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The alveolar pores of Kohn in young postnatal rat lungs and their relation with type II pneumocytes

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Summary. In order to obtain more information on the development, morphology and function of the pores of Kohn, the lungs of Wistar rats are studied during their early postnatal period, up to 3 weeks of age, by scanning and transmission electron microscopy.

The substantial development of the interalveolar pores on days 14 and 21 coincides with the period of septal rearrangement when secondary interalveolar septa become lengthened and thinner. The high frequency of transseptal type II pneumocytes from day 7 onwards, and their typical localization near the pores of Kohn at this period of lung development especially suggests that type II pneumocytes are engaged in the formation of the pores of Kohn. During early lung development, the pores of Kohn seem to serve as passageways for alveolar macrophages.

Key words: Lung, Pores of Kohn, Type II pneumocytes, Macrophages, Electron microscopy, Rat

Introduction

The alveolar pores of Kohn are known as round or oval openings in the interalveolar septa, bordered by epithelial cells, which allow communication between the adjacent alveoli.

It was Hauser (1894) who referred to the openings as the pores of Kohn because in a case of pneumonia, Kohn (1893) had observed threads of fibrin passing from one alveolus into another through these interalveolar openings. As long as the morphology of the alveolar wall was discussed, the nature, structure and function of the pores of Kohn remained a matter of controversy (Hansemann, 1900; Schultze, 1906; Müller, 1907; van Allen, 1932; Macklin, 1936; Loosli, 1937). A decade after the description of the epithelial lining of the alveolar wall by means of electron microscopy by Low and Daniels (1952), Boatman and Martin (1963) determined the fine structure of the pores of Kohn and found them to be lined with the alveolar epithelium, indicating that these structures were not suggestive of pathologic conditions but were developmental in origin.

Earlier observations by Müller (1907), Caradonna (1913) and Macklin (1936) and more recent ones by Martin (1963), Ranga and Kleinerman (1980), Scheuermann et al. (1982), Desplechain et al. (1983), Kawakami et al. (1984), Henry and Ranga (1985) and Shimura et al. (1986) indicate that these pores, absent before birth, develop after birth and increase in number with age. Nevertheless, as long as electron microscopy only provides sequences of a film, their formation cannot be described. The question how these sequences have to be put together remains unanswered.

Based on light microscopic observations, Caradonna (1913) concluded from his experiments on young and growing animals that, while the alveolar wall became thinner with age, the formation of pores was induced by excessive forces during dilatation of the alveolar wall; no comment was made on the cell types involved. However, Loosli (1937) mentioned the presence of nucleated cells scattered over the alveolar wall and in the pores projecting freely into the adjacent spaces; Macklin (1950) suggested the possibility that these «epicytes», leaving their moorings in the wall, left a vacancy, regarded as an interalveolar opening.

Based on electron microscopic observations, Sobin (1981) suggests that the mechanism of pore production exists by a disruption of the enlarged posts of connective tissue and ground substance within the capillary network, whereas Takaro et al. (1982) suggest that the epithelium-covered connective tissue gaps are transitional states in the development of the pores. Concerning the relation of the type II pneumocytes with the alveolar pores of Kohn, Schaefer et al. (1964), Cordingley (1972) and Desplechain et al. (1983) regard

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these cells as forming part of the border of these pores. In the opinion of Takaro et al. (1985), this typical localization of type II cells and even their presence in the connective tissue gaps suggest that the type II pneumocytes contribute to the alveolar septal repair.

In the present paper the structure of pores of Kohn is investigated in neonatal and young rats by means of scanning and transmission electron microscopy in relation to the morphology of the alveolar septa and the presence of type II pneumocytes.

Materials and methods

Neonatal and young male rats of respectively 3 to 8 hours and 7, 14 or 21 days old, were anesthetized with Nembutal^R (Na-pentobarbital, 60mg/100g body weight). After laparotomy and perforation of the diaphragm, in order to create a pneumothorax, the lungs were fixed by the intratracheal instillation of cold 2.5% glutaraldehyde in 0.067M Na-cacodylate buffer (pH 7.4, 380 mosmol) at an end pressure of 20 cm H_2O-column in supine position. After fixation for one to three hours, 1 mm^3 and 10 x 10 x 5 mm^3 tissue blocks of the lower part of the left lung were immersed in the same fixative for another 3 hours.

Transmission electron microscopy

The small tissue samples were rinsed overnight in 0.067M Na-cacodylate buffer with 7.5% saccharose (pH 7.4, 360 mosmol) and postfixed in 2% OsO_4 buffered with 0.038M veronal acetate containing 4% saccharose. Then, two 5 min rinses in 0.05M veronal acetate containing 6% saccharose (pH 7.4, 325 mosmol) were followed by a one hour block staining in 0.5% uranyl acetate in the rinsing buffer. After a final rinse of 2 times 5 minutes in the buffer solution, the tissue blocks were dehydrated in a graded acetone series and embedded in Durcupan^R.

Sections of 70nm were cut with a Reichert OmU_2 or LKB-ultratome III ultramicrotome with glass knives, picked up on 300 mesh formvar-coated grids and additionally stained with 2% aqueous uranyl acetate for 10 minutes and with lead citrate for 15 minutes. Observations were made with a Siemens Elmiskop at 80 KV.

Scanning electron microscopy

The glutaraldehyde-fixed tissue strips were also rinsed overnight, as is the case for transmission electron microscopy, after which they were dehydrated in a graded acetone series, critical-point dried with liquid CO_2, mounted on stubs and coated with a 40 nm gold layer using the diode-sputtering system of Polaron^R type E5000. The specimens were investigated in an Etec^R scanning electron microscope.

Results

Rearrangement of the alveolar septa

Scanning electron microscopy of neonatal rat lungs revealed different sacculi, forming an expanded gas-exchange area, which were situated distally from the terminal bronchioli; recognized by the presence of Clara cells (Fig. 1). As observed in the lungs of 7- and 14-day-old rats, sprouts of secondary septa, protruding from the primary septa, compartmentalized the sacculi in several alveoli. As is seen, the lungs of 3 week old rats showed a well-developed parenchymal area full of alveoli (Fig. 2).

As revealed by transmission electron microscopy, the interalveolar septa became much thinner during the postnatal process of alveolarization. In comparison with the primary interalveolar septa, carrying a double capillary bed in neonatal animals (Fig. 3), the secondary septa in the lungs of 3-week-old rats showed a single capillary network (Fig. 4). These capillaries were sandwiched between the alveolar epithelia of adjacent alveoli. Mainly squamous type I pneumocytes were recognized with in-between polygonal type II pneumocytes containing lamellar inclusion bodies.

From day 7 on, the basal portion of the type II pneumocytes often reached the basal side of the type I cells at the opposite side of the alveolar septum, so that their basement membranes partly fused (Fig. 5). Transseptal type II cells, bordering simultaneously at two and even three alveoli were observed even more frequently (Fig. 6). Although the basal surface of the epithelial cells was mainly occupied by type 1 epithelial cells, the latter cell type rarely contacted another cell of the same type at the opposite side of the alveolar septum (Fig. 7).

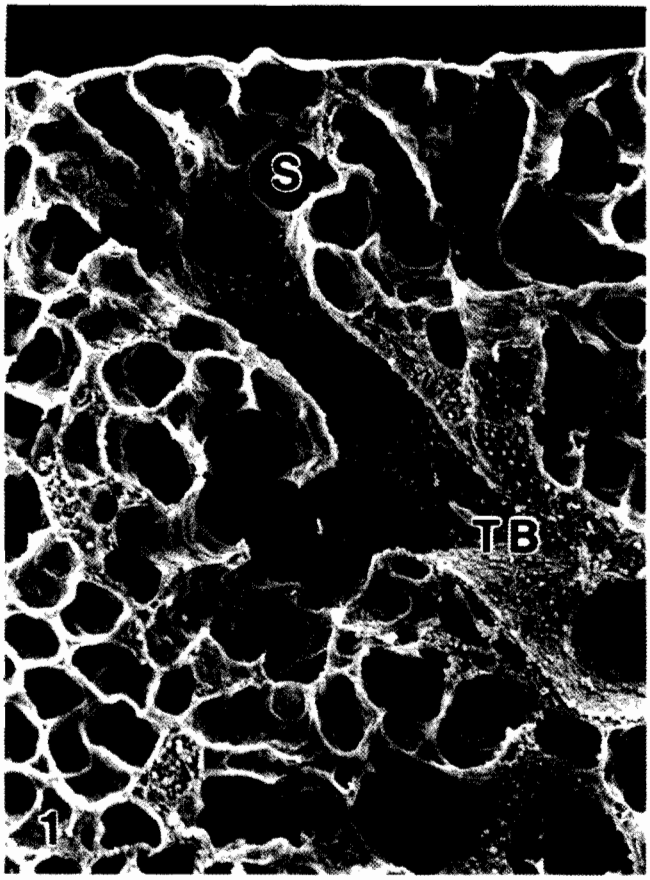
Type I cells may occur as transseptal cells (Fig. 8) so that one squamous cell layer, devoid of small vesicular profiles, forms a cytoplasmic plate in the thin inter-alveolar septum as a slender mechanical barrier between adjacent alveoli.

Occurrence of the pores of Kohn

Openings in the interalveolar septa can be more readily detected with the aid of scanning electron microscopy, which allows the investigation of large areas of the epithelial surface.

In neonatal rat lungs, the pores of Kohn were almost completely absent. The sacculi showed large microvillous areas, typical of type II cells, as well as thick-cut primary septa.

Especially in 14- and 21-day-old rats the interalveolar pores occurred more frequently, whereas the microvillous area became relatively smaller and the septa thinner (Fig. 9). The pores were lined by type I pneumocytes, but in young rats type II cells were frequently found at their border. A clear rim of the epithelial junctional area occurred near the edges of these openings, while the type II cells, if present, were located at one side of the alveolar septum (Fig. 10). The latter observation was confirmed by transmission electron microscopy, showing type II epithelial cells which, together with type I pneumocytes, constituted the border of the interalveolar pores (Fig. 11). The openings mentioned were located in the mid-septal area as well as at the base of the interalveolar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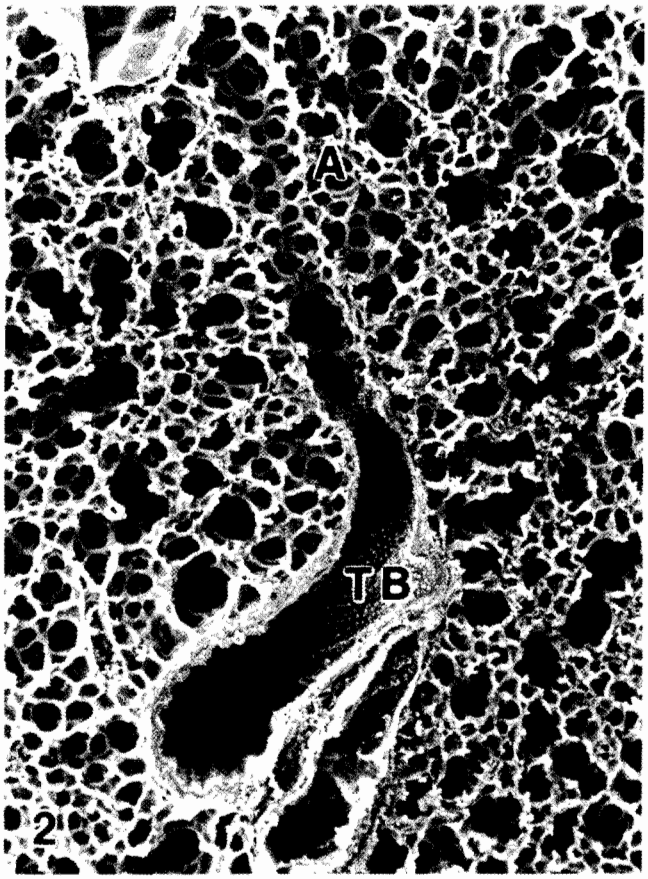
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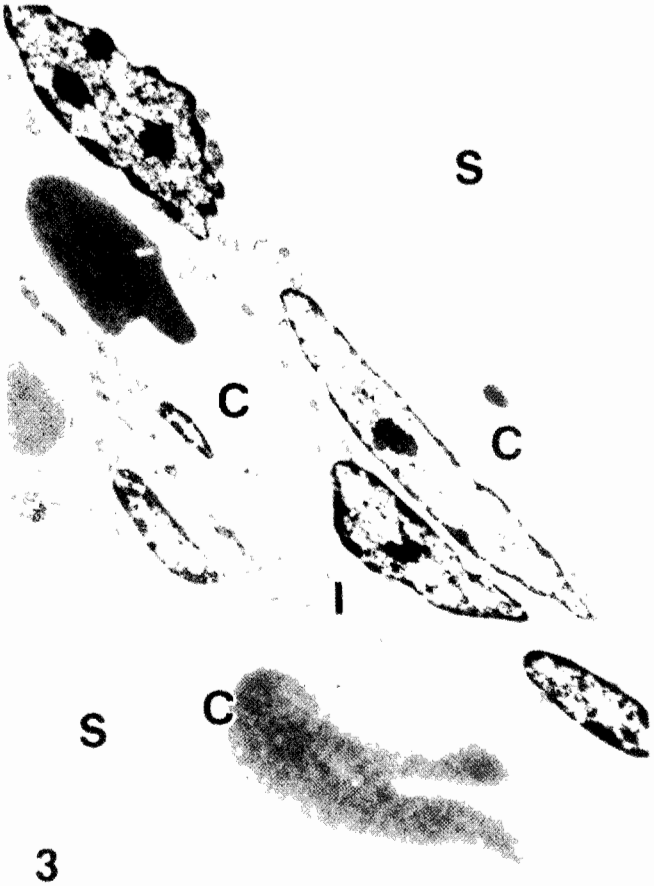
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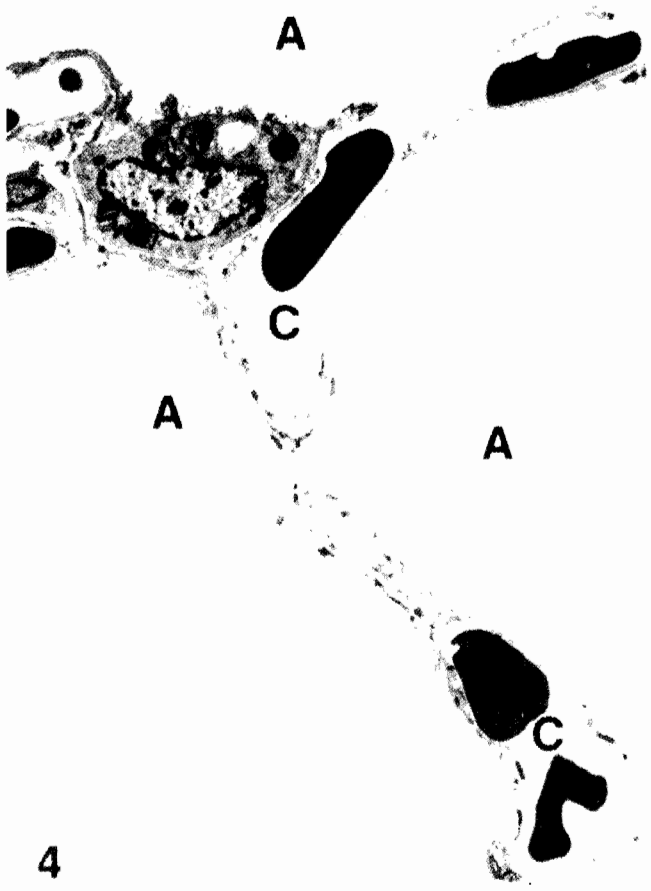
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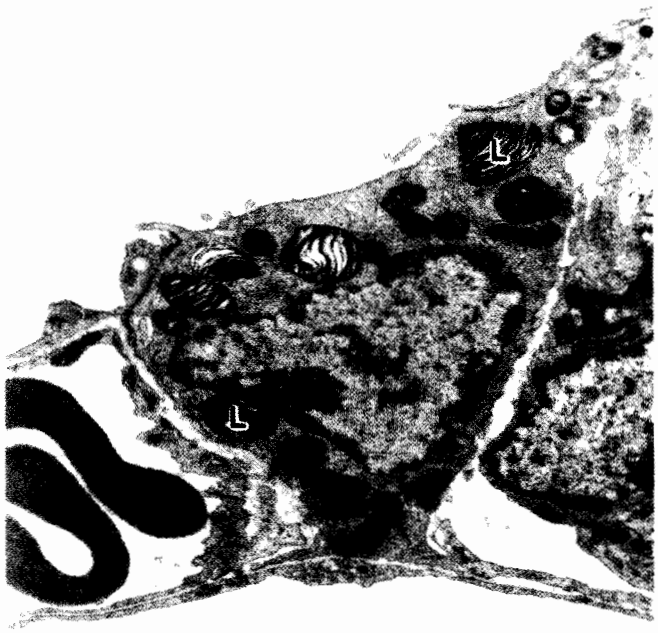

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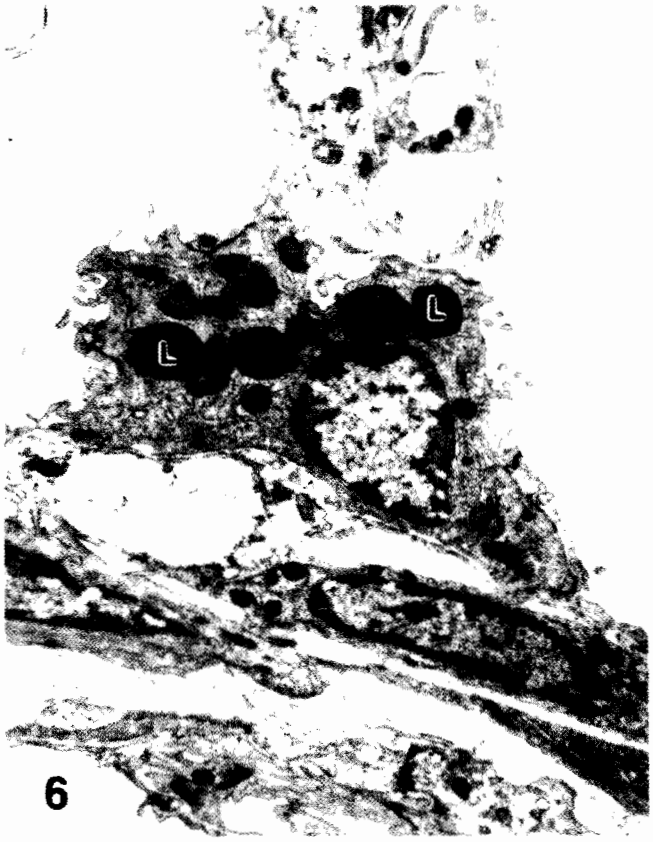

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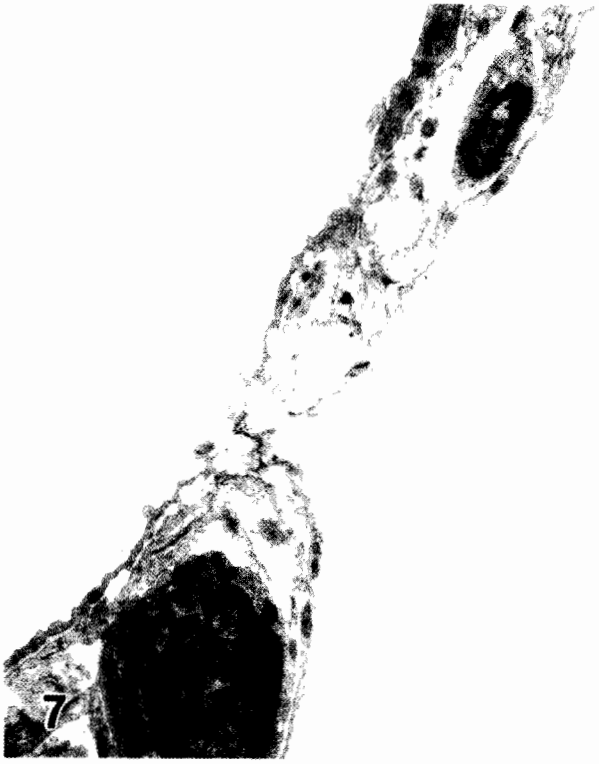

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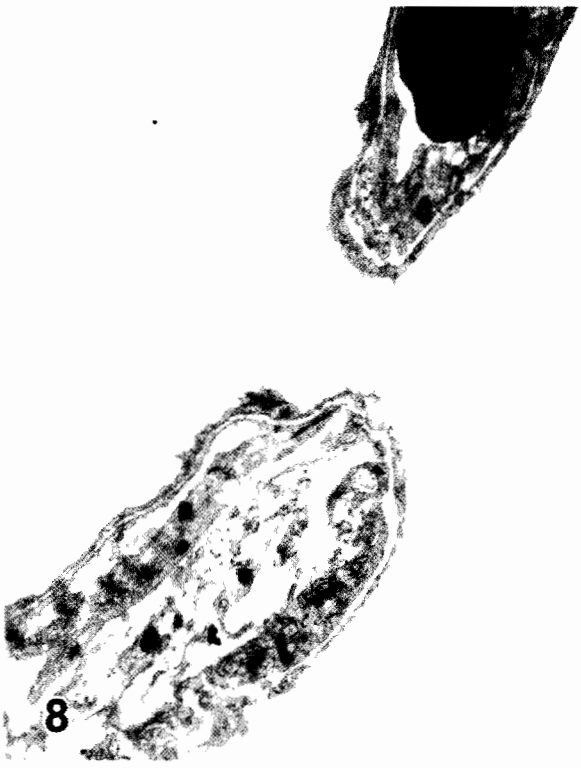

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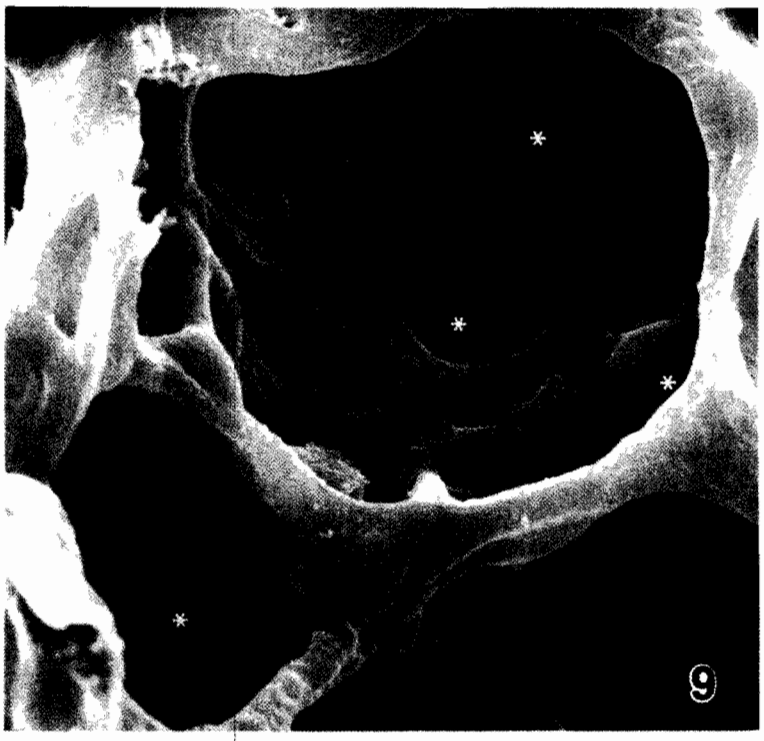
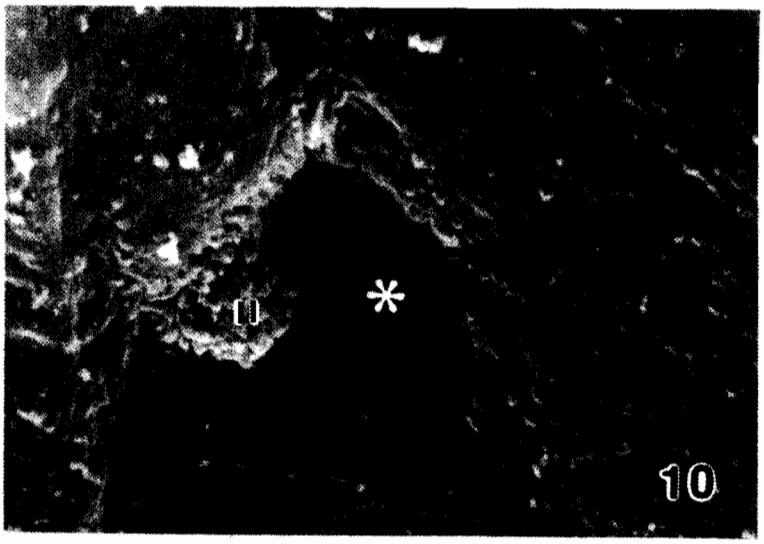
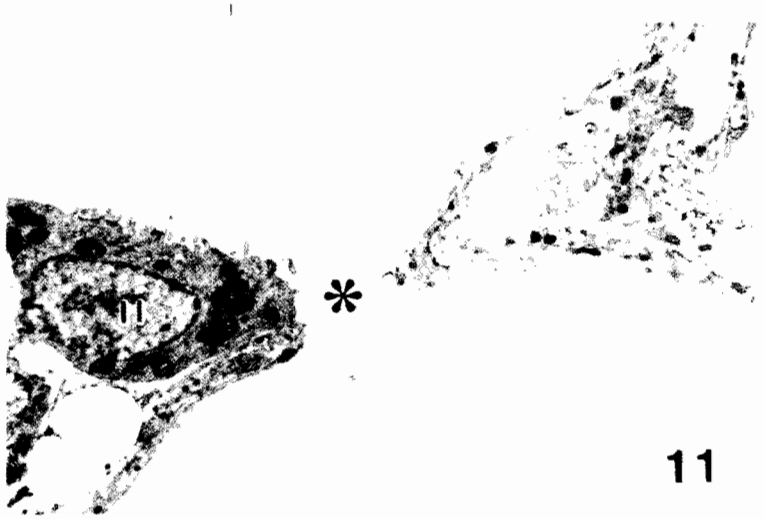






Figs. 1-4 Alveolarization and septal rearrangement. Large sacculi (S) and small alveoli (A) situated distally from a terminal bronchiole (TB) are shown, respectively, in a neonatal (Fig. 1; × 150) and a 21-day-old rat lung (Fig. 2; × 125). The thick septa between adjacent sacculi (S) (Fig. 3; × 6,000) are characterized by a double capillary network (C) and a well-developed connective-tissue core containing a large number of interstitial cells (I). The thin interalveolar septa (Fig. 4; × 3,000) only show a single capillary network (C) and a less developed connective-tissue core.

Figs. 5-8. Contacts between linings of adjacent alveoli. A type II pneumocyte, rich in lamellar bodies (L), makes contact with a type I pneumocyte of an adjacent alveolus in a 7-day-old rat lung (Fig. 5; × 6,000). A transseptal type II cell in a 14-day-old rat lung shows tight junctions with epithelial type I cells of adjacent alveoli (Fig. 6; × 6,000). A close contact between type I cells of adjacent alveoli (Fig. 7; × 7,000) and a single type I epithelial layer forming a cytoplasmic plate between two alveoli (Fig. 8; × 7,000), both observed in a 14-day-old rat lung.

Fig. 9. An alveolus of a 21-day-old rat. The interalveolar pores of Kohn (*) occur more frequently. × 1,300

Figs. 10-11. Pores of Kohn (*) in 21-day-old rat lungs, with the typical appearance of type II cells (II), as observed in scanning (Fig. 10; × 7,500) and transmission (Fig. 11; × 6,200) electron microscopy.

Figs. 12-13. Pores of Kohn (*) as passageways for alveolar macrophages (M) that move by means of lamellipodia (arrow) from one alveolous (A) to another as seen in transmission (Fig. 12; × 2,800) and scanning (Fig. 13; × 4,500) lectron microscopy.

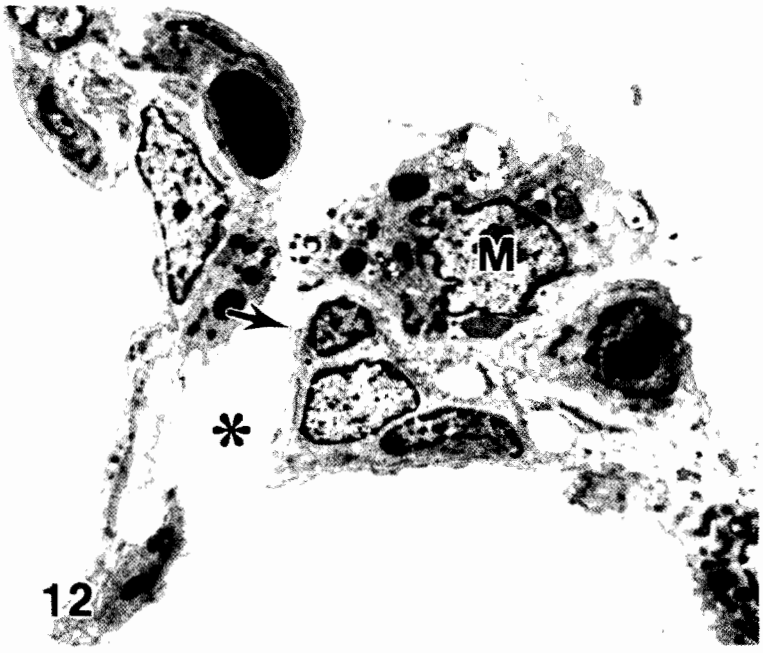
Fig. 14. Diagram illustrating hypothesis proposed in text: **A)** A segment of a normal alveolar septum with two capillaries (C) in cross section; i.e. a type II pneumocyte (II) in the upper epithelial lining and a type I cell (I) in the lower lining. **B)** The type II pneumocyte (of the upper lining) comes into contact with the basal side of a type I cell of the opposite side of the alveolar septum. **C)** Penetrating between the type I epithelial cells of the opposite side of the septum, the transseptal type II cell is now in contact with two adjacent alveoli. **D)** When type I epithelial cells of adjacent alveoli make contact with each other by the movement of the epithelial junctions (arrow) with the type II cell over this transseptal cell up to each other, a pore of Kohn (*) is formed.

septa. Most thin sections through the pores merely revealed a lining of attenuated type I cells, which might indicate that the pores are only bordered by these cell types or that the sections have been made beside the bordering type II cells.

Apart from the presence of the pores of Kohn in young rats, it was striking to note that alveolar macrophages, almost absent in neonatal lungs, were more frequently observed during postnatal development. Their presence on the alveolar surface as well as in the alveolar openings was observed both in transmission and scanning electron microscopy (Figs. 12, 13).

Discussion

Studying the effect of aging on lung structure and looking at the same time at the alveolar pores of Kohn, Martin (1963), Ranga and Kleinerman (1980) and Kawakami et al. (1984) consider the pores of Kohn as developmental in origin. We therefore have to consider the important structural changes occurring during lung growth.



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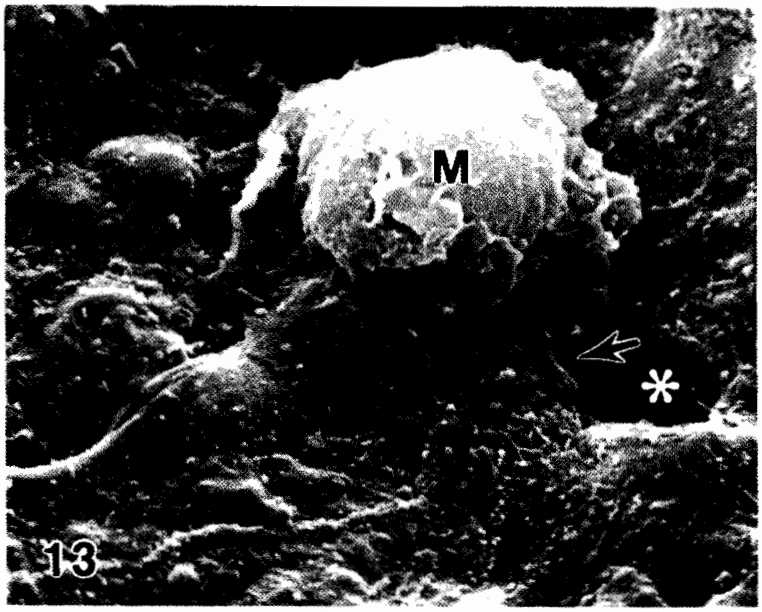

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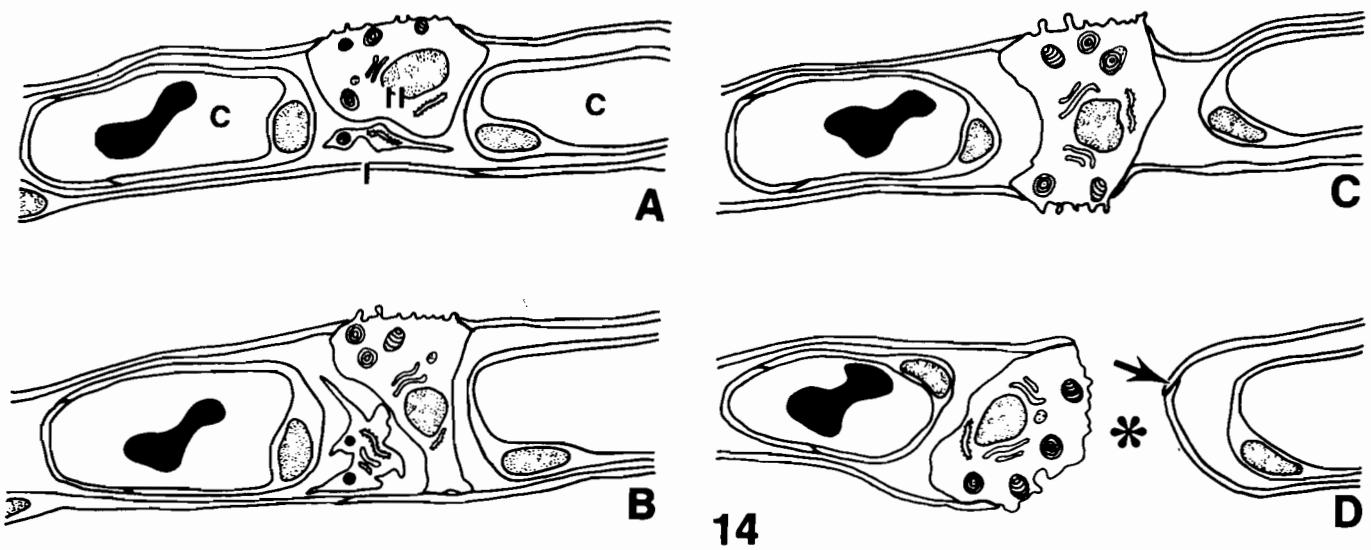
Our observations confirm that, together with the rapid lung expansion, lung development is characterized by the process of alveolarization in early postnatal life. Burri (1974) and Burri et al. (1974) distinguish three phases in lung growth of rats. An initial phase of lung expansion (up to 4 days) is followed by a phase of tissue proliferation (day 4-13) during which the process of alveolarization is characterized by the formation of secondary septa as outgrowths from primary septa, which results in a rapid increase in alveolar and capillary surface areas. This phase can continue for 4 to 10 weeks (Holmes and Thurlbeck, 1979). In a third phase of equilibrated growth (third week to adult age), an important lengthening and thinning of the alveolar septa is followed by a proportionate alveolar growth. Pinkerton et al. (1981) confirmed these results and showed that lung growth was essentially complete at 5 months of age.

The electron microscope studies of Ranga and Kleinerman (1980) and Kawakami et al. (1984) concern the equilibrated growth-phase in mice, where the postnatal lung development closely matches the description in the rat (Amy et al., 1977). Ranga and Kleinerman (1980), Henry and Ranga (1985) and Shimura et al. (1986) notice a significant increase in the number of alveolar pores between 1 month and 3 months of age. Moreover, Kawakami et al. (1984) observed the major increase between 38 days and 68 days in mice.

From early postnatal life no morphometric data are available about the number of interalveolar pores. However, our observations of the rat lung suggest that a substantial development of alveolar pores takes place from the 14th day of postnatal life onwards, confirming the results of Amy et al. (1977) in their study on mice lung. This coincides with the onset of septal rearrangement which results in septal stretching and thinning (Burri, 1974; Burri et al., 1974) and in a substantial decrease in the cellularity of the interstitium (Vidic and Burri, 1983). The morphology of the pores of Kohn in this period of the lung development might teach us something



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about the origin of these structures. As observed by scanning and transmission electron microscopy, the morphology suggests that both types of epithelial cells may be engaged in the formation of these pores.

Studying type I pneumocytes during postnatal morphogenesis in 90-day-old-cats, Mercurio and Rhodin (1984) showed a small pore in this squamous cell type by cell reconstruction after serial sectioning. These investigators also showed the presence of cytoplasmic plates as cytoplasmic extensions of type I pneumocytes lining two alveoli, which is confirmed by our observations in the rat. Studying the pores of Kohn in adult human lung, Takaro et al. (1982) found a correlation between the presence of the cytoplasmic plates and the number of pore profiles. Also, the stepwise increase in size of the connective-tissue gaps bridged by a double layer of type I cells (4.1 μm), the gaps bridged by a single layer of type I cells (5.0 μm) and the mean diameter of the interalveolar pores (6.5 μm) suggest that these cytoplasmic plates might be an alveolar pore in the process of formation. However, Weibel (1971) recognized these cytoplasmic plates as connecting or branching points, establishing transseptal extensions that might bring certain metabolic advantages; such as keeping the spreading distances of the cytoplasmic extensions to the nucleus as short as possible.

Nevertheless, because of the typical appearance of type II pneumocytes near the border of the interalveolar openings (Boatman and Martin, 1963; Schaefer et al., 1964; Cordingley, 1972; Desplechain et al., 1983), the role of type II pneumocytes in the formation of the pores of Kohn needs further attention. Despite the fact that the alveolar connective-tissue gaps are not counted systematically in this study, there are indications that the gaps occupied by type II cells apposed to a type I cell, and the gaps occupied by transseptal type II cells, occur before interalveolar pores can be observed. Up to this moment of lung development, the latter type of tissue gap cannot be the consequence of alveolar septal pore repair, as was suggested by Takaro et al. (1985) in their study of adult human lungs. Our observations of frequent transseptal type II cells and the presence of type II cells at the border of alveolar pores in developing lungs of young rats suggest the possibility that, during septal differentiation, movement of cell contacts over the transseptal type II cells takes place and brings the type I cells of adjacent alveoli together, resulting in an opening on whose border these cell junctions occur (Fig. 14).

The association of type II cells with the septal gaps is not an illusion as may be caused by oblique sections (Scheuermann et al., 1988). The data of Takaro et al. (1985), especially, resulting from a single serially-sectioned hemi-alveolus, revealed that about 69% of all type II cells occupied some type of septal gap, while 24% of all type II cells formed part of the rim of interalveolar pores.

Besides these findings, Vidic and Burri (1983) found a great increase in the type II cell population which represented 58% of the alveolar epithelial volume at 3 weeks of postnatal development in the rat. This coincides with the appearance of the pores of Kohn and suggests that the type II pneumocytes might play a role in the formation of the pores. Pinkerton et al. (1982), studying lung development up to 26 months of age, saw an increase in the type II cell population up to 5 months of age; after this period, type II pneumocytes showed a significant decrease in number, whereas type I cells still increased. These studies and others (Kauffman et al., 1974; Adamson and Bowden, 1975) confirm that type II cells do function as precursors of type I cells in the developing rat lung. This differentiation could also take place after the formation of the pores of Kohn, where type II cells, initially bordering the pores, are transformed into type I pneumocytes.

Additional information from serial sections about differences in septal- and alveolar-pore morphology of young and older animals will give a better insight in interalveolar pore formation.

The functional significance of the type II cells near the pores of Kohn can probably be found in a greater surfactant demand at the sites of interalveolar communication. Gil and Weibel (1969/1970), Parra et al. (1978) and Takaro et al. (1979) observed that in lungs prepared by vascular perfusion, most septal pores were filled with elements of the alveolar lining layer which could explain the presence nearby of type II cells.

Although the role of the alveolar pores in collateral ventilation still remains unclear (Takaro et al., 1979; Desplechain et al., 1983), these structures serve as passageways for alveolar macrophages (Cordingley, 1972; Ferin, 1982). Ferin (1982) suggested that the fully mature macrophages were probably lower in number than the alveoli; for this reason, in circumstances of alveolar pollution, active movement of macrophages through alveolar pores would be necessary.

Nevertheless, our observations on the young animals suggest that the migration of alveolar macrophages through these openings is a common event during alveolarization where septal lengthening and thinning, the appearance of transseptal type II cells, the development of pores of Kohn and the occurrence of alveolar macrophages seems to be connected.

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