PECULIARITIES OF IMMUNOSTIMULATING ACTION PRODUCED BY FOREIGN PROTEIN ON DOGS BELONGING TO DIFFERENT TYPES OF THE NERVOUS SYSTEM AND THE CHOICE OF INDIVIDUAL DOSES OF THE IMMUNOSTIMULANT

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The use of different immune sera and heterogenous protein immunostimulators for prophylaxis and treatment of infectious diseases is becoming more and more widespread in medical practice. However, because of sharp differences in results obtained, a study of individual constitutional peculiarities of reactions of the organism, on the one hand, and of the means of choice of individual doses of these preparations, on the other, is indicated.

Because of this, we have undertaken to study the peculiarities of immunostimulating action of concentrated foreign protein on animals belonging to different types of the nervous system. With this in view, we have investigated the phagocytic activity in peripheral blood of 9 dogs with established types of the nervous system (obtained from the Institute members, G. Ya. Guobis, A. V. Nametkina and A. P. Chesnokova), in response to introduction of various doses of a foreign gamma-globulin. We could not find any published reports dealing directly with this problem. Literature dealing with the study of immune reactions in relation to the type of nervous system is sparse and very contradictory [1-12]. This problem has been investigated mostly by D. F. Pletsityi and his collaborators [2, 9, 10, 11, 12].

METHOD

According to the typological peculiarities of the nervous system, the experimental dogs were classified as follows: Ingul, male, weighing 26 kg, strong, active, with a slight excess of the stimulating process; Volk, male, weighing 21.8 kg, strong, balanced, inert; Seryi, male, weighing 23 kg, strong, active, unrestrained; Pirat, male, weighing 21 kg, strong, active, stimulated; Kuchum, male, weighing 22 kg, weak, inert, retarded; Alma, female, weighing 10 kg, weak, retarded; Malysh, male, weighing 17 kg; Chernyi, male, weighing 14 kg. In determining the type of nervous system in the last two dogs, the first of these was classified with animals of the strong, unbalanced type, and the second with those of the strong, balanced, active type. However, during the past year there occurred in both these dogs a sharp weakening of the stimulating process, and they are considered in this work as having a weak functional state of the brain cortex.

The dog Tsezar' (male, weighing 18 kg) had not been subjected to the study of all the properties of nervous processes; however, the extremely difficult establishment of positive conditioned reflexes by the secretion method (more than 100 combinations), a very slight conditioned reaction, which could not be raised either by starvation or by caffein, and an extreme external retardation of this animal, indicate in it a weakness of the stimulating process.

All these dogs received intramuscularly, in the thigh, 0.14 ml of gamma-globulin per kg body weight. The phagocytic activity was examined for 3 days according to the following method. Blood samples, obtained from cuts on the edge of the ear-lobe, were mixed with a 5% solution of sodium citrate (0.05 ml citrate per 0.1 ml blood) and with 0.05 ml of a suspension in normal saline of a washed 24-hour broth culture of the haemolytic streptococcus.

After mixing by shaking the tube, the mixture was placed in an incubator at 38°C for 30 minutes. After this, smears were made; they were fixed with methyl alcohol and stained with Giemsa. Percentage of phagocytizing leucocytes was determined after counting 100 neutrophils, as well as the average number of bacteria ingested by a single leucocyte (phagocytic number).

RESULTS

The table shows the results of investigation of phagocytic activity in all 9 animals. In dogs of the strong type, Ingul, Volk, Seryi, and Pirat, already one hour after the injection of protein, there was a rapid and considerable stimulation of phagocytosis, while in dogs of the weak type, Kuchum, Alma, and Tsezar', the phagocytic reaction underwent a definite decline. We consider it of interest that in the dogs Malysh and Chernyi, which are animals of the strong type of nervous system, but during the period of investigation showing a weakening of the functional state of the brain cortex, and especially of the stimulating process, we found a reaction to the foreign protein which was identical to that in dogs of the weak type.

Changes of the Phagocytic Number Following Inoculation of γ-Globulin into Dogs Belonging to Different Types of Nervous System

Name of dog	Type of higher nervous activity	Phagocytic number					Phagocytic number			
		before inoculation of protein	after inoculation of 0.14 ml γ-globulin/kg body wt.				before inoculation of protein	after inoculation of 0.07 ml γ-globulin/kg body wt.		
			after 1 hr	after 4 hr	after 24 hr	on 3rd day		after 1 hr	after 4 hr	after 24 hr
Ingul	Strong, active, with slight excess of stimulation	6.1	16.5	18.1	0.8	10.8	13.3	13.8	12.4	14.0
Seryi	Strong, active, unrestrainable	1.8	8.0	9.7	0.85	2.1	-	-	-	-
Pirat	Strong, active, stimulated	4.6	18.1	14.2	1.75	4.35	-	-	-	-
Volk	Strong, inert, stimulated	7.2	14.8	13.4	0.4	8.6	-	-	-	-
Malysh	Strong, unbalanced, with a weakened functional condition	18.0	9.5	12.8	0.5	0.5	-	-	-	-
Chernyi	Strong, active, balanced, with a weakened functional condition	3.2	2.6	0.3	0.3	2.85	8.5	13.9	14.7	2.1
Kuchum	Weak, inert, retarded	3.1	0.35	0.12	0.2	0.3	2.0	8.5	9.3	1.7
Alma	Weak, retarded	7.2	4.3	0.5	0.5	0.25	9.1	10.0	18.2	1.4
Tsezar'	Nearer to the weak type	12.1	9.7	3.2	0.3	5.2	7.1	10.7	10.6	8.0

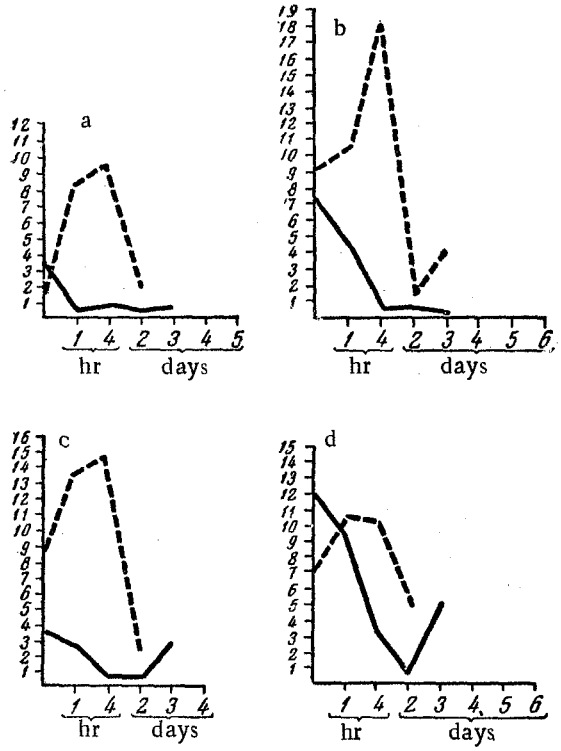
After we had established the differential action of γ-globulin on cellular immunity reaction in dogs belonging to different types of nervous system, we were faced with the problem of elucidating conditions favoring the stimulation of this reaction in animals of the weak type.

Because in dogs of the weak type there was found a decrease of the phagocytic activity, following the same doses of γ-globulin which stimulated this activity in dogs of the strong type, we suspected the appearance of a limiting effect in the former group. Having assumed that these doses of the protein produced a limiting effect in animals of the weak type, we had to consider these doses too high for these animals, and decided to lower them. Sixteen days after the first injection, 4 dogs (Alma, Chernyi, Tsezar', and Kuchum), in which the above-mentioned dose of 0.14 ml/kg body wt. γ-globulin led to a decrease of phagocytic activity, received a second injection of 0.07 ml/kg body wt., which was half of the first one. A dog of the strong type, Ingul, was included in this group, as a control.

Results of this experiment are presented in the same table and in the figure, which shows graphs indicating changes of phagocytic activity following the administration of two doses of the protein. The low dose of γ-globulin produced in all animals, except in the one of the strong type, an activation of phagocytosis. Consequently, this dose of γ-globulin proved to be effective for animals of the weak type and for the weakened one, but insufficiently effective for the animal of the strong type.

This experiment showed that, when using immunostimulatory preparations, it is necessary to consider an individual approach in the choice of dosage of the protein, and that for each animal it is possible to work out best

conditions under which these preparation would give the most favorable results. Equalization of doses of immunostimulators, as is often the case in clinical practice, must invariably lead in some cases to ineffectiveness of this method of treatment and prophylaxis of infectious diseases. In clinical practice, different types of protein-therapy are often used in various chronic and slowly-progressing diseases, for the purpose of stimulating the immunizing forces of the organism. In individuals who are weakened by chronic diseases, the application of protein-therapy may lead in some cases to a limiting effect, as was noted in our experiments on dogs Malysh and Chernyi, and instead of stimulating immunity, may result in its decrease.



Comparative investigation of the phagocytic activity in dogs of the weak type and in those with a weakened functional condition of higher nervous activity, following administration of different doses of γ-globulin. a) Dog Kuchum; b) dog Alma; c) dog Chernyi; d) dog Tsezar'; ordinates - phagocytic number; abscissae-hours and days of investigation; —changes of the phagocytic number following inoculation of γ-globulin in the dose of 0.14 ml/kg body wt.; --- same following doses of 0.07 ml/kg body wt.

Later, dogs Alma and Chernyi received an increased dose of γ-globulin, as compared with the first dose (0.21 ml/kg body wt.), but the result was, as in the first case, a decrease of phagocytic activity. This confirms, in our view, the necessity, in such cases, of reducing the doses of the immunostimulating preparation. At the same time, the use of immunostimulators, apparently, requires definite observations on changes of immunological activity which are brought about by a given preparation.

Thus, the study of phagocytic activity after introduction into animals belonging to different types of the nervous system of a foreign protein, showed a definite relationship of the immunostimulating effect not only with the constitutional properties of the nervous system (type of nervous activity), but with its original functional condition in the animals under study. The changes noted in the effects of immunostimulators in animals belonging to different types of nervous system indicate the necessity to choose individual dosages and to consider the possibility of appearance of the limiting effect in animals of the weak type, following doses of the immunostimulator which are optimal for animals of the strong type.

The development in animals of the weak type, and in animals with a weakened functional condition of the brain cortex, of a limiting effect, which is manifested as a decrease of the phagocytic activity, following the administration of protein, demonstrates a low functional limit of this reaction in such animals. Consequently, it is necessary to use smaller doses of immunostimulators for such animals. After having subsequently investigated the phagocytic activity in the same animals [8], following an experimental bacterial intoxication, we found that these changes were the same as with the previous inoculation of γ-globulin, which, thus, proved to be a prognostic test of the level of the defense reaction. The low functional limit of phagocytic activity in dogs of the weak type was confirmed; this was reflected in the nature of the course and outcome of the disease. We have obtained similar results with experimental streptococcal infections in white mice.

SUMMARY

Experiments were staged on 9 dogs with established types of nervous system. A study was made of the changes occurring in the phagocytic reaction of the peripheral blood after the intramuscular injection of heterogeneous γ-globulin. The protein doses, markedly activating the phagocytosis in dogs of the strong type, provoked a marked inhibition of the phagocytic reaction in animals of the weak type and in dogs with a weak functional state of the brain cortex. Regarding this phagocytosis inhibition in dogs of the weak type as a supraliminal effect, these animals were given protein in reduced doses. Half of the initial dose of the preparation was found to stimulate phagocytosis in animals of the weak type, but as insufficiently effective for dogs of the strong type. Consequently, a relationship was established of immunostimulating activity not only with the constitutional properties of the nervous system (the type of nervous activity), but also with its functional state (experiments on dogs with weakened functional state of the brain).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
