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New Clues for the Emphysemas

KAYE H. KILBURN, M.D.

Columbia, Missouri

"Our ideas are only intellectual instruments which we use to break into phenomena; we must change them when they have served their purpose, as we change a blunt lancet that we have used long enough."

CLAUDE BERNARD

It appears useful to start with a concept so generally accepted as to be practically an axiom that the emphysemas are anatomic lesions characterized by enlargement of distal air spaces with their destruction. They are one of two chronic end-stages of injury and repair in a three phase (gas, liquid, solid) organ. The others are the diffuse interstitial fibroses. Emphysema was first described by Sir John Floyer in 1698 in a horse [1]. He observed, "bladders of the lungs have been extended or broken by some strain . . . and injury done to the membranes." Spontaneous emphysema also occurs in the rabbit [2]. Because it may be induced in animals experimentally by various means, it is thought to have several mechanisms. In the past 16 years dated from the first Aspen Symposium [3], three ideas have dominated research: (1) emphysemas' association with cigarette smoking, (2) its imitation by proteases placed in alveoli and (3) its frequency in homozygotes for deficiency of alpha$_1$ antitrypsin, unfortunately practically to the exclusion of other hypotheses. The objective of this appraisal is to focus attention on certain other observations, the pursuit of which may be as important as those mentioned. These observations have been grouped around four questions.

(1) Is emphysema a developmental defect, specifically a failure of bronchial subdividing?

It is instructive to arrange the defects of pulmonary segmentation which have been described in infants and children and which are thought to be developmental [4] in a continuum ranging from agenesis of both lungs [5]. Included are agenesis of one lung, congenital lobar emphysema, congenital cystic adenomatoid malformation, congenital cysts, congenital bronchiectasis, and bronchiolectasis. In adults there is general or localized roentgenographic hyperlucency of the lung in conditions including "MacLeod's syndrome," "Swyer-James syndrome," "honeycomb lung," and "blebs and

From the Pulmonary and Environmental Medicine Division, Departments of Medicine and Anatomy, University of Missouri Medical Center, and Veterans Administration Hospital, Columbia, Missouri 65201. This study was supported in part by U.S. Public Health Service Grant 2-R01-OH00511 from the National Institutes of Occupational Safety and Health. Requests for reprints should be addressed to Dr. Kaye H. Kilburn, University of Missouri-Columbia School of Medicine, Division of Pulmonary and Environmental Medicine, Columbia, Missouri 65201. Manuscript accepted July 26, 1974.

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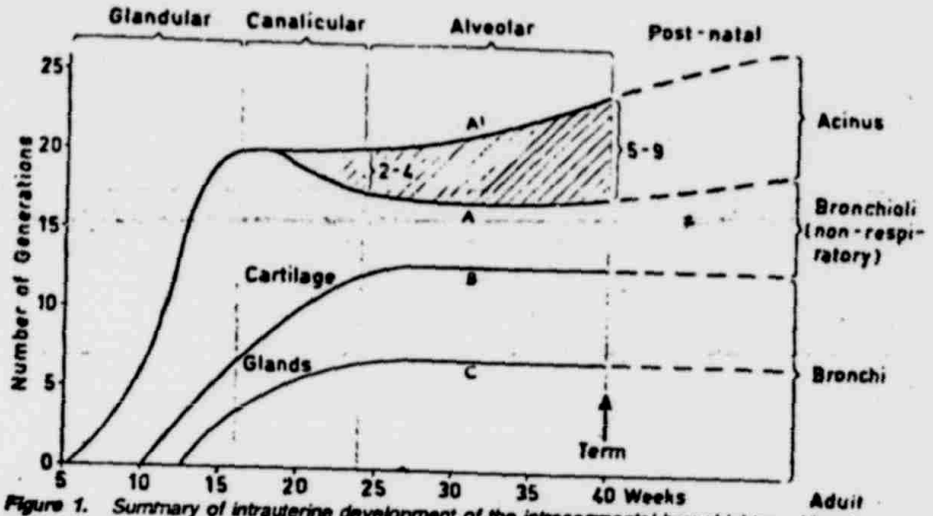


Figure 1. Summary of intrauterine development of the intrasegmental bronchial tree. Line A represents the increase in the number of bronchial generations; shaded area between A and A' the respiratory part of the bronchial tree (i.e., respiratory bronchioles and alveolar ducts); B the extension of cartilage along the bronchial tree; C the extension of mucous glands. A, B and C are taken from mean values of numerous counts. A derives from Engel's studies and Bucher and Reid's own counts. The diagram includes adult counts showing the increase in total generations in the postnatal period. From Bucher and Reid [12].

bullae." Although there are few anatomic studies of such patients, in one series of 69 patients with hyperlucency, 8 had cystic lungs, 3 congenital lobar emphysema and 9 hypoplasia of the pulmonary artery or a branch [6]. Does this continuum extend to the respiratory bronchioles and include centrilobular emphysema?

Congenital lobar emphysema typically presents in infancy, is restricted to a lobe or two, usually the left upper or right middle, and often constitutes a surgical emergency. Approximately half of the lobes removed show bronchomalacia [7]. By 1967, the data on 166 patients were reviewed by Murray [8] who wondered how many other patients who were not symptomatic survived into adulthood without a diagnosis being made. A more common lesion, bronchiectasis is also more common on the left and in the lower lobes as Lindskog and Hubbell [9] observed in 215 patients. Useful studies of congenital emphysema were made by Dr. Lynne Reid and her associates [10–12]. They applied quantitative methods [13], that is, they counted the number of bronchial generations, number of bronchi and the number of alveoli per milliliter of lung. They found four patterns: (1) atresia of branches with the normal number of bronchial generations; (2) a reduced number of bronchial generations, with reduced number of alveoli; (3) normal number of bronchial generations with normal alveoli; and (4) normal bronchial generations with increased number of alveoli [10].

These observations suggest that it would be useful to study the numbers of branches and numbers of bronchial generations together with numbers of alveoli in emphysematous lungs. Because methods are time consuming, only a few such studies have been made in lungs with bronchitis and asthma by Takizawa and Thurlbeck [14], MacLeod and Heard [15], and Sobonya and Kleinerman [16], but these showed differences from normal. Some support for the concept that emphysema in adults may be congenital comes from the medical examiner population studies by Spain et al. [17] and by Kleinerman [18], and from studies of patients who died in hospitals by Pratt and Kilburn [19], Snider et al. [20], Thurlbeck and Angus [21], and Ishikawa et al. [22]. These observers showed variable proportions of people with emphysema across the age range. Perhaps it would be useful to search for toxic agents which, when administered to the mother, would interfere with differentiation of fetal lungs. This would require quantitative morphologic analysis. If subdividing and branching of the lung are sensitive to maternal nutrition and to toxins, it would be susceptible during the period from the 5th through the 28th or 30th week [12] (Figure 1). Bronchial number (atresia) may also be important because, with insufficient subdivisions,

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subsequent growth could produce abnormally large airspaces.

Wide variation in pulmonary diffusing capacity within age ranges after adjusting for height and progressive decrease during aging suggest that lungs vary considerably in their internal surface area [23] or alveoli per cubic millimeter [24]. One wonders whether the degree of alveolarization is controlled after growth is complete, particularly if it is reduced when activity (oxygen demand) falls off incident to inactivity or aging. Although there is evidence that lung volumes are increased in acromegaly and decreased in hypopituitarism, gas exchange is not affected [25]. This presumed correlation is seen in phylogenetic studies from frogs through mammals which show an association between alveolarization and energy use [26]. Perhaps this could be tested in an animal model. Recently, serial studies have shown that the Virginia opossum pursues its pulmonary development largely after birth while breathing air and completes it to a compound complex (mammalian) lung [27]. This suggests that the information for both size-growth and subdividing is built into the primitive outpouching from the foregut. The accessibility of "fetal" lung in marsupials recommends them for experiments to alter its development.

(2) Is the interstitial space or its basal laminae essential for alveolar organization and orderly repair?

Secondary lobular septums provide the boundaries within which the elastic tissue and the distal extensions of smooth muscle define the anatomy of the respiratory bronchiolus and alveolar ducts [28–30]. Within the secondary lobule or acinus, there appear to be two distinct types of alveolar walls: thick ones containing connective tissue fibers mostly collagen and elastin and thin ones of basal lamina with few or no fibers [31] (Figure 2). The thin walls have an interstitial space with one or two basal laminae defined by transmission of electron microscopy of fixed tissue but without structure in freeze fracture-etch prepared rabbit lung [32]. The composition of this interstitial space is even less well known than its anatomy.

Experiments with organoid cultures of lung reveal that both mesenchyma and epithelium are required to form glandular or canalicular structures. Without both types, cells grow in sheets. It is even possible to mix epithelium and mesenchyma from chicken and mouse and achieve differentiation [33]. Explants of lung from young rat fetuses go through several stages of expansion and branching in culture, and even pass into a state of many saccular chambers enclosed by delicate walls [34]. What controls this network of irregular dichotomous branches as it grows? It may be that running out of either mesenchyma or epithelium curtails normal development and forces changes in dimensions during fetal life, after changing to air breathing and perhaps during repair of injury. So little is known concerning the vascular development and differentiation one wonders if the limitation is of uncommitted mesenchymal cells in the proper location [35]. Because the vascular system develops poorly in vitro, damage to it could also limit lung differentiation in vivo [5].

The thinness and structural simplicity of the basal lamina, bounded as it is by the membranes of endothelial and epithelial cells, suggest vulnerability to damage. Even many areas containing collagen and elastin do not seem structurally robust. Little is known of its chemistry, but it is of interest that Laros et al. [36] found that the glucosamine to galactosamine ratio is 0.77 in normal lungs and 2.1 in emphysematous lungs. This represents more of a decrease in the chondroitin component in emphysematous lungs than an increase in the hyaluronic acid component. Total protein, collagen and soluble collagen were all similar in their 30 patients. However, proteolytic enzymes destroy alveoli [37]. Of the fibrillar proteins, elastin appears to be most susceptible not only to papain but also to pancreatic elastase and to elastases from leukocytes. Although the leukocyte enzymes, particularly those in the polymorphonuclear leukocytes, appear capable of destroying lung [38], it is curious that they do so when recruited in pneumonia due to gram-negative bacilli, but do not when attracted by Pneumococci. Perhaps the degree of damage to endothelial membranes accounts for recovery of the circulation through alveoli and is modulated by leukocyte proteases. Certainly some proteases have optimal activities at a pH of 4.5 or below which could be reached in hypoxic lung with blocked airways and an absent circulation. There is even evidence that the lung destruction caused by nitrogen dioxide is due to proteolysis as NO_2 affects lysosome membranes [39]. Weissmann [40] has suggested that vitamin A, by releasing hydrolases from cells, might also produce alveolar hemorrhage, pulmonary edema and death, but emphysema has not been reported [41]. There is a neuraminidase in influenza virus membranes enabling such viruses to fuse with cell membrane proteins and destroy them [42].

Oleic acid [43] produces intra-alveolar hemorrhages, edema and infiltration within a few hours of intravenous administration. By 3 days there are areas of necrosis, with clusters of polymorphonuclear leukocytes. Electron microscopy reveals partial detachment of epithelial cells, bullae formation and, generally, loss of epithelial cells before endothelial cells, al-

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Figure 2. Top, these thin alveolar walls are composed largely of capillaries containing erythrocytes which have one chord attached to a connective tissue armature which contains a few collagen fibrils (C). Bottom, the thicker, more supportive alveolar walls contain bundles of collagen (C), elastin (E) and a fibroblast (F). There is greater separation between capillaries on two sides of the interstitial space and more capillary surface faces it. Glutaraldehyde-osmium tetroxide, stained with uranyl acetate and lead citrate; original magnification X 2,650, reduced by 16 per cent.

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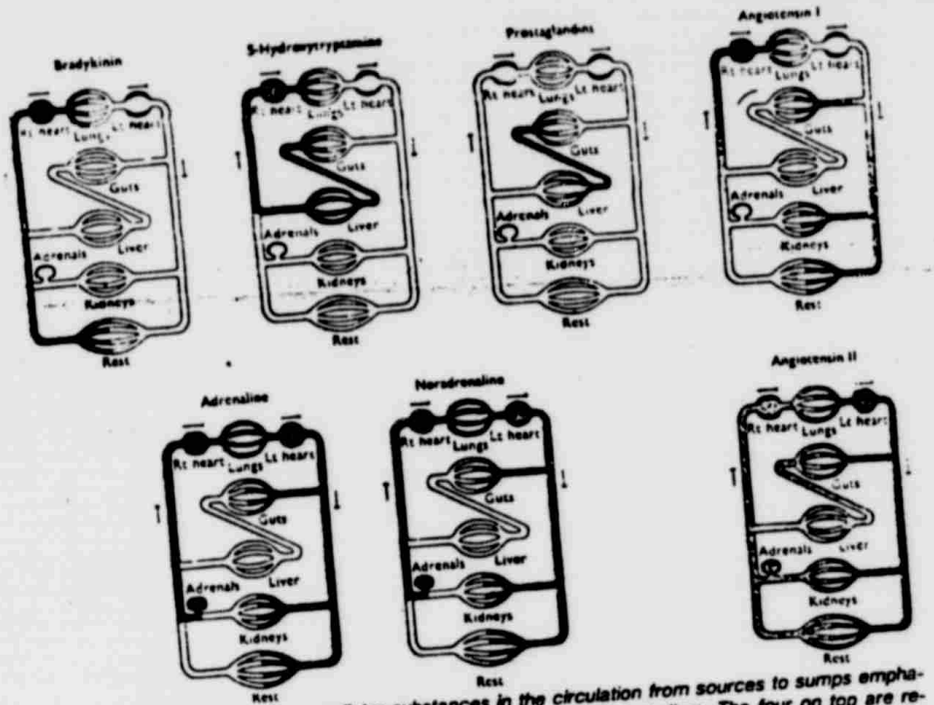


Figure 3. The fate of seven mediator substances in the circulation from sources to sumps emphasizes the converting and metabolizing functions of pulmonary endothelium. The four on top are removed or converted in the lung, some norepinephrine is removed but adrenaline and angiotensin II converted in the lung from angiotensin I is unchanged. From Vane [51].

though both are lost in some areas. Nevertheless, the basal lamina disappeared in 2 weeks. Alveoli may not have been reformed because of retraction by elastic lung away from the destroyed and thus enlarged airspaces. Clearly other organs, such as liver, salivary glands and pancreas, which lack the gas-liquid interphase problem, regenerate after partial extirpation in the liver controlled by a portal blood factor [44–46]. Is there a circulating growth factor for distal lung branching and perhaps even an antifactor?

The addition of collagenase to embryonic salivary gland cultures depatterns or prevents differentiation of the gland so that cells grow as a simple disk [47]. These effects are not duplicated by lipase, elastase, ethylenediaminetetraacetic acid (EDTA) or hyaluronidase. Embryonic lungs from mice and chicks grown in culture show similar effects [48]. Some parallels might be drawn to rheumatic joints from which synovial collagenase has been isolated [49]. It is important to note that collagen is chemotactic for leukocytes [50].

(3) Are blood and lymphatic vessels essential for alveolar preservation?

The new functions ascribed to the pulmonary endothelium have moved it far beyond this circulations reservoir and filter functions of 15 years ago. Certain observations make one ask whether a secondary lobule supplied by a single end artery is as vulnerable to thromboses as are areas of brain and heart. A modern picture of the role of the pulmonary vascular endothelial in handling of circulating mediator substances was provided by Vane [51] (Figure 3).

The endothelium removes 5-hydroxytryptamine (5-HT), bradykinin, angiotensin I, prostaglandins and adenosine triphosphate (ATP). 5-HT or serotonin disappears by uptake and storage which is not dependent on diamine oxidase. Bradykinin and angiotensin 9 (AT-1) are cleaved by dipeptide hydrolase which inactivates bradykinin and converts AT-1 to AT-2 (angiotensin II).

In contrast, epinephrine, norepinephrine, histamine and vasopressin pass through the lungs and are inactivated in peripheral vascular beds; for instance, histamine by N-methyltransferase. Fibrinopeptides A and B released from fibrin clots cause smooth muscle contraction and a pressor effect [52]. Bovine fibrinopeptide B is a small molecule (2,400 mol wt)

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which could raise resistance particularly in an attenuated vascular bed. Fulvine from Crotalaria also raises vascular resistance and has been incriminated in Kimberley horse disease [53]. Finally, microsomes from bovine lung catalyze coagulation and do so better than other microsomes, perhaps because they are already combined with phospholipid which is essential for coagulation [54].

Despite notable progress in understanding coagulation, vascular thrombosis and small vessel disease, a vascular hypotheses for pulmonary emphysema has never been popular. Endothelial damage could expose the collagen in the interstitial space to Hageman factor to initiate the clotting cascade as has been described in vitro by Becker [55], by Ratnoff [56] and by Stecher et al. [57]. When this concept is coupled with intermittent blood flow [58,59], strong forces appear to favor thrombosis in pulmonary vessels, particularly alveolar capillaries. Also, the relative slowness of flow in the whole pulmonary circuit might increase its susceptibility to intravascular coagulation. Both disseminated intravascular coagulation (DIC) and hemorrhagic diathesis associated with generalized thrombosis stress the pulmonary vascular beds filter capacity. As these clotting cascades continue, depletion of fibrinogen and platelets as well as the earlier clotting factors produces hemorrhage, ischemia and necrosis in other vascular beds and probably in the lung as well. However, the question whether thrombotic damage within a secondary lobule can produce necrosis is unanswered.

Recently veno-occlusive disease has been described due to pyrrolizidine alkaloids. For instance, ingestion of seeds or leaves of leguminous plants such as Crotalaria fulva has been associated wth human hepatic veno-occlusive disease [60]. Feeding rats fulvine and monocrotalin produces fatal hemorrhagic centrilobular necrosis of the liver in some. In the survivors hypertensive pulmonary vascular disease and medial hypertrophy of large and muscular pulmonary arteries develop [61]. Emphysema has not been reported. In spontaneous veno-occlusive disease occurring in children and in adults, small pulmonary veins are filled with cellular fibrous tissue which stains like collagen and elastin. Its etiology and relation to emphysema are unknown [62]. However, perhaps Crotalarial disease provides a model to investigate the effect of vascular occlusion on alveolar walls. The description of the vasculitis-granulomatosis syndrome called limited Wegener's appears to place it in this context [63].

Further on the arterial side it has been shown that nicotine stimulates catecholamine release which acts via cyclic adenosine monophosphate (AMP) to induce platelet aggregation. Carbon monoxide has been shown to increase atheroma formation in cholesterol-fed rabbits [64] and squirrel monkeys [65]. Cholesterol feeding in rabbits also produces plaques in the pulmonary artery and increases the numbers of cholesterol laden macrophages in the lung.

The lung can profoundly influence the numbers of circulating leukocytes, particularly polymorphonuclear leukocytes, by sequestering them as was shown by Bierman [66] who infused leukemic leukocytes into normal human subjects. Treatment of plasma with cellophane induces a transient but marked leukocyte sequestration which may be important to patients undergoing renal dialysis [67]. The shock lung syndrome as studied in human subjects [68] and modelled in dogs [69] is heavily influenced by sequestration of leukocytes in pulmonary capillaries. This also occurs in dogs after brief exposure to small doses of nitrogen dioxide [70] and also in rats [71]. Subsequent degranulation of leukocyte lysosomes in these small vessels may damage not only endothelial cells but also interstitial connective tissue [72,73]. The initiation of the coagulation cascade can generate leukotactic factors as has been shown by Stecher, Sorkin and Ryan [57]. The tie-ins between the coagulation and inflammation systems are now so numerous as to not require extensive description. Even the surface contact of neutrophils has been shown to stimulate proinflammatory substances [74]. Cochrane [75] has shown that Arthus-type responses are delayed and practically abolished in the absence of polymorphonuclear leukocytes.

Following wounding or necrosis, fibroblasts or endothelial cells, which are difficult to distinguish morphologically, grow into the damaged area as solid cell cylinders surrounded by basal lamina. They next develop lumens and can be distinguished for some time by a cuff of connective tissue including mature collagen [76]. These are quite different from ordinary pulmonary capillaries which on cross section have only one chord surface attached to connective tissue.

The bronchial circulation has been damaged experimentally by chemicals. McLaughlin et al. [77] found chloropromazine injected into the bronchial arteries of horses produced focal atrophic alveolar changes resembling emphysema. However, Ricketts and Carrington [78] found that ablation of the bronchial circulation in sheep and other species had no effect on alveoli.

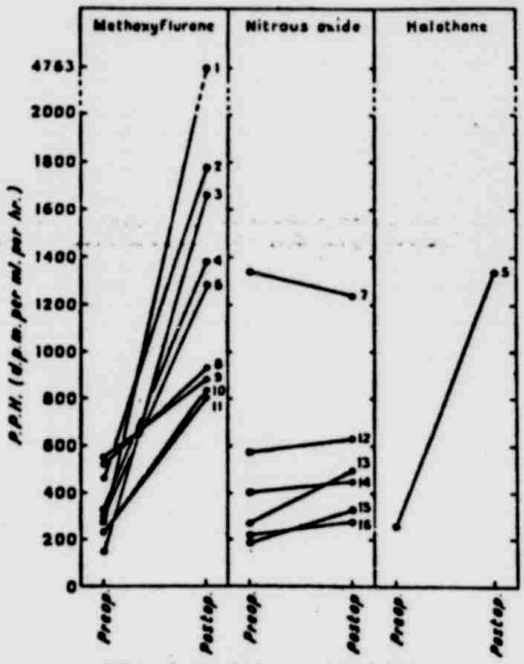
(4) Are there marker substances for alveolar destruction or host susceptibility circulating in the blood?

Lung injury might be distinguished by high concentrations of structural chemicals or of enzymes in serum

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or pulmonary lavage fluid. Although the lungs' complexity in terms of types of cells mitigate against achieving this aim, a few avenues should be pursued. In terms of excesses, collagen and elastin are in high concentration in the lung and probably are mobilized quite easily. So far the excretion of amino acids which are unique to collagen, such as hydroxyproline [79], or the detection of proline hydroxylase has been useful in other diseases. They have not been applied in experimental lung disease, although they will detect lathyrism induced by beta aminoproprionitril. Serum proline hydroxylase activity appears to reflect altered liver function more than changes in tissue levels attributable to disease. A lead worth following is that patients anesthetized with methoxyflurane or halothane show significant abrupt increases in serum proline hydroxylase [80] (Figure 4). Desmosine and isodesmosine, amino acids specific to elastin, have not been explored as markers, but they might be tested in animal models for pulmonary emphysema induced by elastase. An elastase inhibitor has been measured in women before, during and after pregnancy [81]. It rises during each trimester and falls shortly after parturition. That it is distinct from alpha$_1$ antitrypsin has not been established. Studies of rats during uterine involution [82] and studies during changes in the skin of human subjects [83] may serve as models for effects on collagen. Another lead has come from the detection of immunoreactive basement membrane antigens in peripheral blood of normal human subjects using sheep antiserum to human glomerular basement membrane, actually a semirefined glomerular preparation [84,85]. Glomerular and alveolar basement membranes are immunologically cross reactive so this may be a fruitful lead.

Because guanylate cyclase has a higher concentration in homogenized lung than in any other tissue it might reflect lung destruction even though we do not know its cellular source. Also cyclic guanosine 3′,5′ monophosphate (GMP) concentrations are high in lung, but platelets also have high levels so that great care must be taken in handling the blood sample so as to not have cyclic GMP liberated. Cyclic AMP cause selective release of lysosomal hydrolases in cultures [86] and may operate in alveoli or intact capillaries. Because the lungs are rich sources of prostaglandins particularly E1, E2 and F2α, insults to the lung might be reflected in elevations of these mediators [87]. Chemical methods would have to replace bioassays to make these analyses practical. They should reflect endothelial damage, and this may not correlate with damage to the basal lamina or connective tissue [73]. The same argument applies to muramidase [88] or proteases released from leukocytes or to the activity of the aryl hydroxylase in lymphocytes. However, if other organ sources of these materials can be eliminated, perhaps they might reflect alveolar events with fair specificity.



Effect of anesthesia on serum-P.P.H.-activity.

Figure 4. Three inhaled anesthetic agents elevate the serum levels of proline hydroxylase. Although release from the liver is likely, the lung may also be a source. From Stein et al. [80].

There is current interest in another endogenous circulating agent present in apparent excess in some patients. This is the "cystic fibrosis factor." It appears to be a peptide of 7,200 mol wt attached to gamma globulin and associated with polyamines, which may cause glands and goblet cells to secrete. This effect and inhibition of ciliary beating is observed in serum from patients with asthma and allergic diseases as well as cystic fibrosis [89].

A search for deficiencies in plasma has yielded that of alpha$_1$ antitrypsin which has stimulated the interest of biochemists in the lung comparable to that produced by the discovery of surfactant. The methods of detecting deficiency and phenotyping the deficient subjects have been applied to reasonable sized populations and to patients with emphysema. However, the numbers of homozygotes have been 13 per cent or less of selected patients with advanced emphysema and such homozygotes account for less

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than 1 per cent of all patients with emphysema. Thus this is virtually useless as a screening method for susceptible subjects. Most studies of heterozygotes do not show them to be excessively susceptible to emphysema.

Is it logical to neglect the alveolar cell population in these considerations? Are they not an essential line of defense? Clearly, the membranous or squamous type alveolar cells can be damaged by chemicals including viruses, nitrogen dioxide, paraquat and cadmium. However, as long as the basal lamina is not destroyed [43], re-epithelialization occurs by proliferation probably from the lamellar (type II) alveolar cells or from bronchiolar cells. Loosli has shown in mice that influenza PR-8 induces the latter with alveolar obliteration [90]. Lamellar (type II cells) can be induced to proliferate particularly by drugs such as bleomycin [91] or by viruses such as in Maedi or Jaagsekte [92]. These hyperproliferative responses may eventuate in granuloma formation from beryllium in which macrophages play an important role or in adenomas induced by urethane [93,94]. Resemblance of these models to desquamative pneumonia or to allergic extrinsic alveolitis is clear. A relation to emphysema has been suggested only recently in regard to cadmium [95]. Perhaps what has seemed a blind alley should be reexamined.

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