antigen challenge. In the final analysis, the role of mediators
in everyday asthma is the crucial information required, but
studying their role in bronchial hyperreactivity and antigen
challenge is easier and may shed light on the relationship of
induced bronchoconstriction to asthma.

Giving mediator antagonists at different times before and
after antigen challenge will help to determine the timing of
events following inhalation of antigen. The response to
antigen challenge, particularly the late response, is thought
to be a good model of asthma. However, the effectiveness of
drugs currently used to treat asthma does not correlate
particularly well with their effectiveness in inhibiting antigen
challenge.

Experience with the numerous oral anti-allergic drugs
investigated over the last 20 years has shown that undue
emphasis on animal studies and, in some instances, on
antigen challenge in man, has often led to high expectations
which were not realized when more clinically relevant
studies were carried out in asthmatic patients.

**Relationship of Treatment to Bronchodilatation and Bronchial
Hyperreactivity**

It has been claimed that certain drugs are useful for asthma
because they reduce bronchial reactivity or that drugs should
be given in doses which will maintain a reduction in bron­
chial reactivity. Some drugs such as the calcium antagonists
reduce bronchial reactivity without causing bronchodilatation
while others such as atropine appear to cause bronchiodi­
lation with little or no change in reactivity. Bet­
agonists appear to do both and there would seem at present to
be no a priori way of knowing whether the benefit perceived
by the patient is mainly due to the bronchodilatation or to the
reduction in bronchial reactivity. It has also been claimed
that changes in airway caliber may cause an apparent change
in bronchial reactivity when measured by conventional tests,
due to the change in airway size and not to any intrinsic
change in airway responsiveness.

Drugs such as the calcium antagonists which reduce
bronchial hyperreactivity without causing bronchodilatation
have not been found to be of benefit in patients with asthma
and are not recommended as treatment. Drugs such as
atropine and ipratropium which cause little or no change in
bronchial reactivity are used in clinical practice. These
studies raise several important questions.

- What is the relationship between change in airway caliber
  and change in bronchial reactivity with the different drugs
  used to treat asthma? Is there a difference between beta­
  agonists and antimuscarinic drugs, for example?
- If there is a difference, does the patient benefit from the
  change in reactivity and, if so, why are calcium antagonists
  not helpful in asthma?
- If bronchoconstriction in asthma is due to repetitive
  bombardment of hyperreactive Airways by different stimuli,
  why don't drugs which reduce hyperreactivity cause bron­
  chodilatation in the long run, since they are presumably
  reducing the bronchoconstrictor responsiveness to these
  stimuli?

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**Research Needs: Unresolved Questions About the Etiology of
Asthma**

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It is difficult to address the needs for future research into
the causes of asthma without stepping back a bit to examine
how our perceptions of this syndrome have changed over
recent decades. Perhaps a convenient place to begin is
in the latter part of the 1950s when I was a medical student
who was just beginning to learn about clinical medicine.
A standard and well-respected textbook of medicine contained
two pages (out of a total of 1,775) on asthma with a portion of
those two pages devoted to allergic rhinitis. These two pages
were found within a chapter dealing with allergic diseases.
There was a brief description of histopathology. There was no
pathophysiologic description and no mention of mediators,
nerval mechanisms or increased airway responsiveness.
Functional assessment of the patient was not even men­
tioned. The therapeutic portion began with desensitization,
and pharmacotherapeutics were limited to subcutaneous
epinephrine, intravenous aminophylline, glucocorticoster­
oids, sedatives (which were recommended) and a suggestion
that, with regard to opiates, meperidine should be used
instead of morphine.

The most recent edition of that same text contained eight
pages (out of a total of 2,212) comprising a chapter devoted
solely to asthma. Not only was there a greater than 400
percent increase in the space allotted to asthma (as con­
trasted with an overall page increase of 28 percent for the
whole text), the chapter was richly filled with prevalence and
incidence data, pathophysiology, pathobiology and histo­
pathology and contained a sophisticated discussion of medi­
ators (much of which will need to be modified and extended
in the next edition) along with major and logical insights into
the pharmacotherapeutics of this syndrome. Other re­
spected textbooks of internal medicine have shown similar
trends. Thus, even from a general and standard text of
medicine, it was obvious that over the period of a quarter
century, major advances had been made in the understand­
ing and management of asthma.

The advances came from many sources. Of extreme
importance was the recognition that active communication
among persons from diverse disciplines was a requisite for
the current degree of synthesis and application. Future directions of research will, if they are to be productive and ultimately applicable, continue to require active dialogue and collaboration among cell biologists, geneticists, biochemists, pathologists, pharmacologists, immunologists, epidemiologists, pulmonary physicians and allergists. It is clear that progress will continue to come in the form of multiple fragments that relate simple or complex stimuli to single or multiple responses using systems ranging from in vitro cultures of a single cell type (human or subhuman) all the way to persons actually suffering from asthma. Controversies both at the observational and interpretational levels will continue to arise, even when the simplest systems are being used.

The title of this workshop implies that we are discussing a single disease with an etiology that can be defined. I doubt that this is the true state of affairs. If we view asthma as a syndrome whose essential characteristic is increased responsiveness of airways, whereas a preexisting characteristic or an inducible state, we have a point for beginning the next quarter century. We now suspect that this degree of airway responsiveness is a normally distributed attribute among the human population, that the degree of responsiveness can change within the population in response to infections and to pollution in the macro- and microenvironments, and that multiple factors come into play to determine this attribute and its change. We know very little about those who have increased responsiveness but do not have the clinical syndrome of asthma. We suspect that a complex interplay of neural, cellular and hormonal mechanisms plus chemical mediators and smooth muscle characteristics will be involved in producing the syndrome of asthma.

Significant progress has been made in recognizing and defining the similarities among asthmatic subjects in terms of the nonspecificity of increased airway responsiveness. I suspect that we will continue to learn from studying and understanding such similarities. However, it is my guess that we will soon begin a new era and will further learn from the dissimilarities among asthmatic subjects. These dissimilarities may well be related to different degrees and kinds of neural influences, quantitative and qualitative aspects of chemical mediators and hormones, numbers and kinds of cells called into play and, possibly, quantitative and qualitative aspects of smooth muscle as well as its distribution within the tracheobronchial tree. If the dissimilarities are distinct and important, we may now have, and if not we will surely develop, specific treatments for any given subpopulation of asthmatic subjects.

The following is a partial listing of the questions to which I would like to have answers:

- What is the distribution of responsiveness?
- What stimulus (or stimuli) should be used in acquiring such data?
- What is (are) the best functional tactic(s) to define responsiveness?
- What is the meaning of increased airway responsiveness in terms of past, present and future disease?
- How changeable is the degree of airway responsiveness and what makes it change (micro- or macroenvironmental events, infections, endogenous factors)?
- Are there important genetic or familial factors that determine airway responsiveness and its relationship to clinical disease?
- Does increased responsiveness to a series of stimuli in a given subject mean that each of the responses is mediated through some final common pathway?
- Are the determinants of increased responsiveness morphologic, immunologic, biochemical, neural or some combination that may vary from person to person or group to group?
- Does each asthmatic subject have a particular way he/she responds in terms of magnitude, site and effector mechanisms? If these responses vary depending upon the type and intensity of the stimulus, how do they vary?
- Can we develop more appropriate and reliable indices of the effector mechanisms to more fully explore the similarities and/or dissimilarities among asthmatic subjects?
- What is the mechanistic relationship between an acute response evoked in the laboratory to the spontaneous attack?
- What are the qualitative and/or quantitative similarities/dissimilarities in the inflammatory responses to the same or different stimuli among asthmatic subjects?
- If there are inflammatory cell differences (distribution, cell type, mediator production, cell-to-cell interactions), can they be seen in other organ systems?
- I offer this partial listing with full awareness that some investigators think that they have at least partial answers to some of the questions posed. I am also aware that some partial answers are available from different animal species, yet I am also aware of enormous interspecies variations that prevent these partial answers from being straightforwardly applicable to human beings.

Finally, I wish to emphasize that each of the disciplines to which I have referred will need to play a prominent role if we are to make the coming 25 years as profitable and exciting as the previous ones have been.

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Recommendations for Research in the Epidemiology of Asthma

Peter Burney, M.B.; Roger Detela, M.D.; Millicent Higgins, M.D., E.C.P.; Catherine Peckham, M.D.; Jonathan M. Samet, M.D.; and Ira B. Tager, M.D.

Asthma represents a final common response to a variety of stimuli mediated through several pathologic processes including increased irritability of smooth muscle, mucosal edema and mucous hypersecretion. This reduces the likelihood of finding significant associations between asthma and