

Update: Future Directions for Research on Diseases of the Lung

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INTRODUCTION

The Strategic Plan of the American Thoracic Society (ATS) lists, as one of the goals under the heading of "Research," "to identify research opportunities and priorities in pulmonary and critical care medicine." The current report and its predecessor, "Future Directions for Research on Diseases of the Lung" (*Am. J. Respir. Crit. Care Med.* 1995;152:1713-1735), represent the accomplishment of the goal. The current report was developed by the Scientific Advisory Council after solicitation of input from each of the Society's 12 assemblies. The Advisory Council then synthesized the input into a coherent single document. It is intended that there will be dissemination of the document to the Society at large as well as relevant groups within the Society.

This document is a more concise iteration of the earlier paper that was prepared in 1993. It is intended that there will be a regular updating of the "Research Opportunities" to ensure its being timely and reflective of the current thinking of the Society. The intent of the paper is not to present an in-depth discussion of each of the identified areas; rather, it should be viewed as an annotated listing with a concise description of the rationale, questions, and approaches for each of the areas.

The document is intended to be used to guide the Society's research agenda. It will be used by the ALA/ATS Government Relations Committee and staff and by the ATS Research Advocacy Committee to guide advocacy efforts. It will also be used by the ALA/ATS Research Coordinating Committee to identify the current most important research areas and by the Corporate Relations Committee to suggest areas for corporate research support. It is also anticipated that research training program directors will utilize the document to identify areas in which training should be emphasized.

One of the challenges encountered in writing this paper was the reconciliation of a disease-based approach with a discipline- or mechanism-based organization. To effect the reconciliation, both approaches were used. The concept was to use a matrix organization in which different disciplines were applied across a number of specific diseases. With some descriptions or areas, however, there were no specific diseases, leaving these disciplines as freestanding.

This document is intended to be dynamic and to serve as a point of reference for ongoing revisions. Additionally, groups within the Society may wish to amplify on specific areas contained in the report. Finally, it should be emphasized that the value of investigator-initiated research is deemed to be of enormous importance in making progress in research on diseases of the lung.

I. MECHANISMS OF DISEASE

A. Genetic Determinants of Disease

1. **Genetic mapping.** During the 1980s, genetic mapping began to be used to identify genes that cause inherited diseases. This work has led to dramatic advances in our understanding of many diseases, including cystic fibrosis, that have simple mendelian inheritance. Most diseases do not have simple inheritance patterns, but instead are caused by a complex interplay between genetic and environmental factors. Genetic mapping can be used to attempt to identify individual genes that play major or minor roles in the development of these genetically complex diseases. Since this approach makes no assumptions about the biological function of a gene, it can lead to important and unexpected insights into disease pathogenesis.

This may suggest novel targets for drug or gene therapy. In addition, results from gene mapping studies can lead to development of methods for screening populations to identify individuals at risk for development of disease. While much work remains to be done to explore the medical, ethical, and legal issues raised by genetic screening, identification of at-risk individuals could lead to more effective strategies for disease prevention.

Genetic mapping techniques are likely to be valuable for the study of a wide range of pulmonary diseases. Specific examples include asthma, familial primary pulmonary hypertension, sleep apnea and other disorders of respiratory control, and susceptibility to lung cancer or to specific pulmonary infections. Genetic mapping will also be valuable for studying animal models of human disease. For example, mapping can be used to study inbred rodent strains that vary in their frequency of development of pulmonary neoplasms, airway responsiveness, or susceptibility to pulmonary infection or pulmonary fibrosis. Human studies can then be performed to determine whether genes identified in other animals are relevant to human disease.

2. **Genetic determinants of allergic, immunologic, and inflammatory respiratory diseases.** Genetic variability in host response to inhaled and aspirated antigens and to respiratory pathogens has long been recognized, but until recently has largely eluded mechanistic understanding. Considerable progress is being made in physical mapping and sequencing of the genomes of both humans and a range of model animal species. Together with ongoing "classic" genetic studies of sibships with asthma, atopy, and immunodeficiency, these studies promise opportunities to understand at the molecular level and eventually to control host immune responses. Because these genetic investigations are inherently unbiased as to mechanism, it is also likely that new paradigms of immunomodulation will emerge from these interdisciplinary studies. Results of these studies would have broad applicability to asthma, sarcoidosis, and respiratory infections.

The pulmonary immune system plays a central role in defense against infection and neoplasms, the generation of allergic and irritant responses, and the development and repair of acute and chronic inflammatory reactions. The pulmonary immune response must be very tightly regulated in order to protect the vast surface area of the lungs without interfering with their central function, gas exchange. Many pulmonary diseases appear to be caused or exacerbated by dysregulation of the immune response. Dysregulation may be important in the establishment of disease, the resolution of disease, or both. For example, differences in cytokine production in response to allergens have been implicated in the development of asthma, whereas dysfunctional repair following lung injury may contribute to fibrosis and loss of function in asthma, bronchopulmonary dysplasia, cystic fibrosis, pulmonary fibrosis, emphysema, pulmonary vasculitis, and acute lung injury/adult respiratory distress syndrome.

A variety of fundamental issues regarding the normal functioning and regulation of the pulmonary immune response remain to be explored. Better under-

standing of the normal development of the pulmonary immune system is required and could lead to an understanding of how primary abnormalities of immune ontogeny manifest themselves in disease. Additional work is required to further define the early steps in antigen sensitization via the human respiratory tract and to provide a framework for the development of vaccines effective against infectious, and possibly non-infectious, lung diseases. Future studies should define the degree to which the immunologic mechanisms identified in animal model systems can be extrapolated to human physiology and disease. Work in animal models and human populations could help to explain genetic factors that influence the polarized cytokine responses to allergens and other stimuli. Further study is required to determine whether *in vivo* modulation of cytokine networks can be safe and effective in allergic and other diseases, to identify and test pharmacologic inhibitors of inflammatory cytokines, and to evaluate the potential therapeutic role of other immunomodulatory strategies. Gene therapy also raises issues relevant to the pulmonary immune response. For example, gene therapy could be used to directly deliver immunoregulatory genes. Another important concern is that gene therapy may be limited by the immune response to the vector or the gene product, and more study is required to devise strategies to overcome these limitations.

Examples of specific short- and intermediate-term goals of this area of research are:

- a. To investigate the molecular basis of high and low response to inflammatory stimuli among human subjects, especially with regard to production of cytokines, chemokines, eicosanoids, neuropeptides, and other inflammatory mediators. Recent data suggest that variations in the tumor necrosis factor- α (TNF- α) promoter regions influence TNF- α production in critically ill patients and thus may explain, in part, variability in onset of multi-organ system failure in response to infection and trauma. Similarly, variations in production of interleukin-1 (IL-1) and its physiologic inhibitor, IL-1 RA, have been described in patients with rheumatologic disease, but not yet studied in pulmonary fibrosis or asthma.
- b. To facilitate rapid translation of genetic breakthroughs in model animal species to the understanding of human respiratory diseases. The murine response to a variety of pathogens shows highly polarized cytokine responses that vary between mouse strains. The genetic basis for this difference is incompletely defined but should be attainable in the near future. It is plausible that identical, relatively simple modes of inheritance underlie atopy.
- c. To stimulate bidirectional communication between basic researchers in immunology/inflammation research on one hand and pharmaco-chemical researchers on the other, regarding likely fruitful targets for development of novel therapeutics.
- d. To investigate the genetic basis of response to medication, which will continue to be a very important area for research as additional genetic information becomes available. For example, the response to asthma medication may be largely determined by genes.

3. **Genetic bases for sleep-disordered breathing.** Divergence between otherwise healthy individuals occurs in the respiratory responses to increasing carbon dioxide and/or decreasing oxygen levels, and there is strong evidence that these ventilatory traits (e.g., response to chemical and nonchemical drive, and breathing patterns during wakefulness and sleep) have an inherited basis. Estimates of the strength of genetic variance in ventilation, respiration frequency, appearance of sleep apnea, and the ventilatory response to hypercapnia or hypoxia available from human studies and animal models are high (range 40–70%) and are considered to result from the action of a finite number of genes with greater than 4% influence. The techniques now available in molecular genetics through the progress of the Human Genome Project no longer are limiting steps in the identification of this level of genetic influence. These observations and developments lead us to conclude that it is timely and appropriate to begin to directly address the chromosomal bases for ventilation and ventilatory responsiveness. Research is needed to obtain quantitative information about the genetic factors that influence respiratory control at rest and when breathing is stimulated in order to have a more complete understanding of respiratory health and disease. Inferences need to be drawn as to the physical location of genes or gene loci that relate to ventilation and the potential modes of inheritance and the genetic associations among ventilatory traits, cardiovascular physiology, and metabolic control. As in any polygenically determined physiologic system, certain genes will have ontogenic influence on the structural biology of respiratory control, while others may be engaged in normal breathing patterns and the ventilatory response to internal or environmental challenges, including but not limited to occupational exposures, acclimatization to altitude, and cardiopulmonary disease. Knowledge of these genes would identify proteins that could be targets for interventions to control or prevent disorders of respiratory control, like sleep apnea, sudden infant death, dyspnea, and hypo/hyperventilation syndromes.

Early attempts to apply genetic mapping techniques to the genetically complex pulmonary disease, asthma, illustrate the promise and the difficulties associated with this approach. While several groups have linked chromosomal regions to asthma, atopy, and bronchial hyperresponsiveness, the significance of these proposed linkages is still the subject of intense investigation. A number of major methodologic issues confront investigators planning to use genetic mapping to study asthma and other genetically complex pulmonary diseases. For example, consensus must be reached on criteria to be used to establish disease diagnoses within study populations to assure that results from different centers can be compared. Since the genetic component of some diseases is expected to involve multiple genes, each of which has a small individual effect, it will be necessary to devote considerable resources to design and conduct large multicenter trials and to support follow-up studies designed to validate results in independent populations. The Human Genome Project will soon provide a comprehensive accounting of the position of human genes, which will greatly accelerate the process of identifying specific disease genes based on positional information.

B. Regulatory Mechanisms in Immune Response and Inflammation

1. **Molecular determinants, inflammation, the host response to sepsis, and related pathophysiologic conditions.**

The inflammatory process is the core of the most perplexing problems, such as sepsis, acute lung injury, and nosocomial infections, which account for a large number of ICU patient days. The physiologic response to sepsis, trauma, and various other noxious exposures varies substantially from one patient to another. Recent studies suggest that some variations may be understood at the molecular level, including genetic polymorphisms that result in very different responses to sepsis. Other studies, primarily in animals, indicate that a host's recent exposure to endotoxin, heat, or high concentrations of oxygen may alter its subsequent response to similar or more noxious exposures of the same or different agent.

The ATS should support further research into molecular mechanisms of host responses to inflammation in the broadest sense of the word. Large scale epidemiologic studies should be conducted to further define human phenotypes associated with mild versus severe responses to sepsis. These studies, similar to those that defined risk factors for chronic obstructive pulmonary disease (COPD) in cigarette smokers, may point toward specific genetic differences or variations in recent exposures that may alter host's responses. Second, further investigation at the molecular and cellular levels should be focused on the basic mechanisms of tissue injury and repair including the identification of inflammatory mediators, evaluating cell-cell interactions, and further investigations of endothelial and epithelial injury. Further studies to define molecular events that occur between exposure and the pathophysiologic response should be undertaken. These studies may provide useful information to design preventive measures and treatments for patients who are exposed and likely to suffer severe responses.

2. **Regulatory mechanisms and potential immunomodulation of the pulmonary immune response.**

Pulmonary immune responses must be regulated tightly to protect the lungs against pathogens without interfering with gas exchange. The challenge of this regulation is daunting, given the enormous area of alveolar epithelium, the constant threat of aspirated or inhaled antigens, and the presence within pulmonary vasculature of many activated lymphocytes. Until the past decade, understanding of the mechanisms regulating pulmonary immune responses has not led to unique therapies, other than inhaled steroids.

More recently, there have been major advances in the molecular definition of leukocyte recruitment, cytokine and chemokine networks, pulmonary dendritic cells, and the interaction between nonadrenergic/noncholinergic nerves and the immune system. Certain of these areas are relatively mature and well supported by proof-of-concept experiments in experimental systems (e.g., inhibition of leukocyte recruitment by monoclonal antibodies), whereas others (e.g., control of dendritic cell numbers and function) are in their infancy.

Importantly, the respiratory system shares with the skin the unique facility by which topical therapies can be administered. The availability of recom-

binant cytokines and of specific inhibitors of eicosanoid metabolites suggests the potential to selectively up- or downregulate the pulmonary immune response. Nevertheless, early experience with some cytokine therapies (e.g., IL-2, IL-12) indicate the potential for considerable unanticipated toxicity.

Examples of specific short- and intermediate-term goals of this area of research are:

- a. To define more fully the early steps in antigen sensitization via the human respiratory tract. Experimental immunization is feasible and safe (*Am. J. Respir. Cell Mol. Biol.* 1993;11:607-614). Either model antigens or vaccines could be used to address dendritic cell recruitment, peptidergic nerve activation, and regulation of leukocyte apoptosis.
- b. To determine whether the T helper type 2 cell (Th2) cytokine phenotype can be converted *in vivo* by cytokine modulation. This goal must clearly progress from cell lines to whole animal systems before testing in human subjects.
- c. To define the degree to which the immunologic mechanisms derived from animal model systems can be extrapolated to human physiology and disease. Too much attention has been paid in the past to the degree to which such systems mimic the histopathology and respiratory mechanics of human disease.
- d. To use structure-function analysis of cytokine receptors to develop low-molecular-weight inhibitors of inflammatory cytokines. Such inhibitors are needed because monoclonal antibodies are useful to verify concepts but are not feasible for treatment of chronic diseases. Despite the paucity of homology of various cytokines at the amino acid level, cytokine receptors can be assigned to a small number of receptor families based on the physical structures they recognize (e.g., beta trefoil, long-chain 4-alpha helix bundles). This finding suggests that analysis of crystalline structure may be very fruitful.

3. **Developmental immunology of the lung, and its relationship to disease pathogenesis.**

The role of abnormal lung immunology in the pathogenesis of common pediatric lung diseases is being increasingly recognized. Disturbance in local immunity results in inflammatory mediator release that can amplify the disease, resulting in physiologic dysfunction at the organ level. Much work has concentrated on inflammatory mechanisms in asthma, but recent work has implicated abnormal immune regulation in the pathogenesis of bronchopulmonary dysplasia and cystic fibrosis; immune dysregulation is likely to play a role in many of the poorly understood interstitial lung diseases on infancy and childhood as well. Better understanding needs to be achieved in the following areas:

- a. What is the normal ontogeny of the developing lung's immune system, and how do primary abnormalities of this normal ontogeny manifest themselves in disease?
- b. How does the immune system simplify abnormalities due to other primary lung disorders, such as cystic fibrosis, and how can immune system modulation be used to treat disease?

- c. What are the correlations between disease at the cellular level and disease at the organ level? Specifically, do newly developed tests of lung function in infants reflect the cellular and cytokine markers of disease in lung disorders of infancy, and can these tests improve the clinical care of these patients?

C. Lung Injury and Repair Mechanisms

Mechanisms of lung injury and repair are fundamental to an understanding of the pathophysiologic basis of disease and the development of new therapies. With respect to mechanisms of cell injury, there are specific areas that deserve investigation:

1. **The role of nitric oxide in lung injury.** The role of nitric oxide *per se* as an agent of injury, as well as in combination with oxidants, should be elucidated, and similarly the role of oxidants stimulating nitric oxide production by increasing expression of nitric oxide synthetase. For example, ozone can induce tissue injury by its direct effect as an oxidant, but also it stimulates production of nitric oxide. Similarly, the influx of neutrophils and macrophages in inflammatory reaction can induce tissue injury by oxidant release. However, there are mechanisms to be understood with respect to increases in nitric oxide and changes that may occur in the amount and composition of intracellular antioxidants. The interplay of oxidant radicals and nitric oxide and the balance of intracellular antioxidants in setting the stage for tissue injury are all areas requiring further study.

2. **Interactions of agents with oxidants and nitric oxide.** Further clarification is required of how certain agents may modulate the toxic effects of oxidants and nitric oxide. For example, bacterial endotoxin can increase intracellular glutathione in macrophages and reduce nitric oxide synthetase, thereby modulating tissue injury from such agents. In this regard, the concept of a balance between oxidants and antioxidants as a cause for tissue injury in the lung deserves further exploration as a cause for exacerbations in asthma, chronic obstructive lung disease, and the acute respiratory distress syndrome. In this regard, there is a need for accurate and easily utilized methods to assess the concentration of oxidant radicals in tissue and plasma as well as antioxidants. Such a quantitative approach to assess oxidant and antioxidant concentrations could lead to new therapies and the assessment of the efficacy of new therapies.

3. **The role of antioxidant enzymes.** With respect to oxidant injury, much progress has been made in our understanding of the better known antioxidant enzymes (e.g., superoxide dismutase catalase, glutathione peroxidase) in mediating the lung's resistance against oxidant injury. However, it is becoming clear that other oxidant-induced gene products may also play vital roles in the lung's protective response to oxidant stress. One such stress response protein is heme oxygenase, HO-1. Since its discovery in 1968 and recognition that this enzyme catalyzes the first and rate-limiting step in heme degradation, there is much evidence that HO-1 is induced not only by heme but also by a variety of non-heme inducers such as heavy metals, endotoxins, heat shock, inflammatory cytokines, and prostaglandins.

The magnitude of HO-1 induction after oxidative stress and the wide distribution of this enzyme in systemic tissue, coupled with the broad-based biological activities of the catalytic by-products, carbon monoxide, iron, and bilirubin, make HO-1 a highly interesting stress response protein that may play a significant role in mediating protection against oxidant injury. This enzyme has not been investigated with respect to pulmonary injury, but deserves to be.

4. **Apoptosis in lung injury.** One very important aspect of lung injury is apoptosis. Apoptosis plays a major role in homeostasis to maintain a balance between cell proliferation and cell death. However, dysfunction in the processes of apoptosis may cause abnormal tissue reactions, such as inflammation or fibrosis. The agents of injury that induce apoptosis and the precise mechanisms by which apoptosis is induced should be better understood. Of equal significance is an understanding of the steps in cellular injury before apoptosis, i.e., states of cellular dysfunction that go on to apoptosis and other states of dysfunction that are repairable.

The program of physiologic apoptosis is tightly controlled by various genes. A dysfunction in any one of these genes can be associated with pathologic mechanisms leading to disease. The molecular mechanisms by which apoptosis is induced and the results of a failure of apoptotic mechanisms deserves further study.

5. **Cellular and molecular determinants of lung repair following injury.** Dysfunctional repair of the alveolar and vascular architecture after injury appears to explain fibrosis and loss of function in asthma, pulmonary fibrosis, emphysema, and pulmonary vasculitis. Even transient injury appears under certain circumstances to induce long-term phenotypic changes in lung fibroblast populations. Important emerging research topics are regulation of fibroblast migration, proliferation, and survival. Induction of autocrine growth factor receptors, long-term alteration in signal transduction via protein kinase cascades and in expression of COX 2 and upregulation of anti-apoptotic factors, such as scl-2 family members, are all potentially fruitful lines of this investigation. The mechanisms that control repair of the extracellular matrix of the lung following injuries such as the adult respiratory distress syndrome, organizing pneumonia, and idiopathic pulmonary fibrosis must be understood at the molecular level. In addition, further study is needed on how intermediate agents such as versican, decorin, and biglycan influence proteoglycan repair and collagen synthesis.

6. **Growth factors.** Transforming growth factor-beta (TGF- β) belongs to a family of multifunctional polypeptides that regulate normal cell growth, development, and tissue modeling following injury. TGF- β is a potent growth inhibitor of many normal and transformed cell lines. TGF- β is the dominant mediator of the pathologic extracellular matrix accumulation that characterizes progression of tissue injury to end-stage organ failure. TGF- β plays a critical role in cell and tissue growth, development, and differentiation. In the adult animal, TGF- β promotes homeostasis by regulating cell proliferation and in balancing extracellular matrix production and degradation. During wound repair, the inhibitory effects of TGF- β on in-

flammatory and immune effector cells may be important in limiting the magnitude of response to tissue injury. Transient TGF- β production may therefore promote wound healing and restitution of tissue architecture. A persistent expression and/or activation of TGF- β due to repeated tissue injury or to a failure of effective cell clearance may lead to fibrosis and end-stage organ failure. To intervene in this process, mechanisms regulating TGF- β gene expression, activation of latent TGF- β , and TGF- β clearance need to be more clearly defined. The wide range of biologic options of TGF- β suggests many potential therapeutic applications of TGF- β agonist or antagonist therapy.

D. Neural Control

1. *Neurobiological basis of cardiorespiratory integration during wakefulness and sleep: implications for disease.*

Epidemiologic and clinical studies recognize the coexistence of disorders of respiratory and cardiovascular control. For example, 40–60% of individuals with hypertension also have breathing disorders during sleep and loss of circadian and ultradian rhythms. Moreover, a large number of individuals who have obstructive sleep apnea are also at risk for developing cardiovascular dysfunctions. Regions for neural control of breathing and cardiovascular function are located in similar places. In the periphery, the carotid bodies and carotid sinus are in close proximity. Furthermore, integration areas in the brainstem and more rostral brain region receive similar inputs from both sensors. Finally, efferent neural traffic and its control elements, including autonomic nervous system, mechanics (pulmonary and cardiovascular), and humoral factors, influence both ventilatory and cardiovascular parameters. Most studies have focused either on control of ventilation or on cardiovascular function. Additional research is needed to understand the neural basis for cardiorespiratory interaction and how alterations in this integration influence clinical treatment, including pharmacologic interventions, outcome, and the comorbidity of concurrent heart and lung disease.

2. *Developmental aspects of neural control of respiration during wakefulness and sleep in health and disease.*

Sleep-disordered breathing continues to be a major cause of mortality in infants, children, and young and older adults. Infants dying in their sleep from sudden infant death syndrome (SIDS) is the single largest component of postnatal infant mortality. Sleep apnea affects 1–5% of adults resulting in cognitive impairment, poor work and school performance, excessive daytime sleepiness, pulmonary and systemic hypertension, and reduction in life expectancy. Furthermore, it is estimated that obstructive sleep apnea in adults contributes to 38,000 excess deaths per year. Apnea in the premature infant continues to be a major cause of prolonged hospitalization. Although sleep-disordered breathing is a common illness that affects all age groups, the neuroanatomical, cellular, and molecular events that regulate breathing during health and disease in wakefulness and sleep are not well understood. Research is needed to determine the genetic risk, the neurophysiological and neuroanatomical substrates and factors that are important with development in the young and with

maturation in the elderly. Research is also needed to study fundamental cellular and molecular events in central and peripheral neurons that are known to be involved in modulating breathing in sleep and during development—the epidemiologic association of male sex hormones in general and sex steroids in particular on the development of cardiorespiratory control during sleep. Lastly, having a better understanding of neurochemical modulators of breathing during sleep might provide avenues for safe and effective treatment for a disorder that affects an estimated 2–4 million people.

E. Fundamental Mechanisms of Lung Biology

Future directions of lung research should develop a deeper understanding of certain fundamental cellular and biochemical characteristics of the lung that, when deranged, cause disease. Such characteristics determine the structural and functional integrity of the lung and are essential to controlling pathologic mechanisms. Three areas of further biochemical and physiologic study are suggested: (1) the connective tissue matrix of the lung; (2) cytokines that affect lung development in infancy and may be significant factors in lung injury and repair in maturity; and (3) investigation of new biochemical agents that may or may not be unique to the lung but which provide a protective function.

1. **Lung matrix biology.** The tissue substances of alveoli and bronchioles and their interconnections are fundamental to the mechanical behavior of the lung and the distribution of gas and blood in alveoli. The precise relationships between connective tissue elements of the lung parenchyma, such as elastin, collagen, and glycosaminoglycans, which impart the elastic and tensile properties of the lung, have yet to be clearly understood. Previous work has demonstrated the critical importance of elastin fiber structure to alveolar architecture and the pathologic effects of elastin disruption in the development of emphysema. Little is known of the role of collagen degradation, and particularly degradation and alterations of glycosaminoglycans, in the maintenance of normal alveolar structure. These factors are also relevant to the changes in lung structure and function with age. Future directions in research should explore the specific role of pulmonary parenchymal glycosaminoglycans in maintaining alveolar integrity. In this regard, new research should elucidate the mechanisms by which destruction or alteration of proteoglycans leads to alveolar disruption resembling emphysema. Also, investigations are required to better understand the role of proteoglycans and hyaluronan as matrix components that can modulate the destructive effects of proteases, and particularly elastases, in causing alveolar disruption.

Increased understanding is required of how the matrix of the lung parenchyma responds to lung injuries to which the lung is especially susceptible, such as pneumococcal infection, which resolved with little matrix hypertrophy, while inflammatory reactions occurring in the acute respiratory distress syndrome lead to pulmonary fibrosis or bronchopulmonary dysplasia.

More information is required to understand the role of lysyloxidase, which is fundamental to the syn-

thesis of both elastin and collagen in lung parenchyma. The factors that regulate lxyloxydase synthesis and availability with respect to cytokines such as prostaglandins, growth factors, and the gaseous environment of the alveoli deserve further study.

2. **Airway and alveolar injury and repair.** Airway and alveolar epithelial repair is important for resolution of many inflammatory diseases that involve airways. Understanding the detailed processes of airway epithelial proliferation and migration, which involve diverse agents such as neuropeptides, growth factors, bombesin-like peptides (BLPs), and inflammatory cytokines and their relevant signaling systems, could lead to new therapies and offer a significant research opportunity.

Gastrin-releasing peptide (GRP), found in pulmonary neuroendocrine cells, augments epithelial growth and lung branching in embryonic lungs. These compounds, also referred to as BLPs, have been shown to be involved not only in lung development but also in lung repair after injury. In this context, processes concerned with lung development in embryonic life may be repeated in repair from injury in the adult organ, a concept that deserves better understanding.

The role of BLP in tissue repair has been demonstrated in pulmonary airway epithelium, which is especially relevant to cellular regrowth after injury in diseases such as asthma, bronchitis, and cystic fibrosis. GRP specifically has been demonstrated to stimulate airway epithelial cell migration, a process considered to be essential for healing and restoration of function after airway injury. The control mechanisms for epithelial cell migration after injury remain unclear and require a deeper understanding of how agents such as BLP may be linked to the action of matrix proteins which may be concerned with cell migration such as fibronectin, insulin, transforming growth factor-A, inflammatory cytokines, and epidermal growth factor (EGF). The GRB is associated with phospholipase and is known to activate protein kinase-C (PKC) so that GRB receptor ligand interactions can involve several different signal transduction pathways, all of which require elucidation.

3. **Antimicrobial factors and innate immunity.** Defensins are cationic antimicrobial peptides that contribute to an effective barrier on mucosal surface including the tongue, nasal and intrapulmonary airways, and small intestine. They are also concentrated in the phagocytic vacuoles of neutrophils. *In vitro*, defensins exhibit broad spectrum antimicrobial activity against gram-positive and gram-negative bacteria, fungi, and viruses. In some studies hVD-1 protein is expressed in the surface epithelia of the human conducting airways. hVD-1 message has been found in primary cultures of airway epithelia. This class of compounds may play a role in diseases such as cystic fibrosis, chronic bronchitis, sinusitis, and rhinitis. The techniques are available to detect the message for defensins in various cells of the respiratory tract. Studies are needed to evaluate the functional state of such compounds *in vivo* and *in vitro* in the surface lung cells of the respiratory tract.

Surfactant is a lipoprotein that reduces surface tension in the lung and more recently has been found to regulate immune cell function. Both surfactant

proteins and lipids have been implicated as host defense molecules and since the surfactant system is compromised in many disease states, such alterations may have an impact on the immune status of the lung. A deeper understanding of the chemical basis of the antimicrobial properties of defensins and of the mechanism by which surfactant functions in host defense could be important to the development of new antibiotics and related therapies.

4. **Epithelial cell biology.** Epithelial cells are involved in much of the diverse spectrum of lung disease. The ability to culture and study lung epithelial cells *in vitro* has advanced greatly in recent years. This creates the opportunity to describe the mechanisms by which lung epithelial cells play a role in disease processes, both as targets of injury and as active participants in pathogenic mechanisms. The development of alveolar type I and type II and airway cell lines that maintain a functional phenotype is an important research priority. In addition, generation of specific cell surface markers would facilitate the development of cells and provide potential diagnostic tools.
5. **Signal transduction.** Understanding the mechanisms by which cells respond to various signals from their environment and by which they regulate these responses is advancing rapidly. Abnormalities in regulatory mechanisms appear to underlie many disease states. Specific steps in the various regulatory cascades represent potential therapeutic targets. Therefore, it is a clear priority that signal transduction mechanisms in the lung, particularly as they relate to lung diseases, be understood. Such understanding may lead to the development of novel disease treatment strategies.
6. **Gene therapy.** The ability to directly transfer genetic material into humans has created an enormous opportunity for the treatment of lung diseases. These include not only genetic diseases that affect the lung, such as cystic fibrosis and hereditary emphysema (alpha-1-antitrypsin deficiency), but also a wide variety of other diseases involving inflammation and cancer. However, gene therapy is currently in its infancy. Better understanding of the mechanisms and limitations of current vectors, development of new vector technology, and research aimed at using these new approaches to effectively treat lung disease are all areas of high research priority.
7. **Airway smooth muscle.** Airway smooth muscle is the key effector of acute airway narrowing in asthma. The isometric force generating capacity of muscle from asthmatic airways seems to be normal, but the velocity of shortening is elevated. Therefore, it remains unclear whether the airway hyperresponsiveness that is characteristic of asthma is attributable to abnormality of the muscle, abnormality of the load against which the muscle must shorten, or both. Relatively little is known about heterogeneity of smooth muscle phenotypes, their distribution in the lung, or the functional significance of that heterogeneity. Airway smooth muscle has recently been shown to exhibit plasticity by rapidly reorganizing its cytoskeletal architecture or focal adhesion plaques such that it produces its maximum force over a wide range of lengths. However, the specific mechanisms of remodeling, and the factors that regulate that remodeling, are unknown. Also, not enough is known about

- smooth muscle maturation, mitogenesis, and the mechanisms that control them. Finally, it has been reported recently that cytokines have direct effects on G-protein coupled signal transduction pathways in airway smooth muscle, but the role of the inflammatory milieu in modulating signal transduction pathways is not well understood.
8. **Respiratory muscle function.** Compromise of respiratory muscle function, due either to weakness or fatigue, can cause respiratory insufficiency and lead to prolonged dependence on mechanical ventilation. Respiratory muscle insufficiency occurs in diseases that range from corticosteroid myopathy to chronic obstructive lung disease, from sepsis to asthma. Research is needed to establish the mechanisms of muscle failure and to identify novel therapies to complement or replace mechanical ventilation. At the cellular and molecular levels, the factors that limit contractile function of normal respiratory muscle remain enigmatic. The mechanisms that regulate excitation-contraction coupling appear to differ from those observed in limb skeletal muscle and must be determined if we are to understand muscle weakness. The factors that govern muscle fatigue also are incompletely understood. The respiratory muscles adapt to a variety of conditions, including disuse, chronic length change, training, and aging. However, the intracellular mechanisms that control myocyte adaptation remain a mystery. We know nothing of the transcription factors that regulate gene expression in respiratory muscle or the stimuli that alter protein expression. These processes must be investigated in order to understand respiratory muscle wasting and weakness that occurs in chronic disease.
 9. **Lung und chest wall mechanics.** The reintroduction of lung volume reduction surgery (LVRS) as a potentially useful therapy for nearly 2 million sufferers from severe COPD has inspired a resurgence in research on the mechanics of lungs, chest wall, and respiratory muscles. Mechanisms underlying the respiratory dysfunction of emphysema and the improvements in function following LVRS are not well understood and are being explored in theoretical and experimental studies using classic methods of respiratory mechanics and newer techniques of magneto-electric phrenic nerve stimulation and sophisticated electromyography. Only some of the patients with emphysema benefit from LVRS, and selection criteria are controversial. Preoperative measurements such as inspiratory resistance may be important in predicting which patients are more likely to benefit from LVRS. Patients with lung disease may be harmed by too much or too little muscle activity, and too little muscle activity in ventilated patients may cause disuse atrophy. Newer physiologic techniques promise to enable rigorous clinical studies to elucidate the importance of respiratory muscle fatigue and iatrogenic atrophy, and to guide strategies for their prevention.
 10. **Lung structure and pathology.** Two important issues need to be addressed in the histologic classification of lung cancer: neuroendocrine lung tumors and adenocarcinomas. The neuroendocrine lung tumors of atypical carcinoid and large-cell neuroendocrine carcinoma have been recognized in the past two decades. However, due to their rarity, little is known

about the clinical outcome and the response to therapy for patients with these tumors. Histologic subclassification of adenocarcinomas is another major problem. Currently, adenocarcinomas are divided into the subtypes of acinar, papillary, bronchioalveolar, and solid adenocarcinomas with mucin formation. It appears that the only subtype of adenocarcinoma that has a better prognosis is bronchioalveolar carcinoma (BAC). However, the precise definition of this tumor and whether BAC with microscopic foci of invasion should be included in this category awaits further study. Histologic classification of interstitial lung diseases is also problematic in that a sizable percentage of cases do not fit into the major categories of usual interstitial pneumonia (UIP), desquamative interstitial pneumonia, idiopathic diffuse alveolar damage, or idiopathic bronchiolitis obliterans with organizing pneumonia. It has been proposed that these interstitial lung disorders be grouped together under the category of nonspecific interstitial pneumonia. This is a useful concept in that it identifies a group of lesions that should be separated from UIP. However, it represents an ill-defined category with a broad spectrum of histologic findings. More study of the lung pathology and clinical aspects of patients is needed to better define these interstitial disorders.

11. **Pulmonary vascular remodeling.** Isolated pulmonary arteries, even devoid of intima, can constrict to hypoxia, allowing focus of studies on the smooth muscle for the O₂ sensor. O₂ tension appears to affect potassium channels but also may primarily produce calcium release from internal stores. Further studies will delineate the major site of hypoxia sensing and the chemical sensing mechanisms. How vasoconstriction relates to vascular remodeling remains elusive. Multiple important aspects of remodeling are becoming clear, however. The endogenous vascular elastase that alters elastic lamina seems crucial, but exactly why and how is still to be delineated. The media contains multiple different types of smooth muscle cells that vary in appearance, electrical characteristics, and growth characteristics. Why these cells vary and whether it is a response to their environment or a primary change is unknown. New therapies are being developed, aimed at reversing the remodeling, such as heparin or amiloride compounds. Chronic protascyclin infusions may be effecting the reversal of vascular remodeling as much as relaxing vasoconstriction.
12. **Bronchial circulation.** The unique properties of the bronchial vasculature relative to the pulmonary circulation remain undefined. Although the propensity for this circulation to revascularize lung tissue is established, the cellular, molecular, and functional changes leading to neovascularization are poorly understood. Increased vascularity of airways, specifically, may contribute to inflammatory airways disease. Mechanisms of inflammatory cell recruitment by the bronchial circulation need to be addressed. Despite its size relative to the pulmonary vasculature, the bronchial circulation is uniquely positioned to impact airway and lung function.
13. **Pulmonary vascular permeability.** The endothelial cell barrier is a key target in inflammatory and thrombotic processes, which produce vascular permeability and tissue edema. Recent studies have be-

gun to elucidate the molecular mechanisms that link activation stimuli such as leukocyte adhesion, thrombin, cytokines, and growth factors such as VEGF with perturbation of the ED barrier. Disruption of the EC monolayer junctional integrity are highly influenced alterations in the EC cytoskeleton. Future studies directed at understanding the regulation of the paracellular space by competing contractile forces (barrier disruptive) and adhesive forces (barrier protective) will shed considerable insight into treatment of the clinically important pulmonary edema process.

F. Environmental Factors

Epidemiologic evidence indicates that there is a direct relationship between exposure to particulates and morbidity and mortality. Gaseous pollutants such as ozone, sulfur dioxide (SO₂), and organic irritants may be additional factors. The primary causes of death appear to be cardiopulmonary incidents in persons with compromised cardiopulmonary function, and individuals with asthma have greatly increased risk. Identifying the mechanisms whereby particulates may affect cardiopulmonary morbidity and mortality is considered an important research priority. Attention is particularly focused on the leukotrienes as possible mediators in this pathway. Answering this question will require a multidisciplinary approach to include epidemiology (cardiovascular and pulmonary), molecular biology, immunology, and physiology.

II. DISEASES

The previous version of this report "Future Directions for Research on Disease of the Lung" (*Am. J. Respir. Crit. Care Med.* 1995;152:1713-1735), presented a comprehensive description of important pulmonary diseases that were targeted for research in the next decade. Because that document provided detailed information on specific diseases, including etiology, risk factors, and important areas for research, those subjects are only briefly touched upon here, with a priority of providing an update to the previous document to which readers are referred for additional information.

A. Asthma

Pediatric asthma: epidemiology and pathogenesis. Asthma deaths in children have increased 118% between the years 1980 and 1993 (CDC statistics). From 1980-1993 there were 3,850 asthma deaths among persons 0-24 years, with rates highest among African Americans aged 15-24 years. In 1903, among children 0 to 4 years, African Americans were six times more likely than Caucasians to die from asthma. Asthma mortality and morbidity have continued to rise despite advances in understanding of asthma pathophysiology and aerosol pharmacology. Better understanding in the following areas is needed:

1. Why is asthma mortality in the inner city on the rise?
2. Are the educational programs provided for inner city children ineffective because they are not culturally appropriate?
3. What is the role of environmental contributors (e.g., air pollution, dust mite and cockroach antigens) to the rise in inner city asthma, and how can these effectively be lessened'?
4. What are the relative roles of smooth muscle hyper-reactivity and inflammation in the pathogenesis of

asthma, and what are the best pharmacologic approaches to this disease?

5. Why is the prevalence of asthma increasing?
6. What are the risk factors for asthma?

B. Chronic Obstructive Pulmonary Disease

Further information is needed about the role of different risk factors for COPD, in particular:

1. What genes increase the risk for COPD?
2. Are women at greater risk for COPD than men?

C. Cystic Fibrosis

Cystic fibrosis: applications of basic science to clinical care. Recent advances in understanding of the molecular and cellular defects in cystic fibrosis open promising avenues for investigation of treatments. Further research needs to be performed to: (1) identify pharmacologic ways of normalizing defects in sodium and chloride ion transport; and (2) develop vectors capable of delivering the normal cystic fibrosis transmembrane regulator protein (CFTR) gene to target cells in the lung without triggering immunologic-based rejection of the targeted cells. Concurrently, studies of the development of cystic fibrosis lung disease in infants need to be performed to elucidate the extent to which cellular and lung function alterations can precede the onset of clinical disease and to identify the best ways to prevent the development of early lung damage. Further research should explore means of blocking adherence of *Pseudomonas aeruginosa* to the respiratory epithelium.

D. Lung Cancer

Early diagnosis of lung cancer. Despite current therapies, fewer than 15% of patients survive for 5 years following the diagnosis of lung cancer. There is an urgent need for effective screening test(s) to detect this disease at an earlier stage. Recent studies have demonstrated molecular abnormalities in bronchial airway cells that precede the development of frank malignancy. There is a pressing need to identify early cellular biomarkers, such as deletions on chromosome 3p or 9p, that will identify patients likely to develop lung cancer. Intense research efforts are needed to identify early biomarkers for screening so that patients can be monitored carefully to detect neoplasia at a very early stage or to enroll patients into chemoprevention trials in an effort to prevent the development of lung cancer.

E. Infectious Diseases

The following areas have been identified as priorities for research in infectious diseases:

1. Development of a tuberculosis vaccine;
2. Improving tuberculosis diagnostics;
3. Innovative approaches to tuberculosis control;
4. Reducing morbidity and mortality from acute respiratory infections; and
5. Research to develop new classes of antibiotics.

F. Tobacco Addiction

1. **Tobacco use: prevention and cessation.** Tobacco use, a major risk factor for emphysema, chronic bronchitis, and lung cancer, is the single most preventable cause of morbidity and mortality. Although the prevalence of smoking has declined dramatically since 1965, it is estimated that 25% of U.S. adults continue

to smoke cigarettes. Prevalence rates are disproportionately higher among socioeconomically disadvantaged groups, blue-collar workers, and minorities. Most alarming are the substantial increases in smoking among American adolescents. As of 1996, 30% of 15-16-year-old adolescents and 34% of those aged 17-18 reported smoking a cigarette in the last 30 days. Research aimed at the development of effective adolescent prevention and cessation programs must be conducted. Clinician, school, and community-based interventions to reduce adolescent smoking prevalence must be designed and tested. Implementation of legislative policies at the federal, state, and local level that reduce consumption (e.g., taxation, vending machine restriction, underage purchases, restriction of promotional items, etc.) must be evaluated. Formulation and investigation of cessation interventions for parents, especially mothers, who smoke and subsequently place their children at risk for adopting the behavior as well as increasing environmental tobacco exposure of young children in the home, also are necessary. Among adult cessation initiatives, research that examines effective treatment approaches among socioeconomically disadvantaged smokers and other special populations that do not have access to health-promoting care should be undertaken. While nicotine replacement improves treatment efficacy, few studies have examined ways to increase access to this costly therapy, especially among the socioeconomically disadvantaged smoker. Among smokers with lung disease, studies of cessation interventions are limited. The cost-effectiveness of treatment provided by clinicians, i.e., physician, nurse, respiratory therapist, either singularly or in combination, has yet to be tested in pulmonary-related hospital-based environments or outpatient settings, such as health maintenance organizations. Finally, efforts to curb the worldwide spread of tobacco use must be developed and tested by groups of researchers representing international perspectives. (U.S. Department of Health and Human Services. 1995. Healthy people 2000 Midcourse review and 1995 revisions. U.S. Department of Health and Human Services, Public Health Services. 1996. Fiore MC, Bailey WC, Cohen SJ, et al. Smoking cessation. Clinical Practice Guideline No. 18. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, AHCPR Publication No. 96-0692.)

Summary and recommendations:

1. Research aimed at preventing tobacco use among adolescents is a major priority. Cessation programs for adolescents must be designed and tested. Policy-related studies that influence youth access to tobacco are needed.
2. Effective cessation methods have yet to be widely tested among socioeconomically disadvantaged, underserved, and culturally diverse smokers. Studies of clinician-based interventions, especially in combination with nicotine replacement therapy, among patients with active lung disease are needed.
3. Research efforts aimed at curbing the international spread of tobacco are necessary and especially timely due to the rapid increase in smoking in underdeveloped countries.

2. **Tobacco smoke exposure and sudden infant death syndrome.** Sudden infant death syndrome (SIDS) is the leading cause of death in infants between 1 month and the first year of life with an overall incidence in the United States of 2/1,000 live births. Epidemiologic studies have shown a strong association between prenatal and postnatal exposure to environmental tobacco smoke and SIDS. A striking association has been made between exposure to tobacco smoke and SIDS in developing countries. Similarly, prospective studies in the United States have shown a strong dose-response relationship between maternal smoking in pregnancy and SIDS, with an odds ratio of 1.4 and 1.9 for mild and heavy exposure, respectively. A dose-response effect has also been demonstrated for pre- and postnatal exposure to passive tobacco smoke when an adult smokes in the same room as the infant; a striking odds ratio of 8.49 occurred when the adult is the father. Many of the components of environmental tobacco smoke, such as nicotine and carbon monoxide, are neurotoxic and may potentially alter the development of neurotransmitter systems that control respiration. Certainly, the associated risk of SIDS and pre- and postnatal passive exposure to environmental tobacco smoke is compelling and warrants investigating alterations induced by this exposure in neurotransmitter systems that control respiration in developmental models.

C. Pulmonary Hypertension

Mechanisms of primary and secondary pulmonary hypertension. The pathways of initiation, development, and maintenance of both primary pulmonary hypertension (PPH) and chronic pulmonary hypertension are not certain. Current therapy includes administration of vasodilators (e.g., prostacyclin and calcium channel blockers), which are largely unsuccessful. Recently, inhalation of nitric oxide has been used as an alternate therapy with some degree of success, especially with neonatal forms of pulmonary hypertension. Ultimately, lung transplantation, with its associated problems, becomes the only choice. A search for the gene responsible for the development of familial PPH has been initiated and, thus far, studies indicate that such a gene is likely. Studies of gene structure and regulation, as well as determination of whether the same gene contributes to the onset of pulmonary hypertension secondary to chronic lung disease, are an important area of future research. A problem for the latter studies is availability of material, and the need for banking tissue from such patients becomes obvious.

Development of both primary and secondary forms of pulmonary hypertension is associated with restructuring of the pulmonary vascular bed. Studies indicate that restriction of the pulmonary microvasculature is the structural change that results in pulmonary hypertension, while medial, adventitial, and intimal thickening of the large muscular arteries are secondary to the increase in intravascular pressure. Growth factors, the coagulation system, alterations in endothelial and smooth muscle cell receptor populations, lipid mediators, and circulating blood cells have all been implicated in the pathogenesis of this disease. Further studies in animal models are essential for our understanding of the pathogenesis of this disease, and ultimately in patients with primary and secondary pulmonary hypertension. Cognizance of the dis-

ease process is vital to the development of new therapeutic modalities.

H. Sickle Cell Anemia

The acute chest syndrome of sickle cell anemia presents as acute pulmonary distress, fever, chest pain, and focal infiltrates on chest X-ray. The syndrome is a major cause of morbidity and mortality in sickle cell disease and results in chronic lung dysfunction over time. Therapy for this syndrome is not specific for the chest but is the same as for all sickle cell crises. In the acute chest syndrome, the underlying pathophysiology is the hemoglobin S mutation, but many other interactive factors, such as infection, the coagulation system and blood vessel abnormalities, are likely to contribute. The vascular pathology underlying the lung injury is complex and undoubtedly more complicated than the traditional picture, vaso-occlusion through plugging of irreversibly sickled cells, since there is little correlation between the percentage of these cells and clinical severity. Data exist to support multiple mechanisms, such as: uneven distribution of charge on sickle cells; presence of immunoglobulin on sickle cell surfaces that mediate red blood cell attachment to endothelial cells infected with the virus; enhancement of adherent sickle cells to endothelium through various adhesion proteins (e.g., thrombospondin with the red blood cell receptor, CD-36); presence of specific red cell receptors such as vitronectin in microvessels or high molecular weight von Willebrand's factor in large vessel endothelium; and increased adherence of sickle cells to the endothelium through increased expression of endothelin-1. It is obvious that the pathway for increased red blood cell adherence to endothelial lung injury in this syndrome is both complex and largely unknown and warrants further study.

I. Acute Lung Injury/Multi-organ Failure

1. Acute lung injury. The adult respiratory distress syndrome (ARDS) is a substantial health problem with no effective pharmacologic treatment currently available. Endothelial perturbations, oxidant stress, increased cytokine and lipid mediator release, inactivation of surfactant, and inflammation are known to be associated with ARDS, but the initiating pathway(s) is not certain. For example, therapeutic approaches have included anti-inflammatory agents, antioxidants, and antibodies to adhesion molecules and tumor necrosis factor, and surfactant supplementation, and each has proved largely ineffective. These negative findings may represent our limited knowledge of the mechanisms of onset of this syndrome. Therapeutic studies have concentrated on the idea that inhibition of a single event in the inflammatory cascade in the lung will inhibit further progression of the syndrome and lead to recovery. However, it is not certain whether each step of the inflammatory cascade represents a deleterious event. It is likely that some steps of the cascade are beneficial, acting to counteract the harmful inflammatory mediators. The influx of neutrophils into alveolar space, for example, is considered injurious, promoting epithelial injury through release of proteases and oxidants from these cells. It is possible that this migration of cells into the alveolus is a protective event, representing clearance of activated neutrophils from the lung's circulation where they promote endothe-

lial injury and appearance of alveolar edema. Further studies are needed to demonstrate which steps in the inflammatory cascade are injurious and which provide protection against the development of the syndrome and to identify novel therapeutic approaches for treatment of ARDS involving transient gene therapy. Genes for antiproteases or other proteins known to inhibit the pathogenesis of the syndrome can be transiently expressed in the lung and suppress further progress of the disease process.

2. Respiratory support in acute lung injury and ARDS.

Numerous animal and human studies suggest that our traditional methods of respiratory support with positive pressure ventilation may be injurious to the lungs. Uncontrolled studies suggest that outcome from ARDS may improve with small tidal volume ventilation to reduce overdistension-induced lung injury. Other studies suggest that lung injury may be reduced by using higher levels of positive end-expiratory pressure (PEEP) than are traditionally used to support oxygenation. Gas exchange may be greatly improved with fluorocarbon liquids, ventilation with nitric oxide, prostacyclin aerosol, high frequency ventilation, and inverse ratio or airway pressure release ventilation. Beneficial physiologic effects of these modifications or adjuncts to conventional positive ventilation have been demonstrated in animal studies or in clinical trials with relatively small numbers of patients. With the exception of small tidal volume (low stretch) ventilation, there are no large, randomized, controlled trials to demonstrate realistic differences in essential outcome variables such as mortality.

The ATS should support research in further improving our primary means of respiratory support in patients with acute lung injury and ARDS. Research is necessary at several levels, including cellular and molecular levels to elucidate mechanisms of injury and beneficial and deleterious effects of new modalities. Animal studies using realistic models of acute lung injury/ARDS will be necessary to further develop new techniques before human applications. Large-scale multicenter studies will be necessary to determine beneficial effects, if any, and to further refine the techniques.

J. Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a lung injury most often associated with premature birth. Although surfactant replacement therapy has significantly reduced the mortality associated with prematurity, some infants do not respond, and they, as well as others who require ventilatory assistance for multiple reasons, can develop a lung injury that is also associated with inflammation, infection, and nutritional inadequacies. This injury is similar in many ways to ARDS but is significantly impacted by the structural and functional immaturity of the lung. Studies defining the mechanism of lung injury in the developing lung in which alveolar and airway cells do not develop normally and are injured by various mediators are important directions for future research.

III. APPROACHES TO CLINICAL RESEARCH

A. Prevention

Research on the prevention of lung disease goes hand in hand with research on its epidemiology, etiology, and

treatment. Arguably, prevention efforts stand to achieve greater reductions in morbidity and mortality from lung disease at the population level than the most effective therapies. As causal agents and predisposing conditions are identified for lung disease, research is needed on how to translate this knowledge into reduced disease incidence. Among the areas in which prevention research is critically needed are areas such as the following:

1. Reduction of tobacco smoking, especially by children and adolescents;
2. Development of more effective smoking cessation methods;
3. Prevention of asthma;
4. Prevention of occupational and other environmental lung diseases;
5. Prevention of lung disease associated with prematurity; and
6. Prevention of infectious diseases such as influenza, common cold, and tuberculosis.

B. Outcomes Research

1. **Impact of respiratory nursing interventions on patient outcomes, particularly those interventions related to behavioral and psychosocial symptom management (e.g., dyspnea, fatigue).** Nurse clinicians must document the effectiveness of nursing interventions on clinical and cost-related outcomes of care. An examination of teaching interventions for patients that are integral to activities of daily life among patients with chronic lung disorders and studies to evaluate the effectiveness of these teaching interventions on outcomes (e.g., exacerbations of asthma, outpatient visits, and hospitalizations) are necessary.
2. **Functional status/rehabilitation in chronic respiratory conditions.** Over the years, nurses have participated as members of multidisciplinary teams involved in the design and delivery of pulmonary rehabilitation programs. Although programs have experienced a range of support over the years, there has been a renewed interest in pulmonary rehabilitation in the preparation of patients for LVRS and lung transplantation. Quantification of the impact of pulmonary rehabilitation on patients, along with continued characterization of the mechanisms responsible for successful rehabilitation, are necessary.
3. **Cost-effective management of asthma and chronic pulmonary illness.** Despite the introduction of highly effective therapies for asthma, morbidity and mortality have not improved in recent years and in some locales have increased. Suboptimal outcomes in part reflect lack of access to specialty care. Pressures from third parties, insurance carriers, and HMOs have discouraged the use of specialists to diagnose or manage patients with chronic asthma or COPD. A plethora of new technologies and therapies have been introduced in the past decade for managing diverse chronic pulmonary conditions (e.g., cystic fibrosis, alpha₁-antitrypsin deficiency, transplantation, lung reduction surgery, and pharmacotherapeutic regimens). The cost of novel therapies (e.g., DNASE, alpha₁-antitrypsin [Prolastin]) is formidable, and impact on long-term morbidity or mortality is not known. Cost-benefit analyses of the role of novel diagnostic or therapeutic modalities for pulmonary disorders are lacking. Research areas of critical impor-

tance include assessing cost/benefit of these novel and conventional therapies, and the impact of subspecialty providers on appropriateness, cost, and outcomes.

4. **Studies on clinical outcomes.** Critical care is becoming increasingly expensive, consuming a significant proportion of hospital budgets. At the same time, it is becoming clear that the evidence for the efficacy and effectiveness of many investigative procedures and many of our therapies is lacking. As such, an important area of research is in the clinical outcomes and cost-effectiveness/efficacy of diagnostic and therapeutic procedures. The ATS should pursue research under this rubric in at least the following three areas:
 - a. Well-designed studies to further evaluate prognostic scoring systems and to determine how to best incorporate the information provided from the scoring systems into clinical practice;
 - b. Develop a system by which new therapies are tested, validated, and introduced into clinical practice (i.e., develop a procedure so that entities such as the right heart catheter are appropriately studied for both efficacy and cost-effectiveness before they are widely utilized); and
 - c. Investigations into actual clinical outcomes of critically ill patients, which would include better characterizing the patients who are in an ICU, resource utilization, and outcomes including not only mortality but morbidity and quality of life.
5. **Health outcomes research.** The ATS Corporate Relations Committee recently sponsored a two-day meeting on the role of the health outcomes in chronic lung disease, with a focus on the alliance between providers, academic researchers, industry, and the Food and Drug Administration (FDA). The international experts who attended discussed the state of the art in health status assessment, the importance of assessing functional status and health-related quality of life in lung patients, appropriate guidelines for the selection and interpretation of various health status measures, and the use of health status data in the development of new products. Participants recommended that the ATS: (1) establish a committee for the development and implementation of standards in health outcome assessment; (2) develop mechanisms to provide support for research on health status management; (3) develop the means to advocate for outcomes research and quality-of-life assessment in the evaluation of therapy for chronic lung disease; and (4) promote education and training on the measurement of health status. Collaborative research is needed among ATS members, industry, and the FDA to develop, validate, evaluate, standardize, and disseminate measures of health outcomes for patients with chronic lung disease.
6. **Care of the technology-dependent child.** Greater long-term survival of more premature infants at earlier postconceptional ages, along with evolving attitudes toward the home care of children with chronic respiratory failure due to progressive neuromuscular and cardiovascular disorders have led to unprecedented numbers of technology-dependent children. Technology is defined here as levels of support beyond simple nebulizers and monitors, and can include supplemental oxygen, negative pressure ventilation in

cuirass-type ventilators, and positive pressure ventilation by either tracheotomy or bilevel nasal positive airway pressure (BiPAP). The costs of such care are enormous. Research is needed to determine: (1) the long-term outcomes that can be expected for such technology-dependent children; (2) ways of assessing the need for chronic mechanical ventilation, including the assessment of respiratory muscle weakness and fatigue in infants and children; and (3) how the cost of innovative ways of performing care under a case management model and the role of the subspecialist in the care of these children.

C. Epidemiology

1. **Mechanisms of cardiopulmonary responses to allergens and irritants.** Epidemiologic evidence indicates that there is a direct relationship between exposure to particulates and morbidity and mortality. Gaseous pollutants such as ozone, SO₂, and organic irritants may be additional factors. The primary causes of death appear to be cardiopulmonary incidents in persons with compromised cardiopulmonary function; persons with asthma have greatly increased risk. Identifying the mechanisms whereby particulates may affect cardiopulmonary morbidity and mortality is considered an important research priority. Attention is particularly focused on the leukotrienes as possible mediators in this pathway. Answering this question will require a multi-disciplinary approach to include epidemiology (cardiovascular and pulmonary), molecular biology, immunology, and physiology.
2. **Revision of the ATS/D LD Respiratory Symptoms Questionnaire.** The 1978 ATS/DLD Respiratory Symptoms Questionnaire has become the most widely used respiratory questionnaire for epidemiologic studies in the world. The questionnaire evolved from the BMRC questionnaire and was originally designed primarily for epidemiologic studies of COPD. With almost 20 years of experience with this questionnaire, many problems have emerged. One of the most pressing has been the recognition that this questionnaire does not work well for asthma. Also, it does not include any assessment of quality of life for individuals with respiratory problems. Consequently, there has been a great deal of interest in revising the ATS/DLD questionnaire. Several efforts over the past few years have been derailed because of the cost and magnitude of the revision project. Because of the importance of this standardized questionnaire in epidemiologic studies in the United States and throughout the world, starting the process of revision is considered to be of high priority.
3. **Epidemiologic and clinical studies of sleep disordered breathing.** It has only been in the last 10 to 15 years that sleep-disordered breathing (SDB) has been recognized as a common and serious medical condition. It is currently estimated that SDB occurs at least as commonly as asthma, and substantially more in some groups (e.g., middle-aged men, postmenopausal women, elderly patients with cardiovascular disease, African American children and adolescents, etc.). The morbidity associated with SDB includes daytime sleepiness resulting in increased accidents, neurocognitive impairment, hypertension, and cardiac and cerebrovascular diseases. Some data suggest

the SDB may be a modifiable risk factor for vascular diseases that may be at least as important as hyperlipidemia. Much, however, is unknown about the epidemiology of SDB, including its natural history, individual determinants of susceptibility, the relationship between frequency and severity of SDB events and morbidity, and the risk relationships between SDB and vascular diseases. Clinically, there are markedly disparate approaches used for diagnosing and treating patients with SDB, and these clinical approaches are evolving rapidly without evidence that outcomes will be favorably influenced. Current needs include research to define optimal screening and diagnostic approaches, understanding of optimal approaches for treating SDB across its range of severity, improvement of the acceptability and effectiveness of treatment modalities, and defining the levels of thresholds and qualities of SDB that pose the greatest health risks. These approaches need to consider the heterogeneity of patient populations, including potential differences in cultural factors that influence treatment adherence. In addition to well-controlled clinical pathophysiologic research, observational studies (including studies of children, adolescents, and older adults) and rigorously controlled clinical trials will be required to address many of these issues.

D. Educational Interventions for Prevention, Self-management, and Treatment Adherence

1. **Intervention research focused on behavioral change (e.g., tobacco use prevention and cessation in underserved groups and adherence to therapy during illnesses such as tuberculosis).** Very little research has been conducted to determine ways to effectively prevent the use of tobacco among adolescents. In addition, there is only a small amount of information available with regard to cessation among adolescents. The majority of current adult smokers come from socioeconomically disadvantaged backgrounds. The effectiveness of traditional approaches to cessation among underserved groups (i.e., multicomponent behavioral counseling and nicotine replacement) has received little attention, and current cessation treatments have not been adequately tested with these groups. Finally, adherence to therapy, such as self-administration of medication for treatment of tuberculosis, continues to confront public health nurses in practice and deserves further research.
2. **Developing novel approaches for the control of tuberculosis, especially by improving compliance with preventive and curative therapy.**
3. **Patient self-management.** Achieving good control of chronic lung diseases, such as asthma, COPD, and cystic fibrosis, requires complex treatment plans and preventive strategies and careful management by patients and their families. Previous research has shown that good self-management by asthma patients can prevent or attenuate severe exacerbations that might result in emergency department visits and hospitalizations, which represent significant burdens for both the patient and the health care system. Recent advances include the development of a variety of educational interventions aimed at individual patients and groups to increase the effectiveness of self-management interventions, and will draw on recent de-

velopments in behavioral theory, including self-regulation and social support theories. Future research must also determine how effective self-management interventions can be made available to the widest number of patients. New research is focusing on interventions that can be delivered by clinicians during the course of regular patient contacts. It is important to establish the most effective approaches to self-management among patients with chronic lung disease and to determine the most efficient methods for training and supporting patients in self-management.

4. **Treatment adherence.** The magnitude and cost of treating respiratory illnesses in the United States is substantial. Part of that cost can be attributed to inadequate patient adherence to treatment regimens for chronic lung diseases such as asthma and COPD and for communicable diseases such as tuberculosis. There is a rich amount of literature on lung disease and some are authored by ATS members. However, the existing literature on lung disease lacks rigorous intervention research utilizing established approaches to behavior change. By comparison, researchers studying HIV prevention have documented effective behavior change using interventions that draw on social-cognitive theory, social diffusion theory, the stages-of-change model and other established theories of individual behavior change, and on environmental and structural interventions. Research is needed: (1) to study a variety of approaches to improve treatment adherence for chronic and communicable lung disease; (2) that recognizes that adherence as a multifaceted problem; (3) that utilizes rigorous research designs and established social and behavioral theory; and (4) that focuses on a variety of levels, including patients, providers, the health care environment, and legal and economic structures and policies.

IV. CUTTING-EDGE THERAPIES

Exciting advances in the treatment of lung diseases have been made possible by equally important advances in basic lung biology. The traditional surgical and pharmaceutical therapies have been supplemented by the use of genetic and biologic agents. It is impossible to adequately present all areas of therapeutic advances, but the following examples may give a hint as to the direction and scope of therapeutic progress.

A. Nitric Oxide

One of the more exquisite examples of basic biologic research resulting in an unexpected therapeutic advance is the biologic molecule, nitric oxide (NO). This evanescent compound was discovered to be the agent responsible for the relaxation of vascular smooth muscle that could be produced by stimulation of the endothelial cells. Subsequently, NO has proven effective as treatment for elevated pulmonary arterial blood pressure. It is under investigation for use in conditions ranging from neonatal pulmonary hypertension to PPH to ARDS. Thus basic research into lung biology has led to a novel therapy with as yet incompletely developed potential.

B. Pharmacotherapy

In addition, advances in traditional pharmacotherapy continue, with improvements in anticoagulation compounds, experimental use of K channel antagonists, new inhibitors of phosphodiesterase, and use of enzyme in-

hibitors and antagonists. This latter class of agents is nicely illustrated by the compounds utilized to influence the biology of the products of the lipoxygenation of arachidonic acid. Metabolism of arachidonic acid by 5-lipoxygenase enzyme leads to a class of compounds known as leukotrienes, which were identified as the substances comprising slow-reacting substances of anaphylaxis. It soon was determined that leukotrienes had a number of biologic properties important in many diseases, including asthma. Development of inhibitors of leukotriene receptors and the enzyme responsible for production of leukotrienes has provided clinicians with a new class of therapeutic agents for asthma.

C. Optics and Imaging

Technologic advances in optics and imaging have provided better surgical techniques and improved radiologic diagnostics. Video-assisted thoracic operations can be less morbid and provide better diagnostic material. The laser is used for excision of diseased lung tissue, as well as being potentially useful for treatment of intravascular problems. Positron-emission tomography has promise as a means of distinguishing benign from cancerous lung nodules.

D. AIDS Vaccine

The lungs are frequently involved in infectious and immune mediated disorders; advances in immunology have allowed new immunologic-based therapies to be developed. Considerable progress has been made toward the development of a vaccine for AIDS. Attempts are being made in man to decrease the morbidity of allergic diseases such as asthma and hay fever by eliminating the antibody immunoglobulin E (IgE), responsible for initiation of allergic responses. These approaches have included the administration of humanized antibodies to IgE and vaccination against IgE. Many trials are under way to test the efficacy of manipulation of the cytokine cascade, which almost certainly contributes to the multi-organ failure associated with sepsis syndrome.

E. Genetic Therapy

Nowhere has the excitement been greater than in the area of genetic therapies. The biologic revolution in molecular biology has transformed diagnostics and therapeutics of lung disease. The polymerase chain reaction is now in use for the rapid diagnosis of tuberculosis and other infectious diseases. Searches for the genetic causes of lung disease have uncovered the defects in such diseases as cystic fibrosis and alpha-antitrypsin deficiency, and ongoing research is progressing towards elucidation of the genes responsible for diseases such as asthma. Human trials of gene therapy are under way, in which the defect in cystic fibrosis or alpha-antitrypsin deficiency is overcome by delivery of the functioning gene to patients. Not only is the cure of such genetic diseases on the horizon, but considerable effort is under way to broaden the application of gene therapy to acquired lung diseases such as ARDS or asthma. The potential for targeted, triggered, and transient expression of a gene is apparent, and efforts to overcome the technical problems are under way. In theory, it is possible to deliver a gene coding for a beneficial product, which would be expressed only in a particular cell type and only under defined conditions (sepsis for example).

The potential for dramatic improvement in human

lung health is manifold but will require persistent effort to become tangible. Continued research in basic biology up through clinical trials is needed to allow continued benefit from past progress.

SUMMARY

This paper represents the conceptual input of 12 assemblies of the American Thoracic Society and the Scientific Advisory Council of the American Lung Association and the American Thoracic Society to define areas of research that are deemed of special significance to advance the mission of preventing lung disease and improving lung health.

The report is presented in four sections. The first, **MECHANISMS OF DISEASES**, is a predictive perspective focused on cellular and subcellular mechanisms that may predispose or are the cause of cellular and organ dysfunction. Noteworthy in this section are the broad array of mechanisms deemed worthy of further investigation. Many of these mechanisms were not mentioned in the previous document, "Future Directions of Research in Diseases of the Lung," published in 1995, which attests to the accelerated pace of new knowledge in this field. These are areas of investigation in which preliminary studies point to conceptual advances that may be applicable to not only lung disease but also to pathophysiologic mechanisms that can affect many cell or organ systems beyond the lung. Elucidation of such mechanisms therefore has the potential of clarifying cellular dysfunction through understanding of subcellular mechanisms that explore the fundamental mechanisms of disease and therefore have the prospect of not only resulting in major advances in understanding disease, but in devising therapy. Examples of such areas include apoptosis, antioxidants, immune responses, the functions of nitric oxide and genetic determinants of disease.

Increased understanding of these mechanisms of disease at a fundamental level can benefit all of biological science and provide an opportunity for the discovery of new knowledge, which sets the stage for new discoveries for decades to come. It is also to be noted that the areas of study selected are frequently only starting points that will expand, overlap, and interact with other biologic processes, which leads to an exponential growth in new knowledge.

In the second section, **DISEASES**, certain disease entities have been selected for discussion in which questions have been defined that can guide disease-oriented research. For example, for asthma there are still many questions related to environmental triggers, the nature of the defects in airway biology, and the need for new mechanisms of control. For lung cancer, it is clear that the thrust is on an effective screening test for early detection, to improve on what is a poor rate of success of therapy. Research into specific disease entities offers the opportunity to translate information derived from the study of basic mechanisms of disease to the clinical manifesta-

tions of disease and the search for new methods of prevention and therapy.

The third section of the report is **SPECIAL APPROACHES TO CLINICAL RESEARCH**. This section emphasizes the special expertise required for successful clinical research. Research on patients with various disease entities is, and will continue to be, a major need for significant development of new methods of diagnosis and therapy. Clinical research requires a highly disciplined approach to the questions being asked, and this section defines some of those methods of study that require additional development to improve the effectiveness of clinical investigation to answer specific questions in the year to come. As mentioned, improved methods for evaluating clinical outcomes, along with broader application of epidemiologic concepts and patient education as an important therapeutic modality, are examples where significant progress can be made.

The fourth section, **CUTTING-EDGE THERAPIES**, identifies certain areas of study that have reached a sufficient stage of development in which additional resources and added research emphasis can result in real clinical gains in treating disease. The definition of the potential therapeutic role of nitric oxide in various disease settings, along with the development of therapies aimed at correcting genetic defects and a vaccine to prevent the development of AIDS, would have enormous impacts on medical care in the future in all of medical science.

The areas of research selected for inclusion in this document represent the best guesses from a number of individuals in research as to where resources should be expanded and expended to achieve the most effective return in the discovery of new knowledge and its application to lung disease. Hopefully, the fields of study mentioned are still sufficiently broad to leave much leeway for the unexpected and the unpredicted in the process of discovery by individual investigators using their own insights, which, as we have learned by experience, very much underlies the process of progress in medical science.

This report was prepared by the Scientific Advisory Council of the American Lung Association/American Thoracic Society. Members of the Scientific Advisory Council were

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