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Morphological Development of the Human Hypophysis

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= Abstract = The morphological development of the human hypophysis was studied using 142 developing human hypophyses from 19 embryos and 123 fetuses. The adenohypophysis first developed at 4 weeks of gestational age as an upward growing fold of the primitive oral ectoderm Rathke's pouch. At 7 weeks, the configuration of pars distalis and pars intermedia was formed. The Rathke's pouch lost its connection with the oral cavity completely at 8 weeks. Pars tuberalis became evident at 9 weeks. Histologically, capillary formation was found at the end of 7 weeks in adenohypophysis and basophilic lamellated bodies were first identified at 8 weeks. Cells with eosinophilic cytoplasm appeared at 9 weeks and those with basophilic cytoplasm appeared between 10-12 weeks.

The neurohypophysis developed as a downward evagination of the diencephalic floor at 6 weeks. After 9 weeks, capillary formation occurred in the stroma, and primitive neuroepithelial cells became differentiated. Ependymal tubules were also observed at this time. Between 25-29 weeks, suspicious pigment was seen in the cytoplasm of pituicytes and glial cell modification into pituicytes seemed completed. No Herring body-like structures could be identified throughout the fetal period.

Key word: ***Adenohypophysis, Neurohypophysis, Development, Embryo***

INTRODUCTION

The human hypophysis develops from two different embryonic origin. The adenohypophysis is from the oral ectoderm, and the neurohypophysis is from the neuroectoderm. In the embryonic period, the Rathke's pouch and the ventral diverticulum of diencephalon fuse to form the hypophysis. From then, histological differentiation of cells in adenohypophysis and neurohypophysis occurs to become the acidophil, basophil, chromophobe and pituicyte. Regarding the above mentioned statements, Streeter (1951) have contributed greatly on the development of hypophysis in embryonic period, and Arey (1960), Falin (1961) and Conklin (1968) for the development of the adenohypophysis. Shanklin (1940) studied the differentiation of pituicytes in human fetus. In Korea, some anatomical aspect and the pituitary capsule development were reported by Chi and Lee (1980), and histological differentiation of hormone secreting hypophyseal cells was studied by Cho *et al.* (1978) using immunohistochemical and electron microscopic methods.

However, systematic morphological observation using sufficient number of pituitaries of embryos and fetuses encompassing the entire gestational period in human being has not been carried out yet. In this study, we have attempted to elucidate the morphological characteristics of the temporal development of the human hypophysis using sections of hypophyses of embryos and fetuses.

MATERIALS AND METHODS

A total of 142 human hypophyses consisted of those of 19 embryos and 123 fetuses of various age (Table 1). The 19 embryos were distributed from Streeter's horizon XII to XXIII as shown in

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Table 1. Age ditribution of the embryos and fetuses used in this study

Gestational ages (weeks)	No. of cases
4	2
5	4
6	3
7	3
8	7
9	3
10 — 12	2
13 — 18	21
19 — 24	28
25 — 29	28
30 — 34	25
35 — 40	16
Total	142

Table 2. The correlation between the gestational age and the Streeter's developmental horizon used in this study

Gestational ages (weeks)	Streeter's development horizons	No. of cases
4	XII	1
	XIII	1
5	XIV	1
	XV	3
6	XVI	1
	XVII	2
7	XVIII	2
	XIX	1
8	XX	1
	XXI	2
	XXII	1
	XXIII	3
Total		19

Table 2. These were the products of the interrupted pregnancies due to various reasons including ectopic pregnancy, leiomyoma of the uterus, etc. The embryos were examined under the dissecting microscope and full autopsies were done for the fetuses to exclude any diseases affecting the normal development of the hypophysis. The hypophyses were removed en bloc together with sella turcica in fetuses. And all 19 embryos and 3 fetuses of 9 weeks of gestation were serially sectioned in various planes. The hypophysis blocks obtained were fixed in 10% neutral formalin and embedded in paraffin. Sections of 5-7 μm thickness were obtained and stained with hemtoxylin-eosin(H&E), and if necessary, periodic Acid Schiff (PAS) reagent, Orange G and Masson-Trichrome. The adenohypophyses and neurohypophyses of 6 embryos were reconstructed through serial sections. In the fetuses over 10 weeks of gestational age, body weight and crown-rump(CR) length were used to estimate the gestational age together with the last menstrual period. The gestational age was expressed as gestational weeks, the criteria being based on the table by Moore (1978) for embryos and the CR length table by Lee (1975) for fetuses.

RESULTS

1. Embryonic development of the hypophysis

4 weeks:

In the embryos belonging to Streeter's developmental horizon XIII group, early hint of pouch formation was first identified (Plate 1). This represented as a slight upward diverticulation of the stomodeum which was composed of one to two layers of the epithelial cells identical to those of the stomodeum. At this stage, the thyroid diveticulum and tongue bud were also observed in this region. In the brain, three primary brain vesicles and two flexures were found, but no evaginating structure could be identified in the ventromedian portion of the prosencephalon.

5 weeks:

Definite Rathke's pouch was seen at this time (Plate 2). The pouch was composed of three or more layers of the stratified epithelial cells with a few mitotic cells. The mitotic figures were more common around the luminal side of the pouch (Plate 3). However, the lining epithelial cells of the Rathke's pouch were not different from the remaining epithelium of the stomodeum.

6 weeks:

In this period, the brain showed three definite flexures, prominent ventricles and the pineal was first seen in the dorsal diencephalon. The infundibular floor of the diencephalon began to evaginate as the future neurohypophysis (Plate 4). The stratification of the epithelial cells of the Rathke's pouch increased further and the pouch juxtaposed the evaginated infundibular floor. The mesenchymal cells between these two juxtaposing structures

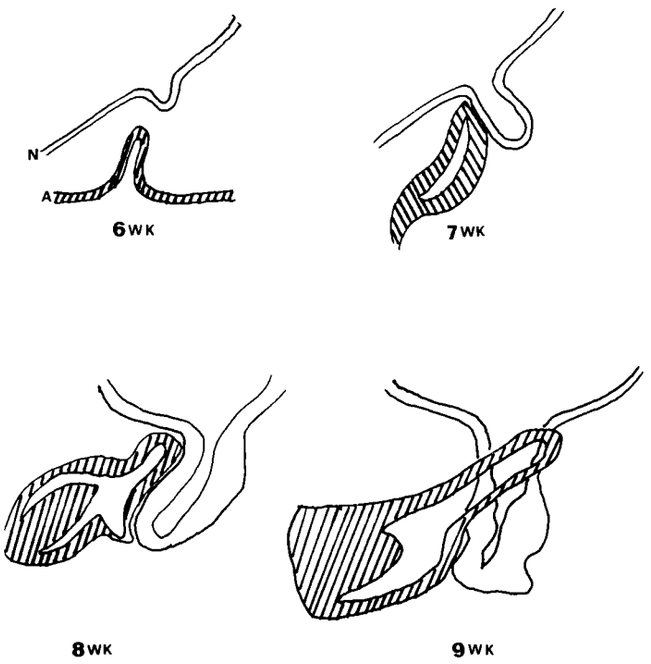

Fig. 1. Schematic reconstruction of spatial relationship between adenohypophysis and neurohypophysis. A: Adenohypophysis N: Neurohypophysis

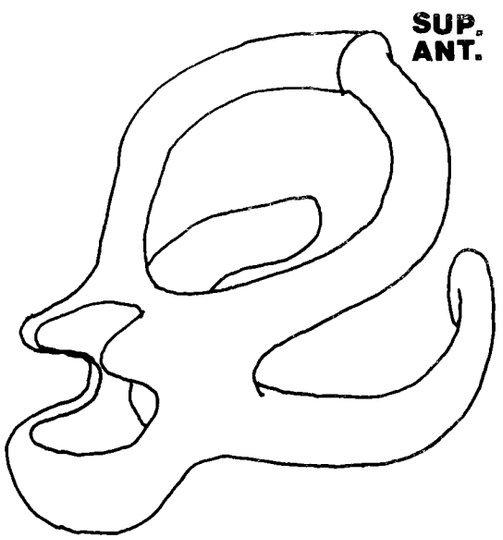

Fig. 2. Schematic reconstruction of Rathke's pouch at its greatest development. (Modified from Stoelting, 1966).

were somewhat condensed and contained some red blood cells without endothelial lining.

7 weeks:

The infiltration of mesenchymal cells and red bood cells in ventral portion of the Rathke's pouch became prominent, and folding of the pouch took place (Plate 5). The formation of capillaries in the mesenchyme could also be observed at the end of this period (Plate 6). At the junction of neurohypophysis and adenohypophysis, the cellular arrangement of the epithelial cells was different from the distal portion of the adenohypophysis. This portion appeared to become the future pars intermedia.

8 weeks:

Rathke's pouch became in its maximal development. The lumen of the pouch became folded to form the limb-like configuration (Fig. 2, Plate 9). Rathke's pouch lost its connection to the oral cavity at the end of this period by complete fusion of the sphenoid cartilage. The cellular differentiation of the anterior portion of adenohypophysis became prominent and formed the lobulating pattern(Plate 8). At this period, the basophilic lamellated bodies appeared first in the luminal side of the adenohypophysis (Plate 11). Some of these bodies were seen in the cavities made by obliterated Rathke's pouch.

2. Fetal development of the hypophysis

9 weeks:

In the glandular tissue destined to form the pars distalis, cell cords and nests formation occurred actively (Plate 13). The cells of the posterior wall of the Rathke's pouch also grew actively. The tubular structure resembling gland could also be observed in these areas. The cells with eosinophilic cytoplasm were first identified at this stage mainly in the anterior portion of the adenohypophysis. The adenohypophysis creeping up toward the infundibulum surrounded the infundibular stalk and formed the pars tuberalis. Pars intermedia was still prominent and showed some tubular structure. The epithelial cell nests of the pars intermedia were often seen in the adjacent neurohypophysis in the interdigitating fashion (Plate 15). In the posterior portion of the neurohypophysis, small rosettes of ependymal cells with small, hyperchromic nuclei were identifed which appeared to be a remnant of the diencephalic pouch epithelium (Plate 19). The capillary formation with red blood cells inside could also be found in neurohypophysis.

10-12 weeks:

In the adenohypophysis, the epithelial cell nests consisted of polygonal appearance with centrally located nuclei and ample cytoplasm. These cell nests and cords could easily be distinguished from the mesenchymal stroma that was already forming a sinusoidal structure by the coalescence of the capillaries. Cells with basophilic cytoplasm were present in small clusters and these cells were stained pink by PAS staining (Plate 16). Mitotic figures were often found in the adenohypophysis. The neurohypophysis that was intially composed of closely packed neuroepithelial cells, became a relatively sparsely populated neuroglial structure. The neuroglial cells with angulated nuclei began to appear in this period. The cytoplasm of angioblasts was amply eosinophilic, and that of neuroglial cells was scanty.

13-18 weeks:

In the adenohypophysis, the cellularity increased more and mitotic figures were more common. The formation of tubules was more prominent and basophilic lamellated bodies impacting tubular lumens were frequently found (Plate 18). In H&E preparation, the distinction of the cytoplasmic stainability between the composing cells became possible. The eosinophilic cells were dominant, and the population of basophilic cells although limited was increased compared to the previous period. Neuroglial cells comprising the neurohypophysis had more than two kinds in terms of the nuclear shape; round and spindle.

19-24 weeks:

The adenohypophysis showed no significant structural change except for the progressive increase of the cellularity.

In the neurohypophysis, the cytoplasm of individual neuroglial cells became abundant seen as cytoplasmic processes. The nucles of these cells were round vesicular, oval or spindle-shaped (Plate 20). None of the neurohypophyseal cells were stained by Masson-Trichrome preparation.

25-29 weeks:

In the adenohypophysis, relative proportion of the mesenchymal component became gradually decreased as the individual gland cells became large and the sheets were widened. The eosinophil, basophil and chromophobe cells were clearly distinguishable. Cytoplasm of cells in neurohypophysis became granular, and suspicious pigment was first identified in pituicytes (Plate 21). The population of the pituicytes with oval or spindle shaped nuclei increased.

31-34 weeks:

The adenohypophysis achieved almost mature form in its structure and cytology. Colloid filled lumens of pars intermedia were found in one case of a 32 weeks fetus (Plate 23). The basophils were often distributed in and near the pars intermedia. Glial cell modification into the pituicytes seemed almostly completed.

35-40 weeks:

The adenohypophysis was not different from the previous period. In neurohypophysis the distinction between pituicytes and non-myelinated nerve fibers was not possible. No Herring body like structures could be identified. In this period, no mitotic figures were found in neurohypophysis.

DISCUSSION

In this study we confirmed that the adenohypophysis first developed as a Rathke's pouch at the end of 4 weeks. At 6 weeks, the pouch juxtaposed the neural lobe, and at 7 weeks, at the junction of the Rathke's pouch and neural lobe formed the pars intermedia. Definite formation of capillaries was found in the embryos belonging to Streeter horizon XIX in this series. Above findings do not coincide with the descriptions of Streeter (1951). According to his observation, capillaries had not appeared in the embryos belonging to the group XIX. These capillaries were supposed to comprise the portal system of the adenohypophysis.

Many important events of morphogenesis and histogenesis in adenohypophysis occurred between 8-9 weeks. Rathke's pouch lost its connection with the oral cavity completely and the remnants of epithelial stalks were completely absorbed. It was understandable that if this process fails, the pharyngeal hypophysis may result. Actually one case of a pharyngeal hypophysis was observed in this series (Plate 14). It was interesting to note that the Rathke's pouch became a limb-like structure by the combination of mesenchymal infiltration from the ventral portion of the pouch and dorsal development of the pars nervosa. We were able to confirm this fact by our reconstructed features that were

similar to those of Conklin (1968). The cellular proliferation occured actively in anterior portion to form the pars distalis (Plate 10).

The upward growing pouch surrounded the infundibular stalk posteriorly to form the pars tuberalis at 9 weeks. And the histological configuration became the glandular pattern at this period. Lobulation, cell nests, strands and tubular structures appeared. The cells with eosinophilic cytoplasm were first identified at 9 weeks. These cells are probably acidophils. Cells with basophilic cytoplasm appeared by 10-12 weeks. Arey (1960) described that all the specialized cell types can be distinguished at 10 weeks. But Cho *et al.* (1978) reported that the first identification of growth hormone secreting cells in adenohypophysis was only possible at 10 weeks by immunohistochemical methods, and would not be possible before 16 weeks by light microscope in H&E preparation. He also reported that TSH secreting cells appeared at 12 weeks by immunohistochemical methods. Our results by light microscopic examination is compatible with the report of Arey (1960), and the results of Cho *et al.* (1978) by immunohistochemical methods. The basophilic lamellated bodies which appeared at the end of 8 weeks seemed to be the calcified materials. These were found throughout the whole fetal period. It is surmised that this is related to the secretions of the gland. Colloids were found in pars intermedia in one case of a 32 weeks fetus. This suggests the possibility of fetal adenohypophysis to function.

The development of neurohypophysis was preceded by that of adenohypophysis. If first appeared at 6 weeks as an evagination of the diencephalic floor. This evagination grew downward as the neuroepithelial cells proliferated, and by 8 weeks, it formed the much more folded neurohypophysis. After 9 weeks, the neurohypophysis began to develop actively. Capillarization became definite at 9 weeks, and the relative ratio of nucleus to cytoplasm of the pituicytes began to decrease. The crowded neuroglial cells became progressively sparse. The primitive homogeneous neuroepithelial cells became differentiated and modified to be the mature, heterogenous pituicytes. Shanklin (1940) reported that modification into the neuroglial cells occurred in the later stages of development. In this study, however, reticulopituicyte, fibropituicyte and micropituicyte could not be distinguished. The increasing amount of cytoplasm and descending nerve fibers from the hypothalamus seemed important for the configuration of the mature neurohypophysis. The phenomenon of the cells in pars intermedia invading the neurohypophysis as a digitating fashion was found. Romeis (1940) speculated that this phenomenon could be resulted from that nervous tissue envelops and submerges the glandular interdigitations of the pars intermedia. We could not confirm this. Pigment in cytoplasm was first identified in the neurohypophysis at 25 weeks. We do not know the significance of it. However, this may suggest tht the pituicytes became mature enough to be able to function at this time. The failure of identification of Herring bodies may indicate that sufficient amounts of the hormones are still not descended to make the nerve endings expanded to form these bodies.

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= 국문초록 =

뇌하수체의 형태학적 발달

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한국인 배아 19예 및 태아 123예 등 총 142예에 대하여 뇌하수체의 형태학적, 조직학적 발달소견을 관찰하였다. 그결과 다음과 같은 결과를 얻었다.

1. 선하수체
   1) 4주령에 원시 구강 외배엽으로부터 윗쪽으로 자나라는 Rathke낭이 최초로 관찰되었다.
   2) 7주령이 되면 겹쳐진 Rathke낭이 pars distalis와 pars intermedia의 배열을 이루게 되고 8주령때에는 원시구강과의 연결이 완전히 소멸되며 잔류조직도 완전히 흡수되었다.
   3) Pars tuberalis의 형성은 9주령에 관찰되었다.
   4) 모세혈관의 형성은 7주령부터 관찰되었고, 8주령이후에는 호염성의 석회질이 나타났다.
   5) 호산성 세포들은 9주령이후에, 호염성 세포들은 10-12주령이후에 출현하였다.
2. 신경하수체
   1) 6주령에 시상뇌부위의 신경관 기저로부터 아래로 돌출되어 나오는 신경하수체 원기가 관찰되었다.
   2) 신경하수체의 발달은 선하수체 발달보다 늦게 진행되어 9주령이후부터 모세혈관형성이 관찰되고, 원시신경세포에 분화가 일어났다.
   3) 25-29주령때 신경하수체 세포의 세포질에서 색소가 관찰되었고 세포의 형태도 성인의 것과 유사해졌다. Herring 소체와 같은 구조물은 발견할 수 없었다.

Plate 1. 4 weeks (GA), sagittal section. The first identification of the Rathke's pouch (arrow) as an upward growing fold of the primitive stomodeal ectoderm. H&E ×100.

Plate 2. 5 weeks (GA), frontal section. Growing Rathke's pouch (arrow) juxtaposes the diencephalic floor. H&E × 100.

Plate 3. 5 weeks (GA). Stratified epithelial cells in Rathke's pouch with the mitotic cells (arrows). H&E ×400.

Plate 4. 6 weeks (GA), frontal section. The neurohypophysis (arrow) first appears as an evagination of the diencephalic floor. R: Rathke's pouch. H&E ×40.

Plate 5. 7 weeks (GA), frontal section. The Rathke's pouch is folded by mesenchymal infiltration and the cellularity is increased. N: Neurohypophysis. i: Pars intermedia. H&E ×100.

Plate 6. 7 weeks (GA). Capillary formation is seen. H&E ×400.

Plate 7. 7 weeks (GA), frontal section. The epithelial stem remnant (arrow) is still not absorbed completely H&E ×40.

Plate 8. 8 weeks (GA), frontal section. Adenohypophysis shows lobulating pattern. Orange G ×100.

Plate 9. 8 weeks (GA), sagittal section. The Rathke's pouch is at its greatest development. The lumen is folded to shows the configuration of 4 limbs. Neurohypophysis is more folded. H&E ×100.

Plate 10. 8 weeks (GA), sagittal sctionl. Cell proliferation is prominent in pars distalis(d). H&E ×100.

Plate 11. 8 weeks (GA). The calcified materials (arrows) are present in the lumen of the Rathke's pouch. H&E ×100.

Plate 12. 9 weeks (GA). The cells in neurohypophysis (arrow) still appear to be the primitive neuroepithelial cells. The cells forming ependymal tubule are different in shape. H&E ×400.

Plate 13. 9 weeks (GA). The lumen of Rathke's pouch is being obliterated and cell nest formation is seen. H&E ×200.

Plate 14. 9 weeks (GA), sagittal section. Pars tuberalis (arrow) and the pharyngeal hypophysis(PH) are seen. H&E ×40.

Plate 15. 9 weeks (GA), sagittal section. Cell nests in pars intermedia (arrow) mingle with the neurohypophysis. H&E ×200.

Plate 16. 12 weeks (GA), Pinkish stained cells by PAS (arrows) appear in cluster. PAS & Orange G ×400.

Plate 17. 16 weeks (GA), sagittal section. Lateral aspect of the hypophysis. Ependymal tubule (arrow) is located in the posterior portion of the neurohypophysis.

Plate 18. 16 weeks (GA). Calcifications (arrows) impacting the glandular lumen of the adenohypophysis are seen. H&E ×400.

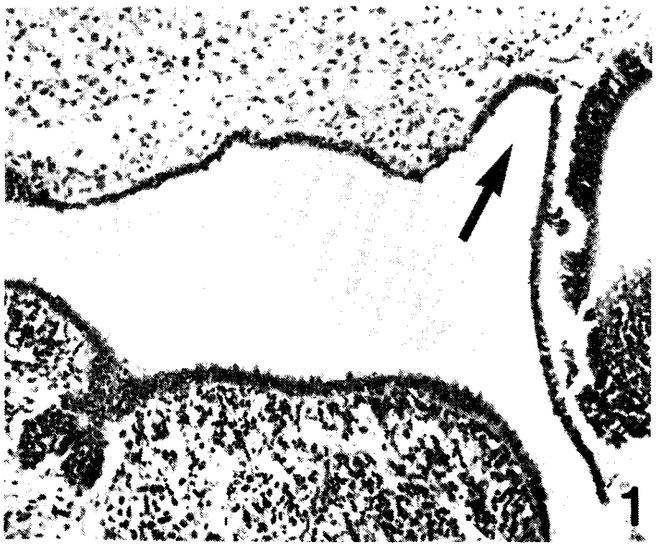
Plate 19. 17 weeks (GA). Ependymal cells with small, hyperchromic nuclei forming tubular structure are seen. H&E ×400.

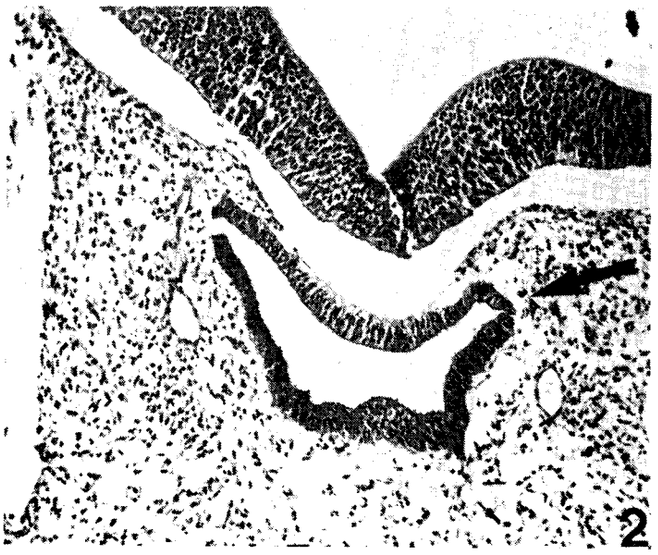
Plate 20. 25 weeks (GA). Nuclear shapes of pituicytes are various and the centrally located angioblasts (arrow) are seen. H&E ×400.

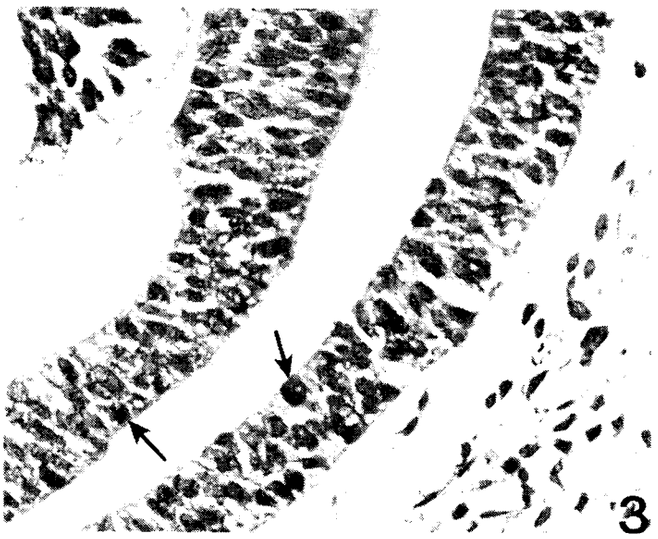
Plate 21. 25 weeks (GA). Pigmentations(arrows) are seen in the cytoplasm of pituicytes. H&E ×1000.

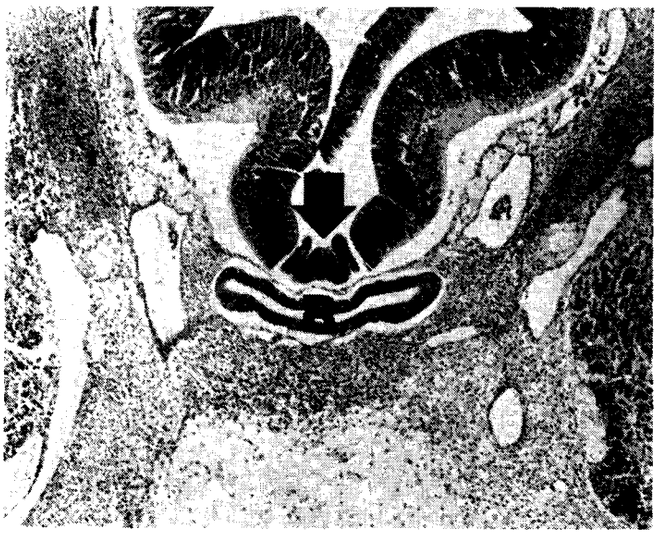
Plate 22. 32 weeks (GA). Neurohypophysis shows the features of maturity. H&E ×200.

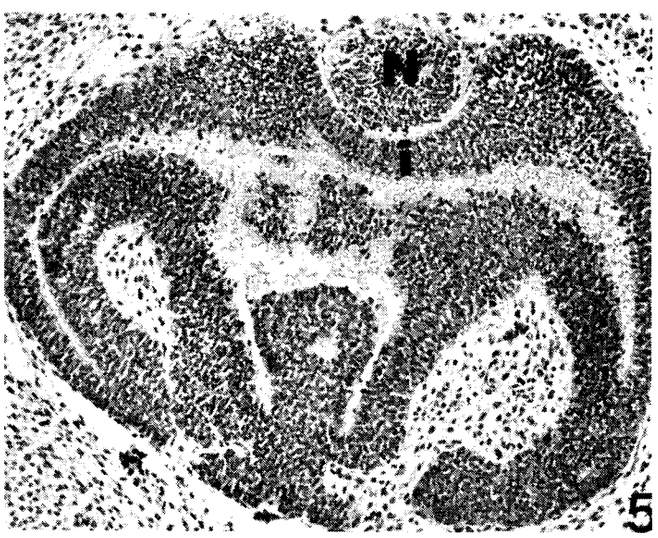
Plate 23. 32 weeks (GA). Colloid filled in the cystic lumen of the pars intermedia (arrow) is seen. H&E ×200.

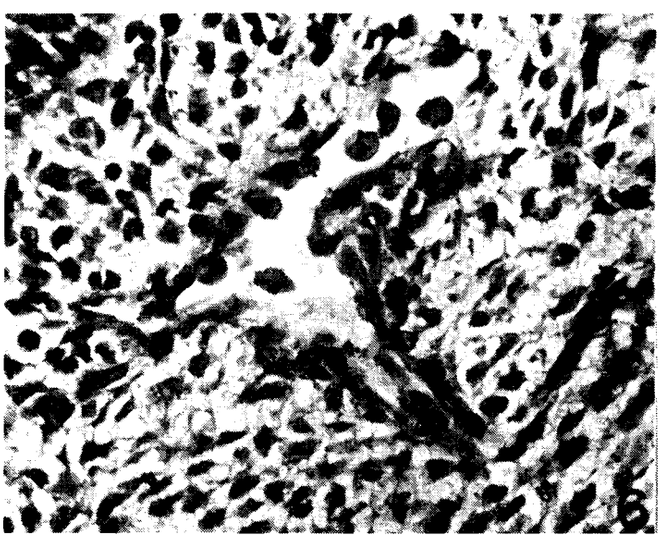


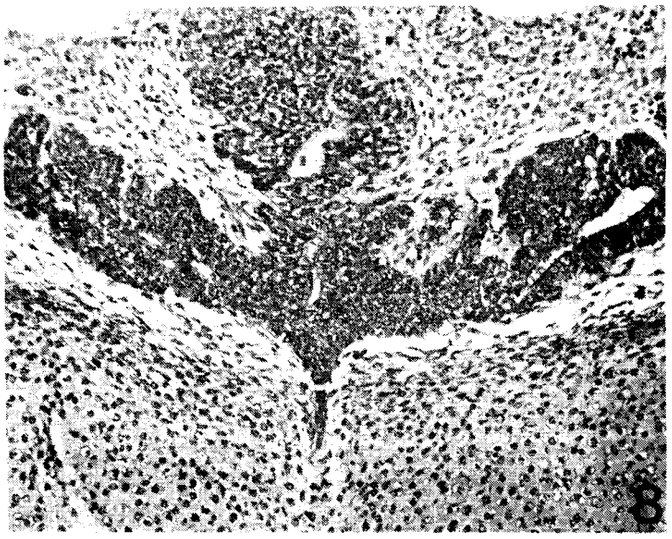


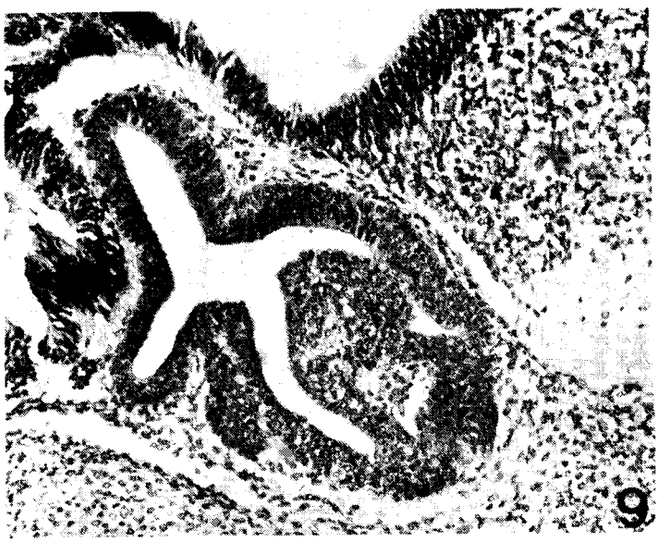


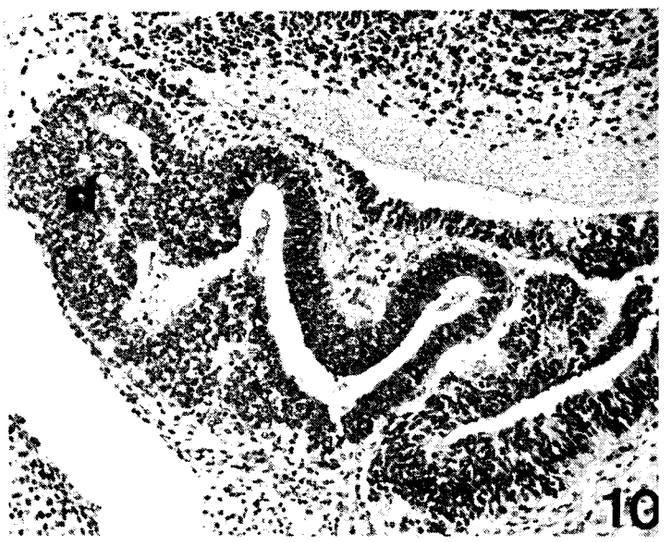


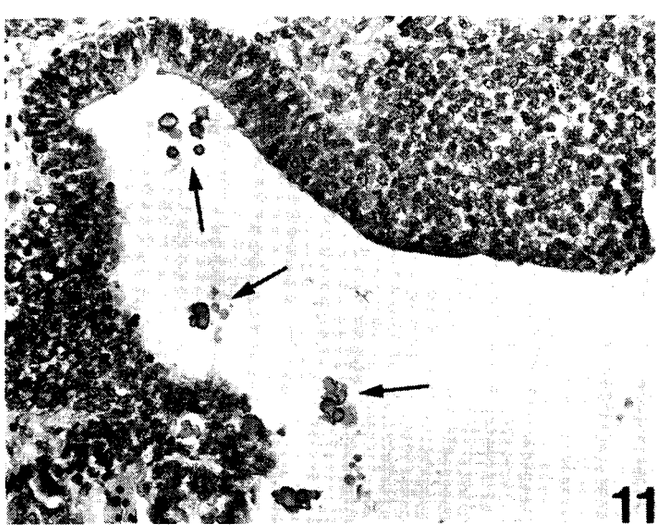


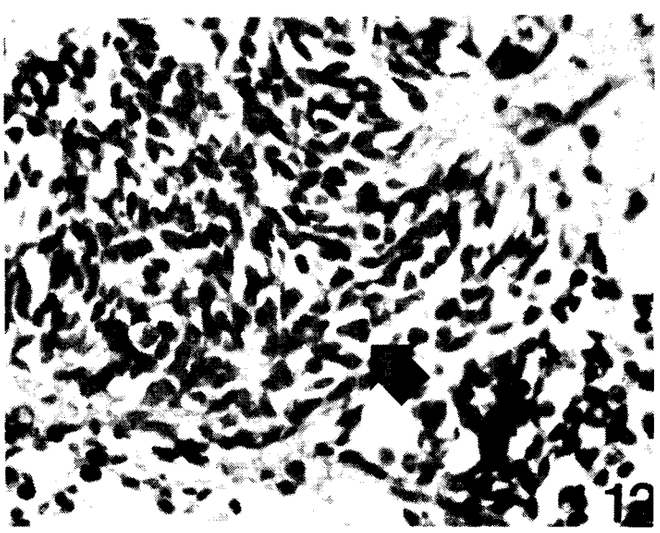


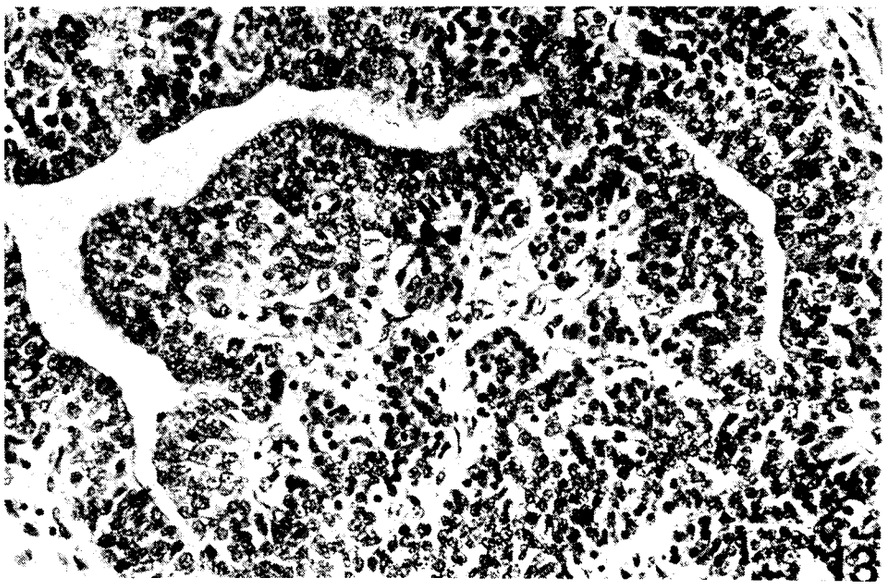


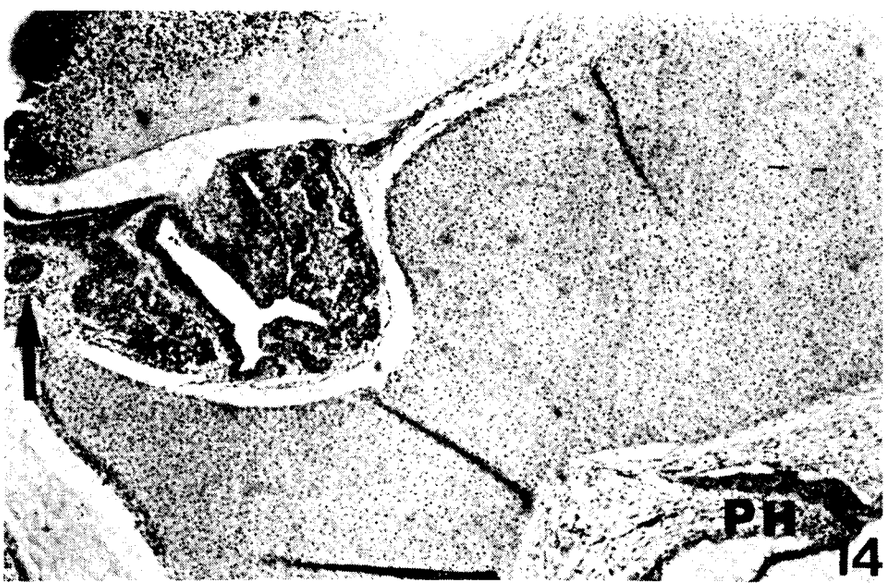








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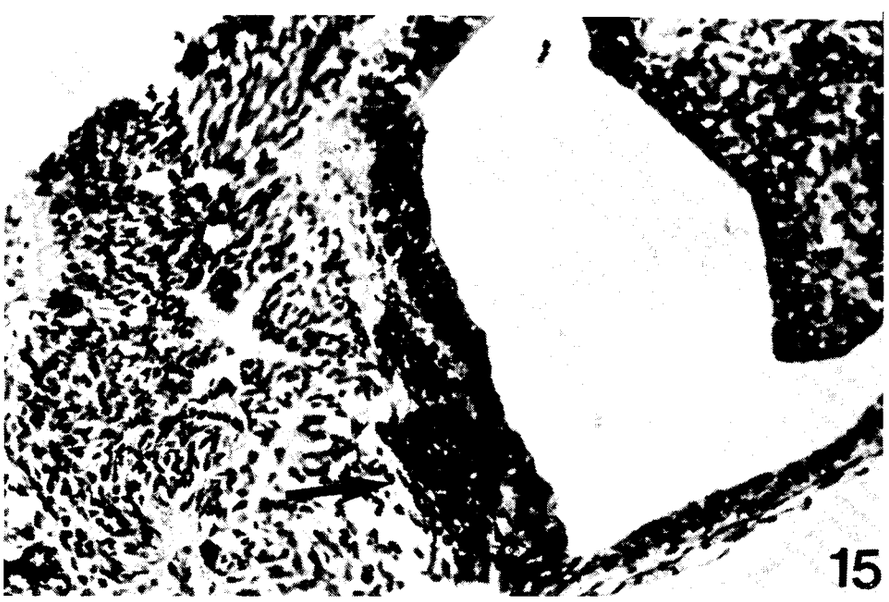
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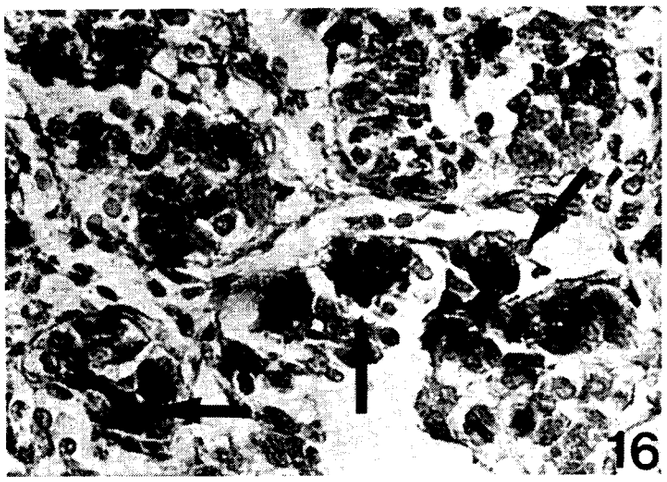
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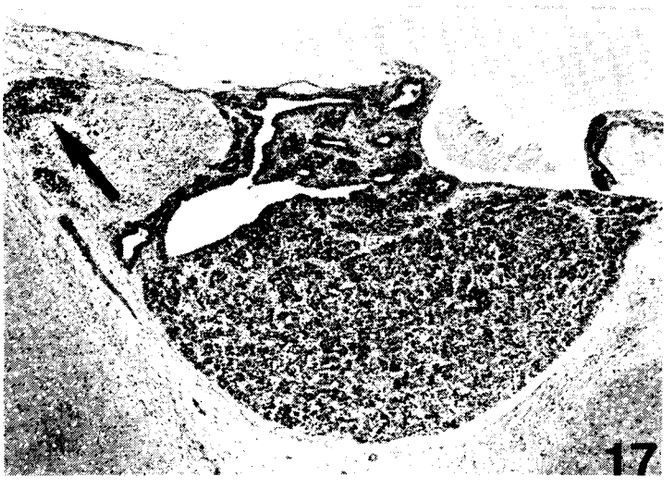
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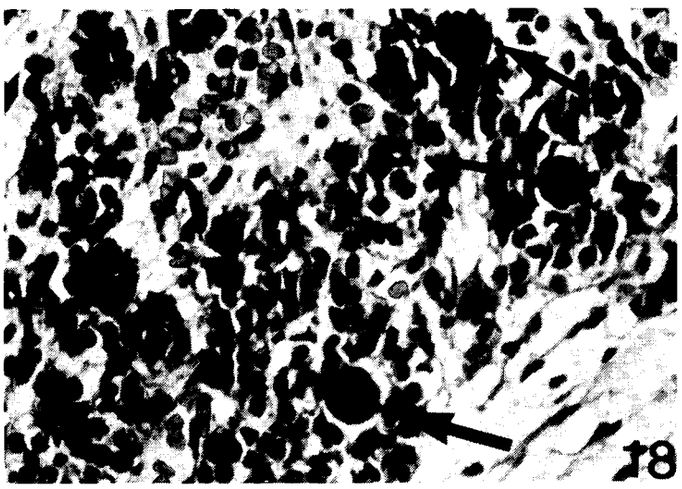
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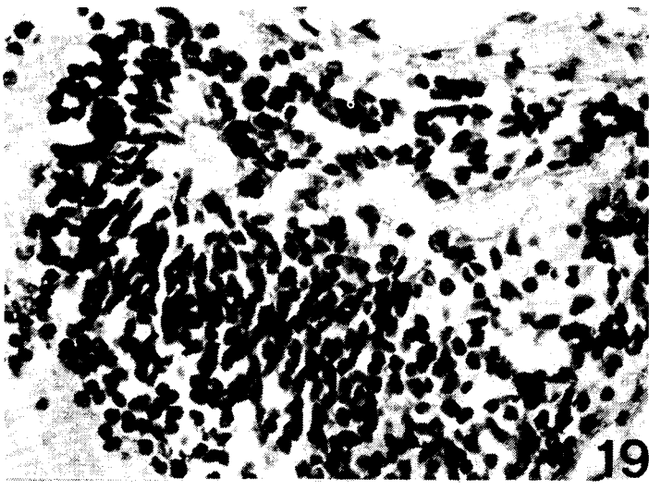
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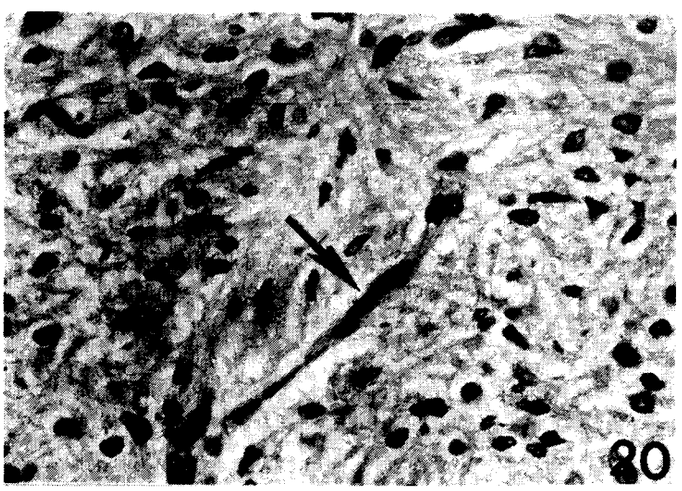
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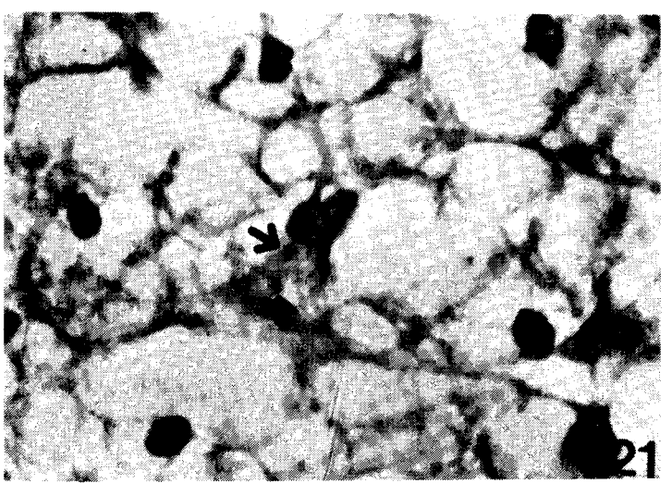
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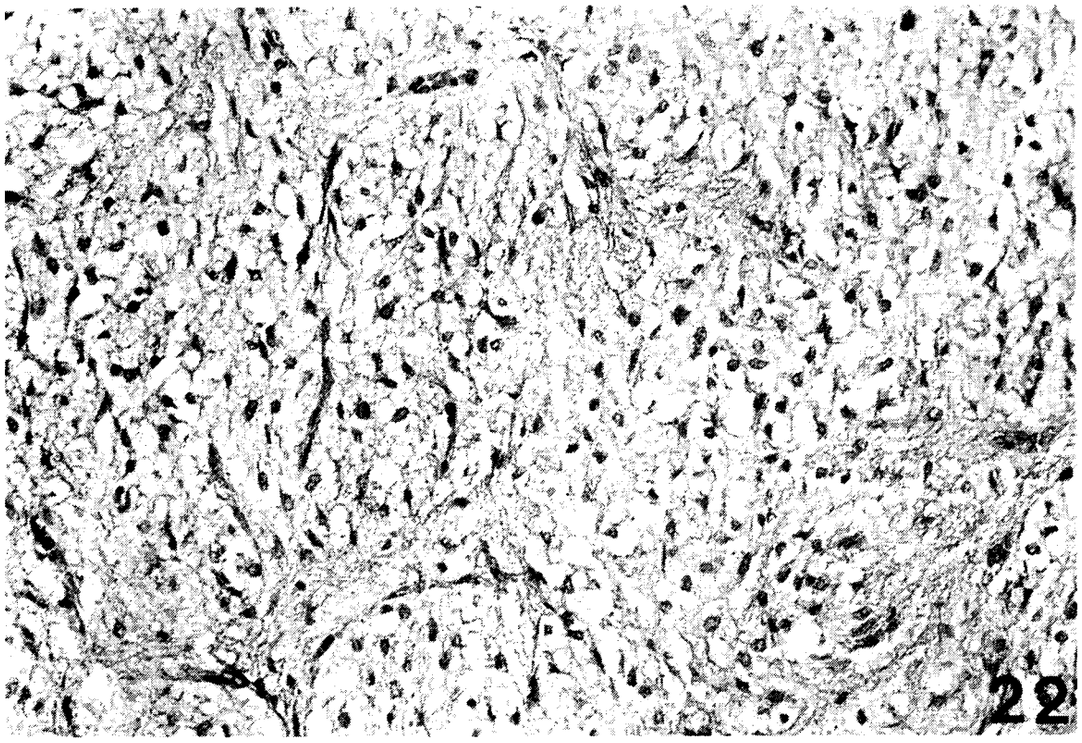
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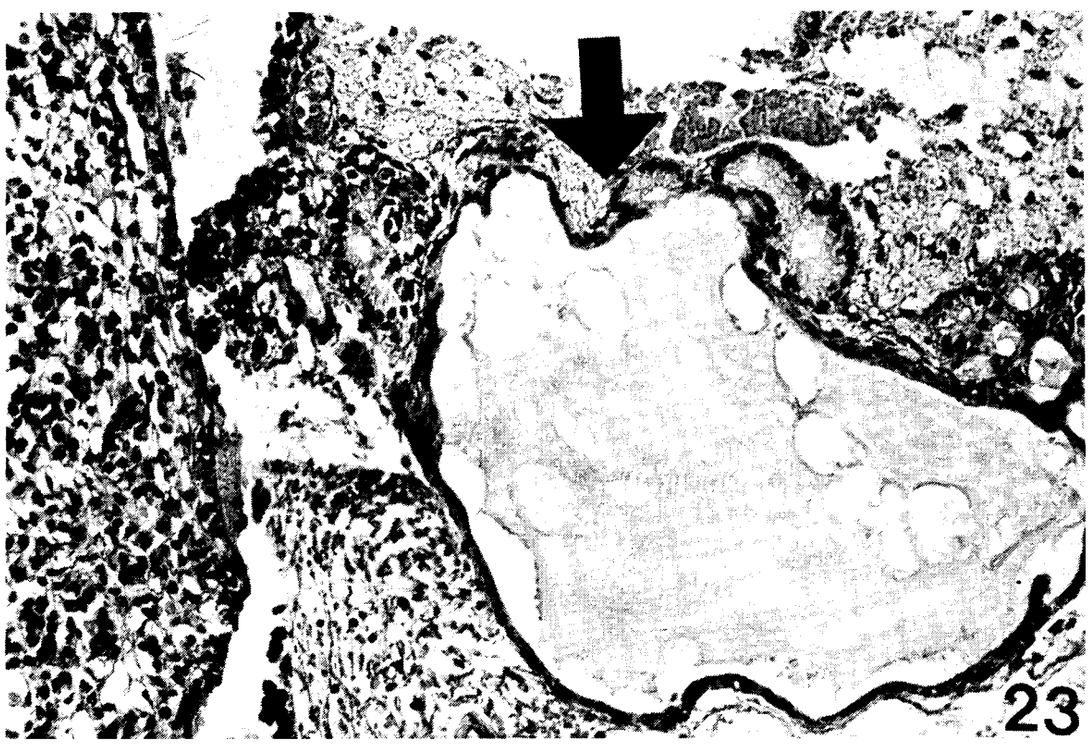
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