THE DEMONSTRATION THAT ALLERGIC INFLAMMATION IS NOT NECESSARY FOR THE OPERATION OF ACQUIRED IMMUNITY

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It is well known that, after recovery from many infectious diseases, the body which was originally susceptible to infection can be shown to have become highly resistant to a second attack of the same infectious agent. It is, however, a remarkable fact that this body, resistant to living bacteria, is nevertheless extremely sensitive as a rule to noxious effects of products of disintegration of the bacteria—so much so that amounts of those products which would be harmless to the normal body can produce distressing symptoms and local damage and death of the tissues, accompanied by severe inflammation, in the hypersensitive, or "allergic" one. In the case of certain infections (tuberculosis, for example) the destruction of tissue resulting from this condition of acquired hypersensitiveness is often one of the most serious aspects of the disease. It is, nevertheless, commonly believed today that the hypersensitive state is necessary for the heightened resistance to bacterial invasion which is acquired during infection. The idea behind this belief is that since the body is more sensitive to the products of the infecting bacteria it responds more promptly with inflammation on contact with the bacteria, which are thereby prevented from spreading and are ultimately destroyed at the site. From this point of view the destruction of tissue resulting from allergy is regarded as an unfortunate, but necessary local sacrifice for the protection of the body as a whole. It is obviously important to know whether the destruction of tissue through hypersensitiveness is actually necessary for immunity, for if it is not the damage may be diminished or even prevented by methods which are effective in reducing or abolishing hypersensitiveness. It is my purpose to present in this paper experimental evidence that allergic inflammation is not necessary for the operation of acquired immunity.

Those who believe that hypersensitivity is necessary for immunity base their belief upon two arguments. In the first place, it is claimed that the two most striking manifestations of acquired immunity—namely, the retardation of spread of the bacteria, and the inhibition of their growth—can both be explained as effects of the acute inflammation which attends the allergic response. This claim is based upon the observation that when certain bacteria are injected into tissues previously inflamed by non-specific irritants, their spread from the site is retarded and their growth is checked. I think that it is important to draw attention briefly to two

facts which interfere with our acceptance of the idea that it is the accelerated acute inflammation of allergy which is responsible for the local fixation and the inhibition of growth of bacteria in the immune body. First, not all of the types of bacteria which can be restrained by acquired immunity are so affected by a prepared inflammatory exudate. Thus, although the activities of the streptococcus, the colon bacillus and bacillus pyocyaneus are inhibited when these bacteria are injected into inflamed areas, such areas offer no protection whatever against the pneumococcus,[1] the diphtheria bacillus,[2] the anthrax bacillus,[2] or the tubercle bacillus.[3] Second, the injection of bacteria into areas inflamed by the preliminary application of an irritant does not actually reproduce the elementary conditions of an allergic reaction, although it is widely assumed to do so. In an allergic reaction the bacteria are deposited in uninflamed tissues, and a period of time must elapse before the irritant antigen arouses an inflammatory response at the site. This situation is comparable to the injection of bacteria together with an irritating agent. Using a bacterium which is readily inhibited when injected into an area of prepared inflammation, Dr. Bull, Miss McKee and I have recently shown that when the time relations of allergic inflammation are really reproduced by injecting the bacteria at the same time as the inflammatory irritant, in spite of the rapid development of inflammation at the site, the growth and spread of the bacteria are accelerated rather than retarded, and death of the animal occurs earlier than in control animals receiving an injection of bacteria alone. As a matter of fact, careful scanning of the protocols of previous investigators who have reported that inflammation inhibits the activities of bacteria reveals the fact that whenever the conditions of an allergic inflammation were reproduced by the injection of the bacteria and the irritant at the same time, the promptly developing inflammation afforded the animal no protection whatever.[2,4,5,6,7] These considerations prevent the acceptance of the claim that it is the prompt inflammation of allergy which is primarily responsible for the retardation of spread and the inhibition of growth of bacteria in the immune body.

The second argument commonly advanced by those who believe that allergy is necessary for immunity is that whenever acquired immunity is demonstrable, allergy is present also. Since little work has been done on the relation between allergy and immunity in infections other than tuberculosis, it seemed important to investigate this matter in different diseases before accepting the current generalization that allergy and immunity are always coexistent. Interestingly enough, in the first disease which we chose for investigation, namely, syphilis, we were able to demonstrate with ease that acquired immunity can act effectively in the absence of allergic inflammation.

That allergy may develop during the course of syphilitic infection was

clearly shown a number of years ago by Noguchi,[8] and has received ample confirmation since. In this disease, as in tuberculosis and in bacterial infections in general, the immunity which develops following infection has been widely assumed to be the result of allergic hypersensitivity. As an example, I need only quote from a recent text book[9] in which it is stated that "immunity (in syphilis) is really a hypersensitiveness.... Persons with syphilis are protected from reinfection by the local hypersensitive reaction which occurs at the site of reinfection." In spite of the dogmatic character of such statements, as far as I have been able to determine there has been no record of an experimental examination of the relation of allergy to immunity in syphilis. The study which I am about to report was carried out in collaboration with Dr. Chesney and Dr. Turner.

Briefly, we rendered animals immune by the injection of spirochaetes derived from human lesions, and at various periods after the immunizing inoculation we injected measured doses of virulent spirochaetes into the skin of these immunized animals and of normal control animals. The results of the injections were studied carefully by gross and microscopic examination of the areas at frequent intervals. Under the conditions of our experiments, acquired immunity manifested itself not by the assumed occurrence of allergic inflammation at the site, but by a remarkable indifference of the tissues to the presence of the injected spirochaetes. After a very slight and transient non-specific inflammation which followed the injection of the emulsion containing the spirochaetes, and which was no different in quantity or in quality in the immune animals from what it was in the controls, the skin of the animals with acquired immunity returned to its normal state and remained so, and no late metastatic lesions appeared, while in contrast, in the control animals a progressive, ulcerating chancre always appeared at the site of inoculation and metastatic lesions developed with the usual frequency. The eye and the testis of our immune animals, sites which are highly reactive in allergic animals, were as indifferent to the injection of spirochaetes as was the skin.

Although, as I have said, allergy undoubtedly may appear under certain conditions during syphilitic infection, the present experiments demonstrate conclusively, we feel, that in this chronic infection, which resembles tuberculosis in so many ways, allergic inflammation is in no sense necessary for the operation of immunity under experimental conditions in animals; and I may add that there is excellent evidence that the same is true of human infection.

What, now, of allergy and immunity in acute infections? For this problem the pneumococcus was the organism selected, for it is well known that animals actively immunized against the pneumococcus become allergic as well as immune, and here, as usual, immunity has been assumed

to be dependent upon the hypersensitive inflammatory reaction. I had, however, occasionally encountered exceptional animals which had acquired a high degree of active immunity to the pneumococcus but which failed consistently to exhibit allergic reactions on reinfection. These accidental observations suggested the possibility of dissociating allergy from immunity in this infection by the method of passive immunization. Accordingly, Dr. Brown and I introduced the serum from immunized animals into the blood stream of normal ones, and then injected measured amounts of virulent pneumococci into the skin of these passively immunized animals and of normal, non-immune controls. In no instance did an allergic inflammatory reaction occur at the site in the immunized animals. All of them survived without developing any appreciable lesion at the site of inoculation or elsewhere. In contrast, the non-immune controls always developed progressive, local inflammatory lesions, and all of them died with septicaemia shortly after the inoculation.[10]

It is clear from these experiments on syphilitic and pneumococcal infection that it is not an accurate generalization to say that acquired immunity is inseparable from allergic inflammation. On the contrary, the experiments demonstrate, in an acute and in a chronic infection, that acquired immunity, whether active or passive, can operate effectively in the complete absence of allergic inflammation.

What, then, is the mechanism which retards the spread of bacteria in the immune body, and what forces are responsible for their destruction? Regarding the first of these problems, I should like to point out that bacteria can frequently be found in the regional lymph nodes as early as five minutes after having been introduced into the normal body. This fact alone should make it clear that the allergic inflammation, which requires a much longer time to develop to any appreciable degree, can hardly be primarily responsible for the local fixation which occurs in the immune body. In a study of pneumococcal immunity I have found that local fixation appears to be effected primarily by a prompt and specific agglutination of the bacteria which impedes their free movement through the tissues; and that this agglutinative fixation (which appears to involve a phenomenon of adsorption to the tissues as well) is just as efficacious in preventing the spread of the bacteria in passively immunized animals in the absence of allergic inflammation as it is in actively immunized, allergic animals. It is significant that this process of fixation can occur in the tissues of immune animals in which no plasma agglutinins are demonstrable by ordinary *in vitro* tests. Furthermore, while I do not mean to suggest that the phagocytes are unimportant in immunity, it is, nevertheless, highly interesting that agglutinated pneumococci can be seen to undergo destruction and lysis in the tissues extracellularly, without the intervention of phagocytosis.

In summary, the studies reported in this paper demonstrate that active immunity in syphilis does not require allergic inflammation for its successful operation; that passive immunity to the pneumococcus acts effectively in the absence of allergic inflammation; and, finally, that the inhibition of spread of pneumococci in the immune body is effected primarily not by allergic inflammation, but by a specific agglutinative process which acts independently of allergy and is in operation before any inflammation appears.

These facts do not support the current generalization that allergic inflammation is necessary for the operation of acquired immunity in bacterial infection. On the contrary, they direct attention to the consideration of abolishing allergy by means of desensitization in diseases, such as tuberculosis, in which hypersensitivity is responsible for untoward symptoms or tissue destruction.

[1] Clark, *Arch. Path.*, **8**, 464 (1929).
[2] Cobbett and Melsome, *Cent. allgem. Path. path. Anat.*, **9**, 827 (1898).
[3] Krause and Willis, *Am. Rev. Tuberc.*, **4**, 563 (1920).
[4] Opie, *Jour. Immunol.*, **17**, 329 (1929).
[5] Rivers and Tillett, *J. Exp. Med.*, **41**, 185 (1925).
[6] Nakahara, *J. Exp. Med.*, **42**, 201 (1925).
[7] Issaeff, *Zeits. Hyg.*, **16**, 287 (1894).
[8] Noguchi, *J. Exp. Med.*, **14**, 557 (1911).
[9] Low, *Anaphylaxis and Sensitization*, Edinburgh, **1924**.
[10] Rich and Brown, *Proc. Soc. Exp. Biol. and Med.*, **27**, 695 (1930).

ON THE SYSTEMATIC AND ACCIDENTAL ERRORS OF MODERN TRIGONOMETRIC PARALLAXES

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1. Some years ago (these PROCEEDINGS, **10**, 1924, 129–132) E. B. Wilson and I discussed two series of parallax determinations, and derived a Lexian ratio of 1.24 for the conversion of the published probable errors to the actual ones. At that time the amount of parallax material available was large enough only in the case of two observatories to be discussed in this manner. Since that time, however, large numbers of parallaxes have been published by nearly all observatories now engaged in this type of work, and it seems possible to apply the same analysis to all photographic trigonometric parallaxes now available.

2. The material used consists of all that could be obtained from published sources by September, 1929, and comprises: