The asthma syndrome: inciters, inducers, and host characteristics

A number of prevailing assumptions about asthma would benefit from re-examination. An example is the view that the host abnormality in asthma is hereditary. Others include the concepts that the abnormality is stable and life-long, the measurement of a normal level of non-specific bronchial responsiveness precludes the possibility of asthma in the individual, and asthma is an entity which is separate and distinct from others such as bronchitis, cystic fibrosis, and pertussis. The position which will be developed here is that these assumptions can now be taken as oversimplifications and, as such, at least partially in error.

Numerous new insights into asthma have emerged from observations of responses to experimental inhalation challenges and observations of the effects of environmental exposures particularly in occupational settings. One type of challenge is the experimental allergen inhalation challenge test in allergic asthmatic individuals—this elicits two basic types of responses, the early (immediate) asthmatic response and the late (non-immediate) asthmatic response. Both may occur in the same individual in the so-called dual asthmatic response.1 These responses are mimicked by responses to non-allergic stimuli including airborne chemicals encountered in the workplace. Some theoretical and practical implications of the patterns of responses to various stimuli will be considered here.

Inciters

Early asthmatic responses develop within minutes of the stimulus and disappear in the first hour or so. The antigen-induced early asthmatic response results from the interaction of antigen with IgE antibody and subsequent release of mediators including histamine and SRS-A which appear to mediate the bronchoconstriction.5,9 Short-latency IgG antibody may replace the IgE antibody in some cases.4,5

Early responses also result from inhaled histamine,6 inhaled methacholine,7 inhaled cold air,6 hyperventilation,9 and exercise.10 The latter three stimuli apparently operate through heat exchange and the resultant cooling of airways.11 The early response to these stimuli, like the early response to antigen,12 is not followed by an increase in non-specific bronchial responsiveness.

The mechanisms underlying the occurrence of early asthmatic responses to non-allergic stimuli remain unclear. Direct evidence of mast cell mediator release is unimpressive despite evidence of inhibition by cromoglycate of the early response stimulated, for example, by exercise.13 A major dependence upon irritant receptor-vagal parasympathetic reflexes has been postulated14 but inhibition by atropine and atropine-like drugs is variable and sometimes unimpressive.15 Whatever the pathogenesis, it is abundantly clear that the pre-existing level of non-specific bronchial responsiveness of the host is a major determinant of the occurrence of early asthmatic responses to both non-allergic and allergic stimuli. The intensity of the stimuli required to provoke a 10 or 20% fall in FEV1 varies in a linear fashion with the level of non-specific bronchial responsiveness.16-18 In other words, the effect of the provoking stimulus is dependent largely upon the pre-existing “twitchiness” of the responding bronchi. These stimuli can be considered to incite an effect of the extent permitted by the pre-existing status of the bronchi. The dependence of early responses upon non-specific bronchial responsiveness and the rapid reversibility of these responses suggest that the airflow obstruction is largely a function of reversible smooth muscle contraction.

Inducers

Late asthmatic responses, occurring as a sequel to an early response (dual response) or in isolation, may be initiated by antigen,11 chemically reactive airborne substances such as toluene diisocyanate,20 or by endotoxin.21 The usual technique of allergen inhalation test in allergic asthmatic individuals is to deliver gradual increases in dose of antigen until there is a 20% early fall in FEV1. In such tests, the early responses are followed by late asthmatic responses in about 50% of subjects.19 The clinical importance of the late responses is indicated by the magnitude, which is often considerably greater than that of the

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corresponding early response, and by the longer duration.

Studies of cutaneous allergic responses have demonstrated that late as well as early responses can occur in reactions in which IgE antibody is the only specific immune reactant.12 23 Rarely, as in bird-fancier’s lung, IgG rather than IgE antibody appears to be the immune reactant.24 Nevertheless, the high frequency of late asthmatic responses after early responses in people with IgE-dependent sensitivity with no other apparently relevant immunological findings, suggests a similar relationship to antibody of the IgE class in the airway that pertains in the skin. The mediators of late responses remain unknown but are a subject of intense investigation.25 26 The observations that chemotactic substances including neutrophil chemotactic factor (NCF) and eosinophil chemotactic factor of anaphylaxis (ECF-A) are released in the IgE-dependent reaction have been taken to indicate the possibility that the resulting wave of inflammatory cell infiltration could be responsible for late responses. The possibility that the response is caused by injury produced by liberation of eosinophil granules of major basic protein27 is clinically attractive in view of the close relationship of the eosinophil to naturally occurring asthma but this remains unproven. In the skin, fibrin deposition has been invoked as a basis for the inflammatory swelling of the late response.28 A number of considerations, taken together, including recent understanding of allergic inflammatory mechanisms, the long duration, the relative resistance to bronchodilators contrasted with susceptibility to adrenocortical steroids suggest a major inflammatory component in the pathogenesis of late responses.

Late asthmatic responses to antigen12 and chemically reactive substances,28 as well as responses to virus infection30 and inhaled pollutants such as ozone,31 are associated with the acquisition of increased non-specific bronchial responsiveness. The increase in responsiveness may extend over days, weeks or even months32 and may occur in people with a previously normal level of non-specific bronchial responsiveness. In effect, these various stimuli induce asthma as an acquired condition. The recognition of the induction of asthma in these defined conditions raises a larger question; is asthma generally acquired as a result of exposure to inducers, many as yet unknown?

A varying susceptibility to late responses and to increased airway responsiveness seems to be a host characteristic which is otherwise undefined. The late asthmatic responses which occur as a result of antigen inhalation tests vary widely in magnitude. However, repeated antigen inhalation tests in the same allergic asthmatic individual with the same dose of the same antigen usually leads to late responses of similar magnitude (Frith et al, unpublished data). Only a limited number of individuals exposed to asthma inducers in the same occupational environment seem to be at risk to develop late asthmatic responses to challenges and increased non-specific bronchial responsiveness with the attendant features of asthma. No characteristic(s) of the host in the form of a correlate or determinant of susceptibility to inducers of asthma has been recognised; in particular, it has not been identified as hereditary. One or more intercurrent conditions on an acquired basis such as an unusual intensity or persistence of a viral infection or autoimmune process could be involved. Admittedly, numerous observations suggest a hereditary basis for asthma. Even in a normal non-asthmatic population, there is a range of responsiveness to inhaled histamine (Thomson and Hargrave, unpublished data). Siblings of asthmatic children have Airways which are more labile than those of control children.33 There is some concordance of asthma between identical twins.34 Unfortunately, these observations are obtained from studies which have not been controlled for the possible influence of known inducers of asthma. The most obvious consideration is that allergy is under major hereditary control35 and the allergic reaction is an inducer of non-specific bronchial hyper-responsiveness. The inheritance of allergy together with a normal airway would be expected to lead to a familial clustering of asthma. A relevant reminder here is that an intensive search for genetic markers of asthma such as histocompatibility types has yielded a plethora of conflicting and unconvincing data.36

Chronicity

Anecdotal observations have long suggested that asthma, once acquired from exposure to asthma inducers, can persist after termination of the exposure. For example, firemen with a heavy exposure to spilled toluene diisocyanate on one occasion experienced acute respiratory symptoms which then persisted for many years.37 Single (carefully graded) challenges with asthma inducers in the laboratory may increase responsiveness but it then gradually returns to normal. A recent study has shown that 50% of western red cedar workers who developed asthma during exposure to western red cedar and then changed their occupation continued to have marked increases in non-specific responsiveness at the time of a four-year follow-up (M Chan Yeung, personal communication). The persistence was observed to relate directly to the duration of the occupational exposure after the onset of symptoms.
Definitive proof of the acquisition of asthma in this type of work and the relationship of the duration of exposure and symptoms to chronicity after the exposure ends will require prospective studies in which subjects are well documented before exposure and are compared with suitable non-exposed controls. It is likely that the intensity and duration of exposure of reacting individuals will prove to be determinants of chronicity.

As a separate issue, the development of irreversibility among some asthmatics, particularly with adult onset asthma, remains problematical. The clinical assumption is that this is part of the disease and is not attributable to alternative potential causes of irreversible airway obstruction including emphysema, cigarette smoking, continuing pollutant exposure, or bronchial infections.

Thus, we know little about the processes operative in the host in asthma induction, chronicity, and irreversibility. It’s enough to take your breath away.

Clinical considerations

The increasingly long list of confirmed inducers of asthma can be expected to continue to lengthen. As a practical point, an increase in non-specific responsiveness demonstrated by repeated histamine or methacholine inhalation tests in association with a particular exposure can be considered to confirm that the substance is relevant to the acquisition of asthma in the individual. Avoidance of offending allergens and chemical inducers can be expected, at least in some cases, to result in a restoration of normal non-specific responsiveness.

Scattered findings indicating increased bronchial responsiveness in conditions such as bronchitis,38 cystic fibrosis,49 and recurrent croup40 are in keeping with the theme, now well supported, that a variety of types of injury can have the common effect of an increase in non-specific bronchial responsiveness. Asthma as defined by Scadding41 is not intended to imply a single disease. But the unqualified term “asthma” seems to lend itself to the assumption of a single disease entity. The term asthma has the benefit of a long history of use and should be retained. It refers to a complex situation involving a multiplicity of stimuli, associated conditions, patterns of responses, and probably pathological processes. When the term asthma is used it should be taken to imply the asthma syndrome.

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