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DEVELOPMENTAL STUDIES ON THE LUNG IN DOG (EARLY INTRAUTERINE LIFE)

(With 10 Figures)

By

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تطور الرئه فى الكلاب
(الحياة الجنينية المبكرة)

محمد نبيل كامل

تم فى هذا البحث دراسة التغيرات المورفولجية والنسيجية التىحدثت فى رئة عشرين من أجنة الكلاب التى تراوحت أطوالها من ١٠-١٢٠مم. فى الأجنة التى تراوحت أطوالها من ١٠-١٥مم ظهرت الرئة الناميه فى الجزء الخلفى لسقف التجويف الصدرى على هيئة أنيبوبات مبطنه بنسيج طلائىمركب كاذب وموجود فى كتلةمن نسيج ميزوديرمى ضام محاطه من الخارج بنسيج طلائى بسيط. وعندما وصل طول الأجنة بين ٢٠-٣٠مم أمتدت الرئة الناميه للأمام حتى وصلت الى مدخل الصدر كما أمتدت من الجهة البطنية حتى أحاطت بالقلب وغشائه التامورى. فى هذا العمر تكونت الرئة من عدة أنيبوبات طلائيه بدائيه متفرعة ومنتشره فى النسيج الضام الميزوديرمى والذى يطلق عليه الجهاز الأنيبوبى الرئوى البدائى. تميزت بشائر الجهاز الأنيبوبى الرئوى البدائى الى نوع داخلى فاتح الصبغة وهو المكون لبشائر الممرات الهوائية المستقبليه وآخر طرفى غامق الصبغة وهو المكون للجزء التنفسى المنتظر وذلك على أساس الموقع التبوجرافى فى الرئة الناميه والتركيب المورفولوجى فى أجنة الكلاب التى تراوحت أطوالها ما بين ٥٠-٦٠مم. وعند طول ٧٠مم ظهرت فصوص الرئة وما بينها من أخاديد بوضوح مما يعكس شكلا مماثلا للشكل الناضج لرئة الكلب فى هذا العمر من التطور. وفى الأجنة التى تراوحت بين ١١٠-١٢٠مم أخذت الرئة الشكل الغدى وتميزت بالأتى: حدوث ارتفاع ملحوظ فى عدد الأنيبوبات المكونه للجزء التنفسى المستقبلى حيث فاقت كثيرا نظيراتها المكونه للممرات الهوائيه المستقبليه. تميز النسيج الطلائى للممرات الهوائيه المستقبليه بوجود عدد هائل من الخلايا المنسلخه. وصلت الأوعية الدموية الرئويه الى مرحلة متميزة من النمو حيث وجد أن الشريان الرئوى وتفرعاته أصبح مصاحبا للممرات الهوائيه المستقبليه.

SUMMARY

The development of the dog lung during the foetal life (10-120 mm CVR length) was studied. At 10-15 mm CVR length, the developing lung appeared in the caudal part of the roof of the thoracic cavity. It was represented by tubular structures lined with pseudostratified epithelium embedded in mesenchymal connective tissue mass which was surrounded by cuboidal or flattened mesothelium. On reaching 20-30 mm CVR length, the lung extended cranially to reach the thoracic inlet and ventrally to enclose the heart and its surrounding pericardium. The epithelial portion of the primordium of the lung appeared as a primitive system of branched epithelial tubules. These tubules became more branched with the advancement of age and differentiated into light and dark tubules (the prospective conducting and respiratory systems, respectively), at 50-60 mm CVR length. The adult form of the lung concerning the lobation and fissures were observed at 70 mm CVR length. Around 110-120 mm CVR length, the dark tubules were increased in their number coinciding with the decreased number of the light tubules. The dark tubules (acinar tubules) had a glandular appearence as they closely resembled glandular end-pieces. The light tubules showed coarse and fine PAS positive granules while the dark ones showed few, fine granules. The epithelium of the light tubules (future bronchial tubules) demonstrated large number of disintegrated cells with pyknotic nuclei. In this period of intrauterine life, the pulmonary blood vessels showed a peculiar stage of development.

Key words: Development- Intrauterine Lung-Dog.

INTRODUCTION

The histomorphological features of the lung during various stages of growth and development have been described in several species. However the dog fetal lung received little attention in the available literatures.

LOSSLI and POTTER (1959) studied the prenatal development of the respiratory portion of human lung. *ALCON, et al. (1981) and*

NOSSEUR, et al. (1987) described the prenatal growth of lung in small ruminants. In addition, the fetal lung development in mouse and rat was studied by *TEN HAVE-OPBROEK (1991) and BURRI and MOSCHOPULOS (1992)* respectively.

Moreover, *SAYED (1994)* described the histogenesis of fetal lung in camel using the light and scanning electron microscopy. However, a preliminary study on the prenatal development of lung in dog was conducted by *LATIMER (1949)*. He studied the increase in the weight of heart and lung with reference to body weight and to body length.

The aim of the present study is to give more informations on the topographical aspects and the histological changes in the dog lung during early intrauterine life.

MATERIAL and METHODS

The material employed in the present study originated from the lung of 20 dog foetuses of both sexes ranging from 10 to 120 mm CVR length. The foetuses were obtained from pregnant bitches (Egyptian-land race) sacrificed at various periods of gestation. The foetuses were removed shortly after evisceration and the crown to rump (CVR) length was measured to the nearest millimeter. The entire embryos (10-60 mm CVR length) as well as the lungs of foetuses ranging from 70 to 120 mm CVR length were removed and fixed in 10% neutral buffered formaline and Bouin's fluid. After proper fixation, the material was dehydrated, cleared and embedded in paraffin wax. Sections at 5-7 µm were stained with Haematoxylin and Eosin, Crossman's trichrome, Weigert's elastic, Van Gieson's stain and PAS technique *(DRURY and WALLINGTON, 1980)*

Tissue blocks from lungs of dog foetuses (110-120 mm CVR length) were fixed in paraformaldehyde and glutaraldehyde *(KARNOVSKY, 1965)*. Osmication was performed for one hour in 1% osmium tetraoxide in 0.1 M phosphate buffer at pH 7.4. Dehydration in ethanol followed by propylene oxide and embedding in araldite was performed. Semithin sections were cut and stained with toluidine blue.

RESULTS

In dog embryos ranging from 10 to 15 mm CVR length, the developing lung appeared in the caudal part of the roof of the thoracic cavity (Fig.1) cranioventrally to the developing kidney separated from the caudally located liver by the septum transversum. On the other hand, it was located caudodorsally to the developing heart. The lung primordium projected into the pleural cavity therefore, it was covered by the prospective visceral pleura where the parietal pleura lined the pleural cavity.

Histologically, the primordium of lung was represented by tubular structures embedded within a mesenchymal connective tissue mass surrounded from outside by a primitive mesothelium composed of one layer of cuboidal or flattened cells representing the future visceral pleura (Fig. 2)

The tubular structures showed irregular or slightly folded lumen and were lined by differentiating pseudostratified columnar epithelium. The cells had vacuolated cytoplasm and large oval or elongated nuclei. Some of these cells showed mitotic activity. Strong PAS postivie materials could be demonstrated within the basal and free apical portions of the cells (Fig. 3) Diastase treated sections showed weak reactions with PAS technique.

The tubular structures were surrounded from outside by concentric layers of undifferentiated mesenchymal cells forming the anlagen of myocytes.

Irregular, wide lumen blood spaces were observed within the mesenchymal tissue. They contained nucleated blood elements and were lined by one layer of mesenchymal cells which represented the primitive endothelium.

In dog embryos ranging from 20 to 30 mm CVR length, the developing lung extended cranially to reach the thoracic inlet, where ventrally it extended to enclose the heart. Therefore, the heart and its surrounding pericardium became in contact with pericardial pleura (Fig. 4,4a).

Caudally, the pleural cavity was enlarged to come in contact with the prospective diphragm, on which the diphragmatic pleura extended ventrally to enclose the phrenco-pericardial ligaments; a serous fold connecting the pericardium with the diaphragm (Fig. 4, 4b). At this stage of intra-uterine life, lobation of the lung was distinct and each lobe became surrounded by its pulmonary pleura and seperated from the adjacent lobe by a wide distinct interlobar fissure.

Histologically, the epithelial portion of the primordium of lung was represented by a primitive system of branched epithelial tubules; the primordial tubular system of the prospective lung (Fig. 5). The primordial tubules were lined by differentiating pseudostratified columnar epithelium. The cells of the lining epithelium showed distinct cell boundaries, slightly basophilic cytoplasm and large oval vesicular nuclei (Fig. 5a) .However, the epithelial cells of the distally situated tubules showed more basophilic cytoplasm (Fig. 5b).

Single layer of circularly arranged myoblastic cells was demonstrated outside the main primordial tubules. These cells contained elongated oval deeply stained nuclei (Fig. 5a).

The cellular elements of the mesenchyme were densely arranged around the primordial tubules where they were loosely arranged elsewhere (Fig. 5). Mitosis was commonly observed in the epithelial cells as well as in the stroma cells (Fig. 5 b).

In dog embryos ranging from 50 to 60 mm CVR length, the primordial tubular system became more branched than those observed at the previous age and exhibited a tree-like formation (Fig. 6). The ramification was centrifugally directed which started from the hilar area and exceeded outward toward the periphery.

The primordial tubules (Fig. 6a,6b,6c) were differentiated into; light and dark tubules (the prospective conducting and respiratory systems, respectively).

The light tubules (the prospective conducting system, the future bronchial tubules) were proximally located in the primordial tubular system. They were numerous than the dark tubules and measured about 130 µm in diameter. They were lined by differentiating pseudostratified columnar epithelium measuring about 23.6 µm in height and overlied a distinct basement membrane. The epithelial cells had distinct cell boundaries and lightly stained cytoplasm. The nuclei were large ovoid or elongated in shape and staggered in the middle portion of the cells. Outside the basement membrane, a thin layer (1-2 cell-thick) of myoblastic cells was circularly arranged. Around the myoblastic cell layers, the mesenchymal cells were condensed into 2-3 cell layers. The latter cells had large ovoid or rounded nuclei.

On the other hand, the dark primordial tubules (the prospective respiratory system, the future acinar tubules) that displayed a peripheral situation in the primordial system measured about 99 µm in diameter. They were lined by basophilic columnar cells measuring about 19 µm in height and rest on a distinct basement membrane, surrounded by a single layer of condensed stromal mesenchymal cells. The nuclei of the cells were rounded or large oval in shape arranged in the lower portions of the cells. Some of these nuclei appeared in more than one level, giving pseudostratified appearance. The mitotic figures were dominant in these cells.

The primordium of the parasympathetic ganglia was demonstrated as small clusters of spherical or polygonal cells located around the developing main bronchus. The cells had scanty basophilic cytoplasm and large, vesicular and spherical nuclei (Fig. 6b).

In dog foetuses of 70 mm CVR length, the developing lung extended from the thoracic inlet cranially to the diphragm caudally. The different lobes; cranial, middle, caudal and accessory lobes were demarcated. The interlobar fissures were deep and lined by plumonary pleura. Moreover, the hilus and its containing structures were located in the medial aspect of the lung dorsal to the base of the heart (Fig. 7).

The caudal lobe was the largest one however the accessory lobe was the smallest and lies medial to the caudal one. On the other hand, the middle lobe occupied an intermediate position between the cranial and caudal lobes concerning the size and position. The contents of the hilus were covered by the pleura forming together the pulmonary root.

In this stage of fetal life, the dark primordial tubules showed a relative increase in their number than at the previous age on the expense of the decreased number of light ones. On the other hand, the light tubules showed further divisions, where each lobar bronchus was divided into successive smaller branches; the prospective segmental and subsegmental bronchial tubules.

On reaching 110-120 mm CVR length the number of dark (acinar) tubules increased pronouncedly in relation to the number of the light tubules compared with the previous age. In this period of intrauterine life, the lung has a glandular appearance where the dark tubules termed the pseudo-glandular acini as they closely resemble glandular end-pieces. They appeared in small groups separated by stromal connective tissue rich in primitive blood vessels indicating the early signs of the beginning of pulmonary lobulation at this fetal age. The mesenchyme in this region of tubule grouping was more cellular, vascularised, and contain fine connective tissue fibers (Fig. 8).

The dark tubules measured about 32 μm in diameter and had smooth narrow lumens lined by columnar or pyramidal cells. The cells had basophilic cytoplasm and large vesicular rounded or oval centerally located nuclei with 1 to 3 nucleoli. Each tubule was surrounded by one or two concentric layers of stroma cells (Fig. 8a, 9, 9b).

The light tubules appeared with different diameters (97 to 213 μm) and exhibited short longitudinal mucosal folds (Fig. 8b). The smooth muscle cells surrounding the light tubules (bronchial wall) appeared more pronounced than that observed at the previous age (Fig.8a).

The tubules lined by columnar epithelial cells with clear cytoplasm and deeply stained oval or elongated nuclei crowded in their apical portions (Fig. 8b). The lining epithelium presented a large number of disintegrated cells with pyknotic nuclei (Fig. 8b, 9a). They showed different morphological appearance. Some of them protruded from the surface epithelium and showed darkely stained apical nuclei. Others, sloughed free cells were also frequently demonstrated inside the lumen. In semithin sections (Fig. 9a) semiscribed homogenous areas of different sizes, stained faintly with toluidine blue were observed in the basal cytoplasm of these cells. On the other hand, the disintegrated cells were rarely demonstrated in the acinar tubules.

The light tubules showed coarse and fine PAS-positive granules while the dark ones showed a few fine granules (Fig. 10).

The pulmonary blood vessels reached a peculiar stage of development. They were differentiated into primitive arteries and veins. The developing pulmonary artery as well as its branches were observed to undergo development satellite to the future bronchial tree (Fig. 8, 8a). Where as, the developing pulmonary veins were observed undergoing development independently to the prospective bronchial tubules.

DISCUSSION

In dog embryos ranging from 10 to 15 mm CVR length, the developing lung appeared in the caudal part of the roof of the thoracic cavity caudodorsally to the developing heart. On reaching 20 to 30 mm CVR length, the developing lung extended cranially to reach the thoracic inlet and ventrally to enclose the heart. Therefore, the heart and its surrounding pericardium became incontact with the pericardial pleura. These results are confirmed by *WENSING (1975)* who stated that, as the mammalian lung primordia enlarged, they displaced the attachments of the pleuro-pericardial membranes ventrally so that the pericardial cavity became more and more confined in its extent to the medial part of the prospective thorax. When the pleuro-pericardial membranes attained their final position they attached to the ventral body wall as well as fusing with each other ventrally. In addition, at the previous age of development, the different parts of the parietal pleura were observed. The diaphragmatic pleura extended ventrally to enclose the phrenco-pericardial ligament. This ligament is a characteristic feature of the dog, unlike other domestic animals which have sternopericardial ligament *(NICKEL et al, 1973).*

In dog foetuses of 70 mm CVR length, the different lobes of the lung, cranial, middle, caudal and accessary lobes were demarcated. The interlobar fissures were deep and lined by pulmonary pleura. Moreover, the contents of the hilus were covered by the pleura forming together the pulmonary root. These morphological features are the criteria of the adult form *(NICKEL et al, 1973 and EVANS, 1993).*

The present investigation revealed that in dog embryos of 20-30 mm CVR length, the tubules of the prospective lung were lined by differntiating pseudostratified columnar epithelium. Similar findings were obtained by *SAYED (1994)* in camel foetuses of 38 mm CRL. On the contrary, *AWAD (1985)* in camel fetal lung and *NOSSEUR et al. (1987)* in goat foetuses mentioned that the lung primordium at the early embryonic phase was formed of tubules lined with stratified columnar epithelium while *TEN HAVE-OPBROEK (1991)* reported that the primordial tubules were lined by undifferentiated columnar epithelium in mouse embryos.

On reaching 50 to 60 mm CVR length dog embryos, the primordial tubular system of the prospective lung became more branched and differentiated into light and dark tubules (the prospective conducting and respiratory systems, respectively). This classification was based on the histomorphological criteria of the primordial tubules together with their topography in the prospective lung. These results support the view that the bronchial and respiratory systems originate from a seperate part of the primordial tubular system *(TEN HAVE-OPBROEK, 1979; and TEN HAVE-OPBROEK et al, 1988* in mouse embryos). *SAYED (1994)* recongized the bronchial and respiratory tubules of the prospective camel fetal lung at the early embryonic stage (50-69 mm CRL). He mentioned that the differentiation of the tubular system coincided with the initial appearance of the argyrophilic and seretonin immunoreactive cells. He suggested that these cells promote differenttiation of the primordial tubular system into two systems of tubules, the prospective bronchial and respiratory tubules.

Mitotic figuers were frequently observed in the cellular elements of the developing lung in all studied stages. This phenomenon reflected the active cellular proliferation and differentiation of the primordial tubular system within the dog lung from 10 to 120 mm CVR length.

The presence of large quantities of PAS positive materials (mostly glycogen) in the epithelium of the tubules of fetal lung can be considered as an energy reservoir,since the liver at this stage of development has not yet fully assumed this function *(ROTHMAN, 1954). MOUSTAFA (1986) and KAMEL et al. (1987),* came to the same explanations regarding the dog fetal epidermis and the epithelium of stomach of goat foetuses respectively. Moreover, this phenomenon confirmed the main role of dog fetal liver in haemopoietic function in this period of intrauterine life *(MOUSTAFA and AHMED, 1995).*

The present study showed that the development of smooth muscle cells appeared to be accompanying the bronchial tree. However the acinar tubules lacked the smooth muscle cell precursors. In agreement with *COLLET and DES-BIENS (1974)* in fetal rat lung, the myoblastic cells and the fibroblasts in dogs probably originate from the same primitive mesenchymal cells and their differentiation depends on the zone where they were located.

The present investigation revealed that in dog foetuses of 110 to 120 mm CVR length, the epithelium of the future bronchial tubules demonstrated large numbers of disintegrating cells with pyknotic nuclei. This is a criteria in all epithelia with basal cells in which the sloughed cells are compensated by the growth and differentiation of basal cells through intrauterine life. Similar findings were obtained by *SAYED (1994)* in the bronchial epithelium of camel foetuses (90-300 mm CRL) and *RHODIN (1966)* in human tracheal epithelium. The latter author reported that the sloughing cells became phagocytosed by macrophages which invade the epithelium from time to time.

In conclusion, a complete study of the developmental changes occuring within the dog lung must involve further investigation to the early postnatal life and throughout the prepubertal age.

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LEGENDS

Fig. 1 : Sagittal section in dog embryo (10 mm CVR length) showing: primordium of lung (U), the developing liver (V), heart (H), kidney (K), pleural cavity (arrow) and septum transversum (st). (Haematoxylin and Eosin, x 40).

Fig. 2 : Lung primordium of 10 mm CVR length dog embryo showing: epithelial tubular structure (E), mesenchymal connective tissue (m) blood spaces (b), visceral pleura (vp) and concentric layers of undifferentiated mesenchymal cells (arrow). (Haematoxylin and Eosin, x 400).

Fig. 3: Lung primordium of 10 mm CVR length dog embryo showing: strong PAS positive materials in the apical and basal portions of the cells of the lining tubular epithelium. (Periodic Acid Schiff and Haematoxylin, X 400).

Fig. 4 ,4a and 4b: Sagittal section in dog embryo (25 mm CVR length) showing: the developing lung (U), heart (H), liver (V) , diphragm (d), interlobar fissure (I), attachment of pericardium with pericardial pleura (↑), sternum (st), pericardium (p), epicardium (ep), visceral pleura (vp), parietal pleura (pp) pericardial pleura (ppl), diphragmatic pleura (dp), phrenco-pericardial ligament (pl), fibrous pericardium (fp), pleural cavity (pc) and pericardial cavity (pca). (Haematoxylin and Eosin , 4: x 25 , 4a : x 250 , 4b: x63).

Fig. 5, 5a and 5b: The primordium of dog lung in 25 mm CVR length showing: the epithelial portion of the primordium of lung is represented by a primitive system of branched epithelial tubule; the primordial tubular system(T), mesenchyme (m), visceral pleura (vp), blood spaces (b), mitosis (o), basement menbrane (bm) and a thin layer of myoblastic cells (arrow). (Haematoxylin and Eosin , 5: x 160 , 5a: x 1000 , 5b : x 1000).

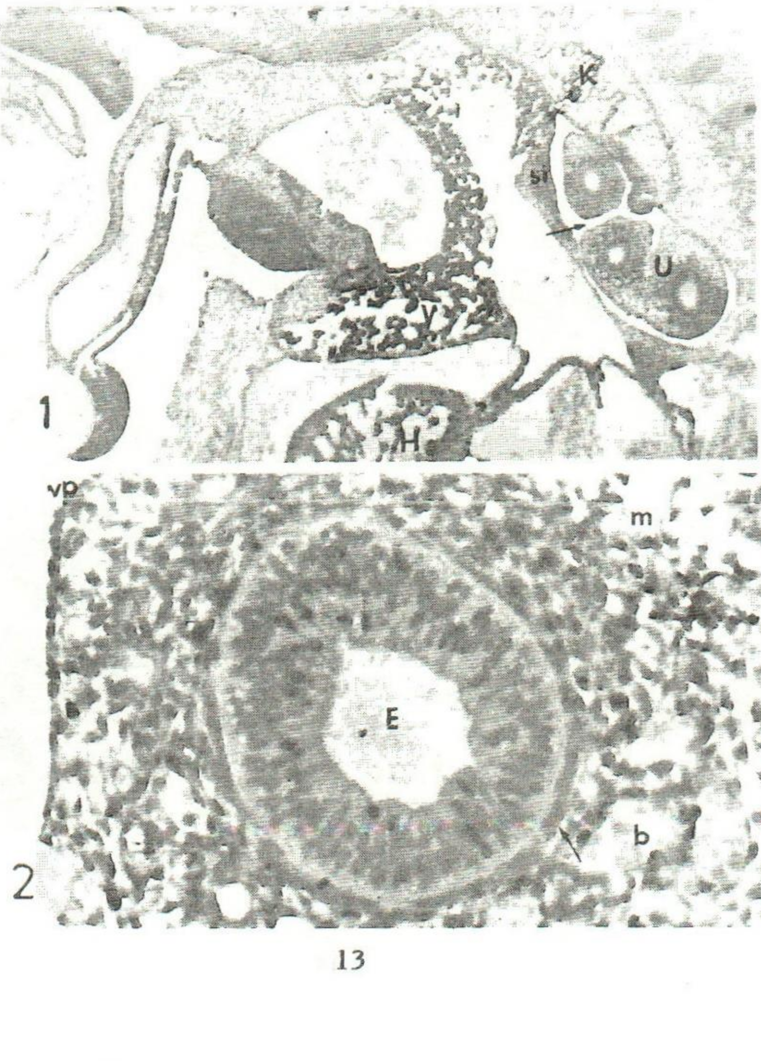
Fig. 6, 6a, 6b and 6c : The primordial tubular system in the prospective lung of 50 mm CVR lung dog embryo. At this stage, the primordial tubules are diffrentiated into proximal light tubules (L) and distal dark tubules (D). Notice: Mitotic divisions (o). concentric layers of myoblaste cells (↓), mesenchyme (m) and the primordium of parasympathetic ganglia (g). (Haematoxylin and Eosin , 6: x 63 , 6a: x400 ,6b: x 400, ,6c: x 400).

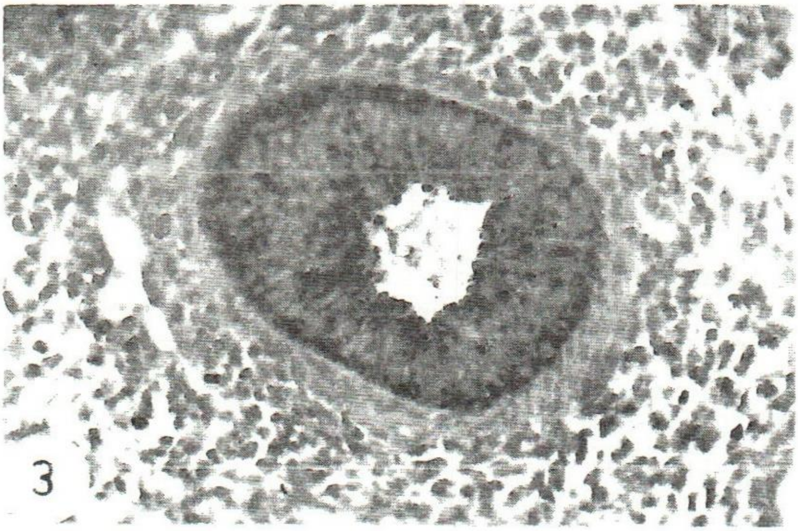
Fig. 7 : Sagittal section in dog foetus (70 mm CVR length) showing cranial (cr), middle (mi), caudal (ca), accessory (ac) lobes of lung, interlobar fissure (I), hilus (Hi), pulmonary root (→), liver (V), diphragm (d) and heart (H), lober bronchus (Lb), caval fold (Cf). (Haematoxylin and Eosin, x 12.5).

Fig. 8 , 8a and 8b: Lung of 120 mm CVR length dog foetus. In this peroid: the fetal lung has a glandular appearance. The dark tubules (D) is pronouncedly increased in number coinciding with the decreased number of the lihgt tubule (L). Notice: the developing pulmonary artery (PA) accompany the future brnochial tree (L), smooth muscle cells (arrow), (Haematoxylin and Eosin, 8: x 63 , 8a: x 250 , 8b: x 1000).

Fig. 9, 9a and 9b: Semithin section in the prospective lung of dog foetus (110 mm CVR length) showing: Light tubule (L) and dark tubule (D). (Toluidine blue, 9: x 400, 9a: x 1000, 9b x 1000).

Fig. 10: Paraffin section in the prospective lung of dog foetus (120mm CVR length) showing: The epithelium of the light tubule demonstrated coarse and fine PAS positive materials while the dark tubules presented few fine granules. (Periodic Acid Schiff and Haematoxylin, x 400).





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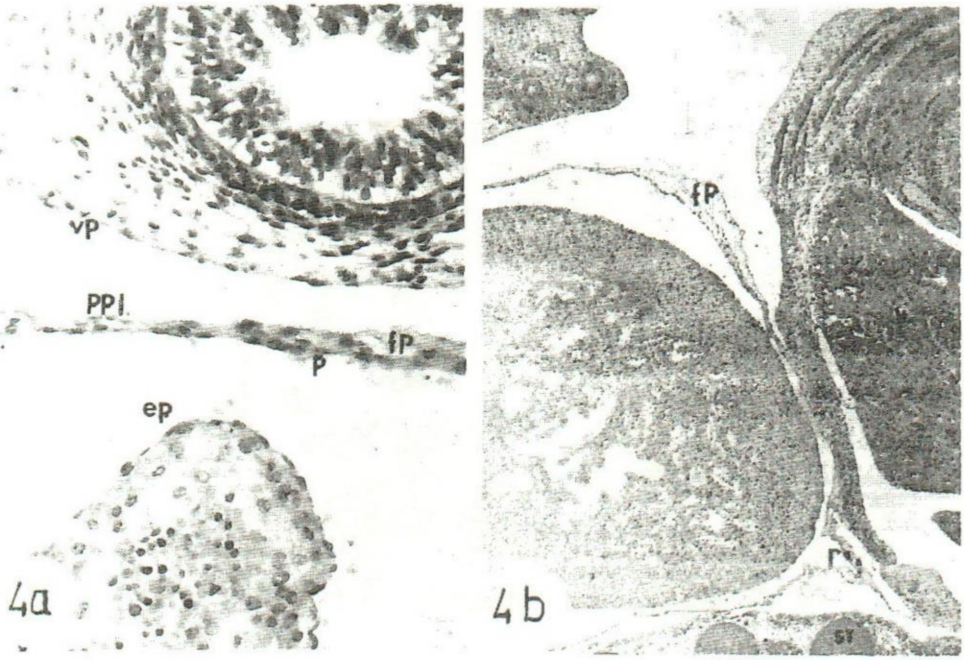
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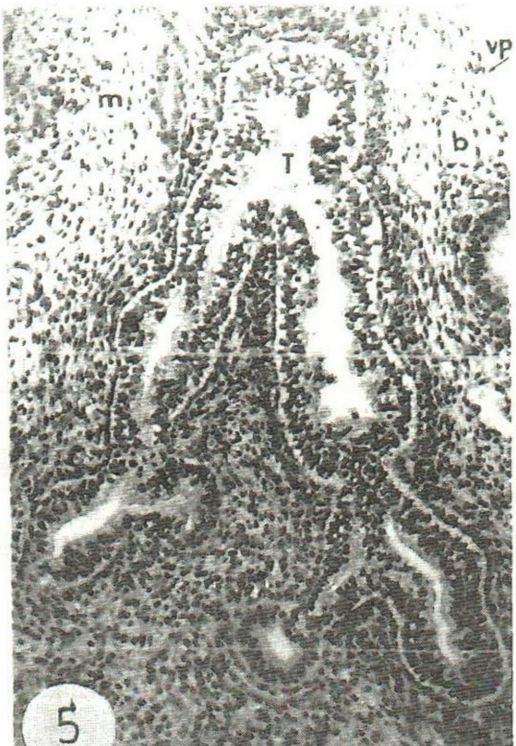
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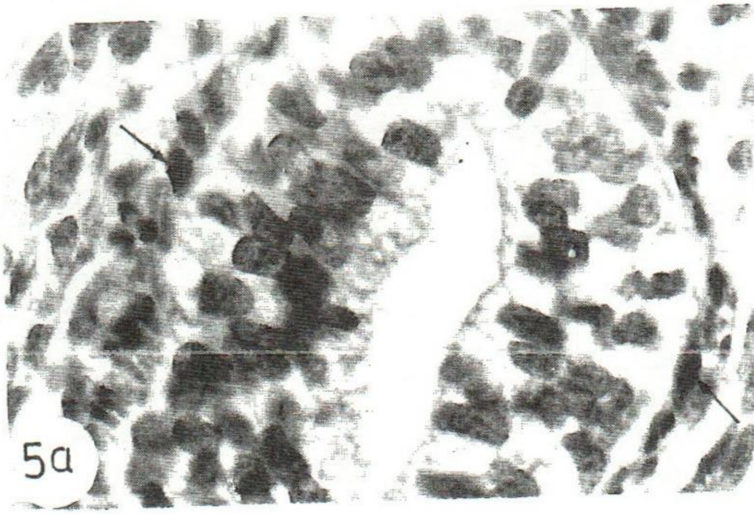
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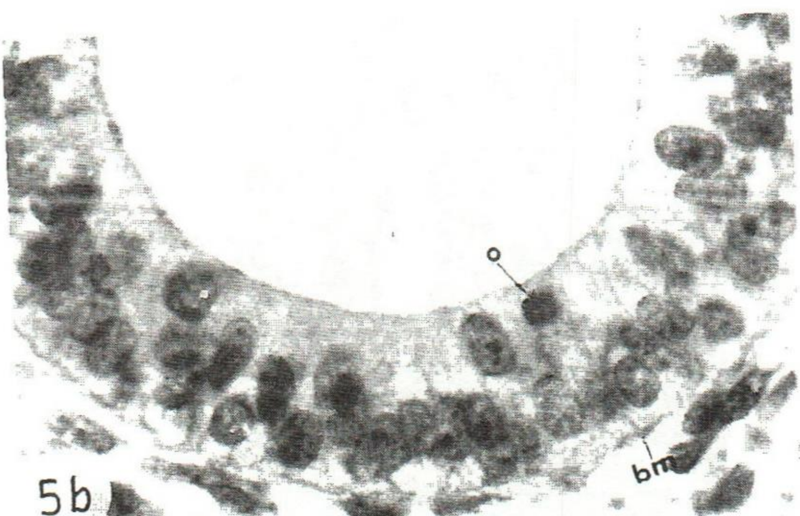
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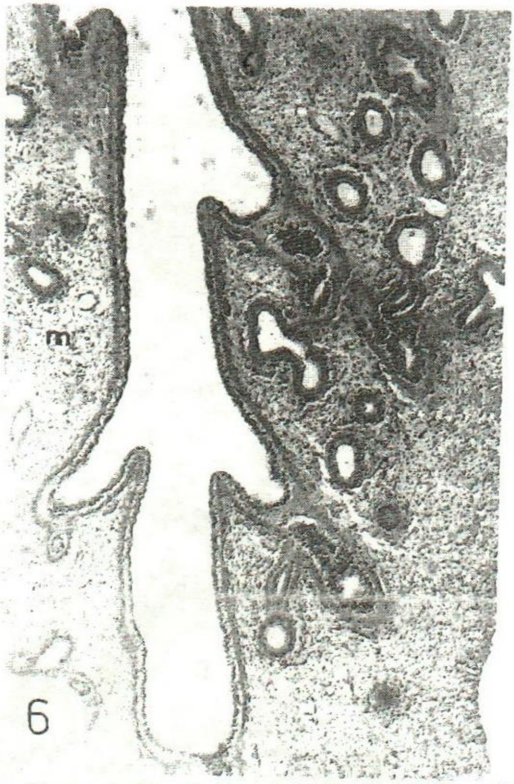
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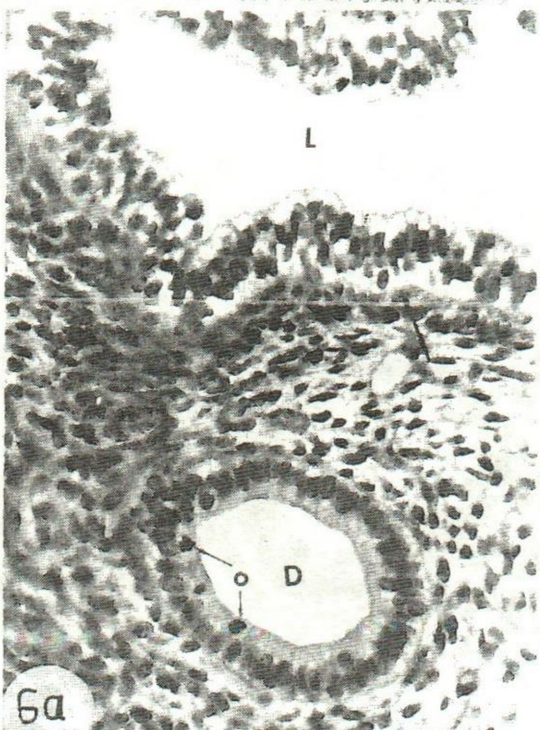
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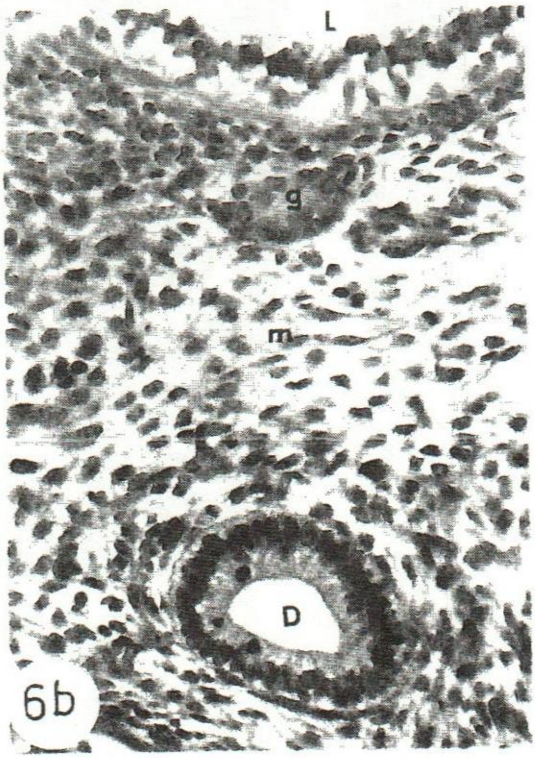
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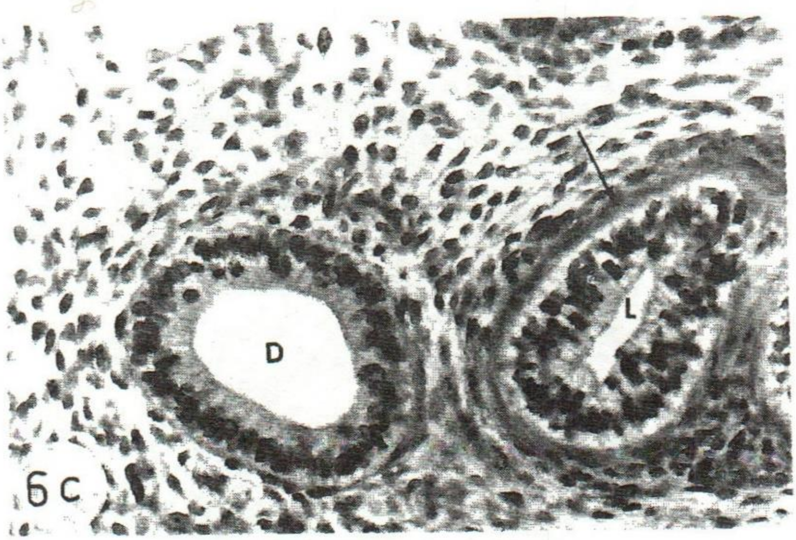
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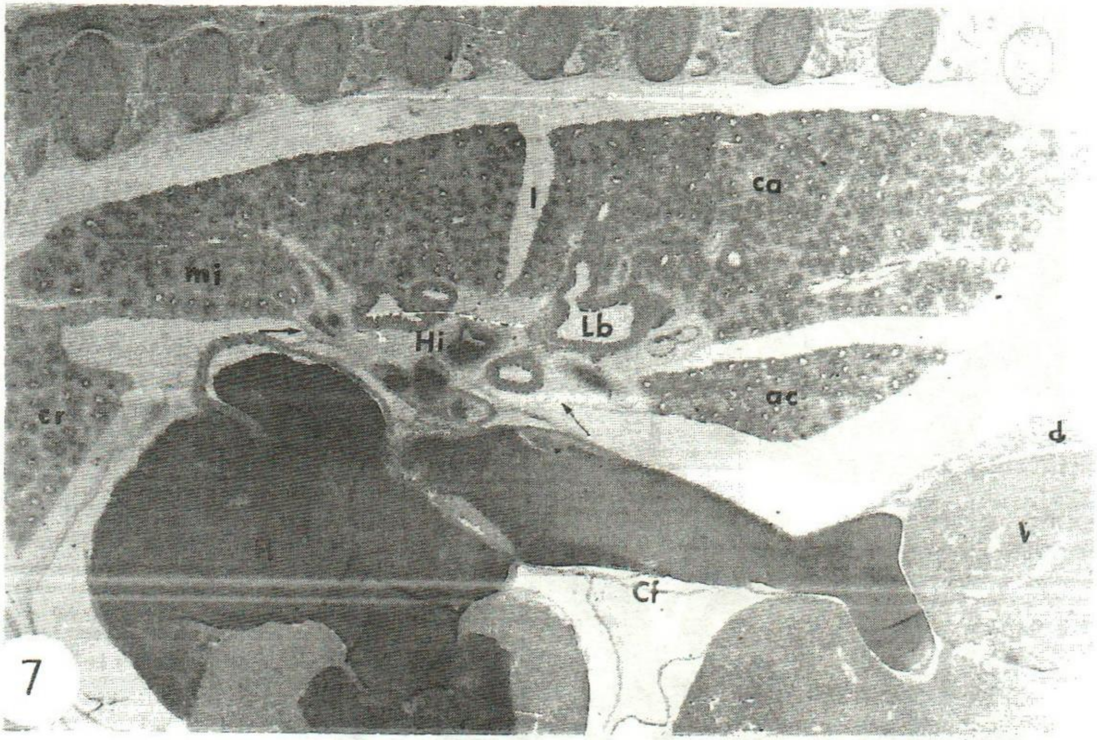

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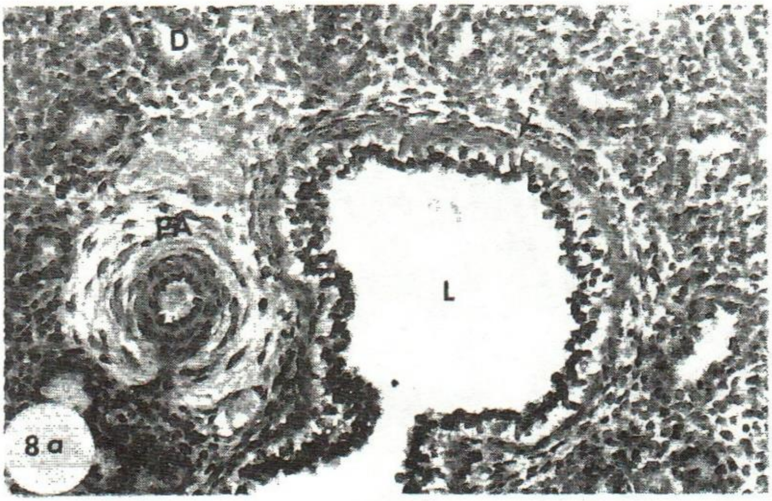
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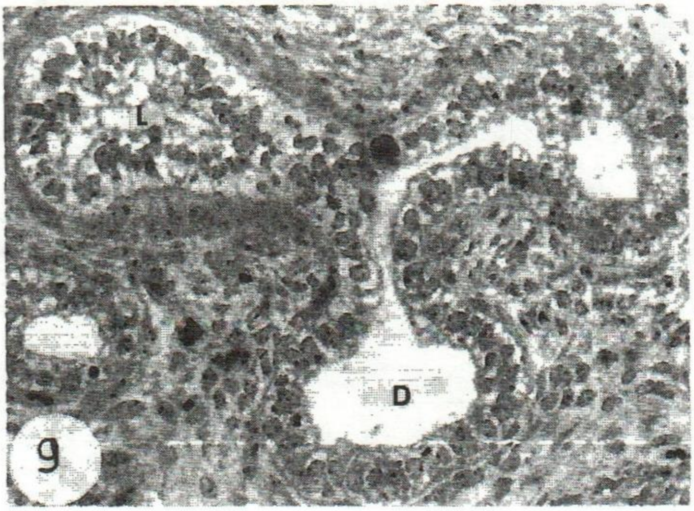
L
8 a


8 b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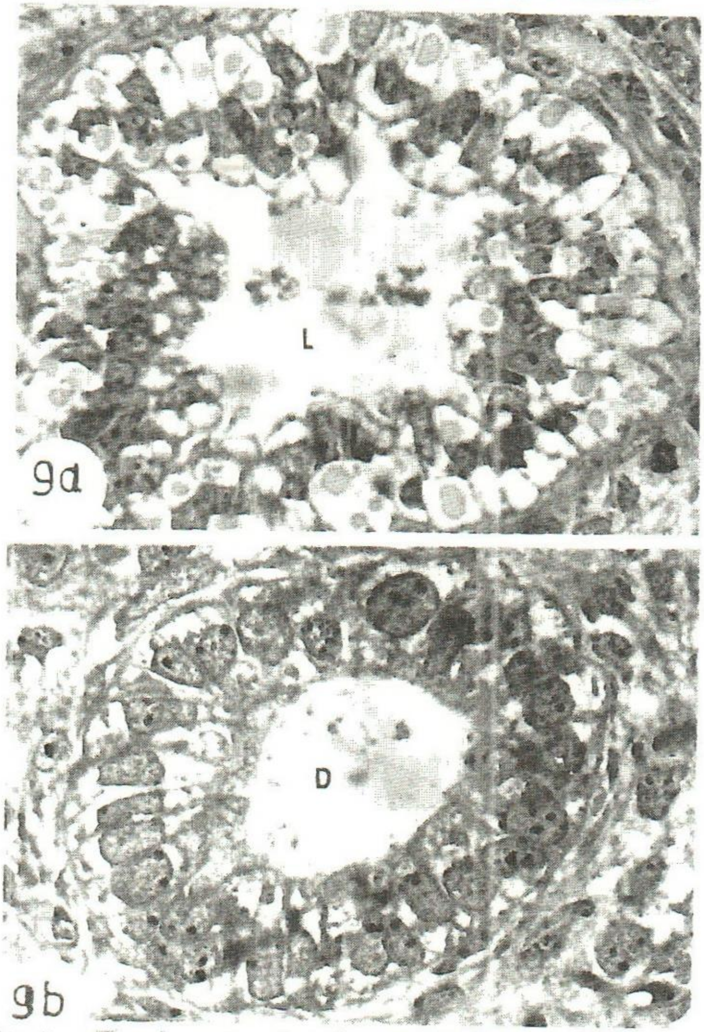
9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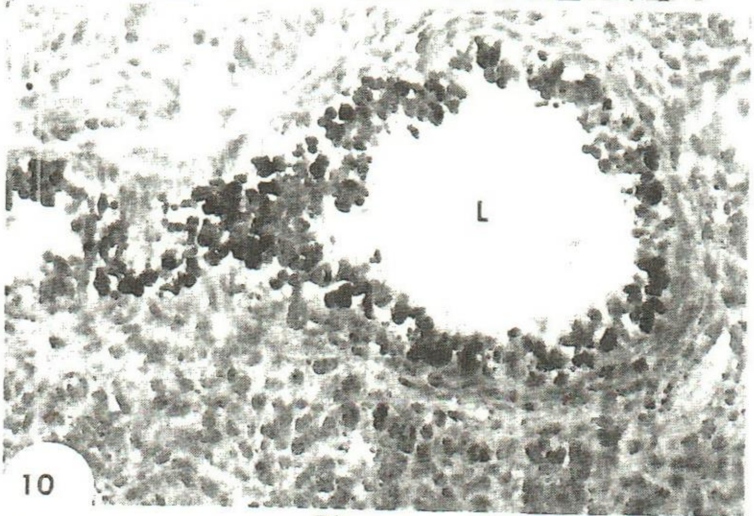
9a
D
9b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10