Dr I Klineberger-Nobel,
With regards.
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The Experimental Production of Bronchiectasis in Rats

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THE EXPERIMENTAL PRODUCTION OF BRONCHIECTASIS IN RATS

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(PLATES XVII AND XVIII)

SINCE Laennec (1819) first described and named bronchiectasis, none of the numerous theories of its pathogenesis (Ewart, 1909 ; Ballon *et al.*, 1931-32 ; Lemoine, 1936 ; Ogilvie, 1941 ; Lisa and Rosenblatt, 1943) has found general acceptance and experimental enquiries have often resulted in conflicting reports (Lisa and Rosenblatt).

In the present investigation, bronchiectasis was experimentally produced in young rats in order to study the pathogenesis of the bronchiectasis which is so prevalent in older rats, and if possible to gain some insight into the pathology of human bronchiectasis. Although the two diseases are not identical (Passey *et al.*, 1936) there may possibly be some common factors in the development of the bronchial dilatation which forms the basic lesion in both diseases.

METHODS

Male albino rats less than 3 months old were used. They weighed 160-220 g., but a few younger rats weighing 50 g. were also used.

Operative technique

Anæsthesia, thoracotomy technique and post-operative care were as previously described (Cheng, 1951). The operations, which were performed with simple aseptic precautions, are described under each experiment.

Bacteriological technique

The left lung was removed aseptically. Lung smears or lung tissue were cultured aerobically on blood agar, MacConkey and papain digest broth, and anaerobically in Robertson's meat broth and semi-solid agar. Direct smears were also examined after staining by Gram's and Ziehl-Neelsen's methods.

Histological technique

The rats were killed with nembutal or coal gas. The lungs were fixed in Bouin's fluid as described by Macklin (1934-35). Paraffin sections were routinely stained with Ehrlich's acid hæmatoxylin and eosin. Selected sections were stained with Weigert's elastic stain and Van Gieson's stain, Lendrum's (1947) reticulin stain and modification of Mallory's method for connective tissue, the Gram-Weigert method for bacteria, mucicarmine stain, and the ferrocyanide method for iron.

To grade the extent of bronchiectasis the following arbitrary scales were sometimes used :—*O*, no bronchial dilatation. *Grade* 1, lung collapsed, surface

smooth, main and secondary bronchi dilated to approximately twice their usual size. *Grade* 2, lung indurated, a few nodules on external surface, bronchi including tertiary branches dilated. *Grade* 3, bronchial dilatation prominent, surface nodular. *Grade* 4, marked bronchial dilatation with displacement of diaphragm and mediastinum, large nodules on surface.

Experiments and results

Total ligation of left bronchus

Method. In rats of 160-220 g. body-weight, the left lung was delivered after severance of its pulmonary ligament through an incision in the 4th left intercostal space. A fine steel wire was tied loosely round the left bronchus in a half hitch and the two ends of the wire were brought outside through the chest wall. The chest wound was then closed. Three days later, when the lung operated on had fully re-expanded, the loose bronchial ligature was tightened under light ether. Controls underwent a sham ligation. The bronchus was also ligated in one stage in some experiments. Some younger rats weighing 50 g. also underwent total bronchial ligation in one stage but only two of them survived the operation.

Results

(*a*) 160-220 *g. rats.* One hundred and twelve rats were used and 2-6 rats were killed at various intervals up to 2 months. After ligation, the left lung became collapsed, with capillary congestion, focal hæmorrhage and œdema. However, bronchitis of varying severity soon developed, sometimes within 2 hours, the bronchial wall showing inflammatory infiltration, vascular congestion and œdema. The bronchial epithelium presented secretory activity, with occasional migrating leucocytes and histiocytes, while mucus or mucopurulent exudate collected in the collapsed bronchial lumen. The change affected all the bronchi but was more pronounced in the large bronchi. Proliferation and desquamation of septal cells and interstitial infiltration by leucocytes also occurred, accompanied by pleural and perivascular inflammation. The primary and secondary bronchi immediately distal to the obstruction, distended by the accumulation of exudate and secretion, then dilated (fig. 1). They might within 6 hours dilate to twice the normal size if their content was purulent, but they generally took about 4 days when their content was mainly mucus. The dilatation then progressed distally to involve the tertiary bronchi and the bronchioles. After about a week the lung had become small and firm and was studded with yellowish or greyish nodules of dilated bronchi, but pleural adhesions were remarkably slight. Large histiocytes distended the alveoli and hæmosiderin pigmentation was present. Purulent bronchitis was associated with more pronounced pneumonitis and abscess formation. The acute inflammation of the lung tissue was gradually replaced by fibrosis. Around the widened bronchi, the fibrotic alveolar walls became stretched more or less parallel with the bronchial wall. From then onwards the bronchiectasis steadily became more pronounced and the lung more fibrotic. After 20-60 days the lung was frequently converted into a large cystic

EXPERIMENTAL BRONCHIECTASIS IN RATS

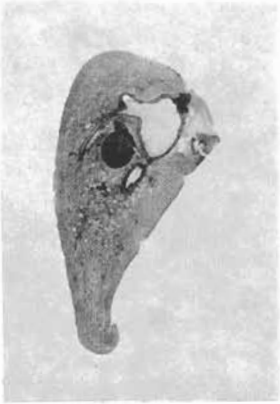

FIG. 1.—Total bronchial ligation; 4 days. Transverse section of lung showing large bronchus beginning to dilate, with mucus content and collapsed parenchyma. Hæmatoxylin and eosin. × 5.

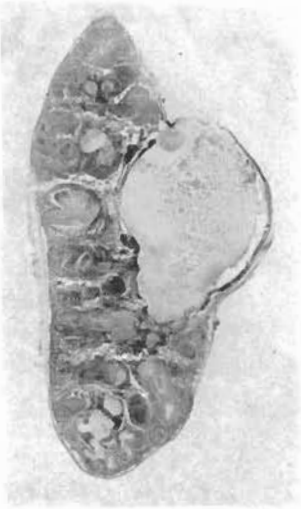

FIG. 2.—Total bronchial ligation; 20 days. Longitudinal section of lung showing advanced generalised bronchiectasis. H. and E. × 2.

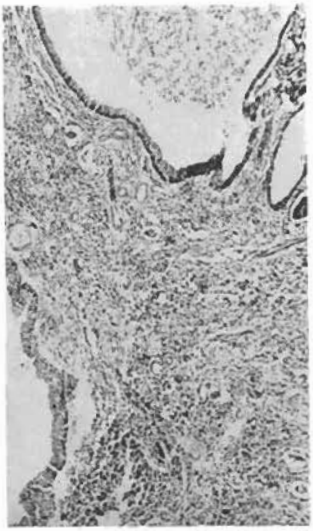

FIG. 3.—Total bronchial ligation; 30 days. Section of lung showing dilated bronchi lined by columnar or stratified flattened epithelium, with inflammatory exudate in lumen; bronchitis. Intervening lung tissue collapsed, inflamed and fibrotic. H. and E. × 45.

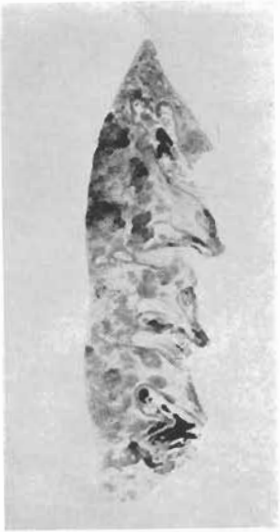

FIG. 4.—Partial bronchial ligation; 30 days. Longitudinal section of lung showing advanced bronchiectasis. The dilated bronchi contain India ink injected through the bronchial constriction. H. and E. × 2·5.

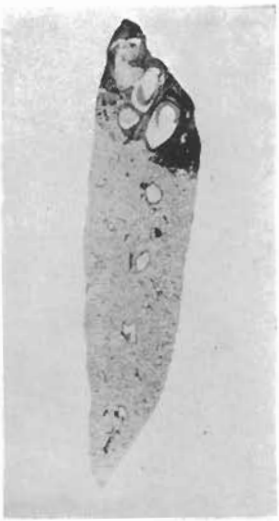

FIG. 5.—Ligation of upper secondary bronchus; 15 days. Longitudinal section of lung showing localised bronchiectasis in the affected pulmonary segment. H. and E. × 2·5.

mass, up to 5×2 cm. in diameter, made up of greatly dilated bronchi filled with purulent or mucopurulent exudate. Little lung parenchyma was left, and what remained was fibrotic and full of abscesses (figs. 2 and 3).

The dilated bronchi were lined by ciliated columnar, cuboid, flattened or hyperplastic epithelial cells, and goblet cells were often prominent. When acute bronchitis occurred the epithelium became shaggy and shrunken, with many migrating leucocytes, but ulceration was detected only in advanced bronchiectasis. Squamous metaplasia was not observed. The bronchial mucosa sometimes showed papillary foldings. The bronchial muscle occasionally appeared hypertrophic in the early stages of dilatation, and both muscle and elastic tissue were usually in evidence around the dilating bronchi for about a week. However, they were eventually replaced by fibrous tissue, which could be traced into the adjacent damaged alveoli, and spaces lined by cuboidal or flattened cells were formed. Lymphoid hyperplasia at the hilum occurred early, but never led to more than very slight obstruction of the lumen of adjoining bronchi. The bronchial elastic fibres were scanty or absent when they traversed the centre of the hilar lymphoid tissue, but this was also observed in the controls. The blood vessels were gradually obliterated by fibrous thickening and the pleura became fibrotic.

The controls showed, at most, slight bronchitis only.

(*b*) 50 *g. rats*. One rat killed after 2 weeks had pulmonary collapse only; bacterial cultures were sterile. The second rat, killed after 3 weeks, exhibited moderately advanced bronchiectasis, accompanied by bronchitis, collapse and pneumonitis. Diphtheroid organisms were cultured from this lung.

Partial ligation of left bronchus

Method. Rats weighing 160-220 g. were used in this and all subsequent experiments. The left bronchus was partially occluded in two stages by means of a cotton thread tied with the special knot previously described (Cheng). When they were killed, patency of the occluded bronchus was estimated by the use of probes, the injection of India ink and by dissection.

Results. Sixteen rats were killed at various intervals up to 60 days. Of these, two rats showed complete bronchial obstruction and advanced bronchiectasis. Eight rats had marked partial bronchial occlusion so that only India ink could be injected through the obstructed tubes. They developed bronchitis, collapse and pneumonitis, followed later by bronchiectasis (fig. 4). The speed of the development of bronchiectasis was variable; for instance, one rat showed grade 2 bronchiectasis after 60 days while another displayed grade 3 bronchiectasis as early as the 10th day or soon after. In the five remaining cases, one lung was normal, two lungs had slight bronchitis and two lungs showed partial collapse, emphysema and bronchopneumonia

only. The bronchi of these rats showed a reduction in calibre ranging from slight to more than half the normal diameter.

Total ligation of left secondary bronchus

Method. The left bronchus was freed from its surrounding lung tissue and pulmonary blood vessels until either its upper or lower secondary branch was exposed. It was carefully isolated and was then either tied immediately, or in two stages, with cotton thread. The lower bronchus was ligated beyond the origin of its first two tertiary branches. When the bronchus was ligated in one stage the left lung, which was partially collapsed at the end of the operation as a result of manipulation, could be reinflated entirely, including the occluded segment, by increasing the pressure of oxygen administered through an intratracheal tube. This indicates that alveolar pores in the rat lung (Macklin) permit collateral circulation of air between the obstructed segment and the adjoining alveoli (Van Allen and Jung, 1931-32) immediately after the ligation of a secondary bronchus.

Results. The left upper secondary bronchus of 7 rats and left lower bronchus of 23 rats were ligated for various periods up to $1\frac{1}{2}$ months. Bronchitis, collapse, pneumonitis and, later, bronchial dilatation constantly occurred in the involved segment. Generally the lower two-thirds of the lung became bronchiectatic when its lower bronchus was ligated, the upper one-fifth when its upper branch was occluded (fig. 5).

Ligation of left main bronchus with subsequent release of the ligature

Method. The left main bronchus was isolated and ligated with a fine steel wire tied with a special knot (fig. 6) ; the two ends of the wire were passed outside the chest wall before the chest wound was approximated. After 1, 3, 5 or 6 days the knot was released extra-thoracically by pulling on the two ends of the wire. Patency of the main bronchus was tested when the animal was killed.

Results. In 26 rats, the ligature round the left main bronchus was released after 5 or 6 days. The animals were then killed after various periods up to 5 weeks. In 4 animals the main bronchus was completely obstructed and they are therefore excluded from the series. In the remainder, the main bronchus was narrowed to a degree ranging from slight to about half the normal diameter at the site of ligation. At first the lung presented dilated bronchi filled with mucopurulent exudate as well as bronchitis, collapse and pneumonitis. However, the bronchial exudate became increasingly watery and was gradually removed. The dilated bronchi therefore became empty after a few days, presenting a condition resembling " dry " bronchiectasis. The bronchial and parenchymatous inflammation also slowly subsided after several weeks. The resolution and removal of the alveolar exudate were frequently followed by an almost complete re-aeration of the alveoli, but sometimes the main outcome was pulmonary fibrosis. The ultimate result thus apparently

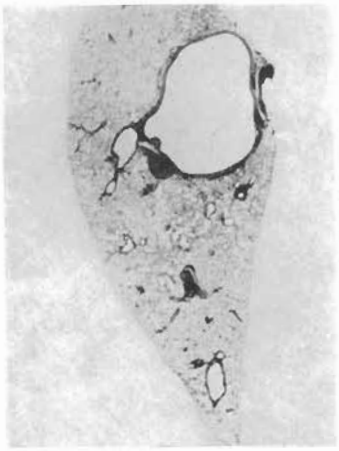

FIG. 7.—Bronchial ligature released after 5 days; 5 weeks. Transverse section of lung showing "dry" bronchiectasis with well aerated lung parenchyma. H. and E. × 4·5.

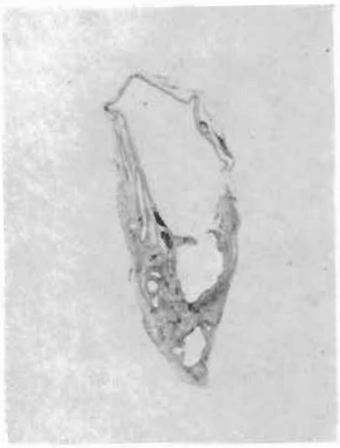

FIG. 8.—Bronchial ligature released after 5 days; 5 weeks. Transverse section of lung showing "dry" bronchiectasis with contracted fibrotic lung parenchyma. H. and E. × 3·5.

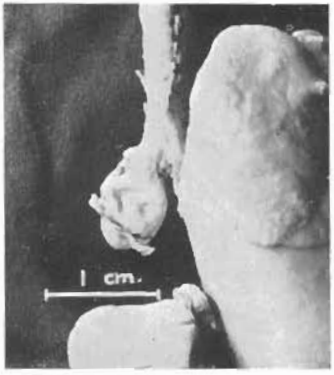

FIG. 9.—Ligation of a segment of left main bronchus with removal of left lung; 20 days. Dilatation of the bronchial segment between two ligatures.

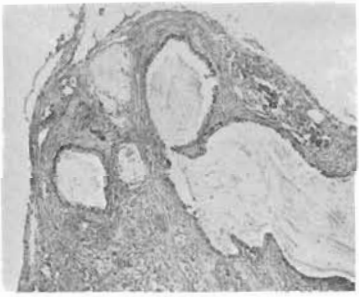

FIG. 10.—Lung graft; 33 days. Section of graft showing dilated bronchi containing mucus; fibrosis of lung parenchyma. H. and E. × 32.

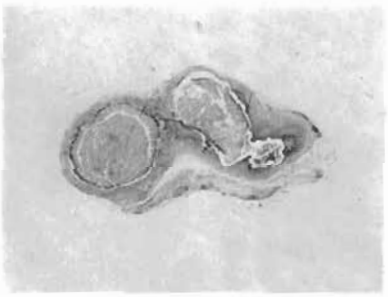

FIG. 11. — Lung graft; 33 days. Section of graft showing grossly dilated bronchi with purulent content. H. and E. × 2·8.

depended on the initial severity of the lesion and the extent of the bronchial obstruction. Of 9 rats killed after 5 weeks, 6 displayed " dry " bronchiectasis with bronchi widened to approximately twice their normal size. In 4 of them, slight to moderate bronchitis was present, but in 2 others the bronchial wall was histologically normal. In all of them the lung tissue was well aerated, with only a few foci of septal hyperplasia, pneumonitis, fibrosis or partial collapse (fig. 7). Two rats also presented " dry " bronchiectasis, with partially fibrotic and somewhat inflamed bronchi dilated up to nearly 4 times their normal diameter. However, the lung parenchyma was replaced by contracting fibrous tissue which was still slightly inflamed (fig. 8). One rat showed slight septal hyperplasia and partial collapse of the lung only.

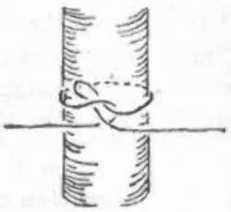

FIG. 6.—Knot of bronchial ligature which can be later released and removed extra-thoracically.

Of two rats killed 3 weeks after the main bronchus had been occluded for 1 day, one presented a normal lung and the other a " dry " bronchiectasis with bronchi four times their normal diameter and fibrotic lung parenchyma. Both rats killed 3 weeks after the main bronchus had been ligated for 3 days exhibited dilated " dry " bronchi twice their normal size, while their aerated lung tissue showed occasional septal hyperplasia only.

Ligation of left main bronchus and antibiotic therapy

Method. The left bronchus was ligated in 2 stages and the following antibiotics were given daily to groups of 4 rats from one day before bronchial ligation : procaine penicillin, 30,000 units intramuscularly once a day ; streptomycin, 25 mg. subcutaneously twice a day ; or aureomycin 5 mg. intramuscularly twice a day. Terramycin, 100 mg. orally, was also given daily to 3 rats from 3 days before ligation. Eight rats which underwent bronchial ligation only acted as controls.

Results. Rats given penicillin, streptomycin or aureomycin, as well as the controls, developed bronchiectasis of grade 2 or 3 in extent after 5-7 days. In terramycin-treated rats killed 7 days after the ligation, one rat displayed grade 3 bronchiectasis, with negative bacterial culture. However, two other rats presented pulmonary collapse with bronchitis and pneumonitis only. Pneumococci and staphylococci were isolated from one of them and staphylococci from the other.

Ligation of left main bronchus and oleothorax

Method. To maintain an intact mediastinal partition, only the apical one-third of the left lung was delivered to expose the hilum for the total ligation of its bronchus in one stage. After the chest wound was sutured, 20 c.c. per kg. body-weight of sterile liquid paraffin, the maximum dose tolerated, was injected into the left pleural cavity. The intrapleural pressure in a few cases after

induction of oleothorax, measured according to the method of Hopkins (1949) with a no. 1 needle, ranged from about −2·5 to 25·0 mm. of water, which is within normal. Controls underwent bronchial ligation only.

Results. Five days after bronchial ligation, 11 rats with oleothorax and 10 controls showed bronchiectasis ranging from less than grade 1 to grade 3 in extent in both groups. Three other rats after bronchial ligation and induction of oleothorax were found dead with grade 3 bronchiectasis after 12, 14 and 17 days respectively.

Ligation of a segment of main bronchus with removal of the lung

Method. In 4 rats, the left lung was delivered outside the chest cavity and the bronchus was tied twice, first near the tracheal bifurcation and next round the pulmonary vessels and bronchus at the hilum. The lung was then cut off and the chest wound closed.

Results. After 20 days, the ligated segment of the left main bronchus was dilated into a cystic mass about 0·5 cm. in diameter containing mucopurulent matter (fig. 9). It was markedly adherent to the chest wall as well as to the mediastinum, which showed a marked shift to the left. Microscopically the bronchial wall was inflamed and fibrotic with a partially ulcerated epithelial layer.

Transplantation of lung tissue into omentum

Method. After ligation of the pulmonary vessels and bronchus the left lung was removed and kept in chilled sterile Krebs-Ringer solution. The chest wound was then closed. The lung was sliced with a sterile Stadie-Riggs tissue slicer and left in the Krebs-Ringer solution. The abdominal cavity was opened and 3 or 4 lung fragments were grafted into a fold of testicular omentum. The abdominal wound was then sutured together. Penicillin was given intramuscularly for 2 days after the operation.

Results. Nine rats were killed after 10-33 days. Only the bronchi in the grafts survived and they were dilated in all but one graft. The dilatation ranged from slight to more than twice the normal diameter when the bronchi contained mucopus or mucus (fig. 10), or it might approach four times the normal size if the content was purulent (fig. 11). The bronchi were lined by ciliated columnar, cuboidal, flattened or hyperplastic epithelium, with frequent goblet cells. There was ulceration when the dilatation was pronounced. Bronchial muscles were still in evidence in some 10-days-old grafts, but the bronchial wall was ultimately replaced by fibrous tissue showing variable inflammatory infiltration. The bronchial elastic tissue was destroyed in the grossly dilated bronchi only. The lung parenchyma was collapsed and degenerated, with inflammatory infiltration and fibrosis. Lymphocytes frequently collected round the bronchi and the blood vessels exhibited obliterative thickening.

Distensibility of normal bronchus

Method. The rat was killed with nembutal and the lungs were removed whole. The left lower secondary bronchus was isolated from the adjacent lung tissue by clamps and bulk ligatures, and then inflated to its maximum distensibility through a tube connected to a gas cylinder.

Results. The isolated bronchus could not be inflated to more than one-fourth of its normal diameter under 10-20 mm. Hg. pressure.

Bacteriology of lung

Fifteen rats were killed 1-20 days after bronchial ligation. *Hæmophilus bronchisepticus* was cultured from 5 cases, *H. bronchisepticus* and pneumococci from 4 cases, pneumococci from 2 cases and diphtheroids and staphylococci from 1 case ; cultures from 4 were sterile. Of 6 sham operation control rats, 3 gave negative cultures and the others had *H. bronchisepticus*, diphtheroids and staphylococci respectively. Pneumococci were cultured from the lung of one normal rat. Gram-Weigert-stained sections of 2 advanced cases of bronchiectasis after bronchial ligation also revealed the presence of Vincent's organisms.

Discussion

The present investigation strongly suggests that bronchitis and stagnation of the accompanying secretions and exudate are two essential factors for the development of bronchiectasis. Bronchopneumonia alone without bronchial stagnation, such as that produced by the intratracheal injection of pneumococci, did not give rise to bronchial dilatation (Gunn and Nungester, 1936), whilst bronchial obstruction in a 50 g. rat produced pulmonary collapse only when it was not followed by bronchitis.

Bronchitis produces bronchial secretion and exudate, and weakens the bronchial wall so that it becomes distensible. But how this weakening is brought about is obscure, because the bronchial muscle and elastic tissues remained histologically intact during the early stage of bronchiectasis. Nor is it clear what causes the bronchitis. Terramycin therapy partially prevents the onset of bronchiectasis after bronchial ligation, suggesting that bronchitis is mainly the result of an infection. Against this view are negative bacterial cultures of some of the lungs. However, the present bacteriological investigation is incomplete and since Nelson (1946) isolated a virus from bronchiectatic pneumonia in rats, infection after bronchial ligation might be viral ; but if it were, a response to terramycin would not be expected. It is therefore tempting to assume that rat lungs are normally contaminated by organisms soon after birth and that bronchial stagnation activates the infection and causes bronchitis and pneumonitis. The diversity of organisms found in the positive cultures would then explain the variation in the severity of the bronchitis after bronchial occlusion. Terramycin therapy seems to have had a bacteriostatic effect only, for organisms were cultured from the lungs

afterwards. The other antibiotics apparently failed to control the infection.

The occurrence of bronchial stagnation seems to depend on the relationship between the extent of bronchial stenosis and the severity of the bronchitis. However, bronchial stagnation probably plays a more important role than bronchitis, since complete bronchial ligation in adult rats always led to bronchiectasis, whereas partial ligation produced bronchial dilatation only when the occlusion was pronounced; otherwise it gave rise to bronchitis and bronchopneumonia only.

Bronchiectasis therefore appears to be due to the pressure of accumulated stagnant bronchitic secretions and exudate on a bronchial wall weakened by inflammation. That it is an expansile type of dilatation is also indicated by the condensation of collapsed alveoli round the dilating bronchi. The production of localised bronchiectasis when a secondary bronchus is ligated would suggest that both localised and generalised types are probably similar in causation.

Collapse and pneumonitis constantly follow bronchial ligation. However, increase of the negative intrathoracic pressure due to collapse does not seem to be an important factor for bronchial dilatation, for bronchi of the omental lung grafts became dilated without this influence, and oleothorax did not prevent the bronchiectasis (*cf.* the results of Tannenberg and Pinner (1941-42) with pneumothorax). Moreover, the dilatation of a segment of bronchus from which the lung has been removed implies that bronchiectasis is primarily a disease of the bronchus, so that pneumonitis appears to be secondary. The alveolar collapse associated with localised bronchiectasis is apparently due to pneumonitis interfering with collateral air circulation through the alveolar pores (Van Allen and Jung).

The persistent epithelial lining of dilated bronchi may be due to the high growth potential of the epithelial cell, as its survival in the transplants in the present study indicates (*cf.* Cameron, 1952). The rapid re-growth of bronchial epithelium after its destruction or removal (Adams *et al.*, 1930; Condon, 1941-42) also supports this view, but the epithelium may not necessarily be resistant to the destructive action of the infective organisms.

Benzançon *et al.* (1924) have described "dry" bronchiectasis in man but its ætiology remains uncertain. In the present experiments it obviously resulted from the re-establishment of bronchial drainage; bronchial exudate was thereby eliminated and the inflamed bronchus and lung tissue healed with ultimate recovery or fibrotic replacement. However, the bronchus usually remained dilated. While there was sometimes an associated bronchial fibrosis, the bronchial wall often appeared histologically normal. No satisfactory explanation can therefore be offered for the persistent dilatation.

Bronchiectasis in rats has been attributed to bronchial obstruction by swollen lymphoid tissue (Cruickshank, 1948). This view is supported

by the present experimental results. Human bronchiectasis too is sometimes associated with bronchial obstruction by foreign bodies, enlarged lymph glands, œdematous mucosa, viscid or inspissated sputum, etc. (Erb, 1933). The present experimental findings, therefore, also appear to have some bearing on the development of at least certain types of human bronchiectasis. Indeed, Laennec (1826) ascribed human bronchiectasis to stagnation of bronchial exudate but his view was not generally accepted because most human cases are not associated with evidence of bronchial obstruction (Mallory, 1947). However, the recent investigation by Whitwell (1952) has revealed more evidence to support Laennec's hypothesis.

Summary

The development of generalised and localised bronchiectasis after bronchial ligation in rats is attributable to bronchitis and bronchial stagnation. The re-establishment of bronchial drainage in bronchiectatic lungs gives rise to " dry " bronchiectasis. Terramycin therapy partially inhibits the development of bronchiectasis after bronchial ligation. In lung grafts, the bronchi survive and dilate. Dilatation occurs in the doubly ligated segment of a main bronchus from which the lung has been removed.

I wish to thank Professor G. R. Cameron and Dr J. M. Barnes for their interest, criticism and help, Dr L. F. Hewitt for the gift of the antibiotics and for help, and Mr M. Roberts for his valuable assistance in the bacteriological investigations.

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