REPLACEMENT OF OVOCYTES IN THE OVARY OF NORMAL AND HORMONE-INJECTED YOUNG RATS

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TWO PLATES (NINE FIGURES)

The observations presented in this paper were made as a series of rat ovaries was studied for their endocrine elements. The peculiar arrangement of the generative tissue in these ovaries has a bearing on certain embryological problems and on views concerning the function of the adult ovary. An interpretation of these findings is substantiated by the literature on ovarian histology and on cases of ovarian regeneration. Insofar as these problems are concerned, first the literature shall be presented briefly and then the development of the generative tissue in the infantile rat ovary shall be described.

(a) LITERATURE

The entire parenchyma (cortical and medullary) of the ovary originally is derived from the germinal epithelium. During an early embryonal stage, ovocytes are spread through the surface epithelium in the germinal ridge as well as in neighboring regions of the dorsal pleura. Nagel (1889) reported that primordial germ cells gather on the germinal ridges and also on the lateral wall of the mesonephros above the ostium tubae and the Wolffian duct in 11–22 mm. human embryos. In older embryos all germ cells are situated within the gonad arranged in zones according to age, the youngest

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ones lying in the neogenic zone just under the germinal epithelium, the oldest ones in the medullary strands. The neogenic zone of the ovary contains ovocytes and the so-called indifferent cells which are a product of the germinal epithelium. Von Winiwarter and Sainmont ('09), having found transitional nuclear structures from indifferent cells (with nuclei protobroque b) to ovocytes (with deutobroque nuclei), conclude that the former are ovogonia. The follicle cells likewise are derived from the indifferent cells. In old embryos the neogenic zone becomes narrow and the mitotic activity in the surface epithelium and the underlying neogenic zone diminishes. After birth, however, the proliferation is resumed (Kingery, '17; Brambell, '27). In the ovary of the infantile rat Cowperthwaite ('25) observes ovocytes arising at some distance from the surface. (For theoretical reasons, because there are no synaptic figures, he doubts that the ovocytes which form after birth ever become functional.) Von Winiwarter and Sainmont report that the proliferation of the surface epithelium is localized. In 34–36 day cat embryos the apex of the ovary at the insertion of the tube is the most active area; subsequently the proliferation spreads outward like a wave and in 45–50 day embryos it reaches the mesovarian border of the ovary. Kingsbury ('13) states that this "marginal growth" of the ovary continues throughout the infantile stage.

In contrast to the condition found in higher mammals, ovogenesis occurs in rats and mice during the reproductive period, and even regeneration of the ovary has been reported. There is no neogenic layer left in the mature ovary, and the main part of the germinal epithelium is flat and inactive. Only in the folds between protruding Graafian follicles or corpora lutea do the cells of the germinal epithelium remain cylindric and undergo mitosis. These "germinal valleys" contain small primary follicles under the germinal epithelium. Free ovocytes are rarely found. A cyclic appearance of new follicles with each estrus is reported by Allen ('23), Butcher ('27) and Allen and Creadick ('36). Papanicolau ('24), from a study of ovogenesis in active regions of the germinal epithelium of the guinea pig, calls the corpus luteum a powerful inhibitory factor. (He remarks that there are not enough mitoses to account for the newly-formed ova.) Swezy ('33), however, observes that more active ovogenesis occurs during pregnancy than in estrus and that even greater activity takes place in pseudo-pregnant rats. Swezy and Pencharz ('32) find that hypophysectomy, chorionic gonadotropin or the luteinizing fraction of the pituitary have a stimulating effect on ovogenesis and Swezy and Evans ('32) find that hypophyseal implants or the follicle stimulating component of the hypophysis have a depressing influence.

Ovogenesis is accompanied by the conjugation of the chromosomes in the embryo, but a synaptic arrangement is not seen in mice and rats older than 4 days (Pratt and Long, '17; Kingery, Cowperthwaite, Butcher, Brambell). Conjugation occurs for some weeks after birth in kittens, then, after the age of 24 days, there is an abbreviated synapsis and in still older animals the process is dropped altogether (von Winiwarter and Sainmont). The rough chromatic figures drawn by Kingery from mouse embryos also represent an incomplete form of meiosis. There is some evidence that meiosis, in contrast to ovogenesis, depends on hypophyseal hormones: after hypophysectomy in rats there arise polynuclear spermatocytes which Gothié and Moricard ('39) explain as resulting from an inhibition of meiosis; the injection of gonadotropic extracts permits development beyond the first maturation division (Moricard and Gothié, '39). In folliculine-induced ovaries of the chick the ovocytes are arrested in meiosis (Dantchakoff, '36 a, b, c).

The observations outlined above have been interpreted in many ways. The germinal epithelium proliferates at various speeds at different ages and gives rise to ovocytes and follicle cells at some times and at other times to strands or a compact layer of indifferent elements. The authors have distinguished several successive proliferations with inherent differences in nature. To the first-formed strands was ascribed a male character from the beginning, since in the mature gonad they occupy the center and produce sperm in the male; and since only the last-formed ova of the outermost layers survive when the animal reaches puberty, it has been believed that the former generations were not viable. The defective character of the ovocytes in the medulla and inner cortex is apparently indicated by their fragmentation at birth and again shortly before puberty (von Winiwarter, '01, rabbit; von Winiwarter and Sainmont, Dederer '34, Sneider '37/'38, cat; Brambell, Engle '31, mouse; Allen '23, Lane '38, rat).

An old controversy exists on the question of determination of germ cells. The theory of the continuity of germ plasm has been substantiated only in lower forms, but several recent authors, Allen, Stanley and Witschi ('40) among them, prove that also in vertebrates ectopic primordial germ cells migrate into the gonad to become the progenitors of germ cells. Other observers, as von Winiwarter and Sainmont and Allen himself, demonstrate the development of ovocytes in loco from cells indistinguishable from somatic cells. The marginal growth of the ovary also implies that part of the peritoneum is converted into germinal epithelium.

(b) ORIGINAL OBSERVATIONS

1. Untreated rats

The infantile ovary is bean-shaped with the hilus at the convex side. The large ovarian vessels and the irregular rete sinuses occupy opposite sides of the broad hilus. In the 7-day ovary shown in figure 1, the distance between rete and vessels is very great. There is a well differentiated epovarium in the fatty tissue of the broad ligament. The capsule folds upward from the broad ligament, and in suckling animals the upper border is attached to the ovary around the depression. In the area not covered by the capsule, the oviduct and the suspensory ligament of the ovary come in contact with the germinal epithelium. The ligament pierces the ovary and continues as the ligamentum ovarii proprium. At the insertion of the ligament the ovary is constricted by a deep furrow and close by, the fimbria makes contact with a broad area of the germinal epithelium. Both fimbria and ligament send connective tissue and fine vessels into the cortex. In the depression and under the insertion of the fimbria the cells of the epithelium and the underlying cortex are very small. This part of the cortex consists of young follicles, many of which possess only a few granulosa cells, embedded in a stroma of minute cells with rod-like dark nuclei. Similar minute cells form the stroma of the fimbria (see fig. 6). The differences between the neogenic zone of the embryo and this germinal focus in the young are in the concentration of neogenic tissue at one point of the ovarian periphery, in the quick enclosure of ovocytes by a follicle, and in the presence of connective tissue. Frequently much of the infantile neogenic tissue, instead of filling the depression, lies beside it, overlapping the older cortex in a cap-like manner. In this part the cells are larger and the epithelium high. The original symmetry of the ovary is thus lost and different topographical relationships become established in the adult.

Mitotic figures disappear from the germinal epithelium soon after birth and the nuclei are often lobulated. While the rats are still suckling, the main portion of the germinal epithelium turns flat like the capsule serosa, and in older animals the ovary even appears enveloped in a multilayered fibrous capsule. A basal and an apical portion of the epithelium retain a more active structure. Apically, over the asymmetrical neogenic cortex, the nuclei are elongated, light, have an irregular outline and no nucleoli (nuclei protobroque a). During the first 2 weeks, a wide region of the germinal epithelium adheres to the serosa of the capsule and the portion of the oviduct inside the capsule. Later the germinal epithelium meets the serosa only at a small apical area and at the bottom of the periovarian space. The borderline between the two kinds of epithelium at the bottom of the periovarian space is not marked. The region of transition corresponds to the white line in mammalian ovaries without a capsule. Here the cells remain cylindrical with vesicular nuclei and closely crowded together. Since proliferation of the germinal epithelium could not be observed, the adjoining organs were searched for mitotic divisions. None were noted in the capsular epithelium and but few were present in the connective tissue around the ovarian border. However, the ciliated epithelium and the stroma of the fimbria abounded in mitoses.

In discrete areas the focal epithelial cells may have vesicular nuclei (deutobroque) and the epithelium invaginates. The focus then contains well differentiated follicles and anovular follicles with vesicular nuclei or tubes still continuous with the surface, the longer ones growing down either along the ligament or under the periphery. In a few instances the plane of section showed that these tubes were connected with the rete and their morphology suggests that they are homologous to seminiferous tubules. The tubes are best developed in prepuberal animals. (Fig. 2 gives an example of an animal in which these male homologues are remarkably well differentiated. This rat also has a prostate.) In very young and in adult rats it is often difficult to say whether similar structures near the focus are plump tubules or anovular follicles. A circular channel derived from the base of the periovarian cavity is always well developed.

Free ovocytes scattered around the periphery are less frequent in young animals than in the embryo. In 12-day females many free ovocytes have nuclei with very finely dispersed chromatin corresponding to an early presynaptic stage (deutobroque). In prepuberal rats free ovocytes are rare and in most of them the nuclear chromatin has the same irregular distribution as in ovocytes surrounded by a follicle. In maturing females there are always a few ova undergoing cleavage in medium or large follicles and in one case a multiple follicle was found in an adult.

At puberty the periovarian cavity completely encloses the ovary except where it rests on the broad ligament. The suspensory ligament and the distal end of the oviduct grow through the capsule. The proliferation of young follicles near fimbria and ligament is less prominent and the germinal epithelium forms multiple germinal valleys. Some months later the original germinal focus has disappeared and the ligament now enters close to the hilus in a region of connective tissue. Indirect cell division in the fimbria continues throughout adult life, but at a lower rate than in the young. The insertions of the fringes of the fimbria become extremely thin, but still seem to promote follicle formation. The focus of proliferation can be seen on one of Allen's sections ('22, fig. 22) through a mouse ovary; it lies opposite the oviduct close to the attachment of a strand of connective tissue. The animal was probably adult. However, with advancing age an increasing amount of the newly formed material assumes the nature of stroma. While the neogenic zone of the embryo contains only indifferent cells and ovocytes, the germinal focus of the young also produces some connective tissue, and the peripheral proliferation of the adult forms a considerable amount of interstitium as well as follicles. As previously pointed out by Swezy, the peripheral growth and luteinization of interstitium is especially marked during pregnancy.

2. *Experimental rats*

The secondary sex organs are masculinized in varying degree after the injection of male hormone or different gonadotropic materials (Bradbury and Gaensbauer, '39). Injections of sex hormones or gonadotropic preparations inhibit the transformation of follicles into corpora lutea and increase the activity of the germinal focus in the ovary. Otherwise the two kinds of hormones exert an opposite influence. In the ovaries of rats injected with gonadotropic substances the number of Graafian follicles is reduced and early growth stages of follicles are very rare. The larger follicles have a prominent theca and after the third week of life the interstitium also becomes abundant. Estrogen or androgen treatment produces minute ovaries consisting mainly of follicles of all stages while the theca and interstitium are atrophic. Many follicles show signs of degeneration. Disintegration of the cumulus and cleavage of the ovum is fairly frequent under the influence of chorionic hormone but much more prevalent in animals treated with sex hormones. After the injection of chorionic hormone, primary follicles in some cases spread from the germinal focus over the ovarian surface and downward along the ligament (see Marx and Bradbury, '40, fig. 7). However, most of the treated rats show only an unusually large amount of neogenic tissue beneath or beside the ovarian cleft. There is also premature proliferation of interstitium from the periphery which consists of epithelial rather than luteinized cells. After the ovary has matured in spite of the treatment, the focus of proliferation is reduced as in controls after puberty.

Mitoses are rarely seen in the germinal epithelium of animals injected with pregnancy urine or anterior pituitary preparations. However, extract of pregnant mare serum definitely provokes indirect cell division in the germinal epithelium and this effect persists after the injections have been discontinued. Since the germinal epithelium in rats injected with chorionic hormone is usually free of mitoses, growth of ovarian tissue from the adjacent organs was suspected and enlarged nuclei in the stroma and epithelia outside, especially in the fimbria, were compared to ovocytes. But as the specific synaptic stages have ceased to occur, no decision could be reached. Ectopic follicles near one of the ovaries stimulated by mare serum extract are most suggestive of ovogenesis outside of the ovary. This ovary (fig. 3) is hypertrophic and contains numerous follicles in all stages; the different components of the cortex contain many mitotic figures. A portion of the serosa on the oviduct inside the capsule and the adjacent capsule lining is packed with primordial follicles (fig. 7). Figure 8 shows a section through the capsule at the margin of this region.

Tubes growing down from the germinal focus are prominent in rats treated with gonadotropic preparations and are lined by an epithelium with the same vesicular nuclei as in the germinal epithelium bordering on the invagination. The membrane between neighboring cells and toward the lumen is well marked. In older rats the clear cytoplasm makes a further contrast between the tubes and granulosa epithelium. In a strand of germinal tissue of a 44 day old rat (fig. 9) tubular parts and a primary follicle are both plainly visible.

The ovaries of sex-hormone-injected rats possess the greatest amount of neogenic tissue. The disproportion between neogenic tissue and rest of the cortex is enhanced by the small size of the ovary. The neogenic cortex encloses numerous primary follicles surrounded by indifferent cells. Fimbria and serosa of the oviduct have broad insertions over the mass of neogenic tissue, a portion of which is shown in figure 6. The neogenic area may protrude from the ovary, as in figure 5. There are no mitoses in the germinal epithelium and only few in the fimbria.

The two rats injected with testosterone developed strong apical tubules (fig. 4). Such tubes are still prominent long after discontinuation of the injections with gonadotropic preparations or male hormone. (That the ovary does not recover from early treatment is apparent from its follicular or cystic structure and the induction of permanent estrus.) One of the rats formerly injected with testosterone has ectopic follicles. They occupy the same location but are less well differentiated than in the mare-serum-treated rat mentioned above. The follicle bearing serosa of the oviduct is connected with the germinal epithelium by a portion of transformed serosa of the suspensory ligament.

DISCUSSION

According to Allen and others, mitoses and young follicles appear in the germinal epithelium of adult rats and mice during estrus, while the germinal epithelium is inactive during diestrus. It is therefore not surprising that in the present study no mitoses were seen in the germinal epithelium of untreated infantile animals. The addition of any new cortical tissue must be from an incorporation of elements from outside into the ovary. This process is reported to occur along the white line in the serosa of the ovarian stalk. In our material an apical germinal focus is far more active than the base of the ovary. The moderate number of mitotic divisions in the connective tissue around the ovary and the intense proliferation in the fimbria parallels the ovogenic activity of the base and apex of the ovary. Because of its location and activity, the fimbria was at first considered as a source for new ovarian cortex. However, the low mitotic rate of the fimbria in sex-hormone-injected rats which have the greatest amount of young apical tissue makes this assumption unlikely. The literature on ovarian embryology and regeneration suggests rather that Müller's duct (among other organs) has inductor properties. Nagel's observation is especially interesting with respect to the fetal and postnatal apical proliferation of the ovary. The ovarian expansion along the white line as well as the occasional development of primary follicles on capsule and suspensory ligament indicate that the serosa has the prospective potentiality to form a gonad and germ cells.

The reports on ovarian regeneration were met with scepticism; but the affirmative data would conform well to the inductor concept. In mice the incidence of regeneration is only 5–17% where the capsule and oviduct was removed at the time of castration but as high as 75%, where only the ovaries were excised (Davenport, '25; Parkes, Fielding and Brambell, '27; Haterius, '27). Parkes, Fielding and Brambell describe the new ovarian tissue as closely related with cystic remnants of the tube and often connected with it by rete cords. Davenport finds the young ovary usually in the old site, near the anterior end of the tube; but there were a few instances in which a new oviduct had grown out in a straight line and the regenerated ovary lay near the uterine end. Butcher twice observes regeneration in rats at the end of the oviduct, but there are only few cases of ovarian regeneration recorded from rats (Heys, '31). It has been assumed that ovarian remnants are responsible for the cases of regeneration, but the possibility of an inductor function of the fimbria remains to be considered along with the surgical possibility of complete castration when the tube and capsule are spared.

The experimental material shows that hormone injections impede the development of the ovary. Whenever the tissue could not differentiate, the proliferation of indifferent material was enhanced. While in normal ovaries embryological growth processes go on until puberty, this proliferation is increased in experimental animals and continues for a longer time. It is probable that such an antagonism between growth and differentiation already exists in the embryo and causes the subsequent proliferations, the medullary cords, Pflüger's tubes and definite cortex which have been reported in higher mammals. In rats and mice the intrauterine growth of the ovary continues smoothly. Brambell records the steady development before puberty to be interrupted by only two breakdown periods, one caused by birth and the other by weaning. There is no reason to assume that the products of early proliferations have a different potentiality from later ones. The ovary grows centripetally, and the ovocytes which still occupy the functional zone when puberty supervenes become definite ova. The male or female character of the germinal elements does not seem to depend on local influences; for ovocytes can arise deep in the medullary cords and the late postnatal proliferation—especially in masculinized females—furnishes long tubes which grow inward toward the rete as well as numerous indifferent cells and ovocytes. Normal development and experimental results alike lead to the opinion that the germinal tissue has a wide potentiality and that its development is determined by outside influences. Dantchakoff ('36 b, c, d) ascribes to estrin the capacity to induce follicles (in bird gonads). This may help to explain the development of ectopic follicles in rats during injections of pregnant mare serum extract or following the treatment with male hormone. The supression of meiosis in postnatal ovogenesis likewise may be caused by hormones; but there remains the problem of how such ovocytes reduce their chromatin.

SUMMARY

In the infantile rat ovary, primary follicles are crowded together in a germinal focus at the apex near the entrance of the suspensory ligament and the insertion of the fimbria. The

germinal epithelium is free of mitotic cells, while they are numerous in the fimbria. The parenchyma is continuously renewed by young elements from the focus. Its close anatomical association with the extra-ovarian serosa suggests that the focal tissue originates on the serosa. After the first days of life, newly-formed ovocytes do not undergo synapsis. The young cortex often encloses vestigial seminiferous tubules, especially in prepuberal females.

The genital tract of rats injected with gonadotropic preparations exhibits signs of masculinization. The ovary of such animals consists largely of theca and interstitium. There is an excessive number of primary follicles, while later stages are scarce. Tubuli are more prominent than in controls. Mare serum gonadotropin is peculiar in that it induces excessive ovarian hypertrophy, a considerable number of mitoses in the germinal epithelium and in one case a layer of primordial follicles on oviduct and capsule.

During the injection of sex hormones the theca and interstitium are inhibited and the ovaries small. Follicles of all stages are numerous and the mass of primary follicles the greatest encountered. Tubules reach a high degree of development under the injection of male hormone.

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PLATE 1

EXPLANATION OF FIGURES

1 Ovary of a 7 day old rat, injected daily with 5 rat units chorionic hormone. The orientation of the section is such that the upper border of the ovary is in the intracapsular space and the lower portion is attached to the broad ligament. At the upper central part of the ovary, the distal part of the oviduct fills the depression. Serosa of oviduct and germinal epithelium are in contact. Below the oviduct the ovary is constricted and the section passes through connective tissue. At the lower left the ovary is connected with the epoophoron and (not as well visible) at the lower right is the entrance of the main vessels. Magnification × 40.

2 Germinal focus of an untreated, 31 day old rat. Upward is the depression and in it part of the fimbria; farther above the oviduct. Germinal tubules run diagonally from the upper left as continuation of the suspensory ligament (not seen in this section). The tubules are unusually well developed in this individual. Neighboring sections are filled with primary follicles. Magnification × 120.

3 Ovary of a 23 day old rat, injected daily from the sixth day with ½ unit of pregnant mare serum extract. Upward oviduct, downward rete. (Hilus vessels not seen.) Most of the parenchyma is hypertrophic theca. Magnification × 14.8.

4 Germinal focus of a 29 day old rat, treated from the eighth day with 0.32 mg. testosterone acetate on alternate days. From the suspensory ligament at the upper right (not seen) comes the fimbria and germinal tubules. They are wide, with well-marked cell membranes. Farther left and below there are numerous primordial follicles. Magnification × 120.


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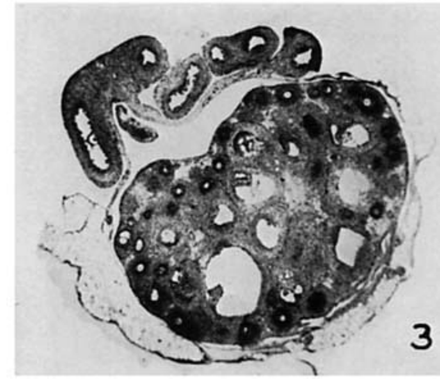
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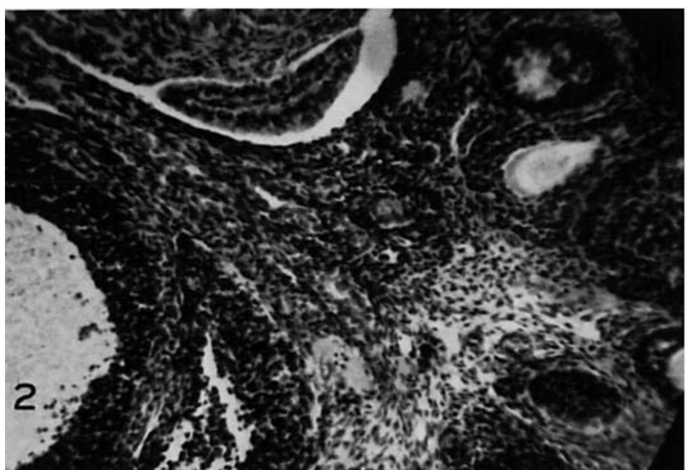
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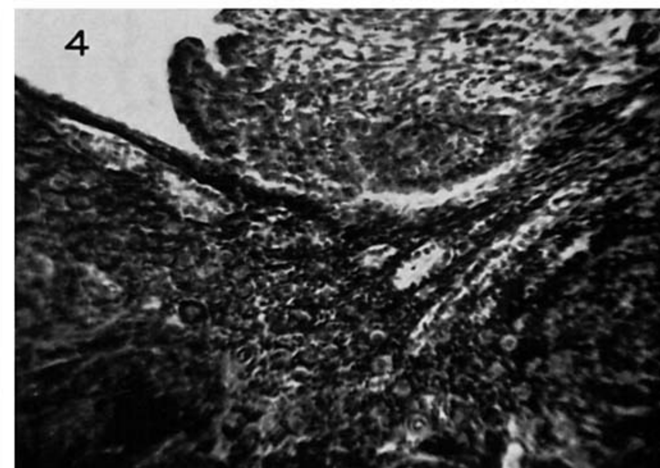
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PLATE 2

EXPLANATION OF FIGURES

5 Another section of the ovary shown in figure 4. The extension of the ovary is neogenic tissue. Its nearness to the fimbria and capsule is clearly shown. Magnification × 66.

6 Insertion of the fimbria in a 29 day old rat, injected from the eighth day with 100 international units estrone on alternate days. The delicate tissue between fimbria and ovary is torn, but stroma and capillaries from the fimbria are seen to enter the ovary. The ovary in this region is filled with primary follicles. Magnification × 440.

7 Oviduct after penetration of ovarian capsule of section shown on figure 3. The serosa of capsule and oviduct has formed ovocytes and follicle cells. Magnification × 280.

8 Capsule of the ovary shown in figure 3. The inner capsular epithelium has differentiated into primordial follicles. Magnification × 440.

9 Periphery of the ovary of 44 day old rat, injected daily from the sixth to the thirty-sixth day with 2 rat units of chorionic hormone. A strand of germinal tissue has formed a primordial follicle and tubules. Magnification × 440.


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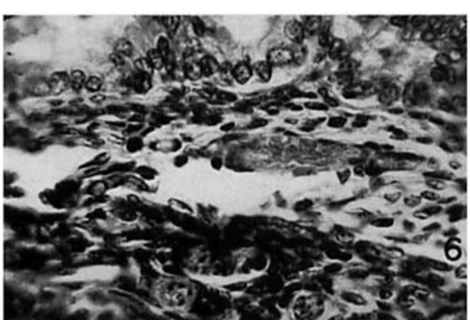
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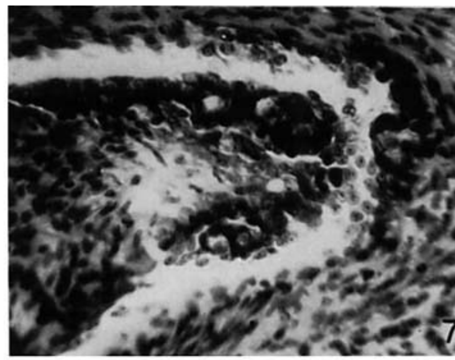
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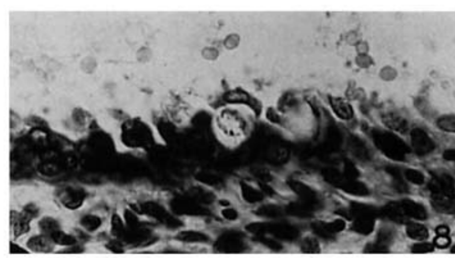
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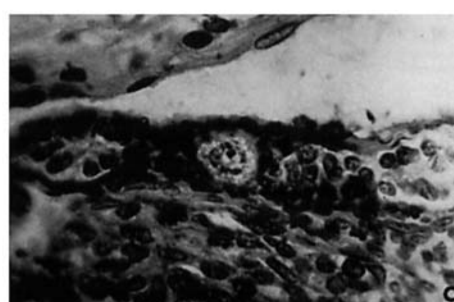
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