AEROSOL IMMUNIZATION WITH DRY POWDER VACCINES AND TOXOIDS. COMMUNICATION IX. FURTHER STUDY OF REACTIVENESS AND IMMUNOLOGICAL EFFECTIVENESS OF THE METHOD OF AEROSOL IMMUNIZATION WITH THE BRUCELLOSIS DUST VACCINE

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Aerozol'naya immunizatsiya sukhimi pylevymi vaktsinami i anatoksinami. Soobshchenie IX. Dal'neishee izuchenie reaktogennosti i immunologicheskoi effektivnosti metoda aerozol'noi immunizatsii pylevoi brutsellieznoi vaktsinoi

[Aerosol immunization with dry powder vaccines and toxoids. Communication IX. Further study of reactiveness and immunological effectiveness of the method of aerosol immunization with the brucellosis dust vaccine]

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(In Russian)

It was mentioned in our previous reports that in aerosol immunization with the brucellosis dust vaccine, in an experiment on animals, its high effectiveness, harmlessness and mild reactiveness, were revealed. The same results were obtained also in the study of the given method in immunization on limited groups of men.[1] After that, with the permission and recommendation of the Serumal-Vaccinal Committee, the study of the cited method of immunization was conducted by us on larger contingents. The results obtained at that time are cited in the present report. We studied the reactiveness and immunological effectiveness of the method of aerosol immunization depending on the inhaled dose of the dust vaccine, as well as on the immunological state of contigents that were subjected to vaccination.

[1] Journal of Microbiology, Epidemiology and Immunobiology, 1960, nos. 6,10,12 and 1961, nos. 1,7,9; Military-Medical Journal, 1958, nos. 10,11,12; 1959, no.8, and 1960, no.12.

During the years 1958-1960, 1201 persons were immunized by the aerosol method with the brucellosis dust vaccine.

Among this number, 305 persons were workers at the sovkhoz "Karmanovo", which during the last 15 years has been registered as a brucellosis focus of the cow type. The aerosol immunization of these workers was conducted as a planned antiepidemic measure. For a considerable part of the vaccinated, essentially, it proved to be a revaccination, since many of them (180 persons) have already been vaccinated against brucellosis in previous years. [Begin p. 96]

Before immunization 619 persons underwent observations at the dispensary, which included medical examination, clinical analyses of blood and urine, as well as x-raying of organs of the chest. The remaining 582 persons underwent only a usual medical examination, without any observations at the dispensary. All those liable to immunization were preliminarily examined for the sensitivity to brucellosis infection with the aid of reactions of "Byurne" [Burnet] and Wright (Huddleson).

As a rule, virtually healthy people were permitted to undergo the aerosol immunization, who showed negative sero-allergic reactions. Only for the purpose of a deepened study of the character of postvaccinal reactions to aerosol immunization 66 persons with positive reactions were subjected to the experiment, as well as a small group (10 persons) with initially chronic metastatic brucellosis in the stage of compensation.

Data, characterizing the state of health of 619 persons that were subjected to the aerosol immunization, obtained in the dispensary are summarized in table 1. [See the table at the end of translation]

It is seen from the cited data that only people with a regular state of health, with the habitual age pathology, who were referred to the category of "virtually healthy" underwent the aerosol immunization with the brucellosis dust vaccine. They were distributed, according to age, in the following manner: 18-30 years -80%; 30-40 years — 14.4%; 40-50 years — 5%, and 50-60 years old — 0.6%.

As it was mentioned earlier, 180 persons, among those who underwent aerosol immunization, were vaccinated previously, between the years 1954-1959, against brucellosis by the subcutaneous method, but before the aerosol immunization the sero-allergic reaction in them was negative.

The aerosol immunization was conducted in ordinary rooms, volume of 40 to 160m^3, cleared from superflous furniture. Up to 200 persons were brought together, simultaneously, in these rooms in a standing position. Atomization [Begin p. 97] of the vaccine was conducted continuously from special apparatuses during the course of the entire session, which continued for 15 minutes[1].

During the aerosol immunization each of the vaccinated inhaled 250-820 million live microbes of the vaccinal strain of Br. abortus bovis 19-BA. This dose proved to be optimal in the aerosol immuni-

[1] A detailed description of the method of aerosol immunization of men has been given in the Journal of Microbiology, Epidemiology and Immunobiology, 1961, nos. 7 and 9.

zation of people, as the specially conducted research has shown.

Medical examination of the state of health of the vaccinated was conducted during the course of 20 days with daily thermometry and questioning. A careful medical observation was conducted for about 2 years on the vaccinated who were in army units (427 persons), while of those vaccinated from the shoe factory and the sovkhoz- during the course of one year.

X-ray examinations of the chest organs were made of 506 aerosol vaccinated on the 1st, 3-4th, 7th, 15th and 20th days. In 159 persons during these periods analysis of peripheral blood was made, and in 36 persons a clinical analysis of the sputum.

The vaccinated with postvaccinal reactions were examined according to a special plan; it specified thermometry every 3-4 hours, electrocardiographic and x-ray examinations, clinical analysis of the peripheral blood, of urine and sputum, biochemical examination of blood (sugar, residual nitrogen, histamine, protein fractions)[2], oximetry, and determination of indices of maximum lung ventilation.

Postvaccinal reactions to the aerosol immunization were subdivided into general and local. To the general reactions were referred the increase of body temperature, changes on the part of the

[2] Results of biochemical research are not included in the present work and will be generalized in a special report.

central nervous system and the cardiovascular system, as well as the shifts in peripheral blood. The general reactions in the degree of manifestation was subdivided into mild (body temperature up to 37.5°), medium strength (body temperature up to 38.5°) and strong (body temperature over 38.5°). To local reactions were referred the changes on the part of the mucous membrane of the upper respiratory tracts, bronchi, lungs and lymph nodes, regional to them, which were revealed by clinical, laboratory and x-ray methods.

Data, which characterize the reactiveness of the method of aerosol immunization with the brucellosis dust vaccine, are cited in table 2 [which is at the end of the translation]: It is seen from it that aerosol immunization with the brucellosis dust vaccine, utilized in optimal doses which ensure a good immunological effect[3], produced general reactions in 7.8% and local in 2.4% of the vaccinated[4]. Whereupon the percentage of the strong and of the medium strength reactions, which led to short (1-2 days), partial loss of the capacity for work, comprised 2.95.

Frequency and degree of manifestation of postvaccinal reactions were in clear dependence on the initial immunological background of the immunized.

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[3] See data, cited in table 4.
[4] Local reactions were registered, as a rule, in persons with general reactions.

In persons with a negative sero-allergic background, independently of the subcutaneous immunization conducted in the past, the general postvaccinal reactions were observed comparatively rare (5.6%), and were expressed for the most part very mildly. Strong reactions and reactions of medium strength were noted in this group of vaccinated only in 1.6%, while the local reactions, in the form of a mild tracheobronchitis, which accompanied the general reaction, disappeared simultaneously with the latter. [Begin p.99]

The aerosol immunization, conducted for scientific research purposes, of persons, sensitized to brucellosis infection, caused, as one should have expected it, more frequent and expressed postvaccinal reactions: among 66 persons the general reactions were registered in 20 or 30.3%; whereupon in 9 (13.8%) among them they referred to the medium and strongly expressed; local reactions were noted in 10.6%. All postvaccinal reactions in this group came to an end in 2-3 days.

Immunization of 10 patients, ill with chronic brucellosis, produced general reactions in all of them. Local, mildly expressed reactions were observed only in 2 persons. All the postvaccinal reactions in this group came to an end in the course of 2-3 days.

Data about postvaccinal reactions are cited in table 3; it follows from them that in the presence in them of sensitization to brucellosis, which can be revealed only by the Wright reaction

(Huddleson), the aerosol immunization by the brucellosis dust vaccine produced development of post-vaccinal reactions considerably more often (13%), than in the immunization on the negative immunological background (5.6%). Aerosol immunization with a positive Burnet reaction caused postvaccinal reactions in 36.7%, and in the combination of positive reactions of Wright and Burnet the frequency of reactions reached 100%.

One can conclude from this that reactiveness of aerosol vaccinations with the brucellosis dust vaccine was determined by a number of persons, sensitized to brucellosis, which were present among the vaccinated. With the revealing of the sensitized persons and their exclusion from the number of the vaccinated, the reactiveness of aerosol immunization with the dust vaccine did not surpass by much the reactiveness of cutaneous vaccinations with the live brucellosis vaccine (Zankova, 1956; Taran, 1960).

We studied the immunological effectiveness of vaccinations with the aid of agglutination reactions (of Wright and Huddleson) and the intracutaneous allergic test of Burnet. The reaction was set up according to the standard method in 7, 10, 15,30,45,90, 180 and 365 days after immunization. Only those persons were examined in whom the sero-allergic reactions were negative before the aerosol immunization. A new group of people was examined during each period. [Begin p. 100]

Results of examinations, conducted in the indicated direction, are cited in table 4 [Table is at the end of the translation]

The positive reaction of Huddleson with a mean titer 1:243 was noted in 13.5% of vaccinated already in 7-10 days after immunization. In 15 days the positive reaction with a titer 1:273 was observed in 53% of the examined. In 30-45 days after immunization the number of persons with a positive reaction increased to 59% (mean titer 1:243), and in 3 months to 8[illegible]% (mean titer 1:308). In distant periods after aerosol immunization (in 6 and 12 months) the number of positive reactions correspondingly comprised 53.2 and 60% with a mean titer 1:200 and 1: 170.

The Wright's reaction in 30-45 days after immunization was positive in 55% (the mean titer 1:170), in 3 months — in 65% (1:166) and in half a year — in 36.8% of the vaccinated (1:95)

The Burnet reaction was registered in 16% of the vaccinated already in 7-10 days after vaccination. In 15 days the number of positive reactions reached 50%, in 90 days — 55.5%, in 180 days — 30% and in a year — 37.6%.

In comparing the indicators of serological reactions and of the intracutaneous allergic test one can see that in the early periods after immunization (7-15 days) they were registered approximately with a similar frequency, while subsequently (in 30-360 days) the positive reaction of Huddleson was observed by 19-27% more often than the positive Burnet test.

If the immunological effectiveness is not to be evaluated on all three tests simultaneously, but just according to one of them, then already in 7-10 days [illegible] after the aerosol immunization approximately

in one third of the vaccinated it is possible to register certain immunological shifts. In 5 days the number of the positively reacting persons increased to 75%, in 30-40 days — up to 80%, while in 3 months — up to 93.5%. After a year the number of positively reacting still comprised 75% [sic].

The obtained results attest that in the aerosol immunization [Begin p.101] with the brucellosis dust vaccine a rapid and long lasting immunological reorganization occurred in the vaccinated persons, which in its intensity and frequency of positive reactions was not surpassed by the reorganization that occurred after the subcutaneous immunization, and exceeded the results that were registered in the cutaneous ministration of the brucellosis vaccine (Abashidze, 1958; Vershilova with co-authors, 1952; Drankin and Malyitin, 1955; Zenkova, 1956; Polyakova, 1954; Taran, 1960; Khalkina, 1956).

Dynamics of the immunological reactions in persons who had a sero-allergic background before the aerosol immunization represent doubtless interest. In this group of people, as it is seen from table 5, after 3 months of immunization clear changes were observed in the Burnet reaction. Sensitization of the organism to the brucellosis antigen increased considerably under the effect of the aerosol immunization. Number of the Burnet reactions increased from 10 to 24 and the number of persons with a simultaneous presence of positive reactions of Huddleson and Burnet increased (from 4 to 20).

Dynamics of the Huddleson reaction were somewhat different. In a part of the persons, who were subjected to aerosol immunization, a clear growth of titers was registered (the mean titer increased from 1:152 to 1:235). Along with this in 8 person, from among the 28 aerosol vaccinated on the positive sero-allergic background, the Huddleson reaction changed to negative from the positive.

Conclusions.

1. All virtually healthy people of both sexes, between the ages of 18 and 60, who have no medical contrindications to inoculations and are not sensitized to the brucellosis infection, can be admitted to aerosol immunization with the brucellosis dust vaccine.

2. The optimal dose of the brucellosis dust vaccine, inhaled by the vaccinated person, is a dose equalling 250-820 (1000) million live Brucella of the vaccinal strain 19BA.

3. In mass aerosol immunization of people with the brucellosis dust vaccine, the reactiveness of vaccinations is determined by the number of persons among them who are sensitized to brucellosis.

4. In the absence of positive sero-allergic reactions in persons, who previously underwent subcutaneous (cutaneous) inoculations with the live brucellosis vaccine, their aerosol revaccinatio with the brucellosis dust vaccine did not produce any increased reaction. [Begin p. 102]

5. Aerosol immunization produced a rapid and long lasting immunologic reorganization of the organism of the vaccinated, which

was registered, during the course of a year (period of observation).

6. It is necessary to continue a comparative deepened study of the character of postvaccinal reactions, which are observed after the subcutaneous, cutaneous and aerosol immunization with the live brucellosis vaccine.

7. It is necessary to recognize as very essential the research for new, more improved methods for the revealing of persons, sensitized to brucellosis.

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State of health of person who went

Diseases			
Total amount of the immunized		619 (100%)	
of internal organs (therapeutic)	neurocirculatory dystonia	4 (0.65%)	
	diseases of the cardiovascular system	4 (0.65%)	
	focal pneumosclerosis	2 (0.32%)	
	chronic bronchitis	1 (0.16%)	
	residual phenomena after pulmonary tuberculosis	5 (0.8%)	
	chronic gastritis	12 (1.93%)	
	other diseases of the gastro-intestinal tract	6 (0.97%)	
	cystitis	1 (0.16%)	
	In all	35 (5.6%)	
Surgical	residual phenomena after operations, trauma and contusions	7 (1.13%)	
	dilatation of veins of the spermatic cord	7 (1.13%)	
	others	5 (0.8%)	

Table 1

who underwent aerosol immunization

Diseases												
urgical				Ear, throat and nose					Neural	Eye	In all
dilatation of veins of the spermatic cord		others	In all	chronic tonsillitis	chronic rhinitis	chronic pharyngitis and laryngitis	chronic otitis in the state of remission	In all	plexitis, neuralgia, and others	chronic conjunctivitis	abs. [absolute]
7 (1.13%)		5 (0.8%)	19 (3.06%)	25 (4%)	11 (1.8%)	12 (1.93%)	2 (0.32%)	50 (8.05%)	5 (0.8%)	2 (0.32%)	111 (17.87%)

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Character of reactiveness, observed after aerosol immunization with brucellosis

Group of immunized	Number of immunized	Number of persons with general reactions								Number of persons with local reactions				
		mild		medium strength		strong		in all		pneumonia	specific lymphadenitis	tracheobronchitis	in all	
		abs.	%	abs.	%	abs.	%	abs.	%				abs.	%
With negative sero-allergic reactions	1,125	45	4	10	0.9	8	0.7	63	5.6	-	-	18	18	1.6
With negative sero-allergic reactions	66	11	16.5	4	6.4	5	7.4	20	30.3	-	-	7	7	10.6
Sick with brucello-	10	2	20	5	50	3	30	10	100	-	-	4	4	40
In all	1,201	58	4.85	19	1.6	16	1.35	93	7.8	-	-	29	29	2.4

Table 2

lesis dust vaccine							
s with	Number of persons who could not work						
n all			Duration (in days)				
bs.	%	bs.	%	1	2	3	4
18	1.6	18	1.6	3	10	5	
				39.7 hours			
7	10.6	9	13.8	1	4	4	1
				44 hours			
4	40	8	80	1	3	3	1
				47.2 hours			
25	2.4	35	2.9	5	17	12	1
				42.8 hours			

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Table 3

Results of estimation of postvaccinal reactions

Group of the immunized	Immunological reaction	Number of vaccinated	Number of persons with general reactions					Inhaled dose (in millions of live microbes)
			mild	medium strength	strong	in all abs.	in all %	
On the positive sero-allergic background	Bright	31	3	-	1	4	13.0	250-820
	Burnet	30	7	2	2	11	36.7	250-820
	Bright + Burnet	5	-	3	2	5	100	250-820
	In all	66	10	5	5	20	30.3	250-820
Ill with brucellosis	Burnet	5	2	1	2	5	100	250-820
	Bright + Burnet	5	-	3	2	5	100	250-820
	In all	10	2	4	4	10	100	250-820
On the positive sero-allergic background, with a small dose	Bright	3	-	-	-	-	-	15
	Burnet	15[1]	-	1		1	-	15

[1] In 4 persons out of 5 the reaction was mildly positive, the postvaccinal reaction was registered only in one vaccinated person who had a strongly expressed Burnet reaction

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Table 4

Evaluation of the immunologic

Day of examination	Number of the examined	Burnet reaction		Huddleson's reaction			Effect
		Number of persons with a positive reaction	% of positive reactions	Number of persons with a positive reaction	Mean titer of reactions	% of positive reactions	Number of persons with positive effect
7 to 10th	156	28	18	21	1:243	13.4	—
15th	60	30	50	32	1:277	53	—
30-45th	73	29	40	43	1:243	59	40
90th	74	41	55.5	61	1:308	82	58
180th	30	9	30	16	1:200	53.4	11
365th	69	26	37.6	41	1:170	60	—

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Effectiveness of inoculations				
[illegible]			Number of persons who had even one positive reaction	
Number of persons with positive reaction	Mean titer of reactions	% of positive reactions	Absolute	%
—	—	—	42	27
—	—	—	45	75
40	1:170	55	53	88
48	1:166	65	69	93.5
11	1:95	36.8	20	67
—	—	—	52	75

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Table 5

Dynamics of immunological reactions in persons with a positive sero-allergic background

Time of examination	Character of immunologic shifts								
	Positive Huddleson reaction							Positive reaction of Burnet	Combination of positive reactions of Huddleson and Burnet
	Number of the examined	Number of positive reaction	Titer						
			1:50	1:100	1:200	1:40	mean		
Before vaccination	28	28	7	9	9	3	1:152	10	4
In 3 months after vaccination	28	20	5	4	2	15	1:237	24	20

5-27-63

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