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, whether 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 diseases 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.

REFERENCES

Recommendations for Research in the Epidemiology of Asthma

Peter Burney, M.B.; Roger Detels, 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...
any risk factors that are independently associated with each of these pathologic processes. In order to overcome this difficulty, researchers should use greater specificity when describing the dependent variable under investigation. Symptoms and functional changes associated with the condition should be described separately so that they may investigate which of these is associated with the independent variables studied. For example, investigators might describe separately the bronchial reactivity, the frequency and severity of such symptoms as wheeze, cough and breathlessness, as well as the presence of physician-diagnosed asthma, and relate these separately to the risk factors under investigation.

One feature of asthma that may be important for determining the etiology is the very great variation in the reported prevalence of the condition. The interpretation of this variation is currently made very difficult by the major problems in comparing reports of “asthma” made in different cultures. There is a serious requirement for research into the international comparability of questionnaires and of other techniques for determining prevalence. Until such research has been completed, comparative surveys using standardized methods should be confined to studying symptoms and lung function, particularly bronchial reactivity.

Different methods have been described for the measurement of bronchial reactivity and these do not all give identical results. Furthermore, there is still little known of the distribution of bronchial reactivity in the general population and of the relationship between bronchial reactivity and “asthma,” and between bronchial reactivity and symptoms. Further studies are needed to establish the relationships between different measures of reactivity, to determine the distribution of increased reactivity in the population according to age, sex, race, socio-economic status, and geographic factors including urbanization, as well as by those factors known to confer an increased risk of developing asthma. Where available, existing data sets should be used, but otherwise non-hospitalized, non-clinic populations should be used. The relationship between increased reactivity and symptoms should be established during the same surveys.

Simple descriptions of the distribution of physician-diagnosed asthma are no longer justified by themselves and even in developing countries, such studies should be linked to tests of more specific hypotheses. There are now a number of interesting and diverse hypotheses and these might be more efficiently tested in case-control studies. Case-control studies based on prevalence surveys would have the added advantage of obviating some of the major problems of sampling in case-control studies, and would, in addition, provide information on attributable as well as relative risks.

Many different disciplines have contributed to an understanding of the nature and etiology of asthma. These contributions from biochemistry, epidemiology, genetics, immunology and physiology, however, tend to be made separately and this is inefficient. Multidisciplinary teams should therefore be formed to tackle the central questions together. Such collaboration is not easy and early results should not be expected, but the ultimate rewards of such a venture are likely to be great.

There is evidence to suggest several genetically determined risk factors in asthma. However, the nature of most of these and their mode of inheritance remain obscure. Their elucidation will require twin studies, as well as family studies. Because those with a shared genotype also often share a common or similar environment, it is particularly important to take account of likely environmental confounding factors in family studies. The identification of biochemical markers for the defective genotype would be a major advance in this area.

The natural history of asthma is poorly documented. At the inception of the condition it is still not clear whether such associated factors as respiratory tract infections and bronchial hyperreactivity are present before the clinical onset or only become more apparent afterwards. This is an important area to clarify and has major implications for research into the etiology of the disease.

Later in the natural history of the disease it is still unclear how far bronchial hyperreactivity is a risk factor for chronic persistent airflow obstruction, and how far the control of either symptoms or bronchial reactivity may affect the final outcome of the condition.

Studies of the natural history of asthma should be carried out on those at high risk of developing the condition and the use of occupational groups is of particular importance in this context. The prospective study of the long-term effects of different methods of treatment should also be encouraged with careful attention being paid to the long-term effects on lung function and bronchial hyperreactivity.

Research Needs in Regard to Determining the Etiology of Asthma

Benjamin Burrows, M.D., F.C.C.P.

The proceedings of this workshop have pointed out many of the problems in research on “asthma.” As a result of the format of the workshop, considerably greater attention has been paid to problems relating to epidemiologic studies than to those involved in more “basic” types of investigations. Indeed, studies of basic mechanisms have received relatively scant attention, and the enormous strides which have been made in our understanding of these mechanisms may not have received sufficient emphasis. The many mediators which may be involved in bronchoconstriction are finally being characterized; cell-to-cell interactions are being much better defined; the roles of the autonomic nervous system and of newly discovered neurotransmitters are being elucidated; and the rapid advances in cell receptor research are now being applied to models of asthma. Admittedly, there is still much to be learned, and further research in these basic areas is needed to understand the interactions of the many factors which appear to be involved in the bronchospastic response. Only by such studies are we likely to discover the specific underlying defect or defects which lead to the exquisite hyperreactivity of the airways which is the hallmark of classic paroxysmal asthma.

One major omission in the workshop was the lack of

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CHEST / 91 / 6 / JUNE, 1987 / Supplement 1955