THE RATE OF DEVELOPMENT OF IMMUNITY AFTER REVACCINATION WITH ANAEROBIC TOXOIDS

R. A. Saltykov, F. F. Rezepov and E. M. Zemskov (Moscow)

(Received April 17, 1958. Presented by Active Member AMN SSSR P. F. Zdrodovskii)

A considerable volume of experimental and clinical evidence has now been accumulated on the rate of development of immunity after revaccination with tetanus toxoid. According to the majority of workers, an increase in the blood antitoxin titers is observed on the 3rd-5th day after revaccination. Separate workers assert, however, that after revaccination, the immunological reorganization of the body takes place much more quickly and an increase in the blood antibody titers is observed during the first 24 hours, or even within a few hours of injection of toxid into the animal [4, 5].

The study of the rate of development of immunity after revaccination is of great practical interest in solving the problem of finding a possible substitute for the prophylactic use of serum to prevent toxic infections in those previously immunized, in the form of revaccination with toxoids, for these preparations are more readily available and cheaper than therapeutic sera. Many workers have indicated that this replacement is possible in the prophylaxis of tetanus [1-3, 5-8]. In the U.S. Army, wounded who have previously been immunized against tetanus are given tetanus toxoid alone for prophylactic purposes [9].

In order to discover the more general character of development of antitoxic immunity after revaccination, in our research we used perfringens, oedematiens, botulinus toxoids in addition to tetanus toxoid.

EXPERIMENTAL METHOD

The investigations were carried out on animals and also on volunteer members of our staff, and these were given primary immunization with concentrated toxoids adsorbed on aluminum hydroxide.

In the first stage we studied the rate of increase of the blood antitoxin titers after revaccination in 12 human subjects. Experiments were also conducted on 38 rabbits and 3 monkeys (Macacus rhesus). Before revaccination and at various times afterwards, starting at 24 hours, the blood concentrations of perfringens, oedematiens, tetanus and botulinus type A antitoxins were determined. The sera were titrated individually by the usual method in white mice. To exclude variations in the titers of the sera due to the method of titration, the blood antitoxin titers in the same animal at different times were determined in the same titration experiment and using the same sample of standard toxin and the same batch of mice.

The animals used in the experiments had received different forms of preliminary immunological preparation (immunized once or twice). We studied the effect of primary and revaccination with different doses of toxids (from 0.1 to 5 ml).

EXPERIMENTAL RESULTS

In all the experiments the pattern of the results was the same for the various antigens: an increase in the blood antitoxin titers was observed not sooner than 3-5 days after revaccination. An increase in the doses of toxoid, replacement of adsorbed preparations by nonadsorbed and the creation of improved condictions for absorption of the toxoid (intramuscular injection) had no essential effect on the rate of increase of the blood

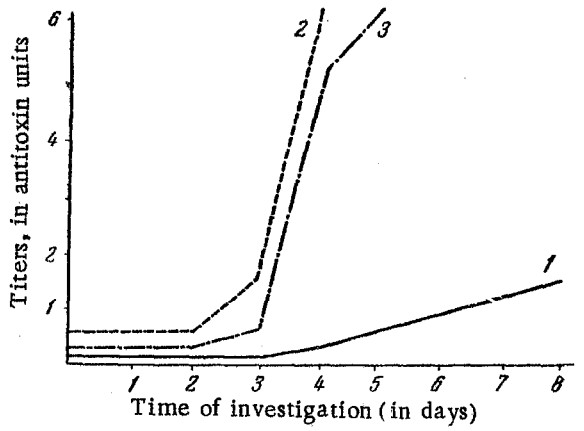

Fig. 1. Increase in the blood titers of perfringens, oedematiens and botulinus type A antitoxins in rabbits after revaccination. 1) Perfringens; 2) oedematiens; 3) botulinus type A.

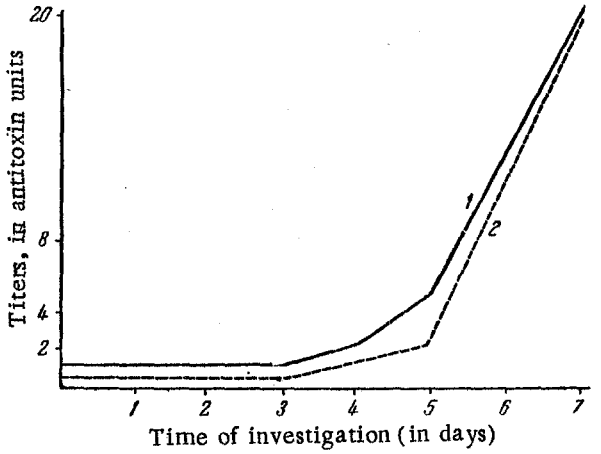

Fig. 2. Increase in the blood titers of tetanus and botulinus type A antitoxins in monkeys after revaccination. 1) Tetanus; 2) botulinus type A.

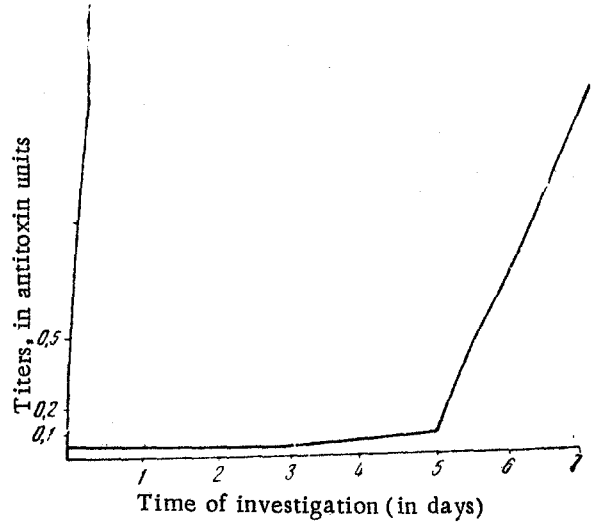

Fig. 3. Increase in the blood titers of tetanus antitoxin in human subjects after revaccination.

antitoxin titers. The experimental results are shown in Figs. 1-3.

It is not only the concentration of antibodies in the blood that determines the state of immunity; besides humoral factors, an important role is also played by tissue insusceptibility. Many workers have established that an increase in resistance after immunization may develop sooner than antibodies can be detected in the blood of the animals.

In view of this, in the next experiments, besides investigating the blood antibody concentrations, we studied the resistance of the animals to toxin at different times after revaccination. Experiments were carried out on rabbits, using perfringens and botulinus type A toxoids and toxins.

The results of the experiments showed that a clear increase in the resistance of the animals to toxin was observed 4-6 days after revaccination, parallel with a considerable rise in the blood antitoxin concentration. Two days after revaccination, no increase in the blood antitoxin titers could be detected by the ordinary methods of titration, but some increase in resistance was observed at this time, as shown by the survival of a larger number of experimental than control animals and by the less severe form of toxic manifestations in the experimental rabbits. Revaccination done at the same time as the toxin was injected has no prophylactic effect: the experimental animals died at the same times as the nonrevaccinated controls. The use of highly concentrated toxoids, increase in their dosage or fractionated injection of the preparations did not increase the effectiveness of revaccination.

Altogether we carried out 7 experiments on 216 rabbits. Similar patterns were obtained in all the experiments.

The increase in the resistance of the animals to toxin after revaccination shows itself only 1-2 days before the increase in the blood antibody concentration is found, and not less than 2 days after revaccination. The results of 2 experiments are shown in the table.

Our results are in agreement with the findings of the majority of workers on the relatively late development of immunity after revaccination (3-5 days). Our investigations did not confirm findings that a very early increase in the blood antitoxin titers takes place after revaccination [4, 5].

Revaccination, as a method of urgent prophylaxis, may evidently be used successfully to replace administration of antitoxic serum when the incubation period of disease is sufficiently long (tetanus). The rapid

Rate of Immunological Reorganization after Revaccination of Rabbits with Perfringens and Botulinus Type A Toxoids

Vaccine preparation	Revaccination		Times of injec. of toxin after revaccination (in days)	Doses of toxin	Blood antitoxin titers		Experimental results		
	doses of toxoid (in ml)	times after primary immunization (in months)			before revaccination	at the moment of injec. of toxin	Total number of animals	developed the disease	died
Perfringens toxoid	0,7—5	4	6	1 MLD	<0,1	0,5—1	5	1	0
			4			0,2—1	10	6	2
			2			<0,1	5	5	1
			Simultaneously with revaccination			<0,1	5	5	3
						<0,1	5	5	3
	Toxin control								
Botulinus type A toxoid	0,1—5	6	4	Minimal dose to overcome the immunity: 10 MLD for fresh animals	<0,025	0,05—0,25	8	0	0
			2			<0,025	15	14	7
			Simultaneously with revaccination			<0,025	5	5	4
						<0,025	5	5	4
	Toxin control								

prophylactic effect of revaccination is very unreliable in gas gangrene, in view of the short incubation period of this disease.

SUMMARY

Investigations conducted on volunteers as well as on rabbits and monkeys demonstrated that following revaccination with anaerobic toxoids (perfringens, oedematiens, tetanus, botulinus) the rise of the antitoxin titers is noted in the blood not earlier than on the 3rd-5th day.

An increased resistance to toxins occurs in the revaccinated animals 24-28 hours before the detectable rise of the antibody titer, but is noted only on the 2nd-3rd day after revaccination.

Replacing the administration of antitoxic serum by revaccination as a method of quick prophylaxis may succed only when the disease has a sufficiently long incubation period.

LITERATURE CITED

[1] B. V. Voskresenskii, O. I. Nikolaeva, Arkh. Biol. Nauk SSSR, 49, 2, 86-101 (1958).

[2] P. F. Zdrodovskii, Reactivity in Infection and Immunity, pp. 151-160. Moscow, 1950 [In Russian].

[3] R. B. Kruk, Experimental Tetanus Revaccination. Candidate's dissertation, 1952 [In Russian].

[4] D. F. Pletsityi, A. S. Labinskaya, A. S. Aksenova, Zhur. Mikrobiol. Epidemiol. i Immunobiol. No. 1, 32-36 (1956).

[5] A. V. Ponomarev, Modern Problems in General Pathology, pp. 100-117, Moscow — Leningrad, 1950 [In Russian].

[6] P. W. Baird, Yale J. Biol. a. Med. v. 21, p. 385-389 (1949).

[7] H. J. Banton, P. A. Miller, New England J. Med. v. 240, p. 13-15 (1949).

[8] J. J. Miller, M. R. Ryan, J. Immunol. v. 65, p. 143-154 (1950).

[9] A. Sachs, Proc. of Royal Soc. of Med. v. 45, p. 641-652 (1952).