Allergic Asthma in Childhood

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Asthma is defined as a disease of the respiratory passages characterized by dyspnoea of an obstructive type which is predominantly expiratory, reversible at least partially, and of varying severity and duration (Meneely *et al.*, 1962). The anatomical and biochemical basis of the bronchial obstruction has been reviewed by Middleton (1959). In the present review emphasis is put on the allergic aspects of the disease.

Pathogenesis

The three mechanical factors giving rise to obstructive symptoms in asthma are: contraction of the smooth muscle in the bronchi and bronchioles, oedema and folding of the mucosa, and secretion of viscid mucus (Fig. 1). A fourth factor may be a reduced activity of the ciliated epithelium, resulting in stagnation of secretion, with plugging of bronchi and bronchioles by mucus (Naylor, 1962).

Whatever the cause of obstruction of the respiratory passages, auxiliary respiratory muscles have then to be brought into use during expiration. This increased expiratory intrathoracic pressure is transmitted to the respiratory passages, further reducing their lumen (Fig. 1). The effect is increased if the pulmonary alveoli are hyperinflated. This mechanism is particularly common in early childhood where a 'pseudo-asthmatic' picture is so often seen in the course of a respiratory infection involving the non-rigid and narrow airways of the young child (Fry, 1961). Thus in young children wheezing commonly accompanies acute bronchitis, and is apt to be labelled 'asthmatic bronchitis'. Repeated episodes of this kind, however, raise the suspicion that the child may eventually prove to be a truly asthmatic subject (Boesen, 1953; Buffum, 1963; Freeman and Todd, 1962).

Allergy and Bronchial Reactivity

The term allergy in this connexion implies the reagin-allergic immune reaction of the immediate

type (Type I hypersensitivity according to the classification of Gell and Coombs (1963)). Antibody (reagin) is present in the serum, and is fixed to cell surfaces in the sensitized tissues. The mast cells are especially important in this respect. Specifically sensitized mast cells are degranulated by the allergic reaction, and histamine, bradykinin, and other transmitter substances are liberated (Graham *et al.*, 1955; Katz and Cohen, 1941; Keller, 1966; Middleton, 1959). Slow-reacting substance A (SRS-A) is among the substances that are liberated in sensitized lung tissues by allergic reactions, but it is uncertain whether or not it origin-

FIG. 1.—Pathogenetic factors in bronchial obstruction (a) Asthma: (1) spasm of smooth muscle, (2) oedema of mucosa, (3) increased secretion of viscid fluid, and (4) forced expiration to compensate for combination of factors 1, 2, and 3, causing increased external pressure on bronchi and bronchioles.

(b) 'Pseudo-asthma': infection in small children causing inflammatory swelling of mucosa with relatively large reduction of lumen of bronchi. As in true asthma, such bronchial obstruction leads to forced expiration, further increasing obstruction from pressure on the child's soft bronchial walls.

ates from precursors in the mast cells (Brocklehurst, 1962). The liberated transmitter substances then initiate the responses in the patient's organs.

In the bronchial walls there are high concentrations of immune globulins available for possible local antigen/antibody reactions (McCarter and Vazquez, 1966), and sensitized respiratory tissues may contain large amounts of the specific reaginic antibodies (Berdal, 1952). The bronchial tree contains a large number of mast cells, the lungs (in the human) being the tissue with the highest concentration of histamine (Stone, Merrill, and Meneely, 1955). This histamine is chiefly bound to the granules of the mast cells, which in asthma become degranulated (Salvato, 1968). The histamine released is a potent transmitter, which causes (1) contraction of the smooth muscles of the bronchi, (2) increased capillary permeability with oedema of the mucosa, and (3) increased secretion of mucus, i.e. the triad of primary reactions characterizing asthma (Fig. 1 and 2).

FIG. 2.—Reagin allergic reaction leads to liberation of histamine, slow-reacting substance A, and other transmitter substances. Symptoms depend on the effects of these transmitter substances on smooth muscle, blood vessels, secreting glands, etc.

Slow-reacting substance A also acts as a powerful bronchoconstrictor (Fig. 2), leading to a bronchial obstruction which comes on more slowly but lasts longer than that provoked by histamine (Brocklehurst, 1962; Herxheimer and Stresemann, 1963). Acetylcholine may also be liberated as a secondary response to the hypersensitivity reaction (Scheiffarth and Zicha, 1967).

Bronchial Hyperreactivity to Chemical Mediators in Asthma

Inhalation of atomized histamine solution causes slight bronchial constriction in normal individuals, but asthmatics similarly tested display a striking hyperreactivity (Aas, 1965; Curry and Lowell,

1948; Tiffeneau, 1959, 1960). Thus, in symptom-free asthma patients, histamine inhalation leads to bronchial obstruction at much lower dosages than in normal individuals (Curry and Lowell, 1948; Tiffeneau, 1959). Similar hyperreactivity of the bronchi to SRS-A (Brocklehurst, 1962), to bradykinin (Mélou and Lecomte, 1962), and to acetylcholine (Curry and Lowell, 1948; Tiffeneau, 1959) is also found in asthmatics. The degree of hyperreactivity varies considerably from patient to patient (Felarca and Itkin, 1966). Tiffeneau (1959, 1960) has shown that the reactivity of the bronchi to histamine and acetylcholine is further increased by infection in the respiratory passages, by allergic reactions, after inhalation of substances that irritate the respiratory mucosa, and possibly also by certain psychological stimuli.

Innervation and Bronchial Reactivity

The respiratory passages are innervated by the autonomic nervous system which is mainly responsible for the maintenance of normal tonus of the smooth musculature, though humoral factors also play a part (Widdicombe, 1964). Parasympathetic stimulation causes bronchoconstriction, sympathetic stimulation causes bronchodilatation. Balanced secretory activity of the glands is maintained by the same system. Bronchial tonus and secretion are thus regulated from central impulse centres, but impulses by shorter reflex arcs are also of great importance, so that bronchial constriction can be caused by either central or peripheral stimuli. The central stimuli causing bronchoconstriction are hypoxia and hypercapnia, whereas hyperinflation of the alveoli and irritation of the respiratory epithelium act as peripheral stimuli (Widdicombe, 1964). Pulmonary hypoxia as well as mediators of allergic reactions induce raised pulmonary vascular resistance, which further aggravates ventilatory insufficiency (Helander *et al.*, 1962). Severe bronchial obstruction can be brought about by epithelial irritation from inhalation of inert particles, gases, tobacco smoke, or cold air, to mention but a few (Burch and Miller, 1967; Middleton, 1959; Tiffeneau, 1959; Wells, Walker, and Hickler, 1960). Bronchial obstruction can also occur reflexly with coughing, strenuous exertion, etc. (Buston, 1966; Sly *et al.*, 1967; Widdicombe, 1964), providing the basis for many vicious circles in the production of asthma.

It is reasonable to assume that the reactivity of a shock organ, and thus the clinical manifestations of disease, may partly depend on the autonomic 'tension' of the organ at the moment it is stimulated

by pharmacologically active transmitter substances of allergy, inflammatory tissue reactions, etc. Smooth muscle, and the mucous glands in the bronchial tree under parasympathetic control, can probably react quickly and thus cause symptoms after quite small histamine stimuli, those under predominantly sympathetic control requiring larger histamine doses before the adrenergic opposition is overcome (Samter, 1959). If so, it is easy to understand how changes in the state of autonomic 'tension' may affect the clinical condition.

Psychosomatic Aspects

While the severity of asthmatic symptoms depends upon the degree and duration of bronchial obstruction, and the consequential ventilatory insufficiency, the patient's subjective registration of the obstruction and his attitude to the disease are extremely important. All these components interact. The established asthmatic—be he acute or chronic—tends to show a confusing picture of psychosomatic features. The disease is clearly accompanied by emotional disturbances in some children (Baraff and Cunningham, 1965; Saul and Delano, 1963). The emotional disturbance is often non-specific, affecting only the child's general attitude rather than the bronchial obstruction as such. But in other children emotional states may precipitate or aggravate the asthma (Saul and Delano, 1963; Stokvis, 1959), whether by causing bronchoconstriction by direct nervous stimulation, or by changing the pattern of breathing, e.g. by hyperventilating, remains unsettled (Gronemeyer and Fuchs, 1959; Purcell, 1965). The literature abounds in hypotheses about psychological traits as primary causative factors in the development of asthma, but fragmentary observations have too often been used to confirm hypotheses rather than to test their validity (Feingold *et al.*, 1966; Purcell, 1965; Swineford, 1962). There is a need for careful prospective studies, and the patients studied should not be limited to those referred because of emotional disorder.

Much could be learned by comparing asthmatic children in whom emotions are judged important precipitating and aggravating factors, with those in whom emotional factors seem to be of no consequence. In some children, emotions seem to influence the disease during the allergen exposure time of year (summer for pollen allergy, winter for house dust allergy), but not in the allergen-free season. Such patients make an interesting subject for study in this context, as do also experimental animals (Tiffeneau, 1960; Friebe, 1954; Noelpp and Noelpp-Eschenhagen, 1952).

The crucial fact which seems to have been established is that there must first exist a somatic substratum for bronchial hyperreactivity before psychosomatic mechanisms can act (Dekker, Barendregt, and de Vries, 1961; Feingold *et al.*, 1966; Freeman *et al.*, 1964; Friebe, 1954; Noelpp and Noelpp-Eschenhagen, 1952; Peshkin, 1963; Purcell, 1965; Stokvis, 1959).

Two Types of Asthma, Extrinsic and Intrinsic

In clinical practice, a distinction is usually made between *extrinsic asthma*, where the disease is thought to be provoked by reaction to allergens, and *intrinsic asthma*, where no such allergy is demonstrable. Both types exhibit the same essential physiological, clinical, and pathological features (Fagerberg, 1958; Middleton, 1959), though intrinsic asthma predominates in cases starting in adult life (Fagerberg, 1958). Immunological techniques may make it possible to distinguish between the two types; Johansson and co-workers (Johansson and Bennich, 1967; Stanworth *et al.*, 1967) have recently found an immune globulin (IgND) which is present in abnormally high concentration in the serum of patients with allergic asthma. IgND appears to be identical with the reagin-containing immune globulin IgE described by Ishizaka, Ishizaka, and Hornbrook (1966).

Extrinsic Asthma

In *extrinsic asthma*, evidence of familial allergy is found in 40–80% of asthmatic children and to a somewhat lesser extent in adult patients (Kantor and Speer, 1963; Leigh and Marley, 1967; Schnyder, 1960; Schwartz, 1952; Spain and Cooke, 1924).

Why an individual should become allergic to certain allergens and not to others equally potent is not known. Nor is it clear why one organ rather than another should become the reacting organ. Animal experiments and clinical observations indicate that infections and other factors disturbing the local micro-circulation probably play an important role as selecting and conditioning phenomena (Fischel, 1967). The significance of the antigenic environment is obvious. Fish allergy with asthma is common in the fish-eating population of Norway (Aas, 1966); flour asthma is frequent in bakers (Diederichs and Lübbers, 1955). The respiratory passages offer an especially large contact surface with an external allergen-containing environment, and the child will inhale airborne allergens more than 30,000 times each 24 hours. Respiratory tract infections are frequent in childhood. These two factors obviously provide ample

opportunity for sensitization of the respiratory passages.

Children with allergic diseases other than asthma develop asthma more frequently than others (Pasternack, 1965), and similarly children with asthma are more liable to present allergic manifestations also in other organs, either at the same time as the asthma or at other times (Kantor and Speer, 1963). The allergic aetiology of the disease comes out very clearly in a large number of cases where it is provoked exclusively by exposure to certain allergens.

Provocative inhalation tests. While positive reactions to allergy tests in the skin, nasal mucosa, or conjunctival sac are indicative, though not conclusive, of an allergic aetiology of asthma, better evidence is provided by bronchial inhalation tests with specific allergens. In practice, provocative

FIG. 3.—Spirographic records from a child given bronchial provocation tests to two different types of house dust, both of which had elicited +++ reactions on intradermal testing. (A) No bronchial obstruction after inhalation of house dust, extract A 1/20. (B) Bronchial obstruction shown by reduced vital capacity and flattened expiratory curve after inhalation of house dust, extract B 1/200: (1) before inhalation test, (2) 10 minutes after inhalation test, (3) 20 minutes after inhalation test, (4) normal respiration 10 minutes after inhalation of isoprenaline. PEF = peak expiratory flow (l./sec.).

inhalation tests are carried out as follows (Aas, 1966, 1967; Citron, Frankland, and Sinclair, 1958; Colldahl, 1952, 1967; Gronemeyer and Fuchs, 1959; Kim, 1965; Vanselow, 1967). Extracts of suspected allergens and controls are atomized. The patient inhales the aerosolized substances through a face mask or in a controlled environment chamber. Reactions are checked by observation

and auscultation, and preferably also by peak expiratory flow (PEF), vital capacity (VC), and forced expiratory volume in $\frac{1}{2}$ and 1 second ($FEV_{0.5, 1.0}$). The test is initiated with low concentrations of the extract, which is then gradually increased, but not to the point of causing non-specific irritation of the respiratory epithelium (Aas, 1967). For control purposes, the child inhales the pure extraction fluids, and preferably also extracts of allergens known from the history to be tolerated. Tests are performed under single blind conditions after initial training and adjustment to the test situation. The child is tested with only one allergen per day, allowing 24 hours' observation time between tests. Antihistamines or bronchodilating drugs must not be given for 24 hours before testing. Positive reactions are shown by signs and symptoms of bronchial obstruction, reduced PEF, reduced VC, flattened and prolonged expiration curve on the spirogram, and reduction of FEV (Fig. 3). An accompanying allergic rhinitis may occur, and a positive reaction is often followed after a few hours by pulmonary and nasal secretions rich in eosinophils. When the reaction proves positive, antihistamines and bronchodilating agents including isoprenaline inhalation are given immediately and continued for 24 hours or more. This type of investigation has been carried out routinely, along with elimination and provocative diets and other diagnostic measures; with adequate precautions there have been no untoward incidents.

The bronchial inhalation test, though time-consuming, is most satisfactory, for it leaves no doubt as to the significance of the allergen tested. Indeed, there is hardly any other disease in which the precise aetiological diagnosis can be made as convincingly. The typical symptoms of the disease can be provoked and recorded by objective means whenever one desires, under conditions that make strict control possible (Aas, 1966; Citron *et al.*, 1958; Colldahl, 1952, 1967; Fagerberg, 1958; Ripe, 1966; Ryssing, 1959). The selection of allergens for the bronchial inhalation test is based on the history and the results of skin tests. The inhalation test may be positive even if the skin test is negative.

The final aetiological diagnosis is made by combining the results obtained after repeated interviews, skin tests, and controlled exposure and provocative tests.

Correlation between skin test reactions and bronchial reactivity. Much uncertainty and misinterpretation of the aetiology of asthma originate from undue confidence in skin tests, for the skin does not mirror bronchial reactivity.

Skin tests are superficial in both senses of the word, though frequently informative. When used with proper extracts, integrated with the clinical history, and interpreted by an experienced person, they can be most helpful as screening tests. For instance, it is seldom possible to obtain a convincing history of reaction to house dust, moulds, and other common inhalant allergens or food allergens, and it is here that skin testing may provide a short cut to diagnosis. The reliability of skin tests depends on the allergens used, on the way the extracts are produced, standardized, stored, and applied, on the individual skin reactivity, and on how the tests are interpreted (Aas, 1963, 1965, 1966; Friedewald, 1952; Horesh, 1959; Miller, 1965; Sobel, 1962; Wilken-Jensen, 1959). Even under optimal conditions they will leave room for doubt as to the aetiological diagnosis, unless the case history is absolutely convincing, in which case the skin test may be unnecessary.

In 534 children with a history indicative of house dust as a cause of asthma, the skin and bronchial reactivities were compared using the same extract of house dust for both tests (Aas, 1969). An aetiological diagnosis based solely on the history and the skin (intradermal) test would have led to an incorrect aetiological diagnosis judged by bronchial reactivity in some 30–35% (Tables I and II). (The exact result would have depended on how an individual doctor defined a 'positive history' and a 'significant, positive' skin test.)

Similar results were found in 500 children with histories indicating that mould allergy might be causing asthma (Tables II and III).

Bronchial allergy to wool dust was frequently proven, despite negative skin tests in children with a suggestive history. On the other hand, children with a history of pollen allergy gave almost 100% correlation between skin and bronchial reactivity (Aas, 1969; Kim, 1965). The higher the skin sensitivity to an allergen, the larger the percentage of positive results from corresponding bronchial provocation tests (Colldahl, 1952). A +++ skin test* in a child with a suggestive history pointing to that allergen will usually correctly predict positive bronchial allergy as shown by provocative inhalation test (Aas, 1969; Colldahl, 1952; Kim, 1965; Ripe, 1966; Ryssing, 1959), but the skin test may only imply the presence of allergy in the skin itself, or in some organ other than the bronchi. If a three-plus skin

*A +++ reaction to the intracutaneous test is equal to that elicited by the injection of the same volume of a 0.01% histamine solution (Aas, 1966).

TABLE I

Intradermal and Bronchial Tests with One House Dust Extract in 534 Asthmatic Children with History Suggestive of House Dust Allergy

Skin Test Reaction	No. of Cases	Bronchial Test Reaction	
		Positive Cases	Negative Cases
—	132	40	92*
+	159	70	89*
++	117	74	43*
+++	93	81	12*
++++	33	28	5
Total	534	293	241

*A total of 23 patients with negative bronchial test reaction to the extract used in skin testing had positive bronchial test reactions to other types of house dust extracts.

TABLE II

Relation of History, Skin Testing, and Bronchial (provocative inhalation) Testing, to Correct Identification of Specific Allergen in Allergic Children

	Sensitivity to House Dust (534 cases)		Sensitivity to Moulds (500 cases)	
	Bronchial Test		Bronchial Test	
	Positive (%)	Negative (%)	Positive (%)	Negative (%)
Positive history, — ve skin test ..	59	41	23	77
Positive history and + ve skin test ..	63	37	67	33
Positive history and ++ ve skin test ..	65	35	77	23
Positive history and +++ ve skin test ..	59	41	75	25

TABLE III

Intradermal and Bronchial Tests with Mixed Mould Extract in 500 Asthmatic Children with History Indicative of Allergy to Moulds

Skin Test Reaction	No. of Cases	Bronchial Reaction		No. of Cases with Positive Bronchial Reaction to Sub-species Only
		No. Negative	No. Positive	
—	303	256	38	9
+	117	82	32	3
++	45	15	23	7
+++	30	8	19	3
++++	5	2	3	0
Totals	500	363	115	22

reaction is arbitrarily set as the lower limit for a test to be read as 'significantly positive', a correct diagnosis will be gainsaid in many patients who happen to have little or no cutaneous allergy, but who yet have pronounced bronchial allergy to the substance in question (Table II).

There is much divergence of opinion as to the importance of food allergy as a cause of asthma (Aas, 1966, 1967). Skin tests are usually of limited value here except for a few allergens such as fish (Aas, 1966; Chobot and Hurwitz, 1937), and the diagnosis must be confirmed or refuted using elimination and provocation diets. Better methods are needed.

***In vitro* Tests for Allergy Diagnosis in Asthma**

In vitro tests on serum for demonstration of specific allergen/reagin interaction are a likely future development, and recent progress is promising (Aas, 1965; Arbesman, 1964; Johansson, 1967; Lichtenstein and Osler, 1964; Stanworth *et al.*, 1967). The presence in serum of a specific reagin is, however, not necessarily of clinical importance, for the allergy may relate to organs other than the bronchi, or possibly to none at all (Aas, 1965; Chobot and Hurwitz, 1937). Though tests on serum may come to replace skin tests, the clinical significance of an allergen/reagin interaction for the asthmatic patient will still need to be tested by bronchial provocation.

Experimental studies. Lung tissue from an asthmatic liberates both histamine and SRS-A into a physiological bath when the allergen in question is added (Schild *et al.*, 1951; Brocklehurst, 1962). In the same way bronchial constriction can be provoked *in vitro*, as was first demonstrated by Schild *et al.* (1951). Rings of bronchial tissue, removed from an asthmatic patient undergoing lung surgery, were suspended in a physiological bath and connected to a kymograph. When the relative allergen was added to the bath, contractions of the smooth muscles of the tissue were recorded. The experiment showed that the allergic reaction led to bronchial constriction independently of innervation. Normal tissues can be made to react in the same manner by sensitization *in vitro* with reaginic serum (Goodfriend, Kovacs, and Rose, 1966; Tollackson and Frick, 1966). Passive transfer experiments have shown the existence of circulating specific reagins in the serum of patients with extrinsic asthma, as first demonstrated by Prausnitz and Küstner (1921) and de Besche (1922). Similar passive transfer of respiratory allergy has also been carried out by intra-

venous infusion of reaginic serum, sometimes by chance during blood transfusions in routine treatment (Ramirez, 1919), and sometimes in controlled experiments (Loveless, 1941). Reagin-allergic reactions cannot be transferred by human serum to animals other than monkeys (Layton, 1966). In primates, however, it is possible after intravenous infusion of human reaginic serum, to provoke bronchial asthma by letting the animals inhale the specific allergens causing the disease in the human donor.

Patterson and co-workers (1967) have shown that specific bronchial reactivity is present after such sensitization, and that provocation causes typical asthmatic dyspnoea, with a spirogram indicating bronchial obstruction, and characteristic relief by adrenaline. Furthermore, allergically induced contraction of the smooth muscle isolated from the respiratory passages of these animals was demonstrable *in vitro*. In other experiments sensitized bronchial mucosa was challenged by allergen, and then showed increased vessel permeability followed by acute local oedema. These experiments are worthy of attention as they provide good experimental models applicable to human allergic asthma.

Intrinsic Asthma: An Exclusion Diagnosis

The immunological and immunochemical mechanisms of extrinsic asthma are fairly clear though many details have to be worked out, but there are many asthmatics in whom an allergic aetiology cannot be demonstrated, at least by current techniques. In other asthmatics, allergies found are insufficient to explain the disease, even when secondary factors are taken into consideration. Do these cases represent allergic asthma where we have failed to find the allergic cause, or are immune mechanisms other than reagin-allergic ones involved, or are they due to non-immunological mechanisms?

In practice, only full investigation of allergy along the lines described can provide a basis for differentiating intrinsic and extrinsic asthma (Fagerberg, 1958). The more limited the investigation, the higher will be the incidence of intrinsic asthma. For example, a patient with asthma caused by allergy to wool dust only, may be assumed to have intrinsic asthma if allergic tests fail to include wool dust, or if he has no cutaneous allergy to wool, and reliance is put on skin tests only. Ripe (1966) has shown that diagnosis of mould allergy in asthma necessitates investigation of the patient's reactivity to individual species of mould; if only a mixed mould extract is used, the diagnosis is

missed in nearly 50% of cases. In our department, the incidence of intrinsic asthma fell from approximately 70% to approximately 15% as diagnostic procedures improved (Aas, 1966; Aas *et al.*, 1963).

Yet it would be naïve to believe that clinical diagnostic tests are adequate; patients can be tested only with a very limited selection of the allergens that might have sensitized the respiratory passages, and there are a number of known or suspected antigens that cannot be satisfactorily applied in the diagnostic tests (Aas, 1967; Chafee and Settippene, 1967; Jimenez-Diaz and Sanchez Cuenca, 1935). This applies, for example, to the vast number of antigens in bacteria and viruses.

Infection and asthma. Many consider that intrinsic asthma is largely due to allergic reactions to antigens in bacteria and viruses, and the many cases of asthma that are precipitated or aggravated by respiratory infections are said to support this view. Such cases may be caused by non-specific, non-allergic mechanisms (Blatt, 1961; Eisen and Bacal, 1967; Feingold, 1959). Respiratory infections may induce an increased hyperreactivity by non-immunological mechanisms. Thus, the injection of an extract of killed influenza virus resulted in increased susceptibility to bronchospasm induced with methacholine in 9 of 10 asthmatics (Ouellette and Reed, 1965).

Skin testing with bacterial extracts is generally regarded as of no value (Barr *et al.*, 1965; Wilken-Jensen, 1959). Better evidence is provided when an injection of a bacterial extract leads to an asthmatic reaction, though this may also be due to other factors, such as extraneous allergens in the bacterial vaccine (Aas, 1963).

Bronchial provocation tests using bacterial extracts have been investigated (Aas *et al.*, 1963; Hajos, 1960; Hampton, Johnson, and Galakatos, 1963). Though bronchial obstructive reactions can be obtained with this type of test, the results tend to be ambiguous, as the respiratory passages may merely be reacting to irritants in the bacterial extracts. In order to investigate this point, 8 children with asthma due only to pollen allergy were tested with the same bacterial extracts as those used by Hajos (1960) and Hampton *et al.* (1963). 5 of the 8 children reacted with asthma, despite the fact that outside the pollen season they tolerated all common respiratory tract infections without asthmatic symptoms. They did not react when tested with double amounts of the extract twice diluted with saline. Their reactions to the bacterial extracts were therefore considered non-specific. One patient, initially reported reacting with bronchial

obstruction to inhalation tests with dilute, non-irritative concentrations of *Neisseria catarrhalis* (Aas, 1966), later showed no such reaction when the medium for culturing these bacteria was changed to potato starch (Aas, 1969).

Protein antigens in bacteria and virus, including non-pathogenic and saprophytic micro-organisms, probably do play a part as respiratory allergens, but the relation has yet to be clarified (Baird, 1966; Feingold, 1959; Hosen and Carabelle, 1954). Well-controlled investigations have failed to support the empirical idea of treating asthma with bacterial extracts, a placebo having proved equally effective (Aas *et al.*, 1963; Fontana *et al.*, 1965; Frankland, Hughes, and Gorrill, 1955; Helander, 1959; Johnstone, 1959; Weil, 1960), except in one study (Barr *et al.*, 1965).

Reactions of the delayed (cyto-allergic) type to bacterial antigens may play a part in chronic asthma (Swineford, 1962). Hypersensitivity reactions of the delayed type are characterized by inflammatory tissue responses, and are thus more likely to lead to bronchitis as a complication of asthma (Feingold, 1959; Gell and Coombs, 1963). Though chronic obstructive bronchitis and bronchial asthma may have similar clinical symptoms, they are quite distinct diseases, each with its characteristic pathology (Salvato, 1968), that of extrinsic asthma, as already stated, corresponding to the pattern of immediate or Type I hypersensitivity.

There is some clinical evidence that asthma may also be caused sometimes by semi-delayed sero-allergic and by delayed cyto-allergic mechanisms (Herxheimer, 1952; Kim, 1965; Pepys *et al.*, 1968).

Mechanisms of intrinsic asthma. Some cases of intrinsic asthma may possibly be caused by immunological mechanisms other than reagin-allergic. The demonstration of precipitating, non-reaginic antibodies in aspergillus and candida asthma cases deserves attention (Longbottom and Pepys, 1964; Pepys *et al.*, 1968). It is suggested that precipitating antibodies may play an important part in semi-delayed asthmatic reactions occurring 4–8 hours after the inhalation of aspergillus and candida extracts, on the basis of Arthus-like hypersensitivity mechanisms. Such cases of bronchial obstructive disease should perhaps be labelled 'obstructive bronchitis with asthma' rather than bronchial asthma (Meneely *et al.*, 1962; Sanerkin, Seal, and Leopold, 1966). This applies also to the bronchial tissue reactions that may possibly be induced by auto-immune hypersensitivity mechanisms (Yagi, Tamanoi, and Pressman, 1960). It is conceivable that the repeated injury

to bronchial tissues occurring in asthma may alter them sufficiently to elicit auto-antibodies responsible for additional tissue damage (Swineford, 1962).

Intrinsic asthma may be due to structural properties of the respiratory tract, or to metabolic disturbances of yet unknown type, and genetic factors seem to be involved (Samter, 1959; Leigh and Marley, 1967). Defects in some regulator mechanism necessary to maintain a balanced function; changes in the bronchial ground substance (Rappaport *et al.*, 1953), or changed permeability conditions there (McCarter and Vazquez, 1966; Samter, 1959); pathological reactivity of β -adrenergic or cholinergic receptors in the bronchi (Kirkpatrick and Keller, 1967; Ouellette and Reed, 1965); or imbalance of local enzyme systems (*Ann. Allergy*, 1965; Ungar and Hayashi, 1958) all merit attention in this challenging field. If increased responsiveness of the bronchi to various stimuli (Meneely *et al.*, 1962; Scadding, 1963) is dependent on structural or biochemical disturbances, it is easy to see that local allergic reactions would be among the first and most important precipitating stimuli. Until more is known about the causes of hyperreactivity of the bronchi, it is better to replace the term 'intrinsic asthma' with 'asthma of unknown origin.'

Comments on Treatment

The logical object of treatment in allergic asthma is the elimination of the active allergens, but unfortunately it is often impossible to carry this out, and in such cases hyposensitization is indicated (Engström and Kraepelien, 1957). If a specific allergen can be identified as a major causative factor, hyposensitization with extracts of that allergen is a valuable adjuvant to treatment. Using maximum tolerated doses, the patient's tolerance to the allergen will usually be increased (Johnstone and Crump, 1961). On immunological grounds one would not expect hyposensitization to protect against very intense exposures to the allergen. Therapeutical trials, using double-blind controlled methods, have shown hyposensitization to be effective when adequately carried out (Johnstone and Crump, 1961; Schon and Gyenes, 1965), and this has been confirmed experimentally (Bernton, Chambers, and Querry 1962; VanArsdel and Middleton, 1961). There is still need for controlled studies of the effect of hyposensitization on the bronchial reactivity to the specific allergen. In allergic diagnostic work, a merely routine search for the more common allergens is hardly adequate. Allergy is characterized by individuality as regards

the immune reaction and must be investigated accordingly.

Furthermore, the interaction of allergic reactions with the many other forces that may affect respiration must be recognized and treated if good results are to be expected. While in 'intrinsic' asthma only non-specific treatment is available, in extrinsic asthma precise allergy diagnosis provides some basis for specific treatment. Better treatment of asthma will only come from better understanding of the disease.

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