Anatomic and Histologic Changes of Early Emphysema*

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Most systems of classifying emphysema grade the lesions according to type, distribution, and extent of involvement from barely visible onward. Clinical and anatomic evidence of progression in these lesions suggests the existence of earlier stages. Thirty-nine lungs were studied. All appeared grossly normal but contained widespread macroscopic foci of early centrilobular and panlobular emphysema. Numerous abnormal brownish pigmented alveolar macrophages were found in the adjacent, otherwise intact appearing parenchyma. They were not found in normal lungs. Identical pigmented macrophages were found in sputum specimens obtained from apparently healthy cigarette smokers. Frequency of occurrence appeared related to the number of cigarettes consumed. The brownish pigment resembled tobacco but could not be identified as such. In heavy smokers, many of these cells also contained iron particles, suggesting the possibility of tissue damage. Such cells are thought to produce proteases. Their occurrence prior to evidence of bronchiolar-alveolar destruction may be of particular significance in the various alpha-antitrypsin deficiency states.

The initial lesion of emphysema is unknown. The transition between normal appearing pulmonary tissue and the earliest recognizable destructive changes attributable to the disease have yet to be described. Serious attempts to discern the nature of this important lesion began with the work of Spain and Kaufman in 1953. Others, including Liebow, McLean, Anderson and Foraker, Snider and coworkers, and Boren, have contributed significantly to our knowledge in the matter. Spain and Kaufman have noted early bronchiolar inflammatory changes. Liebow has suggested focal alveolar necrosis and bronchial obstruction. Anderson and Foraker have described alveolitis and McLean, bronchiolitis. The early, subclinical stages of destruction in centrilobular and panlobular disease have been characterized by Snider and colleagues. Boren has noted the contribution of gradually enlarging fenestrae in the genesis of the already well-developed condition. Progressive capillary attenuation has been found to occur by others. Regardless of the predominant morphologic pattern, virtually every element of the lung, vascular and parenchymal, is eventually involved in this process.

Numerous theories—obstructive, inflammatory, irritative, immune, vascular—have evolved. Perhaps multiple factors are capable of inducing the various changes of emphysema, but none has been proved. Associated with each is the concept that once the disease is fully established, the basic lesion is either unrecognizable or long since has disappeared.

In an effort to overcome this shortcoming, several attempts to produce the disease experimentally in animals have been made. Some may have suffered from use of inappropriate subjects. Marked anatomic differences exist between the lungs of various mammalian species and man. However, other experiments have been remarkably successful in producing histologic lesions similar to those seen in man, but none has resulted in a clear
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The existence of naturally occurring emphysema in species other than man has also been investigated. The horse has been found to develop centrilobular, panlobular, paraseptal, and bullous lesions that are histologically and grossly indistinguishable from those of man. Rabbits are afflicted with the disease to an extent that is, at least, similar to the human variety. These studies have not been extended to the degree necessary to find subjects involved with the disease in its beginning stages. Nevertheless, they represent a potentially rewarding approach. In animal or human lungs possessing beginning destructive changes, the initial lesion might well persist in adjacent, more normal tissues.

With the notable exception of the studies of Snider and associates, most efforts to define the earliest changes in man have been limited to descriptions of grossly observable lesions. These lesions have been graded from those barely discernible to the eye onward in terms of form (panlobular, centrilobular, bullous) and extent of destruction. This system is logical and implies progressive development of the disease in tissues that at one time were actually normal.

The study of lungs by fixed inflation and vascular injection techniques has greatly facilitated the classification and grading of these lesions. Use of such methods has led to the realization that, even in the most severely diseased lungs, marked variation occurs in the development of lesions from area to area. Not only may centrilobular, panlobular, and bullous lesions be seen in the same lung, but also lesions of greatly differing size are frequently noted.

By clinical history, it is frequently possible to determine not only the progressive nature of emphysema and its earliest symptoms of functional impairment, but also the preceding period of apparent functional normalcy. Recent physiologic data from patients showing mild hyperinflation, but normal expiratory flow, have been interpreted to indicate a very early stage of the disease. Morphologic correlations are lacking.

The purpose of this paper is to describe: (1) the morphologic characteristics of early destructive...
lesions that cannot be seen with the naked eye occurring in lungs which, with the exception of black pigment deposits, appear grossly normal; (2) the presence of abnormal brownish pigmented macrophages in relatively intact, adjacent tissues which might represent an interface between normal and obviously destroyed parenchyma; and (3) the presence of similar brownish pigmented macrophages in the sputum of apparently healthy smokers.

**Materials and Methods**

In the past three years, 98 individual lungs were randomly obtained at autopsy. Thirty-nine were included in the present study and classified. Selection was based solely on the presence of widespread panlobular or centrilobular lesions which could not be seen without the use of a dissecting microscope. The lesions varied in development from those with beginning tissue loss, distinct from simple ectasia, to those which were sufficiently advanced to be nearly visible. Lungs possessing lesions visible to the unaided eye were excluded from this group. Age ranged from 32 to 85 years (average 59.2 years). Fifteen of the subjects were women and 24 were men. Adequate smoking history was impossible to obtain in 16 of these patients. Twenty-one were smokers, but only limited history was available. None of these persons died of obstructive pulmonary disease.

A thin slice, multicolored latex injection technique, described elsewhere, was used in the preparation of 32 of these lungs. The remaining seven were treated similarly, except they were not injected with latex, and were fixed with buffered 10 percent formalin, rather than acidified formalin. Slightly improved histologic detail was obtainable in sections prepared from these uninjected specimens. Four normal lungs and an additional five lungs with grossly visible emphysema were prepared by latex injection and studied for purposes of comparison.

To determine the presence of pigmented alveolar macrophages in living individuals, sputum collections were obtained from 21 clinically healthy persons, 14 patients with obstructive pulmonary disease, and one with Hamman-Rich disease. Smoking habits, age, sex, occurrence of pigmented macrophages, and diagnosis are tabulated in Table 1. Induction of sputum by inhalation of heated, hypertonic saline aerosols was frequently employed. Specimens were paraffin mounted rather than smeared.

**Results**

Thirty-nine lungs were found which contained widespread foci of early emphysema. These lesions were not visible to the naked eye (Fig 1). Grossly, the tissues in each of these lung slices were indistinguishable from those seen in normal slices with the exception of increased black pigment deposits. However, with the aid of the dissecting microscope, numerous, well-developed foci of panlobular and centrilobular destruction could be seen. Adjacent to these lesions, large areas of apparently normal parenchyma remained (Fig 1). Twenty-two of these lungs contained mixed centrilobular and panlobular disease. Four contained isolated centrilobular lesions, and 13 contained isolated panlobular lesions. Other anatomic types of emphysema, such as traction, bullous, paraseptal and coal-workers pneumoconiosis, were not found and, as a result, will not be given further consideration in the present study.

Centrilobular lesions (Fig 1, 4, 5, 8) in these specimens consisted of focal tissue loss in the distal portion of the respiratory bronchiole, and just beyond in the proximal alveolar duct. Air spaces were confluent. Their walls were thin, atrophic, and disrupted. Occasional fenestrae were visible, as was capillary attenuation. Macrophages containing...
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FIGURE 5. Macroscopic conglomerate of developing centrilobular and acinar lesions. Note interspersed areas of apparently normal tissue in which proliferative macrophages are found. The pulmonary artery was injected with blue latex (same patient as Figs 1, 3, 6, 7; stain, hematoxylin and eosin; original magnification, ×14.5).

FIGURE 6. Histologic section taken from macroscopically normal appearing areas of same lung as seen in Figs 1, 3, 5, 7. Intact alveolar septa with latex-filled capillaries contain numerous, brownish pigmented alveolar macrophages (stain, hematoxylin and eosin; original magnification, ×250).

FIGURE 7. Histologic section demonstrating individual brownish pigmented alveolar macrophages attached to alveolar wall of latex-injected thin slice (same patient as Figs 1, 3, 5, 6, stain, hematoxylin and eosin; original magnification, ×190).

FIGURE 8. Well-developed, nearly visible macroscopic centrilobular lesion in thin slice showing proximal air-space and bronchial involvement (original magnification, ×14.5).

FIGURE 9. Advanced, nearly visible, panlobular emphysema in thin slice. Note marked tissue loss, fenestration, and attenuation of capillaries. Centrilobular lesions were found elsewhere in this person's lungs (Fig. 8). Blue latex was injected into the pulmonary artery; yellow, into the pulmonary veins (original magnification, ×14.5).

FIGURE 10. Histologic section from sputum of an apparently healthy, heavy cigarette-smoking, 32-year-old man (30 cigarettes per day for 14 years). Numerous brownish pigmented macrophages, as described in text, are seen. These cells are representative of those found in the sputum of other cigarette smokers. They are identical to those found in macroscopically intact appearing regions in thin slices containing adjacent lesions of early emphysema (donor 19, Table 1; stain, hematoxylin and eosin; original magnification, ×375).
black pigment deposits were often, but not always, found in the connective tissues adjacent to the involved bronchiole. Inflammatory cell infiltrates were usually minimal to absent. Involved bronchiolar walls showed atrophy and fibrous replacement of remaining tissue. Usually their lumina were patent.

Panlobular lesions were morphologically distinct from the centrilobular variety. They were characterized by a more uniform involvement of alveolar ducts and alveoli throughout the acinus and with extension of the process to groups of acini displayed a lobular pattern (Fig 1, 5, 9). Atrophy, disruption, and loss of normal air-space walls were noted. Fenestrae were poorly developed but somewhat more frequent, and the capillary bed was diminished (Fig 9). Black pigment deposits remained focal but were much less prominent than in centrilobular lesions at this stage.

Microscopic inspection of the areas adjacent to these lesions revealed generally intact parenchymal architecture. However, attached to the surface of the alveolar walls in these regions many brownish pigmented macrophages were found. Their distribution was variable. They occurred separately, in sheets, or in clusters. The sheets were usually one cell thick, and the clusters were no more than two to three cells thick (Fig 6, 7). Associated infiltration by polymorphonuclear cells, lymphocytes, or plasma cells was minimal to absent.

The cell itself was 10 to 15 microns in diameter with an eccentrically placed nucleus. The nuclei were usually single, but occasionally two to three were present. They contained a strangled, finely reticular chromatin, two to three nucleoli, and were medium blue staining with hematoxylin and eosin. The cytoplasm was finely vacuolar and contained a brownish colored pigment. The pigment was dense and presented an almost homogeneous, ground glass appearance (Fig 6,7,10). Discrete “dust” particle inclusions were not frequently observed. In unstained sections, the pigment retained its brownish cast unchanged, and could easily be seen. It, most often, was entirely negative to iron stains. However, in more severely involved areas, the cell would occasionally contain bluish, iron-positive deposits. Between these deposits the brownish pigment could be observed unaltered. It was not a so-called “heart failure” cell. The pigment was negative to PAS stain. With trichrome stain it appeared somewhat olive drab in color. The cell, therefore, most closely resembles an alveolar macrophage as described by Bertalanffy.22 Electron microscopy was not available to discern the presence or absence of lamellar bodies. Direct stains for tobacco tar, an obvious possibility, could not be found (Luna, LG, personal communication, February, 1970).

Atrophic air-space walls in the adjacent, early emphysematous areas contained very few to none of these cells. This was also true of the similarly atrophic air-space walls in lungs with far advanced emphysema, which were included for comparison. In these severely diseased lungs, such cells could be found occasionally, but only in relatively intact areas. None was seen in normal lungs.

These cells were found in the lungs of two patients with early emphysema who were reported to be nonsmokers by family members. They were minimal in one and moderate in the other. There is no explanation for this finding in the presently available data. The remainder were seen in the lungs of 21 patients who were cigarette smokers and in the lungs of 16 patients in whom smoking history was unobtainable.

Large numbers of identical pigmented macrophages were found in the sputum of apparently healthy smokers (Fig 10). The frequency of occurrence of these cells varied in proportion to the number of cigarettes smoked per day. In heavy smokers (20 cigarettes or more per day) often 60 percent to 80 percent of the alveolar cells seen were pigmented. They were classified as grade III. Specimens from light smokers (less than 10 cigarettes per day) contained 10 percent to 20 percent of these cells and were considered grade I. Grade II distribution was ranked between these ranges. Sputum from nonsmokers contained none of these pigmented macrophages. However, normal appearing nonpigmented alveolar macrophages were present. Age did not appear to be a significant factor.

Patients with chronic obstructive pulmonary disease generally had smaller numbers of these cells in their sputum. A few lightly pigmented macrophages could still be found in the sputum of two patients with obstructive disease one and five years after they had quit smoking. No pigmented cells were found in the sputum of nonsmokers with obstructive disease. These data are shown in Table 1.

**Discussion**

The study of lungs by fixed inflation techniques has led to the systematic classification of emphysematous lesions. They have usually been graded in stages from those barely visible to far advanced and as to extent of involvement of the total parenchyma. Detailed investigations of these lesions as they occur exclusively in lungs at the macroscopic level have not been carried out. However, clinical and anatomic evidence of gradual progression of the disease suggests the existence of earlier, probably
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asymptomatic stages which might not be seen grossly.

In the present study widespread macroscopic lesions have been found in the lungs of 39 individuals in whom gross disease could not be seen. The changes described represent the earliest alterations of emphysema that could be discerned in these specimens with the dissecting microscope.

Clinical and physiologic correlations do not exist for these lesions. However, from a speculative point of view, minimally impaired air flow might be anticipated, residual volume could be increased somewhat, and diffusion capacity might eventually be decreased. Also, the partially destroyed, but patent, distal bronchioles might be unusually susceptible to acute inflammation, as well as transient episodes of obstruction.

The finding of abnormal pigmented macrophages lining the septa was unexpected and cannot entirely be explained. It did, however, constitute a cellular reaction that was not seen in normal lungs. It tended to diminish in intensity as the disease progressed to visible levels and was most commonly found to involve alveoli in areas which were otherwise normal appearing. Considering this, and the fact that several of the lungs were fixed un.injected, the possibility of artefact is highly unlikely.

In sputum specimens the occurrence of these pigmented macrophages was related to the number of cigarettes smoked per day, and none was found among the alveolar cells of nonsmokers. Disappearance rates of the cell from the sputum after cessation of smoking are uncertain. None of the apparently healthy group, who provided samples, quit smoking. In those with obstructive disease who had quit, it was still possible to find occasional lightly pigmented cells in one individual after one year and in another after five years. In two others the cell was absent after one and two years, respectively.

The heavy concentration of these cells in the sputum of cigarette smokers, their absence in nonsmokers, and the very appearance of the pigment itself in unstained preparations infer the possibility of a relationship to some component of tobacco. Unfortunately, it was impossible to investigate this hypothesis further, since a direct stain for tobacco itself in unstained preparations infers the possibility of the pigment to be independent of the presence of iron.

Auerbach and associates have described brownish pigmented granulomata in the lungs of cigarette-smoking dogs, together with induced emphysema-like changes. Dontenwill has found concentrations of brownish pigmented macrophages in the alveoli of hamsters exposed to cigarette smoking and mentions that they have been previously defined as "smoke cells" by Otto.

Factors other than tobacco may be capable of producing a similar reaction. Lungs containing these cells and early lesions of emphysema were obtained from two persons who had never smoked. In 16 others smoking history was unobtainable. A few of these individuals also may have been nonsmokers. It is conceivable that they lived in close proximity to other heavy smoking persons and, thus, were secondarily exposed. However, data do not exist to support this possibility.

Yang in his study of aging rat lungs has found

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*COPD: Chronic obstructive pulmonary disease.

Table 1—Sputum Findings.

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aggregates of macrophages and granular pneumocytes deposited on alveolar walls that blend into emphysematous appearing septa, which are relatively free of this cell. Freeman and co-workers have noted small collections of macrophages in distended alveolar ducts adjacent to areas of nitrogen dioxide-induced centrilobular destruction in rats. The occurrence of pigment was not mentioned in either study, but, as noted above, the brownish pigment may simply indicate the presence of one agent out of many which are capable of evoking this type of response.

Yang considered the adjacent, atrophic septa to represent a later stage in the development of the initial lesion, which gradually disappeared as the disease progressed. The association of these lesions with nearby atrophic septa is similar to the present findings in early human emphysema.

Recent studies in alpha1-antitrypsin deficiency states describe the presence of digestive enzymes in alveolar macrophages. Output of proteases by these cells, unopposed by sufficient quantities of antienzyme, is considered to be a possible mechanism in the production of alveolar damage. The finding of large numbers of brownish pigmented macrophages in lungs afflicted with early emphysema and in the sputum of cigarette smokers tends to support this concept.

Theoretically, increased exposure to an appropriate stress might result in the appearance of increased numbers of these cells. As a result, increased amounts of protease might be produced. In sputum samples the stress appropriate to the production of increased numbers of these cells appeared to be related to the number of cigarettes smoked. If the phenomenon is dose related, then increasing concentrations of enzyme might overcome not only reduced levels of antienzyme, but even normal levels, and, thereby, produce tissue damage. The finding of iron particles in some of the pigmented macrophages obtained from heavy smokers and in tissue sections where deposition of the cell was heavy suggests contact with blood and perhaps some form of tissue damage.

This important cell is also thought to play a significant role in the pathogenesis of the resolution phase of pneumococcal pneumonia, hematite lung, coal-worker’s lung, and silicosis. Recently, Harris and co-workers have investigated the alveolar macrophage in lavages obtained from five healthy nonsmokers and six smokers. In the smoking group, increased numbers of macrophages were found and studied by electron microscopy. Many large lysosomal bodies and crystal or fiber-like structures were present. Endoplasmic reticulum and Golgi vessels were increased. Investigation of glucose metabolism revealed higher energy requirements and phagocytosis was active. The authors considered these cells to represent a protective mechanism allowing for the removal of the irritating components of cigarette smoking. They also proposed that the cell could contribute to the pathogenesis of lung disease by the release of lysosomal enzymes which, in turn, could lead to tissue damage.

Centrilobular disease has been associated with intermediate levels of antitrypsin deficiency and panlobular disease with severe deficiency. In these former states the evidence of a definite relationship between anatomic disease and antitrypsin lack has been inconsistent. Different etiologic factors may also play a role in the genesis of each form.

In the present investigation distribution of macrophages varied somewhat with the type of lesion. Brownish pigmented cells were less prominent in tissues adjacent to early centrilobular disease than in tissues adjacent to panlobular disease, and they were rarely seen in peribronchiolar connective tissues. However, in centrilobular lesions fixed tissue macrophages containing deposits of black pigment were found around the involved distal bronchiole. In contrast, black pigment deposition was usually sparse or absent in early panlobular lesions.

Pratt and associates and Snyder and colleagues have considered centrilobular black pigment deposition to occur secondary to the lesion itself. Both base their conclusion on the finding of concomitant areas of nonpigmented centrilobular disease. Similar, nonpigmented lesions were observed in the present study. The fibrotic, partially destroyed character of the distal bronchiole suggests entrapment of the anthracotic pigment in already present macrophages, and possibly obstructed lymph channels.

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