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HUMORAL MEDIATORS IN LUNG DISEASE

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OUTLINE

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I. INTRODUCTION AND BACKGROUND

The importance of humoral factors in the maintenance of health and in the production of disease has long been recognized. In fact, the ancient Greeks - or was it the Egyptians - first proposed that all human pathology could be explained by the Humoral Theory. This theory[1,2], which influenced medical thought for two thousand years, held that the human body was made up of four humors; one hot and moist (blood), another cold and moist (phlegm), a third hot and dry (yellow bile), and the fourth cold and dry (black bile).

Hippocrates explained the workings of these humors: "Concerning the composite parts of man's body, it has blood, phlegm, yellow bile and melancholy bile (black bile); these make up his parts and through them he feels illness or enjoys health. When all of these elements are truly balanced and mingled, he feels the most perfect health. Illness occurs when one of these qualities is in excess or is lessened in amount or is entirely thrown out of the body."[3]

Though we still make occasional use today of the terms phlegmatic, sanguine, melancholic or choleric, this simplistic theory has long since become obsolete. No one believes any more that the four humors of ancient medicine are at the root of all illness. There is ample evidence, however, that certain chemical compounds, carried in blood or tissue fluids, are important participants in the pathogenesis of pulmonary disease. This discussion will review some of this evidence, with special reference to certain diseases, selected because they are relatively common or because they represent unique types of pathology. The therapeutic implications will be highlighted by examples showing the beneficial effects of agents preventing the formation, release or action of these mediators.

II. PULMONARY DISORDERS IN WHICH HUMORAL MEDIATORS MAY CONTRIBUTE TO CAUSATION OR PATHOGENESIS

Some of these disorders are enumerated in Table 1. This long list is probably incomplete; it includes most pulmonary diseases of adults, as well as some pediatric entities. We will return for a discussion of the probable or possible role of mediators in these clinical conditions or in experimental models that simulate them. But now, we turn our attention to the mediator substances, what they are, what they are capable of doing, and where they originate.

TABLE 1

PULMONARY DISORDERS IN WHICH HUMORAL MEDIATORS
MAY CONTRIBUTE TO CAUSATION OR PATHOGENESIS

A) Immunologic Disorders

Diseases exhibiting 1 or more of the major types of allergic response, including:

Bronchial asthma, Goodpasture's syndrome, hypersensitivity pneumonias (extrinsic allergic alveolitis), eosinophilic pneumonia, pulmonary vasculitis, tuberculosis, and other granulomatous diseases.

B) Fibrosing or sclerosing alveolitis (interstitial fibrosis)

C) Emphysema, especially in association with α_1-antitrypsin deficiency.

D) Vascular Diseases

Pulmonary thromboembolism, pulmonary microembolism (platelet aggregation), pulmonary edema, hypoxic pulmonary hypertension.

E) Conditions associated with Respiratory Distress:

Endotoxin (septic) shock, acute pancreatitis, trauma, burns, intravascular coagulation, mechanical hyperventilation.

F) Paraneoplastic syndromes, due to hypersecretion of peptide hormones by tumors.

G) Congenital Disorders

Cystic fibrosis, patent ductus arteriosus.

III. THE MEDIATORS

In the context of this discussion, humoral mediators are defined as chemical compounds that are either locally released or carried in blood or tissue fluids, and that may participate in initiating, perpetuating or aggravating a disease process. Substances meeting this definition and bearing a possible or likely relationship to lung disease are listed in Table 2. The Table also gives the main action(s) of each of these mediators. Reviews of the pharmacologic effects and biological roles of these agents are given in references 4-18.

IV. CELLULAR ORIGIN OF MEDIATORS

These potent mediators normally occur as inactive precursors or are contained within intracellular sites from which they are discharged only following appropriate stimulation. A discussion of mediators would, therefore, be incomplete without reference to the cells from which they originate, and with which they may interact.

Table 3 summarizes the cellular origin of the major humoral mediators.[19,20] Mast cells and basophils probably contribute most of the mediators of immediate hypersensitivity. Polymorphonuclear leucocytes and, to a smaller degree, macrophages, have lysosomes which contain many proteolytic and other hydrolytic enzymes. Lymphocytes, upon stimulation, release lymphokines. Plasma cells, of course, synthesize immunoglobulins. Finally, platelets are a storehouse of biogenic amines, especially serotonin, but are also rich in prostaglandins, and even more so, in endoperoxides and thromboxanes. The latter group of PG-related compounds are also avidly formed in lung tissue, and in a number of other cells and organs[21-26].

TABLE 2

NATURE AND ACTIONS OF HUMORAL MEDIATORS

MEDIATOR	ACTION
1) Biogenic amines:	
a) Histamine	bronchoconstriction, alveolar-duct constriction, increased capillary permeability; immediate hypersensitivity
b) Serotonin (5-HT)	
2) Polypeptides:	
a) Bradykinin	inflammation, increased capillary permeability
b) Angiotensin	vasoconstriction, raised B.P., aldosterone release
c) Vasoactive lung peptides	bronchoconstriction, systemic vasodilation
d) Hormones, eg, ACTH, ADH, PTH	specific endocrine manifestations
3) Proteins	
a) Proteolytic enzymes, eg, elastase, collagenase, other lysosomal enzymes;	inflammation, hemorrhage, tissue destruction; emphysema
kallikrein	release of bradykinin
b) Complement	immunologic injury (types II & III)
c) Lymphokines	"Cell-mediated" immunity & hypersensitivity
d) Immunoglobulins	Humoral immunity, secretory antibodies; immediate hypersensitivity (IgE)
4) Lipids:	
a) Prostaglandins (PG's), PG Endoperoxides	constriction of bronchi, alveolar ducts; pulmonary vasoconstriction; systemic vasodilation (PGE)
b) Thromboxanes	platelet aggregation, other actions as above (> endoperoxides > $PGF_{2\alpha}$)

TABLE 3

CONTRIBUTION OF CELLS TO MEDIATOR RELEASE

Cell	Associated Mediators
1. Mast cell, basophil	Histamine, other mediators of anaphylaxis
2. Polymorphonuclear leukocyte	Lysosomal enzymes
3. Macrophage	Lysosomal enzymes
4. Lymphocyte (stimulated)	Lymphokines
5. Plasma cell	Immunoglobulins
6. Platelet	Amines, PG's, Endoperoxides, Thromboxanes

V. MECHANISMS OF MEDIATOR RELEASE

Intracellular mediators may be released by either of two distinct mechanisms:[19,20]

1. Cytotoxic Release, where the cell membrane is disrupted and cytoplasmic enzymes and other contents are liberated. Examples of this mechanism are, a) the complement - dependent reaction of antibody directed against the cell; b) the involvement of platelets as "innocent bystanders" in the presence of immune complexes and complement; and c) the lysis of macrophages by the silica they phagocytize.
2. Non-Cytotoxic Release:[5,19] The granules to be discharged are thought to migrate toward the plasma membrane; the granule membrane fuses with the plasma membrane and the granules are extruded by a process of exocytosis.

   Stimuli for this release appear to act at the cell surface, and include: a) immunoglobulins, interacting with specific receptors by the Fc portion of the molecule; b) small proteins or peptides, eg, complement - derived anaphylatoxins; c) certain proteolytic enzymes, eg, thrombin acting on platelets; and d) cell - cell (eg, basophil - platelet) interactions.

   This reaction bears many similarities to the secretory process by which hormones, enzymes and neurotransmitters are secreted. Both require energy (ATP), Ca^{++} in the external medium, and the participation of microtubules and microfilaments. Both processes are also influenced by the cyclic nucleotides, though in opposite fashion: whereas increased cyclic AMP concentration stimulates or enhances glandular and endocrine secretion, it inhibits the release of mediators. The role of cyclic nucleotides and its therapeutic implications will be considered again later.

VI. SOME DISEASES IN WHICH HUMORAL MEDIATORS MAY PLAY A ROLE IN CAUSATION OR PATHOGENESIS

1. Bronchial Asthma:

In allergic bronchial asthma, the basic disease process is an interaction of inhaled, extrinsic antigens with tissue mast cells and basophil leucocytes, in the presence of specific antibodies of the IgE class. This union sets off a cascade of metabolic reactions inside the mast cells, culminating in the release of biologically active mediators that bring about the episodic bronchoconstriction, increased mucus secretion and eosinophilic infiltration[27-29].

The identities of these mediators, and the factors governing their formation and release have been the subject of intensive investigation. While all the answers are certainly not in, this research has nevertheless yielded much valuable information, some of it directly applicable to the treatment and prevention of this disease.

Nature of mediators

The best-known and, in many ways, the prototype of these mediators, is histamine[4]. It is concentrated within the granules of the mast cells and basophils, may be released from these cells or from lung tissue with appropriate immunologic challenge, and can induce some of the changes characteristic of an asthmatic attack -- bronchoconstriction and increased capillary permeability. It seems unlikely, however, that

histamine is the most important mediator, for it is well known that antihistaminics (antagonists of H_1-receptors) are practically useless in the treatment of asthma.

A variety of other chemical agents are now known to be released in the immediate hypersensitivity state, some of which have been fully identified but others only partially purified and characterized. The group includes, in addition to histamine and serotonin, bradykinin, the "eosinophil-chemotactic factor" [29], prostaglandins of the E and F series, and the much discussed, but still unidentified, "slow-reacting substance of anaphylaxis" [30].

Very recently, three new groups of compounds have been discovered as potential mediators of bronchoconstriction and the associated changes in the asthmatic reaction. These are: the endoperoxides[21-25,31], intermediate compounds formed during the biosynthesis of the prostaglandins, and approximately 10 times more potent than the PG's as bronchoconstrictors; the thromboxanes[26,32], which are about 100 times as potent as the PG's; and a newly isolated lung peptide that contracts most smooth-muscle structures, known as the spasmogenic lung peptide[33]. No pharmacologic antagonists are yet available to counter the effects of these new and powerful substances, and so their relative importance as mediators remains to be determined.

2. Goodpasture's Syndrome:[34-38]

This disease, characterized by pulmonary hemorrhage, hematuria, and usually progressive pulmonary and renal failure, is an example of "cytotoxic" or Type II allergic disease. Although some forms of this type of response are strictly cell-mediated, involving specifically sensitized "killer" lymphocytes, in others,including the Goodpasture syndrome, the tissue injury follows the interaction of a circulating antibody with an antigenic component of a cell or tissue, in conjunction with complement, and in the presence of polymorphonuclear leucocytes. In Goodpasture's syndrome, an antibody is produced by the patient against both glomerular and alveolar basement membranes. This antibody is present in the serum and deposited uniformly, together with complement, along the basement membranes of both organs. The tissue-specific autoantibody may also be recovered from the lungs and kidneys of patients with this disease.

Lesions mimicking the human disease may be produced in experimental animals either by active immunization with heterologous basement membrane from lung or kidney, or by injection of serum containing antilung globulins.

3. Extrinsic Allergic Alveolitis:

This term, coined by Pepys, refers to cases of Type III allergic (immune-complex) diseases of the lung that result from inhalation of antigens[39]. The antigens are often thermophilic actinomycetes present

in moldy substances, but may be animal or bird products contained in dusts[40-42]. The list of these diseases, also called hypersensitivity-pneumonitis, is long and is continually getting longer (Table 4).

Among the better-known entities are: Farmer's lung (from moldy hay), byssinosis (from cotton), bagassosis (from moldy sugar cane), and hypersensitivity pneumonitis due to contamination of the air-conditioning system with thermophilic actinomycetes, of which there was a small outbreak at the Dallas Federal Building recently. Some of the less ordinary or downright exotic diseases now included in this group are: tea-grower's lung, coffee-worker's lung, paprika slicer's lung, turkey handler's disease, Furrier's lung, and finally, coptic disease, which afflicts those that handle too many mummy wrappings.

Clinically, there is a history of exposure to appropriate antigens, correlating with the symptoms. Most patients have serum precipitins to the specific antigens and, in many, the acute phase of the illness can be reproduced by inhalation of aerosols containing the offending antigen.

The principal mechanism in these diseases is believed to be the formation and deposition of immune complexes along the alveolar-capillary basement membrane. Injury to the basement membrane may be associated with a necrotizing vasculitis (Arthus reaction). This injury is dependent on the activation of complement and the attraction of neutrophils, which release their lysosomal enzymes[43-48]. There may also be release of histamine leading to increased vascular permeability[44], and the

TABLE 4

CAUSES OF HYPERSENSITIVITY PNEUMONITIS*

Disease	Source of antigen	Probable antigens
Vegetable products		
Farmer's lung	moldy hay	thermophilic actinomycetes *Micropolyspora faeni* *Thermoactinomyces vulgaris*
Bagassosis	moldy pressed sugarcane	thermophilic actinomycetes *Thermoactinomyces sacchari*
Mushroom worker's disease	moldy compost	thermophilic actinomycetes
Suberosis	moldy cork	unknown
Malt worker's lung	contaminated barley	fungi *Aspergillus clavatus*
Maple bark disease	contaminated maple logs	fungi *Cryptostroma corticale*
Sequoiosis	contaminated wood dust	fungi *Graphium* sp. *Pullularia* sp. other fungi
Wood pulp worker's disease	contaminated wood pulp	fungi *Alternaria* sp.
Humidifier lung	contaminated home humidifier and air conditioning ducts	thermophilic actinomycetes *Thermoactinomyces vulgaris* *Thermoactinomyces candidus*
Paprika slicer's lung	moldy paprika pods	fungi *Mucor stolonifer*
Grain measurer's lung	cereal grains	unknown
Thatched room disease	dried grass and leaves	unknown
Tobacco grower's disease	tobacco plants	unknown
Tea grower's disease	tea plants	unknown
Coffee worker's lung	green coffee bean	unknown
Hypersensitivity pneumonitis	sawdust	unknown
Coptic disease	cloth wrappings of mummies	unknown

continued -

CAUSES OF HYPERSENSITIVITY PNEUMONITIS - continued

Disease	Source of antigen	Probable antigens
Animal products		
Pigeon breeder's disease	pigeon droppings	pigeon serum protein (albumin, gamma globulin, and others)
Duck fever	bird feathers	chicken proteins
Turkey handler's disease	turkey products	turkey proteins
Furrier's lung	animal hair	animal proteins
Insect products		
Miller's lung	wheat weavils	*Sitophilus granarius*
Bacterial or viral products		
Hypersensitivity pneumonitis	*B subtilis* enzymes	*Bacillus subtilis*

* Based on references # 38-40

reaction may be accompanied by eosinophilia[49]. As in immune-complex disease of the kidney, eg, systemic lupus erythematosus, the deposits of immune complexes along the basement membrane (alveolar or glomerular) are characteristically granular or nodular (lumpy), as opposed to the linear thickening of the basement membrane seen in cytotoxic (Type II) reactions.

4. "Pulmonary Infiltrates, Eosinophilia and Asthma" (Eosinophilic Pneumonia):

This syndrome, attributable in most instances to sensitivity to Aspergillus fumigatus (allergic bronchopulmonary aspergillosis), is a recurrent febrile illness, characterized by changing pulmonary infiltrates, eosinophilia, sometimes associated with asthma[39,50,51]. Patients with this clinical entity show positive dual skin reactions to the saprophytic fungus: an immediate wheal and flare reaction, followed by an Arthus-type reaction. Challenge with the inhaled antigen leads to an immediate, then a somewhat delayed (4-6 hours later) fall in the vital capacity. The precise immunologic mechanisms mediating the alveolitis of aspergillosis are not fully understood, and there is strong evidence for the participation of cell-mediated (delayed) hypersensitivity[38].

Bronchial asthma and eosinophilia, with or without pulmonary infiltrates, may also occur during the acute, invasive stages of schistosomiasis, ascariasis, ankylostomiasis, and strongyloidosis[38,51]. In these conditions, there is an immediate (Type I) hypersensitivity, and in schistosomiasis, also immune-complex pulmonary vasculitis (that often leads to pulmonary hypertension and cor pulmonale), as well as delayed hypersensitivity.

5. Diseases Related to Cell-Mediated (delayed) Hypersensitivity:

Cellular immunity is probably an important mechanism in the pulmonary defenses against, and disease due to, intracellular organisms, eg, Mycobacterium tuberculosis, Mycobacterium intracellulaire (Battey disease); Histoplasma capsulatum, Coccidioides immitis; Cryptococcus neoformans; certain viruses, eg, varicella, influenza, mumps; and Listeria monocytogenes[52-55].

In these reactions, commonly described as cell-mediated (or delayed hypersensitivity, the dominant role is played by the lymphocyte, acting against other target cells. Though the lymphocyte may exert a specific cytolytic activity (the basis of allograft rejections and tumor immunity), its action against infectious agents is carried out through the mediation of another mechanism. Upon activation or "triggering" by specific antigen, the "committed" lymphocyte liberates a number of humoral mediators, known as "lymphokines" [12,56-58]. These soluble factors, thought to be proteins that are smaller than immunoglobulins, have multiple biological effects, including:

a. Lymphocyte-transforming (mitogenic) factor: recruits other lymphocytes and causes them to undergo blast transformation.

b. Lymphotoxin: a non-specific toxin to a number of target cells. It can cause the release of lysosomal enzymes, leading to tissue damage, necrosis or caseation.

c. Macrophage - activation factor: enhances the capacity of macrophages for phagocytosis and bacterial killing. The activated macrophages can function effectively in a non-specific manner, ie, against organisms other than those provoking the specific release of lymphokines.

d. Migration - Inhibitory factor: related to MAF, it inhibits migration of macrophages, and is perhaps responsible for their accumulation at the site of the lesion, that is typical of the delayed hypersensitivity response. Assay of this factor is now used as a test for assaying cell-mediated hypersensitivity.

e. Transfer factor: [59-60] mediates the transfer of specific delayed hypersensitivity in man. Under the influence of this factor, nonsensitive lymphocytes become antigen - responsive, and when they replicate, their daughter cells are also sensitive. The chemical identity of transfer factor remains unknown. The possible use of this potent agent in the treatment of granulomatous disease of the lung is reviewed later.

f. Chemotactic factors: attract neutrophils, basophils, eosinophils, and lymphocytes.

g. Interferon: inhibits viral replication in infected cells.

These lymphokines not only mediate but also amplify the biological responses of cellular immunity. Thus, it is estimated that a single sensitized lymphocyte can affect several thousand macrophages.

6. Fibrosing Alveolitis:

A wide spectrum of conditions may lead to a process of fibrosing (sclerosing) alveolitis, also known as interstitial pneumonia or interstitial fibrosis. We know that there are dozens of these conditions. We also know a good deal about the pathology of these lesions, especially when they have progressed to the end-stage, scarred or "honeycomb lung". In the vast majority of cases, however, the etiology and the pathogenesis of

the fibrosing alveolitis remain unknown.

It now appears that there may be a link between at least some of the cases labeled as interstitial fibrosis and certain humoral mediators, especially those relating to immunologic reactions. The evidence for such a link is both clinical and experimental. The clinical evidence[38,61,62] includes:

a) Significant proportions of patients with "idiopathic pulmonary fibrosis" have in their serum increased titers of rheumatoid factor, whether or not they have arthritis. Patients with overt rheumatoid arthritis, of course, may have pulmonary complications, including pleurisy, pulmonary nodules and interstitial fibrosis[63,64]. Since rheumatoid factor is a 19S-macroglobulin (antibody) that forms immune complexes in the plasma with gamma-globulin, its association with diffuse interstitial fibrosis has led to the speculation that this clinical condition may, at least in some instances, be a manifestation of the rheumatoid state. According to this notion, the precipitation of immune complexes in the pulmonary capillary bed might provide a mechanism for tissue injury and subsequent fibrosis. Against this speculation are these observations: a) Immune complexes could not be found in the lung on examination with fluorescent microscopy[62]; b) the coexistence of interstitial fibrosis in patients with rheumatoid arthritis is quite rare; and c) rheumatoid-like serological activity is present in a number of other, unrelated human diseases.

b) Although no anti-lung antibodies have been demonstrated in patients with sclerosing alveolitis, non-organ-specific antibodies, and anti-nuclear antibodies have been found in a higher percentage of these patients,

compared with controls[65]. An association has been noted between sclerosing alveolitis and chronic active hepatitis, where multiple non-organ-specific antibodies may be present[66].

c) The majority (88%) of coal-miners with the radiographic appearance of the rheumatoid pneumoconiosis syndrome (Caplan's syndrome), show a high incidence of positive rheumatoid-factor tests[67,68]. Even in the absence of signs or symptoms of rheumatoid arthritis, pulmonary biopsy may reveal rheumatoid nodules, much like the subcutaneous nodules, and rheumatoid endarteritis.

Experimental evidence suggesting a possible etiologic role for immunologic mediators comes from a recently described model of Hamman-Rich fibrosis[69]. In this model, T-lymphocytes in the lungs of rabbits were stimulated by administration of a T-cell mitogen, concanavalin A (con A), in aerosol form. This procedure, in essence, induced a form of cell-mediated or "delayed" hypersensitivity injury. If the con A was coupled with a foreign protein (bovine serum albumin), and given to rabbits that had been previously sensitized to this protein, the animals developed pulmonary lesions closely resembling Wegener's granulomatosis[69].

7. Emphysema:

One of the commoner and more disabling of lung diseases, emphysema remains a medical challenge. Though much is known about its pathologic physiology -- altered gas exchange, lung mechanics, hemodynamics -- little is understood about its causation. Most of us consider the cigarette to be a major factor in the current pandemic, but the disease was known before the discovery of tobacco[70].

The discovery of the association between emphysema and antitrypsin deficiency[71,72] has produced real hope that an understanding of the pathogenesis of the disease may be near. According to the protease-pathogenesis hypothesis, emphysema may result from an imbalance between proteolytic enzymes with a potential for attacking alveolar tissue, and anti-proteases that are available for counteracting the enzymes. In support of this theory:

a) Homozygous hereditary deficiency of α_1-antitrypsin (broad-spectrum protease inhibitor) predisposes to early-onset, rapidly-pregressive emphysema.

b) Airway administration of proteolytic enzymes in animals results in emphysema-like lesions in the lung[73,74].

c) The ability of a given proteolytic enzyme to induce experimental emphysema is proportional to the enzyme's elastolytic activity[75]; elastin is selectively lost in emphysematous lungs[76].

d) The most likely sources of endogenous proteases are the polymorphonuclear leukocytes and alveolar macrophages; homogenates of these cells, given by aerosol, can induce the disease in animals[77], and their proteolytic activity can be inhibited by serum α_1-antitrypsin[78].

This attractive hypothesis, unfortunately, does not really explain more than a small fraction of the emphysema population. Homozygous deficiency of α_1-antitrypsin occurs in only 0.06% of the general population. It is possible, however, that a relative deficiency of protease inhibitors (heterozygous deficiency) may predispose to the development of the disease, especially if protease activity is simultaneously increased.

The possible humoral influence in the causation of emphysema is not limited to proteolytic enzymes. Recent evidence suggests that

individuals with serum α_1-antitrypsin deficiency may also have a deficiency of the naturally occurring "chemotactic factor inactivator"[79]. The latter deficiency could enhance the migration of leukocytes into the lung interstitium.

8. Pulmonary Thromboembolism:

It has been suspected for some time that pulmonary embolism may be associated with a release of humoral mediators from the lung, and that this release contributes to altered hemodynamic and respiratory function. This impression, based largely on indirect evidence, includes:

a) Mechanical vascular obstruction, even with superimposed vagal reflexes, often seems inadequate to explain the full manifestations of pulmonary embolism[80].

b) Certain humoral agents, eg, histamine and serotonin, can simulate some of the vascular and airway changes of this condition[81].

c) It has been possible to transmit some of the cardio-respiratory effects of embolism in one animal to another, through cross-circulation[82].

Recent work, largely in experimental animals, has provided more direct evidence for the release of vasoactive hormones from embolized lung[83,84] - either from lung tissue itself or from platelets contained within the pulmonary vessels. These hormonal substances include: Serotonin, histamine, prostaglandins, and probably also the related endoperoxides and thromboxanes.

9. Pulmonary Microembolism: Intravascular Platelet Aggregation.

An important condition, related to pulmonary embolism, is now recognized, where platelets aggregate and become trapped in the pulmonary

vascular bed, causing pulmonary microembolism.

Platelet reactions include: first, adhesion (adherence) to particles or surfaces, followed by the release reaction, in which their contents are liberated; leading to aggregation (platelets binding to platelets), and usually further release of mediators[20]. It is this chain of reactions that is at the basis of pulmonary microembolism, which is thought to be an important factor in the pathogenesis of the respiratory distress syndrome.

A variety of stimuli may provoke the release reaction and aggregation of platelets. These stimuli include: thrombin, collagen, thromboxanes, PG endoperoxides, ADP, platelet-activating factors (PAF) from basophils or mast cells, antibody, and complement[20,22,26].

Platelet aggregation (and pulmonary microembolism) leads to intense constriction of all smooth-muscle structures in the lung: tracheobronchial tree, alveolar ducts, and pulmonary vessels[85-89]. These effects are attributable in large measure to the release of the many potent vasoactive compounds normally confined within the platelets (please see above).

10. Pulmonary Edema:

There is a two-way relationship between pulmonary edema and humoral mediators. On the one hand, certain mediators, eg, histamine, bradykinin, and anaphylatoxins, can induce pulmonary edema, by increasing the permeability of the pulmonary capillaries. This entity is relatively common among patients with the respiratory distress syndromes; it should be suspected whenever the clinical or radiological picture of pulmonary edema

is associated with a normal pulmonary capillary (wedge) pressure. On the other hand, once pulmonary edema, from any cause, sets in, the lung may release a number of vasoactive substances that can bring about further complications[90]. Such substances have not been fully identified, but they have the capacity to constrict airways and pulmonary vessels, and probably include prostaglandin-like compounds and the vasoactive lung peptides[33].

The presence of edema fluid in alveolar spaces is also known to inactivate pulmonary surfactant, leading to alveolar instability and atelectasis[91].

11. Hypoxic Pulmonary Hypertension:

It is well-known that alveolar hypoxia produces pulmonary vasoconstriction and hypertension, but the mechanism of this response in incompletely understood. Several lines of evidence suggest the mediation of a metabolic event, probably including the release of vasoactive substances. Efforts to identify these mediators have not been totally successful, but prostaglandin-like or prostaglandin-related compounds, as well as the spasmogenic lung peptide, may be involved[92].

12. Conditions Associated with Respiratory Distress:

A syndrome of respiratory distress, progressive hypoxia, falling lung compliance, and spreading infiltrations on chest x-ray, may afflict individuals with previously normal lungs, as a complication of numerous acute medical and surgical conditions. The lungs in this adult respiratory distress syndrome (ARDS)[93,94] show large-scale atelectasis, edema, and hemorrhage, much like the lungs of the neonatal respiratory distress syndrome ("hyaline membrane disease").

The conditions predisposing to the adult syndrome are multiple and apparently unrelated. One common thread between them is the apparent participation of humoral mediators in the pathogenesis of the pulmonary complications. Some of the therapeutic measures often used also tend to provoke the release of additional vasoactive substances, thus compounding the problem. Two conditions relevant to this syndrome, pulmonary microembolism and pulmonary edema, have been discussed earlier. A few others follow:

A) Endotoxin (Septic) Shock:

Shock from any cause, but especially septic shock, is frequently present before the onset of the respiratory distress.

Some understanding of the pathogenicity of endotoxin to the lung and other organs has been gained from investigations in animals. Thus, intravenous administration of endotoxin induces systemic hypotension in all species, often accompanied by pulmonary hypertension. One mechanism of these responses is the release of prostaglandin-like compounds, since both reactions can be reduced or abolished by pretreating the animals with prostaglandin synthetase-inhibitors, such as aspirin or indomethacin[95,96]. This conclusion has recently been confirmed by bioassay[97].

If the lungs are examined after one i.v. injection of endotoxin, fibrin thrombi are found in small pulmonary vessels (also in liver and spleen sinusoids). If a second sub-lethal dose of endotoxin is given intravenously (24 hours later), new fibrin thrombi are found in the lungs, but now also in the glomeruli, leading to bilateral renal cortical necrosis. This pathologic picture is known as the generalized Schwartzman reaction[98,99].

It is now believed that this process of intravascular coagulation is mediated by the granular leukocytes, since the reaction can be prevented by depletion of these cells with nitrogen mustard[100], and leucocyte granules can substitute for the first (preparing) injection of endotoxin[101]. The leukocytes apparently acquire enough procoagulant (thromboplastic) activity in the presence of endotoxin, to trigger intravascular clotting[102], via the extrinsic pathway.

B) Disseminated Intravascular Coagulation:

This clinical syndrome is the result of pathologic activation of blood coagulation and fibrinolysis. When fully expressed, it is manifested by bleeding (due to depletion of coagulation factors and platelets), organ ischemia (due to deposition of fibrin in small vessels), and hemolytic anemia (due to fibrin-induced red cell destruction)[103,104]. Intravascular coagulation may either precede or follow the development of the respiratory distress syndrome. In cases where the coagulopathy occurs first, the lung pathology may be partly related to the small-vessel occlusion and leukocytic enzymes (see above). Conversely, lung injury may itself "trigger" intravascular coagulation as the lung tissue, like brain tissue, granulocytes, and amniotic fluid, is rich in thromboplastin.

C) Acute Pancreatitis[105-108]:

Recent reports have described the occurrence of respiratory complications, especially the respiratory distress syndrome in the course of severe acute pancreatitis. At least some of these patients present a picture of pulmonary edema with normal pulmonary wedge pressures, excluding the possibility of circulatory overload. Speculations on the mechanism of

pulmonary capillary injury in such patients include: release of proteolytic enzymes from the pancreas;or of phospholipase A, which can inactivate alveolar surfactant (and can generate arachidonic acid, a precursor of prostaglandins); elevated levels of triglycerides; and systemic hypotension.

D) Trauma, Burns[109-112]:

Extensive skin burns and other forms of trauma, unrelated to direct thoracic injury, may be followed by diffuse pulmonary lesions and respiratory distress. In these cases, too, humoral mediators may be released from injured tissue and induce pulmonary injury, but these putative mediators remain to be identified.

E) Mechanical Hyperventilation:

One of the therapeutic measures frequently employed in patients with respiratory distress, mechanical ventilation at large tidal volumes , has been shown to provoke the release of vasodilator prostaglandins from the lung[16,113]. This release contributes to the systemic hypotension that often complicates mechanical hyperventilation, and is particularly pronounced in the presence of uncompensated respiratory alkalosis[92].

13. Paraneoplastic Syndromes:

Hypersecretion of hormones by pulmonary tumors may result in a variety of endocrine syndromes. These hormones are usually polypeptides or biogenic amines, and the tumors are most often of the oat-cell variety (Table 5). Since recent reviews of this subject [16.114], another paraneoplastic syndrome -- that of watery diarrhea [115] ("pancreatic cholera") --

TABLE 5

HORMONAL SECRETION BY PULMONARY TUMORS: PARANEOPLASTIC SYNDROMES

	Hormone	Syndrome	Lesion
1.	ACTH	Hypokalemic alkalosis, edema, Cushing's syndrome	Oat-cell carcinoma, adenoma
2.	ADH (arginine vasopressin)	Hyponatremia (SIADH)	Oat-cell carcinoma, adenoma; also, tuberculosis, pneumonia, aspergillosis
3.	PTH or related peptide	Hypercalcemia	Squamous-cell, adeno- and large-cell undifferentiated carcinoma
4.	Gonadotropins	Gynecomastia (adults), precocious puberty (children)	Large-cell anaplastic carcinoma
5.	Calcitonin	No clinical findings	Adenocarcinoma, squamous- and oat-cell carcinoma
6.	VIP or related peptide	Watery diarrhea or no symptoms	Squamous-, oat- or large-cell carcinoma
7.	? Growth hormone	Hypertrophic osteoarthropathy	Squamous-cell carcinoma
8.	Serotonin, kinins (and PG's)	"Carcinoid"	Bronchial adenoma, oat-cell carcinoma
9.	Insulin-like peptide	Hypoglycemia	Mesenchymal cell tumors
10.	Glucagon or related peptide	Diabetes	Fibrosarcoma
11.	Prolactin	Galactorrhea (or no symptoms)	Anaplastic cell carcinoma
12.	Combination of above	Multiple syndromes	Anaplastic cell carcinoma

Abbreviations: ACTH = adrenocorticotrophic hormone; SIADH = syndrome of inappropriate secretion of antidiuretic hormone; PTH = parathyroid hormone; PG's = prostaglandins; VIP = vasoactive intestinal polypeptide.

has been observed in some patients with bronchogenic carcinoma. This syndrome appears to be related to the vasoactive intestinal polypeptide (VIP)[115], normally present in gastrointestinal and brain tissue, or to a similar peptide occurring in normal lung.

14. Cystic Fibrosis[116,117]:

Cystic fibrosis is a common, serious and disabling disease of children. It affects all exocrine glands, but usually kills through respiratory insufficiency. The basic defect of this inherited disease remains a mystery.

One of the promising lines of investigation has been the finding that serum and other fluids of homozygotes and heterozygotes with this disorder contain a number of abnormal humoral factors. These factors: a) inhibit ciliary activity in trachea; b) inhibit sodium reabsorption in saliva and sweat; and c) enhance degranulation of leukocytes and release of their lysosomal enzymes.

None of these factors has yet been isolated in pure form, and it is not known whether they represent primary or secondary metabolic changes. Only one, the sodium reabsorption-inhibitory factor can explain one of the consistent abnormalities in the disease. Nevertheless, these humoral factors are being actively investigated for a possible break in understanding the pathogenesis of this disease.

VII. IMPLICATIONS FOR THERAPY:

Advances in the prevention or treatment of diseases where humoral mediators are involved, may come from: a) use of specific antagonists or blockers of the mediators, and b) inhibitors of their release. Examples follow:

1. Even though the identities of mediators of immediate hypersensitivity are still unknown, agents that inhibit the degranulation of mast cells (eg, disodium cromoglycate "Cromolyn", diethylcarbamazine "Hetrazan") have already proved useful in preventing or reducing the severity and frequency of asthmatic attacks[118].

2. The finding that higher levels of cyclic AMP (especially in relation to cyclic GMP) also inhibit the anaphylactic release of mediators, has provided a sound basis for improved treatment of asthma. This pharmacologic modulation of mediator release can be accomplished by drugs that stimulate cAMP production, inhibit its degradation, or inhibit the formation of cGMP[29].

3. In situations where the release of lysosomal enzymes may contribute to pathogenesis, the use of corticosteroids should be considered, on the grounds that they stabilize plasma and lysosomal membranes[119].

4. An additional important action of corticosteroids has recently been discovered; hydrocortisone inhibits the release of arachidonic acid from cellular lipids[120]. This action would inhibit the formation of prostaglandins and related lipids (endoperoxides and thromboxanes), which are important mediators of inflammatory reactions.

5. If the formation of prostaglandins and other acidic lipids cannot be prevented before the arachidonic-acid step (as above), it may be blocked just beyond that level, with aspirin, indomethacin, and related drugs[121,122]. There are several examples of the beneficial effect of these drugs in experimental preparations (eg, endotoxin shock, platelet aggregation, the hypotension of respiratory alkalosis), but their usefulness in the clinical settings has not been adequately tested.

6. Recently, two groups of investigators have reported the successful closure of patent ductus arteriosus in premature infants, with a single dose of indomethacin[123,124]. Earlier work in animals had determined that PGE compounds dilate the ductus, and that inhibition of prostaglandin synthesis could close it. This simple method of treatment appears to have negligible side effects. It is a substantial step forward in the management of the respiratory distress syndrome of the newborn, in whom the ductal shunt is thought to aggravate the cardiopulmonary dysfunction.

7. The use of transfer factor offers interesting possibilities in the treatment of pulmonary diseases where the host is incapable of mounting an adequate cell-mediated immunity (delayed hypersensitivity). So far, there have been few trials, but some highly successful, especially in disseminated disease (tuberculosis, coccidioidomycosis), that is otherwise unresponsive to therapy[60].

Research in humoral mediators of lung disease is in its early stages. Many of the important mediators have not even been identified. We may, therefore, expect to hear a great deal more about this promising field, and we hope that the best results are yet to come.

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