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Lung Auto-antibodies in the Blood of Children with Bronchial Asthma

By

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Although exogenous antigens, especially inhaled ones, are the principal pathogenic factor in bronchial asthma, dyspnoea due to aspecific or unknown factors may develop in chronic processes without the presence of allergens. Disorders of this nature used to be called endogenous asthma. Since the presence of antibodies reacting with pulmonary tissue has been shown in the blood of adults suffering from chronic respiratory disease or asthma [1, 4, 9, 13, 16, 18], the present experiments were designed to study whether there were such antibodies in the serum of asthmatic children, with the aim to throw some light on the pathomechanism of "endogenous asthma".

Material and Method

Homogenized and the lyophilized human lung served as antigen. Antibodies were determined by the consumption-dilution modification of Steffen's method [15]. The titre of Coombs' serum was invariably 1:1024, and the same antigen was used throughout. Decreases in titre were referred to values obtained with sera of healthy blood donors. The titres registered in dilutions of 1:2 were marked with crosses. If, for instance, the titre of the donor's serum amounted to 1:256 and that of the patient to 1:32, the sign +++ was applied. Reactions with one-tube difference were considered negative.

Determinations were made in the serum of 36 children with bronchial asthma; the number of determinations totalled 43 because four patients were repeatedly examined. Sixteen children, suffering from other (in some cases respiratory) diseases, served as controls.

Results

In the asthmatic group it was in 14 out of 43 cases that the sera contained lung auto-antibodies, against a single case in the control group (Table I). Distribution of the asthmatic patients according to diagnosis showed that the number of doubtful cases was comparatively higher (with only one positive case) in the group with pneumonia (Table II). The sera of patients suffering from other auto-immune diseases (nephrosis, chronic splenomegalic cirrhosis, rheumatic fever) were negative. Of the latter, only the nephrotic patient received steroid treatment when the blood samples were taken.

In the cases in which lung auto-antibodies were demonstrable, the level of gamma globulin was generally higher in the serum of asthmatic than of negative patients (Table III). The gamma globulin level in the positive

TABLE I

	Asthma		Other diseases	
Negative	12 (28%)	29	12 (75%)	15
Positive +	17 (39%)	(68%)	3 (18%)	(94%)
Positive ++	7 (16%)		—	
Positive +++	4 (9%)	14	—	1
Positive ++++	3 (7%)	(32%)	1 (6%)	(6%)
Total		43		16

TABLE II

Diagnosis of non-asthmatic patients

	Negative	+	++	Total
Pneumonia	3	2	1	6
Allergic diseases	2	1	—	3
Auto-immune diseases	4	—	—	4
Diverse	3	—	—	3

sera was invariably above, and that in the majority of negative sera below, 15%.

A comparison of these results with clinical observations failed to show any correlation between the frequency of attacks, the duration of the disease, and the presence of auto-antibodies. Among the positives, there was only one child under 6 years of age, while one third of the negative cases belonged to this age group; so that the presence of auto-antibodies seems to be a rare occurrence in early childhood.

Lung-reactive antibodies were more frequent in blood collected during an attack (Fig. 1). Chronic asthma with lasting dyspnoea often causes thoracic deformity in childhood; it gives

TABLE III

Serum gamma globulin level and lung antibodies

Gamma globulin level	13%	13.1–15%	15.1–17%	17.1–19%	19.1%
Auto-antibodies present	0	0	5	4	2
Auto-antibodies absent	6	8	4	0	2

rise to changes characteristic of rickets and emphysema despite prophylactic treatment with vitamin D (Fig. 2). Its incidence amounted to 62% in the positive, and to 30% in the negative group.

Discussion

Antibodies reacting with the special proteins of a number of different organs have been demonstrated in the serum of patients suffering from various (especially chronic) diseases [7, 11]. Such antibodies do not as a rule constitute the primary pathogenic factors but arise in consequence of the lesion; this notwithstanding, their lasting presence may induce cellular damage demonstrable both in vitro and in vivo [6, 7, 17]. Few investigations have been made with a view to demonstrate lung-reactive antibodies, although Thomas [18] registered numerous positive reactions in cases of primary atypical pneumonia, Stein et al. [16] in patients with mucoviscidosis, and Kalman et al. [9] in cases of silicosis. The last-named authors, as well as Hagedorn et al. [8], found these antibodies to be of IgM and IgG nature.

Employing the antiglobulin consumption test, Burrell et al. [1, 2] as also Quintero et al. [13] found lung-reactive antibodies in the serum of more than 50% of patients suffering from bronchial asthma, while Dinu and Roth [4] in every such case. These authors used lung extract adsorbed to latex in their examinations.

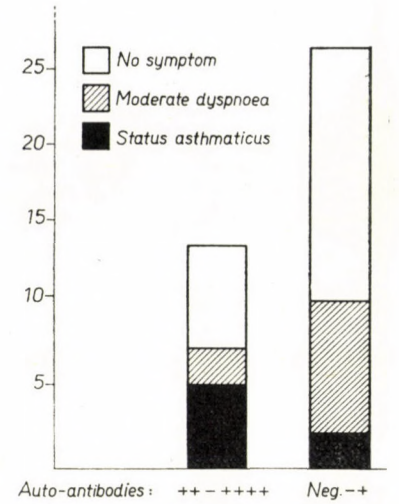

Fig. 1. Lung auto-antibodies and actual condition at blood sampling

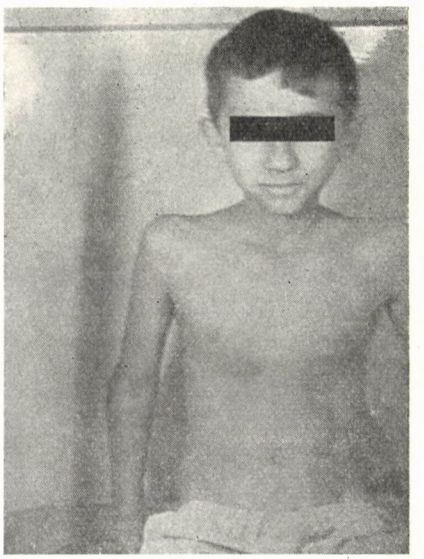

Fig. 2. Thoracic deformity and emphysema in asthmatic child

The proportion of positive reactions in the serum of children is rarer, it amounts, according to our results, to about 50% of that in adults. Antibo-

dies presumably affect the course of the disease in childhood already.

It is not known which component of the lung tissue is that with which auto-antibodies react. MENDES [10] elicited bronchospasm in guinea pigs by means of asthmatic sputum; BÜRGI [3] provoked a positive skin reaction of asthmatic individuals by the mucopolysaccharides of mucus. Employing the immune-fluorescence method, BURRELL et al. [2] found that, of the components of lung tissue, the connective tissue elements, fibroblasts and collagen fibres were reactive in the antiglobulin-consumption test.

Lung antibodies seem to play a pathogenic role in silicosis and chronic bronchitis, although proofs are still lacking in this respect. Besides directly damaging pulmonary function, antibody formation may affect it otherwise as well. It is, for instance, accompanied by interstitial infiltration in the affected organ [7], a phenomenon that was visible in two thirds of the X-ray pictures of our positive cases. Lasting and subsequently cicatrizing interstitial infiltration in childhood leads to thoracic deformity. In chronic asthma, the basement membrane of the bronchial walls grow thicker, presumably owing to a deposition of immune globulins [11] so that auto-antibodies seem to be operative also in this case.

The elevation of the gamma-globulin level was moderate, of a lesser degree than in primary autoimmune disturbances, but even this moderate rise shows that, in cases of asthma, endogenous antigenic stimulation induces a lasting hyperfunction of immune-globulin synthesis.

It is safe to conclude from our results that bronchial asthma causes graver and more lasting sequelae if lung-reactive antibodies are present. This correlation is, however, only a statistical one: daily symptoms over the major part of the year have been registered in 64.3% of the positive, and in 31% of the negative cases. DÓBIÁS et al. [5] observed a rapid decrease in the number of heart-reacting antibodies in rheumatic patients after the institution of prednisolone treatment. This suggests that, in view of its risks, prolonged prednisolone treatment should only be applied if lung antibodies have reliably been demonstrated in the serum of asthmatic patients.

SUMMARY

Lung auto-antibodies have been determined by Steffen's antiglobulin consumption test in 43 instances in the serum of 36 children with bronchial asthma. In one third of the patients could an evaluable level of antibodies be demonstrated; with one exception, all of them were more than six years old. Lung antigen gave no positive reaction in auto-immune diseases, and but rarely in acute respiratory infections. A certain correlation was found to exist between the gravity of asthmatic attacks, the daily occurrence of wheezing and thoracic deformity on the one hand and the presence of auto-antibodies

on the other. The serum gamma globulin level was higher in the presence than in the absence of lung-reactive antibodies. The presence of auto-antibodies seems to mean an unfavourable prognosis in bronchial asthma.

REFERENCES

1. Burrell, R. G., Wallace, J. P., Andrews, C. E.: Lung antibodies in patients with pulmonary disease. Amer. Rev. resp. Dis. **89,** 697 (1964).
2. Burrell, R. G., Esber, H. J., Hagedorn, J. E., Andrews, C. E.: Specificity of lung-reactive antibodies in human serum. Amer. Rev. resp. Dis. **94,** 743 (1966).
3. Bürgi, H.: Vorkommen und mögliche klinische Bedeutung von Fasersystemen im Bronchialsekret von Asthmatikern. Schweiz. med. Wschr. **95,** 1677 (1965).
4. Dinu, I. V., Roth, L.: La présence des anticorps anti-poumon dans le serum des asthmatiques. Med. internal (Buc.) **16,** 1471 (1964).
5. Dóbiás, Gy., Balló, T., Bertalan, T., Lóránt, O.: Studies of the antibodies reacting with human heart muscle in rheumatic fever of the child. Z. Immunforsch. **129,** 452 (1965).
6. Dóbiás, Gy.: Die immunpathologischen Beziehungen der Leberkrankheiten. Dtsch. med. Wschr. **91,** 1836 (1960).
7. Dumonde, D. C.: Tissue specific antigens. Advanc. Immun. **5,** 245 (1966).
8. Hagedorn, J. E., Burrell, R. G., Andrews, C. E.: Immunochemical analysis of lung-reactive antibodies in human serum. Amer. Rev. resp. Dis. **94,** 751 (1966).
9. Kalman, E., Mandi, A., Osztovics, M.: The investigation of anti-lung antibodies in silicosis. Med. d. Lavoro **53,** 165 (1962).
10. Mendes, E.: Experimental asthma of the guinea pig induced by bronchial sputum. Acta allerg. (Kbh.) **18,** 89 (1963).
11. McCarter, J. H., Vazquez, J. J.: The bronchial basement membrane in asthma. Arch. Path. **82,** 328 (1966).
12. Osztovics, M., Marcsek, Z.: Über den Zusammenhang zwischen dem klinischen Zustand und der Antiglobulin-Konsumptionsprobe beim rheumatischen Fieber im Kindesalter. Acta paediat. Acad. Sci. hung. **3,** 211 (1962).
13. Quintero, J. M., Burrell, R. G., Cather, C. H., Wymer, B., Baise, R.: Detection of antibodies to sinus tissue in chronic bronchial asthma. J. Allergy **37,** 84 (1966).
14. Schöngut, L., Turai, L., Cserháti, E., Hüttner, I.: Über einige Probleme der chronischen Corticosteroidbehandlung. Acta paediat. Acad. Sci. hung. **5,** 423 (1964).
15. Steffen, C.: Der Antiglobulin-Konsumptionstest. Klin. Wschr. **40,** 613 (1962).
16. Stein, A. A., Mamlepas, F. C., Soika, K. F., Patterson, P. R.: Specific isoantibodies in cystic fibrosis. J. Pediat. **65,** 495 (1964).
17. Szécsey, G., Dóbiás, G., Végh, M.: Über die Wirkung eines Immunserums gegen Rattenlebermitochondrien auf den Sauerstoffverbrauch von Lebermitochondrien und einige Gewebe von Ratten. Z. Immunforsch. **131,** 390 (1966).
18. Thomas, L.: Circulating Autoantibodies and Human Disease. New Engl. J. Med. **270,** 1157 (1964).

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