. The average figures for this period therefore have little significance.

3. Growth in Weight of the Uterus.

The uterus, being the largest of the divisions of the reproductive tract, can be most accurately dissected out and separated from its fat-laden mesometrium. The uniformly accurate severing of the tube from the extremity of the uterine horn is quite readily accomplished. The transection of the vagina at the tip of the cervix is doubtless subject to somewhat greater variation, but it would seem a variation far less serious than those encountered in the tubes and ovaries. The data from the primiparous rats Nos. 66, 80, 85, 87, 88, 96, 100, and 102 are excluded since the weights of these uteri indicate that the postpartum involution was not complete. When the percentage weights of the uteri of the primiparous rats are plotted a curve is obtained which indicates that about the seventh day after parturition the uterus has reached its lowest weight level. All cases under 7 days have therefore been eliminated.

A glance at the graphs of uterine growth (Chart 3) reveals a general form in the curve and distribution of cases similar to those of ovaries and tubes, with the same four phases. In one respect, however, there is a distinct divergence from the tubes and ovaries: the prepubertal increase in the weight of the uterus begins at about 50 grams body weight instead of at 60 grams. Why this should be the case is not clear and it may be due to accidental variations of no significance. The uterus must, of course, prepare by sufficient growth for its future function, but why the stimuli to this growth should act earlier upon the uterus than upon the closely related tubes, or upon the ovaries, is difficult to understand. As the data stand this point needs further investigation. Similarly the end of the first period appears to come somewhat earlier than in the tubes and ovaries (Chart 5). The percentage curve (Chart 5) indicates that the average values of the relative weight of the uterus (percentage of body weight) are:

In the newborn,-	.032 per cent
At the end of the 1st period,-	.072 " "
" " " " " 2nd "	.050 " "
" " " " " 3rd "	.182 " "
" " " " " 4th "	.075 " "

These values would indicate (by comparison) that the amount of retardation in the second period is less, but that growth during the third period is much greater than in the tubes or ovaries. Comparison of the percentage weight of the uterus at birth with that at the other points in the life cycle seem to indicate also that the uterus is relatively under-developed at birth as compared with the ovaries. Up to the end of the second period the variability has not been great. When the prepubertal growth sets in the variability increases rapidly becoming greater and greater during sexual life, due, of course, to the enormous fluctuations of the organ during the oestrous cycles. The present series would indicate that the greatest variability occurs in rats from 160 to 200 grams in body weight. It may be mentioned incidently that the lower extremes of uterine weight are found associated with extreme involution after parturition, or with distinct undernutrition, or both.

4. Growth in Weight of the Vagina.

In the isolation of the vagina, as previously mentioned, there is considerable difficulty in maintaining a technique sufficiently uniform to give satisfactory weight values. Thus individual cases frequently appear excessively high or low, as seen in Chart 4. In the case of rat No. 28, the weight of the vagina is undoubtedly a positive error. In spite of this defect in the data, a general correspondence in the growth of the vagina with that of the other female organs is obvious, the four phases of growth being quite as distinct.

The vagina likewise shows a correlation with the growth of the uterus, etc., in the depressed curve of the early growth. The first decline in the relative growth rate(Chart 5) occurs, as in the uterus, earlier than the 30 gram stage. The second period of rapid growth also appears somewhat precocious, as in the uterus, a distinct increase in the rate occurring in rats at about 50 grams body weight. Had the vagina shown a compensatory drop in the values at this point it might have been argued that technique was responsible for the unexpectedly high values obtained for the uterus. As the data stand the values for the vagina point to there being some factors other than technique responsible for this precocious beginning of the second acceleration period.

In the newborn rat there is no sign of an external vaginal orifice. In the present series, rat No. 49 (77 grams in body weight) was the smallest to display an open vagina, although in several larger rats the vagina was still closed. In all cases of closed vagina ovulation had not occurred, as shown by sections of the ovary.

In rat No. 50 (79 grams) the vagina was closed but the uterus was considerably congested and distended with fluid. The actual weight of the fluid in this case was not obtained, as it was desired to fix the uterus in the distended condition, but from measurements of relative areas of the human and uterine wall in section, it was calculated to equal approximately 25 per cent of the total weight of the organ. The presence of this fluid, which Long and Evans ('20) have noted as characteristic of the preoestrous and oestrous phases of the cycle, was encountered in 5 additional cases, but in maturer animals. It seems possible that this fluid may play a rôle in the opening of the vagina. Long and Evans ('20) pointed out that this opening of the vagina occurs at the time of the first ovulation and associated with a typical oestrus. Holdeman ('21) has carefully described the histologic processes involved in this opening, but does not mention the condition of uterine distention. Rat No. 50, however, was only 56 days old, which would seem unusually young for immanent sexual maturity. Arai ('20) noted 63 days as the age of his youngest rat at the first ovulation. Sixty-three days of age and a body weight of 85.9 grams are associated in the present series with the earliest ovulation appearing in sections of the ovaries.

5. Discussion.

As appears from the foregoing account, except for minor or doubtful differences, the various parts of the reproductive tract in the albino rat follow a similar type of postnatal growth. After a brief initial period of retardation, growth to the end of the fourth week is very rapid; from the fourth to the seventh week it is distinctly retarded; from the seventh to the eleventh or twelfth week again accelerated, with maturity or first ovulation occurring as early as the middle of this period; and finally, after the twelfth week there is a general retardation with individual secondary fluctuations depending chiefly upon the phase of the oestrus cycle.

If the average absolute weights be determined for the ovaries, tubes, uterus, and vagina in the following groups:

I	Rats Nos. 3, 4, 5, 6	(Newborn groups)
II	" " 23, 24, 25, 26	(30 gram group)
III	" " 35, 36, 37, 38	(60 " ")
IV	" " 68, 69, 70, 71	(120 " ")
V	" " 124, 125	(Terminal group)

the following values are obtained (taken from Table 1)

	Ovaries (grams)	Tubes (grams)	Uterus (grams)	Vagina (grams)
I	.0008	.0008	.0013	.0008 (too low)
II	.0072	.0046	.0198	.0181
III	.0122	.0056	.0376	.0253
IV	.0426	.0167	.2536	.1079
V	.0586	.0210	.2148	.1220

The percentage increase in growth (weight at the end as compared with that at the beginning of each period) then becomes as follows:

Approximate percentage increase in average weight of:

	Body	Ovaries	Tubes	Uterus	Vagina
II	577	828	545	1423	2259 (too high)
III	96	71	23	90	40
IV	100	247	197	573	325
V	130	37	25	-18	13

It is thus seen that during the first period the ovaries have grown (in average weight) at a rate roughly 1-1/2 times that of the body, the tubes at approximately the same rate, the uterus about 2-1/2 and the vagina nearly 4 times the body rate. This value for the vagina is certainly far too high due probably to inaccuracy in determining the weight of the vagina at birth. The vaginal rate of growth should probably be less than that of the uterus.

During the second period the ovaries appear to have grown at a rate only about 3/4 that of the body, the tubes at 1/3. The uterus has practically kept pace with the body (but only because the precocious prepubertal growth has allowed the uterus to make up some of the loss during retardation, as seen in Chart 5. The vagina in turn has grown at about half the body rate.

In the third period the ovaries increase at about 2-1/2 times, the tubes slightly less than twice, the uterus at nearly 6 times, the vagina at more than 3 times the body rate.

In the final period great retardation apparently takes place, but the data are hardly significant in view of the few terminal stages and the fluctuations in the oestrous cycle.

Thus it is seen that while the various parts of the tract grow in a similar manner, the growth is by no means proportionate in amount and perhaps not simultaneous in the various phases. It is therefore conceivable that factors, experimental or otherwise, capable of affecting the growth of the reproductive organs, might have different influence depending on the phase of growth of the organs, and that the organs might not be similarly or proportionately affected.

The present study, as far as the weight changes in the ovary are concerned, agrees in the main with the work of Jackson ('13) and of Hatai ('13). Hatai using the data from Jackson's observations on 136 rats included in the first period all the growth up to about 60 grams body weight. The curve which he plotted included therefore only three phases, the first and last of which he designated as logarithmic curves, the second as a parabolic curve. The principal difference in the present study is therefore that the first period of Hatai appears to have two phases. With this, Jackson's observations are in accord although he derived his curve of percentage growth weights from Hatai's formula. His percentage curve differs from that obtained in this present series chiefly in that the end of the first growth period seemed to come at about 15 grams of body weight, rather than at 30 grams.

In the postnatal growth of the human uterus there occurs a very marked involution during the first two years, an involution with which there appears to be nothing directly comparable in the rat. The relative loss in the weight of the uterus in the rat is not due to any absolute loss as in the human uterus, but only to the greater growth of the body, and the period of its duration is too short to offer satisfactory correspondence.

While much remains to be desired in the way of larger series of observations and more accurate quantitative determinations, these facts regarding the growth of the organs give a basis for consideration of structural changes, which basis otherwise might easily be overlooked.

MORPHOGENESIS OF THE OVARY.

In the consideration of the structural changes which occur in the postnatal ovary of the albino rat the plan will be followed to group these changes according to the periods corresponding with the gross weight changes previously described.

Ovarian changes in the first growth period.

The ovaries of the newborn rats show a rather uniformly characteristic structure in spite of much variation in size of the animal at birth. (Fig. 1) This seeming uniformity is perhaps due to a slowing down of the processes of differentiation during late foetal life, so that for a considerable period the structure of the ovary remains very much the same. There may be distinguished at this time: the germinal epithelium, a subgerminal zone, the tunica albuginea, a combined cortico-medullary region, and at the hilus a core of vascular connective tissue stroma.

The germinal epithelium is characteristically a single layer of cells, varying in shape from more or less flattened to distinctly columnar. Both nucleus and cytoplasm of these cells stain more darkly than do the cells of the subgerminal zone immediately beneath. The nucleus is large for the size of the cell, sometimes nearly spherical, often distinctly elongate, depending upon the degree of compression of the cell, with distinct chromatin masses of small size, packed at the periphery of the nucleus for the most part and connected with each other by fine strands of chromatin. A large nucleolus, sometimes two, is also characteristic. Just below the germinal epithelium one encounters a type of cell, which by comparison is easily recognized as the indifferent type. The cell body and nucleus of the indifferent cell may be slightly or considerably larger than those of the germinal epithelium, but they take the stain much less intensively. The nuclei of these indifferent cells are fairly granular but the granules are less clumped and fail to take the stain strongly. The nucleolus also appears faded. Between the cells of the germinal epithelium and these indifferent cells of the subgerminal zone one may recognize all gradations. One does, however, get the impression that the transformation of germinal epithelial cells into indifferent cells is not particularly active at this time. Here and there the germinal epithelium appears thicker and in such situations it is sometimes possible to make out a group of cells in process of differentiation, with one cell distinctly larger and centrally placed, the others forming a surrounding group. This would indicate that the germinal epithelium is still contributing both oocytes and follicle cells to the underlying region. Similar groups in which no central oocyte can be recognized, and therefore called indifferent cells, are common. This subgerminal zone consisting of indifferent cells and of oocytes just betraying their differentiation, is irregular in thickness, in some places only one cell thick, in others, where grouping occurs, even five or six cells thick.

The tunica albuginea is at this time a more or less complete layer of flattened or spindle-shaped cells distinctly smaller and staining more darkly than the indifferent cells. It consists in reality of the same stromal tissue as one sees penetrating the entire ovary from its hilus and radiating outward toward the periphery as the sheaths of the epithelial cords which make up the cortico-medullary portion of the organ. Here near the periphery this stromal tissue is growing irregularly tangential to the surface of the ovary and forming the tunica albuginea.

The large bulk of the ovary consists of irregular cords and masses of epithelial cells, more or less radially arranged and separated by thin layers of stromal cells which are continuous with the core of similar tissue penetrating the hilus from the mesovarium. One easily recognizes two main types of these epithelial cells: the primitive oocytes and the indifferent cells. The primitive oocytes are large cells, two or three times the diameter of those of the germinal epithelium, with large round nuclei. These nuclei stand out very prominently because of the nature and arrangement of their chromatin. Most of them may be classified as in the pachytene or diplotene stages of von Winiwarter and Sainmont ('08). Occasionally a cell will exhibit something comparable with the synezesis or contraction stage, but for the most part this phase is not very clearly brought out.

If one compares the cells of the peripheral intermediate, and inner regions of this cortico-medullary portion of the ovary, one may convince himself that at the periphery the oocytes are in the earlier (leptotene) stages of nuclear change and furthest in they exhibit the characters of the later (dictyate) stages. At the periphery one observes that the tunica albuginea tends to separate off groups of the oocytes and indifferent cells into "nests". A little further from the surface it appears that the proportion of oocytes is greater, which means either that indifferent cells are differentiating into primitive oocytes or that at the periphery a lower percentage of oocytes is being produced from the germinal epithelium. Perhaps both processes obtain. At any rate, it seems to the writer that one may still witness some production of oocytes at the periphery. This is more than likely the end of the foetal proliferation which is soon to cease and to be replaced by a postnatal proliferation, the oocytes of which, as will be seen, do not exhibit these nuclear changes. It seems likely also that these two proliferative periods are more or less continuous, for it is quite impossible to demonstrate an absolute gap between them.

At this time, then, one may see at the periphery more or less isolated primitive oocytes surrounded by indifferent cells, in the intermediate region a preponderance of oocytes, rather massed together, and in the innermost region oocytes distinctly surrounded by a single-layered follicle. No real division of the ovary into cortex and medulla is possible at this time. Whatever may be the meaning of these nuclear changes they are distinct enough, with exception of the synezisis and synapsis. As has been found in other forms, it is rather interesting that these complex nuclear changes should occur in oocytes that are destined to degenerate. Some of this degeneration is already under way. Especially in the inner regions of the cords various phases of pyknosis are encountered. It therefore appears that proliferation of the primitive oocytes has practically come to a standstill which may account in part for the apparently slow increase in weight of the ovary immediately after birth.

Mainly outside, but projecting into the hilus of the ovary from a cephalic direction, may be seen the tubular rete ovarii. The cuboidal or low columnar epithelium of these rete tubules is characteristic; about each tubule the stromal cells have become circularly arranged to form a sheath one or two cells thick.

During the two or three days following birth the ovary initiates certain definite changes. (Fig.2) The nuclei of the primitive oocytes lose the prominent chromatin character, the distinct chromatin threads which previously filled the nuclei now breaking down into the generally granular character of the 'dictyate' stage. This change proceeds from the deeper regions of the ovary to the periphery. At three days of age only a few of the most peripheral oocytes still show pachytene nuclei and these are the youngest of the primitive ova, the last to be differentiated from the germinal epithelium. It is also noticeable that the stromal tissue is beginning to break up the cortico-medullary cords into smaller groups and that especially in the inner regions of the ovary individual ova surrounded by groups of indifferent or follicle cells are more numerous. Furthermore, mitoses in the germinal epithelium, in the deeper lying follicle cells, and in the stromal cells indicate an increasing activity of growth.

This increased growth becomes still more marked during the latter part of the first week. The cell cords become entirely broken up and the individual primitive ova completely isolated, each with its own follicle. The ova just within the tunica albuginea are but slightly larger than a few days before; those deep within the ovary much larger, a few of them twice their former diameter and nearly one-third of the diameter of the mature ovum. Marked activity is noted in the follicle cells especially, but also in the germinal epithelium and stroma. Mitotic figures are numerous and some of the central follicles already exhibit two layers of cells. The ovarian stroma has plainly increased, forming now a meshwork of septa and trabeculae between the follicles, its previous radial arrangement having become quite obscured. Near the periphery it has contributed to the distinctly thicker tunica albuginea. About the larger follicles distinct thecae of stromal tissue are developing, although no inner or outer portions are yet to be distinguished.

As a whole, the ovary now presents three distinct zones. Outside the conspicuous tunica albuginea lie the germinal epithelium and a new subgerminal layer making up the outer zone. This new subgerminal layer is unequal in thickness but stains feebly as did the earlier primitive subgerminal layer. The major part of the ovary within the tunica albuginea, constituting a middle zone, presents a series of primitive ova and their follicles, the smaller ones peripherally, the others grading in size to the largest occupying the region near the vasculo-stromal zone of the hilus, which may be considered the inner zone. Growth in this zone is therefore centrifugal. The majority of the ova now accumulating in the new subgerminal layer can be distinguished from the primitive ova found about the time of birth and it is now apparent that the tunica albuginea at this time (about one week after birth, body weight of 10 grams) represents a fairly distinct boundary between the primitive ova, produced mainly by prenatal proliferation and now lying internal to the tunica, and the new or definitive ova now being actively produced by a postnatal proliferation, lying external to the tunica. However, an absolutely sharp line between primitive and definitive ova cannot be drawn. At no subsequent time, however, is the distinction any easier. It is, therefore, also apparent that the future growth of the ovary is to consist of a peripheral addition to the mass of primitive oocytes as well as of an expansion of the latter. Up to this point there has been some increase in size of the ovary, but as will presently be seen, subsequent growth far outstrips it. Some of the primitive ova show signs of degeneration by their shrinkage and in intensity of nuclear staining.

In animals 8 to 10 days of age and 12 to 14 grams in body weight one may note that the new subgerminal zone is no longer distinguishable as a lighter staining layer of new definitive ova and their follicle cells lying between the tunica albuginea and the germinal epithelium (Fig. 3). The tunica likewise no longer serves as a boundary between the older and newer generations of oocytes. It has been penetrated by the new definitive oocytes, or rather has extended itself outward peripheral to these, so that now an outer zone of definitive ova lies within the tunica, between it and the mass of primitive ova. The distinction between the new definitive ova which are yet of small size and the primitive ova of relatively large size is still quite readily made but about a particular ovum one may occasionally be in doubt. The germinal epithelium is seen to be very active and numerous groups of ova with the indifferent or follicle cells may be easily recognized. The expansion of the mass of primitive ova and their follicles is conspicuous.

The larger of primitive ova have themselves increased in size until they are nearly one-half the diameter of the mature ovum. Their follicles have grown until the largest are 4 to 5 cells thick, with definitely formed follicular cavities. In the formation of the antrum folliculi, however, the processes are considerably short of normal. The discus proligerous, which normally should enclose the ovum, here fails to do this. Many of the cells of the corona radiata appear to pull away from the ovum and leave fluid filled spaces between the other corona cells next to the ovum. In some cases the egg-cell almost floats free in an irregular space so formed though no typical antrum folliculi has been developed. Even when such an antrum is formed, the cells of the cumulus may slough away leaving the surface of the ovum exposed to the antrum. The normal condition of having the cells of the corona in contact with the surface of the ovum is thus largely destroyed, and this may to some extent be responsible for the degeneration of the larger ova which occurs.

The rapidity of the degeneration has recently been shown by Arai ('20) through careful counts of the number of ova at various ages. Except for the fact that the number of ova seen in a section dwindles so rapidly with advancing age in this early period, one gets little idea of the amount of degeneration that actually occurs. Arai, however, shows that the loss in the first 10 days is approximately 20,000 ova (from 35,000 to 15,000) or nearly two-thirds the total number. As this amounts to 2000 ova per day or 80 ova per hour, it is evident that these changes take place fairly rapidly, for the demonstration of even 80 positively degenerating ova in a single ovary in serial section is by no means an easy task. Not only in the primitive ova but also in the definitive ones can degeneration be shown. In spite of this new proliferation of definitive oocytes, the degeneration goes on at a rate so great as to produce a continued fall in the number of ova present.

In spite of the increase in the number of ova the ovary continues to grow in size and will soon do so at a rate considerably greater than that of the body as a whole. Furthermore, examination of a section of ovary of a 10 day rat reveals an abundance of mitotic figures amongst the follicle cells and stroma cells. It is to the proliferation of these elements that the growth in weight of the ovary must be due, for growth in size of the ova cannot compensate for the loss in their number. One needs but a glance at a section of ovary at this stage to note the large bulk of the organ occupied by the follicular tissue. In the thecae of the larger follicles the interstitial cells are already becoming easily recognizable. Since no special methods of technique have been employed to bring out the interstitial tissue the early cytologic differentiation of these cells has been missed but from this point in the development onward their recognition by ordinary histologic means becomes possible. It was not the purpose of this study to deal with the problem of the origin of these cells, but it may be stated that as far as present methods avail, the evidence here obtained would tend to support the view that at least those of later origin are of stromal or connective tissue ~~origin.~~ derivation.

It is also discernible at this point (10 day rat, 14.5 grams body weight), although it must have occurred earlier as well, that degeneration of ova produces also degeneration of the stratum granulosum of their follicles. The proliferation of the theca interna, producing a mass of interstitial tissue replacing such degenerating follicles and ova, is quite readily recognized a few days later. Recognition of this process in the earlier stages when it goes on on a much smaller scale is more difficult, although special methods would no doubt simplify matters.

If one examines sections of ovaries of rats 15 to 17 days old (body weight 16.9 to 19.5 grams) one finds some of the processes just described in full swing. The germinal epithelium has stretched out into a layer of flatter cells. Although numerous ova may still be found making their way through the tunica albuginea the proliferative activity of the germinal epithelium impresses one as generally somewhat reduced. The younger ova found at the periphery of the sections are scattered considerably farther apart. The cortical zone of definitive ova is consequently not so conspicuous especially since some of the earlier generations of these definitive ova have grown so considerably and have developed follicles so large as to make distinction between them and the more belated primitive ova and follicles quite impossible. Moreover, one is impressed with the larger number of follicles occurring in a particular section as compared with the earlier stages.

This can scarcely mean anything else than that the definitive follicles are now constituting a considerable part of the total follicular apparatus. In fact, the larger part of the primitive oocyte generation must already have undergone degeneration.

All stages of atresia folliculi may now be demonstrated. Practically every one of the larger follicles gives evidence of atresia. They are considerably larger than the follicles of the previous stage (about one-seventh the size of mature follicle) but they consist of fewer layers of granulosa cells; frequently only two layers of cells limit the antrum. These follicles have apparently enlarged chiefly by accumulation of liquor folliculi and distention of the follicle. The majority of the ova, now about six-tenths of the diameter of the mature ovum, lie free in the follicular cavity and exhibit prominent vacuolization of their cytoplasm as definite signs of degeneration. All stages of nuclear and cytoplasmic degeneration may be found and from some of the follicles the ovum has entirely disappeared, the granulosa has shrunken down about the remnant of follicular cavity and the hyperplasia of the theca interna is gradually replacing the follicle with the 'corpus luteum atreticum' of interstitial cells.

In the stromal interstices between the follicles masses of interstitial cells are becoming more and more prominent. The cell bodies of these cells have increased in size and the cytoplasm is distinctly granular, due no doubt to the secretory products of the cells. No special technique was however attempted relative to the secretory activity of the interstitial cells. At this stage, therefore, the ovary does not exhibit a single larger follicle which promises to reach maturity; on the contrary they all furnish positive signs of early dissolution.

In animals 17 to 18 days of age and 21 to 24 grams in body weight a period of reconstruction is seen within the ovary. (Fig. 4) Larger but thicker-walled follicles have made their appearance, follicles about one-sixth to one-fourth the diameter of a mature follicle, some of them 6 to 7 cells thick. Not all these exhibit the beginnings of follicular cavities. On the whole they appear much more robust than earlier follicles and the ova they contain bear a similar character. The follicles are not closely packed but rather widely scattered, though there may be 40 or more of nearly the same size in a single sagittal section of the ovary. Nearly every follicle is enclosed in a mass of interstitial tissue, so that the theca externa appears to lie between an inner and thinner layer and an outer and thicker layer of interstitial tissue. Trabeculae of stroma radiate from the hilus outward carrying blood-vessels. Definitive ova are still being produced from the germinal epithelium.

In rats 22 to 24 days old and 25 to 28 grams in body weight the ovaries have grown very markedly. The follicles have in some cases doubled their diameter so that they measure about half that of a mature follicle. The follicle wall is frequently 8 to 10 cells in thickness. Large follicular cavities have developed. The ova have reached three-fourths to seven-eighths the diameter of the ripe ovum. The variation in size of the follicles, however, is greater than was apparent in the stages just previous. Furthermore the number of follicles per mid-sagittal section is distinctly less. The rather normal appearance of the ova and follicles previously described, is in this 22 to 24 day group distinctly lost. Although the follicles are larger than ever before, almost invariably they exhibit some defect in structure which marks them as destined to degeneration. There is a certain looseness of structure which shades imperceptibly into the phases of distinct disintegration, and stands in decided contrast to the compactness characteristic (especially later) of the follicles capable of more extended growth. In some cases the ovum is shrunken, the nucleus disappeared or nearly so, the cell becoming gradually a homogeneous mass staining unusually pink with eosin. In other cases the cumulus is breaking down and the ovum being liberated into the follicular cavity. The numerous remains of a few granulosa cells surrounding a space, which may or may not still harbor the degenerating ovum, and around which we now see a large compact mass of interstitial tissue, give abundant testimony as to the reason for the apparent reduction in the number of follicles. The amount of interstitial tissue has evidently been considerably augmented, for the amount of ovarian stroma not occupied by compact masses of interstitial cells is relatively slight. Some of the degenerating ova undergo fragmentation, even with nuclear inclusions in the several fragments, which condition is similar to that described by Kingery ('14) in the mouse as the attempted but abnormal first maturation division.

The final chapter of this first conspicuous attempt on the part of the follicles to reach maturity may be seen in Rat No. 25 (30.7 grams in body weight). (Fig. 5) Here one seeks almost in vain for even smaller follicles that may show normal structure. The degeneration is most striking extending throughout the organ. However, at the periphery of the ovary one still sees ova and follicles penetrating the tunica albuginea from the germinal epithelium. One prominent feature of these later stages is that the larger follicles which have so far been produced have not been altogether confined to the cortical regions, but many have been located deeply below the surface of the ovary. It is at this juncture evidently that the first growth period passes over into the second and the ovary suffers a decided retardation in growth.

Ovarian changes in the second growth period.

It is now evident that during the first four weeks, while the first period of accelerated growth of the reproductive tract obtains, the amjor part of ovarian differentiation has been accomplished. All the prepubertal elements of the ovary have been established. Even in this young ovary the development of ova has come near enough to maturity to reveal abortive attempts at the first maturation division. It is further interesting that, while the ovary has been growing at a rate which it will never again duplicate, its all important elements, the ova, have been undergoing great, indeed, their greatest, reduction in number. The decided change in growth rate at the end of the first period Arai ('20) has shown to be associated also with an equally change in the rate of reduction of the ova. Arai's data indicate that during this second period the number of ova is reduced (to take his actual figures) from 10,746 to 10,185, a reduction which is practically insignificant. This must mean, of course, that the production of new oocytes practically keeps pace with the disappearance of older ones.

In the ovaries of rats beyond 30 grams in body weight (33.5, 37.8, 38.7 grams) one still finds numerous young oocytes in the tunica albuginea although the germinal epithelium has thinned out markedly and the changes incident to differentiation of new oocytes are much less evident. The ovaries now assume a more distinct differentiation into a cortical region, in which Graafian follicles are rapidly enlarging, and into a medullary region, characterized by presence of smaller follicles in all stages of atresia, of their associated interstitial tissue and of young normal follicles. The large Graafian follicles are distinctly larger than those previously met with, some of them of more than half the diameter of mature follicles. As they grow in size the follicular wall may thin down to 6 or 8 layers of cells while the younger stages may show walls nearly twice as thick. Their theca interna has become very conspicuous, as much as 6 to 8 cells thick. Some of these larger follicles appear perfectly normal, others show the beginnings of involution. This manifests itself early by the desquamation of the inner cells of the stratum granulosum so that they come to float free in the liquor folliculi along with remnants of chromatin from other degenerated follicle cells. In some cases the desquamation anticipates visible degenerative changes in the ovum; in other cases the egg-cell exhibits marked degeneration, frequently the conspicuous fragmentation previously described. As the animal grows, some of the ova and their follicles approach nearer and nearer the mature condition, but degeneration continues to be their terminal fate. Involution is seen as well in the smaller follicles, even in some of those not yet possessing a follicular antrum. This fills the medullary region of the ovary with round or oval masses of interstitial tissue. In the centers of such masses there are usually found cavities with the remains of the degenerated eggs or granulosa cells and leucocytes. When some of the largest follicles degenerate, a large fluid-filled space nearly the size of the original follicle may be left, the margin of which is bounded by the interstitial cell filled theca.

When the series of ovaries of this second growth period are compared, a general similarity is seen. (Fig. 6) The ovaries have grown markedly in absolute size if not in relative size by the end of the period, and this increase has been mainly in accumulation of interstitial tissue and stroma and in some enlargement of the follicles. The largest of these by the end of the period have attained a size nearly equal to that at maturity. Different ovaries exhibit differences in number and size of the conspicuous follicles and different degrees of intensity of atretic processes. It is quite evident that alternately processes of development and of degeneration hold forth, but the processes are complicated by such factors as inequality in size and age of the follicles, by their different positions in the ovary, and no doubt by extraneous influences such as the state of nutrition, activity of endocrine complex, etc. The interstitial tissue likewise exhibits both progressive and negressive changes, so that while the follicular granulosa is growing and later is degenerating its surrounding theca interna undergoes hyperplasia and hypertrophy; but when the degenerative processes have run their course, regressive changes in the interstitial tissue follow, with reversion of the interstitial cells into stroma cells. One thus observes a complex ~~xx~~ rhythm of morphologic changes in the ovary which on the one hand bring the ova and their follicles successively nearer maturity but still fall somewhat short of this goal, and on the other hand maintain a balance which, it would appear, is both internal, between the ovarian tissues themselves, and external, between the ovaries and the rest of the body. The frequency of this rhythm it would be interesting even to estimate, but for such a purpose the present data are wholly inadequate both in nature and quantity. With this rhythm of morphologic changes there are no doubt related weight changes, which are seen in such data as previously presented, forming variations above and below a certain mean. It is, therefore, not difficult to understand why this variability increases as growth proceeds. Barring individual variation, the upper and lower weight extremes should bear definite relations to the maximum and minimum phases of structural differentiation.

in spite of their large number of follicles, suggest strongly that great reduction in the follicular apparatus is under way. Search for a third proliferation of new oocytes from the germinal epithelium just before maturity, such as described by von Winiwarter and Sainmont in the cat, has failed to reveal even a suggestion of such a process. On the contrary, it is difficult in the present material--though it be confessedly not prepared with a view to the study of finer cytologic questions--to convince oneself that the capacity of the germinal epithelium for the production of new oocytes is not about at an end. Young ova in their primary follicles are, however, demonstrable in the tunica albuginea especially about the margin of the ovarian stalk.

Rat No. 50 (56 days of age, body weight 79 grams) is the first of the series to exhibit the process of maturation. (Fig. 7) In some of the largest follicles the ovum displays the mitotic figure of the first maturation division. Other follicles of about the same size, on the other hand, show degeneration processes under way. This is the rat in which the uterus was distended with fluid while the vagina was still closed.

After ovulation occurs, the size of the ovary is augmented by the development of the corpora lutea. (Fig. 8) It seems clear enough, within the limits of the methods here employed, that the development of the corpus luteum is at least mainly from the stratum granulosum as far as the lutein cells are concerned. The vascularization of the corpus luteum occurs no doubt with the participation of the theca cells which must migrate inward to form the trabecular framework of the organ. As to the possible participation of some of the theca interna cells in the development of the luteal cells, no attempt can here be made to differentiate.

By the end of this third period ovulation may in some cases have occurred a second time, in which case distinction may be possible between the persistent older corpora lutea and the younger ones. In the present series, this must be done on the basis of vascularization and the amount of retrogression which the gland exhibits, but Long and Evans ('20) have reported the use of vital dyes in the more certain establishment of different generations of corpora lutea. It is not possible to state here how many generations of corpora lutea may be found in an ovary at the same time, certainly several may be coincident. As Sobotta ('95) has reported in the mouse and rabbit and van der Stricht in the bat (Marshall, 1910), the ovum may not escape from the follicle during ovulation and has therefore been found (in degenerating condition) within the cavity of the developing corpus luteum.

The advent of the oestrous cycle introduces into the structure of the ovary complexities which furnish ample evidence as to the cause of the great variability in weight of the organ. Atresia continues both in larger and smaller follicles in characteristic fashion. Indications that mechanical pressure becomes a more prominent factor are seen in the not infrequent folded condition of large maturing follicles. Some of these show definite signs of degeneration--whether due to the pressure or not being questionable--others appearing quite normal. The retardation in growth rate of the ovary, at 120 to 130 grams of body weight, is evidently due to its reaching the limit in the number of corpora lutea and follicles which the organ can maintain in proper balance. The interaction of the progressive and regressive changes which take place is too complex for such general methods as here employed to offer any adequate analysis.

Ovarian changes in the fourth growth period.

So far as the present data show, the ovaries continue to grow although on the whole at a constantly decreasing rate. The largest ovaries found occur in a rat of 193 grams. The organs vary in the proportions of their constituent elements according to the phase of the oestrous cycle. In general it may be said that there is a progressive reduction in the relative amount of interstitial tissue, in contrast with the prepubertal periods, where there is a progressive production of this tissue. The amount of follicular degeneration met with in the rat's ovary is rather surprising, and not least so during this fourth period. Occasional animals exhibit ovaries with abnormally large degenerating (cystic ?) follicles. Rat No. 94 showed this condition to an extreme degree, although others approach it. It is at least interesting to speculate whether this condition points to something abnormal in the animal's environment. A further interesting feature of this condition is its occurrence in virgin females and apparently associated with very large uteri. Heape ('05) in his work on the rabbit thought that increased atresia, which might apparently lead to sterility, was noticeable in the does which were kept isolated from the males over several oestrous cycles. In fact the ovaries of such females as Rat No. 94 do appear unduly crowded with both corpora lutea and large follicles as compared with those of the primiparous rats. However, even the latter seem to approach this condition if kept from the males for some months. A quantitative analysis of this condition should be possible although the present data are insufficient to warrant any definite conclusions. The complexity and variability in size and structure of the ovary point to an intricate interplay of the factors involved, but bear witness also to the decidedly effective response by the organ to these factors.

Morphogenesis of the Uterine Tubes.

While the ovary is an organ of great structural differentiation showing a considerably different morphology at the different growth periods, the same cannot be said for the other parts of the reproductive tract. Except for such changes as occur relative to the oestrous cycle, the growth of the tubes, uterus, and vagina are more characteristically quantitative than qualitative.

At birth, as previously mentioned, the uterine tube lies rather simply coiled for the greater part, in the periovarian capsule, no thicker than the tissues of the latter, so consequently quite inconspicuous. Its structure is practically uniform throughout its length. A simple columnar epithelium forms the lining of its lumen, which scarcely exceeds in diameter the height of the epithelium. The oval nuclei of the cells accommodate themselves to different levels, appearing closely crowded, but an inner zone of cytoplasm is distinctly evident. No cilia can be made out. This epithelial lining extends to the upper end of the tube, which opens upon a papilla like extension within the ovarian capsule, and is here reflected back over the entire outside of this papilla. The papilla, lying near the lower end of the intra-capsular space at the side of the mesovarium, is in close proximity to the ovary, and this reflected epithelial covering is seen to become continuous with the germinal epithelium on one side and with the flattened peritoneal lining of the capsule on the other. The height of the epithelium is about the same as in the adult.

Around this epithelial tube, a thick layer (about equal to the outside diameter of the lining) of circularly disposed cells is seen. A very slight differentiation may be noticed into submucosal and muscular elements, the latter cells being arranged in a circular direction. As growth proceeds, the tubes elongate markedly and become more and more convoluted. The differentiation into submucosa and muscular wall becomes more distinct and in two respects the tubes become differentiated into approximately upper and lower halves. The epithelial lining grows into longitudinal folds that become much more prominent in the upper ('ampullary') half of the tube. In the lower half the muscular wall thickens markedly. These distinctions as well as the complex coiling of the tube are very evident in rats 10 days of age. (Fig. 3) The papillary upper end of the tube within the periovarian capsule becomes similarly fluted, not only inside but also on the outside. While this open end of the tube in preserved specimens appears papillary in form, it seems quite likely that, especially in the living adult, it may assume the character of a funnel. The longitudinal folds mentioned become relatively taller and thinner as the tubes enlarge in diameter, finally in transverse section assuming villus-like appearances. They become more numerous in the upper ('ampullary') part of the tube, so that a dozen or more are seen in a cross section. In the lower end of the tube, which grows much less in diameter, they remain lower and usually only about half a dozen in number are seen in cross section. The folds also come to have a spiral rather than a longitudinal direction. (Figs. 10, 11, 12).

While the growth in length has been very considerable, growth in diameter from birth to adult is only about 4 to 5 times in the upper half and 2 to 3 times in the lower half of the tube. The papillary upper end may become quite the largest part of the tube, with the most numerous foldings of the epithelium. The more projecting convolutions come to have only a thin connective tissue externa with its superimposed peritoneum, but the coils deep in the mesosalpinx get a very thick externa. The muscular coat, relatively thin walled in the upper part and thick walled in the lower part of the tube, gradually differentiates into an inner more or less longitudinal and an outer more or less circular layer. Except when oestrous congestion appears, the submucous layer is rather thin and holds the epithelium rather tightly to the muscular wall. The epithelial lining of the tubes in the resting condition may be no taller than that of a newborn, but after maturity the mucosa of the tube apparently responds with that of the uterus to oestrous phases and a prominent preoestrous secretory condition with hypertrophy of the epithelium will be noted. Under these conditions the lining cells may be twice their former size.

Since the differentiation of the tubes is a gradual process, it is not possible to differentiate the growth into structural phases as well defined as in the ovary. It is therefore possible, as much experimental work seems to bear witness, that the ovary is responsible for the quantitative character of the growth of the tube and likewise of uterus and vagina.

Morphogenesis of the Uterus.

In the newborn albino rat the uterus is very small and comparatively undifferentiated. (Fig. 13) The endometrial epithelium is similar to that of the uterine tubes, forming a simple columnar layer with round to oval nuclei less closely packed than in the tubes, and in height quite equal to that of the adult epithelium in the resting condition. The lumen is relatively large. The epithelium is surrounded by a rather thick wall of mesenchymal tissue, limited externally by a characteristically flattened peritoneal mesothelium. The mesenchymal tissue is most cellular in the inner half or two-thirds of the wall. It is just possible at this time to perceive that this inner, more cellular portion is the precursor of the stromal elements of the endometrium, external to which the differentiation has proceeded just far enough to disclose a few young muscle cells circularly arranged.

As differentiation proceeds, accompanied in all the tissues by very active mitosis, the lining epithelium later doubles in thickness, the cells becoming tall and slender with more elongated and closely crowded nuclei. The growth of the wall is such as to flatten the lumen from side to side and give it a more elongated form in transverse section. In a week's time the main layers of the uterine wall have been definitely established. Of these the endometrium remains relatively very thick, and its subepithelial stroma markedly cellular. The endometrial epithelium soon outgrows the other elements so as to form relatively large diverticula projecting outward into the surrounding cellular stroma. These appear in rats about ten days old and represent the first fundaments of the glands. The muscular layers occupy approximately the outer half of the wall. The inner circularly disposed muscle layer is eight to ten cells in thickness, the outer longitudinal layer only about two cells thick. Before the animals are two weeks old the more slender simple tubular glands have developed as extensions of the parent diverticula. These glands soon become coiled enough to give transverse sections of their outer portions in sections across the uterine horns, and they extend out nearly to the muscularis. More prominent intermuscular blood-vessels also appear.

By the 18th day (24.8 grams in body weight) the uterine horn possesses a wall in thickness slightly exceeding that of the entire organ at birth. As many as 6 or 8 glands appear in a section, where at 14 days only about half that number is usually displayed. By the end of the first growth period (four weeks; body weight 30 grams) the structure of the uterus is well established. (Fig. 14) The muscularis has perhaps reached its greatest relative development, although the difference is not great.

<u>During the second growth period</u> (up to body weight of about 60 grams at 7 weeks) the changes are not very marked. Longitudinal sections of the uterine cornua would indicate a slight increase in the number of glands, but these are still simple. The mucosa perhaps is relatively a little greater, the muscularis a little smaller than at the beginning of the period. (Fig. 15)

<u>In the third period</u> (up to body weight of about 120 grams at about 11 weeks) the marked increase in size of the uterus is very noticeable, but during the early part of the period this consists of general growth. (Fig. 16) As the first oestrus is approached, the mucosa as a whole undergoes a decided thickening. This is at first a distinct hyperplasia with some hypertrophy, but later augmented by congestion. The epithelium of the mucosa and (to a lesser degree) of the glands increases markedly in thickness, the cells changing in their staining reaction and revealing the approach of great secretory activity. Finally (as in Rat No. 50) the cells become enlarged to twice their former height or even more, the nuclei become more vesicular and more

oval and the cytoplasm stains characteristically blue (with hematoxylin) as in mucous secretion. As secretion progresses, the uterus distends with the fluid, the epithelial cells increasing in width with the stretching of the lining, the stromal portion of the mucosa and the muscularis being reduced in thickness.

With cessation of the secretion and evacuation of the fluid from the uterus, degenerative changes appear in the epithelial cells, accompanied by immigration of leucocytes. Cytoplasmic and nuclear disintegration with liberation of fragments of chromatin and general desquamation finally take place, the lumen of the organ becoming filled with débris from the epithelial cells and leucocytes. Along with these processes there is no hemorrhage such as occurs in man and in some other mammals. The regeneration of the lost epithelium proceeds from the epithelium of the remaining glands. During these processes, the hyperplasia is especially marked in the mucosa. The hypertrophy of the muscular layers and the general congestion also contribute in causing the greatly increased weights of the uteri during the latter part of this period. The graphs of these weight differences are more impressive than are the microscopic pictures and show more clearly and accurately the quantitative relations involved. These changes taking place during the oestrous cycle of the rat have been reported briefly by Long and Evans ('20). Stockard and Papanicolaou ('17) described the oestrous changes in the ovary, uterus and vagina in the guinea pig. According to Allen ('21), similar changes occur in the mouse.

<u>During the fourth period</u> of growth (up to adult) cycles of the changes above mentioned recur in succession. As a result, the general growth of the uteri is so complicated that it is scarcely advisable to venture an estimate as to what ought to be considered

the normal structure even of the resting uterus. One fact stands out clearly, however: after any oestrous cycle the uteri of the virgin females do not appear to return to a size or structure wholly comparable with that before the oestrus. At least for the earlier part of this period there seems to be a characteristic summation in weight and structure of the uterus. The uterine changes appear to have reached a climax in Rat No. 94 (160 grams in body weight) of the present series. This animal had a uterus of relatively immense size (possibly abnormal?). The mucosa exhibited the desquamatory stage with congestion, leucocytosis, etc. Compared with the uteri of younger animals or with post partum uteri after involution of animals of about the same age, there seem to be several striking differences. First the mucosa is unusually thick--at least four times that of the muscularis--being greatly hyperplastic. The number of glands is markedly increased. The muscularis is reduced at least to half its normal thickness. When the ovaries are consulted one discovers that they are filled with old, small, involuting corpora lutea and huge degenerating follicles. Not one follicle is to be found to suggest possibility of recent or immanent ovulation. Rat No. 94 is not the only case of uterine hypertrophy associated with ovarian follicular degeneration, though it is the extreme one. Others exhibit intermediate conditions. The question arises, are these phenomena common to all female rats during their sexual life or are they expressions of a response to something abnormal in the life of the animal? Is it possible that a succession of active oestrous cycles induces in the organs of these virgin animals a structural condition inconsistent with proper reproductive function? In this connection, one may recall Heape's ('05) suggestion that withholding the male (rabbit) from the female during several successive heat periods induces degeneration of the follicular apparatus, making the female liable to sterility.

Without going into detail it may be stated that there is much in the structure of both ovaries and uterus in the postpartum females to suggest that pregnancy with its subsequent involution restores these organs to a certain balance in structure more like that of younger animals. There is, however, a similar uterine overgrowth in those postpartum animals kept isolated for a longer time from the males.

Morphogenesis of the Vagina.

In the newborn, the epithelium of the vaginal mucosa consists of two layers of cuboidal or low columnar cells, the superficial cells containing large clear vacuoles, resembling those of unruptured goblet cells. (Fig. 47) The highly cellular tissue surrounding may be differentiated into a thicker inner zone, the submucous layer, and a thin outer layer of poorly differentiated muscle cells. In about 10 days the lining epithelium has become three or four layered, the basal layer columnar the surface layer still cuboidal. The epithelium has also been thrown up into longitudinal folds, but, since these are least pronounced in the vaginae fixed in situ, are probably due in part to contraction of circular muscle fibers. At this time there is a fairly distinct demarcation between the very cellular stroma of the mucosa and the more sparsely cellular and more fibrous submucosa. This distinction is shortly obliterated, to reappear later when a zone of looser vascular tissue develops between the two layers. The stroma of the vagina rather early becomes markedly fibrillar and rather sparse in cells. The epithelium remains throughout the first growth period in the three-layered condition. The muscularis also remains thin, consisting of only a few layers of cells. (Fig. 18)

By the end of the second period, the epithelium possesses four or five layers, (Fig. 19) but as the third period of rapid growth sets in and the opening of the vagina approaches, the epithelium thickens rapidly to seven or eight layers of cells, assuming a stratified squamous structure. (Fig. 20) With the advent of oestrus, the surface layer becomes tall columnar, decidedly different in staining reaction from the other cells, taking on the light blue tint of mucous secreting cells. Leucocytes accumulate in the stroma and commence migrating through the epithelium. The tall superficial columnar cells finally begin to degenerate and a general desquamation takes place which with the the leucocytic emigration give rise to the cellular elements of the vaginal smears. Along with the columnar cells, some of the flat, more cornified cells of the underlying epithelium also slough away, leaving a typical stratified squamous epithelium. The process of desquamation in the vagina seems to be completed a little earlier than that in the uterus, although the two processes evidently overlap. The vagina thus undergoes cyclic changes as well as the uterus. In fact the leucocytosis in the vagina appears much the more severe, begins earlier and lasts longer. It is therefore clear why the fluctuations of the weights of the vagina follow those of the uterus. It is also clear thy they are not of equal intensity, the hyperplasia seen in the uterus being so much more extensive. When the sections of vagina are examined it is observed that the thin muscularis has not been uniformly retained, being so scattered as to be seen only with difficulty during dissection. In the oldest rats marked fibrosis of the vaginal stroma takes place.

The cyclic changes during oestrus in the vagina of the rat are thus very similar to those first described by Stockard and Papanicolaou ('17) in the guinea pig, and described briefly by Long and Evans ('20) in the rat.

5. Discussion.

From the foregoing account of the grosser histologic changes of the reproductive tract of the rat during the four growth periods, it is apparent that it is the ovary which exhibits the more specific and intrinsic structural changes. It differs from the other organs in no small degree in this respect. While the growth of the tubes, the uterus, and the vagina is not merely an increase in mass but must to some degree be a matter of self differentiation, yet one cannot in these organs, as in the ovary, point to intrinsic processes of differentiation which exert a comparable influence over their own growth or that of other organs. As has been seen, the differentiation of the uterus, tubes, and vagina is more general. The weights reveal periodic changes in the rate of growth of these organs but there is little in the organs themselves to which one might ascribe the change. They follow the type of growth of the ovary, but without the ovary (as numerous extirpation experiments have shown) they would no doubt grow very differently. That they so follow the growth plan of the ovary is perhaps but the morphologic expression of the dominance of the ovary. It is true that the data seem to show certain differences in time relations in the various growth periods, which might argue against the ovary's having a dominating influence over the other reproductive organs. It is probable, however, that in spite of such discrepancies, which may be in part due to accidental variations, that the correlation between the organs is actually closer than the data indicate.

The oogenesis in the albino rat appears to be very similar, as might be expected, to that of the mouse, described by Kingery ('17). Arai ('20) verified Kingery's observations and similarly came to the conclusion that the postnatal proliferation in the rat furnishes the definitive ova and that the oocytes of the prenatal proliferation undergo complete degeneration. No third or prepubertal proliferation such as described by von Winiwarter and Sainmont ('07) in the cat has been found. The present study confirms Arai's observations on these points. The sharp demarcation between the primitive and definitive proliferation series the writer has been unable to demonstrate. Allen ('21) has observed in the mouse that the production of definitive oocytes may extend into sexual maturity where their proliferation is noted especially during the preoestrous phases of the sexual cycle. The present material indicates that the definitive oocytes continue to be found up till puberty at least; beyond this point, the evidence available is not so convincing.

Of special interest is the great amount of follicular atresia at various ages, with the parallel production of the interstitial tissue. Whatever functions may be ascribed to these interstitial cells, the relationship that exists between the degeneration of the ova and their follicles and this reaction of the surrounding interstitial tissue must be of fundamental significance. It must represent some form of reaction between the two elements and Kingsbury ('14) suggested that it is 'an expression of an altered metabolism'. Evans ('16) has also shown that acid azo dyes are selectively taken up in the living cells of the granulosa destined to undergo atresia, and changes are thus revealed in these granulosa cells before they give any other signs of degeneration. It seems perfectly evident that the interstitial cells are only temporary structures. They are constantly being differentiated and dedifferentiated. They come and go as necessity demands, and it would seem that one of their functions may be the maintenance of a balance of some sort within the ovary itself.

The relation of the interstitial tissue to the blood-vessels is not such in the rat as to suggest in any comparable manner that it constitutes an endocrine gland. The fact that such animals as the rat contain such large amounts of interstitial tissue, while others have so little or none, as has been shown exhaustively by Fraenkel ('05) and Schaeffer ('11), would seem to argue against a universal function of the tissue and to point rather to its specific necessity in the particular species where it occurs. After very careful consideration of the subject, Kingsbury considers that the evidence for the theory of its endocrine nature is too indirect and inconclusive, but the question is still unsettled.

The great amount of degeneration exhibited in the rat's ovary is very striking, sometimes becoming astonishingly extensive. The significance of all these retrogressive processes and their relation to the progressive processes is still one of the large fundamental problems concerning the ovary. That these processes seem to bear fairly definite relationships to the life cycle, that at times they are increasing at other decreasing should offer some encouragement to the view that their rôle may be subjected to analysis. If they are concerned with maintaining some form of balance in the ovary, quantitative methods may yield further evidence upon the question.

In general, for instance, we can state that it is probably to the degeneration of ova and the concomitant great increase of interstitial tissue that the accelerated growth of the first period is mainly due. These processes are then apparently held in check for a period—how or why is still uncertain. What releases this check or prompts the return in the third period it would likewise be interesting to know. That one should consider these processes apart from the body as a whole or apart from the organs which we know to exert positive influence on the reproductive tract, would, therefore, appear irrational.

Valberg ('15) in a volumetric study of the rabbit's ovary, including counts of follicles, observed that the interstitial tissue reaches its relative maximum growth at sexual maturity.

One of the striking phenomena in the rat's ovary is the apparent attempt--if it may be so put--of so many ova and follicles to reach maturity and their failure to do so. The fact that succeeding generations of ova come nearer and nearer attaining the goal would indicate either that the repressive factors are constantly lessening or that the ova themselves are gaining in influence. Robinson ('18), from his study of the development of the follicles in the ferret, suggests that the follicles themselves form a secretion which is responsible for the phenomena of the procestrum and oestrus, and which in the earlier stages facilitates growth of the follicles themselves by cumulative effect of the secretion, carrying successive generations of follicles nearer and nearer maturity until finally some follicles do not degenerate but mature. Exhaustion of this secretion by maturation of one set of follicles produces, he suggests, the anoestrous period with its recurrence of degeneration. There is much in the behavior of the rat's ovary to fit this conception. Accurate quantitative estimation by volumetric methods, cell counts, etc., might afford further evidence on this point. Valberg ('15) in the enumeration and classification of follicles in the rabbit's ovary drew the conclusion that accelerated growth of the follicles occupies a short early prepubertal period and a long postpubertal period which between these two comes a second or retardation period during which the follicles produced in the early period are greatly reduced in number through atresia.

With the intricate relationships of the reproductive organs during postpubertal sexual life, this study obviously cannot deal except in a very general way. Stockard and Papanicolaou ('17) paved the way for more accurate study of reproductive phenomena in their elucidation of the oestrous cycle in the guinea pig. More recently Long and Evans ('20) and Allen ('21) have worked out details in the rat and mouse, which are similar in general principles to the findings of Stockard and Papanicolaou. In the rat therefore there are definite cyclic changes in the uterus with processes analogous to those in the human cycle except for the hemorrhage. Very interesting and significant are, however, the cyclic changes in the vagina, which afford means of identification of stages of the oestrous cycle, reveal the reaction of the vagina to the condition of the ovary and furnish an index as to the latter. Of special interest is the report by Long and Evans ('21) of the rapid maturation of the youthful ovary when transplanted to the body of the adult, indicating the reaction of the ovary to external conditions.

In the growth of the tract before and after puberty there is much to suggest that the changes in size and structure of the uterus and vagina are associated in different manner on the one hand with follicular development or degeneration and on the other hand with that of the corpus luteum. The comparison and evalution of these factors, however, are beyond the scope of the present paper.

Summary.

The results of this study may be summarized briefly as follows:

1. In the postnatal growth of weight in the ovary, uterine tubes, uterus and vagina, four phases in general may be recognized: the first in animals from birth to approximately four weeks of age and thirty grams in body weight; the second to seven weeks of age and sixty grams in body weight; the third, to eleven or twelve weeks of age and one hundred twenty to one hundred thirty grams in body weight; and the fourth, to the adult condition.

2. The first and third are period of accelerated growth, the second and last are periods of retarded growth.

3. These growth phases are approximately correlated in time in the various reproductive organs, the growth of the ovary probably determining the nature of growth in the other organs.

4. Relatively the uterus exhibits the most intensive growth in weight, the vagina the next greatest, the ovary next and the tubes the least.

5. The ovary exhibits fairly definite structural changes characteristic of each period. In the other organs the structural changes, during the second period especially, are less striking and more general in character. Histologic differentiation and size, however, distinguish the first and last periods more definitely.

6. Correlated with the weight changes of the ovary before maturity are the growth of the follicles, their degeneration, and the development of the interstitial tissue. After maturity the ripening or degeneration of follicles and the development and regression of corpora lutea apparently interact.

7. To these various factors thw uterus, tubes, and vagina probably respond in definite manner and to a definite degree.

8. Virginity and parity also probably exert specific effect on both size and structure of the reproductive tract. Environmental factors, such as nutrition, likewise markedly affect the development of the reproductive organs.

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Explanation of Figures.

Fig. 1. Ovary, tube, and periovarian capsule. Rat No. _____ (Not in series of Table I.) Age: Newborn. Body weight 3.6 grams. Bouin, Iron Haematoxylin. X 44.

Ovary shown longitudinally sectioned; uterine tube in periovarian capsule, which is open.

Fig. 2. Ovary, tube, and periovarian capsule. Rat No. _____ (Not in series of Table I.) Age: 3 days. Body weight 5.6 grams. Bouin, Iron Haematoxylin. X 44.

Cortico-medullary cords shown breaking up into smaller groups. Mouth of tube opens inside periovarian capsule at the right of the mesovarium.

Fig. 3. Ovary, tube and capsule. Rat No.____ (Not in series of Table I.) Age: 10 days. Body weight 13.7 grams. Bouin, Haematoxylin-eosin. X 44.

Transverse section of ovary. Shows the great growth of the tube upper ('ampullar') end to the right, lower end above and to the left. Terminal papillary portion shown within capsule.

Fig. 4. Ovary, longitudinal section. Rat No. 38 (020.1) Age: 17 days. Body weight 21.2 grams. Zenker, Haematoxylin-eosin. X 44.

Shows large number of primitive follicles, some atretic, surrounded by masses of interstitial tissue. Peripherally next to the germinal epithelium is seen the narrow lighter staining zone of definitive oocytes.

Fig. 5. Ovary, longitudinal section. Rat No. 26 (O 41.1). Age: 25 days. Body weight 31.9 grams. Zenker, Haematoxylin-eosin. X 44.

Shows extreme degeneration of follicles at end of first growth period.

Fig. 6. Ovary, longitudinal section. Rat No. 41 (O 27.1). Age: 66 days. Body weight 68.5 grams. Zenker, Haematoxylin-eosin. X 44.

Typical ovary of the beginning of the third growth period. Note the large follicles and large amount of interstitial tissue. Observe the various stages of atresia. Three-fourths of ovary shown.

Fig. 7. Ovary, longitudinal section. Rat No. 57 (O 9.1). Age: 63 days. Body weight 85.9 grams. Zenker. Haematoxylin-eosin. X 44.

Ovary in which first maturation spindles are present, therefore, just before ovulation near the middle of the third growth period. About one-half of ovary shown.

Fig. 8. Ovary, longitudinal section. Rat No. 70 (O 8.1). Age: 71 days. Body weight 122.0 grams. Zenker. Haematoxylin-eosin.

Ovary mature, containing at least two generations of corpora lutea. Note the masses of interstitial tissue about the degenerate remains of atretic follicles. About one-half of ovary shown.

Fig. 9. Body of uterus (mid line below, bladder above ureters at the side). Rat No.____ (Not in series of Table I.) Age: newborn. Body weight 5.0 grams. Zenker. Haematoxylin-eosin. X 44.

Shows transverse section through middle of the 'body' of the uterus with its double lumen.

Fig. 10. Uterine tube. Rat No. 26 (O 41.1). Belongs with ovary Fig. 5. Zenker. Haematoxylin-eosin. X 44. Ampullary end below, uterine end above.

Fig. 11. Uterine tube. Rat No. 41 (O 27.1). Belongs with ovary Fig. 6. Zenker. Haematoxylin-eosin. X 44. Portion of the upper'papillary' end of tube within the periovarian capsule shown in the center.

Fig. 12. Uterine tube. Rat No. 70 (O 8.1). Belongs with ovary Fig. 8. Haematoxylin-eosin. X 44. Nearly the whole tube shown. Typical of sexually mature rat.

Fig. 13. Uterine cornu, transverse section. Newborn. Belongs with ovary Fig. 1. X 44.

Fig. 14. Uterine cornu, transverse section. Rat No. 26 (O 41.1). Belongs with ovary Fig. 5. At the end of the first growth period.

Fig. 15. Uterine cornu, transverse section. Rat No. 41 (O 27.1). Belongs with ovary Fig. 6. At the beginning of the third growth period.

Fig. 16. Uterine cornu, transverse section. Rat No. 70 (O 8.1). Belongs with ovary Fig. 8. Uterus of sexually mature rat at end of the third growth period.

Fig. 17. Vagina, transverse section (urethra above to the left). Newborn. Belongs with ovary Fig. 1. Haematoxylin-eosin.

Fig. 18. Vagina, transverse section. Rat No. 26. Belongs with ovary Fig. 5. Haematoxylin-eosin. At the end of first growth period.

Fig. 19. Vagina, transverse section. Rat No. 41. Belongs with ovary Fig. 6. Haematoxylin-eosin. At the beginning of the third growth period.

Fig. 20. Vagina, transverse section. Rat No. 70. Belongs with ovary Fig. 8. Haematoxylin-eosin. At the end of the third growth period, rat sexually mature.

Table I. Data on the individual rats, with absolute and relative weights of the ovary, tubes, uterus and vagina.

Serial No.	Rat No.	Age days	Body Weight grams	Body Length mm.	Absolute weight of Ovaries grams	Tubes grams	Uterus grams	Vagina grams	Percentage of body weight formed by Ovaries %	Tubes %	Uterus %	Vagina %
1	0 46.1	1	2.7	45	.0007	.0008	.0012	.0006	.026	.030	.045	.022
2	0 46.2	2	3.3	42	.0008	.0009	.0011	.0007	.025	.027	.034	.021
3	0 66.1	N	3.4	46	.0006	.0008	.0010	.0006	.015	.020	.025	.015
4	0 64.1	N	4.2	48	.0008	.0008	.0012	.0008	.019	.019	.028	.019
5	0 64.2	N	4.6	49	.0008	.0007	.0015	.0007	.017	.015	.033	.015
6	0 65.1	N	5.1	49	.0009	.0008	.0015	.0010	.018	.016	.030	.020
7	0 64.3	1	5.7	50	.0009	.0007	.0015	.0009	.016	.012	.027	.016
8	0 23.1	1	6.3	52	.0010	.0008	.0025	.0012	.016	.013	.040	.019
9	0 23.2	1	6.5	53	.0006	.0007	.0011	.0009	.009	.011	.017	.014
10	0 64.4	3	7.2	56	.0010	.0008	.0022	.0011	.014	.011	.031	.015
11	0 63.1	5	7.9	59	.0011	.0008	.0028	.0015	.013	.017	.036	.019
12	0 28.1	7	8.1	61	.0009	.0009	.0041	.0016	.011	.011	.051	.020
13	0 21.1	7	10.7	65	.0009	.0009	.0041	.0021	.008	.008	.038	.020
14	0 24.1	8	12.2	76	.0007	.0015	.0058	.0034	.006	.012	.047	.027
15	0 62.1	9	12.3	75	.0020	.0019	.0077	.0044	.016	.015	.063	.036
16	0 19.1	10	14.5	74	.0019	.0021	.0065	.0028	.013	.014	.045	.019
17	0 62.2	15	19.0	78	.0034	.0025	.0111	.0076	.020	.015	.065	.045
18	0 35.1	17	19.5	81	.0026	.0028	.0179	.0080	.013	.014	.092	.041
19	0 19.2	15	20.2	85	.0017	.0030	.0132	.0080	.008	.015	.065	.040
20	0 20.1	17	21.2	86	.0050	.0041	.0171	.0123	.024	.019	.081	.050

21	0	22.1	18	25.0	96	.0046	.0041	.0208	.0148	.019	.017	.084	.060
22	0	60.1	22	26.0	96	.0076	.0038	.0212	.0182	.029	.015	.083	.071
23	0	61.1	24	28.2	98	.0093	.0051	.0256	.0187	.033	.018	.091	.066
24	0	62.3	26	29.8	99	.0098	.0045	.0238	.0178	.033	.015	.080	.060
25	0	33.1	34	30.7	101	.0131	.0050	.0143	.0174	.043	.016	.047	.057
26	0	41.1	25	31.7	103	.0064	.0037	.0159	.0184	.020	.012	.050	.058
27	0	14.1	35	33.5	110	.0047	.0029	.0133	.0170	.014	.009	.040	.051
28	0	17.1	28	37.6	107	.0098	.0032	.0211	.0408	.026	.008	.056	.110
29	0	33.2	48	38.4	112	.0128	.0053	.0183	.0208	.033	.014	.048	.054
30	0	34.1	24	42.2	113	.0108	.0043	.0223	.0234	.026	.010	.053	.055
31	0	40.1	36	45.0	117	.0088	.0041	.0176	.0153	.020	.009	.039	.034
32	0	59.1	38	48.0	119	.0114	.0055	.0240	.0201	.024	.012	.051	.042
33	0	17.2	39	51.4	120	.0104	.0058	.0290	.0325	.020	.011	.056	.063
34	0	58.1	45	54.1	126	.0112	.0051	.0296	.0210	.021	.009	.055	.039
35	0	58.2	46	54.4	125	.0083	.0046	.0335	.0238	.015	.009	.061	.043
36	0	18.1	39	57.6	128	.0121	.0053	.0370	.0286	.021	.009	.064	.050
37	0	57.1	48	62.0	131	.0093	.0039	.0400	.0183	.015	.006	.065	.030
38	0	36.1	50	61.8	132	.0183	.0067	.0422	.0307	.030	.011	.068	.050
39	0	24.2	39	65.6	131	.0161	.0065	.0414	.0353	.025	.009	.063	.054
40	0	57.2	49	68.0	133	.0153	.0078	.0612	.0451	.023	.011	.091	.067
41	0	27.1	66	68.6	130	.0112	.0066	.0294	.0406	.016	.009	.043	.059
42	0	26.1	82	69.1	134	.0132	.0067	.0328	.0308	.019	.010	.048	.045

43	0	30.1	59	70.5	131	.0110	.0062	.0351	.0344	.016	.009	.050	.049
44	0	55.1	53	72.2	135	.0144	.0078	.0678	.0394	.020	.011	.094	.055
45	0	16.1	50	73.3	137	.0136	.0080	.0389	.0454	.019	.011	.053	.062
46	0	35.1	50	74.0	138	.0138	.0066	.0399	.0299	.019	.009	.054	.041
47	0	69.1	56	74.9	139	.0148	.0089	.[illegible]415	.0803	.041	.011	.189	.107
48	0	1.1	56	76.9	136	.0191	.0095	.1189	.0557	.025	.012	.155	.073
49	0	48.1	76	77.3	142	.0226	.0104	.0854	.0399	.029	.014	.111	.052
50	0	13.1	56	79.2	145	.0174	.0115	.[illegible]801	.1048	.022	.015	.228	.138
51	0	56.1	52	80.1	144	.0115	.0093	.1244	.0682	.078	.012	.155	.085
52	0	27.2	70	81.4	137	.0127	.0088	.1622	.0763	.016	.011	.200	.094
53	0	50.1	55	82.[illegible]	144	.0177	.0061	.0383	.0326	.021	.007	.046	.039
54	0	32.1	70	84.1	145	.0134	.0061	.0406	.0423	.016	.007	.048	.050
55	0	48.2	75	85.0	146	.0203	.0088	.0896	.0539	.024	.010	.106	.064
56	0	1.2	56	86.0	145	.0203	.0094	.1850	.0592	.024	.011	.215	.069
57	0	9.1	63	86.0	144	.0158	.0149	.2086	.1017	.018	.017	.243	.118
58	0	67.1	74	90.2	151	.0274	.0105	.1148	.0514	.030	.012	.127	.057
59	0	27.3	65	91.7	151	.0137	.0083	.0507	.0534	.015	.009	.055	.058
60	0	32.2	74	97.0	149	.0313	.0113	.2024	.1051	.032	.012	.209	.108
61	0	29.1	72	98.0	162	.0359	.0116	.1859	.0828	.037	.012	.190	.084
62	0	70.2	67	98.0	152	.0205	.0073	.0745	.0582	.021	.007	.076	.059
63	0	6.1	63	101.0	161	.0269	.0122	.1180	.0784	.027	.012	.117	.078
64	0	70.1	65	105.0	155	.0371	.0210	.2707	.1480	.035	.020	.259	.141
65	0	54.1	97	109.0	179	.0625	.0126	.1949	.0689	.057	.012	.178	.063

66	M	18.3	160	111	157 *2	.0478	.0188	.8396	.0922	.043	.017	.756	.083
67	0	60.2	75	113	163	.0238	.0062	.0854	.0543	.021	.006	.076	.048
68	0	3.1	90	115	161	.0368	.0151	.2378	.1380	.032	.063	.206	.119
69	0	51.1	81	118	162	.0558	.0223	.3285	.1399	.047	.018	.277	.118
70	0	8.1	71	122	163	.0400	.0114	.1390	.0659	.033	.009	.114	.054
71	0	53.1	75	125	165	.0477	.0181	.3093	.0880	.038	.014	.247	.070
72	0	53.2	80	127	164 *15	.0435	.0179	.1480	.0609	.034	.014	.117	.048
73	0	53.3	78	130	172	.0662	.0202	.4382	.1512	.051	.016	.336	.116
74	0	68.1	116	131	170	.0303	.0134	.1653	.0762	.023	.010	.126	.058
75	0	52.1	86	133	173 *9	.0511	.0155	.2038	.1015	.039	.012	.154	.077
76	0	51.2	81	135	175	.0371	.0145	.3450	.0984	.027	.010	.255	.072
77	0	2.1	91	138	167	.0561	.0166	.2551	.1441	.041	.012	.185	.104
78	M	27.1	123	140	173	.0447	.0142	.2159	.0683	.032	.010	.154	.044
79	0	24.3	95	144	176	.0362	.0133	.3818	.0962	.025	.009	.265	.067
80	M	22.1	161	144	174 *1 ½	.0642	.0219	1.0706	.1330	.045	.015	.747	.092
81	M	20.1	213	146	179 *90	.0163	.0065	.0584	.0529	.111	.004	.040	.036
82	M	19.1	189	150	177 *51	.0520	.0174	.4203	.1082	.035	.012	.281	.072
83	M	10.2	183	151	185 *26	.0500	.0109	.1215	.0713	.033	.007	.081	.047
84	M	16.2	179	151	183	.0198	.0086	.0696	.0380	.013	.006	.046	.025
85	M	18.2	171	151	174 * ½	.0606	.0218	2.0098	.1690	.040	.014	.133	.112
86	0	51.3	92	151	179	.0459	.0160	.2083	.0818	.030	.011	.134	.054
87	M	22.2	167	152	154 *2 ¾	.0697	.0208	.6052	.1360	.046	.014	.399	.090

88	M	18.4	171	153	183 *5	.0571	.0157	.3769	.1060	.037	.010	.247	.069
89	M	21.1	220	153	179 *90	.0202	.0066	.0603	.0547	.013	.004	.039	.036
90	M	18.1	208	154	182 *43	.0442	.0116	.1404	.0730	.029	.008	.091	.047
91	M	25.1	137	155	178 *10	.0650	.0152	.4590	.1334	.042	.010	.295	.086
92	M	10.1	176	158	184 *24	.0324	.0114	.1670	.0848	.021	.007	.106	.054
93	M	22.3	168	158	175 *7	.0605	.0143	.2711	.0822	.038	.009	.172	.052
94	0	11.1	108	160	180	.0452	.0226	.7906	.1650	.028	.014	.494	.103
95	M	22.4	175	163	182 *14	.0725	.0226	.3883	.0617	.045	.014	.233	.038
96	M	24.1	---	165	183 *3	.0575	.0108	.3811	.1372	.035	.007	.232	.083
97	0	49.1	157	165	188	.0432	.0175	.3669	.0906	.026	.011	.223	.055
98	M	14.1	170	166	177 *32	.0740	.0215	.4974	.1069	.045	.013	.300	.054
99	0	42.1	152	166	180	.0565	.0150	.2172	.1120	.034	.009	.131	.067
100	M	19.2	145	168	181 *4	.0660	.0207	.6250	.1158	.039	.012	.376	.069
101	M	21.2	196	168	184 *4	.0577	.0203	.5372	.1543	.034	.012	.321	.092
102	M	14.2	141	174	183 *6	.0559	.0169	.3328	.0927	.032	.010	.192	.053
103	M	9.1	---	175	181 *15	.0531	.0233	.4796	.1636	.031	.013	.275	.094
104	0	44.1	144	176	184	.0616	.0170	.4522	.1418	.035	.010	.258	.081
105	0	45.1	140	179	185	.0716	.0223	.5720	.1462	.040	.012	.319	.082
106	0	47.1	162	182	185	.0488	.0178	.3141	.1042	.025	.010	.173	.057
107	0	7.3	200	190	190	.0654	.0160	.2097	.0891	.034	.008	.111	.047
108	0	71.1	184	191	191	.0468	.0218	.3687	.1021	.025	.011	.194	.054
109	M	15.1	---	191	188 *32	.0747	.0273	.4638	.1384	.039	.014	.243	.073
110	0	4.1	161	194	195	.0866	.0249	.6068	.2100	.044	.013	.314	.109

111	M	26.1	135	196	181		.0479	.0138	.1671	.0896	.024	.007	.085	.046
112	0	18.1	280	201	186		.0261	.0061	.1006	.0345	.013	.003	.050	.017
113	0	43.1	156	201	195		.0770	.0219	.5136	.1504	.038	.011	.255	.075
114	0	39.1	175	205	200	*12	.0498	.0126	.1896	.0706	.024	.006	.092	.034
115	M	23.1	153	212	201	*10	.0757	.0169	.2772	.1177	.036	.008	.131	.056
116	0	5.1	142	216	199		.0744	.0191	.3537	.1656	.035	.009	.164	.077
117	0	72.1	---	221	202		.0537	.0141	.3620	.1283	.024	.007	.165	.058
118	M	16.1	173	229	200	*35	.0855	.0236	.3419	.1260	.037	.011	.149	.055
119	0	20.4	254	234	201		.0551	.0177	.4658	.1203	.024	.008	.199	.051
120	0	22.3	248	243	203		.0650	.0185	.2565	.1006	.027	.008	.106	.041
121	M	8.1	---	253	199	*23	.0866	.0182	.2766	.1296	.034	.007	.109	.051
122	M	17.1	---	255	212	*37	.0822	.0189	.1395	.1480	.035	.007	.157	.058
123	M	11.1	---	264	207	*24	.0704	.0212	.4391	.1990	.027	.008	.166	.075
124	0	73.1	300	280	220		.0654	.0235	.2315	.1407	.023	.008	.083	.050
125	0	74.1	300	294	230		.0518	.0185	.1981	.1043	.018	.006	.067	.035

* 24- twenty four days post-partum.

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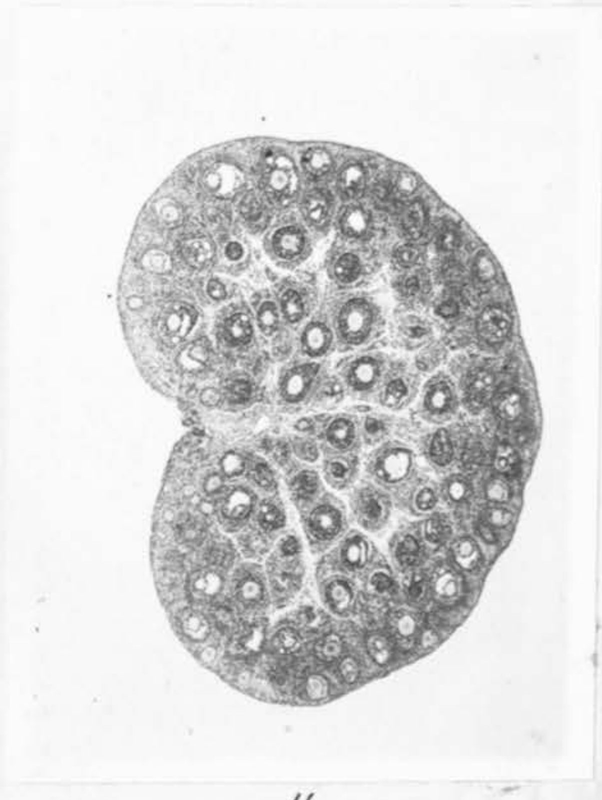

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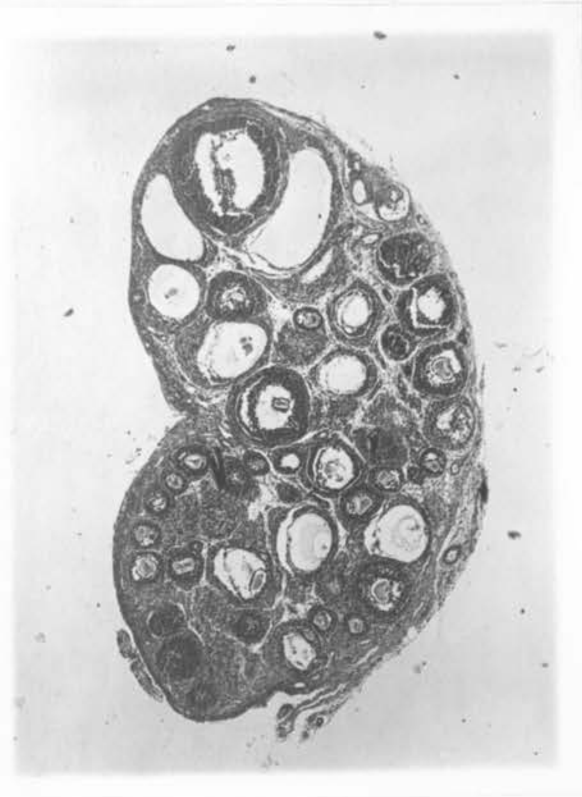
Ostrud



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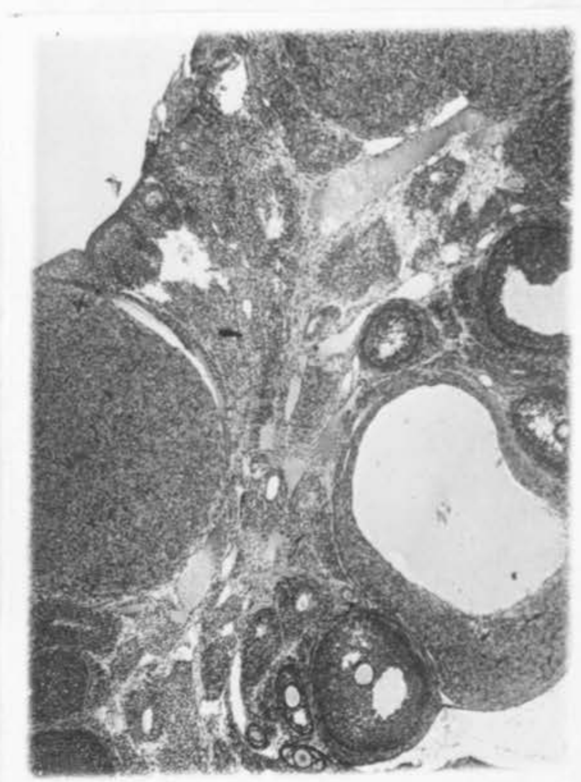

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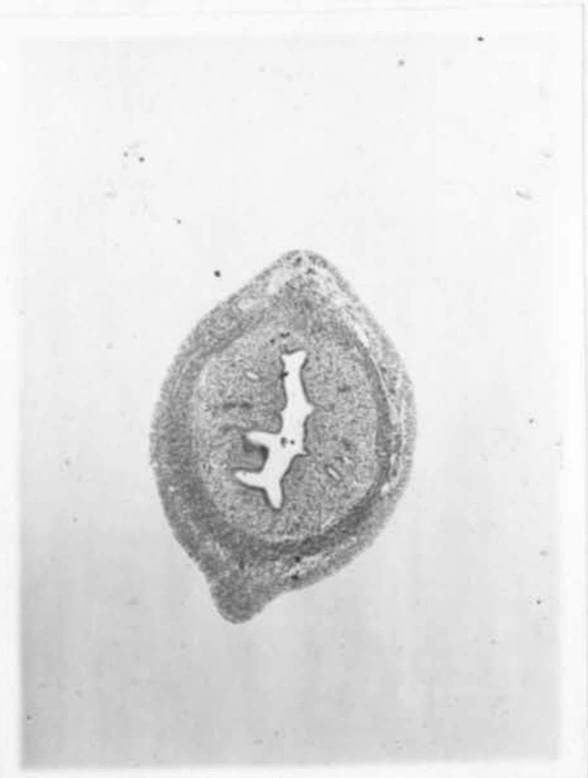

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L. Ostrund

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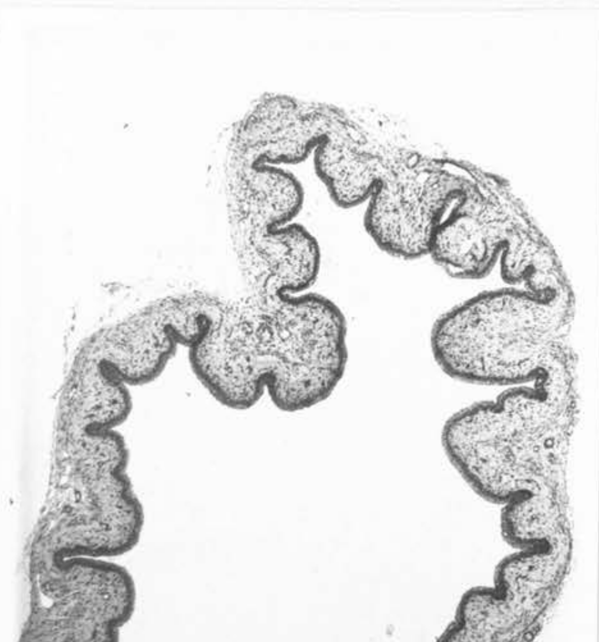

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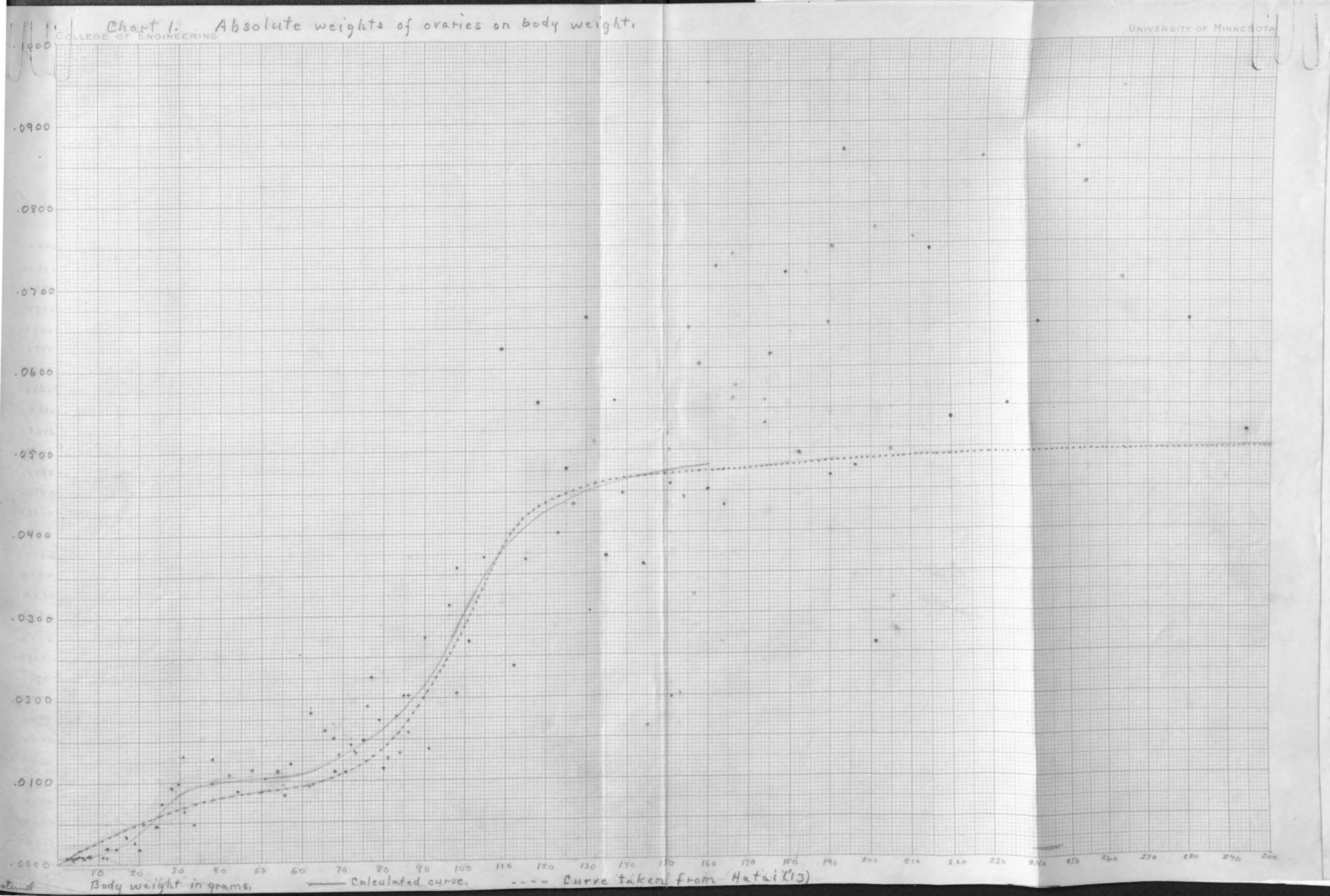
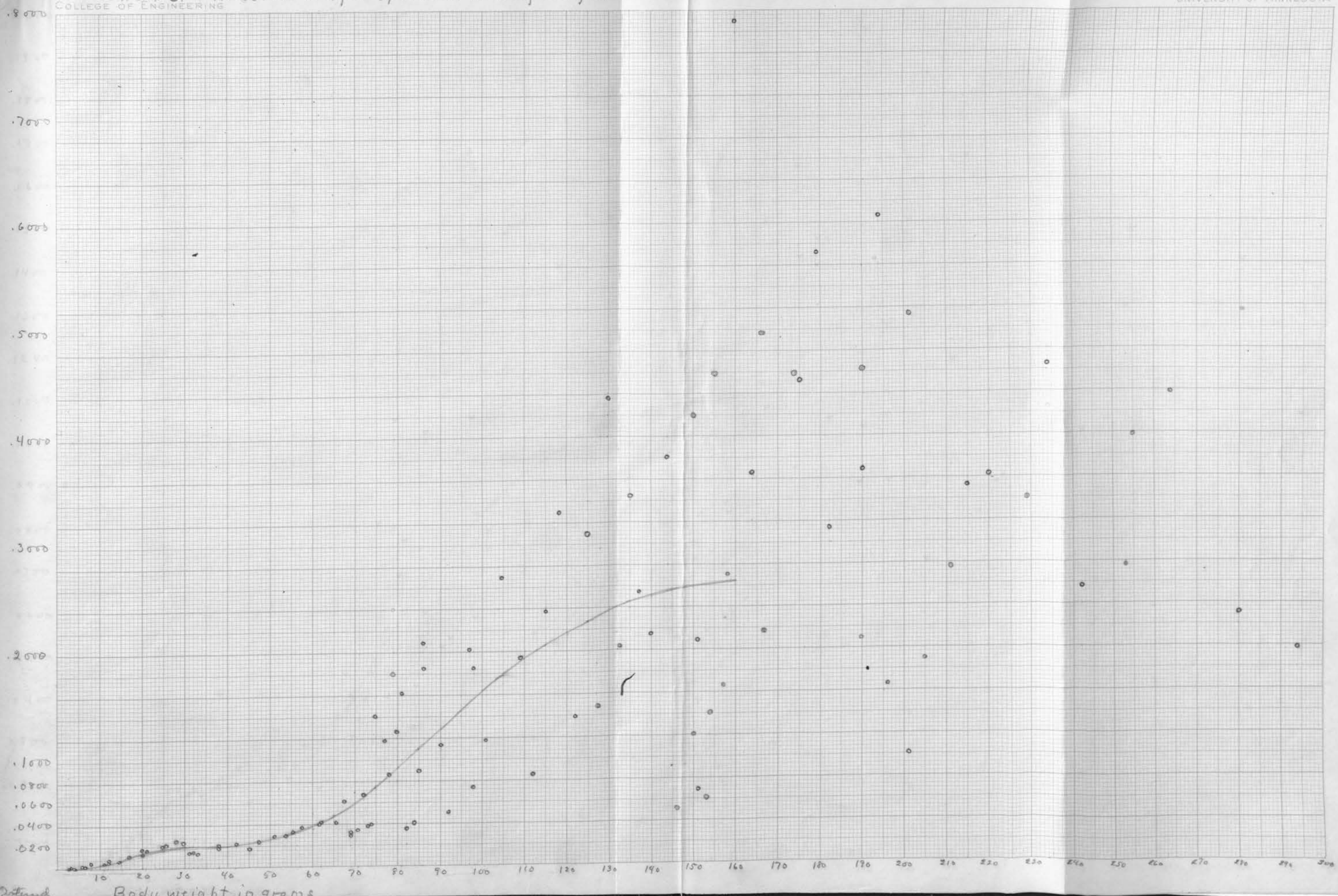


Chart I. Absolute weights of ovaries on body weight.
COLLEGE OF ENGINEERING
UNIVERSITY OF MINNESOTA
.1000
.0900
.0800
.0700
.0600
.0500
.0400
.0300
.0200
.0100
.0000
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
260
270
280
290
300
Body weight in grams.
Calculated curve.
Curve taken from Hatai ('13)

Chart 2 Absolute weight of uterine tubes on body weight.

Osterud

Chart 3. Absolute weight of uterus on body weight.



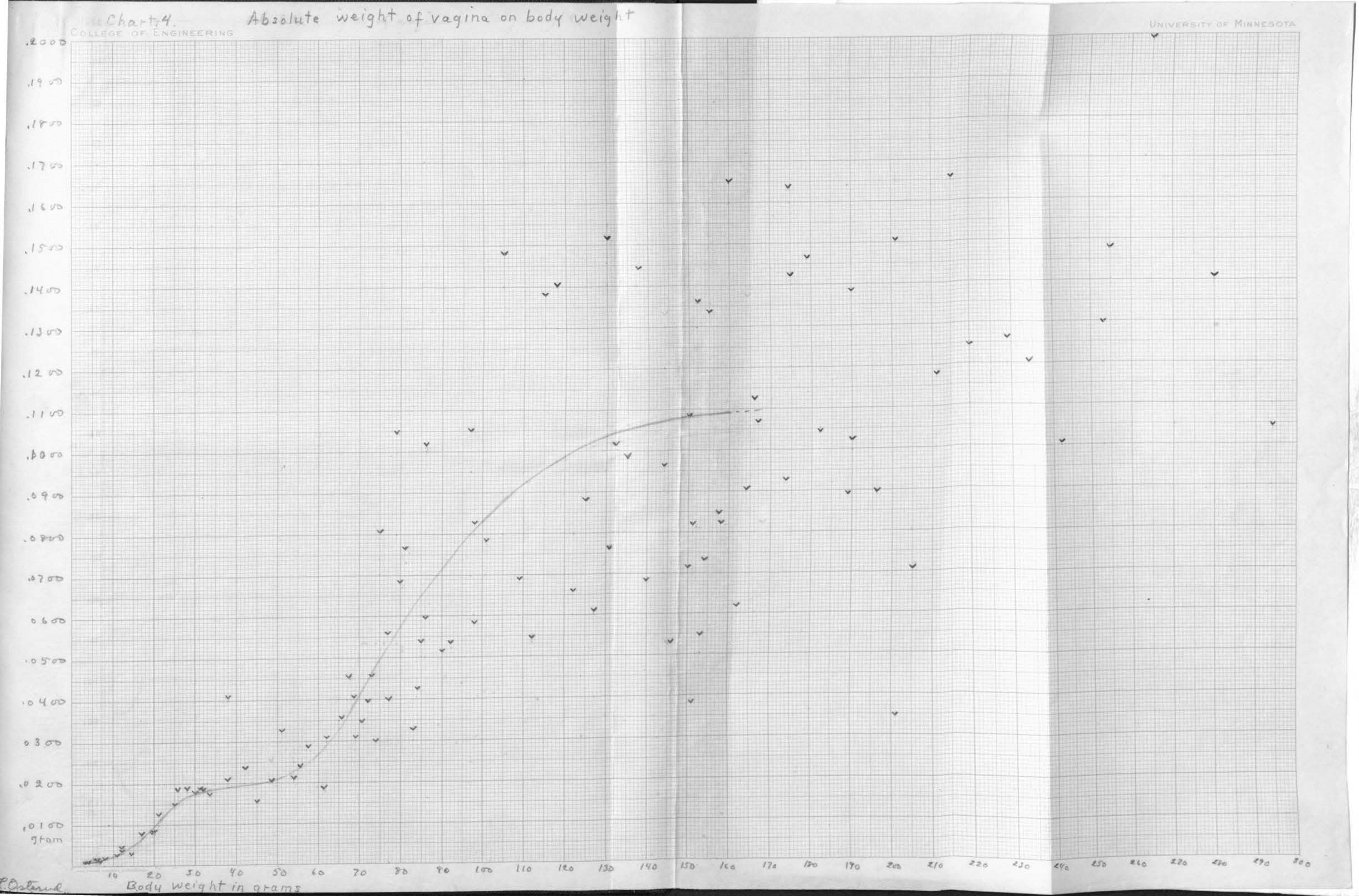


Chart 4.
Absolute weight of vagina on body weight
College of Engineering
University of Minnesota
.2000
.1900
.1800
.1700
.1600
.1500
.1400
.1300
.1200
.1100
.1000
.0900
.0800
.0700
.0600
.0500
.0400
.0300
.0200
.0100
gram
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300
Body weight in grams

Chart 5. Relative (Percentage) Weights.