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THE MECHANISM OF SPECIFIC DESENSITIZATION BY MICROBE ALLERGENS. REPORT I. INDICES OF NONSPECIFIC IMMUNITY IN BRONCHIAL ASTHMA AND CHANGE UNDER THE EFFECT OF DESENSITIZATION BY MICROBE ALLERGENS

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U. S. BOARD ON GEOGRAPHIC NAMES TRANSLITERATION SYSTEM

Block	Italic	Transliteration	Block	Italic	Transliteration
А а	*А а*	A, a	Р р	*Р р*	R, r
Б б	*Б б*	B, b	С с	*С с*	S, s
В в	*В в*	V, v	Т т	*Т т*	T, t
Г г	*Г г*	G, g	У у	*У у*	U, u
Д д	*Д д*	D, d	Ф ф	*Ф ф*	F, f
Е е	*Е е*	Ye, ye; E, e*	Х х	*Х х*	Kh, kh
Ж ж	*Ж ж*	Zh, zh	Ц ц	*Ц ц*	Ts, ts
З з	*З з*	Z, z	Ч ч	*Ч ч*	Ch, ch
И и	*И и*	I, i	Ш ш	*Ш ш*	Sh, sh
Й й	*Й й*	Y, y	Щ щ	*Щ щ*	Shch, shch
К к	*К к*	K, k	Ъ ъ	*Ъ ъ*	"
Л л	*Л л*	L, l	Ы ы	*Ы ы*	Y, y
М м	*М м*	M, m	Ь ь	*Ь ь*	'
Н н	*Н н*	N, n	Э э	*Э э*	E, e
О о	*О о*	O, o	Ю ю	*Ю ю*	Yu, yu
П п	*П п*	P, p	Я я	*Я я*	Ya, ya

* ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ё in Russian, transliterate as yё or ё. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

FOLLOWING ARE THE CORRESPONDING RUSSIAN AND ENGLISH

DESIGNATIONS OF THE TRIGONOMETRIC FUNCTIONS

Russian	English
sin	sin
cos	cos
tg	tan
ctg	cot
sec	sec
cosec	csc
sh	sinh
ch	cosh
th	tanh
cth	coth
sch	sech
csch	csch
arc sin	$\sin^{-1}$
arc cos	$\cos^{-1}$
arc tg	$\tan^{-1}$
arc ctg	$\cot^{-1}$
arc sec	$\sec^{-1}$
arc cosec	$\csc^{-1}$
arc sh	$\sinh^{-1}$
arc ch	$\cosh^{-1}$
arc th	$\tanh^{-1}$
arc cth	$\coth^{-1}$
arc sch	sech^{-1}
arc csch	csch^{-1}
rot	curl
lg	log

GREEK ALPHABET

Alpha	A	α		Nu	N	ν	
Beta	B	β		Xi	Ξ	ξ	
Gamma	Γ	γ		Omicron	O	o	
Delta	Δ	δ		Pi	Π	π	
Epsilon	E	ε	ϵ	Rho	P	ρ	ϱ
Zeta	Z	ζ		Sigma	Σ	σ	ς
Eta	H	η		Tau	T	τ	
Theta	Θ	θ	ϑ	Upsilon	T	υ	
Iota	I	ι		Phi	Φ	φ	ϕ
Kappa	K	κ	ϰ	Chi	X	χ	
Lambda	Λ	λ		Psi	Ψ	ψ	
Mu	M	μ		Omega	Ω	ω	

THE MECHANISM OF SPECIFIC DESENSITIZATION BY MICROBE ALLERGENS

REPORT I

INDICES OF NONSPECIFIC IMMUNITY IN BRONCHIAL ASTHMA AND CHANGE UNDER THE EFFECT OF DESENSITIZATION BY MICROBE ALLERGENS

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(Submitted 11 March 1969)

The state of immunological reactivity in bronchial asthma has been the subject of a small number of works, and the obtained results have been contradictory. Thus, Heilig (1937) observed a drop in the complement titer with bronchial asthma; Mikheyeva and Khomitskaya (1964, 1965) noted an inconsistent index in children ill with bronchial asthma. Paul and Pely (cited by Chistyakov, 1965) observed a reduction in the complement titer, which increased during attacks; Szulczynska (cited by Chistyakov, 1965, on the contrary, observed a complement in high titers, which achieved its maximum during severe attacks. Kaganov and coauthors (1963) in children ill with bronchial asthma of infectious nature observed a reduction in the overall reactivity

of the organism from a series of indices, including phagocytic activity of leukocytes. Mazurek and coauthors (1963) evaluate the change in this index for an analogous contingent of patients as a result of complications of the basic disease. Damaskin (1941) considers the regular increase in phagocytosis during attacks of bronchial asthma, whereas Mikheyeva and Khomitskaya (1964, 1965) observed a reduction in phagocytosis between attacks, an increase before an attack and maximum reduction at the instant of attack. Thus, there is as yet no single opinion as to the changes in nonspecific immunological factors in bronchial asthma.

We studied certain indices of the overall immunological reactivity in patients with infectious bronchial asthma ranging in age from 16 to 60 with duration of disease from 4 months to 20 years and more. According to the severity of the course we distinguished 3 forms of the disease: severe, moderate and relatively light. We judged the infectious nature of the bronchial asthma on the basis of connecting the onset of the disease with infections of the upper respiratory tracts and (or) according to the presence of positive skin tests to microbe antigens. Indices of nonspecific immunity, as was explained, depended neither upon the age of the patients nor upon the duration of the disease.

We simultaneously studied the nature of nonspecific immunological rearrangement, beginning in connection with desensitization by microbe allergens. Certain researchers have explained the effectiveness of this method of medical treatment for bronchial asthma by the intensification of nonspecific protection mechanisms. However, this idea is based only on clinical observations, which have demonstrated an increase in the process of medical treatment of resistivity to intercurrent diseases, primarily catarrhal. Works based on a study of objective indices of nonspecific resistance during medical treatment of bronchial asthma patients by microbe antigens, which would confirm (or reject) the above idea concerning the mechanism of the effect of specific desensitization are not available to us in literature.

Repeated examinations were conducted during the uninterrupted course of desensitization by microbe antigens, a mixture of microbe particles and products of metabolism. The therapeutic mixtures were composed in accordance with positive intracutaneous reactions to antigens of β-hemolytic and Streptococcus viridans, Staphylococcus aureus and Staphylococcus albus, Pneumococcus, Candida albicans, and Neisseria catharralis[1].

The medical treatment followed the procedure of desensitizing therapy. It entailed the systematic parenteral introduction of microbe antigens, beginning with subthreshold (no skin reaction) doses, with subsequent increase and gradual lengthening of intervals between injections. The dosage was increased only after tolerance to the preceding dose developed. During the period of treatment, which lasted from 6 months to 4 years, the patients received from 1 to 15 billion microbe cells. The principles, method and outlines of medical treatment were published previously (Sidorenko and Vershigora, 1965; Sidorenko, 1968).

Phagocytosis (phagocytic activity and phagocytic index) was studied in those patients under observation from a 24-hour culture of Staphylococcus aureus (strain No. 109), titer of complement and blood serum lysozyme, titer of heterophilic agglutinins and general immunological reactivity (Ioffe test).

In the case of bronchial asthma patients particular changes in the nonspecific immunity were noted as compared to healthy patients.

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[1]The antigens were prepared at the Kiev Institute of Otolaryngology by A. V. Vershigora (1966). Temporary interrepublican technical specifications (MRTU-42 No. 172-67) on the preparation of microbe allergens and the manual on their use for diagnostics and medical purposes, developed with our participation, have been sanctioned by the ministry of Public Health USSR 15/V 1967.

Study of phagocytosis in 113 patients disclosed statistically reliable reduction in the phagocytic activity of leukocytes and the phagocytic index as compared with healthy subjects. The mean phagocytosis indicators in the patients were 24 (phagocytic activity) and 5 (phagocytic index), and in the healthy subjects were 37 and 6 respectively. The degree of drop in the phagocytosis indicators is independent of the severity of the bronchial asthma and the medical treatment by steroid hormones.

The complement titer in 107 patients with bronchial asthma was somewhat lower than in the healthy subjects. This reduction is statistically reliable. In comparison of the mean indicators of the complement titer in patients with different severity of disease, the greatest inhibition is observed with the greatest severity of disease, however, statistically this reduction is unreliable. According to our data, therapy by steroid hormones had no effect on the complement titer (difference is statistically unreliable).

In 39 patients an increase in the lysozyme titer in the blood serum was noted, on the average to 1:273 (in healthy subjects 1:176). The lysozyme titer showed a significant decrease under treatment by steroid hormones. In patients with bronchial asthma of the first degree, receiving only systematic therapy, the lysozyme titer was highest (1:452), whereas with patients in the same group, but receiving steroids, it was the very lowest (1:220). The difference is statistically reliable, in spite of the small number in both groups.

The titer of heterophilic agglutinins before treatment was 1:5, i.e., showed no essential difference from the average norm. No dependence was noted between it and the course of the bronchial asthma.

Ioffe's test with "antihuman" serum was given to 26 patients. Negative and doubtful results were obtained from 11, and for 15 of

the patients the tests turned out to be positive (++). Approximately the same number of cases was observed with both normal and reduced general immunological reactivity in the case of bronchial asthma of differing severity.

With prolonged desensitization by small doses of microbe antigens, certain changes were noted in the nonspecific immunity indices. We think it is possible to say that these changes are due to desensitization, in spite of the different periods of patient observation. We were guided by the following considerations: the complex of symptomatic agents used by the patients both before and during the desensitization period was exactly the same; with satisfactory result it was reduced, while with a good result it was entirely eliminated.

Phagocytosis in the desensitization process was determined in the dynamics of 57 patients (see table). With both positive and negative treatment results, there was a marked (and statistically reliable) increase in phagocytic activity of leukocytes, while the phagocytic index decreased in both cases (statistically unreliable). The complement titer studied after treatment of 59 patients dropped to the norms independently of the treatment results; as compared with the complement titer before treatment this decrease is statistically reliable. The lysozyme titer after treatment dropped for all 38 patients, to a greater degree with unsatisfactory results than with satisfactory treatment results. Thus, a certain decrease in nonspecific immunity was noted in bronchial asthma patients as compared with healthy subjects. In particular, the phagocytic activity of leukocytes and the phagocytic index decreased. A decrease in the complement and the general immunological reactivity was noted in half of the patients. An increase in the lysozyme titer was noted at the same time. The titer of heterophilic agglutinins did not change.

The change in level of nonspecific resistance was not directly related to the severity of the course of the bronchial asthma.

Dynamics of nonspecific immunity indicators during treatment by microbe allergens.

	Phagocytosis								Complement titer			Lysozyme titer				
	phagocytic activity				phagocytic index							geo-metric mean	average titer	arith-metic mean		
	M	±σ	±m	n	M	±σ	±m	n	M	p ±t	E ±t	n			p ±t	E ±t	n
Before treatment	25	10,3	1,3	63	5,2	2,8	0,35	63	0,06	0,020	0,003	52	272,7	1:273	2,41	0,28	0,04	39
After treatment	29	11,8	1,26	83	4,4	1,9	0,22	88	0,05	0,017	0,002	77	186,0	1:186	2,27	0,40	0,06	45
positive result	29	12,1	1,45	70	4,5	1,8	0,20	70	0,05			66	199,1	1:199	2,36	0,36	0,05	33
negative result	28	12,2	2,87	18	3,9	2,3	0,54	18	0,05			11	131,5	1:134	2,13	0,45	0,10	8
			$t_{ФА}=2,2$	$P<0,05$					$t=3,3$			$P<0,001$	$t=2,26$			$P<0,05$		
			$t_{ФИ}=1,0$	$P>0,2$														

A lack of difference in the nonspecific indices in patients with different course of the disease makes it possible to consider these changes as secondary. This conclusion completely agrees with clinical observations, which show that susceptibility to any infections, in particular pyogenic and septic infections, in bronchial asthma patients is the same as in patients with other diseases and with healthy subjects. The predisposition of bronchial asthma patients to catarrhal diseases of the upper respiratory tracts, in particular, can be explained by the reduction in the barrier function of the mucuous membrane in the upper respiratory tracts under the constant presence of silent infection.

Steroid hormones have essentially no effect on phagocytosis and the complement activity of blood serum, whereas systematic application of these has a market effect on the lysozyme titer, and results in a decrease.

The purpose of studying the changes in general immunological reactivity under the

effect of treatment by microbe allergens is to explain the role of these mechanisms in specific desensitization. Rackeman (1950) and Rapoport (1959) consider that the positive effect of this method of treating bronchial asthma is related to the increase in the factors of natural immunity, whereas Jones and McLain (1963) and Cornet (1964) assume that small doses of microbe allergens used for desensitization cannot influence the state of natural immunity.

The effect of large doses of microbe allergens (vaccination) on natural protection factors has been studied sufficiently well. It has been established that in animals immunization increases the complement titer (Andrianova, 1966), the phagocytic activity of leukocytes (Specsivtseva, 1965; Zhitova, 1946; Klemparskaya and coauthors, 1968), decreases the lysozyme content in the saliva (Monayenkov and Ostrovskiy, 1961; Pletsityy and coauthors, 1963) and the blood (Elkonin, 1963; Pletsityy and Fidel'man, 1963; Pletsityy and Shaganov, 1965). It has been shown that fluctuation in the nonspecific immunity indices depends upon the vaccine dose (Mikhaylova, 1967).

Analogous changes have been observed under the effect of the vaccinal process in humans. Onishchenko and Kobzeyeva (1962) noted an increase in phagocytosis when whooping cough patients were vaccinated, and Pletsityy and coauthors (1963) noted a decrease in the lysozyme content in saliva and blood after the application of antilyssic vaccine.

At the same time, we have found no published material on how the state of nonspecific immunity is influenced by small concentrations of microbe antigens introduced to the patient over a prolonged period of time for the purpose of desensitization. From the data which we have obtained, it follows that in this case the effect of such nonspecific factors of natural resistance as the complement titer and phagocytosis activity increased,

and the lysozyme titer in the blood serum decreased simultaneously. Thus, the changes detected are qualitatively identical to those observed after immunization. However, changes in the protective reactions of the organism during desensitization are relatively slight, and showed up with both positive results from the medical treatment and also in the case of noneffective results. Consequently, desensitization by microbe antigens had a positive effect on the organism of the patient, increasing his natural protective means; however, this side of its effect did not ensure sufficient medical effect. It follows hence that the mechanism of positive effect in desensitization by microbe allergens cannot be reduced to only the effect of the microbe allergens on the general immunological reactivity of the organism.

Conclusions

1. In bronchial asthma patients a certain reduction in the nonspecific resistance of the organisms was observed, manifested in a reduction of the blood serum complement titer, phagocytic activity of leukocytes and phagocytic index. In this case the titer of heterophilic agglutinins in patients with bronchial asthma was not changed, but the lysozyme titer of the blood serum was raised.

2. Desensitization with microbe antigens according to our plan, independently of the results of the medical treatment, led to a certain increase in the phagocytosis indicators and complement activity of the blood serum and a reduction in the lysozyme titer.

3. The nature of the immunologic rearrangement, which began in the organism under the effect of introduction of small doses of microbe antigens over a prolonged period of times, is analogous to that found in process of immunization.