

A CONTRIBUTION TO THE PROBLEM OF AUTOSENSITIZATION IN BRONCHIAL ASTHMA¹

By

G. BERGQUIST, M.D.

Arboga, Sweden

Intrinsic or endogenous asthma may be perennial, but as a rule it occurs during the colder part of the year and is characterized by exacerbations in connection with upper respiratory tract infections. Analysis of incipient asthma periods shows that there are many different types, but that two main groups predominate. In the one group there is coryza for one or several days, followed by cough of the irritative type which lasts for about a day and then passes over into true bronchitic asthma. In the other group, no particular stages in the onset can be distinguished; possibly, signs may be observed indicating that the throat is the starting point. The former type-group differs from the latter in another respect also. Examination reveals in the majority of cases that the nasal mucous membrane is vasomotorial and that, not infrequently, polypi are present. Sinusitis in some form is not unusual in patients with this type of asthma. The tests are usually negative; on the other hand, these patients are remarkably sensitive to the smell of frying foods, coal and coke smoke and volatile substances (e.g. benzine, aether, etc.).

There has been some discussion as to whether these asthma groups, pathogenically speaking, can be compared to the extrinsic asthmas or not. Waldbott and other investigators main-

¹ From a lecture to the Third European Congress of Allergy, Florence.

tain that they are not comparable, whereas Urbach holds that asthma provoked by an allergen formed within the organism does occur, in chronic infections and focal infections, for instance. The most likely answer to the problem would seem to be that, in the large group of intrinsic asthmas, several different types are distinguishable, among which the purely bacterial allergies are one type. This group also can hardly be called uniform, however. It is not yet possible to decide whether the micro-organism itself, or its metabolic or disintegration products are the allergen. Furthermore, the bacterium's capsule, or its nucleus and/or toxin may be the allergen. Still another possibility is conceivable, namely, that the toxic effect on the mucous membrane changes the cell protein so as to cause it to behave like an allergen for the organism. An illustration of the fact that the body's own protein substances can behave as allergens is provided by the asthma cases described by Salén, in which the allergen was praemenstrual leukorrhoea. Another illustration is found in the observations of Verhoeff and Lemoine, who state that endophthalmitis phaco-anaphylaxis is due to a reaction to the lens protein liberated at the operation. Burky has demonstrated in animal experiments that organ specific proteins (lens protein, muscle protein) may act as allergens, if they have been subjected to the action of toxin-producing micro-organisms. The bacilli he used were toxin-secreting staphylococci.

The present author has already recorded that *Staphylococcus aureus* may be a causative factor in intrinsic asthma. A study of the bacterial flora in the nasal cavity and epipharynx of asthmatic subjects belonging to the type under discussion revealed that *Streptococcus viridans* predominated, whereas, in the flora of healthy persons, *Staphylococcus albus* was the predominant organism. Staphylococci of the aureus type occur in 40 per cent of asthma patients while in healthy persons the corresponding figure is 17.5 per cent. Treatment with an auto-vaccine prepared from staphylococci gives statistically verified better results than when polyvalent autovaccine containing no staphylococci is used. In the opinion of the present author, the

figures mentioned, as well as the result of the vaccine treatment, indicate that *Staphylococcus aureus* has some connection with asthma of the intrinsic type.

In view of these circumstances, there would seem to be reason for believing that, to a large extent, staphylococci in some way or other take a hand in the occurrences which result in intrinsic asthma. Presumably, the bacterial activity, and especially the toxin production, disturbs in some way the normal reaction in the antibody system. Another possible explanation is that the mucous membrane is changed by the action of the bacteria and that its protein substances thereby become transformed into an allergen for its own organism. Asthmatic exacerbations occurring in connection with so-called colds would then be due to the fact that, under the conditions prevailing on such occasions, the allergen is potentiated, or liberated in increased amounts. Thus, the important problem is to try and ascertain whether or not an allergen really is formed, *in vivo*, in the manner described. The investigations reported here were carried out for the purpose of studying this question in the light of the observations made by the afore-mentioned authors.

PERSONAL INVESTIGATIONS

Patients with intrinsic asthma, whose history showed that discomfort from the nose or throat had been the first symptoms at the onset of the constantly recurring asthma periods, were chosen for the investigation. Bacterial samples were taken with a sterile swab, in the usual manner, from the nasal cavity or throat, and were cultivated in inclined agar tubes. When *Staphylococcus aureus* predominated in the flora, these were transferred to a special culture medium prepared in the following manner. Bouillon was mixed with 6-7 per cent of tonsil tissue or nasal mucous membrane. These tissues had been removed directly from the operative field at tonsillectomy and at nose operations. They were thoroughly rinsed with physiological saline and ground with sand into a paste in a mortar. The mass was poured in an undried condition into

bouillon, and agar was added in the usual manner (inclined agar tubes). For bacterial propagation, staphylococci from the tonsillar region were grown on a medium to which tonsil tissue had been added; the bacteria from the nose were cultivated on a nasal mucous membrane medium. When a sufficient quantity of bacteria had grown out, the vaccine was prepared, and an allergen extract was made from the culture in the usual manner with a strength of 1/100. Allergenic extracts were also made from the respective mediums, before cultivation as well as from agar.

The patients who had furnished the bacteria underwent an intracutaneous test in the usual way, with the vaccine and allergen extracts in a dilution of 1/1000, and at the same time a control test was carried out in healthy non-allergic persons. In many instances, a reaction to the different extracts was observed, varying from slight redness around the injection site to considerable oedema in that area. Oedema twice the size of the control wheal produced with physiological saline was counted as a positive reaction. If several wheals (including the control wheal) simultaneously showed a more or less pronounced reaction this was considered to be a non-specific reaction.

Twenty patients whose asthma began with symptoms from the throat, and 20 patients in whom nasal symptoms constituted the first sign of the asthma, were studied first. Among the "throat cases" only 2 showed a definite positive reaction to an extract from the culture obtained after bacterial propagation. The reactions were distinct but not marked. Among the 20 cases in which symptoms from the nose were the first manifestation of the asthma, 8 showed a positive reaction to an extract from the culture resulting from bacterial cultivation. These figures suggest that mucous membranes *in vitro* become changed as the result of the growth of *Staphylococcus aureus* and behave as allergen. The figures show, furthermore, that the nasal mucous membrane is the more susceptible of the two.

After these preliminary studies, the investigation was con-

TABLE
Skin test reactions in patients and control subjects.

Intrinsic asthma cases						Healthy controls				
Nos.	A-v	M-b	M-a	A	S	A-v	M-b	M-a	A	S
19	—	—	+++	—	—	—	—	—	—	—
5	—	—	++	—	—	—	—	—	—	—
2	—	+	+++	—	—	—	—	—	—	—
2	+	+	++	—	—	—	—	—	—	—
1	—	—	+++	—	++	—	—	++	+	—
9	—	++	+++	++	—	—	++	++	++	—
5	+++	++	+++	++	—	—	++	+	+	—
5	+	+	++	+	—	+	+	+	++	—
3	+++	—	—	—	—	—	—	—	—	—
1	—	+++	—	—	—	—	—	—	—	—
12	—	—	—	—	—	—	—	—	—	—

Explanation of the table: Autovaccine = A-v. Extract from mucous membrane culture before bacterial propagation = M-b. Extract from mucous membrane culture after bacterial propagation = M-a. Extract from agar = A. Control using physiological saline = S. Nos. = No. of individuals.

finied to include only those cases in which the asthma began with coryza. From among this category male and female patients between 35 and 45 years of age were selected. The investigation was conducted during the period January 1955 to January 1956, and comprised 21 males and 43 females. Bacterial samples were taken from the nose and bacterial cultures prepared in the manner previously described, but the amount of nasal mucous membrane added to the culture medium was increased to 10 per cent. The testing was also done in the same way as before, and in addition, the Prausnitz-Küstner test was done in all those who showed strong positive reactions to extracts from the medium obtained after bacterial propagation. The results of this investigation have been compiled into a table. The reaction to the different extracts is indicated by the sign + and up to + + +, and a negative reaction is denoted by a — sign. The left column in the table shows the number of patients who reacted in the same way. As regards the patients and healthy controls who have been assembled into common

there was a certain variation in the strength of the reaction in groups, the 6th and 7th groups from the top, for instance, different individuals, which cannot be demonstrated in tabular form. These groups include those who reacted with +, ++ and + + +, as the table would otherwise have been unwieldy.

Before the table is discussed, it may be mentioned that histamine analysis of the culture extracts was done before and after bacterial cultivation. These analyses showed good agreement on different occasions. The mucous membrane culture before bacterial cultivation had a histamine content varying between 1.41 and 2.7 μ gm, and after cultivation the histamine value was between 0.14 and 0.54 μ gm. Thus, it is obvious that the bacterial growth resulted in a change causing destruction of histamine.

DISCUSSION

The table demonstrates that extracts from mucous membrane cultures upon which *Staphylococcus aureus* had been propagated gave a positive reaction in 28 of the 64 patients examined. Looking now at the column for the same extract in the controls, we find that here also, there are ++ positive reactions but that they only occur when the reaction to other extracts is positive also. In 8 of the patients, the reaction to this extract was strongly positive, and there were signs of pseudopodium formation in the wheal. These 8 cases were examined by the Prausnitz-Küstner technique, and the positive reaction could be transferred to healthy, non-allergic persons in 6 instances. It was therefore concluded that the reaction must be due to an allergen formed through the action of the bacteria on the mucous membrane protein in the culture medium. It is the author's intention to supplement this investigation with a comparative cutaneous test using extracts from other tissues (e.g. epidermis) that have been subjected to bacterial action, and thereby to acquire further information on the problem. In 16 cases, the patient had a positive reaction to the extract from mucous membrane agar before bacterial cultivation, and at the same time there was a more or less posi-

tive reaction in the control subject also. This may be due to the fact that the histamine content in the culture medium was higher before cultivation than after bacteria had been grown on it. The significance of these reactions as well as of the simultaneous reactions to different extracts in patients and control subjects cannot be estimated here, in view of the smallness of the material. In all probability, it is a question of non-specific reactions. Three patients showed a positive reaction to vaccine only, in one patient there was only a positive reaction to mucous membrane extract before bacterial cultivation, and in 12 patients as well as in their controls no reaction to the extracts investigated was noted.

SUMMARY

Theoretically, the mucous membrane in the upper respiratory passages *in vivo* can be changed through the action of bacteria so as to act as allergen. The present investigation shows that, *in vitro*, the nasal mucous membrane can acquire allergenic properties through the influence of growing *Staphylococcus aureus*.

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