THE PATHOLOGICAL CHANGES IN CHRONIC BRONCHITIS AND EMPHYSEMA

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Chronic bronchitis defies close definition, just as it has defied all attempts at prevention or cure. Its beginning is innocuous enough, being characterized by cough and clear mucoid sputum; yet this may lead to incapacitating breathlessness, heart failure and death. Pathologically the disease is disappointing in that there is no specific or diagnostic lesion, since in its early or mild stage the only disturbance may be hypersecretion of mucus (an accentuation of the normal function of the bronchial tree) while in the later stages damage to bronchioles and alveoli has serious and far-reaching functional effect but does not produce any specific pathological change.

**Bronchial Hypersecretion**

Hypersecretion of mucus not only holds the key to an understanding of the causes of chronic bronchitis, but its measurement is one of the main difficulties in detecting the onset of the disease and in studying its epidemiological aspects (Stuart-Harris, 1954; Ogilvie, 1957; Oswald, 1957). Without being aware of it, the healthy individual normally forms about 100 c.c. of mucoid secretion in 24 hours (Policard and Galy, 1945), but what increase is necessary before coughing causes secretion to present as sputum is not known, although it is probable that the increase may have to be large, and certain that it varies widely with different individuals. Nor is it known, when there is excess, what proportion of the whole is coughed up as sputum. Clinical, epidemiological, bacteriological and pathological studies suggest no single cause of chronic bronchitis, but rather that responsibility is shared by many, acting either singly or in combination. Infection (May, 1955; Stuart-Harris, 1954), atmospheric pollution (Logan, 1956; Pattle and Collumbine, 1956; Ogilvie and Newell, 1957) and conditions (Pemberton and Goldberg, 1953), smoking (Doll and Hill, 1956), exposure to industrial dusts (Logan, 1956) and familial variation (Oswald, Harold and Martin, 1953) may each contribute to the development of chronic bronchitis.

Mucus is formed mainly in the trachea and larger bronchi. The mucous glands extend along the bronchial tree only as far as cartilage and, like the plates of cartilage, they reduce in number towards the periphery (Miller, 1947). They are numerous in the trachea, in the main and lobar bronchi and in the large intra-segmental bronchi; while it is only at the bifurcations in the small ones that a gland is found adjacent to cartilage. Goblet cells also decrease toward the periphery, being numerous in large bronchi and sparse in bronchioles. In a mild case of chronic bronchitis there may be little in the mucosa to reflect an increase in mucus production sufficient to cause sputum. In a well-established case, however, histological examination shows an increase in the cells distended with mucus (Fig. 1)—in the epithelium of the bronchi, the bronchioles and ducts of glands, and in the glands themselves (Florey, Carleton and Wells, 1932; Reid, 1954).

There is a close relation between the secretion of mucus and the cilia, the upward movement of mucus depending on an effective ciliary 'escalator.' In the absence of acute infection the cilia are usually intact, but if many goblet cells are discharging the effective ciliary area may thereby be reduced. Acute infection not infrequently occurs and here the walls of bronchi are infiltrated with inflammatory cells; also there may be destruction of cilia which, however, re-form with healing.

**Peripheral Changes**

The name 'chronic bronchitis' suggests that the disease is mainly concerned with the large air-tubes, but its progress can be appreciated only if the perhaps more serious changes, those which develop further down the bronchial tree, in the bronchioles and alveoli, are understood (Gairdner, 1850; Amberson and Spain, 1947; Reid, 1954, 1957; Leopold and Gough, 1957). It is in the region of the secondary lobule, the respiratory part of the lung (Fig. 2), that the serious functional damage is done which gives rise to dyspnoea. Recurrent infection, a clinical manifestation of the
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Fig. 1.—On the left the wall of a normal lobar bronchus (cartilage = 2) and on the right one from a patient with chronic bronchitis. There is an increase in the thickness of the mucous glands (1), although even in the right-hand wall it is still just over 1 mm.

Fig. 2.—Lung periphery from a patient who died with a history of chronic bronchitis for many years associated with recurrent bouts of infection in the winter: (1) Remnant of a bronchiole containing denuded epithelium, mucus and pus. (2) Scar consisting of dense fibrous tissue. (3) Pus in lumen and fibrosis in wall of alveoli with, nearby, emphysema associated with disruption of structure.

disease, is probably the chief cause of that peripheral damage which may lead to dyspnoea. It is the pattern of progressive peripheral involvement occurring irregularly throughout both lungs, rather than any single respiratory lesion, which is characteristic of chronic bronchitis (Fig. 2).
types of lesion are many. In the bronchioles there may be hypertrophy of goblet cells or purulent bronchiolitis. This may produce ulceration of bronchioles and alveoli, and give rise to micro-abscess cavities; stenosis of the bronchiole may also occur or even obliteration of its lumen. Alveolar inflammation may give rise to patchy pneumatic consolidation, oedema, mucus and pus in the alveoli, while more permanent damage such as organization of inflammatory exudate, emphysema and collapse may also result. Although the lesions are varied they fall generally into two groups according as they are the direct result of infection or obstruction, though it is often hard to determine the respective role these play in any sequence of changes, particularly since infection may act by obstruction as well as by destruction or consolidation, while obstruction arising from hypersecretion alone probably predisposes to infection.

Some of the changes listed are acute and may resolve, while others represent permanent damage either directly from initial destruction or because, failing to resolve, they proceed to fibrosis. Indirectly damage may also be the result of distortion of lung architecture, distension of air spaces or vascular adjustment in adjacent lung. The pathological changes vary not only in their nature and age but also in their extent. Damage often occurs irregularly within a secondary lobule (Fig. 3) so that within a single unit most of the changes may present, but the disease may involve a lobule or group of lobules uniformly. Scars may, therefore, represent either a considerable volume of lung or rather less than one acinus.

Although bronchioles and alveoli are functionally closely related their changes are not always parallel in severity, and here collateral ventilation is important. Van Allen, Lindskog and Richter (1931) have shown that obstruction of a segmental bronchus may not result in collapse, since air can pass from lobule to lobule by drift across alveolar walls and the change in alveoli may, therefore, be less than would be expected from the associated lesion in the bronchial wall.

**Emphysema**

Where there is shortness of breath the clinician often couples the diagnosis of emphysema with that of bronchitis. At once a new field of diagnostic uncertainty is opened up. Emphysema has a different diagnostic meaning for the clinician, radiologist, physiologist and pathologist, since the different techniques they use measure different aspects of the disease. In order to reconcile the seeming contradictions, it is probably most useful to consider first the pathological diagnosis and then to correlate this with the results of other methods of enquiry. The technique of the pathologist is sensitive in that he can examine the lung directly and minutely. Thus he may justifiably diagnose emphysema where the clinician and the physiologist would not, since the disease is too limited in extent to give rise to such degree of functional disturbance as they would consider significant. The same may apply to the radiologist if the lesion is not extensive enough to give rise to localized hypertranslucency.

The essential feature of the pathological diagnosis of emphysema is an increase in the quantity of air beyond the terminal bronchioles in a given volume of lung and, conversely, a decrease in the amount of alveolar capillary blood (Reid, 1957; Simon, 1957). By emphasising a reduction in the amount of blood as well as an increase in air the pathologist relates the basis of his diagnosis more closely to those features which are significant to other techniques. For example, the hypertranslucency seen by the radiologist results from a relative increase in air, while the decrease in carbon monoxide uptake detected by the physiologist is the result of loss of capillary bed. Within
the above definition two different pathological types of emphysema can be recognized—in the first the structure of the lung is still intact, even though it is distended; while in the second there is destruction or disruption of alveolar walls (Fig. 3). The second includes many different morphological types, ranging from mild to severe disease, from the localized to the diffuse, from the air-containing space of only a centimetre in diameter to one as large as a grapefruit. But to all of these disruption of lung is the common crucial feature.

The overdistension type of emphysema is the less well understood of the two, and in chronic bronchitis it is overshadowed in importance by the second type to which inflammatory damage so often gives rise. Sometimes on opening the chest a whole lobe may appear emphysematous, being fluffy, dry to the touch, failing to collapse and showing evidence of poor elasticity after compression; and yet, throughout the lobe, the honeycomb structure of the lung is still intact even if a little coarser. Overdistension also contributes to the development of emphysema when it occurs unevenly in lung adjacent to scars (Fig. 3) representing considerable condensation of tissue. In some patients with chronic bronchitis fibrotic nodules are frequent, while the total resting volume is normal, or, more often, increased, indicating a relative dilatation of some parts of the lung.

Although ulceration or destruction of pulmonary structure may occur anywhere along the bronchioles or in the alveoli, the region of the bronchiole-alveolar junction is a frequent site of damage, but unless many are involved the damage will not be clinically apparent. With loss of integrity of this part of the lung the normal volume change on respiration is impaired since this is dependent on the structure being intact.

Destruction of part of the wall of the bronchial and of alveoli may bring about an increase in volume, loss of the capillary bed and conversion of the bronchiolar wall to the structure of a flap-valve (Reid, 1957). Such pulmonary destruction may be followed by interference with blood supply to intact alveoli and by trapping of air resulting from the flap-valve action of a distorted bronchiolar wall. The area of such a focus of emphysema may be no more than a few square millimetres.

Large bullae, easily visible to the naked eye, may result if the initial destruction is greater, or if secondary changes are superimposed on small initial lesions. The distension of the smaller space behind the flap-valve of the bronchiolar wall may occur gradually with ordinary respiration, with coughing, because of collapse or fibrosis in neighbouring lobules or by reason of impairment of blood supply to the part beyond.

Although, externally, bullae may appear to contain only air, when cut there may be tags or flimsy strands of lung passing through them. Sometimes a whole lobe or a large part of its volume may be represented only by these shreds, which consist of connective tissue septa, bronchi and blood vessels. Remnants of alveoli may persist as reddish brown tags or they may be compressed against septum or pleura until ultimately, to the naked eye, they appear as fibrous thickening.

Changes in Blood Vessels

The significant disturbance in the vascular system is usually secondary to bronchial damage. Destruction of capillary bed (Fig. 3), arterioles and even larger vessels may be found with emphysema and endarteritis obliterans is frequently seen in arteries supplying fibrotic scars. But histological study is only a preliminary to the more difficult task of interpreting the functional derangement.

Dilatation of the main pulmonary arteries in emphysema is often seen radiographically; at the same time their branches may be abnormally narrow right from their point of origin (Simon, 1957). This dilatation has been confirmed by measurement of the arteries at autopsy, while examination of the wall has confirmed that the change is not due to any associated organic disease. Dilatation suggests that the proximal part of the arterial system behaves like a reservoir, while the intra-pulmonary narrowing points to an alteration in amount or rate of flow through the lung.

The capillary bed in the wall of the bronchial tree is supplied by bronchial artery, that in the wall of the respiratory bronchioles by both bronchial and pulmonary artery, that of the respiratory tissue beyond from pulmonary artery alone. The capillary bed at each of these levels may be reduced by destruction or by scarring of respiratory tissue. The bronchioles seen passing in the flimsy strands of emphysematous lung often have no pulmonary arteriole accompanying them, these having been lost along with the supporting lung. The lumen of pulmonary arteries supplying emphysematous areas is often reduced, perhaps with some degree of endarteritis obliterans. This change may also be seen in vessels supplying scars. In respiratory and terminal bronchioles where the wall is still intact the capillaries are often grossly dilated. The two pathways of venous drainage from the lung do not correspond topographically to the double arterial supply. Normally the true bronchial veins drain only the proximal large bronchi and pleura, pass to the azygos veins and the right side of the heart, while the more peripheral part of the bronchial tree, like the respiratory tissue, drains to the pulmonary veins and the left side of the heart. Marchand and his colleagues
(1950) have shown dilatation of the true bronchial veins in emphysema, while Liebow (1953) and coworkers have demonstrated that there is easier communication between them and the peripheral pulmonary venous system, with an increase in the blood returning from the lungs through the bronchial veins to the right side of the heart.

This is but one feature of the abnormal vascular dynamics in emphysema which gives rise to the clinical features of cor pulmonale. The arterial and venous systems not only communicate with each other through a capillary bed, but pre-capillary anastomoses exist between bronchial and pulmonary artery and between pulmonary artery and veins (Verloop, 1948; Cockett and Vass, 1951; Tobin, 1952). This complexity of the normal vascular arrangements makes the interpretation of changes in disease extremely difficult. In chronic bronchitis the changes are lobular not lobar. The latter may be produced experimentally and their effect on bronchial and pulmonary artery flow determined, but these effects are not necessarily applicable to the conditions found with intralobular disease.

Correlation of Pathological Changes with Radiological and Bronchographic Appearances

The correlation of these changes with those seen in radiographs and bronchograms (Simon and Galbraith, 1953; Simon, 1957) and with the findings of respiratory function tests explains something of the variation in the results obtained by these different methods of investigation which contributes to the difficulties of diagnosis.

A patient may be short of breath and yet, because individual lesions may be small, the lung may radiographically appear normal, although small scars, either singly or in a cluster, may be visible. Hypertranslucency, either localized or generalized, may be evident and it may be demarcated by a line shadow suggesting the wall of a bulla. While individual lesions may not be visible on a radiograph they may yet be so numerous and so serious as to cause secondary changes to the heart, great blood vessels and diaphragm, detectable by radiography.

Bronchography usually reveals more damage than a plain radiograph. The dilated ducts of mucous glands may fill with radio-opaque material and give rise to the linear projections from the outline of main, lobar and segmental bronchi.

In the peripheral part of a bronchogram three changes have been described as characteristic of chronic bronchitis—the absence of peripheral filling, irregular endings of those pathways which do fill, and the presence of pools of radio-opaque material. Although technical inadequacies as the cause of these irregularities must be excluded, they frequently reflect damage in the periphery. Scarring of bronchial pathways and condensation of lung tissue in fibrotic nodules result in loss of peripheral pattern, while delayed filling may result from emphysema because of impaired ventilation.

Irregularities in the outline of the bronchial wall may be caused by narrowing from fibrosis or dilatation from ulceration. Pools of lipiodol several millimetres in diameter represent dilated bronchioles or small bronchi (Reid, 1955). Sometimes a pool has a spiked or irregular outline, resembling normal filling save that it is rather coarser, and here also there is dilatation and obliteration of the bronchioles in the secondary lobule.

**Correlation with Respiratory Function Studies**

In the mild stages of chronic bronchitis there may be no impairment of respiratory function (Bates, 1957), but all too frequently the disease is progressive and in severe cases the pattern characteristic of emphysema is seen (Donald, 1953). There is an increase in total lung volume and in the relative amount of residual air because, with expiration, the lung empties incompletely, air being trapped before the normal level of deflation is reached. Contributing to this phenomenon is blockage of the lumen by sputum, stenosis of the wall of the bronchial tree and destruction of lung tissue converting the walls of bronchioles into flap-valves.

Because of the operation of collateral ventilation (van Allen, Lindskg and Richter, 1931) the lesions in alveoli need not parallel in severity those in bronchioles, so that diffusion of gas may be impaired even where perfusion by blood is normal, and vice versa. Factors which impair ventilation will adversely affect the intrapulmonary mixing of gases. Although there may be free communication between neighbouring bullous areas, allowing for rapid equalization of gas between them, there may still be evidence of poor mixing, because large volumes are uniformly poorly ventilated from the bronchi.

Loss of capillary bed will be associated with reduction in carbon monoxide uptake, but the results of this test must be interpreted in the light of ventilation. Where perfusion of blood is seriously affected there will be decrease in arterial oxygen levels, while impairment of gas diffusion will give rise to retention of carbon dioxide—oxygen desaturation and retention of carbon dioxide are not always proportional.

To conclude, the presence of bronchospasm and the relief given by bronchodilators in certain cases of chronic bronchitis suggest that the dividing
line between this disease and asthma is blurred, but this seems no justification for merging them, because there still exist those many cases in which they are distinct.

In chronic bronchitis peripheral damage is important, and also inevitable where the disease is of long duration. By contrast a patient may suffer from attacks of spasmodic asthma during a long lifetime and yet, at death, the lungs show no emphysema (Gough, 1955). If there is super-added infection as well as recurrent attacks of bronchospasm the same peripheral damage may occur as Seen in chronic bronchitis.

Bronchiectasis and chronic bronchitis may both be characterized by cough and purulent sputum and even bronchographically in both may be discerned peripheral non-filling, irregularity of outline and ending of the filled bronchial pathways, and dilatation. The most important feature distinguishing the two diseases is the level at which the changes occur. In bronchiectasis the brunt falls on the large bronchi, while in chronic bronchitis it is borne by the small bronchi and bronchioles, but there is no sharp dividing line between regions whose involvement is characteristic of bronchiectasis on the one hand and of chronic bronchitis on the other. Even bronchographically, therefore, it is not always possible to be dogmatic in diagnosis. So the difficulty comes back to the clinician for resolution; by weighing the history of the development of the condition in relation to the symptoms and signs, including those of bronchospasm and the finding on bronchography, he will usually be able to place his case in its right category. Although he must accept the nosological challenge presented by each patient his practical problem is to decide which features demand treatment.

The protean features of chronic bronchitis present many puzzles—the long and benign course it takes in many cases, the rapidly fatal course in others; or, again, the no less fatal but more insidious pattern it may present.

The early emergence of hypersecretion of mucus may not be associated with infection, but typically it would seem that in the later course of the disease infection becomes increasingly responsible. The clinical incidents of infection certainly leave their damage and it is probable that the bronchioles may be permanently damaged by infection and obstruction which, though not sufficiently widespread to give clinical evidence, may, nevertheless leave a scar or emphysematous focus in the lung and this, though small, contributes to the cumulative damage which gives rise to the clinical manifestations of emphysema.

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