

Heterogeneity of Bronchial Asthma

Sub-populations – or Different Stages of the Disease

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The concept of bronchial asthma heterogeneity and sub-grouping is far from new. It can be traced back to the first century of the Christian era (4). The very core of heterogeneity and subdivision of the asthma population is regularly touched upon in scientific papers reporting that certain characteristics under investigation are found in one proportion of the patients under study, but not in others. Clinical aspects of this have been discussed in several papers (6, 9, 11, 17, 21, 38, 44, 46, 48, 54, 58). Laros, using different combinations of clinical and laboratory data (31), classified 36 different sub-groups among patients with chronic lung disorders of different kinds, including several sub-groups of asthma. We may be dealing with a number of diseases and could speak of "the asthmas" in the same fashion as the hematologist speaks of the anemias, to cite Leffert (32).

Taken to its extreme, subdivision of the bronchial asthma population could result in each patient presenting as an individual sub-group of one patient. This should indeed be the optimal goal of the clinician in the diagnostic and therapeutic approach in individual patients. The present discussion is restricted, however, to traits which may be used to characterize large sub-populations with asthma.

In this discussion we will be confronted with several difficulties. We have for instance to consider the lack of evidence regarding which degree given traits are reproducible in the same patient during longer periods of time. We have to distinguish between what can be considered characteristic for different types or sub-sets of bronchial asthma, and what are only different stages of a single pathophysiological process. A given trait may be part of a dynamic process

changing with time. In early childhood the disease may initially be triggered mostly by viral respiratory infections in which no allergy can be demonstrated. A few years later, however, the main disease trigger appears to be inhalant allergies, with infections playing a minor role in the same patients. One or two decades later allergy appears to have lost its role, whereas infections and a general non-specific irritability of the bronchi may dominate the etiology. Also the severity of the disease may vary considerably with time.

In studies spanning short periods of time, this kind of disease dynamics may not present any difficulty, but it must be taken into serious consideration in longitudinal investigations covering several years. Hopefully, this difficulty will be a challenge and stimulate longitudinal studies of well-defined patient sub-populations.

For our purpose, we must mainly rely on information compiled from objective studies. There are, however, only three models which are suited for objective investigations in this respect, namely induction of asthma by inhalation of relevant biochemical agents, bronchial provocation tests with allergens, and physical exercise workload tests (2, 13, 20, 21, 27, 28, 35, 52, 53, 55, 57, 58). Many variables may affect the results of such studies (2, 7, 20). Information about the role of other etiological factors such as infection and emotion, is less direct. Much of it is empirical and partly anecdotal. As such it is less reliable, but nevertheless deserves mention in the present discussion.

Definition

In all its imperfection the following definition of

the disease may hopefully serve its purpose for the present discussion (1, 22):

Bronchial asthma is a disease entity characterized by obstructive dyspnea of varying degree and duration, caused by a widespread and more or less reversible obstruction of the bronchi and bronchioles. It is characterized by a more or less pronounced hypersensitivity of the bronchial tissues to physical, chemical, pharmacological and/or immunological stimuli.

Clinical presentation

Bronchial asthma is a protean disease. It may occur with episodic obstruction for short or long intervals during which lung function is normal, or with chronic obstruction with or without bronchitis. Chronic obstruction in asthma may be clinically obvious or of a silent type that can be detected only with certain lung function tests (12, 18, 25, 26, 34, 60).

The disease ranges in severity from very mild forms to life-threatening and incapacitating tragedies. From a clinical point of view the disease may be categorized with respect to severity by means of quite simple clinical criteria (Table 1). Such classification may be valid for a short time only, since the severity can change quite considerably from one year to another in a number of patients. Acute exacerbations of chronic obstructive type asthma or acute episodic attacks with free intervals in between, may be rare, regular or frequent. Logically, the patients can be allocated to different sub-groups with respect to the clinical presentation as such (Fig. 1). Such sub-grouping may be essential in investigations of, for instance, the prognosis, the presence and influence of emotional disturbances, the correlations between disease and social situation, the effect of various therapeutic measures, etc. Further distinction may be made by means of various methods in lung physiology (60).

Asthma starting in early childhood initially presents itself in most cases as a rather moderate disease, corresponding to degree I or II in the clinical sense. Most of these cases remain moderate, and many of the children outgrow their asthma before late puberty. However, some

Table 1

Grading of bronchial asthma with respect to clinical severity

- 1. Less than five episodes per year with less than 7 days duration of symptoms and functional restriction each time, and long symptom-free intervals with apparently normal lung function.*
- 2. Five to 10 episodes per year with less than 7 days duration of symptoms and functional restriction each time, and long symptom-free intervals with apparently normal lung function.*
- 3. More than 10 episodes per year with less than 7 days duration of symptoms and functional restriction each time, and long symptom-free intervals with apparently normal lung function, or more prolonged periods (totalling 12 weeks or more per year) with symptomatic bronchial obstruction or apparently impaired lung function.*
- 4. More than five episodes per year with prolonged obstruction (totalling 6 months or more per year) following most episodes, or chronic symptomatic obstruction with restriction of function. Bronchial asthma in need of institutional treatment and/or continuous use of corticosteroid medication (any route) to classify for grade III or better.*
- 5.** Chronic, incapacitating asthma with severe, acute exacerbations in spite of continuous medication following adequate and safe dosage regimens.

* If the patient has symptoms and signs of more prolonged bronchial obstruction (incl. subclinical obstruction) the next higher grade is given.

* Simple exercise-induced asthma is excluded provided that recovery is complete with rest and/or one single dose of bronchodilator.

* Patients using bronchodilators to prevent or relieve bronchial obstruction belong to the severity grade corresponding to the amount and duration of medication used, and the condition most likely to occur without medication.

** Grade 5 = former grade 4 b (most severe patients in grade).

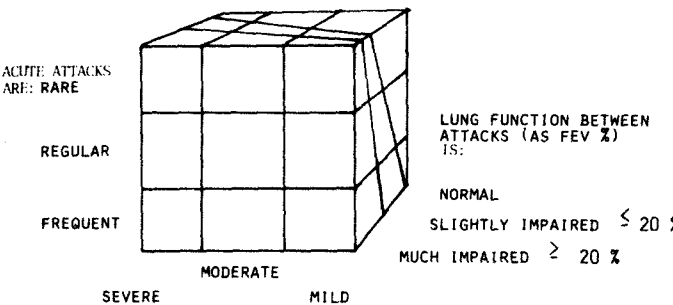


Fig. 1. Sub-grouping of the patients with bronchial asthma with respect to simple clinical parameters and lung function.

cases of childhood asthma follow a more severe course leading to a chronic disabling disease. It is likely that certain risk factors determining this can be identified and taken care of at a quite early stage, be they genetic, immunological, biochemical, environmental, psychological or social characteristics. Thorough broad-spectrum prospective studies are needed to provide information for prognostic differentiation between the different kinds of patients.

Distinction by lung function tests

A number of different lung function tests are available to assist in studies of bronchial asthma, both during spontaneous and experimentally induced bouts of obstruction, and during symptom-free intervals (10, 12, 34, 42, 59, 60). Distinction should be made between patients who demonstrate no obstruction at all in between attacks, and those who constantly have some residual obstruction with or without wheezing. Distinction should also be made between patients with and without residual obstruction located to peripheral airways (10, 18, 26, 34).

Olive & Hyatt have presented evidence of differing sites of airway responses to bronchial provocation tests (BPT), based on different patterns of maximum respiratory flow reduction (42). Similar observations are reported by others (12, 25). It is not here a question of an all-or-none response. Mixed types of obstruction are the most frequent finding, but one or the other type may dominate. The consistency of this in the patients is not sufficiently investigated.

With the use of different adrenergic and anticholinergic substances or blocking agents during pharmacodiagnostic manipulation with analyses of the function of airways, sub-grouping can be achieved also with respect to reversibility of the obstruction (12, 25, 33, 42). Differences in response patterns may, however, be related to the degree of baseline abnormality in pulmonary function, and this must be taken into consideration in this kind of study (20, 33).

A number of more or less sophisticated lung physiology maneuvers are now available for making this distinction (10, 18, 26, 60). They may prove invaluable tools for adequate charac-

terization, for optimization of therapeutic programs and estimation of prognosis. Differences as regards parameters of lung physiology may among others be attributed to the kind of tissues involved (spasm and/or edema), to the site of action of mediator agents and localization of the effects of various drugs. Since smoking, for one thing, affects the reversibility of peripheral airways' involvement in obstructive disease, a distinction between smokers and non-smokers is often mandatory (26).

Pathophysiological reaction patterns

For subdivision with respect to pathophysiology, we have to consider only patients in which distinct patterns dominate the disease and are reproducible from time to time. Otherwise, it may not be a question of heterogeneity, but rather of different stages of progress of the same disease. For example, in early childhood edema and inflammation of the mucous membranes may be particularly important factors contributing to the obstruction of small caliber bronchi. At the same time, the softness of the surrounding tissues predisposes pressures exerted by the expiratory effort to increase the obstruction. The expiratory pressure exerted during forced breathing may compress the particularly soft airways in infants and toddlers more than in young adults (1). On the other hand, closing volumes tend to increase with ageing in adults (60). These phenomena are age-dependent stages in the natural course of the disease.

Lack of data from direct inspection of the pathophysiology in question, leaves us with pharmacodiagnostic maneuvers to differentiate between different kinds of reversible or irreversible pathophysiological phenomena occurring during bronchial asthma. From such studies there appears to be a number of individuals in whom the obstruction tends to be considerably influenced by reversible mucosal edema far beyond early childhood as opposed to those in whom the disease is dominated by spasm of the bronchial muscle. The former may be seen particularly often in allergic asthma as well as in experimental induction of asthma by inhalation

of histamine aerosols. Be it an age-dependent pathophysiological trait or a more long-lasting characteristic trait for a certain subset of patient, this kind of obstruction is not fully relieved by beta₂-adrenergic medication. It is better helped by more broadly acting adrenergic stimulation. Furthermore, when reversible mucosal edema to a large part is triggered by histamine (inhaled or locally released), this subset of patients is more likely to be helped by prophylactic use of antihistamines than patients in whom the obstruction is dominated by muscular spasms.

Exercise-induced asthma (EIA)

Acute bronchial obstruction may be provoked in a large number of patients following strenuous physical exercise. True EIA occurs also when the lung function is normal at the commencement of physical work. Following 5–6 min exercise with a sub-maximal workload, there is a significant increase in resistance to air flow in 60–80% of patients with asthma (16, 21, 37). In another subset of patients (20–40%), EIA is not found following routine procedure. If the workload is increased, obstruction may follow physical exertion even in some of the latter patients, but a distinction can easily be made between responders with high, medium, and low or no EIA-reactivity.

True EIA is thought to be due to release of some unidentified mediator, or possibly due to some faulty metabolism induced by exercise. The biochemical mechanisms are unknown. Transmucosal heat loss has also been implicated (16, 21). In a number of individuals, clinical asthma may be provoked by exercise irrespective of EIA biochemistry, but simply due to increased demands on ventilation when there is already some bronchial obstruction. This results in increase of hyperinflation and more prominent asthma. Combinations of both mechanisms may be found in some patients.

Disodium cromoglycate is effective in preventing true EIA in many – but not all – patients, but has no effect on the obstruction due to exercise hyperinflation. The latter is better helped by bronchodilators, and some patients need both types of premedication to tolerate exercise.

It has been shown that true EIA may also be prevented to some extent by the inhalation of beta₂-adrenergic aerosols as well as by use of theophylline in adequate doses (21). It has also been stated that EIA may be inhibited in a proportion of the patients by means of local anesthesia of the oropharyngeal tissues and by atropine-like drugs (37). There is a wide variation in degree to which the obstruction is inhibited by the various types of drugs. Therapeutic or prophylactic effect occurring in some patients and not in others suggests that there may be different subsets of patients even within the EIA responder sub-population.

Biochemistry

Bronchial asthma appears above all to be a biochemical disease with imbalance of regulatory mechanisms for bronchial tone and hyper-reactivity of bronchial tissues, be it inborn or acquired. Demonstration of hyperreactivity of the bronchial tissues is almost obligatory for the diagnosis of bronchial asthma (1, 3, 7, 27, 40, 50, 58). Hyperreactivity is demonstrated not only to histamine and acetylcholine, but to other biochemical agents as well, including bradykinin, SRS-A and prostaglandin F₂-alpha (1, 35, 55, 58). By means of bronchial provocation testing, differentiation can be made with respect to the degree of sensitivity to these trigger agents. A subdivision may, for instance, be made between patients with high, medium, low or normal bronchial sensitivity to various mediator agents such as histamine and acetylcholine (Fig. 2), provided that exact definitions are given and the methods used are sufficiently reproducible and standardized (2, 20).

In the discussion of this particular aspect, many questions are raised as to methodology. To what extent is the reactivity to different trigger stimuli reproducible? To solve this problem more longitudinal studies are called for. The available information indicates that the reactivity to histamine and acetylcholine is rather unchanged, at least for some time, in the majority of patients (2, 27, 28, 52, 57, 58). As reported by Spector & Farr (54), however, the results may be less reproducible in some patients, particularly

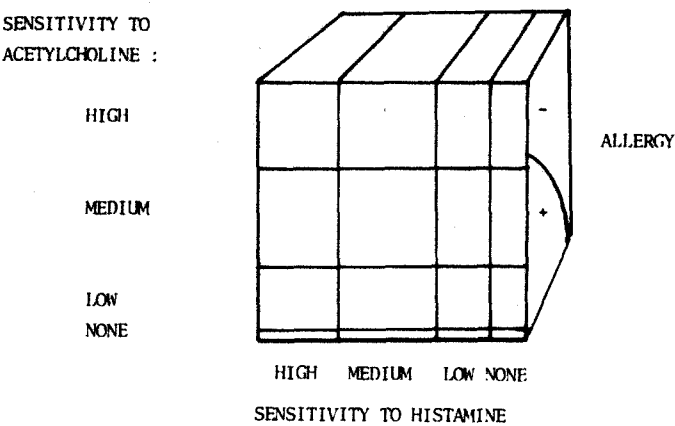


Fig. 2. Sub-grouping of the patient population with bronchial asthma with respect to presence (+) or absence (-) of allergy, and to degree of bronchial sensitivity to acetylcholine and histamine.

regarding histamine. However, this may only be a matter of methodology, since other investigators report a very high degree of reproducibility of bronchial challenges also to histamine (2, 28). The degree of reproducibility has to be assessed in all instances in this kind of study. Maybe there is a call for subdivision of the patients with respect to stability of the bronchi as demonstrated by means of the degree of reproducibility of the reactivity to the agents in question? Care must be taken that reproducibility studies are not carried out during viral infections or acute allergic exacerbations of the bronchial disease, since such phenomena may enhance the bronchial hyperirritability to non-specific triggers.

It is possible to demonstrate a marked disparity in response between different trigger stimuli, be it between histamine and metacholine/acetylcholine (26, 28, 53), or between histamine and prostaglandin F₂-alpha (35, 55). Histamine may act directly on the smooth muscles in the bronchi as well as be a trigger for parasympathetic irritant receptors in the bronchi. Within the asthma population some individuals may therefore be found demonstrating a low or almost normal reactivity to acetylcholine, but high reactivity to histamine and vice versa. In other patients the reactivity to histamine and acetylcholine parallel each other.

Failure to study the appropriate subset of patients may be one of the reasons for the conflicting results reported, for instance, in trials concerning asthma of antihistaminic agents, keto-

tifen, atropine-like agents and so on. If a heterogeneous group of individuals with asthma is investigated with respect to therapeutic effects of, for instance, antihistamines as compared with placebo, the conclusion is likely to be that the effect of the antihistamines is not significantly better than that of placebo. However, if a selection of patients with low acetylcholine but high histamine reactivity is investigated, antihistamines may be found to be highly effective (41). When histamine acts mainly as an irritant trigger of parasympathetic receptors, atropine may prevent or block the reactions to histamine, also when this is released following a local allergic reaction.

Some patients appear to have responses mainly in large airways, and others mainly in small airways although some obstruction is located to other regions. According to Drazen (19) slow-reacting substance seems to have its main action in peripheral airways. Prostaglandin F₂-alpha acts mostly on both the central and peripheral airways in the early stage, but in the latest stage of action mostly in the central and upper airways. The sites of action of histamine and bradykinin are found both in the central and peripheral airways. Atropine could modify to some extent the effects of histamine and bradykinin, while the changes resulting from prostaglandin F₂-alpha and from slow-reacting substance were essentially uninfluenced by atropine. Similar effects of prostaglandin and slow-reacting substance are likely to occur (43). Sub-population differences with respect to reactivity to biochemical mediators may in part be due to differences in mediator availability, in mediator release and the metabolism of mediators in question (1, 3, 5). This is probably influenced by differences in enzyme activities in the sub-populations in question. The importance of enzyme activities is well illustrated by the sub-population suffering from aspirin-induced asthma. These patients most often belong to the so-called non-allergic or "intrinsic" asthma subset.

Acetylsalicylic acid regularly provokes severe asthma in this type of patients. There is evidence that acetylsalicylic acid exerts its effect by interference with the the prostaglandin metabo-

lism due to some deficiency of a prostaglandin inhibitor enzyme.

Szczeklik and coworkers investigated bronchial reactivity to prostaglandins F₂-α, E₂ and histamine, in 55 patients with asthma (55). The patients were divided into two distinct sub-groups. Twenty-seven of them were sensitive to acetylsalicylic acid, and 28 were not. The authors sub-grouped the latter group into so-called atopic (13), infectious (9), and "mixed" (6).

Patients belonging to the atopic group were characterized by vivid reactions both to histamine and prostaglandin F₂-α. In the infectious group significantly higher doses of both histamine and the prostaglandin F₂-α were necessary to induce bronchial constriction. Aspirin-sensitive patients had low thresholds to histamine and were comparable to the atopic group in this respect, but showed high thresholds to prostaglandin F₂-α and were comparable to the infectious group in this respect. Inhalation of prostaglandin E induced much better improvement in the aspirin-sensitive group than in the atopic group or in non-atopic non-aspirin-sensitive controls. This paper demonstrates the value of investigations carried out in well-defined sub-populations rather than in a heterogeneous group of patients. One would have liked to know, however, the repeatability of the threshold dose/responses in the patients in question.

The value of this kind of differentiation into reactivity groups depends on the reliability, precision and reproducibility of the methods used. The bronchial provocation test is considered a very useful tool for this purpose, but must, at its best, be considered only a semi-quantitative test method (2, 20, 52). If the procedures are not sufficiently standardized within the laboratory in question, sub-grouping is not reliable. As long as such tests are not standardized between different laboratories, it is difficult to compare results obtained in different departments (20). Exclusive use of the most distinctive patient sub-groups may minimize this problem, however. Provided that the threshold doses of the agents used and the criteria for the activity as defined are comparable, use of two diametrically oppo-

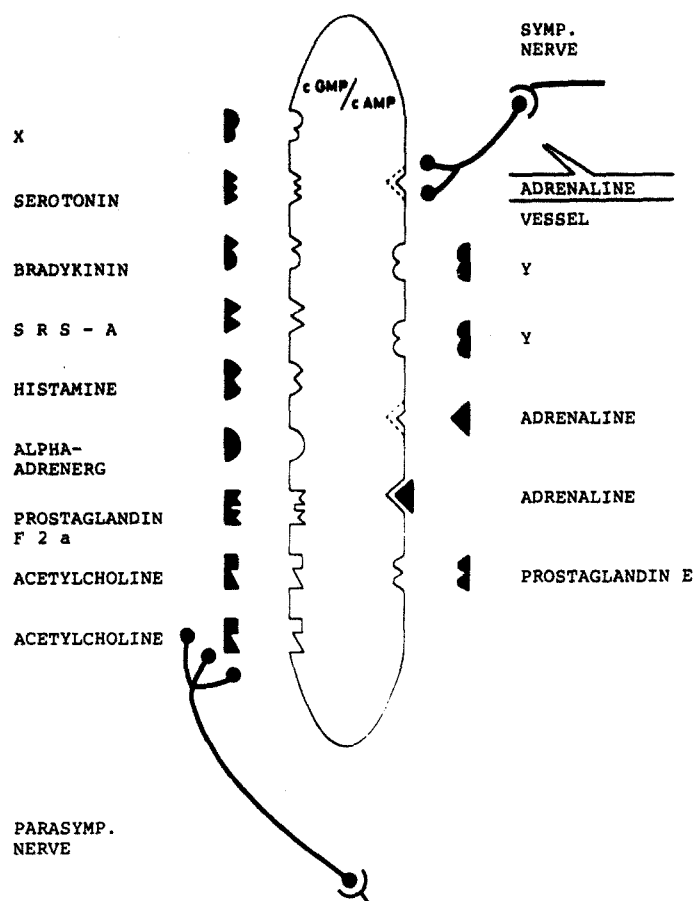


Fig. 3. Schematic illustration of a bronchial smooth muscle cell with mediator agents and specific mediator receptors of importance for regulation of muscle tone. X and Y represent possible unknown mediators or regulator agents.

site sub-groups such as the highly reactive and the non-reactive one within a certain system, probably gives principally comparable results for different departments.

The main effector cells for bronchial hyper-reactivity are the smooth muscle cells surrounding the bronchi and, to some extent, those in the small vessels in the mucosa and sub-mucosa of the lower respiratory passages.

There are many active biochemical mediators acting on this cell, and several specific receptors in the smooth muscle respond specifically to each of the many biochemical agents in question (Fig. 3). This represents the key to the understanding of bronchial asthma. The basic biochemical defect is still an enigma. Abnormal contractile behavior of the smooth muscle may be the result of abnormal mediator stimuli, defective handling of normal mediator stimuli, or combinations of both.

Szentivanyi (56) formulated a concept that ascribed bronchial hyperreactivity to an inherited or acquired partial beta-adrenergic receptor

blockade. Indeed, a malfunction somewhere in the biochemical pathway from the point of beta-adrenergic or similar stimulation to the metabolism of intracellular AMP can explain many prominent features of bronchial asthma in a number of patients, but not in all. Other reasons for hyperirritability have been sought in vagal imbalance (50). What is true for one subset of patients may be irrelevant for another.

One possibility which has not yet been sufficiently investigated is that the asthmatic diathesis may involve deficient interactions between unknown regulatory trigger substances and smooth muscle receptors for this kind of trigger, possibly along two or more different lines for different subsets of patients. In one subset of patients the main mechanism of bronchial asthma might then be due to insufficient beta-adrenergic stimulation, and in another subset, an excess of agents with the opposite (contractile) effects might be most important.

Let us think along the line of the latter hypothesis. Provide that there exists a yet undefined regulator agent (X) that increases the bronchial muscle tone (3, 7, Fig. 3). The effector cell would then have a number of receptors (Rx) for that agent in addition to receptors for other contractile agonists (1, 3). The number of Rx receptors would be limited to a given number. It is likely that in the normal individual or in the symptom-free asthmatic patient a physiologic tone would be maintained by means of balancing dilator agents (A) such as beta-adrenergic agonists, non-adrenergic inhibitor agents (51), and some prostaglandins (43). The number of receptors for the dilators would be limited (nA). A physiologic balance is possible to maintain as long as stimulated Rx is lower in number or equal to (nA) provided that the affinity properties and dynamics of both types of receptors are qualitatively comparable. With a higher production of the regulator agent (X) molecules, the smooth muscle effector cells would react with non-opposed contraction. As long as the number of X molecules is lower than the number of corresponding receptors, most of it may, however, be bound to the receptors in question. With still higher concentrations of X one may anticipate that excesses of unbound X might be found in

the circulation and – possibly – in the urine. This possibility is now under investigation (11).

Without due consideration of the possible existence of sub-populations with distinct differences, also as regards basic mechanisms of the disease, important findings may be overlooked as statistically insignificant.

Anatomy

The morbid anatomy of bronchial asthma cannot be explained only by short reversible mediator actions on the smooth muscles; these must be due to more prolonged inflammatory alterations of the tissues. Among the most important anatomical components involved are smooth muscle cells, the small vessels, the epithelium with tight epithelial junctions, glands, the nervus vagus as opposed to adrenergic and non-adrenergic inhibitor elements, clusters of mast cells beneath the tight epithelial junctions, and a number of viable mast cells in the bronchial lumen. Most or all of the tissue changes seen in asthma can be explained from the biochemistry of mediator agents released from tissue mast cells in the bronchi (5); although these cells may play a minor role in many instances of asthma.

Experimental studies in monkeys and dogs have shown that mast cells can be superficially located or found in the lumen. Hogg and coworkers (23) studied the distribution of mast cells in the lungs of five monkeys. They found mast cells near the surface and also in the epithelium in all of the specimens. The number present in the lumen and epithelium varied from about 0.1% in one individual to 13% in another of the total mast cells present in the five animals studied.

Individual variability in the number of superficial mast cells may be important in determining which individual responds to inhaled allergens, also in the human species. An initial release of mediators from mast cells in the lumen are likely to open up the epithelial tight junctions and allow additional allergenic molecules or irritants to reach the larger number of submucosal clusters of sensitized mast cells, which then may release high concentrations of media-

tors close to the reactive effector cells as well as to irritant receptors.

Unknown characteristic properties of bronchial mast cells, tight junctions, irritant receptors, or other anatomical elements, may be decisive as to bronchial reactivity and type and degree of the disease in asthma.

Immunological aspects

One of the very first efforts to subdivide asthma was based on the demonstration of allergy or not in the patient. With allergy present, the type of asthma was denoted as extrinsic. With no demonstrable allergy, it was labelled as intrinsic or infectious asthma (48).

A demonstration of the presence of allergy by means of skin tests, nasal challenge tests, or the demonstration of specific serum IgE antibodies, does not, however, mean that allergy is important for the bronchial disease. This type of analysis and a thorough history may only distinguish between atopic versus non-atopic individuals.

In many atopic patients with asthma, allergy may play no or only a minor role in the bronchial disease, even if present with high concentrations of circulating IgE antibodies and/or prominent skin test reactivity to inhalant allergens. The latter may, for instance, be important only for allergic rhinitis or atopic eczema concomitant with asthma in the patient. "Intrinsic" components in the form of non-specific bronchial hyperreactivity, precipitation of obstruction by infection, exercise and other triggers may dominate the disease in atopic as well as in non-atopic patients.

Demonstration of the presence of allergy is also a matter of diagnostic activity and capacity as well as a matter of the age and immunological maturity of the patient. In children with bronchial asthma, 90% may be shown to have some or other allergy as compared with only 30–50% in adults (1, 2). It is, however, the threshold reactivity of the bronchi, as combined with the type and degree of exposure, which determines the importance of various allergies for the asthmatic disease. With respect to allergy, subdivision ought to be attempted between those in

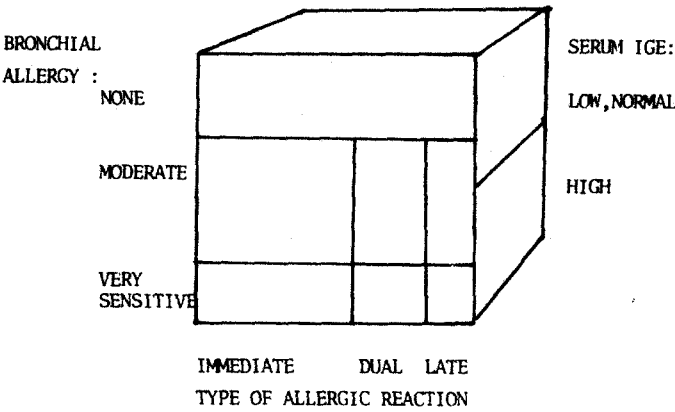


Fig. 4. Subdivision of a pediatric bronchial asthma population with respect to concentration of serum IgE, presence or absence of bronchial allergy, and the type of allergic reaction in the bronchi.

whom allergy is a dominant asthma trigger, those with allergy of little or no importance, and those in whom no allergy can be demonstrated whatsoever (Fig. 4). It is possible to point out many patients in whom bronchial asthma is provoked only by the inhalation of allergens and of seemingly nothing else. Well-known examples are young patients who experience asthma only during the pollen or mould seasons or on exposure to, e.g. certain animals. They may have low or normal reactivity to histamine and acetylcholine, but a marked immunological hypersensitivity in the bronchi. It is also possible to point out patients in whom allergy plays no role at all.

Between these extremes there are many individuals suffering from both forms, i.e. from immunological hypersensitivity and non-immunological or biochemical hyperreactivity combined. In general, the allergic and the non-specific bronchial reactivity are interrelated in the production of allergen-induced asthma (1, 14, 15, 29, 40, 57). Asthmatic individuals may therefore be plotted within a distribution diagram with immunological hypersensitivity along the one axis and biochemical or non-specific hyperirritability along the other.

This means that two subjects could present equally severe bronchial obstruction following allergen challenge by two different mechanisms. One could react most severely in the immunological (allergic) sense with local release of high concentrations of broncho-constrictive mediators. The other could release small amounts of mediators but react excessively due

to non-specific hyperirritability of the tissues (2, 15). With irritants present in the extract used in BPT this kind of patient is even likely to react with broncho-constriction without any local allergic reaction whatsoever. In the former individual, effective anti-allergic treatment would probably have significant effects on the bronchial disease, but not in the latter. The true role of allergy in the individual asthma case can usually be established only by making use of diagnostic bronchial provocation testing. In bronchial provocation testing one can also distinguish between different reaction types (Fig. 4) (2, 13, 29, 44, 52).

There is the one type with immediate reactions and the one with slowly developing obstruction. Some may have a dual response (2, 13, 44). There are those with pure spasmodic reactions to allergen challenge and those with apparent edematous reactions as well. There are the reactions which are fully reverted by beta₂-adrenergic medication and those which are not. You may find those with easily reversible reaction of short duration and those with prolonged ones which need full medication for several days afterwards. Some of these reactions may be mediated by IgE (2, 17), and this is probably so in the majority of instances of allergen-precipitated bronchial asthma. Brostoff and coworkers suggest that some late reactions may be caused by IgE-immunocomplexes with antigen (8). In a smaller subset of patients reaginic antibodies of the IgE STS class may also play a role (9).

Late obstructive reactions may also be associated with signs and symptoms thought to be characteristic of an immunological type III reaction, such as fever and leucocytosis (44). The differences in reaction pattern following BPT with allergens may also be due to differences in the potency of allergen extracts used, and due to differences in challenge procedures, or they may be caused by differences in the availability of various biochemical mediators as well as in the physiological state and degree of reactivity of various receptors in the particular tissues (2). Some late obstructive reactions following BPT may even be due to the portion of the inhaled allergen extract-aerosol that has been swallowed by the patient (39).

Anyhow, from the data presented it seems possible to distinguish sub-populations of asthmatic subjects which have different reaction patterns after allergen exposure. If so, the prophylactic and therapeutic effects of drugs used for allergic asthma should be evaluated in the appropriate sub-populations and not in heterogeneous groups of patients with bronchial asthma of any type.

Psychological aspects

The importance different psychological personality patterns have concerning asthma has been discussed in many papers (6, 45, 46, 47). In this discussion a clear distinction has to be made between psychological factors which influence bronchial obstruction, and psychological phenomena which are only coinciding with the disease or result from it without direct influence on lung function. Many papers give an impression of insufficient knowledge about the somatic substrate for psychosomatic mechanisms in asthma, and contain rather naïve and frequently dualistic concepts as to its etiology, such as for example allergy versus emotion. Retrospective studies tend to ignore factors which may have contributed much to the personality of the patient, such as repeated hospitalization and separation from their mother of infants under more or less dramatic circumstances, effects of restrictions as to environment and activities, and so on. To assess the role of psychological factors and emotion as causative elements, information from prospective studies is needed, but is lacking.

The importance for asthma of different psychological personality patterns deserves investigation, also with relation to pharmacological modification of the disease. Even without objective investigations it is likely that the use or abuse of bronchodilators as well as the techniques of inhalation therapy may be influenced by the personality and by the emotional situation of the patient. Even the physician's attitude may play an important role as to this (30).

Distinction should also be made between emotional factors that cause asthma, and neurovegetative reflexes causing asthma more or less inde-

pendent of the emotional state. More should also be learned about pathways of action for emotional factors in asthma. Two main pathways seem likely, one along the way of breathing and the other along neurovegetative imbalance with parasympathetic overdominance. Distinction should be made between the two, if possible.

Emotion may affect the way of breathing. In a probably small subset of patients, hyperventilation following certain psychological events is an obvious pathway to increased obstruction. Less obvious alterations in the pattern of breathing may result in asthma in other individuals. In patients with slight clinical or sub-clinical bronchial obstruction certain ways of breathing may lead to increased alveolar hyperinflation with asthma exacerbations. During intervals with normal lung function, however, the same way of breathing may have no influence on pulmonary function.

Unless psychosomatic mechanisms act through special ways of breathing, one should expect them to have the most pronounced influence in asthmatic individuals with a low tolerance threshold to the neurotransmitter acetylcholine, whereas psychosomatic mechanisms should be less likely to occur in individuals with high tolerance to this mediator (36). Horton and coworkers (24) used metacholine (acetylcholine) challenges with measurement of airway resistance and specific conductance to identify two groups of patients: those who responded to suggestion and those who did not. The patients with a high degree of reactivity to metacholine challenges were also the ones who responded to suggestion and hypnosis. In accordance with this, anticholinergic drugs have been shown to be more effective in patients with psychogenic asthma than in others (49).

Subdivision of asthma patients has also been successful with respect to psychological response patterns. For example, those with a distinct so-called panic-fear reaction pattern predictably had more severe asthma than the others (30). The patient with severe bronchial asthma can hardly be looked on as detached from his environment and life situation. Various environmental and social influences may have more

or less impact on the disease as such, or on the patients ability to cope with the disease (30, 45). Such factors should also be taken into consideration when selecting sub-populations with asthma for inclusion in various research programs.

CONCLUSION

The prerequisite for an effective therapy is that the diagnosis is correct and precise. The diagnostic label of "bronchial asthma" only, may not be a sufficiently precise diagnosis for optimal treatment. It is necessary in many cases to further characterize the patient according to sub-population criteria. Recommendations as to clinical practice and choice of drugs should specify treatment approaches which take due account of the effects to be anticipated in different subsets of patients. There is a risk that the truth may be concealed as a statistically non-significant finding if an investigation is carried out in a heterogeneous patient population suffering from a protean and multifactorial disease such as asthma. A given drug, for example, could be ineffective in the majority of patients although highly effective in one or another distinguishable sub-population.

For investigational purposes one should select as homogeneous subsets of individuals as possible. Too many conclusions have been drawn from studies of undifferentiated patients and too many generalizations have been made from observations made in small subsets of patients. Conclusions have been drawn that may be correct for some sub-groups, but which may be wrong and harmful to patients belonging to other sub-groups. The use of distinct subsets of asthma patients for study and control purposes might reduce this risk of bias.

It is not possible for one single person to possess detailed knowledge and master the necessary technology in all fields of importance for each subset of the population with asthma. This calls for teamwork, particularly when dealing with severely affected patients in clinical practice, and in research.

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