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Retrogressive Changes of Dental Lamina Rests in Human Fetal Maxilla

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= Abstract =In order to elucidate the retrogressive changes of dental lamina rest (DLR) in human fetuses, 232 human maxillas were examined histologically. In 227 maxillas prepared for light microscopy, the dental laminas were composed of three portions: the dental lamina ridge, the primary dental lamina, and the secondary dental lamina. All of the dental laminas were separated into numerous small islets, i.e., dental lamina rests (DLRs). DLRs of the dental lamina ridge especially showed heavy keratinization in their center. Almost all of the DLRs from the primary and secondary dental laminas became atrophic and degenerative. While abundant capillary proliferation was observed in the vicinity of the DLRs, occasionally small numbers of inflammatory cells infiltrated around the atrophic DLRs. In five cases prepared for electron-microscopy, the degenerating DLRs showed tonofilaments which were reduced in number and considerably aberrant. The basal laminas of the degenerating epithelial cells were gradually destroyed with the increase of gestational age, and a few inflammatory cells containing a large quantity of lysozome adhered to the DLR to destroy the entire basal lamina directly. In this study we confirmed that the DLRs were resorbed by the processes of both self-degeneration and the cytotoxic reaction of inflammatory cells.

Key Words: ***Prenatal retrogressive change, Dental lamina, Human fetus***

INTRODUCTION

Tooth germ is a specific organ that produces dentin, enamel, and periodontal tissue. It is well known that all odontogenic epithelial cells disappear after completion of tooth formation (Bivin and Mcclure, 1975; Garn and Burdi, 1971; Grant and Bernick, 1971). In contrast to the salivary glands or sweat glands the stalk epithelium of tooth germ is separated into numerous epithelial rests called dental lamina rests (DLRs)(Lee and Lim, 1980; Reeve, 1962). DLRs disappear rapidly during the fetal period. These epithelial rests can also be found in other sites of the body, such as in the stalk epithelia of adenohypophysis and in the thyroid gland. The DLR, which belongs to the odontogenic epithelium, lose to keep contact with the odontogenic mesenchyme in the early developmental period. Many authors indicate the hypothetical role of the DLRs in the pathogenesis of various odontogenic tumors, frequently comparing them with Malassez's epithelial rests (Grant and Bernick, 1971; Pindborg and Hansen, 1963; Ritchey and Orban, 1952; Saunders, 1972). Malassez's epithelial rests from Hertwig's epithelial root sheath, which are highly regarded as causative cells of various odontogenic tumors, are partly similar to the DLRs in that they become atrophic and degenerative in the late developmental period after induction of the dental root.

Therefore it seems essential to understand the biologic behavior of the DLR in normal

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fetuses in order to understand the pathogenesis of various odontogenic tumors. We observed the monthly changes of DLR during the fetal period and described the retrogressive alterations of degenerating odontogenic epithelium.

MATERIALS AND METHODS

A total of 232 human maxillas ranging from 10 weeks to 40 weeks of gestation were used. Of these, 227 maxillas were fixed in 10% neutral formalin and decalcified with 5% nitric acid. After decalcification the maxillas were divided into four to six blocks anteriorly-posteriorly, and the frontal planes for serial sections were marked by India ink. The specimens were embedded in paraffin, sected at 4 μm, and stained routinely with hematoxylin and eosin, period acid Schiff (PAS), van Gieson, and Gomori's reticulin stains were also performed.

Five fetal maxillas were prepared for electron-microscopic examination. Their gestational ages were 20, 26, 30, 33, and 35 weeks. Alveolar ridges, in which the DLRs were distributed, were resected serially and fixed in 5% glutaraldehyde embedded in Epon resin.

In the developmental process we classified the dental lamina into three portions, i.e., the dental lamina ridge which shows a continuous plate in the dental arch. It was formed by initial band-like invagination of the stomodeal epithelium. The second is the primary dental lamina for the deciduous tooth germs, which is formed by continuous invagination from the dental lamina ridge. The third is the secondary dental lamina for the permanent tooth germ, which developed from the lingual branch of the primary dental lamina (Fig. 1). In this study we observed the retrogressive changes of the DLRs in each portion of the dental laminas.

RESULTS

Light Microscopic Observation

1) Fragmentation of dental laminas

All of the epithelial stalk of the dental laminas became atrophic and were divided into numerous small islets — dental lamina rests (DLRs). In the process of epithelial separation, the proliferating fibroblasts lay down abundant thick collagen bundles around the DLRs (Fig. 7). The DLRs, which were surrounded by heavy collagen and reticulin fibers, became ovoid or round-shaped. Usually the DLRs in the deep connective tissue were smaller than the superficial ones. DLRs from the dental lamina ridge showed large epithelial nests consisting of keratinizing epithelial cells in the center (Fig. 2). On the other hand, DLRs from primary and secondary dental lamina were tiny epithelial nests consisting of only a few epithelial cells. Inflammatory cell infiltration were not found around the fracturing area of the dental lamina.

The fragmentation of the dental lamina occurred from 20 weeks of gestation, reaching a maximum in the fetal period from 24 weeks to 27 weeks. During the fetal period from 32 weeks to 40 weeks, the fragmentation was almost complete in the primary dental lamina, but continuous fragmentation of the secondary dental lamina continued until term gestation (Table 1).

2) Keratinization of dental lamina rests

From an early gestational age, the DLRs of the dental lamina ridge usually produced many keratin perals which became round-shaped and of various sizes. The keratinizing DLR showed a relatively definite basement membrane in Gomori's reticulin stain, and some of the DLR which was near the oral mucosa developed into huge keratin pearls. The keratin pearl consisted of well aligned cuboidal-shaped basal cells and an abundant central keratinization, the size of which gradually increased, showing occasional cystic change (Fig. 3). Almost all of the keratin pearls were extruded near the oral epithelium, and all of the keratin materials exfoliated into the oral cavity (Fig. 4).

Keratinization of the DLR could be observed from an early gestational age of 10-15 weeks, increasing gradually. In the fetal period from 32 weeks to 35 weeks maximum, keratinization was observed with numerous huge keratin pearls near the oral epithelium. Finally in the fetal period from 36 weeks to 40 weeks, frequent cystic dilatations of the keratin pearls and successive exfoliation of keratin materials into the oral cavity were observed. There was no inflammatory cell infiltration around the huge keratin pearls. Occasionally, small keratin pearls which remained deeply embedded near the developing tooth germ were destroyed by the active phagocytosis of several macrophages (Fig. 11).

Table 1. Changes of dental lamina rests during fetal period

G.A. (Weeks)	Cases	Fragmentation	Keratinization	Resorption
10-15	29	±	−/±	−
16-19	26	+	±	−
20-23	28	++	+/++	±
24-27	46	+++	++	+
28-31	29	++	++/+++	+/++
32-35	35	+	+++	++
36-40	34	+	++	+++
Total	227			

*G.A.: gestational age
−: negative
±: rare
+: mild
++: moderate
+++: severe

3) Resorption

Usually, the DLRs from primary and secondary dental laminas became shrunken and were generally degenerative. The epithelial cells of the DLRs largely lost their cellular polarity, the amount of cytoplasm was remarkably reduced (Fig. 5, 6), and the basement membrane of the DLR was irregularly thin in the PAS and Gomori's reticulin stain (Fig. 9. 10). Mostly the DLRs were resorbed by the processes of both self-atrophic degeneration and active inflammatory reaction. First, the capillary proliferation around the resorbing DLR was prominent in the vicinity of the degenerative DLRs (Fig. 8). Second, mild infiltration of inflammatory cells could be found occasionally around the resorbing DLRs (Fig. 12). The resorption, characterized by the presence of degenerative epithelial islets and the infiltration of some inflammatory cells, could be observed easily from about 32 weeks of gestation. Thereafter almost all of the DLRs from primary and secondary dental laminas were resorbed. But in term gestation there remained only a few DLRs in the deep connective tissue, and some of them showed conspicuous basement membrane in PAS and Gomori's reticulin stains (Table 2).

Electron-microscopic Observation

Atrophic DLRs were characterized by frequent

Table 2. Epithelial rests remained in alveolar tissue

G.A.	Cases	Dental Lamina Ridge	Primary Dental Lamina	Secondary Dental Lamina
10-15	29	+	±	−
16-19	26	++	+	−
20-23	28	++/+++	++	−
24-27	46	+++	+++	±
28-31	29	+++	++	+
32-35	35	++	+	+/++
36-40	34	+/++	±	++
Total	227			

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vacuolization and a decrease and derangement of the tonofilaments. Papillary cytoplasmic projections of the basal cells of the DLRs largely disappeared. In the keratinizing DLR the basal cells showed definite basal lamina and contained well-developed cytoplasmic organelles. The ultrastructure of the cytokeratin in the center of the keratinizing DLR was of a fine granular pattern without keratohyalin granules.

The DLRs were resorbed by the processes of both self-degeneration and cytotoxic reactions of the inflammatory cells. In the resorbing DLR, the amount of tonofilaments decreased, while no tonofilaments were observed inserting into the desmosomes, which were also reduced in number. Only a small amount of tonofilament could be found in the perinuclear area. In the DLRs showing advanced resorption, the nuclear membrane entirely disappeared, and every cytoplasmic organell was mostly destroyed piecemeal into abundant materials. The basal lamina structure, however, relatively persisted during cellular degeneration (Fig. 13).

Inflammatory infiltration of the macrophages, mononuclear cells and polymorphonuclear leukocytes was observed around the DLRs. The inflammatory cells usually contained a large quantity of free and primary lysozome and showed well-developed RER. Some macrophages produced cytoplasmic extensions toward the DLR, mimicing the direct destruction of the related basal lamina (Fig. 14, 15).

DISCUSSION

Based on the observations made in this study, we found that there was no strict histological difference among the three components of the dental laminas. However, it could also be suggested that during the developmental process of tooth germs the dental lamina ridge was formed by the initial invagination of the oral epithelium, and that the dental lamina ridge proliferated more deeply and gave rise to the primary dental lamina, which then produced the primary tooth germ. After the deciduous tooth germ developed, almost up to the bell stage of tooth grm, the stalk epithelium of the deciduous tooth germ produced the secondary dental lamina at the lingual side of it (Churchill, 1935; Gantz, 1922; Pearson, 1974; Provenza, 1964; Schour and Massler, 1940; Shafer *et al.*, 1974; Sofaer, 1975). On the serial sections of tooth germ the histological differences of the dental lamina ridge, the primary dental lamina, and the secondary dental lamina could be identified easily. The epithelium of the dental lamina ridge was characterized by the early and frequent formation of keratin pearls. On the other hand, the primary and secondary dental lamina showed rapid atrophy of their epithelial cells and were separated into numerous tiny epithelial rests that disappeared gradually with the increase of gestational age.

A previous report describes briefly the degenerative processes of DLRs in human fetal jaws as fragmentation, keratinization, and resorption (Lee and Lim, 1980). In the present study we observed inflammatory cell infiltration around the DLRs. Although it was difficult to identify the types of inflammatory cells with histologic findings only, the inflammatory cells contained numerous lysosomal vesicles and well-developed RER ultrastructurally. By these findings we could suppose that even though the fetal immune system was not developed completely in the prenatal period, the native inflammatory cells were able to destroy the degenerative cells effectively. This scavenger activity seemed to be more active than that in the adult periodontium composed of thick fibro-collagenous tissue, accompanying the active proliferation of capillaries. Many authors mention high vascularity as the reason for the nutritional supply around the developing enamel organ, especially observing the capillary invasion into the developing enamel epithelium up to near the layer of stratum intermedium (Addison and Appleton, 1922; Hodson, 1954; Jordan, 1921; Jump, 1938; Kingery, 1924; Maher and Swindle, 1970). Capillary proliferation was commonly observed at the perifollicular connective tissue in the vicinity of the outer enamel epithelium showing numerous papillary projections. In this study prominent capillary proliferation around the DLRs was considered to play the role of scavenger for the cellular debris of the degenerating DLRs or to be a route for the rapid migration of inflammatory cells.

It seems apparent that tonofilament and cytokeratin filament must interact with other elements of the cytoskeleton and with the specific intercellular junctions into which they insert in

order to play a role in stabilizing the cell shape and tissue architecture. The present study showed early degenerative changes of tonofilament in the atrophic cells of the DLRs. Mostly the amount of tonofilament decreased, and little conglomerated tonofilaments were observed at the perinuclear area. DLRs destroyed by cytotoxic inflammatory cells characteristically revealed early destruction of basal lamina.

In this study, the keratinizing DLRs were not resorbed in the alveolar connective tissue and showed definite basal lamina in electron-microscopic observation, and more keratinizing DLRs persisted in the fetal maxillas than the other DLRs. Only a small number of DLRs remained in the fetal alveolar tissue in late gestation, while the remaining DLRs showed a relatively intact basement membrane in the PAS and Gomori's reticulin stains.

We supposed that the initial cause of separation of dental lamina was due to the degenerative state of dental lamina remnant which gradually lost its odontogenic mesenchyme. Also it is very similar to foreign body reaction for the large epithelial rests near the oral mucosa to be exfoliated as keratin pearls into the oral cavity, but many DLRs were resorbed slowly into the connective tissue during the fetal period. However, some atrophying DLRs which were surrounded by thick collagen bundles could be observed dormantly even in the term gestation, and definitly to elucidate the removal of the DLRs may give an important clue to the pathogenesis of odontogenic tumors. In this study the resorption processes of the DLRs included both self-resolution and inflammatory destruction. Particularly, the inflammatory cell was considered to play an essential role in removing the dental lamina rests, even though the fetal immunologic system was still not mature enough.

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= 국문초록 =

사람태아 상악골내에 보이는 치제상피잔사의 퇴행성 변화

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지제근

사람의 태아에서 발생중인 치배의 치제상피 잔사 변화를 관찰하기 위하여 서울대학병원 병리과에 기록되어 있는 232례의 상악골을 조사하였다. 각각의 상악골을 태령별로 분류하였으며 227례는 10% 중성 포르말린에 고정하고 5% 질산에 탈회한 후 전후방으로 4-6개 절편으로 절단하여 파라핀 왁스에 포매하였으며 치배 부위를 4 μm 두께의 연속 절편을 제작하였다. 그리고 신선한 상악골 5례는 전자현미경 관찰을 위하여 치제 상피 잔사를 포함하는 치은 조직을 5% glutaraldehyde에 고정한 후 Epon 포매하였다.

치제 상피는 초기에 치은 상피 함입으로 생긴 치제능(dental lamina ridge), 유치배 형성을 위한 일차 치제(primary dental lamina), 영구 치배 형성을 위한 이차 치제(secondary dental lamina)로 구분되어 지며 치제 상피 잔여 조직은 치제 상피의 위축과 섬유질의 침윤 증식으로 절단되어 다수의 잔사로 나뉘어 지고 상피 잔사 중심부에 각화가 생기면서 치은 상피에 접근하여 비대해지거나 낭종성 변화를 보이면서 구강내로 탈락된다. 심부에 잔존되는 치제 상피 잔사는 활발한 모세혈관의 증식과 함께 점차 위축된 치제 상피 잔사가 흡수되는데 근접 조직에 미만성의 염증세포 침윤이 관찰되며, 간혹 치제 상피 주위에 심한 염증세포 침윤이 보이면서 치제 상피 잔사가 흡수되어 짐을 관찰하였다. 한편 전자현미경 관찰에서 흡수되는 치제 상피 주위에 염증세포 침윤을 확인하였으며 염증세포에 의한 직접적인 세포막의 파괴상을 관찰하였다.

LEGENDS FOR FIGURES

Fig. 1. Photomicrogaph of 25-week-old fetus. The dental lamina are divided into three portions: the dental lamina ridge (R), primary dental lamina (P), and secondary dental lamina (S)(H & E, × 25).

Fig. 2. An example of frequent keratinization of the epithelial rests of the dental lamina ridge is shown, producing keratin pearls (H & E, × 100).

Fig. 3. Increased keratinization of the epithelial rest of the dental lamina ridge is seen. Several keratin pearls showing cystic change are located near the oral mucosa (H & E, × 100).

Fig. 4. A large keratin pearl is extruded out of its keratin plug into the oral cavity (H & E, × 100).

Fig. 5. The tail portion of dental lamina lost its proliferative activity and gradually became atrophic, compared to the other end of actively developing dental lamina (H & E, × 100).

Fig. 6. The atrophic dental lamina is separated and composed of numerous epithelial rests in the stromal connective tissue (H & E, × 100).

Fig. 7. The separated epithelial rests were encircled by thick collagen bundles (arrow)(H & E, × 200).

Fig. 8. Abundant capillary proliferation (arrows) was observed in the vicinity of the degenerating dental lamina rests (H & E, × 400).

Fig. 9. In the reticulin stain, the end of actively developing dental lamina showed conspicuous thick basement membrane (arrows)(Gomori's reticulin, × 400).

Fig. 10. In the reticulin stain, the dental lamina rests disclose inconspicuous and irregular basement membrane (arrows)(Gomori's reticulin, × 400).

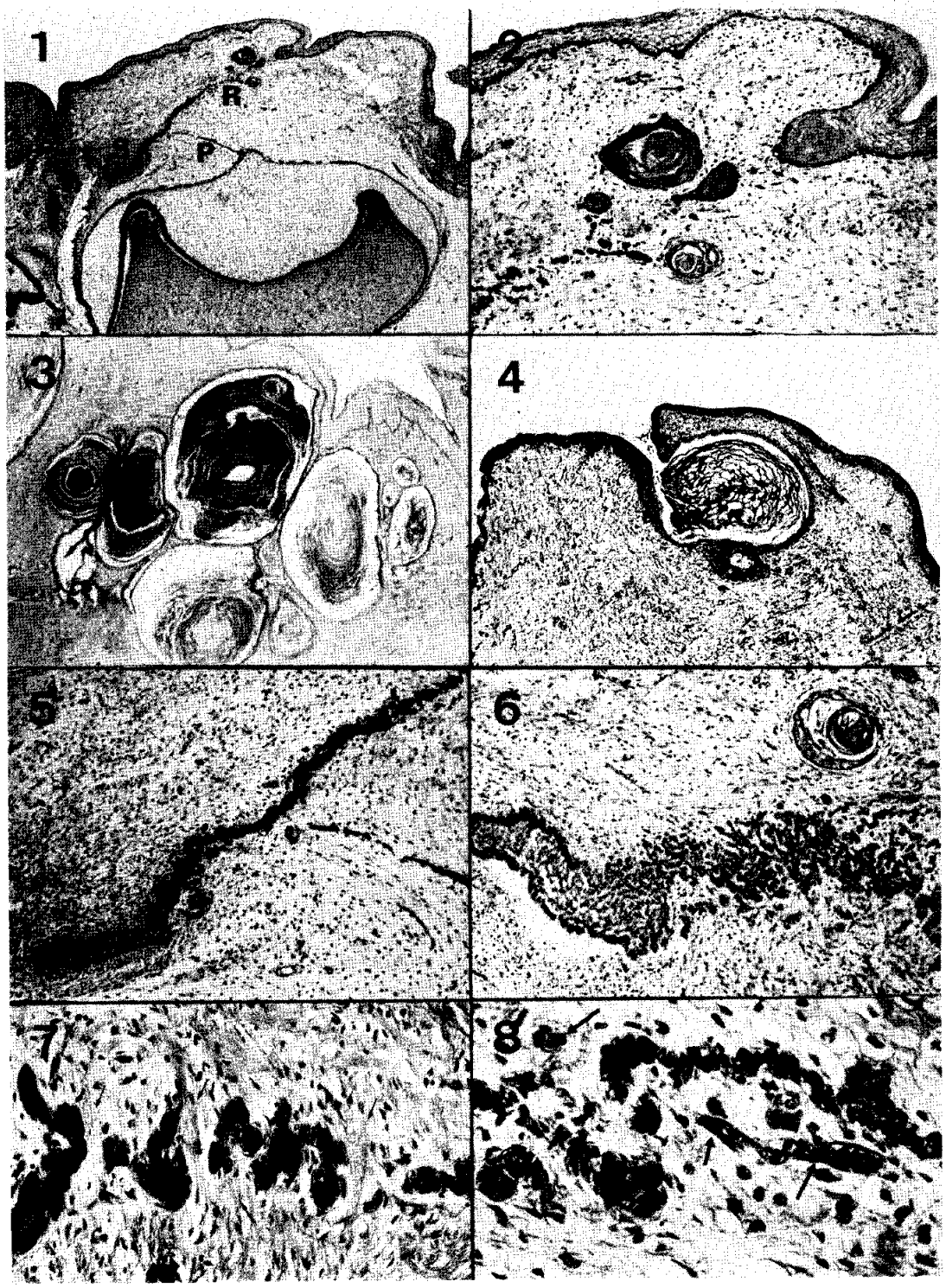
Fig. 11. Some large keratin pearls, located in the relatively deep connective tissue, are actively destroyed by the process of inflammatory phagocytosis (H & E, × 200).

Fig. 12. Small dental lamina rests derived from the primary dental lamina and secondary dental lamina usually persisted until late gestation. Often they were infiltrated by a number of inflammatory cells (H & E, × 200).

Fig. 13. Electron micrograph shows the degenerating dental lamina rest. Generally the cytoplasmic organeles disintegrated, and the necrotic cell shows the karyolysis and derangement of tonofilaments (large arrow). Note the gradual loss of basal lamina (small arrows) and several basal lamina debri (arrowheads).

Fig. 14. A macrophage (M) containing abundant laysozome adhered to the dental lamina rest. The central keratinizing cell contained abundant granular materials (G) and derranged tonofilaments (arrow).

Fig. 15. A polymorphonuclear leukocyte (P) adheres to the dental lamina rest and produces an acitive cytotoxic effect. Note the severe destruction of the basal lamina (arrowheads) and the intense derangement of tonofilament (arrow).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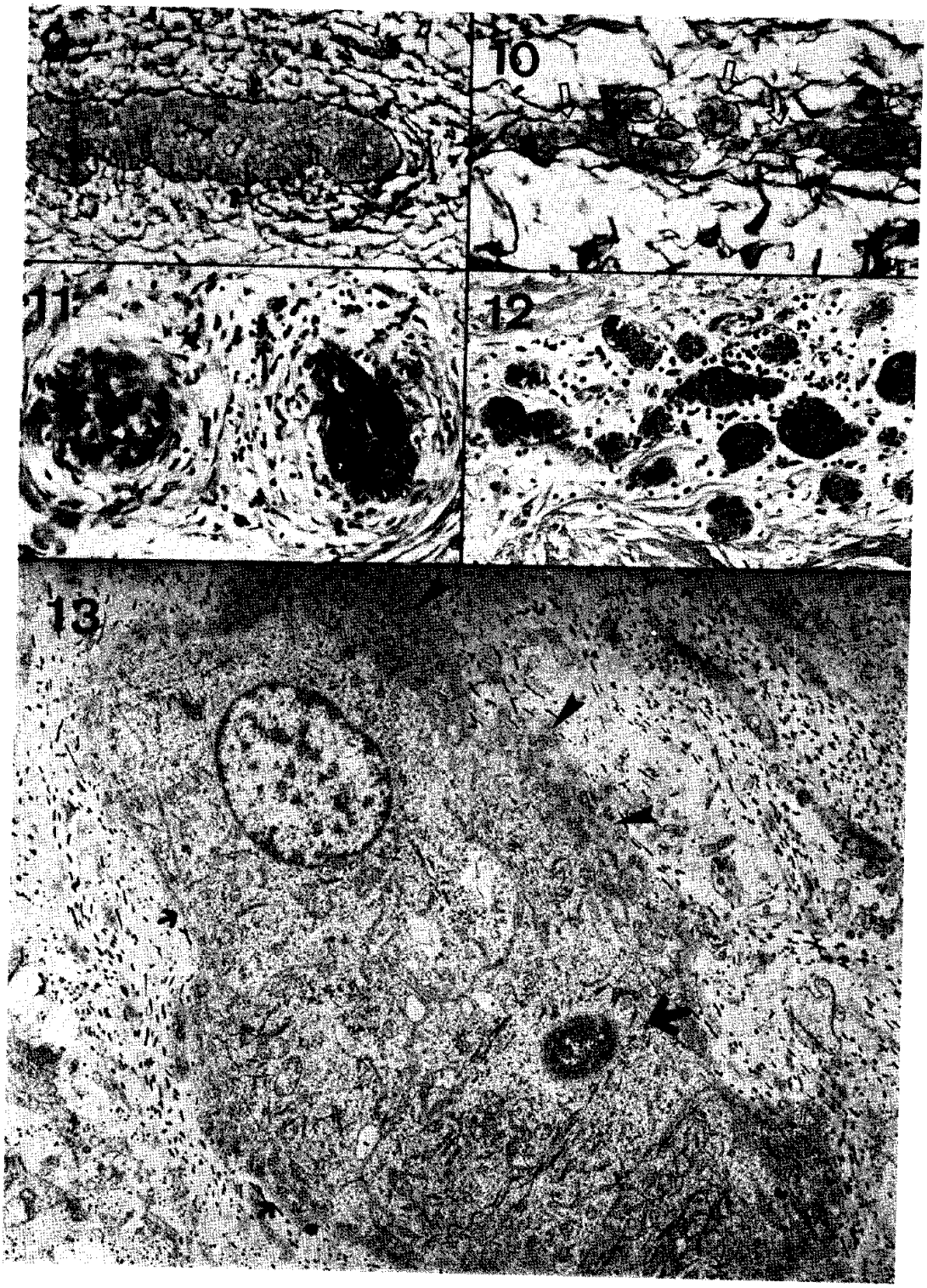
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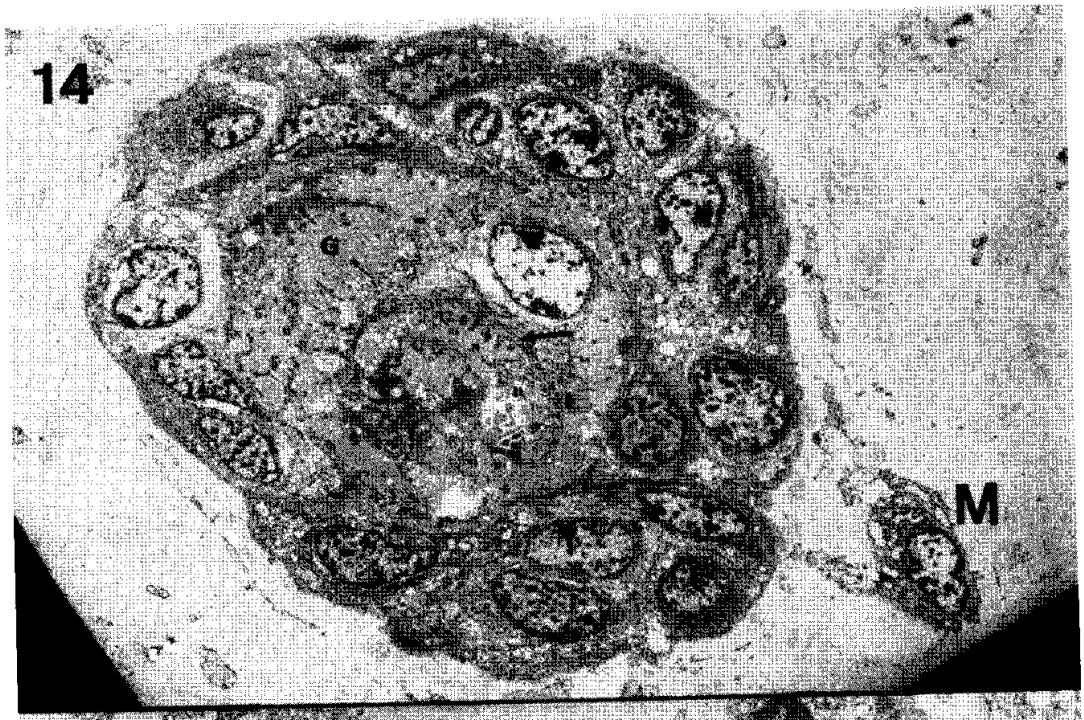
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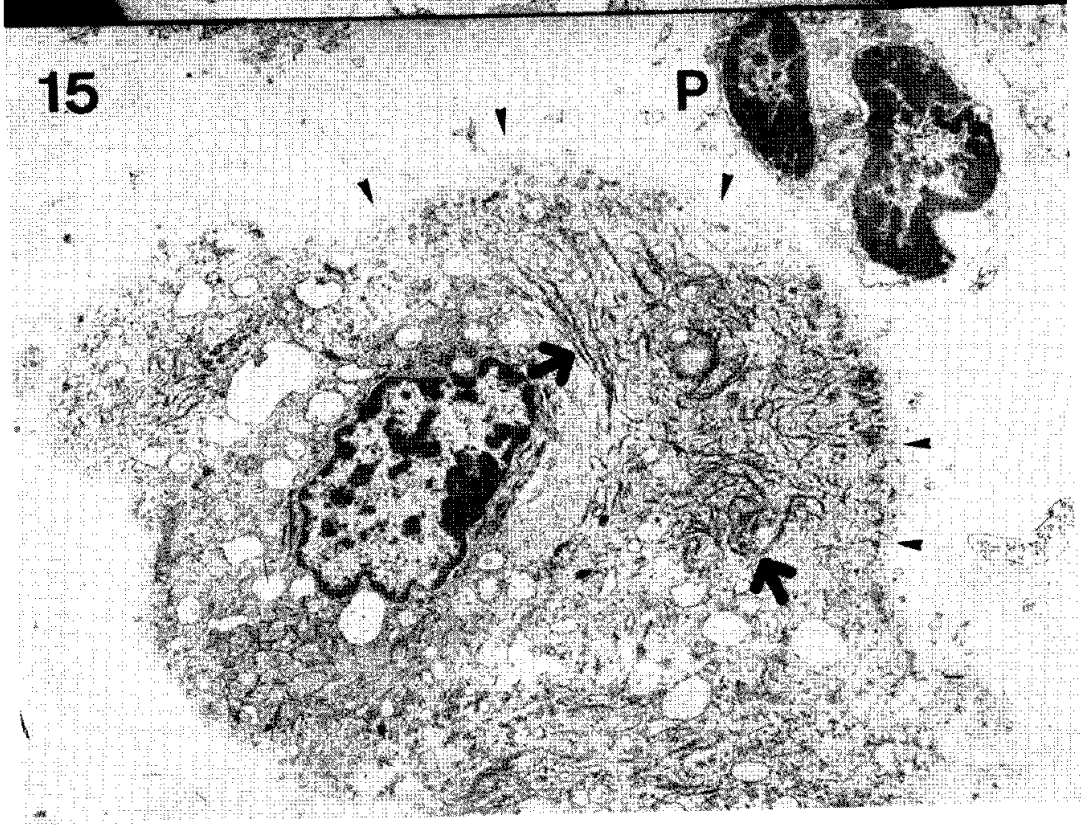
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