those γ-globulins which were formed in the absence of any antigenic stimulus, i.e. the non-maternal γ-globulins occurring in newborns or in germ-free animals may then be regarded as truly natural non-specific antibodies.

In recent years, there has been a renewed interest in other non-specific defense mechanisms, especially after PILLEMER *et al.*[9] described a bactericidal serum factor which they called properdin and which they thought had many of the properties claimed to be essential characteristics of an important non-specific defense mechanism: It had a broad spectrum of activity, it was stimulated by such non-specific and non-antigenic agents as bacterial endotoxins and was thought to be independent in its action of the presence of humoral or cellular antibodies. It was a protein but differed from antibodies in many respects. A great number of studies, too numerous to be reviewed here, have been undertaken to test the validity of these claims. There seems to be fair agreement on the observed facts, but there is disagreement on their interpretation. Especially, one crucial question remains open: Are not many of the effects which were attributed to the properdin system actually caused by properdin *and* antibody; and is not the contribution of properdin rather secondary in importance? Convincing evidence has recently been published showing that a careful new evaluation is needed and that properdin seems indeed to play only a minor role in the so-called non-specific defenses of the host as measured by the bactericidal properties of serum[10,11].

We could dismiss the question as a mere semantic problem and satisfy ourselves with the fact that there are serum factors, whether called natural antibodies or properdin, which have a major function in defense. However, the question which was asked in the title of this essay still remains to be answered. How specific is immunity? Wherever acquired immunity against infection is attributable to circulating serum constituents, it seems that in the great majority of cases the activity rests with antibodies. These are either homologous, i. e. elicited by the infectious agent with which they react, or heterologous for having been brought about by materials which were different, but structurally related to the infectious agent. In regard to the infectious agent, the homologous antibodies are specific, the heterologous nonspecific. However, both types of antibodies are acquired by the same immunologic mechanisms and function alike. The same is presumably true for normal γ-globulins occurring in the serum without any external stimulus. Where antibodies are concerned in acquired resistance, the difference between specific and non-specific immunity rests solely in the nature of the antigenic stimulus which elicited antibody formation. Operationally, specific and non-specific immunity are similar. There is an impressive body of evidence showing that antibodies are indeed responsible for most manifestations of acquired resistance against infection and that the role of other serum factors is far from clear at the present time.

Zusammenfassung

Der vorstehende Artikel enthält eine allgemeine Diskussion über die Grenzen der Spezifität, die der erworbenen Resistenz gegen Infektionskrankheiten zugrunde liegt. Es wird die These vertreten, dass spezifische Mechanismen von grösserer Bedeutung sind als häufig angenommen wird und dass sog. unspezifische Abwehrkräfte in vielen Fällen sich nicht von echten Antikörpern unterscheiden lassen.

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On the Role of Non-Specific Factors in the Pathogenesis of Infectious Disease

By E. SUTER*

After the first discoveries of bacteria as agents of disease the search for pathogenic components produced by these agents resulted in significant findings. Consequently, the ability to produce toxin or toxin-like substances by pathogenic microorganism was assumed to be the major contributory factor in the elicitation of disease. This assumption provided a satisfactory explanation of the pathogenesis of disease in which isolated and purified toxins were shown to reproduce the clinical picture of the disease, as in diphtheria, tetanus, gas gangrene, and others. However, the limitations of this concept were realized when it became apparent that microorganisms, obviously capable of causing severe and often fatal infections, failed to yield products with any striking pathogenic effect. In infections caused by such agents no substances were found which could elicite in a susceptible host a clinical picture similar to the one produced by the living pathogen. Therefore, other mechanisms in addition to those based on toxin production were considered. Disturbances of the normal functioning of the host's tissues were recognized to be caused by the metabolic activity of the pathogen. Furthermore, the interaction of antibodies or antibody-like substances with bacterial components were found to cause severe tissue damage. At least some of the

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functional and morphological lesions occurring during the course of certain infections could be explained on this basis.

Corresponding to the early concept of the specificity of infectious processes, the reaction of the host to infection was recognized essentially as a specific response. This view was based on the discovery of antitoxin in serum of man and animals recovering from various infectious diseases. It was strengthened by the fact that these sera had specific protective power against infection. Recovery from infection and resistance to subsequent reinfection could be explained by this mechanism in a great many instances. However, the response of the host to other infections did not concur with this concept. Subsequent findings revealed the importance of non-specific mechanisms in resistance to initiation of infections and recovery from them. Work in this direction has been reviewed recently[1]. It is evident that resistance to infection is the resultant of specific and non-specific mechanisms which can be influenced by many factors. Besides hormonal imbalance and nutritional status, the injection of various substances such as endotoxins and levans alters resistance to infection in a non-specific manner. In the case of endotoxin the time relationship between preparatory injection and challenge infection, and the lack of antigenic relationship between preparatory material and infective agent, exclude an explanation of the alterations on the basis of antigen-antibody reactions. Further analysis showed that such injections with endotoxin resulted in altered activity of the elements of the reticulo-endothelial system, in fluctuations of the properdin level in the serum, and in increased activity of the antibody producing system[1]. At present, active research on the mechanism of these alterations is in progress. No doubt, some of these reactions are closely related to Shwartzman or Shwartzman-like phenomena.

Our laboratory has been concerned with reactions similar to those described above, but in reverse order. Thus, mice infected with BCG (Bacillus Calmette-Guérin) were found highly susceptible to the lethal action of intraperitoneally or intravenously injected endotoxin or its lipopolysaccharide complex. The difference between normal and BCG infected mice was approximately 100-fold; the LD_{50} of lipopolysaccharide for normal mice being 300–400 µg and 0.5–5 µg for BCG infected ones[2]. This 'hyperreactivity' of BCG mice towards endotoxin appeared to be a non-specific reaction, since lipopolysaccharides from several gram-negative organisms and a preparation of lipid A derived from one of them proved active. Most interestingly, BCG infected mice were also killed by extremely small amounts of a polysaccharide derived from mouse erythrocytes whereas large doses of the same were required to kill normal mice[3]. As findings of other laboratories indicated, the induction of such a state of hyperreactivity was not limited to BCG infection or to the mouse. Similar phenomena were described in mice, guinea pigs, and rabbits with *Hemophilus pertussis*, *Brucella* sp., *Coxiella burneti*, and *Eperythrozoon coccoides*. Mice infected with some of these agents exhibit increased susceptibility not only to bacterial endotoxin but also to biogenic amines and antibody-antigen complexes (for references see [3]).

Obviously it was of interest to explore whether these phenomena had to be treated as laboratory reactions or whether some significance could be attributed to them in relation to pathogenic manifestations during infections. At first it appeared quite paradoxical that infection with an agent, namely BCG, which is known to induce increased resistance to challenge not only with virulent tubercle bacilli but also with non-related agents such as *Salmonella enteritidis* and experimental tumors[4,5], should cause such a strong hyperreaction towards endotoxins. However, observations made during an epidemic of typhoid fever indicated that such hyperreactivity reactions might also occur in man[6]. An intense vaccination program was undertaken in a population, members of which were certainly already infected when vaccinated. Some of these individuals exhibited very severe reactions a few hours after injection of the vaccine and suffered a more protracted course of the infection than was to be expected. This provocative effect of vaccination on an already established infectious process could be reproduced in mouse experiments using various strains of *Salmonella* either as infectious agent or as heat-killed vaccine. This phenomenon was attributed to an enhancement of virulence of the infecting organisms by the injection of vaccine[6]. Our own findings, summarized above, suggest a different interpretation of this observation. It appears likely that the primary infection induced a state of hyperreactivity towards endotoxin and that the vaccination is equivalent to the introduction of a large amount of endotoxin resulting in an acute reaction similar to the one observed with BCG mice injected with lipopolysaccharide. Careful study of the experimental results given in these publications[6] indeed reveals that up to 50% of the infected mice died within 24 h after vaccination, and that the reaction is most apparent when vaccination is done about seven days after infection. This time interval corresponds well with the interval required for hyperreactivity to appear in BCG vaccinated mice. To test this interpretation the following experiments were done.

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Table I: Mortality of Normal and BCG Vaccinated Mice Challenged with Endotoxin, Heat-Killed, and Live *Salmonella typhimurium*

Challenge	Control			BCG [a]		
	Mortality [b]		Number organisms recovered [c]	Mortality [b]		Number organisms recovered [c]
	Numbers	Hours		Numbers	Hours	
Endotoxin 1000 µg	4/4	3–24		–	–	
100 µg	0/10	–		10/10	3–4	
10 µg	–	–		3/5	4–8	
Salmonella typhimurium						
heat-killed: 2×10^{8} [d]	0/10	–		10/10	4–12	
2×10^{7}	0/5	–		5/5	4–24	
2×10^{6}	0/5	–		1/5	6	
2×10^{5}	0/5	–		0/5	–	
Live: 2×10^{8}	10/10	24– 72		10/10	3–5	
2×10^{7}	4/5	24–120		5/5	3–6	
2×10^{6}	4/10	120–144	1.6×10^{6}	3/10	48–144	1.8×10^{6}
2×10^{5}	0/5	–	1.8×10^{4}	0/5	–	1.6×10^{2}
2×10^{4}	0/5	–	5.0×10^{3}	0/5	–	1.8×10^{2}

[a] Mice were injected with 0·2 ml of a BCG culture 8 days prior to challenge.
[b] Number of deaths over total numbers injected. Hours elapsed between injection and deaths.
[c] Survivors challenged with live *S. typhimurium* were killed on the 7th day and the number of organisms in the spleen was determined by plate counts. Numbers indicate organisms per 100 mg spleen.
[d] Number of organisms injected.

Experiment 1: Swiss white mice (Institute for Cancer Research strain) were injected by the intravenous route with BCG (0·2 ml of a 10-day old culture grown on 'Tween'-albumin medium). Seven days later groups of BCG infected and of normal mice were injected intravenously with graded amounts of endotoxin and of living and heat-killed *Salmonella typhimurium*. Deaths were recorded in all groups up to 7 days. All surviving animals challenged with living organisms were killed on the 7th day and quantitative counts of living *Salmonella* were done on their spleens. The combined results obtained in two independent experiments are recorded in Table I. It can be seen that mice infected with BCG were much more sensitive to the intravenous injection of endotoxin. The same was true for heat-killed and live *Salmonella*. All BCG vaccinated mice died within 4–24 h after injection of 10^{7} and 10^{8} live or heat-killed *Salmonella*. Normal mice infected with live organisms died within one to three days when 10^{8} organisms were used and survived somewhat longer than those infected with smaller doses. Culture from the spleens of the survivors revealed that with 10^{6} organisms injected, the content of *Salmonella* in the spleen was approximately the same in normal and BCG infected mice. However, it was much lower in the latter mice than in controls when challenged with smaller inocula. It is apparent that the altered reactivity after BCG infection may have resulted in increased or decreased susceptibility to challenge infection with an immunologically unrelated agent. Hyperreactivity to endotoxin was responsible for acute deaths after injection of large amounts of *Salmonella*, whereas the animals dealt more effectively with small inocula. It is important to emphasize that in this model any immunological relationship between preparatory and challenge infection can be excluded.

Experiment 2: Swiss white mice (Institute for Cancer Research strain) were injected intraperitoneally with *Salmonella typhimurium* and tested 7 days later for hyperreactivity toward endotoxic lipopolysaccharide. The results summarized in Table II indicate that injection with *Salmonella* induced in mice a state of hyperreactivity similar to that after vaccination with BCG.

Table II: Mortality from Endotoxin of Mice Previously Infected with *Salmonella typhimurium* or BCG

Endotoxin µg	Infection					
	Salmonella		BCG		Control	
	deaths/number injected	%	deaths/number injected	%	deaths/number injected	%
1000	—	—	—	—	15/18	83
100	17/18	94	8/12	67	4/18	22
10	10/18	56	5/12	42	0/14	0
1	4/18	22	6/12	50	—	—
0.1	1/12	8	0/10	0	—	—

The observation of RAETTIG [6] on man and our experiments on mice strongly indicate that a state of hyperreactivity towards endotoxin developing during an infection might well contribute to the pathophysiologic processes manifested by this infection. The fact that BCG vaccination may result in increased or decreased susceptibility to an unrelated challenge infection sug-

gest that fluctuations of the host's reactivity to a given infection might occur independent of immunological phenomena. The actual reactivity of the host to a given amount of toxic material and not the absolute potency of the material determines the degree of toxic manifestations during the infection. It can be assumed that such hyperreactivity phenomena need not necessarily be manifested by obvious toxic reactions but may result in subtle disturbances of various systems of the host. It is suggested that physiological and pharmacological studies on such models may be a fruitful approach towards an understanding of pathophysiologic processes in infection. As our experiments show, such studies may also provide information on the relationship between invasive and pathogenic mechanisms.

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Zusammenfassung

Es wird einleitend darauf hingewiesen, dass mehr und mehr die Bedeutung von unspezifischen Faktoren für die Resistenz gegen Infektionen erkannt wird. Solche Faktoren können wohl auch in der Pathogenese von Infektionskrankheiten eine Rolle spielen, so zum Beispiel eine erhöhte Sensibilität gegen Endotoxin, die während den verschiedensten experimentellen Infektionen in Tieren nachgewiesen werden kann. An Hand von Experimenten an Mäusen wird dargestellt, in welchem Ausmass eine vorausgehende Impfung mit BCG den Ablauf einer nachfolgenden Infektion mit *Salmonella typhimurium* in verschiedenster Weise beeinflussen kann. Dies hängt weitgehend davon ab, ob grosse oder kleine Dosen zur Infektion verwendet werden.

Some Remarks Concerning the Ecology of Bedsonia Infections

By K. F. MEYER*

In 1953 in a discussion of the nomenclature of the psittacosis group, sponsored by the New York Academy of Sciences, it was recommended that the system be changed so that the investigator who first elucidated the morphologic, physiologic, and immunologic properties of this group – Sir SAMUEL BEDSON – would be properly recognized (MEYER[1]). It was proposed that the group name *Miyagawanella*, adopted in Bergey's Manual of Determinative Bacteriology, composed by a committee of the American Society of Bacteriologists, be replaced by *Bedsonia*, since the virus of lymphogranuloma venereum can scarcely be regarded as the prototype of the group.

One cannot be satisfied easily in finding even some simple term for reference to members of this group; neither rickettsia nor virus is a perfect fit. In the following remarks they will be given the questionable term virus, since no common appropriate twilight term is at hand.

The recognition of new antigenic relatives of the psittacosis and lymphogranuloma venereum (LGV) viruses has catalyzed investigations on a much broadened front in laboratory and field studies. The relationships of the old and new members, the natural and experimental infections, the virus particles, and the antigenic and chemical structures have aroused a new wave of curiosity and study. The group has been well reviewed recently from several points of view (WEISS[2]; WENNER[3]; MEYER and EDDIE[4]; BEDSON[5]), and this seems the time to integrate the old and new information.

General Characteristics of the Group

During the past 20 years, elaborate and painstaking studies, first of the psittacosis virus, then lymphogranuloma venereum, and later other avian and mammalian viruses, have established the widespread existence of distinct biologic groups which share striking characteristics:

They are large intracellular parasites, responsible for diverse, spontaneous, generalized or local, clinical or latent infections in man, birds, and mammals. They are readily stained by basophilic dyes. They are antigenically related, as evidenced in the complement fixation, cross immunity, and toxin neutralization tests. They are, with one exception, capable of producing pneumonitis in the laboratory mouse when introduced by the intranasal route. They grow well in the yolk sac of the embryonated egg. They are susceptible to the action of certain drugs. The usual infections are probably latent; among susceptible species infection may be commonplace, initially taking place in the young. Mortality rates vary; epidemics sometimes occur. More often the tendency is recovery, with the development

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