

EFFECTS OF ETHER, CYCLOPROPANE, NITROUS OXIDE AND FLUOTHANE UPON THE LUNG ALVEOLI

AN EXPERIMENTAL STUDY ON MOUSE LUNG BY MEANS OF LIGHT AND ELECTRON MICROSCOPE

by

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INTRODUCTION

Diethyl ether has been known to have the most irritant effect upon the whole respiratory tract among the conventional inhalation anesthetics. The patient often suffers from copious secretion of mucus as well as profuse sputum during and after ether anesthesia, which may result in the postoperative pulmonary complications, such as bronchitis, atelectasis or pneumonia. However, few reports have ever been presented concerning the morphological aspect of this fact.

The main purpose of this study is to obtain the morphological evidence of this effect comparing with those of other agents, such as nitrous oxide, cyclopropane and fluothane.

MATERIALS AND METHODS

Adult albino inbred mice weighing 18 to 23 gms of both sexes were employed to this study. Because of the relatively simple pattern of the alveolar structure which enabled us to detect minute transitory changes, and of the great similarity to human lung alveoli, mouse lung was chosen to this study.

The animals were first anesthetized with the following technics:

1) *Open drop ether*: The animals were divided into three groups and each was anesthetized by open drop ether for one, two or three hours respectively. The level of anesthesia was maintained in such a stage that they lay asleep in quiet breathing and did not respond to painful stimuli by pinching their tails with forceps. Immediately after the determined period they were instantly killed by decapitation, and the lungs were taken for specimen.

In order to follow up the process of recovery from the anesthesia two more groups were likewise anesthetized for three hours, then ether was discontinued, the animals were kept awake as long as 24 or 48 hours after anesthesia, until they were sacrificed to the study.

2) *Inhalation of anesthetic agents in known concentrations*: The animals were put in a shallow glass vessel of approximately one liter capacity containing soda lime granules at the bottom, and the vessel was sealed with a vinyl cloth penetrated

with two rubber tubes. Anesthetic gases of known concentrations were delivered through one tube mixed with oxygen at a flow rate of 2 liters per minutes, and the other tube was open for overflow meanwhile. Ether vapor was delivered from a copper kettle in a known concentration of from 3.0 to 5.5 volume per cent in oxygen, nitrous oxide in 75 per cent or more with oxygen, fluothane in 3.0 volume per cent concentration diluted with oxygen using Fluotec vaporizer. Exceptionally, cyclopropane was intermittently delivered with oxygen and the depth of anesthesia was often checked by response to a painful pinch as done in open drop ether. After a certain period of anesthesia the animals were likewise sacrificed.

3) As a control, one group of mice was anesthetized with intermittent intra-peritoneal administration of thiopental sodium, and another group was allowed to breathe in an atmosphere of 30 per cent carbon dioxide in oxygen, and also hypoxic hypoxia was induced in another group confined in a hypoxic atmosphere for a period of three hours.

For electron microscopy small pieces of lung, not exceeding 1 mm in any dimension, were dropped in 1 per cent osmic acid solution buffered by pH 7.4 phosphate immediately after removal of the lung, then placed in an ice-chamber for 60 minutes. Rinsed in running tap water overnight, dehydrated in ascending concentrations of alcohol, and then the tissues were embedded in monomeric methacrylate. Sections were cut at 0.05 micron or less. They were examined and photographed on HIDACHI HU-10 and HS-6 model electron microscope.

For light microscopy the rest of lung specimen was fixed with 10 per cent formol, dehydrated, embedded in paraffin, sectioned at 3 microns in thickness, and stained with hematoxyline and eosin.

RESULTS

1) Normal alveolar structure of mouse lung

A normal view of light microscopy is presented in Fig. 1 a, b. According to the electron microscopic observation of unanesthetized mouse lung in this laboratory, the alveolar wall is generally covered with a thin membranous extension of alveolar epithelial cells as shown in Figs. 12 and 13. The cell nucleus is round or oval, contains a single nucleolus, and clearly raised above the adjacent tissue level into the alveolar space with a thin cytoplasmic covering. The cytoplasm becomes abruptly attenuated on both side of the nucleus as thin as 0.1 micron and further lines up the alveolar surface.

There appears another type of cell, whose cell body is partly buried in the alveolar wall and partly exposed to the alveolar lumen interposed between the above-mentioned thin epithelial cytoplasm (Fig. 14). The cellular feature is quite different from that of the alveolar epithelial cell. It has abundant cytoplasm with jagged cytoplasmic processes (microvilli) on its free surface, and contains various organellae, such as mitochondria and other miscellaneous osmiophilic inclusionsbodies of varied electron densities. A single round or oval nucleus is located rather excentric in the cytoplasm. NAGAISHI and co-workers (18, 19) recently named it "alveolar wall cell".

The interstitium is occupied with respiratory (alveolar) blood capillaries, capillary endothelial cells, other interstitial cells and scanty elastic and collagen fibers (Fig. 15). The capillary wall is lined with a thin cytoplasmic layer which is extended from the endothelial cell in the same fashion as that of alveolar wall surface. Moreover, the cellular features of both cells are in close resemblance with each other as indicated by Low (14), Low and SAMPAIO (17).

It should be emphasized that macrophage, so-called dust cell, or any free cells have scarcely been observed in the alveolar spaces of normal unanesthetized mouse.

2) **Changes in the alveolar structure under ether anesthesia**

a. *Open drop ether for one hour*: The lung is pink colored and macroscopically almost indistinguishable from a normal lung. Under light microscope man can find a slight capillary filling accompanied with a migration of large macrophages (dust cells) into the alveolar spaces (Figs. 2 a, b). The electron microscopic observation revealed that many dust cells are closely resembled to the "alveolar wall cell" (NAGAISHI) in size, shape and osmiophilic behavior of its cytoplasmic ingredients. The cell body is large (from 10 to 30 microns in major diameter), its cell border is jagged and often possesses pseudopodia. The cytoplasm is occupied with a rather smaller number of mitochondria than those of the "alveolar wall cell", abundant osmiophilic bodies, other minute corpuscles and vacuoles (Figs. 22, 23, 27).

b. *Open drop ether for two hours*: The lung has a reddish color and the light microscopic study shows a moderate congestion in blood capillaries, a thickening or swelling of alveolar walls and also a slight tendency of interstitial edema or atelectasis. A small number of erythrocytes is seen in alveolar spaces, and there frequently appear large dust cells in alveolar lumen (Figs. 3 a, b). These changes were also corroborated under electron microscope. Besides, a series of degenerative changes in mitochondria has already commenced in the "alveolar wall cells", such as central transparency (Fig. 16) and vacuolization (Figs. 30 b, c, d).

c. *Open drop ether for three hours*: The surface of the lung is reddish gray, a regional hemorrhage is occasionally found in hilar region. Under light and electron microscope the aforementioned changes are further advanced: Capillaries are dilated and filled with blood, so-called dust cells are more often encountered in the air spaces, and they are more or less subjected to a process of degeneration or destruction, such as rupture of cell membrane, partial loss of cytoplasm or disintegration of cell bodies as demonstrated in Figs. 4 a, b and 21.

Another proof of dust cell migration was obtained by the examination of tissue smears of the lung exposed to ether vapor as long as three hours. The author found a huge cell whose body is stained faint blue by May-Giemsa's azure-eosin, and often includes dusts and vacuoles in its body. It positively be a dust cell (Fig. 11).

The mitochondria of the "alveolar wall cell" are swollen and more spherical, the electron density of central region is diminished and the internal ridges (cristae mitochondriales) become obscure and pushed to periphery. Other osmiophilic ingredients are also subjected to similar changes, and they often look like hollow circles. Occasionally the cell body itself is disintegrated and its inclusionsbodies are scattered

out of the cell. More rarely its cytoplasm is filled up with dense osmiophilic granules and/or vacuoles, most probably derived from mitochondria, as an advanced degenerative process (Figs. 17, 30 c, d, e, f).

Meanwhile, multiple changes are noticed in the interstitium, e. g. vacuoles in the cells of interstitium (Fig. 20), splitted collagen fibers (Fig. 18) and fluid effusion between the basement membranes of capillary endothelium and alveolar epithelium, in other words, the interstitial edema becomes notable (Fig. 19).

After all, the changes in the alveolar structure caused by ether inhalation are progressively intensified as the anesthetic period is prolonged.

d. *Ether inhalation in known concentrations*: The animals were allowed to inhale different percentages of ether vapor in oxygen as described in 2) of the previous chapter. The specimen which exposed to less than 3.0 volume per cent of ether vapor showed no cellular damage but a slight capillary congestion, whereas those inhaled exceeding 4.5 volume per cent ether vapor exhibited a series of the above-described changes, such as appearance of dust cells into alveolar spaces, interstitial edema and multiple degenerative changes in "alveolar wall cells" etc.

e. *Convalescence from ether anesthesia*: Twenty four hours after the emergence from the anesthesia, capillary congestions and red blood cells in alveolar space are almost disappeared, but numerous dust cells are still seen in the lumen (Figs. 5a, b, and 28). Fourty eight hours after the recovery the lung alveoli are almost normal except for a smaller number of dust cells remained (Figs. 6a, b and 29).

3) **Changes in the alveolar structure under cyclopropane anesthesia**

The color of the lung is bloody tinged and the tone becomes darker as the period of anesthesia is longer. The microscopical view is quite different from that of ether inhalation, and characteristic in marked capillary congestion and diffuse extravasation or hemorrhage in the alveolar spaces. The capillary filling is significant even in the first one hour of the anesthesia, and more advanced with the coexistence of marked intraalveolar hemorrhage in 2 and 3 hours of anesthesia (Figs. 7a, b and 24).

On the other hand, few dust cell is found in alveoli (only one incidence throughout the whole investigations), and neither degenerative changes in the "alveolar wall cell" nor edematous swelling in the interstitial tissue spaces are observed even in the lung of three hours cyclopropane anesthesia.

4) **Changes in the alveolar structure under nitrous oxide anesthesia**

The lung exposed to nitrous oxide for three hours is macroscopically almost normal in color. Microscopically, however, there exists a slight capillary congestion after one hour of the anesthesia, and it gradually increases in two and three hours of the anesthesia. A scanty number of erythrocytes are seen, but none of macrophages is found in the alveolar spaces (Figs. 8a, b). Under electron microscope, no significant damage is recognizable in finer alveolar structures, except for a slight filling of blood in respiratory capillaries and a seldom appearance of blood cells in the alveolar lumen (Fig. 25).

5) **Changes in the alveolar structure under fluothane anesthesia**

Fluothane, one of the newest inhalation anesthetics, is said to be nonirritant to the airway. The author examined the effect upon the alveoli as described in the previous chapter. Both under light and electron microscope no trace of reactive or degenerative changes is detectable anywhere in alveolar wall regardless of the time length of inhalation of 3.0 volume per cent fluothane, except for a slight evidence of capillary hyperemia (Figs. 9a, b and 26).

6) **Changes in the alveolar structure under miscellaneous conditions**

In order to rule out the possible effects of various conditions which may intervene in the anesthesia, the lung alveoli were examined under the following conditions: under thiopental anesthesia (Figs. 10a, b), the prolonged hypercapnia and hypoxic hypoxia.

Each specimen thus examined only exhibit insignificant capillary congestion, even if these conditions are sustained as long as three hours.

DISCUSSION

Since a new approach was created through the greater resolving power of electron microscope to clarify the finer structure of the cells, the normal structure of the lung alveoli has been clearly demonstrated by the following investigators: the lungs of rat, mouse and other laboratory mammals were studied by Low (14, 15 and 16), SAMPAIO (26), Low and SAMPAIO (17), KARRER (7, 8, 9, 10 and 11) and NAGAISHI and co-workers (4, 6 and 19), the human lung by Low (15) and NAGAISHI et al. (5, 6 and 18) and others.

The normal electron micrograph of the alveolar structure was also examined by the author in mouse lung as a control of this experiment. As described in the previous chapter, a similar result was obtained in this examination regarding the feature of the alveolar epithelial cells to that obtained by Low (14). As far as the "alveolar cell", (NAGAISHI) is concerned, its presence was also recognized by Low et al. (14, 17), however, Low attributed the cell to a sort of macrophages which happened to be interposed between the epithelial layer, on its way through the alveolar wall into the air space. NAGAISHI et al. first considered it a kind of alveolar epithelium though, they have come to suggest it as a mesenchymal cell, as it is quite different from the alveolar epithelial cell in its feature, and rather akin to a cell of mesenchymal origin. The existence of such cells were also recognized by KISCH (12), POLICARD et al. (20, 21, 22, 23 and 24), TAKAGI (29) and SHIMIZU (28), and called as "specific cell (KISCH)", "large alveolar cell (POLICARD et al.)" etc.

In clinical anesthesia, it has been empirically known that the vapor of diethyl ether possesses an intense irritant effect upon the upper respiratory tract, when inhaled in higher concentration, and often causes multiple complications or sequelae in respiratory system compared with other inhalation anesthetics. As the vapor is inhaled down to the alveoli during anesthesia, it is quite conceivable that the alveolar cells may also be subjected to the direct chemical irritation of the vapor.

The electron and light microscopic investigations in this laboratory revealed that

a series of characteristic changes occurs in the mouse lung alveoli as just described in the foregoing chapter, the appearance of so-called dust cell, a large free cell, in the alveolar air space and degenerative processes in the "alveolar wall cell".

These changes tend to become more marked as the anesthesia is further prolonged, simultaneously combined with the tendency of degenerative processes in the dust cell itself.

The origin of both dust cell and "alveolar wall cell" is still in dispute. In closer examination of dust cells by means of electron micrograph, some of the dust cells represent a similar feature to that of monocytes, whereas the others are very similar to "alveolar wall cell" (Figs. 22, 23). All these cells possess a phagocytic activity, and are mobilized and accumulated to the site of acute inflammation. From these facts, it would be positively concluded that these cells have a similar developmental origin, most probably mesodermal derivatives.

On the other hand, the alveolar epithelial and capillary endothelial cells are both remaining unaltered notwithstanding prolonged exposure to ether vapor. It is of interest to note that the latter have no phagocytic activity and theoretically derive from the endodermal cells, as previously demonstrated by Low and SAMPAIO (17).

In the interstitium, edematous effusion, vacuolization in the cell bodies, break down of collagen fibers are found as a reactive or degenerative process due to ether inhalation.

All these changes are of course reversible and reproducible, as far as adequate anesthetic concentration is used and gradually subside after the emergence of the anesthesia, and the normal alveolar structure is almost completely restored except for the rest of dust cells remaining in the alveolar lumen even after 48 hours.

The threshold of vapor concentration to evoke the specific inflammatory changes in the lung alveoli was estimated approximately 3.0 volume per cent in oxygen by mouse. For that reason it is advisable to use ether in not exceeding 3.0 volume per cent in vapor concentration. ARTUSIO (1, 3), introduced a technic of ether analgesia, in which he used from 0.6 to 1.6 volume per cent of ether in inspired gas mixtures, and achieved total analgesia of patients. The result obtained by this experimental study would support one reason for the advantages of ether analgesia. Practically, a balanced anesthesia in which ether vapor is used in a lowest possible concentration diluted with nitrous oxide or other gases, merely expecting the analgesic effect of ether, would be recommendable to prevent such an undesirable effect of ether.

Cyclopropane is said to be almost non-irritant upon the respiratory tract if not used in excessive concentration. As indicated above, this agent gives rise to a different change in the mouse lung alveoli from that of ether, which is characterized of a notable congestion in respiratory capillaries and diffuse migration or extravasation of blood cell components into the alveolar spaces.

Central venous pressure as well as total peripheral resistance is consistently increased during cyclopropane anesthesia as demonstrated by VOLPITTO et al. (31), BENNETT et al. (2), PRICE et al. (25), and ETSTEN (13) pointed out that there is no

significant change in intrathoracic blood volume during the level of surgical anesthesia. Hypoxia and hypercapnia may readily occur due to central respiratory depression during cyclopropane anesthesia, unless the respiration is adequately assisted or controlled. However, it is unlikely to attribute these changes in lung alveoli to a circulatory derangement due to cyclopropane anesthesia or adverse circulatory effect of intervening respiratory acidosis or anoxia, because the experimental result only demonstrated a slight capillary congestion in mouse lung alveoli under induced hypoxia and hypercapnia, as pointed out in the previous chapter 6).

The true cause of these changes under cyclopropane anesthesia is not clarified yet in the present stage of this experiment though, it would be supposed that cyclopropane may directly affect the capillary epithelium, and may alter the function of vascular walls with no visible microscopic changes so as to permit the displacement of blood cells.

Nitrous oxide and fluothane, particularly the latter, caused no significant effect upon the cells of lung alveoli in electron microscopic observation, and this fact perfectly confirms the clinical experiences.

SUMMARY

1) A series of experimental study was conducted in order to demonstrate the effects of inhalation anesthetics (diethyl ether, cyclopropane, nitrous oxide and fluothane) upon the mouse lung alveoli by means of light and electron microscopy.

2) The normal fine structure of mouse lung alveoli was discussed with special reference to the "alveolar wall cell".

3) The inflammatory changes in the alveolar structure under ether anesthesia are characterized of (1) migration of dust cells into the alveolar spaces, (2) degenerative changes in the "alveolar wall cells" and dust cells, and (3) interstitial edema associated with multiple degenerative changes in the interstitial cells and ground substances.

4) These changes are further advanced as the period of anesthesia is prolonged, especially the mitochondria of alveolar wall cells suffer from considerable degenerative changes.

5) The entodermal derivatives of the alveolar wall, such as the alveolar epithelial cells and capillary endothelial cells are hardly subjected to the changes.

6) The threshold of ether concentration is approximately 3.0 volume per cent in inspired air to evoke the effect upon mouse alveoli.

7) The changes are reversible and the normal pattern of alveolar structure is almost restored 48 hours after the elimination of ether, a small number of dust cells being left in alveolar lumen.

8) In cyclopropane anesthesia, on the other hand, the capillary congestion and blood cell extravasation into the air space are found as the consistent factors of the changes in lung alveoli. The cause of these changes and the mode of action of cyclopropane on lung alveoli were also discussed.

9) No significant change was demonstrable in the alveolar structure under

nitrous oxide and fluothane anesthesia besides a slight filling of the capillary beds with blood.

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EXPLANATION OF FIGURES

Part I.

Light Micrographs of Mouse Lung Alveoli (Figs. 1-11)

Figs. 1-10 : Sectioned at 3 micron, stained with hematoxyline-eosin.

Magnification : a : 675 $\times$, b : the same field, 1500 $\times$

Fig. 11 : Tissue smear, stained with May-Giemsa's azure-eosin. 1350 $\times$.

Fig. 1 : Normal structure in unanesthetized stage.

Fig. 2 : Under ether anesthesia for 1 hour.

Fig. 3 : Ibid. for 2 hours.

Fig. 4 : Ibid. for 3 hours.

Fig. 5 : 24 hours of recovery from ether anesthesia.

Fig. 6 : 48 hours of recovery from ether anesthesia.

Fig. 7 : Under cyclopropane anesthesia for 3 hours.

Fig. 8 : Under nitrous oxide anesthesia for 3 hours.

Fig. 9 : Under fluothane anesthesia for 3 hours.

Fig. 10 : Under thiopental anesthesia for 3 hours.

Fig. 11 : Lung tissue smear under ether anesthesia for 3 hours.

A huge dust cell to the right, 2 leucocytes to the left and below.

EXPLANATION OF FIGURES

Part II.

Electron Micrographs of Mouse Lung Alveoli (Figs. 12-30)

(Note : A bar 1 micron in length is drawn in all figures)

Fig. 12 : Diagrammatical illustration of normal alveolar structure.

Fig. 13 : Normal alveolar structure. Note that the nucleus of alveolar epithelial cell is protruded into the alveolar lumen with a thin cytoplasmic covering. The

surface of alveolar wall is uninterruptedly lined with attenuated cytoplasmic membrane extended from epithelial cell.

Fig. 14 : Normal alveolar wall cell with abundant cytoplasm, in which mitochondria and other osmiophilic inclusionsbodies (arrow) are seen.

Fig. 15 : Normal alveolar structure. An interstitial cell (ISC), alveolar lumen (ALV), alveolar capillaries (CAP) including some erythrocytes (ERY), and its endothelial cell (END) are seen. An alveolar wall cell (AWC) has typical microvilli.

Fig. 16 : Under ether anesthesia for two hours. Slight degenerative changes in the mitochondria (M) of alveolar wall cell (AWC) are seen, such as central transparency and slight swelling of mitochondria.

Fig. 17 : Under ether anesthesia for 3 hours. Advanced degenerative changes in the mitochondria of alveolar wall cell and also those of dust cell (DC) are manifest, e. g. swollen and more spherical mitochondria whose electron densities are diminished a magnified (view is presented in Fig. 30b).

Fig. 18 : Under ether anesthesia for 3 hours. Splitted collagen fibers are visible in abnormal wide tissue spaces.

Fig. 19 : Under ether anesthesia for 3 hours. Interstitial edema, fluid retention are seen between both basement membranes.

Fig. 20 : Under ether anesthesia for 3 hours. Vacuoles are seen in an interstitial cell.

Fig. 21 : Under ether anesthesia for 3 hours. Three giant dust cells (DC) are seen, one (upper right) is disintegrated and its mitochondria are scattered out of the cell. Alveolar epithelial cell (AEC) is intact.

Fig. 22 : A dust cell which closely resembles to alveolar wall cell.

Fig. 23 : A dust cell which is rather similar to monocyte.

Fig. 24 : Under cyclopropane anesthesia for 3 hours. Note the migration of erythrocytes in alveolar lumen. No other significant changes are seen. Endothelial cell and alveolar wall cell seem intact.

Fig. 25 : Under nitrous oxide anesthesia for 3 hours. Two erythrocytes are present in alveolar lumen, elsewhere seems normal.

Fig. 26 : Under fluothane anesthesia for 3 hours. Least changes are seen everywhere in alveolar structure.

Fig. 27 : A single giant dust cell, which structure is quite typical.

Fig. 28 : 24 hours of recovery from ether anesthesia. Two dust cells still exist in alveolar lumen. Interstitial edema is almost ceased.

Fig. 29 : 48 hours of recovery from ether anesthesia. One dust cell with a pseudopodium is still left in the lumen. Note the close resemblance to alveolar wall cell just neighbored in its cellular ingredients.

Fig. 30 : Magnified views of mitochondria in alveolar wall cell.

a : Normal mitochondria. Cristae mitochondriales are discernible in them.

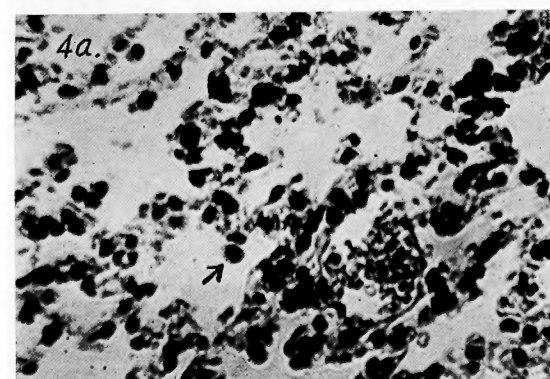
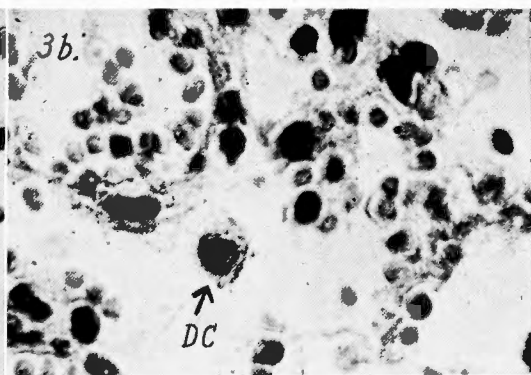
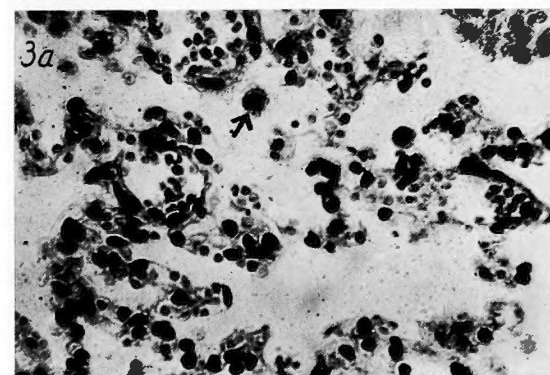
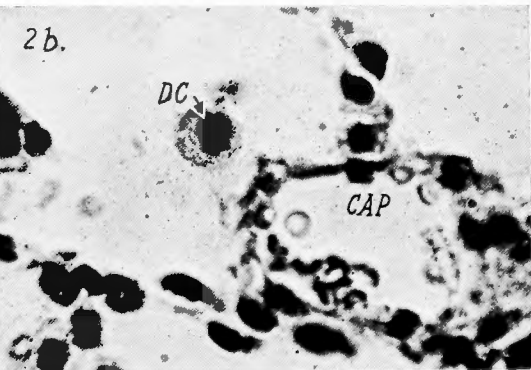
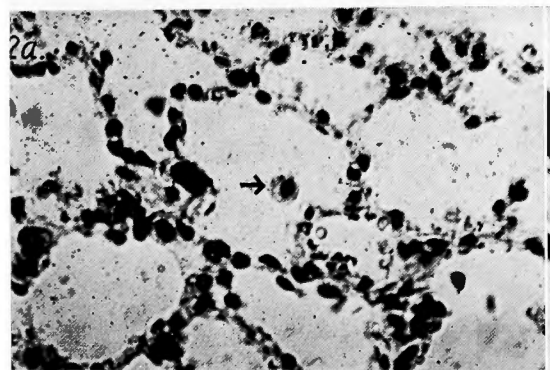
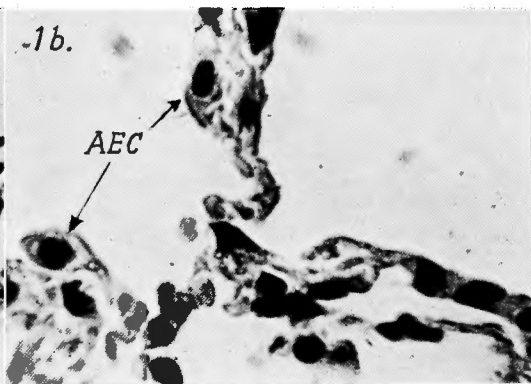
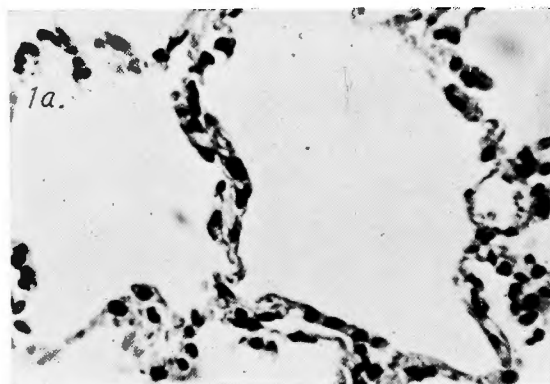
b : Ether anesthesia for three hours. Multiple degenerative changes are seen in mitochondria. Electron density of central region is reduced, cristae mitochondriales are obscure, and pushed to periphery.

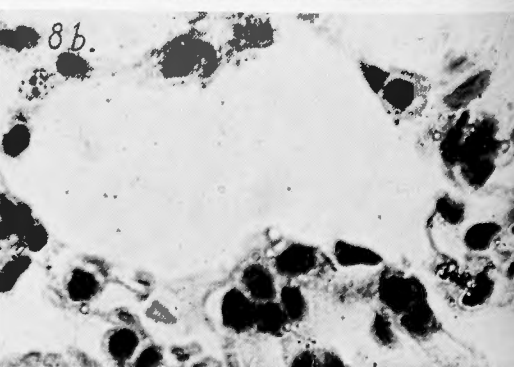
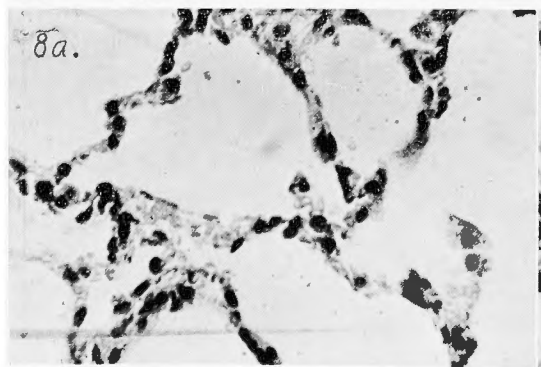
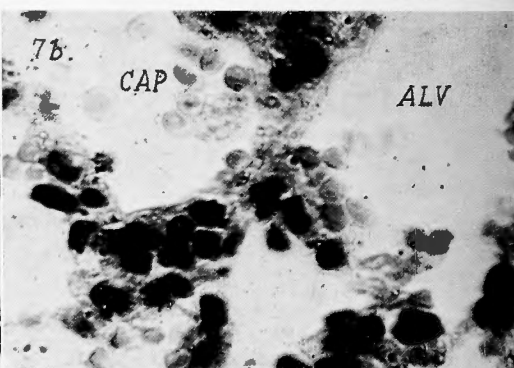
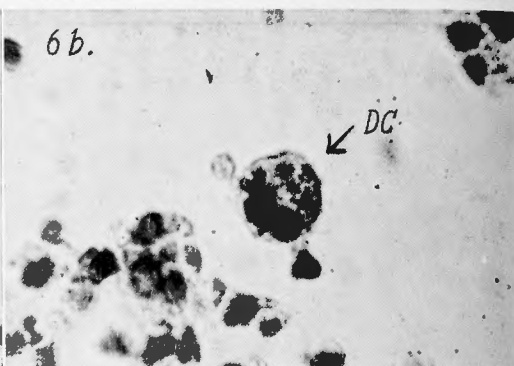
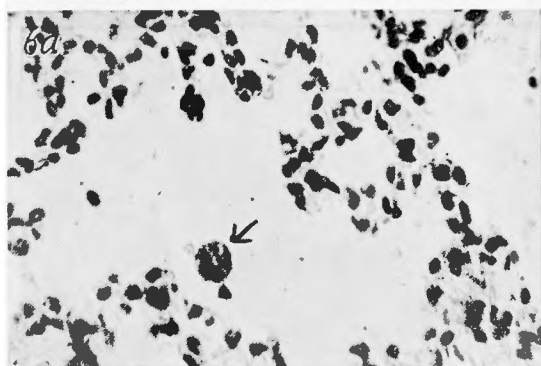
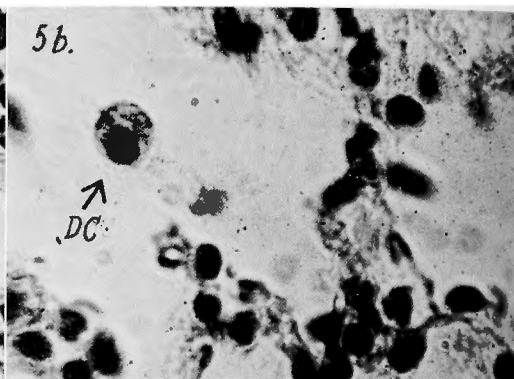
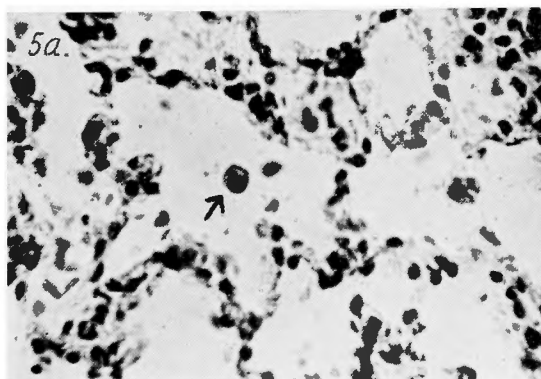
c : Vacuolated mitochondria.

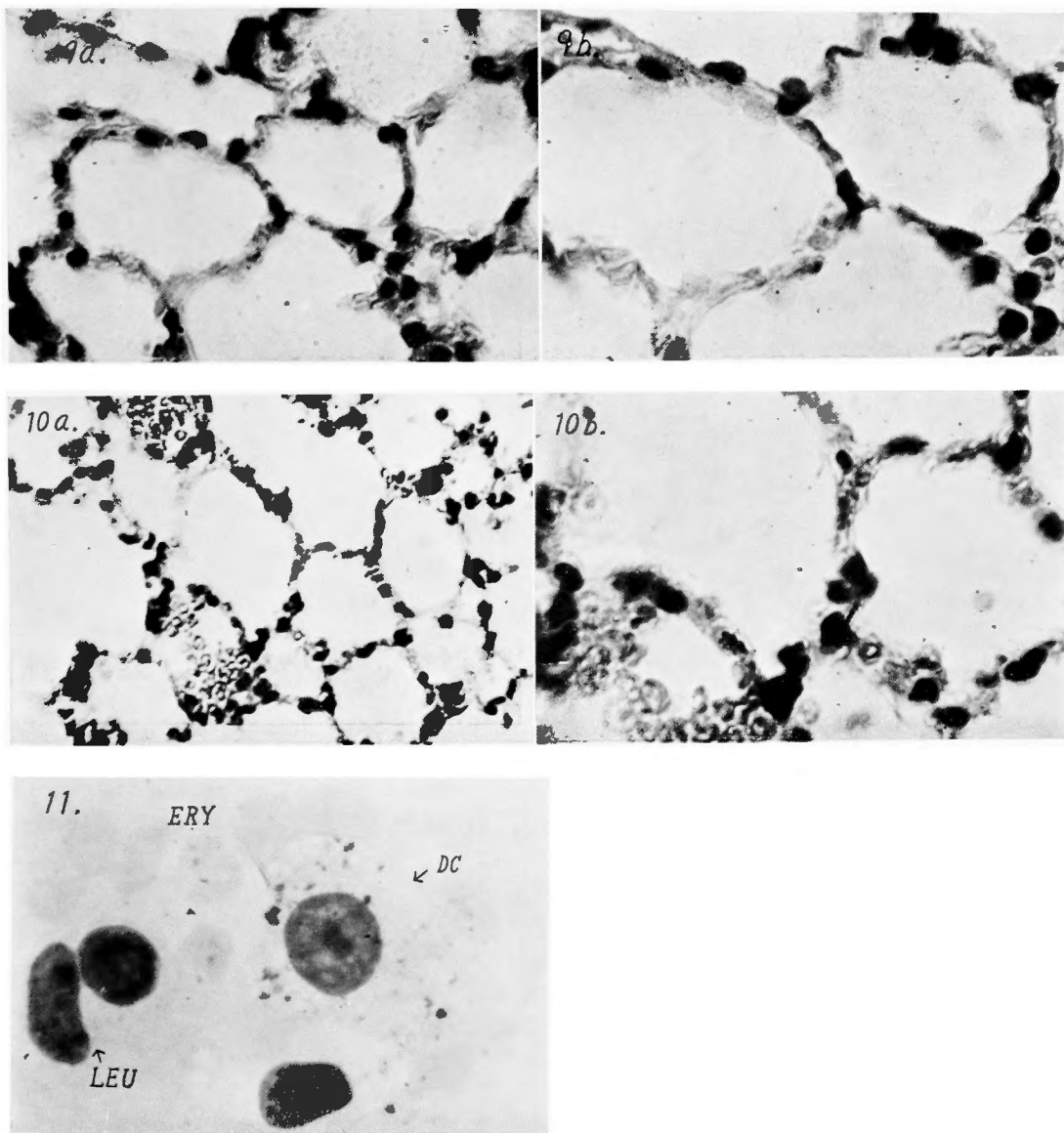
d : A giant vacuole in cytoplasm.

e : Disintegration of mitochondria.

f : The cytoplasm is thoroughly occupied with dense osmiophilic granules and vacuoles probably derived from mitochondria.



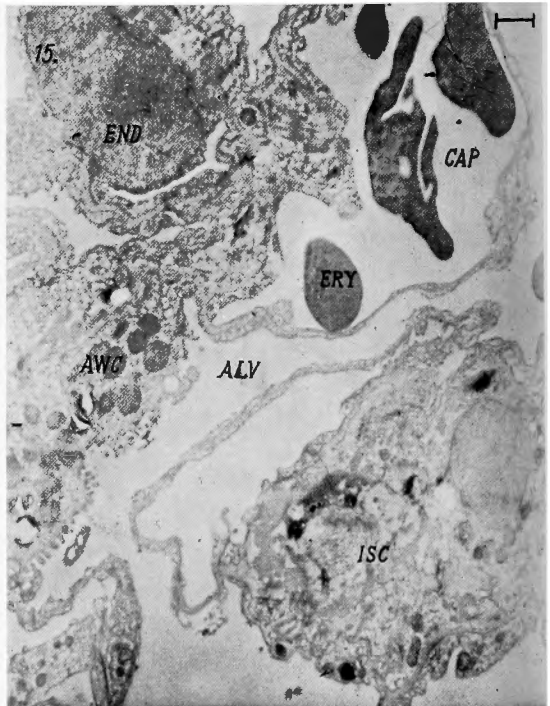
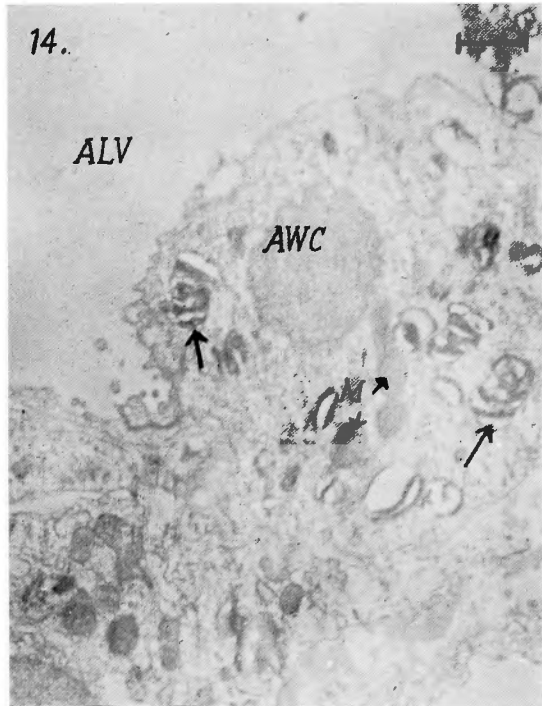
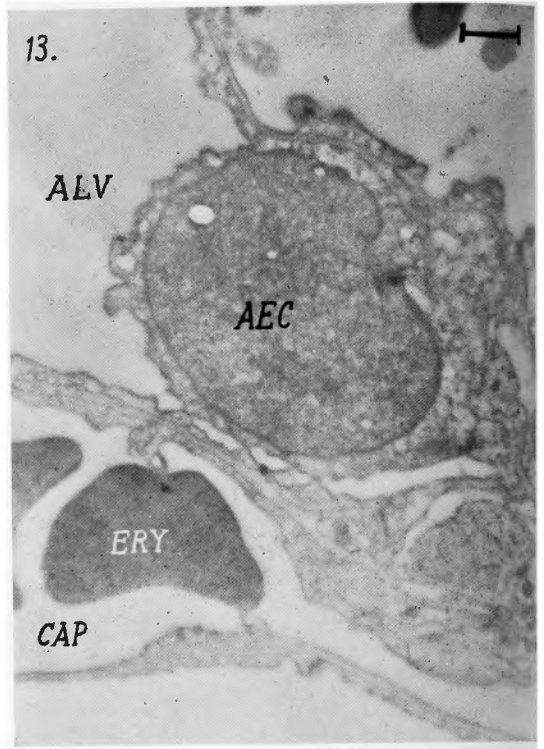
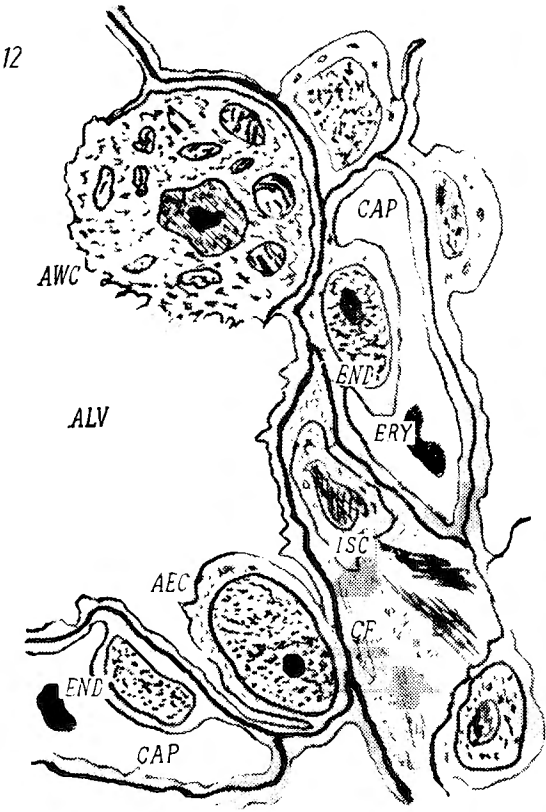


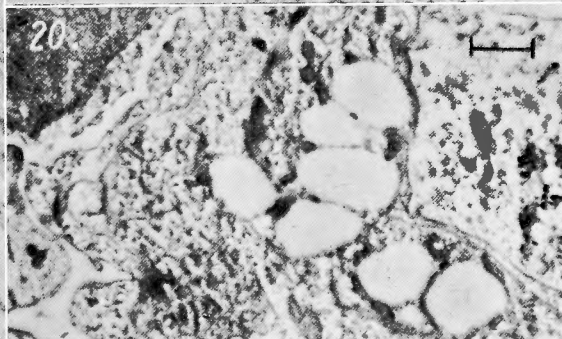
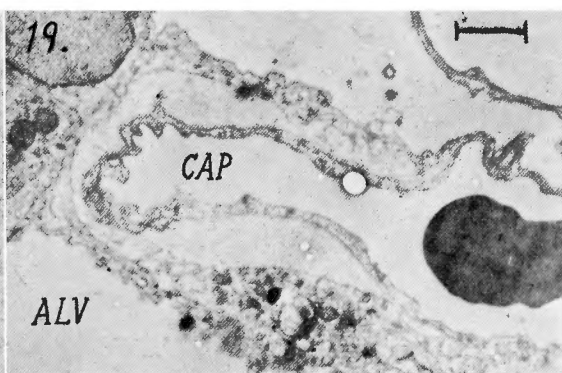
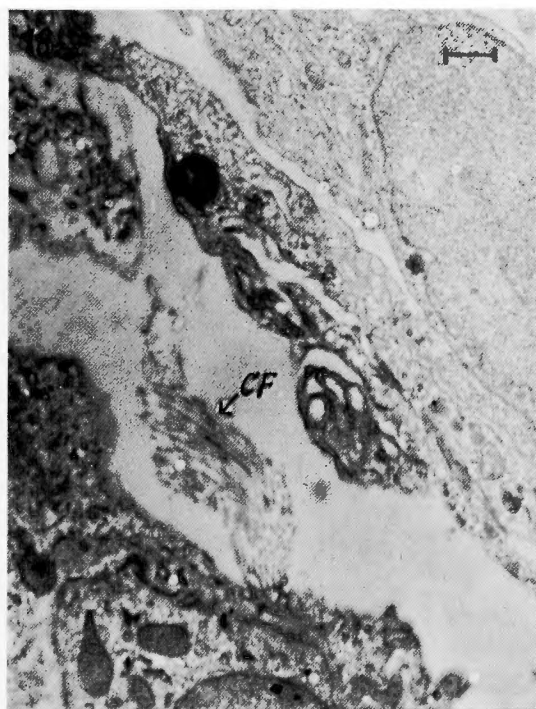
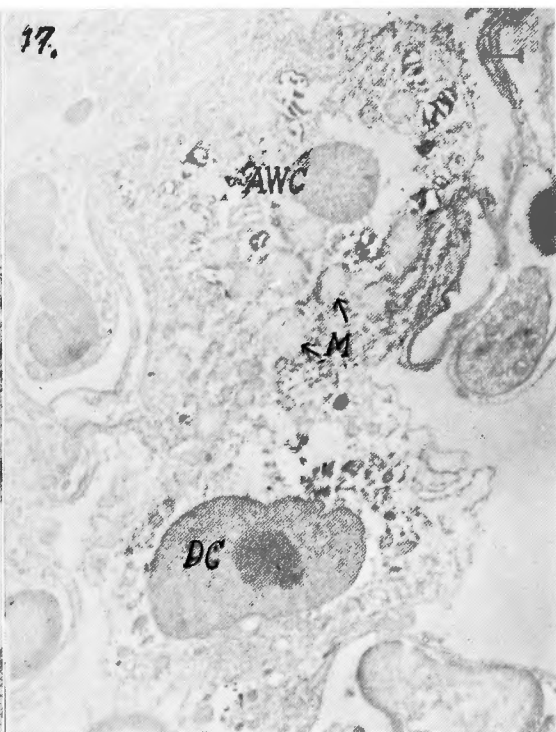
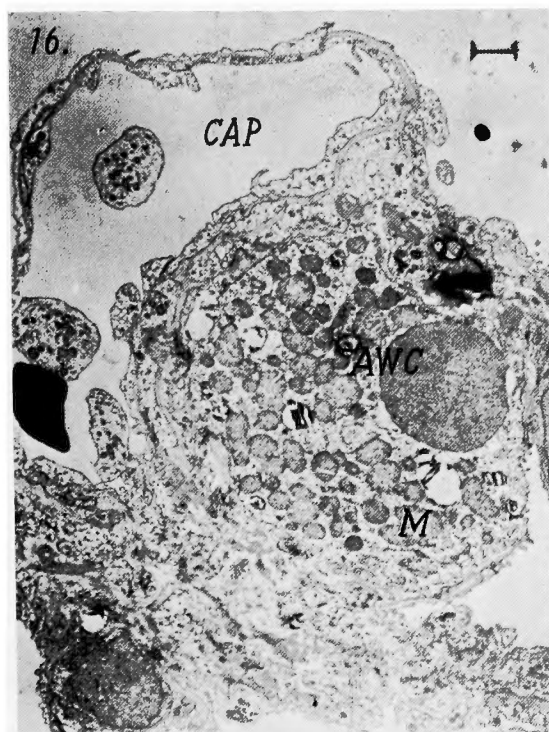


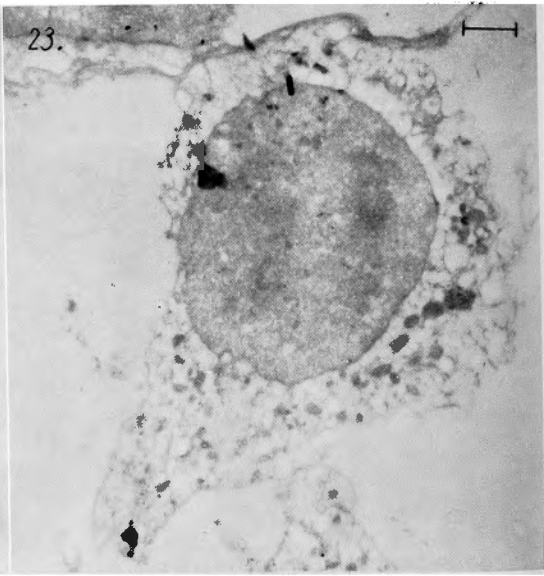
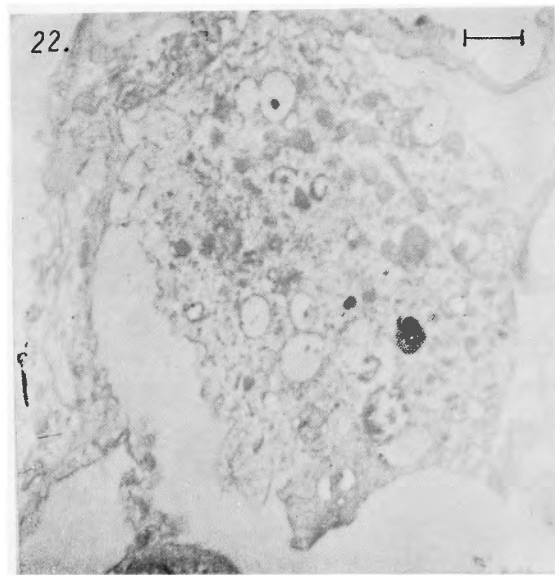
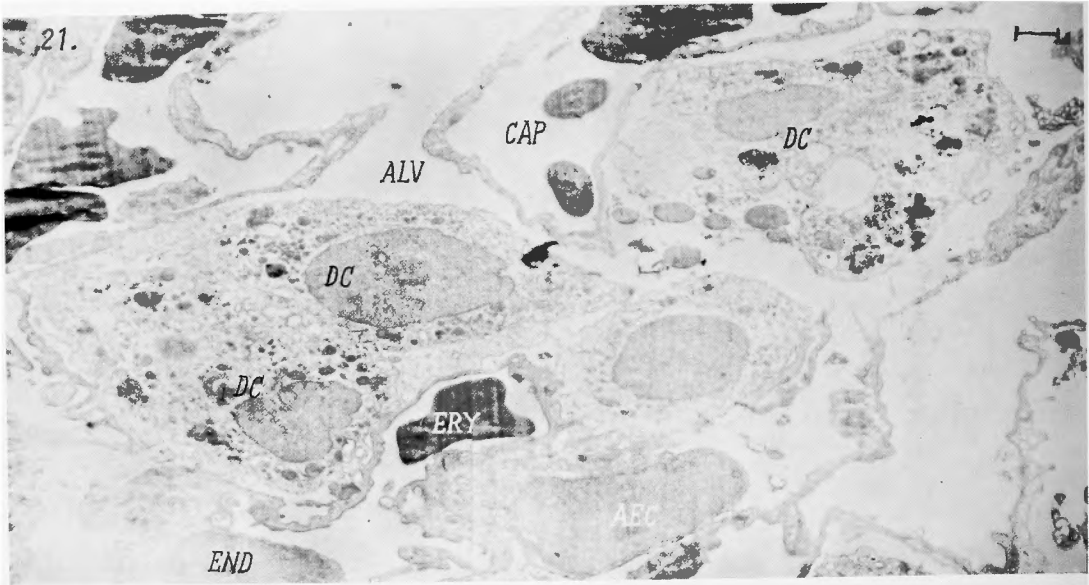
ABBREVIATIONS

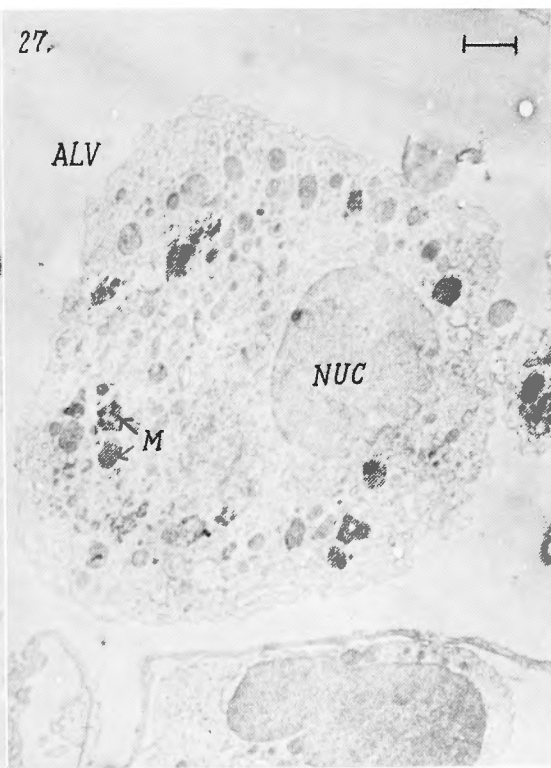
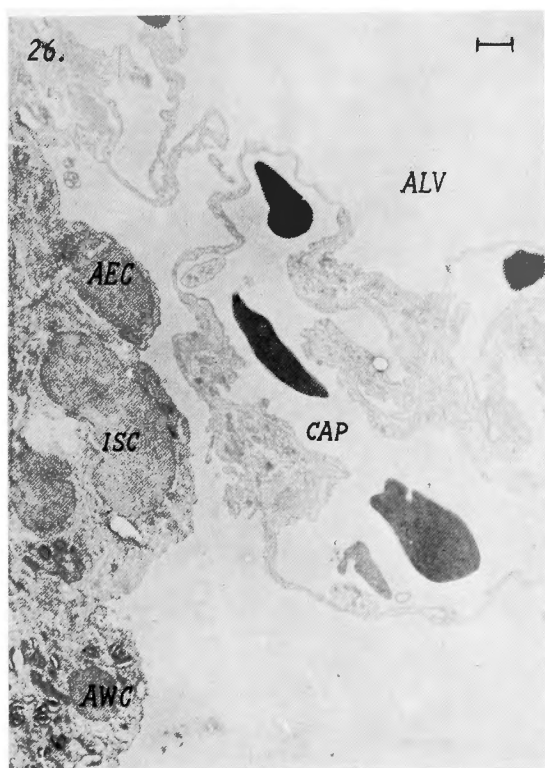
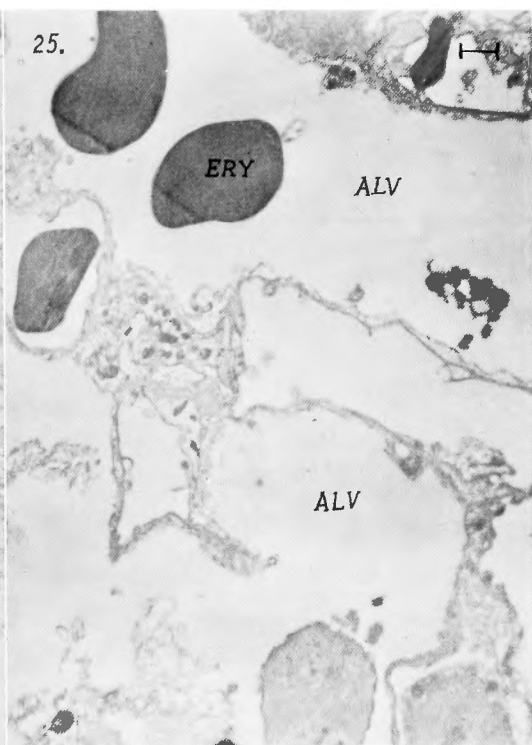
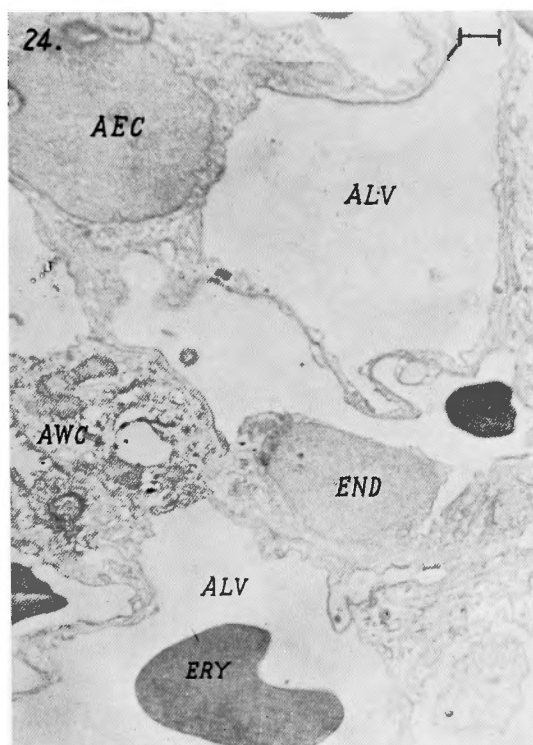
AEC, alveolar epithelial cell
 ALV, alveolar space
 AWC, alveolar wall cell
 CAP, blood capillary
 CF, collagen fiber
 DC, dust cell

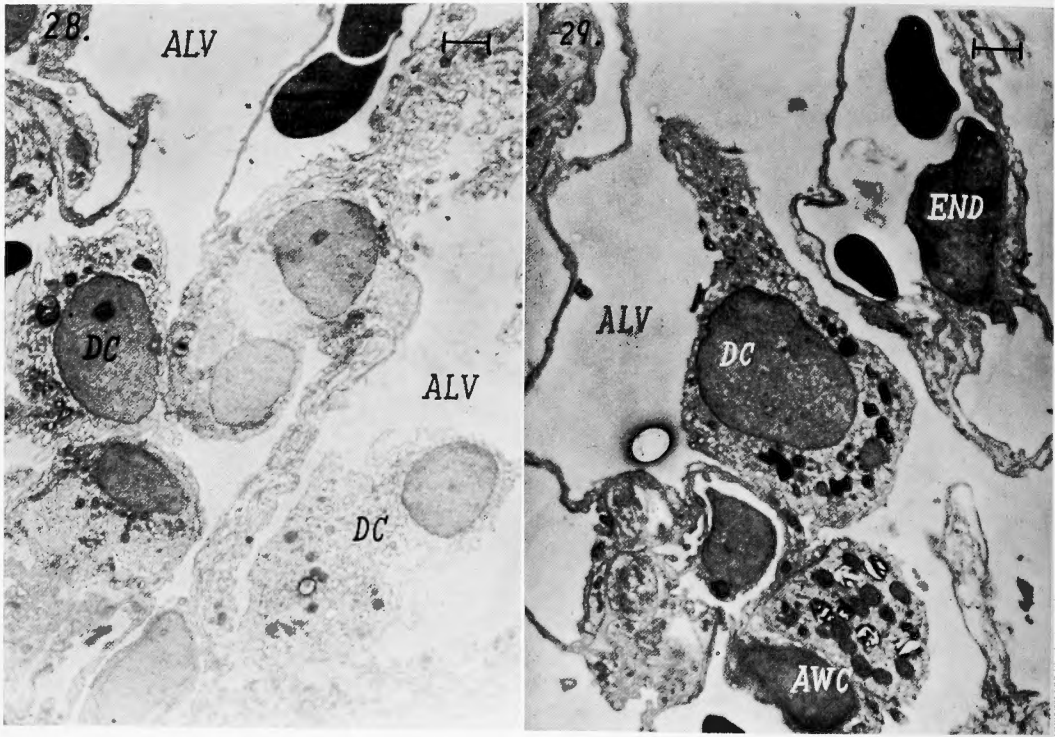
EF, elastic fiber
 END, endothelial cell of blood capillary
 ERY, erythrocyte
 IS, interstitium
 ISC, interstitial cell
 M, mitochondria

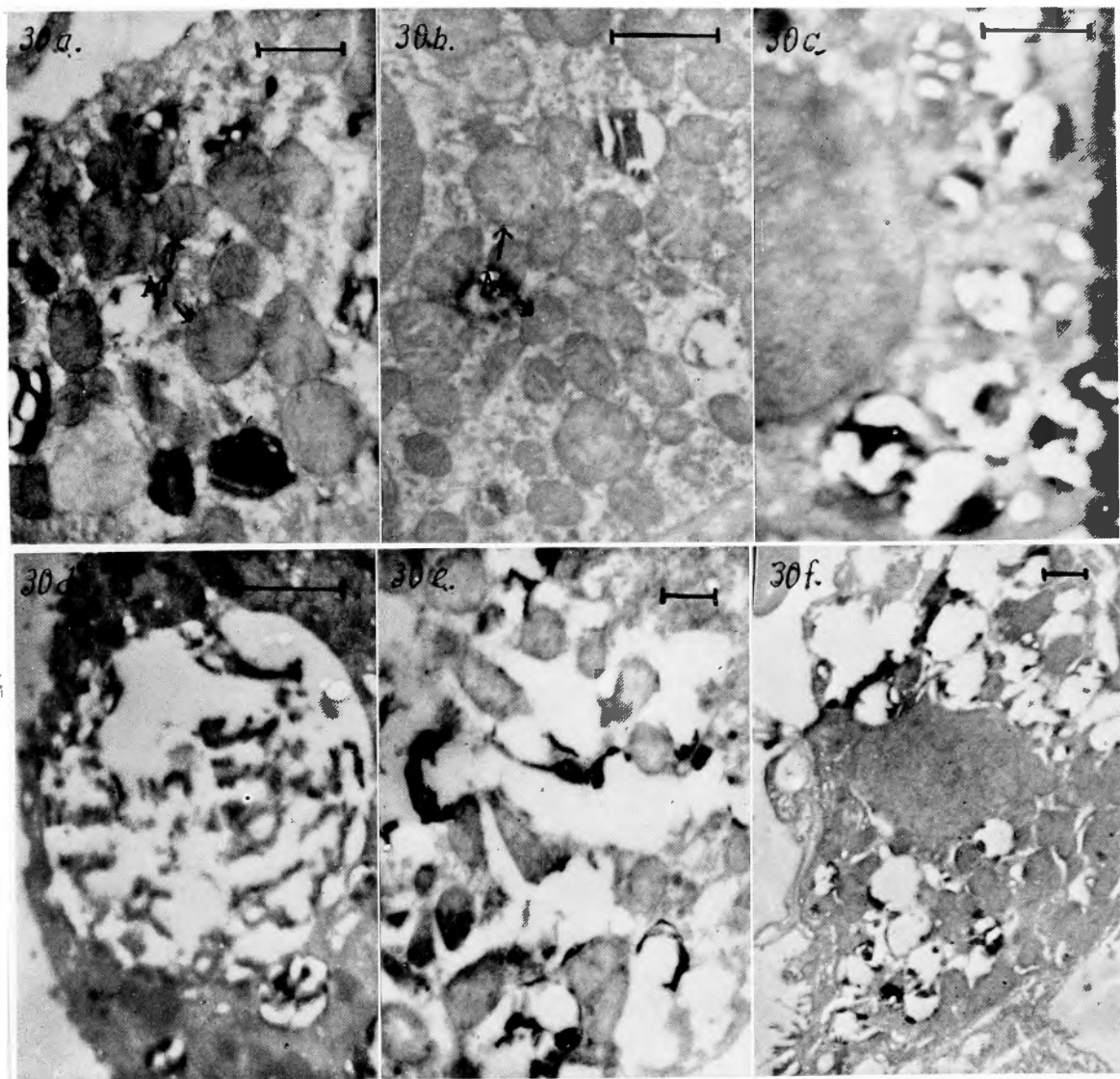












和文抄録

エーテル、サイクロプロペン、笑気及びフルオセンの肺胞微細構造に及ぼす影響についての実験的研究
特にマウス肺胞細胞の電子顕微鏡的变化について

京都大学医学部麻酔学教室（指導：稲本 晃 教授）

中 嶋 日 枝

吸入麻酔中及び麻酔後に屢々遭遇する気道分泌或は喀痰増量、ひいては気管支炎、肺虚脱、肺炎等の術後合併症の頻度から、従来エーテルは気道粘膜に対する刺激性が最も強く、サイクロプロペン、笑気等は比較的少ないと考えられ、又最近輸入せられた新麻酔剤フルオセンもこの副作用が少ないとされている。

著者はエーテル、サイクロプロペン、笑気及びフルオセン麻酔による肺胞微細構造の変化を、光学顕微鏡及び特に電子顕微鏡的に比較し、次の様な所見を得た。

1) 先ず正常肺胞の微細構造をマウスに就て電子顕微鏡的に究明した。即ち肺胞壁は肺胞上皮細胞の薄膜化した細胞質により略々連続的に被覆されているが、其の間に肺胞壁細胞（長石）が其の特徴的な細胞質構造をもつて肺胞壁の所々に顔を出している。この両種の細胞は単に其の構造が本質的に異なるのみならずエーテルの刺激に全く異なつた態度をとることを発見した。又正常マウス肺胞腔内には所謂塵埃細胞は殆ど認められなかつた。

2) エーテル麻酔による肺胞の変化は次の三者に総括される。i 塵埃細胞の肺胞腔内遊出並に其の細胞自身の退行性変化若しくは崩壊、ii 肺胞壁細胞の退行性変化、特に其の絲粒体は膨化し、球形となり、中心部よりオスミウム親和性を失い、次第に空胞化する。iii 間質の浮腫性膨化及び毛細管充盈、毛細管内皮細胞を除く諸細胞及び基質線維の変性、断裂等が見られる。

3) 此の変化はエーテル持続時間に比例して増強し又吸気内濃度が3.0%乃至4.5%を超えると多発する。可逆性であるが、回復後48時間目にも尚塵埃細胞は肺胞腔内に残存する。

4) 肺胞上皮、血管内皮両細胞に全く変化が見られないことは、これらの細胞が何れも内胚葉性起源を有することと、前述の諸変化を認めた諸細胞が何れも中胚葉性と考えられることと対比して興味がある。

5) 上記の所見から、又細胞構造上の相似性、食食能から塵埃細胞と肺胞壁細胞とは同一又は近作した細胞と考えたい。

6) 他の麻酔剤例えばサイクロプロペン麻酔下の肺胞所見はエーテルによるものとは本質的に異り、肺毛細血管の鬱血及び肺胞内出血が時間と共に強度となる。併し塵埃細胞の出現、肺胞壁細胞の退行性変化は認められなかつた。

7) 笑気麻酔では、毛細血管の軽度充盈及び僅少の肺胞内赤血球漏出を来す他認むべき変化がない。

8) フルオセン麻酔下の肺胞構造は、正常肺と何等認むべき変化がない。

9) 夫々の麻酔剤による変化の特殊性を、臨床経緯と照合して考察を加えた。