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U. S. ARMY BIOLOGICAL WARFARE LABORATORIES
Fort Detrick, Frederick, Maryland

A Contribution to the Investigation of Barrier Fixing Manifestations of
Immunity in Dysentery and Cholera

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The immunity mechanisms in dysentery and cholera are still far from being sufficiently investigated. The great hindrance impeding the successful investigation of these divisions were the methodical difficulties in comparing the fate of the specific pathogens in a normergic, and in an immune organism.

In our previous investigations we presented the principally methodical reasons for a differentiated study of the antitoxic and antibacterial mechanisms; and the basic features of antibacterial immunity were defined for such diverse infectious forms as typhus abdominalis, tuberculosis, and brucellosis.

As a result of numerous investigations conducted on the principle of the experimental method that we have developed we were able to show that in all of the infectious forms mentioned, regardless of the particulars of their pathogenesis, uniqueness of the clinical course, or substantial differences in the biological actions of their pathogens, the antibacterial immunity, contrary to the widely accepted theory, is realized not as a result of bactericidal mechanisms, but as a result of barrier fixing mechanisms. This latter is encountered in immune animals where the lymphatic nodes, together with the other components of the reticuloendothelial system, acquire a sharply expressed capacity to fix a great quantity of the bacteria and to prevent their further penetration into the organism. For a quantitative expression of the barrier fixing function we developed a conception about the specific volume (the so-called minimal dose of propagation, Dosis propagationis minima, or DPM) representing the minimum quantity of bacteria that will, in a subcutaneous injection into the inguinal lymphatic node region, break this local barrier and penetrate deeply into the organism, filling the animals' internal organs and blood. After the institution of our concept concerning the minimal dose of propagation, and after the method of its determination was made more precise, there appeared a great possibility for the dosimetry of the barrier fixing function and for its expression in

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quantitative indicators. Further experimental observations allowed us to more closely characterize this function as one of the most substantial manifestations of antibacterial immunity, and to define many aspects that have great importance for theoretical and applied immunology. Thus, we were able to analyze the phenomenon of immunity and allergy in tuberculosis and brucellosis, and to establish that desensitization of animals is not accompanied by a loss of the animals' immunity; we were also able to compare naturally acquired immunity to that induced by vaccination in experimental models of typhoid infection, and, at last, to confirm with complete confidence the capacity of the separate divisions of an integral organism to reorganize to an autonomous immunity. The latter aspect was shown on a special model, which we developed, of the so-called phenomenon of monolateral immunity. There can now be no doubt of the acceptance of this method of investigation in the wide perspectives of study of the various divisions of infectious pathology and immunity.

Our present work was undertaken to determine the possibility of using the method of investigating the barrier fixing function for an investigation of immunity in dysentery and cholera also. During this investigation there were substantial difficulties. As is well known, dysenteric bacteria as well as the cholera vibrio die quickly not only in an immune organism, but also in normal animals. The rates of bacterial ablation for immune and nonimmune organisms differ very little, and this substantially complicates the problem of a precise determination of the character and peculiarities of antibacterial immunity in the indicated infectious forms. We succeeded, however, in solving this problem. The applicable observations are set forth in brief form below according to the individual series.

The investigation of the barrier fixing function as a manifestation of antibacterial immunity is conducted by means of a comparative evaluation of the specific pathogens in the organisms of immune and control animals. It should be completely understood, therefore, that the first stage of this investigation had to be the determination of the peculiarities in the progress of the cholera vibrios and the dysenteric bacteria in the organism of normal mice. For this purpose, as applied to our method, the animals were subcutaneously inoculated in the region of the inguinal lymphatic gland with a measured quantity of bacteria and killed at various time periods, with a subsequent culture of their organs and a quantitative calculation of the colonies grown on the dishes. The results of the experiments pertaining to the cholera vibrio are presented in the table shown below.

In table 1 are presented the data characterizing the progress and retention of a strain of the cholera vibrio No. 72 in white mice with a subcutaneous inoculation (275-310 million bacterial bodies) in the region of the inguinal lymphatic node. The results of these observations are extremely demonstrative. First of all, there is established the fact of the highly invasive properties of the cholera vibrio. Within a few minutes after the subcutaneous inoculation the vibrios penetrate past the boundaries of the lymphatic node and are detected in the internal organs. As seen from the cited table, and from many other analogous observations, which are not shown because of a lack of space, within 30 minutes after inoculation the vibrios regularly fill the blood, and all the organs of the animals. At later time periods, because of the rapid

death of the vibriones, the number of colonies growing on the cultures from the individual organs gradually decrease, and after 24 hours the pathogen, as a rule, is detected in a sharply decreased quantity, and then only in the inguinal lymphatic node. Later, there comes a complete bacterial ablation of the organism.

Concerning the minimal dose of propagation (Dps), our observations showed that this amount varies in the separate strains of the cholera vibrio.

Proceeding from the above stated principally methodical motives, and with the assistance of the same methodical procedure that was used in the experiments to study the invasive properties of the cholera vibrio, we also conducted similar observations related to the individual species of dysenteric bacteria. The data received as a result of these observations can be briefly formulated in the following manner.

The invasive properties of Flexner's bacilli, while showing quantitative fluctuations in the individual strains, are at the same time characterized by an overall and, for this group, regular capacity of rapid penetration into the organism's depths. We observe in our experiments with Flexner's dysenteric bacilli (strain No. 1372, inoculation dose: 90-100 million bacterial bodies) basically the same rates as were found in the experiments with the cholera vibrio (table 2).

A different behavior is displayed in the white mouse organism by Shigella shigae. The basic difference is that in a subcutaneous inoculation of animals the local lymphatic node is filled by the bacilli, however, further penetration into the organism either does not occur at all, or it is registered to a very limited degree. Thus, in comparison with the bacteria of the Flexner group, the invasive capacity of Shiga's bacilli seems to be sharply repressed. Exceptions occur in only a limited number of the Shiga cultures.

The new data that we have established, concerning the existence of expressed differences between the Shiga and Flexner bacteria, in reference to their invasive properties, have great importance for the study of the pathogenesis and immunity in the respective infectious forms.

To determine the barrier fixing properties of an immune organism in relation to cholera vibriones and Flexner's dysenteric bacteria, separate series of animals were immunized with the respective vaccines. At different time periods after immunization the animals were subjected to a subcutaneous inoculation with the appropriate pathogens, and a subsequent culture was taken from the organs by our method. Simultaneously, an analogous experiment was conducted with a control series of normal mice. The data resulting from these observations established with complete clarity the fact of a sharp increase in the barrier fixing capacity of the organism in immunized animals. Thus, the basic problem of our investigation seems to be solved, and the methodical possibility of a systematic study of the barrier fixing manifestations of immunity in cholera and Flexner's dysentery appears to be proved. In reference to Shiga's dysentery the indicated problem remains unsolved. As an illustration, in table 3 is presented one of the numerous experiments that establish the development of the barrier fixing properties in the organism of mice,

which were immunized with cholera vaccine and then subcutaneously inoculated with 108-120 million bacterial bodies on the 16th day after immunization (autopsy within 30 minutes after inoculation).

Conclusions

1. The cholera vibrio and Flexner's dysenteric bacteria, in a subcutaneous inoculation of white mice, manifest a sharply expressed invasive capacity: within a few minutes after inoculation these bacterial species fill the local lymphatic barrier, break through it and penetrate into the internal organs and blood of the animals.

2. The invasive properties of the Shiga bacteria, as compared to the cholera vibriones and Flexner's bacteria, are sharply retarded.

3. In a subcutaneous inoculation of mice that were immunized with cholera and Flexner vaccines the corresponding pathogens did not penetrate deeply into the organism and, as a rule, were fixed at the first lymphatic barrier.

4. The data obtained in this investigation opens the door to a systematic study of the antibacterial barrier fixing manifestations of immunity in cholera, and Flexner dysentery.

Таблица 1

Город прием- ных машин	30 мая		1 авг		2 авг		3 авг		4 авг		5 авг		6 авг		7 авг		8 авг		
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	
Питомец конной...	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Полупитомец...	228	100	872	~	~	~	66	2	7	~	~	~	~	~	~	~	~	~	~
Сезонный...	812	100	232	~	~	~	188	81	14	21	28	2	14	6	0	0	4	1	0
Кровь...	620	120	218	~	~	~	108	200	2	2	2	0	2	6	0	0	0	0	0
Итого коней...																			
Итого машин...																			
Сезонный...																			
Кровь...																			

Удобные обозначения: ~ значок пест, # несуществующее число коней.
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 Таблица 2

Сред. прием- ных машин	30 мая		1 авг		2 авг		3 авг		4 авг		5 авг		6 авг		7 авг		8 авг		
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	
Питомец конной...	#	1350	1220	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#
Полупитомец...	0	0	0	2	8	78	2	2	~	~	~	~	~	~	~	~	~	~	~
Сезонный...	0	8	72	60	18	82	4	10	~	~	~	~	~	~	~	~	~	~	~
Кровь...	8	11	88	10	47	20	2	8	~	~	~	~	~	~	~	~	~	~	~
Итого коней...																			
Итого машин...																			
Сезонный...																			
Кровь...																			

Таблица 3

Опыт	Начало работы						Конец работы					
	1	2	3	4	5	6	1	2	3	4	5	6
Питомец конной...	8	~	14	#	260	732	#	#	508	~	~	~
Полупитомец...	0	0	0	0	0	0	18	12	19	0	0	0
Сезонный...	0	0	0	0	0	0	24	24	9	18	18	0
Кровь...	0	0	0	0	0	0	8	88	23	119	1	22