THE PATHOLOGY OF EMPHYSEMA

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Chapter I

EMPHYSEMA DEFINED AND DESCRIBED

PULMONARY emphysema is best defined by reference to structure. The criteria by which emphysema is diagnosed differ according as the diagnosis is made by the clinician, the radiologist, the physiologist or the pathologist; because of difference in their method, in their discipline, not always will all four in any given case reach the same conclusion. To the physiologist it is the functional changes that matter, while the pathologist can detect a type or degree of structural change which seems not to be associated with any significant functional disturbance and shows no abnormality in the radiograph.

Differences in diagnosis may derive also from difference in scale; a biopsy or autopsy specimen may not be typical of the whole and the pathologist's view, being often limited by the small part of the lung that he sees, may differ from that of the clinician and physiologist who are both concerned with overall functional disturbance. The radiologist has the advantage of seeing the whole lung in light and shade, from which he can deduce functional disturbance. Since it is possible in the light of structural alteration to assess the efficiency of the diagnoses derived from respiratory function studies and radiographic examination, a definition based on structure should make it possible to reconcile any diagnostic contradictions deriving from the different methods necessarily employed.

For ease of distinction the emphysema diagnosed by the four disciplines might be termed clinical, physiological, radiological and pathological. But it is obviously necessary to find a definition to which all four can relate.

Of emphysema Laennec (1826) said that "elle consiste dans la simple dilatation des vesicules ou cellules dont elle compose", which Forbes (1827) translated as "it consists simply in the dilatation of the air cells". This model of simplicity is valid to this day.

Earlier accounts of emphysema had declared that the appearance of the lung was brought about by an infiltration of air into the interstitial tissue, to which Laennec retorts that if this is really what previous authorities saw, their cases were of interlobular, that is interstitial or surgical, not vesicular, emphysema. Although they may have misused the term "interstitial", to Laennec must be given the credit of distinguishing the two clearly and of describing the characteristic features of each. Until the late 19th century the air spaces of the lung were referred to as vesicles or air cells and only from that time was the word "alveolus" applied to them.

Earlier Baillie (1793) had described three conditions: "Lungs Distended

with Air"; "Air Cells of the Lungs Enlarged", and "Air Vesicles Attached to the Edge of the Lungs". Laennec fully quotes Baillie's descriptions of all three (1803), commenting that Baillie had not recognised the mutual dependence of the three, considering them different affections. However, Baillie may have recognised what would be accepted today, that the "Lung Distended with Air" which maintained its volume when the chest was opened might not be associated either with enlargement of "Air Cells" recognisable to the naked eye or with "Vesicules Attached to the Edge of the Lungs". He suggested that "it is not improbable also, that this accumulation (of air) may sometimes break down two or three contiguous cells into one, and thereby form a cell of very large size".

Of later authors, Kountz and Alexander (1934) suggested that "emphysema may be defined as a condition in which the alveoli are distended, with thinning or rupture and loss of elasticity of the alveolar walls". McLean (1956) suggested that to the pathologist the term "pulmonary emphysema" indicated "a chronic destructive lung disease, characterised by enlargement of existing air spaces in the lung parenchyma".

Whatever else may have been thought, the factor common to all is the increase in the size of air spaces. The conflicting diagnoses referred to above, which arise from different ways of examining the lung and its functioning, have recently stimulated the search for a definition and this has led to the restatement of the basic assumption of Baillie and Laennec in more sophisticated anatomical terms.

In discussing the pathological and radiological aspects of emphysema, Reid (1959) and Simon (1959) suggested that the characteristic of emphysema is an abnormal amount of air in the respiratory part of the lung. Put more precisely, "emphysema may be defined as the lung condition in which there is an increase beyond the normal in the size of the air spaces distal to the terminal bronchioli (the acinus)". By using "air spaces" instead of "alveoli" the definition provides for the condition in which alveoli have completely disappeared and, anticipating classification, it adds the qualification "arising either from dilatation or destruction of the walls" (the relevant anatomical details of this region are given separately on pages 15 and 328).

This definition includes "benign" forms such as compensatory emphysema and reversible emphysema associated with a ball-valve obstruction in a large bronchus. It seems useful to keep the definition as broad as this although any satisfactory classification will differentiate them. An attempt to distinguish simply the serious forms from the mild is embodied in the recognition of the two groups, distension and destruction, based on observation of lung architecture.

At the Ciba Guest Symposium in 1959 an attempt to define emphysema in physiological terms was unsuccessful and the following, based on structure, was accepted:

"Emphysema is a condition of the lung characterised by increase beyond the normal in the size of air spaces distal to the terminal bronchiole arising either from dilatation or from destruction of their walls".

The growing significance of chronic respiratory disease prompted the American Thoracic Society in 1962 to adopt the following:

"Emphysema is an anatomic alteration of the lung characterised by an abnormal enlargement of the air spaces distal to the terminal, non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls".

PROPOSED DEFINITION

It is an over-simplification to refer to dilatation and destruction of the walls in such brief terms as are found in the above definitions. These terms imply a mechanism and, further, suggest that within them can be comprehended all cases of emphysema; but this is not so because the atrophic and hypoplastic forms of emphysema are not caused either by dilatation or destruction. Accordingly the definition offered here is close to the earlier ones (Reid, 1959; Ciba Guest Symposium, 1959) but shorn of its reference to distension or destruction:

"Emphysema is a condition of the lung characterised by increase beyond the normal in the size of air spaces distal to the terminal bronchiolus, i.e. the acinus."

The definition is brief and simple but it carries implications which call for comment, especially as they have a bearing on differential diagnosis, among them (*a*) that change in alveolar wall implies disturbance of capillary bed with resulting functional impairment; and (*b*) that rigid criteria of alveolar size are essential in the practical application of the definition—but this is not the case.

(a) Changes in Blood Vessels

Where there is destruction or thinning of alveolar walls there is loss of capillary bed; overinflation of alveoli usually results in reduction in the amount of wall or capillary bed in relation to lung volume except where there is capillary hypertrophy.

In certain types of emphysema the blood vessels are ulcerated, which again means loss of capillary and arteriolar bed; in others the cause of the emphysema may be atrophy of capillaries. This reduction is of paramount significance in certain functional disturbances of emphysema and is, furthermore, relevant to radiological diagnosis. The nature and amount of the blood vessel disturbance varies with different types of emphysema.

(b) Macroscopic and Microscopic Diagnosis

In normal lung, inflated with formalin and fixed for one week, air spaces are so small as not to be detectable on naked eye examination; if,

as in emphysema, alveoli are so large as to produce significant functional disturbance they can easily be detected macroscopically. As long as the lungs are fixed inflated they are satisfactory for examination, but more rigid conditions of preparation may be desirable for investigation of special features of this disease.

In order to relate the severity of emphysema to radiographic appearance and functional disturbance it is necessary to grade air spaces according to size. The basis for such grading is given in detail later (p. 17).

In certain types of emphysema an increase in alveolar size is not the only characteristic of emphysema; microscopically, a simplification or smoothing out of the shape of the alveolus may be seen, which contributes to the appearance of increased alveolar diameter. The alveoli show less subdivision, less angularity, than in the normal although the increase in diameter seen microscopically may be so great that the simpler profile may be overlooked. This simplification occurs in other conditions, such as interstitial fibrosis (see below). Although the increase in alveolar size is the primary change, diagnosis should also take account of the fibrous tissue content of the wall surrounding the air spaces.

A large emphysematous space may represent a single abnormally large alveolus or may be the result of alveoli becoming confluent. The wall may consist of intact alveoli, of straggly alveolar walls, of alveoli condensed in a scar or of connective tissue septa. A ballooning of pleura and fibrous tissue septa can produce a fibrous sac and give the appearance of a cyst, which since it represents alveoli, nevertheless justifies the diagnosis of emphysema.

Certain cognate lung conditions present a problem in differential diagnosis and are accordingly dealt with separately in Chapter XIII: they include pyogenic lung abscess, honeycomb lung, inflammatory conditions of alveolar wall, such as interstitial pulmonary fibrosis and sarcoid, and bronchiolectasis. Interstitial emphysema is discussed on page 238.

The "vesicular" type of emphysema, that is, the type that affects the alveolar part of the lung, is the main concern of this book.

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Chapter II

CLASSIFICATION OF EMPHYSEMA

WITHIN the definition formulated in the previous chapter there must be a breakdown by which the many types of emphysema may be classified, preferably with relevance to clinical problems. The classification offered divides primarily into two—emphysema with and emphysema without airways obstruction.

Only within the past decade have classifications of emphysema been formulated. Before this, types of emphysema were distinguished but there was no formal division into categories; the terms used either described the different pathological features of the disease or reflected theories as to its origin. Today they have been largely superseded, possibly because additional forms of emphysema are now known, calling for a new nomenclature, but also because the old terms were found confusing, contradictory names being applied to the same condition of the lung. For instance, at autopsy, emphysema was usually recognised by the "large" or "hypertrophic" lung which, when cut, disclosed unsubstantial and flimsy alveoli, a condition that was not unreasonably described as both "atrophic" and "hypertrophic".

Laennec (1826 and 1827) used the terms "expiratory" and "obstructive" to describe lung from which air could not escape because of what he called "expiratory obstruction", as opposed to normal lung which deflated at autopsy. He attributed the abnormally large "vesicles" to the expiratory obstruction and thus "expiratory" and "obstructive" became widely used to describe this form of emphysema. It was, perhaps, inevitable that the "expiratory" theory should be countered by the "inspiratory", the basis for which was that excessively "deep breaths-in" did the damage; and so "inspiratory" came to describe the same disease.

Further, Laennec described separately from emphysema the changes in the lung which came with age but, later, "senile emphysema" became an accepted term, which Kountz and Alexander (1934) equated with "postural" emphysema, implying that chest wall change produced emphysema in the underlying lung.

In assessing the clinical severity of the disease, distribution throughout the lung is obviously relevant and even the earliest studies showed that the disease might involve the whole or only part of either or both lungs. In 1956 McLean produced a classification based on localised and generalised emphysema, with or without local accentuation. He distinguished a

"centrilobular" or "focal" from a "diffuse" emphysema according as the lung parenchyma was irregularly or evenly affected.

Again, the disease has been described by reference to its position in the lobule, e.g. centrilobular (Leopold and Gough, 1947), or to its distribution within the acinus, e.g. panacinar (Ciba Guest Symposium, 1959). Still another classification was based on whether or not lung structure was destroyed—destruction and dilatation emphysema respectively (Reid, 1958; Reid and Simon, 1959; Ciba Guest Symposium, 1959); this had certain functional implications. But a purely anatomical classification has little relevance to functional significance; the classification submitted here incorporates both structural features of the disease and its functional implications.

PROPOSED CLASSIFICATION

The chief aim in the classification set out in Figs. 1 and 2 is to relate structural change to functional impairment and hence to clinical signifi-

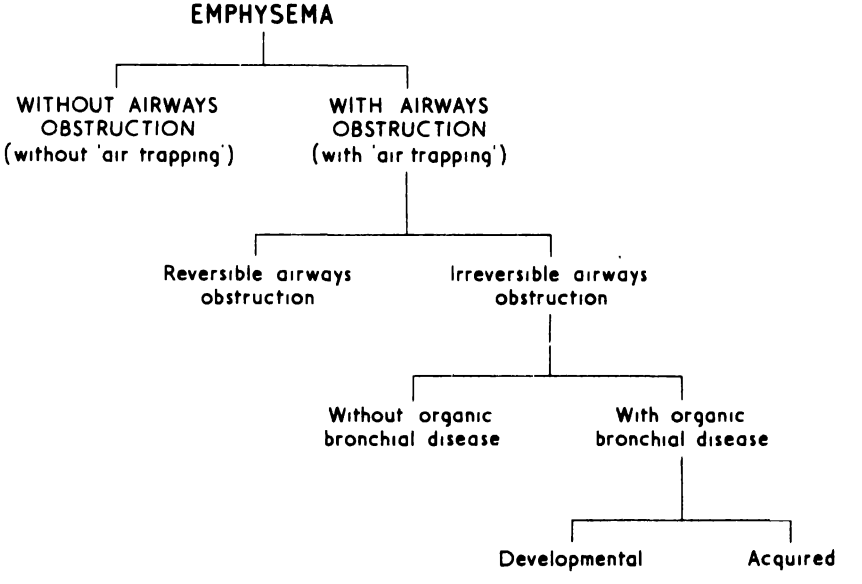


FIG. 1.—Steps in the classification of emphysema. In Fig. 2 this is expanded to include the types of emphysema in each category.

cance; it embraces the obvious extremes of compensatory overinflation and the disabling emphysema which sometimes accompanies chronic bronchitis.

Beginning with a division based on the absence or presence of airways obstruction (Stage I), the classification proceeds to subdivide the latter according as the condition is or is not reversible (Stage II), to whether or

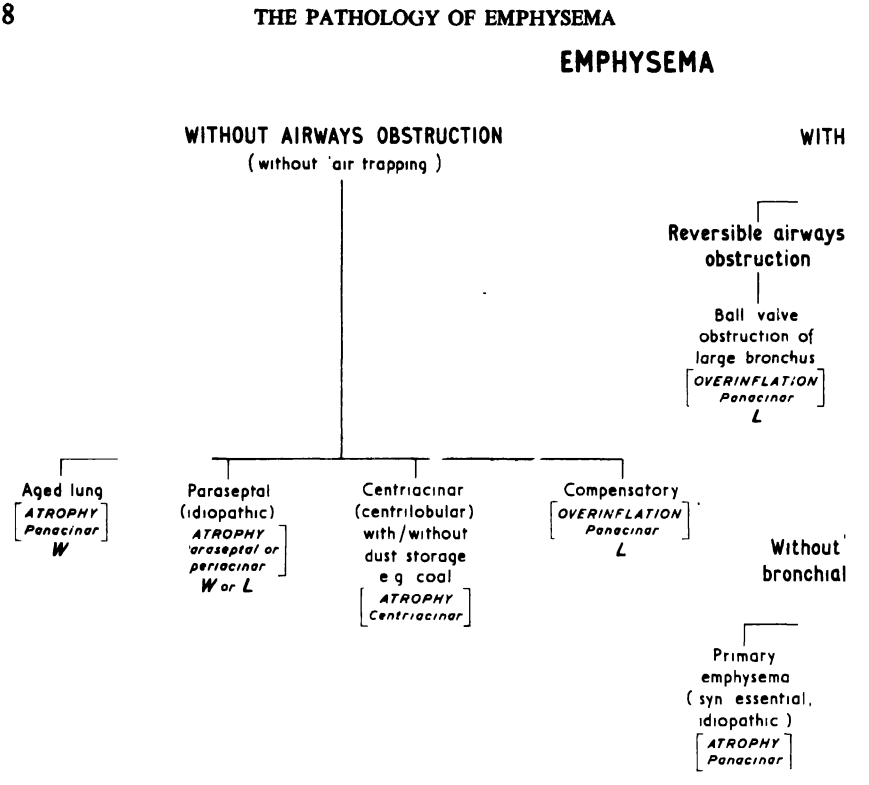


FIG. 2 (*above and opposite*).—Classification of emphysema. Fig. 1 shows the outline of the classification without the types of emphysema. The types of emphysema are mainly described by terms in common usage. Within the square bracket beneath each type is given the mechanism possible, the distribution within the acinus and whether the type is usually localised (L) or widespread (W) through the lung.

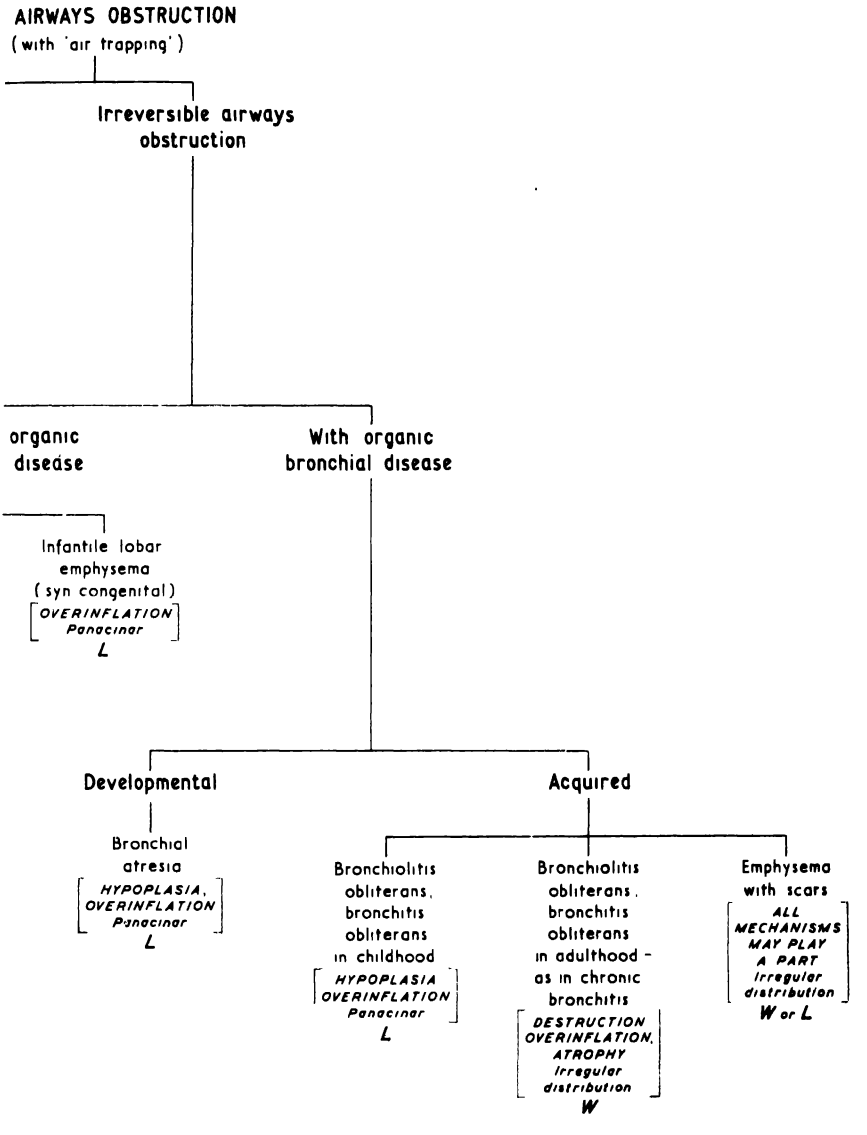
not there is organic bronchial disease (Stage III), and to whether this is developmental or acquired (Stage IV).

STAGES OF CLASSIFICATION

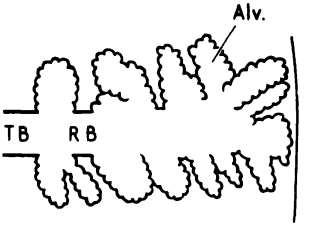
Stage I—Airways Obstruction

Airways obstruction is the key to functional disturbance; even alveolar capillary loss resulting in loss of gaseous diffusion is overshadowed by disturbance in ventilation. Airways obstruction as gauged in life by the respiratory physiologist manifests itself to the pathologist as "trapping"* of air. A lung in which there is trapping does not deflate on removal from the body, but retains its inflated shape and volume. Outside the body the normal lung collapses on release of pressure after inflation. Normal lung

*This term is not used here in the sense in which physiologists use it, as a term of art to describe the premature interruption of air flow on forced expiration.

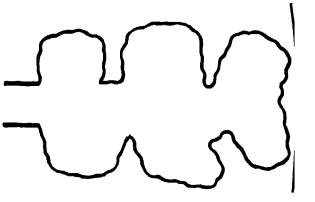


in old age usually deflates rather more slowly than in middle age and youth. The lobe being the smallest lung unit completely isolated by pleura, the effect on function of a given type of emphysema can be assessed only if at least a lobe is involved. That air trapping is characteristic of a given type of emphysema may be based on consideration of lung function studies or on the appearance and behaviour of the lung at operation or autopsy.

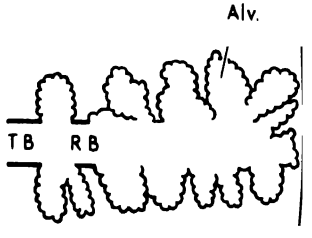


NORMAL

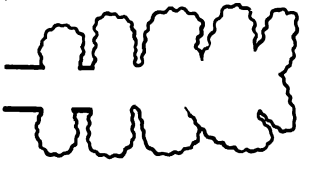
FIG. 3.—Hypoplasia. Failure in alveolar development may lead to alveoli too large and too few in number.



HYPOPLASIA

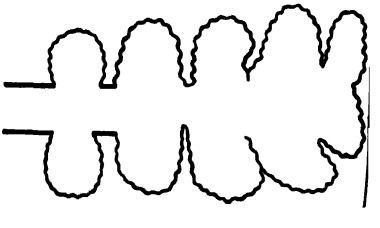


NORMAL



ATROPHY (a)

FIG. 4.--Atrophy (a) Illustrates the atrophy of age without increase in total lung volume or air-trapping; (b) illustrates the atrophy of primary emphysema which is associated with increase in total lung volume and with air-trapping.



ATROPHY (b)

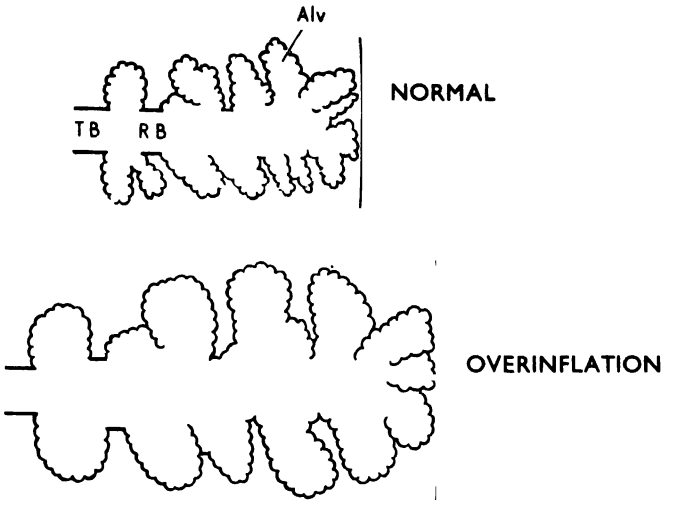


FIG. 5.—Overinflation. Increase in the volume of an otherwise normal lung leads to overinflation emphysema (without air-trapping—compensatory emphysema: with air-trapping—ball-valve obstruction).

Emphysema without airways obstruction.—Emphysema without airways obstruction includes:

1. the aged lung (panacinar);
2. periacinar or paraseptal emphysema;
3. centriacinar emphysema (*syn.* centrilobular)
   (*a*) without dust deposition;
   (*b*) with dust deposition.
4. compensatory emphysema (panacinar).

None of these types necessarily gives rise to functional disturbance.

Of the four basic mechanisms (Figs. 3, 4, 5 and 6) responsible for emphysema—hypoplasia, atrophy, overinflation and destruction—only two, atrophy and overinflation, are exemplified in the above types. The cause of atrophy is not yet known; overinflation develops when lung enlarges to fill that part of the thoracic cage previously occupied by other lung, as in collapse of a lobe. The four types usually give rise to significant respiratory disability only through the complications to which they predispose, such as compression of normal lung by bullae or spontaneous pneumothorax following the rupture of a bulla. They may be present with other disease such as chronic bronchitis and may then reduce respiratory reserve.

This group covers all intra-acinar sites of distribution of emphysema and it follows that no particular intra-acinar localisation is necessarily associated with airways obstruction.

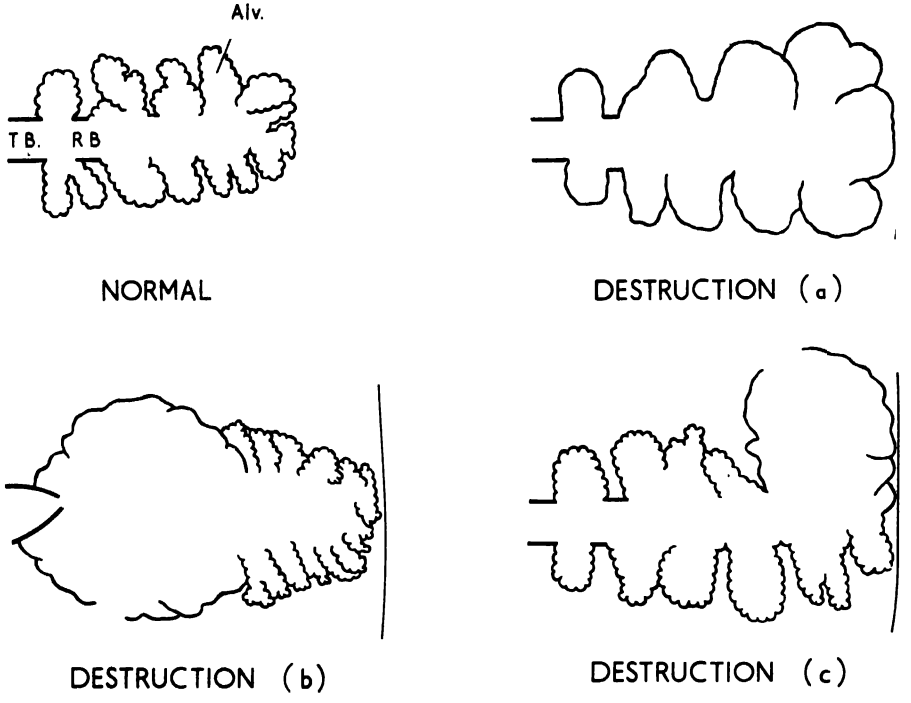


FIG. 6.—Destruction (a) inflammatory damage may reduce the surface or thickness of alveolar wall leaving the overall architecture intact (b and c); ulceration of the full thickness of the alveolar wall may occur anywhere through the acinus. It may be associated with retraction of surrounding normal lung with increase in size of "hole".

Emphysema with airways obstruction.—Emphysema with airways obstruction includes the following, of which the most significant clinically is 6:

1. emphysema from partial obstruction (ball-valve) of a large bronchus;
2. primary emphysema (idiopathic or essential);
3. infantile lobar emphysema;
4. emphysema with bronchial atresia;
5. emphysema from bronchitis and bronchiolitis obliterans of childhood;
6. emphysema with chronic bronchitis;
7. emphysema associated with scar.

The association of alveolectasis with airways obstruction presents the difficulty of decision whether the obstruction is the result of emphysema, that is, the alveolar change, or whether it arises from changes in the airways. Although both may be present together it is useful to consider each separately so that patterns characteristic of each can be established.

Stage II—Reversibility

The next significant stage in the classification depends on the *reversibility or non-reversibility of airways obstruction.* Obstruction is reversible where it is caused by a removable foreign body, or a tumour or an enlarged lymph node, a condition rare in adults but common in childhood. When there is clinical or radiographic evidence of lobar emphysema the clinician reasons that a foreign body may be responsible and that the obstruction may accordingly be reversible. Ball-valve emphysema, incidentally, is the only clear example of airways obstruction causing emphysema.

This classification does not embrace obstruction which is reversible by drugs, as in some cases of asthma, or by resolution of a suffocative bronchitis or bronchiolitis, because such lung changes are not emphysema as defined above, the alveoli not being inflated beyond the size normal in deep inspiration.

Among the types of irreversible airways obstruction is included primary (essential or idiopathic) emphysema where the obstruction seems to derive from the alveolar change. Cases of congenital emphysema may also exemplify this, although some may derive from bronchial change. In neither of these types is there necessarily an obvious structural lesion.

Again, irreversible airways obstruction may be based on irreversible bronchial disease, such as atresia of a segmental bronchus, in which collateral ventilation, by maintaining aeration may offset the effect of the block. By the very nature of the condition the bronchial block is complete and thus the full functional effect of alveolectasis associated with the obstruction cannot be established, This being a developmental anomaly the cause operates at least from birth.

Stage III—Organic Bronchial Disease

Irreversible airways obstruction may be associated with organic disease in bronchial or bronchiolar airways or it may occur even in seemingly structurally normal airways, as in primary emphysema. The classification next subdivides, therefore, on the presence or absence of organic disease. In primary emphysema airways obstruction dominates the clinical picture and air-trapping is seen at autopsy, yet no bronchial stenosis or obliteration is found or even hypersecretion of mucus with airway plugging. The obstruction would seem to be a functional sequela to the alveolar change which causes premature closure of the airways and air-trapping on expiration; in primary emphysema the obstruction is the result and not the cause of the emphysema.

Airways obstruction arises either from organic bronchial disease or from excessive secretion; in either case it may be impossible to estimate the contribution of the alveolar and airways lesions to the obstruction.

Stage IV—Bronchial Disease—Developmental or Acquired

Structural changes in the airways may be antenatal or postnatal, *developmental* or *acquired.* Developmental bronchial disease is often associated with failure of alveolar development. Bronchial atresia is an example of a developmental bronchial defect associated with emphysema in the region supplied by the atretic bronchus (see Chapter X).

The types of emphysema associated with acquired bronchial diseases include such conditions as bronchiectasis, chronic bronchitis and McLeod's syndrome, in all of which the basic pathological lesion is a bronchitis or bronchiolitis stenosans.

Patchy bronchitis or bronchiolitis obliterans is an example of acquired obstructive airways disease. If acquired in childhood the emphysema may be severe and affect ventilation and diffusion; but here again the functional effect of any alveolar change is difficult to assess because of airways disease.

Scar emphysema, even if it is widespread, does not always give rise to airways obstruction. As in this condition lung damage is usually severe and often associated with conditions which cause airways obstruction, it is included in the second rather than the first part of the classification.

Chronic bronchitis can of itself produce airways obstruction, so the same problem presents—of assessing the contribution of the alveolar changes to the obstruction.

TERMINOLOGY

In Fig. 2, types of emphysema are grouped in the subdivisions described in Stages I to IV, their names being mostly those in common use. In the group "emphysema without air-trapping" is included paraseptal or periacinar, and centriacinar, distribution. Centriacinar types of emphysema are further subdivided by reference to the presence or absence of dust.

Congenital emphysema, of which there are doubtless several types, can only be classified provisionally until the essential cause is known.

MECHANISMS

Emphysema may be caused by any of the following four basic mechanisms, to which all types can be related:

1. Hypoplasia—failure of alveoli to develop normally (Fig. 3).
2. Atrophy—atrophy of alveolar walls after normal development (Fig. 4).
3. Overinflation—overinflation of alveoli beyond their normal size in normal maximum inspiration (Fig. 5).
4. Destruction—loss of substance of alveolar wall from a recognisable pathological change, in contrast to the spontaneous operation of atrophy (Fig. 6).

Two types of destruction may be recognised:

(*a*) Partial—partial destruction of alveolar wall, including damage to capillary mesh.

(*b*) Complete—complete rupture of alveolar wall, giving visible interruption in continuity.

Each "mechanism" contemplates a chain of events. Generally it can be stated that alveoli are too large either because they have failed to develop normally or, having developed normally, because they have atrophied, have been inflated to too large a volume, or have had their walls damaged by a trauma, mechanical or infective.

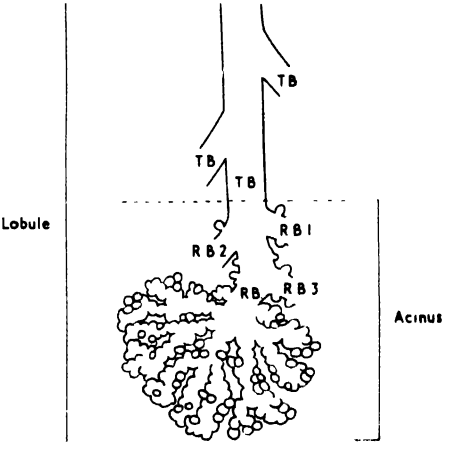


FIG. 7.—Diagrammatic and simplified representation of an acinus. An acinus includes a terminal bronchiolus and the respiratory tissue it supplies. There are usually several orders or generations of respiratory bronchioli. T.B.: terminal bronchiolus; R.B.: respiratory bronchiolus. (For definitions see pp. 324 and 328.)

In Fig. 2 the square bracket after each type of emphysema contains the mechanisms responsible for the condition.

INTRA-ACINAR DISTRIBUTION OF EMPHYSEMA

The acinus is the respiratory unit and consists of that part of the lung (alveoli and respiratory bronchioli) supplied by a terminal bronchiolus (Fig. 7). In emphysema abnormally large air spaces may be found throughout or be limited to some part of the acinus. The distribution (Fig. 8) may be:

(i) centriacinar—i.e. central within the acinus;
(ii) periacinar or paraseptal—i.e. peripheral or marginal;
(iii) panacinar—i.e. universal;
(iv) irregular—i.e. not distinctly falling within (i), (ii) or (iii).

"Centriacinar" is equivalent to "centrilobular" in the present context, but the former term is preferable because by referring to the acinus rather

than the lobule, it is consistent with the definition. As periacinar emphysema occurs only when an acinus is bounded by connective tissue, whether pleural, septal or sheaths around a bronchus or blood vessel, "paraseptal" is an accurate description, especially when distribution throughout the whole lung is considered.

The distribution within the acinus is given in italics, and the overall pulmonary distribution indicated by "W" if widespread, "L" if localised.

GRADING

For precise description of emphysema some method of indicating the degree of air space enlargement is necessary. Any grading is, of course, arbitrary; the one suggested here is based on the size of the average air

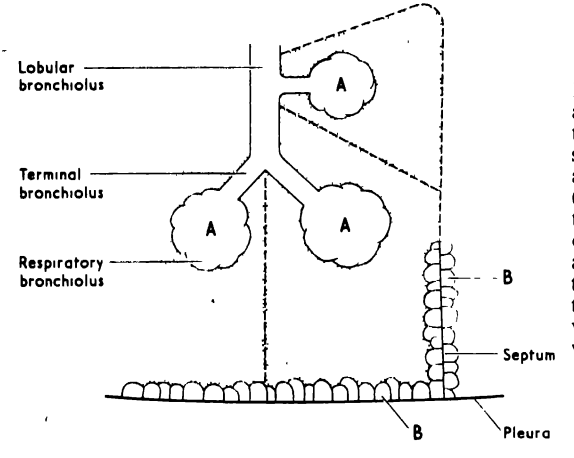


FIG. 8.—Diagrammatic representation of lobule in the angle between pleura and connective tissue septum. Centriacinar emphysema affects the respiratory bronchioli (A). Periacinar emphysema lies at the periphery of an acinus (B) but only where the boundary of an acinus lies against connective tissue—e.g. pleura, septa or connective tissue sheaths around blood vessels. Panacinar includes the whole acinus—i.e. all lung within the dotted line.

space as seen on naked-eye examination. There would seem no practical advantage in grading periacinar or paraseptal emphysema. It is only when an occasional lesion ruptures to produce a pneumothorax or gives rise to a large bulla that there is serious disability. Centriacinar and panacinar emphysema arise from different mechanisms and are each seen in various clinical types: grading of centriacinar emphysema is conveniently considered in Chapter V in which the other features of this type of emphysema are dealt with.

Since most types of emphysema are panacinar in distribution, this type is graded here as a preliminary to a consideration of individual types of emphysema.

Panacinar

Panacinar emphysema, which in its severe forms is most often associated with air-trapping, has been divided into four grades (Reid and Millard, 1964), which have been correlated with the radiographic findings of widespread emphysema (Simon, 1964).

The essential feature of the emphysematous lung is a loss of substance, manifested by an increase in the size of the air spaces and by retraction of the alveoli below the airways and vessels on the cut surface. This retraction is greater in air than in water. Although, by increasing their rigidity, injection of the pulmonary arteries may accentuate retraction, this occurs even in uninjected specimens.

The grading given below is based on naked-eye examination of lung fixed for at least a week, following intra-bronchial formalin inflation until the pleura is tense, at a pressure of 18 inches.

Normal.—The air spaces are so small that they cannot be distinguished clearly without magnification; there is no retraction (Fig. 9).

Grade I.—The air spaces are abnormally large, up to a millimetre in diameter; retraction is slight (Fig. 10).

Grade II.—Retraction is striking; the air spaces are a little bigger than in Grade I but the architecture is still intact (Fig. 11).

Grade III.—The air spaces may be up to 5 mm. in diameter; retraction is such that bronchi and blood vessels appear to be elevated above the surface (Fig. 12).

Grade IV.—The air spaces are "holes" larger than 5 mm. in diameter; these may be confluent and extend through the full thickness of a centimetre slice of lung (Fig. 13).

The milder grades are exemplified in the aged lung, the more severe grades in widespread primary (essential or idiopathic) emphysema and in certain types of bulla.

If the holes are of Grade IV size the type may be difficult both to recognise and to grade. It is probable that some would call Grade IV "irregular", the hole being so large that its situation within the acinus cannot be properly defined. It resembles Grade VI in Snider's grading of centriacinar emphysema (1962). It can be called panacinar since the hole, being so large, probably represents a whole acinus and the damage is clearly not localised to any part of the acinus. The justification for calling this panacinar emphysema of Grade IV severity is that other grades of the same type are often present.

In fact the size of a hole is only one factor to be taken into account in deciding the type of emphysema; if surrounded by normal lung it might be centriacinar and if at the edge of a scar it would be called "scar emphysema".

FIG. 9.—Cut surface of normal lung; arteries white, filled with (barium-gelatin): bronchus and veins. Air spaces are small and there is no retraction away from bronchi and vessels. Male, aged 19. Photomicrograph in Fig. 14. (×2.)

FIG. 10.—Grade I Panacinar. Abnormally large air spaces—slight retraction. At arrow large air spaces seen reaching to edge of acinus against the wall of vein indicating panacinar emphysema. Female, aged 79. Photomicrograph in Fig. 15. (×2.)

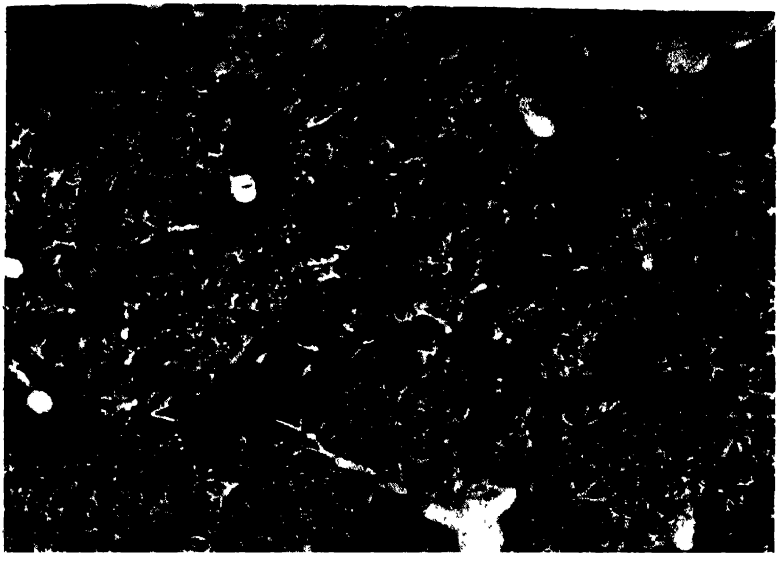


FIG. 11.—Grade II Panacinar. Striking retraction of lung away from blood vessels and bronchi which appear prominent. The size of individual air spaces is not so striking because lung flops. Under water the individual air spaces are more easily distinguished. Female, aged 79. Photomicrograph in Fig. 13. (× 2.)

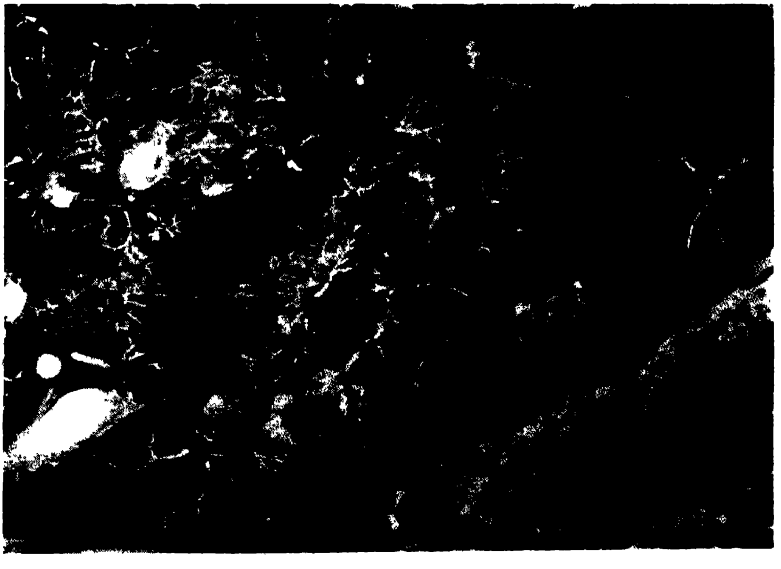


FIG. 12.—Grade III Panacinar. Air spaces are up to 5 mm. in diameter: retraction even more obvious. (× 2.)

FIG. 13.—Grade IV emphysema Air spaces are "holes" more than 5 mm. in diameter and so in some places they extend through the full thickness of the slice of lung. This severe grade may also be called "irregular". Grades III and IV, if widespread enough, may cause fatal disease. (×2.)

The gradings used here can be compared with those used in the Ciba Guest Symposium (1959), which were "mild", "moderate" and "severe". Grade I and Grade II correspond to the "mild" and "moderate" Ciba gradings; the "severe" Ciba grading covers Grades III and IV.

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Chapter III

THE AGED LUNG

In his treatise on diseases of the chest Laennec dealt with the aged lung before he discussed emphysema and his description of the former still stands. He said that in old age the lung was atrophic, that the alveolar walls were thinner, that on opening the chest the lung collapsed but that "strangely the lung no longer has elasticity" and that, prodded with a finger, the dimple smoothed itself out but slowly. Kountz and Alexander (1934) suggested that this "senile emphysema" is essentially postural, resulting from the development of a barrel chest. While in later years the term "senile emphysema" has been widely used to describe the aged lung, of recent years voices have been raised against it (Ciba Guest Symposium, 1959).

The logical consequence of the proposed definition of emphysema which is currently accepted, is that the large air spaces of age (Fig. 10)—alveolectasis of the aged lung—easily distinguishable on naked-eye examination, must qualify as emphysema. The reason for including the "normal" change in a classification of emphysema is that although alveoli are not necessarily enlarged with age, the pathologist has to decide whether large alveoli are due to the aging process or to disease. As will emerge, it is possible to suggest a limit to the degree of alveolectasis which may develop with age. The condition is an example of emphysema without airways obstruction.

Radiographic Features

In a recent survey Edge *et al.* (1964) applied Simon's radiographic criteria (Simon, 1964) for diagnosis of "widespread emphysema" (emphysema with air trapping) to the radiographs of 100 subjects over 75 years of age and free of chest symptoms; none showed the appearance of emphysema (for correlation of the radiographic features of these cases with pathological findings see p. 278). They reported decalcification in the ribs as a common finding, for in only 10 per cent of the cases did they consider rib calcification normal; in 73 per cent it was "poor". This "unmasking" of the lung arising from the ghost-like ribs probably explains the prominent vascular shadows reported by Mayer *et al.* (1958).

In addition they found an increase in the cardio-thoracic ratio, particularly in women, which was not due to an increase in the diameter of the heart but to contraction of the thoracic cage. Total lung capacity, as estimated by respiratory function tests, does not alter with age (Comroe *et al.*, 1962).

Two subjects in the series of Edge *et al.* have since died from non-pulmonary causes; in neither did the overall lung volume seem increased and in both the lungs deflated normally although the alveoli were large (Panacinar Grade I).

Pathological Features

The lungs of an aged subject are lighter and fluffier than in youth. This is typical of primary emphysema also but, which is not typical, the lungs are small in volume and lie against the vertebral body; at post-mortem they deflate normally.

In a series of six lungs from patients (male and female) over 65, the pulmonary artery was injected (Edge *et al.*, 1964); no bullae were seen. In a normal young lung individual air spaces are not usually seen on naked-eye examination, but the cut surface of these lungs showed that the alveoli were abnormally large, 1–2 mm. in cross-section, though the architecture of the lung was intact (Figs. 9 and 10). The cut surface retracted, causing the bronchi and blood vessels to protrude and the pleura to fold over on to the cut surface, which pointed to overall loss of lung substance. The same lung appearance may, however, be seen in patients under 60.

The large air spaces may be somewhat irregularly distributed throughout the lung (Fig. 10) and although some local accentuation is occasionally seen it is not sufficiently widespread or frequent to suggest whether the age change starts from the centre or the periphery of the acinus. The change is, therefore, panacinar in its distribution and, according to the grading described on page 17, is usually Grade I, occasionally Grade II.

In the pulmonary arteriograms the number of branches arising from axial pulmonary arteries was counted, the diameter of successive branches and the distance between them measured by the method described by Millard (1965). The vessels were counted to within 0·5 cm. of pleura, that is, they were mainly pre-acinar. The counts showed no difference between the six aged lungs and the lungs of six normal young controls. The main axial pathways were more clearly distinguished in the arteriogram than in the normal young lung, which probably reflects the reduction in the number of finer blood vessels.

Microscopy.—Microscopic examination of the aged lung confirmed and extended the findings from naked-eye examination (Figs. 14 and 15).

The alveoli were larger than in the normal young lung and the alveolar outline smoother and simpler; the mean alveolar size was several times greater for lungs over 65 than for the normal young lung. The thickness of

FIG. 14.—Photomicrograph of alveoli from normal young lung. Male aged 19. Section of lung seen macroscopically in Fig. 9. Pulmonary artery injected with micropaque and gelatine. No airtrapping. Radiograph in life normal. (× 120.)

FIG. 15.—Photomicrograph of alveoli from aged lung. Female, aged 79. Section of lung seen macroscopically in Fig. 10 and for comparison with Fig. 14. With age the alveoli are less numerous, larger and their outline is simpler. (× 120.)

the alveolar wall was reduced. The elastic fibres were fewer and the number of capillaries identifiable in persisting alveolar walls was relatively less in the aged lung than in the young; thus the capillary concentration per unit of alveolar wall as well as the area of alveolar wall was less, from which also it may be deduced that there was a reduction in capillaries.

Ryan *et al.* (1965) described dilatation of alveolar ducts as being characteristic of age, but although his use of thick lung sections (400 μ) clearly shows the increase in size of the alveolar duct it rather masks the increase in alveolar size which is also present. In fact, the distribution is panacinar.

The blood vessel reduction would seem to affect mainly capillaries and precapillaries. Using microscopic sections from young and aged lungs, an attempt was made to assess the number of precapillaries and to relate them to the number of alveoli. These population counts (Elliott and Millard, 1964) suggested that there was no significant reduction in vessels larger than 70 μ (measurements made in vessels distended by injection).

Respiratory Function Tests

Respiratory function tests in aged subjects usually show some functional impairment even though the subjects are free of symptoms and have never suffered from respiratory disease (Gilson, 1960). The results fall between those which are normal and those which in younger subjects would be taken as evidence of emphysema. However, there is no change in total lung capacity although its volume subdivisions approach the pattern produced in emphysema. Airway resistance is normal but distensibility is increased. The end expiratory lung volume is greater, although the transpulmonary pressure is decreased (Comroe *et al.*, 1962).

Gregg (1965) selected a series of ninety men who not only had no respiratory symptoms but had never smoked and found that any fall in peak flow with age was slight and less than previously reported.

Pathogenesis

The absence of fibrosis and the continued integrity of the structure of the aged lung suggest that atrophy is the mechanism by which this form of emphysema or alveolectasis is produced. The lung does not trap air even though the alveoli are large and smoother than in the normal and though their walls are thin. How far this resembles the atrophy which produces essential or primary emphysema and why it is not associated with premature bronchiolar collapse to produce air-trapping is not clear. That there is a fundamental difference between the atrophy of age and the atrophy of primary emphysema, and that the changes of age do not give rise to serious airways obstruction, seems to be confirmed by the rareness with which subjects over 60 years of age first present with disability from airways obstruction resulting from alveolectasis alone (i.e. without

chronic bronchitis). It remains a crucial question why the structural state of the aged lung which, while milder, is similar to that seen in idiopathic emphysema, has not the latter's functional characteristics and sequelae.

THE AGING PROCESS

These changes in the aged lung raise fundamental problems associated with aging. Why is there a slowing down of activity; is aging the effect of numerous incidents of damage occurring throughout life (Cameron, 1955) or must senescence be considered a peculiar biological process (Comfort, 1954); is the pulmonary change the same as the age change in other organs; is age associated with biochemical differences in the constituents of the alveolar walls?

The number of capillaries per unit volume of tissue at different ages and the extent to which they reduce with age do not seem to have been established for any organ. In the aged lung there is certainly a loss of capillaries (Bastai and Dogliotti, 1938) and, as described above, probably of precapillaries also, but whether the capillary loss is primary or is secondary to a change in the ground substance of alveolar wall is not known.

Biochemical investigation of aging lung has also been disappointing. Pierce and Ebert (1958) and Pierce *et al.* (1959) have studied the amount of collagen and elastin in the adult right middle lobe. The elastic content was found to have increased with age while material from patients with severe emphysema was more or less normal. Although elasticity may not be related solely to elastic fibres, it might have been expected that the reduction with age in lung "elasticity" would be reflected in the biochemical estimations, but a more subtle interpretation of age changes in elastin and collagen may need to be made. Furthermore the relative contribution of blood vessels and alveolar wall to the total amount of elastin is not known.

Biochemical and electron microscope studies of connective tissues elsewhere than in the lung indicate that with age a change occurs that is not as yet equated to function. Verzár (1962) studied the collagen fibres of corium in cattle skin. He found that on thermal contracture in young skin 10–15 times the amount of hydroxyproline is liberated as on contracture in age. But, although the amount liberated on thermal contracture is reduced with age the total content produced by acid hydrolysis is not. Elden *et al.* (1962) have shown that, in the rat tail tendon, aging seems to increase the degree of crosslinking of collagen mucopolysaccharide components. Yu and Ridley (1962) report that the polysaccharides in the connective tissue of the human aorta take up more calcium with age.

The nature of the aging process, whether of the organism as a whole or of individual organs, is poorly understood. Recent chromosome counts (Jacobs *et al.*, 1961) have shown that, in culture, white cells from aged subjects develop a higher percentage of hypomodal cells than do cells

from younger subjects. The chromosomal abnormalities seem more numerous in females than males; yet whether "aging" is assessed by longevity or by the incidence of arterial disease. the female seems to defy age more effectively than the male. A seeming disparity is also shown between the frequency of auto-immune disease in females and their longevity; this denies the theory that aging is associated with the accumulation of substances immunologically undesirable (Comfort, 1963).

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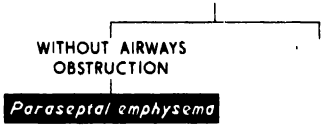
Chapter IV

PERIACINAR OR PARASEPTAL EMPHYSEMA



PERIACINAR or paraseptal emphysema is a condition in which only the alveoli at the acinar periphery are dilated. In fact only certain periacinar sites are susceptible to emphysema—the alveolar regions which lie against connective tissue (Fig. 16), around large bronchi and blood vessels, pleura and connective tissue septa. For this reason it is equally accurate to describe this form of emphysema as "paraseptal" and the two terms are both used here, "periacinar" to draw attention to distribution within the acinus and "paraseptal" to relate to the sites which are susceptible to this type of emphysema.

Periacinar emphysema does not usually give rise to symptoms and signs, yet it can be the beginning of a large bulla or result in a spontaneous pneumothorax; again, it may be sufficiently gross and widespread for some dilated air spaces to be evident radiographically (Figs. 17 and 18). Neither radiographic appearances nor respiratory function tests in this type of emphysema show evidence of widespread air-trapping (Edge *et al.*, 1966). Periacinar emphysema is, therefore, an example of emphysema without airways obstruction.

Pathological Appearances

Macroscopic.—Along a sharp border of the lung, for instance, small elevations of emphysematous lung are often so regular that the lung has a scalloped edge, each elevation being only a few millimetres or so wide at its base (Fig. 19). The sites commonly affected are the sharp edges, such as the anterior edge of the upper or middle lobe and lingula and the costodiaphragmatic rim. These may be called "marginal" as opposed to those which lie over the flat aspects of the lung—the mediastinal surface of either lobe or the flat diaphragmatic surface—which give an appearance of bossing, each circular cushion-like elevation of pleura having a diameter of a couple of centimetres.

Periacinar emphysema is commonly seen in lung which is otherwise intact and it may thus be regarded as a distinct type. It is a common pathological finding. The lesions are usually ignored by the pathologist

for the same reason he ignores small apical bullae, that he is conscious that they rarely lead to the chronic disability usually associated with the diagnosis of "emphysema".

On slicing the lung, these subpleural collections of air are seen to be empty of lung or to contain only atrophic strands. When subpleural they elevate the pleura and are therefore bullae. Often they seem not to extend into the underlying lung; yet their interruption by septa indicates that they are in fact deep to pleura—contrary to Miller's view that they are within it and are thus blebs. A similar appearance is seen along connective tissue septa passing into the lung from the pleura and adjacent to and along a bronchus or a pulmonary artery or vein (Fig. 16). In the angle between the bronchi also, particularly the large bronchi at the hilum, there may be such an area of emphysema, but here it is never large.

FIG. 16.—Paraseptal (peri-acinar) emphysema seen opposite arrow—along fissure and wall of artery. At bottom of figure also along bronchus.

When these lesions are small one striking feature, as seen on the cut surface, is that alveoli throughout the rest of the lung are normal, the bullae representing only a very superficial layer of alveoli. This is well illustrated in the specimen arteriogram (Fig. 20).

Sometimes a row of small bullae is found to be continuous with a large one, as shown in Fig. 21, the large one probably having developed from one, or a series of small ones, especially if the large bulla has a relatively small neck between it and underlying lung. If a single bulla, or even a group of them, expands to produce a large lesion, the base of the bulla—its communication with the rest of the lung—will still be peripheral.

FIG. 17.—Case 1. Paraseptal (periacinar) emphysema. Intersecting hair-line and ring shadows throughout lungs, most marked in basal regions.

FIG. 18.—Case 1. Paraseptal (periacinar) emphysema. Lateral view tomogram. Subpleural position of linear shadows anteriorly and posteriorly. See also Fig. 17.

FIG. 19.—Case 3. Paraseptal (periacinar) emphysema. Radiograph of specimen shows line of small marginal bullae opposite the arrow. See also Figs. 21, 24, and 25. ($\times$ 1.)

In Case 2 (*vide infra*), the bulla was so large and its communication with the lung so small that the surgeon assumed he was within the pleural cavity.

Microscopic.—Small bullae only a few millimetres in diameter sometimes seem to represent no more than a single alveolus, as, for example, when they are subpleural or against a septum or bronchus deep in the lung. Larger bullae may represent a cluster of alveoli, their wall consisting either of pleura or of attenuated alveolar wall. Such alveoli are extremely thin walled and virtually without capillaries or elastic fibres. The alveoli may be confluent and the air spaces accordingly larger. If the bullae are on the flat, rather than the marginal, surface of the lung they may show a bossed appearance; each boss may even be one or two centimetres in diameter and yet seem to affect only the layer of alveoli immediately under the pleura (Fig. 23). The overall lung architecture in such a region may still be intact. Occasionally a hole only a centimetre in diameter is lined by flattened alveolar wall, suggesting that the wall has been ulcerated and there has been retraction of surrounding lung.

Mechanism.—The reason for periacinar emphysema is not certain but as the change is irreversible it would seem to be atrophy and not overinflation. Although it is the subpleural region which favours the development of large bullae, the milder changes of periacinar emphysema are seen even deep within the lung adjacent to fibrous tissue within connective tissue septa or ensheathing broncho-arterial bundles or veins. It is likely that the development of paraseptal emphysema is to some extent facilitated by variations in blood supply. Alveolar walls adjacent to connective tissue have fewer capillaries than those with air spaces on either side (Miller, 1947). Elliott (1964) and Elliott and Reid (1965) have shown that numerous

accessory arteries provide a rich blood supply to the alveoli against the pulmonary artery such as is not enjoyed by peripheral alveoli lying against fibrous tissue septa or pleura—a region of the acinus which by virtue of its reduced vascularity may have a higher compliance.

The periphery of the acinus is deficient also in elastic fibres. These appear first in the mouths of alveoli and alveolar ducts and are not seen at the acinar periphery even at birth (Loosli and Potter, 1959). At twelve years of age the amount of elastic tissue is less than for the adult. Although lung "elasticity" cannot be related directly to the behaviour of elastic fibres, local reduction in their number may help to increase lung compliance in the paraseptal region.

In this region also there are sometimes round holes lined by compressed alveoli, suggesting that ulceration has occurred. Whether the atrophy has proceeded to this stage or whether another factor has supervened to produce ulceration is not clear.

FIG. 20.—Case 2. Paraseptal (periacinar) emphysema at margins of left apical lower lobe. Specimen arteriogram. Normal arterial filling of underlying lung. See also Figs. 22 and 23. (× 1.)

Clinical Features

As stated above, periacinar emphysema usually is not associated with clinical symptoms or signs. A subpleural bulla may rupture and produce a spontaneous pneumothorax (Case 1), or the bulla may enlarge sufficiently to compress neighbouring lung and impair function (Cases 2 and 3). Even if numerous (Case 1), they hardly impair function.

Radiographic Appearances

The lesions of periacinar emphysema are usually too small to be detected in the radiograph and as they do not produce generalised air-

trapping they do not give the signs of widespread emphysema with airways obstruction. The heart, diaphragm (and its movement) and the blood vessels all appear normal.

An individual bulla may be large enough to fill a hemithorax. Smaller bullae may be sufficiently numerous to produce a radiographic appearance characteristic of periacinar emphysema, i.e. many hair-line ring shadows up to 1 or 2 cm. in diameter, or intersecting line shadows (Fig. 17).

Tomograms may show a complete wall to the bulla towards the pleural aspect, but a less well-defined one on the deep aspect leading into the lung (Fig. 18). Even with tomograms it is often not possible to demonstrate air collections deep in lung, as opposed to those subpleural or at the edge of the hemithorax.

There is a similarity between the radiograph in periacinar emphysema and that in some forms of cystic bronchiectasis, but the ring shadows in the former are more numerous and thinner walled. In bronchiectasis the ring shadows usually fill in a bronchogram. In the honeycomb lung of histiocytosis X or of fibrosing alveolitis, the ring shadows are generally smaller; if larger, they may represent bullae, but they are usually not numerous and the nodular shadows of the underlying condition will be evident.

FIG. 21.—Case 3. Operation specimen. Bullae A and B with small neck, represent relatively small volume of lung; C represents the superficial region of large part of the lobe and is continuous with line of paraseptal emphysema opposite arrow. See also Figs. 19, 24 and 25.

Respiratory Function Studies

Minor degrees of periacinar emphysema give no evidence of respiratory function disturbance; even with gross degrees, sufficient to be seen in the radiograph, function studies may be practically normal. Sometimes, however, large bullae compress adjacent lung, limiting ventilation and blood flow to the compressed region and are associated with dyspnoea.

Case 1, below, illustrates the slight effect of numerous small subpleural bullae. Pneumatometric methods showed that there was no gas trapping and that diffusion studies were normal. There was some limitation to forced vital capacity and the forced expiratory volume and maximum voluntary ventilation showed some slight limitation of ventilation. This impairment of function probably arises from relaxation of the bronchial tree. The space occupied by the bullae would seem considerable and as the diaphragm is not depressed, the volume of the remaining normal alveoli is reduced. Even in normal lung the end of expiration is marked by airways collapsing; relaxation of normal lung between bullae probably results in the end of expiration being reached after a smaller volume of air is expired.

Two of the three cases described below have been reported elsewhere with more clinical detail (Edge *et al.*, 1965). The first is unusual in that the periacinar emphysema seemed widespread; as the patient is still alive it is not possible to be certain of the pathological changes. The radiographic changes in Case 2 are more limited but, as it came to autopsy, the pathological appearances could be established and the pathological changes in Case 1 deduced. In Cases 2 and 3 local overdistension of a single bulla or small group of bullae produced giant bullae in lungs otherwise essentially normal.

Case 1

Mrs. G. E. G., aged 33, was without symptoms until after the birth of her second child, when she noticed slight breathlessness on effort. Six months later (September 1961), because of a sudden onset of left chest pain and breathlessness, she was admitted to hospital and found to have a left-sided spontaneous pneumothorax. A few days later she was found to have a right-sided spontaneous pneumothorax as well. Treatment was successful and when she left hospital she thought that she was less dyspnoeic than she had been in the months prior to admission. In April 1962 she returned to hospital for more detailed investigation.

Lung function tests.—Lung function tests showed remarkably little abnormality. There was a ventilatory defect, with mild airways obstruction which improved only slightly after isoprenaline. Surprisingly, her diffusing capacity (steady state CO method) was within normal limits at rest and on exercise.

Respiratory Function Tests

		After Isoprenaline
FEV_1	1500 ml.	1700 ml.
FVC	2600 ml.	2700 ml.
$\frac{FEV_1}{FVC}$	58%	
MVV	77 l./min.	84 l./min.
PEF	300 l./min.	350 l./min.
VC	2500 ml.	2700 ml.

Dco at rest: 18·5 ml./min./mm.Hg (min. vent. 13·8 l./min.)
Dco on exercise: 26·8 ml./min./mm.Hg (min. vent. 17·1 l./min.)
Percentage extraction = 42.
Airways resistance—at 84 breaths/min. = 3·1 cm. H_2O/l./sec.
—at 168 breaths/min. = 1·5 cm. H_2O/l./sec.
Lung volume (pneumometric) = 3·0 l.

On exercise the airways resistance was increased. The lung volumes were virtually the same whether assessed by the body-box or vital capacity, indicating that all parts of the lung were well and directly ventilated.

Radiological findings.—The first radiograph of her chest was routinely taken during her first pregnancy in 1959 (July). It was reported normal, but further scrutiny showed several hair-line and fine ring shadows present medially above both hila. There was also a cluster of curvilinear hair-line shadows in the region of the lower right axilla and adjacent to the upper surface of the diaphragm.

A second radiograph taken fourteen months later (August 1960) during her second pregnancy, showed an increase in the diameter of some of the hair-line ring shadows above the right hilum and at the right base, and a less obvious increase in some of those above the left hilum (Fig. 17).

A third radiograph in September 1961 (before the pneumothorax) showed the hair-line ring shadows in the lower third of both lungs to be larger and that many new ones had appeared, giving the lungs a soap bubble appearance. The diaphragm was lower and flatter, and the heart size had decreased from 11 cm. in the initial radiograph to 9·5 cm. A few small nodular shadows were present in the left mid zone.

After successful treatment of the bilateral spontaneous pneumothoraces the chest radiograph (September 1961) eventually showed complete re-expansion of both lungs, the radiographic appearance being much the same as that taken just before the pneumothoraces. The heart was 10 cm. wide and the diaphragm flat but not low; inspiration and expiration films showed that the right diaphragm moved 4 cm. and the left 4·5 cm. There was good deflation of the lower half of the lungs but not of the apices. In a lateral view there was no increase in the size of the retrosternal transradiant area. The main pulmonary artery and the hilar and mid-lung vessels were not well seen, but appeared normal in tomograms, which showed many hair-line ring shadows, mostly 2 centimetres in diameter, all in a subpleural position. There were also many horizontal line shadows extending to the pleura, but the transradiant space they enclosed was often poorly demarcated on its

deep aspect. Some similar *hair-line ring shadows* were seen deep in the lung, but adjacent to the interlobar pleura and near the hilum (Cut 2—Fig. 18).

When last seen in August 1962, the patient was living a normal life and said she had no dyspnoea. A chest radiograph showed little change in the size and number of the ring and line shadows.

Comment

The radiographic appearances were unusual with numerous 2 cm. hair-line ring shadows mostly subpleural and, although they appeared ring-shaped or polygonal in the plain radiograph, the tomograms revealed that the wall was often incomplete on the deep aspect, suggesting that the ring shadows outlined emphysematous spaces and were not cysts. Respiratory function tests showed the lung to be completely ventilated and supported this interpretation of the radiographs.

The striking feature in this case is that the apparently gross emphysema gave rise to relatively little impairment of function; and yet the clinical course was marked by a nearly fatal incident of bilateral pneumothoraces, occurring some eighteen months after the radiological changes were first seen.

The paradox of gross emphysema with normal diffusion studies and with minimal impairment of ventilation, is explained by lateral tomography which showed that the emphysema was peripheral. As the individual bullae were relatively small, they evidently did not interfere much with bronchial and bronchiolar function. There was probably some relaxation of the relatively normal underlying lung, so that its volume at maximum distension was less than it would have been in the absence of the peripheral emphysema and the airways were, accordingly, partly relaxed. During expiration the bronchi and bronchioli might, therefore, be expected to collapse and "trap" air before the transpulmonary pressure at which this normally occurs was attained, thus accounting for the minimal impairment of ventilation.

The importance of the following case lies in the fact that the radiographic appearance in the left upper lobe was similar to that seen in the last patient and that at autopsy it was possible to establish its pathological basis.

CASE 2

Mr. G. P., aged 53, was perfectly well until 1957 when, while at rest, he experienced a severe attack of breathlessness which lasted a couple of hours. From 1958 he noticed undue shortness of breath on effort. In 1961, following a second attack, he was admitted to hospital. The trachea was found deviated to the left and a large bulla, found in the right lung, was resected after some delay (Fig. 22). The patient died soon after operation because of uncontrollable haemorrhage thought to be caused by hypo-prothrombinaemia.

Lung function tests showed an impaired (50 per cent) diffusion capacity, even during exercise, together with some airways obstruction, partly reversible after isoprenaline. The abnormality was, however, considered insufficient to account for the degree of dyspnoea.

		After Isoprenaline
FEV_1	*1300 ml.*	*1400 ml.*
FVC	2000 ml.	2200 ml.
$\frac{FEV_1}{FVC}$	65%	64%
MVV	49 l./min.	
PEF	260 l./min.	280 l./min.
VC	2200 ml.	2500 ml.

Dco at rest: 12·5 ml./min./mm.Hg (min. vent. 10·8 l./min.)
Dco on exercise: 16·2 ml./min./mm.Hg (min. vent. 18 l./min.).

Radiological findings.—The first radiograph, taken in 1952, showed the diaphragm to be at the 6th rib anteriorly and normal, and that the heart was 14·5 cm. in diameter and normal. The left upper zone was somewhat transradiant and avascular, with hair-line shadows. The right upper zone showed calcification with nearly vertical hair-line shadows. The position of the horizontal fissure was normal. The main, hilar and intrapulmonary branches of the pulmonary artery appeared normal.

In 1961, on admission, both leaves of the diaphragm were lower and flatter, but the heart shadow was unchanged (Fig. 22). In the left upper zone the avascularity and the hair-line shadows were more conspicuous. In the right lung the upper zone shadows were unchanged, the horizontal fissure was raised, and there was a 10 cm. avascular transradiant zone below it.

Lateral views confirmed the flat diaphragm and showed a very large retrosternal translucency, together with a translucency posteriorly demarcated by a vertical hair-line. Posterior view tomograms showed that the calcified lesions in the upper zone lay mainly posteriorly and the hair-line shadows anteriorly. The transradiant space in the right mid zone extended from back to front.

At thoracotomy a large bulla arising from the anterior segment of the right upper lobe filled the hemithorax, stretching forward in front of the heart and aorta. The remainder of the upper lobe was found to be almost completely involved in a system of large thin-walled bullae, whilst the middle and lower lobes showed only numerous small marginal bullae.

Autopsy.—At autopsy the corners of the left lung were rounded even before it was inflated. In the left upper lobe there were eighteen subpleural bullae, rather more than a couple of centimetres in diameter, lying particularly over the mediastinal aspect of the lobe and also at its margins. In addition there were numerous smaller bullae strung along the sharp margin of the lung.

The pulmonary artery was injected with barium-gelatine solution. At the rounded edges of the lung it was evident that the distended region represented only the few subpleural millimetres, certainly not even the depth of an acinus. The underlying pattern seemed normal (Fig. 20). Some pruning of the intra-

FIG. 22.—Case 2. Paraseptal (periacinar) emphysema. Intersecting line shadows left upper lobe. Bulla right mid-zone, found at thoracotomy to extend to pericardium anteriorly. Paraseptal emphysema confirmed at autopsy. See also Figs. 20 and 23.

acinar pattern was seen at the periphery of the filled pathways in the fork between segmental bronchi (Fig. 20).

The lung was cut parallel to the mediastinal surface into slices roughly one and a half centimetres thick. In these the lung appeared essentially normal save for the emphysematous spaces under the pleura, against the connective tissue septa or the connective tissue sheaths of veins or broncho-arterial bundles. Individual air spaces varied between a few millimetres and a centimetre in diameter. There was no evidence of tuberculosis.

The emphysema was all periacinar.

Right upper lobe—resection.—From the right upper lobe two large bullae arose from the anterolateral aspect of the anterior segment. At operation the base of these bullae had been oversewn before resection was decided upon.

In the posterior part of the lobe were half a dozen collections of caseous material, all less than a centimetre in diameter and well encapsulated by dense fibrous tissue. The lung between them was emphysematous, but no subpleural bullae were seen.

In contrast, over the medial aspect of the anterior segment were pouting regions 2 cm. in diameter resembling the bullae described in the left lung.

The distribution was the same as that of the line shadows detected in the tomogram. In this part, the cut surface showed emphysema against the septa deep in the lung.

The distribution of the tuberculous scars and the fact that the emphysema was different from that in the anterior part of the lobe and in the left lung suggests that the paraseptal emphysema is not caused by tuberculosis.

Comment

It would seem likely that the very large bulla on the right had started as one of the small subpleural ones, illustrating another of the complications of this type of emphysema. The value of this case is that it was possible to correlate the ring shadows at the left apex with the presence of the small bullae in the specimen and to show that these were an example of paraseptal emphysema.

The rapid ballooning of a peripheral bulla to an enormous size precipitated the extreme shortness of breath.

CASE 3

Mr. A. C., aged 38, had served in the United States Air Force during the second World War and his duties included regular high altitude flying. His

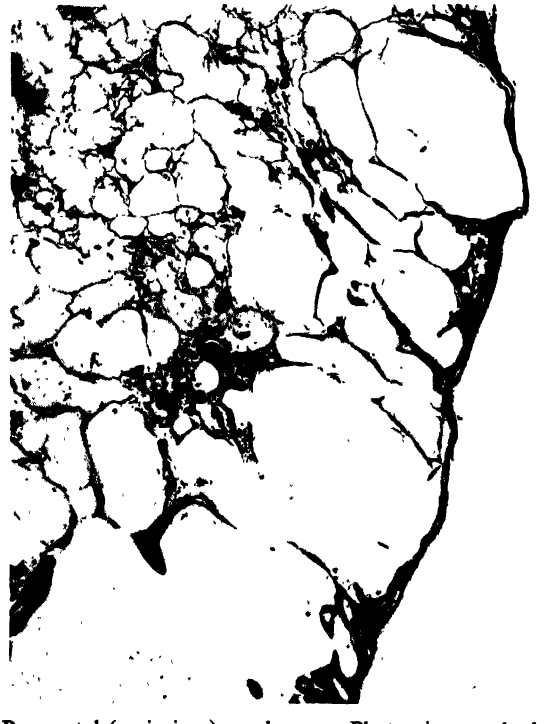


FIG. 23.—Case 2. Paraseptal (periacinar) emphysema. Photomicrograph showing subpleural position of abnormally large air spaces with underlying alveoli relatively normal in appearance. See also Figs. 20 and 22. (×8.)

chest was radiographed routinely on two occasions but nothing abnormal was recorded. From 1950 he noticed increasing shortness of breath which he attributed to heavy smoking (40 cigarettes per day) and to being over-weight. In 1961 his shortness of breath was such that he could only walk slowly on the flat and he then sought medical advice. A radiograph at this time showed bilateral upper zone bullous areas which were subsequently resected on separate occasions (Fig. 24).

FIG. 24.—Case 3. Avascular transradiant area (bullae) right upper lobe. Numerous linear shadows including one near diaphragm, see arrow. Findings confirmed at operation. See also Figs. 19, 21, and 25.

Lung function tests.—Regional lung function tests with gaseous isotope were carried out and showed ventilation to be almost absent at the right apex and much reduced below the left. In the mid zones the ventilation was almost equal on the two sides, but the blood flow was a little lower on the right than on the left. In the lower zones both the blood flow and ventilation were a little reduced on the right compared with the left.

None of these investigations gave a clear cut answer to the nature of the translucency in the left upper zone and, in view of the progressive dyspnoea and the lack of ventilation on the right side, it was considered that right upper lobectomy would very probably bring improvement.

Respiratory Function Tests

(*Ventilation* = ratio between sides. *Clearances* = %/second.)

Breath No.	*Lung Zone*	*Gas*	*Ventilation* (O_2, CO_2) R	L	*Clearance* (O, CO, CO_2) R	L
1	Both second rib	Oxygen	0·2	1·0	—	0·8
2	Both 3″ down from second rib	Oxygen	1·0	0·8	1·6	2·7
3	Both 3″ down from second rib	Oxygen (normal breathing)	1·0	0·5		
4	Both 6″ down from second rib	Oxygen	0·6	1·0	3·0	3·3
5	Both 6″ down from second rib	Oxygen (normal breathing)	0·6	1·0		
6	Both 6″ down from second rib	CO_2			15·2	19·2
7	Both 3″ down from second rib	CO_2			9·3	12·8
8	Both second rib				—	3·2

Note: (i) *Ventilation* from initial peak of O_2 is more reliable than those from initial CO_2 peak.
(ii) *Clearance* CO_2 is best measure of local blood flow.
(iii) *Normal values* vary with position, etc. Horizontal comparisons between two sides at some vertical level generally satisfactory. Interpretation of other readings more complex.

Radiological appearances.—A chest radiograph at this time (July 1961) showed a diaphragm of normal shape, the upper level being opposite the 6th rib anteriorly, a heart of 15 cm. diameter normal in size and shape, and normal hilar vessels.

In the right lung there was a completely avascular translucent area extending from the apex to the lower zone where it was demarcated by an almost horizontal line shadow (Fig. 24). Several other line shadows were present in the lower zone. The lateral view showed that the large transradiant area and the hair-line shadow were present in the anterior half of the thorax and were in the upper lobe. A bronchogram confirmed the upper lobe position of the hair lines (Fig. 25) and showed that the avascular translucent area had caused crowding and downward displacement of the filled bronchi of the middle and lower lobes. Some peripheral bronchiolar dilatations, "pools", were seen in the anterior segment of the upper lobe and one in the middle lobe.

In the left lung there was a long hair-line shadow extending downwards with a lateral convex curvature, which at the lower end merged with a small fluid level medially. There was some doubt at the time whether the hair-line shadow on the left side marked the edge of a huge bulla extending across from the right side as a mediastinal hernia, or the wall of a separate

giant bulla in the left lung. Tomograms showed the transradiant avascular areas on both sides, but no pleural layer between them, though it is unlikely that this could have been demonstrated even if there was. A bronchogram showed poor peripheral filling of the apico-posterior bronchus, but was otherwise normal. A radiograph taken 10 years previously showed very similar appearances on both sides to those seen in the present radiograph.

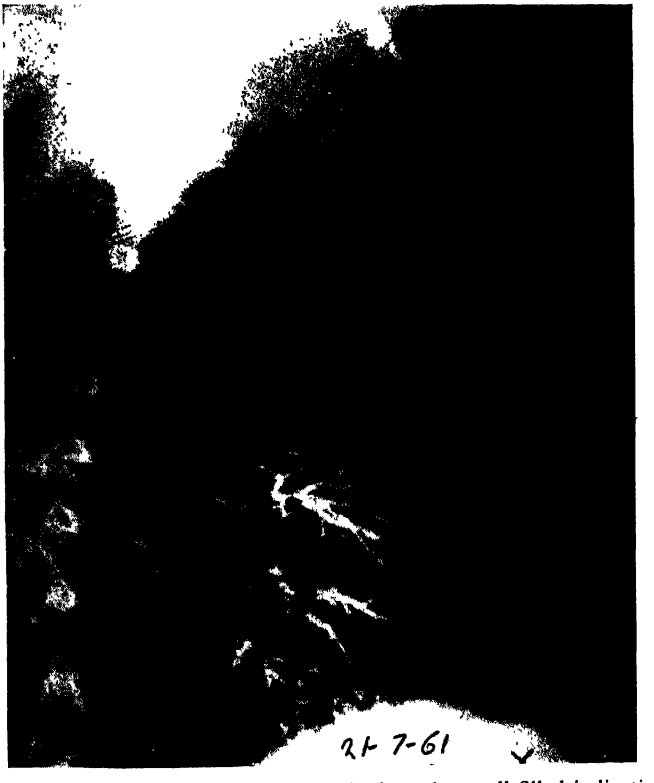


FIG. 25.—Case 3. Right bronchogram. Upper lobe branches well filled indicating superficial position of bullae. No localised compression but slight downward displacement of rest of the lung. See also Figs. 19, 21 and 24.

Thoracotomy.—At right thoracotomy (1961), the right upper lobe was seen to be almost completely replaced by large bullae. One of the largest was herniating into the mediastinum far across the mid line and it was felt that this bulla was responsible for the X-ray appearance of a curvilinear shadow on the left side. Between the anterior segment of the upper lobe and the middle lobe the fissure was incomplete; collateral drift was found to occur at this site, filling even the bulla at the apex, although it did not abut on to the intersegmental plane.

Both the middle and lower lobes were compressed and showed heavy coal impregnation. They inflated and deflated well, the only evidence of emphysema being a row of marginal blebs over the lateral segment of the

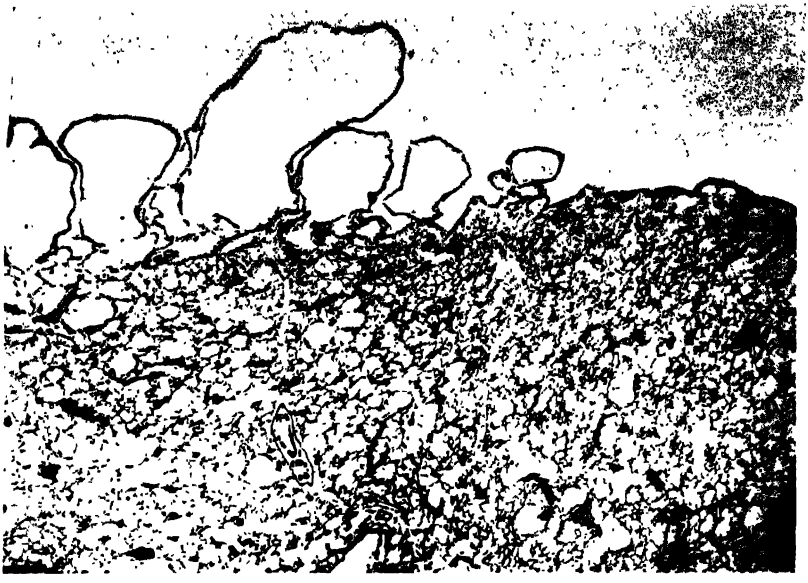


FIG. 26.—Photomicrograph of marginal emphysema as in Figs. 19 and 21. Individual bullae represent one, or no more than a few alveoli; stretching affects pleura mainly; underlying alveoli normal. For comparison with Fig. 22 where the lengthening of the alveolar walls is greater. (×4.)

middle lobe. The diaphragmatic surface of the lower lobe and the fissural surface of the middle lobe were relatively free of carbon pigment. Over the lateral aspect of the lower lobe dilated lymphatics were visible. The lower lobe seemed slower to expand than the middle lobe and possibly did not achieve its normal volume during the operation, as the middle lobe overlapped it by several centimetres.

Right upper lobectomy was performed, and the lower and middle lobes expanded to fill the right hemithorax quite well.

The patient recovered uneventfully and said that he was less breathless than before operation, but the cough and sputum persisted and then for the first time he noted attacks of sharp pain in the left upper chest anteriorly. Radiography confirmed satisfactory expansion of the right mid and lower lobes, that the blood vessels were of a good size and that diaphragmatic movement was full. The cystic space in the left upper lobe persisted, however, and in February 1962 showed for the first time a small fluid level. It was concluded that this was in fact another bulla, and in view of the persisting symptoms, *left thoracotomy* was carried out on 1st June, 1962.

A very large bulla about 12 cm. in diameter was found, arising from the lingular portion of the left upper lobe, and there was a collection of smaller bullae about 3–4 cm. in diameter rising from the apical segment of the upper lobe. Both sets of bullae were excised and the bases oversewn. There were small marginal bullae along the edges of the left lower lobe, but otherwise this portion of the lung appeared to be fairly healthy.

The patient again recovered quite uneventfully but experienced no

further improvement in his effort dyspnoea. He still has considerable cough and sputum, though this disappeared during a short period when he discontinued cigarette smoking.

Examination of Resected Specimen—Right Upper Lobe

Macroscopic.—The right upper lobe was distorted and compressed by three bullae arising mainly from the anterior and apical region and measuring 8, 12 and 24 cm. in the long axis respectively (Fig. 21). Along the inferior edge of the lobe there was a line of marginal emphysema, tiny air spaces each only a few millimetres in diameter (Fig. 19). There were also localised vascular pleural adhesions.

On inflation the largest of the bullae expanded first and it was only by compressing its base that it was possible to inflate the other two. The base of the large bulla was unusually long and seemed to have no true pedicle, the row of marginal emphysema shading into the edge of it.

One branch of the pulmonary artery was injected; the arteriogram showed that the vessels at the base of the bulla had filled and also those in the compressed region of the lung, which inflated and collapsed with ease. This fact, together with the large amount of coal pigment in this region, suggested that the bullae originated during adult life.

On section, the cut surface of the lung showed the three bullae. The two posterior arose near together rather behind the apex and each had a narrow communication to the underlying lung, while the anterior one, which at first sight seemed to have a broader base, was found to have part of its deep wall formed by a septum. A dense white scar was seen in the base of one of the posterior bullae but otherwise this segment seemed normal. The largest, the anterior, bulla was found to have a very large base which was fairly continuous with underlying lung. The whole of the anterior region seemed to have been expanded with the immediately subpleural region maximally affected. Most of the bulla was empty but there were strands of varying size running across it, some like shoelaces, representing blood vessels, while the more sheath-like bands represented major connective tissue septa. The tiny marginal (paraseptal) bullae were continuous up to the edge of the largest bulla. The lung in the region of the marginal bullae was normal.

Microscopic.—Although at its base the smallest bulla was continuous with emphysematous lung, to one side a solid collection of fibrous tissue was seen which could have been compressed lung or lung condensed in a scar and evidence of old inflammation. Associated with this was a region of interstitial fibrosis in alveolar walls and also of bronchiolar deformity and fibrosis. Forming the base of one of these bullae was a sheet of dense fibrous tissue, probably a septum, smooth on one side but with ragged lung attached to the other—typical of apical bullae. The large anterior bulla would seem to have been different in type from the other two. This bulla appeared to represent overinflation of a row of small bullae, which would explain its broad base communicating with lung and also the shallow layer of lung involved.

Comment

The patient presented with progressive effort dyspnoea, a productive cough and several incidents of acute bronchitis; these symptoms were accompanied by radiological evidence of bullae.

Resection of the right upper lobe was followed by a reduction in effort dyspnoea, but there was no further improvement after excision of the bullae on the left side, perhaps due to the patient's continued heavy cigarette smoking.

It would seem that on both sides the larger bullae derived from a series of paraseptal emphysematous lesions.

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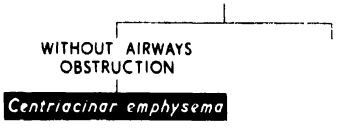
Chapter V

CENTRIACINAR EMPHYSEMA

(*a*) *Without Coal Storage*
(*Syn. Centrilobular Emphysema, Focal Emphysema*)



IN centriacinar emphysema only those alveoli near the centre of the acinus are dilated (Fig. 8), while those at the periphery are normal.

Centriacinar emphysema has been called "centrilobular" (Leopold and Gough, 1947). While, however, it is central to the lobule rather than peripheral, it is somewhat to the side of the centre and thus is more accurately described, in relation to the acinus (see Figs. 7 and 8), as central. Furthermore, the term "centriacinar" is consistent with the current definition of emphysema based on the acinus and with the other terms describing anatomical distribution.

PATHOLOGICAL TYPES OF CENTRIACINAR EMPHYSEMA

Apart from emphysema with accumulation of dust, two different types of centriacinar emphysema can be recognised by their naked-eye appearance. In the first type, Atrophy (Fig. 27), the "hole" consists of a group of dilated air spaces traversed by flimsy strands of lung, with architecture roughly intact; in the second type, Destruction (Fig. 28), the "hole" is complete and empty of tissue and about a centimetre in diameter. It appears like a cyst with a complete and smooth wall and may resemble a region of bronchiolectasis (Fig. 29).

Microscopically the centrally-placed alveoli of the atrophy type show flimsy alveolar walls while the architecture of the region is essentially intact; this points to an atrophic condition. In a microscopic or paper-mounted slice of lung such as a Gough-Wentworth (1949) section, the persistent alveolar structure is evident as points of tissue within the region of dilatation.

In the destruction type the wall or lining of the hole consists of flattened alveoli; interruption of the alveolar wall by ulceration or tearing allows retraction of surrounding lung, which can happen even if only a small part of the wall of the respiratory bronchiolus is interrupted (Fig. 29). In both

types of centriacinar emphysema the alveoli between the foci of emphysema are usually normal, but occasionally a mild degree of panacinar emphysema may be present.

The atrophy form would seem to be much commoner than the destruction. They are not usually found together. It is probable that neither causes airways obstruction. Cases of the destruction type occurring alone throughout a lobe are few, and although evidence that it can of itself produce air-trapping is lacking, this possibility must still be entertained.

Snider and his co-workers (1962) have studied centriacinar emphysema in autopsy material from 52 patients with no history of chronic pulmonary disease. They distinguished six grades of severity of the lesion (which they illustrated) and their grading can be related accordingly to the types described here. Grades I–IV would be atrophy emphysema; only the severest grades, Grades V and VI, are destruction emphysema. Centriacinar emphysema, Grades I–IV, was found in 30 of 52 autopsy specimens, and Grades V and VI in none. In Grade VI the whole acinus is affected and it is

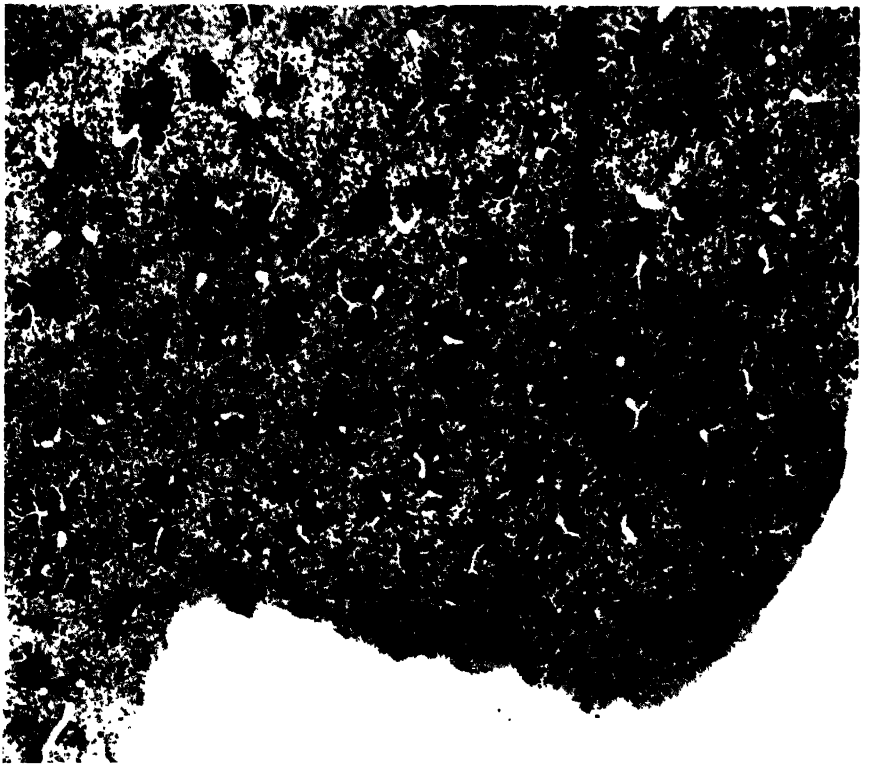


FIG. 27.—Centriacinar emphysema (atrophic), with and without coal. Some lesions are free of soot, the lung being creamish grey in colour, others are outlined by soot (e.g. those indicated by arrows). Woman, aged 50, died of cirrhosis of the liver.

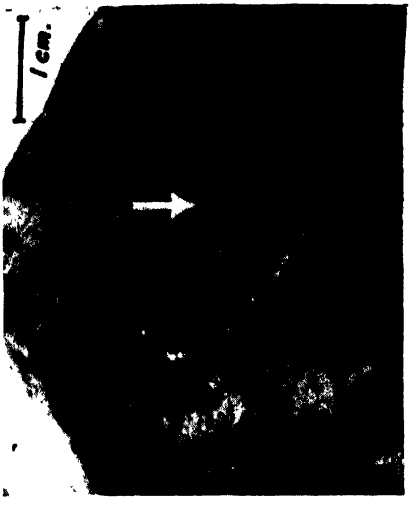


FIG. 28.—Centriacinar emphysema (destructive). Dilated spaces opposite arrow, up to 1 cm. in diameter with lobulated shape and smooth lining (see Fig. 29). Panacinar Grade I also present opposite arrow.

FIG. 29.—Lining of dilated space from Fig. 28. The alveolar connections to bronchiolus (1) are disrupted, surrounding lung has retracted, flattened alveoli line the space. Black pigment present upper part.

therefore indistinguishable from panacinar Grade IV or from a severe grade of irregular emphysema.

The importance of the study of Snider and his colleagues is that it confirms that even well-developed and widespread atrophy centriacinar emphysema does not give symptoms. It is not associated with air-trapping or with disability and would seem to have little to do with chronic bronchitis. On the other hand a lung with such lesions may well be susceptible to damage by other disease such as chronic bronchitis.

PATHOGENESIS

Atrophy Centriacinar

As atrophy seems the most likely way in which this type of emphysema develops, the description "atrophy" would appear justified. The fact that the lesion is localised would seem to preclude infection or other inflammation as a cause. There is no evidence that the lung is hypoplastic and centriacinar emphysema has not been reported in childhood. As there is no air-trapping, overinflation also would seem to be ruled out.

Destruction Centriacinar

Serial sections through a lesion of destruction centriacinar emphysema demonstrate interruption of the continuity of the lung. Complete destruction of some alveoli may follow inflammatory damage or tearing. The

strange thing about destruction centriancinar lesions is that the surrounding lung seems relatively unaffected, which suggests that any inflammation has been confined to the proximal part of the acinus. Again, coughing may produce a tearing; while in the normal lung cough does no damage, in a bronchial tree affected either by bronchiolitis or bronchiolar blockage it may be less innocuous.

Relation of Atrophy to Destruction Centriacinar Emphysema

The development of destruction emphysema does not depend on the existence of atrophic lesions. In one operation case (a pneumonectomy for carcinoma of the left lower lobe) numerous lesions of the destruction variety were seen in the left upper lobe and none of even a mild atrophy type. Whether, on the other hand, the atrophy type progresses to a condition indistinguishable from the destruction type is not known, but again there is no evidence that it does.

Relation of Coal Storage to Centriacinar Emphysema

In either the destruction or atrophy type of centriacinar emphysema, the walls of the central alveoli are sometimes black from coal stored in them. The role of dust in causing emphysema is still a matter of doubt, the evidence as to which is discussed later, but certainly the holes may be present without dust.

A satisfactory description of emphysema central in the acinus should, therefore, take account of any dust present as well as any ulceration of the alveolar walls, and centriacinar emphysema can then be grouped as follows:

Type I.—Atrophy—with dust
without dust
Type II.—Destruction—with dust
without dust

For completeness, the description should also refer to any bronchial or bronchiolar lesions present.

Relation of Bronchial and Bronchiolar Disease to Centriacinar Emphysema

In 1947, Leopold and Gough diagnosed chronic bronchitis in their cases of centrilobular emphysema, but they gave no criteria for their diagnosis of chronic bronchitis. In only two of forty patients with chronic bronchitis who died from lung disease was centriacinar emphysema widely distributed (Reid and Millard, 1964). As the forty cases were nearly all badly disabled chronic bronchitics, severe grades of centriacinar emphysema would still be expected if it was an important cause of disability. There would seem then to be no firm evidence that centriacinar emphysema is a frequent sequela to chronic bronchitis.

Furthermore there is little evidence that centriacinar emphysema is associated with severe bronchiolar lesions. In the emphysema associated with bronchiolitis obliterans acquired in childhood there is no centriacinar accentuation. In this condition the respiratory bronchioli as well as the peripheral acini are hypoplastic.

Relation to Panacinar Emphysema

There is little evidence that centriacinar atrophy emphysema is a precursor of panacinar emphysema or that they are associated, whereas the centriacinar type is more common in the cranial two-thirds and the panacinar is roughly uniform, commonly involving the basal regions. This distribution was reported also by Snider (1962) and Thurlbeck (1963*a*). Thurlbeck found panacinar as often in women as men, while the centriacinar was more common in men.

Moreover, in our study of the aged lung no centriacinar accentuation was found, nor in cases of primary (or essential) emphysema in which the lung changes are panacinar.

Radiographic Appearances

Centriacinar emphysema of whatever type may be widespread and even of Grade IV severity (Snider *et al.*, 1962), without the radiograph showing any abnormality. The absence of radiographic disturbance is closely linked with the absence of any impairment of respiratory function. From the few cases available it would seem also that even Grade V does not produce an abnormality in the radiograph.

These statements are supported by findings in coal-workers' radiographs (see p. 54).

Respiratory Function Tests

No satisfactory correlation has been made between respiratory function tests and the pathological findings in centriacinar emphysema without dust. Such knowledge as there is of the effect of this type of emphysema on respiratory function is derived from studies of coal-workers' lungs, or from patients with chronic bronchitis. It has been suggested that centriacinar emphysema produces impairment of diffusion, but as this has not been described in the absence of chronic bronchitis its significance is difficult to assess. In his pathological studies Thurlbeck (1963*b*) groups centriacinar and panacinar together according to their overall severity so that their relative importance cannot be distinguished. Nor has centriacinar emphysema been established as a cause of death in the absence of other lung disease as has been shown for panacinar emphysema.

(b) With Coal Storage (or other dust)
(Syn. Simple Coal-miners' Pneumoconiosis; Focal Emphysema; Centrilobular Emphysema)

Gough (1940) and Gough *et al.* (1949) described changes in the lungs of coal-workers and Heppleston (1954) described dilatation of the respiratory bronchioli associated with dust in the lungs of coal-miners and also town-dwellers. He originally called this "simple pneumoconiosis in coal-workers". But although alveoli opening into respiratory bronchioli may be dilated and contain dust, they may also be dilated without dust storage (Fig. 27), and dust may be present without dilatation (Fig. 30).

Accumulations of dust in the respiratory bronchioli may be associated with the characteristic dust foci which are so striking on naked-eye examination of the lung. That an increase in the diameter of these bronchioli may be associated with coal is undenied. But as coal may be present without dilatation, and vice versa (Figs. 30 and 31), and as emphysema is not necessarily associated with coal, even when it is present in considerable quantities, it would seem that some other factor may account for the emphysema. Cases of massive fibrosis are not included in this discussion.

Pathological Features

The pathological features of centriacinar emphysema with dust are essentially the same as those of centriacinar emphysema without dust (Fig. 31). The nature of the black pigment in the lungs of non-coal workers is not fully known but is generally assumed to be "soot". In coal-workers' lungs, Rivers and his colleagues (1960) have investigated the carbon, quartz, mica and kaolin content of the lungs. Interesting results emerge from their studies, bearing on the nature of the dust and the shadows to which it gives rise in the radiographs. Although on naked-eye examination of dust lesions they may appear to be the same in size, in city-dwellers as in coal-miners the total amount of dust is greater in the latter. Comparing the carbon and the mineral (that is, the non-carbon) content, the mineral is greater in the coal-miner than in the city-dweller and, although the absolute amount is small, it has relatively greater radio-opacity than the carbon and makes a relatively larger contribution to the shadows in the radiograph.

In the same study Rivers and his colleagues show that although the number of nodular radiographic shadows correlates closely with the amount of dust, the degree of pathological emphysema does not. Perhaps their most striking finding was the relatively infrequent occurrence of pathological emphysema, either centriacinar or panacinar, in association with dust storage and the absence of correlation between the amount of dust and the presence or severity of pathological emphysema. Unfortunately the radiographs were not assessed for signs of emphysema in these cases.

FIG. 30.—Accumulation of "coal" without emphysema. South Wales collier, aged 44, working at coal face 25 years. No disability. Gough-Wentworth section. (× 2.)

Caplan (1962) in his study of the "correlation of radiological category with lung pathology in coal-workers' pneumoconiosis" produces evidence that emphysema is not related to the amount of dust accumulated in the lung. Two hundred and thirty cases were selected, from each of which a large lung section was available and a chest radiograph taken no more than two years before death. He divided his categories of pathological emphysema into "none", "slight", "moderate" and "severe"; he did not distinguish centriacinar from panacinar. The incidence of pathological emphysema was analysed in relation to two groups of coal-workers—those under and those over 60 years of age. In both groups the pathological emphysema was more prevalent in pneumoconiosis category 0; those in

FIG. 31.—Centriacinar emphysema (atrophic) with black pigment in a non-miner. Gough-Wentworth section. (×2.)

category 1 had least and there was some increase in categories 2 and 3. Certainly here again there was no direct relation with dust accumulation.

Although there is an increasing interest in the role of pigment or dust in the production of emphysema, particularly in the United States, work has largely been directed to the relation between dust and the presence of fenestrations in the alveolar walls (Boren, 1962), but the presence of dust in macrophages near these does not necessarily mean that dust has caused them. In two recent surveys from the United States, those of Sweet *et al.* (1961) and of Thurlbeck (1963*a*), no mention is made of the presence of pigmented dust. These authors describe a lesion as "centrilobular" whether or not coal pigment is present. Sweet and his colleagues give two illustrations of centrilobular emphysema; one figure, the early stage of centrilobular shows a large amount of dust, and another "a close-up of centrilobular emphysema" with "normal appearing alveoli around the centrally placed 'cystic foci'," also shows pigmented dust. Although these authors do not attempt to group the lesions as they are described here: Type I—atrophy, Type II—destruction, this second illustration of Sweet would seem to be of Type II; the hole seems empty and the wall to consist of flattened lung.

Radiological Features

The radiographic appearance of coal-workers' pneumoconiosis is that of small circular shadows widely distributed, each between 0·5 and 2 mm. in diameter. Each circular shadow would seem to represent a summation of nodular lesions in which dust is concentrated (Gilson and Hugh-Jones, M.R.C. Report, 1955; Carstairs, 1961). The severity of simple pneumoconiosis can be graded by the frequency and distribution of these shadows. (I.L.O. Classification 1959.) In "complicated pneumoconiosis" there are in addition much larger shadows, often in the upper third on each side.

Relation of Pneumoconiosis to the Radiographic Diagnosis of Widespread Emphysema

The radiographs have been shown to be a satisfactory method of diagnosing widespread emphysema associated with airways obstruction (Simon and Galbraith, 1953; Simon, 1964; Reid and Millard, 1964).

To relate the category of pneumoconiosis to the incidence of radiological emphysema, both features were recorded in a series of four hundred radiographs from subjects with pneumoconiosis, one hundred from each of categories 0, 1, 2, and 3 (Caplan *et al.*, 1965). As all radiographs were of men applying for compensation, it was felt that if pneumoconiosis contributed to the development of emphysema the radiographic appearances of emphysema should be found more often in categories 1, 2, and 3 than in 0 and with increasing frequency.

In fact, the incidence of radiographic emphysema was found to be extremely low in all categories, but highest in category 0; it was of roughly the same severity in each of the other categories. Thus there was no evidence that the severity of pneumoconiosis influenced the incidence of emphysema.

Storage of other dusts.—No particularly damaging effect of coal has ever been demonstrated. Evidence of the benign nature of coal storage might be deduced from the behaviour of other dusts. Tin or iron, for example, can be stored in large amounts in the lung without any radiographic, functional, or structural evidence of emphysema (e.g. Robertson and Whitaker, 1955; Robertson *et al.*, 1961).

Bonnell and his colleagues (1965) in a "follow up study of men exposed to cadmium oxide fumes" reported a higher incidence of emphysema in these men than in controls. This diagnosis was based in part on respiratory function tests suggesting airways obstruction and they reported emphysema in the radiograph in only a small number (Bonnell, 1955). The airways obstruction may have been due to chronic bronchitis.

Respiratory Function Tests

Respiratory function tests, even in the presence of radiographic changes of advanced categories of simple coal-miners' pneumoconiosis, may not show disturbance. There may be no disability and no air-trapping (Gilson and Hugh-Jones, 1955; Higgins, 1960; Cochrane and Higgins, 1961). This is not to deny that many coal-miners are incapacitated, but it throws doubt on the role of dust storage alone in any respiratory disability, in particular on the theory that centriacinar emphysema is the cause of airways obstruction.

Where the pneumoconiosis is complicated by the scarring of progressive massive fibrosis, or by infection, other factors come into play.

Surveys, such as those of the Coal Board (Rogan *et al.*, 1961; *British Medical Journal*, 1961 and 1962) have investigated the relationship between disability and radiographic appearances and many discrepancies have been found. Respiratory function tests also fail to establish any relation between the amount of coal in the lung and the presence of airways obstruction. One explanation of the discrepancy is that the pneumoconiosis is associated with chronic bronchitis, which is responsible for disability—a possibility now under study (Rogan *et al.*, 1961).

In conclusion, then, it would seem that:

1. In coal-miners' pneumoconiosis the dust is not necessarily associated with pathological emphysema. Furthermore, it would seem that neither the presence nor the severity of emphysema shows any clear correlation with the amount of dust.
2. Although in some coal-miners the association of dust with emphysema

suggests that the dust may cause emphysema, it certainly does not often do so; other factors will need to be taken into account. For example, it may be the same centriacinar emphysema as seen in those who are not coal-miners.

3. Respiratory function studies show no consistent correlation between the amount of coal present and the patient's disability or tests of airways obstruction—suggesting that centriacinar emphysema with coal storage does not cause airways obstruction.
4. No correlation is found between the radiographic evidence of pneumoconiosis and of widespread emphysema with air-trapping. In a pilot study the incidence of emphysema was low, but higher in category 0 than in any other category; in each of the other categories it was roughly the same.
5. When there is progressive massive fibrosis other factors than dust must be taken into account.
6. Where there is disability, chronic bronchitis may be the cause.

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Chapter VI

COMPENSATORY EMPHYSEMA

"COMPENSATORY emphysema" is the term used to describe the condition in which lung overinflates to fill the thoracic region previously occupied by other lung before resection or collapse. The behaviour of normal adult lung when overinflated is first described because, in childhood, compensatory emphysema has to take account of further growth of the overinflated lung. Normal and diseased lungs behave differently when overinflated.

Little attention has been paid to the structure of the human lung in which there is compensatory emphysema. As the lungs themselves are not available, knowledge of this condition can only be obtained indirectly, from radiographs, respiratory function tests, and extirpation experiments. Compensatory overinflation may properly be called emphysema because it represents an increase in alveolar volume. If it occurs in childhood, "compensatory" changes will produce increase in alveolar volume but, later, normal growth of alveoli may be such that the remaining lung becomes populated by a larger number of alveoli than it would ordinarily contain. Thus the "compensatory" changes in this condition may include both overinflation and hypertrophy.

Radiology

The most satisfactory radiographs for the study of compensatory emphysema are those from patients in whom the overinflation follows prolonged lobar collapse without infection, such, for instance, as results from an adenoma of the bronchus or pressure on the bronchus from a nearby tuberculous lymph node. After a lobar resection the radiographic picture of compensatory emphysema is usually complicated by the presence of pleural shadows, elevation of the diaphragm, and shift of the heart. A survey of thirty-one cases was made (Simon and Reid, 1964) to define the radiographic features of compensatory emphysema with lobar collapse. Five patients were under eight years of age, three between eight and twenty, fourteen between twenty and fifty, and nine above fifty. The overinflated lobes were:

Left upper—12
Left lower—3
Right upper—6
Right upper and middle—3
Right middle and lower—7

Transradiancy was judged by the greater blackness of the lung field between individual vascular shadows as compared with a similar area in the opposite and normal side. The diaphragm was considered normal if the left dome was about half an inch lower than the right; the blood vessels were examined for their distribution, size, and direction; bullae or bullous areas were looked for but none was found.

Transradiancy.—In twenty-one cases the overinflated lobe was normal (Fig. 32); in seven patients a slight increase in transradiancy was detected; in three, there was a moderately severe increase. The transradiancy seemed not affected by the age of the patient, the age of onset of the condition, or the particular lobe affected.

Diaphragm.—The diaphragm on the affected side was elevated in nine patients, depressed in two, and normal in the remaining twenty. Elevation of the diaphragm did not prevent transradiancy; of the nine cases in which the dome was raised, there was transradiancy in four.

Blood Vessels.—In the region of the overdistended lobe the radiograph showed a spreading out of the blood vessels so that there were fewer per unit area than in the normal side, but there was no alteration in their size or in the balance between hilar and mid-lung vessels, such as in widespread emphysema. In overinflation a segmental artery occupies the position of a lobar artery and may give the impression of arterial narrowing. In all cases the blood vessels ran in the expected direction; no avascular area was seen (Fig. 32).

The most important fact established was that the transradiancy of the overexpanded lobe was in most cases normal, whether the collapse was due to a carcinoma or an adenoma and, therefore, of recent onset, or whether it was of long standing.

Of the three cases in which the transradiancy was moderate no cause could be seen in two; the third case was of a child of 5 in whom the left lower lobe was collapsed from bronchiectasis and the diaphragm raised. In a bronchogram the left upper lobe showed an appearance suggesting a patchy bronchiolitis obliterans in the lingula only; the rest of the lobe was normal with good peripheral filling, save that the bronchial pathways were less concentrated. Together with the fact that the diameter of the blood vessels was normal, these appearances would seem to preclude the possibility of air-trapping in the upper two-thirds of the lobe.

Of the five cases under 8 years of age, only in the child of 5 described above was the overinflated lung relatively transradiant and this was of

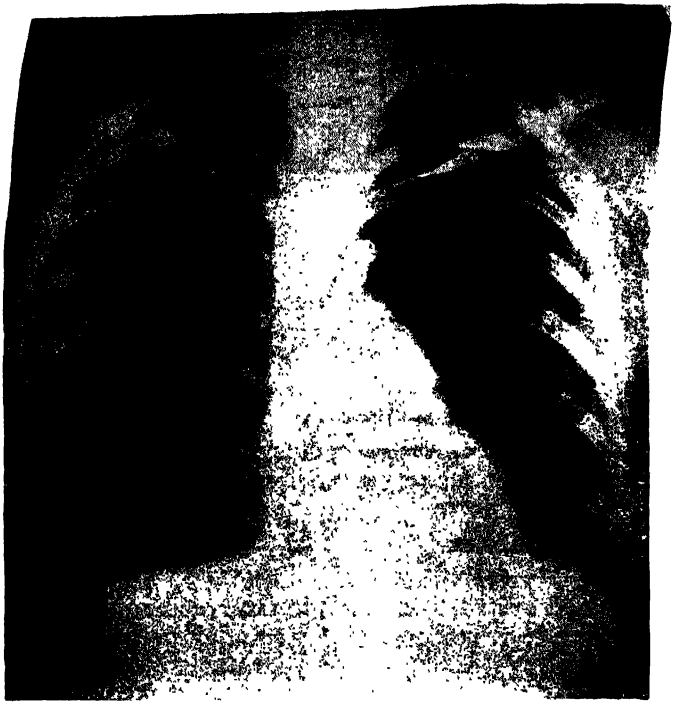

FIG. 32.—Compensatory emphysema left upper lobe. Vessel pattern spread out but no change in transradiancy. Adenoma left lower lobe bronchus with lobar collapse.

moderate severity. Of those under 20, one child of 10 showed some relative transradiancy but the bronchogram was normal.

Bronchographic findings.—Bronchograms of overinflated lungs were available in thirteen cases and showed that the number of large bronchi per unit area was much fewer than in a normal bronchogram, because the branches were more spread out. Although good peripheral filling was achieved in most cases, this did not give as crowded a picture as in the normal (Fig. 33). Unfortunately, contra lateral filling was not sufficient for a comparison of acinar size.

Although less crowded, the peripheral pattern, as well as the depth of the "unfilled rim", which represents intra-acinar structures, seemed in all other respects normal. There is a two- or three-fold volume increase in an overinflated lobe, but the depth of the unfilled rim, like the diameter of an alveolus, is increased only by the cube root of 2 or 3, a change which would not be detectable in a bronchogram.

Pathology

Operation specimens in which there was carcinoma as well as a collapsed lobe have shown no obvious change in the overinflated lobe, but no detailed reports are available of the overinflated lobe in compensatory

emphysema. The fact that there is no obvious change is not surprising, as the diameter of an alveolus is only increased by perhaps the square root of 2 or 3. As the blood flow is maintained, if not increased, the capillaries in the alveolar walls are well filled.

(For experimental findings see p. 298.)

COMPENSATORY EMPHYSEMA IN CHILDHOOD BEFORE GROWTH COMPLETE

Agenesis of One Lung

Absence of one lung bud at the very beginning of intra-uterine lung development, means that the other bud will grow to fill both hemithoraces and will occupy a space roughly twice the volume of a normal lung. There is no evidence to show whether or not in this single lung there is alveolectasis, i.e. emphysema, but, as the function of such a lung may equal that of two normal ones (Smart, 1946), it shows the degree of functional compensation which can take place where overinflation occurs before growth is completed. Of this condition detailed structural studies are also lacking; but some reports show that the alveoli were normal (e.g. Rienhoff, 1937), others that emphysema was present (e.g. Gross, 1905).

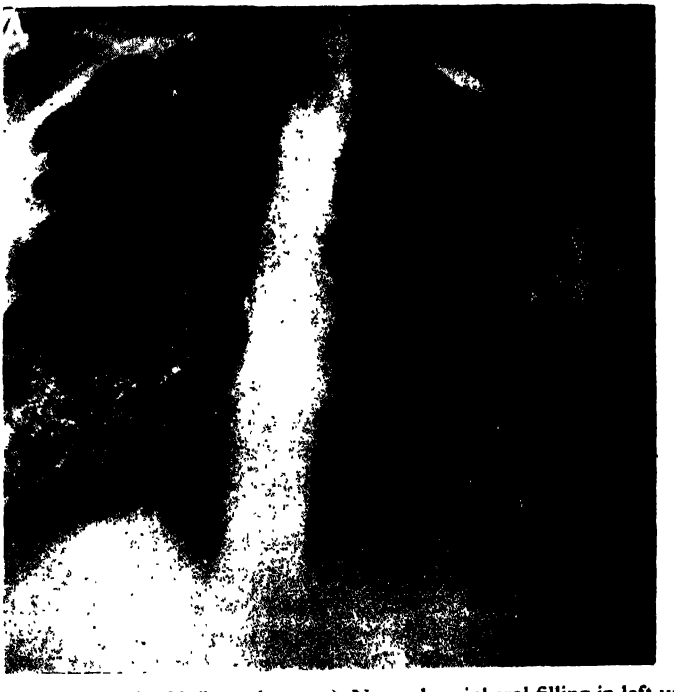

FIG. 33.—Same case as Fig. 32 (bronchogram). Normal peripheral filling in left upper lobe.

Radiology

In agenesis of the lung the diaphragm is often normal, the blood vessel pattern is more spread out than usual, but the "hilar and mid-lung vessel" pattern is normal and the lung not unduly transradiant; there is no evidence of widespread emphysema with airways obstruction. As the heart is displaced laterally by the single lung, there can be no comparison of the two hemithoraces.

Respiratory Function Tests

Respiratory function tests confirm the absence of airways obstruction and demonstrate that the lung tissue behaves normally, that the one lung is capable of the work of two (Smart, 1946).

Pathology

No count has been made of the number of branches from an axial bronchial pathway in a single lung which fills both hemithoraces and thus it is not known whether the pathways characteristic of one lung are doing double the work or whether the bronchial tree has branched even more as more space was available. The same question arises in relation to the number and size of the alveoli.

Growth in Lung Overinflated in Childhood

The cases described early in this chapter include children in whom the overexpansion was of a few years' duration, as well as adults in whom the onset was in childhood. It was a fair assumption that the lobes were normal before being overexpanded. Radiographic evidence suggests that the lobe expanded in childhood has by maturity achieved a normal blood-gas balance and shows no sign of air-trapping. These and many similar cases raise the questions whether such good function is achieved with the number of alveoli present in childhood at the time of overinflation or whether by growth the normal adult number of alveoli for the lobe is achieved or, again, whether an increase beyond this occurs, the number approaching that for the whole normal adult lung. Both experimental studies and the behaviour of normal adult lung tend to show that there is no reason why growth should have stopped or been reduced at the time of overinflation. Hence the normal adult number of alveoli per unit would seem to be achieved in a lung overinflated in childhood. Ignorance of the mechanisms which produce postnatal growth of the lung leads to the surmise that increase in thoracic volume with normal ventilation and adequate blood flow encourage multiplication of alveoli.

Experimental studies on dogs by Longacre and Johansmann (1940) indicate that overinflation, before growth of lung is complete, leads to an

increase in alveoli beyond the normal. Lung was resected in some dogs when they were puppies and in others when they were full grown; in the former the alveolar diameter (measured when they were full grown) was less than in the latter. If even the normal number of alveoli was achieved in the "puppy" group, their alveolar diameter would be roughly the same as in the adult group, so that the fact that it was smaller points to an increase in the number beyond the normal for the lobe.

Pathogenesis: Factors in the Development of Compensatory Emphysema in the Child and Adult

Enlarged air spaces are produced in compensatory emphysema in otherwise normal lung by overinflation without airways obstruction. Following overinflation a normal intrapleural pressure is rapidly achieved. As the airways are patent and the volume and pressure range during the respiratory cycle normal, the blood flow increases so that ventilation and perfusion are still appropriate to each other and hence the alveolar walls appear normal.

The adult number of alveoli is achieved by the age of eight (Willson, 1928; Dunnill, 1962). If overinflation without airways obstruction occurs before eight years of age, it is probable that the alveoli will develop normally and may even exceed the normal number. After the age of eight the vascular bed generally continues to increase but not the number of alveoli, which indicates that the alveolar diameter increases. It may be that compensatory expansion before or even after eight years of age leads to development of new alveoli and it is likely that the number of capillaries increases.

Overinflation of Adult Lung

When compensatory expansion occurs first in the adult, respiratory function seems well compensated. A small increase in the diameter of blood vessels will accommodate a surprisingly large volume of blood. Cournand (1950) has estimated that a one-sixteenth increase in diameter will provide for double the blood flow. Whether new capillaries are formed is not known.

It is difficult to assess the functional behaviour of residual tissue in the aged lung after resection; any atrophy of the capillary bed may mean that residual lung does not compensate well.

Comparison with Ball-Valve Obstruction Emphysema

Compensatory expansion does not necessarily entail any increase in transradiancy. This would suggest either that doubling the volume of air may not be detectable or that the volume of blood has also been doubled, so that within a unit the balance is maintained. In cases in which a ball-

valve mechanism has operated to double the volume of air, the radiograph shows hypertransradiancy. As the amount of air is similar in these two examples it must be the volume of contained blood that is significant.

In the compensatory expansion there is probably little reduction in the amount of blood per unit volume of lung. Inspiration and expiration films normally show a striking difference in transradiancy; but it is likely that there is no significant change in the volume of blood, although the distribution of blood in the vascular tree varies. As in expiration the volume of the lung may be reduced to half, it will contain much less air and, therefore, a relative increase in the amount of blood. This suggests that halving the amount of air while the blood volume stays the same is radiographically detectable.

Compensatory Emphysema in an already Diseased Lobe

It would thus appear that after compensatory overinflation the functioning of a normal lobe may be even better than before; but this may not be so in the case of a previously diseased lobe. In bronchiolar disease associated with air-trapping there is a local reduction in pulmonary artery flow (see p. 127). It is unlikely that overinflation would lead to compensatory growth.

The effect of over-expansion of diseased lung is illustrated by the behaviour of the residual lung after resection of regions of bronchiectasis. The over-expanded lobe sometimes shows evidence of emphysema or bronchographic evidence of bronchial or bronchiolar disease, which raises the question whether this represents "spread of bronchiectasis" or evidence of pre-operative disease. In some cases, because of incomplete or irregular filling, the pre-operative bronchogram suggests that airway and alveolar disease was already present.

Respiratory Function Studies

As respiratory function studies have been carried out mainly following pneumonectomy resection, they are of little value in studying overinflation of a lobe after collapse of adjacent lung, since the increase in the volume of residual lung is usually less than that of a lobe which has expanded to fill a hemithorax. Most post-operative physiological studies have been directed to studying lung which has maintained a roughly normal volume although called on to receive twice its normal pulmonary blood flow. Sometimes, after pneumonectomy, as after lobectomy, the volume of the remaining lung increases to produce compensatory emphysema.

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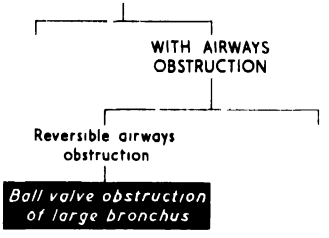
Chapter VII

EMPHYSEMA FROM OBSTRUCTION OF A LARGE BRONCHUS

(Syn. Ball-valve Emphysema; Obstructive Emphysema)



OBSTRUCTIVE or ball-valve emphysema means overinflation of lung arising from a ball-valve obstruction in a large bronchus. The ball-valve may be produced by a foreign body in the lumen, by disease of the bronchial wall, or by pressure from outside the bronchus; the obstruction allows air to enter the lung but impedes its escape. Airways normally dilate and lengthen on inspiration and contract and shorten on expiration; but where there is a "ball-valve" obstruction some air will pass it as the lumen widens and will not escape on expiration, with the result that the region supplied by the blocked bronchus becomes overinflated and does not deflate satisfactorily. Eventually, the lobe may become several times its normal size, the remaining lobes being relatively compressed or relaxed. In compensatory emphysema there is overinflation, but deflation on expiration is normal.

If the block is complete and persistent, the lung will collapse. The margin between collapse and emphysema is narrow; Chevalier Jackson (1950) has described a change from collapse to emphysema within a few days. The two changes may even alternate.

Radiology

The chest radiograph shows increased transradiancy in the region of the affected lobe and if this is greatly overinflated the vessels are spread out and narrowed. The heart, trachea, and any visible fissure are displaced away from the transradiant area, the diaphragm may be depressed, and the rib spaces widened. Further, there may be increased opacity of relaxed (or compressed) lung nearby.

Sometimes there is little increase in lobar volume but the region is nevertheless transradiant and the blood vessels appear narrowed. Whether or not the volume of the affected lobe is markedly increased on inspiration, on expiration the transradiant region does not deflate to show the increased opacity normally seen. All these signs point to air-trapping.

Overinflation, if untreated, may prove fatal but, particularly in adult cases, the process of inflation may stop when roughly stable pressures are reached. The determining factors are a matter of conjecture, but rigidity of large airways, blood vessels and mediastinum and the lengthening and consequent narrowing of the airways must at some stage prevent further inflation. Overinflation itself may also contribute by impeding airway dilatation on inspiration.

Pathology

No detailed description is available of the structural change in the human lung resulting from ball-valve obstruction since, usually, neither bronchoscopic removal of a foreign body nor even resection of a gland pressing on a bronchus necessitates resection of lung; nor are angiograms reported in this condition. The alveoli are certainly dilated and, as a lobe may be so inflated as to fill a hemithorax, displacing the heart and trachea, the increase in lobe volume may be greater than in compensatory emphysema. The minute blood flow is probably much less owing to reduced ventilation and air-trapping, which causes ischaemia of the alveolar wall and stretching and narrowing. There is also vaso-constriction which may be due to a reflex from the alveolar wall to the large arteries, or to proximal spreading of constriction from peripheral vessels. This mechanism has been described in systemic arteries (Hilton, 1959).

Experimental studies have shown that, in animals into whose main or lobar bronchi a ball-valve has been inserted, the alveoli of the obstructed lobe are, as a result of the overinflation, abnormally large and thin-walled and their outline smoothed out (see p. 300).

Level of bronchus affected.—Ball-valve obstruction leading to emphysema usually involves the bronchus to a whole lung or a lobe, but emphysema may still develop if a more peripheral airway is affected, depending on whether collateral air-drift can cope with the air trapped. Collateral air-drift has been described on page 334, but knowledge of the factors influencing its operation is still incomplete. It may not only prevent collapse of a segment or sub-segment but, by means of such drift, air trapped behind a sub-lobar ball-valve obstruction may pass into neighbouring lung, thus reducing or preventing the overinflation in the region of the obstructions. On the other hand, if a distal blow-up follows too quickly on the blocking of even a first or second division of a lobar bronchus, the overinflation may then, perhaps, by compressing adjacent lung, prevent the effective operation of collateral air-drift.

"Ball-valve" Obstructions

The luminal narrowing which gives rise to a ball-valve obstruction may be caused by:

(*a*) an intraluminal object—e.g. a foreign body (particularly in children) or a tumour such as a pedunculated adenoma;
(*b*) disease of the bronchial wall causing stenosis—e.g. tuberculosis, the most common inflammatory cause. Commonly the bronchial wall is infected from a nearby caseous node;
(*c*) extramural pressure on the bronchus—e.g. inflammatory enlargement of lymph nodes, particularly in childhood, tuberculosis again being a common cause. Measles and whooping cough may act in a similar manner. Rarely the glandular enlargement is neoplastic. Congenital vascular anomalies also have been shown to be associated with a ball-valve effect (see p. 96).

It may here be mentioned that in idiopathic infantile emphysema a lobe or part of one behaves as if a ball-valve obstruction were present; whether the reason is an inherent defect in a large or small bronchus or in alveoli is not known.

Pathogenesis

Ball-valve emphysema is overinflation with air-trapping, which latter carries far-reaching implications for blood flow (see p. 127).

The minute blood flow to the lobe is chiefly dependent on ventilation; obstructive emphysema will reduce it considerably. Total blood volume in the lobe is similarly reduced, especially in the region of the alveolar capillary bed, which fills principally on expiration (Riley, 1959). Inspiration draws blood into arteries and arterioles but it is during expiration that the capillary bed receives its main flow. As in obstructive emphysema the pressure within the alveoli is increased and the expiratory phase absent or diminished; the alveolar capillary filling is likely to be impeded. The greater the overinflation the greater is the stretching both of the capillary web in the alveolar walls and of the small blood vessels.

The cases illustrated in Figs. 34 to 38 show that with bronchial ball-valve obstruction and air-trapping the transradiancy increases out of proportion to the increase in the lung volume which suggests that reduction in blood in the lobe may be the most important single factor in bringing about transradiancy.

To judge from resected specimens, great overinflation can occur in childhood emphysema without tearing, but if overinflation were prolonged it might well lead to atrophy of the capillary bed and alveolar wall. In granulation tissue absence of flow through a capillary for twenty-four hours results in the disappearance of the capillary (Sandison, 1928); it is not known if this applies to the normal capillaries of other organs, but

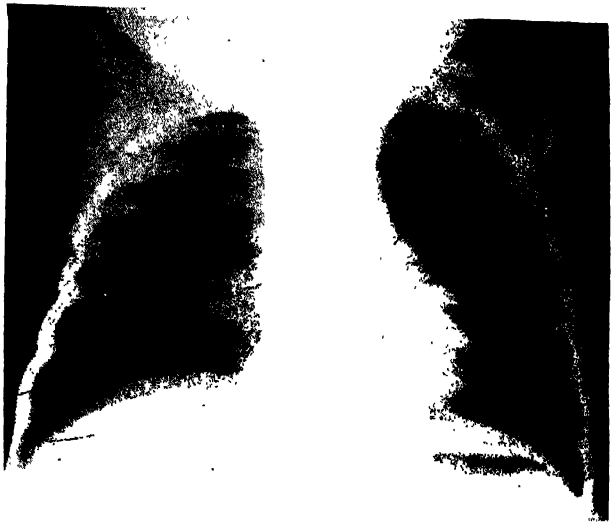


FIG. 34.—Case 4. Primary tuberculosis. Opacity to right of superior vena cava. Lung transradiancy normal. Child, aged 1½ years. See also Figs. 35 and 36.

FIG. 35.—Case 4. Radiograph five months later than Fig. 34. Hypertransradiant right lung without displacement of heart or trachea, suggesting the cause is reduction in blood, not increase in air. Inspiration-expiration radiographs showed air-trapping in right lung. At thoracotomy caseous lymph nodes pressed on the bronchus but were not related to the artery. See also Figs. 34 and 36.

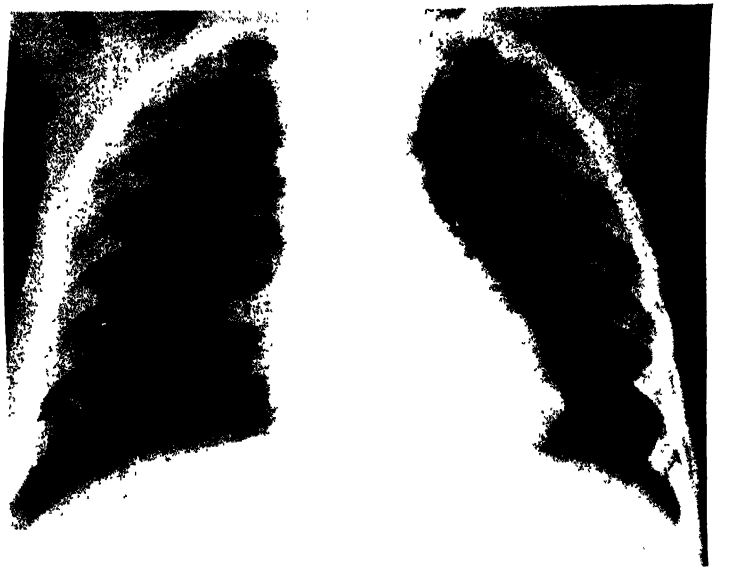


FIG. 36.—Case 4. One month post-operatively. Transradiancy of right lung virtually normal. See also Figs. 34 and 35.

it poses the question of long-term damage to alveolar walls where there is chronic overinflation and air-trapping.

Long-term damage to lobes.—After removal of the obstruction the overinflation rapidly disappears and the radiographic appearances may return to normal. The scarcity of long-term radiographic or respiratory function follow-up studies in cases such as these rather suggests that the lobe has come to no harm. In the two cases illustrated in Figs. 34 to 38 the narrowing of blood vessels was largely reversible and the radiograph returned to normal.

If a ball-valve obstruction develops in a child before lung growth is complete, and persists, it is probable that hypoplasia will supervene to bring about an irreversible emphysema as follows an occlusive lesion (see p. 126).

Function Disturbance

Disability probably stems from two main disturbances—the shift and compression of the heart and great vessels and the relaxation or compression of adjacent normal lung. The larger volume assumed by the overinflated lung leaves less space to the normal or residual lung, which then operates under a mechanical disability; even on full inspiration the normal lobes may be greatly below their normal volume and nearer to the size at which airways normally collapse. The function of the lung under a pneumothorax is similar; both ventilation and blood flow are reduced. The impaired ventilation may be followed by interference with venous

return arising from mechanical obstruction to the veins due either to distortion of the great vessels or to the increased pressure around them.

Comment

As the cause of obstruction is usually curable and the lung change reversible, pathological material is rarely available for detailed examination, but the radiograph and animal experiments permit certain deductions to be made.

Hypertransradiancy results from both overinflation and reduced blood flow and if the overinflation is considerable, the excessive air is the more important factor. Bronchial ball-valve obstruction and air-trapping produces increased transradiancy out of proportion both to the increase in lung volume and to decreased vascular markings. This suggests that reduction in blood volume is mainly responsible for the transradiancy, as the following cases indicate:

Case 4.—Obstruction in Childhood from Tuberculous Lymph Node

A child was seen by a physician because his mother had pulmonary tuberculosis; his radiograph showed enlarged lymph nodes but the transradiancy was the same on both sides (Fig. 34). A subsequent radiograph (Fig. 35) disclosed increased transradiancy of the right lung with a reduction in size of the vascular shadows and no detectable displacement of the heart and trachea. After removal of the enlarged hilar nodes, which relieved the pressure on the right main bronchus, the hypertransradiancy decreased and this together with the vascular shadows became almost the same as those in the other lung (Fig. 36). As there was no evidence at operation that lymph nodes were compressing the pulmonary artery and thus contributing directly to the vascular change, it would seem that the latter was secondary to the reduction in ventilation resulting from bronchial obstruction.

Case 5.—Obstruction in Childhood from Adenoma

A girl aged 11 years in 1963 had had a cough for 8 years and for 2 to 3 years had complained of slight sputum production and wheezing, these being worse in the winter. The left side of the chest was flat, moved poorly compared with the right and a wheeze was heard.

A radiograph taken in 1957 was normal, the blood vessels being equal on the two sides. In 1963 another radiograph (Fig. 37) showed a transradiant left lung with small vessels, particularly in the upper zone; the diaphragm was at a normal level and moved rather more than 1 cm. on the right and rather less on the left; the heart and trachea were in normal position. On expiration the diaphragm movement was poor on both sides. The main pulmonary artery was normal, the left pulmonary artery and the left hilar and mid-lung vessels smaller than on the right. Tomograms revealed that the left lower lobe arteries were not as small as the upper.

Bronchoscopy disclosed an oedematous polyp which acted as a ball-valve and completely blocked the left main stem bronchus. The mass, which proved to be a carcinoid adenoma, was removed through an incision in the posterior part of the main bronchus. Nothing abnormal was noted in the left pulmonary artery. Within a few months of operation the radiograph was normal and the hypertransradiancy of the left lung had disappeared (Fig. 38); and the blood vessels were the same on both sides.

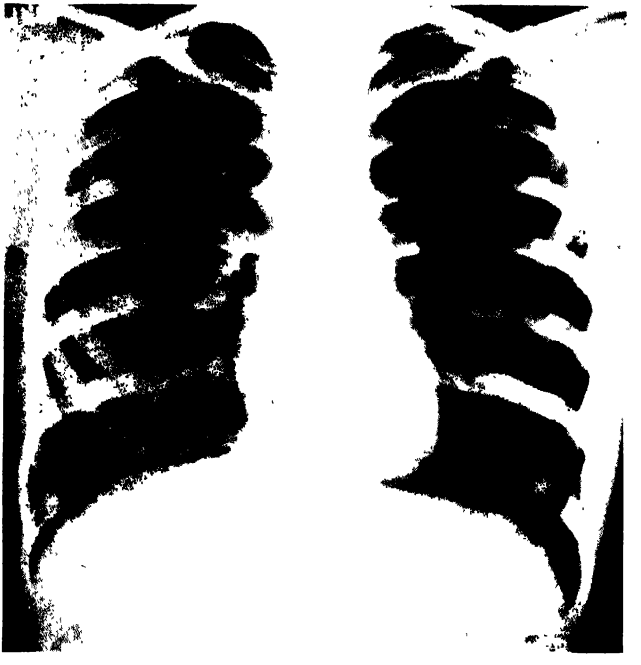


FIG. 37.—Case 5. Pre-operative radiograph. Hypertransradiant left lung, particularly upper lobe. Narrow blood vessels without displacement of heart or trachea suggest the probable cause of hypertransradiancy is reduction in blood not increase in air. At thoracotomy adenoma obstructing left upper and to a lesser extent left main bronchus and not related to pulmonary artery.

CASE 6.—OBSTRUCTION IN ADULT FROM ADENOMA

A woman aged 44 presented with a history of frothy sputum up to 2 ounces a day for one year and of wheezing for seven months. Bronchoscopy revealed a mass occupying most of the crescent of the right upper lobe bronchus and encroaching on the right main bronchus.

The radiograph showed that the right dome of the diaphragm and the horizontal fissure were depressed. As the patient was rotated the real position of the heart and trachea could not be assessed. In the right upper lobe the vessels were narrowed and those at its hilum were small.

When the chest was opened the upper lobe did not collapse, indicating that air was trapped in it. The mass, an adenoma, was removed through the posterior wall of the bronchus.

Within a few weeks of operation the fissure was back to its normal position and the upper lobe vessels were larger and normal, being the same on both sides.

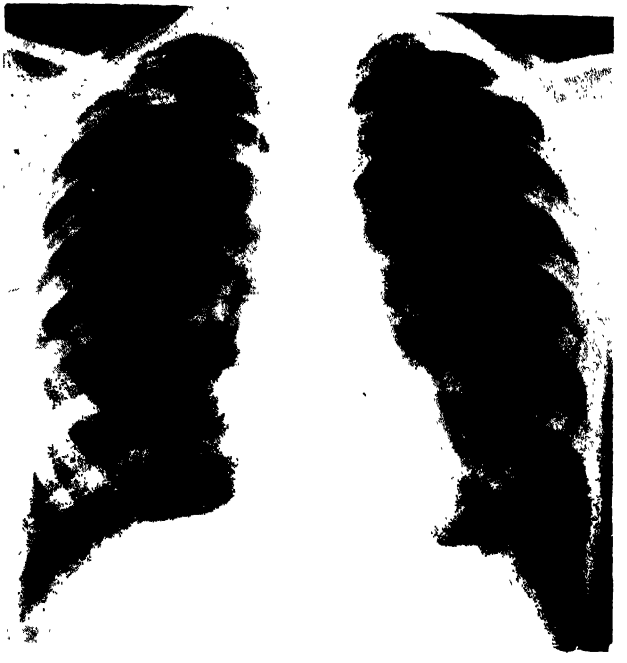


FIG. 38.—Case 5. Radiograph, a few months after removal of adenoma. Transradiancy of left lung, now virtually normal. Lung vessels larger. See also Fig. 37.

Comment

These cases illustrate the following points:

Transradiancy may occur with little change in lung volume, suggesting that it derives from decrease in blood rather than from an increase in air. The hilar vessels are small, the axial vessels within the transradiant lobe are narrower, and fewer side branches can be seen. As these changes are reversible when the obstruction is removed, it seems that narrowing arises from a functional change in the vessels. The narrowing may be true active vasoconstriction or the radiographic diameter of the artery may reflect the reduced blood flow during the time of exposure. Blood flow through the artery is the key factor. If the flow is decreased the artery may appear narrower because of decreased pulsation.

The next point is whether the local vasoconstriction is secondary to local anoxia or results from the mechanical effects of air-trapping. Although there is a relatively small change in volume the minute blood flow to the lobe is reduced. Anoxic alveoli may produce vasoconstriction of proximal vessels, either through a nervous reflex or a humoral mediator; but the

change in diameter may spread proximally from the dilated alveoli along the vascular smooth muscle (Hilton, 1962) until it involves the vessels at the hilum.

Hilton (1959) suggested that in the systemic arteries the conducting elements for vasodilatation after peripheral muscular contraction are situated in the media of the artery and are not nervous. In man, as well as in vertebrates, there is evidence, in the systemic arteries, of a peripherally maintained conduction system in the walls of blood vessels which can be actuated by a variety of stimuli. There is no reason why this should not apply to the pulmonary arteries also, although as yet this has not been established.

Comparison with Compensatory Emphysema

Though in some respects ball-valve emphysema resembles compensatory emphysema the latter is yet fundamentally different in that it is overinflation without air-trapping, the airways being normally patent. Accordingly, the blood flow to the lobe and to the alveolar capillaries is more or less normal. By contrast, in ball-valve emphysema these are reduced and the lung is oligemic.

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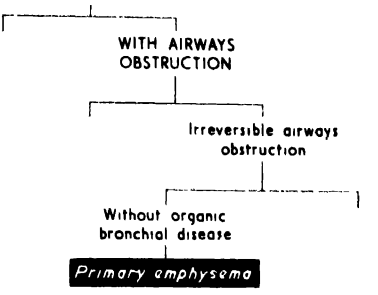
Chapter VIII

PRIMARY EMPHYSEMA

(Essential Emphysema; Idiopathic Emphysema)



THE TERM "primary (or essential or idiopathic) emphysema" describes the condition of widespread emphysema or alveolectasis which has developed from some unknown cause and is unaccompanied by structural airways disease or chronic bronchitis. Being widespread it may prove fatal. Occasionally the same pathological type of emphysema may be encountered in a localised form—affecting a single lobe as in a resected "bulla".

The condition may be present with chronic bronchitis, without having either caused it or been caused by it. Particularly in this country, however, where cough and sputum are common, it is likely that primary emphysema is often designated "chronic bronchitis with emphysema" (see p. 84), while for instance in Australia, where sputum production is not as common, the cases of primary emphysema are more numerous, as witness the large series of cases reported by Fitts in 1958.

An interesting feature of this type of emphysema is that there is airways obstruction deriving, it would seem, from the alveolar change alone, whereas in chronic bronchitis and emphysema it is difficult to assess the individual contributions of the airways and of the alveoli.

Primary emphysema affects women as often as men, in striking contrast to "chronic bronchitis and emphysema" which predominantly affects males. Primary emphysema is often found in relatively young people, especially those in the 30's and 40's (Fitts, 1958). Of cases of chronic bronchitis or emphysema seen personally, probably less than 6 per cent have fallen within this group of primary emphysema (Reid, 1962).

Pathological material from six cases has been personally studied, selected because there was no previous history of cough and sputum. The thickness of bronchial mucous glands was measured to eliminate cases of

mucous gland hypertrophy and, therefore, chronic bronchitis (Reid, 1960). Additionally, five living patients were studied, in whom the diagnosis of primary emphysema was based on clinical features, radiographic appearance and respiratory function tests, but from whom no pathological material was available.

Clinical Features

The usual symptom of primary emphysema is shortness of breath, which may present at a comparatively young age. Patients are often athletic and have enjoyed excellent health until shortness of breath supervenes on exertion (Fitts, 1958). It may come on suddenly but is often insidious and a patient may only seek advice when he has become seriously disabled. Shortness of breath in a patient who is hyperventilating, but is not producing sputum, often results in the diagnosis of psychosomatic dyspnoea. Case 17 presents many of the features typical of this disease.

Acute infection or spontaneous pneumothorax may cause a great increase in dyspnoea.

If there is cough it is usually of an irritating nature but non-productive. Although a small amount of sputum may be produced months or even years after the onset of dyspnoea, the patient on presenting might well be diagnosed as "chronic bronchitis and emphysema," although a careful history might point to primary emphysema with mild chronic bronchitis of later onset (e.g. Case 17).

Radiology

The radiographic features of primary emphysema are illustrated in Figs. 39, 40, and 41 and are those of widespread emphysema described on page 276. They include (*a*) a low flat diaphragm with poor movement and a large retrosternal translucent area; (*b*) a narrow vertical heart and large hilar vessels with small mid-lung vessels; and additionally (*c*) localised areas of hypertransradiancy not necessarily clearly demarcated, with few or no vessels and indicating a bullous region. Of the eleven cases studied radiographically there was localised accentuation at both bases in five, in the upper zones alone in one, and at both apices and bases in four.

In several of the patients an upper or lower zone appeared to have abnormally large vessels (Fig. 40). In one patient this was particularly marked at the apices, and in another in one of the mid-zones. This appearance of regional plethora in the lungs was in striking contrast to what is seen in cases of chronic bronchitis where it is often more local, an occasional vessel appearing enlarged (Simon, 1964).

Pathology

The lungs in the six cases studied pathologically were large and bulky and did not deflate easily (Fig. 42). Several of the cases had been operated upon for removal of bullae and the anaesthetist had reported that the

lungs were easier to inflate than those commonly found in chronic bronchitis with emphysema, but that deflation was incomplete and slower than in the normal. These changes indicate air-trapping.

Slicing the lung disclosed a loss of substance, manifested by an increase in the size of the air spaces and by retraction of the alveoli below the airways and vessels on the cut surface (Fig. 43). In the cases which had proved fatal all lobes were usually affected, but the severity of the change was not uniform. The airways were usually free of secretion.

The emphysema was panacinar and its severity was at least Grade III through most of the lung, with some areas of Grade IV.

Often a lobe is uniformly affected by emphysema but bullae, sometimes large, are not uncommon. Bullae were sometimes empty of alveolar remnants, being a sac of air with a base of lung showing panacinar emphysema of Grade III or IV severity. In other bullae the lung architecture was still recognisable. The bullae are characteristically of Type II and Type III (see p. 212), both of which have a broad base in relation to their size; but occasionally they are of Type I.

FIG. 39.—Case 7. Primary emphysema. Low flat diaphragm, large hilar shadows, small mid-lung vessels, avascular area in right upper zone. Insidious onset and progression of shortness of breath over years. At autopsy panacinar emphysema Grade III or IV throughout both lungs.

In many cases, unless the lungs were inflated, the pathologist might easily miss the presence of primary emphysema as there are no such "holes" in the lung as in centriacinar emphysema. Even if inflated, the lung, on cutting, may collapse and present a surprisingly intact appearance.

FIG. 40.—Case 8. Chronic bronchitis and probably primary emphysema. Low flat diaphragm, large hilar and small mid-lung vessels, except for left mid-zone where lung vessels are normal. See also Figs. 41, 42 and 45.

Microscopic examination.—*The bronchi.*—The bronchi of the six cases showed no signs of inflammation or fibrosis. As stated previously the mucous glands were examined for evidence of hypertrophy, pointing to chronic bronchitis, but the acinar count was normal. In one case, the gland wall ratio showed a minor degree of hypertrophy but, in view of the acinar count, was considered normal. In these cases of primary emphysema the hypertrophy of mucous glands seen in chronic bronchitis was absent.

Cartilage.—The size and shape of the plates of cartilage in normal hilar bronchi vary greatly. The six cases were no exception. In most, the cartilage plates were clearly within the normal range but in the case reported on page 84 the main bronchi seemed hypoplastic in that the out-

FIG. 41.—Case 8. Lateral radiograph. Low flat diaphragm, large retrosternal transradiancy. See also Figs. 40, 42 and 45.

FIG. 42.—Case 8. Specimen illustrating air trapping in the left upper lobe (seen from medial aspect), deflation in apical region of lower lobe but basal region is grossly emphysematous. See also Figs. 40, 41 and 45.

line of the airways lumen was almond, rather than horse-shoe, shaped. Whether this indicated an overall defect in lung development or whether it was coincidental cannot be said. It has been suggested that this hypoplasia might lead to excessive bronchial collapsibility and thereby cause the alveolar change of emphysema but, as in most cases the cartilage clearly seemed normal, this hypothesis would appear untenable. (For further discussion of the significance of cartilage see p. 177.)

FIG. 43.—Panacinar emphysema Grades III (A) and IV (B) as in Case 8. Left upper lobe. Lung slice 1 cm. thick; at B the light is showing through ragged lung.

Bronchioli.—The peripheral airways also seemed normal. Small bronchi and bronchioli showed no increase in goblet cells and there were no fibrotic lesions pointing to previous inflammatory damage.

Alveoli.—The alveoli were abnormally large and their walls too thin (Fig. 44), and there were too few capillaries. The profile of the alveoli in microscopic section was too smooth. The number of elastic fibres per length of wall was below normal.

Alveolar diameter in two normal lungs was assessed by measuring the diameter of the largest alveolus in each of eight fields; the mean of the sixteen measurements was 2·6 units. Similar measurements were taken in three lungs with primary emphysema from mildly affected regions and the mean alveolar diameter for each case was 4·4, 5·6, 5·25 units. Thus in these three cases of primary emphysema the average alveolar diameter was rather more than twice the normal, which means a roughly eightfold increase in volume; this suggests that there may be a considerable reduction in the

number of alveoli, perhaps only an eighth of the normal number remaining in those regions most severely affected. Since scarring or collapse is not a feature of this type of emphysema, compensatory overinflation of residual lung is not significant.

The mean thickness of the emphysematous alveolar wall was usually less than one unit, compared with one to two units in the normal. Even the capillary wall that persists shows a loss of capillaries.

In summary, the lungs in primary emphysema show air-trapping and alveolectasis of a severe degree, which is panacinar in its distribution and is associated with an essentially normal and patent bronchial tree.

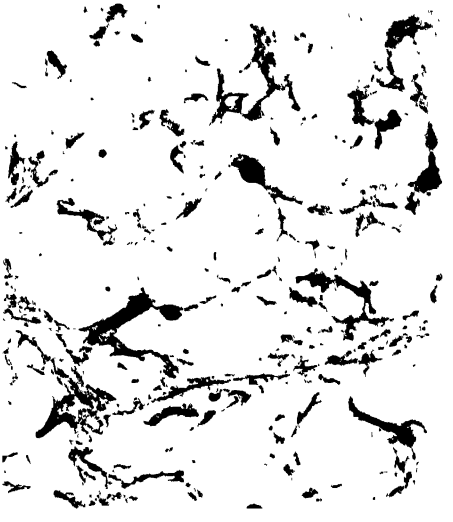


FIG. 44.—Photomicrograph of panacinar emphysema Grade III. (× 4.)

Pulmonary Arteriogram

In primary emphysema, unless there is pulmonary hypertension, the large pulmonary arteries are normal; and there is no abnormal cross filling to bronchial arteries. Within the acinus there is a reduction in the number of pulmonary artery branches (Fig. 45). In a case of primary emphysema (panacinar, Grade III) counts of the side branches (Millard, 1964) arising from axial pulmonary arteries between the hilum and a point 5 mm. from the pleura showed no significant reduction. However, in thin slices of lung or at the thin edge when the lung is only one or two lobules thick, a reduction in the fine intra-acinar pattern was evident (Fig. 45). As the alveolar duct arteries are reduced and even those with respiratory bronchioli, arteries as large as 500 μ may be lost (see p. 353). This over-all reduction in the pulmonary artery bed means that the central vessels stand out more distinctly in the arteriogram, there being less radio-opaque injection medium in the encasing lungs.

The opening of anastomoses between adjacent pulmonary arteries may be seen in this type of emphysema. Vessels of 1–2 mm. in diameter may form an interlacing mesh.

PATHOGENESIS

This type of emphysema is in striking contrast to that associated with chronic bronchitis, in that women are as often affected as men and it

is rather a young person's disease. This points to different causes. The absence of childhood infection or of previous inflammatory damage and the disease's distribution throughout a lobe or lung, point to an intrinsic deficiency in the alveolar wall. This is unlikely to be congenital, however, since alveolar development is mainly postnatal, whereas it is likely that adolescent lung growth is mainly in blood vessels (see also p. 127).

In the series of eleven cases there was no evidence and little likelihood of any familial incidence of primary emphysema. Further, if the alveoli were abnormal at birth it is improbable that childhood development would be normal. What is not clear is whether primary emphysema represents

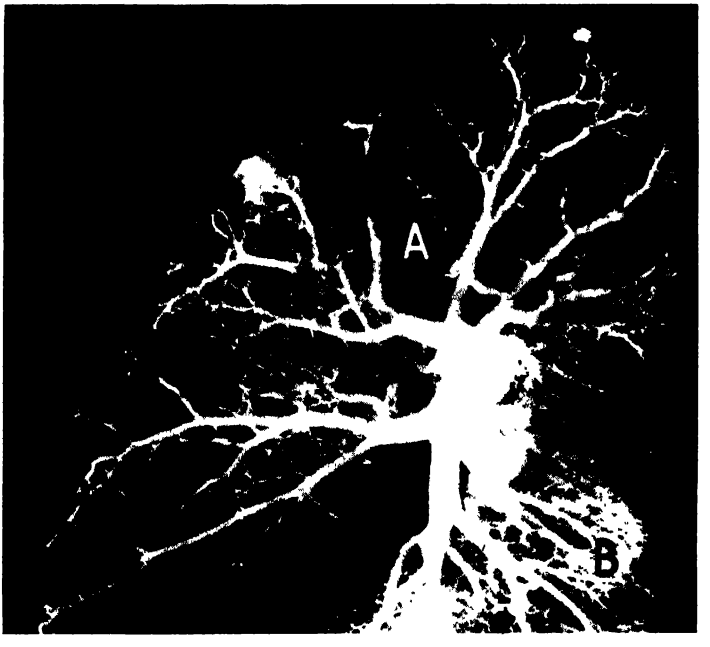


FIG. 45.—Case 8. Specimen arteriogram of left lung, showing reduction in peripheral side branches in region A, with normal pattern in region B (apical lower) corresponding to normal vessels in the radiograph. See also Figs. 40, 41 and 42.

an atrophy of lung normally developed or failure of adolescent development. The considerable reduction in the number of alveoli which can be deduced from the increase in alveolar size may point to incomplete childhood growth. That the condition has not been reported in childhood or early adulthood suggests that it develops later after normal lung development.

It would seem, then, that the basic change is atrophy of the alveolar wall and the capillary bed. It is not known whether both result from the same cause or whether either causes the other.

Air-trapping

Air-trapping or airways obstruction in primary emphysema would seem to be secondary to the alveolar change. Dayman (1951) suggests that collapse of the bronchial tree—and consequently air-trapping—occurs in the normal subject at the end of deep expiration, although it is not known at what level of the bronchial tree this happens. In primary emphysema bronchial collapse may occur prematurely since, without excess of bronchial mucus or organic obliteration, the functional effect of airways obstruction is present. Airways collapse in this disease probably derives from structural alveolar change.

Patency of the normal bronchial tree depends on anatomical integrity, which may be interfered with by ulceration or tearing of alveoli or by weakening or atrophy of alveolar walls. Airways without alveolar connections float free, resembling a flap valve (Reid, 1958); alveolar recoil on expiration is weakened by atrophy, the airways achieving a given state of collapse in the expiratory phase more quickly than in the normal (Dayman 1951). It is submitted that in primary emphysema the bronchial tree closes prematurely, the abnormally large air spaces allowing such excessive relaxation. It was suggested that the minor changes in respiratory function sometimes seen in periacinar emphysema can be similarly explained (see p. 35).

A recurrently discussed theory of causation of emphysema hinges on this functional disturbance—whether the airways obstruction (i.e. the bronchial tree collapse) is the primary change and the alveolar overdistension and atrophy a secondary one, or vice versa? That airways obstruction by itself causes irreversible widespread emphysema is not acceptable; in asthma and in chronic bronchitis it can be present for years without disturbance to the alveoli. Not only this, but the emphysema associated with ball-valve obstruction is reversible. Thus the basic change would seem to be an atrophy of the alveolar wall, including its capillary bed, this, in its turn giving rise to the respiratory disturbance characteristic of emphysema, particularly to the ventilatory disturbance associated with trapping of air. The changes may be widespread or localised.

Respiratory Function Tests

In primary emphysema respiratory function studies show evidence of airways obstruction; air is trapped in the lungs and both residual and total lung volumes are increased (see results in Case 17).

Blood gas disturbance would seem to occur relatively late in the disease and it may be that the lung, even if underventilated overall, is more uniformly ventilated. The greater ease with which collateral airdrift occurs in an atrophic lung may contribute to this.

Association with Chronic Bronchitis

Primary emphysema is probably often misdiagnosed. If a patient is absolutely free of sputum the correct diagnosis may be made but, if small amounts of sputum are produced, "chronic bronchitis" is probably diagnosed, in the United Kingdom at any rate. In the United States it would seem that the reverse more often happens, the diagnosis of emphysema being made without mention of chronic bronchitis, even if cough and sputum have been present for many years.

There are cases of emphysema and chronic bronchitis in which the severity of the former is much greater than that of the latter. The history of shortness of breath may considerably antedate that of cough and sputum, and there may be no infection to explain the development of the emphysema; these suggest that the emphysema is primary. The clinical diagnosis of primary emphysema must rely heavily on the radiograph, as function studies can be confused by causes of airways obstruction other than emphysema.

Association with Right Ventricular Hypertrophy

There was evidence of increased pulmonary vascular resistance in several of the present series. In two patients the heart was available for examination; in one, a woman, no right ventricular hypertrophy was present; in the other, a man, it was of mild degree (R.V. 82·5; L.V. 117·5; Ratio 1·42—Normal 2·3–3·3) and it was detected in the electrocardiograph. Of three other cases an electrocardiograph was available and two showed right ventricular hypertrophy (Millard, 1965).

Thus right ventricular hypertrophy is found in cases of primary emphysema, but if this type behaves as the emphysema associated with chronic bronchitis it is unlikely that severe degrees of right ventricular hypertrophy occur (see p. 244). Fitts (1958) found in his series that evidence of cardiac failure was not as common in primary emphysema as in emphysema associated with chronic bronchitis, which may explain the suggestion of Fletcher and his colleagues (1963) that emphysema did not cause right ventricular hypertrophy. (For further discussion see page 255.)

Case 7.—Primary Emphysema

The patient was fit in 1940 and passed category A1 into the Army, to become a Commando. In 1942, at the age of 23, he noticed, on extreme exercise, shortness of breath, perhaps greater than his companions experienced, and he had three or four "black-outs". Careful physical examination, including lung function studies, revealed no cause. It was thought that he was malingering and so he returned to active operation, taking part in the campaigns in Italy and Sicily. He managed to continue until 1944. He was then re-examined and interviewed by Boards and downgraded. Shortly afterwards he had an appendectomy complicated by post-operative pneu-

monia on the left side. He recovered from this and resumed non-combatant duties till discharged in 1945.

He became a fireman and for two years (1945–7) managed to perform his duties, but found that on severe exertion (running and climbing ladders) he was again very breathless, so he changed over to being a sales representative. This lighter occupation was well within his capability till he was 31 (1950), when he again began to be short of breath. This condition became worse and he was away from his work for increasingly long periods. Between the age of 33 and 39 the dyspnoea slowly progressed until he was confined to the house. He had no sputum or cough and had never noticed wheezing.

Respiratory Function Tests

	1956	*1957*	*1958*	*1959 (pre-operative day)*
VC	2330 ml.	1600 ml.		
FVC			760 ml.	
MBC	16 l./min.			
Inspiratory capacity	1440 ml.			
Expiratory reserve	790 ml.			
FRC	8200 ml.			
RC	7410 ml.			
TLC	9640 ml.			
RC/TLC × 100	77%			
Mixing efficiency	63%			
Poorly ventilated space	3710 ml.			
FEV_1			315 ml.	
$\frac{FEV_1}{FVC}$		55%	41%	85%
O_2 saturation		85%		
CO_2 content		60 vols.%		
pH		7·23		7·311
Po_2				55 mm.Hg
Pco_2				84 mm.Hg

In 1957 after a pneumothorax the patient was found to be cyanosed; a further year after this he presented with a raised jugular venous pressure and swelling of the ankles.

The first radiograph in 1955 showed that the diaphragm was low and flat and between the sixth and seventh rib; the transverse diameter of the heart was 10·5 cm. and the transhilar measurement 11·5 cm. (normal). The main trunk of the pulmonary artery and its branches at the hila appeared large while the vessels within the lung were narrow. In both upper zones there were avascular areas not demarcated by line shadows. The diagnosis was widespread emphysema with localised accentuation. There was virtually no change in the radiographs over the next four years (Fig. 39).

The electrocardiograph in 1958 showed a sinus rhythm and a low voltage tracing; the frontal plane mean QRS axis was −90°. (Millard, 1965, has taken more than +90° to indicate right ventricular hypertrophy.)

In 1959 he was readmitted cyanosed, with no oedema and no elevation

of jugular venous pressure; there was slight finger clubbing. His oxygen saturation was 85 per cent, Po_2 55 mm.Hg, Pco_2 84 mm Hg and pH 7·3. The radiograph showed that the transradiancy and avascularity in the right upper zone had extended.

At right thoracotomy (1959) the pleural cavity was free apart from a few fibrinous adhesions over the right lower lobe. There was a huge bulla under tension, some 20 cm. in diameter and filling the whole of the upper chest. It arose from the antero-lateral aspect of the right upper lobe. Another bulla 10 cm. in diameter arose from the apical lower segment with numerous smaller bullae up to 2·5 cm. in diameter over the right upper and middle lobes.

When the large bulla was incised immediate improvement in the ventilatory capacity occurred. The bulla was mainly empty of tissue although at its base were flimsy remnants of lung. The two bullae were oversewn and although the residual lung occupied more space than it had before the operation it did not inflate to fill all the chest.

A tracheostomy was performed and the patient was maintained on the Blease respirator. Two days post-operatively cardiac arrest occurred which was corrected by open-heart massage, but on the tenth post-operative day he died.

At autopsy all the lobes showed panacinar emphysema, in the upper and middle lobes, mainly Grade IV, while the lower lobes, though Grade III, were not quite as atrophied as the upper lobes. The membranous part of the right main bronchus was wider than that of the left as the cartilage plates were less curved. At operation the surgeon commented that it felt flaccid. The left ventricle weighed 117·5 grams, the right 82·5 grams, giving a ratio LV/RV of 1·4. Both the weight of the venticle and the ratio point to right ventricular hypertrophy.

Case 8.—Primary Emphysema with Chronic Bronchitis

In this case the history of cough and sputum for eight years justified the diagnosis of chronic bronchitis, but the shortness of breath which persisted, and even worsened when the sputum decreased, suggested that emphysema was the main cause of the disability. The emphysema being only panacinar without scars or alveolar ulceration, chronic bronchitis could not clearly be blamed, which suggests that the patient had a severe degree of primary emphysema (a rare condition) with a mild degree of chronic bronchitis (a common condition). A history of childhood infection prompts the question whether lung development was impaired during adolescence, but although in cases such as this hypoplasia may be a factor, it cannot explain all cases of primary emphysema.

At the age of 55 (1962) this patient was admitted to hospital with the history of eight years' shortness of breath. He had had more or less continuous cough and sputum from an attack of pneumonia at the age of 10, until five years previously. He then gave up smoking the 30 to 40 cigarettes which had been his daily consumption, and this produced a dramatic reduction in his sputum though his shortness of breath persisted. It gradually became worse until he was forced to retire at the age of 54 from his job as an administrative

engineer. On admission he had a troublesome cough but with no more than a trace of mucoid sputum. After climbing seven stairs he was short of breath. He reported that his ankles occasionally swelled and that he was 3½ stone lighter than ten years previously. He was short of breath at rest. His blood pressure was 180/110; no peripheral oedema was detected. His lung function studies revealed:

Respiratory Function Tests

FVC	2400 ml.
FEV_1	600 ml.
$\frac{FEV_1}{FVC}$	25%
MVV	23·1 l./min.
PEF	125 l./min.
V.C.	2300 ml.

Dco at rest: 4·5 ml./min./mm.Hg (Minute Ventilation 12·4 l./min.)
Dco on exercise: 6·3 ml./min./mm.Hg (Minute Ventilation 19·6 l./min.)
Percentage extraction 19·1.

His chest radiograph showed evidence of widespread emphysema (Fig. 40). The diaphragm was seen to be between the 6th and 7th rib and had a low flat configuration, the heart was 11·5 cm. in transverse diameter and had a narrow vertical configuration. The hilar arteries were large, and the vessels within the lungs were small. All regions of both lungs were avascular except for the left apical lower lobe which was well vascularised in the lateral view (Fig. 41). The radiograph remained unchanged until the patient's death in 1964 save that the diameter of his heart had increased to 14 cm.

He had improved during his stay in hospital but had to be readmitted in 1964 when he died.

In 1962 the electrocardiograph showed left axis deviation of −30°; by 1964 this had increased to −90°. His haemoglobin was never more than 112 per cent of the normal. His sputum during his final admission was 25 grams/day and his peak flow 155 litres/minute.

At autopsy the immediate cause of death was found to be a retroperitoneal haemorrhage associated with a perforation of the ileum; the hepatic flexures of the colon and ileum were adherent to each other.

The coronary arteries were patent and the right ventricle dilated. The weight of the left ventricle was 140·5 grams, of the right 40 grams, with a LV/RV ratio of 3·6 (i.e. no right ventricular hypertrophy). On naked-eye examination there was no clear evidence of cardiac ischaemia but microscopic sections revealed a mild and patchy fibrosis.

The lungs were pale and bulky.

The right pulmonary artery was injected and the lung fixed by formalin vapour (Figs. 42 and 43). The lung distended greatly at the pressure used (40 mm.Hg) and when it was released the volume was maintained save for that of the apical lower lobe, which deflated normally to give a waist between the greatly overinflated upper lobe and basal regions of the lower lobe. The latter gradually deflated but the upper lobe remained overinflated.

The arteriogram in Fig. 45 was taken after the apical lower lobe had deflated and shows reduction of side branches from the axial pathways of the pulmonary artery in all regions save the apical lower lobe and the inferior part of the posterior segment of the upper lobe. The reduction is greatest distally but can be detected even over the proximal half. Even making allowance for the stretching of the emphysematous region, narrowing of some of the axial pathways reaches close to the hilum.

On cutting the lung, panacinar emphysema, Grades III and IV, was found to be present throughout; only in the apical region of the lower lobe was it not as severe.

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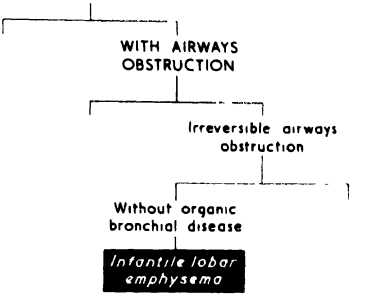
Chapter IX

INFANTILE LOBAR EMPHYSEMA

(Congenital Lobar Emphysema; Congenital Obstructive Emphysema)



INFANTILE lobar emphysema may present a striking clinical picture as it may cause acute respiratory distress. It is a condition in which part of the lung becomes so grossly distended with air that it compresses the rest of the lung, perhaps displacing the heart so much that the functioning of the contralateral lung is also affected. The chest wall may bulge on the affected side. Knowledge of the pathogenesis of this type of emphysema is far from complete but it certainly includes several types; only rarely is it possible to deduce the cause. Its place in the classification can therefore only be provisional.

The condition may be present from birth, or arise within a few months after. Most reported cases (Cottom and Myers, 1957; Silver *et al.*, 1956; Bolande *et al.*, 1956; and Jewsbury, 1955) have presented with symptoms under six weeks of age and, in most, operation was urgently necessary. In other cases (relatively few of which are reported) the onset may be later, the course of the disease less acute, and operation can be postponed. Silver and his colleagues report a case under observation from soon after birth until one year eight months, when operation was performed; and a series of young children with clinical symptoms milder than those usually reported has been observed by Drew (1965) for several years without operation being necessary. The radiographs are similar to those of the more acute cases save that the overinflation is less.

Radiology

In the radiograph (Figs. 46 and 47) there is a large, hypertransradiant, completely avascular area occupying most of the left side and displacing

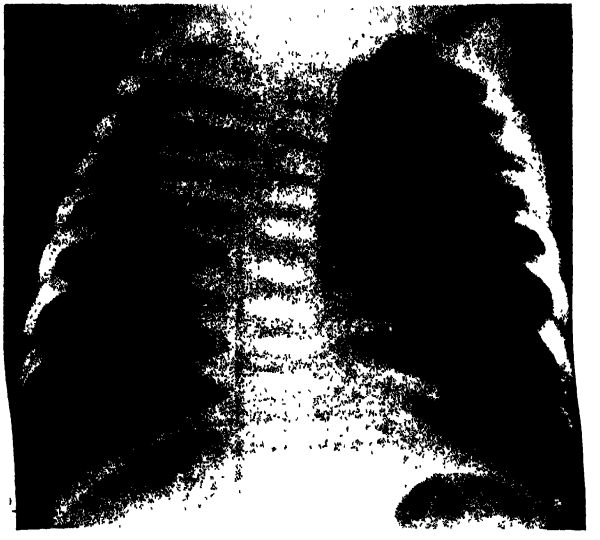


FIG. 46.—Case 10. Idiopathic emphysema of childhood. Left upper lobe. Hypertransradiant, avascular left hemithorax, heart and trachea displaced to right. Left lower lobe displaced medially and opaque (opposite arrow). Girl aged 3 months. See also Figs. 47, 48, 49 and 50.

the heart and trachea to the opposite side. In addition the diaphragm may be depressed and the rib spaces widened on the affected side; an affected lobe may occupy the whole of the hemithorax, compressing normal lung and rendering it invisible. The lobes commonly affected are the upper and the middle.

An angiogram carried out on a child (Case 12), in whom the symptoms were subacute, showed that the artery to the affected side was smaller than that to the opposite side, that flow was reduced, and that only the main arterial pathways were filled, no peripheral vessels being identifiable.

FIG. 47.—Case 10. Lateral radiograph. Transradiant avascular region lies in anterior half and is sharply demarcated by compressed lung posteriorly. See also Figs. 46, 48, 49 and 50.

Pathology

Distribution.—In cases of idiopathic infantile emphysema the distended part of the lung bulges into the wound at thoracotomy, the unaffected lung being compressed against the vertebrae. The lobe does not usually collapse at operation but its herniation out of the wound will result in the patient's immediate improvement. As the emphysema does not seem reversible the offending lobe has generally to be removed. Although when the chest is opened it would seem that the condition has a lobar distribution, eight cases of infantile emphysema personally studied (Table I) revealed either that the whole lobe is not affected or, if it is, that the change is not uniform in severity (Fig. 48).

TABLE I

INFANTILE LOBAR EMPHYSEMA

Case No.	*Age*	*Sex*	*Lobe Affected*	*Comment*
9	1 month	M	LUL RML	
10	3 months	F	LUL	
11	4 ,,	M	RML	
12	4½ ,,	M	LUL	Transradiancy without displacement—suggests decompression. Segmental lesion.
13	8 ,,	M	LUL	Associated rib anomaly.
14	10 ,,	M	LUL	LUL vein drains to superior vena cava.
15	16 ,,	M	RML	Hiatus hernia.
16	6 years	F	LUL	

In a child's lung a region of collapse or compression can be easily overlooked because, there being no coal pigment, the collapsed part is roughly the same colour as the rest. In the adult, on the other hand, condensation of carbon pigment would produce increased blackness. For example, the lingula if collapsed is little more than the size of a walnut tucked into the hilum, while the rest of the upper lobe may be a tense balloon more than large enough to fill the hemithorax.

A child of three months (Case 10) had acute symptoms and when the chest was opened the left upper lobe herniated through the wound. By the time this lobe reached the pathology laboratory the lingular and posterior regions had deflated (Fig. 48), but air remained trapped in the apical and anterior region. On inflation, the whole lobe increased excessively in volume but the apical and anterior regions bulged over neighbouring lung so much that an appearance of incomplete fissures was produced. A similar appearance was seen in a picture taken at operation. This suggests either that the initial disturbance was in the apical and anterior segments and that the other segments were only secondarily involved, or that if the "cause" operated throughout the lobe it was stronger in one

region. Even in Cases 9, 14, and 15, from which only microscopic sections were available (these fortunately represented large blocks of tissue), part of each of the sections was much more inflated than the rest.

In Case 12 the clinical features were less acute and only in the apical region of the left upper lobe was emphysema present. This case was strange, the radiograph showing a region of hypertransradiancy, without displacement of mediastinal structures or compression of neighbouring lung. No main interlobar fissure was found at operation, but only a shallow

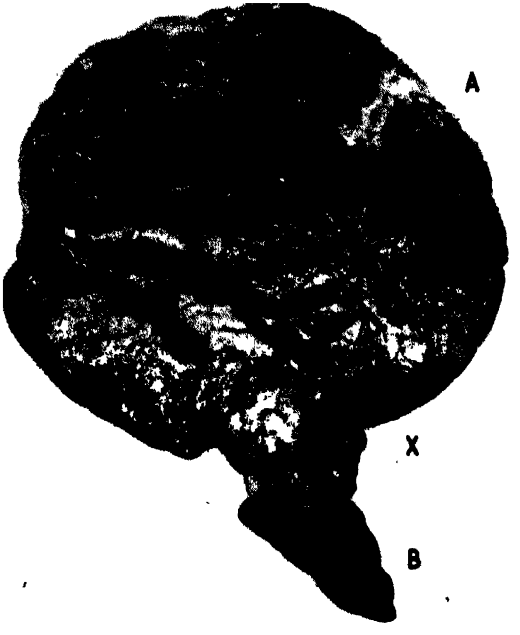


FIG. 48.—Case 10. Resected left upper lobe. At operation all regions were greatly distended. Spontaneous deflation least in apical region (A) simulating a fissure at X–X; the inferior region (B) deflated well. See also Figs. 46, 47, 49 and 50.

indentation from the diaphragmatic surface unrelated to the affected part of the lung. The emphysematous region was recognised by the size of the air spaces visible through the pleura; although the lobe was well aerated and the apical region tense, the latter was not elevated above the neighbouring pleura, the area of emphysema seeming to decompress itself into the adjacent lung. Although the segment as a whole was not enlarged the presence of enlarged air spaces in the apical region pointed to the emphysema having developed as the result of hypoplasia, and not from an increase in volume of this part of the lobe at the expense of neighbouring lung. Whether this region was already hypoplastic at birth cannot be said.

Alveoli.—The alveoli are emphysematous, very large and with extremely thin walls (Figs. 49 and 50). Although occasionally fibrosis of alveolar walls has been reported it is not usually seen in cases of idiopathic infantile emphysema. In Case 10, although the lingula deflated

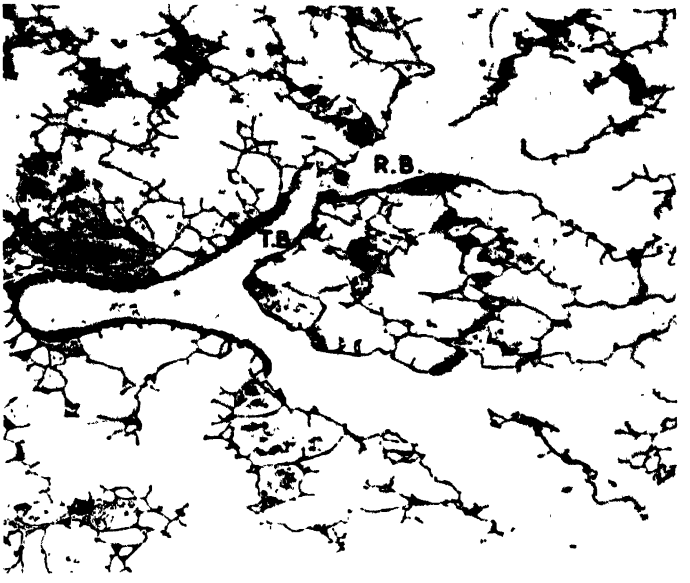


FIG. 49

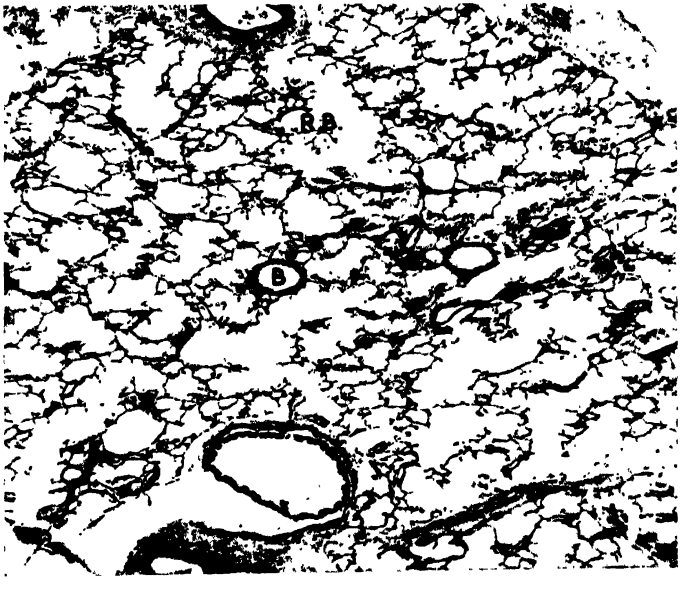


FIG. 50

FIGS. 49 and 50.—Case 170. Photomicrographs from regions A and B respectively in Fig. 48. The number of alveoli included gives an indication of the degree of dilation. T.B. Terminal bronchiolus. B. Bronchiolus (more proximal than T.B.). R.B. respiratory bronchiolus. Fig. 49 apical region. Scarcely the width of an acinus included. Fig. 50 several lobules included in the same area. See also Figs. 46, 47 and 48. (Both × 25.)

normally, the most affected region, the apical, did not and it would thus seem that the emphysema is irreversible. Whether this difference in behaviour reflects other, basic, differences in the lung or points to a time difference is not certain. While thinning of the alveolar walls is seen with sparse capillaries and elastic fibres it is not certain whether this loss is real or due to overinflation.

Pathogenesis

Mucous plug.—Whether or not plugging of bronchi with mucus contributes to idiopathic infantile emphysema is impossible so far to decide. In order not to interfere with the bronchus to the affected region, the surgeon in Case 9 cut the bronchus without clamping it. In its mouth was a piece of firm mucus, the size of a rice grain and of the same shape. The possibility that this may have contributed to the emphysema cannot be ruled out.

Functional bronchial obstruction.—In most cases idiopathic infantile emphysema resembles ball-valve emphysema although there is no organic block; and it would seem, therefore, that the obstruction is functional. In two cases (Cases 10 and 12) radio-opaque material allowed to run into the bronchus passed to the respiratory bronchiolar level.

Bronchial cartilage abnormality.—In this series of eight cases the cartilage in the bronchi to the affected region was examined in frequent sections and not by stripping the epithelium along the whole length of the bronchus. This was done by Hayward and Reid (1952) in describing the normal distribution of cartilage, and by Stovin (1959) in a case of infantile emphysema. In none of the cases was cartilage absent.

In Case 10 the plates of cartilage were of a rather queer shape, similar to the prolongations from the body of the cartilage plate described by Stovin, though only in the bronchus to the anterior segment where the emphysema was maximal and seemed irreversible. This might have had a bearing on the cause of the emphysema or it might have been the result of over-stretching the bronchus.

Cases are recorded where cartilage is missing from the affected region (e.g. Bolande *et al.*, 1956).

It is difficult to assess the importance of variations in the amount of cartilage and in its compressibility. Harris (1959*a* & *b*) has shown that by extending the neck during respiration the trachea is lengthened, thus increasing the distance between the plates of cartilage. In childhood emphysema the volume of a lobe is greatly increased, and although the greater part of the increase is probably borne by the alveoli there is doubtless some lengthening of bronchial pathways. Accordingly, in a given length of bronchus, the number of cartilage plates may be reduced while over its entire length the number would be normal. One can only be sure that an

affected region has no cartilage by sampling the whole pathway and not merely a single section.

The best method is probably to prepare mounts of the whole of a bronchial pathway and stain cartilage (see Hayward and Reid, 1952). In this way allowance can be made for the variation in bronchial branching. The normal airway with which comparison is made should come from the same segment and start as nearly as possible at the same level. In surgical removal of a right middle or upper lobe for infantile lobar emphysema the bronchus is divided some distance from the parent stem to allow adequate suture of the bronchial stump. A control is almost certainly taken at autopsy when a more generous amount of the supplying bronchus is available.

In examining the cartilage of the bronchial wall pathologists have usually compared the bronchus and particularly the cartilage plates with similar ones from a normal lung of the same age. Where this discloses hypoplasia of cartilage further information should be sought by comparing the "emphysematous" bronchus with a bronchus to the same region from the lung of a newborn at term. Any hypoplasia can thus be interpreted in the light of the normal appearance at birth. If cartilage is deficient, even in relation to the newborn lung, this points to the anomaly having developed antenatally. If the cartilage development is greater than at birth this would point to the deficiency being postnatal and the result rather than the cause of the emphysema.

Because of the great variation in the amount of cartilage in the normal, the significance of any variation is hard to estimate. The development of cartilage in the bronchial tree has been studied by Hayward and Reid (1952) and Bucher and Reid (1961), and it was found that the penetration of cartilage along different pathways in the same segment in the same lung varied enormously, and for this reason minor differences in the amount of cartilage should not be given too much weight. Further, although proximal plates of cartilage have commonly developed basophilia at birth, more distal ones are eosinophilic. After birth, there is maturation of the cartilage ground substance as well as growth in size of the plates. Adult distribution is described on page 326.

In short, cartilage anomalies cannot be invoked to explain all cases of childhood emphysema.

Cause and Pathogenesis

Occasionally inflammatory stenosis (Case 3 in Bolande's series) or absence of cartilage (Case 6 in the same series) may be sufficiently gross to be accepted as the cause; less satisfactory are mucous plugs and redundant folds of mucosa. In most cases of infantile emphysema there is no obvious cause. The primary cause probably lies within the alveoli and not in the airways.

In cases in which there is also a cardiac anomaly, such as a patent ductus, it is doubtful whether there is any direct relation between the anomaly and the emphysema. The significance of associated congenital anomalies is always difficult to establish, except where a minor degree of emphysema through a whole lung responds to repair of an anomalous artery seen to be mechanically interfering with a bronchus (Contro and his colleagues, 1958*a* & *b*).

The fact that in seven of the eight cases here reported the condition was either limited to or was predominant in less than a lobe, suggests that even where the whole lobe seems affected special attention should be directed to any regional accentuation and a comparison made with less affected regions.

It would seem that infantile emphysema is essentially a condition of localised air-trapping. If one segment is the site of the original change the behaviour of adjacent segments which may be compressed or overinflated may depend on the speed with which the original emphysema develops. This overinflation may be due either to direct or to collateral ventilation.

The question arises whether the site of the airways obstruction is at the hilum or at the periphery. The acceptance that this disease is lobar in nature has concentrated attention on the lobar bronchus. But although the lobar bronchi may collapse it may not be assumed that the collapse is the cause of the emphysema, because once air is trapped the increase in transpulmonary pressure may be transmitted even to widely patent, cartilaginous bronchi. Abnormal collapsibility of bronchi has not, it seems, been demonstrated in life in any case in which the alveoli are normal. (This question is also discussed on page 177 in reference to air-trapping in the adult lung.)

The primary disturbance may be in the alveoli of the affected region; a local increase in distensibility or compliance, perhaps because of variation in blood flow or even a developmental defect in the alveoli, may have allowed relative overinflation of the region sufficient to give trapping of air from bronchial relaxation or compression.

Related Conditions

Lobar transradiancy presenting in a child in the first weeks of its life is most likely to be due to emphysema for which no cause can be found, although an anomaly, particularly of cartilage development in the bronchial wall, may be suspected.

In an older child a lobar emphysema is more likely to be subacute. At such an age the cause and mechanisms may be the same as in the acute form, but the subacute nature of the symptoms points either to the emphysema affecting less than a lobe or to the emphysema being localised and associated with another bronchial anomaly. An example of this is

given in the chapter on bronchial atresia (p. 99). Cysts in the lung may be associated with emphysema of adjacent lung and may present with acute symptoms.

When emphysema is of long-standing it is complicated by hypoplasia. Where emphysema has been present from babyhood, besides the original cause of emphysema there may be interference with growth and maturation in the lung. As a result the final state of emphysema derives also in part from local hypoplasia. Although the affected segment is abnormally large a stable volume seems to be reached, as in none of the subacute cases had there been any increase in dyspnoea, and in those where several radiographs were available the appearance was unchanged.

Classification

Infantile lobar emphysema probably includes several distinct conditions. They have been grouped together in the proposed classification as emphysema with airways obstruction, which is irreversible, and without organic bronchial disease. Although in some cases there is evidence of bronchial abnormality, in most it is impossible confidently to regard structural bronchial change as the cause of the emphysema. The possibility of primary alveolar abnormality cannot, therefore, be ruled out.

Additional Case

Since this chapter was printed unilateral hypertransradiancy in a newborn child with a ventricular septal defect has been shown to be due to emphysema in a *small* lung—pointing to an abnormality present at birth.

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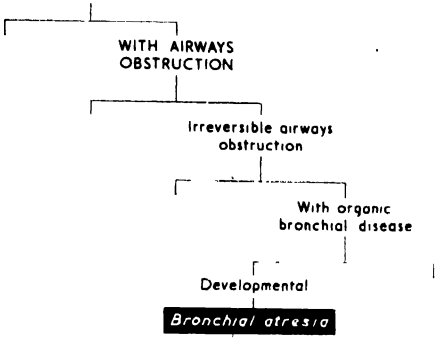
Chapter X

EMPHYSEMA WITH BRONCHIAL ATRESIA



DEVELOPMENTAL bronchial disease associated with emphysema is well exemplified in atresia of a bronchus, at segmental or presegmental level. The bronchus is blind on its hilar aspect but branches normally into the lung and supplies alveoli aerated by cross-ventilation. In the adult, this form of emphysema probably arises from a combination of two mechanisms—early overinflation and hypoplasia, the latter being the more important. The emphysema associated with bronchial atresia is a good example of emphysema arising from hypoplasia, the interference with alveolar development having been present from birth.

Four specimens of this condition have been described, three by Simon and Reid, 1963, the fourth by Waddell *et al.*, 1965. A fifth case (Waddell *et al.*, 1965) has been diagnosed radiologically (Cases 17–21, Table II). The examination of the first specimen diagnosed illustrates the value of tracing the length of bronchial pathways. It was in the light of the careful study of this specimen that Cases 2 and 3 were re-examined and diagnosed. In the fourth the diagnosis was suspected before the specimen was cut.

Only two further cases having a similarity to the above could be found reported in the literature. Falor and Kyriakides (1949) described a case with several bronchial and arterial anomalies of the left lung, which included four or five bronchi radiating into the upper lobe from a hilar "cyst" 2 cm. diameter. The bronchial supply to the rest of the upper lobe was abnormal, however, seeming to arise from bronchi to the lower lobe.

Belsey (1958—Case 7) describes a boy of 6½ who was diagnosed as having "obstructive" emphysema of the left upper lobe. At bronchography the region failed to fill and at bronchoscopy only a dimple was seen on the

lateral wall of the left main bronchus, representing the left upper lobe stem. There was an abnormal arrangement of the pulmonary arteries and the proximal end of the bronchus to the upper lobe was represented by two cartilaginous masses. This would seem to have been an atresia of a lobar bronchus (those described here are segmental), and the oblique fissure was presumably incomplete, permitting aeration by collateral air drift.

Clinical Features

All cases were young adults, three male and two female, and all were virtually asymptomatic except one in which the affected area eventually became infected (see Table II).

TABLE II

BRONCHIAL ATRESIA IN THE ADULT

Case	*Sex*	*Age at Resection*	
17	M	19	Symptomless—picked up on routine films.
18	F	25	
19	M	18	At age 16, thin-walled cavities, diagnosed radiographically. Recurrent infection.
20	M	25	Symptomless. Mass Miniature Radiograph diagnosis.
21	F		Diagnosis, at age 16, from radiographic appearance. Not resected.

Radiology

The radiographic features of all cases were similar and in all a region of increased transradiancy and avascularity was seen in the left upper zone (Fig. 51). A radiograph showed that this region in full expiration failed to deflate normally and the heart and trachea in some cases were displaced to the opposite side, indicating air-trapping (Fig. 52).

All showed at some time a shadow which probably represented the atretic bronchus. In Case 17, the 3 mm. wide shadow was arborising; in Case 18, lying centrally, there was a 2 cm. hair-line ring shadow containing a fluid level. In Case 19 several thin-walled cavities were seen, one with a fluid level. In Case 20 from a hair-line ring shadow there radiated three lines, each about 3 cm. long. In Case 21 the radiograph in 1955 showed a rather band-like shadow near the hilum unlike a consolidation. In 1962 the band-like shadow appeared as a 1·5 cm. circular shadow proximally with a 2 cm. shadow lateral to it, from which branches radiated outward and upward. The transradiancy had enlarged, pointing to an increase in emphysema, while the change in the shadows suggested atresia of a bronchus whose branches were now distended with secretion and unable to drain.

FIG. 51.—Case 17. Hypoplastic emphysema with atresia of bronchus to apico-posterior segment left upper lobe. Left upper zone hypertransradiant and relatively avascular (anterior view on inspiration). See also Figs. 52, 53, 54, 55 and 56.

Bronchographic Appearances (Cases 17–19); Angiographic Appearances (Case 20)

Bronchography was carried out in the first three cases; in none did the transradiant region fill and the nearby bronchi were compressed and displaced downward (Fig. 53).

Pre-operatively the filled bronchi had been assumed to represent the whole lung. With hind-sight the bronchograms could have given an important lead to the correct diagnosis. In Case 17, in the left bronchogram the left main bronchus was seen to divide into an upper and lower lobe bronchus, the latter and its branches being normal. The upper lobe bronchus divided in an orthodox manner into another common division

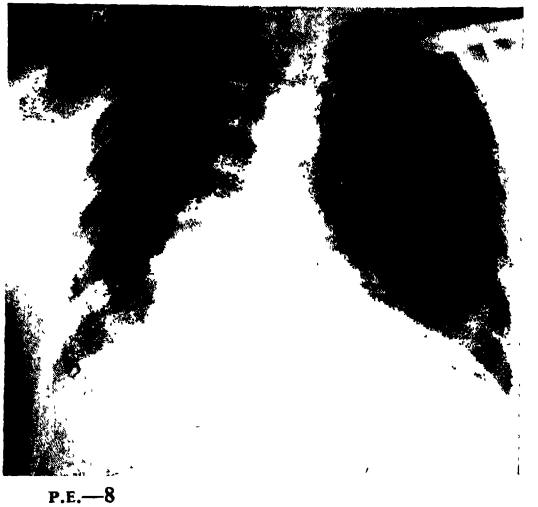


FIG. 52.—Case 17. Anterior view on expiration. Both domes of diaphragm moved up, and heart and trachea displaced to the right. Right lung and left base now opaque while transradiant area unchanged, indicating air-trapping in apical region. See also Figs. 51, 53, 54, 55 and 56.

FIG. 53.—Case 17. Bronchogram, oblique view. Lower lobe normal; main upper division and anterior and lingular bronchus displaced downwards, otherwise normal; apico-posterior bronchus small and no apical division. No filling in emphysematous region. Atresia of bronchus to apico-posterior segment left upper lobe. See also Figs. 51, 52, 54, 55 and 56.

and into the lingula, the latter and its branches being normal. The common upper division divided into an anterior division which, apart from being displaced downwards, appeared normal. The apico-posterior division was small and no apical branches arose from it, while the posterior branches were small and displaced posteriorly.

The left bronchogram of Case 18 showed a normal main bronchus which divided into an upper and a lower division. The latter was marked by a normal but small apical branch, but the basal divisions were abnormal and only two instead of three main trunks could be identified. Their branches were small and narrow and the pattern of branching was abnormal, there being fewer divisions, some of which came off at unusual

FIG. 54.—Left upper lobe seen in Fig. 53. Atresia of intralobar bronchus, seen as empty cyst below A and B. A—emphysema with no coal pigment; B—aerated, small amount of pigment not evident in reproduction, veins filled; C—alveoli small, suggesting longstanding partial collapse, white because of concentration of veins injected with micropaque gelatin.

Most of the slice is emphysematous witnessed by the infolding of the pleura. Regions B and C probably the apico-posterior, and A the anterior segment. See also Figs. 51, 52, 53, 55 and 56.

angles. The upper lobe division was very short and small. A small branch coming off near its point of origin might well represent an abnormally placed posterior bronchus. No branch corresponding to the apical bronchus could be seen and the translucent area was not filled. The final divisions of the abnormal upper lobe bronchus were displaced downwards and were abnormally small, while their branches were fewer than normal; and it was not possible to determine from their shape or position which represented the anterior and which the lingular segment. Thus the filled left bronchial tree was very abnormal and suggested hypoplasia.

In Case 19 the left bronchogram was similar to that of Case 17 save that the posterior division of the apico-posterior bronchus was rather better developed and was displaced downwards; the apical division was not seen and the transradiant area did not fill. Bronchography was not performed in Case 20. Angiography (Fig. 57) showed poor filling in the transradiant area with stretching and narrowing of the arteries in the left upper lobe and compression of the arteries in the left lower lobe.

Pathology

Resection was carried out in four of these five cases (Cases 17–20, Table II).

Case 17.—The apical region seemed more fluffy and emphysematous than the posterior region (although no pleural projections indicative of bullae were seen). On the anterior part of the bare surface there was a firm, round, hollow lump about 1 cm. in diameter. Air or formalin injected through the wall, which contained cartilage, dispersed into the lung without building up any pressure or leaking out around the needle. Thus this cyst-like space seemed blind on its hilar aspect but was distally in continuity with alveoli. Posteriorly the lung seemed compressed and relatively airless.

On slicing the lobe three regions could be identified (Fig. 54); the most anterior (A) was emphysematous and free of carbon pigment, the middle region (B) was emphysematous but with carbon, and the posterior part (C) was small in volume and relatively airless (Figs. 55 and 56). The absence of carbon pigment distinguished the region supplied by the abnormal bronchus from that supplied by the posterior branch.

Bronchi.—Reconstructing from the sliced lung, it was evident that there was a "blind" bronchus two to three centimetres in diameter at its broadest and that from it opened four or five airways, showing a roughly normal distribution, into the anterior part of the specimen. The walls of these airways were thinner and smoother than usual, lacking the longitudinal striation characteristic of the ordinary bronchial pathway. Dissecting one to the apex it was possible to count with the naked eye nine orders of branching, or fourteen if the side branches from the cystic bronchus were included.

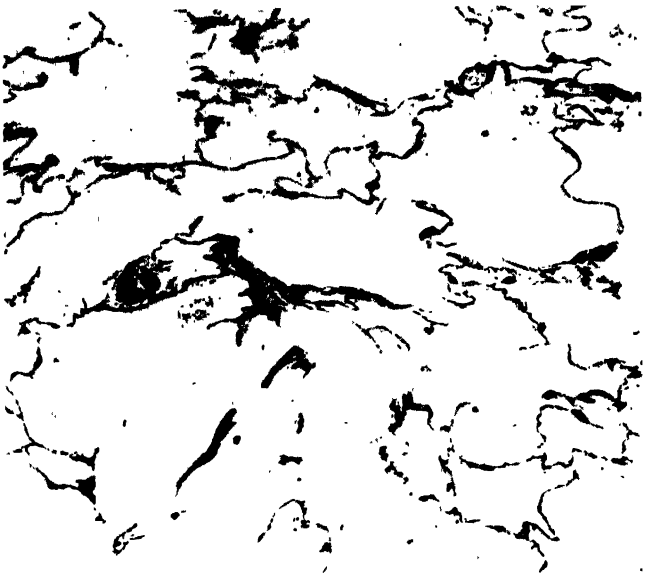


FIG. 55.—Region A of the specimen in Fig. 54, showing emphysema and poorly developed bronchiolus.

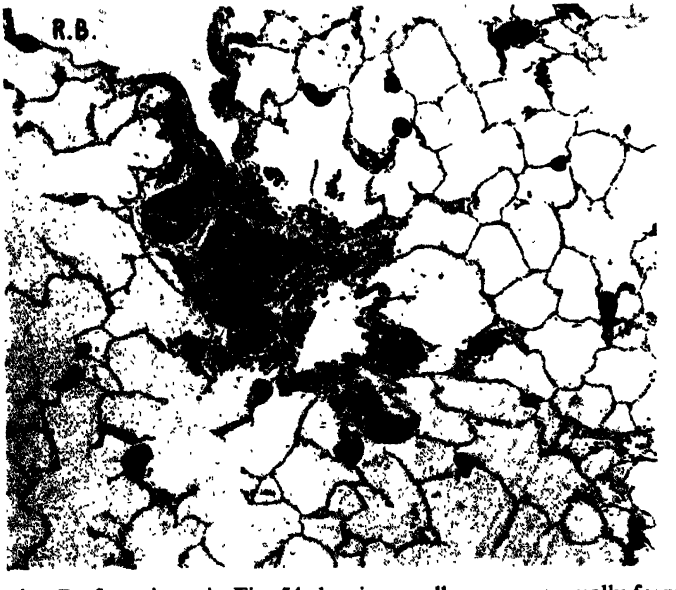


FIG. 56.—Region B of specimen in Fig. 54 showing smaller, more normally formed alveoli. Black pigment. Veins in alveolar and bronchial walls filled. (×40.)

FIG. 57.—Case 20. Angiogram. Radiograph taken for life insurance. Atresia of bronchus and emphysema in apico-posterior segment left upper lobe. Arteries in left upper zone narrower and few in number, in lower zone well filled. See also Figs. 58, 59 and 60.

Posteriorly a patent bronchus of about 6 mm. lumen diameter was found at the hilum: it supplied regions B and C. Its first side branch was very small and only a couple of millimetres in diameter, and supplied the compressed part, region C, while the main pathway supplied region B.

The bronchi in region C were counted and even on naked-eye dissection as many as twelve branches could be identified, which suggested that there was here no very great impairment of bronchial development. Microscopy confirmed that carbon was present in the posterior compressed part of this lobe as well as in the adjacent emphysematous region.

Microscopic examination of the blind bronchus and its side branches showed that the wall, although thinner than normal, included cartilage, muscle, and mucous glands. Special stains for acid mucopolysaccharide showed that in the cartilage this was concentrated around the chondrocytes and was less in amount than is usual in plates of cartilage at the hilum of a segment. The same stain showed that the mucopolysaccharide of the glands and goblet cells of the epithelium were within normal limits. A nerve was seen outside the cartilage in the wall of the cystic part of the bronchus.

Step sections through a block of tissue distal to the level at which naked-eye dissection was no longer possible, showed that the number of branches from the axial pathway was thirteen or eighteen according as the side branches from the cystic bronchus were or were not excluded. Since the mean number of bronchial generations or branches arising from an axial pathway of the apical segment of the right upper lobe is normally fifteen (Bucher and Reid, 1961) this suggests that there is little antenatal impairment of bronchial development.

Vessels.—One blood vessel thought to be an artery and subsequently shown to be a vein was identified posteriorly and injected with barium-gelatin solution. Its tributaries drained normally from neighbouring segments, some vessels being filled in the anterior carbon-free part. The concentration of filled vessels was much less in the emphysematous than in the compressed region. On microscopy it was seen that the bronchial venules around even the "blind" bronchial system had filled—the normal pattern of venous drainage. Pulmonary artery branches could be seen running with these airways. Neither in this case nor in any of the others did the surgeon comment on a bronchial artery running to the emphysematous region.

The alveoli were emphysematous (Fig. 55)—i.e. abnormally large, with attenuated walls and simple profile. Although individual alveoli were clearly emphysematous on microscopic examination this might be the result of over-distension of the segment and did not necessarily mean that the number of alveoli was reduced. However, even assuming that the volume of this segment was four times that of a normal anterior segment—which is probably an exaggeration—it means that the diameter increase in individual alveoli would be only the cube root of four and therefore scarcely discernible on ordinary microscopic examination. Thus the dramatic increase in diameter, even in the relatively collapsed state when removed from the body, must mean that the affected segment has less than the adult quota of alveoli. Fewer respiratory bronchioli than usual were seen in the step sections taken from the end of a pathway.

In the compressed posterior part of the lung the alveoli were small, well formed and round, and not elongated as in collapse (Fig. 56); there was no evidence of the haemodynamic changes which are characteristic of chronic collapse. In view of the naked-eye appearance of the lung and the small but round form of the alveoli seen microscopically, this region would seem to be hypoplastic rather than a region of collapse.

Case 18.—In the second case, at thoracotomy, the apical region of the upper lobe was grossly emphysematous, though clearly demarcated from the normal lung tissue which formed the lingula. No bullae were evident on the surface nor was any cyst palpable in the lobe. The lower lobe and hilum appeared normal. Dissection of the left pulmonary artery from above revealed a small atrophic branch to the diseased area. A small

pulmonary vein draining the diseased area was also dissected and divided anterior to the artery. The lingular bronchus was dissected free but, since it was impossible to identify the apical bronchus with certainty, the whole of the left upper lobe was removed. Subsequently the remaining lung filled the left hemithorax.

The specimen consisted of the whole of the left upper lobe and showed on section that the posterior and apical part of the lobe was largely free of carbon while the anterior part contained a good deal. At the junction of the carbon-containing and carbon-free areas there was a 2 cm. cystic cavity lined by smooth epithelium. No hilar communication between this cavity and proximal bronchi was demonstrated, but branching from it into the emphysematous, carbon-free, part of the lung were a number of peripheral bronchial branches which, on dissection, showed a normal branching pattern within the lung and normal communication to the alveoli.

On section the alveoli were seen to be emphysematous, that is, abnormally large and with thin, attenuated walls. Microscopic examination showed that the wall of the cyst-like space contained cartilage and mucous glands and was lined by ciliated columnar epithelium, indicating that it was a dilated bronchus. In the emphysematous part of the specimen the alveoli were large and their outline simpler and less subdivided than in the normal.

Case 19.—The third specimen was discarded before detailed anatomical dissection was possible, but it also showed bronchi in the anterior part of the lobe not in communication with the hilum, but branching to alveoli. The alveoli as well as the airways in this region were the site of acute inflammatory changes.

Case 20.—On opening the chest the surgeon reported that the left upper lobe was emphysematous and occupied most of the chest, the lower lobe being only about one quarter the normal volume. During the operation the lingula collapsed but the apical region remained distended. The whole left upper lobe was removed, no abnormal bronchial artery and no extra arteries going to the emphysematous area being seen.

On arrival in the laboratory the lobe had deflated, save for the apical region which was raised above the neighbouring segments to a height of several centimetres, but was less in volume than in the body. The elevated region was free of carbon, while over the remainder some carbon was distributed in the usual way in bands related to the line of the ribs.

At the hilum the main bronchial branches lay on the cut surface anterior to the emphysematous area: they had not been clamped. On probing, it was found that neither of these two cut bronchi supplied the region of emphysema, attached to whose hilar aspect was a firm, well-defined mass about 2·5 cm. in diameter.

The lobe was cut in a roughly sagittal plane into slices about one

FIG. 58

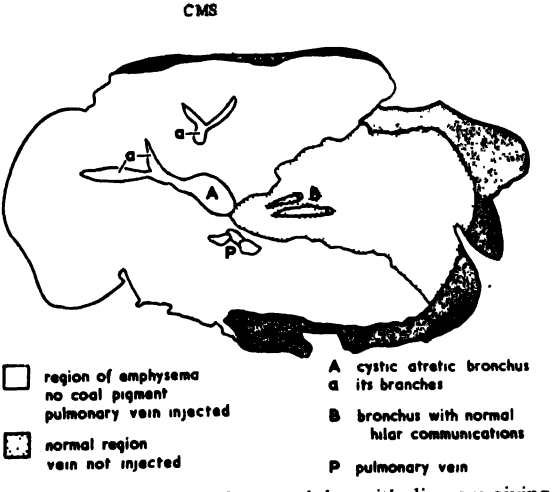


FIG. 59

FIGS. 58 and 59.—Case 20. Specimen of left upper lobe, with diagram giving key to structure. See also Figs. 57 and 60.

centimetre thick (Figs. 58 and 59). This revealed that the mass was cystic and represented a bronchus blind on its hilar aspect which branched distally into five main bronchial pathways, each branching in a more or less normal manner and which could be traced even with naked-eye dissection until it finally dissipated into respiratory tissue. There was no carbon present in the emphysematous area, which occupied roughly the posterior two-thirds of most of the slices; but some carbon was seen in the anterior third.

The pulmonary vessels on the surface were injected by cannulating them separately. Unfortunately they all proved to be veins, the artery having retracted below the level of the cystic bronchus (Fig. 60). One region in the anterior segment was not filled, which accounted for the appearance of the venogram; the relatively normal region is seen at "A" in the illustration, while the emphysematous region is seen at "B". The pulmonary veins are thinned and sparse in the emphysematous region and the number of intra-acinar tributaries reduced. Anteriorly the appearance

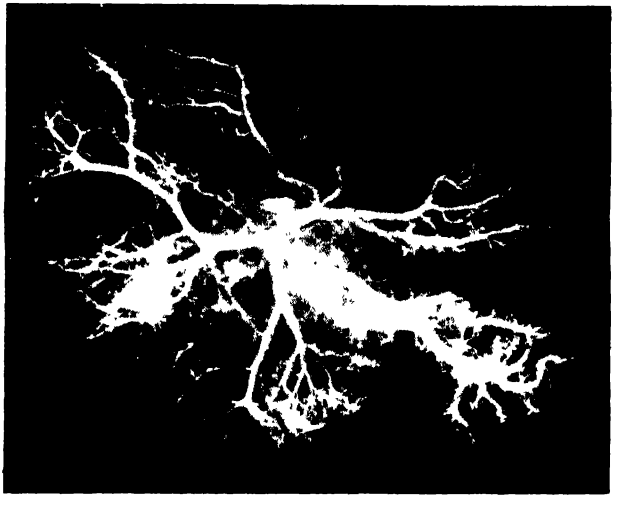


FIG. 60.—Case 20. Specimen venogram of lobe shown in Fig. 58. Region of emphysema to left hand, more normal region to right. See also Figs. 57, 58, and 59.

suggests some degree of collapse inferiorly; cranially the lung is aerated and, while not as emphysematous as posteriorly, contains carbon and well-filled pulmonary veins. The tributaries in the wall of the bronchi in the anterior and posterior regions were filled. No bronchial artery to the posterior region was seen by the surgeon.

Microscopy.—The epithelial lining of the atretic bronchus (A) was thin. Mucous glands were present and contained some basophilic but predominantly eosinophilic cells: the cartilage was eosinophilic. Nerves could be identified. In the anterior region the airways seemed better developed, the cartilage, for example, being basophilic.

In the emphysematous region the alveoli were very large and very thin-walled; few elastic fibres could be identified and the concentration of capillaries in the alveolar walls was reduced. Postero-inferiorly there was a region of alveoli compressed against pleura; anteriorly, although the size of the alveoli was more normal, the walls seemed to have less than the normal quota of capillaries.

Comment

In all these cases the alveoli were abnormally large, that is, they were emphysematous, but the essential or primary disturbance was in the bronchial tree. In all cases the antero-apical region of the left upper lobe was supplied by a bronchus which, at its proximal end, was "blind" and not in communication with the lobar bronchus; atresia, that is absence of lumen, would, therefore, seem a proper description. No fibrous cord between the proximal and the blind bronchus was found in Cases 1 and 4, the two in which it was possible to examine the specimen for this feature. Nor is such a fibrous remnant necessary to justify the use of the word "atresia".

In all three cases the site of the atresia was the apical anterior region of the true upper lobe and might represent atresia of the anterior or apical bronchus, or of their common bronchus. In other words, the lesion can properly be considered as affecting a recognised segmental bronchus rather than representing an accessory bronchus. Therefore the term "atresia" is more appropriate than "supernumerary" or "sequestrated" segment.

The left upper lobe branches are notorious for the variation in their arrangement. Boyden (1955) has demonstrated the variations that occur in this region from displacement of the segmental and presegmental branches in relation to the main upper lobe bronchus. This may indicate an underlying embryological instability.

Bronchial development.—The development of the bronchial tree is completed *in utero* (Bucher and Reid, 1961), and thus its degree can be used as a measure of antenatal development (Reid and Simon, 1964); while alveolar development being mainly after birth (Willson, 1928; Dunnill, 1962) its degree can be used as a measure of postnatal development.

The segmental bronchi normally appear at about the fifth week of intra-uterine development, which may point to the age at which bronchial atresia occurs. In Case 1, in which the bronchial generations or branchings could be counted, it was found that the number arising from the cystic bronchus was within the normal range, as was the count in the posterior compressed region. This suggests that between the fifth and fifteenth week of intra-uterine life, at least, bronchial development was normal.

Pathogenesis

(a) Bronchial atresia.—It is not certain whether atresia represents a disturbance of growth or whether it develops in an airway which has previously been normal. The surgeon's failure to mention bronchial arteries running to the emphysematous region may mean that they are absent, which, if they are, may be the cause of the condition, or the atresia may be secondary to some other disturbance. Speaking generally, blood flow increases with growth and interference with the bronchial development could easily produce a secondary change in the arterial bed, especially

at the fifth or sixth week of antenatal growth, when a segmental bronchus would be budding and the communications of the capillary plexus to the right or left side of the heart would not be stabilised.

Experimental studies in the dog by Louw and Barnard (1955) have shown, on the other hand, that when, near term, a mesenteric artery to the small gut is tied and the puppy returned to the uterus, atresia of the gut develops within sixteen days. It is suggested, therefore, that a vascular accident late in intra-uterine life may be the cause of atresia of the gut.

The bronchial anomaly may be accounted for by disturbance in the blood supply to the region of the atresia, such as would occur late in intra-uterine life, after the sixteenth week, for example, when the bronchial tree is already complete. That interference with a bronchial artery is the primary cause is, understandably, hard to accept because lung damage resulting from interference after birth is difficult to establish. It may be that antenatal damage would have a more far-reaching effect.

(b) Emphysema.—The alveoli in the region supplied by the blind bronchus were free of carbon pigment and were emphysematous; they were not only abnormally large but had an extremely simplified profile. This was so, even when the lung was sliced and the affected region occupied an even smaller volume than in life. The type of emphysema present with atresia is a good example of emphysema caused by hypoplasia, as the bronchial abnormality has been present since birth. Alveolar hypoplasia may mean—

(i) a reduction in the total number of alveoli;
(ii) alveoli which are too small; and
(iii) alveoli which are too large but whose walls may be too thin and whose outline is less folded and abnormally simple.

The condition in which alveoli are too few and too small is not emphysema; as an example, a large congenital diaphragmatic hernia compressing the lung is an antenatal disorder causing hypoplasia without emphysema (Areechon and Reid, 1963). A postnatal instance of a condition in which alveoli are too few and too small is severe kyphoscoliosis (Reid, 1965). If the curvature is uncorrected growth of the compressed part of the lung is disturbed.

Where there is atresia of a segmental bronchus, alveolar hypoplasia can arise from impaired growth, the affected region having been aerated by collateral air drift. Culiner and Reich (1961) have demonstrated that air admitted to a region by collateral drift does not, during expiration, leave the lung as easily as the air from adjacent directly ventilated lung. The indirectly ventilated lung is maintained continuously in a state which approximates to that on inspiration. The air-trapping in this region is demonstrated on the radiographs. Although the depth of inspiration is probably the main factor in establishing a good minute flow of blood to

the lung (Cournand *et al.*, 1935), it is during expiration, not inspiration, that the maximum capillary flow is achieved (Riley, 1959). Thus, in these cases, because the lung is always in inspiration the alveolar capillary flow, and hence the flow through the more proximal vessels, will be reduced.

Cases such as are here described give some indication of the mechanisms whereby normal lung growth is achieved. In hypoplasia associated with congenital diaphragmatic hernia the number of alveoli per terminal bronchiolus is less affected than is alveolar diameter.

Study of bronchial atresia and of congenital diaphragmatic hernia (Areechon and Reid, 1963) would seem to show that the number of bronchial generations and the volume of an alveolus reflect space available for lung development during the antenatal period, while the number of alveoli at birth and their differentiation is relatively independent of it.

In the postnatal period it is otherwise. To a significant extent lung growth is a work hypertrophy, "work" being represented by the volume change with each respiration. This depends on normal ventilation; a reduction in ventilation not only means less work, but also a diminished blood flow, thereby aggravating the hypoplasia.

Growth consists initially of an increase in the number of alveoli, in the complexity of their walls, and in the number of capillaries they contain; and later, an increase in alveolar diameter. The total number of alveoli is achieved by about the age of eight (Dunnill, 1962) and thereafter any increase in thoracic volume results in an increase in alveolar diameter; thoracic volume increase does not of itself suffice to bring about an increase in the number of alveoli and capillaries, which more directly results from the amount of work done.

In the two uninfected cases reported here, the cystic bronchus was empty save for a small amount of clear mucus. This and the fact that their structure appeared normal indicated that the bronchial mucous glands were secreting. Under certain conditions secretion accumulates, because a fluid level may be seen (as in Cases 18 and 19).

Hypoplasia of Non-emphysematous Regions

In Cases 17 and 20 part of the non-emphysematous regions of the lobe also were hypoplastic. The alveoli of the posterior region in Case 17 were small, and in Case 20 the walls of those in the anterior region were thin, with the venous pattern rather less dense than in the normal. Hypoplasia might be a manifestation of partial compression of the region so that, although ventilation and circulation are better than in the emphysematous region they still do not achieve normal levels.

Other Congenital Anomalies

Bronchial atresia is an example of the effect of indirect aeration on developing alveoli. The cases described here involve at least one segment

and therefore the distribution is clearly seen. A different type of distribution may be found in a sequestrated segment. In a recent case (personally studied) a multilocular cyst occupied the postero-inferior border of the lower lobe; when sliced, three regions could be recognised roughly encircling the cyst. The alveoli adjacent to the cyst wall were different from those elsewhere in being free of carbon and they were also emphysematous; the next layer was emphysematous but contained carbon; while the next layer was normal. This suggests that the region ventilated by collateral drift was emphysematous and that this to some extent affected adjacent alveoli.

Congenital lobar emphysema of childhood may be subacute and the lobe accordingly left *in situ* for some years. In these circumstances not only has the overinflation contributed to the emphysema but, as the result of impairment of ventilation and interference with alveolar development, hypoplasia also may have contributed (see Case 47, p. 232, where the adult appearance of what was probably lobar emphysema of childhood is illustrated).

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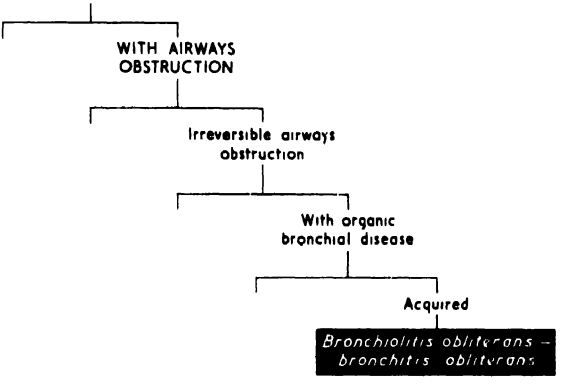
Chapter XI

EMPHYSEMA WITH BRONCHIOLITIS AND BRONCHITIS OBLITERANS

Acquired in Childhood: Macleod's Syndrome (Unilateral or Unilobar Hypertransradiancy)



MACLEOD in 1954 described nine patients with an X-ray appearance in which one lung was more transradiant than the opposite lung. His cases were usually asymptomatic and without evidence of collapse, bronchiectasis, or old tuberculosis.

Evidence from resected specimens in similar cases and from bronchograms shows that there is widespread bronchitis or bronchiolitis obliterans on the affected side (Reid and Simon, 1962), and this appears to be the cause of widespread emphysema and hypoplasia of the alveoli and pulmonary arteries. It would seem likely that in most cases the bronchial occlusions took place in childhood as a result of infective damage and the consequent air-trapping interfered with the growth of the lung. In the light of the pathology of most cases, it is only natural to include in Macleod's syndrome similar pathological conditions even if their distribution is different and they arise from other infective agents; this means that unilobar forms can be included and even bronchitis obliterans if caused by a tuberculous infection—which has the agreement of Dr. Macleod.

Unilateral hypertransradiancy may occur from local accentuation of the adult form of emphysema, but can be distinguished from Macleod's syndrome because the lung is larger, or as large as, not smaller, than the opposite lung and the early branches of the pulmonary artery will be large and not small and hypoplastic.

Another condition *not* to be included will be rare cases of hypoplasia but without hypertransradiancy.

Detailed pathological studies of unilateral hypertransradiancy have been few (Swyer and James, 1953; Reid and Simon, 1962; Culiner and Reich, 1961; Decroix et al., 1963), but reports of its radiographic and functional features are numerous. (Some of these are included in the bibliography and marked with an asterisk.)

Study of a series of six resected specimens and many bronchograms revealed that obstructive or obliterative lesions of airways are always found in the hypertransradiant lung, patchily distributed; it is suggested that these are acquired in childhood before growth is complete and have interfered with lung development (Reid and Simon, 1962). This explains the presence of emphysema in a lung of normal or sub-normal size, associated with a reduction in pulmonary artery flow. During growth impaired ventilation may follow either obstructive disease of the airways or pleural disease causing restriction of ventilatory movement.

Radiology

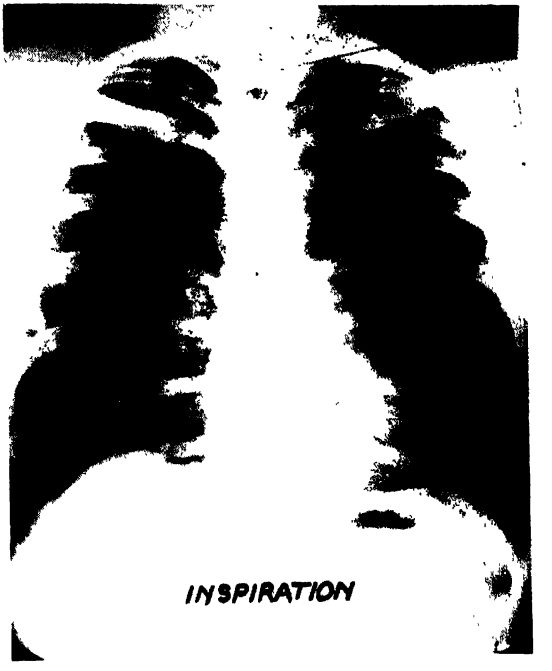
In unilateral hypertransradiancy the patient is usually without symptoms and accordingly the radiographic appearances are dramatic.

The plain radiograph reveals hypertransradiancy in one lung with small blood vessels both at the hilum and within the lung (Fig. 61). There being no lobar collapse, the distribution of the main arterial pathways is normal. The heart and trachea may be drawn to the hypertransradiant side, and the level of the diaphragm on the affected side may be normal or somewhat low. Comparison of films taken on deep inspiration and deep expiration reveals that there is trapping of air in the hypertransradiant lung (Fig. 62), as the diaphragm on that side moves less than on the other, normal, side, while on expiration the heart and trachea are displaced away from the hypertransradiant side which fails to become opaque as does a normal lung.

Tomography and angiography.—Because of the vascular findings, tomographs (Fig. 63) and angiograms (Fig. 64) have usually been performed before bronchography. They confirm the finding in the plain radiograph, angiography showing a small pulmonary artery with filling of the proximal branches only, in contrast to the normal peripheral filling which will be seen on the other, normal, side. The main pulmonary artery to the affected side usually has a smooth outline but, presumably because of reduced blood flow, appears much smaller than on direct examination either at operation or in the resected specimen.

Bronchography.—In the light of the pathological findings that this condition is essentially a patchy bronchiolitis obliterans throughout the lung, the bronchogram becomes increasingly important, helping to detect the changes in life. In many cases no very obvious changes may be seen;

FIG. 61



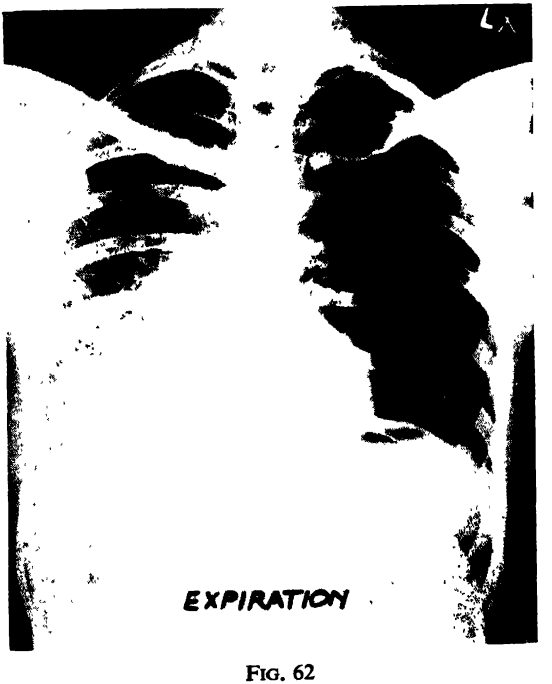


FIG. 62

FIGS. 61 and 62.—Hypertransradiancy of left lung. Radiographs in inspiration and expiration showing displacement of heart and trachea to unaffected side on expiration, with relative increase in transradiancy on the left. Left hilar shadow small; no collapse in left lung.

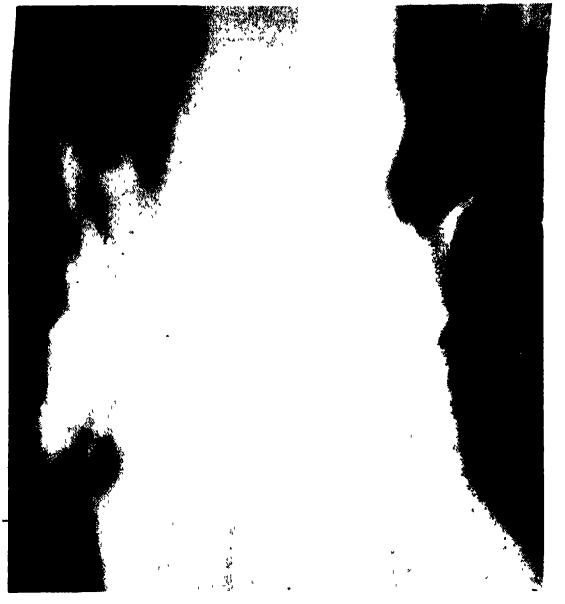


FIG. 63.—Small left pulmonary artery and its intrapulmonary branches seen in tomogram. Man aged 41, known to have had radiographic hypertransradiancy for 15 years.

many reports mention only that "no bronchiectasis was seen". However, from a careful survey of reported cases and of many personally observed, it would seem that an abnormality is always present.

In a normal bronchogram the contrast medium is usually conducted to the smaller bronchi and bronchioli (a normal peripheral bronchogram

FIG. 64.—Hypertransradiancy of left lung. Angiogram. Great reduction in blood flow to lung and in intrapulmonary vascular pattern.

is illustrated in Fig. 65), where it produces the "centimetre" pattern, so named because the branches are regular and lie roughly 1 cm. apart. More distally, within the secondary lobule itself, the branches arise a few millimetres apart, are a few millimetres long and, when filled, produce the "millimetre" pattern representing terminal or near-terminal bronchioli (Reid and Simon, 1958).

In unilateral or unilobar hypertransradiancy the following changes may be found:

I. Poor peripheral filling.—In none of the bronchograms reviewed did filling in the more transradiant lung reach a peripheral level (Figs. 65 and 66), indicating a failure of normal conduction. The filling might extend as far as the middle level, i.e. the eighth to the tenth generation, though an occasional pathway filled to a more distal level. This evidence of abnormality is often ignored, perhaps because it is ascribed to technical faults such as too little contrast medium or too little time for it to flow distally; more often the cause is a structural damage; or again, the passage of the

FIG. 65.—Case 22. Hypertransradiancy of left lung. Bronchogram. Filling in left lung ceases in bronchi and at much the same level in all pathways; filling on right side normal. Most of endings of the filled bronchi are square, suggesting level at which filling ceased, not necessarily a point of organic obliteration. Hypertransradiancy appeared two years after childhood tuberculosis. Bronchograms at 12 and 22 years showed virtually same bronchographic pattern save that bronchi larger.

contrast medium to the peripheral bronchi may be impeded by an excess of mucus or by diminution in inspiratory "suck".

The inspiratory suck will be poor if there is airway obstruction from organic occlusion of small peripheral bronchi or bronchioli, a change found patchily in the five specimens. These occlusions may be associated with air-trapping, arising from distal emphysema and bullae, which will themselves hinder the respiratory suck in nearby branches.

II. Dilatation.—In some cases the normal reduction in calibre of bronchi between the third and sixth generations was lacking, and in a few there was a more positive dilatation (Figs. 66 and 70).

III. Irregular endings.—In many cases the contrast medium ended either in an irregular tapering fashion, in a bulbous expansion, or in a small circular "pool". Such end irregularities are frequent and indicate an organic occlusion.

Respiratory Function Tests

Breath sounds are usually difficult to hear over the affected lung and the percussion note may be hyper-resonant. Bronchospirometry reveals that ventilation to the affected lung is greatly impaired, there being scarcely any ventilation or oxygen uptake at rest. On deep inspiration there is usually only 5–10 per cent of total ventilation to that lung and a lower percentage of oxygen uptake. Overall ventilation tests commonly give sub-normal values which, with an increase in residual volume, may be similar to those in widespread airways obstruction. Blood gas studies are usually normal, even after a period of forced respiration.

Dornhorst and his co-workers in 1957 investigated the mechanical properties of the abnormal lung at bronchospirometry. Enforced ventilation produced only a slight improvement. Respiratory function studies indicated "a severe non-valvular obstruction to the small airways on the affected side".

Radio-active gas studies (Dyson *et al.*, 1960) confirmed these findings and demonstrated that ventilation to the affected lung occurred either not at all, or at a higher opening pressure in quiet respiration than in the normal lung and with a lag even on forced inspiration. Slow clearance demonstrated gross air-trapping and the low level of blood flow through the affected lung was also confirmed.

In some cases radio-active studies revealed that a "unilateral" condition affects less than a whole lung. Evidence of this was also found radiographically. The radiograph, or particularly the tomogram, showed the vessels to be of normal size in the less affected regions.

In one case in a series investigated by bronchospirometry, Fouché *et al.* (1960) found that "hyperventilation resulted in over-inflation and temporary suspension of oxygen uptake on the affected side"—further

evidence of the reduction in capillary blood flow in a lung in which air is held trapped at inspiratory levels.

Pathology

This account of pathological findings is based on resection material from six cases of unilateral hypertransradiancy, in one of which it probably followed tuberculosis. In addition, other specimens are described later which throw light on the pathogenesis and cause.

Macroscopic.—The behaviour and the macroscopic appearance of the hypertransradiant lung can be studied at operation. On opening the thorax the lung is seen as a tense bag of air which will not deflate even on pressure from the surgeon. On inflation by the anaesthetist the affected lung sometimes increases in volume and tenseness, which makes its subsequent deflation even more difficult.

The distribution of coal pigment both on the surface and through the lung is often bizarre; it may be scattered, with the rest of the lung appearing pink and fluffy. In one of the six cases, for example, the basal segments were completely free of carbon, which was seen over the apical segments of the lower lobe and the upper lobe, in which, again, the lingula was free. In another case the cut surface of the lower lobe showed half a dozen dense collections of carbon with pink fluffy lung in between. In view of the obliterative changes in some of the bronchioli the absence of carbon indicates the areas ventilated by collateral drift since, although in life air passes across the alveolar walls, particulate matter evidently does not. Occasionally pleural adhesions were present, but in most the pleural space was surprisingly free of them.

The bronchi at the hilum may be normally rigid and roughly normal in size, or they may feel flabby, that is, the plates of cartilage seem unduly compressible. In assessing the significance of such flabbiness it is essential to take into account the wide variation in size, shape, and rigidity of the hilar bronchi in normal lungs. There was no obvious correlation between the behaviour of the cartilage and any other aspect of the disease. (For further discussion of cartilage structure and behaviour, see pp. 94, 177 and 326.)

Specimen arteriograms.—In all six cases the pulmonary artery to the affected side was injected (Fig. 67), in four of them under the carefully controlled conditions described on page 311. The pulmonary artery in all was much larger at the hilum than would be suggested by the appearance in the angiogram, although it might not be quite normal for the patient's age. In the specimen arteriogram, the peripheral filling was roughly normal and penetrated well within the acinus. In comparison with the absence of filling in the clinical arteriogram, the filling in the specimen arteriogram was striking, though the arterial pattern was not as dense as in the normal. The diameter of the axial arteries along their course was smaller than

normal, indicating hypoplasia, and there were fewer intra-acinar vessels detectable as fine lines. In none of these cases was there any striking filling of the pleural vessels or of those to hilar bronchi.

Alveoli.—On cutting the affected lungs which, as mentioned above, were normal or small in volume, the air spaces were found to be abnormally large, that is the lungs were emphysematous. The appearance was that of a panacinar emphysema in that there was no accentuation and no particularly large holes. In none of the resected lungs have bullae been seen, although in the radiographs of two cases which did not come to operation linear shadows at the base suggested them.

Bronchi and bronchioli.—The bronchograms are the best means of studying bronchi and bronchioli as they show a cast of the whole of the bronchial tree. In some cases in which the bronchogram suggested blocking in large bronchi it was possible by dissection along the airways to demonstrate the points of obliteration. In other cases the damage was patchy and in fine airways, so that the points of distortion or obliteration could be identified on the cut surface of the lung by the stellate arrangements of grey scar tissue (Fig. 68).

Sometimes larger areas of scarring were seen, as in one patient where what appeared to be a subsegment of lung, about 50 cu. cm. in size initially, had been reduced to only a few. This was subpleural and hence not visible in the radiograph.

Microscopic.—*The bronchial tree.*—The bronchi at the hilum were within normal limits in five cases; in one there was evidence of mucous gland hypertrophy. The patient had been known from the serial radiographs to have had unilateral hypertransradiancy for 20 years, but persistent cough and sputum for only seven. It would seem, therefore, that the mucous gland hypertrophy in the one lung was part of a generalised hypertrophy acquired many years after the incident responsible for the peripheral damage. In some bronchi the amount of fibrous tissue in the wall seemed increased, but the significance of this is not known. Even in quite large bronchi, filling of small bronchial arteries has been shown.

Sometimes the site of distortion and obliteration is within the bronchi. In one of the resected lungs the site was in the large bronchi and in another it seemed to be in the distal smaller bronchi.

To assess the antenatal development of the bronchial tree, the number of bronchial generations within the lingula in one case was counted. A bronchus was traced to its obliteration in the tenth generation, which lay closer to the pleura than would be expected in the normal. Serial sections of the lung between the intra-bronchial block and the pleura revealed numerous fine scars and nine extra generations, 19 in all. As this is just below normal for this segment and as, in the scarring, one or two branches might have been completely effaced, it would seem that there is no evidence of impairment of the development of the bronchial tree, indicating that it

FIG. 66.—Case 27. Hypertransradiancy right lung. Bronchogram shows poor peripheral filling, stenosis of right main bronchus. Probably the end result of tuberculosis in childhood. See also Figs. 67 and 69.

FIG. 67.—Case 27. Specimen pulmonary arteriogram of right lower lobe. Peripheral vascular filling greater than suggested by poor filling in angiogram. See also Figs. 66 and 68

FIG. 68.—Case 27. Specimen from left lower lobe. Emphysema and dilated bronchiolus. At arrow bronchioli choked in scar tissue. At X pulmonary artery injected with barium-gelatine. See also Figs. 66 and 67. (× 60.)

was not hypoplastic at birth (in contrast with the hypoplasia associated with congenital diaphragmatic hernia, in which the affected lobe may show only a third to a half of the normal bronchial number of branches (Areechon and Reid, 1963). In other cases, where the scarring was too fine to be demonstrable to the naked eye, microscopic examination revealed peribronchiolar fibrosis with narrowing and obliteration of bronchioli. In these areas cross-filling to the bronchial artery branches from the pulmonary artery was usually obtained, but this had not sufficed to fill the bronchial arteries back to the branches at the hilum.

Pulmonary arteriogram.—Comparison of the pulmonary arteriogram of these resected lungs with a normal specimen arteriogram revealed that the larger arteries running with bronchi were somewhat narrower. Detailed measurements of arterial wall thickness and the area of the medial muscle coat have been made in one of these cases (Elliott, 1964*a* & *b*; Elliott and Reid, 1965). Elliott has shown that in assessing muscular hypertrophy in diseased lung, comparison with normal arteries must be made on the basis of the external diameter of the injected artery (see also p. 353). Within the block of tissue on which these detailed measurements were made two arterial pathways were traced, the one showing much greater hypertrophy of the medial muscle coat than the other, suggesting that the arterial changes are not regular in distribution. Within the lobule and the acinus, injection of the pulmonary artery had revealed a virtually normal pattern save that the intra-acinar vessels were too small and too sparse. Within the region of the acinus, microscopic counts were made of the number of blood vessels (i.e. between 30 and 100 μ in diameter) in the walls of a given number of alveoli, and these showed that there were fewer vessels than normal (Elliott, 1964*b*). This count was made in relation to field size as well as to the total number of alveoli and suggests that there was a relatively greater hypoplasia of the pulmonary artery bed than of the alveoli.

Alveoli.—The degree of emphysema varied from case to case. In some the alveoli were extremely large while in others, although there was no doubt that emphysema was present, alveolar size was not as great. This may reflect the age at which the initial damage occurred, but it is not yet possible to relate the age of onset to the degree of emphysema.

The alveolar walls were abnormally thin and the outline smooth; there was no evidence of tearing or ulceration of alveoli. In one lung only an occasional section showed ragged alveolar walls. No count was made but whereas normally large numbers of respiratory bronchioli are clearly seen in the respiratory region, even in serial sections it was difficult to identify more than one or two. Thus the development of respiratory bronchioli would seem impaired in some cases.

In summary the pathological findings are of a patchy bronchiolitis and bronchitis obliterans with emphysema from hypoplasia, evidenced by alveoli which are larger and simpler in outline than in the normal. The

pulmonary artery bed within the acinus is also affected by the hypoplasia, so that small arteries are less numerous and the volume of the capillary bed reduced.

Pathogenesis

Airway lesions.—The essential change in the six patients seemed to be multiple bronchial or bronchiolar obliteration acquired in childhood. When obstruction is acute, the secondary effects on ventilation and on the blood content of the lung are probably reversible, but if the lesions progress to organic obliteration, all the components for the adult picture of unilateral transradiancy are present.

A patient will rarely volunteer that he has suffered a childhood respiratory illness because he sees no reason to connect his abnormal radiograph with a bronchial infection twenty, thirty, or fifty years earlier. By contrast, in bronchiectasis the persistent production of sputum usually starts near enough to a childhood illness for the patient or a parent to link the two. Clinical notes, sometimes a pathologist's only source of information, often fail to indicate whether the patient or his relatives were questioned as to a childhood chest illness in these cases.

Not all airways are obliterated or the lung would collapse; the patency of some can be assumed because of the presence of carbon pigment. That there are regions free of carbon suggests that ventilation to them is by collateral air drift. Radio-active gas studies and radiographic appearances indicate that air is trapped in the lung. What proportion of airways must remain patent to aerate the alveoli of the whole lung is not known, but it doubtless depends to some extent on their distribution; nor is it known how many airways must be blocked to give the overall effect of air-trapping and the vascular effects in the lung. Too few lungs with this condition have been examined pathologically to establish the patterns of distribution of airways disease.

Since the number of branches of the bronchial tree in these cases seems normal, antenatal development was probably normal, but the reduction in the number of alveoli and in the finer branches of the pulmonary arteries indicates that there was impairment of postnatal development, or hypoplasia, suggesting that the bronchial obliterations most likely occurred between birth and the age of 8 when alveolar number is normally complete. Certainly the effect of bronchial damage at this time before the total number of alveoli have developed could be most serious.

The suggestion that unilateral hypertransradiancy in the adult is the result of disease acquired in childhood would be strengthened if the condition could be demonstrated in a patient known earlier to have been normal. Three such cases have been seen. In one studied by Simon and reported by Darke *et al.*, 1960, the hypertransradiancy developed some two years after the region had been passed as normal: in another hyper-

transradiancy developed after measles, although an earlier radiograph was normal (Simon and Reid, 1966).

The following is a third case.

CASE 22.—DEVELOPMENT OF HYPERTRANSRADIANCY

This patient developed a primary tuberculous infection but there was no hypertransradiancy of either lung. Eighteen months later the left lung was seen to be hypertransradiant and a bronchogram showed bronchial (or bronchiolar) obliterations, while 5 and 15 years later bronchograms showed an increase in diameter of the patent bronchi although the pattern of filling on the bronchogram had not altered.

The boy, aged 6, was admitted to hospital because of fever and found to be suffering from primary tuberculosis; he developed a left spontaneous pneumothorax and the left lower lobe was found to be collapsed. Radiographs showed a progression from consolidation and collapse of the lower lobe to re-aeration. The initial radiograph showed collapse of the left lower lobe but no abnormal transradiancy of the left upper lobe; films taken two years later, after re-expansion of the lower lobe, showed increased transradiancy of the whole of the left lung and this has persisted since. The bronchogram taken at the age of 7 showed good peripheral filling in the right lung, but none in the left (Fig. 65) and, although the upper lobe showed mainly a broken bough appearance, in the lower lobe dilatation and irregular tapering endings were evident.

The bronchogram was repeated at 12 and 22 years of age and these showed that the level of the blockages in the bronchial tree remained unchanged, although the length between certain bronchial levels had increased. The distance between two points on the upper part of the left main bronchus, identifiable in the bronchograms taken at the ages of 7, 12, and 22, had increased from 9 to 11·5 to 14 cm. The chest length, measured between the first rib and the diaphragm, was 18, 23, and 29 cm. respectively, the proportion of supra- and infra-hilar regions being the same at all ages. Between the ages of 12 and 22 the diameter of the left main bronchus had increased from 1·3 to 2 cm.

The radiograph has since remained unchanged, as also in other reported cases with long follow-up. (See Dornhorst *et al.*, 1957 on Macleod's cases.) (For further discussion of prognosis see p. 143.)

Alveolar lesions.—The individual air spaces in cases of hypertransradiancy are abnormally large, that is, they are emphysematous. In spite of the increase in volume of individual alveoli the lung volume is usually normal or less, pointing to a hypoplasia. Since the development of the thoracic cage is not retarded as, for example, in kyphoscoliosis, the cage increases normally in volume whereas, because of disease, the increase in number and substance of the alveoli is less than normal.

The development of alveoli is mainly postnatal, about 20 million being

present at birth, rising only at the age of 8 to the adult number of some 300 million (Dunnill, 1962). When, therefore, infection occurs in early childhood the lung is small. Growth is a work hypertrophy, each respiration bringing a volume change. If there is less ventilation (and less blood flow) to the hypertransradiant side the alveoli lack the stimulus to multiplication (Reid and Simon, 1962 and 1964). After the age of 8, growth results in an increase not in the number of alveoli, but in their size and in the complexity of their walls as well as in the number of blood vessels.

Hypoplasia of the Pulmonary Artery and Capillary Bed.—The diameter of the pulmonary artery on the hypertransradiant side (as shown in the plain tomogram and angiogram) is less than that of the artery on the normal side but, in the specimen, though somewhat smaller than in the normal, the diameter is much greater than in the angiogram, and so nearly normal that a great increase in size must have occurred since birth.

Probably no single factor explains the final haemodynamic state of the lung. It may be that the factors that operated during the first incident of damage (Case 23) are different from those that maintain it. It has been shown that acute anoxia causes vasospasm (Fritts and Cournand, 1959) which, if it involved both lungs, would produce pulmonary hypertension, but, because it involves only a local area, deflects flow from the whole of one lung to the other side. Fouché and d'Silva (1960) showed narrowing of the pulmonary arteries in cats, after unilateral "miliary embolisation of pulmonary arteries". It is not known what effect vasospasm has in perpetuating reduced blood flow.

The reduced ventilation which results from the bronchiolar damage will persist when the acute inflammation subsides and so help to prolong the reductions in flow. Cournand and his colleagues (1935), from a series of experiments on the effect of collapse on circulation, concluded that it was the depth of ventilation rather than the degree of collapse that affected the minute volume of blood flow through the lung. This suggests that the pumping action of respiration contributes to the pulmonary circulation. Recently Riley (1959) indicated that although deep inspiration might increase minute volume blood flow to the lung as a whole, the size of the capillary bed is reduced during the inspiratory phase. From this it would seem that a lung in which air is trapped, i.e. one relatively hyperinflated, offers mechanical resistance to flow through its capillaries, contributing, possibly, to hypoplasia or atrophy of the capillary bed in cases of unilateral transradiancy.

Reduction in alveolar capillary blood content can clearly take place in acute bronchiolitis and if continued will probably retard lung growth. A secondary effect will be to reduce flow through the large vessels of the lobe (see the report of Hilton's findings, on p. 74).

From the specimen arteriogram (Fig. 67) it is clear that there is hypoplasia of the intra-acinar vessels. Counts of the number of vessels between

FIG. 69.—Case 23. Posterior view; angiogram showing injection pulmonary artery. Bronchiolitis obliterans—early effect. Reduction in blood flow to left lung, eighteen months after onset of recurrent left-sided bronchiolitis. Right side normal: hardly any filling on left.

30 and 100 μ in relation to alveolar number and size, points to the peripheral small vessels being more affected than the alveoli by the hypoplasia (Elliott, 1964*b*.)

Childhood cases of acute suffocative bronchiolitis (unilateral) demonstrate decreased pulmonary blood flow in the early stages of the disease. In Case 23 resection before emphysema had developed revealed a virtually normal pulmonary artery and a subacute or chronic bronchiolitis, and it was clear that bronchiolar lesions interfering with pulmonary blood flow before any alveolar or pulmonary artery structural change had developed, pointed to the airway lesions as the primary cause.

FIG. 70.—Case 23. Bronchogram. Absence of peripheral filling through left lung; irregular endings to filled airways. The plain radiograph had shown the vessels smaller and relative hypertransradiancy of the left lung.

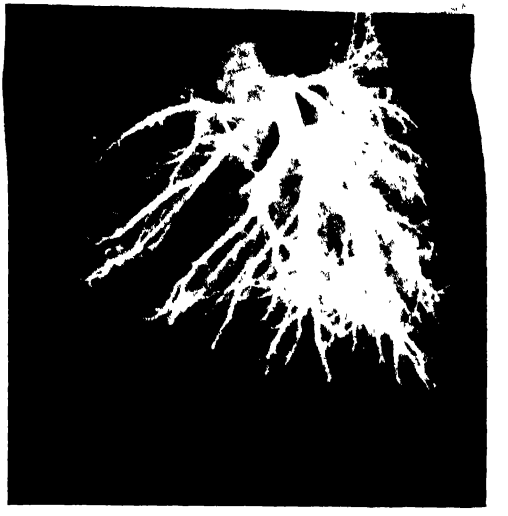


FIG. 71.—Case 23. Specimen pulmonary arteriogram showing good filling and normal sized pulmonary artery of left lower lobe and lingula. For comparison with angiogram in life, Fig. 69. See also Figs. 70, 72 and 73.

CASE 23.—ACUTE SUFFOCATIVE BRONCHIOLITIS

A boy aged one year was admitted to hospital with bilateral bronchopneumonia, worse on the left side. On discharge a few weeks later his radiograph was normal, but over the next 18 months he had recurrent pulmonary infections on the left side and there was some suspicion that the left lung was hypertransradiant. An angiogram (Fig. 69) showed hardly any blood flow to the left lung; a bronchogram revealed that filling had occurred in only the first 5–6 generations along an axial pathway and that these were irregular in outline (Fig. 70).

The left lung was removed and the size of the left pulmonary artery was seen to be the same as the right. Injection of the pulmonary artery with micropaque (Fig. 71) revealed normal filling to within the acini, indicating that the dramatic reduction in blood flow seen in the pre-operative angiogram was functional and not due to structural changes in the vessels. There was some filling of the bronchial arteries from the pulmonary artery injection.

Alveolar development seemed normal, and the only emphysema was a few abnormally large alveoli adjacent to the bronchioli. The walls of the bronchioli were thickened, partly by fibrous tissue and partly with inflammatory cells, so that widespread bronchiolitis obliterans was present (Figs. 72 and 73).

The hypertransradiancy appeared before structural emphysema could have developed, indicating functional change particularly in blood flow.

A reduction in the pulmonary artery flow, as in embolism of a main pulmonary artery branch, does not necessarily give rise to hypertransradiancy; an embolus or thrombus has sometimes been found in a patient with a normal chest radiograph. In bronchiolitis obliterans the associated air-trapping probably reduces the alveolar capillary flow below that which is present after embolic block without air-trapping, that is, the air-trapping

FIG. 72.—Case 23. Same case as Fig. 69. Low power magnification of distal 3 cm. of lingula showing bronchiolitis—thickening of walls of bronchioli, irregularity of lumen, small airways choked in scar tissue at arrow, but alveoli mainly normal. See also Figs. 69–71 and 73. (× 4·5.)

has interfered with the amount of alveolar blood. Presumably, in pulmonary embolus without transradiancy, the normal ventilation allows the bronchial system to maintain a normal alveolar blood content.

The cases, described on p. 71, of ball-valve obstruction to large bronchi with little volume increase in the affected lung, illustrate the development of hypertransradiancy with air-trapping. Both air-trapping and hypertransradiancy in these cases were reversible. It is suggested that the interference with blood flow to the lobe was the main cause of the hypertransradiancy.

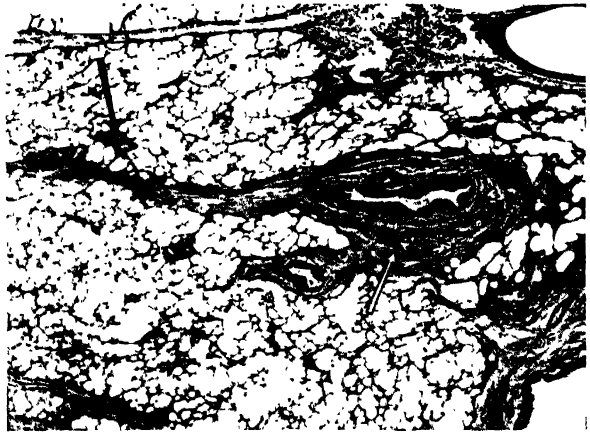


FIG. 73.—Case 23. Photomicrograph. Normal alveoli but bronchiolitis with peribronchiolar fibrosis of peripheral airways in lingula at white arrow; at black arrow remnants of small airways obliterated in scar tissue. No emphysema. See also Figs. 69–72. (× 15.)

Restrictive Pleural Disease

By causing airways obstruction, bronchiolar disease before lung growth is complete may result in hypoplasia. However, hypoplasia may develop through ventilatory restriction caused otherwise, as by pleural disease. The following case is one of hypoplasia without hypertransradiancy and hence it is not an example of Macleod's syndrome.

Case 24.—Hypoplasia with Restrictive Pleural Disease

A woman, aged 46, presented with slight cough as the only symptom. The radiograph revealed that the left dome of the diaphragm was flat, the trachea central, and the heart displaced somewhat to the left: the right lung appeared normal save for apical scars: the left lung showed small pulmonary vessels. There was loss of transradiancy in the axilla and at the base, and peripheral line shadows indicated that this was due to pleural change which would hide any lung hypertransradiancy.

A left bronchogram showed no narrowing of the upper lobe bronchus such as had been reported at bronchoscopy, but all branches were very small. Peripheral filling was poor in the upper lobe and in the basal region of the lower lobe where it was associated with numerous "pools"; in the apical region of the lower and the proximal part of the anterior basal lobes, peripheral filling was good.

The radiographic appearances point to hypoplasia of the left lung with pleural thickening and patchy areas of localised bronchiolitis obliterans. As stated above, lung hypertransradiancy (if present) was masked by the pleural shadow; peripheral filling was normal in a much larger area than is usual in unilateral hypertransradiancy. The hypoplasia was probably the result both of the restrictive pleuritis and of the bronchiolitis obliterans.

Hypoplasia of bronchial cartilage.—In cases of hypertransradiancy the main bronchus may appear quite normal and its cartilage plates well-developed and rigid; or the plates may be thin. The variation in thickness of cartilage plates in the adult is very great. If there is hypoplasia of cartilage it is probably an expression of general hypoplasia of the lung resulting from reduced "work" during the growth period. Since hypoplasia of cartilage is not always found, it would seem not to be the cause of emphysema.

Macleod (1954) excluded from his series patients with excessive collapse of the airways, i.e. those in whom at bronchoscopy the walls of the larger bronchi fell together. Why this occurs in some cases, but not all, is unknown, but it would not seem necessary to exclude these. (See p. 177 for further discussion of the relationship of cartilage changes to airways collapse.)

The following case illustrates excessive collapsibility of the walls of the airways in unilateral hypertransradiancy.

CASE 25.—COLLAPSE OF AIRWAYS

This woman, a nurse of 24 (1954), had been chesty as a child and early had "bronchopneumonia" and "double pneumonia". During her training she had had several haemoptyses and some years later developed a cold with sputum production; a diagnosis of "doubtful bronchiectasis" was made following a bronchogram. Her nursing career terminated because of her shortness of breath and the diagnosis was "chronic bronchitis and emphysema".

As revealed by the radiograph (1957), the right leaf of the diaphragm was flat but at the normal level: the heart was displaced slightly to the right; the trachea was central. The right lung showed a slight relative transradiancy and the horizontal fissure was normal. The hilar vessels and lung vessels were small but their distribution normal. This was confirmed by the angiogram (Fig. 74), which showed a poor flow to the right lung and a poor venous return. The angiogram of the left lung showed a reduced flow to the left lower lobe, but was otherwise normal.

Bronchograms revealed poor peripheral filling on the right side with some cystic dilatations of upper lobe side branches; the right main bronchus was of normal calibre. On the left side, the upper lobe was normal with good peripheral filling, while in the lower lobe, which was reduced in volume, peripheral filling was poor and slight side branch bronchiectasis was seen in the left apical lower and the basal bronchi.

In 1954 the respiratory function tests were as follows:

VC	1890 ml.
FRC	3370 ml.
TLC	4420 ml.
RC/TLC	57%
MVV	42 litres

Bronchospirometry	*Right Lung*	*Left Lung*
VC	750 ml.	900 ml.
Ventilation	3·1 l.	5·0 l.
O_2 consumption	117 ml.	250 ml.

Dco at rest: 7·2 ml./min./mm.Hg.
Dco on exercise: 15·9 ml./min./mm.Hg.

Radioactive xenon studies showed that the ventilation and perfusion in the right upper zone were reduced as compared with the left upper zone, but that both lower zones were about the same.

On bronchoscopy the walls of the bronchi on the right were seen to collapse on expiration. Because it was thought that this might contribute to disability the right main bronchus was splinted. At thoracotomy the right lung was less pigmented than usual, failed to collapse spontaneously, and could not be compressed. The right main bronchus was easily compressed, and even when it was splinted by wire the lung did not deflate. The left main bronchus also felt soft.

This case illustrates hypoplasia of the right lung and probably also of the left lower lobe, following bronchiolar lesions in childhood. In these regions the angiograms showed that blood flow was reduced. The failure

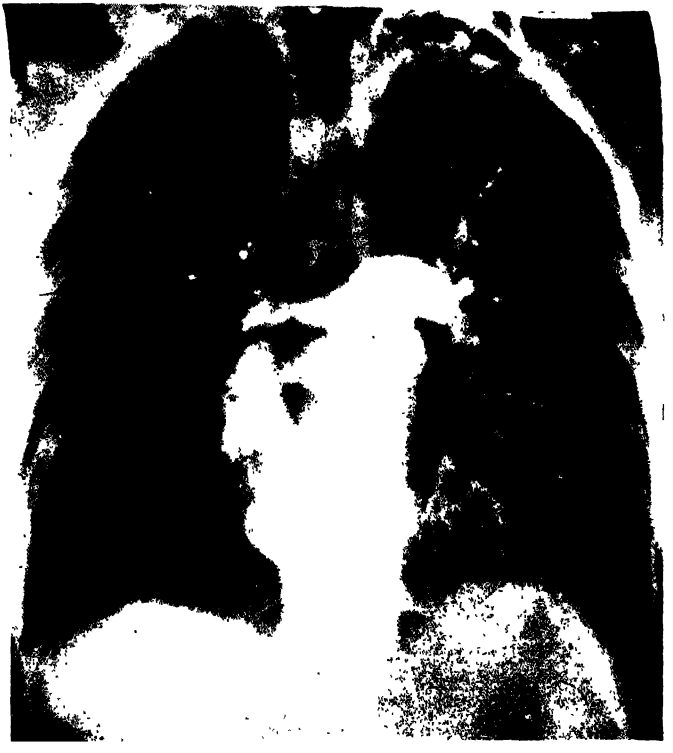


FIG. 74.—Case 25. Hypertransradiancy of right lung, reduction in volume of left lower lobe. Blood flow very reduced through right lung and some reduction through left lower lobe. Bronchogram showed evidence of bronchial disease throughout right lung and left lower lobe.

of the splint to correct the air-trapping would suggest that collapse of the central airways follows the trapping of air at a peripheral level.

Causes

Any condition which produces patchy damage to the bronchial or bronchiolar tree may give rise to unilateral hypoplasia with emphysema. Infection is the most obvious cause of bronchitis or bronchiolitis stenosans, presenting as unilateral or unilobar transradiancy. Chemical damage might produce essentially the same pathological picture but is less likely to be localised.

Infection.—The bacterium responsible for infection cannot usually be identified with certainty. For example, measles, whooping cough, bronchopneumonia, lobar pneumonia, tuberculosis or bronchitis may be the

clinical diagnosis but, even if a specific virus or bacterium is associated with the primary condition, it does not follow that it is responsible for the bronchiolar lesions.

In tuberculosis, for instance, secondary invaders rather than the primary organism are likely to be responsible (e.g. Cases 22 and 27), but the effect of inflammatory products which are essentially sterile has also to be considered. The non-caseating giant cell pneumonia (Miller *et al.*, 1963) which produces a "large white lobe" in the radiograph is evidently a response to the caseous material aspirated from the lymph nodes (Case 26). The chemical constituents of dead tubercle bacilli and necrotic tissue seem able to produce the inflammatory response without the necrosis characteristic of multiplying tubercle bacilli. The details of the mechanism involved in this are not clear, but the damage that may arise is described below (Case 26). Once the fibrosis has developed it is usually impossible to be certain which of the above mechanisms was involved, but it is unlikely that living tubercle bacilli in any number have contributed, for if that were so more serious and acute tuberculosis would be expected.

Case 26.—Lobar Consolidation in Childhood Tuberculosis—Bronchiolitis Obliterans

Bronchitis obliterans may be the residual change from pneumonic consolidation of the lobe during childhood tuberculosis.

A girl, aged 12, seen because of contact with pulmonary tuberculosis, was found to have enlarged right hilar glands. Some weeks later there was radiographic evidence of consolidation of the right lower lobe. This cleared, but within a few months the lobe was resected because of the serious changes seen in lobes resected during the consolidation stage from other patients. At first sight the lobe in this case appeared normal, although the air spaces were coarse and irregular, but sections showed a peribronchiolar fibrosis with bronchiolar obliteration and distortion as well as some emphysema (Fig. 75). The bronchiolar changes, though widespread, had not been obvious on naked-eye examination, nor had they become apparent on the radiograph. What the effect on growth would have been in this child cannot be certain, but the pathological changes suggest that this is one type of childhood tuberculosis, asymptomatic at the time, which could lead to localised radiographic hypertransradiancy associated with hypoplasia.

Case 27.—Unilateral Hypertransradiancy following Childhood Tuberculosis

Hypertransradiancy in an adult may follow childhood tuberculosis, the alveolar changes being associated with stenosis of large bronchi.

A Cypriot male of 32 years, presented because of recurrent haemoptyses during the previous five years. He admitted to shortness of breath since

FIG. 75.—Case 26. Photomicrograph. Right lower lobe some months after resolution of consolidation associated with caseating tuberculosis in hilar lymph nodes; peribronchiolar fibrosis and stenosing bronchiolitis in scar (B); emphysema present. (× 35.)

childhood and to recurrent febrile chest illnesses for seven years, after each of which he had coughed up muco-purulent secretions. A radiograph showed that the right diaphragm was low, the heart and trachea displaced to the right, the right lung hypertransradiant, with small hilar and midlung vessels, and the left lung normal. Bronchograms (Fig. 66) showed that there was a stricture at the junction of the right main, upper and intermediate bronchi, occlusion of the middle lobe and, in most areas, no peripheral filling in spite of much contrast medium proximally.

When the right lung was resected the lower lobe was found to be pink, fluffy, and emphysematous: no bullae were present. Large scars lay under the pleura in the anterior and posterior segments of the upper lobe and the middle lobe showed the carnified appearance of chronic massive collapse. A calcified node lay between the main and upper lobe bronchus. The pulmonary artery was 8·5 mm. in diameter, the bronchus 11 × 8 mm., with the cartilage 2 mm. thick. In the specimen arteriogram (Fig. 67) the pulmonary artery filled to within the acini although the number of intra-acinar branches was below normal. Bronchial arteries both in large bronchi and bronchioli filled from the pulmonary artery through pre-capillary anastomoses.

No mucous gland hyptertrophy was found on microscopic examination of the bronchi. Throughout the aerated lower lobe the alveoli were emphysematous and many bronchioli were obliterated (Fig. 68). The lymph node excised from near the stenosis showed no caseation, only fibrosis.

The lower lobe was more transradiant than would be expected with

collapse of the middle lobe and through it there was widespread bronchiolitis obliterans. Although tuberculosis was presumed to be the cause, no characteristic histological evidence for it could be found in the resected specimen and it may be that the changes were produced by secondary invaders.

The pulmonary damage may well have followed childhood tuberculosis. It is of interest that there was no radiological evidence of calcified lymph nodes. Davies (1961) found that patients known to have severe lymph node involvement in childhood were not necessarily left with calcification visible in the plain radiograph. Although the right middle lobe was collapsed the transradiancy of the rest of the lung was much greater than would be caused by such collapse alone; as might be expected a childhood infection can give rise to a variety of lung changes including lung collapse and obliterative airway lesions.

RADIOLOGICAL DIFFERENTIAL DIAGNOSIS

Differences in Soft Tissue Cover

Transradiancy may be more definite in one lung than in the other because of difference in the density of the overlying soft tissues. They may be less dense on one side because of muscular atrophy from paralysis; or one group of muscles may be absent because of a developmental defect, or removed during a mastectomy operation; or the distribution of the soft tissue masses may be altered by rotation or scoliosis; or because the other side is larger as a result of muscular hypertrophy or a tumour. In all these instances the diagnosis of bronchitis obliterans with emphysema can be excluded because the two sides of the diaphragm lie at a normal level relative to each other and, if a radiograph is taken on expiration, they will move equally, so that there is no air-trapping. This test is not really necessary because the vessel pattern will be the same on the two sides.

Compensatory Emphysema

In compensatory emphysema of one lobe arising from collapse of the rest of the lung, any difference in transradiancy is usually slight, while the abnormality in size and shape of the hilar vessels and the more widely-spaced lung vessels serve to differentiate the condition from bronchitis obliterans, even when the shadow of the collapsed lobe is difficult to see without a penetrating or a lateral view radiograph.

Local Accentuation of Widespread General Emphysema

More difficult to differentiate from unilateral hypertransradiancy is widespread general emphysema with air-trapping and local accentuation of bullous areas in one lung (Cases 28 and 29). Unlike emphysema with

hypoplasia the hilar vessels are likely to be large on both sides and not merely small on the relatively transradiant side, while the diaphragm will be low and flat on both sides. The heart will tend to be narrow and vertical and may even in deep inspiration be displaced towards the less transradiant side. In a lateral view the retrosternal translucent zone will be much enlarged, which again will differentiate the condition from emphysema with hypoplasia in which the lung is in fact small and the retrosternal space normal.

Congenital Absence of One Pulmonary Artery

In congenital absence of a main pulmonary artery to one lung (Case 30) the difference in transradiancy is often relatively slight, the heart is in the normal position and the diaphragm moves normally on both sides because there is no airways obstruction.

Abnormalities of Blood Distribution in Congenital Heart Disease

In congenital heart disease the blood flow may be less to one lung than the other, and the vessels on one side may appear smaller. Alternatively, particularly after a Blalock type of operation, in which the pulmonary artery has been anastomosed with the sub-clavian artery, the flow in one lung may be increased. The abnormality of heart contour and of vessel size, the normal diaphragm, and the clinical findings will serve to indicate the correct diagnosis.

Unilateral opacity

Pathological opacity of one side may be even and relatively slight, so that the normal side is the more transradiant and is mistaken for the diseased side. Such opacity may be caused by a thin layer of pleural exudate. The diaphragm on the opaque side is often flattened and high while, if the condition is of long standing—following a therapeutic pneumothorax for instance—the vessels on the opaque side will, because of the poor lung function, be smaller than on the normal, more transradiant, side.

Hypoplasia without Hypertransradiancy, Air-trapping, or Emphysema

Hypoplasia of a lung is not necessarily associated with hypertransradiancy, air-trapping, or emphysema (Case 31). The diaphragm may be raised and the heart and trachea displaced toward the affected side, but on respiration the position of the heart may be unchanged and the diaphragm move normally. A bronchogram reveals normal airways as far as the lung periphery, and an angiogram shows a normal but small pulmonary artery and smaller branches.

The following cases illustrate problems of differential diagnosis.

CASE 28.—UNILATERAL ACCENTUATION OF EMPHYSEMA

In widespread emphysema bullae may produce a unilateral hypertransradiancy.

This patient presented with a severe attack of acute bronchitis in 1957 at the age of 47. Thereafter he became progressively more short of breath. Bronchospirometry revealed no oxygen uptake by the right lung and 230 cc. by the left. FVC 1000 cc.; FEV_1 400 cc., 40 per cent; MBC (calculated) 14 l./min.

In the radiograph the diaphragm appeared low and flat at the level of the seventh rib anteriorly; the heart had a narrow vertical configuration with a diameter of 11·5 cm. The main pulmonary artery and hilar vessels were large while the intrapulmonary vessels were small. Avascular areas not demarcated by line shadows were seen throughout the whole of the right lung and in the upper third of the left.

The diagnosis of Macleod's syndrome was made but pathological examination of the resected lung showed widespread panacinar emphysema with many regions of Grade IV severity (p. 17), while the lower lobe was compressed by two bullae, one at its apex, the other on its diaphragmatic surface. Between the right upper and middle lobes there was no fissure.

The large hilar shadows in this case should have led to the diagnosis of widespread emphysema with large bullous areas in the right lung.

CASE 29.—UNILATERAL ACCENTUATION OF EMPHYSEMA

Large bullae localised to a single lung may be diagnosed as "unilateral transradiancy" or Macleod's syndrome. In the following case the diagnosis was based on radioactive gas studies showing hardly any function.

The patient, aged 67 in 1962, had complained of winter cough for twelve years and had produced as much as a cup of frothy sputum each day. During the previous year he had become increasingly short of breath.

The chest radiograph showed that the diaphragm was flat and at the level of the sixth rib. The heart was 13·5 cm. in transverse diameter. The main pulmonary artery was normal in size, both hilar shadows were large, and the vessels within the lung fields were small. The whole of the left lung appeared avascular and hypertransradiant, but no line shadows were seen. The distribution of the vessels suggested that some were displaced. In the right lower zone avascular areas demarcated by line shadows were seen.

The dominant appearance in the left lung radiograph was that of a large bulla; yet, the rest of the lower lobe being compressed postero-medially, the blood vessel pattern was seen through the bulla so that the bulla was at first overlooked. Xenon studies showed that ventilation in the left upper zone was about half that on the right. In the left lower zone it was not possible to establish a ratio as no clearance was recorded and it took about 6 seconds to reach 90 per cent of the final counting rate. It was reported that "the mechanics and blood flow and also mass spectrometric analysis at bronchoscopy were typical of a Macleod's syndrome".

In this patient the radiographic appearance should have precluded the diagnosis made of emphysema associated with bronchiolitis and bronchitis obliterans of childhood, and the case illustrates the value of adequate study of the radiograph. Respiratory function studies revealed hypoxia (PO_2 73 mm. Hg) and CO_2 retention (P_{CO_2} 49 mm. Hg).

The patient was convalescing when he suddenly died. At autopsy thick mucus was found blocking the lower lobe bronchi. The left lung was largely replaced by bullae; the lower lobe consisted of a large bulla with a few strands of tissue across it, while the rest of the lobe, which was small in volume, was compressed. The apex of its upper lobe was bullous and included candy floss lung. Carbon was distributed throughout the lung save for the tip of the lingula which was pink and fluffy. The right lung contained much carbon with some centriacinar emphysema, but mostly panacinar Grade III or IV; at its base there was a bulla about 15 cm. in diameter and containing candy floss lung.

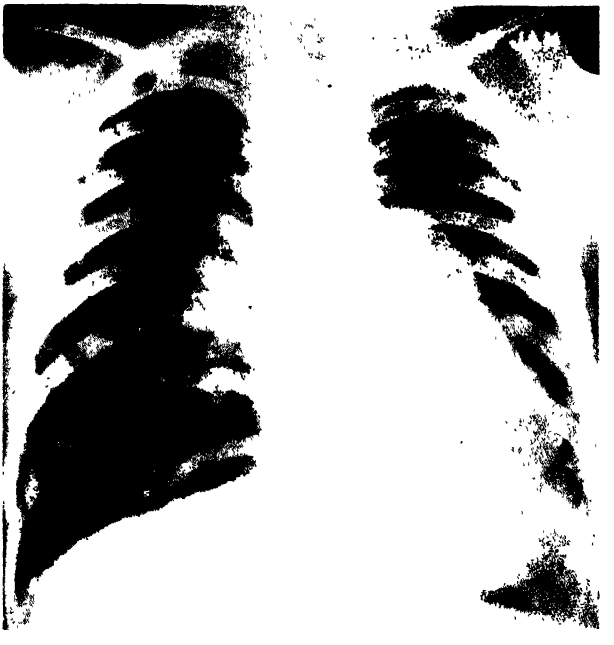


FIG. 76.—Case 30. Absent left pulmonary artery—no hypertransradiancy on the left. Absence of artery detected by angiography and confirmed at thoracotomy.

CASE 30.—ABSENCE OF PULMONARY ARTERY

The absence of a pulmonary artery does not necessarily produce hypertransradiancy. In the following case the anatomical anomaly was confirmed at thoracotomy.

A child of six years was investigated for congenital heart disease. The postero-anterior radiograph showed a normal diaphragm with the trachea

central and the heart to the left (Fig. 76). The right lung was normal save for enlarged hilar vessels; the left lung was rather more opaque than the right; no hilar vessels could be seen and the mid-lung vessels were small.

Angiography showed no evidence of a left pulmonary artery and the right pulmonary artery was narrow at its origin and with a post-stenotic dilatation. A patent ductus arteriosus and a right-sided aortic arch were identified. Radioactive gas studies, using radioactive oxygen (O^{15}) revealed no gas clearance in the left lung and negligible circulation. There was a high clearance in the right lung with an approximately equal blood flow top and bottom.

At thoracotomy the patent ductus arteriosus was closed and it was confirmed that there was no pulmonary artery to the left lung but that venous drainage was normal.

Case 31.—Hypoplasia with Small Pulmonary Artery without Hypertransradiancy, Air-trapping, or Emphysema

This young woman from the Potteries presented at the age of 20 years with a history of recurrent infections causing her to lose time from work. Although she had been "chesty" as a child she had not lost time from school.

The resonance of the left side of the chest was impaired, breath sounds were weak, and there were numerous rhonci.

In the radiograph (Fig. 77) the right dome of the diaphragm lay between the 6th and 7th rib and lower than the left dome. On expiration the right dome moved up to the 5th rib and the left moved the same amount. The heart and trachea were displaced to the left, their position being unchanged during respiration, suggesting that there was no air-trapping. This was confirmed by the normal clouding of both lungs on expiration. The right lung had normal fissures and normal blood vessels. The left lung was less transradiant than the right and had a peripheral line shadow over the apex and down to the axilla. Only peripheral vessels were visible because of the displaced heart and these were normal in number though small.

Bronchography (Fig. 78) confirmed that the left bronchi were small with a normal hilar and segmental arrangement. Filling extended well into the region of the centimetre pattern but to the millimetre pattern only in some regions. Filling was slow. The filled airways showed a squared ending and all filled pathways were normal. The bronchogram was more normal than any of the cases seen with hypertransradiancy.

At pneumonectomy the pulmonary artery was found to be very small, only 8 mm. in diameter; there was little carbon pigment in the lung, a rare finding in the Potteries. Adhesions were divided in removing the lung.

The specimen was inflated through the bronchus. The pleural surface revealed an extraordinary appearance of white lines several millimetres in diameter passing particularly in a craniocaudal direction—histologically these suggested lymphatics.

The lung felt firmer than normal and on cutting was rather tough, although there was no evidence of scarring (Fig. 79). The pulmonary artery

FIG. 77.—Case 31. Hypoplasia small left pulmonary artery; no hypertransradiancy; no air-trapping. See also Figs. 78, 79 and 80.

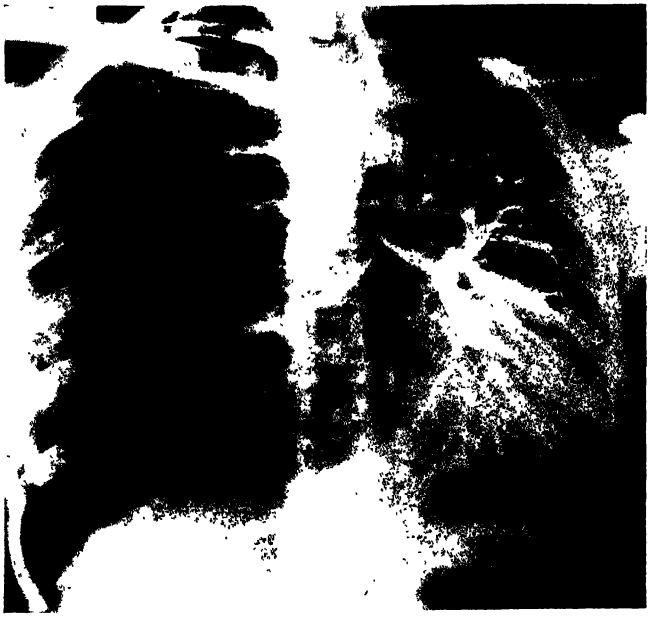


Fig. 78.—Case 31. Bronchogram shows left lung normal but small, with filling to the centimetre pattern. See also Figs. 77, 79 and 80.

FIG. 79.—Case 31. Cut surface of lung showing no emphysema, no scarring. Large pleural vessels seen at arrow. See also Figs. 77, 78 and 80.

FIG. 80.—Case 31. Photomicrograph showing normal alveolar structure. Pleura includes collections of muscle, suggesting hamartomata. See also Figs. 77, 78 and 79. (×40.)

and bronchi appeared small and the veins were difficult to see (Fig. 80). The architecture appeared intact and not only was there no emphysema but the air spaces seemed smaller. There were only scattered foci of pigment.

PROGNOSIS AND DISABILITY

The prognosis in unilateral hypertransradiancy associated with obliterative bronchial disease acquired in childhood would seem to be surprisingly good. So many cases are first diagnosed as the result of mass miniature radiography that even by a late age symptoms have usually not developed.

On the other hand, as more cases are seen, the radiographic appearance gives rise to problems in the diagnosis and assessment of associated disability, such as the reduction in pulmonary reserve produced by the absence of function in one lung. Any disease in the sound lung, such as pneumonia or acute or chronic bronchitis, might thus render the patient more short of breath.

If chronic bronchitis is present in a patient who also shows unilateral hypertransradiancy it is more difficult to decide the cause of dyspnoea when there is no evidence of pus in the sputum and no temperature. A case illustrating this is that of a woman producing a few ounces of sputum a day and short of breath, who was distressed by climbing stairs and even by bathing. She was not cyanosed and her blood gases were normal. The radiograph disclosed no bullae or other evidence of widespread emphysema, but her left lung was hypertransradiant. Her sensation of dyspnoea, not in keeping with normal blood gases even on exercise, may have been produced from blockage of airways by secretions.

Whether there can be dyspnoea if one lung is normal is not known. Most patients with dyspnoea and Macleod's syndrome have other reasons for airways obstruction in the contralateral lung. Cases 33 and 34 were complicated by the presence of chronic bronchitis.

Mediastinal shift might contribute to disability, but the air in the transradiant lung is not under a ball-valve type of pressure and there is no evidence that mediastinal shift is enough to hinder filling and emptying of normal lung. If bullous disease is present it may cause mechanical interference. Bullae in addition to the hypertransradiancy are rare.

CASE 32.—BULLAE, WITH UNILATERAL HYPERTRANSRADIANCY

This case is one of only two examples of bullae seen in a large series of radiographs of unilateral or unilobar hypertransradiancy.

At the age of 53, the patient presented with a three years' history of shortness of breath and of sputum production of a quarter cupful per day. He had had a cough since childhood.

The radiograph showed a flat left diaphragm with lower lobe collapse, hypertransradiancy of the left upper lobe with avascular areas, some demarcated by line shadows indicating bullae. The cause of emphysema in this lobe was in part compensatory overinflation and in part hypoplasia associated with bronchiolitis obliterans.

A bronchogram showed collapse of the left lower lobe, tapering and irregular endings of bronchitis obliterans in the lingula, and poor filling of the rest of the upper lobe.

Relation of Unilateral Hypertransradiancy to Right Ventricular Hypertrophy

Usually the vascular bed in a normal lung is well able to accommodate the blood flow of two lungs. In the first of the cases reported by Rivett (1960) there was plethora of the contralateral lung and, unlike other reported cases, the patient's condition was steadily deteriorating. His shortness of breath started at the age of twenty-seven when he increased from ten to fifty the number of cigarettes smoked daily. Since his respiratory function tests revealed widespread airways obstruction, which responded to broncho-dilator drugs, even the functioning of the plethoric lung could not be considered normal.

Case 33.—Polycythaemia and Right Ventricular Hypertrophy

The development of polycythaemia and right ventricular hypertrophy in a patient known to have had unilateral hypertransradiancy for many years is rare. It is illustrated by this case:

In 1959, at the age of 50, this man presented to hospital because of a chest infection associated with a week's swelling of the ankles. He reported that for twelve years he had suffered from increasing breathlessness on exertion. "Sometime in his twenties" he spent five months in hospital for lung trouble, since when he had had several attacks of pneumonia.

In 1959 he was cyanosed, his legs were oedematous to the knees, the jugular venous pressure was + 3 cm., and the liver was palpable. His haemoglobin level was 15 grams per cent. The heart failure was associated with atrial flutter and a 2:1 block. Respiratory function studies revealed gross impairment of ventilation and reduction in diffusion capacity. It is unlikely that at this time the patient had polycythaemia or right ventricular hypertrophy of severe degree.

The radiograph showed bilateral pleural effusion with, possibly, middle lobe shrinkage and patchy clouding in the left middle zone (Fig. 81). The heart was enlarged to a diameter of 16·5 cm., having been 13 cm. in 1958. After three weeks' treatment the diaphragm was lower, the heart 13 cm. in diameter, and both lungs were clear except for the changes described below in the 1964 film. By 1963 the heart measurement was 15·5 cm. The ventilatory tests did not change between 1959 and 1964.

In 1964 the radiograph showed a hypertransradiancy of the right lung, which was small; on inspiration the heart and trachea moved toward the right. The right diaphragm moved 1·5 cm., the left 3 cm. The right hilar vessels and lung vessels were small; on the left they were large, since the left lung was plethoric, and between 1958 and 1964 the left hilar vessels had doubled in diameter.

The haemoglobin was 19·2 grams per cent, the packed cell volume 63 per cent, and the mean corpuscular haemoglobin content 30; the electrocardiogram showed evidence of right ventricular hypertrophy, but there was no longer any evidence of the right bundle branch block present in earlier tracings. Xenon studies revealed greatly impaired ventilation and perfusion of the right lung compared with the left. Although he had developed polycythaemia and right ventricular hypertrophy this patient has continued in better clinical state than Case 34.

FIG. 81.—Case 33. Unilateral hypertransradiancy of the right lung with pulmonary oedema only in left. Chronic bronchitis as well as unilateral hypertransradiancy. Shadows in left lung disappeared as oedema responded to treatment.

Between 1958 and 1964 he had had recurrent bouts of infection and he would seem to have qualified as a case of chronic bronchitis. The bronchogram in 1964 showed narrowing of the right upper lobe bronchus and no filling anywhere in the right bronchial tree beyond the 6th generation, whose endings were sometimes tapering, sometimes broken bough. Irregularities of the filled airways were seen, but no collapse. On the left the overall filling was good, with filling to the centimetre pattern in many regions.

The chronic bronchitis with airways obstruction associated with unilateral hypertransradiancy probably accounts for the development of

polycythaemia and right ventricular hypertrophy. Only the "normal" lung appeared plethoric, although during an incident of heart failure a pleural effusion and, possibly, pulmonary oedema had affected the hypertransradiant lung.

CASE 34.—HYPOPLASIA OF RIGHT LUNG—EMPHYSEMA—CHRONIC BRONCHITIS

The following case illustrates hypoplasia of the right lung, accompanied in the upper and middle lobes by airway disease and in the lower with restriction to ventilation because of pleural disease, as in Case 32. The patient developed chronic bronchitis. (This case was described at a Clinicopathological Conference, reported *Brit. med. J.*, 1965.)

FIG. 82.—Case 34. Hypertransradiancy of right lung, particularly right upper lobe. Patient also suffered from chronic bronchitis. See also Figs. 83, 84 and 85.

All his adult life the patient had been a heavy smoker. In 1957, at the age of 56, he first came to hospital because of respiratory symptoms, in particular, shortness of breath on exertion, with cough and mucoid sputum. The production of sputum first became chronic during the Second World War. He was a thin man and had neither cyanosis nor finger clubbing.

Breath sounds were diminished over the whole of the right chest. The radiograph of 1957 revealed hypertransradiancy of the right upper and mid zones. Bronchoscopy showed no abnormality.

In 1958 he was admitted to hospital cyanosed and short of breath at rest, with no peripheral oedema and a jugular venous pressure 1½" above the sternum. His electrocardiogram was normal. His sputum was purulent, but the pus disappeared with the administration of antibiotics. Two years later, when oedema of the ankles had appeared and he complained of angina of effort, the electrocardiograph showed evidence of right ventricular hypertrophy. His haemoglobin was 14·4 grams. Between 1961 and 1963 he had recurrent bouts of cardiac failure with purulent sputum.

In the chest radiograph (Fig. 82) the left leaf of the diaphragm was normal and higher than the right; both were between the 6th and 7th ribs. The right leaf had a "low flat" configuration; the right half of the diaphragm barely moved, but was not paralysed. The heart was 13·5 cm. in diameter and somewhat to the right (but the patient was not straight). The left hilar vessels were prominent but were perhaps normal because of this displacement. The upper half of the right lung was seen to be transradiant and avascular, the upper hilar vessels small, the lower descending artery within normal limits, though smaller than the left. The horizontal fissure was slightly depressed and just above the right dome of the diaphragm was another avascular area.

FIG. 83.—Case 34. Poor peripheral filling in right bronchogram—worse in upper than lower lobe. See also Figs. 82, 84, and 85.

The above were confirmed in the lateral radiograph and the tomograms. A right bronchogram (Fig. 83), the only one performed, showed no peripheral filling; the endings, being broken bough except for one branch of the lateral basal bronchus, where filling penetrated to the region of the centimetre pattern.

Respiratory function tests.—Arterial blood gas studies showed desaturation and carbon dioxide retention. The respiratory function tests were as follows:

	1960
FVC	1400 ml.
FEV_1	700 ml.
$\frac{FEV_1}{FVC}$	50%
PEF	220 ml.
VC	1650 ml.
FRC	2900 ml.
RC	1250 ml.
TLC	3920 ml.
RC/TLC	58%

Mixing efficiency—7 mins. (i.e. impaired)

Dco at rest	6·1 ml./min./mm.Hg	(ventilation—8·0 l./min.)
Dco on exercise	8·7 ml./min./mm.Hg	(ventilation—18 l./min.)
	28% extraction	

FIG. 84 (*see opposite*)

Blood gases

	Sept. 1960	*March 1961*
O_2 satn.	71·5%	83·5%
Po_2	42	56
Pco_2	70	58
pH	7·31	7·29
HCO_3	31	25

The haemoglobin level in 1961 was 85 per cent of the normal value, in 1963 108 per cent; the packed corpuscular volume was 55 per cent at both times.

Treatment for bronchial infection, hypoxia, and heart failure enabled the patient to continue to work, although dyspnoea persisted until signs of heart

FIG. 85.

FIGS. 84 and 85.—Case 34. Specimen pulmonary arteriogram—radiograph of 1 cm. slice of lung. Fig. 84 left and Fig. 85 right lung. Left lung (2,100 ml.) larger than right (900 ml.) and better arterial filling than right. The slice of left lung represents a relatively smaller proportion of lung than the right slice. See also Figs. 82 and 83.

failure developed again in March 1963. In October he died, at the age of 62.

At autopsy, adhesions were found over the right lung, which was small. The pulmonary artery to each lung was injected (Figs. 84 and 85) and confirmed the hypoplasia of the right lung (water displacement 900 ml.) and its arterial bed. The left lung (water displacement 2100 ml.) showed no evidence of emphysema but the airways were filled with secretion.

The sliced right lung showed sparse and irregular deposits of carbon in the upper and middle lobes; in the lower lobe, carbon was widely distributed. In the upper and middle lobes panacinar emphysema was present; the basal region of the lower lobe, although much smaller than that of the left and therefore hypoplastic, did not show the same degree of emphysema as the right apical regions.

Microscopy showed mucous gland hypertrophy in the large bronchi of both lungs, and in the small airways of the left lung. The peripheral airways of the right lung were scarcely affected.

It is probable that this patient had a hypoplastic right lung as the result of childhood infection, impairment to ventilation, and hence to growth, having followed obliterative bronchial lesions as well as restrictive pleural fibrosis. Chronic bronchitis developed in adult life and although the left lung remained free of emphysema the widespread airways obstruction resulting from the bronchitis was associated with blood gas disturbance, polycythaemia, right ventricular hypertrophy, and failure.

Case 35.—Macleod's Syndrome and Development of Bronchiectasis

Infection in a lung already the site of bronchiolar distortion may cause further bronchial damage, as illustrated in this case, altering the bronchogram and leading perhaps to persistent sputum production. Francis (1961) has reported the complication of pneumonia in a "hyperlucent lung".

This patient presented at the age of 36 because of an attack of "bronchitis". The radiograph was typical of Macleod's syndrome and a bronchogram was done at this time. The patient admitted to an acute respiratory illness in childhood. Between 1952 and 1964 he had repeated incidents of infection after one of which the bronchogram was repeated.

The radiograph in 1952 showed that the right dome of the diaphragm was at the level of the sixth rib and normal. The left dome was at the same level. The heart was 11·5 cm. in diameter and the heart and trachea seemed displaced to the left, although the patient in fact was not very straight. The right lung appeared normal but the left lung showed relative hypertransradiancy with normal arrangement of the left hilar vessels which were small. It seemed therefore that the pulmonary artery was present with hilar branches and mid lung vessels, though small, distributed normally.

The bronchogram in 1952 showed in the upper lobe a few side branches with dilatations in the anterior segment. The lingula showed proximal dilatations and occlusions, but filling in the rest of this lobe was reasonably normal. The apical segment of the lower lobe appeared normal, while in the

basal segments penetration of the radio-opaque medium reached the centimetre pattern but in no place into the millimetre pattern. The filled airways were dilated and their endings tapering, concave or broken bough in appearance. The picture was thus of scattered bronchial disease with probably occlusive lesions in some regions, while in the others the implication was that the ventilatory "suck" was poor.

A radiograph in 1964 revealed an opacity in the left lower zone. The bronchogram after this incident of infection showed that in the lingula the dilatations were much more gross and that, although the apical lower lobe was still relatively normal, the changes in the basal segment were worse. Filling nowhere penetrated as far as in the previous film and the reason for this failure was to be seen in proximal dilatations which were gross. This meant that bronchi which had previously been reasonably normal were now dilated and obliterated.

UNILOBAR TRANSRADIANCY

The pathological basis for unilobar hypertransradiancy is essentially the same as for unilateral hypertransradiancy; the radiographic picture is the same within the lung and at the lobar hilum, but not at the hilum of the lung. This means that the lobar artery is reduced in size, while the hilar artery appears normal, which is why involvement of a whole lung seems so dramatic.

Unilobar hypertransradiancy may be:

(*a*) an isolated change, that is, affecting one or two lobes. the remainder of the lung being normal;
(*b*) associated with collapse of a lobe or lobes on the ipselateral side;
(*c*) associated with disease on the other side, e.g. contralateral hypertransradiancy.

Figures 86 and 87 illustrate a case in which one lung and one lobe in the other lung were diseased, and Fig. 74 a case where the right middle and lower lobes were affected.

CASE 36.—HYPERTRANSRADIANCY OF RIGHT LOWER AND MIDDLE LOBES

(a) Isolated Lobar Change

In this patient the right lower and middle lobes were both affected:

From the age of seventeen, this patient, a female, had occasional attacks of cough, particularly in the winter, with thick green sputum and wheezing. At thirty-seven a radiograph of her chest showed a large transradiant avascular area at the right base, with the heart somewhat to the right, and the right dome of the diaphragm low and flat (Fig. 86). At bronchography (Fig. 87) the radio-opaque material entered the transradiant zone in the right middle and lower lobes, but did not go beyond the 6th or 7th genera-

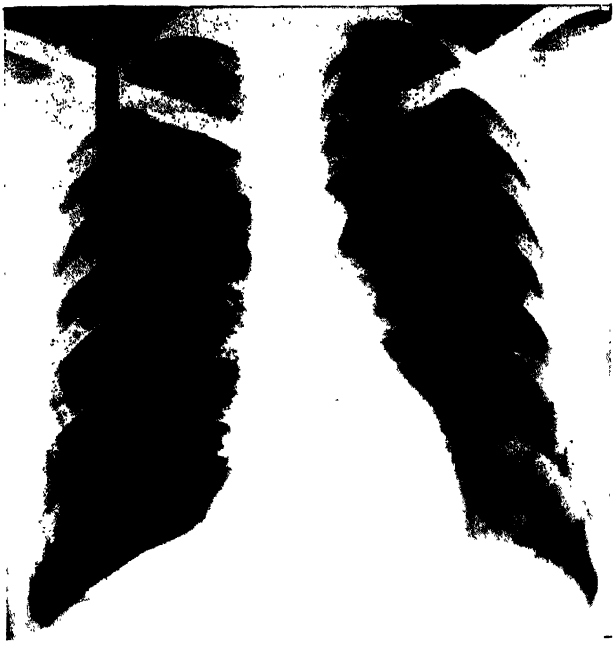


FIG. 86.

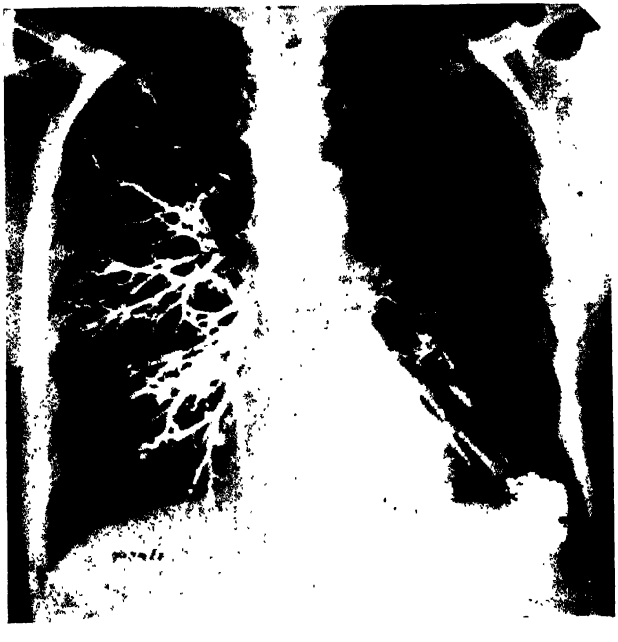


FIG. 87.

tion and showed a normal spatial distribution. Some of the endings of the filled pathways were rather clubbed, but dilatation was not striking.

By contrast, the right upper lobe showed good peripheral filling to the region of the millimetre pattern. Angiography showed a normal arterial branch to the upper lobe and a small one to the right lower and middle lobes.

When these latter were removed the bronchial artery was found to be of normal size though the pulmonary artery was small. The total volume of the lobes was within normal limits. Some carbon pigment was present in both, less distally than proximally; they were fluffy to the touch. On cutting, they showed Grade III widespread panacinar emphysema. The bronchial pathways were patent well to the periphery, when it became difficult to dissect them. The apical and medial basal segments were least affected. Step sections through a typical pathway revealed a bronchiolitis obliterans.

(b) Lobar Collapse with Hypertransradiancy

Macleod (1954) expressly excluded any case in which unilateral hypertransradiancy was associated with collapse. It has been emphasised that in compensatory emphysema there is usually no hypertransradiancy, so that overinflation does not explain it. From the pathogenesis of Macleod's syndrome it would seem likely that the disease can produce collapse in one lobe and patchy bronchiolitis obliterans in another, the latter causing a localised hypertransradiancy.

Case 27 illustrates a case of lower lobe emphysema with patchy bronchiolitis obliterans, massive collapse of the middle lobe, and dense scarring of most of the anterior segment of the upper lobe, findings which were confirmed at operation.

(c) Unilobar Hypertransradiancy with Contralateral Disease

If it is accepted that infective inflammatory disease acquired in childhood is the basis of radiographic hypertransradiancy associated with lung hypoplasia, it is unlikely always to be confined to one lung. Not only are the nature and distribution of lesions through one lung irregular but both lungs may be affected.

Case 25 (see p. 132) illustrates the same change throughout the whole of the right lung and the left lower lobe. It is worth repeating that, in spite of the widespread distribution of the bronchial disease, this patient produced no sputum.

BRONCHITIS OBLITERANS OF CHILDHOOD— LEVEL OF BRONCHIAL TREE AFFECTED

For convenience, the term bronchiolitis obliterans has been used in this chapter although obliterative lesions may affect not only the bronchioli but

FIGS. 86 and 87 (*see opposite*).—Case 36. Unilobar hypertransradiancy, with bronchiectasis, right lower lobe (bronchogram). No peripheral filling, dilated bronchi obliterated in region of medium and small sized bronchi.

bronchi also, producing a bronchitis obliterans. In patients whose radiographs show hypertransradiancy but who have no sputum production, bronchiolar lesions are the most characteristic finding. In surgical bronchiectasis associated with great sputum production the typical lesion is bronchitis obliterans, the term which Churchill uses (1952) to describe bronchiectasis, in order to focus attention on the nature of the critical lesion. If all bronchi are obliterated massive collapse will follow (Hayward and Reid, 1952); it is when obliteration of the bronchial tree is incomplete that the diseased airways, as outlined in a bronchogram, are separated by hypertransradiant lung.

In emphysema deriving from bronchitis obliterans occurring before growth is complete, the alveolar regions show the same characteristics of hypoplastic emphysema as in bronchiolitis obliterans. The lobes are usually normal or small in volume, even if transradiant and, furthermore, the pulmonary artery flow to them is small (Belcher *et al.*, 1959; Belcher and Pattinson, 1957).

Obliteration of large airways seems more often to be associated with persistent infection causing mucous gland hypertrophy than does bronchiolitis obliterans. Gland hypertrophy, while common, is not inevitable in bronchiectasis (Reid, 1960). The production of sputum may occur with either bronchial or bronchiolar lesions.

Bronchial Arteries

Pulmonary artery injection in cases of Macleod's syndrome has not revealed large bronchial arteries or particularly large pulmonary artery to bronchial artery anastomoses. In bronchiectasis, presumably because bronchial supply to large airways is greater, the bronchial artery anastomoses are usually very much larger and more numerous than in peripheral disease. This may reflect that infection is more persistent in the former.

"Congenital Bronchomalacia"

Fig. 88 shows a case of bronchitis obliterans with hypertransradiancy which are complications of infection in early childhood. A series of cases showing similar radiographs was reported by Williams and Campbell (1960), who showed that the airways filled to the region where cartilage became sparse. They suggested that a developmental defect in the cartilage was the cause of this pulmonary abnormality. But the abnormality might be the end result of the infections from which the children had suffered. The bronchial tree being diseased, alveolar development is impaired and although the lung volumes may increase, the number of alveoli will not rise normally nor will cartilage develop normally.

Correlation of Lung Hypoplasia with Age at Initial Incident

No correlation has been made between the size of the alveoli, that is the degree of emphysema, and the age at which the initial airways damage

from infection takes place. The younger the patient at the time of initial damage the greater the alveolar disturbance is likely to be.

Bronchiolitis Obliterans—Chemical Damage

The above cases have mostly been concerned with obliterative lesions following an infection. However, damage to small airways may also be produced by chemical fumes—nitrous oxide fumes are one of the industrial hazards which can cause acute ulcerative bronchiolitis (Darke and Warrack, 1958). Cases reported in the literature have been concerned only with the acute cases; no long-term effect, such as the development of air-trapping or hypertransradiancy has been reported.

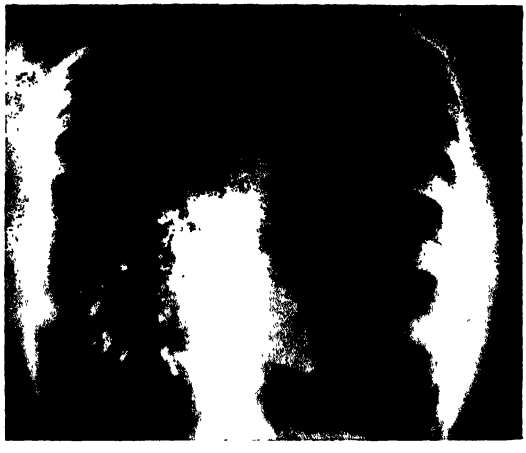


FIG. 88.—Hypertransradiancy right lower zone. Bronchogram shows dilated bronchi of first several generations with no filling beyond. Female, aged 23: occasionally green sputum.

Bronchiolitis Obliterans or Bronchitis Obliterans Acquired in Adulthood

If bronchiolitis obliterans develops patchily throughout a lobe in an adult, air-trapping with reduction in blood flow and hypertransradiancy may follow. Illustrations of this are ball-valve emphysema with no increase in lobe volume, and in Case 23, an example of bronchiolitis in childhood, hypertransradiancy supervened before structural changes had had time to develop. Hypertransradiancy following infection in a lobe of normal volume in the adult is rare. A young male (Case 37) was radiographed two years after an attack of pneumonia at the right base and it was found that the lower third of the right chest was hypertransradiant. A film previous to the pneumonia was available and was normal, but no bronchogram was available. The radiographic features would seem to be consistent with the deduction from Case 23, that hypertransradiancy can develop before alveolar structural changes, as the effect of change in blood flow.

The long-term effect on the alveolar walls of the reduction in blood content and flow is not known, or whether it could produce emphysema by atrophy of the alveolar walls.

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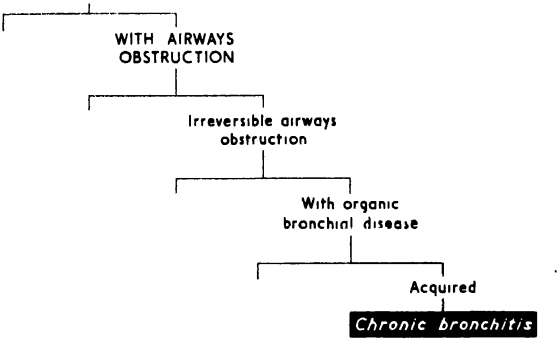
Chapter XII

EMPHYSEMA WITH CHRONIC BRONCHITIS



WHERE emphysema and chronic bronchitis are found together, the emphysema may have been caused by the chronic bronchitis or each may have developed independently of the other.

The clinical stigma of chronic bronchitis is the production of mucoid sputum; its pathological counterpart is an increase in the number of cells secreting mucus. Thus hypertrophy of the mucous glands in the large airways offers a pathological yardstick for diagnosis (Reid, 1960). In addition goblet cells are found in large numbers in the fine peripheral airways, a fact of significant functional implication and of help in diagnosis.

The diagnosis of emphysema by itself is incomplete unless it has taken into account the presence or absence of chronic bronchitis—and vice versa. Clinically the difficulties are very real since the same ventilatory disturbance may be found in chronic bronchitis as in emphysema. Airways obstruction may be found in primary emphysema, i.e. without structural bronchial changes, and in chronic bronchitis without emphysema, i.e. without any alveolar change. Thus all the functional disturbance associated with "emphysema" may be present without abnormally large air spaces, i.e. "structural" emphysema.

The chief cause of emphysema developing in chronic bronchitis is the damage to small airways and alveoli caused by infection.

DIAGNOSIS OF CHRONIC BRONCHITIS

CLINICAL AND EPIDEMIOLOGICAL

Clinical definitions of chronic bronchitis have varied. When epidemiological studies first demanded clear-cut criteria for diagnosis, there was

generally a feeling that disability or "sickness" must be included. Early definitions incorporated a reference to recurrent respiratory infections (Higgins, 1957) or to shortness of breath (Oswald, 1958); Stuart-Harris and Hanley (1957) grouped patients with "cough and sputum" separately from those with disability. Though the feature common to all was the chronic production of sputum, different limits were set to its duration. Ogilvie and Newell (1957), in a survey in Newcastle-upon-Tyne, were the first who insisted that cough and sputum alone justified the diagnosis of chronic bronchitis. This criterion has since been widely accepted (e.g. Medical Research Council questionnaire. 1960), and has been incorporated in definitions formulated by the Ciba Guest Symposium (1959) and the American Thoracic Society (1962).

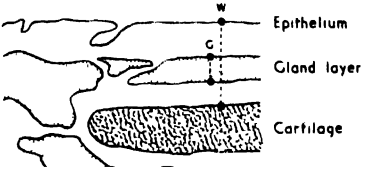


FIG. 89.—Gland wall (G/W) ratio. At a site where epithelium roughly parallel to cartilage, gland thickness (G) is measured and at same point wall thickness (W), i.e. distance from perichondrium to basement membrane of epithelium.

PATHOLOGICAL DIAGNOSIS OF CHRONIC BRONCHITIS—HYPERTROPHY OF MUCUS SECRETING STRUCTURES

Hypertrophy of Mucous Glands

In a case of persistent sputum production the mucous glands are hypertrophied throughout the trachea and large and small bronchi.

A quick and simple method of gauging gland hypertrophy is by reference to the ratio between gland thickness and bronchial wall thickness (Reid, 1960) (Fig. 89). This method may be augmented by estimating the hypertrophy of individual acini either as a count of the number of acini within the field of a microscope or as a measurement of acinar diameter (de Haller and Reid, 1965).

Measuring the largest acinus in the field avoids the necessity for formulating a convention for deciding what is "an acinus", as is required for the method of counting the number of acini in a field. There is a further method, that of establishing a ratio between the number of distended, and the number of granular, cells; while this points to a gland change which is characteristic of chronic bronchitis, the ratio is difficult to establish and is, therefore, of less value in a mild case. If a patient shows a gland/wall ratio falling between the normal and bronchitic limits these additional measurements may help in diagnosis.

Ratio of gland thickness to wall thickness (G/W ratio). Method of measuring.—At a site where cartilage is roughly parallel to the surface

epithelium of the bronchus the distance from the epithelium to the cartilage, the "internal wall thickness" (W) is measured and, at the same point, the depth of the mucous gland layer (G); the two are then expressed as a ratio, G/W—the gland/wall ratio (Table III: Fig. 89).

TABLE III

THICKNESS OF MUCOUS GLAND LAYER IN NORMAL AND CHRONIC BRONCHITIC BRONCHI

Group	*Cases*	*Bronchi*	*Thickness of Wall (mm.)*	*Gland (mm.)*	*Mean Gland/Wall Ratio and Range*	*Standard Error of Mean Ratio*	*Mean Acini*	*Standard Error of Mean Acini*	*Difference from Normal*
Normal	7	8	0·64	0·17	0·26 (0·14–0·36)	0·026	24	1·4	
Chronic Bronchitis	20	26	1·07	0·64	0·59 (0·41–0·79)	0·020	14	0·88	Significant P = <0·001

Measurements are made by means of a graticule set in the eyepiece of the microscope; they are expressed in "graticule units" and converted to millimetres. In routine examination of bronchi, however, a satisfactory estimate of gland size can often be made without a graticule and without the need for absolute measurement.

The main or lobar bronchi are most suitable for these measurements as the glands are distributed more or less evenly around their walls and the ducts open over the plates of cartilage as well as between them. The trachea, by contrast, is not always satisfactory as the ducts are concentrated between the plates of cartilage and, in the posterior wall, cartilage is missing; sites suitable for measurement are accordingly hard to find. The main and lobar bronchi are usually available in autopsy or resection specimens and are large enough to offer several sites.

The wall thickness of bronchi varies with the size of the person from whom they are taken and the more proximal airways have thicker walls than distal ones. The gland/wall ratio allows a valid comparison of bronchi in spite of these variations and also of any variation in gland size due to the glands passing between and outside the plates of cartilage. This distribution influences absolute gland measurement. The total gland area is greater where cartilage plates are separated by gaps and less where cartilage is continuous around the wall.

Other measurements tried were the maximum and minimum depths of glands and the area of gland and of bronchial wall, which were related to the maximum diameter of the bronchus and to that of the lumen; but none was as accurate and practicable for diagnosis as the G/W ratio (Reid, 1960). Gland area has been used by Restrepo and Heard (1963).

Range of gland/wall ratio in the normal and in chronic bronchitics.—The gland/wall ratio not only offers an objective basis for diagnosis but pro-

vides a quantitative assessment of the severity of the gland hypertrophy. Measurements made on bronchi from a group of subjects with no history of cough and sputum, not even a "smoker's" cough, showed that as far as could be established the range of the gland/wall ratio, even of older persons, was between 0·14 and 0·36 (Fig. 90). In patients with chronic bronchitis the range was 0·41–0·79. The details are shown in Table III and Fig. 89. There was no overlap between the normals and those chronic bronchitics whose cough and sputum had been present for five years or more.

In a survey of sections of bronchi taken from routine autopsy material Thurlbeck and Paré (1963) related the gland/wall ratio to sputum history taken from the notes. Their results for the "normal" group were higher than those indicated above, which is not surprising, seeing that their controls were judged "non-bronchitics" by the case notes.

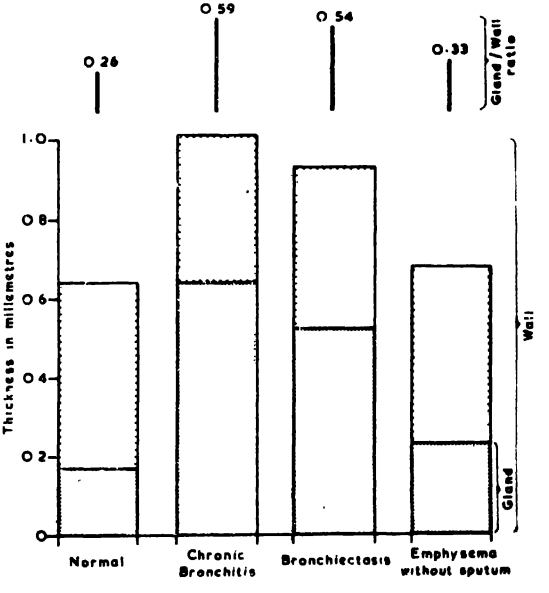


FIG. 90.—Histogram showing gland (G) and wall (W) thickness and G/W ratio, in normal, chronic bronchitis, bronchiectasis and emphysema without sputum. Gland thickness, fine stippling; wall thickness, coarse stippling In normal, gland less than 0·2 mm. and about a quarter of wall thickness; in chronic bronchitics gland thickened and G/W ratio increased.

In cases of primary emphysema with dyspnoea but no cough and sputum, the gland/wall ratio was within normal limits (Reid, 1960). Some cases of bronchiectasis showed a gland size within the normal range, but most were in the chronic bronchitic range.

In an established chronic bronchitic mucous gland hypertrophy would seem to affect most bronchi. There is no evidence that one lobe is more affected than another, but this is not certain (Reid, 1961).

As indicated above, in intermediate cases additional measurements may be of assistance in diagnosis.

Acinar diameter.—Measurement of acinar diameter can be made quite quickly and may be more sensitive than the count of acini in a microscopic field. As the acini enlarge they encroach upon the interacinar space so that acinar enlargement could be considerable before the gland diameter is affected.

In a series of normal and bronchitic patients de Haller (de Haller and Reid, 1965) has measured the largest acinus entirely composed of distended cells in each of twenty fields. His analysis showed that five fields sufficed to give the same results as the twenty. A circular acinus was obviously preferable but if not available the transverse (shorter) diameter of an oblong acinus was used. He found that the mean diameter of distended acini in the controls was 52 μ and in the bronchitics 77 μ. The values for the bronchitics overlapped those of the controls but it was estimated that only 2·5 per cent of the controls were larger than 65 μ. For this reason 65 μ was chosen as the upper limit of the normal.

Acinar count.—In chronic bronchitis the size of individual acini (taken as a clump of cells seen around a tubule in cross section) is increased, as well as the overall size of the gland, which means that there are fewer acini per unit area.

In the normal gland the acini are packed loosely and the interacinar areas are large, while in a chronic bronchitic the acini are packed more closely and may in section be almost contiguous.

Accordingly the number of acini included in a microscopic field of given size (Reid, 1960) provides another means of estimating gland size. With the microscope used for the original counts, an ocular $\times 6$, and objective 4 mm., gave a field of area 0·36 sq. mm. Such a field contained about twenty-four acini for a normal subject; but in patients with chronic bronchitis most acini were so enlarged, being distended with secretions, that the field gave only twelve or so. The acinar count is useful as additional diagnostic evidence in a case where the gland/wall ratio is only slightly above the normal.

Distended and non-distended acini.—In the normal, many acini are composed of cells containing mucus in granular form (McCarthy and Reid, 1964), while in a chronic bronchitic these are fewer, and cells distended with secretions predominate (de Haller and Reid, 1965). (Figs. 91 and 92.)

Maximum gland/wall ratio.—In a patient with chronic bronchitis the bronchial wall may here and there yield a low or even normal gland/wall ratio; but in a normal subject it is rare to find a high ratio such as in a chronic bronchitic. Thus even if the mean of several counts is normal or in the intermediate range, the finding of one high count at the bronchitic level is a fairly sure sign of the presence of chronic bronchitis (de Haller and Reid, 1965).

It would seem right, even if the gland/wall ratio falls in the intermediate

FIG. 91 (*left*).—Normal bronchial mucous gland (1) opening into surface of bronchus by duct (2): cartilage at lower edge.

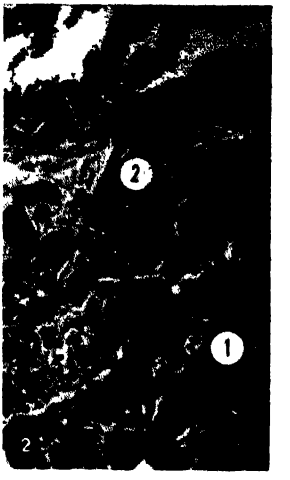


FIG. 92 (*right*).—Bronchial mucous gland (1) from chronic bronchitic, hypertrophied and showing discharge of mucus from duct (2).

FIG. 93.—Bronchiolus (1) from chronic bronchitic, with numerous goblet cells in the lining epithelium where the mucus appears black. This is near the bronchiolus where it opens into alveoli (2 and 3); this part of an airway is normally free of goblet cells.

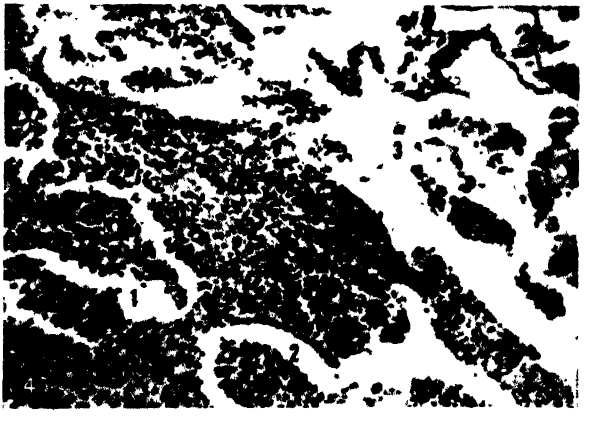


FIG. 94.—Infection in an airway (1 and 2) and in alveoli beyond (3) showing ulceration of alveolar and bronchiolar walls.

range, to place the case in the chronic bronchitic group provided any of the additional three tests produces the characteristics of a chronic bronchitic.

Goblet Cells

With chronic bronchitis the goblet cells of the surface epithelium increase in number. In the large airways the increase in the size of the glands deep in the wall is greater than the increase in volume of goblet cells. In the finer airways—the bronchioli—in which goblet cells are normally sparse, the epithelium consists almost entirely of goblet cells (Fig. 93). The bronchioli include the last ten or so airways along any pathway which, being only about a millimetre in diameter, may be effectively blocked by a small volume of secretion.

Distribution of goblet cell increase.—In the walls of the bronchi and bronchioli goblet cells are increased in number, but the increase is not uniform throughout. Even in large bronchi in which goblet cells are always numerous the distribution is patchy with concentrations within a millimetre or two above and below the average.

In the peripheral bronchioli there is a similar disparity in concentration. Counts of goblet cells were made in a series of sections from different parts of the lungs of twelve of the bronchitic cases in which glands were measured (Reid, 1961). Five to twelve small airways are found in a piece of tissue several square centimetres in area. In all sections there was some increase in goblet cells, but with wide variation. In only two of the twelve cases did all the bronchioli show as high a concentration of goblet cells among the epithelial cells as 50 per cent. In the others there were several in which goblet cells were one in three to five, but there was also an occasional bronchiolus in which none was seen, though the lumen might contain mucus. In a normal lung most bronchioli would be free of goblet cells and the larger airways would have only one in twenty or thirty cells.

The hyperplasia of the goblet cells in the epithelium of peripheral airways varies in proportion to the degree of hypertrophy in the glands. Of four patients with a gland/wall ratio of more than 0·7, three showed a marked increase of cells in almost all bronchioli examined; in the fourth, while some bronchioli showed a considerable increase there were several in which hardly any was seen. On the other hand, in cases in which the bronchioli showed a marked increase there was an occasional case associated with a relatively low gland/wall ratio.

The different parts of the lungs examined showed no constant pattern in this respect. Bronchioli in emphysematous areas may contain numerous goblet cells, so may scars. In either case the presence or absence of cells doubtless reflects the degree of hypertrophy which had occurred before the damage supervened which produced the scar.

In general, the goblet cell increase is not as uniform as is the change in gland thickness.

Correlation of Gland Hypertrophy with Sputum Production

The volume of mucous glands in a normal adult is roughly 4 ml., of the goblet cells 0·1 ml. A two-fold increase in thickness means an eight-fold increase in volume. The glands are probably responsible for more of the sputum produced than are goblet cells. Yet goblet cells may be indirectly responsible for much of the disability, since they are mainly responsible for secretions which block the finer airways, which may explain why some patients with comparatively little sputum have much dyspnoea, while others with much sputum have comparatively little.

Nor is there any obvious relation between the degree of disability and the time for which sputum has been produced. Some patients with a history of cough and sputum of only a few years are severely disabled; others suffer no great disability and yet have produced sputum for thirty years or more.

To sum up, the gland/wall ratio, acinar size, and excessive goblet cells in the bronchioli each furnishes reliable pathological data for the diagnosis of chronic bronchitis and, being objective, may be more reliable than the sputum history, which is often difficult to obtain with accuracy.

INFECTION IN THE PRODUCTION OF EMPHYSEMA

The hypertrophy of mucus secreting tissue which has been described above can occur without inflammatory cell infiltration and may well result from irritation without infection (Reid, 1954, 1963). Hypersecretion is usually the first and major change, infection following.

Hypersecretion of mucus may leave bronchiolar and alveolar structure intact, even though giving rise to functional disturbance, and may accordingly be reversible. But where infection supervenes, permanent damage to pulmonary structure is likely. Acting as an irritant, infection may induce hypersecretion, thus causing chronic bronchitis. or aggravate existing hypersecretion and through the agency of pus may obstruct airways. But it is by bringing irreversible damage to bronchioli and alveoli through ulceration, stenosis, and fibrosis that, superimposed upon chronic bronchitis, infection leads to emphysema.

In chronic bronchitis infection may be entirely luminal, that is confined to the mucus, and while this may result in purulent sputum, it does little damage. The distribution of infection in chronic bronchitis is patchy as in bronchopneumonia and may involve any region of the lung or the acinus.

Infection in Bronchioli

The damage done by infection in the bronchial tree ranges from the mild and reversible to complete destruction. In the mildest form the bronchial wall may be infiltrated with inflammatory cells, congested with dilated capillaries (the blood supply to the bronchial wall being the bronchial artery) and dilated lymphatics, but still have an intact epithelium.

There may also be damage to the epithelium and cilia and epithelium shed from small or large areas. The basal cell layer may be intact or all cells destroyed or shed. The above stages may be found with an otherwise intact wall structure, the muscle and even the basement membrane being structurally unimpaired.

In the most severe form of bronchial wall infection an abscess may develop, i.e. pus may accumulate and necrosis involve muscle and connective tissue as well as epithelium and basement membrane (Fig. 94). As a result, epithelium may be left with a hole or the damaged wall replaced by fibrous tissue, over which the surface epithelium may grow. The result of healing may be bronchiolitis deformans, stenosans or obliterans, or bronchiolectasis, either singly or in combination, as where there is bronchiolectasis proximal to a point of bronchiolitis obliterans. These changes are not necessarily associated with alveolar changes and may only be detected on microscopic examination (Reid, 1954 and 1958).

The importance of bronchiolar infection in relation to alveolar damage, and in particular to emphysema, lies in the possible extension of the infection to cause ulceration of alveoli either through the wall or from the end of the airway into the alveoli it supplies. Sometimes pus and mucus lying in the alveoli must have been aspirated, since the alveolar walls are not inflamed. Blockage of the small airways, arising either from pus or from the organic disease mentioned above, results in disturbance of ventilation and of blood flow which, in turn, may cause further damage to alveolar walls. Bronchiolar damage, by leading to collapse of distal lung beyond, is one cause of the small scars which may develop in chronic bronchitis.

Bronchiolar changes may thus be associated with distal normal lung, with condensation into scars, or with emphysema.

Infection in Alveoli

The alveolar changes in chronic bronchitis illustrate the types of damage which may follow any infection—an inflammatory cell infiltration in which the architecture is essentially intact or in which it is destroyed through necrosis; an outpouring of fluid rendering the alveoli oedematous, resembling lobar penumonia. Usually individual foci of any type of damage are small.

The outcome of the infection may thus be:

(i) resolution;
(ii) fibrosis of alveolar wall with an essentially intact architecture;
(iii) damage which leaves the alveolar outline intact but the components of the wall so reduced that healing leaves them thinner than normal, with more collagen and fewer capillaries—partial destruction;

(iv) a hole, in part alveolar, with ragged edges, perhaps with a fibrous tissue lining representing complete destruction;
(v) scarring giving rise to scar emphysema to which overinflation and atrophy both may contribute.

Infection in the Production of Scars

Infection is a common cause of scarring in the lungs, although one has the impression that scarring is seen less frequently today in patients who die in hospital from chronic bronchitis, which may be due to the greater use of antibiotics. A series of thirty-three lobes were examined macroscopically for "scars" or nodules (Reid, 1956). They were found to contain 233 nodules of which about 160 were subpleural and 73 deep in the lung. The distribution of nodules varied from patient to patient and as between the lobes of the same lung. Seven was the average number of nodules in each lobe, but seven lobes contained none and nine had more than ten; from one patient one lobe contained eighteen, one contained five and the remaining three none.

Seventy-six nodules were examined microscopically; in one third the changes were still acute and the increase in fibrous tissue minimal. The microscopic pattern in about one half of the nodules pointed to the scars being caused by infection; in rather more than one quarter the cause was collapse and in the remainder the scar was so dense that it was not possible to decide the cause.

Collapse was particularly evident in the subpleural nodules and could have resulted from compression of lung by adjacent emphysema. Foci of damage close to the pleura may contribute to the development of bullae. The local factors which influence such development are discussed later on page 198.

Distribution of Peripheral Lung Damage

Infection has little respect for the anatomical arrangement of the lung, any unit of which may be destroyed either wholly or in part.

Within the acinus.—The acinus, being the region supplied by the terminal bronchiolus, includes the respiratory bronchioli, alveolar ducts, and alveoli. Its proximal part may bear the brunt of infective damage or only a small cluster of alveoli at the periphery. As not all acini are bounded by connective tissue septa, infection may spread through alveolar walls from acinus to acinus, leaving ragged communications between them.

Within the lobule.—As in the case of the acinus, a lobule also may be evenly or irregularly affected.

Infection penetrating the bronchiolar wall may involve alveoli contiguous with it, producing emphysema around more proximal bronchioli and small bronchi. The accessory bronchiolo-alveolar communications described by Lambert (1955) are an additional cause for the spread of

infection from the bronchioli to alveoli. Lambert has described pus passing through these openings. An abscess developing here would probably quickly obliterate evidence of the communication.

Functional Disturbances following from Infection

The changes produced by infection may result in disturbance to lung function in a variety of ways.

Reversible Airways Obstruction

Pus and mucus may block airways at any level, but small airways are particularly prone and, by interfering with alveolar ventilation, will temporarily affect the functioning of the alveoli. An acute inflammatory response may cause vascular dilatation and oedema, blocking airways and effecting a similar temporary impairment of function. Infection may lead to altered functioning of muscle and elastic fibres; as broncho-dilators bring about an improvement in function it would seem that there is reversible broncho-constriction in chronic bronchitis. Altered function from any of these causes does not give rise to changes in the radiograph.

Irreversible Airways Obstruction

At autopsy emphysema may not be found even in a patient in whom airways obstruction has proved irreversible, which would indicate that the cause of the obstruction lies in the airways and not in the alveoli. The excessive mucus production associated with an abnormally widespread distribution of goblet cells and with hypertrophied glands could cause it.

Organic narrowing or complete obliteration of airways, producing bronchitis stenosans or obliterans, will obviously interfere with aeration. Again, alveolar destruction due to infection may leave small peripheral or even large airways unsupported. At the periphery unsupported airways operate as flap valves; larger proximal airways may collapse like a bicycle tyre.

Reversible Alveolar Damage

Although an acute inflammatory lesion with consolidation or oedema may resolve completely, it may yet temporarily impair function.

Irreversible Alveolar Damage

Infective erosion may result in permanent loss of alveolar surface, either partial through thinning and scarring of the alveolar wall or complete by ulceration, all of which changes reduce the efficiency of gaseous exchange. Condensation of alveoli from destruction or scarring may result in blood flow through areas of unventilated alveoli and contribute to a disturbance of the perfusion/ventilation ratio. If the alveoli, the guys and

slings which maintain lung architecture, are destroyed, some airways will no longer remain patent and there will be local air-trapping, interfering with the blood circulation to some of the alveoli, predisposing them to atrophy.

EMPHYSEMA ASSOCIATED WITH BUT NOT CAUSED BY CHRONIC BRONCHITIS

In subjects over forty years old, one or more of the types of structural emphysema already described may be found as well as chronic bronchitis. But they are not necessarily caused by it. The enlarged alveoli of old age, or centriacinar (atrophic) emphysema with or without dust deposition are common examples and neither causes significant air-trapping, changes in the radiograph, or disability.

Even primary idiopathic emphysema with air-trapping may be associated with chronic bronchitis and be attributed to it, but there is no evidence that chronic bronchitis is responsible for it.

Where there is bronchiolar or alveolar ulceration widespread emphysema with air-trapping can be traced to the destructive damage from infection in chronic bronchitis. The severe atrophic forms of emphysema cannot be so certainly related to the chronic bronchitis even though large regions of the lung are affected.

It cannot be concluded, however, that emphysema not caused by the chronic bronchitis will have no effect on the latter. For example, centriacinar idiopathic emphysema may predispose to ulceration if infection occurs or may dilate more easily if scarring develops nearby.

EMPHYSEMA IN FATAL CASES OF CHRONIC BRONCHITIS

Detailed radiological and pathological correlation in forty cases of patients who died of chronic bronchitis is summarised in Table IV (see also Reid and Millard, 1964).

TABLE IV

CORRELATION BETWEEN RADIOLOGICAL DIAGNOSIS OF EMPHYSEMA AND STRUCTURE

Radiographic Assessment	*Number of Cases (40)*	*Pathological Grading* found in these Cases*	*Extent of Emphysema on Largest Slice*
No Emphysema	19	Normal (4)	
Localised		I & II (15)	
Emphysema	9	III & IV	In corresponding region
Widespread			
Emphysema	10	III & IV	At least $\frac{1}{3}$ to $\frac{2}{3}$
"Possible"			
Emphysema	2	III & IV	$\frac{1}{3}$ to $\frac{1}{2}$

* of panacinar emphysema.

In nineteen of these cases the radiograph was normal, but because of their long history of cough and sputum they could be regarded as cases of chronic bronchitis without gross emphysema. Pathological examination disclosed no emphysema in four cases, panacinar Grade I in seven, Grade II in two and Grades I and II in six. A mild degree of widespread centriacinar emphysema was found in only two. It has been claimed that centrilobular (centriacinar) emphysema is usually present in patients who die of chronic bronchitis (Leopold and Gough, 1957), but in the above series this was not so. As centrilobular emphysema occurs in "normal" lungs (Snider *et al.*, 1962), it is unlikely that it contributes seriously to death from chronic bronchitis. A mild degree of panacinar emphysema of Grades I and II was present in fifteen cases, but this type and degree of change is seen increasingly with age and thus it cannot be assumed that it played a dominant part in the disability or the fatal outcome.

In nine cases the radiograph showed localised emphysema, without evidence of widespread emphysema, and in the corresponding area of lung there was panacinar emphysema of Grades III and IV evenly throughout the region which, in the radiograph, appeared bullous. The rest of the lung was fairly normal. In these nine cases no single large intrapulmonary air space with complete destruction and compression of nearby lung was found.

In ten cases the radiograph showed widespread emphysema with panacinar emphysema of Grade III or Grade IV predominant and affecting between a half and two-thirds of a lung slice.

From a study of necropsy cases Thurlbeck (Thurlbeck, 1963; Thurlbeck and Angus, 1963) concluded that emphysema is always accompanied by chronic bronchitis and that, if emphysema cases were grouped in increasing order of severity, there was a similar increase in the severity of bronchitis as measured by the gland/wall ratio.

This is only broadly true; it fails to take account, for instance, of the small but significant group of patients with primary emphysema.

RADIOGRAPHIC APPEARANCE IN CHRONIC BRONCHITIS WITHOUT AND WITH STRUCTURAL EMPHYSEMA

In many cases of chronic bronchitis, so severe as to cripple the patient and to give respiratory function results indicating severe airways obstruction, the plain radiograph is normal. This is not surprising since even in fatal cases no structural emphysema may be found at autopsy and, apart from the mucous gland hypertrophy, no thickening of the wall of the bronchi large enough to be seen in a radiograph. Since many of the alveolar scars are subpleural, and thus without air all round to give them contrast, these too are invisible in the radiograph, but occasionally a deep scar may give a small ill-defined circular shadow in the lung (Simon, 1959) which cannot

be distinguished radiologically from the scar of an old tuberculous infection.

Where there is airways obstruction due to an excess of mucus, perhaps with pus, some cases of severe chronic bronchitis develop a disorder of the pulmonary circulation and, eventually, right ventricular hypertrophy. If, also, there is dilatation of the hilar vessels, particularly the descending artery on either side, this change may be visible in the radiograph (Fig. 144). There may also be some enlargement of the heart shadow. Hilar vessel enlargement will be particularly gross if the patient develops marked polycythaemia with a PCV of more than 60 per cent; it will also be greater if there is a thrombosis of a descending artery, which is usually unilateral. The incidence of these circulatory changes at different stages of the disease is not known. They are relatively uncommon in patients with cough and sputum only, but common in patients with cough and sputum who are admitted to hospital in an acute episode of anoxic heart failure, with CO_2 retention.

When the chronic bronchitis is complicated by a large bulla it will appear as an avascular transradiant area, the rest of the lungs being normal. There may also be evidence of gross widespread emphysema, the radiographic changes then being those described on page 276 (Simon, 1964*a*).

In a group of 299 patients with cough and sputum, with a record of absence from work because of chronic bronchitis (Medvei and Oswald, 1962; Simon and Medvei, 1962) the radiographic findings were:

Radiological Diagnosis			
No emphysema		177	59%
Local emphysema		35	11%
Widespread emphysema			
with bullae	33	87	29%
without bullae	54		

(from Table I, Simon and Medvei, 1962)

In a smaller series of patients referred to an outpatients' clinic in the usual way, with cough and sputum apparently due to chronic bronchitis, the incidence was similar (Batten and Chappell, 1964):

No emphysema	86	59%
Local emphysema	20	14%
Widespread emphysema	30	21%
Possible emphysema	9	6%

In a series of forty fatal cases of chronic lung disease (Reid and Millard, 1964) diagnosed as chronic bronchitis, the radiographic findings were as follows:

No emphysema	19	47%
Local emphysema	9	23%
Widespread emphysema	10	25%
Possible emphysema	2	5%

In all of this group there was pathological confirmation of the radiographic findings.

Bronchographic Abnormalities in Chronic Bronchitis

Even though the plain radiograph of a chronic bronchitic is normal, a bronchogram may reveal a variety of changes (Simon and Galbraith, 1953; Reid, 1955; Simon, 1962), the most common being evidence of hypersecretion of mucus. Whereas in a normal person the ducts of the mucous glands are expanded within the wall of the bronchus, the actual opening into the lumen is very small, and does not fill with the rather viscid contrast medium used in bronchography; in a chronic bronchitic the mouths of the ducts are much widened and may appear as pointed projections 2–3 mm. long from the inferior aspect of the lobar and segmental bronchi. Though relatively common they are not always seen. They may be present in other conditions which cause excessive mucus secretion, such as long-standing tuberculous cavitation or bronchiectasis.

Not to be confused with the dilated ducts of the mucous glands are larger and more pouch-like diverticula of epithelium arising from the posterior wall of the trachea or main bronchi in the angle between the plates of cartilage and the attachment of the muscle bands to the cartilage (Morlock and Pinchin, 1933). They are usually seen in old persons and are not very common.

Proximal Bronchi

Excessive calibre change.—In a normal person the bronchi and trachea narrow on expiration. On coughing the narrowing is accentuated so that the walls of the trachea and some parts of main bronchi almost touch. In cases of chronic bronchitis the inspiration-expiration difference may be much greater, being due especially to the increase in calibre on inspiration (Simon and Galbraith, 1953). Usually only an occasional lobar, segmental or subsegmental bronchus, and perhaps the next two branches, are affected. The change is not particularly common and is seen only in one or two areas. It is probably caused by alterations in the support offered by the surrounding lung (which by its attachment to the bronchial wall forms a series of guys and slings) rather than by disease of the bronchial wall itself.

Concertina deformity.—Sometimes a segmental bronchus is somewhat dilated and shows a concertina-like deformity along its length. The muscle bundles are concentrated at the apices of the folds which may reflect change in the muscle or in the pull of surrounding lung. Elastic fibres are grouped beneath the basement membrane and damage to these may contribute to the bronchial deformity.

FIG. 95.—Bronchogram prepared on autopsy specimen from lower lobe showing absence of peripheral filling, irregularity of filled bronchi.

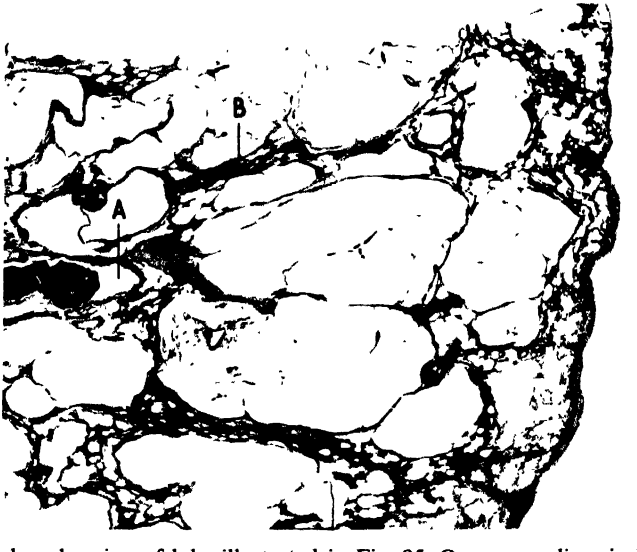


FIG. 96.—Subpleural region of lobe illustrated in Fig. 95. Opaque medium in bronchus (A) which ends blindly; remnants of one of its branches included in linear scar (B). (×2·5.)

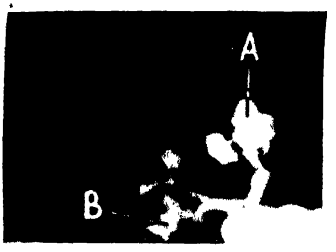


FIG. 97.—Bronchogram prepared on specimen showing "pool" at (A) with smoothly lobulated outline, at (B) a more irregular angular shadow.

Changes in the Peripheral Part of the Bronchial Tree

Poor Peripheral Filling

Normally the level to which contrast medium extends is much the same over a wide area but, in chronic bronchitis, peripheral filling is frequently poor. Peripheral filling may be prevented by a mucous plug (which will show as a concave indentation at the end of the contrast medium) or an organic occlusion. In either case the normal suck is diminished by reason of the block, and filling may, therefore, stop proximal to the point of blocking, with a square terminal appearance like a broken bough. In severe chronic bronchitis regions of poor filling are usually irregularly distributed.

Organic bronchiolar occlusions.—If the contrast medium finishes with a tapering, irregular, or bulbous end (Fig. 95), it will indicate an organic occlusion of the pathway deriving from a previous inflammatory episode which has produced destruction and fibrosis (Fig. 96).

Pools.—Sometimes the contrast medium ends in a small smooth dilatation or pool 3–5 mm. in diameter, arising at the end of a small side branch (Fig. 97). These represent dilated bronchioli (Reid, 1955). The

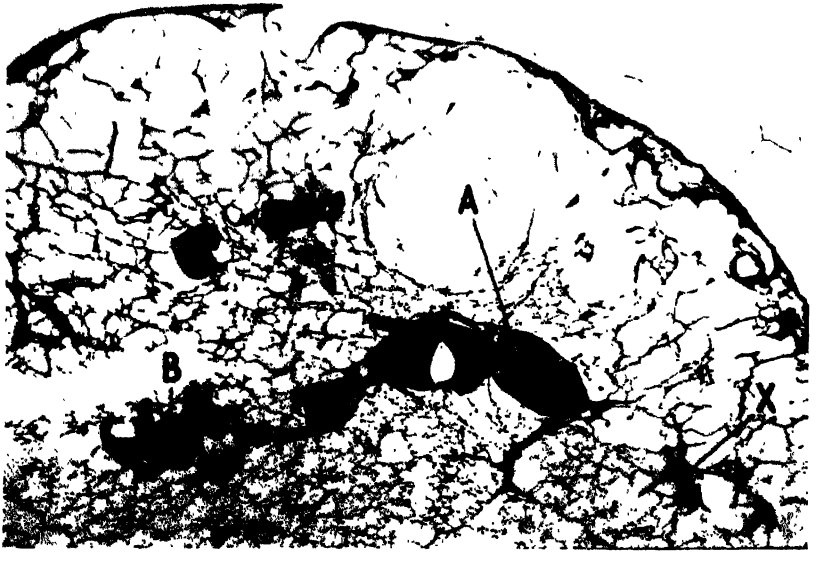


FIG. 98.—Section through (A) and (B) seen in Fig. 97. (A) represented a dilated and obliterated bronchiolus whose continuation is included in scar (X); at (B) the radio-opaque medium is in alveoli. (×6.)

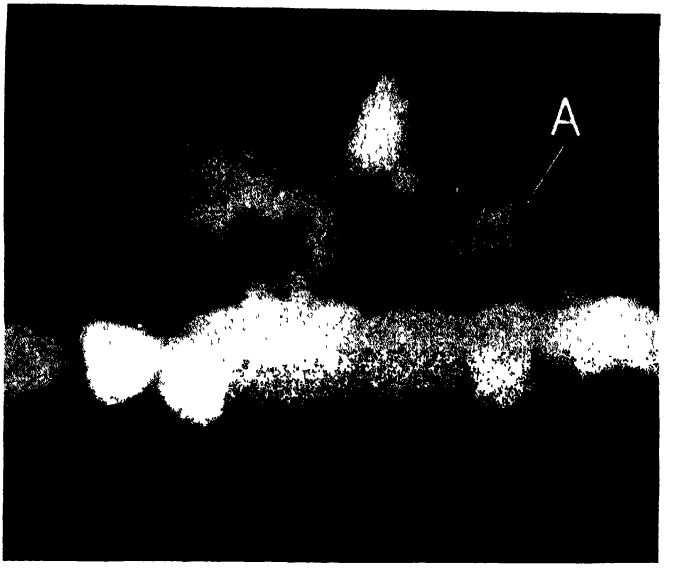


FIG. 99.—Bronchogram, prepared on specimen showing "mimosa" pattern at (A). (× 2.)

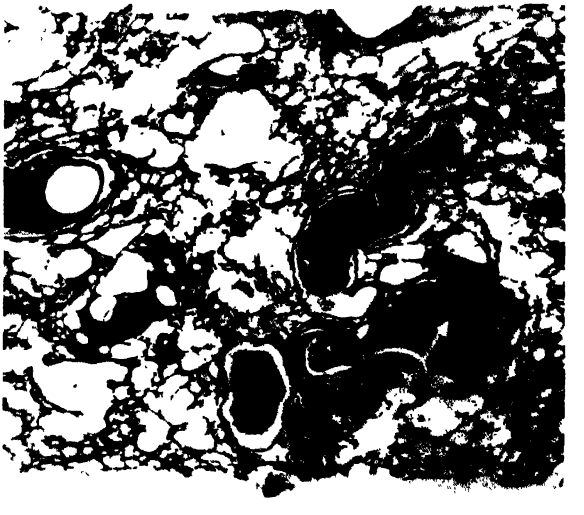


FIG. 100.—Section through (A) in Fig. 99 showing mimosa, represents radio-opaque medium in region of panacinar emphysema (at arrow) Grade III. (× 5.)

dilatation is usually associated with obliteration, so that there is no filling of the pathway beyond (Fig. 98).

"Spider."—Sometimes the pattern is that of a central line shadow with several lateral spikes resembling a spider. Microscopic examination shows that the small lines represent terminal bronchioli.

These bronchographic appearances have been described by other authors (Freimanis and Molnar, 1960; Rayl *et al.*, 1961; Sammons *et al.*, 1957).

"Flowers" or "mimosa" pattern.—One further shadow, not seen in the material originally examined pathologically (Reid, 1955), although Simon and Galbraith (1953) had reported it as "mimosa", has been described bronchographically by Duinker and Huizinga (1962) as "flowers" or "mimosa". These shadows are larger than the "spider", being 1 cm. or more in diameter, with an irregular edge and consisting often of blobs. A lobe removed from one of their patients revealed slight emphysema and dilated terminal and respiratory bronchioli. They suggest on the circumstantial evidence, as do Leopold and Seal (1961), that centrilobular emphysema is responsible for the bronchographic shadow.

The "mimosa" shadow shown in Fig. 99 is from a patient with chronic bronchitis and emphysema. In Fig. 100 is shown the microscopic section of this "shadow". This demonstrates that the radio-opaque medium is within dilated alveoli but not in fact in an area of centriacinar (centrilobular) emphysema; that this type of shadow is cast by centriacinar emphysema is not proved. In a radiograph the "mimosa" may reach the lateral chest wall, indicating that the alveoli immediately subpleural are filled, and suggesting that here again the area is not one of centriacinar emphysema.

In a patient with chronic bronchitis none of these changes may be seen, which probably means that there is no infective damage; but most severe cases show one or other of them. None are completely specific to chronic bronchitis. An occasional pool, for instance, may follow damage to a bronchiolus by a tuberculous lesion but, when pools are numerous or several other types of change are present as well, they will be very suggestive of infective damage having occurred during the course of chronic bronchitis.

Irregularity of Changes through the Lungs

In chronic bronchitis the distribution of all these changes varies. They may be throughout all lobes, but are never really evenly distributed and some regions are spared. The irregular distribution applies to the acute and subacute infective lesions, the scars, bronchographic abnormalities and emphysematous changes.

COLLAPSE OF AIRWAYS AND RIGIDITY OF CARTILAGE SUPPORT

Localised Reduction in Calibre

Fraser (1961) has shown localised reduction in calibre of airways on expiration, which may occur in the intra- or extra-pulmonary part of the airways. The decrease in calibre on coughing does not affect the bronchus uniformly throughout its length.

Pathological Basis

The pathological basis for the excessive calibre change is not altogether clear. In many cases of chronic bronchitis with emphysema the peripheral small airways are completely unsupported by alveolar attachment, the loss of which converts the structure of the bronchiolar wall to that of a flap-valve, with the result that on expiration the obstruction to outflow of air occurs at the most peripheral region.

The excessive calibre change of even more proximal airways may arise from a similar lack of alveolar attachment and support. But it would seem that in the case of proximal airways no such structural change need occur; the collapse of proximal airways may be a functional disturbance secondary to collapse of peripheral airways. Dayman (1951 and 1964) has postulated that with a block at peripheral level the build up of the intrapulmonary extrabronchial pressure will suffice to collapse the whole length of the airways—i.e. collapse in the distal airways will be transmitted to proximal airways.

Campbell and his colleagues (1957) have studied the maximum effective intrathoracic pressure and maximum expiratory flow rate in normal subjects and in patients with asthma or emphysema during forced expiration. As a result of their analysis they suggest that in emphysema the critical narrowing occurs first in small airways, while in asthma it occurs in large airways.

Trachea and Main Bronchi

In the normal subject, although the lumen decreases at one phase of coughing, on quiet respiration there is little change. Using bronchography in cases of emphysema, Gandevia (1963) has demonstrated expiratory collapse of the trachea and main bronchi at lesser expiratory effort than in the normal.

Campbell and Young (1963) found bronchoscopy necessary for positive diagnosis, as notching in the spirogram was sometimes present without tracheo-bronchial collapse. Herzog (1960) has described a condition of narrowing from expiratory intussusception of the membranous part of the trachea and of the main bronchi into the lumen, the narrowing being

proportional to the intensity of expiration. On cineradiography a reduction in the sagittal diameter of the trachea may be observed. The clinical disability is an irritating cough and nausea. The ridged linear striation normally seen on the posterior wall of the trachea is lost. These ridges represent collections of elastic fibres which Herzog has reported as being lost in patients with a pouting membranous trachea.

The collapse of the trachea in cases of emphysema may be the continuation, as it were, of the intrapulmonary changes described above or it may reflect changes in the trachea itself. The collapse of the trachea raises two important questions: first, whether tracheal collapse may be the cause of the emphysema, and second, whether even if the trachea collapses it represents simply a secondary effect of the peripheral block or contributes to the disability? In at least one case the early notching in the spirogram reported by Gandevia has been seen in a patient with chronic bronchitis but without radiographic evidence of emphysema (Simon, 1964*b*).

Recent experimental studies on dogs with normal lungs (Bryant, 1964) have included circumferential replacement by pericardium of a segment of trachea, up to 8 cartilage rings in length. The trachea showed abnormal mobility bronchoscopically but the animals suffered no disability, suggesting that the mechanical abnormality did not matter. The radiographs remained normal. Compressibility tests were also carried out on tracheas from normal and emphysematous subjects and revealed no difference in results between the normal and disease. Two patients with emphysema did not show improvement in expiratory flow rate when an endotracheal tube was used as an internal splint. In the study reported on page 94, of cases of unilateral hypertransradiancy, main bronchi from adult lungs were examined and the variation in size and shape of the cross-section of the main bronchus was striking. Bryant found distribution of C-shaped and almond-shaped tracheal cross-section both in normal subjects and in cases of emphysema. Liddelow and Campbell (1964) estimated tracheal flatness by a width/depth ratio and found definite flattening in an unexpectedly high proportion; the tracheal flatness was not necessarily associated with chronic bronchitis.

Wright (1960) has reported an atrophy of cartilage in cases of emphysema. Restrepo and Heard (1964) report no difference in the staining properties of cartilage in the intra-pulmonary bronchi as between normal and bronchitic subjects. This suggests that the tracheal change does not reflect any cartilage abnormality.

RESPIRATORY FUNCTION TESTS

Although the results of respiratory function tests and blood gas analyses on patients with cough and sputum may prove normal, there is often evidence of airways obstruction. One of the commonest findings,

equally in patients with chronic bronchitis without emphysema and in those with widespread emphysema alone, is a reduction in rate of expiratory air flow.

Mild Chronic Bronchitis

The production of sputum, the characteristic of chronic bronchitis, is not necessarily associated with disability or with any detectable disturbance of respiratory function (e.g. Brille, 1961; Gaensler, 1962). The disturbance may be detected before the patient is conscious of disability.

Recently Gregg (1963 and 1964), using the Wright Peak Flow Meter for serial measurements, has studied a group of patients with cough and sputum, many of whom had never complained of disability. Even in cases of hypersecretion the PEF may be normal; a deterioration in the level of PEF can occur without associated clinical infection and, again, particularly in smokers. Sputum production sometimes ceased when smoking was stopped and the PEF returned to normal levels; in other cases the deterioration persisted. It is thus possible to distinguish a stage of chronic bronchitis characterised by hypersecretion without airways obstruction, hypersecretion with reversible airway obstruction, and hypersecretion in which the obstruction can no longer be reversed by the stopping of smoking or by the administration of bronchodilator drugs.

Pathological and Radiological Findings associated with Disturbed Respiratory Function

Emphysema does not necessarily give rise to disability or to detectable disturbance of respiratory function. This is the case with centriacinar (centrilobular) emphysema, whether with coal deposition or not, and with compensatory emphysema. Disturbance of function may be minimal also with the aged lung.

At the same time ventilation may be impaired and respiratory function show extreme hypoxia, without any structural emphysema (Hentel *et al.*, 1963; Simpson *et al.*, 1963; Reid and Millard, 1964). Thus such tests fail to distinguish cases of airways disease from those of diseased alveoli.

Where there is gross structural emphysema there is always impairment of function as, for instance, in the case of panacinar emphysema severe enough to be widespread radiographically. In chronic bronchitis, with or without emphysema, the D_{CO} may be low. Simon (1964*b*) found that in all patients whose radiographs showed widespread emphysema, alveolar diffusion tests were sub-normal (D_{CO} about 10 ml./min./mm.Hg—steady state) and ventilation impaired ($FEV_1 < 1200$ ml.).

Improvement

In cases of chronic bronchitis alone, if respiratory function is impaired treatment for infection and heart failure may be effective; but if there is

widespread emphysema as shown radiographically, treatment will not bring the same improvement and function tests will certainly not return to normal.

Reports of respiratory function have generally used the term "emphysema" to indicate airways obstruction; in this context the term does not properly mean structural emphysema. In considering obstruction in cases of chronic bronchitis any structural emphysema there may be must be taken into account. In life, structural emphysema can only be detected by the radiograph.

Additional methods of investigating lung function and discussion of the changes in chronic bronchitis and emphysema are given for example in Gaensler, 1962; Comroe, 1962; Dollery and Hugh-Jones, 1963; Batten, 1964; Bates and Christie, 1964.

Case 38.—Chronic Bronchitis—Airways Obstruction—(No Structural Emphysema)

This patient died at the age of 73 without any emphysema radiologically or pathologically, but with a 25 year history of persistent cough and sputum which started after an attack of pneumonia. For 15 years he was short of breath, which was severe only in the 4 weeks prior to his admission, with purulent sputum and in heart failure. He was gassed during the first war and had smoked 60 cigarettes a day until 2 months before admission.

On admission he was cyanosed; his haemoglobin was 126 per cent, PCV 62 per cent, blood pressure 150/85. His blood gases, which improved with treatment, were as shown below.

His electrocardiograph was within normal limits with a mean frontal QRS vector of 30° and mean T vector of +45°.

Radiology.—The radiograph (Fig. 101) showed the diaphragm was between the 5th and 6th ribs and normal. The heart was 16·0 cm. in diameter and after recovery it reduced to 14·5 cm. The radiograph was in other respects normal.

Respiratory function tests.—The peak flow was 80 l./min. on admission and improved to 140 l./min. after treatment.

His hypoxia, carbon dioxide retention, and compensated respiratory acidosis responded to treatment for infection and heart failure.

Arterial Blood Gas Studies

		pH	P_{CO_2} *mm.Hg*	HCO_3 *mg./l.*	O_2 *Sat.*	P_{O_2}
Day of admission	5.11.63	7·37	105	46 mm.Hg	47%	26 mm.Hg
Day after admission	6.11.63	7·23	63	23·5	81%	56 mm.Hg
Nine days later	15.11.63	7·36	59	29	100%	over 100 mm.Hg

Progress.—A year later, following a respiratory infection, he was again admitted to hospital in heart failure. Because of his satisfactory response to

treatment on the previous occasion a tracheostomy was performed and he improved but, two weeks later, he developed a polyneuritis whose cause, though not satisfactorily determined, was presumed to be viral. His condition deteriorated and he died.

Autopsy findings.—At autopsy the lungs deflated normally and a pulmonary arteriogram was normal (Fig. 102). On slicing, the lungs appeared normal with no evidence of emphysema. The gland/wall ratio was 0·7, showing evidence of mucous gland hypertrophy.

An old myocardial infarct was found. The left ventricle weighed 213 grams, the right 57 grams, giving an LV/RV ratio of 3·7 and indicating an absolute left ventricular hypertrophy.

FIG. 101.—Case 38 Chronic bronchitis without emphysema. Radiograph—diaphragm normal; heart large. hilar and lung vessels normal. No emphysema at autopsy. RV. 57 gm. See also Fig. 102.

CASE 39.—CHRONIC BRONCHITIS AND "POSSIBLE EMPHYSEMA"

In the following patient chronic bronchitis was associated with radiographic features suggesting, but not conclusive of, widespread emphysema. Autopsy confirmed that the amount of emphysema present fell short of that necessary to produce evidence of widespread emphysema.

The patient presented in 1957 with a nine-year history of cough and sputum with mild shortness of breath on exercise. During the severe fog of 1952 he had been disabled and since that time his shortness of breath had steadily increased. He produced up to two ounces a day of mucoid sputum.

On admission he was found to be cyanosed, there was no clubbing of the fingers and no oedema, but his jugular venous pressure was raised, his peripheral pulses were full, and his extremities warm, the forearm veins being dilated. A loud diastolic gallop was audible. His haemoglobin was 97 per cent.

He responded to oxygen therapy and antibiotics. Thereafter he returned home, but during the following three and a half years until the time of his death he was too disabled to leave the house.

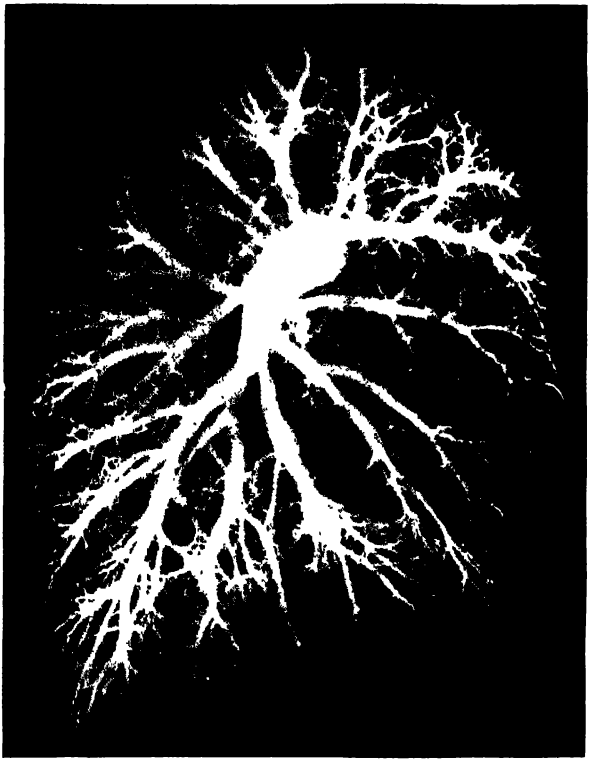


FIG. 102.—Case 38. Specimen arteriogram. See also Fig. 101.

On his final readmission in 1960 he had sacral oedema, low oxygen saturation of his blood, and high levels of carbon dioxide. His response to treatment was only temporary.

Radiology.—Radiographs taken in 1951 and 1953 showed a low flat diaphragm but were otherwise normal. By 1957 the hilar vessels had enlarged and the heart measured 12·5 cm. By 1960 (Fig. 103) it was 14 cm. and, although the hilar vessels seemed normal, the veins from the upper lobe were enlarged. Two months later the heart had reduced to 12·5 cm., the hilar vessels were normal but the upper zones now appeared rather avascular. A diagnosis of "possible emphysema" was then made.

Respiratory Function Tests

	1957	*1959*	*1960*	*1960*
FEV_1	400	580	400	
FVC	1010	1950	1200	
$FEV_1/FVC\%$	40	30	33	
MVV		31	18	
D_{CO} at rest		10·2	5·0	
(ml./min./mm. Hg)		(Min. Vent. 9·9 l./min.)	(Min. Vent. 4·2 l./min.)	
D_{CO} on exercise		11·6	9·2	
		(Min. Vent. 15·1 l./min.)	(Min. Vent. 9·6 l./min.)	

Arterial blood gases:

				After oxygen
Oxygen saturation %	52	85	74	100
P_{CO_2} (mm. Hg)	103	66	94	110
pH	7·13	7·27	7·27	7·23

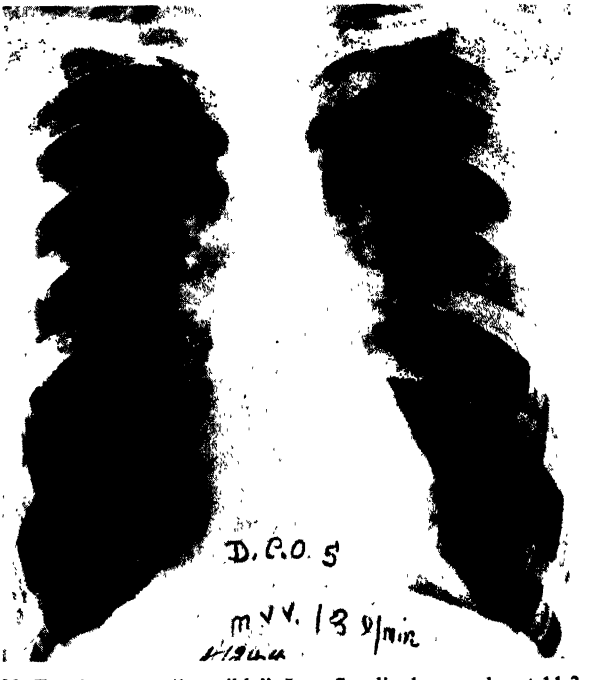


FIG. 103.—Case 39. Emphysema—"possible". Low flat diaphragm; heart 11·3 cm., large hilar but normal mid-lung vessels, with some vessel narrowing in the upper zones. Cough, sputum and increasing dyspnoea, 13 years. At autopsy panacinar emphysema, Grade III, affected half of the slice of lung through hilum.

Autopsy findings.—At autopsy the lungs were bulky. After inflating them under negative pressure, deflation was abnormally slow. The left pulmonary vein and right pulmonary artery were injected; the axial pathways were not dilated and the number of vessels was within the normal range. Emphy-

sema was present through both lungs. Through the left lung, save for regions of Grade IV at the left apex, the emphysema was panacinar, Grades II and III. In the right lung panacinar emphysema Grade II predominated with patchy areas of Grade IV in the right upper and lower lobes. The regions of Grades III and IV comprised about one third of the area of the largest slice of each lung.

The gland-wall ratio was 0·5, showing evidence of mucous gland hypertrophy.

The right ventricle was hypertrophied as the wall was 1 cm. thick, and the wall of the left ventricle was also thickened. The heart was not available for weighing.

Case 40.—Chronic Bronchitis and Emphysema

In this patient chronic bronchitis was associated with radiological features of widespread emphysema; his response to treatment, in spite of his youth, was not as good as in Case 38.

The patient was first admitted to hospital at the age of 37 (December, 1960), with a history of cough for many years, which was usually worse in the winter and produced small amounts of mucoid sputum. During the previous twelve months he had become very short of breath with swelling of the ankles.

On admission his sputum was purulent; his fingers were not clubbed, his haemoglobin concentration was 15·3 gm. per cent. The electrocardiograph showed a mean frontal QRS vector of 110°, QR in V_{1-3}, dominant S in V_5, T wave inversion in 2,3 AVF and V_{1-3}, these indicating right ventricular hypertrophy; additionally P pulmonale was present.

Radiology.— The radiograph showed evidence of widespread emphysema; the diaphragm was low at the level of the seventh rib, and flat; the heart was of a "narrow, vertical" configuration and 11 cm. in diameter; the pulmonary artery and its hilar branches and the arteria basalis to each lung were large, otherwise the intrapulmonary vessels were small; there were avascular regions, some demarcated by line shadows and some not.

The respiratory function tests are summarised below. He improved in hospital and although his hypercarbia responded, there was no great improvement in his oxygen saturation. Ten months after discharge, during the following winter (October, 1961), he caught a cold—his sputum became purulent and he had swelling of the ankles for six weeks. He was readmitted in 1961 with signs of cardiac failure and it was found that his liver was enlarged and his jugular venous pressure raised. Once again he responded, but after a similar incident in the winter at the end of 1962 he died.

Autopsy findings.—At autopsy the lungs were bulky so that they met in the mid-line and air was trapped in them. Only a few marginal bullae were seen. An arteriogram of the left pulmonary artery showed pruning of the peripheral branches with only very slight dilatation of the axial arteries. On slicing the lung panacinar emphysema, Grade IV, was found throughout the left upper lobe; the left lower lobe was similar except for occasional regions of Grade III.

The gland/wall ratio was 0·7, showing mucous gland hypertrophy.

The left ventricle weighed 111 grams, the right 75 grams, giving an LV/RV ratio of 1·7, and indicating right ventricular hypertrophy.

Respiratory Function Tests

	December 1960
FVC	1100 ml.
FEV_1	400 ml.
$\frac{FEV_1}{FVC}$	36%
MVV	17 l./min.
D_{CO} at rest	6·9 ml./min./mm.Hg (min. vent 9 l./min.)
D_{CO} on exercise	9·4 ml./min./mm.Hg (min. vent 10 l./min.)
% extraction	32

Blood gases

O_2 saturation %	87
CO_2 content (v.p.c.)	63·4
pH	7·39
P_{O_2} (mm. Hg)	56
P_{CO_2} (mm. Hg)	60
pl.CO_2 content (v.p.c.)	76
HCO_3 (mm./l.)	32

Case 41.—Chronic Bronchitis, Emphysema, and Right Ventricular Hypertrophy

In this case chronic bronchitis was associated with widespread emphysema, shortness of breath having developed many years after the production of sputum.

This patient presented at the age of 63 with a history of cough and sputum for 20 years and shortness of breath on exertion for six. During a fog in 1962 his breathlessness increased and he was unable even to dress himself. He had slight clubbing of the fingers and polycythaemia (haemoglobin 116 per cent, PCV 59 per cent, MCHC 29 per cent). The electrocardiograph showed a mean frontal QRS of +110°, indicating right ventricular hypertrophy; also present was P pulmonale and a dominant S in V_5.

Initially he improved with antibiotic treatment, then he developed peripheral oedema and in spite of treatment he died.

Radiology.—The radiograph (Fig. 104) revealed a low, flat diaphragm at the level of the seventh rib, and a narrow vertical heart, 11 cm. in diameter. The main trunk of the pulmonary artery and its hilar branches were enlarged while the branches within the lung were small, except in the medial

FIG. 104.—Case 41. Emphysema. Diaphragm low and flat, between 6th and 7th ribs; heart narrow and vertical, 11·5 cm.; pulmonary and hilar arteries enlarged, lung vessels small; avascular areas not demarcated by line shadows at both bases.

region of the upper lobes where they were enlarged. Throughout the right lung and at the left base were avascular regions not demarcated by line shadows.

Respiratory function studies.—Spirometry revealed that his FVC was 300 ml., his FEV_1 150 ml. These did not improve.

Autopsy findings.—At autopsy the airways were stuffed with mucus, the lungs failed to deflate and were so emphysematous that they met in the midline. In the left lung there was pulmonary oedema with capillary engorgement, worse in the upper lobe.

An arteriogram of the right lung showed pruning of the peripheral branches, the number along an axial pathway being 24 (normal range 33–42). This is as would be expected with right ventricular hypertrophy, but on the other hand the diameter of the artery was not increased but within the normal range and well below the mean for the group of severe hypertrophy. It was the only case of widespread emphysema in the group of severe hypertrophy.

On slicing the lung, panacinar emphysema of at least Grade IV severity

was found throughout—roughly 90 per cent of the largest slice. The gland wall ratio was 0·6, thus showing mucous gland hypertrophy.

The ventricles were weighed separately, the right ventricle weighing 105 gm., the left 150 gm. and the LV/RV ratio being 1·5 (severe right ventricular hypertrophy).

Case 42.—Chronic Bronchitis, Emphysema, Polycythaemia, Bilateral Pulmonary Artery Thrombosis, Right Ventricular Hypertrophy

In this patient emphysema and chronic bronchitis were associated with polycythaemia over several years and bilateral pulmonary artery thromboses at least over some months. This patient was Case 1 in the series reported by Chamberlain and Millard (1963).

In 1955, at the age of 52, the patient was first admitted to hospital with a history of cough and sputum for six years. The radiograph showed evidence of widespread emphysema. He had further incidents of acute infection and was readmitted in 1956 and 1959. During these years he improved with antibiotic treatment given for up to six months at a time.

He was again admitted in 1961 and for the first time showed clubbing of

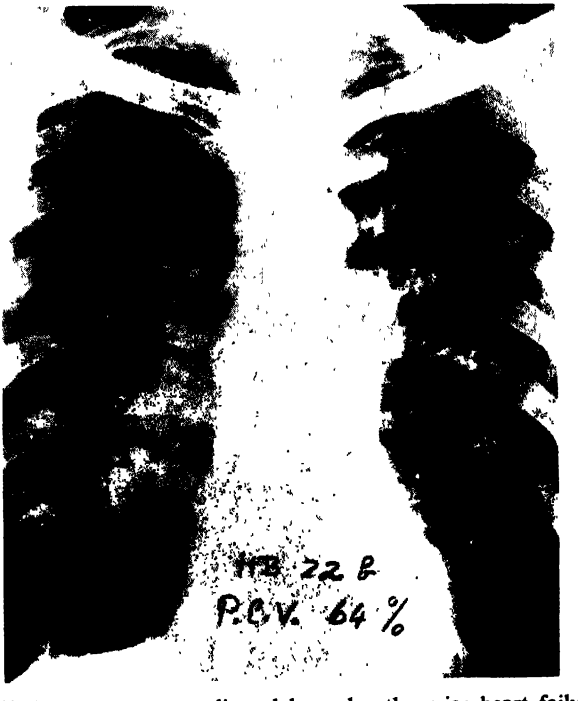


Fig. 105.—Case 42. Emphysema complicated by polycythaemia; heart failure. Radiograph 6 years earlier showed evidence of widespread emphysema. Now heart, hilar vessels and some lung vessels larger. Cough, sputum and increasing dyspnoea. Hb 22 Gm. PCV 64%, right ventricular hypertrophy. Emphysema panacinar Grade III and IV.

the fingers, signs of heart failure and he was polycythaemic. The electrocardiograph showed a mean frontal QRS of +110°, indicating right ventricular hypertrophy; P pulmonale and a dominant S in V_5 were also present. He was cyanosed and his ankles had been swollen for one month. He was treated with oxygen continuously for six weeks by Venturi mask, with a satisfactory fall in his packed cell volume.

Radiology.—The radiograph was virtually unchanged between 1956 and 1962 (Fig. 105). It showed the heart to be 12·5 cm. in transverse diameter, the diaphragm to be at the level of the 7th rib and to have a low flat contour. The pulmonary artery and its hilar branches were large, including the arteria basalis on the right, while the intrapulmonary vessels were small. Avascular areas not demarcated by line shadows were visible at the periphery in both upper zones and at the left base. The right lower lobe was the best vascularised region and here the peripheral vessels were conspicuous. The left upper lobe veins were dilated. The hilar arteries enlarged further between 1956 and 1962.

Haemoglobin 136%	20·1 gm. %
PCV 60%	MCHC 33%

The blood volume as calculated from height and weight was 5·4 litres, by Cr^{51} to be 4·8 litres. The red cell mass was 2·5 litres. The polycythaemia may have arisen in part from the reduced blood volume. The circulation time was 22 seconds.

Respiratory Function Tests

FVC	2100 ml.
FEV_1	500 ml.
$\frac{FEV_1}{FVC}$	24%
MVV	19·7 l./min.
PEF	130 l./min.
D_{CO} at rest	8·4 ml./min./mm. Hg
(Minute ventilation	7·4 l./min.)
D_{CO} on exercise	5·3 ml./min./mm. Hg
(Minute ventilation	11·0 l./min.)

Blood gases

O_2 content (vol. %)	23·0
O_2 capacity (vol. %)	27·9 (=151% HbO_2)
O_2 saturation	83%
O_2 content (v.p.c.)	55·4
pH	7·39
P_{O_2}	50 mm. Hg.
P_{CO_2}	57 mm. Hg.
pl. CO_2 content (vol. %)	73·2

After treatment the lung function studies hardly altered; the patient's haemoglobin fell to 111% and his PCV to 49%.

In 1962 and again in 1963 polycythaemia was again present. It was treated not with oxygen but by radioactive phosphorus on the first occasion and by pyrimethamine on the second occasion. The latter induced a thrombocytopenic purpura.

Autopsy findings.—At autopsy bilateral pulmonary artery thromboses were found, the ante-mortem thrombus being layered and adherent and extending into the major pulmonary artery branches. The lungs showed air-trapping and met in the mid-line. Regions of fibro-caseous tuberculosis were present at both apices. The bronchial tree was full of purulent secretion. The basal part of the segments of the right lung were infarcted. The lungs showed panacinar emphysema, predominantly Grade IV throughout. The lungs were not obtained for injection of the pulmonary artery or section of the bronchus.

The ventricles were weighed separately, the right ventricle weighing 143 grams, the left 171 grams and the LV/RV ratio being 1·2 (severe right ventricular hypertrophy).

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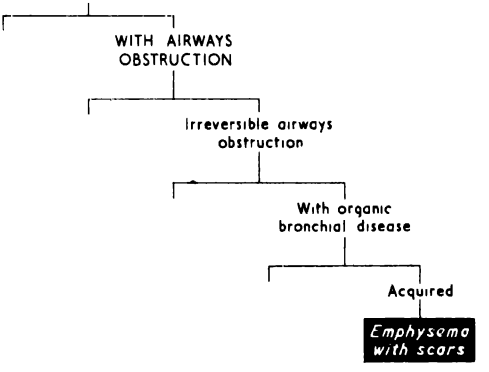
Chapter XIII

EMPHYSEMA WITH SCARS

(Focal Emphysema, Irregular Emphysema)



A SCAR is "the trace of a healed wound, be it traumatic or infective". This definition would include fibrosis, but a scar is not necessarily fibrous. In a lung, "scar" usually refers to a unit of airless tissue incorporating the elements of the lung structure, principally the alveoli. Such a scar is usually encircled by dilated and distended air spaces, which sometimes have fibrosed walls. The airless region and the emphysema are both the trace of a previous lesion, but for convenience scar will here be taken to refer to the airless region of lung, and "scar emphysema" to any surrounding emphysema. The abnormally large alveoli are usually apparent on naked-eye examination and are here called scar emphysema to distinguish the condition from its former name "focal emphysema", which has recently been applied to emphysema with dust storage.

In 1850, Gairdner aptly described the essential nature of lung scar as "condensation" of lung. The most common cause of a scar associated with emphysema is infective damage and less commonly other inflammatory changes, infarction or collapse. Small scars with surrounding emphysema are seen in pulmonary tuberculosis and in long-standing chronic bronchitis, and larger ones in sarcoidosis, tuberculosis and progressive massive fibrosis in pneumoconiosis.

PATHOLOGY OF SCAR

Macroscopic Appearance

A scar may be white, grey, reddish brown or black and may have a smooth or an irregular outline. It may be bounded by pleura, a connective

tissue septum, a vein or a bronchiolus, in which case the outline of the scar tends to be regular. Scars are irregular in distribution and size (Figs. 106, 107 and 108).

Histology

As a scar represents condensed lung, it contains remnants of alveoli, airways, blood vessels, normal collagen and collagen formed in the process of healing. Such remnants and even a reasonably intact architecture may be recognisable in a haematoxylin-eosin stained section; on the other hand, particularly in old and fibrosed scars, it may be possible to pick up only an occasional nucleus of a fibrocyte in an otherwise dense homogeneous and pink-staining area. Special stains usually reveal a surprisingly complex structure within a scar (Mallory, 1948; Reid, 1956); the combined Weigert

FIG. 106.—Panacinar emphysema Grade III and irregular emphysema: cut surface of lung, bronchi and vessels protruding and pleura infolded: two scars at (S). Male aged 59. Cough and sputum many years, shortness of breath 4 years; treated with antibiotics only in his last winter.

(elastic) and van Gieson (collagen and muscle) stain is probably best for recognising bronchiolar and vascular remnants. In addition, it may be possible to detect other substances such as caseous material in cases of tuberculosis, and pigment in clefts of fibrous tissue where there is dust storage.

If condensation has followed intra-alveolar exudate the outline of shrunken alveoli may be detected by the elastic stain; and in an old infarct the staining reveals a densely tangled mass of elastic fibres. In chronic collapse the lung is solid, the collapse having obliterated the alveolar space and allowing the capillaries to dilate, thus giving the appearance of vascular sinusoids (Adams *et al.*, 1935; Macpherson *et al.*, 1960).

Distribution within acinus.—The distribution of small scars within the

FIG. 107.—Subpleural scar (pleura—P) showing dilated bronchiolus (B) entering scar and artery (A) showing endarteritis. Connective tissue septum at (S). (× 7.)

acinus has been little studied but, from personal examination, the distribution, as might be expected, is irregular (Figs. 108 and 109).

A large scar will include many acini, lobules or even subsegments. At the scar edge obliteration of respiratory units is incomplete, which gives rise to the irregularity of scarring within the acinus. The acute inflammatory changes which give rise to the scarring may not affect the whole of an acinus and no part is particularly prone to it. This is perhaps not surprising in pneumonia, which spreads from alveolus to alveolus, and the process may stop before the whole of an acinus is affected. Even with a bronchiolar block airlessness may not be uniform throughout the subtended respiratory region, because of collateral air drift from adjacent units.

Volume of lung represented by scar.—As a result of condensation there is represented within a scar a much greater volume of normal lung and,

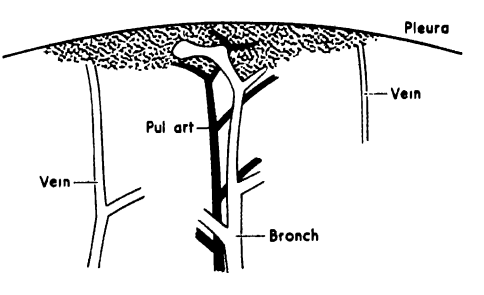


FIG. 108.—Diagrammatic representation of features of scarring commonly seen in subpleural region (as in Fig. 107). The pulmonary artery and airway enter centrally the veins drain from the periphery.

since the overall volume of the lobe may not be reduced, overinflation of the remaining unscarred lung may occur and produce a compensatory emphysema.

Any scar representing a volume of normal lung greater than an acinus must include at least one terminal bronchiolus. The greater the volume of lung affected the larger the number of airways within the scar. Sometimes the bronchioli are obliterated, sometimes they remain patent for some distance within a scar, although surrounded by condensed lung, giving rise to a region of bronchiolectasis within the scar (Figs. 107 and 108). A periodic-acid-Schiff stain, by staining mucus, may help to identify bronchiolar remnants and the van Gieson stain the characteristic muscle bundles of the bronchiolar wall. With the condensation of airways and vessels, muscle may be very obvious.

Circulation in Scars

The vascular bed within a scar is partly obliterated, bronchial and pulmonary arteries as well as pulmonary veins being affected. On in-

FIG. 109.—Diagrammatic representation of development of scar. Region of consolidation: the central region of more severe damage (stippled) condenses into a solid scar while the surrounding alveoli, with partially damaged walls, showing a mixture of emphysema and fibrosis.

jecting the pulmonary or bronchial artery system vessels may be seen within the scar, often with anastomoses between the two systems. The pulmonary artery to the scar and the pulmonary vein draining it may both show an endarteritis obliterans (Figs. 106 and 107), which means obstruction to the pulmonary artery even more proximal than the level of partial or complete bronchiolar block.

DEVELOPMENT OF SCAR

Scarring may follow necrosis, but an intra-alveolar exudate without necrosis can lead to organisation of the affected lung and its condensation into a solid scar (Fig. 109). On the other hand the exudate may be incorporated into the alveolar wall to produce an alveolar wall fibrosis, i.e.,

interstitial fibrosis. Thus the process of healing does not always produce a solid scar.

Exudate may consist of inflammatory cells and fluid as in consolidation of bacterial pneumonia and sarcoidosis, or of fluid alone, as in oedema. Although the oedema usually absorbs, under certain conditions it can be fibrogenic as in uraemia.

Organisation of inflammatory exudate by granulation tissue begins with fibroblastic proliferation, proceeding to the production of reticulin and its conversion to collagen, with consequent reduction in cell numbers. In the earlier stages a region of scarring appears grey and glairy; later it becomes denser and whiter in colour. Red cells may predominate in the exudate as in infarction and thus haemorrhagic exudate may proceed to dense scarring. Lesser degrees of infarction may disappear completely from a radiograph, presumably as the result of a process of resolution.

As indicated above, collapse of alveoli does not of itself lead to an increase in fibrous tissue, but it is dealt with here as condensation of lung may contribute to "scar emphysema". When the lung collapses the alveolar walls fall together and fuse, and there is dilatation of capillaries within the alveolar walls (Adams *et al.*, 1935). These alterations in the haemodynamics of the airless lung produce a region of condensation with an appearance, both to the naked eye and on microscopic examination, not unlike spleen. Blood flow through the region is probably reduced. These changes are best seen when a lobe is affected, but a lesser volume of lung may show it. A small region of lung may collapse when the efficiency of collateral ventilation is impaired, as in a region where connective tissue septa are numerous or when collapse is associated with infection.

SCAR EMPHYSEMA

Macroscopic Appearance

Scar emphysema takes the form of a zone of emphysematous alveoli around a core of condensed lung. If the scars are small and numerous, each being surrounded by a wide zone of emphysema, the lung gives the appearance of a massive emphysematous region dotted with scars. If they are near the pleura, bullae may form. Enlarged alveoli may be recognised but the alveolar pattern is often lost altogether.

Histology

Histological examination of the emphysema discloses air spaces having a simple profile and, usually, loss of capillaries in the alveolar wall. The alveoli may be so tenuous that little structure is recognisable, even using special stains; or they may consist mainly of collagen in walls of reduced thickness.

PATHOGENESIS OF "SCAR" EMPHYSEMA

Scar emphysema may be the result of any of the basic mechanisms—destruction, overinflation, atrophy and hypoplasia. The original damage is usually an inflammatory process and destruction of alveolar walls is part of this original damage; overinflation and atrophy may play a part as the scar develops, and hypoplasia where scarring has occurred before lung growth is complete.

In considering these mechanisms, certain subsidiary factors are relevant, such as the irregular distribution of the lesions, collateral ventilation and retraction of scar tissue.

Blood Supply and Irregular Scar Distribution

Incomplete and irregular distribution of inflammation within an acinus means that alveoli around a scar may be isolated from their direct blood and air supply—in which case they may either collapse or stay aerated. Interference with blood supply can thus occur even if the alveoli were not directly damaged by the initial inflammation. Where alveolar walls are dependent for or receive their direct blood supply from vessels obliterated in a scar, the resulting interference with blood supply may induce alveolar atrophy.

Similarly interference may also arise from local distortion and stretching of a blood vessel as where local condensation overinflates adjacent alveoli. Where they are aerated by collateral ventilation there is usually air-trapping, which may also reduce blood supply. These factors operate even if the initial alveolar damage has been minimal (for discussion of collateral ventilation see p. 334).

Retraction of Scar Tissue

Studies such as those of Sandison (1928*a* and *b*) demonstrated the intrinsic contracting power of a collagen fibre and showed that the direction of collagen fibres laid down is largely dictated by local physical forces. The physico-chemical changes in collagen fibres which result in contraction of a scar can be studied in a skin wound; even within 10 days of the incision, the tensile strength of the wound is largely dependent on collagen and is of the order of about 200 grams per sq. mm. and after six months 2000 grams (Howes *et al.*, 1939).

Although collagen may under certain conditions as in pericarditis be capable of great stretching, in a healing scar it would seem able to contract greatly and against high pressures. Although inspiration tends to maintain the volume even of inflamed areas of lung, a region healing by organisation contracts down on itself and alveoli at its edge will, therefore, be subject to additional pull.

Destruction of Alveoli

Original inflammatory damage may cause *complete destruction*, that is, complete ulceration of the alveolar wall, or only *partial destruction*, affecting only part of the alveolar wall such as the capillary network. The initial damage, e.g. a pneumonia, will certainly have affected a larger mass of lung than is represented by the final scar. Any acute inflammatory lesion shows a falling off from the centre to the periphery in the severity of damage as well as in the degree of inflammatory infiltration (Fig. 109). By the time the process of healing is complete the damage is represented by a dense central scar with a halo of dilated and distorted air spaces, either with tags of alveoli pointing to a complete destruction, or a roughly intact architecture indicating only a partial destruction.

A few inflammatory lesions associated with an increase in fibrous tissue fail to show this surrounding emphysema; a "tuberculoma" in the pathological sense is one of the rare examples (Macleod and Tait-Smith, 1952). As a tuberculoma is probably a slowly expanding lesion it does not show a halo of emphysema.

Vascular Damage by Inflammation

One puzzling feature of the resolution of inflammation is that although during the acute stage the number of blood vessels may be greater than the normal, after resolution fewer remain than there were originally. This is particularly serious in the lung since not only nutrition but proper alveolar function is dependent on a sound capillary bed.

During inflammation two types of capillary are present—those of the normal capillary bed and those of the newly-formed capillaries of the granulation tissue. It is not known whether the normal capillaries are functionally distinguishable from those of the granulation tissue and whether they also will disappear with the resolution.

With the reduction of inflammation the blood flow decreases, stasis of blood being followed by disappearance of the cells from the walls of the capillary until threads of endothelium pass across its lumen (Sandison, 1928*a* and *b*). These threads become attenuated and interrupted, the tag ends disappear and the wall of their vessel of attachment becomes smooth.

Consideration of the haemodynamic changes characteristic of inflammation is further complicated by the fact that in certain circumstances the blood supply to granulation tissue in the lung comes from the bronchial artery system. Interaction between the pulmonary and bronchial artery systems is thus an additional complication.

Emphysema may develop around scars from partial damage to alveolar walls, including their capillaries. This partial destruction will give rise to alveoli with abnormally thin walls and with a smoothed-out shape. The distensibility of such alveoli may be greater than normal, thereby further increasing their resting volume.

Overinflation

The retraction of scar tissue with condensation will give rise to overinflation of unaffected lung according to the volume of lung absorbed.

It has been emphasised that in compensatory emphysema overinflation of a normal lobe following resection, or massive collapse of the adjacent lobe, may leave the remaining lung functionally indistinguishable from normal, although there is some slight dilatation of alveoli evenly throughout. If damage by numerous small foci of condensation is distributed irregularly throughout both lungs, the effect may be more serious functionally and structurally. The assessment of the volume of normal lung affected in multiple small foci of damage is technically difficult, but usually the volume of the lobe is not reduced. This means that overinflation has occurred in the remaining aerated parts of the lung, but the degree of this may vary as those alveoli close to the retracting scar would seem to bear the brunt of damage and distortion. The reduction in blood flow to these alveoli could have increased their distensibility or compliance.

Atrophy

Atrophy may be a consequence of collateral ventilation (for a fuller discussion see p. 334). It is likely that in lung in which air is trapped, reduction in capillary flow will occur and if this persists for long it may lead to atrophy of the alveolar wall capillary bed. This is less likely to happen with small scars, but it is not known at what volume of scar this would be critical.

Hypoplasia

If there is scarring before lung growth is complete the disturbance in blood supply and ventilation may also impede the development of new alveoli and the formation of new capillaries in their wall.

Relative Importance of the Above Factors

There is no means of judging the relative significance of the above mechanisms, except by analysing the development of scar emphysema in relation to them. For example, sarcoid would commonly seem to produce partial destruction of the alveolar wall, evidenced by the frequent reduction in diffusing capacity which is found even after resolution of the nodular shadows and return to a normal radiograph. Atrophy is probably particularly important when subpleural acini or lobules are irregularly affected, for these are isolated by pleura from the protective influence of cross ventilation and cross circulation from adjacent units. In addition to the basic mechanisms the size of the scar also plays a part; a very small

intra-acinar scar, for instance, will not interfere with large blood vessels (Fig. 110), but one affecting several lobules will certainly do so.

SCAR PATTERN IN LUNG DISEASES

The relative importance of the different mechanisms in different diseases varies characteristically. For example the original acute inflammation may cause partial ulceration of the alveolar wall or implicate the bronchioli. The diseases described below occur in the absence of chronic bronchitis and are sufficiently widespread to allow some deductions to be drawn from respiratory function tests and radiographs of the effect of scar emphysema on function.

Histiocytosis X (Eosinophilic Granuloma of Lung)

Evidence of complete or partial destruction of alveolar walls is often seen in granulomata of histiocytosis X. A single acute granuloma may be a centimetre in diameter, affecting a group of neighbouring bronchioli and alveoli. Usually, a whole acinus is not involved, which means that distal alveoli may be spared the acute inflammatory infiltration, but are nevertheless cut off from their proximal airway and vascular connections.

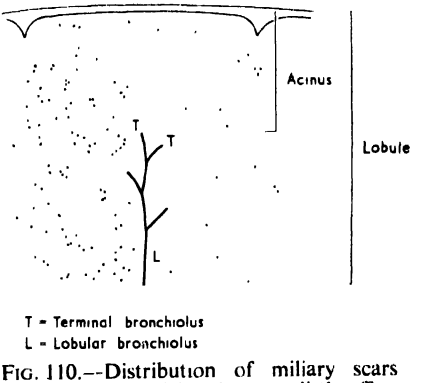


FIG. 110.—Distribution of miliary scars through acini and lobule cause little effect in large blood vessels

Histiocytic infiltration may be ulcerative over quite large areas of alveolar and even of bronchiolar wall (Grant and Ginsburg, 1955). At the edge of an eosinophilic granuloma ragged alveoli may often be seen, suggesting that alveoli have been ulcerated at the edge of the lesion as well as centrally. In the acute stage the solid central granuloma is surrounded by a nimbus (a halo in cross-section) of alveolar walls thickened by inflammatory exudate and the alveolar space may be filled with it. Although the acute changes may resolve, complete destruction of alveolar wall will leave a residue of emphysema. The central region of the granuloma may be densely scarred and surrounded by emphysematous alveoli, alveoli with walls thickened by fibrous tissue or dilated air spaces with torn ragged alveoli in their walls. Bronchioli also may be condensed into the scars or be ulcerated, leaving tags of bronchiolar wall.

Where so many pathological features are found together some idea of the predominant changes and their overall effect on function can be gained from serial radiographs and function studies. The radiograph may clear,

but when it remains abnormal, it shows either nodular or linear shadows as in interstitial fibrosis or a coarse honeycomb appearance; the diaphragm is usually normal. Respiratory function tests show little evidence of air-trapping (Hoffman *et al.*, 1962; Lewis, 1964). Rarely the radiographic appearance and respiratory function studies point to widespread emphysema.

Sarcoidosis

In sarcoidosis the distribution of granulation tissue may vary widely, from myriad microscopic granulomata [in berylliosis, Dudley (1959) counted 1013 in a microscopic section of lung 2 sq. cm. in size], to uniform pneumonia-like consolidation of several segments. Between the granulomata there may be normal alveoli or alveoli with diffusely thickened walls but without focal accentuation of the inflammation.

As a rule these lesions resolve but, occasionally, scarring may occur and follow the pattern of the acute changes—large dense scars, scattered pinpoint scars or recognisable alveolar walls either fibrosed or emphysematous.

A ragged appearance in the alveoli is less often seen with the naked eye in sarcoidosis than in histiocytosis X. So-called "cavitation" in sarcoidosis is occasionally seen. In one case personally studied the walls of the space were so dense, and the scars of which they formed part so large, that identification of the anatomical site represented by the space was virtually impossible. The predominant damage from the original acute inflammation would seem to be a partial destruction. In sites such as the skin the reduction in substance of the original tissue as the result of healing is apparent, although necrosis is not a feature of sarcoid.

In sarcoidosis there is essentially infiltration and replacement of the original tissue by characteristic granulation tissue which would seem to be relatively avascular, suggesting that the granulomata draw their blood supply from the blood vessels to the part. It may be that the capillary blood flow becomes adapted to the needs of this new tissue and with resolution of the inflammation the capillaries may close down in response to the needs of the inflammatory tissue and without reference to the original function of the lung.

This process leads to an enlarged alveolus with probably some increase in collagen. The combined result may be that the wall is still obviously thinner than in the normal and the condition would unquestionably come within the term "emphysema"; or it may be so thickened that it is clearly an example of interstitial fibrosis. In between come degrees about which it is not possible to be dogmatic. In such cases it is better to diagnose both pathological findings.

Radiology.—Sarcoidosis affecting the lung may resolve and radiograph and respiratory function studies both return to normal. But though the

radiograph usually returns to normal, showing that there is no air-trapping, the function studies often remain abnormal indicating, by impairment in gas diffusion and reduction in compliance, that alveolar walls have been irreparably damaged.

Sarcoidosis is usually widespread. A series of radiographs from 48 cases selected at random were examined to obtain information on the radiographic features of the scarring which succeeds the acute granulomatous stage, and in particular, for evidence of emphysema (Simon and Reid, 1964). The cases included a range of radiographic appearances in the acute and chronic stage illustrating the course taken by the disease. In all cases the diagnosis had been proved by biopsy and clinical details were available.

In acute cases of sarcoid showing nodular shadows no evidence of widespread emphysema was seen, whether the nodules were small or large. If shadows were numerous and confluent the diaphragm was often raised. Of sixteen acute cases in which there was gross nodular shadowing, most resolved to a normal radiograph, the diaphragm, heart, and vascular shadows being normal; the exceptions were three cases in which localised emphysema (an avascular area) was seen. In one, both upper lobes were affected in this way, in another one apex and in the third the left base. In a case with massive shadows throughout the lungs, these resolved completely in two years, there being then no evidence even of localised emphysema.

Of fourteen chronic cases, that is, those in which radiographic shadows persisted for more than two years, localised emphysema was rather more frequent. The shadows that persisted were massive, but in none were there signs of widespread emphysema with air-trapping and in six there was no evidence of localised emphysema. Localised emphysema was seen in eight cases, in four of these both apical regions showed bullous areas; in two, both apices and one base were affected; in another, one apex and in the other the base of one lung. Of four cases with small residual shadows localised emphysema was seen in two.

In several patients bronchograms showed filling well into the periphery of the bronchial tree to the region of the centimetre pattern, this also indicating satisfactory ventilation.

Comment.—The radiographic appearances of these patients suggest that widespread emphysema with air-trapping is not the usual sequela of sarcoidosis. Of the few cases in which autopsy material was available the alveolar damage seemed to be widespread; this was corroborated by function studies which demonstrated diffusion defects, even when the radiograph was normal (Smellie and Hoyle, 1960; Smellie *et al.*, 1961).

Collagen in the alveolar walls may, by reducing compliance, prevent an increase in total lung volume such as is commonly seen in certain other types of emphysema, e.g. primary emphysema or that associated with chronic bronchitis.

Avascular areas may remain in a region from which shadows have disappeared, but when such regions of localised emphysema are seen they are more often associated with residual shadows. A common pattern is for these to fan from the hilum to the mid-zones, leaving apical and basal regions unaffected; or the upper lobes may retract and the lower lobes show compensatory overinflation.

In conclusion—in no case of sarcoidosis was widespread general emphysema with air-trapping found.

Tuberculosis

Although necrosis is a common feature of tuberculosis, producing lung abscess cavities, these "large air spaces" are no longer continuous with alveoli but are separated from them by fibrous tissue. Caseous foci are also walled off by dense fibrous tissue. Elastic fibres are absent within the granuloma of histiocytosis whereas even in regions of tuberculous caseation the elastic fibres may remain. Thus it would seem that the lysis of elastic fibres is not as extensive in tuberculous lesions as in histiocytosis X.

Unlike sarcoidosis and histiocytosis X the upper lobes are usually much more seriously affected in tuberculosis and, with resolution and healing, scarring commonly reduces their volume and causes overinflation of the lower lobes, which usually are also diseased to some degree.

To a varying extent, between and around the caseous foci encapsulated in fibrous tissue, regions of emphysema are found. Partial destruction of alveolar walls would seem to have taken place, the mechanisms, even the nature of the granulation tissue, being similar to that in sarcoidosis. Tuberculous lesions, like any other infective damage, are distributed irregularly throughout an acinus.

Radiology.—With resolution, even if extensive damage was present the radiograph may return to normal, as in miliary disease, for example.

Individual small scars, even if only the size of a peanut, may be associated with bullae. The lung in the scar probably represents only a small part of the originally damaged lung, so that the initial infective damage has doubtless contributed. A subpleural position is probably more prone to the local development of the bulla, a condition commonly seen at the lung apex.

Compensatory emphysema also is not infrequently seen in pulmonary tuberculosis, as retraction of an upper lobe is often accompanied by overinflation of the lower lobe. In such a case the diaphragm may be low but, often, its range of movement is good, indicating little airways obstruction. Figure 112 illustrates the lower lobe shown in the radiograph in Fig. 111; the lobe had been inflated but, as shown by the wrinkled pleura,

FIG. 111 (*see opposite*).—Emphysema with tuberculosis. Left lower zone, localised emphysema, hypertransradiant, relatively avascular and diaphragm low.

FIG. 112 (*see opposite*).—Left lower lobe seen in Fig. 111, bullae against diaphragmatic surface. Lung showed gross emphysema, panacinar Grade III and IV on naked-eye examination.

FIG. 111.

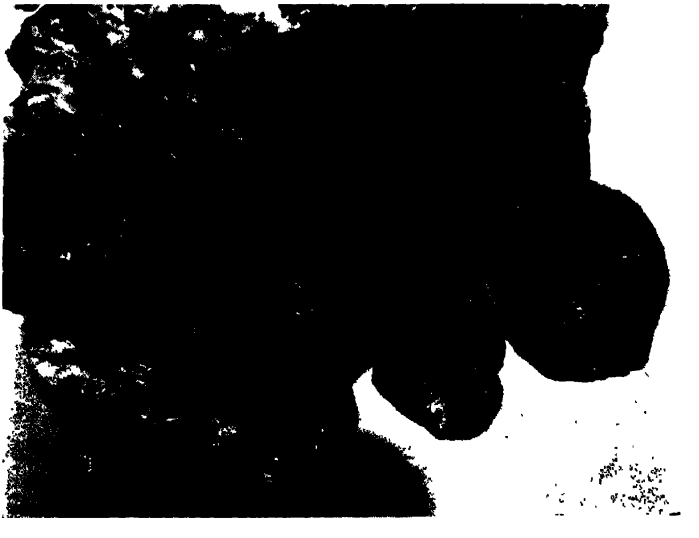


FIG. 112.

immediately deflated on release of pressure. Bullae are seen on the diaphragmatic surface.

Sometimes emphysema with air-trapping follows tuberculosis, the diaphragm being low and flat and moving poorly. One possible cause of this is the residual bronchiolar lesions which, though numerous, may be unsuspected until bronchography is performed. If sufficiently profuse they may be distributed in such a way that within a lobe or lung there is overall airways obstruction and the region relatively avascular and hypertransradiant.

Related to this is the localised emphysema remaining after pulmonary tuberculosis in childhood. Bronchiolar and alveolar lesions can produce a reduction in blood flow which over the years interferes with growth and causes hypoplasia, contributing to the development of emphysema. The mechanisms are described in the discussion of bronchiolitis obliterans in childhood on page 127.

General Comment

Scars of the order of 0·5 cm. in diameter may be visible in a radiograph if they are deep in the lung, but not if they are subpleural. This means that often they cannot be diagnosed or their number assessed while the lung is in the body. The thoracic surgeon will always be able to palpate more tuberculous lesions at thoracotomy, for example, than could be identified in the radiograph.

Scar emphysema may of course be associated with other types of emphysema. Figure 111 illustrates a case in which both upper and lower lobes were affected in the stage of acute tuberculous infection. The upper lobes were severely affected and cavitated and these retracted, causing overinflation of the lower lobes in which little shadowing persisted. In one lower lobe the appearance is that of overinflation with air-trapping, while in the other there is no trapping.

The size of scar seems important in the development of a bulla; miliary scars do not commonly produce them unless a subpleural lobule or small group of them is affected.

RESPIRATORY FUNCTION STUDIES

As might be deduced from the pathological changes described above, the functional disturbance varies. Respiratory function may be almost normal after healing of any of these diseases, yet damage may be enough to affect it permanently. In sarcoidosis the findings are typical of a restrictive lesion—reduction in lung volume, in compliance and in inspiratory volumes. There may be an increase in residual capacity as a fraction of total lung capacity, but because of the overall reduction the absolute figure may not be raised. There is not usually airways obstruction, but diffusing capacity is reduced (Smellie *et al.*, 1961).

So also in tuberculosis; destruction and damage may be great but do not necessarily produce airways obstruction. It is difficult to assess what pathological changes have taken place in patients in whom tuberculosis has healed. If this were possible we should know more of the mechanisms involved in the development of complications of chronic lung disease, polycythaemia and right ventricular hypertrophy, for example.

FIG. 113.—Bronchiolectasis. At (A) "large air spaces" lined by bronchiolar epithelium; therefore examples of bronchiolectasis and not emphysema.

Scar emphysema will cause loss of diffusion and reduction in compliance, but without airways obstruction. It may be that the fibrosis which is a feature of this type of emphysema and which causes reduction in lung compliance may operate to prevent airways collapsing.

DIFFERENTIAL DIAGNOSIS

Certain types of inflammatory damage and of scarring may make differential diagnosis of emphysema difficult. For instance, destruction without fibrosis comes within the definition of emphysema, but if the fibrosis is appreciable it might be argued that the condition is not emphysema. Certain problems of differential diagnosis are accordingly mentioned here.

Lung abscess.—A lung abscess represents destroyed alveoli but the cavity, while usually in free communication with a patent bronchial tree, is not continuous with adjacent alveoli. An intermediate condition may occur where a space brought about by ulceration is lined in part by fibrous tissue and in part by alveoli, as in certain healed tuberculous cavities, air-

containing although no longer in communication with the patent bronchus and with a lining which, to the naked eye, is smooth and complete (Keers *et al.*, 1956). Step sections through the thinnest part of the lining may show that a microscopic part of the wall of the healed cavity is formed by enlarged alveoli, few in number, which allow air to leak in. Such alveoli may reasonably be called emphysematous but the overall condition does not come within the definition.

Bronchiolectasis.—By definition bronchiolectasis of terminal or more proximal airways is excluded from emphysema. On naked-eye examination, however, bronchiolectasis may be indistinguishable from certain sorts of emphysema such as the centriacinar destructive type in which the retracted alveoli are so flattened that, to the naked eye, the "hole" in the lung is lined by a thin smooth wall (Fig. 113). Microscopic examination makes it possible to distinguish the epithelium in bronchiolectasis from the flattened alveoli in destruction emphysema (Fig. 29).

It has recently been suggested that the term "bronchiolar emphysema" would embrace both bronchiolectasis and emphysema (Siebert and Fisher, 1957), but this would seem to have no merit and merely to confuse; associated bronchiolar changes can be described separately from emphysema (pp. 116 and 172). To accept that any part of the acinus may become emphysematous entails including the respiratory bronchioli, and in the sense that alveoli open into their lumen this would seem justified. Only if it were shown that the respiratory bronchiolus became dilated without causing any change in its associated alveoli might such a condition be called bronchiolectasis and there is little advantage in divorcing the respiratory bronchiolus from the respiratory part of the lung for so rare a condition.

Interstitial pulmonary fibrosis.—Certain inflammatory conditions may leave alveoli large but with extremely thin walls; if the alveolar walls are thickened there is no difficulty in diagnosis. A simplified alveolar outline gives alveoli an abnormally large diameter. This may be the case in diffuse interstitial fibrosis of Grade I severity (Livingstone *et al.*, 1964), the stage at which change is confined to the alveolar wall. When the stage of acute inflammatory exudate within the alveolar wall or in the alveolar space is reached (Grade II) there is little likelihood of confusion with emphysema. It is when fibrosis (Grade I) has supervened and there is a thin collagen layer confined to the alveolar wall that the loss of alveolar complexity with thin walls may give rise to the diagnosis of emphysema.

Honeycomb lung.—Even more difficult to diagnose may be cases of fine scarring, in a "honeycomb" lung (used here to signify a naked-eye appearance of lung and not a particular disease) in which small holes have walls consisting of dense fibrous tissue and dilated alveoli. While some of the abnormally large air spaces may properly be called emphysema the primary diagnosis should be fibrosis.

Similar confusion may arise in other states of alveolar wall fibrosis as in

diffuse systemic sclerosis (scleroderma) and even muscular cirrhosis (von Stossel's disease, 1939), where alveoli are simple and large. In this condition emphysema is clearly not the basic diagnosis and "abnormally large air-spaces" must be interpreted in relation to the alveolar wall structure.

After resolution of inflammatory processes as in sarcoidosis, alveoli may be left abnormally large with walls too thin and perhaps with an increase of fibrous tissue. It is where the wall is very thin that it may be difficult to put a name to the condition and perhaps here the right diagnosis is not a critical matter. It is unknown whether these fibrous alveolar walls are associated with airways obstruction as in the atrophy of primary emphysema, but the circumstantial evidence described above suggests that they may not.

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Chapter XIV

BULLAE

(Localised emphysema, limited emphysema, pneumatocoele, vanishing lung, anepithelial cyst)

EMPHYSEMA, affecting a whole lobe, may distend it uniformly, but if only part of a lobe is involved the pleural contour is locally expanded and a bulla is produced. The term bulla is taken to refer to the local elevation of the pleura above the surface of the lung.

Three types of bullae can be distinguished. In the first (Type I) the bulla projects like a mushroom above the pleural surface and communicates with the lung by a narrow neck. This type represents a great overinflation of a relatively small volume of lung. The second type (Type II) has a broad base as it represents overdistension of a shallow subpleural layer. The third type (Type III) represents overdistension of a much deeper region of lung, perhaps extending back to the hilum.

Different types of bullae have been recognised on the basis of various features, for instance, according as they are congenital or acquired (Allbritten and Templeton, 1950), "on the state of the bronchial communication" with underlying lung (Baldwin *et al.*, 1950), or of anepithelial cysts and other emphysematous bullae (Belcher and Siddons, 1954). With particular concern for prognosis Kaltreider and Fray (1939) subdivided patients according to any increase in total lung volume and Baldwin *et al.* (1950) by reference to respiratory function tests. Siebens *et al.* (1957) thought compression of neighbouring lung by the bulla was significant and that the "patency of communication" was the critical factor in its production. Jensen *et al.* (1961) used angiography to assess compression. The condition of the remaining lung was thought the most important factor in prognosis by Woo-Ming *et al.* (1963) who have suggested that the features which should encourage operation are the large size of the bulla and the degree of dyspnoea.

Recently Davies *et al.* (1965) have applied the above method of classifying bullae in a study of forty resection cases. They have taken into account the symptoms of chronic bronchitis, shortness of breath, radiographic evidence of widespread emphysema, the size and type of the bulla, and whether or not it causes compression or displacement of adjacent lung. They found that all patients with dyspnoea suffered from chronic bronchitis or widespread emphysema or other disease; displacement or compression of lung adjacent to the bulla did not improve the chance that

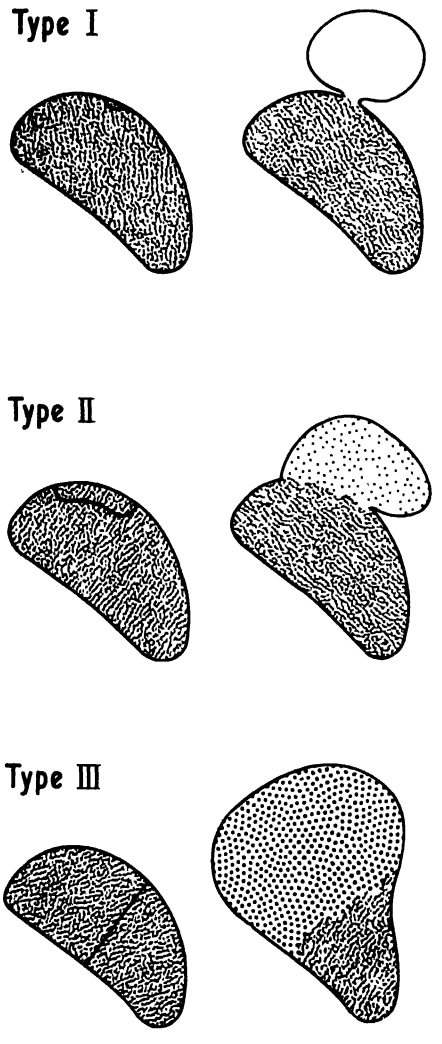

FIG. 114.—Diagrammatic representation of types of bullae. I—small amount of lung greatly overinflated giving narrow neck and empty sac; II—relatively less overinflation of shallow layer of lung giving broad neck and usually at least lung remnants; III—relatively less overinflation of large amount of lung, usually extending back to hilum giving no well defined neck and usually lung evenly through bulla.

operation would benefit the patient. The size of the bulla was no guide to prognosis or to the possible success of the operation. Symptoms of bronchitis or radiographic evidence of widespread emphysema did not rule out benefit from operation.

Because of the importance of large bullae in radiographic diagnosis, and their being capable of surgical treatment, the use of the word "bulla" has been limited to describing a particular macroscopic appearance rather than applied to all holes in the lung above a certain size (Ciba Guest Symposium, 1959).

Within the chest the shape of the lung, including any bullae present, necessarily conforms to the smooth ovoid contour of the hemithorax (Fig. 115), though occasionally bullae migrate across the mid-line or into the neck, but on removal a bulla usually projects above the lung contour as a spherical or ovoid prominence. Lungs removed at autopsy or surgical specimens are usually inflated before they are examined and this may expand lung which in the body was compressed by the bulla, giving the impression that the bulla sits on the surface of the lobe whereas in the body it is usually embedded within and indents the underlying lung, causing compression of varying degree. Figure 21 shows the indent for the bulla on the upper surface of the lobe.

DEVELOPMENT OF BULLAE

Given a region of emphysema in a subpleural position its increased distensibility will result in a bulla. Increased distensibility, i.e. compliance,

may arise in a variety of ways. Emphysema from each of the four basic mechanisms that have been described as producing emphysema (p. 288)—atrophy, hypoplasia, overinflation, or destruction—can give rise to bullae. Reduced vascularity in the paraseptal region has been mentioned as a contributing anatomical feature.

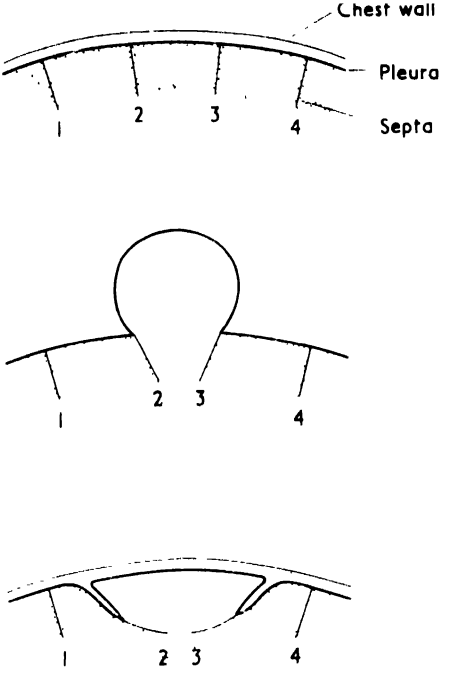

FIG. 115.—Diagrams illustrating one way in which bullae produce line shadows in the radiograph. Out of the body the bulla between 2 and 3 projects from the surface; within the body it conforms to the chest wall contour, invaginating lung. The outline produced by pleura and septa.

As a result of the emphysema the affected region occupies a larger volume than it did when the lung was normal, that is, there has been a stage when more air has entered the bulla than has left it. But having achieved a new stability, there need not be trapping of air in the usual sense as a bullous region may be ventilated normally.

As a consequence of the formation of a bulla there is a yielding of surrounding structures. A bulla expands mainly into the pleural space. To understand the final size of the bulla the resistance of the lung—blood vessel, bronchus and fibrous tissue—to stretching, must all be taken into account, as well as the opposition of surrounding structures.

An example of a bulla in emphysema caused by hypoplasia can be seen in a case of unilateral hypertransradiancy associated with bronchiolitis obliterans acquired in childhood (Case 32, p. 143).

Atrophy is presumed to have been responsible in cases of primary emphysema such as is illustrated on pages 39 and 224.

Overinflation as a solitary cause of emphysema often operates through a whole lobe because it follows ball-valve obstruction of a lobar bronchus, so bullae are not so commonly a feature of this type of emphysema. It may be seen in childhood emphysema. Whether long maintained overinflation such as might occur in relatively isolated subpleural lobules ultimately produces a region of increased compliance is one of the unanswered questions.

Destruction as the result of infection is probably the factor responsible for the bullae seen in chronic bronchitis and tuberculosis, although it is sometimes difficult in a given case to prove the type of initial lesion.

Destruction and atrophy are mainly responsible for emphysema giving rise to bullae.

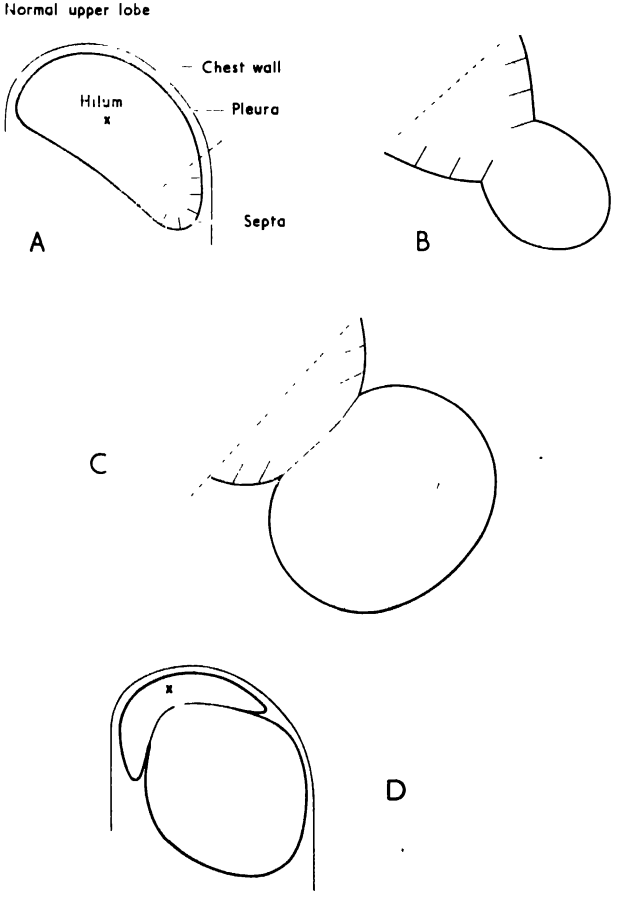

FIG. 116.—Type I bulla—diagrammatic representation of its development. A D lung within chest wall. A—normal lung; B and C increase in size of bulla developing from small volume of lung between two septa; D within chest wall this compresses neighbouring lung.

Of the anatomical types of emphysema, centriacinar emphysema has not been seen in a bulla, but panacinar and periacinar and irregular emphysema commonly occur.

PATHOLOGICAL APPEARANCES

Type I Bulla—Narrow Neck

A mushroom bulla is attached to adjacent lung by a narrow neck (Fig. 116). Its characteristics can be summarised as follows:

Neck	— small
Wall and deep surface	— mainly pleura and connective tissue septa
Contents	— only gas or a few flimsy strands of lung
Lung represented	— a small amount of lung (probably a small cluster of lobules) greatly overinflated
Blood vessels	— may be absent or a few tags
Distribution	— commonly at the lung apex and where septa are numerous

Neck.—The size of the neck or base gives some idea of the amount of tissue represented in the bulla. The neck may be only a centimetre in diameter, suggesting that the bulla represents only one lobule, or the base may still be narrow and yet represent several lobules.

Wall including deep surface.—The wall commonly consists of pleura which has been converted to featureless hyaline connective tissue. Irregular thickening of the pleura may be apparent and special stains often reveal blood vessels, collections of elastic fibres, and compressed lung within the thickened regions. The junction with the lung is often connective tissue septa of which the deep surface of the bulla consists, with a relatively small contribution from adjacent emphysematous or compressed lung.

Contents.—The bulla is usually empty except for gas; it may contain flimsy strands or remnants of alveoli and tags of tissue floating free at one end which represent blood vessels.

Lung represented.—The amount of normal lung represented is much smaller than the volume of the bulla itself—a relatively small volume of lung is greatly blown up, in contrast to a scar which represents much more normal lung than its own volume.

Blood vessels.—When the bulla is empty the pulmonary artery capillary bed and some arteries have been lost. A specimen pulmonary arteriogram does not usually outline the wall of a bulla.

Distribution.—This sort of bulla is commonly seen at the apex of the upper lobe, associated with apical scars, and at other sites where septa are common—e.g. along the edge of the lingula and middle lobes, and the costo-diaphragmatic rim.

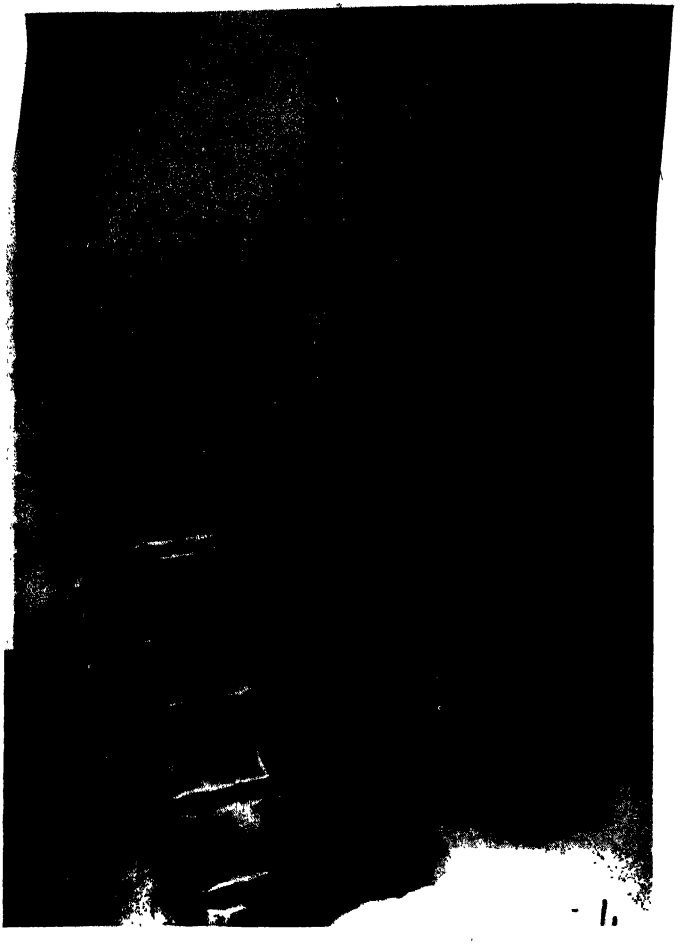

FIG. 117.—Case 43. Type I bulla, representing great overinflation of small volume of normal lung. Lateral view shows size and anterior position. At thoracotomy, bulla found to arise from tip of middle lobe by neck only a cm. or so in diameter. No symptoms.

Development.—An area of emphysema may arise from any of the four mechanisms, but where septa are numerous these tend to isolate a bullous region and may act as a funnel (see diagram) which favours air-trapping in the region and gross local distension. At the base of the bulla there is often a scar which suggests that there has been some previous infection and lung damage, leading to partial or complete destruction of alveolar walls. This, as well as the scar itself, may have contributed to the development of the bulla. In addition, the subpleural site of this damage where the blood supply is also more isolated predisposes to additional atrophy.

Even if there are no septa, underlying normal lung compressed by the emphysema may be mostly airtight and can act at least as an intermittent obstruction.

CASE 43.—TYPE I BULLA—ASYMPTOMATIC

A male of 57 had his right shoulder radiographed because it had been hurt in a car accident. As part of the right lung field was included and showed a hair-line shadow, a routine chest radiograph was taken. This revealed that the right dome of the diaphragm was flat and lower than the left, the heart and trachea being displaced to the left. The left lung was normal, the right lung more transradiant than the left. The right hilar vessels were normal but the lower zone showed either small vessels or no vessels at all. A hair-line shadow ran downwards and outwards from the hilum to the costo-phrenic angle. In the lateral view (Fig. 117) the hair-line was seen in the middle of the lung, showing a posterior convex curve with a transradiant zone between it and the sternum. Scars were seen at the apex of the right lung.

At operation it emerged that the bulla arose from the medial tip of the middle lobe; the apical scars were seen and the bulla was found against the mediastinum, adherent to the diaphragm and the pericardium, and to the under surface of the upper and middle lobes and anterior surface of the lower. The thin-walled cyst some 25 cm. in size was dissected away from its attachment without air leak from either lung or cyst until the medial tip of the middle lobe was reached, when an attachment had to be cut and there was a small leak. The cyst had not increased in size while the anaesthetist inflated the lung, nor could it be deflated. The residual lung, especially the lower lobe, was slow to inflate after resection of the bulla.

It is suggested that this cyst represents a Type I bulla—striking because of the size of the "mushroom" and the smallness of the neck.

TYPE II BULLA—BROAD BASE AND SUPERFICIAL

The characteristics of this second type of bulla are:

Neck — very broad

Wall and deep surface — the pleura, with the deep surface being a region of emphysematous lung

Contents — usually emphysematous lung

Lung represented — a superficial layer of lung

Blood vessels — usually blood vessels still cross the bulla

Distribution — anywhere through lung

Neck.—The neck of the bulla is usually so wide that any constriction present at the base is only slight. This is demonstrated in Fig. 118.

Wall and deep surface.—Because the neck is so wide it is virtually the same as the deep surface of the bulla. This type of bulla seems to grow by progressively implicating the base so that the lung within the bulla becomes stretched and atrophies until it may be represented by mere remnants.

Contents.—The bulla often contains architecturally intact lung with a *panacinar Grade III* emphysema within it, but may be only a bag of gas.

Lung represented.—*The amount of lung represented by a bulla of this type is relatively less than that by a Type I bulla of the same size. The bulla may still be greatly overinflated so that a small amount of lung is considerably over-distended.*

Blood vessels.—An arteriogram may show numerous vessels within the bulla but these are narrow, stretched, and lacking the usually numerous side branches. There are, however, still more vessels than suggested by an angiogram in life.

Distribution.—This type of bulla is commonly seen over the anterior edge of the upper and middle lobes and over the diaphragmatic surface,

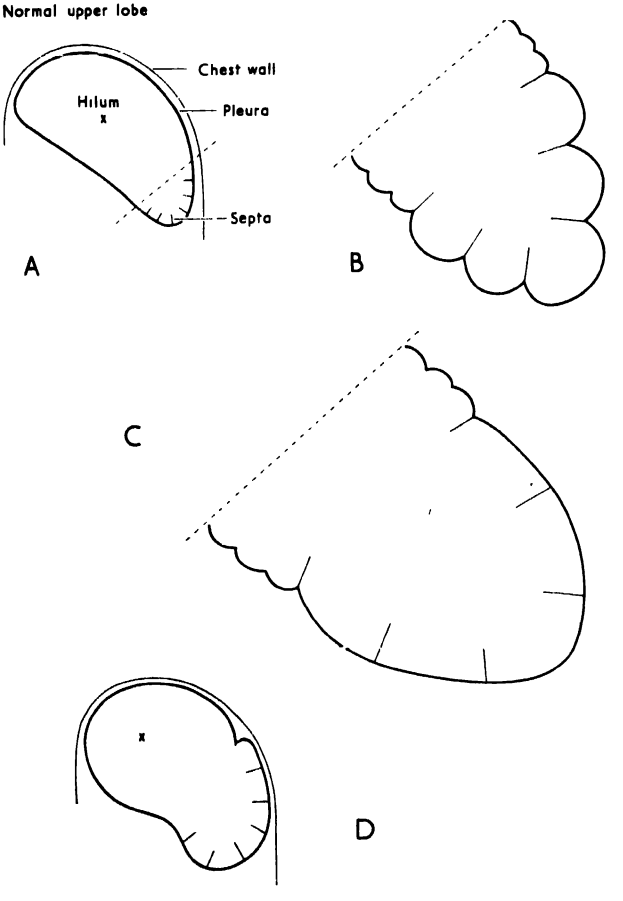

FIG. 118.—Type II bulla—diagrammatic representation of its development. A D lung within chest wall. A—normal lung; B and C, development of bulla in shallow subpleural layer with broad neck; D within body demarcation by line shadow is incomplete.

but it may be found in any part of the lung including the flat lateral surfaces.

Development.—These bullae may arise from any type of emphysema.

Case 44.—Type II Bulla

After a mass miniature radiograph in 1957 had revealed a bulla the patient gave up smoking. The small amount of sputum that he had been producing each day then ceased.

The radiograph (Fig. 119) revealed that the heart was normal and that the diaphragm was of normal contour and was between the 6th and 7th rib.

The upper half of both lung fields showed relative transradiancy with no visible vessels, these regions being demarcated below by hair-line shadows. The lung vessels below this area were crowded but the lung was otherwise normal. Bronchograms (Fig. 120) showed no filling in the transradiant areas and the bronchi in the lung below were crowded but otherwise normal. In the lower lobe the peripheral filling was fairly good, but was poor in the right upper lobe below the bullous area. After right upper lobectomy the right lung vessels occupied their usual site and appeared normal.

Respiratory Function Tests

VC	3700 ml.
FRC	4620 ml.
RC	3820 (predicted 1620 ml.)
TLC	7620 ml.
RC/TLC	50%
Mixing efficiency	3 mins.
FEV_1	2400 ml.
FVC	3975 ml.
FEV_1/FVC	61%
PEF	520 l./min.
$D_{(CO)}$ at rest	17·3 ml./min./min.Hg (Min. ventilation 10 l./min.)
$D_{(CO)}$ on exercise	41·5 ml./min./mm.Hg (Min. ventilation 31 l./min.)
% extraction	49

Gas flow measurements during bronchoscopy showed that there was virtually no gas flow from the right upper lobe, a big flow from the middle lobe, and a small one from the right lower. On the left side there was also some impairment. Regional lung function studies indicated that no gas entered the upper zones. Ventilation and blood flow were reduced in the right lower lobe compared with the left.

At operation a large bulla more than 20 cm. in diameter with no carbon in its walls was found occupying the posterior and apical segments (Fig. 121). The anterior segment was somewhat bullous and contained carbon.

The middle lobe was normal except for its lateral fringe which showed a row of small marginal bullae. A bulla, 4 cm. in diameter, was found at the apex of the lower lobe but the remainder appeared normal. The bronchial

FIG. 119.

FIG. 120.

FIG. 121.—Case 44. Specimen. Large bullae from superficial lung of apical and posterior segments. Anterior segment compressed and displaced by bullae. See also Figs. 119 and 120.

and pulmonary arteries seemed normal, the cartilage of the main airways soft.

The right upper lobe was removed and contained a bulla 20 cm. in diameter even in the fixed condition, with a region of compressed lung attached to it. The pulmonary artery was injected segment by segment. On cutting, the bulla was seen to be multiloculated with connective tissue septa and compressed lung subdividing *the cavity*—which is situated in the apical segment. The anterior and posterior segments were compressed but still aerated and slightly emphysematous. The base of the bulla consisted of compressed lung. Marginal bullae were present at the edges of the anterior and posterior segment. Five months after operation the RC/TLC had fallen to 32·5 per cent. Otherwise there was little change.

TYPE III BULLA—BROAD BASE AND DEEP

The third type of bulla is similar to the previous type save that a greater depth of lung is involved.

Its features can be summarised as follows:

Neck — broad

Wall and deep surface — emphysematous lung

Contents — emphysematous lung

FIG. 119 (*see opposite*).—Case 44. Type II bulla. Transradiant avascular areas both upper zones; long linear shadows right mid-zone and another inferiorly, demarcating affected area. Vessel crowding in lower zone. See also Figs. 120 and 121.

FIG. 120 (*see opposite*).—Case 44. Bronchogram. Bronchi displaced forwards and downwards. Bullae represent only peripheral lung. See also Figs. 119 and 121.

Lung represented — large amount of lung relatively little overinflated

Blood supply — relatively normal

Distribution — any lobe may be affected

Neck.—The neck or base is very wide, and as most of a segment is affected the bullous regions often extend close to the hilum. This is demonstrated in Fig. 122.

Wall and deep surface.—The base of the bulla is usually the junctional region between the normal and emphysematous lung.

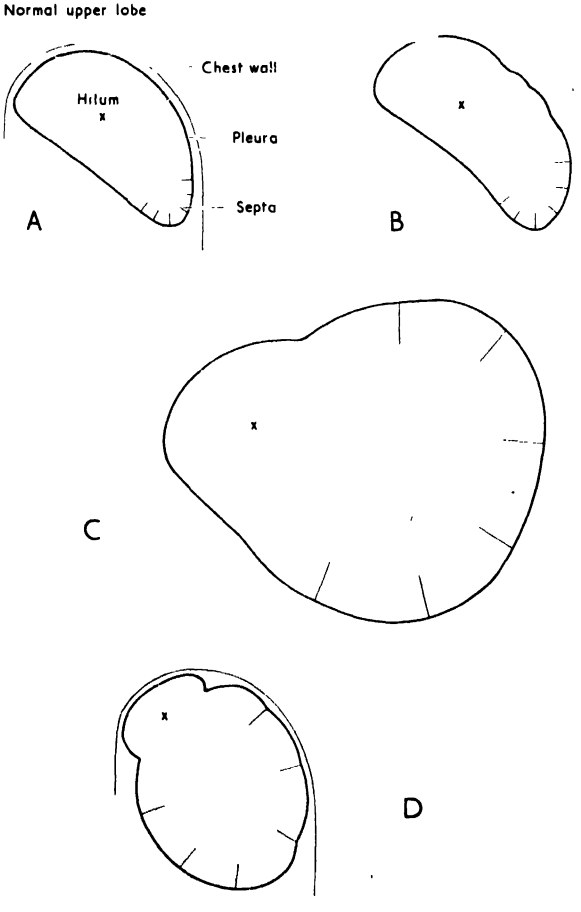

FIG. 122—Type III bulla. Diagrammatic representation of its development. A D lung within chest wall. A—normal lung; B and C, gradual increase in volume of half of lobe; D within body usually no demarcation by line shadow; relaxation of adjacent lung.

Contents.—Within the bulla emphysematous lung with an overall architectural pattern intact is seen, usually panacinar Grade III or IV severity. It may not be apparent in the radiograph that such a bulla contains so much lung issue.

Lung represented.—Such a bulla represents a large amount of lung relatively little overinflated, as seen in Fig. 122. In this case it is roughly 250 cc. blown up to 500 cc. This can be compared with the bulla illustrated in Fig. 117 on page 216, which probably represents lung about 1 cm. deep, 1 cm. wide and 5 cm. long, i.e. 5 cc. which has blown up to 500 cc.

Blood vessels.—The blood vessel pattern through this region may be more normal than in bullae of types I or II. Fig. 124, a specimen arteriogram, illustrates the roughly uniform pattern of vessels through the bulla. The pleura may show a mesh of inter-communicating blood vessels, each 1–2 mm. in diameter.

The apparent avascularity of such a region in a plain radiograph points to a reduction in blood flow through this region. A specimen arteriogram may produce a degree of arterial filling which the radiograph failed to indicate. Figs. 123 and 124 illustrate a bulla in the right upper lobe in a radiograph and the specimen arteriogram of the corresponding region. The arterial arrangement is unusual since throughout the emphysematous region anastomoses between adjacent pulmonary arteries have opened up to form "arcades". The significance of this is not clear. It may be that in these pulmonary artery arcades lies the cause of the emphysema—atrophy of the capillary bed is perhaps the result of its being by-passed by the blood in these larger vessels. Or it may be that as the capillary bed atrophies the proximal channels dilate. The case illustrated in Fig. 124 is a well-developed example of these arcades.

Distribution.—This type of bulla may be seen in any region.

Development.—The cause is unknown. The basic pathological change is an atrophic type of emphysema—panacinar in distribution—proceeding to a severe grade (see also p. 17).

Once this type of emphysema has developed, increased distensibility will favour relative overdistension. Upper or lower lobes may be affected. Of cases considered clinically as localised emphysema, it is a not uncommon pathological type. In some cases, however, the later history has revealed that the region represented a localised accentuation of what was widespread emphysema of the primary (essential of idiopathic) type.

Case 45.—Type III Bulla—Probably Early Clinical Manifestation of Primary Widespread Emphysema

The patient, a man aged 45, used to smoke 15–20 cigarettes a day. He had been well until 1953 when he started to have recurrent attacks of bronchitis. He was exposed to fumes in a gasworks. He had noticed shortness of breath for 3 years.

The radiograph (Fig. 123) showed that the diaphragm was low (7th rib) and flat, and the range of movement less than 2 cm. The heart was 10·5 cm. transverse diameter. The main and hilar pulmonary arteries were normal; avascular areas were present in the right upper half and base and at the left base. The horizontal fissure was somewhat depressed. The appearances were those of widespread general emphysema with local accentuation.

FIG. 123.—Case 45. Type III bulla, right upper zone. A vascular hypertransradiant region. Diaphragm low and flat and basal lung vessels small, suggesting apical region is localised accentuation of generalised emphysema. See also Fig. 124.

Respiratory Function Tests

Pre-operative (January 1961)		*Post-operative* (December 1961)
VC		2500 ml.
FEV_1	1200 ml.	800 ml.
FVC	2833 ml.	2400 ml.
$\frac{FEV_1}{FVC}$	41%	33%
MVV	39·5 l./min.	
PEF	175 l./min.	100 l./n
D_{CO} at rest	8·6 ml./min./mm.Hg (minute ventilation)	
% extraction	33·5%	

Xenon studies showed that neither ventilation nor blood flow occurred in the right upper zone. The CO_2 clearances were generally low. The regional test revealed that gas flow was reduced in the right upper and also the left lower lobe.

At operation the anaesthetist found that for the lungs as a whole inflation was easy and that recoil seemed satisfactory with the maximum expiratory pause allowed for on the Blease machine. On opening the right chest much of the lung, particularly the upper lobe, did not alter but the middle and anterior basal segments deflated. The whole of the posterior region of the upper lobe was occupied by what seemed an empty bulla; in the anterior region air spaces, visible through the pleura, were enlarged compared with those visible in the lower lobe; the enlargement increased progressively towards the posterior region.

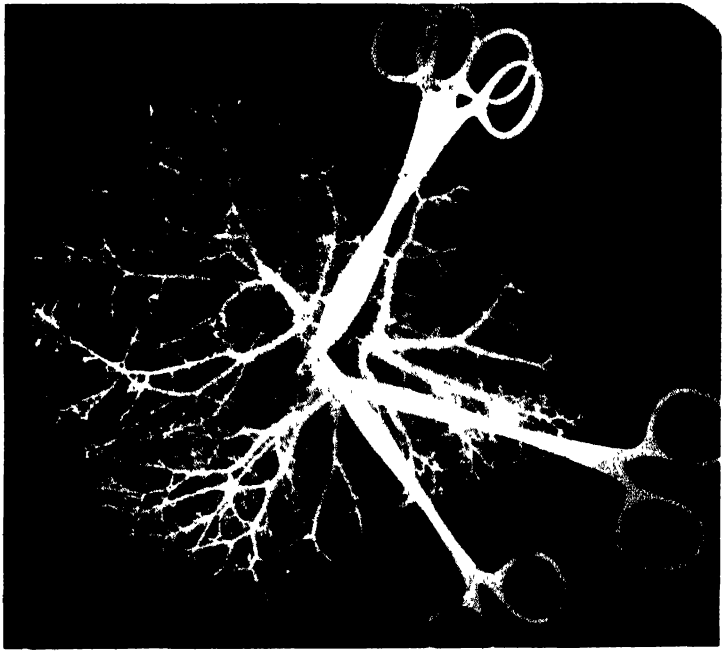

FIG. 124.—Case 45. Micropaque pulmonary arteriogram of right upper lobe. Bullous region represents posterior and apical region lobe and involves a relatively large amount of lung. Panacinar emphysema Grade III. See also Fig. 123.

The volume of the upper lobe ultimately reduced with handling. Starting from a deflated position, gradual inflation of the upper lobe by the anaesthetist then increased its volume on each inflation without any reduction in between. When its original volume was reached there was no further increase.

Inspection of the other lobes showed that the middle lobe was normal. The cardiac segment was separated by a complete fissure and this and the apical segment of the lower lobe appeared normal; the anterior and posterior basal segment showed larger air spaces through the pleura and the lateral basal even larger—clearly emphysematous. The upper lobe was removed.

Injection of the pulmonary arteries of this specimen (Fig. 124) revealed not only that the posterior region was not a sac of air, but that throughout there was emphysema, panacinar in type and Grades III and IV in severity, which gave a surprisingly uniform appearance in the arteriogram. The pulmonary arteries throughout this region anastomosed to form numerous pulmonary arcades.

EFFECT OF BULLA ON ADJACENT LUNG

While a small bulla may simply encroach on the pleural space, a bulla of any size will fill space in the thorax usually occupied by normal aerated lung and to do this it must to some extent displace the remaining lung. In this case the compression may be concentrated in a small amount of adjacent lung or spread over a much larger volume of lung, perhaps the whole of the remainder. The transradiancy in the remaining lung may be little altered, and the displaced lung may be described as relaxed. If the displacement is great enough there may be vessel crowding and opacity of lung, which suggests that the lung is compressed as well as relaxed.

The degree of compression and relaxation varies. For example, in the case of the bulla illustrated in Fig. 123, the horizontal fissure is displaced downwards, indicating relaxation of the middle and lower lobe. By contrast, in Fig. 119 a large bulla has displaced the vessels in the other lobe and caused some lung clouding.

In Case 45, displacement of the oblique fissure shows that the upper lobe is affected, that is, the rest of the lung is relaxed. In this instance throughout the right side of the chest the resting volume of each lung unit is reduced. Ventilation and perfusion are thereby reduced, probably in the same proportion. Finally the effects may be localised, so that immediately adjacent to the bulla the lung is opaque (Fig. 125).

A bulla does not always encroach much on a lung, the pleural space being such that the bulla may extend into it with relatively little resistance. It may even spread to the opposite side in front of the aorta or up into the neck (Tubuku-Metzger, 1961).

For a bulla of a given size the degree of compression of the rest of a lung will vary with the amount of lung represented by the bulla. For example, if a bulla the size of a left upper lobe represents only a few apical lobules, virtually the whole of the lung will be compressed to the size of a lower lobe. If on the other hand the bulla or bullous region represents almost the whole of the upper lobe, there will be relatively little compression of the lower lobe. Respiratory function tests may show whether or not a bulla is ventilated during quiet respiration.

Clinical Features

Even though a bulla is large enough to compress one lung and encroach across the mediastinum on the other, the patient may be free of

symptoms. Much probably depends on the condition of the remaining lung. If the bulla is an isolated change and the rest of the lung is normal the bulla may have no effect detectable by the patient even if it occupies most of one side.

If the remainder of the lung is diseased the patient may be incapacitated, partly because the respiratory reserve is already so reduced by the bulla that any further diminution suffices to tip the balance, or because slight compression of lung in which air-trapping is already occurring will greatly accentuate the disability (Case 46). Disability may also be caused by the speed with which a bulla develops. A sudden increase in size may be sufficiently inconvenient to cause the patient to seek medical advice.

Case 46.—Type II Bulla—Sudden Increase in Size—Associated with Chronic Bronchitis

The patient, aged 44, had had a productive cough since childhood. At 24 years, while he was in the Army, he first noticed shortness of breath and was discharged because of chronic bronchitis. During the next twenty years he had recurrent attacks of bronchitis and increasing dyspnoea which kept him confined to the house. He smoked 5 cigarettes a day and there was no finger clubbing. Haemoglobin was 106 per cent, packed cell volume 50 per cent; mean corpuscular haemoglobin concentration 31 per cent.

Respiratory Function Tests

		After operation
VC	1400 ml.	2200 ml.
FEV_1	400 ml.	500 ml.
FVC	1200 ml.	2200 ml.
$\frac{FEV_1}{FVC}$	33%	22·7%
MVV	20 l./min.	23·9 l./min.
PEF	60 l./min.	70 l./min.
D_{CO} at rest	9·4 ml./min. mm. Hg (Minute ventilation 9·25 l./min.)	7·1 ml./min./mm. Hg (Minute ventilation 9·6 l./min.)
D_{CO} on exercise	12·5 ml./min./mm. Hg (Minute ventilation 15·5 l./min.)	7·7 ml./min./mm. Hg (Minute ventilation 11·7 l./min.)
% extraction	24	30

The radiograph (Fig. 125) showed evidence of widespread emphysema with avascular areas partly demarcated by line shadows in both upper zones and also at the left base. The lower half was relatively transradiant and only a few narrow vessels were seen. The hypertransradiant area was demarcated above by a broad band-like horizontal shadow. Between 1962 and 1963 the radiograph had altered, the bullous region at the left base having increased to reach the apex of the left lung. The bronchogram of the left lung showed poor peripheral filling in both lobes, but was worse in the lower, and

nowhere was it further than the fourth generation. Tomograms suggesting collapse of the left upper lobe showed some narrowing of vessels in the right apical and basal regions, but the mid-zone had a more normal appearance. At operation the left lower lobe was found to be filling most of the left hemithorax and compressing the left upper lobe.

The specimen consisted of the left lower lobe. A large bulla arising from the apical region seemed to compress most of the rest of the lobe, but on the diaphragmatic surface there was another smaller bulla. Most of the basal segments and part of the apical were compressed against the bronchi at the hilum. Injection of the pulmonary artery (Fig. 126) revealed that blood vessels, thin and shorn of most of their side branches, were distributed throughout the bullae. Cutting the lobe not only confirmed this but showed that the compressed region was emphysematous. Airways could be traced right into the bullae, indicating that the bullous region represented a large volume of lung.

A bulla may give rise to pain but how it does so is not clear. A bulla may also become infected. While the clinical course may be little different from that of any other lung infection, the shadows in the radiograph may be very slow to resolve, lagging a long time behind clinical response. A fluid level, thickening of the wall of the bulla, or a solid shadow may persist for months.

The question whether a patient should be told that he has a "harmless lung cyst" is a difficult one for the clinician, since it is not unlikely in future that any chest sensation will be magnified by the knowledge. Several of the patients in the present series, given the news following a mass miniature radiograph, were back within two years complaining of shortness of breath, possibly iatrogenic, and raising the question of resection.

Resection or plication of a bulla will sometimes relieve disability but on the other hand it may do little to help a patient suffering from disease in other parts of the lung and causing disability. It would seem that the ultimate success of the operation depends on the amount and nature of disease in the residual lung (see p. 278). At present it is impossible to predict which of the severely incapacitated patients will benefit.

RADIOGRAPHIC APPEARANCES

Reduced vascularity and hypertransradiancy are radiographic evidence of the presence of a bulla. In addition there may be seen a hair-line shadow cast by the walls of the bulla or again a shadow produced by compression of lung—both of which would accentuate the hypertransradiancy.

FIG. 125 (*see opposite*).—Case 46. Type II bulla, left base, with widespread emphysema. Widespread emphysema, avascular hypertransradiant areas through left lung, right apex and extreme right base. Horizontal band-like shadow left side, represents compressed alveolar tissue in left upper lobe (established by bronchography). See also Fig. 126.

FIG. 126 (*see opposite*).—Case 46. Specimen pulmonary arteriogram of basal segments only: left lower lobe. Reduction in peripheral branches throughout; bulla (B) represents lung from lateral aspects of basal segments displacing apical lower lobe (A). See also Fig. 125.

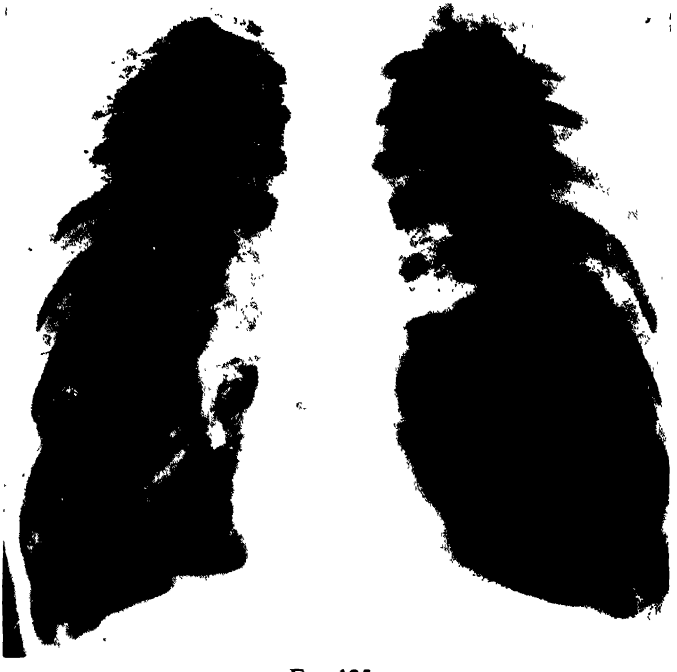

FIG. 125.

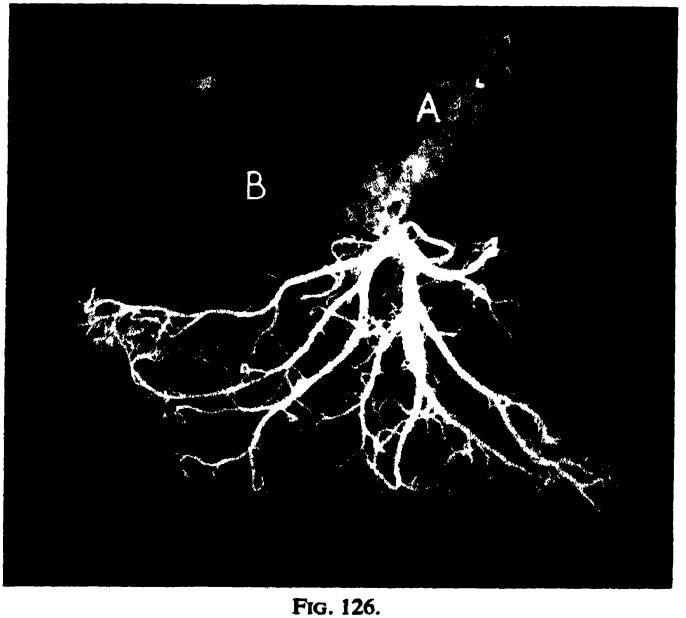

FIG. 126.

Whether a bulla is detected in a radiograph will depend on its size and the degree to which it is obscured by overlying lung. For example, a bulla may be striking if at the apex of the lung, but if in the apical region of the lower lobe may be missed in a posterio-anterior radiograph, though clearly detectable in a lateral view.

In all three types of bulla described above the concentration of blood vessels is reduced. If the bulla is of Type I it is virtually a bag of air and the hypertransradiancy is well marked. Probably also because such a bulla has a narrow neck, the air is almost completely enclosed and the pleural walls may be clearly seen.

In Types II and III the contents of the bulla include an abnormal concentration of air and also remnants of lung—blood vessels and respiratory tissue which, particularly as they are drawn out and distorted, may appear as solid strands of tissue within the region of increased transradiancy.

Correlation between the radiographic and pathological findings (Reid and Millard, 1964) revealed that when a bulla is radiographically detectable panacinar emphysema of at least Grade III is present.

Wall of Bulla

The hypertransradiant region is not necessarily clearly defined; it may shade gradually into adjacent lung. For example, a Type III bulla (Fig. 123) typically has no linear demarcation in the radiograph.

At the other extreme, in a bulla of Type I the sac of air has a narrow neck, is almost completely demarcated by pleura and, on the deep aspect, the aspect away from the chest wall, the wall consists of a double layer of pleura thin as a hair-line or it may be 2–3 millimetres thick (Fig. 117).

Between these two extremes are found those locally prominent bullae which cause creasing of the pleura so that, depending on the plane of the wall in relation to that of the X-ray beam, the wall shows as a more or less complete ring shadow or as a straight fine line.

The line shadows of the pleura may be seen with bullae at any site, but they are particularly evident at sites where connective tissue septa are numerous and form part of the wall of a bulla. For example, at the base the infolded pleura and its continuation into connective tissue septa often cast linear shadows running at right angles to the diaphragm. The wall may also be demarcated by shadows arising from the effect of the bulla on adjacent lung.

Effect on the Diaphragm

Large apical or mid-lung bullae usually have no effect on the level or movement of the diaphragm. Of 25 cases treated surgically, in five the adjacent lung was compressed or the bulla had encroached on the contralateral side, while the diaphragm was normal.

On the other hand quite small bullae against the diaphragm may

depress it even when the rest of the lung is normal. In one case personally studied the only emphysema present was represented by small basal bullae. These included lung showing Grade III panacinar emphysema and were elevated several centimetres above the diaphragmatic pleura, yet the diaphragm was low.

Effect on Mediastinum

It is rare for bullae to displace the heart or trachea, though they may encroach on the retrosternal mediastinum, especially large bullae of Type I with a small neck. There are virtually air cysts with a very small communication with lung.

Distribution

Bullae may be found throughout the lung. Table V gives the distribution of bullae or bullous areas in 103 cases with widespread gross emphysema.

TABLE V

DISTRIBUTION OF BULLAE

Radiographic Evidence of Widespread Emphysema

Zone	*Present*
Upper	33
Lower	27
Upper and lower	16
Not obvious	27
	103

A bulla or bullous area was considered present if a large avascular, relatively transradiant area was seen, whether or not demarcated by a white line shadow. All cases had severe dyspnoea and showed the other criteria (see p. 276) for the radiographic diagnosis of emphysema. Large bullae without widespread emphysema were not included.

Bronchography

Airways displaced and distorted by bullae and large or medium sized airways entering the region of increased transradiancy may be revealed by bronchography. It can often give additional evidence of the amount of lung represented by a bulla.

In the case of a Type I bulla, for example, the bronchogram may show filling of all segments, the bronchial tree being displaced in a manner that reflects the size of the bulla, although not the amount of lung it represents. The bronchogram often shows filling of most of the bronchial tree indicating that the bulla represents only a small part of the lung.

In Type II the bronchogram may be similar to that in Type I. If this

type of bulla is large, displacement may be accompanied by compression of nearby lung. As only a subpleural layer is involved this is beyond the level at which filling normally occurs.

In the case of Type III bulla the bronchogram may show within the transradiant region quite large airways but with deficient peripheral filling. The bronchogram indicates that the bulla represents a large volume of lung with architecture more or less intact, while in the case of Types I and II the presence of all segments in the bronchogram and the relatively normal pattern adjacent to the bulla indicates that only a superficial layer of lung is included within it.

The bronchogram of the rest of the affected lung is useful as a guide to the presence of disease. Filling of adjacent lobes is often poor because of the reduction in ventilation associated with air-trapping in the bulla, the visible airways often appearing narrowed but otherwise normal; in such a case the bronchogram is a poor guide to the state of the peripheral airways. Peripheral irregularities and pooling of radio-opaque medium may be seen and suggest the presence of bronchial disease in the non-bullous areas.

Tomography

The blood vessel pattern revealed by tomography may reveal how much lung is involved in a bulla. Type I is usually seen to be empty of vessels; in Types II and III some vessels may be seen within the hyper-transradiant region. Tomography may also reveal the degree and nature of the compression or displacement of adjacent lung and thereby help to elucidate the nature of the bulla.

UNILOBAR EMPHYSEMA

Certain types of unilobar emphysema can usefully be considered in context with bullae. Type III bullae may affect a whole lobe and not merely two-thirds as in Case 45. In the radiograph this cannot be distinguished and the surgeon's first intention of removing "a bullous cyst" may have to give way to the performance of a lobectomy.

The following case is an example of a rare form of bullous cyst. The whole of the left lower lobe was affected and although the size of the emphysematous region had recently increased, a large area of emphysema was known to have been present since the age of seven. This probably illustrated "congenital" or infantile lobar emphysema of the lower lobe, which was the site of air-trapping through some period of postnatal growth and early adulthood.

CASE 47.—TYPE III BULLA—ONSET IN CHILDHOOD

This patient was found at the age of 7 to have a cyst on the left lung; he had no symptoms, the diagnosis being made from a routine chest radiograph. On a further mass miniature radiograph in 1963 when he was 28 a large "cyst"

was again noted and resection was advised. He reported that in the intervening years his respiratory function was normal and that it was only while mountaineering and climbing heights up to 10,000 feet that he became more breathless than his companions.

Not only was respiratory movement on the left poor but the chest was asymmetrical with a greater antero-posterior diameter through the left than through the right hemithorax. The trachea and heart were grossly deviated to the right.

The radiograph (Fig. 127) showed that the left dome was depressed, the

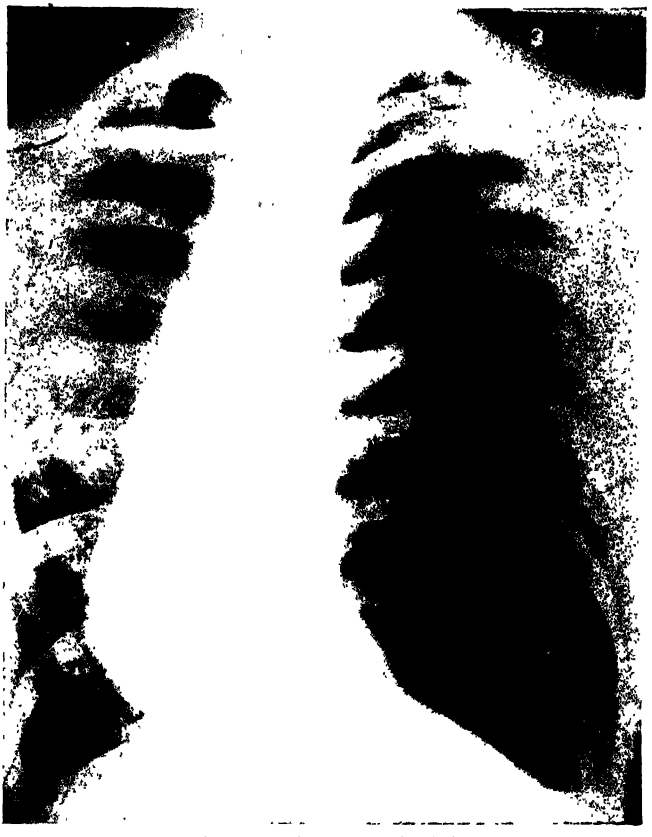

FIG. 127.—Case 47. Hypertransradiancy and avascularity left hemithorax. "Bulla" represents whole of left lower lobe; compressed left upper lobe invisible and obscured by central shadows. This probably represents a lobar emphysema of childhood since a "lung cyst" was known to have been present since age 8. See also Fig. 128.

heart and trachea displaced to the right. The right lung was normal while the left was completely avascular and hypertransradiant. In a bronchogram the left bronchi were displaced over the spine and, although distorted beyond certain identification, the findings later at operation showed that the left upper lobe as it lay against the mediastinum was responsible for the filled airways.

Respiratory Function Tests

VC	2000 ml.
FRC	1300 ml.
RC	600 ml.
TLC	2500 ml.
RC/TLC	24%
Gas mixing efficiency	normal
FEV_1	1500 ml.
FVC	2000 ml.
$\frac{FEV_1}{FVC}$	75%
MVV	79 l./min.
PEF	350 l./min.
D_{CO} at rest	21·1 ml./min./mm.Hg (Min. vent. 12·5 l./min.)
D_{CO} on exercise	30 ml./min./mm.Hg (Min. vent. 34·6 l./min.)
% extraction	50

The vital capacity is about half the normal value and presumably is the vital capacity of only one lung. Airway resistance was high (3·1 cm. H_2O/1./sec.). Plethysmographic studies indicate that the emphysematous region in this lung did not take part in respiration, its volume being probably 1·5 l. (plethysmographic lung volume—helium lung volume).

At operation the left chest was found to be filled with a large balloon-like structure representing the left lower lobe; patches of flimsy lung were visible in it through the pleura (Fig. 128), particularly on the diaphragmatic aspect and in the region of the apical lower lobe. The left upper lobe was small and lying in a mediastinal hernia. Although less than is usual, some pigmentation was present in it. The pulmonary artery was small, the bronchial artery of normal size.

On inflation after left lower lobectomy, the left upper lobe filled only a third of the chest cavity; the sternum had bulged pre-operatively but not afterwards. Post-operatively the left lung re-expanded quite well, but the heart is now to the left and there is peripheral pleural shadowing.

This would seem to be a case of childhood emphysema of the left lower lobe which has interfered with the development of the left upper lobe. The bulla's final size may have been due to the patient's strenuous exercise in a rarified atmosphere.

Effect of Bullae on Blood Vessels

Bullae always represent a loss of capillary bed and also of much larger vessels. In Type III there is intra-acinar pruning of arteries; in Types I and II the arteries affected will depend on how proximally the bulla encroaches and could mean loss of arteries of lobular size or more.

In addition to the damage represented by the bulla itself there is the effect of compression of neighbouring lung; this will reduce blood flow even if capillaries are structurally intact.

Behaviour of Base of Bulla

Any bulla is in communication at least intermittently with underlying lung. Many, however, have so small a communication that they do not participate in ordinary respiration and pneumometric tests suggest that they are virtually not ventilated. Such a bulla is illustrated by the case in

FIG. 128.—Case 47. Arteriogram of resected "bulla"—i.e. of whole of left lower lobe. Hypoplasia and overinflation of left lower lobe. See also Fig. 127.

Fig. 117, where a sac the size of a melon was in communication with lung over the length of a cluster of alveoli at the tip of the right middle lobe. In contrast are cases such as those illustrated in Figs. 123 and 124, where the bullous areas are in free communication with the rest of the lung so that pneumometric tests show that the volume of ventilated lung is the same as the total lung volume.

It is likely that compressed lung at the base of a bulla may be just as air-tight during quiet respiration as is pleura or connective tissue septa. A bulla may be cut off from inspired air because its size is such that more proximal bronchi are compressed and ventilation to the lobe reduced.

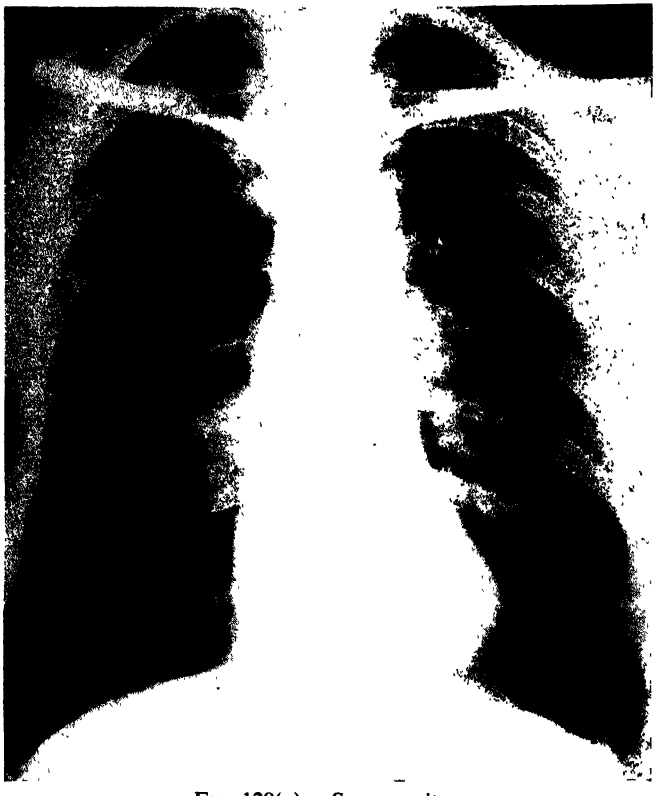

FIG. 129(*a*).—*See opposite.*

An example of such compression is described on page 138, where a large left-sided bulla so compressed the rest of the lung that there was virtually no ventilation or perfusion to the left lung revealed by studies with radioactive xenon. Figs. 129*a* and *b* illustrate lung compression in the base of a bulla only on expiration.

The size and ventilation of most bullae tend to remain fairly stable, but sometimes a dramatic change in size occurs, often with distressing symptoms. It is rarely possible to account for this, but in some way the pressure equilibrium is disturbed, as where temporarily the base of the bulla must have operated as a ball valve, so that an increasing volume of air is trapped within it. This can happen with a broad-based bulla as well as with a narrow-necked one.

"STABILITY" OF A BULLA

If a bulla is artificially deflated at operation, and then released, it usually returns rapidly to its original size. At operation a bulla against the base was inadvertently punctured early in the operation and deflated.

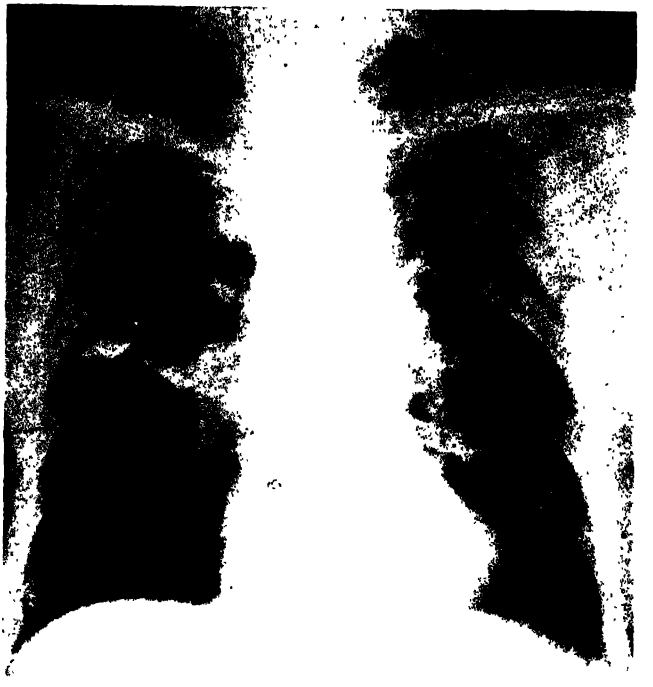

FIG. 129(b).

FIG. 129(*a*) and (*b*).—Air-trapping in bulla. (*a*) In inspiration, low flat diaphragm, large hilar, and small mid-lung vessels at bases; line of horizontal fissure normal; (*b*) On expiration diaphragm moves up well, horizontal fissure displaced upwards and adjacent lung in upper lobe becomes opaque while base remains hypertransradiant, indicating air-trapping.

The surgeon first turned his attention to the region of the lingula, the lower lobe being packed out of the way. On returning to it he found that the opening had sealed itself off and, even with the quiet respiration provided by the anaesthetist, the bulla had returned to its previous volume.

In another patient the upper lobe was compressed by bullae in the middle lobe. Thoracotomy was performed for another condition and since the post-operative film revealed that the upper lobe was now aerated and that the bullae occupied a much smaller volume, surgery for the bullae was deferred. A film taken three months later showed that the bullae had returned to their previous volume and that the upper lobe was again compressed.

SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax is a not infrequent result of emphysema, in particular of bullae. A spontaneous pneumothorax may develop during

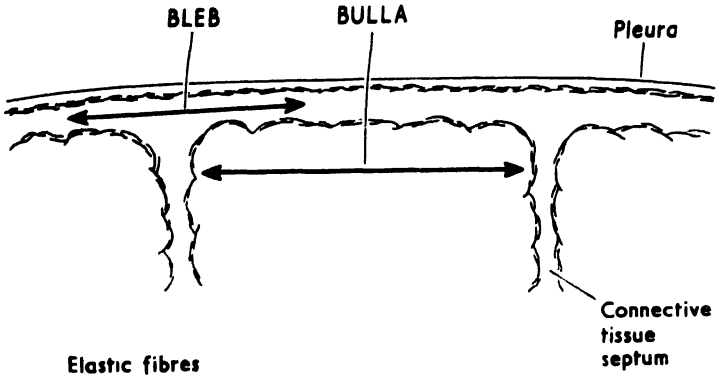

FIG. 130.—Diagram showing difference between bleb and bulla; being within pleura, a bleb is external to the internal elastic layer and not confined by connective tissue septa.

lung infection but more often occurs without any obvious cause. Pain may be the presenting symptom, but the sudden development, or worsening, of shortness of breath are more serious threats to life. Radiographic difficulties in distinguishing between a bulla and a pneumothorax may be considerable. That thoracoscopy may be misleading is illustrated in Case 2, page 37.

A pneumothorax may develop from a hole in the lung which quickly seals itself so that the pneumothorax absorbs quickly and thoracoscopy will fail to disclose the hole. On the other hand a leak may stay open for a very long time and the hole may be revealed either at thoracoscopy or thoracotomy. Usually it appears as a round puncture in the pleural sac of a bulla, no more than one to three millimetres in diameter. A similar appearance may be seen at autopsy, but the site of leakage may be difficult to identify if the condition has been intermittent or the hole has sealed itself off, or if the pleura has been the site of inflammatory damage.

The development of spontaneous pneumothorax with emphysema sufficient to produce radiographic changes, either localised or widespread, is usually associated with bullae and is brought about by a different mechanism and is of different significance from the "cuckoo-spit" appearance on the adolescent pleura described by Brock (1948).

INTERSTITIAL EMPHYSEMA (SURGICAL EMPHYSEMA)

Interstitial, as applied to emphysema, refers to the connective tissue framework of the lung, although when applied to fibrosis it implies an affection of the alveolar walls.

Air within the connective tissue framework of the lung is usually only seen in the connective tissue sheath surrounding large bronchi and veins. From these sites the air not uncommonly spreads along the connective

tissue planes to reach the mediastinum and thence can spread to the neck and skin. These are stages of surgical emphysema.

It is rare to see air in the connective tissue septa of the adult lung; interstitial emphysema seems more common in childhood.

In the child the septa are more often affected and a condition in which air tracks through the lung and over the pleura is seen. As fewer alveoli are present in the child it means that the connective tissue septa are much closer to the broncho-vascular sheaths.

This has some bearing on the description that has been given by Miller (1947) of a bleb, and its difference from a bulla. Miller has described a bleb as being an accumulation of air within the pleura, but at the same time he demarcated it by connective tissue septa (Fig. 130). Reference to the arrangement of the elastic fibres in the pleura makes this difficult to understand. The inner layer of elastic fibres is in fact part of the wall of the alveoli, while the outer layer of elastic fibres only lies in the pleura and does not drop into the lung. Hence any collection of air to be outlined by connective tissue septa must be deep to the inner elastic layer or within the lung, while anything outside this or within the layers would be within pleura and not under the connective tissue septa. If the pleura is stripped from the lung, as can happen if a lung is overinflated at great pressure, the pleura may be stripped from the underlying alveoli.

It has been mentioned that the cow's lung, because of its complete septa, may present a different appearance from that seen in man. In the cow interstitial emphysema commonly occurs—air tracking along the connective tissue septa which completely subdivide the lung. These air bubbles may delineate the pattern of septal attachment to the pleura without elevating pleura over the whole lung.

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Chapter XV

CHANGES IN HEART AND PULMONARY ARTERIES IN CHRONIC LUNG DISEASE

THAT lung disease can affect the heart is not in doubt, but why some patients with similar lung lesions develop right ventricular hypertrophy and others do not is unknown; nor why cardiac failure develops in some and not in others. Neither the duration nor the severity of the lung disease serves to explain this, and clinical assessment has been difficult because the electrocardiographic changes have been an uncertain indication of right ventricular hypertrophy. Chronic bronchitis without emphysema; emphysema, idiopathic or with chronic bronchitis; scar emphysema; fibrosis and bronchiectasis, are the lung lesions mainly responsible for right ventricular hypertrophy and certain changes in the pulmonary artery bed. Pulmonary hypertension from emboli, being primarily concerned with blood vessels, does not fall within the scope of this book.

Cor pulmonale.—The term "cor pulmonale" has at times been applied to a variety of heart manifestations. For instance, Stuart-Harris and his colleagues (1957) used the term only in relation to congestive heart failure in association with disease of the pulmonary parenchyma or with deformities of the thoracic cage. Wood (1956), on the other hand, applied the term to cases where there was evidence that the right heart had been affected by pulmonary disease, i.e. he included right ventricular hypertrophy, peripheral oedema, raised jugular venous pressure and so on. In this book the term "cor pulmonale" is avoided and the individual aspects which it has hitherto embraced are here dealt with separately.

RIGHT VENTRICULAR HYPERTROPHY WITH CHRONIC LUNG DISEASE

Pathological Diagnosis

Right ventricular hypertrophy can be diagnosed pathologically in two ways—(*a*) by relating it to the thickness of the wall of the right ventricle, a method which can be misleading because dilatation may result in a wall of normal thickness even when it is severely hypertrophied; and (*b*) by weighing the right ventricle, which will give a more certain result. Lewis (1914) separated the septum from the right and left ventricle, weighed the three components separately and apportioned the septum between the

other two. But the most satisfactory method of ascertaining the weight of the right ventricle is that of Fulton (1953), and recently recommended by a W.H.O. Committee (1961), who demonstrated that the septum was never very enlarged, save in the case of the left ventricular hypertrophy, and accordingly included the septum with the left ventricle. The manner in which the septum and left ventricle hypertrophy together is illustrated in transverse section of the heart in aortic stenosis.

The *Fulton method* dissects away fat and pericardium, divides the heart at the auriculo-ventricular junction, and dissects the right ventricle from the septum, leaving the latter joined to the left ventricle. The separate weights of the ventricles are expressed as a ratio. Fulton and his colleagues consider the heart normal only if:

(*a*) the total ventricular weight is less than 250 g.
(*b*) the free wall of the right ventricle (RV) weighs less than 65 g.
(*c*) the left ventricle (LV) and septum (S) together weigh less than 190 g., and
(*d*) the ratio (LV + S)/RV lies between 2·3:1 and 3·3:1.

The criteria for right venticular hypertrophy are stated as follows: "Right ventricular hypertrophy is considered to be present when the free wall of the right ventricle weighs 80 g. or more. In isolated right ventricular hypertrophy the ratio (LV and S)/RV is always less than 2:1. If left ventricular hypertrophy is also present, the ratio may be within normal limits or even raised." With isolated right ventricular hypertrophy the total heart weight was within normal limits in 50 per cent of their 202 cases, in contrast to left ventricular hypertrophy which was always associated with a total weight above the normal.

Millard (1965) used this method to assess the right ventricular weight in a series of forty-five cases (the largest to date) of chronic respiratory disease. He also studied the chest radiograph and electrocardiogram and from roughly a half of the cases he prepared a pulmonary arteriogram. His findings were related to the clinical details, including the haemoglobin levels. He divided his cases of right ventricular hypertrophy into three grades of severity, which are used throughout this account:

(*a*) mild, the ratio LV/RV being less than 2 even if the weight is not above 80 grams.
(Weights between 65 and 80 grams were regarded as normal if the ratio was within normal limits.)
(*b*) moderate, the weight being between 80 and 100 grams.
(*c*) severe, the weight being above 100 grams.

Electrocardiographic Diagnosis

The electrocardiogram has failed to give a very consistent guide to the clinical state of the patient with chronic bronchitis and emphysema; nor

has it proved helpful in prognosis in deciding which patients will develop heart failure and which will not (Wood, 1956). Correlations between heart size and electrocardiographic signs are scarce in chronic lung disease, most of the work on right ventricular enlargement having been concerned with congenital heart disease in which the degree of enlargement is much greater than is usually seen in chronic lung disease. In Millard's series the features of electrocardiograms were analysed and the results interpreted by several of the currently used methods. The individual signs and the diagnostic evidence suggested by various workers were then related to the heart weights.

From his study the following conclusions can be drawn:

(1) The most reliable evidence of right ventricular hypertrophy is a frontal plane mean QRS axis between and including $+91°$ and $\pm 180°$ (Table VI).

TABLE VI

ELECTROCARDIOGRAPHIC AXIS AND RIGHT VENTRICULAR HYPERTROPHY

R.V.H.	*Cases*	*Mean age*	*Mean axis (s.e.)*	*Difference between group and next below*
Nil	14	62	+47 (9·6)	significant
Slight	3	58	+90 (17)	not significant
Moderate	7	48	+114 (8·0)	significant
Severe	9	50	+131 (7·2)	

(s.e.—standard error)

(2) This criterion did not give any false positives in Millard's series and enabled the diagnosis to be made in 85 per cent of cases where hypertrophy was confined to the right ventricle. It therefore seems the most reliable single sign and also is more reliable than any other group of signs suggested for diagnosis. The method closest in accuracy achieved 75 per cent (Goodwin and Abdin, 1959).

(3) The degree of right ventricular hypertrophy cannot be assessed with certainty by Millard's or any other method of interpretation of the E.C.G.

(4) From this material it was not possible to deduce the significance of a frontal plane mean QRS axis between $-91°$ and $\pm 180°$. (There were only two patients with a mean QRS axis of $+90°$; one had right ventricular hypertrophy and the other a normal heart.)

(5) The presence of left ventricular hypertrophy or of ischaemic disease—common in elderly bronchitics—will mask the signs of right ventricular hypertrophy and so limit the usefulness of the electrocardiogram in diagnosing right ventricular hypertrophy.

(6) The presence of emphysema in the overlying lung seems to have little effect on the electrocardiograph.

Radiographic Diagnosis

Hypertrophy of the right ventricle without dilatation is not diagnosed from the radiographs. Where there is also gross emphysema the heart shadow will remain narrow and vertical with a transverse diameter of 11·5 cm. or less. If dilatation occurs, it is rarely confined to the right ventricle, so that the heart shadow as a whole is enlarged, and the dilatation is usually seen only when heart failure is present or imminent, or has recently occurred.

Correlation of Right Ventricular Hypertrophy with Clinical Features

To investigate the factors associated with right ventricular hypertrophy in chronic bronchitis and emphysema, Millard's patients included seventeen cases (ten male, seven female) of chronic bronchitis, some with gross emphysema, in all of whom the lung condition was the cause of death. These formed part of a larger group.

On the basis of the pathological findings the cases were divided into four groups, those with (*a*) a normal right ventricle, and those in whom the right ventricular hypertrophy was (*b*) mild, (*c*) moderate, (*d*) severe. These four groups were related to the following clinical features:

Sex of patient.—No correlation was found between the sex of the patient and the disease.

Age.—The degree of right ventricular hypertrophy varied inversely with age, tending to be most marked in the younger age groups.

Duration of cough and sputum.—Allowing for any inaccuracy of the history given by the patient, no difference was found in the four groups between those with a long, and those with a relatively short, history of cough and sputum.

Shortness of breath.—Patients with a long history of shortness of breath tended to have a greater degree of right ventricular hypertrophy than the others.

Clubbing of the fingers.—Clubbing of the fingers was found in three patients, who had polycythaemia as well as severe right ventricular hypertrophy. None showed an emphysema pattern in the radiograph.

Radiological grouping.—The seventeen patients were also grouped according to whether or not the chest radiograph showed the classical appearance of widespread emphysema as described on page 276. Table VII shows the incidence and severity of the right ventricular hypertrophy when the patients are grouped by the radiographic appearances.

TABLE VII

RIGHT VENTRICULAR HYPERTROPHY AND RADIOGRAPHIC EMPHYSEMA IN SEVENTEEN CASES OF CHRONIC BRONCHITIS

X-ray	*No*	*Mild*	*Moderate*	*Severe*
No Emphysema (8)	—	2	2	4
			6	
Widespread Emphysema (9)	4	2	2	1
			3	

Of the group of nine patients with the emphysema pattern (severe emphysema was found pathologically in all) four had no right ventricular hypertrophy, while in the five who did, it was mild or moderate in four, and severe only in one. In contrast to these findings, all those without gross emphysema radiologically and pathologically showed right ventricular hypertrophy of a severe degree, save only two in whom it was mild.

It would thus seem that if a patient with chronic bronchitis has widespread emphysema the clinical picture is unlikely to be dominated by cardiac complications, and severe hypertrophy of the right ventricle is unlikely to be found at autopsy, whereas a patient with similar symptoms but little morbid anatomical emphysema, is likely to die from cardiac rather than respiratory failure, and may show gross right ventricular hypertrophy.

TABLE VIII

RADIOGRAPHIC APPEARANCE OF EMPHYSEMA AND ELECTROCARDIOGRAPHIC EVIDENCE OF RIGHT VENTRICULAR HYPERTROPHY IN 112 PATIENTS WITH CHRONIC BRONCHITIS

Radiographic Evidence of Emphysema	*Number of Patients*	*Right Ventricular Hypertrophy (Millard)*
Widespread	24	4 (17%)
Possible, localised or no emphysema PF < 200 ml. FEV_1 < 1200 ml.	43	7 (16%)
Possible, localised or no emphysema PF > 200 ml. FEV_1 > 1200 ml.	45	—

The high incidence of right ventricular hypertrophy in these patients, all fatal cases, should be considered in relation to findings in patients with chronic bronchitis before they enter the final stage of the disease. In a series of 151 patients with chronic bronchitis studied by Chappell and Batten (1964) (see Table VIII), thirty-nine were rejected because of the presence of systemic hypertension or incomplete data. In the remaining 112 cases the incidence of right ventricular hypertrophy from the evidence of the electrocardiogram alone was four in twenty-four (17 per cent) of those

with radiological evidence of gross emphysema; in those with either a normal radiograph, localised or slight emphysema, seven of forty-three patients (16 per cent) with an FEV_1 <1200 ml. showed right ventricular hypertrophy and none in those whose FEV_1 was above this figure. As has been mentioned above the severity of right ventricular hypertrophy cannot be assessed from the electrocardiogram.

Peripheral oedema.—Millard found that the greater the degree of right ventricular hypertrophy the higher the incidence and the longer the duration of peripheral oedema.

Polycythaemia.—All patients with polycythaemia had severe right ventricular hypertrophy; and all patients whose right ventricle was above 105 grams had polycythaemia. The polycythaemia was judged by a haemoglobin of more than 120 per cent or a packed cell volume of more than 55 per cent.

Unfortunately the total blood volume in these patients was not known. Chamberlain and Millard (1963) in a small series of patients with chronic lung disease and polycythaemia found that the plasma volume was not increased, thus any increase in blood volume derived purely from the increase in the red cell mass.

Polycythaemia is a rare complication of chronic bronchitis, although Millard's series, representing fatal cases, includes several examples. Shaw and Simpson (1961) found that polycythaemia was rare in cases of incapacitating chronic bronchitis unless judged by the size of the red cell mass. Fielding and Zorab (1964) had a similar experience. In the series of Chappell and Batten (1964) there are four cases of polycythaemia.

To summarise, in Millard's series of cases of chronic bronchitis who died in hospital the presence of radiographic evidence of widespread emphysema serves to distinguish two groups of patients. Those without radiographic evidence of emphysema often had a history of peripheral oedema which was comparatively long; polycythaemia was relatively common and at post-mortem right ventricular hypertrophy was usually present and often severe.

In those subjects whose radiographs showed widespread emphysema, oedema was less often present and was of shorter duration; none had polycythaemia and right ventricular hypertrophy was less severe. One case with polycythaemia and emphysema was seen during the time Millard was collecting his cases but was not included because the lungs were not available for injection (see Case 42, p. 187).

Thus, although chronic bronchitis complicated by emphysema is often associated with mild and moderate degrees of ventricular hypertrophy, it is in cases of chronic bronchitis with alveolar damage not severe enough to produce radiographic evidence of emphysema that severe grades of right ventricular hypertrophy may develop. These are associated with polycythaemia (and clubbing). Cromie (1961), using ventricular wall thickness

as a measure of hypertrophy, failed to show any correlation between the amount of emphysema and the degree of ventricular hypertrophy.

It would seem that the alveolar walls through most of the lungs must be intact for these sequelae to develop.

The Arteriogram in Chronic Bronchitis and Emphysema—with and without Right Ventricular Hypertrophy

The normal specimen arteriogram is described on page 343. Comparison between this (Fig. 131) and that of a patient with emphysema and pulmonary hypertension (right ventricular hypertrophy) shown in Fig. 132, shows an obvious difference. In the extreme degree of such disturbance the axial pathways stand out clearly, being bare of their normal complement of side branches. To measure this change Millard (1965) counted the number of side branches from representative pathways to within 5 mm. of the pleural edge; in arteriograms prepared by his technique it is difficult to be certain of individual lines more distally. Because of variations in arterial branching the segmental artery is not a satisfactory hilar starting point and the main pulmonary artery just distal to the first branch running in a caudal direction was therefore chosen. The distance between branches

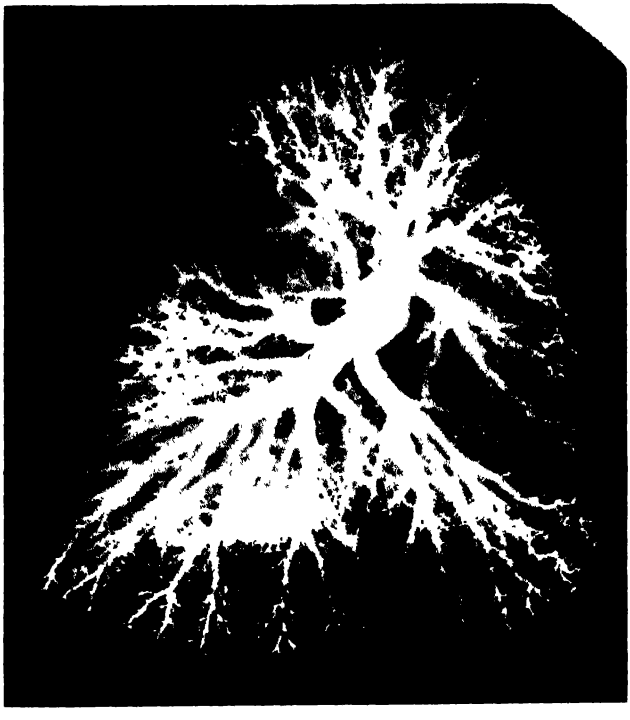

Fig. 131.—Normal specimen pulmonary arteriogram.

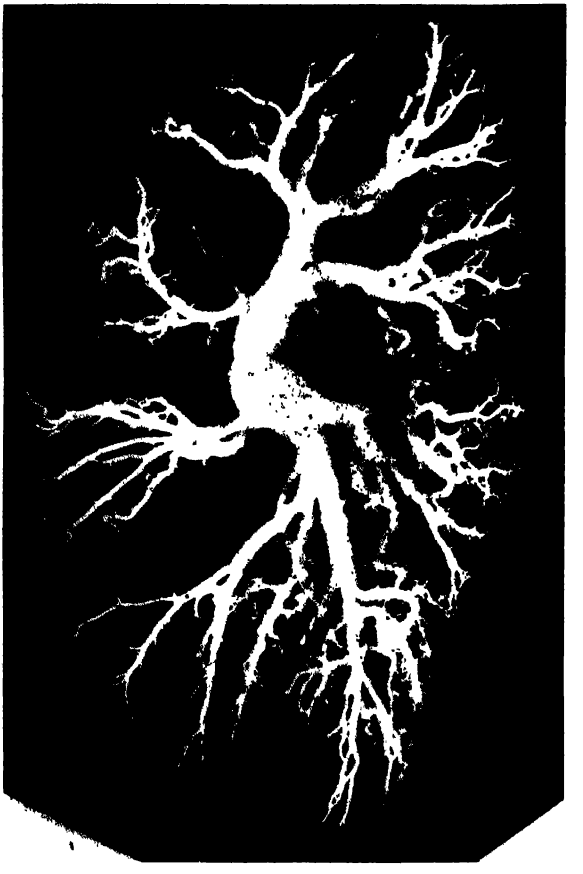

FIG. 132.—Specimen pulmonary arteriogram in pulmonary hypertension showing duction in side branches and dilatation of axial pathways. (LV/RV = 106/83 gm. -- Ratio 1·4, i.e. RVH.)

was measured, and the diameter of the axial pathway immediately after each branch. As the total length of each pathway was different, to make comparison possible the length of each pathway was taken as 100 units and the branching and diameters charted according to their position on this scale.

The arteries counted included only the proximal part of the acinus, and as the number was found to be in excess of bronchial branches, clearly some of the supernumerary arteries recently described (Elliott, 1964; Elliott and Reid, 1965; Reid, 1965) are included (see p. 349).

Without Right Ventricular Hypertrophy

In patients with chronic bronchitis but no right ventricular hypertrophy the arteriogram is likely to be normal. In patients with emphysema (Figs. 133 and 134) but no right ventricular hypertrophy the arteriogram shows a varying reduction in side branches in the emphysematous regions (Figs.

135 and 136). These changes occur mainly within the acinus and are confined to the distal centimetre or so of any pathway.

Panacinar emphysema in its mild grades causes little change to the arteriogram—Grades I and II show a roughly normal pattern. With Grade III panacinar emphysema (which will produce radiographic changes) an arteriogram change is apparent; peripherally the short fine lines of the blood vessels are reduced in number, the vessels are drawn out and more clearly seen as separate lines. In Grade IV the reduction in number of the short fine lines is even more marked. Cases of emphysema show hardly any reduction in side branches as counted by Millard's method since the main change is very peripheral, but it can be detected by direct inspection of the arteriogram.

With Right Ventricular Hypertrophy

In patients with right ventricular hypertrophy the changes in the arteriogram are greater than those described in either chronic bronchitis or emphysema without right ventricular hypertrophy. Millard related the presence and degree of right ventricular hypertrophy to the appearance of the specimen pulmonary arteriogram. Two features in the arteriogram were found to be associated with ventricular hypertrophy, (i) dilatation of the axial arteries and (ii) a loss of side branches.

TABLE IX

ARTERIAL DIAMETER AT PROPORTIONATE INTERVALS (mm.)

		Percentage of Pathway										
	Cases	1 (s.e.)	10	20	30	40	50 (s.e.)	60	70	80	90	100 (s.e.)
Normal	6	15·5 (·8)	11·1	8·3	7·3	5·5	4·8 (1·4)	3·8	3·0	2·2	1·2	6 (·06)
R.V.H.:												
Nil	6			8·7	5·9	4·8	3·7	3·3	2·7	1·9	1·5	·5
Mild	4			10·1	7·1	6·3	5·1	4·3	3·1	2·5	1·4	·6
Moderate	4			12·6	10·2	8·1	6·4	4·6	3·6	2·9	1·7	·5
Severe	8			13·1	11·0	8·1	6·9 (·8)	5·8	3·4	3·3	2·2	8 (·2)

(s.e.—standard error)

Dilatation of arteries.—The diameter along the length of an axial arterial pathway showed widening at all levels (Table IX) and its degree increased with the severity of right ventricular hypertrophy. It is usually stated that in pulmonary hypertension the large proximal vessels are dilated, but the finding of dilatation of an axial pathway to within a few millimetres of the pleura was unexpected. Measuring diameters revealed that the dilatation affected virtually the whole length of the artery visible in a specimen arteriogram.

As the normals were injected at "hypertensive" pressures, the effect of the injection might be expected to increase the diameter of the normal

FIG. 133.—Widespread emphysema. Diaphragm low and flat, at level of 7th rib; large hilar and small lung vessels; avascular areas not demarcated by lines in right upper zone and at both bases.

arteries relative to the diseased ones; certainly it would not exaggerate the difference between normal and hypertensive lungs.

The greater diameter and, presumably, greater distensibility of the filled vessels could be a secondary effect from the loss of peripheral vessels as from a change in the pulse wave through these vessels, or a redistribution of blood volume. That this proximal dilatation occurs to some extent before any side branch loss can be recognised may mean that the method was not sufficiently sensitive to detect mild degrees of reduction in the number of side branches, or it may mean that, in the early stages, the peripheral resistance is functional and reversible and not associated with irreversible structural alterations.

Reduction in side branches from axial arteries.—In cases of right ventricular hypertrophy the number of side branches was found to be reduced (Table X). The reduction was detected in the distal half of an axial pathway and was greatest in the distal 10–20 per cent of the pathway, where the branches are normally most numerous. In Millard's groups of moderate and severe right ventricular hypertrophy the side branch reduc-

FIG 134.—Widespread emphysema—same case as Fig. 133. Lateral view, diaphragm low and flat, retrosternal translucent area large, 5 cm., and reaching to diaphragm. (Normal figures 2·5 and 7 cm. respectively.)

tion was significantly greater than in the milder grades (seen best in the right-hand columns of Table X); that is, the more severe grades of ventricular hypertrophy were associated with the greater peripheral cut down, but the severity of the ventricular hypertrophy was not proportional to the

TABLE X

ARTERIAL BRANCHES IN PROPORTIONATE PARTS OF PATHWAY

		Percentage of Pathway									
		10	20	30	40	50 (s.e.)	60	70	80	90	100 (s.e.)
	Cases										
Normal	6				7	11 (·8)	13	15	18	23	36 (1·4)
R.V.H.											
Nil					6	6 (1·1)	0	12	13	22	37 (2·1)
Mild					6	7 (·7)	8	10	13	18	30 (4·9)
Moderate					5	7 (·5)	9	11	13	15	20 (1·5)
Severe					6	7 (1·0)	9	11	13	17	27 (1·7)

(s.e.—standard error)

The number of branches is significantly lower for the moderate and severe right ventricular hypertrophy groups, and for all the abnormals this can be detected at the halfway level: in the group with no ventricular hypertrophy the number of branches (6) at 50 per cent of the pathway is much lower than in the more distal stretches and is probably a chance finding.

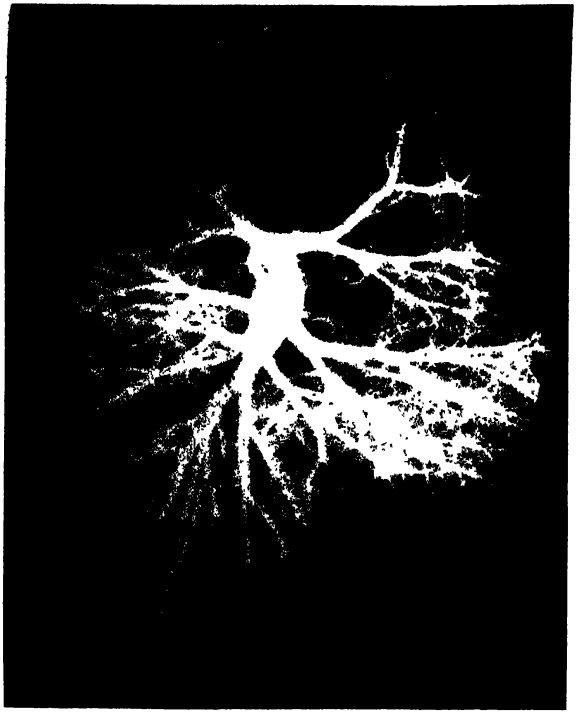

FIG. 135.—Specimen pulmonary arteriogram. Right lung shown in Fig. 133. Reduction in side branches throughout lung, most marked in upper lobe. Panacinar emphysema—Grade IV upper lobe—Grade III rest of lung.

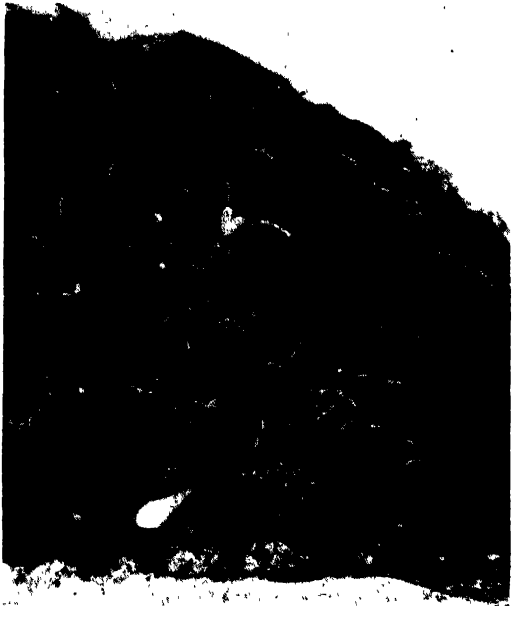

FIG. 136.—Specimen. Cut surface of lower lobe of right lung, as in Fig. 135. Panacinar Grade III.

number of side branches lost. An exception to the general pattern (Fig. 137) was a case of severe right ventricular hypertrophy in which the vessel count was within the normal range (Fig. 138). This patient, a young woman, had polycythaemia.

When right ventricular hypertrophy is present with either emphysema or chronic bronchitis it is usually associated with reduction in side branches in the arteriogram. It is worth reiterating that right ventricular hypertrophy bears no relation to the alveolar damage of emphysema, so that these arterial changes do not directly reflect alveolar damage.

The technique of arterial injection is designed to overcome any contraction of the blood vessels, and as the elastic laminae appear smooth in microscopic sections it is unlikely that the absence of vessel filling in the arteriogram is the result of technical inadequacy. It is probable, therefore, that the reduction of side branches in the specimen arteriogram means that normally visible arteries no longer have a large enough lumen, even if filled with micropaque, to be detected on the radiograph; their lumen is narrowed beyond the critical diameter to be visible with the focal spot of the X-ray tube and the type of film used.

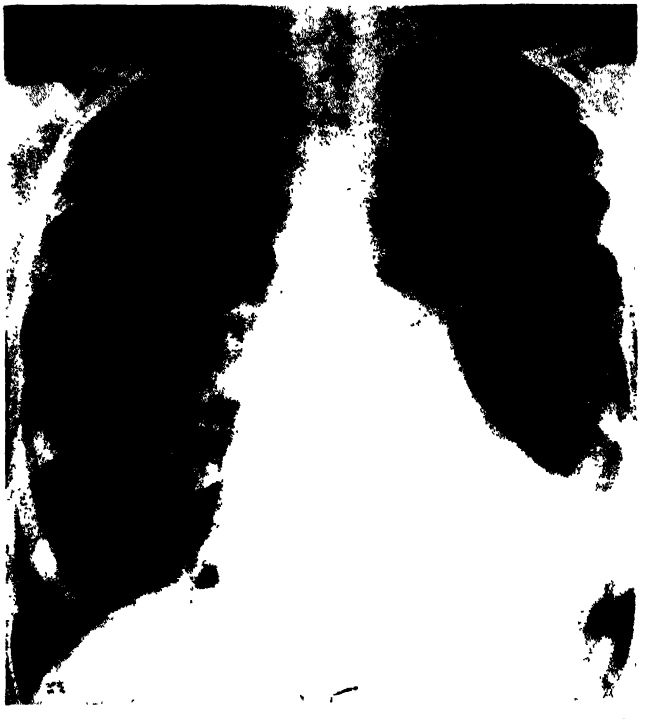

FIG. 137.—Chronic bronchitis complicated by polycythaemia. Small region localised bronchiectasis. Female, aged twenty-nine. Cough, sputum, severe dyspnoea. Hb 144% (21 G), PCV 72%. Large heart, pulmonary artery and hilar vessels (right), otherwise normal. (LV/RV = 150/204 = 0·8, i.e. RVH.)

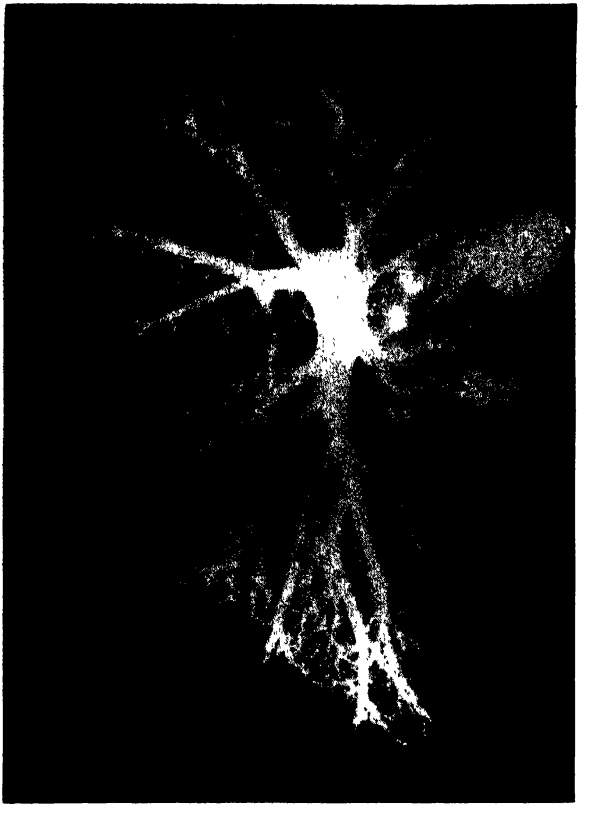

FIG. 138.—Specimen pulmonary arteriogram nearly normal (same case as Fig. 137). No appreciable reduction in side branches; increase in diameter of axial arteries.

With the technique employed in this study it is probable that vessels of the order of 200–500 μ can be detected as separate lines (Elliott and Millard, 1964). Within the region of the lobule and the acinus most arteries are in this range, but throughout the length of an artery there are also branches of this size (Elliott, 1964), many of them "supernumerary" (see p. 349). Thus the reduction, which was detected through the distal 50 per cent, probably affected muscular arteries similar to those associated with the most distal region of any arterial pathway, that is within the lobule.

The reduction in arterial diameter may arise from:

(i) encroachment on the lumen by hypertrophied muscle, affecting particularly the media, but longitudinal muscle may appear in the intima and the media;
(ii) endarteritic changes—either hyalinisation of the intima or mural thrombi;
(iii) resistance of vessels to distension may be associated with hypertrophy, e.g. the "contracture" described by Short (1956).

It would seem that thrombi are not essential to the development of this appearance as the same arteriographic changes are found in cases of primary pulmonary hypertension with no evidence of thrombosis (Reid, 1963). This is supported by the widespread reduction in arterial branches and the relative absence in the arteries of chronic lung disease of the tortuosity and irregularity associated with multiple emboli and thrombi (e.g. mitral stenosis, Doyle *et al.*, 1957).

Microscopy.—The advantage of the specimen arteriogram is that differences in the arterial bed throughout the whole lung can be visualised, a coverage scarcely possible by microscopy. It enables suitable material to be selected for microscopy, whose role is to establish the structural basis for the changes seen in the arteriogram.

Region of dilatation.—Elliott (1964) made microscopic measurements of a length of the artery seen in the specimen arteriogram to be dilated, and showed that the medial wall area and percentage wall thickness were increased, indicating that the arterial wall was hypertrophied and not just overdistended.

Reduction in side branches.—Microscopic examination has revealed severe hypertrophy of the media in vessels no longer visible on the arteriogram. Even in the normal, the wall of the small muscular arteries may be as much as 15 per cent of the external diameter; in the example mentioned above an artery of less than 100 μ diameter had a wall percentage of 31·5 and the medial area was increased four-fold. Three arteries between 1000 and 1500 μ had a percentage wall thickness of 4·1 (the normal range being 0·6–1·8).

The medial hypertrophy affected not only the circular muscle but longitudinal muscle was present both internal and external to the circular coat. In some cases hyalinisation of the intima was also severe.

It would thus seem that in chronic bronchitis the development of right ventricular hypertrophy does not depend on the presence or the degree of emphysema, but on the structural narrowing of the pulmonary arteries. But this is not the only cause, as narrowing is not always present and the degree of "pruning" of arteries, at least as determined from the arteriogram, does not correlate with the degree of right ventricular hypertrophy. These changes are being further studied.

Development of Right Ventricular Hypertrophy in Chronic Bronchitis and Emphysema

Hypertrophy is a response to increased work. In patients with chronic lung disease many factors may contribute to increased effort of the right ventricle resulting in hypertrophy. The following factors are not given in

order of frequency or importance but rather in order of convenience for discussion:

(*a*) Polycythaemia;
(*b*) Increased blood volume;
(*c*) Increased cardiac output;
(*d*) Pulmonary vascular resistance increased by functional vasoconstriction or organic narrowing, partial or complete—i.e. a "reversible" and a "fixed" element in vascular resistance.

Figure 139 illustrates schematically the relation between the various factors.

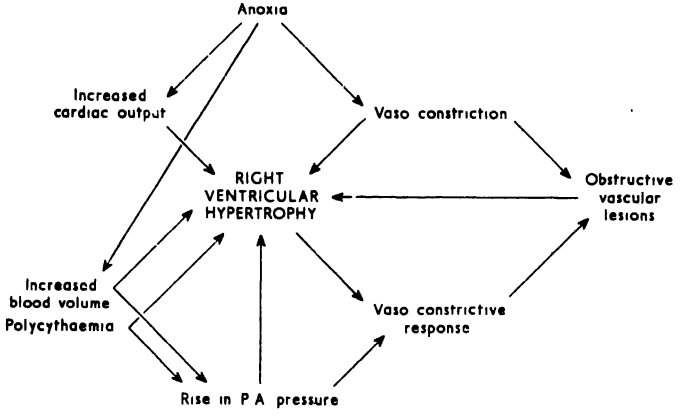

FIG. 139.—Diagrammatic representation of the interplay of some of the factors leading to right ventricular hypertrophy.

Polycythaemia.—As polycythaemia also was present in all of Millard's cases of severe right ventricular hypertrophy in chronic bronchitis, there is clearly an association between the two. Whether they arise from a common cause or whether the polycythaemia is in some way responsible for the right ventricular hypertrophy is unknown. Its effect could arise from increased blood viscosity or volume (see below). A ventricular weight above 105 grams was always associated with polycythaemia and vice versa. As in all problems of blood flow, it is difficult to analyse the relative contributions of the various factors, but Whittaker and Winton (1933) showed that when the PCV was above 55–60 per cent the rate of increase in viscosity rose sharply, and Chamberlain and Millard (1963) suggested that unless the PCV was 60 per cent or more a reduction in PCV offers little relief to the patient. Polycythaemia of these levels is a rare complication of chronic bronchitis or emphysema, but when it occurs it seems to be associated with the most severe degrees of hypertrophy seen in these diseases. The only case of emphysema with severe RVH was also the only case of emphysema with polycythaemia, thus underlining the

over-riding importance of the complication in severe degrees of RVH. In a young case of chronic bronchitis with polycythaemia the reduction in the number of peripheral side branches in the micropaque arteriogram was not great, suggesting that polycythaemia does not necessarily follow blood vessel changes. Rather it would seem that vasoconstriction and polycythaemia may each be a response to blood gas disturbance, though not necessarily proportional to it.

Increased blood volume.—Shaw and Simpson (1961) have shown that in many bronchitics, even if they are not in heart failure, although a haematocrit reading is normal, the blood volume is increased, the red cell mass and plasma volume staying roughly proportional. In thirty-three hypoxic patients included in their study the peripheral red cell count, packed cell volume, and haemoglobin concentration were similar to three other patients with normal arterial saturation. In the hypoxic patients the red cell volume and plasma volume were larger than in the normals. The red cell volume was similar to that of normal people who are hypoxic from residence at high altitude. In Millard's cases haematocrit levels were available but plasma blood volumes were not, and it may be that the milder degrees of right ventricular hypertrophy resulted largely from blood volume change, though it seems unlikely that this alone gave rise to the more severe degrees.

The polycythaemia and blood volume changes are probably related to anoxia and, therefore, represent a load on the heart resulting indirectly from lung disease. They may not develop if the patient is deficient in iron, for Fielding and Zorab (1964) have recently shown that the administration or iron may further increase blood volume and red cell mass in patients with chronic bronchitis.

Cardiac output.—Chronic lung disease is widely accepted as one cause of "hyperkinetic" circulation, but its degree and cause are still the subject of controversy.

Patients with airways obstruction may not have an increased output. Stuart-Harris, discussing the difficulties of assessing cardiac output, reaffirms the conclusion of Mounsey and his colleagues (1952) that patients with emphysema do not at rest have an increased cardiac output if their high resting oxygen consumption, because of laboured breathing, is taken into account. It is not a condition of "high output", but of normal physiological response; hence the paradox that the heart may show signs of failure while the output is within the normal range.

This does not alter the fact that in at least some patients even at rest the cardiac output is higher than in the normal. During incidents of failure the output is often higher in patients with chronic lung disease than in those with valvular disease. In the former there may be a fall in output with recovery; in the valvular group it is usually a rise.

Some patients with heart failure from lung disease respond normally

to exercise with increased cardiac output, but the rise in their pulmonary artery pressure is probably greater than usual. Some patients may not achieve any increase in cardiac output on exercise and this may be the phase that represents failure (Ferrer and Harvey, 1959; Harvey, 1965).

Increase in blood volume as the result of hypoxia may affect the heart through increase in cardiac output.

Pressure and blood flow.—Normally, increase in blood flow from exercise is not associated with a rise in pulmonary artery pressure until roughly three times the normal level of flow is achieved and thereafter pressure rises proportionally to flow and therefore with little increase in vascular resistance (Cournand, 1950; Burton, 1959 and 1962). At moderate exercise there may be no pressure rise (Hickam and Cargill, 1948; Riley *et al.*, 1948; Cournand, 1950). Exercise in the erect posture is associated with less rise in pulmonary artery pressure than exercise in the supine position (Dexter *et al.*, 1951). Donald and his co-workers (1955) showed a rise in pulmonary artery pressures at high levels of exercise but without any change in vascular resistance.

Vascular resistance.—Vascular resistance is a load arising directly from changes in the lung vessels and, although it may be functional, it is probable that in long-standing cases structural changes also contribute; but it is difficult to decide their relative importance.

Vasoconstriction—functional.—Vasoconstriction may play an important role in the complications of chronic bronchitis and emphysema. Its effect on vascular resistance is assessable only where it is reversible. Being functional and reversible it may operate intermittently and any effect on the right ventricle may be expected to be of a minor degree. It is probable, however, that vasoconstriction by itself is able to produce an overaction and hypertrophy of the vessel wall and, ultimately, predisposes to internal hyalinisation, both these changes resulting in thickening of the walls.

There seems little doubt that acute hypoxia can cause a rise in pulmonary artery pressure in the normal (Motley *et al.*, 1947; Doyle *et al.*, 1952), a fall of pulmonary arterial oxygen saturation below 85 per cent being necessary for a rise in pulmonary artery pressure to occur (Fishman *et al.*, 1960; Fritts *et al.*, 1960). The height of pulmonary artery pressure in patients with chronic lung disease has been shown to be related to the reduction in partial pressures of oxygen as well as the rise of partial pressures of CO_2 (Fishman *et al.*, 1952; Whitaker, 1954). Von Euler and Liljestrand (1946) concluded from experiments in the cat that the rise from oxygen lack was greater than that from excessive carbon dioxide. Their results also suggest that the effect of these blood gases is produced directly on the small blood vessels and is not prevented by vagotomy, sympathectomy, or drugs. Elliott (1964) has shown that the small precapillary vessels are muscular, with a high degree of muscularity in the vessels just proximal to them and running with respiratory bronchioli (see also p. 349). The

constriction of the muscle at this latter region where the effect on resistance will be great may, therefore, be mediated quickly and directly through the muscle. This supposes that conduction through the medial muscle of the pulmonary artery is similar to that in systemic arteries (Hilton, 1959 and 1963.

In the normal this rise in pulmonary artery pressure would seem to be produced by a severe reduction in oxygen saturation. Although it is tempting to assume this reflex in anoxic cases of chronic lung disease, it is by no means the whole answer. In incidents of acute infection it may be so applied (Wood, 1956), but in cases of long-standing anoxia the contribution of low oxygen levels is doubtful.

It is not always possible in patients with anoxia to produce a fall in pressure by raising the oxygen saturation, but since pressure falls on recovery from the incident, so also the pulmonary artery pressure is not dependent only on structural or "fixed" resistance (Mounsey *et al.*, 1952; Whitaker, 1954).

Thomas (1951) found that on exercise, patients with chronic lung disease breathing oxygen doubled the pulmonary artery pressure without changing the oxygen tension. This suggests that hypoxia is not the only factor and that the "fixed" or structural contribution may be important.

Arterial narrowing—structural.—Millard found a reduction in the number of peripheral vessels in most cases with moderate or severe RVH, suggesting that structural changes are associated with these degrees of effect on the heart; but the reduction in side branches is not proportionate to heart weight. This may mean that the technique of counting is inadequate to detect a small reduction in side branches or that functional vasoconstriction occurs before any structural change. Thus structural changes are not the primary disturbance, but a manifestation of its long duration.

It is probable that an increase in plasma volume gives only a mild degree of hypertrophy.

The cut down in side branches associated with moderate and severe degrees of hypertrophy probably means that at this stage there is always some organic narrowing, some "fixed" resistance, together with some functional or reversible resistance.

There would seem no reason to regard this organic narrowing as primary. Rather it would seem that vasoconstriction if sufficiently severe or of long standing may produce enough muscular hypertrophy and endarteritis to result in a narrowing of the lumen.

The reduction in peripheral branches is also seen in cases of pulmonary hypertension such as derive from congenital or acquired heart disease. In cases of chronic bronchitis the reduction occurred both with and without polycythaemia.

Functional Significance of Structural Changes

The functional significance of the reduction in branches is not easy to determine. It is known that lung can compensate for an increase in blood flow through it; that, for example, after pneumonectomy no rise in pulmonary artery pressure occurs at rest (Brock, 1940; Cournand, 1950), but that the rise on exercise is greater than normal.

Söderholm (1959) suggests that the state of the remaining lung is important. He found that, following occlusion of one pulmonary artery, exercise produced a rise of pressure in the other pulmonary artery, greater if the lung was diseased than if it was normal. This fits with the behaviour in emphysema, in which there is an abnormal rise with exercise (Hickam and Cargill, 1948; Riley *et al.*, 1948).

In the arteriogram the reduction in vessel number is at the periphery and is generally widespread. The maximum reduction in side branches is within the lobule that is over the distal 1–2 cm. of a pathway. In this region the artery narrows fastest, the muscularity of the vessels increases sharply, and as the number of side branches is great the volume of the pulmonary artery bed increases at its greatest rate. This region of the artery, roughly at the level of respiratory bronchioli, has been described by Elliott as a "stop-cock". Thus even if the capillary bed is intact, the reduction of the arterial bed by organic narrowing at this particular level may represent a change of major functional significance.

Dilatation of proximal vessels.—Dilatation of the filled vessels, that is, with a diameter more than 0·5 mm., was a feature of the changes in chronic lung disease. This occurred between the hilum and the subpleural level at which vessels were no longer visible in the arteriogram. That it occurred also in a patient with primary pulmonary hypertension suggests that it is secondary to peripheral constriction and is not peculiar to chronic lung disease.

It is usually accepted that hypertrophied vessels resist distension on injection and this may apply to the arteries which are not visible. In injected vessels, of above 2000 μ in diameter, the total thickness of the wall is less than 4 per cent of the external diameter and although there is hypertrophy of the muscle in this region dilatation still occurs, the increase in diameter may reflect a shift in distribution of intrapulmonary blood volume and that in life the volume of these vessels was greater through much of the cardiac cycle.

Between 2000 and 500 μ diameter the wall thickness falls to nearer 2 per cent and then in smaller vessels rises, at about 100 μ, to 4 per cent.

Vasoconstrictive response.—If the pressure in an artery is raised, it leads on occasion to a further rise (Byrom, 1954) associated with an increase of resistance in the vascular bed, referred to as a "vasoconstrictive response" of the vessels. The clinical manifestation of this response is

seen in the cases of "reactive hypertension" (Wood, 1956) in valvular heart disease, either congenital or acquired. The puzzling feature is that some patients develop pulmonary hypertension while others with a similar valvular lesion do not.

The relative importance of this response in emphysema is not clear. That severe degrees of right ventricular hypertrophy in chronic bronchitis or emphysema have been found only with polycythaemia suggests that the vasoconstrictive response is not as severe or significant as in primary heart disease.

The Angiogram in Emphysema and Chronic Bronchitis

Angiography is not often carried out in patients with emphysema and chronic bronchitis. Scarrow (1965) has described angiograms in such cases but as he does not mention the postero-anterior plain radiographs it is not possible to relate his results to those described here. Jensen and his colleagues (1961) show illustrations of radiographs and angiograms from eight cases of emphysema, in four of which it appeared to be gross and widespread and four localised (Simon, 1964). These illustrations, so far as it is possible to judge, show that their cases appear typical of those dealt with here, which present the following features (Simon, 1965).

Enlargement of the hilar and lobar arteries may reflect a rise in pulmonary resistance. Where there is right ventricular hypertrophy a zone of rather abrupt arterial narrowing sometimes occurs close to the hilum, near where the arteries enter the lung. In emphysema, the tapering is gradual, although the intrapulmonary arteries are narrower. In regions of gross emphysema the penetration of the dye is poor; very few side branches are seen and penetration along axial pathways is less than normal. In patients with chronic bronchitis and right ventricular hypertrophy but no emphysema, the penetration and the number of side branches are roughly normal, but the concentration of dye is less, suggesting a reduction in the amount of blood in these vessels.

It is not yet possible to express these radiographic differences in terms of haemodynamic variation, but from the comparisons shown in Table XI certain tentative deductions can be drawn. For instance, the narrowing along an intrasegmental axial pathway in the radiograph and angiogram corresponds to a dilatation of these pathways in the specimen arteriogram, which suggests that the appearance during life arises from a functional and not a structural change.

A normal *in vivo* angiogram is shown in Fig. 140.

Case 48.—Chronic Bronchitis—Localised Emphysema—Pulmonary Artery Pressure Normal

The patient was admitted at the age of 57 with a 20-year history of cough and sputum and gradual increase in shortness of breath over the previous 10

FIG. 140.—Normal angiogram.

TABLE XI

ANGIOGRAPHIC APPEARANCE IN CHRONIC BRONCHITIS AND EMPHYSEMA

	Radiograph	*Angiogram*	*Specimen Arteriogram*	*Specimen*
Chronic Bronchitis with Right Ventricular Hypertrophy	Large hilar arteries	Large hilar	Large hilar	Obliterative arterial lesions (pre- and intralobular)
	Normal intra-pulmonary arteries	Small intra-pulmonary arteries relative to hilum	Large intra-pulmonary segmental arteries	
	No hypertrans-radiancy	Good peripheral filling but poor flow	Loss of side branches at intra- and prelobular level	No emphysema
Emphysema	Normal to large hilar arteries	Normal to large hilar arteries	Normal hilar arteries	Capillary bed largely disappeared and also pre- and intra-lobular arteries
	Small intra-pulmonary arteries	Small lung-No peripheral filling and loss of side branches in most regions	Normal or small intra-pulmonary arteries	

years. During this time he had often been off work for up to two months from an attack of acute bronchitis. One month before admission he had noticed swelling of the ankles. He produced about half a cupful of mucopurulent sputum a day.

The radiograph showed the diaphragm to be low and flat, and at the level of the 7th rib. The heart was 11 cm. in diameter. The pulmonary artery was prominent, the hilar arteries large, and the intrapulmonary vessels normal save for an avascular region, not demarcated by line shadows, at the left base. Thus the radiograph gave evidence of localised emphysema but no more than "possible" widespread emphysema.

Respiratory Function Tests

		After isoprenaline
FVC	1600 ml.	1700 ml.
FEV	700 ml.	900 ml.
$\frac{FEV_1}{FVC}$	44%	
MVV	22 l./min.	35 l./min.
PEF	—	160 l./min.
VC	2400 ml.	2850 ml.
D_{CO} at rest	4·8 ml./min./mm.Hg (Min. vent.	6·8 l./min.)
D_{CO} on exercise	7·8 ml./min./mm.Hg (Min. vent.	18·1 l./min.)
% extraction	32%	
Blood Gases		
P_{O_2} (mm.Hg)	100	
P_{CO_2} (mm.Hg)	36·0	

Cardiac catheterisation showed the pulmonary artery pressure to be 20·0 mm.Hg. The mean pulmonary artery pressure did not rise on exercise (comparing wedge pressure before and after exercise).

The angiogram (Fig. 141) showed the hilar arteries somewhat enlarged with narrowing of the intra-pulmonary vessels in the lower lobes and reduction in the number of side branches.

The electrocardiograph was normal, haemoglobin 98 per cent (14·5 grams), and packed cell volume 46 per cent.

Case 49.—Primary Emphysema—Bullae

At the age of 51 the patient was admitted to hospital with a history of shortness of breath. She had never smoked and occasionally produced a small amount of yellow sputum. Twelve years before admission during her convalescence from right inguinal hernia she had developed a deep vein thrombosis in the left leg and her shortness of breath had become worse from this time. There was no finger clubbing or cyanosis but she was breathless at rest. The haemoglobin was 97 per cent. The oxygen saturation 85 per cent and respiratory function tests were as follows:

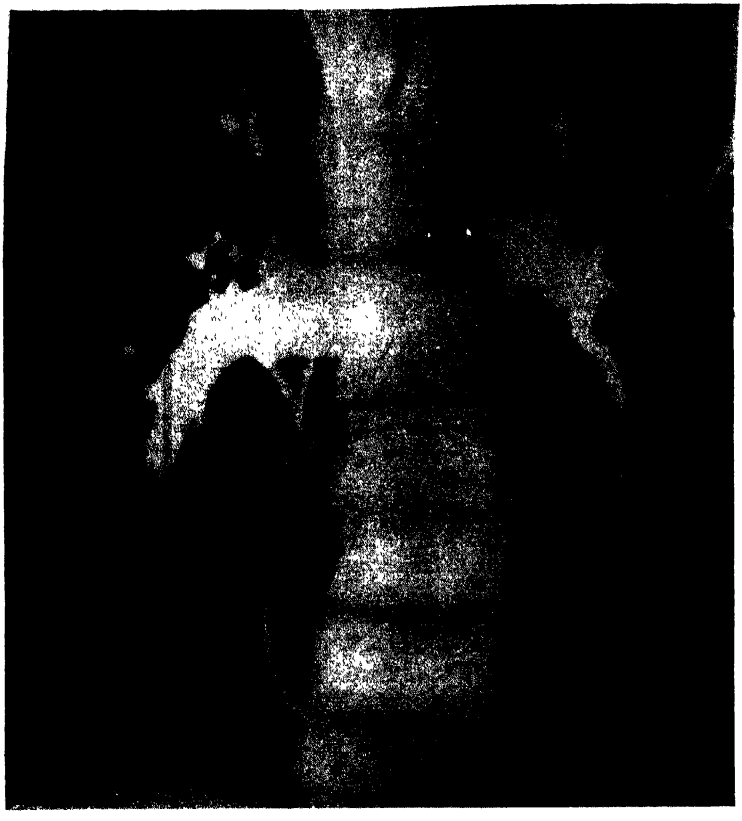

FIG. 141.—Case 48.—Chronic bronchitis and localised emphysema. Hilar arteries not as large as those in Fig. 143, intrapulmonary vessels narrow in lower lobes with fewer side branches. E.C.G. normal. PA pressure, 20/0 mins. Hg, D_{CO} 4·8 ccs./min./mm.Hg.

FVC	1350 ml.
FEV_1	450 ml.
$\frac{FEV_1}{FVC}$	33%
MVV	17·4 l./min.
The peak flow was not recordable.	
D_{CO} at rest	3·8 ml./min./mm.Hg
(Min. vent.	8·3 l./min.)
D_{CO} on exercise	7·0 ml./min./mm.Hg
(Min. vent.	16·8 l./min.)

The radiograph showed the diaphragm to be low and flat and at the level of the seventh rib. The heart was 10 cm. in transverse diameter and of a "narrow vertical" configuration. The main trunk, pulmonary and hilar arteries were

normal, the intrapulmonary vessels small and throughout the right lung and at the left base were avascular regions. The right upper lobe was compressed against the mediastinum. The lateral film confirmed the low flat diaphragms and showed an abnormally large anterior retrosternal space.

The electrocardiogram showed the QRS frontal axis to be +105°, suggesting right ventricular hypertrophy.

Radioactive xenon studies confirmed that the best diffusion and ventilation was in the left upper lobe. Pulmonary arteriography (Fig. 142) was per-

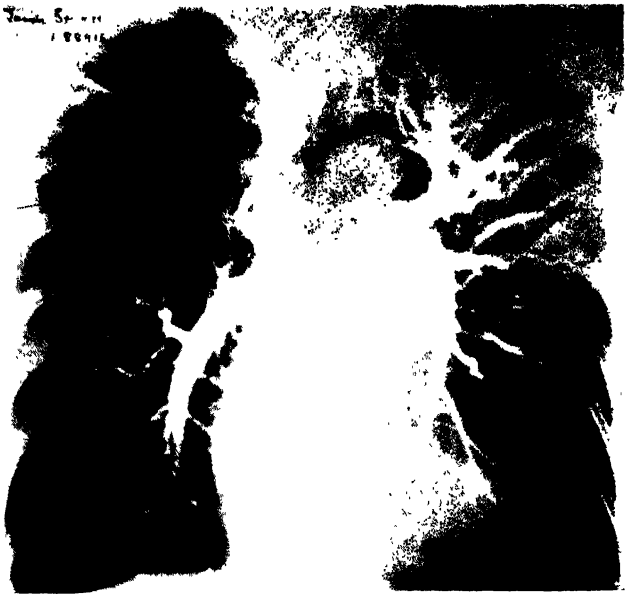

FIG. 142.—Case 49. Primary emphysema. Diversion of blood flow to left upper lobe; right upper lobe compressed medially by large bulla; in both lower lobes poor arterial filling. Radioactive xenon studies showed that diffusion was best in left upper lobe. D_{CO} 3·3 ccs./min./mm.Hg. Pulmonary artery pressure 35/8 mm.Hg. E.C.G. evidence of R.V.H.

formed with the catheter in the main pulmonary artery. The circulation to the left upper lobe was faster than elsewhere and the vessels were of good calibre. The collapse of the whole of the right upper lobe was confirmed and that there was a good circulation through it. The middle lobe artery and vein appeared considerably displaced upwards and medially, presumably by bullae. The pulmonary vessels in both lower lobes were attenuated because of the emphysema. In the right upper zone, the region of the bulla, very few vessels were visible.

The pulmonary artery pressure was 35/8 mm.Hg. The right ventricular pressure varied between 50/0 and 46/0 mm.Hg.

Right middle lobectomy was performed since this lobe contained a huge bulla which was found to be compressing the upper lobe; the latter then expanded well. Bullae were seen in the lower lobe.

CASE 50.—CHRONIC BRONCHITIS

The patient was admitted to hospital at the age of 61 with the sudden onset of swelling of the ankles, following shortness of breath which had developed during the previous few weeks. The patient had produced cough and sputum for the previous eight years. He had smoked ten cigarettes a day for forty years. On admission there was some cyanosis but no clubbing of the fingers.

The radiograph showed that the diaphragm was between the sixth and seventh rib and normal. The transverse diameter of the heart was 14·5 cm.; the pulmonary artery and hilar arteries were eniarged but the intrapulmonary vessels were normal. There was no evidence of widespread emphysema.

Respiratory function as follows:

Respiratory Function Tests

	30.3.62.	25.4.62.
VC		2340 ml.
FEV_1		1040 ml.
FVC		2070 ml.
$\frac{FEV_1}{FVC}$		45%
PEF	110	180 l./min.
RC		3460 ml.
TLC		5480 ml.
RC/TLC		63%
D_{CO} at rest		10·8 ml./min./mm.Hg
D_{CO} on exercise		14·0 ml./min./mm.Hg
$PaCO_2$	74 mm.Hg	65 mm.Hg
PaO_2	41 mm.Hg	59 mm.Hg
SaO_2	70%	86%
Dead Space/Tidal volume	72% Tidal volume	310 ml.
	Rate	25/min.
	Minute volume	7·7 l.
	Alveolar ventilation	2·15 l./min.
	Ventilation Perfusion Ratio	0·4
Haemoglobin	14 G.	
E.C.G.	Evidence of right axis deviation	

Cardiac catheterisation.—Cardiac catheterisation two months after admission revealed the following:

Pressures

P.C.	Mean 16 (poor trace)
M.P.A.	Resting varied between 35/15 and 55/25 (means 23–30)
M.P.A.	On exercise: 90/40 (mean 50 and 70/35) (mean 45)
M.P.A.	Breathing O_2: mean 23 before and during
M.P.A.	Breathing O_2 on exercise: 56/28 (mean 30)
R.V.	50/0
R.A.	Mean O.

O_2 Saturation	*L.B.A.*	*M.P.A.*
1. Resting	86%	61%
2. Exercise	82%	42%
3. Breathing O_2	98%	75%
4. Exercise $+O_2$	97%	69%
5. Breathing 14% O_2	81%	68%

Cardiac Output: 4·8 l./min.
Pulmonary Vascular Resistance: 2 units.

Angiography.—Angiography (Fig. 143) demonstrated the enlarged hilar arteries. The intrasegmental axial arteries were narrowed relative to the main arteries and also to the normal but they were not as narrowed as in emphysema. (50 ml. Urografin was injected into the main pulmonary artery.)

RIGHT VENTRICULAR HYPERTROPHY IN OTHER LUNG DISEASE

The above discussion of right ventricular hypertrophy has so far been mainly concerned with primary emphysema and emphysema associated with chronic bronchitis, but there are rare cases in which right ventricular hypertrophy is associated with bronchiolitis obliterans (see p. 144). In the patients described it seems likely that airways obstruction was present in the radiographically normal lung; thus the right ventricular hypertrophy would not appear to be a complication of the obliterative lesions in the emphysematous region.

Right ventricular hypertrophy may arise in cases of scar emphysema. The role of the emphysema in producing right ventricular hypertrophy is difficult to determine, as the amount of lung lost in the scars needs to be taken into account as well as any residual damage in the aerated lung between them.

The following diseases are here described for their bearing on scarring, emphysema, and airways disease. In few of them have studies of cor pulmonale included weighing the right and left ventricles.

In sarcoid death is not uncommonly due to right heart failure, mostly secondary to pulmonary fibrosis, rarely to sarcoid myocarditis. The reports of heart failure do not usually state whether there is also hypertrophy. Of the twenty-six fatal cases in Rubin and Pinner's series (1944) eight died of myocardial failure, one of sarcoid of the heart, the others of the complication of pulmonary fibrosis; Riley (1950) reported thirteen fatalities, four from "cor pulmonale"; the only death in Scadding's sixteen cases (1950) was due to right heart failure; in Nitter's series (1953) ten of the sixteen deaths were due to complications of pulmonary fibrosis—bronchopneumonia and cardiac insufficiency; Israel and Sones (1961) report on twenty deaths, including five from "cor pulmonale" and one from myocardial sarcoid.

In localised tuberculosis pulmonary hypertension is not likely to

FIG. 143.—Case 50. Chronic bronchitis with cor pulmonale. No radiographic evidence of widespread emphysema. Large hilar vessels, normal sized intrapulmonary vessels but poor flow in all regions. Man aged 60. Cough, sputum, dyspnoea. No polycythaemia. E.C.G. evidence of R.V.H. Airways obstruction severe. PA 35/15—55/25. D_{CO} 10.8 ccs./min./mm.Hg ventilation.

develop. Söderholm (1959) concluded that it is in patients with widespread tuberculosis giving severe and widespread scarring that the rise in pulmonary artery pressure is particularly seen: he measured pulmonary artery pressures by catheterisation and the pressure rather than the size of the right ventricle was his evidence of "cor pulmonale". On the other hand Zimmerman (1951) had reported a rise in pulmonary artery pressure after thoracoplasty in patients whose disease was considered unilateral.

Uggla (1957) measured pulmonary artery pressure in cases of pulmonary tuberculosis by cardiac catheterisation including the pressure after unilateral occlusion of the pulmonary artery. This test was carried out at rest and during work, and the pressures related to the fitness of the patient for work after surgical treatment. It was found that higher pressures were associated with a poorer prognosis. Müller (1960) studied respiratory function in patients with pulmonary tuberculosis and concluded that air-

ways obstruction is more important in the development of right ventricular hypertrophy than restrictive ventilatory insufficiency such as may follow tuberculosis.

In histiocytosis X in Lewis' series (1964), two of the four cases coming to autopsy showed evidence of right ventricular hypertrophy.

It would seem that simple penumoconiosis does not cause right ventricular hypertrophy, although this is not uncommonly found when massive fibrosis is present (Thomas, 1951; Wells, 1954). James and Thomas (1956) using Herrmann and Wilson's criteria (1922)—the septum is divided between the ventricles—analysed the findings, including ventricular weights in eighty, and concluded that it is the massive fibrosis which is associated with right ventricular hypertrophy and suggested that stenosing arteriolar lesions were responsible for the effect on the heart.

The frequency of right ventricular hypertrophy and heart failure in bronchiectasis is difficult to assess. Recent surveys such as those of Strang (1956), Helm and Thompson (1958) and Clark (1963) make no mention of either. Both are mentioned in the earlier reports of the natural history of bronchiectasis, before antibiotics were introduced and postural drainage was exploited. Of 110 cases of fatal bronchiectasis Jex-Blake (1930) reported three as due to heart failure. Franklin (1953) followed a series of cases admitted to the Meath School of Recovery for management of bronchiectasis and reported three deaths in 171 cases, of which one was from cor pulmonale. Earlier, Perry and King (1940) reviewed 400 cases of bronchiectasis from the Massachusetts General Hospital. Of the 260 not treated surgically sixty-six deaths occurred, six from cor pulmonale; there were nine deaths in the whole series and in these the disease was widespread, in six of them bilateral. Field (1961) reported four deaths from cor pulmonale in 224 children followed for periods ranging from eight to twenty-one years.

Although in the fatal cases of bronchiectasis infection was by far the commonest complication (Lee Lander, 1950) and cause of death, there is surprisingly little mention of heart failure, considering how common it is in cases of chronic bronchitis. It may be that the airways obstruction must affect virtually all airways before this complication can develop or that ventricular hypertrophy developing in early life may "protect" the patient from heart failure.

Right ventricular hypertrophy in cystic fibrosis is described in two patients under two years of age (Tomlin *et al.*, 1952; Royce, 1951); and Anderson (1938) considered that the complication of lung infection including cor pulmonale was the commonest cause of death.

Recently Goldring and her colleagues (1964) have investigated the development of pulmonary hypertension in cases of cystic fibrosis and found that the pulmonary arterial pressure was directly related to the degree of hypoxia and that increasing the blood oxygen levels caused a fall in the

pressure. In a number of cases this did not return to the normal range, suggesting the presence of an additional or contributing factor.

In diffuse interstitial fibrosis cardiac failure is the cause of death in a minority of cases. For example, of the forty-five patients described by Livingstone *et al.* (1964) twenty-one died, eight from cardiac failure. At autopsy hypertrophy of the right ventricle had been reported in seven of the cases with cardiac failure and five of the twelve with respiratory failure.

FIG. 144.—Case 51. Chronic bronchitis; large left pulmonary artery found to be almost entirely blocked by thrombosis. E.C.G. showed evidence of ischaemia. At autopsy, emphysema and R.V.H. (right ventricular wall 1·5 cm. thick).

THROMBOSIS OF THE MAIN RIGHT OR LEFT PULMONARY ARTERY

Thrombosis of a main pulmonary artery to a lung is often overlooked, largely because it gives rise to no special radiographic appearance. In some cases the thrombus is in a dilated descending artery which may be unduly conspicuous in the radiograph. Probably the thrombus not infrequently causes deterioration in the patient's condition and heart failure but, as there are usually other features which might be blamed, its presence is not suspected.

Thrombosis of the main pulmonary artery probably occurs more often

than suspected, being usually overlooked during life and perhaps even at death. In a fatal case of chronic bronchitis (Fig. 144) in which a pulmonary arteriogram was performed the pulmonary artery was well filled and large (Fig. 145); it was not until the lung was sliced that it was realised that the

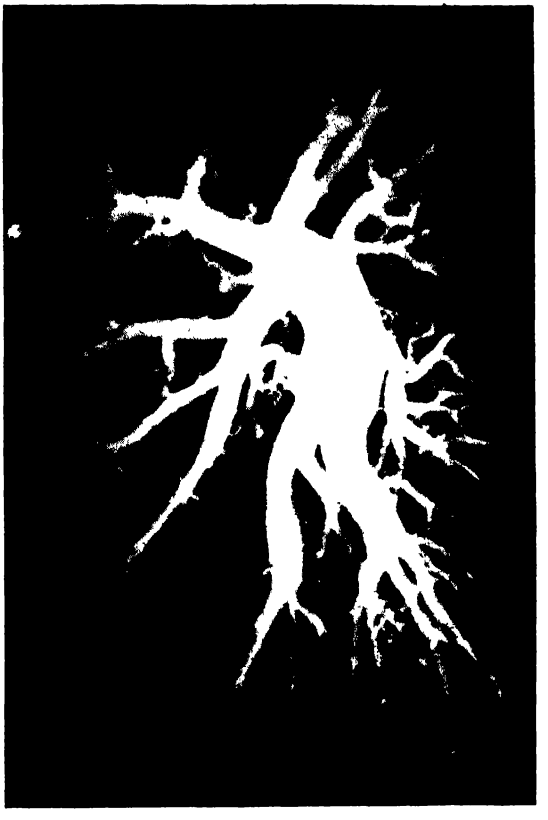

FIG. 145.—Case 51. Specimen arteriogram. A thrombus which almost entirely blocked the artery was not detected until the specimen was sliced. Note large proximal arteries, large intrasegmental pathways and poor peripheral filling.

lumen of the artery was almost occluded by a thrombus. In many cases there is no reason to postulate an initial embolus and the possibility that these are primary thrombi seems more likely.

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Chapter XVI

CORRELATION OF RADIOGRAPHIC AND PATHOLOGICAL FEATURES OF EMPHYSEMA

RADIOGRAPHIC FEATURES

THERE are no radiographic abnormalities in emphysema without airways obstruction such as the aged lung, centriacinar emphysema and compensatory emphysema, except that in this last the vessels are spread out. Paraseptal emphysema may show the hair-line shadows of the walls of bullae (Fig. 17), but, again, the rest of the lung is normal. Localised emphysema with air-trapping, however, such as that arising from a ball-valve stenosis of a bronchus, will give rise to a localised relatively avascular transradiant area (Fig. 35), the rest of the lungs being normal.

By contrast, panacinar emphysema if severe enough to be associated with airways obstruction and sufficiently widespread will almost invariably give rise to abnormal radiographic appearances. These are summarised here and given in more detail in his Skinner Lecture by Simon (1964*a*). The criteria for the radiographic diagnosis of this condition are threefold:

I. An Excess of Air in the Lungs

This may be inferred if the diaphragm is low and flat, lying at or below the seventh rib anteriorly (the sixth rib is acceptable as low in a broad stocky person). A large retrosternal translucent zone 3–5 cm. deep (normally it is 2–3 cm. deep) and reaching to within 3 cm. of the diaphragm, would be additional evidence of excessive air. The air being trapped, the diaphragm rarely moves more than 3 cm. between deep inspiration and expiration, against a normal range of 3–10 cm., even in the age group 45–65. With excessive air the retrosternal translucent area remains large on expiration. The flatness of the diaphragm is the most important sign of excessive air. This means loss of curve, although the diaphragm may be horizontal or oblique.

II. Cardiovascular Changes

The cardiovascular changes resulting from emphysema with air-trapping may not be very obvious on pathological examination, but can be detected by cardiac catheter studies, in pulmonary *in vivo* angiograms and in the plain radiograph. The heart is often narrow and vertical with a transverse diameter of 11·5 cm. or less; by reason of the low position of

the diaphragm its lie is probably dependent and it often remains narrow and vertical even when right ventricular hypertrophy develops.

The main pulmonary artery may be somewhat dilated, exaggerating the bulge below the aortic knuckle on the left border of the heart. This dilatation may be confirmed on morbid anatomical investigation.

The hilar arteries are seen to be dilated in the radiograph, and the majority of the larger intra-pulmonary vessels appear by contrast unduly small. The severity of these changes throughout the lung varies; where it is severe enough to cause blood diversion to less affected areas, the major vessels in this area may appear large in contrast to the other lung vessels which are small.

III. Bullae

The presence of bullae can be inferred from the appearance of a relatively transradiant avascular area whether it is demarcated by a white hair-line shadow or not. The disappearance of vessels in an area not demarcated by line shadows is sometimes referred to as a pruning of the vessel pattern (Laws and Heard, 1962).

Diagnosis

When all three criteria are present, the diagnosis is certain. A large heart with large hilar and small lung vessels is also seen in pulmonary hypertension without emphysema—hence the significance of finding the first criteria. Bullae are present in only about one-third of the cases, but tend to justify the diagnosis if the cardiovascular changes are relatively slight.

On the basis of these criteria the radiographs can be divided into the following groups:

(1) No emphysema
(2) Gross widespread emphysema; all three criteria are present or there is excessive air and the cardiovascular change; or excessive air and bullae, the cardiovascular change being uncertain.
(3) Localised emphysema: an avascular translucent area with neither widespread excessive air nor widespread cardiovascular changes (and often without symptoms).
(4) "Possible emphysema": where the radiograph shows excess of air with trapping, but equivocal or incomplete cardiovascular changes, and no large bullae.

The features characteristic of widespread emphysema in the plain radiograph may also be seen in tomograms, on which it is possible to measure the larger hilar vessels and sometimes to detect avascular areas of bullae invisible in the plain radiograph. Tomograms may therefore be of use for diagnosis in doubtful cases (Fraser and Bates, 1959).

BULLAE

The incidence of bullae in widespread emphysema is shown from the following studies.

All cases had severe dyspnoea and showed the other radiographic criteria of widespread emphysema (see p. 276). Large bullae without widespread emphysema were not included.

(1) Simon and Medvei (1962)	87	cases with pattern of widespread emphysema
No bullae	54	(63%)
Obvious bullae	33	(37%)
(2) Chappell and Batten (1965)	30	cases
No bullae	14	(47%)
Obvious bullae	16	(53%)

The sites of large bullae or bullous areas in 76 unselected patients (Simon, 1964) with widespread gross emphysema and bullae were:

Upper half	33
Lower half	27
Upper and lower zones	16

CORRELATION BETWEEN RADIOLOGICAL DIAGNOSIS AND STRUCTURE

To correlate the radiographic appearance of widespread emphysema with structure, three points must be determined:

(1) the type of emphysema;
(2) the degree of severity; and
(3) the extent of the disease.

It is first necessary to define the type of emphysema because not all large air spaces are clinically significant. In centriacinar or paraseptal emphysema, for example, the air spaces may be large but are not associated with air-trapping or radiological changes of widespread emphysema. The type which is most often clinically significant is panacinar emphysema.

The degree of severity of this type of emphysema must be established (see p. 17), because mild grades of panacinar emphysema are seen in the aged lung (Chapter III), but do not give rise to air-trapping.

The above features were considered in relation to forty cases of fatal chronic bronchitis (Reid and Millard, 1964) already referred to in Chapter XV. In none was a large bulla present, so that interpretation was not complicated by compression of adjacent lung. The results are summarised in Table IV and are dealt with in the following description, according to the grouping given on page 277.

No Emphysema

In nineteen patients the chest radiograph showed no evidence of emphysema; on pathological examination four still showed no emphysema, seven showed Grade I panacinar emphysema, two Grade II and six both Grades I and II. In the two cases of Grade II the emphysema was widely and uniformly distributed. In the six cases with Grades I and II the distribution was irregular; in two of these, small patches of Grade III emphysema were found in both upper or lower lobes, but the total area of Grade III in each was considerably less than one-third of the area of the largest lung slice. (The lung was divided into slices 1 cm. thick, the plane of cutting being parallel to the medial surface of the lung.)

In one patient Grade III emphysema involved about half the total area of the largest lung slice but, in addition to emphysema, the patient had suffered from chronic left ventricular failure for several years which probably prevented the radiograph from showing the signs of emphysema (see p. 283).

Gross Widespread Emphysema

In ten of the cases the radiograph showed the signs of widespread emphysema. On pathological examination Grade III emphysema was found in all while in some there were also patches of Grade IV emphysema. In eight cases the emphysema was widely distributed throughout both lobes. In two cases the upper lobes showed Grade III and extensive Grade IV; the lower lobe of one showed Grade I, and of the other Grade II. In all ten cases more than half of the area of the largest lung slice was found to contain Grade III or Grade IV panacinar emphysema.

Localised Emphysema

From 6 of 9 patients with a radiological diagnosis of localised emphysema the affected lobes were available. The regions corresponding to the transradiant areas showed Grade III or Grade IV emphysema, the rest of the lung being either normal or showed only Grade I or Grade II emphysema.

"Possible" emphysema

In two patients the radiographic appearances showed "possible" emphysema. The diaphragm was low and flat in both cases and the hilar vessels large but, because the mid-lung vessels were normal, the diagnosis of widespread emphysema was not justified and the radiographs were graded as "possible" emphysema. Both lungs were available in these cases. In one patient (Fig. 103) the right lung showed patches of Grade III emphysema in the upper and lower lobes, while the middle lobe showed only Grade I; the left lung showed Grades I and II but the apical region of both the upper and lower lobes showed Grade III. In the other patient

the lung slices showed Grade III and IV at the apices of both lungs, the remainder showing mainly Grade II but with patches of Grade III.

The total amount of Grade III emphysema in each case was between a third and a half of the area of the largest slice.

In summary then, panacinar emphysema was present in all cases with radiographic evidence of widespread emphysema. Only Grades III or IV will produce radiographic changes of widespread emphysema and then only if at least half to two-thirds of the largest lung slice is so affected.

Not only are the type, the grading, and the total amount of emphysema important but so also is its distribution. A given amount of Grade III emphysema may be detectable in a radiograph if it is localised, but not if it is spread patchily throughout the lungs.

Clearly if Grade III emphysema is widespread throughout both lungs the radiograph would show the signs of it. The distribution of Grades III–IV need not necessarily be even throughout all the lobes to show the radiographic pattern of widespread emphysema. In two patients in whom this picture was seen, Grade III was predominant in only 4 lobes, with a lower lobe showing mainly Grades II–III.

Grade III panacinar emphysema if concentrated in part of a lung will produce the appearance of localised emphysema in the radiograph. Localised emphysema in the upper lobe does not affect the position of the diaphragm but when against the diaphragm usually depresses its level.

BASIS OF RADIOGRAPHIC APPEARANCE

Relative Transradiancy

Excessive transradiancy arises from an increase in air relative to the tissue or blood through which the X-rays pass. It may occur when part of the lung increases in volume as in compensatory distension, although in this condition it does not necessarily occur since increase in blood to the region compensates for the increased volume. It would seem that the relative reduction in the amount of blood is the main cause, since there may be transradiancy with little change in lung volume, as in some cases of ball-valve obstruction (p. 71). There is little or no fissure displacement and the cause of the transradiancy must be vascular and functional, since it develops and disappears so quickly. Bronchitis and bronchiolitis obliterans are other conditions in which transradiancy may be seen early in the disease, before there is much effect on the number or size of the alveoli (see p. 129). Similarly in a ball-valve obstruction blood vessels may be narrowed.

The radiograph may be the most successful means of diagnosing a localised region of emphysema, as the alteration of the blood/air ratio may be readily assessed. A specimen arteriogram may reveal a pulmonary artery and branches more intact than suggested by the radiograph in life (Figs. 69 and 71).

The radiograph may show hair-line shadows demarcating a bulla cast by folds of pleura, pointing to a local stretching and indentation of pleura.

Pathological Basis of a Transradiant Area

From the radiograph it is not always clear whether a bulla is an empty air sac or whether it contains surprisingly intact lung, albeit showing panacinar emphysema Grade III. If blood vessel shadows can be seen within the transradiant area, this must include lung; but the converse does not hold, since a transradiant region may include lung even if blood vessel shadows are not visible in the radiograph (see Case 47, p. 232).

Diaphragm and Lung Volumes

The radiograph has the great advantage over pathological examination of the lung out of the body in that the size of the lung can be seen in relation to the thoracic cage. A low flat diaphragm is evidence that on inspiration the lung volumes are greater than is normal in health. If the area of the diaphragm is taken as 250 sq. cm. its descent by 4 cm. will increase lung volume by one litre.

Failure of the diaphragm to move up well on expiration is evidence that there is air-trapping and obstruction to expiration; it is the end-expiratory volume which is, therefore, often most significant for the recognition of emphysema.

The amount of diaphragmatic movement can be estimated by fluoroscopy, cine-radiography or by the use of films taken on inspiration and expiration. In emphysema the movement may be only 2–3 cm., representing a tidal air of perhaps 750 ml.—normally 3–10 cm. and 2500 ml. respectively.

Airways obstruction may occur even with a normal inspiratory diaphragm level, as in cases of chronic bronchitis, the results of respiratory function tests being characteristic of this condition. Airways obstruction of extreme degree can develop without the level of the diaphragm being depressed. The depression of the diaphragm and the other features of a large lung volume seem to be evidence of increased compliance (Christie, 1934) of the respiratory tissue rather than to the presence of airways obstruction.

Limitation of Diaphragm as Index

Kyphoscoliosis may cause the diaphragm to be low and flat on one side but its movement is not impaired. Normal subjects sometimes show a diaphragm which on inspiration is at a low level, but whose movement is excellent. In patients with asthma, particularly older children or adolescents, the diaphragmatic features of emphysema may occasionally be seen on inspiration but not the blood vessel changes of emphysema (Lodge,

1946) and inspiration/expiration films show that their diaphragmatic movement is greater than in a patient with emphysema.

If localised bullae are present against it, the diaphragm may be unusually low and flat and move but little, although the blood vessel pattern may be within normal limits throughout the upper two-thirds of the lung.

If heart failure develops in a patient with emphysema the diaphragm moves up; this has not yet been explained but it is usually associated with the increase in diameter of the heart in this condition. It may be that because of the congestion in the lung there is time for trapped air to be absorbed from the lungs with a consequent reduction in lung gas volume.

Narrow Vertical Heart

The anatomical basis for the radiographic phenomenon of a narrow vertical heart is not clear. Often the transverse diameter of the heart is 2 cm. or so less than the normal. There is an increase in the length of the chest but this is not likely to account for all the heart change, as in a normal subject even with the maximum inspiration a heart of less than 11·5 cm. is not common. The narrowness may be due to the heart's working at a smaller filling volume. Even if the right ventricle is hypertrophied the heart may appear "narrow and vertical".

Large Hilar and Small Mid-Lung Vessels

The large hilar and small mid-lung vessels may represent either an absolute or a relative alteration in diameter of the vessels. On the tomograph the hilar arteries appear increased in diameter, which suggests an absolute increase in size (see Table XII) but to some extent the narrow vertical heart "unmasks" hilar vessels.

Table XII

Comparison of Arterial Measurements (in mm.) from Standard Tomograms at Hilum; in Normal Subjects, in Patients Showing Radiographic Features of Widespread Emphysema and in Patients with Chronic Bronchitis and no Radiographic Emphysema.

	Transhilar		*Left Main Pulmonary Artery*		*Right Main Descending Artery*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*
Normals	119	100–145*	24	18–32	12·8	10–15
Obstructive Airways Disease without Emphysema	134	125–150	32	22–49	15·5	11–20
Widespread Emphysema	147	125–170	36	29–47	18·0	15–25

* only 2 above 135.

Another basic disturbance of pattern is that the side branches appear fewer and the blood vessels of the peripheral lacy network are less in bullous areas.

Basis of Vascular Signs

Tomograms.—A series of measurements of the more proximal pulmonary arteries have been made in tomograms of normal subjects and of patients with chronic bronchitis, some with and some without evidence of widespread emphysema on the radiograph (Simon and Millard, 1964). The transhilar measurement was taken as well as the diameter of the left main pulmonary artery and right main descending (basalis) artery.

For all three measurements, the average, both for "emphysema" and "bronchitis without emphysema", was larger than for the normals. As shown in Table XII the range overlap with the normals was less marked in the emphysema group than in the bronchitic, the latter being as wide as the normal and emphysema groups together. Amongst the bronchitics the presence of pulmonary hypertension is probably associated with the wider hilum measurement, whereas in some patients in this group (probably without either pulmonary hypertension or polycythaemia) the measurements are virtually normal.

Specimen arteriogram.—Specimen arteriograms are of little use for measurement of main and hilar arteries because of the ligature on the artery at the point of cutting. In cases of emphysema without pulmonary hypertension the intrasegmental arteries show no significant narrowing, which suggests that the radiographic appearance in life reflects a functional modification.

The "small mid-lung vessels" may represent a contraction in diameter, a reduction in flow, or less systolic expansion. Unfortunately it is not known to what extent the shadows cast by a blood vessel are dependent on the amount of blood passing through it as well as on its diameter.

EFFECT OF HEART FAILURE ON CARDIOVASCULAR SIGNS

If a patient with emphysema develops heart failure the radiographic picture is altered. The diaphragm may then come to lie at the normal level and have a normal shape, the transverse diameter of the heart shadow increases and the blood vessels are large, not only at the hilum, but into the lung. The change in the circulation may allow trapped air to be absorbed. With recovery from the heart failure the features of emphysema may again be seen, but while failure is present the appearance of emphysema is completely masked. If the patient with chronic bronchitis and no emphysema develops polycythaemia, the radiograph will often show enlargement of the hilar vessels and perhaps the heart shadow but, unlike emphysema, there is no narrowing of the blood vessels within the lung.

Polycythaemia may also be a complication, albeit rare, of gross widespread emphysema and then the typical emphysema pattern will be seen, but with particularly large hilar vessels and often large lobar and segmental arteries well into the lung fields.

COMMENT

Once the typical pattern has been seen, the usual course of events over the years is that further radiographs show no change but the dyspnoea gets worse. It is probable that the radiographic "emphysema pattern" only develops when the emphysema is pathologically so gross that the respiratory reserve is almost used up. Further loss of lung tissue, though small and insufficient to alter the radiographic appearances, will nevertheless result in a considerable increase in the dyspnoea.

In his Skinner Lecture, Simon (1964*a*) considered the development of the radiographic features of emphysema. The pattern is commonly seen for the first time between the ages of 45 and 60 and rarely in a younger person or in one over the age of 70. It is rare to trace its development. In over 200 cases with the "emphysema pattern" it was possible to find a radiograph before the appearance of widespread emphysema in only one patient. A normal radiograph was available of a man at the age of 21; seven years later at the age of 28 a second radiograph showed the appearance of widespread emphysema. Cough and sputum and dyspnoea had been present for only two years. The dyspnoea became worse, and the radiograph was unchanged save for the enlargement of a bulla, which appeared at the right apex.

In some cases a bulla or bullous area has been seen to enlarge.

The radiographic changes which have been described may be produced by the changes of primary emphysema in the absence of bronchiolar disease; this means that the radiographic features depend essentially on the alveolar and not the bronchiolar changes.

Close correlation can be shown between the radiographic features of emphysema, the findings of airways obstruction in respiratory function studies and the presence of structural emphysema as seen on pathological examination. It follows from what has been described here that radiographic evidence of widespread emphysema is always associated with airways obstruction and disability, but equally that severe disability and impairment in respiratory function tests may arise from airway changes without structural emphysema.

From a series of cases of chronic bronchitis Batten *et al.* (1965) found that the peak flow was always below 180 litres per minute (normal 300–500) in patients whose radiographs showed evidence of widespread emphysema; while in those with a normal radiograph the peak flow was only occasionally equally low (see p. 179).

Relation Between Radiographic Appearance and Prognosis

A statistical survey, such as the follow-up of Medvei and Oswald (1962) and Simon and Medvei (1962) showed that the prognosis in a patient with cough and sputum is worse when the radiographic features of emphysema are present than if the chest is normal. Table XIII shows the five-year mortality rate related to the radiographic appearance in their 299 patients (Simon and Medvei, 1962) brought up to date to include the ten-year mortality (Simon and Medvei, 1965).

TABLE XIII

CHRONIC BRONCHITIS SURVEY—10 YEAR MORTALITY

		Number of Deaths		
Radiographic Appearances	*Number in group at start*	*At 5 years*	*Additional 5–10 years*	*Total at 10 years*
No Emphysema	177	38 (21%)	32	70 (40%)
Local Emphysema	35	7 (20%)	4	30 (30%)
Widespread Emphysema	87	46 (53%)	15	61 (70%)

Twenty-one per cent of the patients with a normal radiograph had died at the end of five years, as compared with 53 per cent of those with the radiographic appearance of widespread emphysema. Local emphysema alone carried no worse a prognosis than the normal radiograph; the mortality in this group was 20 per cent. On the other hand, of those cases with widespread emphysema the prognosis was rather worse if bullae also were present—73 per cent mortality in patients with bullae, 41 per cent in those without.

The importance of evidence of widespread emphysema on the radiograph is emphasised by the fact that most of those who died with emphysema were under 60 at the beginning of this trial whereas many of those with a normal chest radiograph who died were over 60. Furthermore the cause of death in cases of emphysema was usually respiratory or cardiorespiratory; in the others it was usually "other disease".

In a patient with chronic bronchitis and shortness of breath, respiratory function tests may show gross airways obstruction and blood gas disturbance; yet no structural emphysema may be found at autopsies. If a radiograph reveals signs of widespread emphysema it may be accepted that the alveolar damage is such that the prognosis is worse.

ASTHMA

Livingstone and Davies (1961) have described a series of 71 patients with asthma sufficiently severe to justify steroid therapy. Simon (1964*b*) reviewed the films and found that in no case was there the appearance of widespread emphysema.

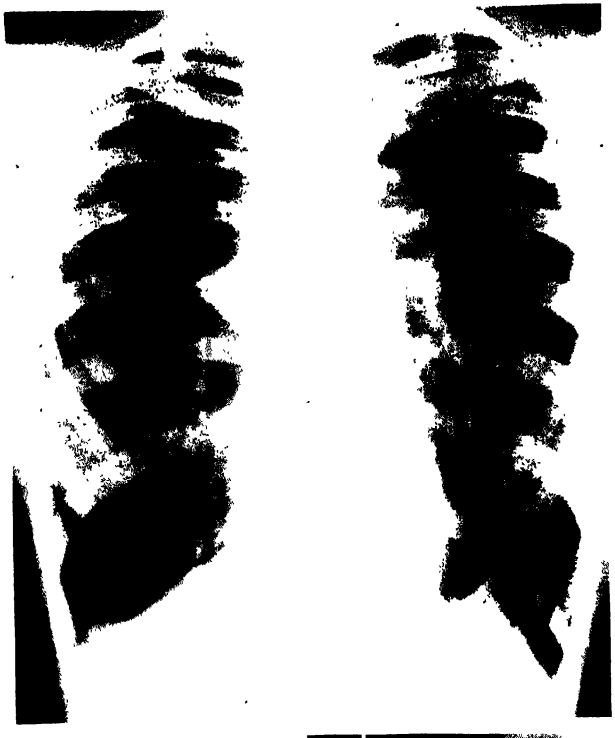

FIG. 146.—Radiograph of adult woman with asthma since childhood; low flat diaphragm suggests widespread emphysema.

FIG. 147.—Bronchogram of patient in Fig. 146 showing excellent peripheral filling, which excludes occlusive airway disease and suggests ventilation is satisfactory and airways obstruction not the cause of the radiographic appearance. The pathological basis for this appearance is not known.

Asthma persisting from childhood may occasionally give in an adult radiograph an appearance similar to that of widespread emphysema, as in Fig. 146. The pathological basis for this is not known, but the bronchogram in Fig. 147 suggests that the appearance does not result from emphysema with air-trapping, because the filling proceeds to the level of terminal bronchioli and there is no reason to believe that the lung is hypoplastic.

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Chapter XVII

PATHOGENESIS OF EMPHYSEMA

EMPHYSEMA can be attributed to no single mechanism. Four types, each deriving from a different mechanism, may be distinguished; they include most pathological types of alveolectasis or emphysema. Each mechanism would seem to imply a different process. In this chapter are summarised certain aspects of pathogenesis, discussed previously in relation to the various types of emphysema. In the next chapter experimental studies are related to the four basic mechanisms dealt with here.

In general terms alveoli may be larger than normal because they have failed to develop normally; or because having developed normally the walls have atrophied; or, again, because the alveoli have been overinflated or their walls have been destroyed. These processes, which may operate individually or in combination, may be described as:

(i) hypoplasia
(ii) atrophy
(iii) overinflation
(iv) destruction
  (*a*) partial — partial destruction of alveolar wall including damage to capillary mesh
  (*b*) complete — complete destruction of alveolar wall.

TABLE XIV

TYPES OF EMPHYSEMA—ARRANGED BY MECHANISM

HYPOPLASIA	Developmental Bronchial Anomalies e.g. Bronchial Atresia	M
	Scar Emphysema in Childhood	M
	Bronchitis or Bronchiolitis Stenosans in Childhood	M
ATROPHY	Aged Lung	S
	Idiopathic Centriacinar	S
	Idiopathic Periacinar	S
	Coalminer's Pneumoconiosis	S
	Primary Essential Emphysema	S
	Bronchitis or Bronchiolitis Stenosans in Adult	M
	Scar Emphysema	M

OVERINFLATION	Compensatory Emphysema	S
	Ball-valve Obstruction	S
	Idiopathic Emphysema of Childhood	S
	Developmental Bronchial Anomalies e.g. Bronchial Atresia	M
	Bronchitis and Bronchiolitis Stenosans in Childhood or Adult	M
	Scar Emphysema	M
DESTRUCTION	Partial as in Alveolar Wall Damage by Inflammation—e.g. Sarcoidosis, Alveolitis as in Chronic Bronchitis, Tuberculosis	S
Complete (ulcerative alveolitis)	as in Chronic Bronchitis	S

M = Mixed—i.e. more than one mechanism operating
S = Single—i.e. single mechanism operating.

HYPOPLASIA

A state of underdevelopment—this term implies that the lung has failed to develop normally.

Alveolar hypoplasia may suggest that alveoli are (i), too few or (ii), too small or paradoxically (iii), too large. It is this last which qualifies as emphysema; these alveoli are probably too few also as the impairment may well have begun in early childhood so that the normal number of alveoli has not developed.

A smooth alveolar outline may also be an indication of hypoplasia. As the normal number of alveoli is achieved by the age of eight and subsequent growth produces an increase only in alveolar diameter and in the capillary number, impairment at this later phase produces alveoli that have a simplified outline.

Emphysema applies to hypoplastic alveoli which are too large. In contrast are the following two examples of hypoplasia with small alveoli, that is hypoplasia but without emphysema. An antenatal disorder causing hypoplasia without emphysema is a large congenital diaphragmatic hernia compressing the lung, a condition in which at birth the alveoli are too small and too few (Areechon and Reid, 1963); a postnatal cause is severe kyphoscoliosis supervening in childhood before lung growth is complete. Growth will then be impeded and the alveoli will again be too few and too small (Reid, 1966).

As bronchial tree development is completed *in utero*, it is a measure of antenatal development; alveolar development being mainly after birth, is a measure of postnatal development (p. 335).

Hypoplasia with emphysema is mainly associated with conditions characterised by obstruction to airways, either organic or functional. Organic obstruction is exemplified in atresia of the bronchus arising

before birth, or in bronchitis obliterans or bronchiolitis obliterans acquired after birth. An example of a functional block is seen in the "air-trapping" of acute lobar emphysema of childhood.

The mechanism involved is best seen where there is an organic bronchial obliteration. If the lung distal to the block is aerated, ventilation must be effected by collateral air drift, and as such lung does not deflate as satisfactorily as lung ventilated directly (Culiner and Reich, 1961), the region may therefore remain in the inspiratory phase.

The reduced ventilation which results from the bronchiolar damage will persist when the acute inflammation subsides and will help to prolong the reduction in flow. Cournand and his colleagues (1935), from a series of experiments on the effect of collapse on circulation, concluded that it was the depth of ventilation rather than the degree of collapse that affected the minute volume of blood flow through the lung. This suggests that respiration has a pumping action increasing pulmonary blood flow. Recently, Riley (1959) indicated that although deep inspiration might increase minute volume of blood flow to the lung as a whole, the capillary blood volume is reduced during the inspiratory phase. This suggests that a lung in which air is trapped, i.e. one relatively hyperinflated, offers mechanical resistance to flow through its capillaries, a further possible contribution to unilateral transradiancy and to atrophy of the capillary bed.

A secondary effect of the reduction in capillary blood flow is to reduce flow through the large vessels of the lobe (see the report of Hilton's findings, on p. 74).

ATROPHY

The wall of an alveolus consists essentially of capillaries with their supporting connective tissue, hence it is particularly to the vessels that one must look both for the cause and the effect of alveolar wall atrophy, meaning the disappearance of alveolar wall substance.

Aging is one example of atrophy and is seen in most tissues. In considering the cause of atrophy whether in relation to the loss of skin elasticity or the "fluffiness" of the aged lung, the first questions which spring to mind concern the blood vessels. Unfortunately very little is known about age changes in the capillary bed.

In the lung it has been established that there is a reduction not only of capillaries but of precapillaries and arterioles—of vessels up to about 70μ in injected and fixed tissue (see p. 25). Although this disappearance of small vessels is obviously a crucial change it is not clear whether it is primary or whether it follows alteration in the elastic fibres or basement membrane of the alveolar wall. But even so it is probable that in aging lung the capillary loss is functionally the most significant.

A loss of capillaries would seem of similar importance in primary emphysema and yet, for the reasons given in the description of this

condition (p. 81), the two cannot be regarded as the same; primary emphysema seems not to be simply an accentuation of the aging process.

Aging, like primary emphysema for that matter, is an atrophy which usually involves the whole of the acinus and affects the whole of the lung. There are two further types of emphysema, paraseptal and centriacinar, to which atrophy would seem to be the key and in which certain parts of the acinus are particularly affected. One suspects that the anatomical arrangement peculiar to these regions may be responsible. It is those parts of the alveolar walls which are not "buffered" by adjacent lung as in the central part, or against fibrous tissue and therefore "isolated", that tend to develop this type of emphysema.

The "peripheral" may be designated periacinar but "paraseptal" is probably more appropriate since the edge of acini not clearly demarcated by fibrous tissue seems not to develop this type of emphysema.

In the central region atrophy of the free margins of alveolar walls may be associated with enlargement of the spaces lying centrally in the acinus—centriacinar emphysema.

It is likely that reduction or absence of flow through capillaries will result in their disappearance. More detailed knowledge of intra-acinar blood vessel arrangement may throw light on the question of reduced blood flow resulting from disappearance of capillaries. But it would seem that within an acinus there may be shunts—some of the branches being larger and more capable of carrying the blood through faster than the side branches (p. 29), which are by-passed.

Destruction also means loss of substance but, whereas in the case of atrophy we are ignorant of its cause, destruction in pathological terms means interruption of a surface and implies a known cause.

OVERINFLATION

In overinflation the alveoli are essentially normal but have become enlarged. The cause is thus a simple mechanical one. Two types of overinflation can be distinguished. The first is exemplified by compensatory emphysema; as there is no obstruction to ventilation the normal alveolar volume and pressure changes occur throughout the respiratory cycle. In the second, overinflation follows a ball-valve obstruction in the airways to a lobe whose ventilation is obstructed, as the result of which the normal alveolar volume and pressure are disturbed.

Although both forms of overinflation may similarly affect alveolar size their effect on vascularity of the lobe would seem to be different. Lobes overexpanded to the same degree by the two types appear different radiographically. If there is ventilatory obstruction in addition, the lobe will appear transradiant and with small vessels, whereas a lobe overinflated

but without ventilatory obstruction shows normal transradiancy and vessels of normal calibre. The transradiancy reflects an alteration in the air/tissue ratio, probably explained by a reduction in vascularity. The narrowed vessel reflects either reduced blood volume or blood flow—the consequence of ventilatory disturbance.

Overinflation may cause tearing but, to judge from resected specimens in cases of childhood emphysema, the alveolar volume may increase three- or four-fold without causing tearing.

Compensatory overinflation with normal ventilation may produce hypertrophy (see p. 298); whether over a long time the reduced vascularity associated with impaired ventilation and compensatory overinflation leads to detectable atrophy is uncertain.

DESTRUCTION

Destruction also means loss of substance but, whereas in the case of atrophy we are ignorant of its cause, in the case of destruction there is either clinical evidence from which the cause can be deduced or pathological evidence of the way in which the damage has occurred.

It would seem justified to divide complete from partial destruction. "Complete destruction" of the alveolar wall is ulcerative in the general pathological sense of ulcer, as an interruption or tearing, associated with loss of integrity of alveolar architecture; in "partial destruction" there may be loss of alveolar wall substance, particularly from damage to capillaries, but the architecture may still be intact even if the alveolar outline becomes simpler. The difference between the two types is partly a difference in scale.

In complete destruction a "hole" may be visible either to the naked eye or only on microscopic examination. This most commonly arises from infection—from proteolytic enzymes of pus cells or bacteria. Further details are given in the account of the damage of infection in bronchitis.

The pathological details of "partial" destruction still await elucidation. Conditions such as sarcoidosis or pneumonic infiltrations leave lung architecture broadly intact but with a loss of alveolar surface and of capillary volume. This is presumably the result of an alveolitis in which the inflammation has resulted in local damage to the capillaries; the wall may be as thin as a normal alveolar wall but probably contains more collagen. Inflammatory changes may not only cause a direct loss of the capillary bed but, with abatement of the inflammatory process associated with closure and atrophy of capillaries, the pre-existing capillaries of the part seem to be also affected.

A more detailed discussion of this is included in Chapter X on scar emphysema (see p. 193).

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Chapter XVIII

EXPERIMENTAL PRODUCTION OF EMPHYSEMA

WHILE understanding and treatment of disease often follow on the discovery of a means of producing it experimentally, this has hardly been the case with emphysema. This is largely because it has so often been assumed that it is enough to produce abnormally large air spaces, ignoring the mechanisms which can cause the disease in man, and whether there is disability and, again, whether the disability is reversible.

Without these last considerations the experimental production of emphysema in the artificially narrow structural sense indicated above may have little relevance to the real disease.

While emphysema is basically defined as abnormally large air spaces, its production experimentally, if it is to have any value at all, must be considered from the standpoint of the clinical manifestations and the four basic mechanisms operating in man—hypoplasia, atrophy, overinflation and destruction—and of the resulting functional behaviour of the lung.

Thus, to relate experimentally produced emphysema to human clinical problems it is essential to know from each experiment:

(*a*) whether abnormally large air spaces are produced;
(*b*) if they are, whether this condition is irreversible;
(*c*) what mechanism is responsible;
(*d*) what functional impairment arises; and
(*e*) the type of human emphysema it resembles.

Very few experiments have provided the answers to these questions; some of the more important are considered below.

HYPOPLASIA AND ATROPHY

The literature discloses no case in which experimental emphysema has reproduced the effect of hypoplasia as seen in man; nor are there examples of what can be called simple atrophy (see below, Strawbridge, 1960*a*, *b*, *c*).

DESTRUCTION—PARTIAL

Partial damage to alveolar walls can be illustrated by the application to mice of NO_2 adsorbed to carbon. Boren (1964) exposed mice to NO_2 adsorbed to carbon, and to carbon and NO_2 separately; in the first group, and only in this group, a loss of alveolar wall structure was produced with-

out evidence of inflammation. It would seem from this report that there could also be an increase in alveolar size, but it is not known whether this caused air-trapping or produced any detectable functional disturbance.

Kleinerman and Wright (1962) exposed guinea-pigs, rabbits and rats intermittently to NO_2 for periods up to 21½ months and produced dilatation in the region of the respiratory bronchiole in the guinea-pig only. The terminal bronchiole was patent and free of fibrosis and the distal alveolar ducts were normal. These authors' brief report emphasises the similarity to centriacinar emphysema in man but does not say whether the lungs trapped air.

Thurlbeck and Foley (1963) have administered cadmium chloride to guinea-pigs by intratracheal injection. Haemorrhage and oedema were seen after one injection and, after several, the lung became condensed into scars, around which were thin-walled overinflated alveoli, an example of scar emphysema. There is no mention whether in the later stages the lungs trapped air, but the fact that they needed to be inflated in preparation for microscopic examination suggests that they did not.

With the current interest in auto-immune phenomena and their possible role in disease, attempts have been made to produce emphysema with lung antibody. Experiments producing immunological damage have not yet succeeded in this, but whatever damage does occur would probably fall within the "partial destruction" group, since it is predominantly an allergic pneumonitis (Crowle, 1959; Balchum *et al.*, 1964). Circulating antibodies to human lung have been detected in patients with lung disease, and at higher levels of concentration than in controls (Hennes *et al.*, 1961; Balchum and van Dyke, 1964). Homologous normal lung tissue has been used (Crowle) as well as "damaged" lung taken from animals after heavy exposure to NO_2 (Balchum *et al.*, 1964). Scheel and his colleagues (1959) reported that ozone reacts on the protein of rabbit tissue to form an antigenic structure. These findings are not conclusive; to date emphysema has not been produced by the use of lung homogenates.

Strawbridge (1960*a*, *b* and *c*) injected into the ear vein of the rabbit Caledon blue R.C. (an anthroquinone dyestuff) insoluble in water and giving particles, size 10–25 μ, which lodged in capillaries and precapillaries. The presence of emphysema was judged microscopically by the presence of alveolar fenestrae characteristic of the naturally occurring changes. Unfortunately here also there is no mention of air-trapping, so that if, as the author claims, "atrophy" has produced large air spaces, this gives no indication of the type of emphysema it resembles.

COMPLETE DESTRUCTION

Complete destruction is illustrated in two series of experiments; in one the large air spaces are produced by mechanical tearing, in the other by infection.

Mechanical Tearing

Moolten (1935) used bronchoscopy forceps to punch holes in lungs, "to produce cavities mechanically". Although this can hardly be considered a re-enactment of what happens in disease the result is similar to the appearance of lung in emphysema with complete destruction. In lungs from human subjects and from cows, Moolten produced mechanical laceration in bronchial walls and surrounding lung, lacerating the tissue in some and in others punching out varying amounts. The lobes were then inflated, in the human lungs a suction pressure of 20–30 cm. of water being used. Where the laceration was along the bronchial wall the resulting cavity was elongated and tortuous, an extension of the bronchus. Where a "measurable amount of lung tissue" was removed balloon-like cavities of large size were produced, sometimes showing ridges of thin tightly stretched bands of fibrous tissue or vessels. The cavities had a definite wall caused by a narrow zone of collapsed lung and their final size varied with the pressure rather than the amount of lung removed initially. It was in the sub-pleural region that Moolten found the maximum bulging of lung with inflation. With deflation, he says, the cavity "decreased proportionately" but did not return to its pre-inflation size unless suction was used.

The connective tissue septa in the cow's lung are much more numerous than in man, the lobules being completely surrounded by connective tissue; for this reason the cow commonly suffers from interstitial emphysema throughout a lobe. It was doubtless a collection of air in one of the septa that gave rise to Moolten's finding in the cow that, on occasion, a cavity refused to deflate no matter what pressure was applied. On section, he found that such cavities, often the size of a billiard ball, were within the interstitial tissue of the lung.

Moreover, histologically the narrow zone of collapsed lung was found to consist of alveoli, connective tissue and "flaring openings of small bronchi". In most cavities two or more draining airways were found without any appearance of valve-like narrowing; in fact, they seemed to enter the cavity by funnel-shaped openings. In the literature the absence of any structural narrowing is often stressed, which implies that there is no airways obstruction; but this overlooks the possibility that such unsupported airways have the structure of and, doubtless behave as, "flap-valves" (Reid, 1958).

Moolten concludes that "any solution of continuity in lung tissue produces an area of lowered resistance to inflation", a region of increased compliance. Discussing the spherical contour of the holes, he quotes Reinders' finding (1928) that in sheets of rubber any laceration assumed a round shape; similarly, the elastic pull of surrounding normal lung produces a recoil from the area of dissolution.

With known interruption of continuity—"complete destruction"—the

retraction of surrounding lung has produced holes larger than can be accounted for by the original loss of tissue, holes roughly spherical in shape and lined with compressed lung tissue. Ridges containing blood vessels and fibrous septa are seen in cases of human emphysema also.

INFECTION

In the second destruction type the cause of the ulceration is infection. Studying the effect of chemotherapy on tuberculosis in rabbits, Steenken and Wolinsky (1957) stated that "bullae or cyst-like" spaces developed only in those animals given chemotherapy. As these spaces are within the alveolar region of the lung they do not represent airways and, not being walled off by fibrous tissue, are an example of emphysema.

In two-thirds of the animals successfully treated with chemotherapy, bullae were seen in the radiographs between three and eight weeks after treatment was started, in a region where there had previously been caseous foci. It seemed that a caseous focus had evacuated itself leaving a space not yet walled with fibrous tissue and lined only by ragged alveoli. When, at autopsy, the lungs were inflated and the pressure in the trachea then released, the lung tissue deflated although air remained trapped in the bullae. The wall of these spaces consisted of a few compressed alveolar walls without cellular reaction. Steenken and Wolinsky ascribed the cause to inflammatory reaction in the bronchus acting as a check valve mechanism. With continued antibiotic treatment many of these holes disappeared.

Bell (1958) and Yesner *et al.* (1960), also produced similar emphysematous changes by tuberculous infection.

Enzyme Digestion

In a preliminary report Gross *et al.* (1964) describe the development of centrilobular emphysema in rats as the result of intratracheal injection of papain and quartz dust, the papain seeming to be the significant inoculum. The changes were not confined to the centrilobular region. It would seem from the illustrations that ulceration of alveolar walls occurred without inflammatory infiltration or fibrosis.

OVERINFLATION

A large number of experiments have been concerned with some form of overinflation, especially with overinflation without airways obstruction, and have reproduced compensatory emphysema. With the extension of thoracic surgery in the thirties and forties the surgeon was anxious to know the effect of overinflation on the remaining lobe or lung after resection. Did the lung simply overinflate or was there hypertrophy as well,

and if there was, were both airways and alveoli affected? In the last century interest was also shown in changes exemplifying the general features of hypertrophy in relation to the lung.

Overinflation Without Airways Obstruction

Overinflation of lung without airways obstruction has been produced by:

(*a*) allowing residual lung to overinflate after resection;
(*b*) plicating the diaphragm to increase the volume of the thoracic cage.

Hyperventilation is included in this section.

Lung Resection

Haasler (1892) excised the left lung from a week-old puppy and found that after six months the right lung filled the thorax; as it showed a histologically normal structure with alveoli of normal size and normal epithelium he considered it "a true hyperplasia in Virchow's sense of the word".

Rienhoff and his co-workers (1935) performed left pneumonectomy in 10 adult dogs. They set out to find whether the residual lung would show (*a*) hypertrophy, (*b*) hyperplasia, (*c*) emphysema (by which they meant torn alveolar walls), or (*d*) simple dilatation of pre-existing respiratory units.

The lungs were fixed *in situ*. Bronchial generations were counted but no increase in the number of bronchial branches was found. The number of alveoli in a given field was measured and, whereas 101–105 was the range of the mean figures for the control animals, after resection the range was 66–68. The mean alveolar diameter was also determined, for the normals the range being 75–82μ and for operated animals 125–140μ. The lungs showed dilatation of respiratory bronchioli and dilatation but no tearing of alveolar walls and no increase in the number of airways. No indication of the functioning of the lungs is given.

Cohn (1939), by assessing the weight of the exsanguinated lobes of rats, followed the effect on growth of various procedures which altered volume. He found that the weight of the residual lung increased rapidly after resection. This points to an increase in tissue bulk, not just a stretching of pre-existing structures.

Bremer (1937) excised one lung from a cat and one from a kitten a week old. Normally the alveoli are the same size in both, but after excision the remaining alveoli in the adult cat became abnormally large—evidence of overinflation. In the kitten, even after a month, there was evidence of new alveoli. This could be normal postnatal growth.

Longacre and Johansmann (1940) described a series of resection

experiments in the dog, designed to compare the fate of residual lung in animals operated upon as puppies and as adults and to determine how effectively residual lung bore the additional strain. Two types of measurement were taken as an index of lung efficiency. The first was the swing of intrapleural pressure; as this became less negative it was considered to indicate reduction in recoil of the remaining lung. In the normal dog the swing is from −5 to −9 cm. H_2O; in animals four years after pneumonectomy the swing in animals operated upon as puppies was −3·5 to −6·5 cm., while in those from which lung was removed as adults −4 to −7 cm. H_2O.

The second measure of cardio-respiratory reserve took into account oxygen saturation as well as disturbance of heat mechanism on enforced exercise. Immediately after pneumonectomy function was found reduced by 50 per cent, but within nine months 75–80 per cent of this had been recovered. During the following 2–3 years, function in the "adult group" fell away somewhat.

On opening the thorax it was found that the residual lung had herniated across the mediastinum to occupy both sides of the chest. The mean diameter of alveoli was 116μ for the normal puppy and 106μ for the normal adult dog. In animals operated upon as adults 129μ was the mean alveolar diameter while in those operated upon as puppies it was below the normal—93, 96 and 104μ being the figures for the three animals. This points to hyperplasia of alveoli in those operated upon as puppies. In the adult operated group the authors describe "a breaking of alveolar walls". Hartroft (1945) suggests that such an appearance could arise from dilatation rather than tearing.

From the ability of these animals to perform hard exercise after resection it is unlikely that there was any air-trapping, or that the pulmonary circulation was unable to deal with the excess of blood. These aspects of function are not mentioned.

The experiments seem to suggest that in rat, cat and dog the expansion of residual lung after resection in the adult gives abnormally large air spaces in the residual lung; if the overinflation has started in young life there is an increase beyond the normal complement of alveoli as well as in the volume of tissue—hyperplasia of alveoli as well as hypertrophy. The function of the residuary lobes in the adult even after resection would seem surprisingly good.

Plication of the Diaphragm

By plicating the diaphragm in dogs Paine (1940) increased the volume of the thorax. This doubtless increased the volume of alveoli but any increase would be slight compared with that following resection. There is no evidence that disability or air-trapping develops, that, in other words, the effect simulates disabling human emphysema.

Low Oxygen Pressures and Hyperventilation

Various experimental methods have been used the effect of which cannot be said to increase the alveolar volume beyond normal, though by increasing the mid-respiratory volume they simulate one feature of emphysema with air-trapping. Campbell (1927) thought "emphysema" had followed acclimatisation to low oxygen pressures; and Prinzmetal (1934) claimed to have produced it in rats by keeping them hypoxic in low pressure atmosphere. Chillingworth and Hopkins (1919) placed animals under a negative pressure in a body plethysmograph; in other animals (1920) insufflation by positive pressure was carried out through an endotracheal tube. Rasmussen and Adams (1942) also increased depth of inspiration by positive pressure insufflation without increasing lung volume or causing airways obstruction. They obtained no evidence to support the "inspiratory theory" of emphysema, i.e. that repeated forcible inspiration is the cause of disabling emphysema.

Overinflation with Airways Obstruction

Mechanical Obstruction

In another group of experiments overinflation is produced by obstructing respiration, the result of which is that lung volume may be larger than would be achieved on normal respiration.

The placing of valves in airways can be used to impede either inspiration or expiration, the latter being more often studied. If expiratory resistance is increased the functional residual capacity of the lung may be increased (Comroe *et al.*, 1962). While such valves are in place the chest will clearly expand and operate at an increased mid-respiratory volume.

It has not been substantiated that valves produce irreversible changes in the lung, that on removal "emphysema" persists. To assess the significance of these experiments for human disease the structure of the alveoli after the valve has been removed must be known and whether, if any changes persist, there is still airways obstruction. Usually only the behaviour of the lung while the valve is in place is known, although often the reports do not say whether the valve is in place or not.

Facial masks with valves produced no overinflation (Schall, 1909). Tracheal stenosis in the rabbit by partial ligation was reported by Köhler (1877) and Nissen (1927) as producing alveolar dilatation.

Harris and Chillingworth (1919) described an attempt to produce piratory obstruction. In twenty-five dogs a ball-valve was introduced into the trachea and the animals were sacrified at times varying from twenty-four hours to three weeks. No blocking of the trachea with mucus was found. The thorax gradually enlarged and became prominent. Exercise or the presence of atmospheric irritants increased dyspnoea; the former,

particularly, resulted in slower deeper breathing and a striking change occurred in expiration which was forced, prolonged and incomplete.

When the animals were sacrificed it was found that the gross appearance was "that of human emphysema". The lungs were distended with no tendency to collapse; evidently the ball-valve was still *in situ* as the authors make no mention of its removal. The organs were pale and there was "distinct vesicular wall rupture" with small bullae particularly over the anterior edges. The alveolar walls were thin. The reduction in blood flow which affects a lung in which expiration is obstructed has already been mentioned and the appearance of these lungs could reflect the avascularity (p. 127). The tearing of alveoli is probably real, although some of it may be accounted for by the ragged appearance usually seen in overinflated alveoli (Hartroft, 1945). Harris and Chillingworth are still concerned with the relative claims of the "inspiratory" and "expiratory" causes and conclude that it is the degree and duration of impediment to expiration which is most important. Unfortunately their illustrations of the "emphysematous alveoli" are not convincing.

Krahl (1959) produced "emphysema" in the rat by placing a ball-valve in the bronchus of the right lower lobe. On resection the lobes were pale and the alveoli dilated microscopically, but the behaviour of the lobes when the valves were removed is not stated.

Hinshaw (1938) left a valve in place for some months and Friedman and Jackson (1917) in the trachea in dogs for only a few hours under an anaesthetic. In both cases the lung volumes were increased. Kountz *et al.* (1929) produced in the dog an interstitial emphysema by considerable tracheal obstruction.

Paine (1940) placed a hinge-valve in the trachea. He estimated the distensibility coefficient of the lungs and found, immediately on removal of the valve, that distensibility had increased; what he measured, therefore, was really the behaviour of lung behind an obstruction rather than irreversible changes to the lung. Experiments with airways obstruction are of some interest in relation to the comment above that the blood flow to alveoli is impeded by the presence of airways obstruction. Paine has measured the increase in the distension coefficient associated with this and found that reduced vascularity leads to increased compliance.

The disadvantage of ball-valve experiments lies in the fact that an expiratory obstruction will alter the mechanics of respiration and of the blood flow to the part. Emphysema caused by expiratory block is relevant to disabling emphysema in man only if airways obstruction persists when the valve has been removed.

Valve experiments must be concerned with at least a lobe if distension behind the block is to be uniform, in view of the operation of collateral respiration (van Allen *et al.*, 1930; van Allen and Jung, 1931). In most experimental reports both lungs have been obstructed.

It would seem that no clear answer can be given to the question whether or not the presence of an expiratory obstruction can give rise to emphysema which would prove to be irreversible notwithstanding the removal of the obstruction, and whether there would be resultant air-trapping. That recurrent attacks of status asthmaticus and chronic bronchitis with airways obstruction can be found with virtually normal alveoli shows that airways obstruction does not necessarily cause emphysema in man. What is less certain is whether in those cases of chronic bronchitis which develop emphysema, airways obstruction has contributed to it.

Muscle Spasm

A further series of experiments have produced overinflation of the lung associated with muscle spasm. This simulates asthma and as the alveoli are not increased above the size achieved in deep inspiration the overinflation is not accepted within the definition of emphysema. The experiments are mentioned here as illustrating reversible air-trapping with airways obstruction.

Brown-Sequard reported in 1885 that he had produced "emphysema" by causing spasm of bronchiolar muscle in dogs and rabbits through the stimulation of the brain stem. Earlier attempts had produced this effect by stimulation of the vagi, but the advantage of brain stem stimulation was that forced inspiration or expiration was avoided as the thorax was not opened. Lungs treated in this way "trap" air but current opinion would not accept the alveoli in these lungs as emphysematous.

Auer and Lewis (1910) in their study of anaphylaxis in the guinea-pig noted that the lungs did not collapse when the chest was opened and were "in the inspiratory position so that the diaphragm is pushed down". These authors did not consider emphysema a good description for these lungs, thereby disagreeing with the earlier reports of Gay and Southard (1908).

Mucus Obstruction

An increased lung resting volume has been produced by airway obstruction from an excess of mucus, resembling chronic bronchitis—in which hypersecretion of mucus is the important feature—rather than asthma. By daily exposure to sulphur dioxide, hypertrophy of the mucus-secreting cells was induced in rat lung after 6 weeks' exposure (Reid, 1963). Recently Freeman and Haydon (1964*a*) have produced a similar hypertrophy by the use of nitrogen dioxide with exposures up to twenty-six weeks of 12·5 and 2·5 ppm, while producing the increase in mucus-secreting structures, were tolerated best by the animals.

Some fibrosis occurred around terminal bronchioli after exposure but no other sign of infection or inflammation was usually seen. Animals which died twenty weeks or more after the beginning of exposure showed strikingly voluminous lungs, which failed to deflate spontaneously as in the

normal and weighed more than the control. The authors describe the changes produced as "emphysema", but it would seem better to call this airways obstruction because emphysema implies that the alveolar volumes are greater than might occur during the normal respiratory cycle.

In a subsequent experiment (Freeman and Haydon, 1964*b*) the rats after long periods of exposure to fumes were removed from the noxious environment. Those killed at the height of the exposure showed voluminous lungs in which air was trapped. The behaviour of the lungs of animals killed after exposure ceased was found to have become more normal in proportion to the duration of freedom from exposure. The lung volume became less with an increasing degree of spontaneous deflation. This would seem to resemble the airways obstruction of chronic bronchitis without structural emphysema. It is significant that the air-trapping was at least in part reversible.

Overinflation combined with Chemical Damage

Anderson and his colleagues (1964) produced hyperinflation in a group of greyhounds by an intratracheal venturi valve; no more emphysema was found in them than in the controls. In another group hyperinflation was combined with inflammation produced by intratracheal installation of a dilute solution of nitric acid (30–50 ml. of a 1 per cent solution) which produced a peripheral effect from the nitrogen dioxide liberated. There was more emphysema in this group and also alveolar fibrosis.

PULMONARY ARTERY OBSTRUCTION

Experiments dealing with pulmonary artery flow and the effect of obstruction are relevant to problems of emphysema because, although the disease is not exactly reproduced, a particular aspect of the appearance of the lung in emphysema is shown.

Experimental studies in dogs have indicated that the capacity of the small blood vessels is such that a several-fold increase in blood flow may be accommodated with negligible pressure changes (Drinker *et al.*, 1926; Brofman *et al.*, 1957). Thus the effect of resection of part of the lung does not significantly alter the resistance to flow. The flow increase may account for the arterial muscle hypertrophy reported in resection experiments (Bremer, 1937).

Obstruction to a pulmonary artery has little effect on the capacity of the opposite lung to deal with the additional flow. As regards the deprived lung, a main pulmonary artery embolus in man cannot usually be detected radiologically (Simon, 1964); that is, an arrest of pulmonary artery flow does not alter the vascularity of the lung—the bronchial artery and pulmonary veins seem to readjust.

Bloomer *et al.* (1949) have traced experimentally the great expansion

in bronchial circulation which occurs after ligation of the pulmonary artery, with no interference with air flow to the lung.

By contrast, Rosenberg (1952), studying unilateral "collapse" of the lung (the lobe was not massively collapsed but rather "relaxed"), left the bronchus open but tied the lung in a cotton mesh, thus interfering with ventilation. Although air remained in the lung it showed only 3 per cent of normal function. No great increase in the size of bronchial vessels occurred even in animals which lived three months after operation, although a marked reduction in pulmonary artery blood flow through the constricted lung was shown in life; the pressure in the main pulmonary artery was not elevated and, presumably, the peripheral resistance in the unaffected lung was decreased while that in the constricted lung was increased. Soon after operation the intrapleural pressures were abnormally negative but, ultimately, they returned to normal with the distension of the normal lung to fill the thorax—further evidence of the compensatory change in the contralateral lung. In unilateral transradiancy the bronchial arteries to the affected lung are not greatly dilated, although the pulmonary artery flow is reduced; nor is there clinical evidence of a shunt from left to right through the lungs. The impairment of alveolar ventilation seems to reduce pulmonary artery flow and prevent any major increase in bronchial flow.

Cloetta (1911 and 1913) showed that alveolar distension decreased blood vessel calibre and flow through the capillaries. Riley (1959) and his colleagues (Permutt *et al.*, 1961) have also shown recently that the capillary blood flow is maximal during the expiratory part of the cycle, while it is during the inspiratory part that the more proximal arteries are filled.

Fouché and d'Silva (1960) were concerned to show the basis of the narrowing of pulmonary arteries in unilateral emphysema. In each of fifteen cats they injected one pulmonary artery with starch emboli 20μ in diameter. Hourly angiograms were carried out for three hours, then the animal was killed and an arteriogram made of the specimen. The angiogram to the affected lung in 10 of the 15 showed progressive reduction in flow and narrowing of the large arteries. The authors describe this as vasoconstriction, but it may be that the shadow cast by an artery is in part the result of the blood flow and pulsation. In the proximal arteries no block was seen in the specimen arteriogram, which would appear to indicate that reduction in peripheral flow produces reduction of flow through proximal arteries—perhaps by vasoconstriction.

NATURAL EMPHYSEMA IN ANIMALS

Reference may be made here to naturally occurring emphysema in animals.

In a study of the lungs of seven horses which had been diagnosed in life as cases of heaves, Thurlbeck and Lowell (1964) failed to find any widespread emphysema. The main features were a bronchiolitis with

excessive mucus within the bronchial tree and plugging of small airways. In addition there was an eosinophil infiltration often widespread and severe. On the basis of these findings and the fact that exacerbations are usually associated with the feeding of dusty and mouldy hay, he agreed with Alexander (1959) that the condition resembled the human condition of farmer's lung.

However, it would seem that insofar as there is excessive mucus and airway plugging, the condition resembles chronic bronchitis, but these features are not usual in cases of farmer's lung. The element of airways obstruction, in addition to the allergic element may explain the respiratory disturbance from which the animals suffer. Alexander (1959) had illustrated patchy areas of microscopic emphysema irregularly distributed within the lung. These may have followed scarring from granuloma such as in farmer's lung or may represent the end stage of bacterial damage. It would seem that the condition comes closer to chronic bronchitis than to emphysema. Right ventricular hypertrophy seems a not infrequent finding in these animals.

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Appendix A

EXAMINATION OF LUNG

IT is essential for satisfactory examination of the lung that it be fixed in the inflated position. A variety of suggestions have recently been made as to the pressure at which lung should be inflated, the medium to be used for fixation and whether the lung should be fixed dry and so on but, although these may sometimes be useful, for purposes of special investigation and certainly for adequate routine study, inflation and fixation are the twin requirements.

Removal of Specimen

In relation to operation specimens surgical technical considerations will determine the length of the bronchus and so on. Examination of the specimen is greatly helped if the surgeon leaves ligatures long and of different colours on artery and vein, especially if it is planned to inject them, as the blood vessels on cutting retract far into the lung.

If the specimen is taken at autopsy not only should the pleura be preserved intact, but also an adequate length of bronchus or pulmonary artery. If, as may happen, the pleura has been damaged, small rents may be repaired by covering them with artificial skin such as is used in wound dressing ("Nobecutane"), if necessary, with gauze reinforcement (Millard, 1964).

It should be standard practice, certainly in cases of chronic bronchitis or emphysema (see p. 158), to examine the main bronchus microscopically and accordingly a cuff of bronchus should be taken for section before further manipulation.

Aspiration of Mucus

Particularly in fatal cases of chronic bronchitis pus and mucus in large airways may interfere with the preparation of the lung, in which case aspiration of the secretion, by means of a catheter attached to a water pump from a laboratory tap, can be carried out with little trauma. In asthma this may not be possible and fixation fluid may be introduced through the pulmonary artery or vein.

Inflation and Fixation

If no injection techniques are to be employed, for routine purposes inflation and fixation are best achieved by the intrabronchial inoculation of fluid fixative. Formalin (4 per cent formaldehyde) is satisfactory for this

and can be run into the lung from a bottle, placed on a shelf 18 in. above the bench, through rubber tubing which can be compressed by a clip. A catheter attached to the end makes injection easier as it can be inserted into lobar and segmental bronchi. The fluid is allowed to run in until the edges of the lung are rounded.

The lung is then placed in a bowl of formalin in which it can float freely, the bronchus being packed lightly with cotton wool to prevent the formalin escaping too easily. The lung should be covered by a piece of gauze or a thin layer of cotton wool to prevent its surface drying. It is usually fixed for a week before being cut, although two or three days are probably adequate (Aspen Conference, 1959).

To localise small lesions in the lung or to investigate structures responsible for particular radiographic shadows, fixation by formalin vapour (Cureton and Trapnell, 1961) is easy and renders the lungs suitable for radiography. The vapour is obtained from a carboy containing 40 per cent formaldehyde at a pressure of 40 mm.Hg. A rubber bung is tied firmly into the main bronchus and through it a transfusion needle is introduced. It is essential that the bung be airtight and that the inflation be made slowly—about twenty minutes for a whole lung. The needle is then removed and, with the bung still in place, the lung is floated on formalin solution for 48 hours. The lung is then satisfactory for radiography; it can be cut and will maintain its shape. Microscopy also is satisfactory. This is an easy method of dry fixation and has most of the advantages of more complicated techniques. Dry fixation may not be satisfactory if there is much fibrosis or infection in the lung.

Dissecting and Slicing Lung

With certain specimens, particularly operation specimens, the way in which the lung is examined will depend on what one is looking for and on the expected diagnosis. Tracing the bronchi of each segment may be the major interest, in which case the insertion of two or three probes into main airways will ensure that the plane of slicing will expose a considerable length of large airways near the hilum. If necessary further dissection can be made with scissors.

If disease is widespread throughout a lobe or lung its distribution is best assessed by cutting the lung into slices 1 cm. thick. This can be done by surrounding the lung with four strips of cork, 1 cm. deep, along which a knife can be guided. A model can be made in perspex or other material with the ribs to guide the knife attached or adjustable to vary the thickness of the slice (Silverton, 1963).

Comparison of Specimen with Radiograph in Life

Whether the lung is placed hilum up or down does not much matter but cutting is usually easier if the hilum lies uppermost. In life the hilum

points more or less antero-medially, whereas after fixation the mediastinal surface points medially. For comparison with a postero-antero radiograph or tomogram the slice should as nearly as possible be coronal; with a lateral view, the slice should be sagittal and run from apex to base.

PULMONARY ARTERY INJECTION

For pulmonary artery injection the lung must not have been previously fixed. It may be kept for a few days in a refrigerator at a temperature just above freezing, but if it is necessary to keep it longer it should be deep frozen. Lungs can be kept in deep freeze for months and be satisfactory for injection as well as histological examination but, in such cases, they must be thawed completely before injection. This is ensured by transferring them to a refrigerator at 0° for three days, then leaving them at room temperature overnight and finally placing them in an incubator at 40° for one hour.

Clots in the main pulmonary arteries can be removed by manipulation and gravity, but washing the lung with saline will not force clots forward and has the disadvantage that the lung becomes waterlogged.

Before injecting the pulmonary artery the lung can be inflated under negative pressure. Positive pressure can be used with little damage to lung if it is applied intermittently.

Injection Medium

A barium-gelatine injection mixture is suitable as it permits microscopic examination and is also radio-opaque. The mixture used is as follows:

500 ml. "Micropaque" (Damancy & Co.)
(as used in clinical gastro-intestinal radiology)
50 grams gelatine powder (Hopkin and Williams)
200 ml. water
A few menthol or phenol crystals.

The gelatine is dissolved completely in warm water and the "Micropaque" is then added slowly, stirring meanwhile. Finally the menthol crystals are added. If the neck of the flask in which this medium is stored is plugged with cotton wool it can be kept for weeks at room temperature. Using Short's method (1956) this medium penetrates to vessels between 10 and 30μ. With a thread and needle a ligature is sewn right through the wall of the pulmonary artery or in the adventitia (Millard, 1964) thereby avoiding leakage through needle holes. A cannula is then tied into the pulmonary artery. The medium at a temperature of 60°C. is injected at a pressure of 120 cm. water, which is maintained for seven minutes. It is better to use the same pressure for both normal and diseased lungs. The use of hypertensive pressures would perhaps underestimate the differences but certainly not exaggerate them. If the medium cools too quickly, the injection may be inadequate and therefore it is important to have the lung

warm. The cannula is plugged and the injection medium allowed to set. (The lung can be radiographed either at this stage or after formalin fixation.) It is then fixed by intrabronchial inoculation of formalin or by formalin vapour and sliced in the way described above.

Radiography

The whole lungs or slices illustrated in this book were radiographed using a tube film distance of 36 in. For slices, 40 KVP, 5 ma and 2 seconds were used, for whole lungs 45 KVP. Kodirex or Ilfex films are suitable. The specimen is placed on a thin sheet of celluloid, made from a cleared film, with the unexposed film beneath.

Bronchial Artery Injection

Bronchial arteries can be injected in the same way as the pulmonary arteries but it is difficult to find the arteries and to get a sufficiently wide bore cannula into them; for this reason it is best to remove the whole thoracic block and inject the bronchials through the aorta, having clamped the other side branches and the cut aortic ends (Turner-Warwick, 1963*a* and *b*).

If broncho-pulmonary anastomoses have opened up, the bronchial artery will, of course, fill from the pulmonary arteries.

BRONCHOGRAM

Whereas the capillaries and small blood vessels offer a natural obstruction to extreme peripheral filling of arteries, filling of the airways can easily cause flooding of the alveoli. This overfilling does not matter much if it is hoped merely to pick out diseased areas, but detail in the unaffected regions may be obscured. Injection under fluoroscopy until the bronchioli are outlined, is probably the easiest way of controlling the degree of filling.

Bronchography is usually valuable to show regions of bronchiolar disease, as in Figs. 65 and 66. To choose lesions deep in the lung for sections, a parallax method can be used to localise the lesion (Reid, 1955), after inserting a pin into the lung, provided it is parallel to the film.

OTHER METHODS

Casts, while excellent to show distribution through the lung and as illustrations (Tompsett, 1952, 1954 and 1956), have the disadvantage for research that detailed microscopy is not possible; but if the disease has been diagnosed microscopically, casts give an idea of overall distribution of any pathological change.

Whole lung paper sections (Gough and Wentworth, 1949) are valuable

to indicate the localisation and amount of coloured dusts. It is also easier to store a slice of lung mounted on paper than floating in formalin.

In addition to the techniques mentioned here the use of a wide variety of methods of preparing lungs has been advocated—drying techniques with air, Tobin, 1952; Oderr *et al.*, 1958; Pratt and Klugh, 1961; Pratt *et al.*, 1961; formalin fume fixation, Blumenthal and Boren, 1959; formalin and alcohol fume, Jones, 1960; and formalin steam, Weibel and Vidone, 1961; Greenberg *et al.*, 1964. For particular research some of these may have an advantage, but any impression that exotic techniques are necessary for worthwhile examination of the lung is quite unjustified. Barium sulphate impregnation has been used by Heard (1960) to reduce the translucency of lung and facilitate examination of lung slices.

MEASUREMENT OF THE EXTENT OF LUNG CHANGE

The perennial problem of describing how much lung is affected by any change has recently reasserted itself in the numerous attempts to correlate "the amount of emphysema" with the disturbance of respiratory function, this has usually meant estimating the air/tissue ratio. Unfortunately, as has been indicated earlier (p. 51), the size of the air space has little to do with the disability produced.

The amount of emphysema may be estimated by covering the slice of lung with a grid ruled into 1 cm. or 1 in. squares. The emphysema in each square is graded and from this a figure for the whole lung slice is derived. It would seem, however, that the air/tissue ratio alone is not a satisfactory criterion and this method has not thrown much light on the problem of disability in emphysema. The type of emphysema must first be taken into account.

A grid can be of help also in establishing the area of lung affected by a given type of emphysema. Using a grid with 1 in. squares and estimating by inspection the fraction of the area affected, it has been shown that one-half to two-thirds of the area of a slice of lung was affected in cases showing the radiographic changes of emphysema (Reid and Millard, 1965).

The use of the point-counter method has been applied by Dunnill (1962, 1964) both to normal and diseased lungs. The results he obtained with normal lung will be referred to later (p. 339). In centriacinar emphysema he has used these methods to count the number of lesions within a lung—in panacinar he has suggested that the overall reduction in the number of alveoli is slight. The statistical basis for the study of the morphometry of the lung has recently been described by Weibel and Gomez (1962).

Sweet and his colleagues (1961) analysed the presence of panlobular and centrilobular emphysema in large lung sections from 194 cases. They used a grid method and grouped the cases as centrilobular, panlobular, and combined centrilobular and panlobular. In thirty-six cases pulmonary

function studies had been carried out. They found that the "average percentage emphysema in lung" was fifty-four in a group of forty-three cases in which emphysema caused death. In the group "emphysema contributing to death", the figure was 35 per cent.

The striking thing is the range in the forty-three cases in which death was ascribed to emphysema, i.e. the assessment of the amount of emphysema ranged from 10 per cent to 80 per cent. In six of the cases it was 35 per cent or under. These figures suggest that disability is not related simply and directly to the amount of emphysema present.

In an earlier paper Sweet and his colleagues (1960) had correlated the amount of emphysema revealed by a macrosection with certain respiratory function tests carried out during life. These included vital capacity, total lung capacity, residual volume, maximum breathing capacity, oxygen consumption per litre of air ventilated and alveolar nitrogen percentage after seven minutes of oxygen breathing. The results were available in thirty-one cases who died from a variety of causes. In twenty, one lung only was available. The lungs were fixed with 10 per cent formaldehyde introduced at a pressure of 20 cm. H_2O. After fixation, 1 in. thick slices of lung were embedded in gelatine and frozen. Whole lung sections 250μ in thickness were then cut from the thick slices and mounted.

In all thirty-one cases multiple sections were made from separate parts of one lung, five to ten sections from each lung being examined. In eleven cases sections were available from both lungs.

To determine the percentage of lung which was emphysematous, a transparent plastic grid, ruled into 1 cm. squares, was used. This grid was placed over large lung sections on an X-ray view box and each square centimetre examined with a hand lens and graded to ten, to represent the amount of emphysematous, scarred and normal lung (e.g. emphysema four, scar one, normal five). From the totals percentages were obtained and used for correlation with the various pulmonary function studies. Later, however, these authors used only the figure for emphysema. Two investigators interpreted separately all macrosections. In all but one agreement was within 8 per cent. The correlation coefficient for the separate reading was +0·89.

The amount of emphysema estimated in the macrosections in this way showed the closest correlation with the residual volume expressed as a percentage of total lung capacity, the correlation coefficient being +0·75, the ratio of the residual volume to the normal giving a coefficient of +0·80. Both the total lung capacity and vital capacity showed poor correlation with the amount of anatomic emphysema (+0·41 and −0·4 respectively). The maximum breathing capacity showed a rather better correlation −0·62. The authors assert that "the percentage of alveolar nitrogen shows fair correlation" (+0·52), that is, the greater the alveolar nitrogen after seven minutes of oxygen breathing, the greater the degree of emphysema.

Oxygen consumption per litre of ventilation showed no correlation at all with the degree of emphysema.

As no cases present had an RV/TLC of less than 30 per cent and those between 30 and 40 per cent had less than 20 per cent macro-emphysema, the authors suggest that with a ratio of less then thirty, macroscopic emphysema is not present. The range of the findings also emphasises that it is not the emphysema alone which affects this test of lung function. In no case is any mention made of the type of emphysema.

Thurlbeck (1963) also estimated the amount of emphysema in lungs, by dividing each lung into ten zones and grading each zone 0–3—absent (0), mild (1), moderate (2) and severe (3) giving a maximum of thirty units of emphysema for each lung. On the resulting figure cases were placed in four groups, 0 units, 1–5 units, 6–15 units, 16 or more units. Of the twenty-six cases in group 4 only 80 per cent had been diagnosed in life, of the twenty in group 3 only 35 per cent. In only 50 per cent of the cases in group 4 was emphysema included on the death certificate.

Thurlbeck points out that the relationship between the clinical and anatomical state is not constant, since one of the patients with mild emphysema and four with moderate emphysema were considered to have emphysema as their major disease. The patient with mild emphysema had also a long-standing history of chronic bronchitis and at death was found to have broncho-pneumonia in addition to old and new myocardial infarcts.

In 1961, Cromie, by the grid method, analysed Gough sections from thirty patients. He was concerned to find the relationship between the degree of right ventricular hypertrophy (measured by thickness of ventricular wall) and the amount of emphysema, to test the assumption that right ventricular hypertrophy is associated with loss of lung alveoli. Whole lung sections were covered with a plastic sheet ruled in 1 cm. squares. Assessment was made by comparing a square with samples of eight standards, 0–7, 0 representing normal young lung, and grade 7 complete absence of lung marking. The mean value per square was estimated for the whole lung. The author does not analyse his results in relation to the total volume of the lung or to the type of emphysema present. His illustrations of standards show varying degrees of atrophic emphysema and no mention is made of scars although these are seen in the illustrations. Right ventricular hypertrophy was graded by inspection as present or absent, the total heart weight is given and the thickness of the right and left ventricles.

Of the fourteen patients who had mild grades of emphysema with an average rating per lung square of 1·7, right ventricular hypertrophy was present in eight; of the sixteen in the second group where the emphysema was worse, the rating was 3·5, in seven, right ventricular hypertrophy was present and in nine absent. In the first group there was little to choose as regards the amount of emphysema present between those with and those

without right ventricular hypertrophy. In the second group those with right ventricular hypertrophy had a lesser degree of emphysema. There seems no relation between the presence or severity of emphysema and the development of pulmonary hypertension.

In all these reports there is a failure to show correlation between the air-tissue ratio on the one hand and the respiratory function tests, right ventricular hypertrophy or the patients' disability on the other. This is not surprising in view of the finding of severe airways obstruction associated with chronic bronchitis, presumably arising from a suffocative bronchiolitis in the absence of any emphysema. Disability by no means implies emphysema. Furthermore, if cases of structural emphysema are considered it is clear that there may be large air spaces as in atrophic centriacinar emphysema (see p. 47), without any airways obstruction.

The correlation that has proved helpful has been between the radiographic signs of widespread emphysema and structural emphysema. But in cases with widespread emphysema, in seeking a correlation between the radiograph and lung structure the tissue/air ratio is not enough; it is necessary to take into account the type of emphysema present, its severity and its distribution.

In this latter respect Reid and Millard (1964) found that radiological evidence of widespread emphysema was associated with the presence of panacinar emphysema, of severity Grade III or IV (the latter could occasionally also be called irregular—see p. 17) and its distribution through half to two-thirds of the area of a lung slice taken through its longest diameter. Centriacinar emphysema of atrophic form or panacinar emphysema of less severity was not responsible for the radiographic picture of widespread emphysema. No case with centriacinar (destruction) emphysema sufficiently widespread was found.

ALVEOLAR LINING SUBSTANCE

Although it has not been shown to be significant in the development of emphysema, mention must be made of the surface tension-reducing substance (surfactant) described by Pattle (1955; Pattle and Burgess, 1961). He devised a simple method of estimating the amount of this substance by measuring the stability of bubbles squeezed from the lung. Clements (1957) used a lung extract in a surface tension balance to detect the presence of surfactant. There is as yet no evidence that an excess of this substance increases compliance—a hypothesis suggested by its nature. The only disease in which its effect, a deficiency, can be invoked as important would seem to be hyaline membrane of the newborn (Avery and Mead, 1959).

Brown (1965) concluded that the emphysematous lung did not differ significantly from a normal lung in its surface tension or its content of certain lipoproteins. As he used autopsy material this result must be accepted with some reservation.

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Appendix B

NORMAL STRUCTURE OF THE LUNG

CERTAIN features of the normal anatomy of the lung have been referred to in earlier chapters; they are now dealt with in more detail for their bearing on the localisation and description of all lung lesions, including emphysema, and their mechanism of development.

AIRWAYS OF THE LUNG

The behaviour of the airways in emphysema, the diagnosis of chronic bronchitis, the localisation of inflammatory changes and bronchography are some of the aspects whose interpretation depends on knowledge of the structure of the trachea, main bronchi and intra-pulmonary airways.

THE TRACHEA AND MAIN BRONCHI

The large airways are supported by cartilage. In the trachea and main bronchi the cartilage is arranged in C-shaped plates opening posteriorly, the gap containing the muscle of the trachea. Bundles of muscle fibres interlace and attach laterally to the posterior ends of the cartilage, but the regions near and between the tips of the cartilage are unsupported and are the sites at which diverticula arise.

The sub-mucosa of the trachea is thin, the cartilage plates being clearly visible through the mucosa. Anteriorly, elastic fibres are scattered irregularly, but posteriorly they are collected into dense bands running the length of the bronchus and seen as longitudinal striae on the tracheal surface.

The mucous glands overlying the cartilage are few and small but between the plates of cartilage and posteriorly they are larger and more numerous.

The main bronchi have a similar structure to the trachea proximally but, in the region where the bronchi enter the lungs cartilage is distributed round the entire circumference and consists of irregularly shaped plates (Hayward and Reid, 1952*b*). At this level the muscle also extends around the wall of the bronchus and is no longer attached to the cartilage. The submucosal elastic fibres concentrated into striae are evenly arranged around the bronchus but are narrower than those in the posterior wall of the trachea.

Fig. 148 illustrates the cartilage arrangement of the left main bronchus and shows the transitional region where the bronchus is encircled by

plates of cartilage. In other respects the main bronchi resemble the intra-segmental bronchi, described in more detail below.

The branching pattern of the segmental bronchi at the hilum and its numerous variants have been established by Boyden (1955), and its clinical importance by Brock (1954). A nomenclature and system for numbering the individual segments has been formulated by an international committee and is reported in *Thorax* (Brock, 1950). Details with summaries of variations in the pattern of branching are given by Foster-Carter (1963).

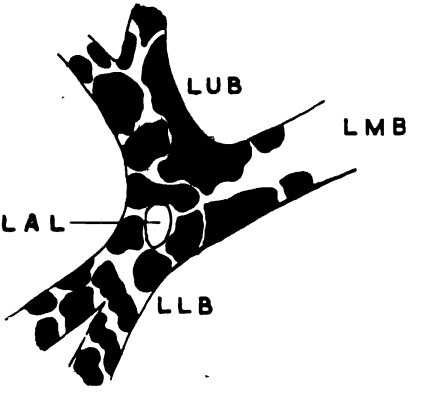


FIG. 148.—Posterior view of the arrangement of the cartilage (black) at the termination of the left main bronchus (LMB) and around the origin of the bronchi to the left upper lobe (LUB), with its lingular branch and its apical branch (LAL) and lower lobe (LLB). In the wall of the main bronchus are open rings of cartilage separated posteriorly by the membranous portion. As the bronchus branches, the rings are replaced by plates of cartilage distributed around the entire circumference of the wall. The membranous part of the main bronchus narrows progressively over its distal portion.

INTRA-SEGMENTAL AIRWAYS

The designation of airways by size is unsatisfactory since they vary with the size and sex of the subject, with the state of contraction of the muscle and the phase of inspiration. To describe airways adequately they must be designated as large or small bronchi or bronchioli and by position, that is, the number of generations from the hilum and the type of bronchial pathway of which they form part.

Axial and Lateral Pathways

Broadly speaking, two sorts of intra-segmental pathway can be recognised (Fig. 149). The first is an axial pathway, which runs the longest possible course within the segment and passes directly from the hilum of the lung to the distal pleural surface. The second is a lateral pathway, supplying regions between the hilum and the distal pleural surface.

Some of the branches which arise along an axial pathway are themselves axial pathways in the sense of the above definition, but most are

lateral branches. Figure 150 illustrates an axial pathway of the anterior basal segment; axial and lateral branches are interspersed and of twelve branches before the lobular bronchus is reached nine are lateral and only three can be considered axial. The axial branches to the beginning of the lobule at least can be described as "conducting", and the lateral as "distributing", branches supplying one, perhaps two, lobules. The distributing branches are, therefore, only a short distance from alveoli.

Angle of Branching

The angle of branching of these two types of airway differs as they proceed to the periphery. When a bronchus divides into two axial pathways they form a relatively acute angle; lateral pathways, on the other hand, diverge roughly at right-angles to the bronchus.

Number of Bronchial Generations

If a generation of the bronchial tree is taken as the length of bronchus between two branches of the tree, by counting the number of generations (or branches) along a bronchial pathway, an estimate of its total length can be made. Longer pathways have more generations, that is more branches.

Comparison by Generations

The number of generations can be used to make comparison between airways and between segments. For this purpose it is best to count the

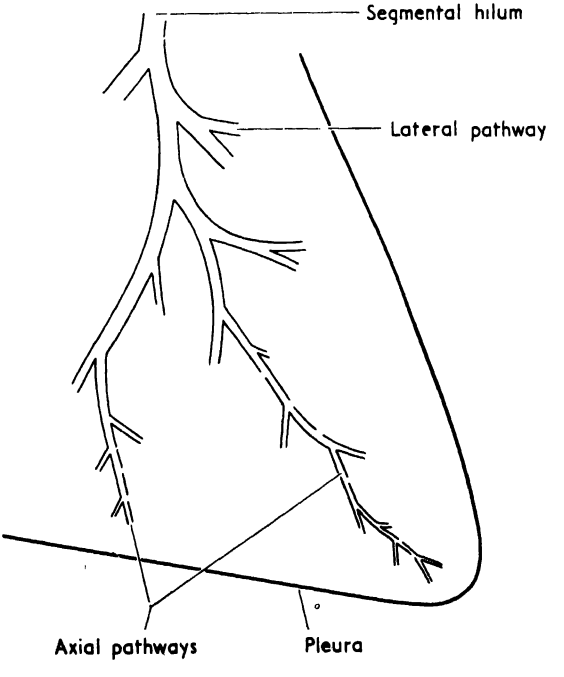


FIG. 149.—Diagram to illustrate bronchial pathways and angle of branching. Axial pathways run to the distal pleural surface, lateral pathways have shorter course to supply the proximal regions.

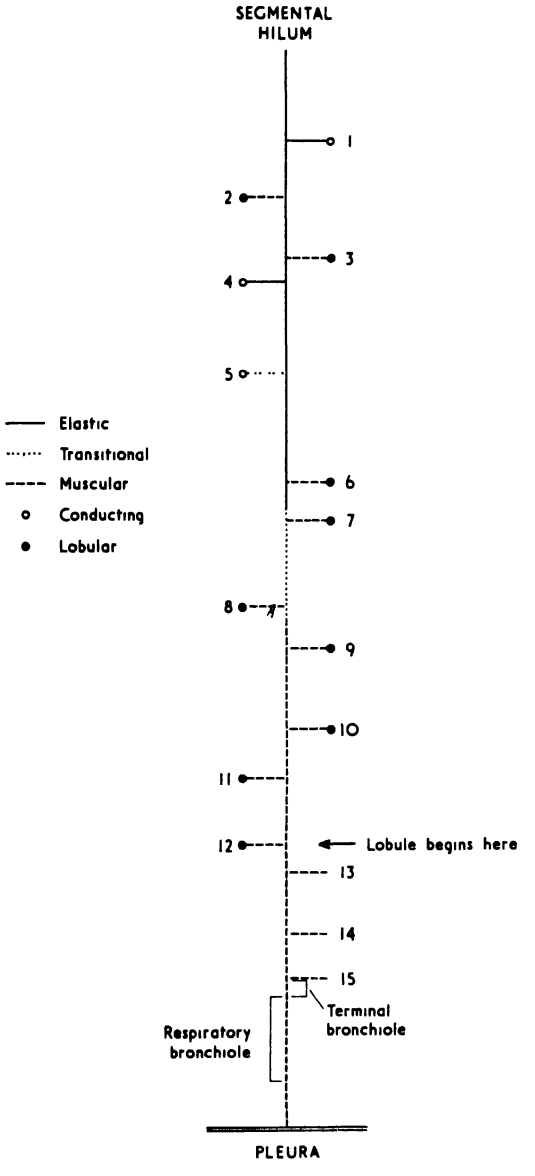


FIG. 150.—Side branches of an axial bronchus of basal segment; "lobular branches" supply one or perhaps two lobules, "conducting pathways" are either axial or, if lateral, supply more than two lobules.

segmental bronchus as the first (Hayward and Reid 1952*a*); the older method of counting the trachea as the first has the disadvantage, when comparing intra-segmental structures, that, because of the complex hilar arrangement, a segmental bronchus in the upper lobe is made the same generation as the right lower main bronchus (Fig. 152).

DEFINITION OF AIRWAYS

The airways are divided into bronchi and bronchioli according to their distribution of cartilage.

By definition *bronchi* are those air tubes lying proximal to the last plate of cartilage found along an airway (Fig. 151); *bronchioli* are found distal to the bronchi, beyond the last plate of cartilage and proximal to the alveolar region of the lung.

It will be evident from Fig. 151 that along the proximal parts of a pathway the cartilage is so abundant that any cross-section must include it and the pathway would clearly be a bronchus. In the region between A and B the cartilage is so sparse that a cross-section of the airway might miss a plane which includes cartilage, in which case the airway would not obviously be a bronchus. It is useful to describe the bronchi as large or small by reference to the amount of cartilage in their wall. In this diagram region A represents large bronchi and region B small.

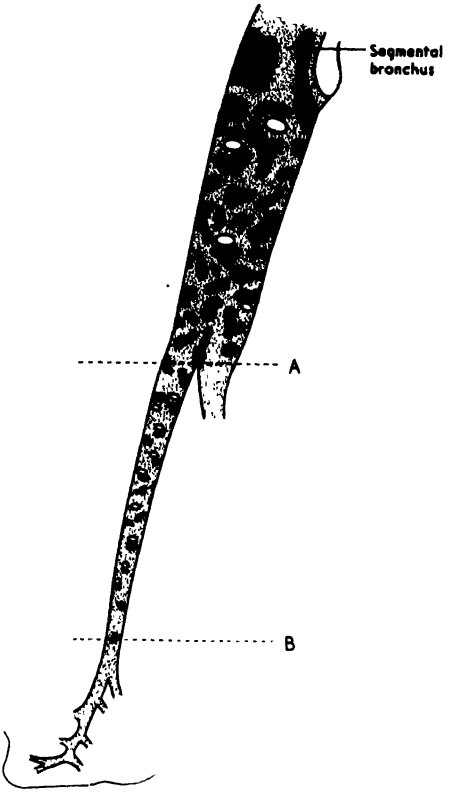


FIG. 151.—Diagrammatic representation of the plates of cartilage (black) in the wall of an axial bronchus of the posterior basal bròncho-pulmonary segment of an adult. The bronchus has been laid open longitudinally and is displayed flattened. Proximal to point A the cartilage supports the entire circumference of the bronchial wall continuously along its length ("large bronchi"). Distal to the last plate of cartilage at B are bronchioli. Between A and B are "small bronchi".

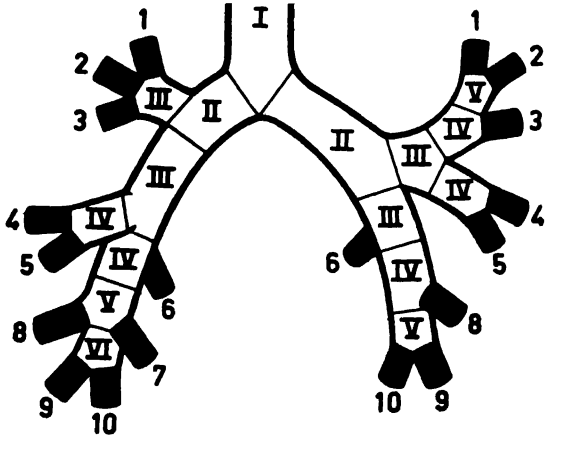


FIG. 152.—Variation in number (Roman numerals of presegmental generations). Segmental bronchi, shaded black, number (Arabic) 1–10 standard nomenclature (*Thorax*, 1950, **5**, 222).

The large bronchi behave differently from the small. In massive collapse of a lobe the large bronchi are inherently rigid enough to stay patent (Hayward and Reid, 1952*a*), whereas the small bronchi and bronchioli behave like the alveoli—their walls collapse and come into apposition. One structural feature that distinguishes the small bronchi from the bronchioli is that the presence of cartilage in the former is associated with mucous glands, which means that glandular mucus is secreted into small bronchi; while in bronchioli there are no glands and mucus is secreted into them only from the occasional goblet cell.

Pursuing an airway to the distal limit of the bronchial tree:

a respiratory bronchiolus, while having the structure of a bronchiolus in part of its wall, is an airway with alveoli opening into its lumen;

the terminal bronchiolus is the airway immediately before a respiratory bronchiolus, and is the most distal bronchiolus with a complete epithelial lining.

The branching pattern in the region of the terminal and respiratory bronchioli is rather complex. The terminal bronchiolus sometimes divides into two or three respiratory bronchioli; or it may transform itself within a generation (i.e. between successive branches) into a respiratory bronchiolus; or, again, from it there not infrequently arises a respiratory bronchiolus, i.e. a bronchiolus with an incomplete epithelial lining, while itself continuing with a complete epithelial lining and perhaps giving rise to another respiratory bronchiolus before becoming itself transformed into one. This arrangement can be identified in both adult (Elliott, 1964) and newborn lung (Bucher and Reid, 1961*a*) and is illustrated in Fig. 153. Respiratory bronchioli (A to F) are shaded. Bronchiolus 1 is the terminal bronchiolus to A but it divides into two further terminal bronchioli, 2 and 4. Bronchiolus 2 is terminal in respect of B, bronchiolus 3 is terminal in respect of C and D. The division of 1 into A and 2 is unequal, as is not unusual. Even if 2 and 3 may both be regarded as terminal bronchioli, in defining an acinus, below, it would seem reasonable to describe as the acinus all lung distal to 2 or 4.

A respiratory bronchiolus in its turn may branch several times into further respiratory bronchioli—as many as nine generations have been reported—before it is transformed into alveolar ducts and alveoli. The frequency of alveolar openings from respiratory bronchioli is probably greater distally than proximally.

A situation similar to that in Fig. 153 may be seen when a proximal respiratory bronchiolus arises from a lobular bronchiolus, the former usually supplying a smaller volume of lung than a terminal bronchiolus. To describe them as acini might give a false impression of their size and it would therefore seem better to call them "incomplete" acini.

In cat, rabbit and human lungs Lambert (1955) has described narrow tubular communications lined with epithelium connecting distal bron-

chioli with adjacent alveoli—accessory bronchiole-alveolar communications.

Divisions of the Bronchial Treb

Axial Pathways

The length of an axial pathway and the number of its generations vary with the size and shape of the segments (Hayward and Reid, 1952*a*). In short segments, such as the apical segment of the lower lobe, as few as fifteen generations may be counted along an axial pathway before the terminal bronchiolus is reached, whereas in the case of long segments such

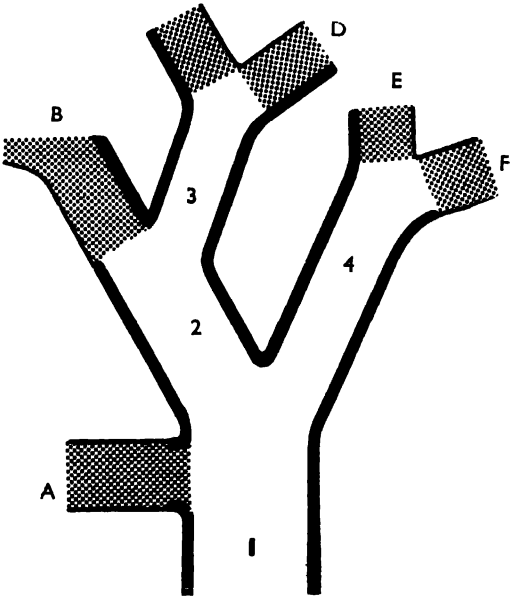


FIG. 153.—Diagrammatic representation of branching in terminal and respiratory bronchiolar region. Reconstruction from serial sections of a 32-week foetus of arrangement of terminal bronchioli. A to F respiratory bronchioli; 1 terminal bronchiolus to A; 2 to B; 3 to C and D, 4 to E and F.

as the inferior lingula or posterior basal, there may be as many as twenty-five. The most medial axial pathway of the medial segment of the right middle lobe is sometimes longer than the lateral pathway of this segment. Even between axial pathways of the same segment there are minor differences. In a study of segmental development Bucher and Reid (1961*a*) found that the maximum count for the superior lingular segment was twenty-five and the mean twenty-two.

These counts are for all branches from an axial pathway and, as illustrated in Fig. 149, some are themselves axial.

Lateral Pathways

Along lateral branches fewer generations are passed before alveoli are reached than with axial pathways. Hayward and Reid (1952*a*) reported

alveoli within eight generations of the posterior basal segmental bronchus; but in the reconstruction of the anterior basal segment shown in Fig. 150, the second lateral branch supplies a lobule and alveoli are within three generations of the segmental bronchus.

Lateral branches have themselves a varying number of side branches, the number gradually increasing towards the distal surface of the segment.

Distribution of Cartilage—Axial Pathways

The distribution of cartilage and its variation in the normal are essential factors in deciding whether or not airways are normal.

The extent of cartilage even along axial pathways varies considerably; generally, the longer the pathway the more generations with cartilage there will be. The extent of cartilage along axial pathways in adult lungs is indicated in Table XV.

Table XV

Cartilage Distribution

(by reference to bronchial generations in 12 adult lungs)

Segment (No. International Classification)	*Apical Upper* (1)	*Medial Middle Lobe* (5)	*Inferior Ling.* (5)	*Posterior Basal* (10)	*Apical Lower* (6)
Large Bronchi (Generations of bronchi with circumferential cartilage.)	4	4	5	6	4
Total Bronchi (Generations in which cartilage can be identified.)	9	10	11	10	8

If counts are made between the point where cartilage disappears and the end of the pathway a similar variation is found (Reid, 1958). In an adult lingula in that study, six generations were found distal to the last plate of cartilage; while in the apical segment of the lower lobe a small rod of cartilage was found within two generations of the end.

More numerous counts were made on the foetal lung and it appears that from the thirtieth week these were the same as those for the adult (Bucher and Reid, 1961*a*); the same variability of cartilage was found. Counts in lungs at term along an axial pathway of the anterior segment of the left upper lobe showed thirteen, thirteen, fourteen and fifteen generations with cartilage. The maximum number of generations with cartilage was twenty-one, in the segment of a foetus at term, and this pathway had twenty-six branches.

In foetuses over thirty-two weeks, counts of generations free of cartilage may be as high as fourteen and as low as three. The distribution of cartilage along lateral branches seems to show much the same variation as in

axial pathways, i.e. the distal generations are usually free, indicating that cartilage is not usually present within the lobule.

MUCOUS GLANDS

Mucous glands have roughly the same distribution and concentration as cartilage; hence no glands are normally seen in bronchioli. Distally they do not extend as irregularly as does the cartilage, as Bucher (Bucher and Reid, 1961*b*) found they were present in roughly two-thirds of the generations of an axial airway. They are abundant in large intra-segmental bronchi, both within and external to the plates of cartilage; in the small bronchi the glands are much sparser and may be found with cartilage only at a carina.

RESPIRATORY UNITS

The units comprising the lung are each designed for its particular site. The lobes vary widely in size, shape and arrangement of segments; the respiratory units within the segment also vary. To divide the lung into units must be arbitrary, but the justification for the following subdivision is that the units described are based not merely on size but on the branching pattern of the airways and are related to function.

Broncho-pulmonary Segments

The broncho-pulmonary segments are the lung units most used for topography. The lung contains nine or ten segments, each consisting of a roughly pyramidal chunk, the apex of the pyramid being at the hilum where the bronchus, artery and vein, lympathics and nerves makes their entrance or exit.

The variation in the pattern of branching of the bronchi at the hilum is so great that the segments cannot be satisfactorily described by reference only to the position of the supplying bronchi; the significant factor is the position of the segment in the lung (Boyden, 1955).

Boundaries

The segments, although recognised as units, are not isolated functionally; adjacent segments share the same venous drainage, and lymphatic communication between them is free. The pulmonary artery capillary bed is not interrupted by the segmental boundaries, and there is certainly collateral air drift across them (van Allen and Jung, 1931; van Allen *et al.*, 1931).

Segments are grouped into lobes—three on the right, two on the left—which are surrounded by pleura and each contains between two and five segments. Because the lobes are isolated by pleura they form functional end units of the lung.

It is only in the subpleural region that the segments are separated from each other by a barrier of fibrous tissue; in the subpleural region a septum may penetrate the lung for 1–2 cm. All segments are to some extent bounded by pleura; the medial segment of the right middle lobe, for example, is mostly bound by pleura while the right lateral basal segment may have pleura on only two sides.

Intersegmental Plane

Where a segment is not bounded by pleura there is no continuous sheet of fibrous tissue separating segment from segment, but the intersegmental plane is marked by a vein and its tributaries.

This is the anatomical basis for resection of a segment; the segmental bronchus is divided and the corresponding branch of the artery ligated. The intersegmental vein is then ligated at the hilum and by blunt dissection the surgeon can proceed along the plane mapped out by the vein and its tributaries, tearing the veins in the process from the segment to be resected. No pulmonary or bronchial artery is thereby affected.

The intersegmental junction is not straight; it is saw-toothed, as interdigitation of lobules occurs.

Intra-segmental Respiratory Units

The Acinus

Although the respiratory part of the lung may be anatomically subdivided in a number of ways, it is most useful to include in the respiratory unit all the lung distal to the terminal bronchiolus (Fig. 7). The acinus can then be defined as the lung distal to one terminal bronchiolus, i.e. respiratory bronchioli, alveolar ducts and alveoli. Acini vary in their size and shape, as do the segments.

The Secondary Lobule

While the concept of the lobule as a lung unit is useful, the word is still widely used without being adequately defined. Because methods of preparing lung tissue or casts may cause considerable change in the size of lung units it is essential that the basis for comparison between available techniques should be the pattern of bronchial branching rather than measurement.

The secondary lobule was for long defined as the unit demarcated by septa of connective tissue passing into the lung from the pleura. Because of the irregular distribution of septa (see below), however, the size of the unit so designated, in particular the number of acini it contains, has been shown to vary widely. Rindfleisch (1878) suggested that the acini in a lobule varied from two to thirty, while Laguesse and d'Hardivillier (1898), whose diagram is still included in current textbooks, selecting the lateral

aspect of the lower lobe where septa are sparse, gave a range of thirty-six to 100. While reflecting the irregular distribution of septa these figures give little idea of any intrinsic pattern of bronchial branching. Perhaps because of the embarrassing numerical diversity, modern accounts of lung anatomy (Miller, 1947) make no reference to the acini, but still describe the lobule in terms of septa.

It was hoped that the extent of cartilage would offer a more satisfactory way of defining the lobule but, as shown above, this also varies too widely.

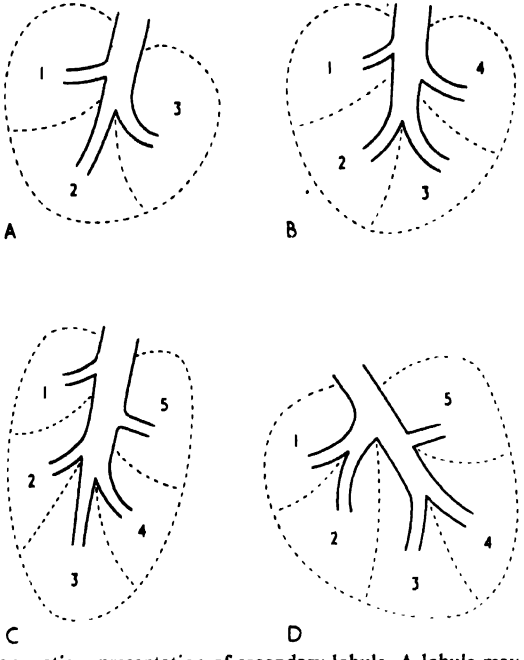


FIG. 154.—Diagrammatic representation of secondary lobule. A lobule may consist of three, four or five acini (i.e. terminal bronchiolus and tissue it supplies) arranged around a central or forked bronchiolar pathway.

On the basis of study of bronchograms (Reid and Simon, 1958) and of serial sections of lung, from injected and uninjected specimens, the secondary lobule is defined in terms of the pattern of branching of the bronchial tree as the cluster of three to five terminal bronchioli together with the part of the lung that they supply (Fig. 154). This usually includes three to five acini (Reid, 1958). Terminal bronchioli arise usually at intervals of about 2 mm. and are arranged about a single or forked pathway.

CORRELATION OF STRUCTURE WITH BRONCHOGRAPHIC APPEARANCE

In a normal clinical bronchogram (Figs. 155 and 156) the peripheral part of the airways shows up as parallel-walled line shadows. Along an

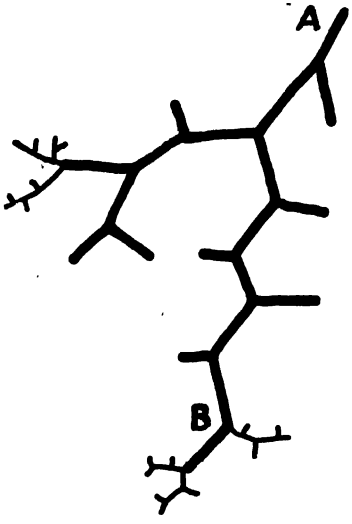


FIG. 155.—Diagram showing the pattern of branching of the end of a bronchial pathway. At first the branches arise at intervals of approximately 0·5 to 1 cm.—A to B—and then beyond B they arise at intervals of approximately 2 mm. (approximately natural size).

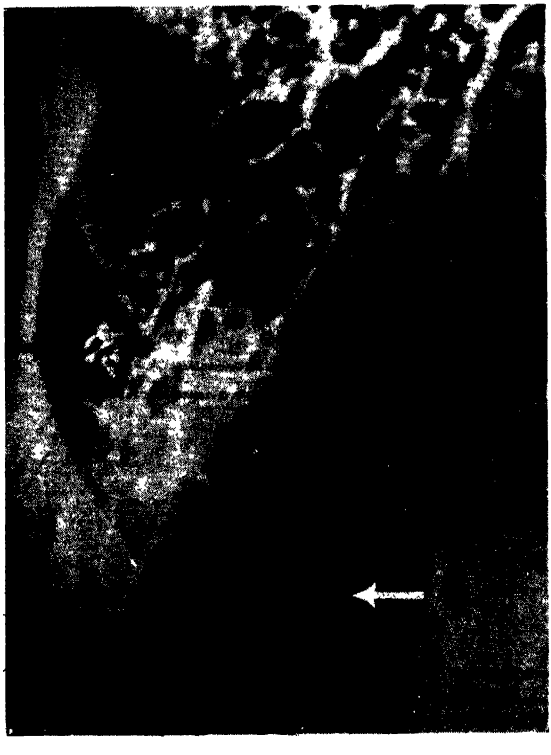


FIG. 156.—Anterior view bronchogram of the lower part of the right chest. The ultimate lines are short and fine, being about 2 mm. long and arising at intervals of about 2 mm. This is an example of the "millimetre" pattern (top arrow) and shows also the "unfilled rim" of lung under the ribs. The "centimetre" pattern is seen opposite the lower arrow. (×1.)

axial pathway, after the eighth to the tenth division from the segmental bronchus, branching occurs at intervals of 0·5 to 1·0 cm. until near the end, when the branches occur every 2–3 mm. and are only 2–3 mm. long (Fig. 155). These two patterns have been called respectively the "centimetre" and "millimetre" patterns (Reid and Simon, 1958).

Correlation with structure shows that the centimetre pattern generally begins in the region of small bronchi but is comprised mostly of bronchioli; while the closer-set millimetre pattern comprises terminal bronchioli. Even in a well-filled normal clinical bronchogram the alveoli opening into respiratory bronchioli usually appear free of contrast medium, and are represented by an unfilled rim in the subpleural region. This can be well seen against the chest wall or the interlobar fissure. The "unfilled rim" occurs at the edge of every acinus whether deep in the lung or subpleural. The woolly appearance sometimes seen in a clinical bronchogram is usually due to superimposed line shadows. Woolly shadows may on occasion be the result of pathological changes; these are discussed on page 172.

CONNECTIVE TISSUE SEPTA

The bronchi and blood vessels of the lung are ensheathed by connective tissue; but in some places connective tissue septa arise from the pleura and pass roughly at right-angles to it into the lung (Fig. 157). They appear to the naked eye as white lines, as thin as a hair's breadth, but may resemble a fissure like fascial planes elsewhere in the body.

The septa are sheets of fibrous tissue connected to the pleura along one edge and passing into the lung for a depth of 1–2 cm. Over part of its length the septum ends free in the lung, while elsewhere it is continuous with the sheaths around veins, arteries, lymphatics and bronchi. Where septa are near an angle of lung or near the hilum they stretch right across the lung from one pleural edge to the adjacent one.

Microscopically the areolar tissue forming the core of the septa is seen to be bounded by a thin layer of elastic fibres common to the pleura and to the underlying alveoli. The external or true elastic layer of the pleura has no connection with the septa, for it passes parallel to the pleural surface across the base of the septa without dipping into them. Since the septa lie at the periphery of a unit they outline the plane in which the veins run. Often the veins and the lymphatics are at the edge of the septum rather than deep within it.

Septa are of two types, the first being shallow with a maximum depth in the adult of only 2 or 3 mm., the second having a depth of 2–3 cm. The shallow septa vary considerably in the length of their attachment to the pleura and often contain a blood vessel or lymphatic at their intrapulmonary edge. They do little to subdivide the lung and are of less functional importance than the larger septa.

Relation of Large Septa to Pleural Lymphatics

In the adult lung the distribution of septa (Reid, 1959) does not reproduce the mosaic pattern of pleural lymphatics recognisable by the naked eye. Over the lateral aspect of the lower lobe, for example, septa are sparse and yet the pattern of lymphatics is visible on the lobe's surface. Elsewhere, as over the inferior tip of the lingula, the pleural pattern corresponds more to that of the underlying septa, which are usually less complete than that pattern would suggest. Serial sections cut parallel to the pleura often show that, although immediately subjacent to it there is a pattern of septa resembling that of the lymphatics, this is gradually lost, so that at a depth of half a centimetre there may be no septa.

Distribution of the Septa

The most striking feature of septa in the lung (child and adult) (Reid and Rubino, 1959; Reid, 1959), is the regional variation in number (Fig. 157). They are confined to the subpleural region, particularly at the margins and sharp edges of the lung—the anterior edges of the upper lobes and lingula and middle lobes, the costo-diaphragmatic rim, the postero-medial margin. The costal or flat aspects of the lobes are relatively free. Where the edge is sharply angled the septa dipping in from both surfaces almost meet.

Over the edges of the lung, compartments separated by septa are triangular; over the blunt postero-medial margin the compartments are oval or cylindrical.

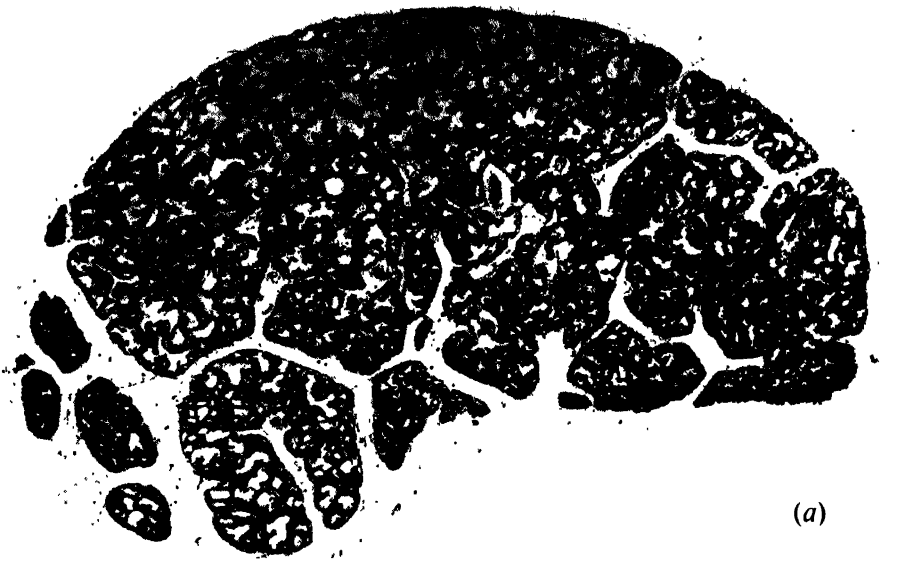
Regional Arrangement of Septa

The apex.—The apical part of the lung is usually well subdivided by septa. Horizontal slices through the apex often show a septum of considerable length passing caudally into the lung in an antero-posterior direction, with several small ones approaching it from the lateral aspects.

Fissures.—Save where they approach the angles of the lobe, the fissural surfaces of the lung are usually free of septa.

Diaphragmatic surface.—From the diaphragmatic surface a number of septa arise, particularly at its edge; the costophrenic edge is angled acutely and resembles the sharp anterior margin of the upper lobe in that it is only about one lobule thick. Over the central, flatter, part of the diaphragm septa are less frequent than at its rim. If the lung is sliced parallel to the diaphragmatic surface several septa may be seen arising from the postero-medial angle and radiating into the lung at a depth of perhaps 3 cm.

Hilum.—At the hilum, septa may meet the areolar tissue surrounding the blood vessels and bronchi, so that in this region also the subdivision into units may be well marked.



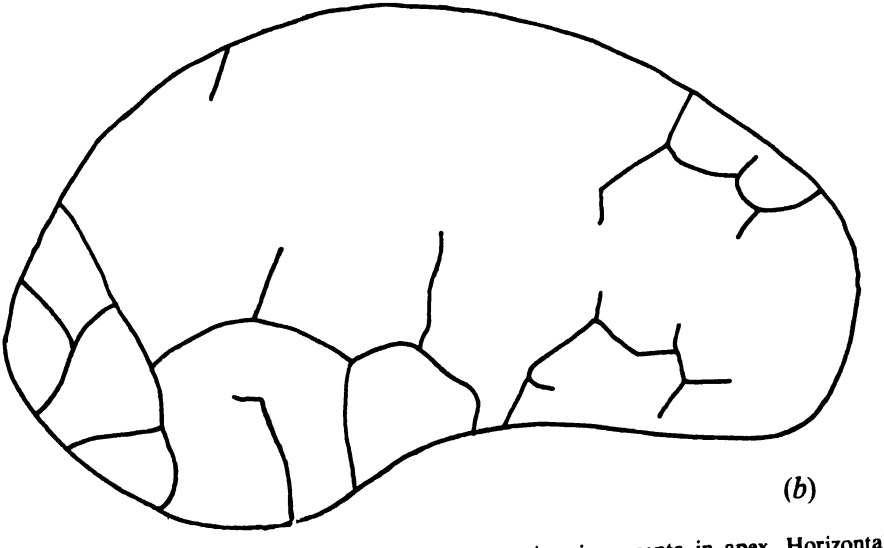


FIG. 157(*a*) and (*b*).—Slice of lung to illustrate connective tissue septa in apex. Horizontal section of the apex of the right upper lobe, with diagram, of a 24-week foetus, showing few septa over the lateral aspect of the lobe.

Subdivision of Lung

Even in the foetal lung, serial sections showed no compartment to be ever completely isolated from its neighbour; a bridge between adjacent lung compartments can always be identified (Reid and Rubino, 1959). Nevertheless some parts of the lung are relatively more isolated by septa than others; septa interfere with the continuity of the capillary bed.

Numerical Counts of Septa

Reid (1959) gave the average number of septa for each lobe, indicating the frequency of the septa and emphasising their regional variation. In this study the lobe was sliced; each side of the lobe was divided into two roughly equal parts and as a lobe is more or less triangular in section, six counts were possible at each level. The average for each edge was established, all five lobes studied giving similar counts.

Often the lung enclosed between adjacent septa is as small as a lobule, but it may represent much more.

Relation of Septa to Collateral Air Drift

The incompleteness of the septa in man is essential to "collateral air drift", the term used by van Allen and Jung (1931) to describe the phenomenon whereby air can drift across alveolar walls. This means that air can pass from acinus to acinus, lobule to lobule, and segment to segment without the intermediary of airways. Using fresh specimens van Allen *et al.* (1931) demonstrated that air injected into one segment escaped through the bronchus of a neighbouring segment even before the former was maximally distended; that furthermore, applying negative pressure to one bronchus did not result in collapse if the bronchus to an adjacent segment was patent. This phenomenon has been demonstrated in the normal intact lung of both man and of several species of animals, the only exception being the calf, in which the connective tissue completely encloses units of the lung (Reid, 1958), with no alveoli to serve as interlobular bridges.

The significance of collateral air drift in normal healthy lung is not known. That it operates under conditions of disease has been shown in pathological specimens in which lung may be well aerated and normal to naked-eye examination, although its supplying airways are obliterated. Even if alveoli appear normal it does not follow that the supplying airway is normal or, of course, that the reverse applies. The pathological importance of collateral air drift is thus obvious, because it renders airway and alveoli to some extent independent of each other.

The absence of pigment in an aerated region, the rest of the lung being pigmented, suggests the operation of collateral ventilation behind localised airways disease.

The specimens illustrated in Chapter XI, particularly, show the operation of collateral ventilation.

The regional variation in the concentration of septa means that there are parts of the lung where air drift is less effective. The "protective" action of cross ventilation can best be illustrated by reference to bronchial obstruction at lobar and segmental level and to collapse occurring behind it, the cross ventilation acting both to prevent collapse and over-inflation. As the right middle lobe has only two segments (4 and 5), each is continuous with only one other, unlike the lateral basal segment (9) which is continuous with three or four others and has only two surfaces "isolated" by pleura. Where a segment is isolated, the liability to collapse is obviously greater.

Like the segments of the right middle lobe, the inferior segment of the lingula (5) is continuous with only one surface of one other segment and, particularly at its tip, airlessness is frequent if the lung is diseased. In this region the high concentration of septa combines with isolation of the segment by pleura in predisposing it to collapse. Obstruction to the apical segment of the upper lobe or lateral basal segment of the lower lobe rarely leads to collapse.

The irregular operation of collateral ventilation in the subpleural zone is illustrated by the distribution of the minute foci of fibrosis and collapse seen in chronic bronchitis (Reid, 1956). These foci are twice as frequent immediately under the pleura as in the deeper part of the lung (p. 167), suggesting again that ventilation is less effective where lung is isolated by pleura.

Septa and Development of Bullae

It would seem that collateral ventilation also contributes to the development of bullae in emphysema. The structural isolation which impedes the entry of air may equally hinder its escape. Although emphysema occurs throughout the lung, the local over-distension which gives rise to bullae is seen dramatically in the subpleural region, and the characteristic fringe of bullae along the anterior edge of the lung, at the apex and on the diaphragmatic surface, suggests that the development of bullae is, at least in part, the consequence of the high concentration of septa at these sites (Reid, 1959).

It is in Type I bullae (see p. 212) and to some extent in Type II, that septa contribute most to their development.

DEVELOPMENT OF LUNG STRUCTURE

The development of the bronchial tree as measured by the number of bronchial branches is one indication of whether or not intra-uterine bronchial development has been normal. The bronchial tree seems to show

no increase in branching after birth, although the alveoli increase greatly. In certain congenital deformities the beginning of the primary disturbance can thus be gauged by the extent to which development of the bronchial tree has been retarded (Reid, 1966).

The trachea grows as a pouch from the foregut at about the fifth week of intra-uterine life and branches within the mesenchyme. The airways are hollow tubes blind at the distal and growing end, culminating in solid buds of epithelial tissue that divide as they develop. As the pleural space is part of the coelomic cavity the lobes, from the earliest stage of development, are surrounded by pleura.

In a five-week foetus (crown-rump length 8–10 mm.) the lobar bronchi are present as small outgrowths. In what Boyden (1955) has described as a "burst of activity", these lobar bronchi subdivide so that segmental bronchi are recognisable from the sixth week. Lung development during the weeks following is commonly described as "glandular" (Fig. 158), because its air spaces are enclosed by epithelium surrounded by solid mesenchyme, i.e. the bronchial tree is still blind at its distal end and completely lined by epithelium. It is in this phase that all airways to the end of the terminal bronchiolus are formed.

The "canalicular" phase follows, lasting from roughly the sixteenth to the twenty-fourth week, in which period the ingrowth of capillaries through the epithelium opens the distal airways. The next phase continues until birth and is called the "alveolar" (Dubreuil *et al.*, 1936; Palmer, 1936; Loosli and Potter, 1959).

The number of generations of the bronchial tree present at different stages of intra-uterine life has been established by Bucher and Reid (1961*a*). In the shorter segments branching is completed by the fourteenth week, but for certain long segments such as the lingula and the posterior basal, branching continues until the sixteenth week (Fig. 160). In Fig. 159 the number of generations counted along axial pathways in the different segments is related to the glandular, canalicular and alveolar phases and also to the emergence and distribution of cartilage and mucous glands. The counts were made to the last generation of a "blind airway" (Fig. 159). In the canalicular phase the count of generations dropped, because alveoli had by this time opened into the terminal generations. This fall is represented in Fig. 160 by line A, the space between A_1 and A representing the lung distal to the terminal bronchiolus.

In man the number of airways to the end of the terminal bronchiolus seems not to increase after the canalicular phase. It would appear that the development of the branches of the bronchial tree is complete by the sixteenth week (Fig. 160). It may be that there is even some reduction after birth as alveoli open into additional distal generations of the bronchial tree (Boyden and Tompsett, 1962).

The maximum burst of activity as judged by new generations formed

PHASES OF DEVELOPMENT OF THE LUNGS

Glandular: 5th–16th Week.

Canalicular: 16th–24th Week.

Alveolar: 24th Week-Term.

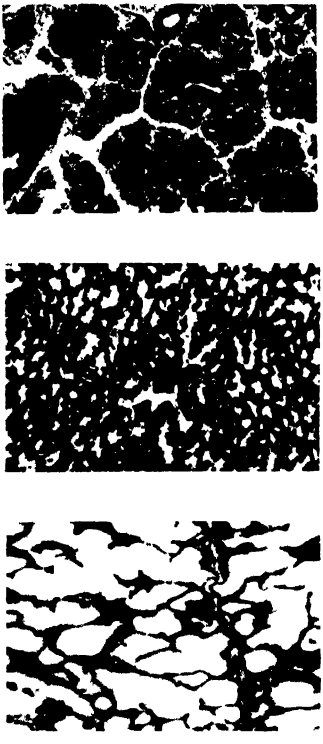


FIG. 158.—Development of lung. Appearance of lung in cross section at various stages of development.

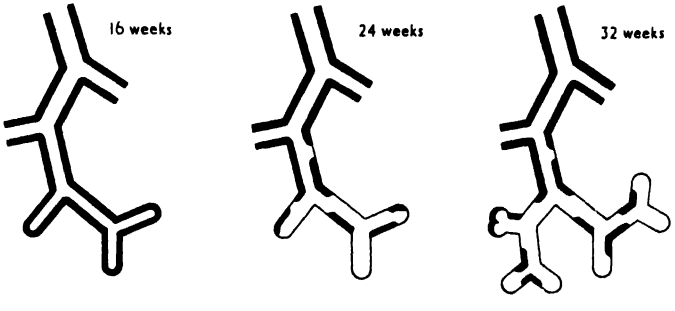


FIG. 159.—Ultimate generations of the bronchial tree at various stages of intra-uterine development; 16 weeks, bronchial tree completely lined with epithelium; 24 weeks, epithelium interrupted by ingrowth of capillaries, i.e. respiratory or alveolar part arises from transformation in the terminal branches; 32 weeks, additional growth respiratory part.

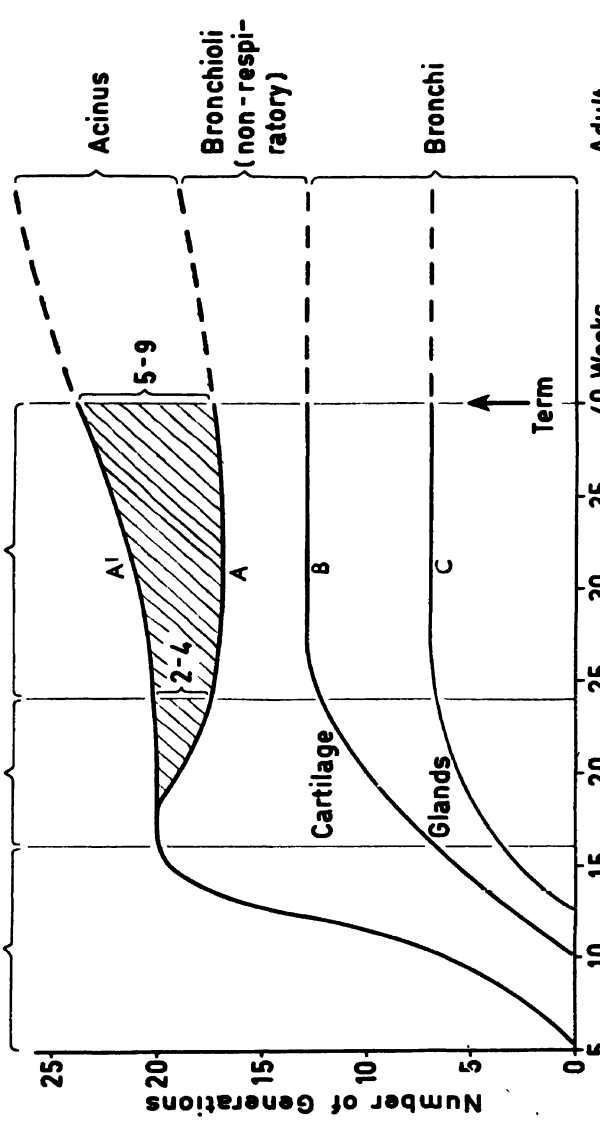


FIG. 160.—Summary of intra-uterine development of the intrasegmental bronchial tree. Line A represents the increase in the number of bronchial generations; shaded area between A and A^1 the respiratory part of the bronchial tree (i.e. respiratory bronchioles and alveolar ducts); B the extension of cartilage along the bronchial tree; C the extension of mucous glands. A, B, and C are taken from mean values of numerous counts. A derives from Engel's studies and our own counts. The diagram includes adult counts showing the increase in total generations in the postnatal period (data from published figures—ref. see text).

would seem to happen between the tenth and fourteenth week, during which period are formed 70 per cent of the generations present at birth.

Development of Cartilage

Cartilage continues to grow after bronchial branching is complete, until the twenty-fifth week of intra-uterine life, but with no burst of activity such as characterises the branching of the bronchi.

Plates of cartilage can be identified in the trachea and main bronchi at the age of ten weeks, but they are not found in segmental bronchi until the twelfth week, that is about six weeks after the bronchi are formed. Thereafter cartilage appear in steady progression further to the periphery, but its extent in different axial pathways of a single segment varies considerably (Fig. 160).

At ten weeks the plates of cartilage of the main bronchi are developing in zones of pre-cartilage—concentrations of large cells with round darkly-staining nuclei, the cytoplasm being palely eosinophilic. The cellular formation of cartilage is achieved in two weeks, but its full development with its final histochemical properties takes much longer, perhaps 15–20 weeks. This means that even at birth the distal plates do not have a mature intercellular matrix. Acid mucopolysaccharide stains are positive some time before either basophilia develops or the periodic-acid-Schiff stain becomes positive (Bucher and Reid, 1961*b*).

Postnatal Development

Bucher and Reid (1961*a*) found no evidence that further airways develop between the sixteenth week of intra-uterine life and birth or between birth and adult life. Boyden and Tompsett (1962) have made a study of the medial segment of the right middle lobe in infants of two days, thirty-seven days, eighty-eight days, and six years eight months respectively, of postnatal age. They found that counts along an axial pathway—including terminal but not respiratory bronchioli—vary from twenty to twenty-six generations, which, as these are within the adult range, suggests that new bronchi do not form in the postnatal period.

Alveoli

It would seem that new alveoli form until the age of eight years or so, after which they increase in size (Willson, 1928). Dunnill (1962), using the point-counting system of Weibel and Gomez (Weibel, 1963), estimated a figure of twenty million alveoli present at birth, increasing to three hundred million, the adult figure, by the age of eight.

Another way of ascertaining the stage of development of alveoli is that described by Emery and Mithal (1960), who counted the number of alveoli present between a terminal bronchiolus and the edge of the acinus marked by pleura or connective tissue septum—the "radial alveolar count".

This increased from a mean of 2·5 at twenty-eight weeks of gestation to 4·4 at full term. By the age of one the count was nearly 7, at eight years 8·2, and at twelve, 9·3.

Little is known of the development of the respiratory bronchioli. They cannot be anatomically recognised by Dunnill's technique. His alveolar counts include alveoli arising from respiratory bronchioli.

The recent work of Boyden and Tompsett on the newborn shows that new alveoli form first in the central part of the acinus (Boyden and Tompsett, 1965).

Arrangement of elastic fibres

Loosli and Potter (1959) have reported that elastic fibres are present in the pulmonary artery and airways by the third month of intra-uterine life. In the alveolar region they appear first in the mouths of alveolar ducts, then in the alveoli just beyond, and only later in the walls of the peripheral alveoli where even at term they are sparse.

THE LYMPHATICS

Study of the lymphatics of the human lung has been neglected until recently. Trapnell (1963; 1964*a* and *b*) investigated the extent to which they produce abnormal shadows in the chest radiograph. His review of previous work is valuable in bringing to light reliable work that had been displaced by more recent ill-founded comments.

The technical difficulties in examining lymphatics are considerable. As they are furnished with valves, injection along ordinary routes of flow shows up only a limited number of lymphatics because the medium will not pass from large to smaller channels. Retrograde injection is thus of very limited value and the smallest vessels must, therefore, be injected. Hitherto the subject has been studied mainly in animal lungs and the results should be accepted for the human lung with reserve.

In the human lung, lymphatics are numerous around airways and arteries (the broncho-arterial bundles), around veins and in the pleura. Trapnell discarded the terms "subpleural", "septal" and "communicating," preferring to classify lymphatics as:

Pleural
Interlobular
Peribronchial (including periarterial)
Perivenous
Anastomotic (these lie deep in the lung but are not in the same connective tissue sheath as vessels or airways and they pass between broncho-arterial and venous groups).

Where interlobular septa are present the lymphatics run in them.

That there are pleural and "deep" lymphatics in the human lung is agreed. By the end of the last century it was accepted that there were "superficial" and "deep" groups of lymphatics and it had been shown that the superficial or pleural group communicated freely with those deep within the lung and that the direction of flow from the pleura, as well as within the lung, was towards the hilum (Mascagni, 1784; Cruickshank, 1786; Sappey, 1885).

In 1900 Councilman described numerous lymphatics in and under the pleura of the human lung, particularly in the connective tissue septa. His conclusion was unfortunate, that the valves pointed to the pleura and that the flow was from the subpleural and deep systems, though this he had not been able to demonstrate. Miller (1900), mainly from a study of the dog which, being a "thin pleura" species, has no interlobular septa did not find any communication between the pleural and the deep systems. He described a deep set of lymphatics without valves and a pleural set well supplied with valves which ultimately directed flow over the surface of the lung to the hilum. Although the flow in the deep lymphatics was claimed to be direct to the hilum they were said to have no valves. These reports suggested a watershed between subpleural and deep lymphatics, the latter draining direct to the hilum, the former draining to the pleura and thence over the lung surface to the hilum.

This description has been widely accepted although it was contrary, not only to earlier descriptions, but to Franke's view (1912) that the deep lymphatics filled from the pleura and that the inoculum reached the hilum without filling the network in the pleura. Trapnell found that there were numerous anastomoses between pleural lymphatics and also free communication with deep lymphatics; that the pleural lymph reached the hilum via these deep lymphatics and that free anastomosis occurred between the peribronchial and perivenous lymphatics; further that valves were numerous, usually only a millimetre or two apart, in all types of pulmonary lymphatics.

Trapnell (1964*a*) found small lymph nodes deep in the lung radiographically in 6 of 90 lungs examined, and in 5 of 28 lungs in which the lymphatics were injected sufficiently well to fill the hilar lymph nodes.

Distribution

It is often suggested that the distribution of lymphatics through the lung is even. Comparing the number visible to the naked eye on the pleura of different lobes both at operation and at autopsy, in healthy and diseased lungs, Trapnell found that pleural lymphatics were much more numerous over the lower lobes than over the upper lobes, the middle lobe or the lingula. Some pleural lymphatics were seen on the surface of all the right lower lobes, but of only 31 per cent of the upper lobes and only 23 per cent

of the middle lobes. A comparative assessment of the number of pleural lymphatics seen gave the following counts for each lobe:

RUL	38	RML	23	RLL	123
LUL	18	LL	14	LLL	148

No such regional difference for other types of lymphatics was detected.

It would seem that lymphatics are not present in alveolar walls, appearing first around terminal and respiratory bronchioli; this has been confirmed in man by Teichmann (1861), Miller (1900) and Policard (1938).

PULMONARY CIRCULATION

The lung receives blood from the right side of the heart through the pulmonary artery and from the left side of the heart through the bronchial artery, the latter supplying the walls of airways, while the pulmonary artery supplies the respiratory tissue beyond the terminal bronchiolus. There are also two systems of venous drainage, the first by which blood passes through the pulmonary veins and returns to the left heart, the second in which it passes through the "true bronchial veins" to the right. The two systems of venous drainage do not correspond exactly to the arterial systems. The pulmonary veins drain the respiratory tissue as well as most of the bronchial tree; the true bronchial veins receive the blood from only a small region of lung around the hilum.

Distribution of Vessels

The bronchial arteries arise from the aorta or from its intrathoracic branches and run within the connective tissue sheath of the bronchus, supplying the capillary bed which invests the bronchial tree from hilum to terminal and respiratory bronchioli. The pulmonary artery is also associated with the bronchus and bronchial artery in that all are included within a common connective tissue sheath, the broncho-arterial bundle, running centrally in any unit of the lung, be it segment or acinus. When the pulmonary artery accompanies the bronchus it branches with the bronchial tree but does not divide into capillaries until the respiratory part of the lung is reached.

The pulmonary veins, on the other hand, are distributed at the periphery of lung units (Fig. 161). The veins draining the bronchus pass away from it at right angles to join the larger veins which are also centrifugal in relation to the lung they drain. Two veins leave the bronchial wall at each division of a bronchus and pass from it in opposite directions (Miller, 1947). This arrangement is the anatomical basis for a segmental resection, as the veins mark the intersegmental plane.

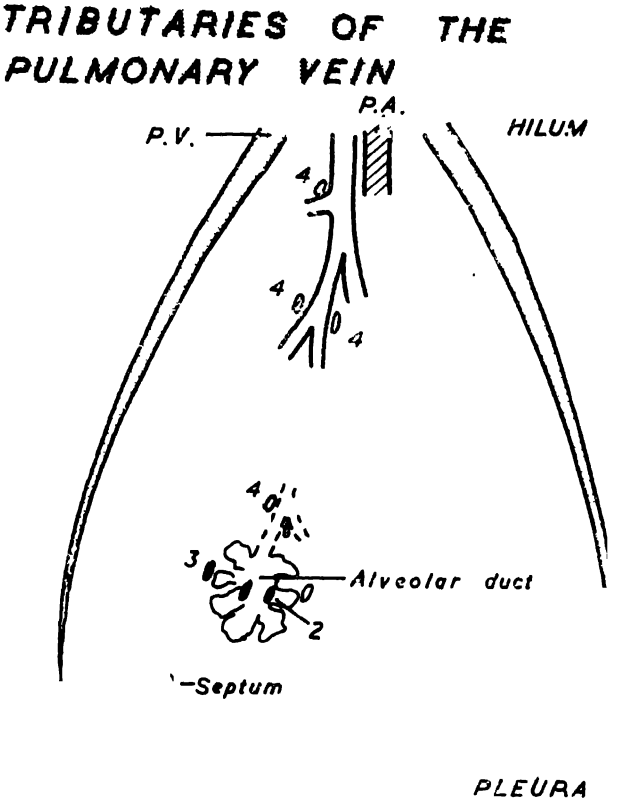


FIG. 161.—Diagrammatic representation of broncho-pulmonary segment. Pulmonary veins (P.V.) lie at periphery of any segment. Tributaries from pleura and connective tissue septa, from within the acinus (2, 3) and from the bronchial wall (4). From points of bronchial branching, two veins arise and pass in opposite directions.

STRUCTURE OF PULMONARY ARTERIES

Presegmental

The trunk of the pulmonary artery and of its right and left branches is similar to that of the aorta—a so-called elastic artery. The media consists of laminae of elastic fibres, the spaces between which are filled with muscle fibres. In the aorta these alternating layers are sufficiently regular to give the wall a fenestrated appearance, although the fibres of the elastic laminae to some extent branch and link with adjacent sheets of elastic fibres.

In the pulmonary artery the thickness of the media is less, that is, there are fewer layers of elastic and muscle fibres, and the fenestration is not quite as orderly. Before birth blood pressure in both systems is the same and so is the structure of the pulmonary artery and aorta. If there is pulmonary hypertension at birth the aortic pressures in the pulmonary

FIG. 162.—Specimen pulmonary arteriogram. Anterior basal segment (segmental artery 8) in slice of lung 1 cm. thick. White arrow corresponds in position to the black arrow in Fig. 165.

artery maintain its structure similar to that of the aorta (Heath and Edwards, 1958).

The right and left pulmonary arteries in the cadaver are about 2·25 cm. in diameter (Belcher *et al.*, 1959). (Diameters in tomograms are given on p. 282.)

Intra-segmental

Brenner (1935) reported that in the lung arteries over 1000μ are elastic, those between 1000 and 100μ are muscular and those under 100μ are free of muscle. These figures were based on uninjected material. This broadly has been the accepted basis for most normal and morbid anatomical studies of lung until the present.

Using injected material (Fig. 162) which offers a more satisfactory basis for comparison than uninjected lung, Elliott (Elliott, 1964; Elliott and Reid, 1965) recently carried out a detailed study of the normal pulmonary arterial tree. He traced axial pathways from hilum to distant pleura and

FIG. 163.—Elastic artery. Wall consists of laminae of elastic fibrils with muscle between. (× 250.)

established the structure and size of the artery along its length, as well as identifying and measuring all its side branches. This reconstruction of the pulmonary artery along its length not only revealed new facts about structure but also showed the great disparity between the bronchial and pulmonary artery branching. Furthermore the overall muscularity of the pulmonary artery system was found to be much greater than Brenner's description implies.

Structure

Three main types of pulmonary artery can be recognised according to the variations in the structure of the media—elastic, transitional and muscular. Two additional, smaller, types of artery are also considered separately—a "partially muscular arterial vessel" and a "non-muscular arterial vessel"; these are sometimes called arterioles, but this term has been here avoided since it has different significances for anatomist and physiologist. Traced from the hilum to the periphery any axial artery passes through each of these stages in turn.

The following definitions broadly follow those of Brenner (1935), but they are given here in greater detail and the transitional type is added. Brenner's descriptions of diameter were not acceptable since he used uninjected lungs; moreover, it emerged in the course of Elliott's study that Brenner's range of diameters for different structural types needed modification.

Elastic artery (Fig. 163).—The media lies between internal and external

limiting elastic laminae; seven or more elastic laminae are found within the media. Not only are these laminae more numerous than in muscular arteries but their arrangement is more orderly, as they run parallel and are frequently continuous around the greater part of the circumference. This is in contrast to the ragged appearance of the elastic fibrils seen in muscular arteries. Even an elastic artery has a considerable quantity of muscle, muscle fibres being sandwiched in the interstices between the elastic fibrils.

Transitional artery.—The structure of a transitional artery is intermediate between an elastic and a muscular artery; it contains five or six elastic laminae in addition to the internal and external elastic laminae.

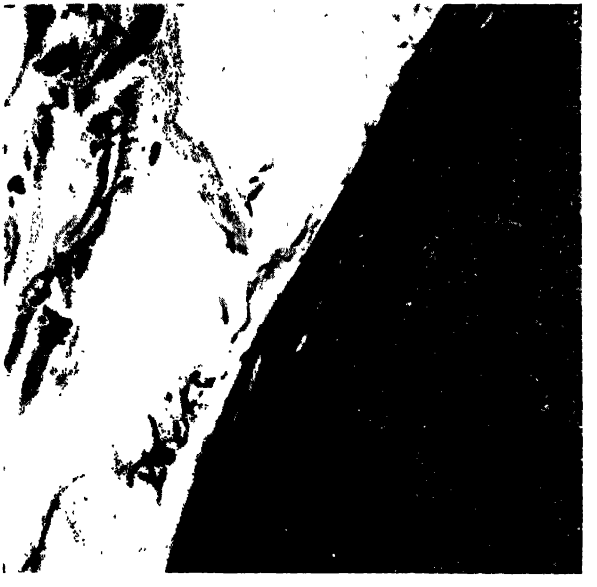


FIG. 164.—Muscular artery. Wall consists of muscle coat between an internal and external limiting elastic membrane. Fragmented elastic fibrils are mixed with the muscle. Artery filled with barium-gelatine mixture. (· 500)

Muscular artery (Fig. 164).—In a muscular artery the media consists of a continuous muscle coat. All muscular arteries except the smallest have, in addition, an internal and an external elastic lamina with up to four scattered elastic fibrils at any point of the circumference. Although the limiting elastic laminae are seen in larger muscular arteries they are not an essential element.

"Partially muscular" arterial vessels.—A "partially muscular" arterial vessel is one in which such muscle as is present in the wall is not continuous around the circumference in any given cross section; the rest of the wall consists of collagen and elastic fibres.

"Non-muscular" arterial vessels.—A "non-muscular" arterial vessel is one lying proximal to and larger than a capillary, with no muscle in its wall, which consists of collagen and an occasional elastic fibril.

Distribution

The elastic and transitional arteries extend roughly halfway along an axial pathway (Figs. 165 and 166), which represents 9 generations of the bronchial tree (elastic for 6 and transitional for 3). The muscular region begins in arteries which in injected material are roughly 2 mm. in diameter. This is larger than that suggested by Brenner and might reflect the arterial distension associated with injection, but Elliott has established that arteries as small as 30μ in diameter may have a complete ring of muscle in their walls. Even vessels up to the beginning of the capillaries which are smaller than 30μ have some muscle in their wall. The reconstruction by serial section of the pulmonary artery branching was supplemented within the acinus by the use of "population studies" of arteries. Figure 167 summarises the distribution of the muscular, partially muscular and non-muscular arteries in arterial vessels below 130μ in diameter, at which all vessels are wholly muscular; at about 100μ 50 per cent of vessels are wholly muscular, while at roughly 50μ, 50 per cent are partially muscular (Reid, 1965).

Muscularity (Wall Thickness as a Percentage of External Diameter) and Medial Area

The amount of muscle in the different regions was also assessed by measuring the thickness of the artery wall, doubling it (because the external diameter includes two walls) and expressing this as a ratio of the external diameter $\left(\frac{2 \times \text{wall thickness}}{\text{external diameter}} \times 100\right)$. The medial area was also calculated.

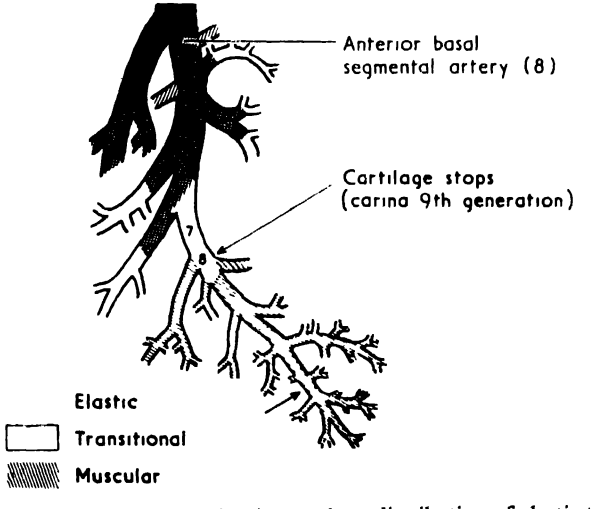


FIG. 165.—Same pathway as Fig. 162. Tracing to show distribution of elastic transitional and muscular arteries. Small black arrow corresponds in position to the white one in Fig. 162. ($\times \frac{1}{3}$.)

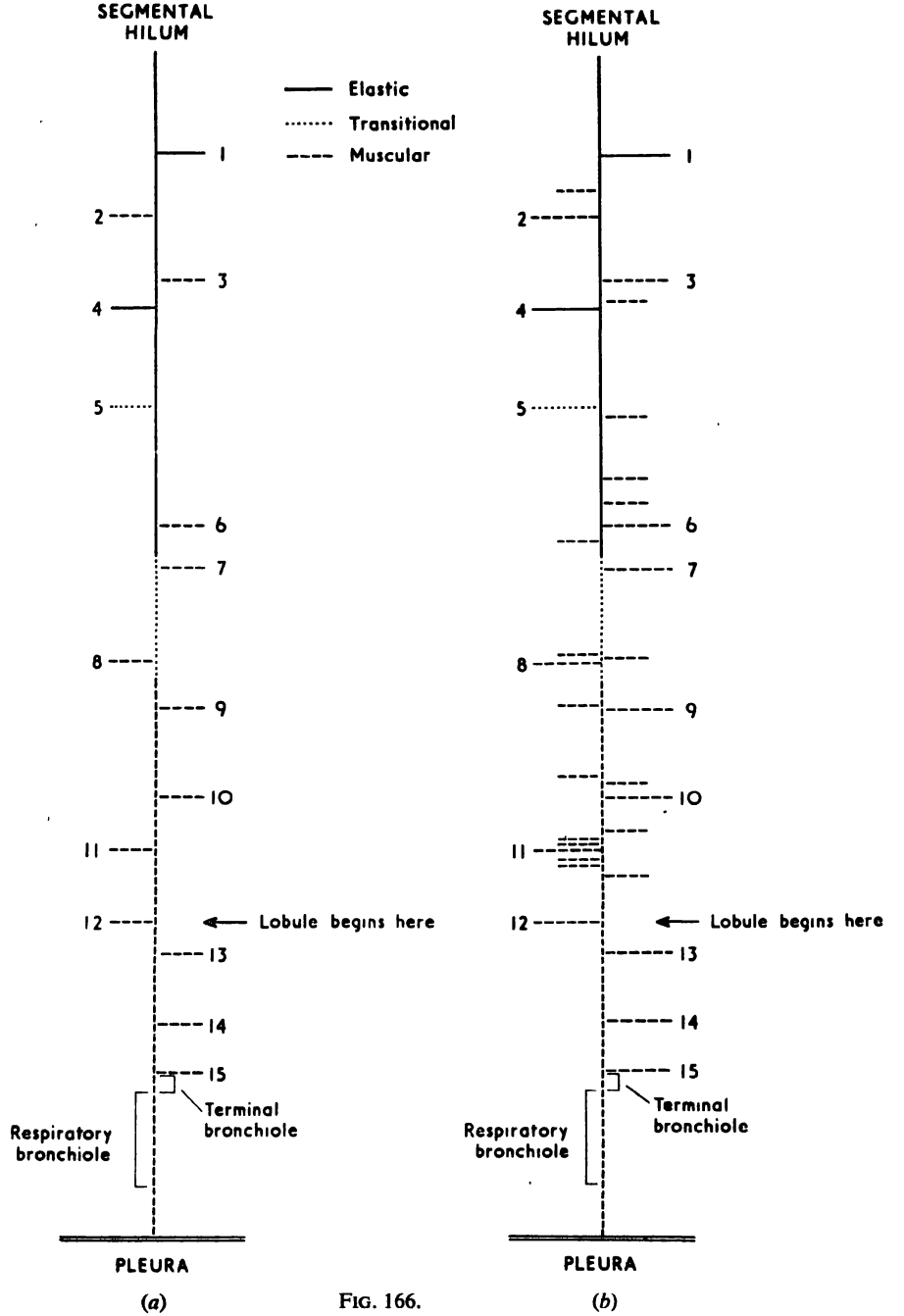

SEGMENTAL HILUM
Elastic
Transitional
Muscular
1
2
3
4
5
6
7
8
9
10
11
12
Lobule begins here
13
14
15
Terminal bronchiole
Respiratory bronchiole
PLEURA
(a)
SEGMENTAL HILUM
1
2
3
4
5
6
7
8
9
10
11
12
Lobule begins here
13
14
15
Terminal bronchiole
Respiratory bronchiole
PLEURA
(b)

FIG. 166.

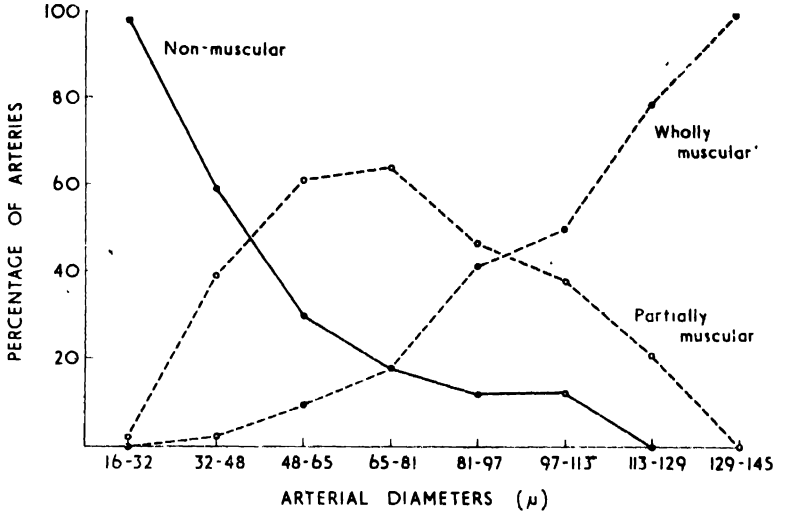


FIG. 167.—Distribution of arterial types in vessels below 142 μ. Completely muscular arteries are gradually replaced by partially and non-muscular arteries.

At the hilum of a segment the wall thickness, calculated as above, is 3–5 per cent of the external diameter. This falls gradually until at the beginning of the muscular region it is 1·5–2·5 per cent; the lowest figure is in the prelobular region in arteries between 1500 and 1000μ where it is about 1 per cent. Elliott has described this as the "downward trend"; distal to this the wall thickness then increases rapidly (the "upward trend") and achieves a higher figure than found anywhere more proximally. In arteries below 1000μ the wall thickness increases and in arteries below 100μ may be as much as 20 per cent. These results are illustrated in Fig. 168. That the medial area no longer reduces as rapidly indicates that in this part of the artery muscularity is increasing.

The pulmonary artery system has a low pressure compared with the systemic and, in the pulmonary as in the systemic, the smaller vessels need little strength in their wall to resist internal pressures. The relative increase in muscularity points not to theirs being a supporting function but suggests control through vasoconstriction.

CONVENTIONAL AND SUPERNUMERARY ARTERIES

"Conventional" arteries are those which run for their whole length with a branch of an airway. Elliott (1964) found, however, that the pulmonary artery branched many more times than the bronchial tree (Fig.

FIG. 166(*a*) and (*b*) (*see opposite*).—Same pathway as Figs. 162 and 165. Diagrammatic representation drawn to scale. Conventional arteries (those running with airways) and numbered. Muscular arteries start at the seventh generation and continue to within the acinus. FIG. 166(*b*). —The supernumerary (i.e. aberrant and accessory) arteries added also.

166) and that these "supernumerary" vessels, as he called them, occur throughout the length of an artery starting from the hilum. The supernumerary arteries are of two types: aberrant and accessory (Fig. 169).

(1) **Aberrant arteries** are distributed with an airway but have not risen from the parent artery at a point corresponding to the bronchial branching. They usually avoid the rather circuitous course taken by the airway and are found along the whole length of the pre-acinar length of an artery.

(2) **Accessory arteries** start only in the immediately prelobular region

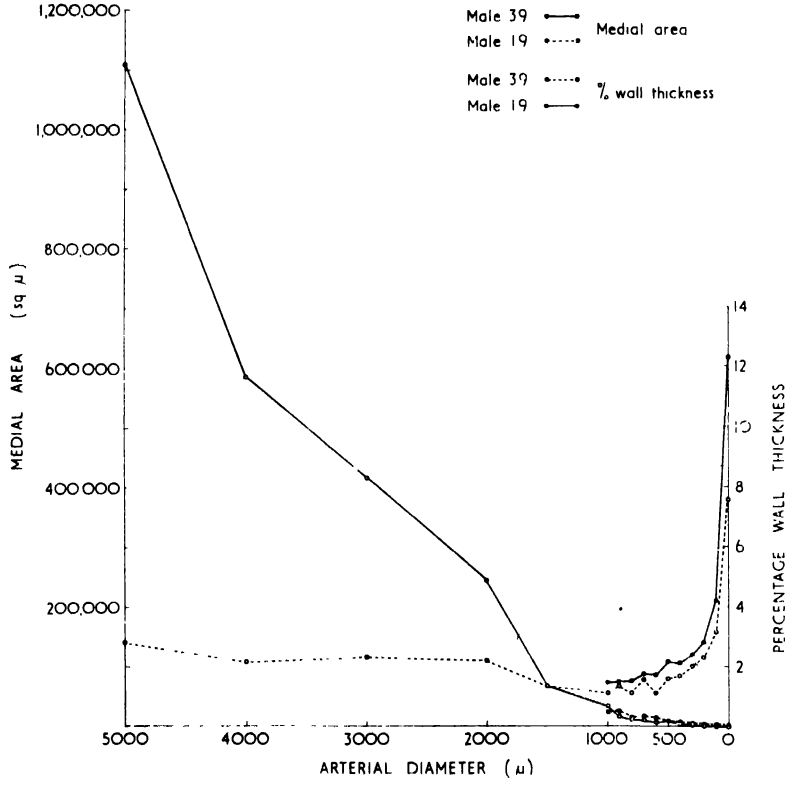


FIG. 168.—Medial area and wall thickness showing relative increase in wall thickness in smaller arteries. Medial area falls with size of artery but at point where wall thickness is increasing the medial area falls less sharply, suggesting that the wall thickness increase is not the result of incomplete distension.

and do not run with airways. They are distributed to respiratory tissue, usually passing directly to alveoli, occasionally to alveolar ducts and respiratory bronchioli. Both aberrant and conventional arteries may give rise to accessory branches.

Frequency.—Even proximal to terminal bronchiolar level, supernumerary arteries far outnumber conventional branches (Fig. 166) but as the former are usually smaller than the conventional, the latter make

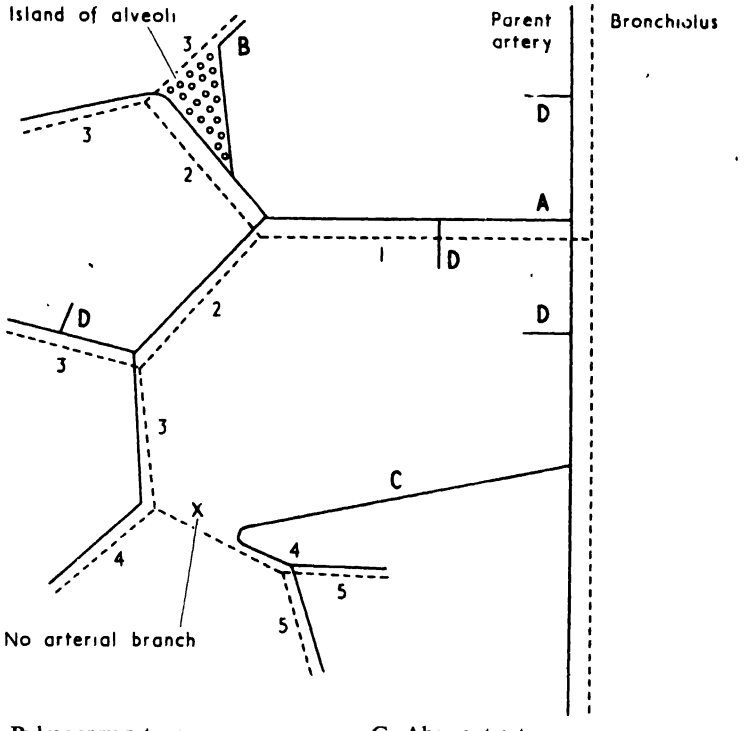


FIG. 169.—Diagrammatic representation of the pattern of pulmonary artery branching—conventional arteries (A and B) and supernumerary arteries (C, aberrant; D, accessory).

the largest contribution to the total cross-sectional area of the side branches. Nevertheless the supernumeraries contribute between 20 per cent and 45 per cent, depending on the region, of the total area of side branches.

Within the acinus the accessories are even more numerous than in the pre-acinar region (Fig. 170). Pump (1961) had described an occasional additional artery at the edge of the lobule.

Almost all side branches of an axial artery are muscular. The exceptions are in the most distal region of the acinus where a muscular artery may give rise to a non-muscular or partially muscular artery and near the hilum where an occasional branch from the elastic region of an axial artery may be elastic or transitional, although even in the elastic region of the artery most side branches are muscular.

It is the external diameter of an artery rather than its proximity to the hilum or its position in the branching pattern or the nature of the accompanying airway, from which the structure of an artery and its percentage wall thickness can be predicted.

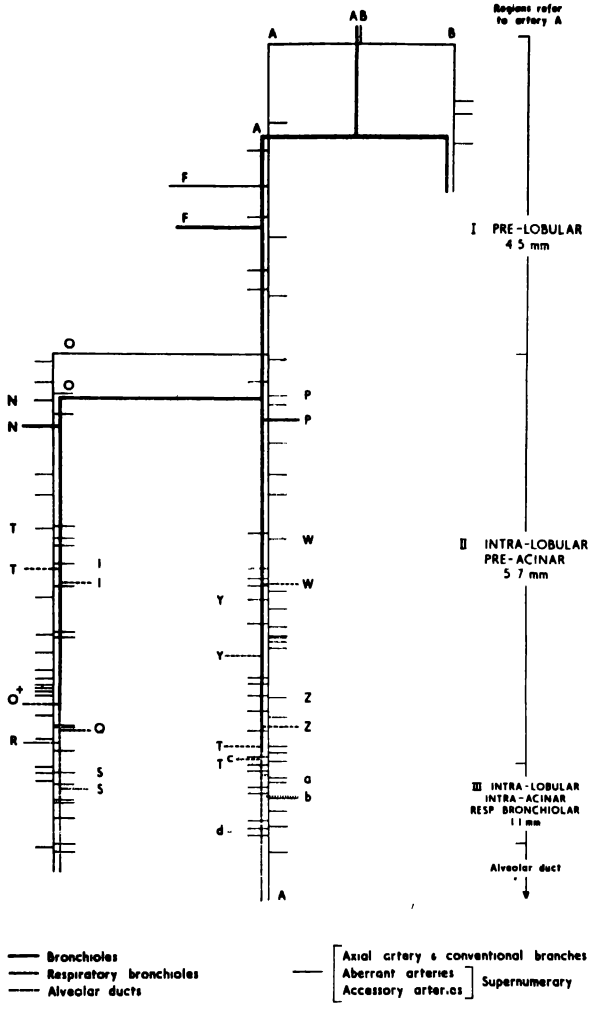


FIG. 170.—Tracing of pulmonary artery branching within the lobule, the arterial branches are designated by reference to the bronchial tree.

INTRA-SEGMENTAL ARTERIAL BRANCHING

Figure 150 illustrates an arterial axial pathway and indicates those side branches which are axial (conducting) pathways and those which supply lobules. It is seen that of the 12 conventional branches nine are lobular supplying one or perhaps two lobules.

The size of an artery accompanying an airway cannot be gauged from the nature of the airway. Figure 171 indicates the size range of arteries accompanying airways within the lobule, the different sizes reflecting different degrees of muscularity.

Comparison of Arteries in Normal and Diseased Lung

It is generally accepted that satisfactory comparison of arteries in normal and diseased lung can be made only between arteries distended by injection. Moreover, it is necessary to establish criteria for valid comparison. In 1955, O'Neal and his co-workers chose arteries running with respiratory bronchioli. This was Elliott's intention but, as Fig. 171 demonstrates, the range of normal wall thickness is too wide for the purpose.

The diagram also shows that in small arteries percentage wall thickness may range from 1–20 and hence no single measurement can be taken as the basis for comparison. Figure 168 illustrates the range of percentage wall thickness for arteries below 8000μ diameter. Within the range 8000μ –200μ it is possible to give 5 per cent as the upper limit of normal, but even within this range subdivision gives a better basis for comparison.

Medial Area

The medial area of arteries of given size is illustrated in Fig. 168. According as the external diameter of the artery is less, so the medial area

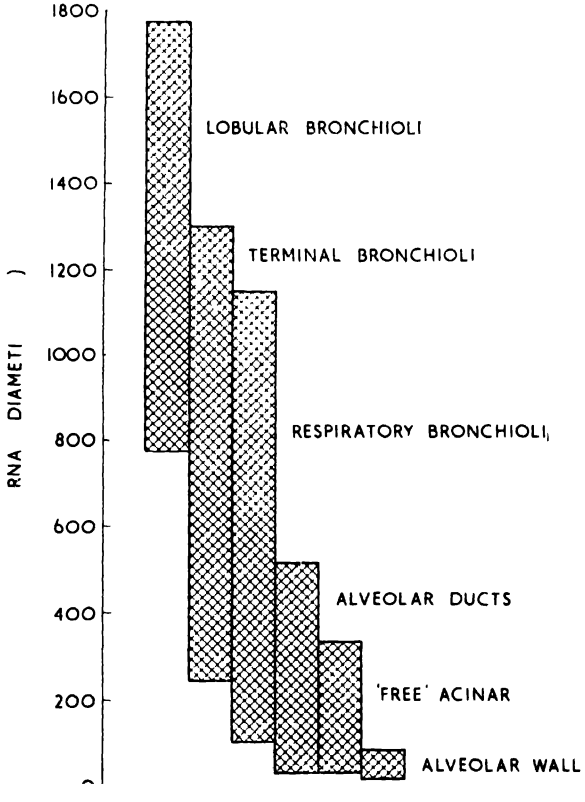


FIG. 171.—Diameter of arteries accompanying peripheral airways and within the acinus.

drops abruptly although the percentage wall thickness (related to the external diameter of the artery) changes little. As the percentage wall thickness rises the medial area drops less sharply, indicating that the rise is due to a real increase in muscularity and not to inadequate injection. The medial area is an important arterial dimension as the medial area is independent of arterial contraction (Ernst, 1925). In an uninjected or inadequately injected artery the percentage wall thickness may rise even though the medial area remains virtually unchanged.

These considerations, summarised below, point to the following as the most satisfactory means yet known of comparing arteries in normal lungs, or in normal and diseased lungs, to asess the size of the media:

(1) Use of injected material.
(2) Comparison by arterial diameter. (Subdivision into 1000μ groups between 8000μ to 2000μ; between 2000 and 1000μ by 500μ; between 1000 and 100μ by 100μ; between 100 and 10μ by 10μ).
(3) Use of both wall thickness and medial area, as these two check each other.

In cases of hypoplasia comparison of external diameter of arteries according to their accompanying airways may reveal vessels with a smaller diameter than in the normal (see p. 124).

The Functional Significance of the Structure of the Pulmonary Artery

Supernumeraries

The supernumerary vessels are an additional blood supply to respiratory tissue. At the periphery of a lobule where this abuts on to a pulmonary artery there is an additional blood supply because of supernumerary vessels. But these are not present where pleura and connective tissue septa are present and it may be that such areas as these are relatively "dry" areas.

Alveolar Wall Arteries

The alveolar walls contain numerous blood vessels larger than capillaries. Up to 83μ in diameter the small vessels may be within the alveolar wall without any particular adventitia identifiable by light microscopy. Then there are vessels surrounded by a thin connective tissue sheath often lying at the junction of several alveoli. These vessels are between 50 and 90μ in diameter.

Elliott's "population studies" of the vessels within the lobule show that roughly 90 per cent of the vessels injected by his technique are within the alveolar wall without an adventitial sheath, while 10 per cent are within the alveolar wall but surrounded by a connective tissue sheath.

Pulmonary Artery Anastomoses

In emphysema and other lung disease the pulmonary arteries often form arcades, both on the pleural surface and within the lung. A striking example of this is seen in Case 46, in which pulmonary arteries of more than 100μ diameter open up to form arcades. It is possible that, at least in part, the supernumeraries contribute to these communications.

The axial arteries of the acini under the pleura often continue to the pleura as vessels of considerable size. They are frequently muscular throughout.

Bronchial Artery

The normal bronchial artery on injection fills only those arteries which run with the main bronchial pathways. At the hilum the bronchial arteries supply the lymph nodes and visceral pleura. Within the bronchial wall they supply an arterial arcade lying within and without the muscle from which the capillaries arise.

Parts of the bronchial artery have a layer of longitudinal muscle as well as a layer of circular muscle. The former has a spiral arrangement suggesting the structure of a sphincter, which develops soon after birth (Verloop, 1948 and 1949), and may reconcile the difficulty in filling the bronchial artery from the pulmonary artery in the normal lung with the opening up of anastomoses in disease.

In the region of the respiratory bronchioli the bronchial artery and pulmonary artery capillary beds are continuous with each other. Both systems drain to the pulmonary veins and so are continuous through the venous capillaries also.

Figure 172 illustrates the points at which conditions within the pulmonary and systemic circulation influence each other, the capillary bed in the respiratory bronchioli and the pulmonary veins. A rise in pressure in the left auricle, as in mitral stenosis, will lead to congestion of the bronchial wall as well as of the alveoli.

The pulmonary artery is responsible for the blood supply of the alveolar capillaries and although, if the pulmonary artery is blocked, the bronchial artery may supply the capillary region, there is no evidence that disease of the bronchial artery can produce alveolar, or for that matter bronchial, disease.

Pre-capillary Anastomoses

The term pre-capillary anastomosis refers to communications larger than a capillary and lying proximal to capillaries in the arterial ramification.

There is no doubt that bronchial artery–pulmonary artery anastomoses develop in disease through the opening up of normal channels, i.e. not through granulation tissue. What is not known is whether these channels

represent dilated capillaries which, because of increased flow, develop arterial walls or whether such vessels are present in normal lung. Verloop, amongst others, has reported muscular walled spiral vessels between the pulmonary and bronchial artery systems within the bronchial wall.

An argument denying the presence of these anastomoses is that they do not open on injection of either system, even with medium which penetrates to vessels of 10–30μ. But in normal lungs injected by Short's method it is not uncommon to find in lung slices length of bronchial artery in the region

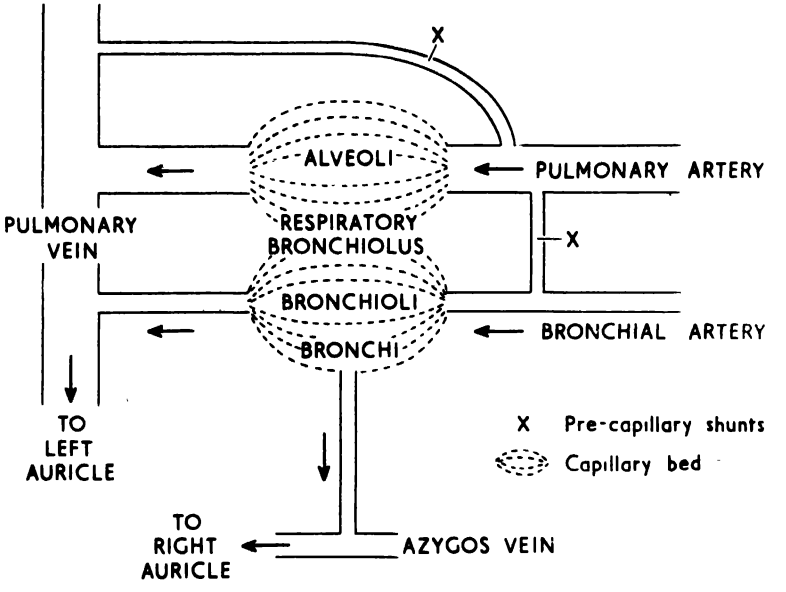


FIG. 172.—Diagrammatic representation of the double arterial and venous systems of the lung. The capillary bed of the bronchi is supplied by the bronchial artery, of the respiratory region by the pulmonary artery; both drain to the pulmonary veins. Only from the bronchi at the hilum does blood drain through the "true bronchial veins" to the right auricle. Precapillary anastomoses are described between pulmonary and bronchial arteries; they may also be found between pulmonary artery and pulmonary vein.

of the small bronchi which have filled. Up till now (by dissection and step sections) the communications have not been demonstrated—suggesting that they are small (Elliott, 1964). The injection technique used generally fills arterial vessels of 30μ and occasionally even those of 10μ (paraffin embedded), but the veins are not filled. It is likely that the cross filling arises from a small pre-capillary anastomosis occurring through small arterial vessels in the broncho-pulmonary sheath.

In disease large communications are frequently and easily demonstrated (Liebow *et al.*, 1959). In general any pathological lesion, be it inflammatory or neoplastic and primary or secondary, is supplied by the bronchial artery system. Any except a small intra-acinar lesion will abut

on to a bronchial wall at some level and therefore impinge on both the bronchial and the pulmonary artery capillary systems. For instance, in cases of bronchiectasis, anastomoses have been described in the fifth generation of bronchi, but these were probably bronchi which were obliterated and saccular; hence the formation of new vessels in granulation tissue may have played a part.

Hilar anastomoses open up in conditions such as interstitial fibrosis. These are probably based on the presence of pre-existing vessels, as with pleural anastomoses. Within the lung they may develop through granulation tissue.

Clubbing

Turner-Warwick (1963*a* and *b*) has recently described the types of anastomoses seen in both acquired and congenital lung disease. In a high proportion of patients with digital clubbing the diameter of the bronchial arteries was seen to be increased; while this points to increased flow, it is not necessarily associated with the opening up of pulmonary artery-bronchial artery anastomoses.

Arterio-venous Anastomoses

The presence of arterio-venous anastomoses is uncertain. As there is a capillary bed between the arterial and venous systems these might enlarge to form a pre-capillary vessel. Tobin (1965) has suggested that pulmonary artery-pulmonary vein anastomoses occur at pre-capillary level in the dog and in man.

ALVEOLAR WALL

Under the light microscope the alveolar wall appears as a continuous membrane and includes numerous capillaries. Special stains reveal collagen, reticulin and elastic fibres in it. The reticulin network is dense, as reticulin fibres seem to support the capillaries, appearing in cross-section like a brush. Elastic fibres are less abundant and are seen as short curly segments.

Electron Microscopy

Electron microscopic studies have as yet contributed little to our understanding of emphysema, though they have elucidated normal structure (Fig. 173). The alveolar wall would seem to consist of:

(*a*) alveolar lining epithelium;
(*b*) ground substance with elastic collagen and reticulin fibres embedded, and
(*c*) capillary endothelium.

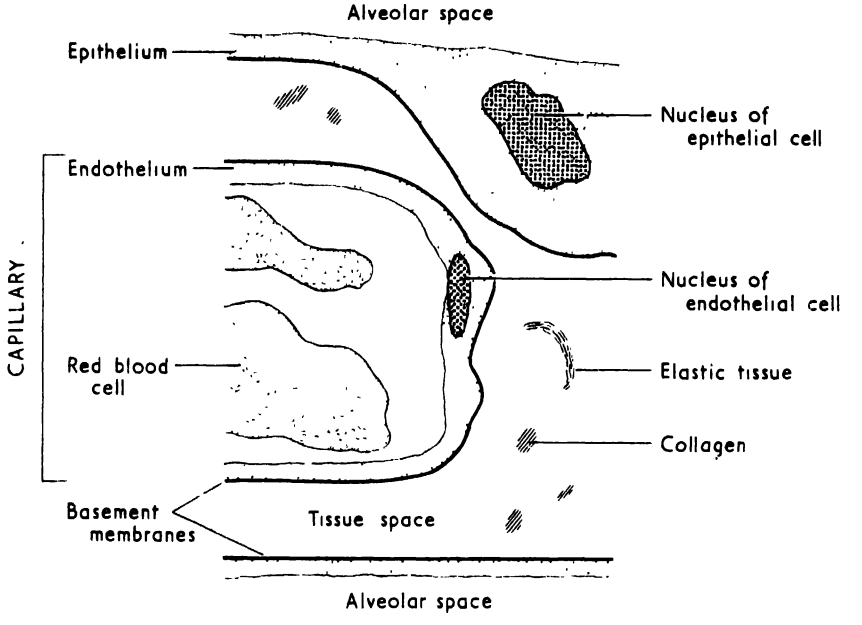


FIG. 173.—Diagrammatic representation of the structure of the alveolar wall revealed by electron microscopy. This diagram follows a part of the alveolar wall which was about 9μ thick in the section prepared for electron microscopy.

Alveolar structure is illustrated diagrammatically in Fig. 173.

Two types of pneumocytes or cells lining the alveoli have been described. Type I covers most of the alveolar surface (Low, 1953); Type II is characterised by osmophilic inclusions (Karrer, 1956) which may be the source of the surfactant lining the alveoli (Buckingham and Avery, 1962; Klaus *et al.*, 1962). From their studies of the foetal lung Campiche *et al.* (1963) suggest that both types are endodermal in origin.

Reynolds (1965) examined the end stage of mixed centriacinar and panacinar emphysema in which the "alveolo-capillary membranes" were lost, and described the residual fibrous trabeculae. The electron microscope revealed that they were covered by Type I and Type II alveolar epithelial cells. The trabeculae included thick elastic fibres and much collagen thought to be the result of the collapse of the connective tissue framework of the lung around the broncho-vascular bundle. Martin and Boatman (1965) reported that in emphysema in the rabbit and in man there was loss of capillary endothelium and partial or complete filling of the capillary lumen with collagen. The very smallness of the amount of tissue examinable by electron microscopy makes it hard to relate what is seen to the lung as a whole.

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