Surface Epithelium of the Developing Ovary

Possible Correlation With Ovarian Neoplasia

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The surface epithelium of the fetal ovary undergoes diffuse proliferation during the fourth and fifth months of gestation, after which it reverts to a single layer separated from the developing cortex by a tunica albuginea. The proliferation is associated with marked nuclear irregularity and pleomorphism similar to that seen in surface epithelial neoplasms. The epithelial changes occur during the same time period that interstitial cells with ultrastructural and histochemical properties of steriod-secreting tissue appear in the ovarian stroma. The possible role of steroid hormones in stimulating surface epithelial proliferation is discussed. (Am J Pathol 81:303–320, 1975)

TUMORS OF THE SURFACE EPITHELIUM account for 80 to 88% of ovarian neoplasms.[1,2] These include the common epithelial tumors of serous, mucinous, and endometrioid type, the clear cell ("mesonephric") tumors, the Brenner tumor, and the less common solid adenocarcinomas, carcinosarcomas, and malignant mixed müllerian tumors.[3] While this is by far the most common group of ovarian tumors, it is the least well understood in terms of pathogenesis and the least amenable to experimental study. Granulosa cell tumors and luteomas have been produced by a variety of experimental methods, including chemical induction, irradiation, and intrasplenic transplantation,[4] and represent the most frequent form of ovarian cancer occurring in animals.[5] Germ cell tumors have been examined in animal models [6] and cytogenetic studies,[7] and exhibit distinctive microscopic features indicative of their origin and development.[8] In contrast, epithelial cell tumors are not associated with special endocrine or cytogenetic abnormalities, occur rarely in animals, and do not appear in response to the various forms of experimental carcinogenesis. The variety of neoplastic patterns that can be derived from the surface epithelium has thus far defied experimental study and pathogenetic analysis. Since the pathologist is increasingly being called upon to make a specific histologic classification and prognostic evaluation in this diverse group of tumors, more precise information about the development and behavior of these tumors is needed.

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An approach to the problem of surface epithelial neoplasms occurred to us in the course of studies on the ultrastructural development of the human fetal ovary. While examining the role of the surface epithelium in the development of germ cells and granulosa cells, we became impressed by the marked proliferative capacity of the epithelium during the early gestational period. Previous studies of the human fetal ovary, using light microscopy, had also described developmental changes in the surface epithelium.[9,10] With the additional use of electron microscopy in animal studies, the proliferative changes were found to be associated with severe nuclear irregularity and pleomorphism.[11,12] Similarity of the cellular changes in both the animal and human ovaries to those accompanying neoplasia in the adult prompted us to perform a detailed fine structural analysis of the development of the surface epithelium in the human fetal ovary and to compare the findings with previous electron microscopic observations on tumors of the surface epithelium.[13-18] The present report describes the electron microscopic observations and also considers possible mechanisms responsible for the proliferative changes.

Materials and Methods

Specimens were obtained following therapeutic abortion by hysterotomy or by prostaglandin induction. Gonadal tissue was dissected from the aborted fetus and processed for electron microscopic study. Fixation was accomplished by direct immersion in 1% ice-cold buffered osmium tetroxide for 1 hour[19] or by immersion in 2.5% glutaraldehyde in 0.1 M sodium cacodylate at pH 7.4 for 3 to 4 hours[20] followed by postfixation in osmium tetroxide. All specimens were dehydrated in graded alcohols, embedded in Araldite, and sectioned with an LKB II or Porter Blum MT-2B ultramicrotome. After staining with uranyl acetate[21] and lead citrate,[22] sections were examined with a Hitachi HU11C or Siemens Ia electron microscope. Sections for light microscopy were stained with toluidine blue and photographed with a Zeiss Ultraphot II microscope.

Altogether, 42 ovarian specimens were examined. Age of the fetus was calculated from the crown-rump and crown-heel length. Numbers of specimens obtained at various stages of development, as defined by fetal age and appearance and arrangement of germ cells, are shown in Table 1. Up to 12 weeks, the crown-rump measurement was used as the more accurate indicator of fetal age, while after 12 weeks the crown-heel length is considered more reliable.[23] The stage of ovarian development could be consistently correlated with

Table 1—Ovarian Specimens Examined at Different Stages of Development

Stage of Development	Fetal length (cm)	Age (wk)	Number of specimens
Primitive germ cells	2–4 (CR)	7–9	3
Oogonial multiplication	4–8 (CR)	9–12	7
Sex cords, onset of meiosis	12–18 (CH)	12–16	18
Meiosis, extensive degeneration	18–26 (CH)	16–20	14
Primary follicles	26+ (CH)	20–38	—

CR = crown-rump, CH = crown-heel.

fetal age, as indicated by previous studies of the human fetal ovary using light [24] and electron microscopy [25] The specimens examined include the period from early ovarian differentiation up to the time of beginning follicle formation. No specimens from fetuses more than 20 weeks of age were used in this study.

Results

Light Microscopy

At 7 to 9 weeks, the ovarian cortex consisted of confluent sheets of primitive germ cells and pregranulosa cells without apparent organization (Figure 1). The surface epithelium was distinguished only by its columnar arrangement; a tunica albuginea was not present, and consequently there was no distinct separation between the epithelium and the underlying cortical elements. The surface cells were generally oriented vertically with uniform-appearing, regular oval nuclei. In areas where germ cells were present within the epithelium, the epithelial cells bent around them, somewhat distorting the otherwise regular arrangement.

At 9 to 12 weeks, there was still no clear indication of cellular organization in the cortex; however, a basement membrane underlying the surface epithelium had begun to appear (Figure 2). At this stage, it could be seen that the surface layer was generally of single cell thickness, with occasionally a double layer. There was still no tunica albuginea, and the separation of the surface epithelium from the cortex was patchy, with large areas of direct confluence remaining. A few stromal connective tissue elements were present within the cortex. The epithelial cells remained vertically oriented, and the nuclei were regular in appearance as previously. Mitotic figures were frequently seen.

At 12 to 16 weeks, definite organization of the cortex into sex cords resulted from the ingrowth of connective tissue and blood vessels, and there was a clear separation of the surface epithelium from the cortical cords, although this separation was incomplete (Figure 3). Several layers of epithelial cells were present, generally no more than three or four. The outer cells retained a regular, columnar appearance, with some loss of polarity and irregularity evident in the basal layers. Most of the germ cells in the lower cortex had entered meiosis and were in close association with adjacent pregranulosa cells. Zones of confluence of variable size and distribution between the surface epithelium and the cortical cell groups provided free cellular continuity between the surface epithelium and underlying areas.

At 16 to 20 weeks, marked proliferation of the surface epithelium together with increasing development of the tunica albuginea resulted in the formation of a clearly distinguished thick surface epithelium in which multiple cell layers were present (Figure 4). Areas of bridging between

the surface and the cortex were still present, but they were smaller and much fewer in number than previously. Some germ cells were found within the deeper layers of the surface epithelium. There was diffuse thickening of the epithelium in a fairly uniform manner, but occasionally with irregular papillary projections, as shown in Figure 4. The cellular arrangement was jumbled, with many different directions of orientation evident (Figure 5). Nuclear infolding, pleomorphism, and nucleolar prominence were visible, even at low magnification, but at higher magnification these changes were quite striking (Figure 6). Bizarre nuclear shapes, deep indentations, and irregular coarse clumping of chromatin were evident.

Electron Microscopy

Findings by electron microscopy confirmed and extended the above observations. Prior to 12 weeks, the epithelial cells had regular nuclei with smooth borders, small nucleoli, and evenly distributed chromatin (Figure 7). Cytoplasm was well stocked with organelles, including numerous ribosomes, branching elongated mitochondria with transverse cristae, occasional strands of rough endoplasmic reticulum, a supranuclear Golgi area, and rare lipid droplets. Cell surfaces were also well developed, with many randomly distributed short, blunt microvilli, rare cilia, and consistently present terminal tight junctions. Desmosomal attachments were frequently present (Figure 8A), as were occasional broad intercellular spaces. The formation of a basement membrane after 9 weeks, as suggested by light microscopy, resulted from deposition of a thin basal lamina directly beneath the base of the epithelium and underneath this some bands of collagen (Figure 8B). A basal lamina also overlay the outer surface of the cortical cell groups.

Between 12 to 16 weeks, slight nuclear changes were noted in the epithelial cells. Chromatin was distributed in irregular coarse aggregates, centrally as well as peripherally (Figure 9), and nucleoli were prominent (Figure 10). Generally, nuclei retained their regular oval shape and columnar arrangement, although there was some distortion at the base of the epithelium. In areas where germ cells were present, the epithelial cells curved around them producing variations in nuclear contour (Figure 11). Cytoplasmic organization was similar to that seen previously, except for a slight increase in amount of lipid and rough endoplasmic reticulum (Figure 9). Also noted were prominent intercellular lacunae lined by numerous microvilli (Figure 9). The lacunae were most conspicuous in areas of several cells' thickness. The appearance and distribution of sur-

face microvilli, cilia, and terminal tight junctions were unchanged. The developing tunica albuginea included fibroblasts and fairly abundant collagen (Figure 11).

During the 16- to 20-week period, the nuclei of the epithelial cells showed marked distortion, characterized by bizarre convolution, irregular infolding, deep grooves, and pseudolobulation (Figure 12). In some cases the irregularity was so severe that it gave an appearance of nuclear cavitation (Figure 13). Irregular chromatin distribution was evident, as was a general loss of polarity within the epithelium (Figure 14). Cytoplasmic and cell membrane features were similar to previous stages, although occasionally there was a rather extensive development of microvilli, and desmosomal attachments were fewer in number. The tunica albuginea was filled with fibroblasts, capillaries, and abundant collagen.

Discussion

Proliferative changes in the fetal surface epithelium result in cellular stratification, loss of polarity, nuclear pleomorphism, nuclear irregularity, coarse aggregation of chromatin, and nucleolar prominence during the fourth and fifth months of gestation. The present study was limited to the initial 20-week period. A previous ultrastructural investigation of the adult surface epithelium (including observations on later stages of fetal development) indicated that by 24 weeks' gestation the epithelium is reduced to a single layer similar in appearance to the surface epithelium of the adult ovary.[26] Thus, just as in the rabbit [11] and hamster,[12] the period of epithelial proliferation is restricted to the stage of ovarian development prior to follicle formation.

The marked proliferation and associated nuclear changes in the fetal ovary produce a picture closely resembling that seen in surface epithelial neoplasms (Table 2). By electron microscopy, there are distinct similarities in cellular arrangement and appearance in the fetal epithelium and serous cystadenocarcinoma.[13,14] The presence of multiple jumbled layers of columnar cells containing large irregular nuclei and prominent nucleoli and lined by short blunt surface microvilli is characteristic of both the fetal ovary and papillary serous tumors. Similar nuclear features are seen in clear cell carcinoma,[16] where there is also prominence of blunt microvilli and terminal tight junctions and abundance of rough endoplasmic reticulum and ribosomes; a notable difference is the presence of large aggregates of glycogen granules in the clear cells, not seen in the fetal tissue. Projection of microvilli into intercellular lacunae, such as described here, is characteristic of Brenner tumors and mucinous neo-

Table 2—Comparison of Fetal, Adult, and Neoplastic Surface Epithelium

	Fetus (12–20 wks)	Adult[15,26]	Neoplasms[13–18]
General appearance	Diffuse thickening, with multiple cell layers, jumbling, loss of polarity, occasional papillary formations	Single layer of low cuboidal cells	Multiple cell layers, frequent papillary formations, jumbling, loss of polarity; other features depend on type of tumor
Nuclei	Severely irregular infolding, high N/C ratio, pleomorphism, prominent nucleoli	Uniform small size, moderate infolding, small nucleoli	Severely irregular infolding, high N/C ratio, pleomorphism, prominent nucleoli
Cytoplasm	Numerous ribosomes, elongated mitochondria, abundant rough endoplasmic reticulum, occasional lipid	Scattered ribosomes, elongated mitochondria, occasional rough endoplasmic reticulum, rare lipid	Numerous ribosomes, elongated mitochondria, abundant rough endoplasmic reticulum, occas. lipid; glycogen (clear cell); mucus (mucinous); secretory granules (serous)
Cell membranes	Short, blunt microvilli, prominent terminal bars, wide intercellular spaces with intralacunar cytoplasmic projections, few desmosomes	Numerous, often branching microvilli, terminal bars, prominent desmosomes, generally close apposition of adjacent cells	Short, blunt microvilli, terminal bars, decreased desmosomes, widened intercellular spaces with occas. intralacunar cytoplasmic projections

plasms of the ovary.[15,17,18] It appears, therefore, that in many respects the differentiation of fetal surface epithelium and surface epithelial neoplasms involve similar morphologic changes.

The latter observation is not in itself particularly useful, since there are obviously fundamental differences between a normal self-limited developmental process and an abnormal uncontrolled neoplastic process. The changes described most likely reflect cellular activity associated with growth and proliferation, and the fact that certain similarities exist between differentiation and cancer has been well recognized.[27] However, occurrence of the proliferation of the fetal epithelium during a well-defined time period provides an opportunity to consider possible regulatory mechanisms.

What particular influences might be acting on the fetal ovary during the 12- to 20-week period? The first inclination is to implicate chorionic gonadotropin, as has been done in the case of Leydig cell differentiation in the testis.[28] Leydig cells undergo extensive proliferation beginning at 8 weeks' gestation,[29] just when HCG reaches its peak level.[30] While this is

strong evidence supporting the influence of chorionic gonadotropin on Leydig cell development, the fact that the testicular surface epithelium does not undergo proliferation during this time, but remains a single layer of inactive cells,[31] indicates that HCG does not promote epithelial development.

In fact, the sharp divergence in growth patterns of the surface epithelium of the ovary and testis suggests an alternate hypothesis. At the time of gonadal sex differentiation, early separation of the surface epithelium from the underlying sex cords by a tunica albuginea is characteristic of the testis, while in the ovary there is no such separation. Parenchymal elements are in close association with the surface epithelium in the ovary, but not in the testis. Thus, it is possible that some substance present within the gonadal parenchyma might be responsible for inducing epithelial proliferation in the ovary, while in the testis the tunica albuginea provides a barrier. Proliferation in the ovary is, however, terminated when the tunica albuginea has become well formed, separating the epithelium from the underlying cortex.

Could this substance be a steroid hormone? Contrary to earlier views, it is now known that the fetal ovary is capable of steroid synthesis.[32,33] Such activity has been found in the 4- to 5-month period. Fetal granulosa cells could be the source of such activity since they exhibit histochemical evidence of 3β-hydroxysteroid dehydrogenase activity;[34] however, they lack ultrastructural features associated with steroidogenic activity.[25] Another, more likely source is provided by the interstitial cells which differentiate from stromal cells in the fetal ovary.[35] Interstitial cells with characteristic features of steroid-secreting cells are present in the human ovary between 12 and 20 weeks' gestation.[36] The cells show elaborate development of smooth endoplasmic reticulum and an abundance of large tubular mitochondria during this period. Furthermore, histochemical studies have localized high levels of glycolytic and NADPH-supplying enzymes as well as 3β-hydroxysteroid dehydrogenase in the intersitial cells beginning in the fourth month.[37,38] At the present time the nature of the secretory activity of the fetal ovarian interstitial tissue is not known, nor is there any evidence that the fetal surface epithelium is responsive to steroid hormones.

It is generally considered that the ovarian surface epithelium shares fundamental biologic properties and potentialities with müllerian epithelium,[39-42] and it is therefore relevant that the various types of müllerian epithelium (tubal epithelium, endometrium, endocervix) are normally responsive to steroid hormone stimulation. Definite evidence implicating steroids in the development of malignancy in these sites remains

to be established, but the association of endometrial and endocervical hyperplasia with steroid administration is well known.[43,44] In addition, recent reports have described the occurrence of endometrial cancer in patients with gonadal dysgenesis treated with nonsteroidal estrogens.[45,46] The studies of Forsberg demonstrating that injection of estradiol-17β or diethylstilbestrol in newborn mice results in atypical proliferation of müllerian epithelium in the vagina producing a picture of adenosis,[47,48] and the recent recognition of cases of clear cell adenocarcinoma of the vagina and cervix developing in young women often in association with vaginal adenosis,[49] following maternal stilbestrol administration,[50] suggest that müllerian epithelium may be especially responsive to estrogenic stimulation during early development.

While no conclusions can be drawn from the present study regarding the factors responsible for surface epithelial development in the fetal ovary or in ovarian tumors, the observation that the fetal proliferation occurs at the time that steroid-secreting cells differentiate in the ovarian parenchyma may be significant. Further work is needed on the possible relation of steroid hormones to the proliferation of surface epithelium in the fetal ovary. Such information could be useful in understanding the development of surface epithelial tumors.

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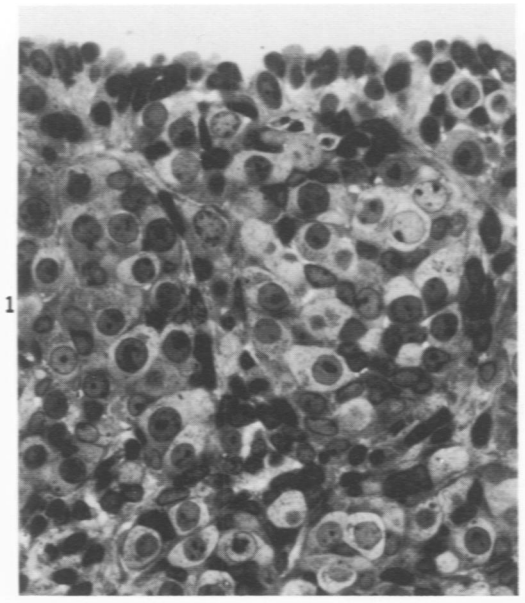

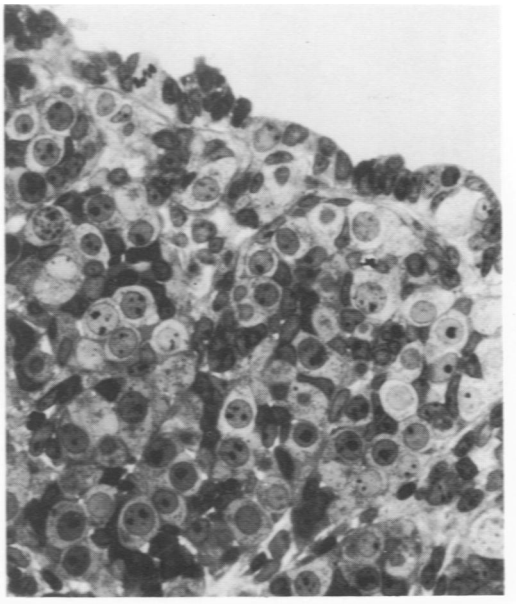

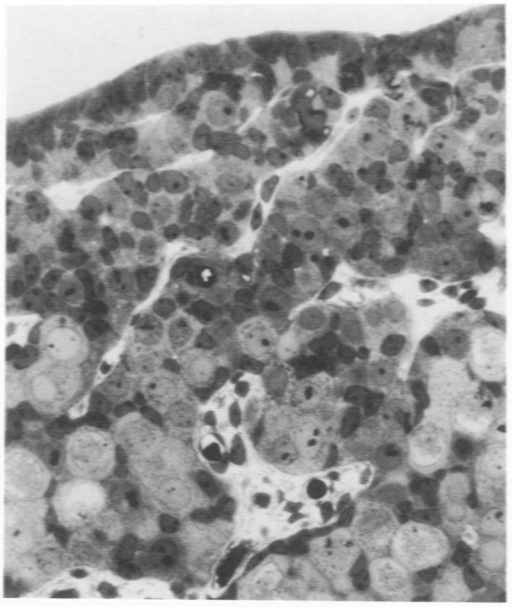

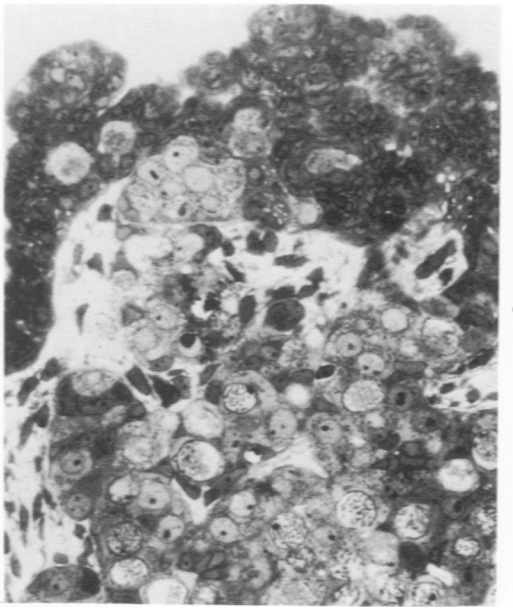

Figures 1-4—General appearance of ovarian cortex and surface epithelium at different stages of development (see Table 1). **1**—Nine weeks. **2**—Ten and one-half weeks. **3**—Sixteen weeks. **4**—Nineteen weeks. (× 250)

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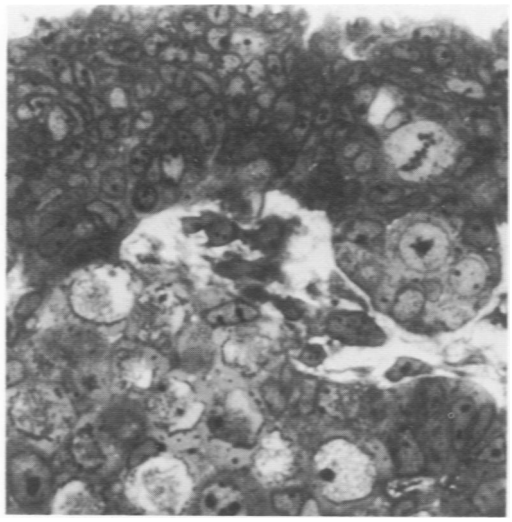

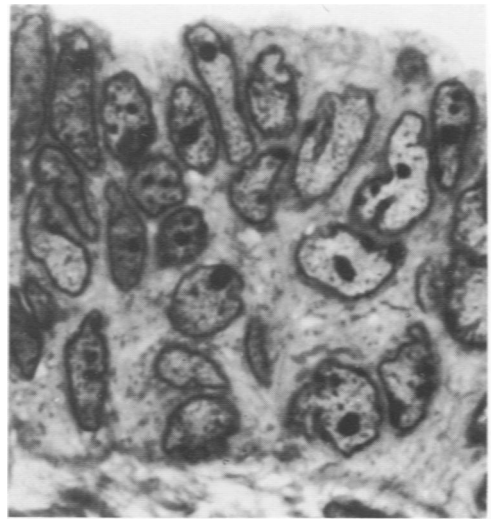

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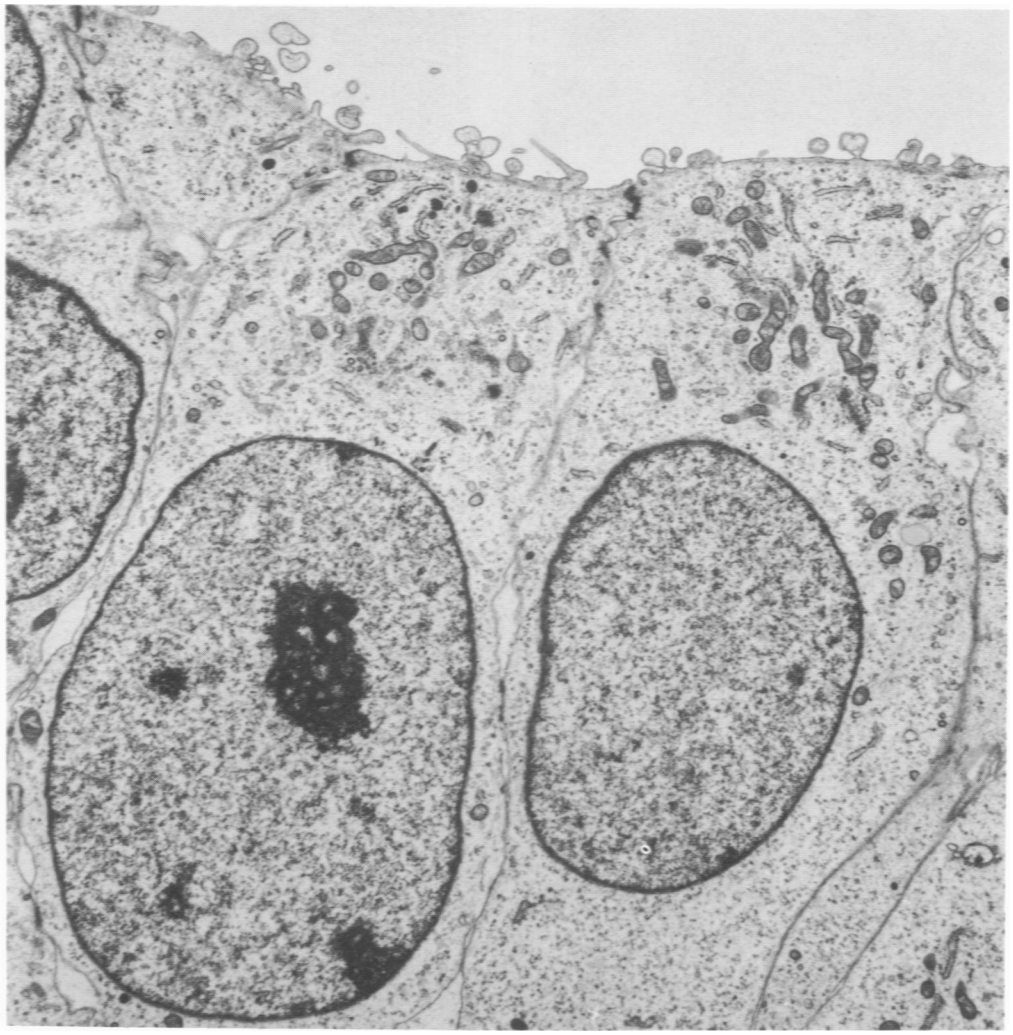

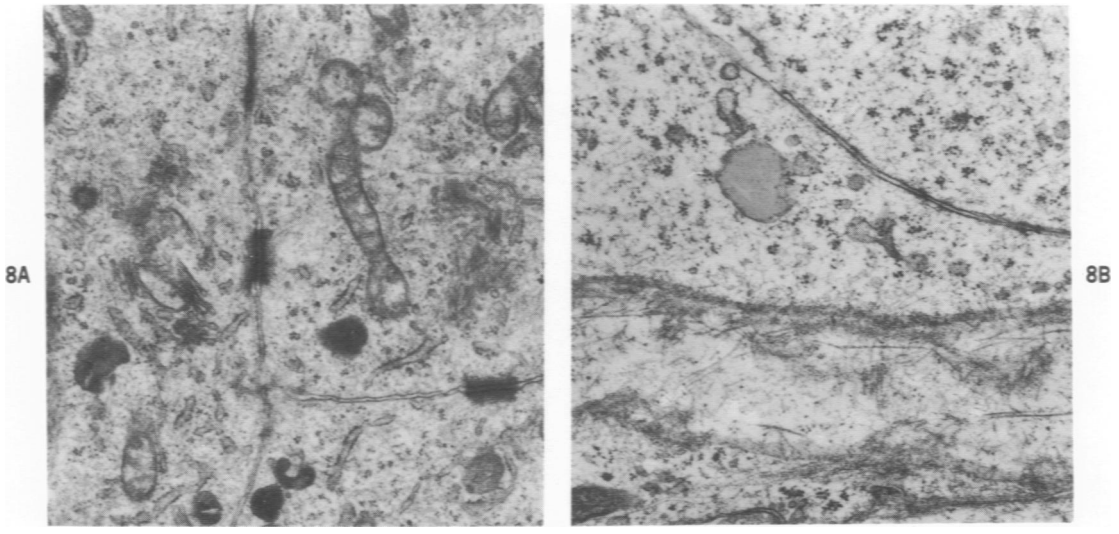

Figure 5—Diffuse thickening of surface epithelium, with jumbling and disorientation, 19 weeks. Tunica albuginea is well developed, but connection can still be seen between surface epithelium and cortical cell groups at left. A few germ cells remain in the surface epithelium. (× 400)

Figure 6—Higher magnification light micrograph of surface epithelial cells at 19 weeks, indicating marked nuclear infolding and pleomorphism (× 1000).

Figure 7—Electron micrograph of surface epithelial cells at 10½ weeks showing columnar arrangement, oval nuclei with smooth borders, elongated mitochondria, and strands of rough endoplasmic reticulum in apical cytoplasm, and scattered short, blunt microvilli (× 10,500).

Figure 8A—Close apposition of adjacent cell membranes with multiple desmosomal attachments, 9 weeks (× 18,000). **B**—Basal lamina and underlying collagen fibers beneath surface epithelial cells, 10½ weeks (× 16,000).

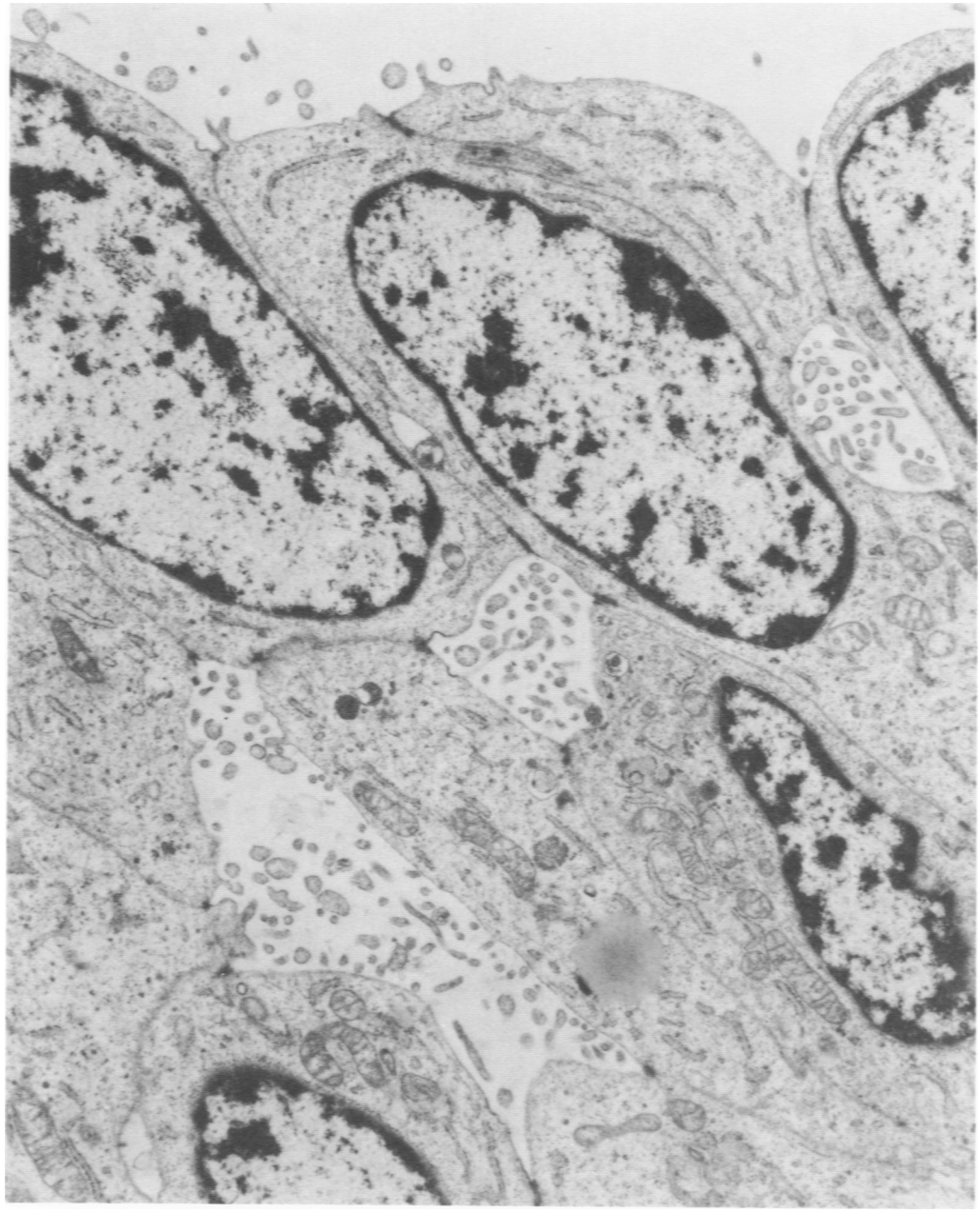

Figure 9—Stratified columnar arrangement, 14 weeks. Nuclei retain regular borders but show irregular distribution of chromatin. Note intercellular lacunae filled with cytoplasmic projections. (× 14,500)

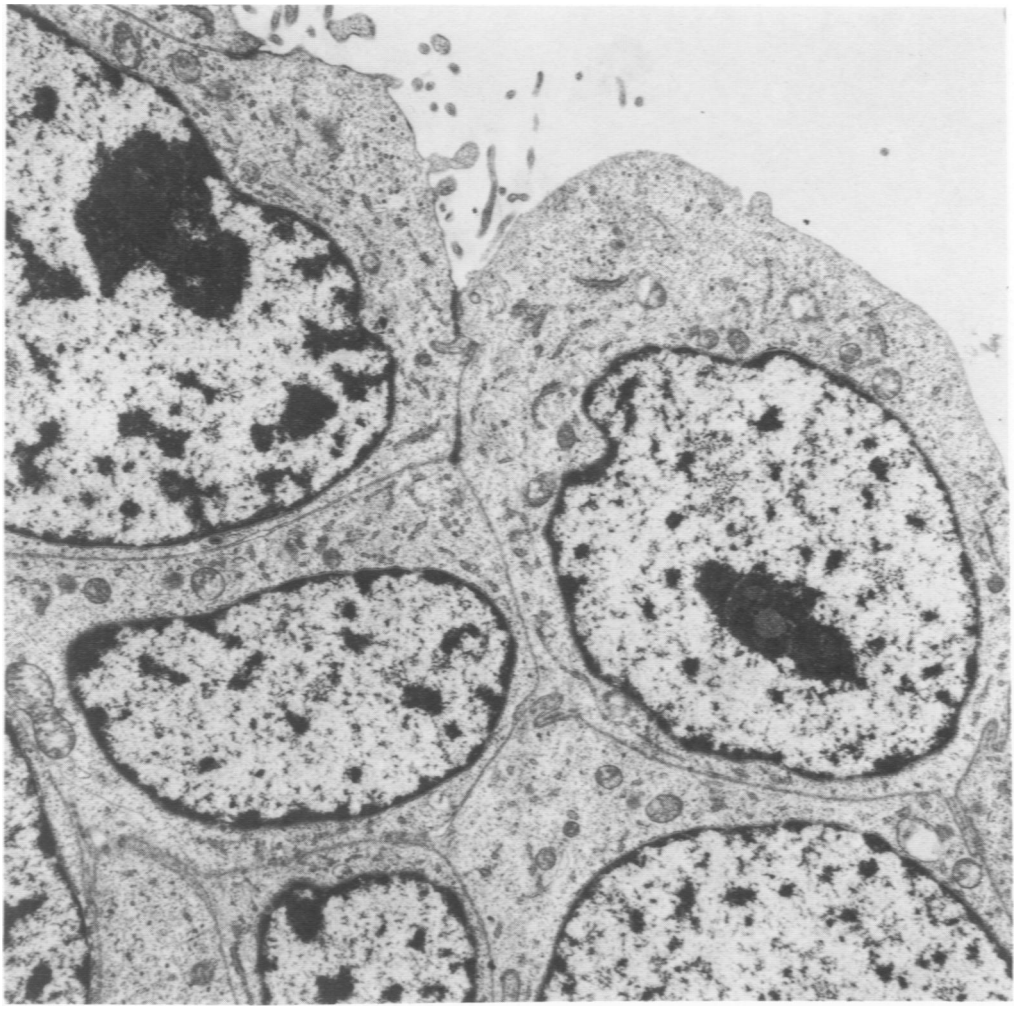

Figure 10—Apical surface at 14 weeks is flattened, with relatively few microvilli present. In contrast with previous electron micrograph, adjacent cell membranes are closely apposed. (× 10,000)

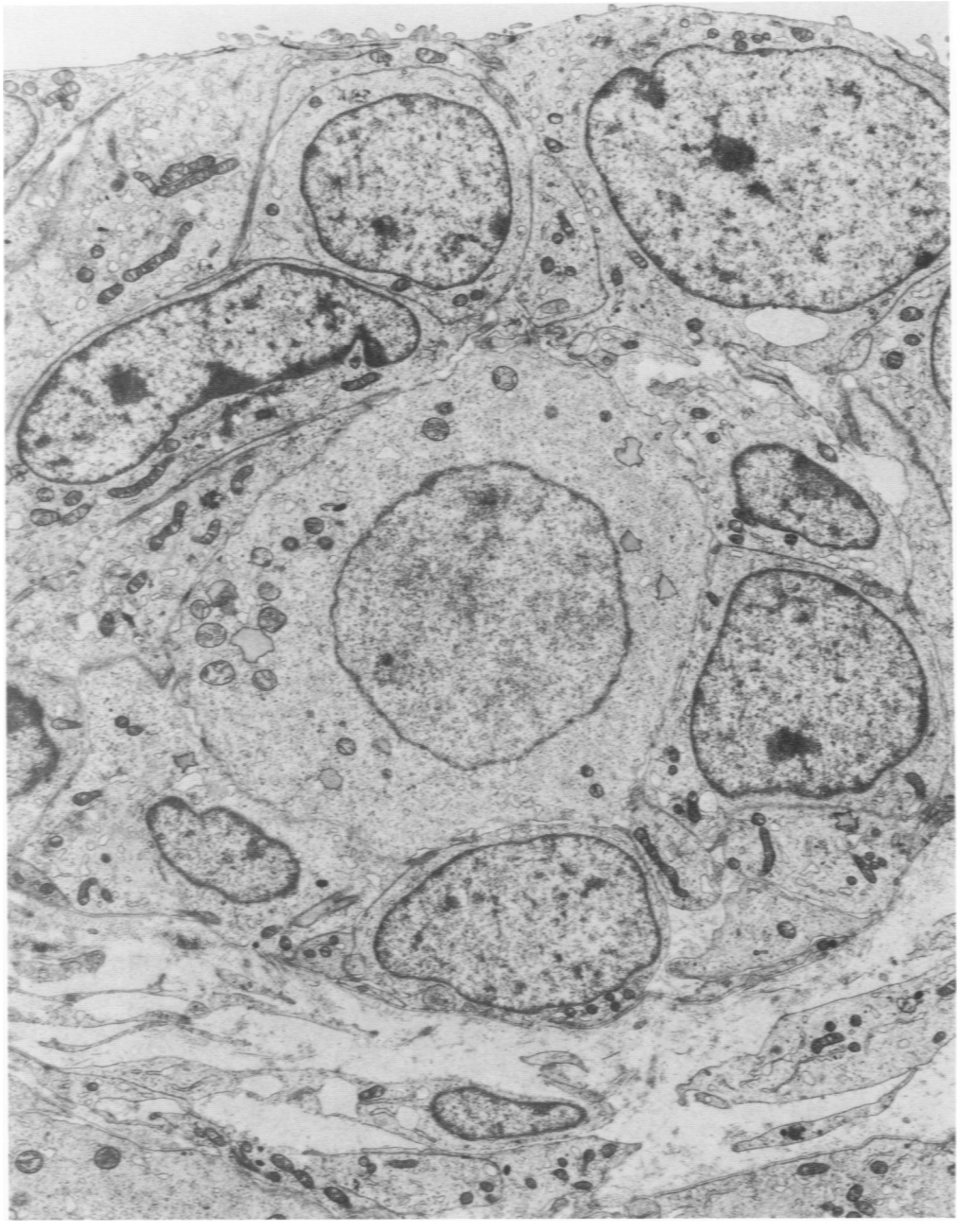

Figure 11—Surface epithelium and developing tunica albuginea at 16 weeks. Note the manner in which epithelial cells bend around the intraepithelial germ cell. (× 5000)

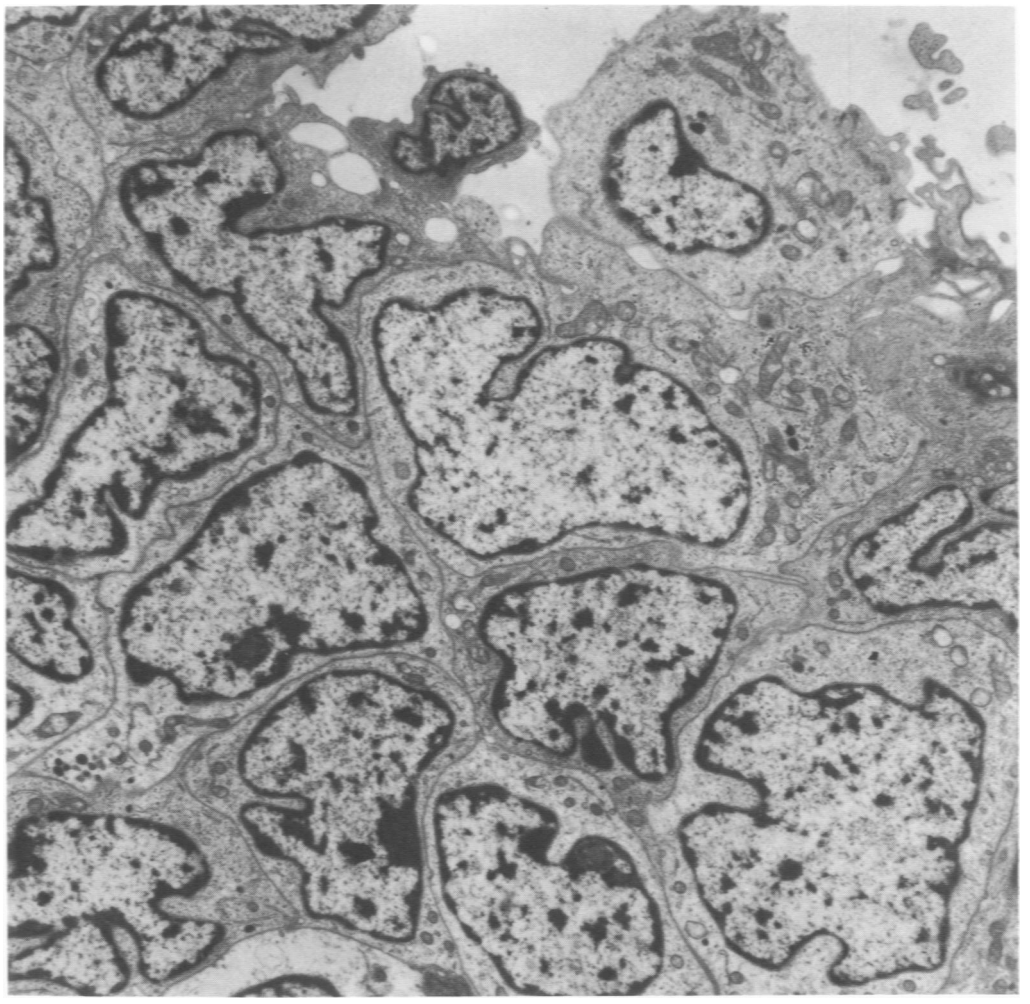

Figure 12—Surface epithelial cells at 19½ weeks, showing severely irregular nuclear infolding, high nucleocytoplasmic ratio and disorderly arrangement. (× 7500)

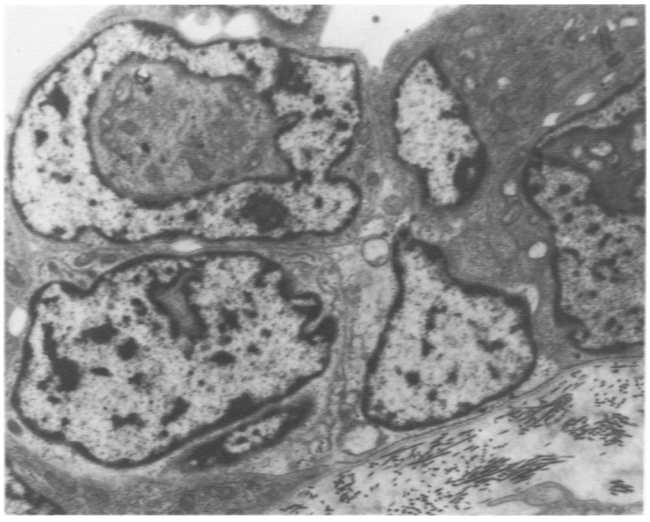

Figure 13—Bizarre nuclear shapes producing pseudocavitation, 19½ weeks (× 7800).

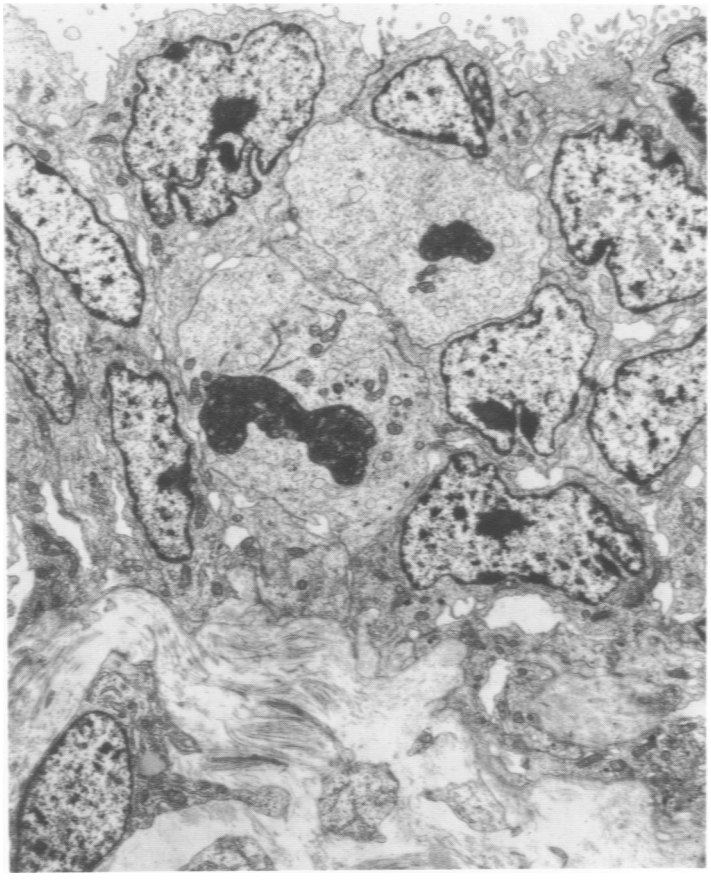

Figure 14—Irregularly shaped epithelial cells, with wide intercellular spaces, 20 weeks. Mitotic figures are present. Dense collagen bands can be seen in tunica albuginea. (× 7500)