Cellular events in alveolitis and the evolution of pulmonary fibrosis

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Summary. "Alveolitis", as opposed to "pneumonia" *sensu strictiori*, is a term used to denote diffuse inflammatory changes of the pulmonary parenchyma, excluding those that result from local bacterial, fungal or other extracellular microbial growth. The various types of alveolitis are classified according to their histological characteristics and range from "luminal phagocytic" or "mural lymphoplasmacellular" and "exudative" to "fibrosing" alveolitis. In this overview, various exogenous and endogenous causes of different types of alveolitis, and the cellular events in their pathogenesis are briefly discussed to illustrate the complex mechanisms involved. Particular emphasis is placed on the possible transition from diffuse exudative to fibrosing alveolitis. It appears that pulmonary fibrosis, which is usually patchy rather than truly diffuse, does not have a uniform pathogenesis. Besides the possibility of a certain degree of a diffuse fibrosis three major pathways are evident: (1) granulation tissue budding into alveolar lumina (luminal fibrosis) (2) exudate incorporation into alveolar walls (mural fibrosis) and – at least equally important – (3) so-called collapse (atelectatic) induration (obliterative-interseptal fibrosis), a process that has largely been neglected so far.

Key words: Alveolitis – Pulmonary fibrosis – Diffuse alveolar damage – Pulmonary alveoli

Introduction

Pulmonary alveoli are superbly equipped to carry out their function of gas exchange during respiration. This is particularly evident from their ultrastructure (reviewed in Kuhn 1980). Flat type I pneumocytes, the fused epithelial and endothelial basement membranes and the endothelium constitute the respiratory membrane, which in humans is less than 0.5 μm thick at its thinnest parts (Bachofen and Weibel 1977). Type II pneumocytes which, after appropriate stimulation can enter the mitotic cycle, are able to transform into type I cells and thus to replace the latter when they are damaged and/or desquamate. Clearance of inhaled materials from the alveoli is predominantly the task of alveolar macrophages. A minute fraction of inhaled, nondigestible particles, usually within macrophages (Adamson and Bowden 1982), enters the pulmonary lymphatics and is passed to regional lymph nodes. Along this route the particles may accumulate, especially within lymphoid nodules in the lung (Cottier et al. 1987). So-called interstitial cells in the alveolar walls are usually mononuclear phagocytes on their way from the capillaries to the alveolar lumen. Lung tissue, particularly the extraalveolar interstitium, is extremely distensible due to the special arrangement of elastic and various types of collagen fibers (Amenta et al. 1988). The alveolal wall contains only a small number of fibroblasts/myofibroblasts, which helps to explain the limited capacity for fibroplasia inherent in the interalveolar septa per se unless fibroblasts or their precursors are attracted from neighboring structures.

Inflammatory changes in the pulmonary parenchyma are frequent and relevant clinical problems. Those caused by local growth of bacteria, fungi or animal parasites are commonly referred to as pneumonias. Inflammatory reactions not caused by extracellular microorganisms have traditionally been regarded as separate entities. There is, however, no generally accepted, uniform nomenclature to denote these disorders usually caused by a more or less "*diffuse alveolar damage*" (*DAD*, Katzenstein et al. 1976; reviewed in Burkhardt 1989).

Scadding (1964, 1967, 1974, 1978) and Fishman (1978) proposed the term "*alveolitis*" for the inflammatory consequences of DAD, a description which offers the advantage of a clear linguistic separation from "pneumonia". It also corresponds to reality inasmuch as the pathologist is rarely in a position to actually see the true initial alveolar damage, while inflammatory sequelae are more easily detectable. It is well recognized that both pneumonia and alveolitis can result in a fibrosing process. However, since only alveolitis is defined as a diffuse inflammatory change in the lungs, pulmonary fibrosis, in the sense it is commonly used, originates from fibrosing alveolitis. If the causative agent or agents initiating the fibrosing process are unknown, we speak of "idiopathic pulmonary fibrosis" or "Hamman-Rich syndrome" (Hamman and Rich 1944).

Most of our knowledge on alveolitis in humans is empirical. The site of initial damage – endothelium, pneumocytes, phagocytes, and/or other structural elements – is important for possible preventive measures but often can be deduced only from indirect evidence and for many agents remains speculative (review: Burkhardt 1989). Current concepts of pathogenesis are mainly based on experimental models or – as far as cellular phenomena are concerned – on findings in vitro.

In the following, various causes and types of alveolitis and their pathogenesis will be reviewed briefly, although the innumerable agents which may be responsible for such disorders will not be listed in detail. Rather some prototypes of alveolitis will be mentioned to exemplify the complexity of the cellular events initiating the disease process and the factors promoting the transition from alveolitis to pulmonary fibrosis, which includes the hitherto largely neglected process of so-called 'collapse induration', will be discussed.

Exogenous causes of alveolitis, with comments on possible sites of primary damage

Inhaled noxious agents

We need not emphasize that the human lung is exposed repeatedly to a vast array of potentially hazardous exogenous agents, in particular gases, vapors, fumes, dusts, poisons and microbes. This may in part be responsible for the fact that pulmonary function in Man deteriorates with age at a faster pace than that of other major organs (Astrand et al. 1973). With increasing air pollution and inhalation of potentially hazardous agents, particularly in industrialized countries, this phenomenon has gained great clinical relevance and

one could question if a clear distinction can be made in this respect between health and disease.

Gaseous components of polluted air such as nitrogen oxides, ozone and sulfur dioxide constitute, even in low concentrations, a generally recognized health hazard (reviewed in Cottier 1980). For obvious reasons, oxygen poisoning, in particular hyperoxic lung damage, has been studied in more detail, especially in animals (Kistler et al. 1967; Kapanci et al. 1969; Kaplan et al. 1969; Adamson et al. 1970; Weibel 1971; Bowden and Adamson 1974; Hayatdavoudi et al. 1981). Neutrophils do not seem to be needed to mediate this type of injury (Raj et al. 1985; Smith et al. 1988), so that most evidence points to direct damage to cellular components of the alveolar wall by the production of oxygen radicals (reviewed in Taylor et al. 1986). Many authors have gained the impression that in these animal model systems the capillary endothelium is the primary target cell (Porte et al. 1989). However, alveolar epithelial cells are also damaged to a considerable extent, directly or as a consequence of the endothelial lesions and hypoperfusion. Evidence for this is shown by the consequent marked regenerative activity of type II pneumocytes ("cuboid metaplasia"), which – at least in certain model systems – appears to originate near the first alveolar duct bifurcation (Brody and Overby 1989). In a cultured mouse lung system, which offers the advantage of avoiding the presence of blood components and of dealing with only a relatively small number of macrophages, hyperoxia produced marked damage and subsequent repair of the alveolar epithelium, sufficient to promote a "fibrotic process". Less severe hyperoxia affected the endothelium only and was not associated with fibrosis (Adamson et al. 1988). Although this artificial system does not reflect the true situation in vivo since it largely circumvents the activation of inflammatory cascades, these findings stress the importance of partial alveolar denudation, due to the destruction of pneumocytes, in promoting the appearance of "thick fibrous septa".

In the intact organism, hyperoxic lung damage involves, of course, much more complex mechanisms (see below). At this point, it may suffice to remember that the pathomorphic appearance of acute hyperoxic pulmonary lesions is a diffuse exudative alveolitis with edema, the appearance of hyaline membranes and – simultaneously or consecutively – "cuboid metaplasia", which can be regarded as an expression of pneumocyte regeneration. After inhalation of highly toxic gases or aerosols, such as the ones used in chemical warfare, the damage is even more dramatic ("necrotizing

and hemorrhagic alveolitis") than after exposure to pure oxygen.

Prolonged cigarette smoking, in addition to other, well known risks, is often associated with the accumulation of pulmonary alveolar macrophages that are larger than in nonsmokers (Müller and Hirschberg 1984), have an enhanced cytotoxic potential for normal lung parenchymal cells in vitro (Davis et al. 1988) and, mainly with the help of complement component C5 (Robbins et al. 1987), can attract (Hunninghake et al. 1978; Hunninghake and Crystal 1983) and activate (Pennington et al. 1985) neutrophils. It seems safe, therefore, to accept that cigarette smoking may damage the alveolar epithelium (Jones et al. 1980), at least in part, by the cytotoxic effects of phagocytes. The latter seem to include the damaging action of oxygen-derived radicals, which may be released from alveolar macrophages (see Cassatella et al. 1989). An imbalance between pro-inflammatory proteases and antiproteases, such as alpha-1-antitrypsin, may not only promote chronic obstructive pulmonary disease with consecutive chronic emphysema (Niewoehner 1988) but can also contribute to alveolitis and the evolution of fibrosis. In view of these findings, we could speak of a "chronic luminal phagocytic alveolitis".

Inhalation of inorganic dusts in large amounts and over a prolonged period of time represents a well known hazard (reviewed in Walton and McGovern 1977) and may result in nodular fibrotic changes, known as pneumoconiosis (reviewed in Morgan 1986). Mechanisms of fibrogenesis in these lesions have best been studied in silicosis (Reiser and Last 1979) and asbestosis (Lemaire et al. 1986; Chang et al. 1988). It should be recognized, however, that a certain degree of "chronic luminal phagocytic alveolitis" due to dust inhalation is widespread. The medical relevance of such discrete changes may be difficult to assess. Translocation of the dust particles to septal lymphoid nodules (Cottier et al. 1987) may explain the typically focal distribution of fibrosis/scarring in pneumoconiosis, which is predominantly macrophage-mediated and essentially different from diffuse pulmonary fibrosis developing from alveolitis, as will be discussed later.

Inhalation of organic particles has divergent effects, depending on particle size, nature, amount, antigenicity and solubility of the material as well as the duration of exposure. Poorly soluble or insoluble, barely antigenic particles, such as vinyl and polyvinyl chlorides (Cardasco et al. 1980; Antti-Poika et al. 1986) or hairspray (Gebbers et al. 1979), may cause accumulation and a certain degree of stimulation of alveolar macrophages, similar to the changes mentioned above. If, however, the inhaled dust exhibits antigenic properties, as is the case with many materials of microbial, plant or animal origin, an immune reaction may be elicited, with the possible result of a "*hypersensitivity alveolitis*" or "*extrinsic allergic alveolitis*" (formerly "lymphocytic and/or plasmacellular interstitial pneumonia", reviewed in Gaensler et al. 1972; Richerson 1983; Spencer 1985 and Fink and DeShazo 1987).

Blood-borne noxious agents

Another group of causative agents comprises toxic substances (toxons) that – at least in part – reach the lung by the blood stream rather than by inhalation, and appear to affect this organ preferentially. Under physiological conditions the lung is the only organ that is perfused by all the circulating blood. Furthermore, the pulmonary capillary system receives the bulk of venous blood without possessing a detoxifying capacity comparable to that of the liver.

Of particular interest in this context are certain drugs used for chemotherapy in humans, for instance the cytostatic antibiotic bleomycin, which has been recognized as pneumotoxic years ago (Delena et al. 1972; Krous and Hamlin 1973; Burkhardt et al. 1976; Burkhardt and Gebbers 1986). There are certain indications that pulmonary capillary endothelium may be the primary site of attack of bleomycin. Microthrombi appear in small blood vessels of the lung very early, and the damage can be mitigated by heparin therapy (Burkhardt et al. 1976, 1977). Pneumocytes also suffer severely, which leads to partial denudation of alveoli, the formation of hyaline membranes and, with a short latency, the development of "cuboid metaplasia". These and additional lesions, characteristic of severe exudative alveolitis, can also be found after treatment with other "cytostatic" drugs, e.g. cyclophosphamide (see experiments in mice, Allalunis-Turner and Siemann 1988). Dog lungs perfused in situ with doxorubicin also exhibit dose-dependent damage to endothelial cells and alveolear epithelium (Minchin et al. 1988). Earlier postulates that cytostatic drugs, such as bleomycin, inhibit surfactant production by type II pneumocytes (Burkhardt et al. 1977), have been confirmed using hamster lung slices in vitro (Giri 1987).

Radiation

Penetrating ionizing radiation from external sources has long been known to cause a diffuse lung damage that – in its initial stage – may well

be termed alveolitis. The time course of these lesions has been studied in detail in animal experiments (Cottier 1956; reviewed in Cottier 1966; Watanabe et al. 1974; Penney et al. 1981; Maisin et al. 1982) and the importance of endothelial damage and repair has been stressed (Adamson and Bowden 1983) as has the occurrence of alveolar collapse induration (Cottier 1956, see also below).

Somewhat different patterns of lung injury may be expected from inhalation of radionuclides (International Commision on Radiological Protection 1980). Since human data are virtually lacking, our knowledge in this field originates essentially from animal experimentation. Long-term studies have been carried out to evaluate the effects of inhaled alpha-emitting particles, especially plutonium oxides and salts. In evaluating the results of such experiments, a number of variables must be taken into account, for example specific activity of radionuclide, the type of radiation emitted, radioactive decay, the concentration of radionuclides in particles, the size and degree of aggregation of particles, the solubility of the inhaled material, the presence or absence of other toxic substances, particle-tissue interactions, translocational events, and the characteristics of the tissue concerned. Although such studies focused mainly on carcinogenic action (Park et al. 1986), it became evident that these highly toxic particles also have non-stochastic effects, in particular progressive pulmonary fibrosis (International Commision on Radiological Protection 1980). Since the initial deposition of the radioactive material is diffuse, it is easily understood that – depending on the burden – a more or less severe alveolitis will ensue. Highly soluble compounds, such as plutonium nitrate, then rapidly gain access to the blood stream and are fixed to bone or other tissues and – to a considerable extent – finally excreted. Conversely, insoluble particles, e.g. $^{239}PuO_2$, translocate over the years mainly by the pulmonary lymphatics, where focal accumulations of radioactive material occur and are apt to create "hot spots" (reviewed in Cottier and Zimmermann 1986; see also Cottier et al. 1987).

Other extrinsic or presumably extrinsic causes

The question whether diffuse virus-induced pulmonary changes, that are associated with morphologic signs of immune reactions, should be included under the heading of "alveolitis", is not yet settled. The same pertains to certain disorders of unknown etiology with considerable lymphocytic infiltration, e.g. the early phase of sarcoidosis (reviewed in Chrétien et al. 1983). It would certainly help international communication if a consensus in this field could be reached.

Endogenous, complex and/or unknown causes of alveolitis

The so-called adult respiratory distress syndrome (ARDS)

In terms of clinical relevance, causes of alveolitis other than the ones discussed so far are probably of greater importance. This may best be exemplified by the wide range of disorders or events that can lead to what is now commonly known as "adult respiratory distress syndrome (ARDS)" (Ashbaugh et al. 1967; review: Rinaldo and Rogers 1982; Simon and Ward 1988). The common features of this syndrome include rapid and progressive development of respiratory impairment. Autopsy studies on 301 individuals who died in the Intensive Care Unit of the University Hospital in Bern revealed that severe, fibrosing alveolitis developed mainly in patients requiring prolonged mechanical ventilation, and that among this group preceding abdominal complications were predominant (Ruchti 1986). This is in line with other observations that gram-negative rods are the most important infectious cause of ARDS (Hyers and Fowler 1986). It thus appears that endotoxin-containing bacteria play a particular role in the initiation of ARDS.

Prolonged *shock* as such, which may be defined as a condition resulting from critical hypoperfusion of vital organs, can injure the lungs ("shock lung", see Bleyl and Büsing 1971; Schulz and Schnabel 1975; Heene and Lasch 1977; Sandritter et al. 1978; Riede et al. 1981), although progressive ARDS following acute hypovolemia does not appear to be a frequent event. Possibly, shock-induced damage to the intestinal barrier, comparable to ischemic colitis, could add an infectious component in such situations. Structural changes in the lungs in cases of uncomplicated shock may be viewed as mild variants of the severe alveolitis encountered in progressive ARDS. They include, among others, an early and often transient accumulation of neutrophils in pulmonary capillaries (Schlag et al. 1976; Heine 1981), endothelial swelling and injury at these sites (Gross 1967; Freudenberg 1978), microthrombi or -emboli (Saldeen 1983), alveolar epithelial damage, and the formation of hyaline membranes. Usually there is also a varying degree of luminal and interstitial edema, which ensues – at least in part – from increased vascular permeability and may cause the normally fused subendothelial and subepithelial basement membranes to separate (Riede et al. 1978; Riede et al. 1979, reviewed in Burkhardt and Gebbers 1983). It is thus understandable that a certain de-

gree of alveolo-capillary block can be observed in shock patients showing no overt ARDS.

The structural changes summarized above are much more pronounced and complicated by additional, progressive changes in patients with the so-called "*septic shock syndrome*". We write this term in parentheses because all these individuals show signs of severe infection, usually caused by gram-negative rods, but not all have sepsis *sensu strictiori*. There is most often a marked, although transient, aggregation of neutrophils in pulmonary capillaries (Tate and Repine 1983; Elliott et al. 1985), with at least a fraction of these cells in an activated state (Zimmermann et al. 1983). These cells can mediate tissue destruction (reviewed by Weiss 1989). Endothelial damage appears to be important (Tomashefski et al. 1983), however, it is probably of short duration due to a high regenerative capacity of the endothelium. In fact, ultrastructural studies on human lungs revealed astonishingly little vascular damage, platelet thrombi or neutrophil accumulation, while luminal and interstitial edema, partial destruction of pneumocytes (especially type I), the formation of hyaline membranes and the beginning cuboidal metaplasia are obvious 20–24 h after onset of ARDS (Bachofen and Weibel 1974, 1977). In these cases, actual lung damage was probably initiated before an overt ARDS developed.

The pathogenesis of severe, progressive alveolitis in the "septic shock syndrome" is obviously highly complex. Bacterial endotoxins seem to be of great importance. However, although these lipopolysaccharides (LPS) from gram-negative microorganisms, with their toxic component lipid A, are able to directly damage cellular constituents of the pulmonary alveolar wall (Meyrick 1986; Meyrick et al. 1989), this does not appear to be the only, or even the most important, mechanism responsible for alveolitis in "septic shock syndrome". Animal experiments have demonstrated that activation of complement (C), with the subsequent accumulation of neutrophils in pulmonary capillaries and the release of oxygen-derived free radicals, in particular OH·, can cause severe lung damage (Till and Ward 1986; Doherty et al. 1988). Leukotrienes, in particular LTB_4, appear to contribute to chemotaxis of neutrophils (Heidel et al. 1989), while adhesion molecules, such as the endothelial leukocyte adhesion molecule 1 (ELAM-1), seem to be instrumental in intracapillary sticking of these cells (Bevilacqua et al. 1989). Other factors, such as tumor necrosis factor (TNF; reviewed by Ziegler 1988), can serve as activators of granulocytes (Yuo et al. 1989) and endothelial cells (Cavender et al. 1989).

Since LPS is able to activate complement by both classical and alternate pathways (Morrison and Kline 1977) and to enhance neutrophil-mediated effects stimulated by chemotactic factors (Worthen et al. 1986), we have to reckon with more than one mechanism of endotoxin-induced injury to pulmonary alveoli. The problem became further complicated with the observation that ARDS may develop in patients with severe neutropenia (Ognibene et al. 1986; Ward and Johnson 1987; Heine et al. 1989), so that an accumulation of granulocytes in the lungs does not seem to be a strict prerequisite for shock-induced lung damage. Other mechanisms apt to contribute to injurious effects on alveolar wall constituents comprise activation of the coagulation system, as is often observed in intensive care patients (Wilde et al. 1988). Clotting of blood usually goes in parallel with a stimulation of the kinin system (reviewed in Kaplan and Silverberg 1987) and the appearance of serum factors that promote aggregation, adherence to endothelium and oxygen radical production by neutrophils (Lo et al. 1988). The mechanisms responsible for initiating coagulation in such conditions are not clear. Proteins of the contact system seem to be more extensively activated than proteins that contribute to later reactions in intravascular coagulation and fibrinolysis (Carvalho et al. 1988). It should also be mentioned that tissue factor (reviewed in Nemerson 1988) is liberated in such lesions, that LPS primes neutrophils for the production of platelet activating factor (PAF; Worthen et al. 1988), and that activated alveolar macrophages express a marked procoagulant activity, which may be important for fibrin deposition in hyaline membranes and in the interstitium (Tipping et al. 1988). The role of coagulation in the development of ARDS is still disputed. Treatment of mice with epsilon-aminocaproic acid, which inhibits the breakdown of fibrin clots, did not enhance cyclophosphamide-induced lung damage in mice (Allalunis-Turner and Siemann 1988). Conversely, the administration of recombinant alpha-1-antitrypsin Pittsburgh, a mutant with a loss in antielastase activity but a marked increase in antithrombin activity, to piglets attenuated the effects of septicemia induced with gram-negative bacteria (Colman et al. 1988). Little is known on the behavior of naturally occurring anticoagulant proteins (reviewed in High 1988) in "septic shock syndrome". The role of an inhibition of fibrinolysis in ARDS (Saldeen 1983) also remains to be further examined. Another group of mediators that appears to be instrumental in the development of "toxic shock syndrome" are products of local cellular arachidonic acid metabolism, i.e. certain pro-

staglandins (PG) and leukotrienes (LT). Mono-cytes/macrophages are among the cells that can be stimulated to enhanced production of such substances (Balter et al. 1989). As regards alveolitis, thromboxan B_2 (TXB$_2$), LTB$_4$ and LTC$_4$ are of special interest (Morganroth et al. 1988; Schönfeld et al. 1988). Although in certain animal models, nonsteroidal antiinflammatory drugs had a mitigating effect on the development of lung lesions (Begley et al. 1984), the relative importance of arachidonic acid products in the pathogenesis of lung damage discussed here should probably not be overestimated (Simon and Ward 1988).

More recently, interest has focused on certain cytokines as mediators of lung damage, in particular interleukin-1 (IL-1), TNF and interferon-γ (IFN-γ). For instance, monoclonal antibodies directed against TNFα abrogated TNF-mediated macrophage cytotoxicity (Lefkowitz et al. 1989), and prevented the development of septic shock in baboons if given 2 h before the injection of an LD 100 of live E. coli (Tracey et al. 1987). Similarly, monoclonal antibody to IFN-γ, which seems to enhance TNFα and IL-1 activities independently of cyclo-oxygenase products (Hart et al. 1989), protected mice against lethal effects of LPS injections (Billiau 1988). However, if we consider the vast number of cytokines known (reviewed in Hamblin 1988), their possibilities of autoregulation (e.g. IL-1; Manson et al. 1989), their in part antagonistic or synergistic actions (Sporn and Roberts 1988), and their divergent effects on different cell types (Warren et al. 1988), it is as yet impossible to assess their relative contribution to the pathogenesis of severe, exudative alveolitis in vivo. Experiments in vitro, for instance on the multitude of cytokine effects on cultured vascular endothelium (Pober 1988), support this view. Analogous difficulties arise if we try to evaluate actions of other substances released from cells, e.g. proteases (reviewed in Scher 1987), peroxidases (Shellito et al. 1987), peptide defensins (Lichtenstein et al. 1988), macrophage activation-associated proteins (MacKay et al. 1989), or vasoactive substances such as histamine (for lung mast cells, see Heard et al. 1989), PGI$_2$, nitric oxide or endothelin, a vasoconstrictor factor (De Nucci et al. 1988). Furthermore, regulatory circuits, such as the one including the hypothalamus-pituary-adrenal axis, have to be taken into account. In vitro, glucocorticoids reduce the LPS-induced monocyte IL-1 levels but have only minimal effects on endothelial cell IL-1 (Zuckerman et al. 1989).

To summarize the complex pathogenetic events leading to severe alveolitis in "septic shock syndrome": there is no single agent that could be made responsible for all the damage caused, rather, an overwhelming activation of various inflammatory cascades appears to be important.

In ARDS caused by other events, e.g. thermal burns, disseminated intravascular coagulation, multiple injuries with or without fat embolism, pancreatitis and others, the pathogenesis may differ in certain respects; however, several of the mechanisms mentioned above are probably also relevant. Autoimmune processes (see Schwartz and Rose 1986) should also be considered, although their role in alveolitis and pulmonary fibrosis is as yet poorly understood.

Idiopathic or cryptogenic alveolitis

It should be remembered that in about 50% of human cases with diffuse fibrosis of the lungs no causative agent(s) could be identified. This condition, known as "Hamman-Rich syndrome" (Hamman and Rich 1935), "idiopathic pulmonary fibrosis" (Crystal 1976) or "cryptogenic fibrosing alveolitis" (Scadding and Hinson 1967), is thought to be associated with a chronic immune reaction of unknown origin and progresses from an early "cellular" to a late "fibrotic" stage (reviewed in Hance and Crystal 1983; Crystal et al. 1984). However, since the initial phase of this disorder – or group of disorders – is still obscure, the pathogenesis cannot be discussed based on the data available. Lung fibrosis in scleroderma most probably represents a separate entity, related to a defective collagen metabolism.

From alveolitis to pulmonary fibrosis, with special reference to collapse (atelectatic) induration

By comparing the various types of alveolitis and their pathogenesis, the impression is gained that the reaction pattern to injury depends more on the severity of damage than on the nature of causative agents. It seems that the further course of the process is to a great extent determined by the degree to which the alveolar epithelium has been impaired. Death of pneumocytes, in particular of the type I cells, results in a more or less pronounced alveolar denudation, an erosive lesion, concomitant with partial disintegration of the underlying basement membrane and fibrin deposition. If the blood flow through capillaries is reduced, e.g. by accumulation of leukocytes, endothelial swelling and/or microthrombi, hypoxic damage ensues. At this stage, and with limited initial damage, reconstitution of the alveolar structure by resolution of

the exudate and regeneration of pneumocytes by proliferation of type II cells and their transformation into type I cells still seems possible. An intact basement membrane rich in fibronectin may be relevant for epithelial regeneration (Vracko 1974; Torikata et al. 1985), and reperfusion of capillaries after dissolution of microthrombi and endothelial regeneration may ensue. Such minor reparative events are probably quite frequent. Conversely, pneumocytes can cover hyaline membranes and thus lead to incorporation of fibrin-rich material into the thickened septa. If, for one reason or another, such as secondary bacterial infection, larger amounts of fibrin-rich exudate within alveoli are not resolved in due time, organization by granulation tissue ("onion-scale type of fibrosing alveolitis"; Otto 1975) and focal scar formation follow. Such changes seem to occur more often in respiratory bronchioli ("alveolitis with bronchiolitis obliterans"; Katzenstein et al. 1986a) than in alveoli sensu strictiori. This particular localization of scars could in part be related to the initial impact site of exogenous noxious materials.

If the pulmonary parenchyma has undergone severe and/or repetitive damage, fibrosing alveolitis (diffuse pulmonary fibrosis) may develop. Observations made on humans and in animal experiments indicate that in most – if not all – such cases "cuboid metaplasia" of the alveolar epithelium is a prominent feature. This phenomenon, which can even lead to squamous epithelial metaplasia and dysplasia (Spencer 1968; Burkhardt et al. 1977; Wang 1983; Menne and Müller 1984; Katzenstein et al. 1986b; Hartmann et al. 1987) and/or ingrowth of bronchiolar epithelium ("bronchiolization"; Kawanami et al. 1982), must be regarded as a distinct sign of preceding pneumocyte type I necrosis, alveolar denudation and subsequent regeneration. It can also be assumed that in such conditions the alveoli have experienced an at least transient lack of surfactant and surfactant-associated proteins. Normally, type II pneumocytes and alveolar macrophages express high-affinity receptors for pulmonary surfactant protein A (Kuroki et al. 1988), which helps to prevent alveolar collapse and seems to also be instrumental in avoiding inappropriate immune and other inflammatory reactions (Catanzaro et al. 1988). Available information strongly suggests that the initiation of fibrosing alveolitis depends on the severity and the duration of exudative inflammatory processes in the pulmonary parenchyma, concomitant with alveolar denudation, inflammatory infiltrates and unresolved deposits of fibrin. It is of interest in this context that fibronectin (see review by Var-

tio 1983) seems to augment the binding of fibrin to the surface of mononuclear phagocytes (Kaplan et al. 1989), which may be instrumental in the degradation of this material.

The question then arises what mechanisms lead to fibrosis. Results of studies on cultured mouse lung subjected to hyperoxic attack, a model system that avoids most inflammatory reactions and their effects, are of interest in this respect. They indicate that severe injury and retarded repair of alveolar epithelium disturb normal epithelial-fibroblast interactions and are sufficient to promote the fibrotic process, while less severe damage involving the endothelium only, is not associated with fibrosis (Adamson et al. 1988). However, the situation in vivo is certainly much more complex. A number of lymphokines and monokines are instrumental in fibroblasts chemotaxis, proliferation and matrix synthesis (reviewed in Wahl 1985; Lemaire et al. 1986). In particular, activated macrophages are known to produce and release one or several factor(s) that stimulate(s) fibroblast proliferation (Leibowich and Ross 1976; Bitterman et al. 1982; Bitterman et al. 1983; Kumar et al. 1988) and modulate collagen production (Kelley et al. 1981; Clark and Greenberg 1987). Alveolar macrophages from patients with idiopathic pulmonary fibrosis seem to exhibit an exaggerated spontaneous release of "platelet-derived growth factor (PDGF)" (Martinet et al. 1987). Immune interferon has also been shown to act as a growth factor for human lung fibroblasts (Hunninghake et al. 1986). Furthermore, several proteases, including thrombin, promote fibroblast proliferation and differentiation (reviewed in Scher 1987). One may thus be satisfied with the mechanisms mentioned so far as sufficient to explain the development of pulmonary fibrosis. In fact, it has been proposed in the past that severe exudative alveolitis of a certain duration results in a rather early "generalized fibrotic thickening of the alveolar septa" (Bachofen and Weibel 1977).

Several observations, however, argue against these being the only, or even most important, mechanisms involved in the development of pulmonary fibrosis. The latter, although commonly described as "diffuse", at the light microscopic level often exhibits a marked focal pattern, with coexistence of virtually unchanged alveoli and thick fibrotic septa. This fact has struck many investigators (Jones and Reeve 1978; Bachofen and Weibel 1982; Hammar et al. 1985; Snider 1986) and has remained unexplained on the basis of a truly diffuse fibrosing process. Attempts at relating these inhomogeneities to regionally different vasomotor and bronchomotor functions (Snider 1986) lack

documentation. There is thus a need to reconsider other possible causes of patchy fibrosis in such disorders. One mechanism has already been mentioned, i.e. the appearance of "onion-scale" type of granulation tissue ("intraluminal buds"; Basset et al. 1986) organizing excessive amounts of fibrinous exudate in an expanded alveolus. Another possibility is the incorporation of murally attached fibrinous masses into the denuded alveolar wall, which can then become covered by regenerating pneumocytes and elicit local fibroblastic responses (Spencer 1968; Katzenstein et al. 1985; Basset et al. 1986). Results of experiments on mice indicate that the transfer of macrophage-derived growth factor(s) to fibroblasts is more efficient when it occurs within the pulmonary interstitium than from alveolar macrophages (Adamson et al. 1989).

The third, and probably most important, mechanism resulting in focal septal fibrosis is the so-called collapse induration or atelectatic induration, a process that has largely been neglected in the international literature (reviewed in Burkhardt 1989). Yet as early as 1922, Kaufman, in a widely used textbook on pathology, wrote under the heading of "obliteration and fibrosis of atelectatic lung tissue, so-called collapse induration" the following: "If collapse of alveoli persists for some time, expansion may no longer be possible. The denuded alveolar walls stick together and coalesce. The alveoli are obliterated. In the interstitial tissue proliferation of fibrous tissue ensues, resulting in cicatricial induration". There have been only sporadic references to this mechanism in the literature (Lauche 1928; Cottier 1956, 1961, 1966, 1980; Heppleston 1956; Otto 1975; Cottier and Zimmermann 1986; Burkhardt 1986), although its importance for the evolution of lung fibrosis was stressed in the last edition of a German handbook of pathology (Burkhardt and Gebbers 1983). More recently, attention has been drawn to collapse induration in the United States (Katzenstein 1985) and in Japan (Fukuda et al. 1985, 1987). Katzenstein pointed out in 1985 that "other factors than collagen deposition may be important in producing the interstitial thickening... one, which was not reported previously, involves partial or complete collapse of alveoli and permanent apposition of their walls."

Recently Burkhardt et al. (1986) were able to demonstrate by means of morphometry the importance of collapse induration in experimental alveolitis induced by bleomycin: in the early stages (until day 60) an increase in the thickness of the alveolar walls and loss of surface area was not accompanied by a true increase in total alveolar wall volume or by an increase in the hydroxyproline content of lung tissue.

Strong evidence in favor of an important role of collapse induration in the pathogenesis of pulmonary fibrosis can also be taken from a number of observations reported in the literature (review: Burkhardt 1989), although these were not interpreted by the authors in terms of collapse induration. Thus Fulmer et al. (1980) concluded that in idiopathic pulmonary fibrosis, the lungs did not contain more collagen than normal lungs in spite of a histologically "unequivocal septal fibrosis".

Alveolar collapse in a lung with DAD may in part be reversible and does not necessarily result in atelectatic induration. For the latter to occur, as mentioned before, probably requires prior alveolar denudation, with loss of surfactant and deposition of fibrinous exudate at the eroded inner surface of alveoli. Fibrin may thus serve as an adhesive, apt to attach the walls of collapsed alveoli to each other. Fibronectin, which accumulates in developing lung fibrosis (Torikata et al. 1985), could exert a similar function. Fibrin and fibronectin (Fukuda et al. 1987) are also candidates for attracting fibroblasts into the collapsed space and thus for contributing to fibrosis at this site, a process that may be termed "obliterative interseptal fibrosis".

Possible consequences of collapse induration and its recognition are manifold. They comprise a reduction of the intact inner respiratory surface and the exclusion from gas exchange of a considerable portion of pulmonary capillaries. These alterations may contribute as much – or more – to the respiratory insufficiency of patients with pulmonary fibrosis as/than an "alveolo-capillary block" sensu strictiori. Since collapse induration results in patchy rather than diffuse fibrosis, the compliance of lung tissue cannot be expected to be uniformly reduced. For the same reason, the imbalance between ventilation and perfusion may vary markedly from one small area to another. Furthermore, alveoli not affected by collapse induration are apt to expand, producing a pattern of alternating small foci of emphysematous change and fibrosis. It should be recognized, however, that even a lung with advanced fibrosis is subject to constant remodeling (reviewed in Murray and Laurent 1988). Macrophages stimulated to enhanced procollagenase production may be instrumental in this process (Cury et al. 1988), and mast cells, which accumulate in experimental, bleomycin-induced pulmonary fibrosis (Tomioka et al. 1989), probably also play a role. The structural

changes mentioned above may become exaggerated to form what is commonly known as "honeycomb lung". Attempts to explain the evolution of this cystic remodeling have alluded to various possible mechanisms (reviewed in Witek 1970; Gross and Goodwin 1976), but not to collapse induration. The multifocal lung fibrosis resulting from the latter also offers one plausible explanation for the non-uniform particle deposition and clearance in fibrosing pulmonary disorders (Tryka et al. 1985). Another problem relates to the interpretation of small lung biopsy specimens in such diseases, as recommended for the diagnosis of pulmonary fibrosis (Crystal 1976): these may not be representative for the entire lung tissue. It seems desirable that the recently proposed systems for morphometry (Gil et al. 1988) or grading (Ashcroft et al. 1988) of pulmonary fibrosis will be modified to include an assessment of the type and degree of "patchiness" of the lesions.

From a clinical point of view, recognition of collapse induration as an essential mechanism in the pathogenesis of pulmonary fibrosis helps towards a better understanding of the beneficial effect of exogenous surfactant administration in children with ARDS (Davis et al. 1988). It is also apt to further encourage forced inspiratory breathing exercises to be included in the therapeutic program in such conditions, as some pysicians have always done. These exercises should be continued for a long time, because fibrosing lung disorders have a tendency to progress with time even after cessation of the causative influence (Bleyl and Büsing 1971; Burkhardt et al. 1977; Burkhardt and Gebbers 1983; Burkhardt 1989). The mechanisms responsible for this phenomenon of protraction ("perpetuation") are not clarified. Persistent inflammation, hypoperfusion and ischemic damage to lung tissue seem to be important. Other or additional possibilities are: remodeling of the diseased pulmonary parenchyma, prolonged imbalance of collagen turnover with predominance of fiber deposition over removal, frequent infectious complications, and others. It should be mentioned in this context that in progressive pulmonary fibrosis type I collagen is increasingly prevalent over the more elastic type III (reviewed in Laurent 1986). Finally, obstructive changes in pulmonary lymphatics with consecutive, possibly discrete, lymphedema, a pathogenetic factor rarely mentioned in the literature, should be considered. A longstanding edema may favor diffuse fibrosis ("lymphsclerema"). It also remains to be studied which mechanisms are responsible for the beneficial effects of polyinosinic-polycytidylic acid (Po-

ly I:C), an inducer of interferons, on developing, bleomycin-induced lung fibrosis in hamsters (Giri and Hyde 1988).

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