The Effect of Age Upon the Connective Tissue of the Uterus, Cervix, and Vagina of the Rat*

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Recently Loeb, Suntzeff, and Burns (7, 8) reported that advancing age in the mouse is accompanied by changes in the stroma of the uterus, cervix, and vagina. The most significant of these is an increase in the amount of fibrillar and hyaline connective tissue, which is first manifest in the earliest months of life, progressing only slightly throughout the sexually active period, but becoming pronounced after the age of 18 months. In studying the effects of age and endocrine factors upon certain tissues in the rat, we have found, in general, changes similar to those described by Loeb and his associates in the mouse. In addition, evidence was obtained which indicates that the reproductive history of the animal plays an important role in the determination of the amount of connective tissue deposited in the genital organs and, furthermore, that this effect may vary somewhat in different strains of rats.

MATERIALS AND METHODS

Two hundred and twenty rats were sacrificed at ages ranging from 30 to over 800 days. Approximately half of these were from the Albany (A-S) strain, which is characterized by low fertility and a fairly high incidence of spontaneous fibroadenomas (3). The remaining half were from the Vanderbilt (V-S) strain, in which tumor incidence is low and fertility high (4). No animals with tumors were used for these particular studies. Up to 1 year of age, all rats were virgins. The groups of animals over 1 year of age consisted of breeding females and nonbreeders which were virgins of either strain, or sterile females of the A-S strain (12).

The reproductive tract was fixed in Bouin’s fluid. Representative sections were taken from the uterus and vagina of each rat, and complete serial sections of the cervixes of 54 rats were cut. Sections from all tissues were stained routinely with hematoxylin and eosin. In addition, Goldner’s modification (6) of the Masson trichrome method was used for staining the connective tissue. By this technic both collagen and reticulum are stained green, smooth muscle and epithelium red or orange-red, and nuclei brownish-black to reddish-brown. The method does not differentiate collagen from reticulum, and in this paper, therefore, no effort will be made to separate the two. In the descriptions to follow, the term collagen is employed in a collective sense for both reticular and collagenous tissue.

CHANGES IN THE UTERUS WITH ADVANCING AGE

Alterations in the endometrium.—The entire endometrium of the immature animal (30-40 days) in both strains is strikingly cellular. The stromal cells appear round or oval, with scant cytoplasm, which can only infrequently be observed, and large round or oval nuclei which have clearly defined nuclear membranes, prominent nucleoli, and chromatin scattered in coarse aggregates. There is a greater abundance of cells in the inner portion of the endometrium than in the outer region near the muscle layer.

A fibrillar meshwork lies between the stromal cells. Immediately beneath the epithelium which lines the uterine lumen, the fibrils are delicate, separate, and lightly staining, but deeper in the endometrium they become thicker, more dense, and stain more deeply. This is especially true in the outermost portion, near the myometrium, where the cells are relatively less abundant and the fibrillar connective tissue is more conspicuous than elsewhere.

From the immature to the 3-month stage there is a noticeable increase in collagenous tissue in the endometrium. Immediately beneath the lining cells the fibrils remain comparatively thin. More deeply, however, they have a tendency to become aggregated into fiber bundles. This process is most pronounced in the neighborhood of glands, about which the fibers are arranged in concentric rings, and in the outermost portion of the endometrium, where the individual fibers

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are thicker and the fibrils which compose them are more dense than elsewhere.

The stromal cells are generally more abundant in the subepithelial portion of the endometrium and become progressively less numerous as the myometrium is approached. Beneath the lining epithelium they still resemble those seen in the younger animals, but deeper down they become somewhat elongated, probably from compression by the denser collagenous fibers; the cell nuclei in most instances, however, remain quite large and vesicular.

In the period from 3 to 6 months there is a steady but highly variable further increase in the deposition of collagen in the endometrium, which differs regionally in its cellular composition and structure. While the cells directly under the lining epithelium usually retain their round vesicular nature and lie in a loose and relatively fine fibrillar network, the extent of this type of tissue varies in different animals; in some all or part of this superficial endometrium is composed of a dense meshwork of thickened fibrils in which are embedded fusiform cells. In the middle portion of the endometrium, where the glands are situated, the connective tissue may be composed of a dense meshwork of coarse fibers between which lie stromal cells with round or oval vesicular nuclei. Sometimes the collagenous fibers are arranged in whorl-like lamina- tions around the glands, compressing the cells between them. Sometimes they appear to form a homogeneous sheet of tissue which, under high magnification, is found to be a closely knit network of extremely fine fibrils (Fig. 1). In these areas the cells have no discernible cytoplasm, but do have characteristic hypertrophied, vesicular nuclei containing scant chromatin, prominent nucleoli, and indistinct nuclear membranes (Fig. 1). In the outermost region of the endometrium the collagen usually becomes much more dense and consists of coarse undulating fibers which interlace or run in parallel bundles and compress the stromal cells which lie between them. These cells are for the most part oval or spindle-shaped and have elongated nuclei, which are usually vesicular, although they may often appear shrunken and pyknotic.

From the age of 6 months on, there is an intensification in the formation of endometrial collagen. The rate of production, the amount laid down, and the manner in which it is arranged depend, apparently, not only on the age of the animal but also upon its reproductive history. In the virgins of both strains, and in A-S sterile females, there is, as age advances, a relatively rapid increase in the deposition of collagenous tissue (Fig. 2). In old virgin rats, particularly those of 18 months or over, the most superficial endometrial connective tissue, which in younger animals is loose and finely fibrillar, containing an abundance of characteristic cells with large vesicular nuclei, is replaced by denser collagenous tissue. Although there is considerable variability in the extent of this replacement and in the abundance of the stromal cells, the tendency for the condensation of collagen in this region is unmistakable.

The middle portion of the endometrium is not uniform in character. In some situations this is composed of coarse, deeply staining fibers which are wrapped around the glands like sleeves, compressing the cells lying between them. In intervening areas the character varies from well stained, definitely fibrillar tissue to lightly stained islands which only on very high magnification are seen to be composed of an extremely fine fibrillar meshwork. Indeed, not infrequently a considerable portion of this part of the endometrium is composed of sheets of the lightly staining, delicately fibrillar collagenous tissue, the cells of which, as in the younger group, are hypertrophied and contain relatively large, pale nuclei with scant chromatin and prominent nucleoli (See Fig. 1).

Finally, in the deepest portion of the endometrium the connective tissue consists of coarse, deeply staining fibers. With advancing age, particularly after 18 months, there is a tendency for the collagenous tissue
to become increasingly condensed into thick fibers or broad bands (Fig. 4). Sometimes the central portions of the wide bands appear homogeneous or hyaline and may display an alteration in staining properties, showing, in sections stained by the modified Masson technic, a greater affinity for the red instead of the green dye (Fig. 6). The fiber bundles are usually closely packed together and in most instances compress the stromal cells lying between them.

In fertile breeding animals of both strains the rate of collagen deposition in the endometrium is slower than in females which have never borne young. In the breeding V-S rats, which were uniformly very fertile, the uterus remained fairly small in diameter as compared with the size in virgins of the same age (Figs. 2 and 3). The endometrium was characterized by a much greater compactness of the fibrillar meshwork as a whole and by the presence of dense collagenous tissue in the inner portion instead of the loose, delicate network commonly seen in the younger animals. In most instances the entire endometrium was remarkably cellular, and frequently the majority of the cells had nuclei of the vesicular type.

In about one-half of the animals comprising the V-S breeding group over 18 months of age, the endometrial stroma appeared to be composed of dense, almost hyaline collagen. Careful examination with the oil immersion lens, however, revealed that this consisted actually of a sheet of very fine fibrils, although it was extremely difficult, if not impossible, always to discern the fibrillar architecture. Frequently—and this was particularly true in the peripheral portion of the endometrium—the collagen was demarcated into broad interconnecting bands by the stromal cells.

In the A-S breeding animals there was less uniformity in the size of the uterus. In a number of instances this was of large diameter and contained a generous amount of connective tissue, thus resembling those of virgin rats. In seeking an explanation for these observations, examination was made of the reproductive histories, and also of vaginal smear records when such were available. It was noted that the animals with large uteri had not been pregnant more than once or twice, usually because of an ovarian dysfunction which manifested itself by a vaginal hyperestrus (12). On the other hand, those which had given birth to from 5 to 7 litters had small uteri, similar to those of V-S animals whose reproductive capacity was about the same. These observations tended to confirm the general impression that the deposition of large amounts of connective tissue is associated with the nonpregnant state.

To check on the observations further, the thickness of the endometrium and the myometrium of breeding and nonbreeding animals of both strains was measured. The results are summarized in Table I. The findings must be regarded as only suggestive, since
Altered sections from uterus of an A-S rat 17 months old, showing wide bands of collagen in the outermost portion of the endometrium. Mag. X 210.

Table I: Summary of Quantitative Data Giving the Average Width, in Millimeters, of the Endometrium and Myometrium of the Various Groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of animals</th>
<th>Age (months)</th>
<th>Endometrium</th>
<th>Myometrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-S virgins</td>
<td>14</td>
<td>12</td>
<td>1.72 ± 0.07</td>
<td>0.80 ± 0.02</td>
</tr>
<tr>
<td>V-S breeders</td>
<td>15</td>
<td>12</td>
<td>0.97 ± 0.05</td>
<td>0.81 ± 0.05</td>
</tr>
<tr>
<td>V-S breeders</td>
<td>18</td>
<td>19</td>
<td>1.10 ± 0.05</td>
<td>0.78 ± 0.04</td>
</tr>
<tr>
<td>A-S breeders</td>
<td>20</td>
<td>19</td>
<td>1.36 ± 0.07</td>
<td>0.74 ± 0.03</td>
</tr>
<tr>
<td>A-S virgins</td>
<td>16</td>
<td>19</td>
<td>1.81 ± 0.10</td>
<td>0.70 ± 0.03</td>
</tr>
</tbody>
</table>

1 The average number of litters was 5 to 6.
2 The average number of litters was 5 to 4.
3 In this and the following group, each animal was 12 months old.
4 In this and the following 2 groups, the ages ranged from 14 months to 2 years, the average being 19 months.

The significance ratio is the ratio of the difference between the means to the probable error of the difference. If it is 3 or over, the data are considered reliable.

The number of animals in each series is small, but the results confirm the impression obtained from histologic examination. Comparison of 1 year old V-S virgins and V-S breeders shows that the mean width of the endometrium in the virgins is significantly greater than that of the breeders. In groups in which the mean age is 19 months, the average width of the endometrium of the A-S breeders exceeds that of the V-S breeders, but is in turn exceeded to an even greater degree in the A-S females which had never borne young. In contrast to the differences noted in the endometrium, the measurements of the myometrium show no significant variations among the groups.

Alterations in the myometrium.—Equally striking changes occur in the myometrium with advancing age. Frequently in breeding rats the condition of the muscular coats suggests the age of the animal when it is impossible to assign the uterus to any particular age group on the basis of endometrial changes. Up to the age of 6 months there is no significant increase in the interstitial tissue of the myometrium, and only infrequently is there found a noticeable increase in connective tissue surrounding the larger arteries present between the 2 muscular coats. As age advances, however, the myometrial stroma becomes progressively more abundant, and in the oldest age group (1.5 to 2 years) constitutes a considerable portion of the muscular wall.

Invariably the earliest changes are noted in the inner or circular smooth muscle. In the large uteri the muscle cells in this region often appear atrophied, and the muscular ring may give the impression of being stretched, as if distended by the pressure of the enlarging endometrium. In virgins and breeders of both strains the circular muscle layer becomes in most instances extensively invaded by connective tissue before significant alterations are observed in the outer longitudinal muscle coat (Fig. 5). In old rats, however, the collagenous bands which surround the muscle bundles of the longitudinal layer are decidedly thicker,

The increase in perivascular connective tissue which forms in sleeve-like fashion around the blood vessels in the myometrium is clearly demonstrated in animals which have reached 1 year of age, and it becomes more pronounced in progressively older females. Sometimes this connective tissue is composed of well-formed, fairly thick fibers which not only surround

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the arteries but also produce a continuous wide ring of collagenous tissue between the 2 muscular coats. In most cases, however, this connective tissue is arranged more irregularly and actually replaces muscle cells in both muscular layers (Fig. 6). It consists of fairly fine interlacing fibers or of sheets of pale staining hyaline collagen.

**CHANGES IN THE CERVIX WITH ADVANCING AGE**

As we have not been able to find any satisfactory description of the cervix of the rat, it may be pertinent to mention its main features here. The rat cervix may be said to begin at the point where the uterine horns fuse. It contains 2 canals which are prolongations of the uterine lumina. Each canal communicates independently with the vagina (Fig. 7). In approximately the upper third of the cervix, which represents the uterine portion (Fig. 7, a), the epithelium lining the cavities is columnar in type, but at the point where the obliquely directed lumina become the relatively narrow, straight cervical canals (Fig. 7, b), there is an abrupt change of epithelium to the vaginal or stratified variety. It is at this level (Fig. 7, b) also that the outer longitudinal uterine muscular coats diminish in width rapidly and disappear in the loose connective tissue surrounding the cervix. The circular smooth muscle of the uterine horns is continued into the cervix, and in the vertical portion of the organ (Fig. 7, c), consists chiefly of circular bundles. These are especially prominent in the upper half of the vertical cervix (Fig. 7, c), but in the distal portion they begin to be diluted by an increased amount of connective tissue which forms the chief bulk of the cervical lips (Fig. 7, e). Throughout the length of the cervical canals an inner longitudinal muscle coat is developed on either side. On the medial aspect these longitudinal muscle layers flank a central core of circular muscle bundles, with which they merge obliquely at the tip. On the lateral sides they are continued into the lips, mixing with the circular muscle present and extending into the vagina to form its longitudinal muscle coat.

The stroma of the rat cervix at all ages, but especially in the young, is quite cellular. In its uterine portion...
the connective tissue beneath the epithelium lining the canals, like that of the superficial endometrial stroma, is delicate and fibrillar and persists in this form for variable distances beyond the point where the uterine (columnar) type of lining epithelium gives way to the vaginal (stratified) form. It then changes gradually, becoming a dense matrix of fibers, which run parallel to the longitudinal muscle layer and crowd the cells lying between them. The connective tissue surrounding the bundles of circular muscle consists of irregularly arranged collagenous fibers which become increasingly dense and more conspicuous in the region of the outer cervical lips, where the muscle bundles become sparse. Under the epithelium of the lateral walls of the cervical lips the pattern most frequently observed is that of fairly thick fibers which interlace freely; it then changes either gradually or abruptly to the finely fibrillar meshwork that usually characterizes the vaginal folds with which the cervix becomes continuous.

In the cervix, as in the uterus, there is a considerable increase in collagenous tissue from the immature to the 3-month stage, resulting in enlargement in all three dimensions. As age advances the collagenous tissue increases in amount and density, the most striking acceleration occurring in those animals which do not breed. Thus, discounting the usual variations of biological material, the cervices of 1 year old virgins are in the main decidedly larger than those of breeders of the same age (Figs. 8 and 9). Indeed, the outer lips of the cervical canals may become so enlarged and thickened that they project into the vagina, not infrequently converting the normally separate openings of the 2 canals into a common outlet (Fig. 8).

**Changes in the Vagina with Advancing Age**

The connective tissue even in the immature animals is usually a closely interwoven collagenous meshwork in which are embedded a considerable number of fibroblasts containing large vesicular nuclei. Occasionally it is difficult to make out any fibrils in this meshwork, but where the section chances to be thin the fibrillar character is quite clear. As age progresses the connective tissue becomes more dense. In some regions there is a tendency for the collagen to become aggregated into coarse, closely packed fibers. This is observed most often in the anterior wall near the urethra. In other areas, the connective tissue may resemble a dense, almost hyaline sheet in which the fibrillar structure cannot always be made out even with high magnification. The proportions of the coarse, deeply staining fibrous tissue and the very finely woven, lightly staining, fibrillar type vary widely not only in different animals but also in different regions of the vagina in the same animal. While the connective tissue near the urethra is usually coarse, that which is present in the vaginal folds is of the finely fibrillar or hyaline-appearing variety. The differences in the number and nature of the fibroblasts characterize for the most part the young and old vaginae. In the young the cells are abundant and large, with typical vesicular nuclei. In the old they are relatively few in proportion to the amount of collagenous tissue, and appear predominantly flattened and shrunken. Between these two extremes wide variations in cellular composition exist. In some 1 year old females, for example, both breeders and virgins, the stroma may contain relatively few cells, whereas in much older animals a remarkable cellularity may be observed.

**Abnormal Staining Reactions by the Trichrome Stain**

In some of our sections prepared by Goldner's modification of the Masson trichrome stain (6), as well as in sections stained by Masson's original technic (9), we have encountered unusual staining reactions in connective tissues. Whether or not these reactions are significant and result from actual biochemical modi-
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fications of the tissue, or whether they are artifacts, we do not know. To date, the results of our investigations as to the cause of the phenomenon are confusing, and the final solution is not yet at hand. Brief mention will be made, however, of our observations in order to call attention to the difficulties which may accompany the use of this technic for the study of connective tissue in the female reproductive system, at least of the rat.

The unusual finding is that in places the connective tissue, instead of being stained by the light green dye, as is to be expected, is stained red by the fuchsin. If a connective tissue fiber is fairly broad, the central portion may be red while the peripheral portion is green (Fig. 6). Sometimes almost the entire fiber may stain green but with red tinges in its course. If the stroma is finely fibrillar, as so frequently occurs in the vagina, many of the fine fibrils in irregular areas appear red and fade gently into others which are green. In the vagina the change occurs most frequently under and parallel to the epithelium but not immediately adjacent to it. Other sections, from different animals or from different regions of the same organ, stained in the same dish with sections which give the peculiar staining reaction, fail to show the unusual affinity for fuchsin. Studies of serial sections and modifications of procedure have thus far not yielded clarifying results. Whatever may be the basis for this tinctorial abnormality, it is apparently not related to the age or sexual activity of the animal, for it is observed in immature animals as well as in the old and at all phases of the estrous cycle in sexually mature rats.

Discussion

These studies in general confirm those of Loeb and his associates with respect to the increase in the amount of collagen and in the density of the collagen fibers with advancing age. There are, however, several minor points of difference between their observations in the mouse and ours in the rat, which suggest species variations. Whereas they found only "a gradual slight increase in the relative amount of connective-tissue fibrillae from the age of three weeks to the age of four months" (8), we have been impressed with the striking increase in the rate of connective tissue deposition which occurs between the ages of approximately 30 days and 3 or 4 months. In the mouse the increase in collagenous tissue "appears to make little advance throughout the sexually active interval, but it progresses again during the later period of life" (8), while in the rat the deposition of collagenous tissue appears to continue throughout the sexual
period and is influenced by the sexual history. Thus it was noted with striking frequency that the uteri and cervices of virgins were manifestly larger than those of breeding females of comparable age. This cannot be attributed to any direct relation of the size of individual organs to general body weight, for the body weights of virgin animals are on the average distinctly lower than those of breeding females (2, 5, 13).

In a previous study of the estrous cycles of rats in the A-S and V-S strains (12) it was observed that in the virgins of both strains vaginal smears containing only epithelial or cornified cells, or a mixture of these two, occurred during approximately 45 per cent of the almost lifelong observation period. In contrast, such smears were found in the V-S breeding animals for only about 13 per cent of the time, and in the A-S breeding rats for approximately 30 per cent. The increased proportion of the observation period during which the A-S breeding animals showed smears characterized by epithelial and cornified cells as compared with the V-S rats was due to the generally poor reproductive abilities of the former.

In the virgin rats the presence of epithelial and cornified cells can safely be taken as an index of estrogen activity, and the large amounts of collagenous tissue found in the accessory reproductive organs of these animals can probably be associated with the long-continued action of estrogen. These observations strongly suggest that estrogen stimulates the formation of collagenous tissue in these organs. This view is supported by the findings of Sundtzeff and his associates (10), who reported that in mice receiving injections of estrogen a homogeneous hyaline substance having the staining properties of collagen was deposited in the uterus, cervix, and vagina. By using a method which differentiates collagen from reticulum, we have found that, as age advances, there is a transformation of the latter into the former in the endometrium (11). In preliminary studies of the effect of estrogen on the reproductive organs of the immature rat (unpublished data) a considerable increase in collagenous tissue, with a concomitant decrease in reticulum, has been observed after 2 weeks of intensive administration of estrogenic substance. All these findings point to estrogen as the determining factor in the formation of connective tissue in these organs.

The factors which induce the more restricted deposition of collagen in the breeding animals are not clear. This restriction, associated with the more limited period during which such animals have only epithelial or cornified cells in the vaginal smears, would superficially appear to be due to the decreased time during which estrogen acts on the accessory reproductive organs. It is known, however, that estrogens are abundant in pregnancy in certain species, and it is quite possible that this is true in the rat as well. If so, it seems probable that the action of estrogen on the connective tissue of the accessory reproductive organs is held in abeyance by some factor produced during pregnancy, probably progesterin. This is considered likely, since progesterin is known to restrict the action of estrogen on the vaginal mucosa (1).

In the V-S strain there were highly significant differences in width of the endometrium in virgins and fertile breeders of the same age. In the A-S animals, the differences between groups of breeders and virgins in which the average ages were comparable were not great but were nevertheless significant. Examination whenever possible of both the reproductive histories and vaginal smear records of the animals which were used for the histologic studies revealed that the A-S females which had given birth to from 5 to 7 litters usually had relatively small uteri. On the other hand, the animals with large uteri had had only 1 or 2 pregnancies and long periods of predominantly epithelial smears, indicative of a prolonged estrogenic activity. This is interpreted as supporting the concept that the proliferation of collagenous tissue is influenced by estrogen, and that the amount deposited is related to the length of time and extent of estrogenic stimulation, at least in the nonpregnant state.

**Summary**

In studies concerning the effects of age and endocrine factors upon certain of the connective tissues of the body, the uteri, cervices, and vaginas of rats, sacrificed at ages ranging from 30 to over 800 days, were examined histologically. Two strains of rats were employed, the (A-S) strain, characterized by low fertility and a fairly high incidence of spontaneous mammary fibroadenomas, and the (V-S) strain, in which fertility is high and spontaneous development of tumors is low.

It was found, in general, that as age advanced there was an increase in the amount and condensation of the collagenous tissue in the uterus, cervix, and vagina of the normal rat. In the endometrium this increase was observed to be greatest from the immature to the 3-month stage. From then on there was great variability in the further deposition of collagen. Furthermore, the rate of formation, the amount deposited, and the manner in which the collagen was arranged depended, apparently, not only on age but also upon the sexual history of the animal. In virgins the growth of connective tissue was greater than in breeding animals and resulted in the frequent development of strikingly larger uteri and cervices than were usually found in highly fertile breeders of comparable age. The observations in general tended to associate the deposition of collagenous tissue in the accessory reproductive organs of the rat with the long-continued, unmodified influence of estrogen in the nonpregnant state.
Beginning with approximately 1 year of age there was a progressive increase in the amount of connective tissue in the muscle layers of the uterus. The earliest changes were invariably observed in the inner or circular smooth muscle coat, although in old rats significant replacement was also frequently seen in the outer or longitudinal layer. Large amounts of collagenous tissue also developed around the arteries, especially between the muscle coats.

REFERENCES

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