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Postnatal growth of the mouse lung

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INTRODUCTION

Postnatal growth of the lung has been the subject of investigation and controversy for many years. Koelliker (1881) believed that the adult structure of the lung was already present in the newborn infant and growth involved expansion only. This view was supported in part by Short (1950), who considered that lung growth was determined by purely physical factors, and thought that simple distension of the newborn rabbit lung resulted in a structure resembling that of an adult lung. More recent work has indicated that the lungs of newborn animals are qualitatively different from those of adults of the same species in that alveoli are few or absent at birth. Thus most or all alveoli are formed after birth in rats (Weibel, 1967; Burri, Dbaly & Weibel, 1974*a*), rabbits (Engel, 1953), cats (Engel, 1953; Dingler, 1958), and man (Dubreuil, Lacoste & Raymond, 1936; Boyden & Tompsett, 1965; Reid, 1967). The way that alveoli are formed is controversial. Subdivision of peripheral lung units, alveolarization of non-alveolated airways (bronchioles), peripheral airway branching and alveolar 'sprouts' have all been described. Boyden & Tompsett (1961, 1965) have stressed the fact that the peripheral airways are different in the newborn dog and human from adults of the same species. They have termed the relatively large, simple units in newborn puppies 'terminal saccules'. Similar observations have been made by Weibel (1967) and, in his laboratory, Burri and his colleagues (1974*a*, *b*) have recently made a systematic survey of the postnatal growth of the lung in the rat. They demonstrated that the neonatal rat has no true alveoli, and that respiratory exchange is carried out in large smooth-walled sacs ('primary saccules'). The walls of these saccules were called 'primary septa'. Primary saccules differed from alveoli by their large size and lack of complexity, and primary septa from nature inter-alveolar septa by the presence of a double capillary system in the former. They thought that the primary saccules were subdivided in the postnatal period by slender crests (termed 'secondary crests or septa') into alveoli. Secondary septa consisted of a covering of Type I alveolar epithelium and a core of interstitial cells, capillaries and connective tissue. Subsequent development of the lung was marked by a decrease in interstitial tissue and an increase in lung complexity.

The purpose of this paper is to amplify these observations concerning postnatal growth, using the scanning electron microscope, to provide data concerning lung

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Table 1. *The number of animals, their mean lung and body weight and lung weight/body weight ratios are shown at various times*

(The animals are grouped by age in days and, for example, 0 indicates animals of less than 24 hours of age, and 1 indicates animals 24 hours to just less than 48 hours of age.)

Age (days)	No. of animals	Lung weight (mg)		Body weight (g)		Lung weight / Body weight (mg/g)
		Mean	Standard deviation	Mean	Standard deviation	
0	14	25·4	3·2	1·428	0·202	17·8
1	19	32·5	5·7	1·832	0·244	17·7
2	10	37·2	4·1	2·198	0·159	16·9
3	10	47·1	10·6	2·634	0·426	17·8
4	10	54·7	11·8	2·983	0·616	18·3
5	7	55·5	7·3	3·151	0·263	17·6
6	17	72·4	11·7	4·621	0·767	15·7
8	17	97·7	10·2	6·642	0·713	14·7
10	13	101·5	19·1	6·465	1·421	15·7
12	14	97·6	12·7	7·449	1·551	13·1
14	11	112·0	13·1	9·493	2·385	11·9
17	5	115·3	5·5	11·302	0·399	10·1
19	7	98·3	13·0	9·986	2·182	10·0
21	7	97·0	26·3	10·697	3·997	9·4
23	0	—	—	—	—	—
25	5	115·9	11·9	16·140	2·890	7·3
27	9	120·3	21·3	16·423	5·028	7·6
29	6	136·7	21·0	19·484	3·325	7·0
33	4	151·1	7·2	23·475	1·690	6·4
37	6	147·4	8·7	25·463	1·636	5·8
	Total 191					

growth in a different species (the mouse) and to emphasize the role of elastic tissue in alveolar formation.

MATERIALS AND METHODS

Swiss–Webster albino mice of both sexes were weighed, anaesthetized with ether and killed by exsanguination at various times from birth to adult life.

Lung weights were determined by removing the chest contents, carefully separating the lungs from other tissue (when necessary using a dissecting microscope), blotting the lungs on a non-absorbent surface, and weighing them separately. The number of animals used, average body weight and wet lung weight, ages and the ratio of the weight of lungs (combined, in milligrams) to body weight in grams is recorded in Table 1. Two litters were studied to assess lung growth during the first day of life: six mice from the first litter and four from the second litter were killed within 2 hours of birth and their lung and body weight determined. The remaining six mice from each of the litters were killed between 24 and 26 hours after birth.

Separate animals were used for morphological studies of the lung and were killed as above. Lungs were fixed by cannulating the trachea, opening the diaphragm from below, and attaching the tracheal cannula to a pump and reservoir system providing a constant pressure of 20 cm of H_2O. For light microscopic examination the fixative

Table 2. *The number of animals examined by light and electron microscopy and then scanned at each age is shown (age indicated as in Table* 1)

Age (days)	Number of animals	Number 'scanned'
0	21	5
1	18	4
2	13	5
3	11	2
4	8	3
5	5	1
6	17	3
7	8	1
8	1	0
9	1	1
10	3	0
11	2	0
12	4	1
13	7	1
14	2	0
15	23	2
Adult	7	4
Total	151	33

used was a 3·5 % solution of laboratory grade glutaraldehyde in 0·1 M cacodylate buffer at pH 7·2 (562 m-osmol), and fixation time *in situ* was 1 hour. The lungs were removed, trimmed and stored overnight in the glutaraldehyde solution. They were then processed and embedded in paraffin. Approximately 4 μm thick sections were prepared from the block and stained with haematoxylin and eosin and with an elastic stain (Miller's elastic stain (1970), Lambs/Difco and light green counterstain). For electron microscope examination the fixative used was a 5 % solution of electron microscope grade glutaraldehyde in 0·1 M cacodylate buffer at pH 7·2 with 2 mM calcium ion (840 m-osmol), and fixation time *in situ* was 30 minutes. The lungs were removed and stored in the glutaraldehyde solution for 2 hours. Selected blocks were post-fixed in osmium tetroxide, block stained with uranyl acetate, and embedded in epon, following standard procedure (Luft, 1961). Semithin (1 μm) sections were stained with Richardson's stain (Richardson, Jarett & Finke, 1960) for light microscope examination and ultrathin sections were stained with lead citrate (Reynolds, 1963) for electron microscope examination. For scanning electron microscopy blocks fixed with 5 % glutaraldehyde, approximately 3 × 1 × 1 mm, were treated by a thiocarbohydrazide and osmium tetroxide technique (Kelley, Dekker & Bluemink, 1973), critical point dried using acetone and carbon dioxide, and coated with gold–palladium. The number of animals used, their ages, and the number 'scanned' are recorded in Table 2.

RESULTS

Examination of the newborn mouse lung showed that true alveoli were absent at birth and the gas exchanging units of the lungs were the 'primary saccules', similar to those described in the rat (Burri, 1974*b*), and characterized by having smooth walls

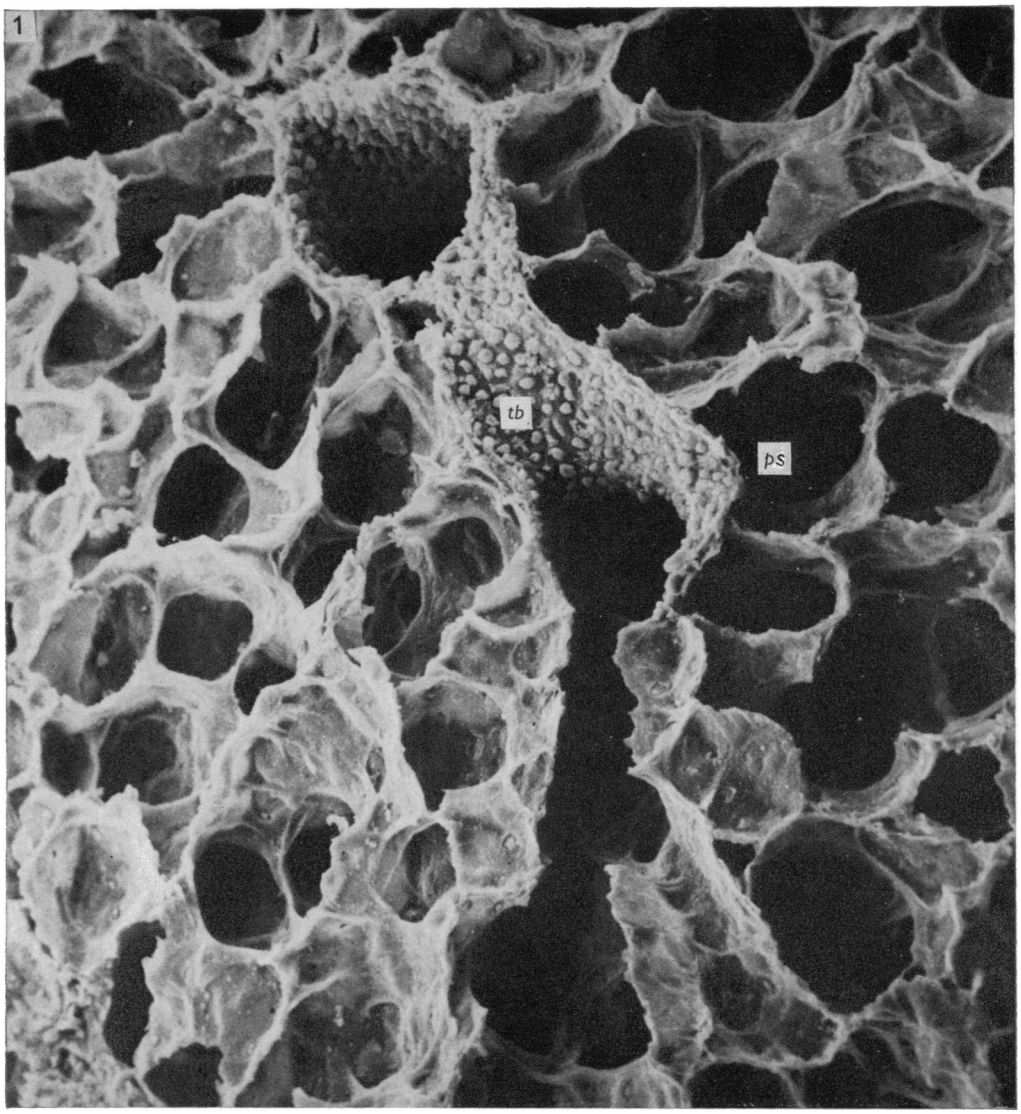


Fig. 1. Day 1 mouse. A terminal bronchiole (*tb*) is in the centre of the photograph. The large, smooth walled air saccules surrounding the terminal bronchiole are primary saccules (*ps*). Note the numerous bulging Clara cells constituting a prominent part of the terminal bronchiolar mucosa. Scanning electron microscope photograph. × 300.

and being larger in size than alveoli (Figs. 1, 8). Primary saccule walls had a wide capillary system, frequently forming a double layer, and were composed of a layer of Type I alveolar epithelial cytoplasm separated by a continuous basal lamina from an interstitial layer (Fig. 12). The interstitial layer consisted of capillaries with their enveloping basal laminae, ground substance and interstitial cells. Interstitial cells (O'Hare & Sheridan, 1970) contained large vacuoles that were probably lipid, cytoplasmic areas rich in rough endoplasmic reticulum, glycogen granules and optically

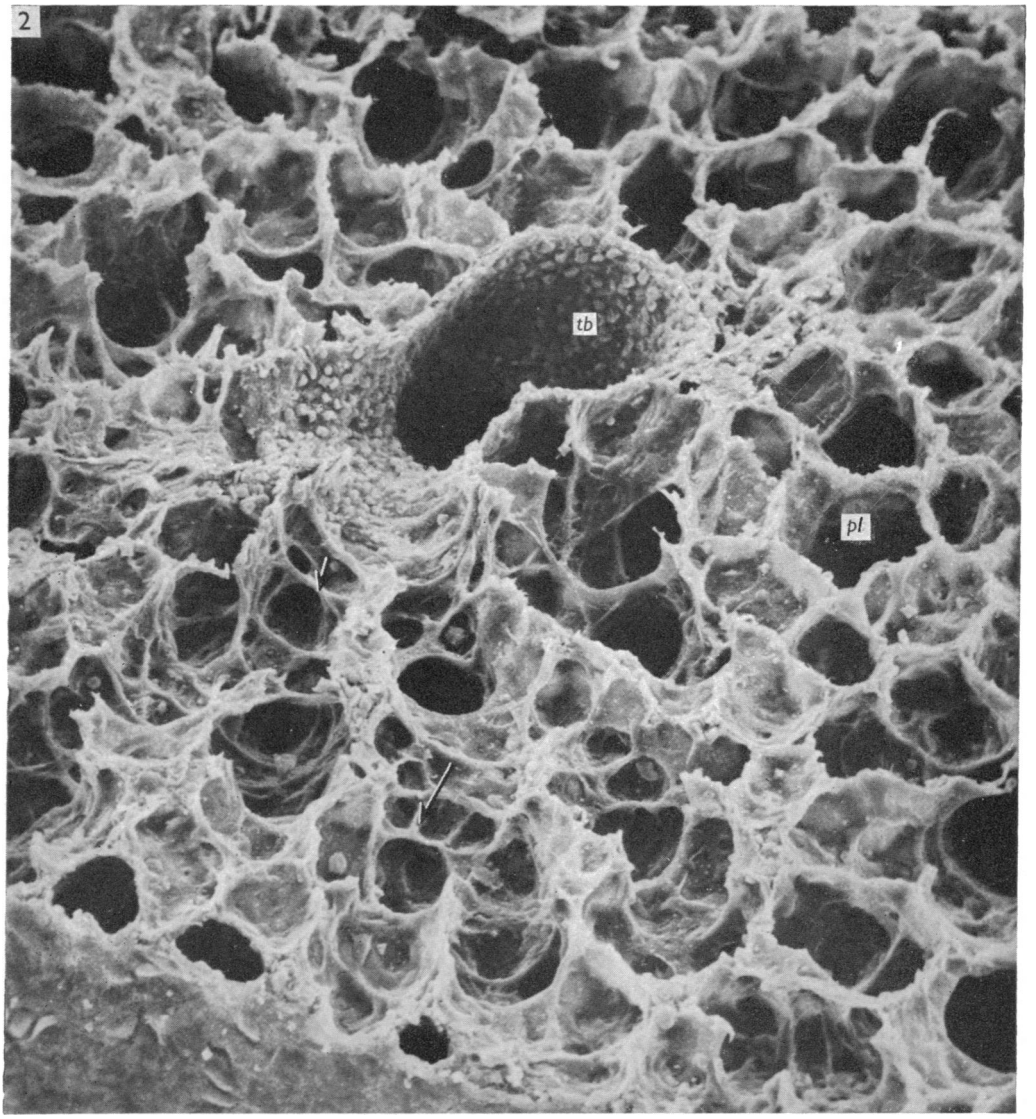


Fig. 2. Day 3 mouse. A terminal bronchiole (*tb*) has a prominent central position. The smooth walled primary saccules seen in Fig. 1 now are modified by prominent low secondary crests (short arrow). Clara cells are numerous in the terminal bronchiolar mucosa. In the lower left hand corner of the photograph is a triangular-shaped fragment of pleura (*pl*). Scanning electron microscope photographs. × 300.

empty areas that probably represented dissolved glycogen; these cells had irregular cytoplasmic extensions (Figs. 12, 13, 14). Type II alveolar epithelial cells were numerous in the saccule wall and, like Type I cells, were separated from the interstitial layer by a continuous basal lamina. Examination of the newborn lung by scanning electron microscopy proved to be the best method for visualizing the large, simple primary saccules (Fig. 1).

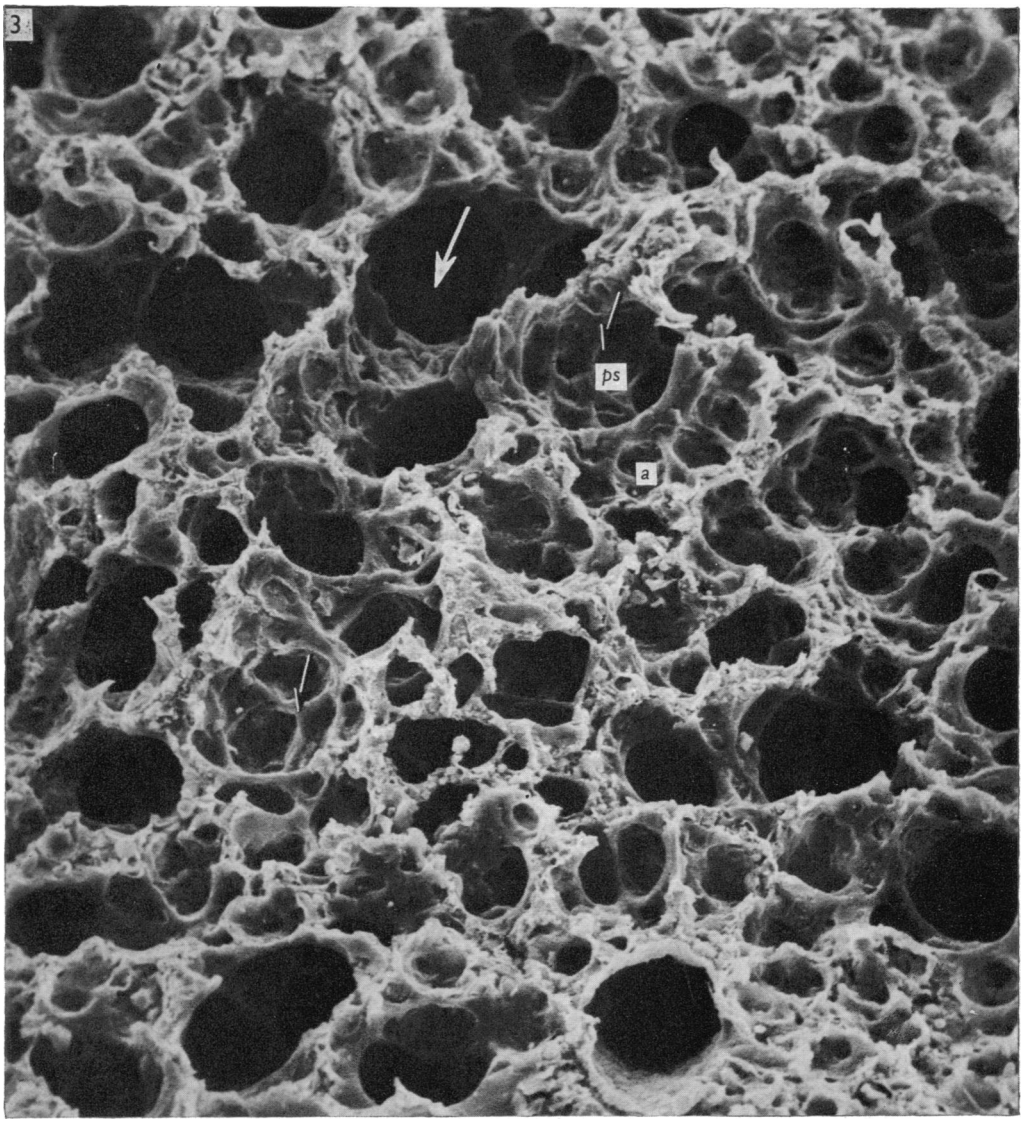


Fig. 3. Day 4 mouse. Primary saccules (*ps*) have been further subdivided by secondary crests (thin arrows). Shallow alveoli (*a*) are recognizable. Some primary saccules appear less subdivided by secondary crests than others (broad arrow). Scanning electron microscope photograph. × 300.

During the first 2–3 days of postnatal life the size of the primary saccule enlarged somewhat and the previously smooth saccule wall was modified by the development of very low 'secondary crests' (Fig. 2). In a three-dimensional visualization a secondary crest was a ridge running along a primary saccule wall dividing the saccule into two or more parts, whilst in a two-dimensional visualization it was a triangular-shaped elevation arising from a primary saccule wall. A secondary crest consisted of a layer of Type I alveolar epithelial cell cytoplasm separated by a continuous basal

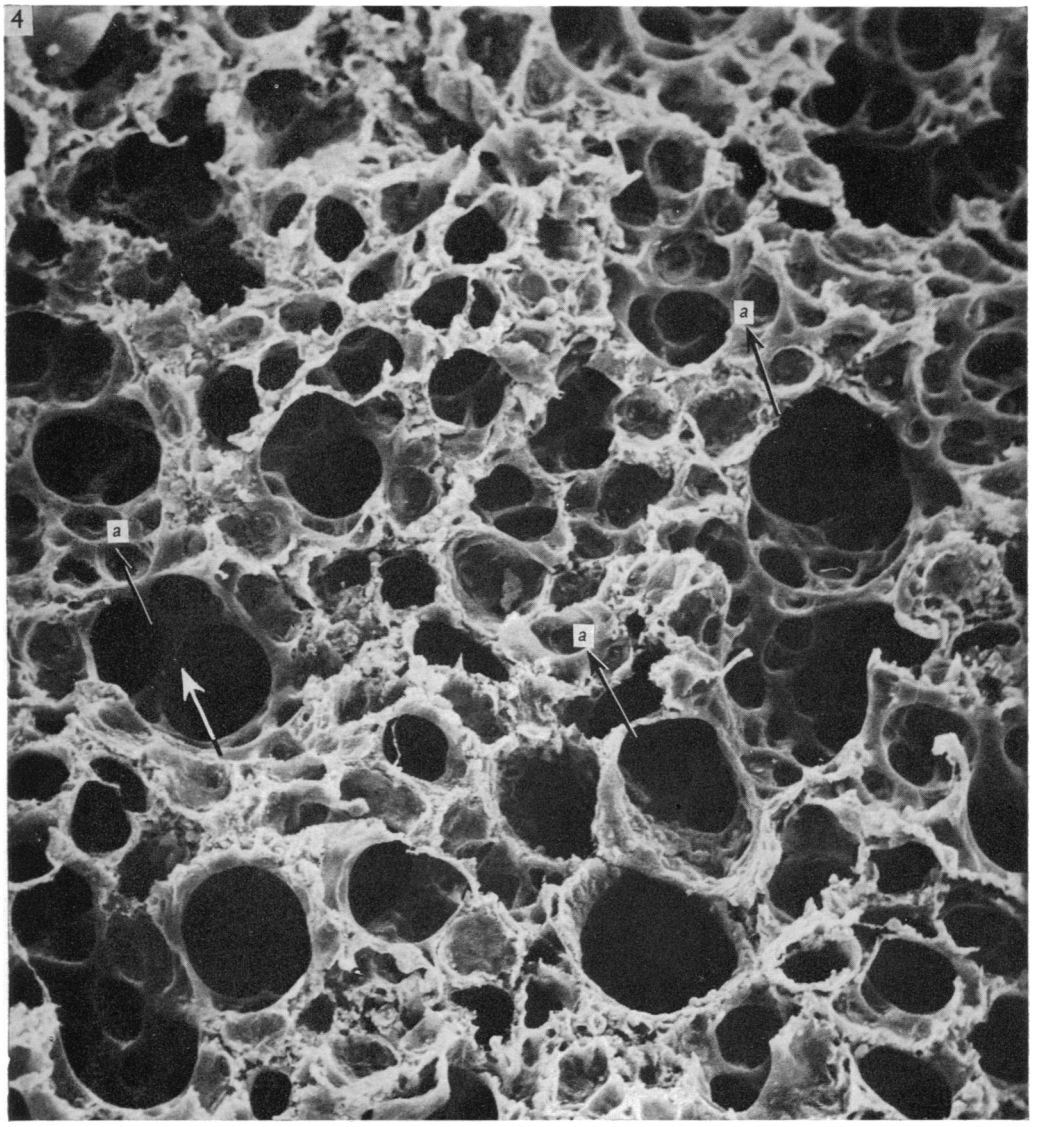


Fig. 4. Day 6 mouse. Most of the primary saccules have been subdivided into alveoli (*a*) by secondary crests (thin arrows). Some of the alveoli are quite deep. A few primary saccules appear less subdivided than others (broad arrow). Scanning electron microscope photograph. × 300.

lamina from an interstitial layer consisting of interstitial cell cytoplasm, ground substance and portions of one or two capillaries together with their enveloping basal laminae (which fused at points of contact with the basal lamina separating alveolar epithelial cell cytoplasm from the interstitial layer) (Figs. 13, 14). At the apex of the interstitial layer were one or more elastic fibres often found in an interstitial cell cytoplasmic bay (Fig. 13). The elastic fibres were within ground substance and in close apposition to the basal lamina. They had a homogeneous, amorphous centre

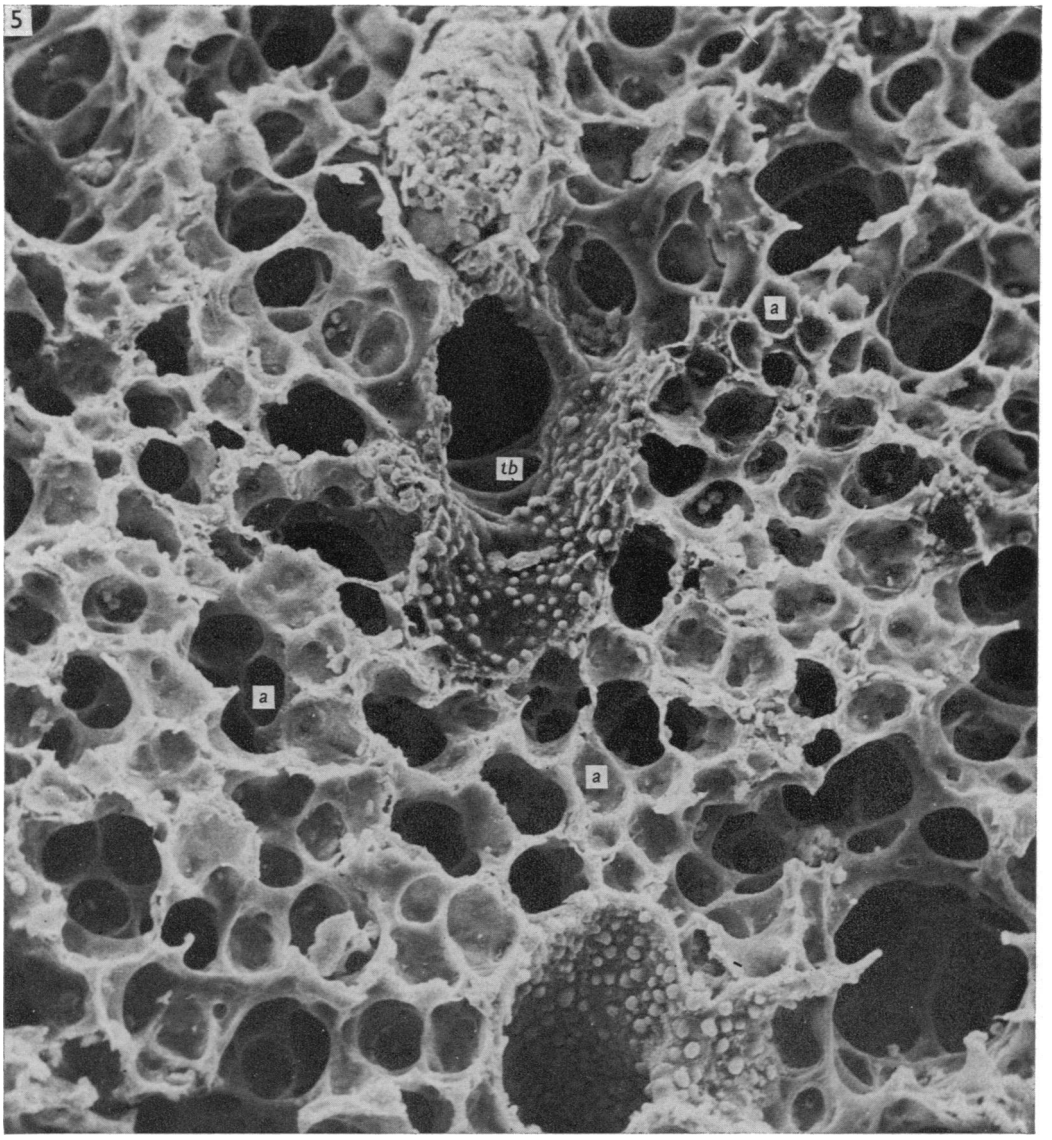


Fig. 5. Day 10 mouse. Two terminal bronchioles (*tb*) occupy prominent central positions. Most of the respiratory portion of the lung parenchyma consists of alveoli (*a*). Scanning electron microscope photograph. × 350.

surrounded by microfibrils (Collet & Des Biens, 1974) (Fig. 13). Collagen fibres were also present at the apex of the interstitial layer within ground substance (Figs. 14–16).

On the 3rd and, more so, on the 4th day of postnatal life the appearance of the lung changed markedly (Figs. 3, 9). Primary saccules became subdivided into alveoli by the rapid elongation of secondary crests. The change was patchy, i.e. not all primary saccules were subdivided to the same extent at the same time. The elongated

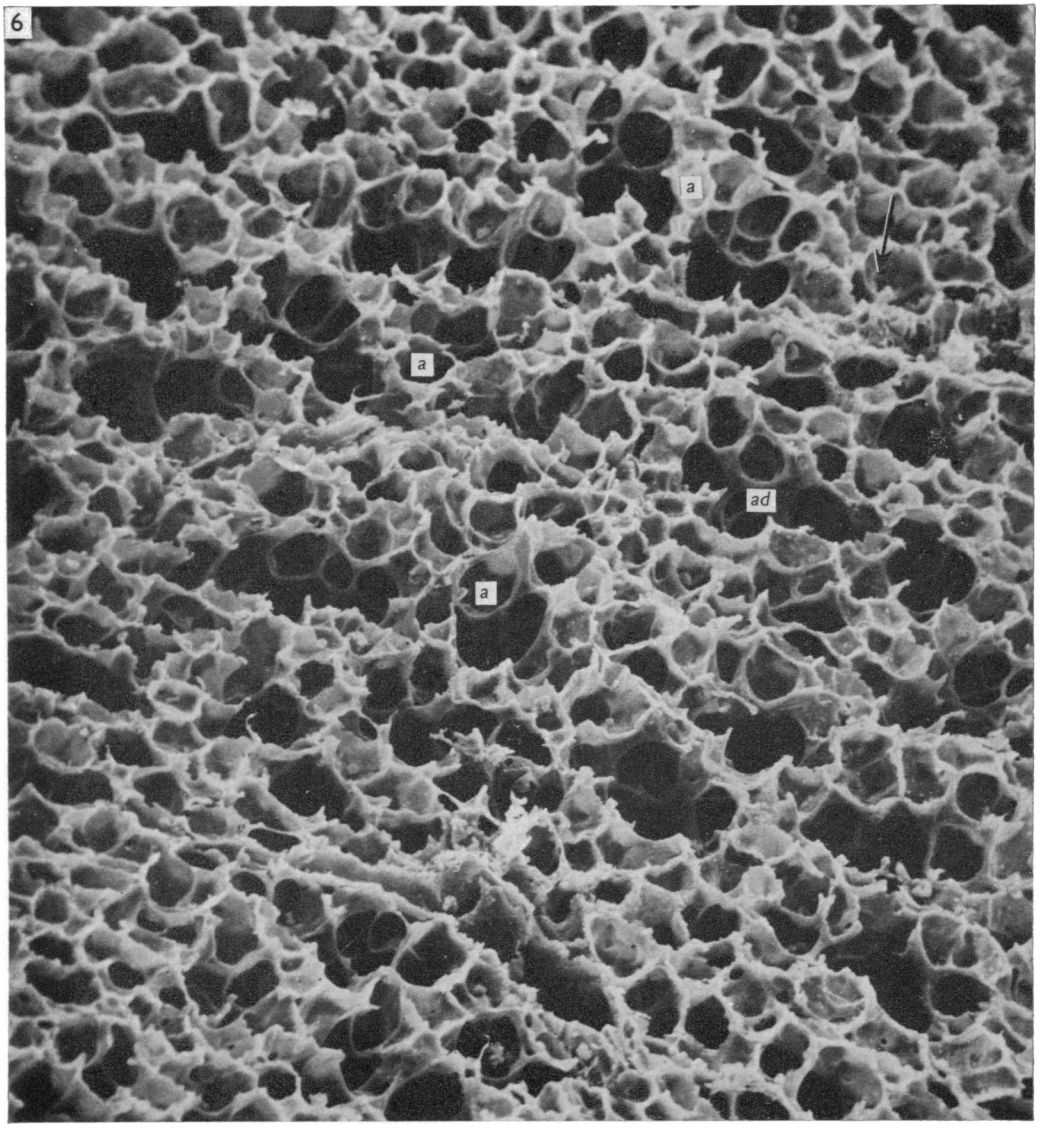


Fig. 6. Day 14 mouse. Alveoli (*a*) and alveolar ducts (*ad*) are present. Pores of Kohn (thin arrow), though present, are infrequent. Scanning electron microscope photograph. × 280.

secondary crests (Fig. 15) had structures similar to the very low secondary crests found during the first 2–3 days of life (Figs. 13, 14). All secondary crests appeared to have apical elastic and collagen fibres within the interstitial layer ground substance near the basal lamina separating alveolar epithelium from the interstitial layer, and contained interstitial cell components and one or two capillaries (Fig. 15). Mitotic figures were occasionally seen in interstitial cells (Fig. 15). The basal lamina surrounding a capillary was often in close apposition to the elastic and collagen fibres

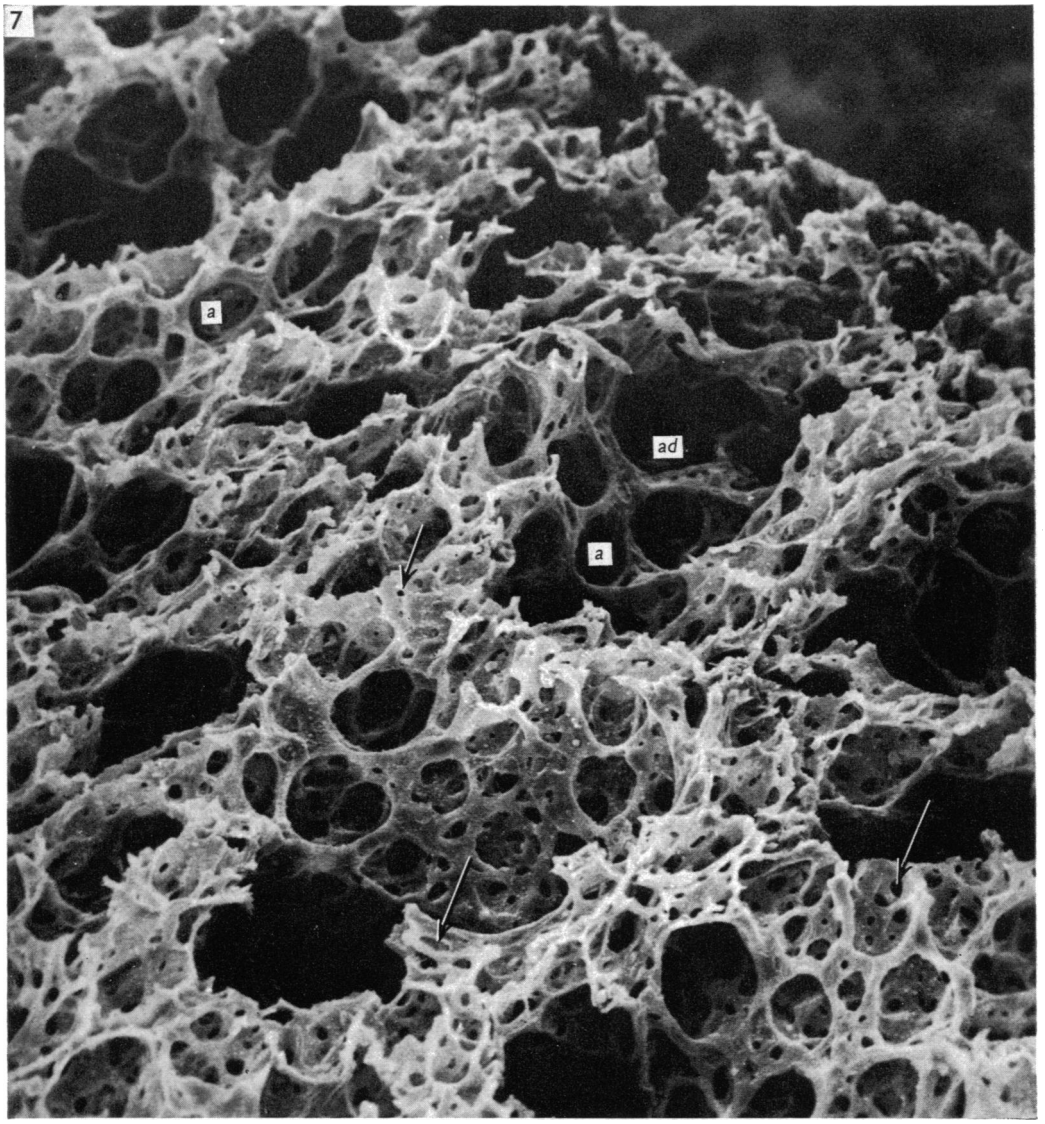
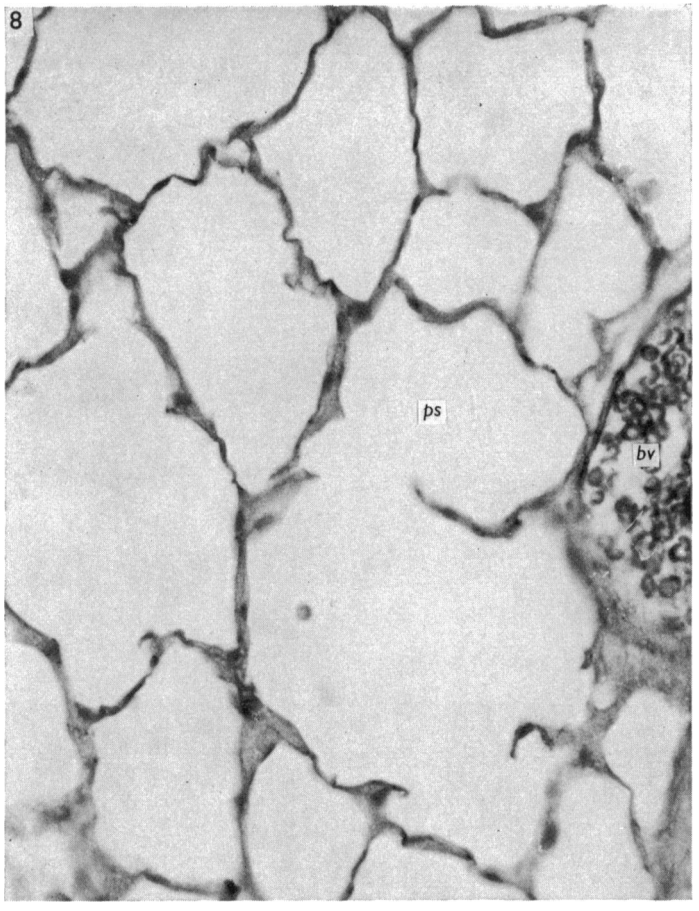


Fig. 7. Adult mouse. Alveoli (*a*) and alveolar ducts (*ad*) are present. Pores of Kohn (thin arrow) are very numerous, giving the lung a fenestrated appearance. Scanning electron microscope photograph. × 300.

(Fig. 15). Capillaries often had a very narrow lumen toward the apex of a secondary crest, frequently being represented in this area by a solid, bilayered, endothelial sprout (Fig. 15). Elastic fibres that marked the apices of secondary crests that had developed within a single primary saccule tended to lie about the same distance apart as the original primary saccule walls (compare Figs. 8, 9 and Figs. 10, 11).

The process of rapid alveolarization with subdivision of all primary saccules into



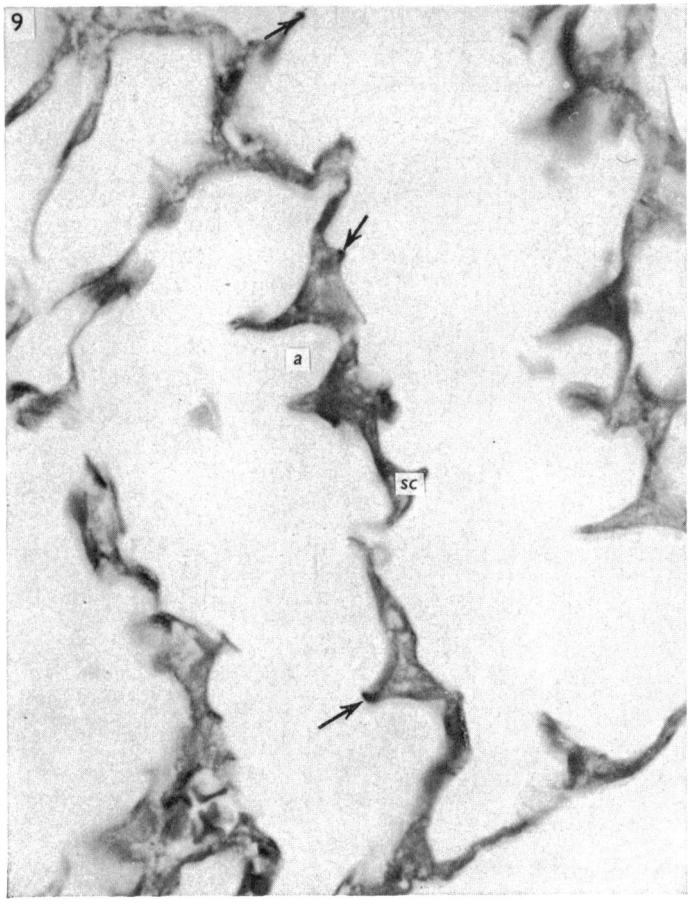
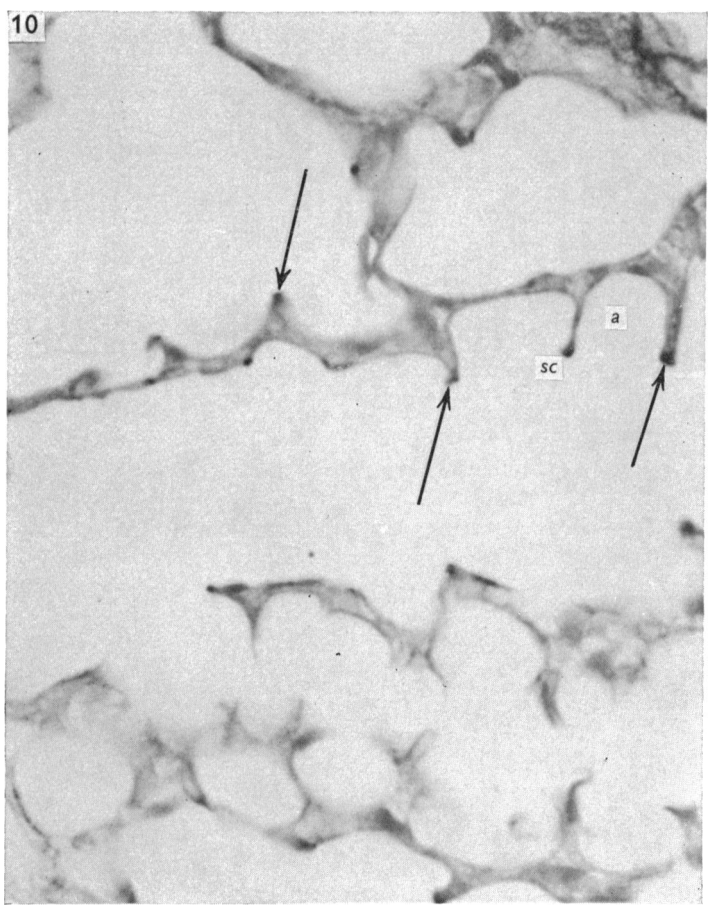


Fig. 8. Day 2 mouse. Shows large, simple primary saccules (*ps*) with smooth walls. A blood vessel (*bv*) is present. Elastic tissue is not prominent. Miller's elastic stain. ×470.

Fig. 9. Day 4 mouse. Secondary crests (*sc*) appear as triangular-shaped elevations on primary saccule walls. Section crests all have elastic stain-positive material (short arrows) at their apices. Shallow alveoli (*a*) have formed. Miller's elastic stain. ×470.



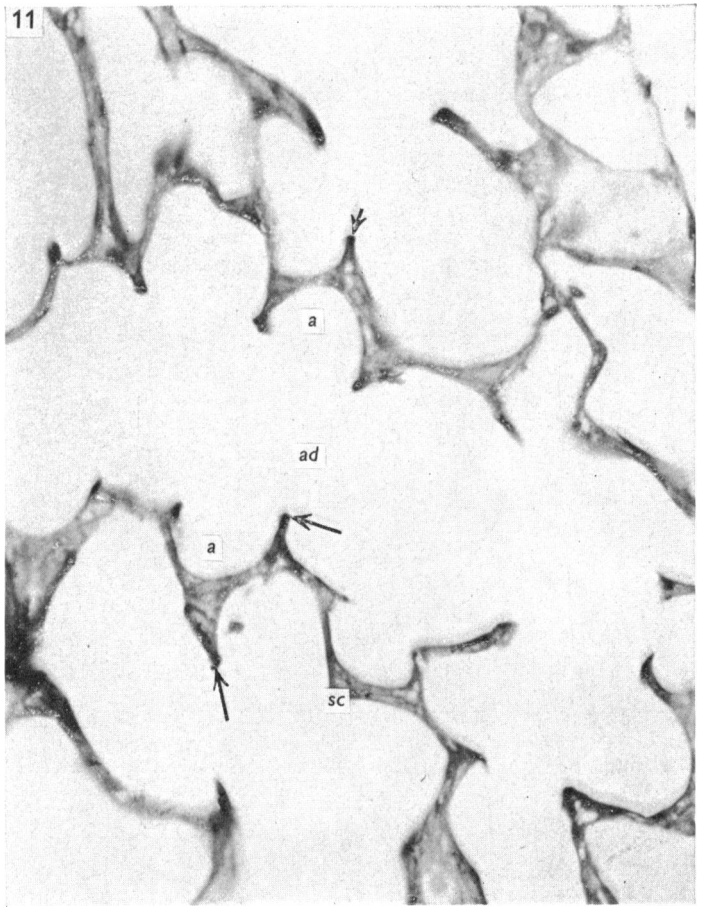


Fig. 10. Day 6 mouse. Elongated secondary crests (*sc*) and deep alveoli (*a*) are present. All secondary crests have elastic stain-positive material (long arrows) at their apices. Miller's elastic stain. × 585.

Fig. 11. Day 8 mouse. Deep alveoli (*a*) and an alveolar duct (*ad*) are present. Note the constant presence of elastic stain-positive material (short arrows) at the apices of secondary crests (*sc*). Miller's elastic stain. × 585.

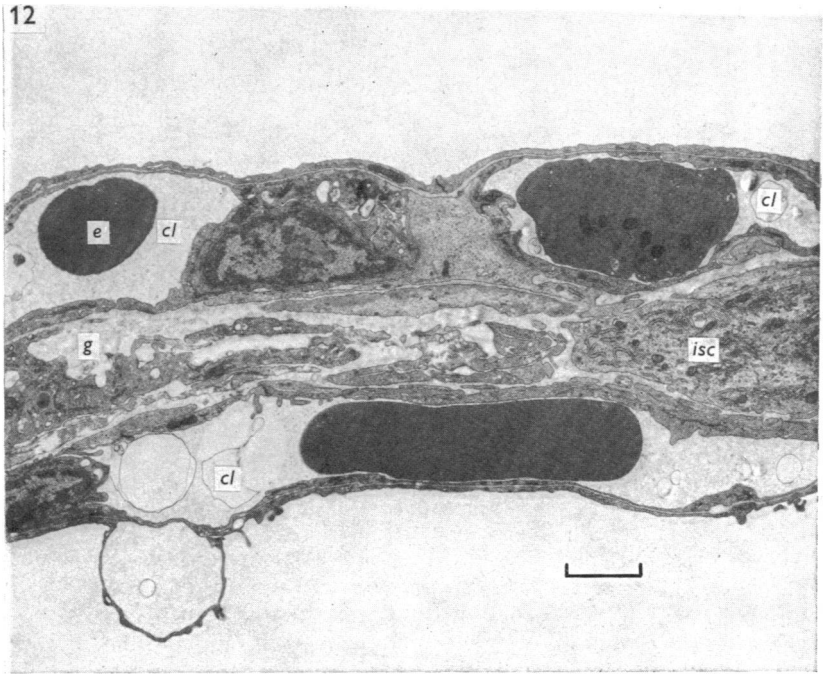


Fig. 12. Day 3 mouse. The primary saccule wall illustrated is composed of a layer of Type I alveolar epithelial cytoplasm separated by a continuous basal lamina from an interstitial layer. The interstitial layer consists of three capillaries (*cl*) containing erythrocytes (*e*) and forming a double capillary layer, together with their enveloping basal lamina, ground substance (*g*) and a portion of an interstitial cell (*isc*). Transmission electron micrograph. Scale = 1 μm. $\times$10000.

alveoli continued from the 4th (Figs. 3, 4, 5, 6, 11) to approximately the 14th day (Fig. 6) of postnatal life when an appearance similar to adult lung (Fig. 7), except for rarity of pores of Kohn, was attained. Pores of Kohn, which, though present, were infrequent during the first 10 days of life in the few animals studied, increased in number rapidly after the 14th day (Fig. 6) and came to resemble adult lung in their frequency by day 22 (Fig. 7). During this period the double capillary system frequently seen in the primary saccule wall (Fig. 12), and the immature secondary crest, disappeared leaving a single capillary system, and interstitial cells became much less prominent (Fig. 16). Capillaries 'rounded-out' and lost their narrow lumina. Elastic and collagen fibres remained prominent at the apices of the mature secondary crests.

A plot of lung weight (in milligrams) against postnatal age (in days) showed a fairly rapid increase in lung weight up to about 10 days (Fig. 17) and a less rapid increase after that date. Table 3 shows that lung weight did not increase during the first 24 hours of life, although body weight increased, and thus the ratio of lung weight to body weight decreased.

The ratio devised of lung weight (in milligrams) to body weight (in grams) plotted against age (in days) showed that in the first 6 days of postnatal life the increase in lung weight roughly paralleled the increase in body weight (i.e. the ratio remained

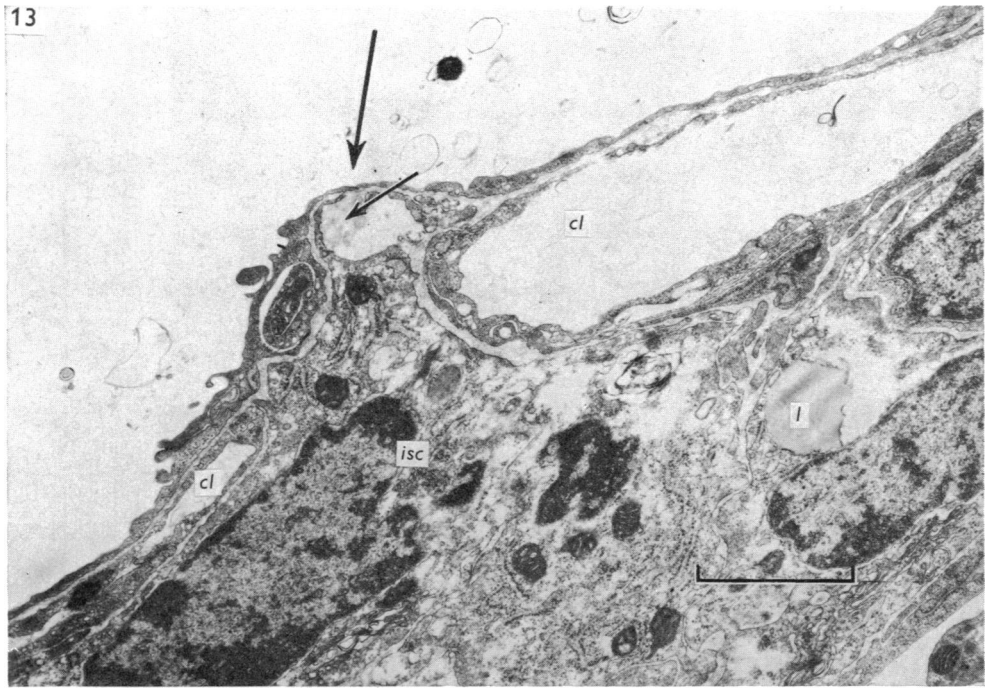


Fig. 13. Day 1 mouse. Present is a secondary crest (broad arrow) arising as a triangular-shaped elevation from a primary saccule wall. At its apex, within a cytoplasmic bay of an interstitial cell (*isc*), are elastic fibres (thin arrow). Portions of two capillaries (*cl*) are present. The lower interstitial cell contains a lipid vacuole (*l*). Transmission electron micrograph. Scale = 1 μm. $\times$20000.

constant), while after that date the increase in lung weight was progressively less than the increase in body weight (Fig. 18).

DISCUSSION

This study has demonstrated that true alveoli do not exist in the mouse lung at birth, and that gas exchange in the newborn mouse takes place in large, simple primary saccules. Primary saccules are larger than alveoli and have smooth walls. The primary saccule wall frequently has a double capillary network, thus differentiating it from the septa of a mature lung, which has an apparently single capillary system which runs alternatively on either side of a connective tissue framework (Weibel, 1973). Burri *et al.* (1974*a*, *b*) described the morphometric and morphological appearance of the developing rat lung and concluded that true alveoli do not exist in the rat lung at birth, a conclusion also drawn by Willson (1928) for mouse lung, Engel (1953) for mouse and rat lung, Boyden & Tompsett (1961) for dog lung and Weibel (1967) for rat lung. Respiratory exchange in the newborn rat took place in large primary saccules. The primary saccules described in this study are identical with the primary saccules described by Burri (1974*b*) and are probably identical with structures referred to as 'primitive air sacs' (Willson, 1928), 'lobulated saccules

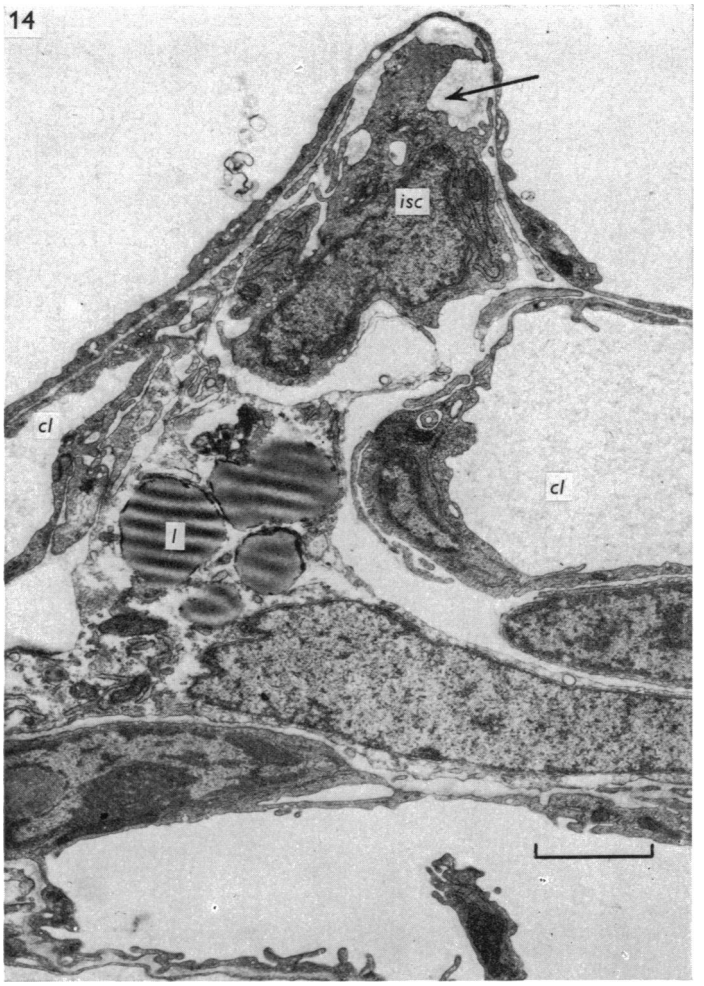


Fig. 14. Day 3 mouse. The elongating secondary crest illustrated has the same elements as the early secondary crest (Fig. 13). At its apex, within a cytoplasmic bay of an interstitial cell (*isc*), are elastic and collagen fibres (arrow). Portions of two capillaries (*cl*) are present. The interstitial cell contains lipid vacuoles (*l*). Transmission electron micrograph. Scale = 1 μm. ×15000.

without alveoli' (Engel, 1953), 'terminal saccules' (Boyden & Tompsett, 1961) and 'primary saccules' (Weibel, 1967).

Within the first 2–3 days of postnatal life the smooth primary saccule walls of the mouse lung became modified by the elevation of very low secondary crests, appearing as narrow ridges. The apex of a secondary crest, both by light and transmission electron microscopy, appeared always to contain elastic and collagen fibres. On the 3rd, and more so on the 4th, day of postnatal life the secondary crests rapidly elongated, thus subdividing each large primary saccule into many smaller units or alveoli. Subdivision of primary saccules into alveoli was not complete until about the 14th postnatal day. Before this date subdivision was patchy, with some areas

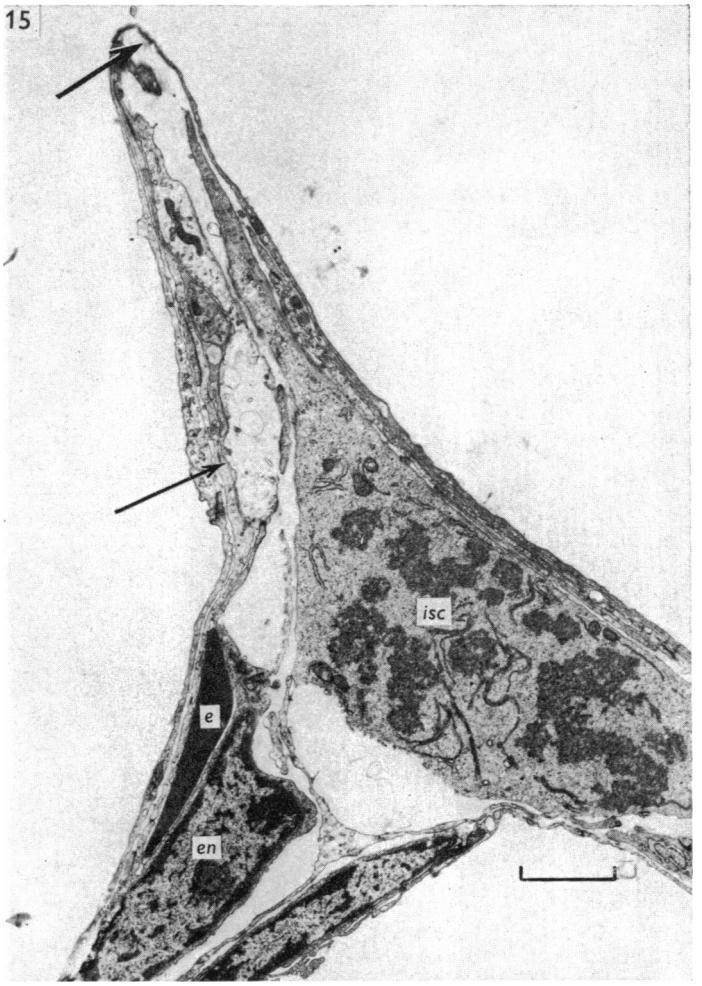


Fig. 15. Day 3 mouse. This secondary crest contains an interstitial cell (*isc*) undergoing mitotic division. Elastic and collagen fibres (broad arrow) are present at the apex of the crest. A capillary with an endothelial cell nucleus (*en*) and containing an erythrocyte (*e*) is present. Note the bilayered endothelial tube appearance (thin arrow) of the capillary toward the apex of the crest. Transmission electron micrograph. Scale = 1 μm. ×12000.

resembling adult lung whilst some primary saccules were only partially subdivided. Burri (1974*b*) and Kaufman, Burri & Weibel (1974), studying developing rat lung, felt that subdivision of primary saccules into alveoli started on or about the 4th postnatal day and was complete by the 13th postnatal day, a result in keeping with our mouse studies.

The secondary crests subdividing primary saccules into alveoli had a constant structure. The crest surface was composed of Type I alveolar epithelial cytoplasm (with an occasional Type II cell), separated by a continuous basal lamina from an interstitial layer. At the apex of the interstitial layer, just under, and sometimes

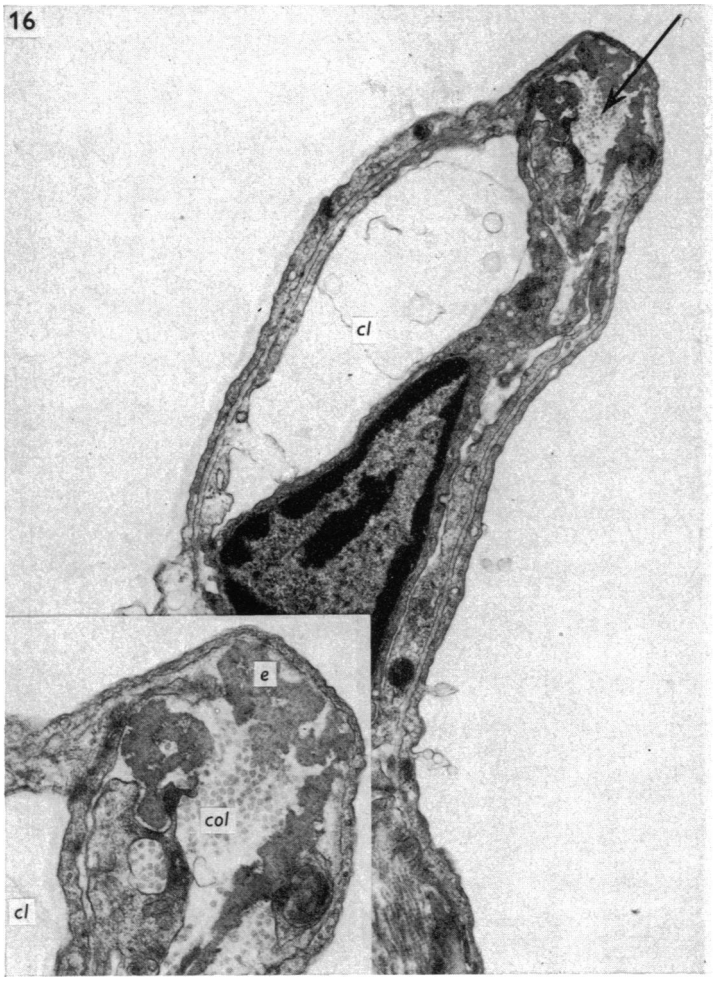


Fig. 16. Day 24 mouse. The mature secondary crest illustrated has a single capillary (*cl*). Elastic and collagen fibres are prominent at the crest apex (arrow). Transmission electron micrograph. ×20000. Inset Fig. 16 (lower left hand corner). Note elastic (*e*) and collagen (*col*) at the crest apex. ×40000.

seeming to fuse with, the subepithelial basal lamina, were one or more elastic fibres. Collagen fibres were also present. The basal lamina of the one or two capillaries constantly found in a secondary crest was frequently in close apposition to apical elastic and collagen fibres. An interstitial cell, or portions of interstitial cells, were also constant components of the secondary crest.

A secondary crest appeared to originate at a point of deposition of elastic tissue fibres at the site of juxtaposition of a capillary, interstitial cell and Type I alveolar epithelial cell. Juxtaposition of these three elements was not invariably followed by elastic tissue deposition and the development of a secondary crest, and elastic tissue

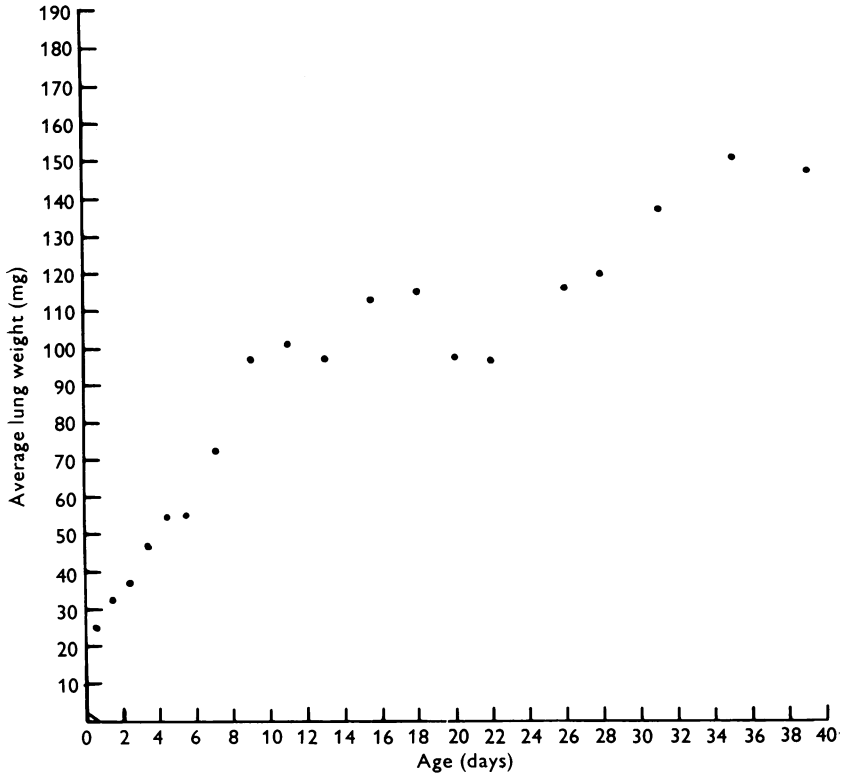


Fig. 17. Average lung weight (in milligrams) plotted against age (in days). Note that lung weight increases most rapidly in the first 10 days of life.

deposition occurred elsewhere in the absence of epithelial cell and/or capillary, but secondary crest formation and development occurred only when these three elements were juxtaposed. During secondary crest elongation, occasional mitotic figures were seen amongst interstitial cells. Capillaries round, or ellipsoidal in cross section in early secondary crests, had narrow lumina toward the apices of elongating crests, and were frequently represented in this area by seemingly closed, bilayered endothelial tubes. Apical elastic and collagen fibres were often in close apposition to the basal lamina of the bilayered endothelial tube.

Apically situated elastic and collagen fibres appeared to be an essential component of all secondary crests, and the initial stage in crest formation may well have been the deposition of these fibres. The importance of elastic tissue in lung development has been emphasized by Loosli & Potter (1959), and by Emery (1970). In company with these authors we believe that elastic tissue plays a major role in postnatal lung development, and that collagen may well be equally important. To paraphrase Emery (1970), elastic tissue probably acts to prevent the completely free movement of parts of the primary saccule wall so that alveolar development extends beyond the elastic tissue net. Elastic fibres that marked the apices of secondary crests that had

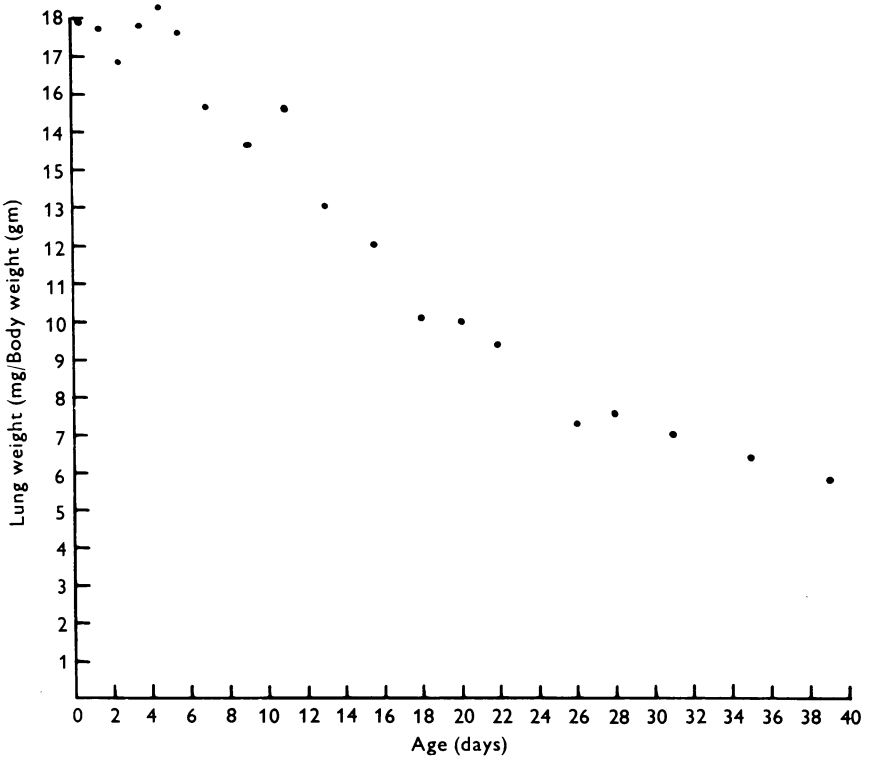


Fig. 18. The ratio of lung weight (in milligrams) divided by body weight (in grams) is plotted against age (in days). The ratio of lung weight/body weight remains nearly constant for the first 6 days of life, indicating that the increase in lung weight roughly parallels the increase in body weight during this period.

Table 3. *During the first day of life, lung weight does not increase significantly, although there is an increase in body weight, thus the lung weight/body weight ratio decreases*

Age (hours)	*n*	Mean lung weight (mg)	Body weight (g)	Lung wt/body wt (mg/g)
0–2	10	37·1	1·615	23·0
24–26	12	39·4	2·052	19·2

developed within a single primary saccule tended to lie about the same circumference as the original primary saccule wall, suggesting that, as the growing lung expanded, the secondary septal apices remained in approximately their original position in the primary saccule wall, whilst the remaining crest components elongated behind the apices. The apical elastic and collagen fibres in a secondary crest probably have a tethering action in this process.

As the mouse lung matured the double capillary system frequently seen in both

secondary crest and primary saccule wall disappeared, and previously 'flattened' capillaries 'rounded out' and took on the appearance typical of adult lung. Interstitial cells became less prominent. Crests and saccule walls became thinner and adult in appearance. A double capillary system could be lost in part by 'stretching' the crests and saccule walls so that vessels originally overlying one another became separated. Stretching could also account for decreased interstitial cell prominence. There was no morphological evidence of destruction or necrosis of capillaries or interstitial cells during any period of lung development studied, but fusion of capillary lumina might occur, though this would be difficult to observe.

Pores of Kohn, infrequent in the first 10 days of postnatal life, increased rapidly in number after the 14th day (in the few animals studied) and came to have a seemingly adult number by day 22. The reason for such an increase over such a short period is uncertain, but it may reflect a stretching and thinning phenomenon.

During the first day of life no significant increase in lung weight occurred, although average body weight increased 27 % during this time. This finding is consistent with the observation that nuclear labelling with tritiated thymidine is low in the first day of life in mice (Crocker, Tieter & Nielson, 1970). Thus the first phase of lung growth is primarily one of expansion, but this phase is very short in duration. Subsequently, lung weight increased rapidly and the most rapid rate of growth was in the first 6 days of life when lung weight increased in parallel with body weight. This probably reflects preparation by the lung for, and the beginning of, the 'explosive restructuring' (Burri, 1974*b*) of lung parenchyma which begins about day 4 of postnatal life. The rate of lung tissue growth then gradually falls and, in general, the rate of growth is slower than general body growth. There is, however, a greater growth in lung volume than in lung weight, and this is reflected in the increasing proportion of air in the lung that occurs throughout the period of somatic growth (Thurlbeck, 1975).

SUMMARY

We have followed the morphological changes that occur in mouse lung from birth to adult life. Alveoli are absent at birth, and the gas exchanging units of the lungs then are primary saccules, characterized by smooth walls and a wide capillary system, frequently forming a double layer. During the subsequent 3–4 days the smooth primary saccule wall is modified by the elevation of very low secondary crests, appearing as narrow ridges. Secondary crests have a constant structure. An outer surface composed of alveolar epithelial cell cytoplasm is separated by a continuous basal lamina from an interstitial layer composed of interstitial cells, ground substance, portions of one or two capillaries and apical elastic and collagen fibres. It is postulated that elastic and collagen fibres play a key role in alveolar development. Secondary crests rapidly elongate after the 4th day, subdividing the primary saccule into alveoli, a process that appears substantially complete by the 14th day. Pores of Kohn, infrequent in the first 10 days of postnatal life, increase rapidly after the 14th day, coming to have a seemingly adult number by day 22. The rate of increase in lung weight is greatest during the first 6 days of life, reflecting cellular proliferation in the walls of primary saccules.

Scanning electron microscopy, was carried out at the Structural Studies Unit, Department of Metallurgy, University of Surrey, Guildford, Surrey.

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