network of immune and inflammatory cells and additional proteinases that contribute to emphysema have subsequently been identified.

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

Upon exposure to oxidants from cigarette smoke, macrophages and epithelial cells become activated, producing proteinases and chemokines that attract other inflammatory and immune cells. One mechanism of macrophage activation occurs via oxidant-induced inactivation of histone deacetylase-2, shifting the balance toward acetylated or loose chromatin, exposing nuclear factor-κB sites, and resulting in transcription of matrix metalloproteinases, proinflammatory cytokines such as interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α); this leads to neutrophil recruitment. CD8+ T cells are also recruited in response to cigarette smoke and release interferon-inducible protein-10 (IP-10, CXCL-7), which in turn leads to macrophage production of macrophage elastase (matrix metalloproteinase-12 [MMP-12]). Matrix metalloproteinases and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin also serve as a macrophage chemokine, fueling this destructive positive feedback loop.

Autoimmune mechanisms may promote the progression of disease. Increased B cells and lymphoid follicles are present in patients, particularly those with advanced disease. Antibodies have been found against elastin fragments as well; IgG autoantibodies with avidity for pulmonary epithelium and the potential to mediate cytotoxicity have been detected.

Concomitant cigarette smoke–induced loss of cilia in the airway epithelium and impaired macrophage phagocytosis predispose to bacterial infection with neutrophilia. In end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory response, suggesting that mechanisms of cigarette smoke–induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation.

Cell Death Cigarette smoke oxidant-mediated structural cell death occurs via a variety of mechanisms including rt801 inhibition of mammalian target of rapamycin (mTOR), leading to cell death as well as inflammation and proteolysis. Involvement of mTOR and other senescence markers has led to the recent concept that emphysema resembles premature aging of the lung. Uptake of apoptotic cells by macrophages results in production of growth factors and dampens inflammation, promoting lung repair. Cigarette smoke impairs macrophage uptake of apoptotic cells, limiting repair.

Ineffective Repair The ability of the adult lung to repair damaged alveoli appears limited. It is unlikely that the process of septation that is responsible for alveologenesis during lung development can be reinitiated. The capacity of stem cells to repopulate the lung is under active investigation. It appears difficult for an adult human to completely restore an appropriate extracellular matrix, particularly functional elastic fibers.

PATHOLOGY

Cigarette smoke exposure may affect the large airways, small airways (≤2 mm diameter), and alveoli. Changes in large airways cause cough and sputum, while changes in small airways and alveoli are responsible for physiologic alterations. Emphysema and small airway pathology are both present in most persons with COPD; however, they do not appear to be mechanistically related to each other, and their relative contributions to obstruction vary from one person to another.

LARGE AIRWAY

Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production that define chronic bronchitis, but these abnormalities are not related to airflow limitation. Goblet cells not only increase in number but in extent through the bronchial tree. Bronchi also undergo squamous metaplasia, predisposing to carcinogenesis and disrupting mucociliary clearance. Although not as prominent as in asthma, patients may have smooth-muscle hypertrophy and bronchial hyperreactivity leading to airflow limitation. Neutrophil influx has been associated with purulent sputum of upper respiratory tract infections. Independent of its proteolytic activity, neutrophil elastase is among the most potent secretagogues identified.

SMALL AIRWAYS

The major site of increased resistance in most individuals with COPD is in airways ≤2 mm diameter. Characteristic cellular changes include goblet cell metaplasia, with these mucus-secreting cells replacing surfactant-secreting Clara cells. Smooth-muscle hypertrophy may also be present. These abnormalities may cause luminal narrowing by fibrosis, excess mucus, edema, and cellular infiltration. Reduced surfactant may increase surface tension at the air-tissue interface, predisposing to airway narrowing or collapse. Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may cause proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts where the fibers are concentrated as rings around alveolar entrances. Narrowing and drop-out of small airways precede the onset of emphysematous destruction.

LUNG PARENCHYMA

Emphysema is characterized by destruction of gas-exchanging air spaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli. Their walls become perforated and later obliterated with coalescence of small distinct air spaces into abnormal and much larger air spaces. Macrophages accumulate in respiratory bronchioles of essentially all young smokers. Bronchoalveolar lavage fluid from such individuals contains roughly five times as many macrophages as lavage from nonsmokers. In smokers' lavage fluid, macrophages comprise >95% of the total cell count, and neutrophils, nearly absent in nonsmokers' lavage, account for 1–2% of the cells. T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers.

Emphysema is classified into distinct pathologic types, the most important being centriacinar and panacinar. *Centriacinar emphysema,* the type most frequently associated with cigarette smoking, is characterized by enlarged air spaces found (initially) in association with respiratory bronchioles. Centriacinar emphysema is usually most prominent in the upper lobes and superior segments of lower lobes and is often quite focal. *Panacinar emphysema* refers to abnormally large air spaces evenly distributed within and across acinar units. Panacinar emphysema is usually observed in patients with α_1AT deficiency, which has a predilection for the lower lobes.

PATHOPHYSIOLOGY

Persistent reduction in forced expiratory flow rates is the most typical finding in COPD. Increases in the residual volume and the residual volume/total lung capacity ratio, nonuniform distribution of ventilation, and ventilation-perfusion mismatching also occur.

AIRFLOW OBSTRUCTION

Airflow limitation, also known as airflow obstruction, is typically determined by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to total lung capacity. Key parameters obtained from spirometry include the volume of air exhaled within the first second of the forced expiratory maneuver (FEV_1) and the total volume of air exhaled during the entire spirometric maneuver (forced vital capacity [FVC]). Patients with airflow obstruction related to COPD have a chronically reduced ratio of FEV_1/FVC. In contrast to asthma, the reduced FEV_1 in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common. Asthma patients can also develop chronic (not fully reversible) airflow obstruction.

Airflow during forced exhalation is the result of the balance between the elastic recoil of the lungs promoting flow and the resistance of the airways limiting flow. In normal lungs, as well as in lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil and because the cross-sectional area of the airways falls, raising the resistance to airflow. The decrease in flow coincident with decreased lung