ON THE TITRATED ALLERGIC TEST FOR BRUCELLOSIS

(Preliminary Report)

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The intradermal allergic test proposed by Burnet in 1922 found, as is known, wide application in the diagnosis of brucellosis in clinical medicine and during epidemiological investigations. Many investigations [1, 2, 3] showed that the allergic test has a substantial diagnosis significance in the later stages of the illness, when the number of positive reactions increases noticeably and exceeds the percentage of positive results obtained during examination of the blood with the agglutination reaction. The significance of this method is also great in the demonstration of hidden forms of the disease (in foci and brucellosis) and for the evaluation of the immunological change of the system of those who have been inoculated with attenuated live vaccine.

The skin allergy test is carried out, as is known, by introducing a certain standard dose of brucellosis antigen and subsequently following the local reaction. The latter is read from weakly positive (when the diameter of the inflamed area is 1-2 cm) to positive (when the diameter of the inflamed area increases to 3-6 cm) and strongly positive (when the inflamed area is larger and when generalized symptoms appear). Suggested also (by I. V. Seppi) has been reading the severity of the reaction by the area of edema, considering the reaction doubtful when the endematous area does not exceed 4 cm^2, weakly positive when the edematous area is 5-10 cm^2, positive if the endematous area reaches 11-25 cm^2, and strongly positive when the area is larger still.

As is known, the intradermal toxicity tests – Schick's and Dick's tests – are based on the same principle, i.e. on the introduction of a definite dose of poison, while the sensitivity of the system is evaluated according to the intensity of the local reaction, depending on the size of the reddened area. In the works of V. I. Ioffe [4] and coworkers on the immunology of scarlet fever, there is a critique of this method and the advantage of another method, based on the determination of the threshold and sensitivity of the toxin, is shown. The threshold of sensitivity is found by using the so-called titrated skin tests, when the testing is carried out with fractional doses of toxin, as well as with a standard dose (in the investigations of V. I. Ioffe – one skin dose of scarlet fever-streptococcus toxin, 1/3 and 1/10 of the dose).

The problem of the applicability of a similar principle to the study of the degree of sensitization of the system was the subject of N. N. Rubel's [6] investigations, which showed, in animal experimentation, the quantitative relationship between a decreasing area of the zone of the reaction and a dose of allergen administered intradermally into an immunized animal. The titrated allergic test was also tested in the clinic. Thus, for instance, L. M. Model and E. F. Sidelnikova [5], in evaluating the allergy tests of Mantoux and von Pirquet, produced data which indicate the worth of determinations of the system's degree of sensitivity to various doses of tuberculin not only for the purpose of diagnosing tuberculosis, but also for the characterization of its course. B. L. Ittsikson studied the dynamics of streptococcal sensitization during scarlet fever with the help of the titrated test.

The problem of the present work was the testing of the titrated allergy test during brucellosis.

The Burnet reaction was studied in its usual form in 675 healthy persons who lived in foci which are unsafe as regards brucellosis, on 195 persons inoculated against brucellosis within 30 days to 6 months after inoculation, and in 118 patients who had been ill from 1 month to 2 years.

The results which were obtained (Table 1) correspond with the data in the literature regarding the high percentage of positive reaction in patients, the possibility of demonstrating hidden immunization in foci of brucellosis, and the pronounced immunological change in inoculated persons. In addition, the noticeable increase in the number of positive reactions half a year after inoculation and the almost identical results obtained in investigations of inoculated and healthy persons during this time attracted attention. These two groups were subjected to additional investigations with the help of titrated allergy tests.

TABLE 1

Results of Intradermal Allergy Tests using the Usual Method

Group under investigation	Number under investigation	Number of investigated (in %) by severity of reaction			
		+++	++	+	–
Clinically healthy persons, found in a focus of brucellosis	398	10.3	9.5	10.5	69.7
Clinically healthy persons who had lived in a focus of brucellosis (varying lengths of time after leaving)	277	14.0	3.6	10.8	71.6
Inoculated persons (30-40 days after inoculation)	114	6,1	7.9	10.8	75 2
Inoculated persons (6 months after inoculation	81	30.0	26.7	19.6	23.7
Patients	118	33,1	33 1	20.3	13.5

Symbols +++ area of edema $> \pi\frac{20}{4}$; ++ $\pi\frac{10}{4}$ to $\pi\frac{20}{4}$; + $< \pi\frac{10}{4}$;

Correlation of the results of the usual and titrated allergy tests on 102 patients (180 tests) are presented in Table 2.

As could be expected, the definite correlation between the results obtained in both methods of investigation is preserved. However, the coincidence is not complete. Thus, of 24 patients whose reaction was read as one plus (+), 6 patients reacted to 1/50 dose of allergen; on the other hand, of 39 patients with a strong reaction (+++), 3 reacted only to the full dose of allergen, and 12 other patients to 1/10 dose only. Similar deviations were observed also in the group of patients whose reaction was read as two plus (++). It is evident that of 49 patients who reacted to 1/50 dose of allergen, only half responded to administration of a full dose with a severe reaction (+++), while of the 13 patients with low sensitivity, i.e. those reacting to the full dose only, 3 showed severe reactions (+++).

At the same time, the titrated test reflected the changes in the system's level of sensitivity more accurately. This can be illustrated by several examples of patients and, especially, by comparison of the results obtained with patients and inoculated persons.

Examples of the changes in the allergic reactions of 4 patients ill for varying lengths of time – from 4 months to 2 years – are shown in Table 3. If patient K.'s reaction to the single dose were considered alone,

TABLE 2

Correlation of Data from the Usual Allergy Tests and of Determinations of Sensitivity Thresholds to the Allergen in Patients.

Severity during the usual test	Number of patients				Number of reactions			
	Total	Reaction to 1/50, 1/10, and 1 dose	Reaction to 1/10 and 1 dose	Reaction to 1 dose	Total	1/50, 1/10, and 1 dose	To 1/10 and 1 dose	To 1 dose
+++	39	24 (61.5)	12 (30.7)	3 (7.6)	77	43 (55.8)	31 (40.2)	3 (3.8)
++	39	19 (48.7)	16 (41)	4 (10.2)	71	26 (36.6)	36 (50.7)	9 (12.6)
+	24	6 (25)	12 (50)	6 (25)	32	7 (21.8)	16 (50)	9 (28.1)

Note: Percentages are indicated in parentheses.

TABLE 3

Changes in the Signs of Allergic Reaction in Patients Ill for Varying Periods of Time

Dose of allergen	Years		Patient K-va 10 months		Patient Z.; 2 years				Patient O.; 2 years	
	13/X	10/XI	16/II	2/III	17/XI	1/XII	15/XII	29/XII	15/XII	29/XII
1	$\pi\frac{20}{4}$	$\pi\frac{16}{4}$	$\pi\frac{16}{4}$	$\pi\frac{16}{4}$	—	$\pi\frac{12}{4}$	$\pi\frac{29}{4}$	$\pi\frac{10}{4}$	$\pi\frac{55}{4}$	$\pi\frac{35}{4}$
1/10	$\pi\frac{10}{4}$	$\pi\frac{15}{4}$	$\pi\frac{5}{4}$	$\pi\frac{6}{4}$	—	$\pi\frac{2}{4}$	$\pi\frac{6}{4}$	$\pi\frac{2}{4}$	$\pi\frac{4}{4}$	$\pi\frac{14}{4}$
1/50	—	$\pi\frac{3}{4}$	$\pi\frac{4}{4}$	—	—	$\pi\frac{2}{4}$	—	—	—	$\pi\frac{4}{4}$

Note: The severity of the reaction is indicated by the size of the area of edema which was calculated by the formula for an ellipse.

one could think that her sensitivity to the allergen on the second test would be less, while the titrated test revealed the system's growing sensitivity. The changes in the sensitization of the system of patient K-va could only be demonstrated by determination of the threshold of sensitivity to the allergen by the titration method. A marked increase in the area of edema in comparison with the reaction of 2 weeks before was observed in patient Z. on December 15; this, however, did not indicate a significant rise in sensitization since her reaction was negative to 1/50 dose while her reaction to 1/10 dose remained almost the same as before. Subsequent tests two weeks later confirmed this. Finally, in the last example, one could think that the sensitivity to the allergen had decreased, since the area of edema had become noticeably smaller when the full dose of allergen was used. In actual fact, the sensitivity to the allergen increased, and this could be found only by determining the threshold of sensitivity.

Comparison of the results of tests on patients and inoculated persons is very indicative (Table 4). With the usual allergy test, the percentage of positive reactions was almost the same in both groups. However, the titrated test uncovered substantial differences. While 75.7% of the patients reacted to 1/10 dose of allergen, a positive reaction was found in only 9.8% of the inoculated persons; not one inoculated person reacted to 1/50 dose, while 41.5% of the brucellosis patients showed a positive reaction. Thus, the patients and persons inoculated against brucellosis possessed different sensitivities to brucellosis allergen, and these differences were clearly demonstrated by the titrated allergy test based on the determination of the threshold of sensitivity.

TABLE 4

Determination of the Threshold of Sensitivity to Allergen in Patients and Inoculated Persons

Subjects	Number of subjects	Percentage reacting positively		
		To undiluted brucellergin	To diluted brucellergin	
			1:10	1:50
Inoculated persons.	81	76.3	9.8	0
Patients	118	84.4	75.7	41.5

The data presented indicate that the titrated allergy test (determination of the threshold of sensitivity to the allergen) can be used as a more exact method for the clinico-immunological and epidemiological investigations of brucellosis.

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