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POSTVACCINAL PATHERGY IN BRUCELLOSIS  
REPORT I

Following is a translation of an article by G.A. Balandin and S.P. Sazykin of the Rostov-on-the-Don Scientific Research Anti-Plague Institute in the Russian-language periodical Zhurnal mikrobiologii, epidemologii, i immunobiologii (Journal of Microbiology, Epidemiology, and Immunobiology), No 8, 1963, pages 44-48. The article was submitted on 22 October 1962.

There is a considerable number of reports by both scientific and practical workers (Vershilova, 1956, 1960; Zdrodovskiy, 1949; Vershilova et al., 1952, etc.) which give sufficiently convincing evidence that the live brucellosis vaccine is harmless to man. The local or general reactions which sometimes occur not only in subcutaneous but also in epidermal introduction into the organism of man are based not on its reactogenousness but rather on the reactiveness of the inoculated persons themselves who had been sensitized through the previous artificial (upon vaccination) or natural (upon infection) penetration of *Brucella* organisms into their organism (Vershilova, Feder, and Polyakova, 1952; Polyakov et al., 1959). It should, however, be emphasized that all these observations were conducted either immediately after vaccination or during the course of a relatively short period of time after it, which in this case is particularly important only after a one-time administration of the vaccine. Clinically indicated brucellosis connected with the development of a microbial (purely infectious) factor was not found in these persons. With respect to the

development in persons inoculated against brucellosis or a state of pathergy in the broad sense, where the brucellosis was connected with their sensitization by live Brucella organisms of the vaccine strains Br. abortus No 19 and 19-BA, in this sense there is only one report by Vershilova, which itself is not sufficiently concrete, which she made in December 1960 at the scientific-practical conference of veterinary and medical personnel of the oblasts of the Urals and Western Siberia on the questions of the occurrence of brucellosis and tuberculosis in farm animals and the lowering of the incidence of these diseases among people. She calls the indicated phenomenon vaccinal pathology in the case of brucellosis.

Considering the unclearness of this problem, we undertook a study of it at one of the sausage plants which were located outside the main area of a meat combine. The workers of this plant had, without sufficient basis, been vaccinated (first subcutaneously and then epidermally) and revaccinated over the course of a number of years against brucellosis with live vaccine.

Altogether 271 persons at the plant were subjected to immunological and clinical investigation, including 198 who had been vaccinated against brucellosis and 73 who had not.

In a one-time sero-allergic investigation of the 73 persons who had not been vaccinated against brucellosis, in three Huddleson's agglutination reaction was positive only with 0.02 ml of serum, while at the same time there were negative results from Wright's reaction and from Boerne's skin allergy test. In all these cases the agglutinate was finely fibrous and was located in the center, which, as was established by one of us (Balandin, 1958), is characteristic of the non-specific positive results of this diagnostic reaction. In addition to this, the index of opsono-phagocytic reaction for these three persons was zero. Everything taken together gave us a basis for not considering them to be infected with brucellosis.

Only in the case of one female worker who had come to the plant 28 days prior to the investigation was the Boerne allergic skin test weakly positive (area of skin edema of 6 x 3 cm with a maximum thickness of its fold of 3 mm), while the results of the Huddleson, Wright, and opsono-phagocytic reactions were negative. All this gave

sufficiently convincing evidence that the person being investigated had been infected with brucellosis in the remote past. The epidemiological anamnesis made it possible to assume that the infecting took place on one of the collective farms of Krasnodarskiy Kray which had an unfavorable situation with respect to brucellosis of the cattle type, where she had worked for a number of years as a milkmaid.

The remaining 69 unvaccinated persons who had worked at the sausage plant for 1 or 2 up to 26 years reacted negatively with respect to all diagnostic reactions.

In addition, it was established that at one of the canneries where they processed the same meat as at the sausage plant there was not a single case of brucellosis, although no one had ever been vaccinated.

Upon considering that which has been said, we came to the conclusion that conditions did not exist at the sausage plant which would threaten the workers with the possibility of infection with brucellosis. Kosilov and Seleksiya (1962) showed that in the case of the experimental infection of sheep with Brucella organisms of the melitensis type, Brucella organisms were not found in the carcasses of these animals, even when they were killed during the acute period of the development of brucellosis but with the parenchymatous organs and lymph nodes having been removed.

All the indicated situations led us to consider the positive results of immunodiagnostic reactions for brucellosis and changes in the state of health characteristic of brucellosis (see above) in workers of the sausage plant who had been vaccinated against this infection as being the result of their vaccination and revaccination with live brucellosis vaccine.

Of the 198 persons who were vaccinated against brucellosis, 79 were vaccinated once, 57 were revaccinated once, 35 were revaccinated twice, 19 were revaccinated three times, 6 were revaccinated four times, and 2 were revaccinated 5 times. All were examined serologically (Huddleson's reaction and Wright's reaction) allergically (Boerne's test); in addition the phagocytic activity of their polynuclear neutrophils was determined (according to Streeter); we noted subjective complaints and objective symptoms characteristic of brucellosis in its allergic

phase (Zirodovskiy, 1949, 1953, 1961; Rudnev, 1949, 1955; Vershilova, 1961). Finally, all entries in the journal of the medical point of the plant concerning the state of their health and the basis (diagnoses) for issuing temporary disability slips were considered. They were examined within a minimum of one to two years (160 persons) and a maximum of seven to eight years (7 persons) after the completion of the administration of live brucellosis vaccine.

From Table 1 it is most clearly evident that the degree of seroallergic reactivity of persons vaccinated against brucellosis was in direct relation to the degree (multiplicity) of their antigenic stimulation by live *Brucella* organisms of vaccine strains Br. abortus No 19 and 19-BA. The phagocytic activity of the leukocytes also followed this pattern, although its average value for vaccinated persons of all groups was within the range of the second degree of this activity.

However, the determination of the degree of specific sensitivity of persons vaccinated against brucellosis which, as was later established, plays a basic role in the development of postvaccinal allergy in the case of brucellosis was clearly inadequate if based only on the fact of positive reactivity to Boerne's test. This circumstance led us to consider the average values of the maximum dimensions (areas) of the inflammatory edema of the skin and the degree of its thickening within 24 or 48 hours after setting Boerne's test for each group separately. In addition, the degree of their general reactivity to the cutaneous administration of brucellin was considered.

Table 2, in which the data obtained in this case is totalled, gives even clearer evidence of the direct relation of the degree of sensitivity of persons vaccinated against brucellosis to the extent of specific antigenic stimulation (even in those cases where the individual groups which we investigated were represented by a small number of persons).

What is more, in a series of cases it was only the revaccinated in whom local skin reactions to brucellin ended with clearly expressed necrosis, which we never observed in persons with natural brucellosis infections, including those of the goat-sheep type. This also was evidence of their high degree of specific sensitivity.

Table 1

The degree of sero-allergic reactivity to brucellosis in workers at a sausage plant who had been inoculated with live brucellosis vaccine

Group of persons investigated	Number investigated	Nature of reaction				Number reacting positively		Index of opsono-phagocytic reaction					Average
		Huddleson				Serology - cally	Allergy - cally	0-4	5-25	26-50	51-75	Not determined	
		-	+	+	-								
		Boerne				Serology - cally	Allergy - cally	0-4	5-25	26-50	51-75	Not determined	
Vaccinated. . . .	79	16/20	6/8	35/44	22/28								41/52
Revaccinated one time	57	5/9	9/16	29/51	14/21	38/67	43/75	25/45	5/9	11/20	14/26	2	41
" 2 times	35	1/3	1/3	22/63	11/31	23/60	33/51	13/41	7/22	5/15	7/22	3	50
" 3 times	19	1/5	1/5	12/63	5/27	13/68	17/89	3/17	6/33	6/33	3/17	1	50
" 4 times	6	-	-	6/100	-	6/100	6/100	-	-	3/50	3/50	-	45
" 5 times	2	-	-	1/1	1/1	1/2	2/2	-	1/1	-	1/1	-	-

Symbols: + positive result, - negative result, numerator -- absolute numbers, denominator --- percents (arbitrary)

Table 2

The degree of sensitivity of persons who have been vaccinated against brucellosis in relation to the degree of their antigen stimulation by live brucellosis vaccine

Group of persons investigated	Number investigated	Average values		Number who showed a general reaction to Boerne's test (in arbitrary percentages)
		Area of inflammatory edema of the skin according to Boerne's test (in cm <sup>2</sup> )	Thickness of the cutaneous fold of the edema (in mm)	
Vaccinated. . . . .	79	22	6.3	6.3
Revaccinated	57	24	7.2	12.3
"	35	35	11.1	20
"	19	30	14.5	42.1
"	6	34	12.8	Two of six
"	2	12 and 48	2.1 and 13.4	Two of two

Upon questioning the persons who had been vaccinated against brucellosis we devoted particular attention to their subjective evaluation of their state of health (complaints of pain in the extremities, joints, lumbar area, changes in ones feelings with change in weather, etc.) and also on some objective symptoms of these changes (an increase in the body temperature, the degree of perspiration, the painfulness of various parts of the body including the paravertebral points upon palpitation, etc.). In a series of cases not only the objective symptoms but also the subjective symptoms of brucellosis, including those confirmed in the laboratory, served as a basis for freeing persons vaccinated against this disease from work according to temporary disability which, as is apparent from Table 3, also depended on the degree of sensitivity from the live brucellosis vaccine and considerably exceeded these indices in a group of workers who had not been vaccinated against brucellosis. In all these cases disability slips were issued because of myositis, radiculitis, mono- and polyarthrits, tendo-vaginitis, lumbago, pleuralgia, ischialgia, neuralgia, chronic brucellosis, and its aggravations.

In addition, in the journal entries of the medical point of the sausage plant for the last 5 years it was found that disability slips had been given to 11 persons who had formerly worked at the plant; the total number of days of the disability slips was 559 (an average of 51 days for each of them); the reasons for giving the slips were "chronic brucellosis," "aggravation of chronic brucellosis," "residual effects of chronic brucellosis," "chronic polyarthrits of brucellosis etiology," and one person receiving 14 days due to "acute brucellosis." In a number of cases these ailments were the reasons for the worker leaving the sausage plant. In comparing the names of these persons with the lists of those who had been vaccinated against brucellosis and upon visiting them at their homes it was found that during the time they had worked at the sausage plant they had all been vaccinated and revaccinated more than once with live brucellosis vaccine.

Table 3

Relation of changes in the state of health of persons who have been vaccinated against brucellosis to their immunological reactivity to this infection

Results of determining the reactions		Number investigated	Changes in the state of health		Disability in man-days	
Huddleson	Boerne		Subjective (in arbitrary percentages)	Objective (in arbitrary percentages)	For each person	For each of the group
-	-	23	34.8	17.4	19.8	6.9
+	-	17	53	17.6	14	6.8
+	+	105	51	18.1	16.6	5
-	+	53	45.3	18.9	21.6	6.5
			} 49.4	} 18.4	} 18.2	} 5.5
Nonvaccinated (control)		93	27.4	8.2	7.8	1.3

### Conclusions

A specific sensitivity is observed in persons upon vaccination and revaccination with live brucellosis vaccine. As a result a pathergic state develops in them; its expression is in direct relation to the degree of specific antigenic stimulation.

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