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Preventive Efficacy of Rabies Serum in Experiments on Rabbits and Dogs

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Abstract

The results of the studies showed that the administration of rabies and dogs anti-rabies hyperimmune serum after 3.5.7 and 8 days after infection with street rabies virus, 100% of them protect against rabies, while all control animals that did not receive such serum got rabies for 13-15 days of experience. At the same time, the administration of experimental rabies hyperimmune serum to experimental animals 10 and 12 days after infection with the street rabies virus does not protect them from this disease. It was also established that these periods (10-12 days) were sufficient for complete reproduction of the street virus in the brain, and the anti-rabies antibodies found in hyperimmune serum were not able to put the already developed infectious process.

Keywords: *anti-rabies hyperimmune serum, rabbit, dogs, donkey, rabies, street virus, antibody, titer, hyperimmunization, cycle*

RELEVANCE

The problem of combating rabies as a highly dangerous infection is relevant for most countries of the world, including Uzbekistan. In the Republic, rabies is annually recorded among farm, domestic and wild animals. The incidence of farm and domestic animals is mainly associated with areas of natural foci of rabies. World wide distribution nosoareal, natural focality, extreme contagiousness, vector transmission by carnivores, susceptibility of all warm-blooded animals, social and economic significance inherent in rabies made it possible to include it in the list of especially dangerous infectious diseases of the OIE. From 55 to 70 thousand people die from rabies every year, half of which are children. This means that 171 people die from this disease every day. Up to 6.5 million people in the world are subjected to post-exposure anti-rabies treatments annually (A. Gulukin, 2018). In Uzbekistan alone, 50-55 thousand people receive anti-rabies assistance annually after being bitten by dogs, cats and rodents. Of all sick people, 96.1% of cases, the disease occurs after a dog bite. More than 1 million animals of various species become ill and die annually in the world (Samoilenko A.Ya. et al., 2006).

Until today, the epizootic staging on rabies of farm, domestic, and wild carnivores in some regions remains moderately difficult. It is due to the fact that in these territories all available dogs are not fully covered for preventive vaccination, but without domesticated stray dogs and wild carnivorous carnivorous animals, which are natural reservoirs of rabies, they are not vaccinated at all. Unfortunately, effective methods of treating rabies in humans and animals have not been invented even by scientists from the medical and veterinary science of highly developed countries; the basis for the fight against this terrible, especially dangerous disease is its timely diagnosis and prevention. For specific prophylaxis, there is only a vaccine that protects the animal and human body from the virus, and even that does not always protect them from developing the disease.

In a forced vaccination against rabies after a bite of rabid animals, some researchers have used hyperimmune anti-rabies serum with a positive effect, especially when they are late with vaccination (Vedernikov V.A. et al., 1974; M.A. Selimov, 1978; Samoilenko A. Ya. And et al., 2006).

With the bite of high-value thoroughbred horses, bulls, cows, camels and dogs with rabid animals, to ensure rabies protection, along with forced vaccination to ensure quick confrontation against the introduced street viruses, the introduction of the ready-made neutralizing antibodies found in hyperimmune rabies serum is required. Virus-neutralizing antibodies against rabies of animals occurring in the body of a bitten animal with a street virus, they are neutralized - they are not allowed to penetrate into nerve cells (neurons) and the infection process does not develop. Therefore, the development of a technology for producing hyperimmune

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serum against rabies in animals and verification of its effectiveness in acute experiments on rabbits and dogs, followed by testing under veterinary practice, is of great economic importance. Because Uzbekistan does not produce anti-rabies hyperimmune serum, which guarantees the well-being of high-value (horse, bull, cows, dogs, etc.) animals bitten by rabid animals. All this predetermined the need for a study to develop a technology for producing hyperimmune anti-rabies serum with a high titer of antibodies, their testing in acute experiments on rabbits and dogs.

PURPOSE OF THE STUDY

The aim of the research was to develop a technology for producing hyperimmune rabies serum with a high titer of antibodies and to study its prophylactic efficacy in rabies and dogs infected with street rabies virus in acute experiments on rabbits and dogs.

To achieve this goal, we set the following tasks:

1. To develop the most optimal variant of the immunization schedule for obtaining active hyperimmune anti-rabies serum with a high antibody titer;

2. To find out the prophylactic effectiveness of hyperimmune rabies serum in animals infected with street rabies virus in acute experiments on rabbits.

3. To establish the prophylactic effectiveness of hyperimmune rabies serum in animals infected with street rabies virus in acute experiments on dogs.

Scope and research methods. To obtain hyperimmune rabies anti-rabies serum with a high antibody titer and to study its prophylactic efficacy in animals infected with street rabies virus, in the experiments 3 heads of 2-year-old donkeys, 3 heads of 8-10-month-old sheep, 12 heads of annual rabbits, 18 heads of one-year-old dogs were used in the experiments. ages and 220 goals 16-20 gram white mice. Infection of experimental rabbits and dogs was carried out with a street virus (pcs ST-02) with a titer $LgЛД_{50}$ $10^{-4,63}$ 0,03 ml at a dose of 1 ml intramuscularly in the lip. The laboratory diagnosis of experimental rabies and dogs rabies was carried out comprehensively: by microscopic examination of smears of brain prints, detection of viral antigen in the RIF and bioassay on 10 heads of white mice. In order to obtain anti-rabies antibodies with a sufficiently high titer, according to the chosen scheme, we started immunization of 3 donkeys with a liquid inactivated rabies vaccine, manufactured under the conditions of the Virology Laboratory of the NIIV. This vaccine has been introduced into veterinary practice to immunize farm, domestic (dogs and cats) animals against rabies.

For the hyperimmunization of donkeys, along with the rabies vaccine, the inactivated antigen of fixative virus O-73-02 was also used. The completeness of virus inactivation in the antigen was checked by intracerebral injection of a suspension in a dose of 0.03 ml to 10 heads of white mice and clinical observations were made for them for 10 days. No clinically visible changes were observed in mice during this period. Then 5 of them were killed and from the brains of which a 10% suspension was made. This suspension was administered intracerebrally to another 10 clinically healthy mice. In the remaining five mice of the first passage and the newly introduced mice of the second passage, clinical observations were made for 15 days. As a result of clinical observations over a 15–25 day period, 15 mice showed no pathological changes characteristic of rabies. Thus, complete inactivation of the virus in the antigen was established.

In order to determine the possible presence of precipitating antibodies in the blood serum of clinically healthy donkeys, 5 ml of blood were taken from them before the start of immunization and the serum was separated. The ring precipitation reaction was performed with these sera in small Ulungut tubes. The reaction used antigen prepared from the fixed virus "O-73-02" inactivated with ethanol. As a result of studies in the blood serums of three donkeys, precipitating antibodies were not detected before the start of hyperimmunization, which made it possible to start immunization of donkey-producers to obtain hyperimmune rabies serum.

To obtain active hyperimmune anti-rabies serum with a high titer of antibodies, the P.N. method was used. Kosyakova (1967) in our modification. At the same time, donkey hypermunization consisted of three cycles. The first cycle consisted of three periods. Each period consisted of three injections at 3-day intervals. Between periods, the interval was 5 days (chart). In the first period, consisting of 3 injections, three donkey heads were injected subcutaneously with 5 ml of liquid inactivated rabies vaccine 3 times at 3-day intervals. In the second period, which also consisted of 3 injections, the donkeys were subcutaneously injected with the

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same vaccine, 8 ml 3 times at 3-day intervals. In the third period, the vaccine was also similarly injected subcutaneously, but not with 8, but with 10 ml, and they were also injected intradermally with 1 ml of fixed-virus antigen. In total, in the 1st cycle over 33 days, donkeys were hyperimmunized 9 times. Then, on the 9th day after the last injection of the vaccine and antigen of the third period, blood was taken from the jugular vein of donkeys, serum was isolated from it to study the titer of precipitating antibodies in the ring precipitation reaction.

Donkey hyperimmunization scheme for obtaining hyperimmune rabies serum

№ № periods in the cycle	**Immunization days**	**Routes of administration and doses**	
		Subcutaneous dose of the vaccine (in ml)	**Intradermally, doses of antigen (in ml)**
1st period	1	5	-
	4	5	-
	7	5	-
2nd period	12	8	-
	16	8	-
	20	8	-
3rd period	26	10	1
	29	10	1
	33	10	1
	42	Blood sampling	

As a result of studies in the blood serum of hyperimmunized donkeys after the 1st cycle, it did not exceed 1: 1024, so donor donkeys were given a 2-month respite before the 2nd immunization cycle. In the second cycle, experimental donkeys were injected 3 times at 3-day intervals with a viral antigen at a dose of 2 ml subcutaneously. 8 days after the last immunization, donkey blood was taken from the jugular vein of donkeys, serum was separated from it to study the titer of antibodies with a homologous viral antigen in the ring precipitation reaction. After the second cycle of immunization in the blood serum of donor donors, the antibody titer in the ring precipitation reaction did not exceed an average of 1: 1200. Therefore, before the start of the 3rd cycle of immunization, donkeys were again given a month's rest. Then they started the third cycle of immunization, which consisted of three injections with a 3-day interval. In the third cycle, donor donors in each injection were injected simultaneously with 3 ml of the rabies vaccine intramuscularly and 2 ml of the viral antigen subcutaneously. 8 days after the last immunization, donkey blood was taken from the jugular vein of donkeys, serum was separated from it to study the titer of antibodies with a homologous viral antigen in the ring precipitation reaction. As a result of studies in the blood serum of hyper immunized donkeys, after the 3rd cycle, a rather high titer (1: 1800) of precipitating antibodies in the ring precipitation reaction was established. After obtaining a high titer of precipitating antibodies in the blood serum of experimental donkeys, studies were conducted to study the titer of neutralizing antibodies in this serum in the neutralization reaction in white mice.

After making sure that all hyper-immunized donkeys gave a sufficiently high titer of antibodies, after another 6 days, 1-1.5 L of blood was taken from each donkey under sterile conditions, and serum was separated. All hyperimmune anti-rabies sera of three donkeys were combined into one sterile flask and preserved with 0.1% phenol. To evaluate the prophylactic efficacy of hyperimmune anti-rabies serum in animals infected with street rabies virus, acute experiments were performed (animals were subjected to experimental infection with a street virus with an Lg LD50 titer of 10-4.63 0.03 ml, intramuscularly in the lips at a dose of 1 ml) before 12 heads of rabbits and 18 heads of dogs.

When setting up the ring precipitation reaction, two controls were necessarily set: in the same row as the serum of the non-immunized donkey and the second, physiological saline was used instead of the serum for the reaction. The reaction took place at room temperature. The reaction results were evaluated after 5, 10, 30 and 60 minutes. With a positive reaction, the antigen and antibodies, connecting together formed a precipitation ring. This ring is clearly visible with the naked eye. After 60 minutes, these precipitates settle to the bottom of the tube. Therefore, the results of the reaction should be evaluated no later than 60 minutes.

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RESEARCH RESULTS AND DISCUSSION

The sterility of the liquid rabies vaccine produced at the NIIV Virology Laboratory was verified by inoculation on artificial nutrient media (meat-peptone broth, meat-peptone agar, Saburo and Kitt-Tarozzi media), harmlessness and immunogenicity by administration to white mice, and reactogenicity - on the sheep.

When sowing hyperimmune anti-rabies serum (GIAS) on artificial nutrient media: meat-peptone broth, meat-peptone agar, Saburo and Kitt-Tarozzi media, no microorganisms germinated in them for 10 days and thereby established its sterility. When studying the safety of this serum by administering subcutaneous injection to 10 heads of white mice at a dose of 0.2 ml for a month, no pathological changes in the condition of the mice were also detected, which made it possible to consider it harmless. A study of the reactogenicity of this serum on three heads of sheep showed that they had no clinical changes during 10 days of observation, thereby establishing its harmlessness.

The results of studying the titer of antibodies in the combined hyperimmune anti-rabies donkey serum of donkeys in the ring precipitation reaction are presented in table 1.

In order to assess the prophylactic efficacy of hyperimmune anti-rabies serum in animals infected with street rabies virus, acute experiments were performed on 12 heads of rabbits, divided into 4 groups of 3 heads in each (Table 2). At the beginning of the experiment, all rabbits (12 goals) were infected with a street virus with a titer $LgЛД_{50}$ $10^{-4,63}$ 0,03 ml intramuscularly into the lip at a dose of 1 ml. Group 1 rabbits 3 days after infection, group 2 rabbits 5 days later and group 3 rabbits 7 days after infection with street virus were given hyperimmune rabies serum at a dose of 1 ml / kg (1 ml contains 200 ME), subcutaneously. Group 4 rabbits were not given hyperimmune rabies serum; they served as a control. All rabbits were followed up for 4.5 months. Based on the results of clinical observations, an assessment was made of the prophylactic effectiveness of this anti-rabies serum.

Table 1. The results of a study of the titer of rabies antibodies in hyperimmune donkey serum in a ring precipitation reaction

№ p / p	Dilution of antigen in saline	Reaction results
1	1:10	++++
2	1:50	++++
3	1:100	++++
4	1:200	++++
5	1:400	+++
6	1:600	+++
7	1:800	++
8	1:1000	++
9	1:1200	++
10	1:1400	++
11	1:1600	+
12	1:1800	+
13	1:2000	-
14	1:2400	-
15	control is a physiologist. solution	-
16	control - blood serum of non-immunized donkey	-

The intensity of the manifestation of the reaction was evaluated in the following order:

++++ is a very dense ring and it forms a precipitate at the bottom of the tube;

+++ very dense ring and it does not form a sediment at the bottom of the tube;

++ transparently visible ring;

+ transparently invisible ring;

- the ring is not formed, the reaction is negative.

In control tubes, reaction results should be negative.

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The results of studying the prophylactic effectiveness of hyperimmune rabies serum in experiments on rabbits are presented in table 2. As can be seen from the data in table 2, rabbits of the 1st, 2nd and 3rd groups infected with street virus received hyperimmune rabies serum after 3, 5 and 7 days after infection, in 100% of cases they remained alive, while control rabbits not receiving such serum died on 12 and 13 days of the experiment with obvious clinical signs of rabies. Therefore, when a bite of highly valuable animals, rabid animals, the introduction of this serum at a dose of 1 ml / kg, even after 3, 5, and 7 days after the bite, completely protects against rabies.

Table 2. The results of the prophylactic effectiveness of hyperimmune rabies serum in experiments on rabbits

№ групп	Days of administration of hyperimmune rabies serum after infection with street virus	The number of infected rabbits (goals)	Doses of GIAS (ml / kg)	Research results (the fate of the rabbit Cove)
1	3 days after infection	3	1 ml / kg	3 goal stayed alive
2	5 days after infection	3	1 ml / kg	3 goal stayed alive
3	7 days after infection	3	1 ml / kg	3 goal stayed alive
4	A control group that did not receive GIAS	3	-	3 goal died

The results of a study of the immunogenicity of hyperimmune rabies serum for each rabbit are presented in table 3. From the data of the 3rd table it is clear that rabbits of the 4th control group infected with street virus, but did not receive hyperimmune rabies serum, one head after 12 days and two heads through 13 days after the start of the experiment with clearly clinical signs of rabies, they died. At the same time, 9 goals of rabbits of the 1st, 2nd and 3rd experimental groups receiving GIAS, respectively 3, 5 and 7 days after infection with street virus, remained alive for 4.5 months (observation period).

Thus, in acute experiments on rabbits experimentally infected with a street virus, it was proved that administering them 3, 5, and 7 days after infection with hyperimmune rabies serum completely protects against rabies. At the same time, control rabbits not receiving this serum developed clinical signs of rabies. The sick rabbits tried to be in the dark corner of the iron cage, their condition was depressed, apathetic, their appetite was absent. They often lie down and jump up, the pupils were dilated, salivation was observed. Over time, patients noted increased reflex excitability to light, noise, rustling and shortness of breath appeared. They observed a quiet form of the disease and they died 1.5 to 2 days after the onset of clinical signs. Pathological material from all parts of the brain was taken from all the dead rabbits and, as a result of a comprehensive laboratory study, the diagnosis of rabies was confirmed.

Table 3. The results of a study of the immunogenicity of hyperimmune rabies serum for each rabbit

Name of groups	Clinical days for infected street virus and GIAS-treated rabbits																						
	1	3	5	7	10	11	12	13	15	20	25	30	35	40	45	50	55	60	70	80	90	105	135
1st experienced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2nd experienced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3rd experienced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4th control	-	-	-	-	-	-	+																
	-	-	-	-	-	-	-	+															
	-	-	-	-	-	-	-	+															

Note: + died; - stayed alive.

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Finding out the prophylactic efficacy of hyperimmune rabies serum in experimental rabies rabies, the same studies were conducted in dogs. However, at the same time, an additional task was posed - to determine the time (limits) beyond which the risk of developing the disease inevitably grows. To assess the prophylactic effectiveness of hyperimmune anti-rabies serum in animals infected with street rabies virus, acute experiments were performed on 18 heads of dogs, divided into 6 groups of 3 heads in each (Table 4). At the beginning of the experiment, all dogs (18 goals) were infected with the ST-02 street virus with an Lg LD50 titer of 10-4.63 0.03 ml intramuscularly in the lip at a dose of 1 ml. Dogs of the 1st group 3 days after infection, dogs of the 2nd group after 5 days and dogs of the 3rd group after 8 days, dogs of the 4th group after 10 days, dogs of the 5th group 12 days after infection with street virus hyperimmune rabies serum was introduced at a dose of 1 ml / kg, subcutaneously (in 1 ml contains 200 ME). Dogs of the 6th group (3 heads) were not given hyperimmune anti-rabies serum, they served as a control. All dogs were monitored for 4.5 months. Based on the results of clinical observations, an assessment was made of the prophylactic effectiveness of this anti-rabies serum.

The results of the prophylactic effectiveness of hyperimmune anti-rabies serum in experiments on dogs are presented in table 4. As can be seen from the data in table 4, dogs of the 1st, 2nd and 3rd groups infected with street-virus anti-rabies serum at a dose of 1ml / kg, subcutaneously , 3, 5, and 8 days after infection, in 100% of cases they remained alive, while parallel experiments on the 4th group of dogs receiving the same serum 10 days later died on the 16th and 17th days of the experiment. Experimental dogs of the 5th group receiving GIAS after 12 days also died on the 18th, 19th and 20th days, like control dogs of the 6th group, died of rabies 12-13 days after the start of the experiment with clearly clinical signs of the disease.

Table 4. The results of the prophylactic effectiveness of hyperimmune rabies serum in experiments on dogs

T. p	Days of administration of hyperimmune rabies serum after infection with street virus	Number of infected dogs (goals)	Doses of GIAS (ml / kg)	Research results (the fate of the dogs)	Efficiency
1	3 days after infection	3	1 ml / kg	3 goal stayed	100 %
2	5 days after infection	3	1 ml / kg	alive	100 %
3	8 days after infection	3	1 ml / kg	3 goal stayed	100 %
4	10 days after infection	3		alive	0 %
5	12 days after infection	3	1 ml / kg	3 goal stayed	0 %
6	A control group that did not receive GIAS	3	-	alive	0 %

An analysis of the results showed that due to the relatively late introduction (10 and 12 days after infection with the virus) GIAS to dogs, did not give the opportunity to protect them from the disease. Consequently, the virus-neutralizing antibodies present in the hyperimmune anti-rabies serum, 10 days after infection with the virus, do not have time to prevent the already vigorously reproducing virions in neurons and the developed pathological process in the brain of dogs, although experimental dogs of the 4th and 5th groups died on 4-8 days later compared with the control group (table 5).

The results of a study of the prophylactic effectiveness of hyperimmune anti-rabies serum for each dog are presented in table 5. From the data of the 5th table it can be seen that from dogs of the 6th control group infected with street virus, but not receiving hyperimmune anti-rabies serum, one head after 13 days and two heads 14 days after the start of the experiment with clearly clinical signs of rabies died. In the same way, dogs from the 4th group died, one head after 18, 19 and 20 days after infection with the virus, although they received GIAS 10 days after infection. A similar result was obtained by dogs of the 5th experimental group, also receiving GIAS 2 days later (12 days after infection with the virus) than the 4th group. In the 5th group, two dogs fell after 16 and one after 17 days after experimental infection with the virus. At the same time, 9 goals of dogs of the 1st, 2nd and 3rd experimental groups receiving GIAS, respectively 3, 5 and 8 days after infection with the street virus, remained alive for 4.5 months (observation period).

The results of these studies suggest that in the case of a bite of healthy especially valuable thoroughbred animals (production bulls, cows, horses, dogs) with rabid animals, they can be protected from the occurrence

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of the disease if they are given hyperimmune rabies serum for 8 days. It is appropriate to say here that the dogs of the control group died on 13 and 14 days of the experiment with obvious clinical

Table 5. The results of a study of the preventive effectiveness of hyperimmune rabies serum for each dog

Name of groups	Clinical days for infected street virus and GIAS dogs																						
	1	3	5	7	1	11	12	13	15	16	17	18	19	20	30	40	50	60	70	80	90	105	135
1st experienced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2nd experienced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3rd experienced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4th experienced	-	-	-	-	-	-	-	-	-	-	-	+											
	-	-	-	-	-	-	-	-	-	-	-	-	+										
	-	-	-	-	-	-	-	-	-	-	-	-	-	+									
5th experienced	-	-	-	-	-	-	-	-	-	+													
	-	-	-	-	-	-	-	-	-	+													
	-	-	-	-	-	-	-	-	-	-	+												
6th control	-	-	-	-	-	-	-	+															
	-	-	-	-	-	-	-	-	+														
	-	-	-	-	-	-	-	-	+														

Note: + died; - stayed alive.

signs of rabies. Sick dogs did not respond to commands and retired to a dark corner of an iron cage. Dogs started hallucinating, vomiting, increased salivation, noted pupil expansion, severe loss of eyes, and appetite decreased significantly. Barking became muffled, hoarse. Dogs became increasingly anxious over time, gnawing at themselves, an iron cage, followed by the onset of paralysis of the hind limbs, lower jaw, tongue crawled out of its mouth. They had a paralytic form of the disease and they died after 1.5 - 2 days after the manifestation of clinical signs of rabies. Pathological material was collected from all dead dogs from all parts of the brain to confirm the diagnosis of rabies using laboratory tests. As a result of a comprehensive laboratory study, the diagnosis was confirmed.

The mechanism of formation of immunity in rabies has not been sufficiently studied. On this issue of immunity, scientists of the world have two directions. According to proponents of the first direction, anti-rabies immunity depends entirely on the titer of antibodies, especially the neutralizing antibodies found in the blood serum of animals and humans, which are formed in reticuloendothelial cells - plasmocytes. At the same time, virus-neutralizing antibodies against rabies in animals, when encountered in the body with a virus, neutralize them - they are not allowed to penetrate into nerve cells (neurons) and thereby prevent the development of an infectious process. In fact, after rabies vaccination in the body, a high titer of neutralizing antibodies is established in the blood serum of animals and humans.

Proponents of the second direction, the body's resistance to the rabies virus is associated with cellular immunity. Indeed, in the body of animals immunized against rabies, animals and humans, nerve cells have high degree of virocidal properties. Scientists of the second direction believe that humoral factors of immunity (virus neutralizing antibodies) are involved as an accompanying element to cellular immunity.

According to L.P. Gorshunova (1968) in case of forced rabies vaccination, immunity is not associated with the actions of virus-neutralizing antibodies found in blood serum. Therefore, in vaccinated animals, there is no direct correlation between the intensity of immunity and the titer of neutralizing antibodies. At the same time, in the presence of a high titer of neutralizing antibodies in vaccinated animals, their experimental infection with a rabies virus usually does not lead to rabies. In her experiments, starting from the third day to

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three months after immunization with the rabies vaccine, the fix virus antigen was detected in brain neurons, which indicates the direct involvement of nerve cells in the formation of immunity. It is appropriate to emphasize here that in our experiments after infection of rabbits and dogs with street virus within 3-8 days, the introduced virus through nerve cells must reach the brain neurons, because already on the 10th day of the experiment in control rabbits and on the 11th day - the first clinical signs characteristic of rabies were observed in control dogs. However, after 3, 5 and 8 days after infection, the administration of hyperimmune anti-rabies serum to dogs at doses of 1 ml / kg, the virus-neutralizing antibodies available in this serum, 100% of cases protected them from rabies. Consequently, virus-neutralizing antibodies against the virus, available in serum, completely neutralized the virus, found in neurons and prevented the development of the disease in dogs. At the same time, when GIAS was introduced a little later (after 10-12 days), the dogs of the 4th and 5th groups started to show the first clinical signs of rabies and they died 16-20 days after the start of the experiment. In these cases, virus-neutralizing antibodies against the virus do not have time to prevent the virions already intensely reproducing and the pathological process that has developed in the brain of dogs. Summarizing the above, we can conclude that when animals are infected with a rabies virus, the administration of a hyperimmune anti-rabies serum to them for 8 days (threshold day) completely protects them from the onset of the disease, and starting from day 10, this serum no longer saves animals from rabies.

CONCLUSION

As a result of the studies, it was found that in acute experiments on rabbits experimentally infected with a street virus with an Lg LD50 titer of 10-4.63 0.03 at a dose of 1 ml in the lip, he introduced hyperimmune rabies serum 3, 5 and 7 days after infection, fully (100%) protect them from getting sick with rabies, with obvious manifestations of the disease in the control. It has been proven that when dogs are infected with a rabies virus, administering a hyperimmune anti-rabies serum to them for 8 days (threshold day) completely protects them from the onset of the disease, and starting from day 10, this serum no longer saves animals from rabies.

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