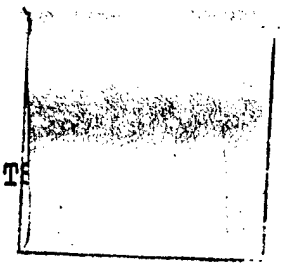

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IMMUNOGENESIS AND TYPES OF HIGHER NERVOUS ACTIVITY

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IMMUNOGENESIS AND TYPES OF HIGHER NERVOUS ACTIVITY

[Following is a translation of an article by S. I. Vovk in Fiziologichnyy Zhurnal (Physiology Journal), Vol. V., No. 6, Kiev, 1959, pages 781-786.]

The problem of the influence of the type of higher nervous activity on the formation of immunologic reactivity and on the course of various immunobiologic reactions has given rise to frequent controversies in the journals and has become the object of special experimental investigations (Gordiyenko, 1949, 1954; Monayenkov, 1954; Kotlyarevskiy, 1957; Yevseyev, 1957; Kazantsev, 1957; Kryachko, 1957, 1958; Berezhna, 1957, 1958, and others). However, this problem has not yet been solved and remains at the stage of the preliminary accumulation of experimental material. The data which do exist are contradictory in many instances, and are occasionally altogether in opposition.

Starting with the position that the immunobiological reconstruction of the organism depends on known physiologic laws and takes place through the participation of the central nervous system, including the higher divisions - the cortex of the brain (Metal'nikov, 1934; Gordiyenko, 1948, 1954; Puchkov, 1945, 1948; Zdorovskiy, 1950; Uchitel', 1950, 1951, 1954; Ado, 1952, and others), it should be thought that the typological peculiarities of the higher nervous activity would be reflected very definitely in the course of this composite biological process. Unfortunately, the practical solution of this problem is confronted with a number of difficulties, which, to a considerable degree, reduce the reliability and credibility of the data at hand. First of all, it should be recognized that, for the performance of immunobiological studies, a large number of experimental animals are needed, whereas the possibility of this is frequently limited in connection with the length of time and the laboriousness of the work required for precise determination of the type of higher nervous activity. It must also be kept in mind that the initial physiologic reactivity of the experimental animals may be changed markedly under the influence of antigens which have acted on them during the course of their individual growth even prior to their being used for experimental purposes. The source of such antigens and of allergization [sensitization] of the organism, aside from the external environment, may include the intestine which is very rich in antigens. In this, the changes in reactivity may be so marked as to

obscure the typological characteristics.

We undertook to study the influence of the type of higher nervous activity on the course of different immunobiologic reactions due to immunization, under conditions in which there was a complex reorganization of reactivity induced by exposure to an antigen. The latter we regarded as an extraordinary stimulus which could dislodge the organism from its state of physiologic equilibrium.

Methods

The studies were carried out on dogs. Twelve dogs were used. Initially, using the food-secretion method in the dogs, we studied the conditioned reflex activity and the type of higher nervous activity. Two of the dogs belonged to the strong equilibrated type (Kashtan, Tarzan); two to the strong, unequilibrated, stimulatory type (Polkan, Druzhik); four to the weak type (Butuz, Dzhek, Dzhim, Dzhek$_1$); and four to the intermediate type (Byel'chik, Brovko, Lisichka, Zeta).

For immunization we used a typhoid vaccine, one ml of which contained three billion bacterial cells, as judged by an optical standard. The vaccine was given intravenously, at a dose of 0.01 ml (30 million bacterial cells) per kg body weight.

For appraisal of the state of immunologic reactivity, we used the following indices: the content in the blood of specific agglutinins to the typhoid bacillus, the complement activity of the blood, and the phagocytic activity of the blood leukocytes with respect to specific (typhoid bacillus) and non-specific (staph. aureus) antigens. All indices were studied "on the curve", i.e., were repeated every seven days.

The agglutination reaction wasset up on the basis of the usual, well-known method, using 0.5 ml of fluid in the test tube. As antigen we used the diagnostic typhoid bacillus prepared at the Kiew Institute of Epidemiology and Microbiology.

The complement activity of the blood (the titer of the complement) was studied by titrating decreasing amounts of the sera being investigated in the presence of 0.2 ml of a hemolytic system in a volume of 0.5 ml of fluid in the test tube.

The phagocytic reaction was set up with citrated with whole. Wqshings of the specific antigen - the typhoid

bacillus - were prepared from the diagnostic culture by washing it with physiologic saline solution, with subsequent dilution to the desired concentration. Non-specific antigen was prepared from a 24-hour agar culture of staph. aureus No 209. In both instances, one ml of the bacterial washings contained two billion bacterial cells, according to the optical standard. The data from the first study, which was carried out prior to immunization, were taken as unity. The phagocytic numbers obtained from studies performed during the process of immunization, and again after its completion, were divided by this number, and by this means we obtained the index for the phagocytic activity of the leukocytes.

Results of the Studies

As can be seen from Table 1, before immunization, in the majority of the animals, agglutinins to the typhoid bacillus in the blood were either absent or were present only in very small titer (1:10 to 1:40). The only exception was dog Tarzan, in which the agglutinin titer was 1:240. It is of interest that, in this dog, the agglutination reaction was positive in a dilution of 1:40 to the Flexner dysentery bacillus, as well.

After immunization, the content of agglutinins in all animals was markedly increased and, in isolated instances, reached titers of 1:8600 and even 1:12,800 (Butuz, Tarzan, Lisichka). The level of the titer of agglutinins and the character of its increases and decreases varied within wide limits. In the majority of animals, the agglutinin titers increased only after the first two injections of antigen, and then, after the third, either remained at the elevated level (Tarzan, Dzhim) or began to drop (Dzhek, Druzhok, Lisichka, Zeta). In some of the animals (Kashtan, Polkan, Brovko), the content of agglutinins increased with each immunization and began to drop only 14 days after the last (third) injection of antigen. In dogs Butuz and Dzhekl, the titer of agglutinins only increased after the first injection of antigen, and later, after the second and third injections, there was a regular decline. In dog Byel'chik, the content of agglutinins after the first injection reached a titer of 1:2400, and remaind at this level throughout the course of immunizations, despite further administration of antigen. The highest titer of agglutins was reached in dogs Lisichka (1:12,800), and Butuz and Tarzan (1:9600). Relatively low titers were seen in Dzhim (1:600), Byel'chik and Dzhekl (1:2400).

As can be seen, individual variations in the content of agglutinins in the blood of the dogs showed no regular association with the type of higher nervous activity of these animals. It should, however, be noted that an early drop in agglutinins after the third, and especially after the second, injection of antigen, was most frequently observed in dogs of the weak and intermediate types. Obviously, their immunogenic apparatus, and also their regulatory mechanisms, were less resistant to antigenic stimulation, as compared with animals of the strong type. The dose of antigen used by us for animals of the weak type was clearly too large and caused an excessive stimulation of the immunogenic apparatus, with ensuing protective inhibition.

The results of the studies of the complement activity are shown in Table 2. (see end of this translation).

As can be seen from Table 2, the complement activity of the blood was to remain at a constant value, maintained throughout the course of the entire experiment. The titer of complement prior to immunization in individual dogs varied, on the average, within the limits of 0.013 to 0.017 ml, with the exception of dogs Tarzan and Dzhim, in which it was somewhat lower (0.027 ml). After injection of the antigen, we observed a tendency to reduction in the complement titer of the blood, but these reductions were only slight and were not stable. After immunization, the titer of complement quickly reverted to the original level. Individual variations in the complement activity of the blood showed no association with the type of higher nervous activity.

The peculiarities of the changes in the phagocytic activity of the leukocytes of the blood are shown in Table 3. The phagocytic activity of the leukocytes with respect to the typhoid bacillus was very low prior to immunization. The phagocytic number for individual dogs did not exceed 0.11 to 0.27 and was much lower than that with respect to the non-specific antigen - the staph. aureus. Such a slight activity was, perhaps, due to the pathogenicity of the bacteria and to the presence in the bacterial washings of toxic products of disintegration. A certain suppressive influence may also have been exertex by the preservative used in the preparation of the diagnostic culture, traces of which could not be eliminated. Upon immunization, the phagocytic activity of the leukocytes with respect to the typhoid bacillus was considerably increased. In individual cases the phagocytic indices reached values of 3.0 to 4.2 (Kashtan, Polkan, Brovko, Butuz, Lisichka, Dzhek$_1$). As a rule, this

increase began after the first injection of antigen and continued throughout the period of immunization and even persisted after its termination. 35 days after the last injection of antigen, the phagocytic indices in the majority of the dogs were greater than unity

Changes in the phagocytic activity of the leukocytes with respect to the non-specific antigen - the staph. aureus - were considerably different from the changes with respect to the typhoid bacillus. First of all, it should be noted that staphylococci were phagocytosed with extraordinary intensity. The phagocytic number for them piror to immunization varied within the limits of 3.8 to 17.5, which was considerably greater than for the typhoid bacillus, which number did not exceed several tenth parts of unity.

After the first injection of antigen, there was a slight increase in the phagocytic activity of the leukocytes in some animals with respect to the staphylococcus aureus, whereas in others this remained unchanged. However, beginning with the second injection of antigen, in the majority of animals it dropped, as a rule, and remained at a low level for a long time after immunization. 35 days after the last injection of antigen, the phagocytic index in all animals was less than unity and varied within wide limits - 0.3 to 0.9. Therefore, the increase in the phagocytic activity with respect to the specific antigen in our studies was accompanied by a reduction in it with respect to the non-specific antigen. This fact merits particular attention.

In analyzing our data on the phagocytic activity of the blood leukocytes, note should be taken of the singular individual variations of this immunobiological index in different animals both before immunization and afterward. These variations apparently exhibited no dependence on the type of higher nervous activity. In animals of the strong type, they frequently exhibited the same character as in the weak type.

Our findings are completely in accord with those of Berezhna (1957, 1958). Studying the process of the formation of agglutinins and phagocytic activity of the leukocytes in rabbits of different types following immunization of them with Flexner dysentery vaccine, she likewise was unable to demonstrate typological peculiarities in the course of their immunobiologic processes. Our findings also differ only slightly from the results of studies by Yevseyev and Kazantsev, who, first in rats and then in dogs, did

did not demonstrate any marked dependence of the formation of dysentery antitoxins on the type of nervous system of the experimental animals. In contrast to this, Monayenkov (in rats) and Kryachko (in rats and dogs)obtained data which testify to the fact that the character of the different immunobiologic reactions depends to a considerable extent on the typological peculiarities of the higher nervous activity. According to the findings of these authors, animals of the strong equilibrated type are characterized by a high intensity of different immunologic reactions (production of agglutinins, phagocytic activity of the leukocytes, leukocytic reaction, etc.), which ensures greater resistance in them to different intoxications and infections. In animals of the weak type, the formation of antibodies, phagocytosis and other protective reactions take place, on the contrary, at a lower level, so that intoxications and infections proceed with greater severity in them. Animals of the strong unequilibrated type occupy an intermediate position in this respect.

It is important to note the cause of the controversy among authors, and the contradictions in the findings. First of all, it should be pointed out that one must take into account the methodological difficulties mentioned earlier. A certain importance may also attach to the fact that the majority of these studies were carried out on small animals, the typological features of the higher nervous activity of which have not been clearly defined.

Conclusions

1 - Upon immunization of dogs with typhoid antigen, there was a significant increase in the content of specific agglutinins, as well as a change in the phagocytic activity of the leukocytes of the blood. The latter increased to the specific antigen - the typhoid bacillus - and either remained unchanged or decreased to the non-specific antigen - the staphylococcus aureus.

2 - The complement activity of the blood following immunization showed no essential changes. After a slight reduction of it during immunization, later, with discontinuation of the injections of antigen into the organism, the titer of complement reverted to the original level and remained there.

3 - The content of specific agglutinins in the blood and the specific phagocytic activity of the leukocytes in the

process of immunization showed individual variations within wide limits. In dogs of the strong type, the course of individual immunobiologic indices was characterized by considerable regularity and stability, as contrasted with animals of the weak type. However, no clear dependence of the indices investigated here on the type of higher nervous activity can be demonstrated.

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Table 1

Content of Specific Agglutinins in Dogs Immunized with Typhoid Vaccine (Dilutions of the Sera

Dogs' Names	Before Immunization	Days after injection of vaccine								
		First	Second	Third						
		7 days	7 days	7 days	14 days	21 days	28 days	35 days	42 days	49 days
Тарзан Tarzan	240	6400	9600	9600	4800	4800	2400	2400	—	—
Каштан Kashtan	10	2400	3200	4800	2400	1200	800	600	400	200
Полкан Polkan	—	3200	3200	4800	3200	1600	1600	1200	600	400
Дружок Druzhok	—	3200	6400	4800	2400	1600	800	600	—	—
Бельчик Byal'chik	30	2400	2400	2400	2400	800	400	300	200	150
Бровко Brovko	10	2400	3200	4800	3200	2400	2400	1200	1600	1200
Лисичка Lisichka	—	3600	12800	4800	3200	2400	1200	1200	—	—
Зета Zeta	—	1600	4800	2400	1200	800	400	300	—	—
Бутуз Butuz	40	9600	6400	4800	1600	2400	1600	1600	—	—
Джек Dzhek	15	4800	6400	3200	2400	2400	1200	1200	—	—
Джім Dzhim	—	800	1600	1600	1600	800	600	600	—	—
Джек, Dzhek,	—	2400	1600	1600	1600	800	600	300	—	—

Table 2

The Content of Complement in the Blood of Dogs Immunized with Typhoid Vaccine (Amount of Sera in ml)

Dogs' Names	Days after injection of vaccine							
	Before Immunization	First	Second	Third				
		7 days	7 days	7 days	14 days	21 days	28 days	35 days
Тарзан Tarzan	0,027	0,033	0,030	0,030	0,023	0,023	0,030	0,030
Каштан Kashtan	0,013	0,017	0,015	0,017	0,013	0,013	0,017	0,013
Полкан Polkan	0,013	0,013	0,015	0,013	0,013	0,013	0,010	0,010
Дружок Druzhok	0,017	0,023	0,020	0,023	0,017	0,013	0,017	0,020
Бельчик Byal'chik	0,013	0,017	0,015	0,020	0,017	0,017	0,017	0,010
Бровко Brovko	0,013	0,017	0,015	0,017	0,017	0,013	0,017	0,010
Лисичка Lisichka	0,013	0,017	0,017	0,017	0,010	0,013	0,013	0,010
Зета Zeta	0,013	0,013	0,020	0,017	0,013	0,017	0,013	0,017
Бутуз Butuz	0,017	0,023	0,017	0,017	0,023	0,017	—	0,017
Джек Dzhek	0,013	0,010	0 013	0,013	0,013	0,010	—	0,013
Джім Dzhim	0,027	0,023	0,027	0,030	0,023	0,023	0,023	0,027
Джек, Dzhek,	0,017	0,023	0,020	0,020	0,017	0,017	0,020	0,017

Table 3

The Phagocytic Activity of Leukoxytes of the Blood in Dogs Immunized with Typhoid Vaccine, with Respect to the Typhoid Bacillus (Numerators) and to Staphylococcus Aureus (Denominators)

Dogs' Names	Before Immunization	Days after injection of vaccine: First 7 days	Second 7 days	Third 7 days	Third 14 days	Third 21 days	Third 28 days	Third 35 days
Тарзан . . Tarzan	1,0	1,4 / 0,8	1,5 / 0,7	1,4 / 0,8	1,2 / 0,7	1,8 / 0,5	2,2 / 0,5	1,2 / 0,4
Каштан . . Kashtan	1,0	1,1 / 0,6	2,8 / 0,2	3,2 / 0,1	2,7 / 0,2	3,4 / 0,2	1,9 / 0,4	1,1 / 0,3
Полкан . . Polkan	1,0	3,3 / 1,1	3,2 / 1,1	3,6 / 1,0	2,8 / 0,5	3,0 / 1,1	2,3 / 0,7	1,8 / 0,7
Дружок . . Druzhok	1,0	2,0 / 1,7	2,3 / 1,3	1,3 / 0,7	1,6 / 0,9	1,5 / 0,5	1,2 / 0,7	1,7 / 0,8
Бельчик . . Byel'chik	1,0	1,0 / 1,0	1,1 / 0,6	1,1 / 0,7	1,9 / 0,2	2,1 / 0,7	2,0 / 0,8	2,5 / 0,6
Бровко . . Brovko	1,0	0,9 / 1,2	2,0 / 1,2	3,8 / 1,0	2,1 / 1,0	3,5 / 1,1	2,3 / 0,9	2,3 / 0,7
Лисичка . Lisichka	1,0	2,7 / 1,1	2,7 / 1,0	4,2 / 1,0	1,6 / 0,9	0,9 / 0,5	0,8 / 1,1	1,6 / 0,7
Зета . . . Zeta	1,0	1,3 / 1,0	1,8 / 0,7	1,0 / 0,7	1,5 / 0,6	1,9 / 0,7	0,5 / 0,7	0,7 / 0,8
Бутуз . . Butuz	1,0	2,2 / 1,7	3,4 / 0,4	2,4 / 0,8	1,5 / 0,3	2,0 / 0,5	1,5 / 0,9	1,6 / 0,3
Джек . . . Dzhek	1,0	1,0 / 1,2	2,0 / 0,9	1,3 / 1,0	2,3 / 0,7	1,9 / 0,7	1,9 / 0,9	1,8 / 0,9
Джім . . . Dzhim	1,0	1,6 / 1,2	1,0 / 0,7	2 3 / 1,0	1,8 / 0,6	1,3 / 0,8	1,2 / 0,4	0,9 / 0,8
Джек$_1$ . . Dzhek$_1$	1,0	1,2 / 0,8	1,9 / 0,9	3,1 / 0,5	1,7 / 0,4	0,8 / 0,7	0,4 / 0,4	0,7 / 0,5

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