ALMOST seventeen billion granulocytes enter and exit the lungs each minute. Although the numbers of granulocytes in pulmonary artery and systemic artery blood are equal under normal conditions, they are not all the same cells, since a sizeable marginated pool of granulocytes in the lungs is constantly exchanging with the pool of circulating cells (Bierman et al., 1952, 1955; Cohen et al., 1979; Staub et al., 1981; Cohen et al., 1982). Some relatively innocuous interventions (for example, hemodialysis) cause sudden, dramatic stasis of granulocytes in the pulmonary circulation—granulocytes virtually disappear from the blood briefly—without severely compromising lung function (Craddock et al., 1977). In other circumstances, activated granulocytes sequestered in the lung appear to cause severe injury which may be either acute or chronic (Heflin and Brigham, 1981; Loyd et al., 1983; Newman et al., 1983). There is even some evidence that, under normal conditions, leukocytes sequestered in the lungs may be preferentially located along the walls of small arteries (Staub et al., 1981). There are several possible explanations for the presence of excess granulocytes in the lungs' microcirculation.

Schmid-Schoenbein et al. (1980) presented convincing evidence that the physics of particulate flow in small vessels would favor retardation of granulocytes relative to the smaller erythrocytes, and such behavior has been shown in some microvascular beds by cinemicroscopy. Additional evidence favoring a physical explanation for the intrapulmonary pool of granulocytes has been presented by Martin et al. (1982) who demonstrated that the number of granulocytes present in the lung is inversely related to pulmonary blood flow. This phenomenon could explain the relatively greater numbers of leukocytes in the microvasculature of isolated lungs under zone 2 conditions than under zone 3 conditions where flow is higher (Perlo et al., 1975).

It is not yet clear whether physical factors are adequate to explain completely the number of granulocytes normally present in the lungs. Some studies have suggested specific interactions between the microvascular endothelium and granulocytes. Granulocytes adhere preferentially to endothelium in vitro (Beesley et al., 1978), and this adherence requires divalent cations (Beesley et al., 1978; Hoover et al., 1980). Endothelial cells have surface receptors for chemotactic peptides, and incubation of endothelium with complement fragments increases granulocyte adherence (Hoover et al., 1980). Endothe-
lium may secrete a pro-adhesive factor, particularly when incubated with plasma (Pearson et al., 1979), and both adherence of granulocytes to endothelium (Pearson et al., 1979) and migration of granulocytes through endothelium (Beeley et al., 1978) may be interactive processes between the two cell types, rather than functions of granulocytes alone. Unstimulated granulocytes adhere to cultured endothelial monolayers (Buchanan et al., 1981), and this spontaneous granulocyte adherence is not affected by prostacyclin (Gimbrone and Buchanan, 1982), but is inhibited by agents which may prevent generation of lipoxygenation products of arachidonic acid (Buchanan et al., 1981; Gimbrone and Buchanan, 1982). The lung is a potential source of lipoxygenation products, so it is possible that these chemotactic products of arachidonic acid (Palmblad et al., 1981) play a role in the normal interactions of granulocytes with the lungs. There is evidence that mobilization of the marginated granulocyte pool by epinephrine is a result of generation of cAMP by endothelial cells after stimulation of β-adrenergic receptors (Boxer et al., 1980). These findings also suggest humoral communication between granulocytes and vascular endothelium, which affects granulocyte margination and migration.

Is there any effect of the normal interactions of granulocytes with the lungs on the organ’s function? Recent evidence suggests that there may be. Snapper and associates studied airway reactivity to aerosolized histamine in chronically instrumented, unanesthetized sheep (Hinson et al., 1982). They found a broad range of airway responsiveness in normal sheep similar to that seen in other animals (Snapper et al., 1978) and in humans (Orehek and Gayrard, 1976). However, when animals were depleted of circulating granulocytes, airway reactivity uniformly decreased and the variability among animals was reduced considerably (Hinson et al., 1982). In addition, there was a clear correlation between airway reactivity and the peripheral blood leukocyte count under baseline conditions. The suggestion is that interactions of granulocytes with the lung may affect important functions of the lung even under normal conditions.

Acute Lung Injury

Inflammation is a characteristic response of the lung to injury. Granulocytes accumulate in the lungs of patients who die of acute diffuse lung injury (adult respiratory distress syndrome) (Bachofen and Weibel, 1977; Pratt et al., 1979), and this is also true
of several experimental forms of the syndrome (Staub et al., 1982b; Johnson and Ward, 1982; Loyd et al., 1983; Meyrick and Brigham, 1983; Newman et al., 1983).

Figures 1 and 2 illustrate the rapid and profound accumulation of granulocytes in the lungs of animals infused with gram-negative endotoxin (Meyrick and Brigham, 1983). Not only do granulocytes accumulate, but, at least with endotoxemia, they undergo a sequence of interactions with the peripheral lung vessels which temporally coincides with physiological responses. Figure 3 shows a series of electron micrographs of peripheral lung tissue from a sheep, depicting the temporal sequence of leukocyte behavior in the lungs' microcirculation after endotoxin infusion (Meyrick and Brigham, 1983). Soon after endotoxin is infused, there is margination of leukocytes in the small vessels and degranulation of polymorphonuclear neutrophils. Later, there is migration of leukocytes between endothelial cells and, finally, endothelial cell injury with gaps appearing between endothelial cells. Table 1 juxtaposes the time course of the structural and functional changes.

Granulocytes accumulate in the lungs in other animal models of diffuse lung injury, for example, extensive microembolism (Staub et al., 1982b) and

**Table 1**

<table>
<thead>
<tr>
<th>Time following start of endotoxin infusion</th>
<th>Structural changes</th>
<th>Physiological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>Accumulation, margination, degranulation and fragmentation of granulocyte and accumulation of activated lymphocytes in pulmonary microcirculation</td>
<td>Increase in Ppa and protein-poor lung lymph flow; decreased P02 and leukopenia; early alterations in lung mechanics</td>
</tr>
<tr>
<td>30 min</td>
<td>Migration of leukocytes into interstitium; some interstitial edema</td>
<td>Peak pulmonary hypertension and alterations in lung mechanics</td>
</tr>
<tr>
<td>60 min</td>
<td>Endothelial and vessel wall damage; damaged type I and interstitial cells; perivascular edema</td>
<td>Ppa and lung mechanics returning toward baseline</td>
</tr>
<tr>
<td>2 hr and onwards</td>
<td>Endothelial layer disruption</td>
<td>Ppa and lung mechanics stable; increased lung vascular permeability</td>
</tr>
</tbody>
</table>

[Reprinted with permission from Meyrick and Brigham (1983).]
FIGURE 3. A series of electron micrographs from lung biopsies taken at different times following infusion of E. coli endotoxin into sheep. Panel a: accumulation and margination of both granulocytes (g) and lymphocytes (l) in the microcirculation 15 minutes after endotoxin infusion 550X; panel b: fragmentation (*) and degranulation of granulocyte-specific granules into vessel lumen 30 minutes after endotoxin infusion 3800X; panel c: a granulocyte in the process of migration 30 minutes after endotoxin infusion. The nucleated portion of the granulocyte (g) lies beneath the capillary endothelium (e) but superficial to its basement membrane (bm) 6,700X. Endothelial cell damage (e) seen as increased electron density, 60 minutes after endotoxin 9,700X. [Reprinted with permission from Meyrick and Brigham (1983).]
Granulocytes also accumulate in the airspaces in humans with acute lung injury, and bronchoalveolar lavage fluid from such patients contains proteolytic enzymes derived from leukocytes (Lee et al., 1981; Cochrane et al., 1983a, 1983b).

In addition to circumstantial evidence implicating granulocytes as mediators of acute lung injury (the granulocytes are there and present in increased numbers), infusion of agents which activate granulocytes causes pulmonary leukostasis and lung injury in some experimental preparations (Henson et al., 1979; Hosea et al., 1980; Kunkel et al., 1981; Shasby et al., 1982b; Loyd et al., 1983). Some forms of lung injury can be shown to be granulocyte-dependent (Craddock et al., 1977; Johnson and Malik, 1980; Flick et al., 1981; Shasby et al., 1982a), and there is substantial data implicating the generation of oxygen-free radicals by activated granulocytes as a mechanism by which injury of lung cells occurs (Sacks et al., 1978; Nathan et al., 1979; Johnson et al., 1981; Shasby et al., 1982b; Till et al., 1982). Release of proteolytic enzymes by granulocytes may also be an important determinant of injury (Janoff et al., 1979; McDonald et al., 1979; Carp and Janoff, 1980b; Lee et al., 1981; Cochrane et al., 1983a, 1983b).

What specific functional abnormalities of the lung depend on the presence of granulocytes? Based primarily on studies of responses to gram-negative bacterial endotoxemia in sheep, we will discuss three areas: pulmonary vasoconstriction, abnormalities of lung mechanics, and increased lung vascular permeability.

Pulmonary hypertension is a common response of the lungs to diffuse injury (Helfin and Brigham, 1981; Staub et al., 1982a; Loyd et al., 1983; Meyrick and Brigham, 1983), and patients with severe diffuse lung injury also usually have pulmonary hypertension (Zapol et al., 1977; Zapol and Snider, 1977; Brigham et al., 1979; Esbenshade et al., 1982). After endotoxin infusion in sheep, there is an early, marked pulmonary vasoconstriction which is accompanied by increased concentrations of a metabolite of thromboxane A2 in lung lymph and blood plasma (Frolich et al., 1980; Brigham and Ogletree, 1981; Brigham et al., 1982b; Snapper et al., 1983). The initial vasoconstriction is attenuated by cyclooxygenase inhibitors which prevent generation of thromboxane (Ogletree and Brigham, 1982; Snapper et al., 1983). Could granulocytes be the source of the cyclooxygenase metabolite of arachidonic acid which appears to cause the vasoconstriction?

Figure 4 shows pulmonary vascular resistance in sheep after endotoxin infusion, before and after depletion of the peripheral blood granulocyte count to less than 300 cells/mm³ with hydroxyurea (Helfin and Brigham, 1981). Granulocyte depletion did not prevent the vasoconstrictor response. In a similar model, other workers showed attenuation of endotoxin-induced pulmonary hypertension in sheep after granulocyte depletion with nitrogen mustard, but the early-phase pulmonary hypertension was not abolished (Huttemeier et al., 1982). At least in this model, granulocytes do not seem essential to the vasoconstrictor response to diffuse lung injury.

Marked abnormalities of lung mechanics are typical of both the human syndrome of acute lung injury (Petty and Ashbaugh, 1971) and animal models of the syndrome. For example, early in the response to endotoxemia in sheep, there are marked reductions of lung compliance and marked increases in resistance to airflow across the lungs (Esbenshade et al., 1982; Snapper et al., 1983). There is some evidence that these changes in airway function are major contributors to the abnormalities of gas exchange (Esbenshade et al., 1982). The maximum abnormalities of lung mechanics occur coincident with the peak pulmonary hypertension and the peak thromboxane concentrations in lung lymph and plasma, and, as with the pulmonary hypertension, the changes in lung mechanics after endotoxemia in sheep are attenuated by cyclooxygenase inhibitors (Snapper et al., 1983). However, unlike the vasoconstriction, changes in lung mechanics after endotoxemia in sheep are attenuated by granulocyte depletion with hydroxyurea (Hinson et al., 1983) (Fig. 5). These data implicate granulocytes as mediators of the alterations in airway function and may suggest that the response is produced by granulocyte generation of cyclooxygenase metabolites of arachidonic acid. The cell source of the cyclooxygenase products which mediate vasoconstriction in response to endotoxemia is apparently different. Most studies of the role of granulocytes in acute lung injury have concentrated on microvascular injury (increased vascular permeability). Evidence is accumulating that granulocytes are essential participants in the response to several interventions which result in increased permeability. Figure 6 shows lung lymph protein clearance in sheep in response to the intravenous infusion of gram-negative endotoxin.
before and after depleting the animals of granulocytes with hydroxyurea (Heflin and Brigham, 1981). Lung lymph protein clearance in this preparation indicates an increase in vascular permeability, reaching a plateau several hours after endotoxin infusion. This increase in permeability is substantially reduced in granulocytopenic animals. Similar results have been shown with microemboli in experimental animals (Johnson and Malik, 1980; Flick et al., 1981).

Also, in isolated perfused lungs, edema resulting from agents which activate granulocytes (e.g., phorbol myristate acetate) to produce oxygen-free radicals, depends on the presence of normal granulocytes in the perfusate (Shasby et al., 1982a). Granulocyte interactions with the lungs have also been linked to the microvascular injury resulting from prolonged breathing of high concentrations of oxygen. Animals dying of pulmonary oxygen toxic-
ity have large numbers of granulocytes in their lungs (Crapo et al., 1980), and some investigators have found that granulocyte-depleted animals tolerate high oxygen breathing better than normal ones (Shasby et al., 1982a). Alveolar macrophages exposed to high oxygen pressures in vitro generate granulocyte chemotaxins, providing a possible mechanism for the pulmonary leukostasis (Harada et al., 1980). Lung endothelial cells cultured under hyperoxic conditions are more susceptible to granulocyte-mediated injury than endothelial cells grown under normoxic conditions (Suttorp and Simon, 1982). However, other investigators have not shown an essential role for granulocytes in pulmonary oxygen toxicity (Raj and Bland, 1982), and it is not yet clear whether the immigration of granulocytes into the lungs is the cause of, or a response to the injury.

**Chronic Lung Diseases**

**Asthma**

Slow-reacting substance of anaphylaxis (SRS-A) has long been thought to be an important mediator of bronchoconstriction (Orange et al., 1971). The discovery by Samuelsson and his co-workers that SRS-A is a lipoxxygenation product of arachidonic acid, synthesized by leukocytes (Samuelsson et al., 1980; Samuelsson and Hammarstrom, 1980) has resulted in several investigations of possible relationships between granulocytes and asthma.

In experimental animals, interventions which increase the numbers of granulocytes in the lungs may cause bronchoconstriction (Esbenshade et al., 1982; Snapper et al., 1983) and increased airway reactivity to inhaled bronchoconstrictor stimuli (Lee et al., 1977; Irvin et al., 1982; Hutchison et al., 1983). In some animal models, granulocyte depletion attenuates both the bronchoconstriction and the airway hyperreactivity. One report of studies in unanesthetized sheep showed consistent decreases in baseline airway responses to aerosolized histamine when animals were depleted of granulocytes (Hinson et al., 1982).

In humans with asthma, granulocyte chemotaxins have been detected in systemic blood coincident with aerosol-induced bronchoconstriction (Nagg et al., 1982). Humans with exercise-induced bronchoconstriction also generate circulating chemotaxins coincident with the airway responses (Lee et al., 1983).

The role, if any, of granulocytes in mediating lung dysfunction in asthma is not yet clear, but data presently available suggest the possibility that interactions of granulocytes with the lungs may be at least part of the pathophysiology of this disease. Whether eosinophils, basophils, mast cells, or neutrophils are selectively involved, or whether all of these cell types contribute to the airway hyperreactivity, is not known.

**Pulmonary Emphysema**

With the discovery that a subset of patients with the onset of pulmonary emphysema at an early age had an inherited deficiency of circulating proteins which inhibit proteases (α1 antitrypsin deficiency), the hypothesis emerged that the destruction of lung parenchyma might be due to the local digestion of lung tissue by proteases. Inflammatory cells, especially granulocytes, are sources of proteases which may digest elastin (elastases) (Lee et al., 1981; Cochrane et al., 1983b). Inhaled cigarette smoke recruits granulocytes into the lungs (Hunninghake et al., 1980) and recent reports indicate that even asymptomatic cigarette smokers (presumably at risk for development of emphysema) have elastase activity in bronchoalveolar lavage fluid which originates predominantly from granulocytes (Janoff et al., 1983). Decreases in the antiprotease activity in lungs of cigarette smokers has also been shown which apparently results from oxidation of antiproteases by oxidants generated by activated inflammatory cells, including granulocytes (Gadek et al., 1979; Carp and Janoff, 1980a; Carp et al., 1982).

In experimental animals, purified neutrophil elastase instilled into the lungs can cause emphysema (Janoff et al., 1977; Senior et al., 1977). In addition, a number of experimental insults to the lung which result in prolonged abnormalities in lung structure and function are characterized by influx of large numbers of granulocytes into the interstitial spaces and alveoli (Johnson and Ward, 1982; Loyd et al., 1983; Meyrick and Brigham, 1983; Newman et al., 1983), and repeated lung inflammation over a prolonged period in primates may produce widespread alveolar disruption (Wittels et al., 1974). Some of the responses of the lung can be shown to be granulocyte-dependent (Johnson and Malik, 1980; Flick et al., 1981; Heflin and Brigham, 1981; Shasby et al., 1982a).

In summary, a leading hypothesis explaining the pathogenesis of pulmonary emphysema proposes that local release of proteases or inactivation of antiproteases, or both, in the lung is primarily responsible for destruction of lung parenchyma. Polymorphonuclear neutrophils are a likely source of proteases and of oxidants which inactivate antiproteases. Repeated local inflammation in the lungs with influx of activated neutrophils could be a key event in the development of emphysema.

**Interstitial Pulmonary Fibrosis**

Although the pathogenesis of interstitial pulmonary fibrosis is complex, several lines of evidence suggest a role for interactions of granulocytes with the lungs as important in the pathogenetic process (Snider, 1983). The possible role of granulocytes in diffuse acute lung injury resulting in the adult respiratory distress syndrome is discussed above. In some patients who present with adult respiratory distress syndrome but undergo a prolonged course, increased collagen synthesis occurs in the lungs.
eventuating in a pathological and clinical picture of severe interstitial fibrosis (Zapol et al., 1979). This sequence of events could be perceived as rapidly progressive pulmonary fibrosis, and it is tempting to suggest a similar pathogenetic sequence for the more common, slowly progressive form of the disease. However, experimental studies implicating neutrophils in fibrosis indicate that the relationship is complex.

In experimental lung fibrosis induced by bleomycin, depletion of neutrophils seems to increase the amount of collagen synthesis in the lungs (Thrall et al., 1981). Airway instillation of phorbol myristate acetate, an agent which stimulates neutrophils (and other phagocytes), causes an acute influx of granulocytes into the airspaces, and the reaction may proceed to pulmonary fibrosis. However, depleting animals of neutrophils prior to phorbol instillation does not prevent the fibrotic response (Johnson and Ward, 1982). Beige mice, whose neutrophils can generate superoxide but cannot release proteolytic enzymes (Bennett et al., 1969), show a very high rate of lung collagen accumulation in response to lung injury (Fhan et al., 1983).

In summary, although in human and experimental models of interstitial pulmonary fibrosis, granulocytes migrate into the lungs where they may release both proteolytic enzymes (Lee et al., 1981; Cochrane et al., 1983a, 1983b; Janoff et al., 1983) and generate oxidants (Nathan et al., 1979; Shasby et al., 1982), the precise role of neutrophils in the pathogenesis of fibrosis is not yet clear.

Chronic Pulmonary Hypertension

Both chronically increased pulmonary vascular resistance and structural changes of pulmonary hypertension (medial hypertrophy of arteries and extension of muscle into smaller vessels than normal on the arterial side causing a reduction in lumen diameter) develop in humans with several kinds of chronic lung disease (Voelkel and Reeves, 1979; Meyrick and Reid, 1983). Chronic pulmonary hypertension also develops without apparent cause in some patients, and this syndrome of primary pulmonary hypertension is sometimes familial (Loyd et al., 1984). The functional and structural alterations in the lungs with chronic pulmonary hypertension—both secondary and primary—have been described in humans (Anderson et al., 1973; Semmens and Reid, 1974; Ryland and Reid, 1975; Shelton et al., 1977; Reid, 1979), and several animal models of the disorder have been studied, but the causes of these changes remain obscure (Kay and Heath, 1969; Abraham et al., 1971; Meyerick and Reid, 1978; Meyerick et al., 1980).

Although the major cause of chronic pulmonary hypertension may be hypoxia, recent evidence suggests that chronic pulmonary hypertension may also be linked to chronic inflammation of the lung. Pulmonary hypertension occurs in patients with chronic bronchitis (Semmens and Reid, 1974; Shelton et al., 1977), cystic fibrosis (Ryland and Reid, 1975), the adult respiratory distress syndrome (Tomasheshki et al., 1983), idiopathic urticarial vasculitis (Falk, in press), and patients receiving radiation or chemotherapy, all conditions with a known inflammatory response in the lung. In addition, histological examination of the lungs of many of the patients in the outbreak of pulmonary hypertension after use of the appetite suppressant, Aminorex, showed evidence of an inflammatory response (Wagenvoort and Wagenvoort, 1977).

Experimental conditions also suggest a link between inflammation and chronic pulmonary hypertension. Monocrotaline, when given to rats, results in an inflammatory response in the lungs followed by the development of the structural and functional changes of chronic pulmonary hypertension (Kay and Heath, 1969; Meyrick et al., 1980), and carrageenan (Irish peat moss), used originally as an experimental agent to produce pneumonia (Wagenvoort and Wagenvoort, 1977), when administered repeatedly, leads to a persistent increase in pulmonary artery pressure and the structural changes of pulmonary hypertension (Herget et al., 1981). In addition, air emboli are known to be associated with intravascular accumulation of granulocytes (Staub et al., 1982b), and these, too, when administered repeatedly, have been shown, in rabbits, to lead to an increase in the medial thickness of the pulmonary arteries (Wright, 1962), one of the characteristic changes of chronic pulmonary hypertension.

Physiological vs. Pathological Interactions of Granulocytes with the Lungs

As discussed earlier, it appears that, even under normal conditions, there is a large pool of granulocytes margined in the small vessels in the pulmonary circulation. In addition, there are some clinical situations in which an intervention causes large numbers of granulocytes to sequester in the lungs, usually without severe consequences—for example, in patients undergoing hemodialysis (Cradock et al., 1977) or cardiopulmonary bypass (Chenoweth et al., 1981).

There are also experimental interventions that are analogous to the relatively benign pulmonary leukocyte sequestration that occurs clinically. Intravenous infusion of a bolus of autologous plasma which has been incubated in vitro with zymosan to activate complement, causes dramatic sequestration of granulocytes in the lung circulation. This intervention also causes pulmonary hypertension and, perhaps, modest evidence of increased lung microvascular permeability, but not severe diffuse lung injury and edema (Shaw et al., 1980; Meyrick and Brigham, 1984a).

In contrast, several experimental interventions that were discussed earlier cause granulocyte leukostasis and more severe microvascular injury in the lungs, and such injury appears to depend on the
presence of granulocytes (Johnson and Malik, 1980; Flick et al., 1981; Heflin and Brigham, 1981; Staub et al., 1982a). Infusion of exogenous agents that stimulate granulocytes (for example, phorbol myristate acetate) also causes severe lung injury (Loyd et al., 1983).

The structural consequences of infusion of an agent which produces granulocyte-dependent lung injury (endotoxin) (Meyrick and Brigham, 1983) are contrasted with the consequences of a different agent which produces quantitatively similar granulocyte sequestration in the lungs, but much less evidence of lung injury (zymosan-activated plasma) (Meyrick and Brigham, 1984a) in Figure 7. The difference between relatively benign pulmonary sequestration of granulocytes and granulocyte-mediated severe lung injury is not simply explained by quantitative differences in the number of granulocytes sequestered, but rather seems to be a qualitative difference in the nature of the granulocyte interactions with the lungs, possibly related to the duration of the activating stimulus.

Some investigators have postulated possible factors which may determine whether granulocytes sequestered in the lung cause injury. Low concentrations of oxygen and infusions of vasodilator prostaglandins have been shown to potentiate lung injury resulting from intratracheal instillation of chemotactic stimuli (Henson et al., 1982). It is also possible that lung injury depends on some specific activity of granulocytes (for example, free radical generation or release of proteolytic enzymes) and that granulocytes may be stimulated to adhere to pulmonary vascular endothelium without releasing injurious products (Becker et al., 1981).

There is good evidence that the simple process of granulocyte migration across vascular endothelium toward a chemotactic stimulus is not a sufficient explanation of granulocyte-mediated endothelial injury (Shaw et al., 1980; Meyrick and Brigham, 1984a; Meyrick and Brigham, 1984b). Figure 8 shows a granulocyte in the process of migrating between endothelial cells of a pulmonary artery intimal explant. The chemotactic stimulus was homologous zymosan-activated plasma. Although there is intimate contact between migrating granulocytes and endothelial cells as large numbers of granulocytes move toward the chemotaxin, there is no evidence of endothelial injury by ultrastructural studies and no evidence of increased permeability of the endothelial layer (Meyrick and Brigham, 1984b).
Granulocytes and Humoral Mediators

At least when stimulated, granulocytes are capable of producing several chemicals which can profoundly affect the function of both blood vessels and airways in the lungs without necessarily producing structural injury. Metabolites of arachidonic acid are especially interesting in this regard (Goldstein et al., 1977; Becker et al., 1981). Granulocytes can produce both cyclooxygenase and lipoxygenase metabolites of arachidonic acid, and a number of both classes of metabolites may cause bronchoconstriction, vasoconstriction, and perhaps even increases in microvascular permeability (Brigham and Ogletree, 1981). Thus, it is possible that some of the functional consequences of granulocyte interactions with the lungs are a result of humorally mediated events, rather than a result of lung cell injury. The fact that interventions which produce little evidence of structural injury to the lungs can produce changes in lung function supports this view (Fountain et al., 1980; Brigham et al., 1982a; Meyrick and Brigham, 1984a).

Summary and Conclusions

Under normal conditions, there is a sizeable pool of margined granulocytes in the lung circulation which is in dynamic equilibrium with the circulating granulocyte pool. The number of granulocytes in the lungs' microcirculation may depend on pulmonary blood flow or biochemical interactions between granulocytes and pulmonary vascular endothelium, or both. There is some evidence that normal lung function may be affected by granulocytes.

Several acute and chronic diseases may result, at least in part, from interactions of granulocytes with the lungs. Acute diffuse lung injury (adult respiratory distress syndrome) is characterized by diffuse pulmonary inflammation, and, in animal models, some of the lung dysfunction depends on the presence of granulocytes. Bronchoconstriction and airway hyperreactivity, characteristic of asthma, may be influenced by granulocyte-generated products of arachidonic acid. Granulocyte-derived proteases and oxidants may contribute to the pathogenesis of pulmonary emphysema and may affect connective
tissue synthesis in interstitial pulmonary fibrosis. There is some evidence suggesting a connection between granulocytes and chronic pulmonary hypertension.

The fact that some interventions which cause pulmonary leukostasis do not cause severe, persistent lung injury indicates that as yet unknown factors may determine whether interactions of granulocytes with the lungs are benign or pathological. Such factors could include the generation of humoral substances, and metabolites of arachidonic acid are particularly interesting in this regard.

Research related to interactions of granulocytes with the lungs suggests strongly that such interactions are integral to the pathogenesis of several lung diseases. Understanding those diseases will require further basic studies of granulocyte behavior and the modes of communication between cells intrinsic to the lung and granulocytes.

References


Buchanan M, Vaquero M, Gimbrone M (1981) Influence of the lipoxigenase on the adhesion of human leukocytes to cultured vascular endothelial cells (abstr) Blood 58: (suppl) 70a


ulation due to oxygen toxicity: Involvement of chemotactic factors and polymorphonuclear leukocytes. Am Rev Respir Dis 123: 521-523


Henson P.M., Larsen G., Webster RO, Mitchell BC, Goinis AJ, Henson JE (1982) Pulmonary microvascular alterations and injury induced by complement fragments: Synergistic effect of complement activation, neutrophil sequestration and prosta-


Hoover R., Folger R., Haring W., Ware B., Kornovsky M. (1980) Adhesion of leukocytes to endothelium: Roles of divalent cat-


Hosea S., Brown E., Hammer C., Frank M. (1980) Role of complement activation, neutrophil sequestration and prosta-

McDonald J., Baum B., Rosenberg D., Kelman J., Brin S., Crystal R. (1979) Destruction of a major extracellular adhesive glycopro-

tein (fibronectin) of human fibroblasts by neutral proteases from polymorphonuclear leukocytes granules. Lab Invest 40: 350–357


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Interactions of granulocytes with the lungs.
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