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Chapter 9

The Pathogenesis of Emphysema

JETHRO GOUGH

My thesis is that a reasonable interpretation of causation can be assigned to those types of emphysema that have a selective distribution. This idea is based on a modification of the Ciba classification.[8] On the other hand, the types that are unselective belong to the group that are designated as primary, constitutional or atrophic, and cannot at the present time have a cause assigned to them. "Primary" emphysema can be described in terms of anatomical changes, but as far as its pathogenesis is concerned we are probably no further on than Waters[37] was in 1862, when he wrote that "I believe that emphysema is the result of some degenerative process and although it would be very satisfactory to be able to speak positively as to the exact nature of the degeneration, yet for all practical purposes it is sufficient to point out the general pathology of the malady." After excluding diseases associated with a previous history of cough, he concludes that "the frequency with which the disease attacks both lungs and the uniformly equal characters of the morbid changes observed throughout all parts of the lung" convinced him of the degenerative characteristic of the disease. There seems to be little doubt that this type is the condition that we speak of as primary generalized panacinar or paniobular emphysema, which is unselective in its distribution in terms of the components of the acini or lobules.

SELECTIVE EMPHYSEMA

In types with selective distribution we can come more to grips with causation. We can be most sure about types resulting from deposition of dust. These dust depositions can be conveniently divided into two main groups, those from industrial dust and dust from general atmospheric pollution.

Industrial Dust, Coal—Focal Dust Emphysema (FDE)[14, 15]

A study of thousands of lungs from coal workers has shown a sequence of events leading to a characteristic emphysema. In the young coal miner with short exposure to dust, dying of accident or of nonpulmonary disease, there is an accumulation of coal dust specifically related to the terminal and respiratory bronchioles (Fig. 59). The lungs can evidently withstand this deposition without harm for some years. Emphysema then develops, and, in miners who have been exposed for 20 years, some degree of dilation of the proximal orders of respira-



FIG. 59. From a young coal miner. Deposition of dust around terminal and respiratory bronchioles. This is the pre-emphysema stage. (× 2.)

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tory bronchioles is usual and may be marked. After 40 years of dust exposure, the majority of miners will show FDE, although there is a surprising range in the quantity of dust deposited and the degree of emphysema in miners working under similar conditions. FDE refers to dilation of the respiratory bronchioles and there can be no doubt, because of the time sequence, that the dust deposition precedes the emphysema. Typical examples occur without any other contributory causes, and in characteristic cases there is a strict anatomical relationship between the emphysema and the dust foci. Furthermore, FDE was produced by Heppleston[19] in rabbits exposed to coal dust in mines. Heppleston[20] later concluded that FDE is a selective dilation of respiratory bronchioles, resulting from atrophy of the smooth muscle in their walls together with contraction of the small amount of connective tissue which develops in response to the dust deposition. Other relatively inert dusts, that is, inert in the sense of not producing much fibrosis, may likewise produce focal emphysema, but usually to a far lesser degree than that seen with coal. Hematite, and iron oxide as in welders, are examples of such dusts. There are two anatomical forms of FDE that result from coal.[15] In one there is very little fibrosis and the lesion consists of a cluster of emphysematous spaces with black walls (Fig. 60). In the other, there is a stellate fibrous nodule with a circle of emphysematous spaces (Figs. 61 and 62). The latter is sometimes called perifocal emphysema. In advanced cases of focal dust emphysema, destructive changes are added to the distensive ones, and severe disintegration of the whole lung structure occurs (Fig. 63).

Dust in General Atmospheric Pollution, Soot

In the lungs of city dwellers, carbon in the form of soot is a usual finding; in older people these deposits are in the walls of emphysematous spaces in the centers of lobules. The soot, or some material associated with it, seems to be the cause of the emphysema because in younger people these deposits can be found without emphysema. The soot is derived mainly from the burning of coal. The localization of emphysema and dust coincides in the respiratory bronchioles, and is most marked in the upper lobes. This type is very similar to the type that is the result of coal. In London, and particularly in Glasgow, the amount of dust deposited is much greater than in Cardiff, which has the cleanest atmosphere for a city of its size in Britain. In 1914, Klotz[21] reported that in Pittsburgh, Pennsylvania, the carbon content of lungs from the general community ranged from 1.2 to 5.3 gm., but in control cases from salubrious Ann Arbor, Michigan, there was only 0.145 to 0.405 and the latter figure represented one person who was 68 years old.

Heard and Izukawa,[18] in London, called emphysema associated with soot "distensive," pointing out its similarity to the focal dust emphysema of coal miners. Soot emphysema alone causes little or no disturbance of respiratory function. Figure 64 shows the typical appearance in a man aged 91, a nonsmoker who died after a prostatectomy.

Centrilobular Emphysema (CLE)

Although focal dust emphysema develops in the centers of lobules, I prefer to reserve the name "centrilobular emphysema" for a condition occurring commonly

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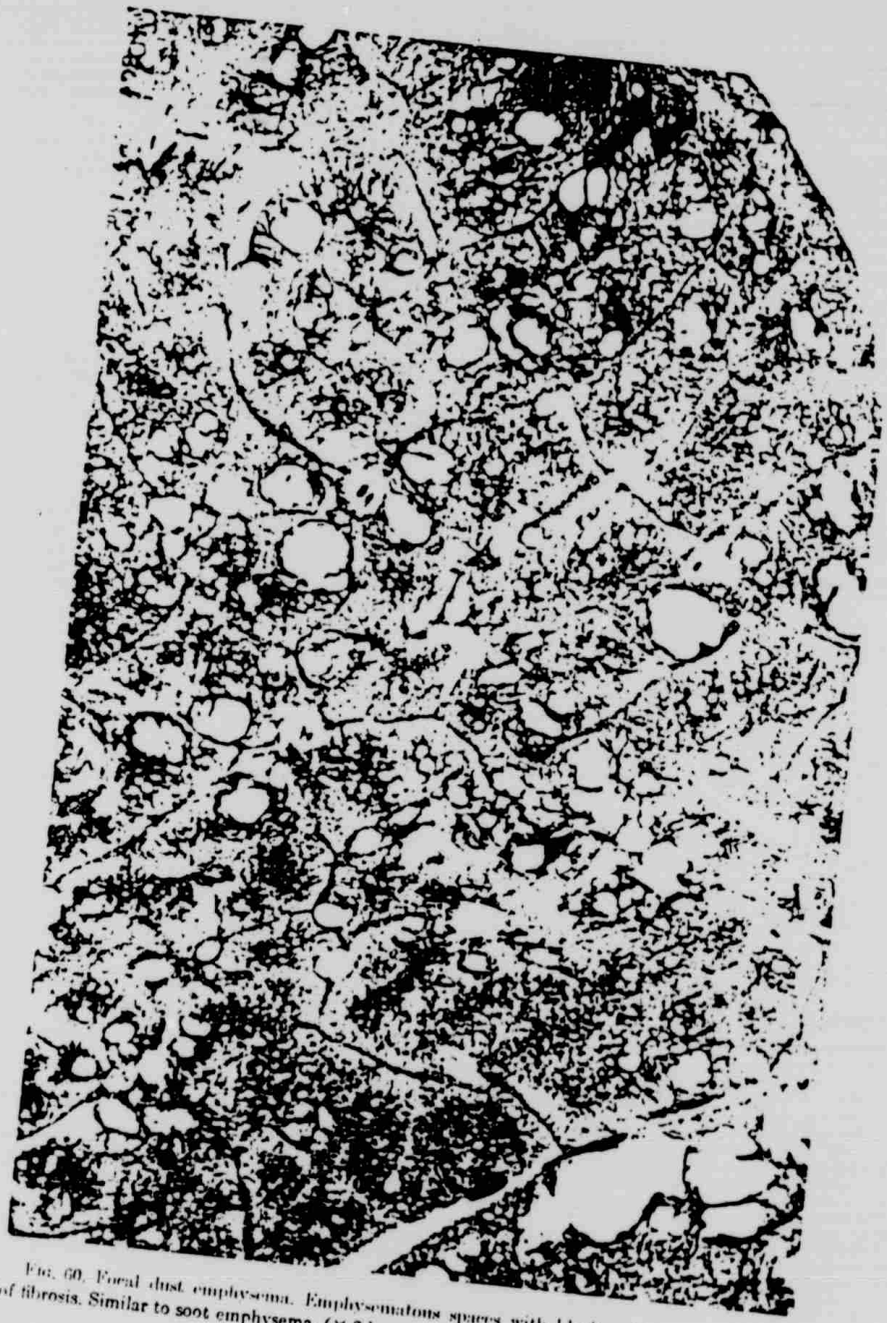


FIG. 60. Focal dust emphysema. Emphysematous spaces with black walls. Little evidence of fibrosis. Similar to soot emphysema. (× 2.)

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FIG. 61. Focal dust emphysema. Central stellate dust nodule and surrounding (perifocal) emphysema. (× 36.)

in the general population and associated with histologic evidence of bronchiolitis. I regard centrilobular emphysema as a distinct pathologic condition resulting from a variety of causes, but mainly as a disease of the 20th century, as judged from the historical evidence discussed below. CLE can be distinguished from panacinar emphysema in lungs fixed in expansion.[18] Its detailed structure has been described by Leopold and Gough.[28] Figure 65 shows the appearances in a

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FIG. 62. Stellate coal nodules surrounded by emphysematous spaces (dilated respiratory bronchioles). (× 2.)

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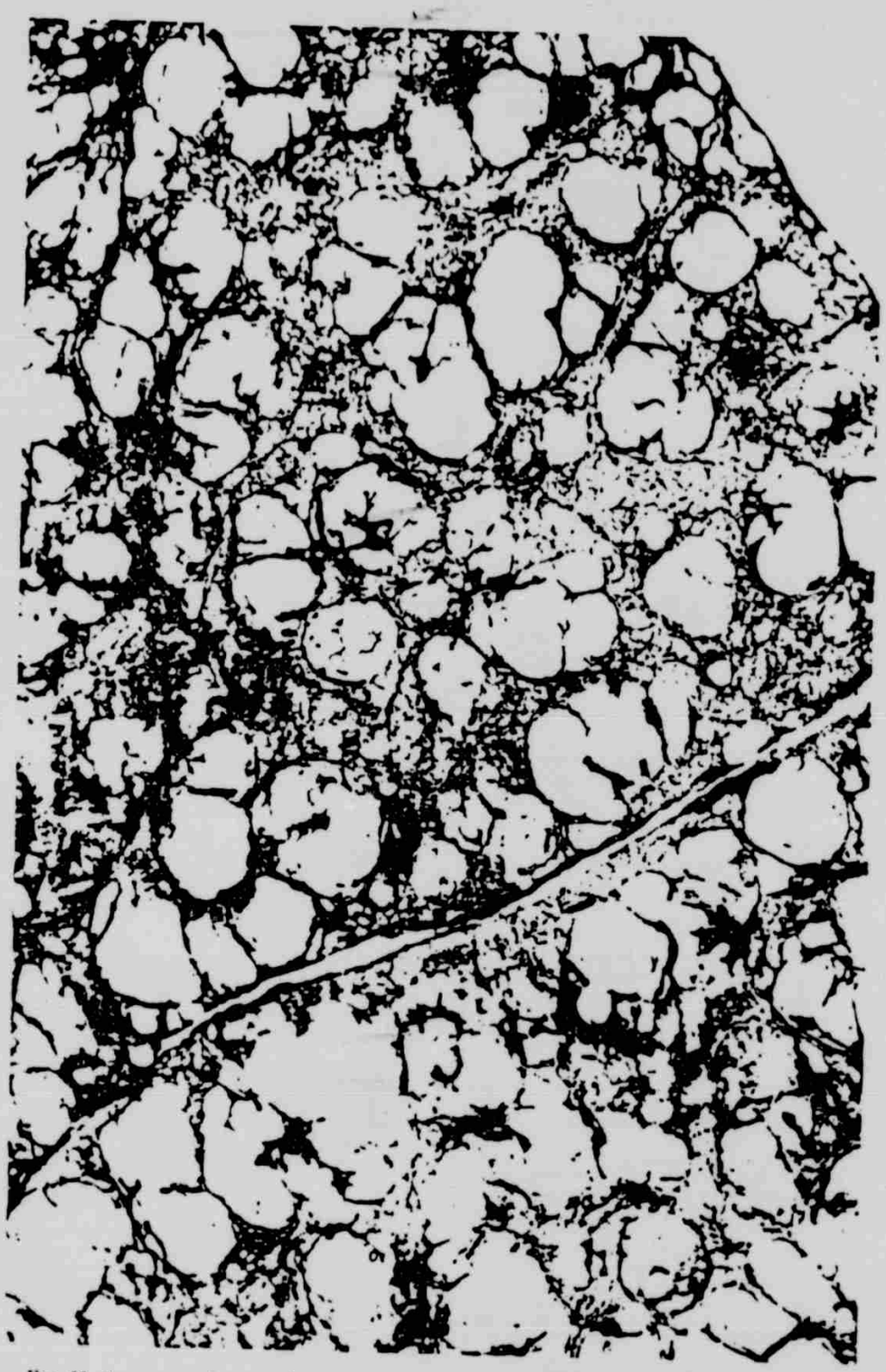


FIG. 63. Severe emphysema in a coal miner. This is common in older miners. It appears to be a combination of focal dust emphysema and panacinar emphysema. (× 2.5.)

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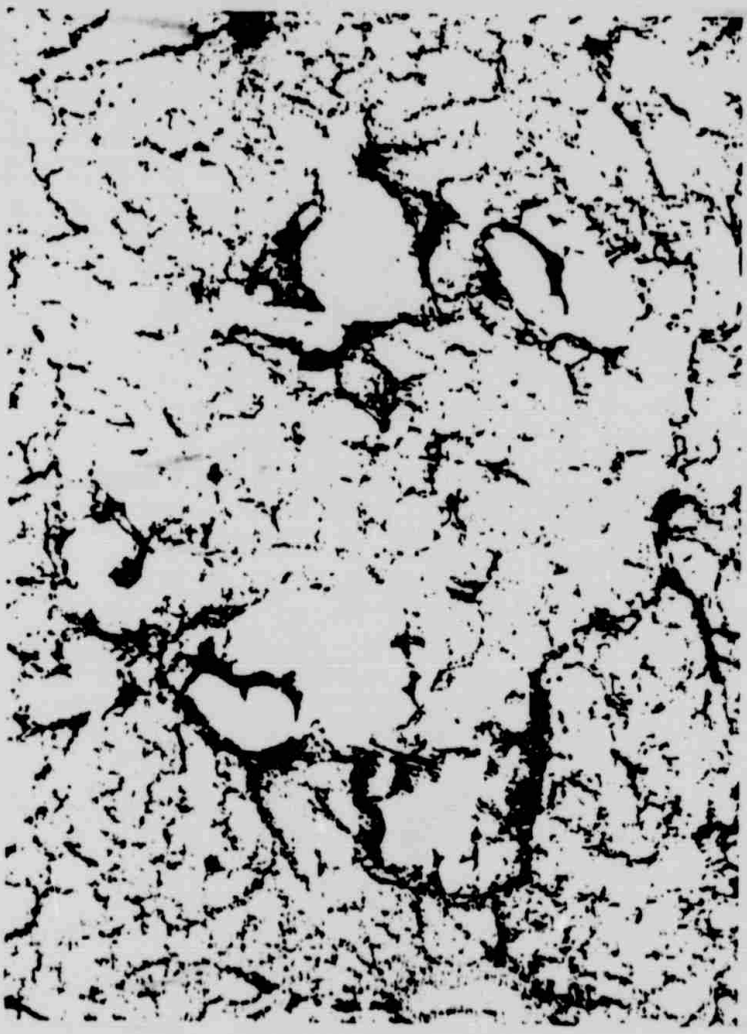


FIG. 64. Soot emphysema. Man aged 91. Nonsmoker; died after prostatectomy. (× 6.)

wet slice of lung fixed in expansion. When one looks into their depths, the centrilobular spaces appear to be black in contrast to the normal peripheral parts of the lobules. Figure 66 shows the structure of an early lesion in a routine histologic section taken from a lung fixed in expansion. Figure 67 shows a plastic cast of a single lesion, showing the distended respiratory bronchiole, with only an occasional alveolus remaining in the wall but with characteristic normal alveolar ducts and sacs located distally. (This cast was made with a liquid plastic silicone rubber monomer made by Flexico Developments, Ltd., London. It has the

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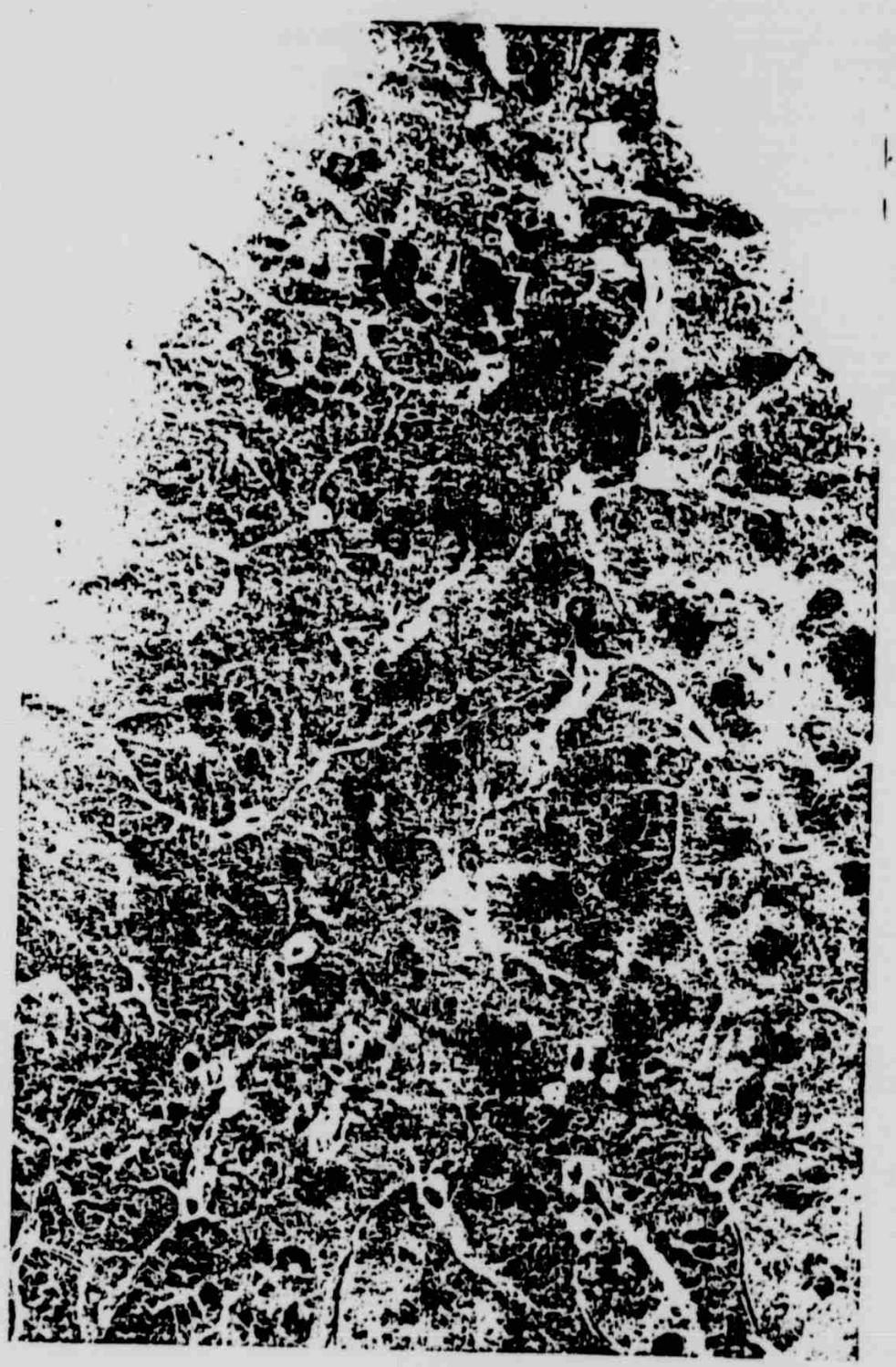


FIG. 65. Slice of lung fixed in expansion. The centrilobular emphysematous spaces appear to be black because of their depth. The outlines of the lobules are white. (× 1.3.)

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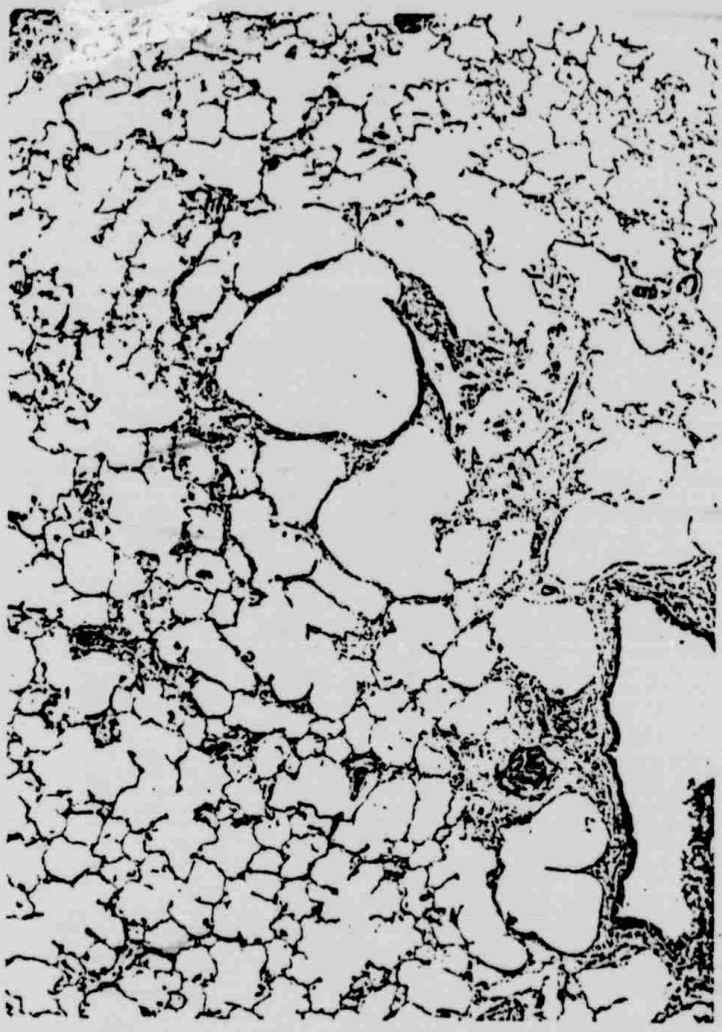


FIG. 66. Early centrilobular emphysema. Man aged 26, killed instantly in a road accident. Cigarette smoker from age of 17. A merchant seaman. There is evidence of inflammation in the terminal and respiratory bronchioles with dilation of respiratory bronchioles but not of distal alveoli. (× 32.)

advantage over vinylite that it does not shrink and remains supple, whereas vinylite casts are brittle.)

In CLE, an inflammatory infiltration is found in the walls of the proximal order of respiratory bronchioles. Lymphocytes and plasma cells, and sometimes

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FIG. 67. A plastic cast of centrilobular emphysema with intact, more distal, alveolar ducts and sacs. A few individual alveoli survive on the wall of the centrilobular emphysematous bulla. The mouth of the supplying bronchiole can be seen cut across as it enters the space. (× 22.)

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polymorphonuclear leukocytes, are present. Eosinophils are few or absent. The inflammation may be represented by fibrosis only. Because the inflammation is limited to the proximal part of the acini, it may be missed in random histologic sections if the section is oriented in such a way that it does not include the respiratory bronchioles. Serial sections, however, will show it. The emphysema is obvious in expanded lungs, but may be completely overlooked in lungs cut at the time of autopsy in the unexpanded postmortem condition. The inflammation must be looked for carefully with good histologic technics. Macrophages containing dust are present in varying numbers, depending on the dustiness of the environment in which the individual lived and worked. The very common association of chronic bronchitis, and especially bronchiolitis, with CLE suggests that infection, atmospheric pollution and cigarette smoking might be the primary causes. These various possibilities are discussed below. Individuals from cities with heavy atmospheric pollution have a great deal of soot in the walls of the emphysematous spaces, but I have also been fortunate in studying CLE in citizens of the relatively unpolluted city of Cardiff. The pathogenesis of CLE is evidently not dependent on the quantity of visible pigment, but may have to do with the kind of pigment. Cases of characteristic CLE occur with little carbonaceous dust, although some "pigment" is present, consisting of brown particles of an uncertain nature. Soot emphysema can easily be mistaken for CLE, but the difference is the presence of bronchiolitis in CLE. The exogenous agent causing CLE is not at all likely to be carbon itself, but this does not exclude associated toxic substances present in the atmosphere from industrial sources, domestic fires and cigarette smoke. These substances may be adsorbed on the carbon.[4]

CLE AND INFECTION RELATED TO AGE INCIDENCE

Children and adolescents 20 years and under. We have previously suggested[26] that CLE might be the result of the "pedunculer" pneumonia that has been described in children. This is a pneumonia surrounding respiratory bronchioles. From a further study of a large number of cases, however, I have concluded that this is not the cause. I have not seen a single example of CLE in childhood or adolescence. The lungs used in the study have come from young people dying of a variety of diseases or from accidents, and they have also included fatal cases of bacterial lung infection of great severity associated with mucoviscidosis. In these latter, although there was very severe bronchitis and often cylindrical and saccular bronchiectasis and large cystlike spaces, CLE was not present. It is true that Williams, Scheuer, and Heard[28] have reported one case that they regard as being centrilobular emphysema in an infant, but they doubted whether it was the same condition as CLE of adults. Furthermore, Leopold[26, 27] has examined lungs of individuals dying of virus influenza, some with and some without complicating bacterial pneumonias, and has found no evidence of the commencement of CLE in cases from the 1957 epidemic or from the 1918–1919 epidemic. This series included children and adolescents. It would seem, therefore, that virus and bacterial pulmonary infections in early life are not an immediate cause of CLE.

Age group from 20 to 40. The youngest individuals whom I have found affected

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have been in the age group between 20 and 40. These have demonstrated slight degrees of the condition seen in deaths from other causes, and also instances of very advanced CLE associated with fatal respiratory failure. The characteristic early lesion shown in Figure 66 represents a 26-year-old man killed instantly in a road accident. He had been a cigarette smoker from the age of 17. There is cellular inflammatory infiltration of a terminal bronchiole and of respiratory bronchioles leading to a centrilobular emphysematous space, whereas the more distal air passages and alveoli are intact. Figure 68 comes from the youngest case of marked CLE that I have seen. It comes from a 20-year-old woman. She was evidently in good health until the age of 18 and was working in the British Women's Land Army, *i.e.*, doing farm work. She had to leave this work, however, because of respiratory symptoms; she died with histologic evidence of bronchiolitis and bronchopneumonia. She was a cigarette smoker.

As Liebow has said "When we look at the lung in advanced emphysema, we are already looking at ashes and can gather all too little regarding the transformation of the structure that was there." I have, therefore, concentrated on early cases coming to autopsy. In this age group between 20 and 40, some of the cases have had a definite history of infection, bronchitis or pneumonia, but there was also a high incidence of cigarette smoking in the women, as well as the men, affected. Cigarette smokers usually have more than normal amounts of pigment in their lungs. This is most obvious in smoking women compared with non-smoking women.

Age groups of over 40 with special reference to smoking. In older age groups, the incidence of CLE rises rapidly, being much more common in men than in women. Its interpretation in terms of pathogenesis, however, is complex. Some of the cases have pulmonary infection as the primary incident of respiratory symptoms. CLE can be found, in characteristic form, restricted to an area of lung around localized areas of bronchitis or bronchiectasis. In these cases there is distinct inflammation of the terminal and first order of respiratory bronchioles. Nevertheless, if we take the group as a whole, there is a striking incidence of cigarette smoking which, if it is not a primary cause, would at least seem to play an important part in perpetuating bronchitis, increasing its severity, and damaging the lung parenchyma. I have rarely found CLE in the lungs of elderly women. In the few instances in which there has been CLE with bronchiolitis, I have found that the women have been cigarette smokers.

It is possible to identify CLE during life. By chance, during bronchography, the radiopaque material used may become trapped in CLE spaces. This is a specific appearance referred to as the "flowers," or "mimosa" or "lily of the valley" appearance (Fig. 69). It has been possible to prove in resected lungs[28] and also by postmortem bronchography[27] that these appearances represent CLE.

Simon[32] found that these appearances, which he called "peripheral pooling," are a common appearance which seem to bear direct relation to other radiologic evidence of emphysema; they were present in 14 out of 21 bronchograms of patients whose standard radiographs suggested emphysema.

Buckley, Tucker, Thorne and Sieker[7] reported six instances of mimosa pattern seen during bronchographic examination. The patients ranged in age from

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FIG. 68. A 20-year-old woman. Good health to the age of 18. Left land work because of respiratory symptoms. Cigarette smoker. Centrilobular emphysema. (×2.)

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FIG. 69. Postmortem bronchogram. This is the mimosa pattern of CLE. It shows that there are patent bronchioles directly supplying the centrilobular emphysematous spaces. (× 3.)

44 to 57. Of them, two were women and four were men, and all were cigarette smokers. They had smoked at least one pack of cigarettes a day. Four of these patients were under 50 years of age, including the two women. In one of Hirschfeld's[22] cases, the pattern was present in a 32-year-old woman who had frequent colds and coughs and had smoked more than 20 cigarettes a day since early adulthood. Leopold and Seal's case[28] was a man aged 50 who had a "smoker's cough"

and smoked 30 cigarettes a day. I have not found any instances where the authors have said that the person was a nonsmoker. On the other hand, authors have, in some reports, drawn particular attention to the fact that individuals were cigarette smokers.

Anderson, Hernandez, Eckert and Foraker,[1] in Jacksonville, Florida, found a particularly close relationship between smoking and CLE as estimated in whole lung sections, but found no such relationship between panacinar emphysema and smoking.

If cigarette smoking is an important cause of CLE, then its incidence should be related to the rise in cigarette smoking in this century. It is fortunate that there is an excellent account of the pathologic anatomy of emphysema as it occurred in Britain a century ago. Waters,[37] mentioned above, a physician *cum* anatomist *cum* pathologist, practicing in Liverpool, England, published his monograph in 1862. He based his classification on lung lobules. He recognized forms of emphysema in which individual lobules were affected, and in a subdivision mentioned partial lobular involvement, but, when he found that only part of the lobule was affected, it was the peripheral part which was involved; *i.e.*, this was the reversal of CLE. Nowhere in his publications does he refer to the center of the lobules being especially affected. It would be very surprising for such an able observer to have overlooked CLE if it had existed commonly in England at that time, if we bear in mind that he described and accurately depicted alveolar wall fenestration, which is the prime pathologic change in the development of the emphysema as he saw it. From his descriptions, what we now call panacinar or panlobular emphysema can be readily identified. Villemin,[34] in France, however, made reference to emphysema commencing in the centers of lobules and extending to the periphery, but did not distinguish CLE as a distinctive type. I would expect that CLE occurred before the cigarette smoking habit commenced, because undoubted cases occur as a result of infection, but the increase in cigarette smoking could account for the apparent great rise in incidence. Atmospheric pollution was severe in Britain a century ago, and thus it would seem that smoke from coal perhaps plays a lesser part in the development of this emphysema than does cigarette smoking. CLE is common in Cardiff, where general atmospheric pollution is low, but the latter cause would account for the particularly high incidence in highly polluted cities and industrial areas.

In summary, CLE is a disease of adults associated with inflammatory changes in the bronchioles. Infection, as in bronchiectasis, can undoubtedly be the cause. Exogenous factors including cigarette smoking and atmospheric pollution are important primary or contributory causes.

Cadmium emphysema

A good example of emphysema due to an inhaled toxic substance is that due to the fumes of cadmium oxide. A zone of normal lobules is present beneath the pleura. This sparing of the periphery can be seen in acute cadmium lung (Fig. 70). Lane and Campbell[25] have described the chronic emphysematous cadmium lung, and illustrated it with whole lung sections that my department prepared.

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FIG. 70. Acute cadmium poisoning. Death on 5th day after exposure. The subpleural lobules show less damage than deeper lobules. (× 1.5.)

FIG. 71. Chronic cadmium emphysema—sparing of peripheral lobules. Similar to confluent CLE. (× 1.5.)

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Figure 71 shows the distribution of the emphysema. In the lobules that are affected, the appearances are those of CLE.

CLE in experimental animals

I have contended that in man CLE is due to external agents and there is confirmation of this view from animal experiments. Several investigators who have administered toxic substances by inhalation or by direct injection have noted that the respiratory bronchioles are particularly vulnerable to damage. Wright and Kleinerman[39] produced CLE in guinea pigs by exposing them to nitrogen dioxide, which is a common constituent in polluted atmospheres and in cigarette smoke. Boren[4] produced a focal destructive effect in mice with nitrogen dioxide adsorbed onto carbon. Gross, Babyak, Tolker and Kaschak[17] produced CLE in rats by the action of papain given by intratracheal injection. Rossing and Clay[31] found that phosgene given to dogs in sublethal doses produces a chronic bronchoalveolitis which is followed by emphysema that is selective in distribution, involving distal respiratory bronchioles and alveolar ducts. Although the bronchioles in these animals were affected by chronic changes, the bronchi were essentially normal in appearance. Bell and Elmes[3] produced CLE in rats by chlorine gas.

Tissue destruction and airway obstruction in the causation of CLE

Leopold and Gough[26] have discussed reasons for believing that destruction of the walls of respiratory bronchioles and adjacent alveoli is an essential lesion in CLE. The lack of support to the bronchioles which results leads to airway obstruction and air trapping. CLE spaces continue to expand selectively as a result of functional obstruction, according to the formula of Green and Shield. On application of this physical principle, emphysematous spaces, being larger than normal air spaces, will tend to expand to a greater degree with respiration, and, once expansion has started, a progressively diminishing expanding force is required for futher expansion.

Alveolar Duct Emphysema

A common occurrence in lungs from the general population is a selective dilation of the alveolar ducts. Heppleston and Leopold[21] noted that increase in diameter of these airways occurs largely at the expense of the associated alveoli, which become wider at their mouths and shallower in depth. The age incidence of this common condition was investigated by Vincent *et al.*[35] The youngest patient who showed it was 45 years old at death. It was uncommon between 40 and 50 years of age, but occurred in about 50% of those dying in the sixth and seventh decades and in more than 81% of subjects dying after 80 years of age. It was not associated with any abnormal clinical symptoms, sign or radiographic finding. I have always considered this to be a simple dilation associated with aging. Giese and Hartung[13] described dilation of the alveolar duct as the beginning of primary atrophic (senile) emphysema, and referred to the "ironing out" of the alveoli. Giese[12] has referred to this condition in several of his earlier pub-

lications. The view that alveolar duct enlargement is an age change resulting from flattening of the alveoli, so that the internal diameter of the ducts is increased, has been confirmed by microradiography.[36]

Lobar Emphysema (Unilobar, Unilateral)

In the Ciba[7] classification of emphysema, the designation "selective" was used in relation to the acinus and thereby to the lobule. In the present context of pathogenesis I am using "selective" on the basis of the acinus and lobules and also in terms of the lobes. Emphysema may be limited to one or more lobes. Lobar emphysema can be considered as consisting of two types.

Type 1, neonatal. The neonatal type is due to a congenital defect in the bronchus supplying a lobe. The newborn child becomes severely dyspneic, and the affected lobe continues to expand and compresses the remainder of the lung and the opposite lung. The condition constitutes a surgical emergency. The cause is to be found in the supplying bronchus. In some cases there is deficiency of the bronchial cartilage,[33] so that the bronchus is flaccid, collapses and acts as a valve. It may also be found in association with congenital heart disease.[23] Other defects, however, such as flaplike folds in the bronchial wall, occur and also give rise to a valvelike action.

Type 2. The second type of unilateral or unilobar emphysema is discovered by routine radiography; the affected part is hyperlucent. These cases may be found in childhood or in adult life. They are thought to be the result of childhood infections, not of maldevelopment, but in some instances that I have seen the bronchi are extremely flaccid, possibly as a result of developmental abnormality. In other instances, however, there has been good evidence of severe chronic bronchiolitis. Although the term "unilobar" is applied, more than one lobe may be affected, leading to total unilateral hyperlucency.

Linear Emphysema, Related to the Framework of the Lung

This form of emphysema has been recognized for a long time. Loescheke[29] described it as occurring under the pleura and along interlobar septa. I have referred to it as linear.[16] In all of the situations in which it is found, it consists of lines of bullae, usually 0.5 to 1 cm., but ranging up to 2 cm., in diameter. Included in this form is what German writers call *subpleural Mantel-emphysem*. Heard and Izukawa[18] refer to it as paraseptal.

Linear emphysema is associated with fibrosis of the pleura and of the interlobular septa. It also occurs along branches of the pulmonary blood vessels. I regard it as being more closely related to honeycomb lung than to emphysema, and in my collection of honeycomb lungs I have all grades from the linear form to fully developed highly characteristic honeycomb lung. I suggest, therefore, that linear emphysema is a "honeycomb" lung of limited extent. It simulates honeycomb lung in that the bullae have distinct fibrous walls (Fig. 72). It is, therefore, likely to have an inflammatory cause. It may be a developmental abnormality, but this is unlikely because it is most common in older age groups. A similar distribution of bullae is, however, found in association with rare developmental conditions, particularly neurofibromatosis. Giese and Hartung[13] also

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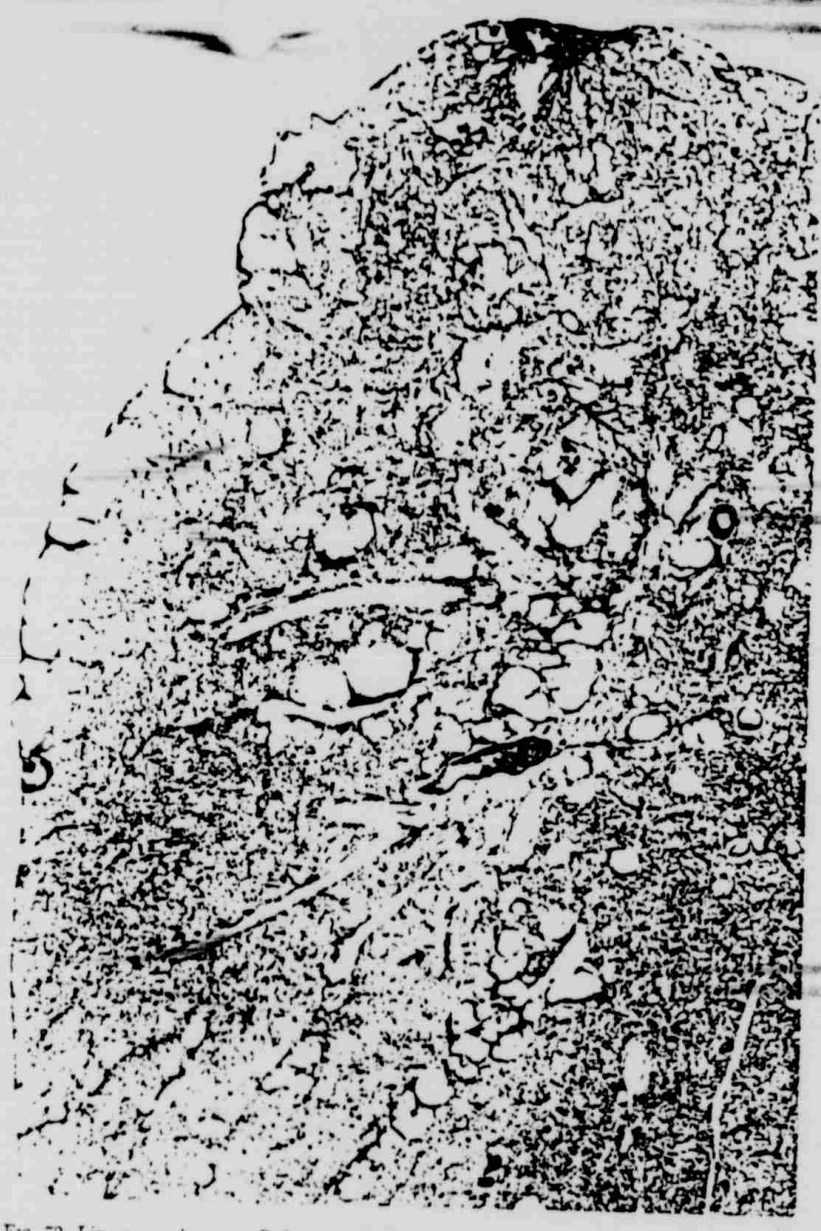
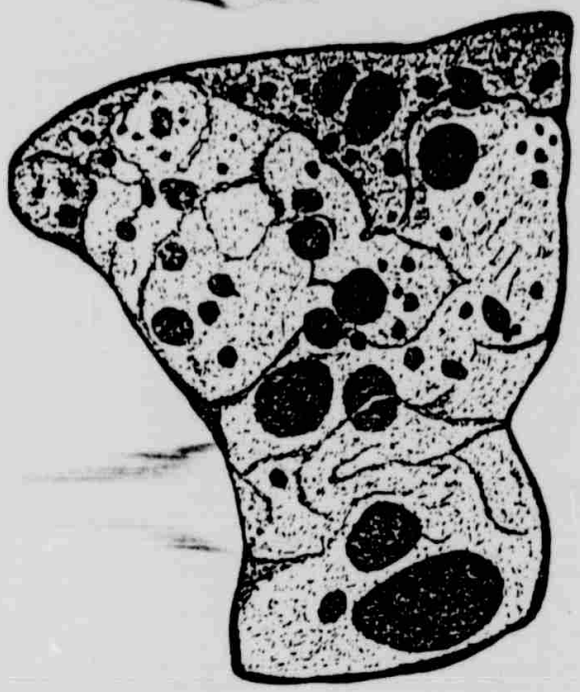


FIG. 72. Linear emphysema. Strings of bullae seen beneath the pleura and along septa. Part of whole lung section. (× 1.)

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Taken from a portion of lung very emphysematous. It shows the appearance of the air-sacs in a dilated condition, with their partitions much ruptured, and full of large perforations. (Drawn by means of the camera lucida.) The black spots shew the perforations. The cavities—the distended and broken-down air-sacs—in the piece of lung from which this was taken had a diameter of 1-16th, 1-20th, and 1-27th of an inch.

FIG. 73. Exact reproduction from Waters' monograph on emphysema of 1862. Shows his familiarity with fenestration as a feature in development of emphysema. The *legend* is his original one. Reproduced with permission (A. T. H. Waters. *Emphysema of the Lungs*. London, J. and A. Churchill, Ltd., 1862).

regard this type of emphysema as being due to scarring and related to the diffuse interstitial fibrosis which causes honeycombing.

UNSELECTIVE EMPHYSEMA

The causes of panacinar and panlobular emphysemas are unknown. Their synonyms are: primary, idiopathic, and constitutional. Contemporary descriptions of primary emphysema emphasize the melting away of alveolar walls, beginning with fenestration. This process was well described and depicted by Waters,[37] more than a century ago. Figure 73 comes from his 1862 monograph. The destruction which eventually arises can be very considerable, leading to bullous changes in many instances. The process of destruction can sometimes be followed by serial

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roentgenographs. To me, the distinguishing characteristic of these cases is the absence of inflammation. It is true, as Waters pointed out, that in some instances there are macrophages containing fatty material. These changes seem, however, to be a result of the breakdown of tissue, and not of a primary fatty degeneration. What metabolic process leads to the thinning and wasting away of the lung tissue is unknown, but study of the enzymes in the lungs may give the answer.

Primary emphysema is known to have a familial incidence. In one family, Eriksson[9] has observed α_1-antitrypsin deficiency in the serum. These observations suggested the possibility of a recessive type of inheritance. In three siblings emphysema occurred early in life, and in two of them the α_1-antitrypsin concentration was less than 10 per cent of normal. No determination was possible in the third case.

An investigation has been made to see whether the surface active agent of Pattle (surfactant) plays a part in the development of emphysema, but the results have been negative. Surfactant has been found in emphysematous lungs by Brown,[5] although he did not describe the type of emphysema that he examined.

The relative frequency of primary emphysema compared with those forms secondary to other processes seems to vary considerably from one country to another. There is so much bronchitis associated with emphysema in Britain that it may obscure some of the cases of the primary type. If we equate primary emphysema with dry emphysema, *i.e.*, that without a prior history of cough and sputum, it is somewhat more common in the United States than in Britain. Fletcher, Jones, Burrow, and Niden[10] say that dry emphysema is more frequent in Chicago (12 per cent), which is a similar prevalence to that described by Gaensler and Lindgren[11] in Boston, Massachusetts (14 per cent). Such cases are relatively uncommon in London. In a recent study in Lyon, France,[6] it was found that 30 per cent of patients with emphysema syndromes did not have initial signs of bronchitis. In Germany also, Professor Giese of Münster (personal communication) tells me that he sees CLE less frequently than we do in Britain, but that "bullous" emphysema is more common.

Associated with the destruction of alveolar walls there are changes in the capillaries, but whether capillary destruction is a primary or a secondary feature is not known. Breakup of elastic tissue could also be a secondary change.

CONCLUSION

I have attempted to assign pathogenesis to some kinds of emphysema, but must agree, a century and a half later, with Matthew Baillie,[2] who wrote in 1803, "It is very much to be regretted that the knowledge of morbid structure does not lead with certainty to the knowledge of morbid actions." However, I take comfort in his next sentence, "Yet surely it lays the most solid foundation for prosecuting such enquiries with success."

Classification of Emphysema Based on Pathogenesis

The Ciba classification of emphysema is based on pathologic anatomy. It can, however, be readily adapted to include pathogenesis where this is known.

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SELECTIVE DISTRIBUTION

Within lobules

1. Focal dust emphysema—dilation of respiratory bronchioles due to industrial dust, like that in coal workers. Destructive changes in the later stages.
2. Soot emphysema—dilation, especially of respiratory bronchioles resulting from soot, particularly from coal burning in atmospheric pollution.
3. Centrilobular emphysema due to bronchiolitis—caused by exogenous agents including cigarette smoking, infection, toxic substances from general atmospheric pollution or special toxic substances, *e.g.*, cadmium oxide fume.
4. Alveolar duct emphysema—simple dilation of alveolar ducts common in older people, probably a simple aging process.

Lobar emphysema

1. Neonatal lobar emphysema due to congenital abnormality of supplying bronchus, either a deficiency of cartilage or abnormal valvelike folds of bronchial mucosa.
2. Hyperlucent lungs of older ages due to same causes as 1 and also a sequela of infection.

Related to the framework of the lung

1. Linear emphysema, also including subpleural micro bullae. Probably same causes as honeycomb lung.

UNSELECTIVE DISTRIBUTION

1. Primary emphysema. Cause unknown. Sometimes familial.

SUMMARY

A reasonable interpretation of causation can be assigned to the types of emphysema that have a selective distribution. This idea is based on a modification of the 1959 Ciba classification. Focal dust emphysema is seen most commonly in coal miners. A similar but less severe form results from general atmospheric pollution. In these instances, the deposit is soot, not coal. Centrilobular emphysema (CLE) occurs in the general population. This condition was distinguished as a specific type from other emphysemas by Gough in 1952.[18] There are multiple causes for it, bronchitis and particularly bronchiolitis being the immediate causes. Neither the bronchiolitis of infectious diseases in childhood nor virus influenza appears to initiate the lesion. CLE is found from the age of 20 onward. Severe examples may be found in the age group between 20 and 40 in both men and women. The incidence increases in older age groups. Cigarette smoking appears to be an important cause whether it is primary or ancillary. CLE can be recognized during life in bronchograms, giving the specific appearance called "flowers" or "mimosa" or "lily of the valley." As evidence in support of the view that inhaled irritant or toxic substances cause CLE, the noxious effect of cadmium oxide fumes in man is quoted. Reference is made to experimental work done by

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others who have found the centrilobular type of emphysema in animals resulting from nitrogen dioxide, paraquat, phosgene, and chlorine. The common alveolar duct emphysema is apparently an age change. Lobar emphysema can be unilobar or unilateral. This group is subdivided into the neonatal type and a type which is discovered for the first time in adult life. Linear emphysema is related to the framework of the lung and includes the subpleural mantle emphysema of the Germans. This type appears to be more related to honeycomb lung than to emphysema. Emphysema with unselective distribution is the primary idiopathic or constitutional type for which no cause is known.

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Gough, J.

00 The Pathogenesis of Emphysema

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SUMMARY

A reasonable interpretation of causation can be assigned to the types of emphysema that have a selective distribution. This idea is based on a modification of the 1959 Ciba classification. Focal dust emphysema is seen most commonly in coal miners. A similar but less severe form results from general atmospheric pollution. In these instances, the deposit is soot, not coal. Centrilobular emphysema (CLE) occurs in the general population. This condition was distinguished as a specific type from other emphysemas by Gough in 1952.[18] There are multiple causes for it, bronchitis and particularly bronchiolitis being the immediate causes. Neither the bronchiolitis of infectious diseases in childhood nor virus influenza appears to initiate the lesion. CLE is found from the age of 20 onward. Severe examples may be found in the age group between 20 and 40 in both men and women. The incidence increases in older age groups. Cigarette smoking appears to be an important cause whether it is primary or ancillary. CLE can be recognized during life by bronchograms, giving the specific appearance called "flowers" or "mimosa" or "lily of the valley." As evidence in support of the view that inhaled irritant or toxic substances cause CLE, the noxious effect of cadmium oxide fumes in man is quoted. Reference is made to experimental work done by others who have found the centrilobular type of emphysema in animals resulting from nitrogen dioxide, papain, phosgene, and chlorine. The common alveolar duct emphysema is apparently an age change. Lobar emphysema can be unilobar or unilateral. This group is subdivided into the neonatal type and a type which is discovered for the first time in adult life. Linear emphysema is related to the framework of the lung and includes the subpleural mantle emphysema of the Germans. This type appears to be more related to honeycomb lung than to emphysema. Emphysema with unselective distribution is the primary idiopathic or constitutional type for which no cause is known.