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Particles Causing Lung Disease

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The lung has a limited number of patterns of reaction to inhaled particles. The disease observed depends upon the location: conducting airways, terminal bronchioles and alveoli, and upon the nature of inflammation induced: acute, subacute or chronic. Many different agents cause narrowing of conducting airways (asthma) and some of these cause permanent distortion or obliteration of airways as well. Terminal bronchioles appear to be particularly susceptible to particles which cause goblet cell metaplasia, mucous plugging and ultimately peribronchiolar fibrosis. Cancer is the last outcome at the bronchial level and appears to depend upon continuous exposure to or retention of an agent in the airway and failure of the affected cells to be exfoliated which may be due to squamous metaplasia.

Alveoli are populated by endothelial cells, Type I or pavement epithelial cells and metabolically active cuboidal Type II cells that produce the lungs specific surfactant, dipalmytol lecithin. Disturbances of surfactant lead to edema in distal lung while laryngeal edema due to anaphylaxis or fumes may produce asphyxia. Physical retention of indigestible particles or retention by immune memory responses may provoke hyaline membranes, stimulate alveolar lipoproteinosis and finally fibrosis. This later exuberant deposition of connective tissue has been best studied in the occupational pneumoconioses especially silicosis and asbestosis. In contrast emphysema a catabolic response, appears frequently to result from leakage or release of lysosomal proteases into the lung during processing of cigarette smoke particles.

The insidious and probably most important human lung disease due to particles is bronchiolar obstruction and obliteration, producing progressive impairment of air flow. The responsible particle is the complex combination of poorly digestive lipids and complex carbohydrates with active chemicals which we call cigarette smoke. More research is needed to perfect, correct and quantify our preliminary picture of the pathogenesis of lung disease by particles, but a useful start has been made.

Many gaps exist in our knowledge of the structural pathology of the reactions produced in the lung by inhaled particles. There are even fewer data about their biochemical effects. Evidence concerning human responses consists largely of symptom frequencies, of physiological abnormalities and of X-ray changes. In only a few instances has the pathology been carefully studied. There are several reasons for this, but the major one is that human lung tissue is infrequently available for study because the immediate effects are usually clinically mild, or inapparent, often insidious, and usually do not require a lung biopsy for management. Human occupational exposure is frequently to particles composed of mixtures of chemicals representing commercially useful materials. Thus exposures to pure materials such as toluene diisocyanate, vinyl chloride or to cadmium are less frequent than to mixtures like coal, welding fumes, foundry dust, cotton dust, paint aerosols or diesel exhaust. The probable structural changes in human lungs from such complex mixtures must be inferred from single agent diseases which have similarities in symptoms and histories, chest X-ray studies, and pulmonary physiological measurements.

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In this field the animal exposure studies have been limited, used small numbers and short periods. Thus accurate information with which to extrapolate to human disease due to long-term exposure is relatively rare. However, it is possible to piece together what is known and provide some plausible estimates concerning the pathological changes at the cell and tissue levels. Particles may be innately harmful, as are cobalt and cadmium, and many organometallic agents or they may be practically harmless but adsorb gases to hold active chemicals in or near cells to produce ill effects beyond those of the particle or gas alone; for example formaldehyde on carbon or polyurethane.

Natural and man-made particles constitute a wide variety of agents which produce acute and chronic changes in the lung. The list of agents is so long (Table 1) that even a brief discussion of the changes associated with each would be beyond the scope of this paper. However, an even better reason for taking a different approach is the fact that the lung has limited number of patterns of reaction. This paper will describe these patterns and relate the agents to them.

A useful first step is to divide the lung into three zones: conducting airways, terminal bronchioles and alveoli. The former are airways down to the preterminal and terminal bronchioles which constitute the second zone. The alveolar zone includes respiratory bronchioles

Table 1. Sources and occupational groups affected by particles.[a]

Source	Workers affected	Site affected		Reference
		Airways	Alveoli	
Bacteria				
Aerobactor cloaceae Phialophora species	Air conditioner, humidifier		+	(1)
E. coli endotoxin	Textile workers (mill fever)	+	+	(2)
Pseudomonas sp.	Sewer workers	+	+	(3)
Fungi	Farmer's lung group			
Aspergillus sp. Micropolyspora faeni	Farmers	+		(4)
Aspergillus clavatus	Malt workers	+		(5)
Cladosporium sp.	Combine operators	+	+	(6)
Verticillum sp.				
Alternaria sp.				
Micropolyspora faeni	Mushroom workers	+	+	(7)
Penicillium casei	Cheese washers	+		(8)
Penicillium frequentans	Suberosis (cork)	+		(9)
Thermoactinomyces (vulgaris) sacchari	Bagassosis, sugar cane products	+	+	(10)
Amoeba				
Acathamoeba castellani	Air conditioning and humidifier	+	+	(11)
Acathamoeba polyphaga				
Naegleria gruberi				
Vegetable origin				
Castor bean (ricinine)	Oil mill	+		(12)
Coffee bean	Roasters	+		(13)
				(14)
Cotton, hemp, flax, jute, kapok	Textile workers	+		(15)
Flour dust	Millers	+		(16)
Grain dust	Farmers	+		(17)
Gum, arabic, gum	Printers	+		(18)
Papain	Preparation workers		+	(19)
Proteolytic enzymes from *Bacillus subtilus* (subtilisin, alcalase)	Detergent workers		+	(20)
Tamarind seed powder	Weavers	+		(21)
Wood dust	Canadian red cedar, South African boxwood, rosewood (*Dalbergia* sp.)			
Animal origin				
Ascaris lumbricoides	Zoologists	+		(23)
Ascidiacea	Oyster culture	+		(24)
Dander	Farmers, fur workers, grooms	+		(25)
Feathers	Turkey and chicken farmers	+		(26)
Insect citin				
Sitophilus granarius	Flour	+		(27)
Mayfly	Outdoorsmen	+		(28)
Screwfly	Screw-worm controllers	+		(29)
Pancreatic enzymes	Preparation workers	+	+	(30)
Rat serum, urine	Laboratory workers	+	+	(31)
Inorganic chemicals				
Alumina abrasives	Manufacturing workers		+	(32)
Aluminum (fluorine)	Smelter workers	+		(33)
Brick dust	Fire brick makers	+		(34)
Calcium hydroxide, tricalcium silicate	Cement workers	+		(35)
Chromium	Casters	+		(36)
Copper sulfate and lime	Vineyard sprayers		+	(37)
Fiberglass	Production, Insulation	+		(38)
Foundry	Foundry workers	+		(39)
Nickel sulfate	Platers	+		(40)
Platinum, chloroplantinate	Photographers	+		(41)
Tungsten carbide (cobalt), hard metal	Hard metal workers	+	+	(42)
Vanadium pentoxide	Refinery workers	+		(43)
Welding, stainless steel	Welders	+		(44)
Zinc, copper, magnesium fumes	Welders, bronze (metal fume fever)	+		(45)
Zinc chloride	Tunnel workers	+		(46)
Organic chemicals				
Aminoethyl ethanolamine	Solderers	+		(47)
Chlorinated biphenyls	Transformer manufacturers		+	(48)
Cigarette smoke	All	+	+	(39)
				(49)
Colophony (pine resin)	Solderers	+		(50)
Diazonium salts	Chemical workers	+		(51)

Table 1. Sources and occupational groups affected by particles (continued).[a]

Source	Workers affected	Site affected		Reference
		Airways	Alveoli	
Diesel	Miners	+	+	(52)
Diisocyanates, toluene, diphenylmethane	Production workers	+		(53)
Formalin	Permapress, urethane foam	+		(54)
p-Phenylenediamine	Solderers	+		(51)
Paraquat	Sprayers	+	+	(55)
Penicillin, ampicillin	Production workers, nurses	+		(56)
Parathion	Sprayers	+		(57)
Piperazine	Chemists	+		(58)
Polymer fumes (polytetrafluoroethylene)	Teflon manufacture, use	+	+	(59) (60)
Rubber	Curing	+		(61)
Synthetic fibers (nylon, polyesters, Dacron)	Textile workers		+	(62)
Trimellitic anhydride	Chemical workers, plastics	+		(63)
Vinyl chloride (phosgene) (hydrogen chloride)	Meat wrappers (asthma)	+		(64)
	Firefighters		+	(65)
	Polymerization plant		+	(66)

[a] Adapted from Last (67).

Table 2. Pathological changes in various zones of the lung.

Pathological change	Zone of lung (and protective coating)		
	Conducting airways (mucus)	Terminal bronchioles (surfactant-serous)	Respiratory bronchioles and alveolar ducts (surfactant)
Vascular			
Fluid	Catarrh	Edema, obstruction	Edema—cardiogenic, alveolotoxic
Smooth muscle	Reversible airway		
Contraction	obstruction		
Leukocytes			
Cell products	Mucus (GCH)	Serous, pituitous catarrh	Hyaline membranes
		Mucus (GCM)	Lipid pneumonia
			Lipoproteinosis
Cells	Asthma (lymphocytes, eosinophils)	Obstruction (neutrophils, macrophages)	Neutrophils (allergic alveolitis)
			Macrophages (desquamative interstitial pneumonia and lymphocytic interstitial pneumonia)
Destruction	Bronchiectasis (proteases)	Bronchiolectasis, obliteration (proteases)	Emphysema (proteases)
Organization granuloma	"Sarcoidosis"	"Sarcoidosis"	"Sarcoidosis"
Proliferation			
Fibrosis fibroblasts	Distortion and obstruction	Obliteration	Interstitial fibrosis
Epithelial cell carcinoma	Squamous, poorly differentiated carcinoma	Bronchial cell carcinoma (adenocarcinoma)	Alveolar cell carcinoma

and alveolar ducts. The acute, subacute and chronic inflammatory reactions and neoplastic changes can be described in these three sites (Table 2). The size, the structural components and epithelium are clearly different in the three zones. Their protective coatings are respectively mucus, serous fluid and transported surfactant and tidal surfactant. Together these features provide a conceptual scaffold on which to erect a logical description of the reaction possibilities in the three principal lung regions.

Conducting Airways

Normal Structure

These airways from the nose to the twelfth bifurcation from the trachea are cartilage-supported distensible tapering tubes with many dichotomous branches. Beneath the cartilage is a fibroelastic sheath. Above the cartilage the lamina propria contains smooth muscle, blood and lymph vessels, glands, elastin and collagen fibers, mast cells, plasma cells and a few macrophages,

lymphocytes and polymorphonuclear leukocytes. The epithelium is pseudostratified, ciliated, columnar, meaning each cell has a foothold on the basal lamina. There are four major cell types. The proliferative lower layer of basal cells is obviously incomplete. It consists of polyhedral cells with rather prominent nuclei and few organelles except for ribosomes. Immediately above the basal cells are intermediate cells, pyramidal in shape with bases upon the basal lamina and nuclei above the basal cell nuclei, mitochondria are more numerous and Golgi, ribosomes, and tonofilaments are present. The most numerous cells are the ciliated ones, distinctive by reason of 200 or more cilia. Cilia average 5 μm in diameter, contain nine pairs of microtubules in the periphery and two single central ones. The cell apices contain many mitochondria, a large Golgi zone, many ribosomes and lysosomes. Goblet cells are less numerous, and occur singly in a ratio of one to five or six ciliated cells. The nuclei are basal and the Golgi apparatus occupies the midcell zone with secretory vacuoles above. These cells undergo cycles of synthesis, accumulation and discharge by fusion of membrane of mucous droplets to the cell surface membrane and discharge to the lumen.

Reaction to Particles

Local stimulation causes secretion, as do cold, heat and particles. The mucous and serous (mixed) glands which provide the bulk of airway secretion are under cholinergic control. Tips of beating cilia transport the more viscous, sticky mucus which traps particles while their recovery stroke is in a serous-surfactant layer. The transport rate of particles with mucus may exceed 20 mm per minute in larger bronchi compared to 2 mm in small bronchi (*68,69*). This system, the mucociliary escalator, traps particles in mucus and excretes them from the lung. Thus, it is a major defense against particles. It is damaged acutely by influenza and similar respiratory viruses which cause exfoliation of ciliated cells, disturb clearance and break the barrier. When loss of cells is extensive, serous fluid exudes from the epithelium and gaps in the ciliary escalator retard clearance. Repair by replacement of mature pseudostratified epithelial cells takes 14 days or more. Failure to reestablish epithelial contiguity may permit fibroblasts to proliferate into the lumen and produce a polypoid or eccentric scar (Fig. 1). Direct ventilation and ciliary clearance are lost, and the acinus or larger lung unit ceases to function. Luminal obstruction also occurs by concentric scarring without destruction of the epithelium.

Recruitment of polymorphonuclear (PMN) leuko-

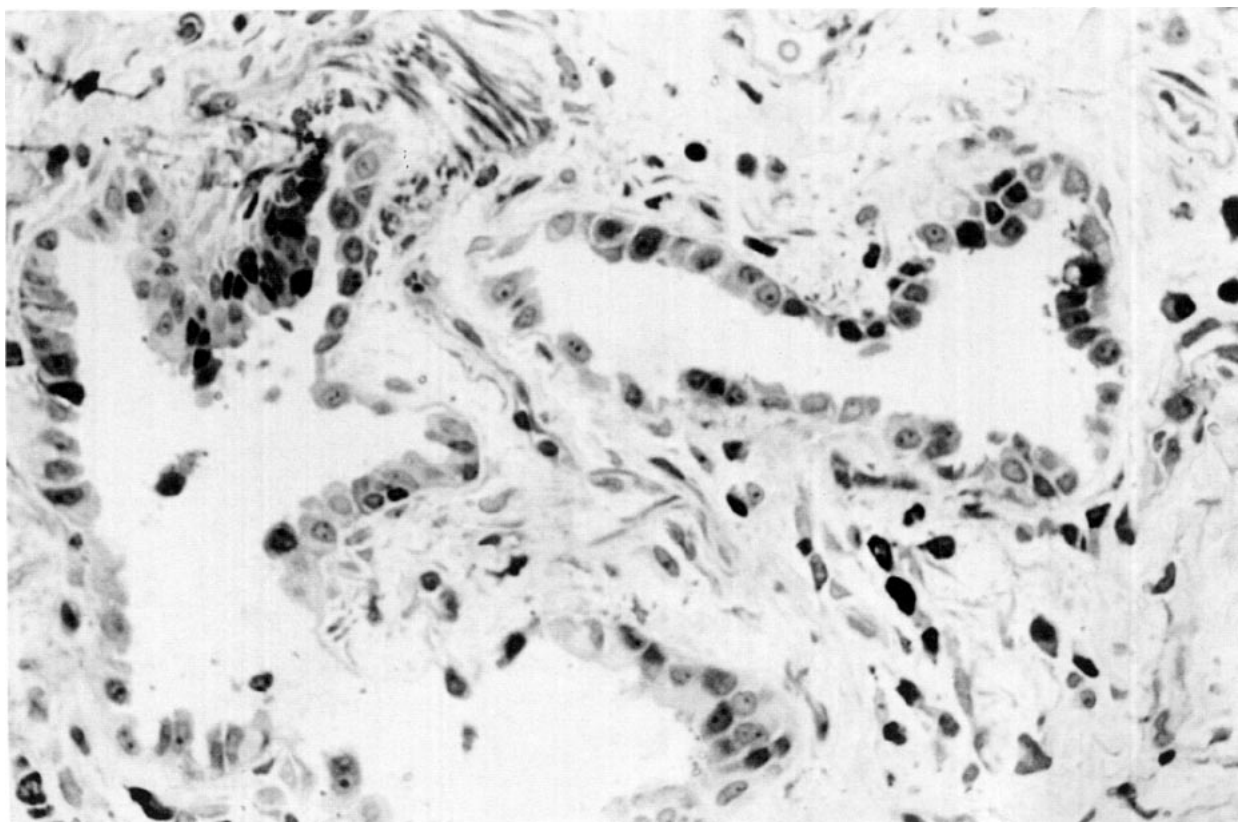

FIGURE 1. A small airway, a terminal bronchiole, showing to the left eccentric scarring; a subordinate lumen appears at the right. Original magnification 200×.

cytes through the intact respiratory epithelium is a major response to particles. Exposure to Gram negative endotoxin (*70*), cigarette smoke, its particle phase or the gas phase adsorbed on carbon (*71*), cotton dust and partially purified derivatives (*68*), aldehydes adsorbed on carbon (*72*) and SO_2 adsorbed on carbon (*73*) recruit PMN leukocytes at doses in hamsters approximating human exposure. In contrast, without a particle phase, SO_2 and formaldehyde levels must be 100 times higher to recruit granulocytes. It is probable that fumes of oxides of copper, zinc, cadmium and magnesium (*74–77*), which produce fever and other systemic as well as respiratory symptoms, recruit PMN leukocytes in airways. A suggested mechanism is that some recruited leukocytes leak or die and their pyrogens are released, absorbed and transported to produce systemic effects while local mediators act via mast cells to release histamine and other mediators to produce airway narrowing. This may be a mechanism by which a large number of agents cause occupational asthma (Table 1). These range from simple chemicals, such as formaldehyde, toluene diisocyanate, (TDI), and trimellitic anhydride, to bacterial and fungal products and complex mixtures, such as cigarette smoke, cotton dust, welding fumes and foundry dust.

Continued exposure to particle mixtures particularly to cigarette smoke but probably many complex dusts —cotton, welding, foundry—produces goblet cell hyperplasia in conducting airways, glandular hyperplasia and conversion from mixed serous and mucous glands to predominantly or entirely mucous glands (*78–81*). This metaplasia proceeds onward to layering of a less differentiated cell type resembling squamous cells called squamous metaplasia. The epithelial cells are heaped up, ciliated cells are absent and so are goblet cells. Although these changes are important in producing phlegm and cough so long as only larger airways are involved, respiratory function is not impaired. The major risk is for further dysplasia of cells, followed by carcinoma *in situ* and invasive carcinoma.

Terminal Bronchioles

Alterations of the nature of the epithelium and its principal secretions and structural integrity are most critical in small bronchioles, those without cartilage plates and with luminal diameters below 1 mm. The several generations of terminal bronchioles are lined by a single layer of cuboidal cells of which an equal number are ciliated and secretory. Only a few goblet cells are present. The cilia are similar to those in the large bronchi. The nonciliated cells have domed apices loaded with vacuoles or granules which have variably dense, homogeneous contents that are composed of both lipid and protein (*82*). The Golgi zone is prominent above a perinuclear area rich in microsomes and endoplasmic reticulum. Both cells rest on a basal lamina and hence upon elastin fibers arranged longitudinally and smooth muscle concentrically, together with blood and lymph vessels, mast cells, lymphocytes and plasma cells.

In peripheral airways where goblet cells are not present, they may be stimulated by inhaled particles. Such metaplasia of goblet cells occurs in terminal bronchioles (*83*) to produce mucus plugging and functional loss of the secondary lobule. It is impossible to distinguish by physiological tests between airways that are obstructed by mucus and those that have been distorted and functionally impaired by scarring or smooth muscle hyperplasia in their walls. There is a gradation from acute to chronic obstruction. One might predict that loss of the protective epithelium in small airways or failure to respond in a proliferative fashion by the epithelial layer would render the underlying connective tissue susceptible to stimulation by inhaled particles to produce obliterative bronchiolitis. Such stimulation can be produced experimentally by the administration of nitric acid or of neuraminidase (*84*). Proliferation of fibroblasts or smooth muscle cells is stimulated, and they produce polypoid lesions which bulge into airways, quickly occupying the lumen —particularly if the epithelium has been lost—or cause concentric narrowing or eccentric loss of luminal integrity, even if the epithelium remains intact or is reconstituted (Fig. 1).

This type of lesion, which can be seen often in the biopsies from current cigarette smokers who have had 20 or more pack/years of exposure, probably account for the decreasing values of FEV_1 observed in long-range studies such as those of Fletcher and colleagues (*85,86*). The changes in small airways are accompanied frequently by mucous production in larger airways so that cough and sputum accompany the reduction in functional capacity over time, as measured by spirometry at yearly intervals. However, either change may occur alone (*86*). Structural changes in the larger airways, because of their much larger lumens appear less important but bronchograms in subjects who are chronic cigarette smokers show pruning of airways as large as tertiary bronchi as well (*87*). Such lesions resemble those due to trauma, disturb the connective tissue framework and produce collapse or obliteration and thereby irreversible impairment of airway function. In foundry workers, 45 years of occupational exposure of nonsmokers caused equal functional impairment to that of 25 years of cigarette smoking alone (*39*). Tungsten carbide, hard metal, used for drill bits, is a sintered tungsten and carbon mixture prepared with a flux of cobalt (*88*). Cobalt appears to be the toxic agent (*89*) because when cobalt is administered to guinea pigs by intratracheal injection, acute pulmonary edema was produced within 24 hr. Bronchioles showed epithelial desquamation. After 8 months, peribronchial fibrosis and eosinophil-rich granulomas surrounded and obliterated bronchioles, and at 12 months the lesions had foci of multinuclear giant cells, fibronodular changes and hyperplasia of Type II alveolar cells surrounded pig-

ment deposits in obliterated terminal or respiratory bronchioles. Changes in four human lungs without a known interval from initial exposure have been described as desquamative interstitial pneumonia which was accompanied by interstitial fibrosis and hyperplasia of alveolar Type II cells (*88,90*).

Beryllium produces in experimental animal and human lungs a "granulomatous pneumonitis" but an important feature is the bronchiectasis and perifocal emphysema because of localization of interstitial fibrosis around bronchioles while granulomas characterize only 40% of cases (*91,92*).

The lesions resulting from human exposure to "thin," less than 1 μm diameter, flame-attenuated, glass fiber, are also characterized by bronchiectasis and bronchiolectasis (*38,93*), although detailed descriptions are not available. In experimental animals, bromobenzene (*94*) and various hydrocarbons (*95,96*), including chlorinated ones (*48*), produce acute necrotic lesions of terminal airway epithelium. Vinyl chloride dust produces granulomatous bronchiolitis (*97*), while the fumes produce resultant decreases in expiratory flow rates (*65,98,99*). Such fibrotic and frequently granulomatous lesions of bronchioles are found in biopsies of human subjects with farmer's lung (*100*). Apparently the deposition, but more importantly clearance of fine particles deposited in the secondary lobule back to the terminal bronchiole, when coupled with the high sensitivity of these epithelial cells to damage, produces these lesions. Poorly digestible plant material contributes materially to chronicity of these lesions in animal experiments (*101*). Cotton dust produces symptoms of chest tightness, shortness of breath and cough in textile workers and in naive persons which are accompanied by neutrophilic leukocyte recruitment to airways, peripheral leukocytosis and temperature elevation. Experimental animals show leukocytosis and increased neutrophilic leukocytes in airways demonstrable by tissue sections of airways and by bronchopulmonary lavage. Several chemicals, including lacinilene methyl ether, may combine with minute plant parts to produce these effects (*68,102,103*). Pathological changes are confined to airways which show enlarged mucous glands, goblet cell hyperplasia and squamous metaplasia, increased smooth muscle and leukocytic infiltration, terminal bronchioles show goblet cell metaplasia and mucous plugs in lumens (*79,80*). Limited data show more rapid decrements in expiratory flow rates with years of exposure, even in nonsmoking workers, and lack of restoration when exposure ceases. This pattern suggests functional and usually structural loss of small bronchioles. Similar patterns of a more rapid reduction in $FEV_{1.0}$ over time have been reported in many dusty occupations, including grain handling, baking, cement, foundries, coal mining, brickmaking, wood dust and firefighting (*67*). It is probable that Canadian red cedar, enzyme detergents and the host of particles causing occupational asthma produce similar lesions (Table 1).

The last pathological change in the airways, that of neoplasia, is an epithelial lesion in which the basal cells of this pseudostratified columnar epithelium show unbridled growth. It is still unclear whether the major exposure to the basal cells is via the luminal side by agents passing through the intact ciliated or goblet cells or via the lymphatics and across the basal lamina. In any case, the crucial matter seems to be prolonged retention of carcinogen at a site by particle (*104,105*), and the failure of these cells to be exfoliated in their normal time (*71*). The prior development of squamous metaplasia above the dysplastic cells which would prevent orderly desquamation may be the critical effect of cigarette smoking, which requires in most cases 20 years or more of exposure. The need for such a mechanism is supported by the observation that in experimental animals changes in epithelium such as doubling of nuclei in cells and invasion across the basal lamina occur after brief exposure to cigarette smoke (*71*) but do not produce tumors. If these changes occurred without disposal of malignant cells by exfoliation, the forbidden clone could have a permanent home. The cooperative role of particles, which by themselves are not carcinogens, and molecular chemical carcinogens has been shown repeatedly (*105,106*).

Alveoli

The most numerous cells in the alveolar zone are capillary endothelial cells, which have a large surface area to volume ratio and thus an extensive attachment to basal lamina. The nuclus is flattened, and the cytoplasm contains mitochondria, microsomes and smooth endoplasmic reticulum. Pinocytotic vesicles are a prominent feature. On the opposite side of the basal lamina are the flat or Type I alveolar cells that resemble the endothelial cells but have an even more extended cytoplasm. They have few organelles, many pinocytotic vesicles and many more junctional overlaps than nuclei. Large alveolar cells, Type II, are recognized by cuboidal shape, many microvilli, numerous lamellar bodies composed of highly organized and regular electron dense lipid arrays, numerous mitochondria and a prominent Golgi zone. These cells contain lipidase and proteinase and synthesize the unique surfactant dipalmytol phosphatidylcholine. This material provides the lungs' wet surfaces with a surface tension approaching zero so that the sharp angles of curvature of alveoli do not draw fluid into the alveolar spaces. Addition of native or extraneous particles of cholesterol, fatty acids or hydrocarbons to this layer raises its surface tension from near zero as measured on the surface balance (*107*) so that the equilibrium is shifted from favoring gas-filled to favoring fluid-filled alveoli, and pulmonary edema results.

Pulmonary Reactions

Edema

The rapidly fatal pulmonary reactions are due to edema. In the larynx or tracheobronchial tree, edema

can cause asphyxia following massive exposure to fumes, especially from plastic fires (*65*). Blood vessels with increased permeability leak fluid into the airways diluting or displacing the mucus or surfactant. Mediators are released from tissue mast cells and from platelets and leukocytes (*108*) to produce edema. Experiments done in a variety of animal models suggest that, irrespective of whether the particle is an immunological stimulus or a chemical one such as cigarette smoke, vinyl chloride, hydrocarbon, silica or asbestos, or an active principal such as an aldehyde adsorbed on carbon (*72*) as in diesel exhaust or fry cooking smoke (*109*), that the alveolar response is leakage of plasma into the air spaces. Although some agents damage small vessels directly, this is augmented by massive release of mediators including histamine, serotonin, slowly reactive substance of anaphylaxis (leukotriene), platelet aggregating factor (PAF) and prostaglandins. These agents also constrict smooth muscle and produce airway narrowing, resulting in "asthma" after particles such as toluene diisocyanate are inspired. Particles of about 1 μm in diameter as complex as *Micropolyspora faeni* (*110*) and gram negative bacilli may produce at the same time a small airway reaction so generalized as to reduce air flow during expiration, reduce pulmonary diffusing capacity and thus decrease arterial blood oxygen. These changes cause dyspnea and produce alveolar clouding on the chest X-ray. If the exposure is single and limited, the edema clears and function is restored without residual ill effects. However, if damage is repeated or protracted because of retention of particles that damage cells or evoke mediators and are poor digestible (hydrocarbons) or indigestible (silica or asbestos) or the stimulation of the immune system is such that memory is evoked or the response is simply widespread (*111*), there may be sufficient deposition of larger molecular weight proteins in alveoli to produce hyaline membranes. Such proteinaceous hyaline membranes are less easily mobilized from alveoli and may take from days to a few weeks to clear.

Agents such as toluene diisocyanate, endotoxin, fungal spores, vinyl chloride fumes, beryllium, zinc chloride, cadmium, asbestos and silica, which have well-known toxic effects, including the narrowing airways or production of fibrosis in alveoli, often produce pulmonary edema when the exposure is massive. Therefore, when trying to attribute specific effects to components of mixtures, one should consider as strong contenders such biologically active agents.

Lipidosis

Two types of lipids—hydrocarbons and membrane phospholipids—which are highly resistant to digestion by the lipases from lysosomes recruit macrophages to the lung and, at least in the case of hydrocarbons, sequentially attract lymphocytes, produce granulomas and cause fibrosis. Thus, exogenous hydrocarbons, including animal fat (*109*), kerosene and mineral oil (*112*), produce a distinctive alveolar reaction characterized by masses of macrophages laden with lipid vacuoles, lymphocytes, diffuse fibrosis both interstitial and interlobular and small giant cells granulomas. Because similar pathological changes occur in lung zones distal to obstructed bronchial lumens from tumors, foreign bodies and diffuse bronchiolitis, the role of clearance obstruction in the pathogenesis seems secure (*113*).

Lipoproteinosis

In a probable continuum, silica, silicates and other particles that are poorly digestible stimulate endogenous lipid pneumonia without obstruction of airways. This lipid-glycoprotein mixture can be removed by bronchopulmonary lavage (*114*). The predominant lipid is dipalmitol phosphatidylcholine (DPL). Alveolar lipoproteinous in which poorly soluble glycoproteins accompany DPL has been related to particles (*115*) and certainly characterizes the exposure to silica (*116,117*).

In the alveoli, chronic exposure to inhalants or exposure to those with an immunologic or physical memory produces either proteolytic destruction of connective tissue, emphysema (*118*), or stimulates collagen and elastin causing fibrosis. Fibroblast activity is usually accompanied by epithelial stimulation in the terminal bronchioles or alveoli producing bronchiolization of alveoli or hyperplasia of large alveolar cells (*119*). Peripheral adenocarcinomas, the so-called bronchiolar cell cancers and much less commonly, alveolar cell tumors, may reflect the ultimate irreversible stimulation of these cells.

Emphysema

It appears that elastin is crucial for the preservation of structural integrity in the peripheral parts of the lung, that is, the terminal bronchioles and beyond. Elastin can be digested by lysosomal enzymes, especially collagenases and elastases derived from polymorphonuclear leukocytes and macrophages (*120*). Furthermore, that there are proteolytic systems in these cells that can (*121*) further digest structural proteins after the initial steps (*122*). Thus, it appears that to produce emphysema there must be retention of cells in lung and their stimulation to digest particles. During this attempt at digestion, lysosomal enzymes are liberated into alveolar spaces, where they digest the structural fibers of the lung. To be effective at this level, the particles must be carried to the alveoli in sufficient dosage or repeated frequently enough to keep cell recruitment going or to persist because of indigestibility (*101*) or stimulation of memory (immune persistence and potentiation), to call up cycles of cellular response (*111*). In any case, after loss of structural proteins defining the alveolar interstitial spaces, the acinar organization appears to be incapable of being reconstituted so that what is left is either a proliferative fibrotic lesion or a loss of alveoli, usually the latter. It is not yet clear why

some stimuli produce digestion of alveolar walls without apparent stimulation of repair leading to emphysema. Cigarette smoke best exemplifies this stimulus (*78,123,124*) and coal dust may operative (*125*) but evidence is substantial that cadmium, fly ash and other agents cause emphysema.

Fibrosis

There appear to be several steps between reception of particles by the macrophage and the stimulation of fibroblasts (*126–129*) and there are many questions: Is the macrophage an essential intermediate? Are other cells involved? If the mediators are macrophage products, does one stimulate proliferation of fibroblasts and another stimulate the smooth muscle cells in capillaries or small airways to lay down an elastin network which is then collagenized (*130*)? Such a sequence is suggested in some of human disease sequences, particularly the exuberant fibrosis after influenzal pneumonia, and after chemicals including paraquat (*131*), bleomycin (*132*) and doxorubicin (Adriamycin). The experience with lipid pneumonia, both the exogenous type usually due to hydrocarbons (*112*) and the endogenous type in which the lipid is a human product (*113*) are instructive, in that these materials, in contrast to tobacco smoke, stimulate fibrosis rather than digestion. There are large numbers of macrophages and some leukocytes attracted to the site, and certainly the material is indigestible; thus it appears, by and large, that the indigestible particles stimulate fibrosis. Cadmium (*133*), beryllium (*91*), cobalt (*89*), nickel, titanium, fungi and similar complex materials stimulate fibrosis. Although fungi alone stimulate recruitment of macrophages to alveoli, the addition of plant fibers causes fibrosis (*101*). From animal experiments it is clear that neoplasia at the alveolar level can be stimulated by chemical agents such as vinyl chloride monomer (*134*), urethane (*135*) and viruses, especially the Jaagsiekte agent (*136*).

Specific Particle Effects

By far the most important effect of particles in human subjects is chronic progressive functional impairment and death from pulmonary insufficiency. These are chronic effects in small bronchioles and alveolar ducts leading to departitioning or to functional amputation of pulmonary units of acinar size or larger by obstruction or destruction of airways. Cigarette smoke is the particle of the twentieth century which has taught us more than any other about the range of this disorder and the complexity of particle–lung interactions from irritation to chronic airways, obstruction, fibrosis, emphysema and cancer. The cigarette smoke story is most instructive and may be applicable to other complex particles, such as coal, fly ash, welding fumes, smoke from plastic fires and solid waste reduction and diesel exhaust.

Cigarette smoke contains most of the classes of compounds found in tobacco leaf plus pyrolysis products (*137*). These include inorganics (cadmium, nickel, chromium, lead, silicates), simple and complex carbohydrates (cellulose, lignin, dextrin and starch), pectins, organic acids, oils waxes and resins, polyphenol (tannins) and nitrogen compounds including the alkaloids (nicotine and continine). Combustion entrains the volatile fractions of these plus combustion products, biologically active gases, including hydrogen cyanide, aldehydes and nitrogen dioxide, and polycyclic hydrocarbons which condense or adsorb on particles of ash or lipid to enhance toxicity. Exposure of a variety of cells to condensate of cigarette smoke produces stimulation, inhibition, cytotoxicity and neoplasia. The fractions attract neutrophilic leukocytes to airways (*71*), and inhibits them (*138*). Condensates attract and stimulate macrophages to migrate, phagocytize (*139*), induce and depress various enzymes (*140*). Ciliary beating is inhibited by smoke (*141*) and tracheobronchial clearance is decreased (*142*). On the airway epithelium, smoke condensate causes hyperplasia with pleomorphism (*143,144*), and it transforms hamster lung fibroblasts in culture (*145*). Chronic exposure of bronchial epithelium *in vivo* causes bronchial gland hyperplasia, increases goblet cells (*78,146*), and produces pigment deposition and ectasia of respiratory bronchioles to produce emphysema in dogs (*124*). Human studies show many effects of cigarette smoke besides lung cancer. The most important are irreversible losses of airway function over time (*86*) and emphysema (*147*).

Coal will be a major energy source until at least the end of the century, so a strategy for preventing particle toxicity is an important concern—not only in mining and shipping of coal but in its combustion and gasification. Coal and its combustion product, fly ash, constitute other extremely complex mixtures. Up to 55 elements and a vast array of organic compounds are in coal. A considerable amount has been learned about the pulmonary toxicity of the major coal compounds. These include mellitic acid (hexacarboxyl benzene), polycyclic aromatic hydrocarbons, metallocenes (ferrocene), arene carbamyl complexes, metal carbonyls ($Ni[Co]_4$), metal alkyls (tetraethyllead, trimethyltin), metal porphyrins and metal chelates. Attribution of effects of single components is so difficult and time consuming that the best estimates for coal are based upon large to massive occupational exposures (*125,148*). Chronic bronchitis, including insidious reductions in pulmonary function, and emphysema are observed in coal miners and handlers when cigarette smoking effects are factored out. Also there is unquestionably a pneumoconiosis featuring stellate fibrotic nodules that can be attributed to silica plus a particle burden.

Fly ash, a generic name for coal combustion particles, contains many of the metals known to be toxic, and their concentrations increase greatly as particle size decreases in the critical respirable range (*149*). In the United States, eastern coal has a greater number and concentration of metals known to be toxic than does western

coal. These metals include cadmium, selenium, arsenic, antimony, molybdenum, lead, cobalt, nickel, manganese, beryllium and copper (*150*).

Useful comparisons between *in vitro* cytotoxicity using alveolar macrophages, cultured macrophage lines and lymphocytes in short-term preparations (*151*) and animal toxicity (*152*) have begun to provide some guidance in predicting the human effects of coal processing (*153*). Also, insight is being gained into the crucial role of the alveolar macrophage and its breakdown products (*154*), in transducing particles and producing fibrosis and neoplasia. For example, killing of rat lymphocytes (*in vitro*) by tributyltin and dioctyltin has predicted the lymphopenia with atrophy of thymus and spleen in rats (*155*). In addition to the organometallic compounds, the importance of silicates, especially kaolin and mica as components of coal mine dust, has been shown (*153*), which appears to strengthen the concept that particles which can be phagocytized but are indigestible have a critical role in pulmonary toxicity. For example, carbon alone had an almost trivial effect in recruiting neutrophilic leukocytes into airways of hamsters but small quantities of formaldehyde or acrolein added to it caused prompt recruitment of these cells at 0.001 part of the aldehyde dose (*72*).

To establish a firm line of evidence, an orderly progression from cytopathology to human disease should be shown. The intermediate steps might include organ-directed analysis of effects after multiple doses given intraperitoneally compared to intratracheally for alveolar effects. Subsequently, multiple doses or airborne administration is needed to establish the pattern of chronic effects. Finally, a larger animal, dog, sheep or primate, should be used to confirm the pattern of the long-term or more insidious effects.

The redistribution of particles in the lung and body after deposition is frequently ignored. Movement on the surfaces of alveolar ducts and bronchioles causes removal and concentration. These movements are accompanied by and coupled to lymphatic redistribution in the lung, removal to local and regional lymph nodes and systemic distribution. Knowledge of these processes is fragmentary, at least in part, because of the inaccessibility of distal lung to direct examination. Simpler lungs, like those of the bullfrog (*156*), have provided insight into possible mechanisms of particle redistribution and removal by surface forces prior to their gaining access to the mucociliary escalator. Dynamic methods which express particles removed as equal to those present after deposition minus those remaining after a period of time during which there is clearance fail to distinguish between physical removal from the body via the mucociliary escalator, removal via lymphatics (from the lung but relocation within the body), and digestion, that is, solubility and processing usually within cells (*157*). Studies in beagle dogs of radioactive isotope-labeled $BaSO_4$, MnO_2, Fe_2O_3 and UO_2 adjusted for initial size and deposition showed that lung clearance was predictable from ultrafiltrability (*158*). Serial studies in rats with the use of titanium oxide (TiO_2) showed that clearance of deposited particles retained beyond 24 hr had two curves, with retention half-times of 14 days and 88 days, respectively (*157*). As far as transposition is concerned, Morrow (*159*) observed that TiO_2 and Al_2O_3 —materials which do not produce cytotoxic effects —appear promptly in the pulmonary lymph after inhalation while silica, which is cytotoxic, is less quickly cleared to lymphatics. However, lymph node concentrations of silica typically exceed those in the lung in workers after 7 to 20 years. Tin, graphite, carbon and coal also clear to lymph nodes. Interpretation of differences in lung–lymph node concentrations are difficult. The most important principle to keep in mind is that the lymphatic system translocates materials out of the lung to local and regional lymph nodes and hence via the blood circulation to many body organs. Thus asbestos, silica and other particles have been measured in brain, spleen, kidney, bone marrow and distant lymph nodes (*160*).

Careful analysis of many natural and man-made dusts show that the fibrosis in workers exposed to kaolin, diatomaceous earth, firebrick, cement, foundry dust, anthracite coal, stone quarrying and fly ash is silicosis modifed by the less active insoluble noncrystalline components of the dust. Asbestos, as a general term for serpentine rock, is also widespread in nature, contaminating talc, road-surfacing gravel, nickel ore in New Caledonia and building stone in central Turkey (Anatolia). Thus it is sound advice to regard most natural materials as impure and search carefully for known agents before embracing causal connections for new ones. In the same sense, radiation sources are nearly ubiquitous, so that radon daughters contaminate materials not considered to be primary hazards for radiation.

Excess cadmium and nickel were found in the lungs of patients with emphysema and chronic bronchitis (*161*), then in the lungs of cigarette smokers (*162*) and finally traced to the cigarette tobacco (*163*). These observations are instructive in showing that an adequate examination of known agents should precede attribution of new etiological relationships for particles.

Another difficulty is posed by the diverse exposures which occur in occupations such as shipyard work or building construction, in which the working space and air are shared by workers from many trades.

Awareness has been growing since before World War II that exposures to welding, painting and metal grinding are added to asbestos exposure for the 13 or more shipyard occupations, including shipfitters, boilermakers, machinists, painters, welders, electricians, engine fitters, caulkers and riveters, engineers, laggers and plumbers. Thus, asbestos disease arises not just in specific occupations but also in specific workplaces. As welding exposures to manual electric arc, inert gas protected arc and consumptive gas have been more completely investigated, effects of exposure to nickel, chromium, cadmium, zinc, manganese, titanium, copper and lead, plus ozone and nitrogen oxides, have been

distinguished from exposure to iron, which has little ill effect (*164*). It appears that most of the airway symptoms, including cough and sputum, colds, hoarseness, sore throats and wheezing, are due principally to the nickel and chromium but also to aluminum, cadmium, zinc and copper. Painters are exposed to pigments, of which chromates —especially lead chromate—are most toxic; to solvents, drying oils, hydrocarbons, naphthols, terpenes and to inert materials, frequently silica and silicates, such as diatomaceous earths. The application of paints creates aerosols, but their pulmonary effects have received little study.

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