An invisible microbe that is antagonistic to the dysentery bacillus

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d'Herelle, F. 1917. Sur un microbe invisible antagoniste des bacilles dysentériques. *Comptes rendus Acad. Sciences*, Vol. 165, pages 373–375.

FROM THE FECES OF SEVERAL PATIENTS convalescing from infection with the dysentery bacillus, as well as from the urine of another patient, I have isolated an invisible microbe endowed with an antagonistic property against the bacillus of Shiga. This discovery is particularly easy to make in cases of ordinary enteritis following upon dysentery infections. In convalescent cases in which enteritis does not occur, the antagonistic microbe disappears very soon after the disappearance of the pathogenic bacillus. In spite of a number of examinations, I have never found this antagonistic microbe in the feces of dysentery cases during the period of infection, nor in normal subjects.

It is very simple to isolate the anti-Shiga microbe. A tube of broth is seeded with four to five drops of feces, and the tube is placed in the incubator for 18 hours at 37°, and the contents then filtered through a Chamberland candle filter, L_2. When a small quantity of an active filtrate is added to a broth culture of the Shiga bacillus, or

an emulsion of this bacillus in broth or in physiological saline, the culture is inhibited and the death of the bacillus through complete lysis occurs after a period of time which varies from several hours to several days, depending upon the amount of filtrate added and the size of the bacterial inoculum.

When the invisible microbe is cultivated in a culture of Shiga bacillus and transferred to a new culture of Shiga bacillus by a drop of the liquid, it reproduces the same phenomenon again with the same intensity. Up until today I have carried the first isolated strain through 50 successive transfers. Moreover, the following experiment offers visible proof that the antagonistic action is produced by a living germ. If one adds to a culture of the Shiga bacillus a dilution of a previously lysed culture such that the new culture contains only one-millionth of a part of the original lysate, and then, immediately, a small drop of this is spread on an agar slant, one obtains, after incubation, a layer of dysentery bacilli covering the surface, but in which there are a certain number of clear areas of about 1 mm. diameter, in which there are no bacteria. These clear areas can only represent colonies of the antagonistic microbe: a chemical substance would not be able to concentrate itself in such definite spots. By doing this experiment with measured quantities, I have been able to show that a lysed culture of Shiga bacillus contains around 5 to 6 billion filterable germs per cubic centimeter. One three-billionth of a cc. of a lysate of Shiga bacillus, containing therefore a single germ, fully inhibits a culture of Shiga bacillus similarly seeded. The same quantity added to a 10 cc. culture sterilizes and lyses it in 5 or 6 days.

Various strains of the antagonistic microbe which I have isolated were originally only active against the bacillus of Shiga. By culture in symbiosis with the dysentery bacilli of Hiss or Flexner, I have been able, after several passages, to render them active against these bacilli. I have never obtained an activity against other microbes: typhoid and paratyphoid bacilli, staphylococci, and so on. The appearance of antagonistic activity against the bacilli of Flexner and Hiss is accompanied by a reduction and then a loss of power against the Shiga bacillus. This power reappears with its original intensity, however, after several transfers in symbiosis with the latter. Its specificity of action is therefore not inherited in the nature of the invisible microbe, but is acquired in the organism which is attacked during the symbiotic culture with the pathogenic bacilli.*

The antagonistic microbe can never be cultivated in media in the absence of the dysentery bacillus. It does not attack heat-killed dysentery bacilli, but is cultivated perfectly in a suspension of washed cells in physiological saline. This indicates that the anti-dysentery microbe is an obligate bacteriophage.†

The anti-Shiga microbe exhibits no pathogenic action against experimental animals. Lysed cultures of the bacillus, which are in reality cultures of the antagonistic microbe, exhibit the property of immunizing rabbits against doses of the Shiga bacillus which kill the controls in five days.

I have attempted to discover evidence for an antagonistic microbe in convalescents from typhoid fever. In two cases, one in the urine, the other in the feces, I have isolated a filterable microbe able to lyse nicely the paratyphoid A bacillus but always less markedly than in the cases of the

* [This statement is not exactly true. Bacterial viruses continue to breed true.]

† [Apparently the first use of this word.]

Shiga bacillus. These latter properties were attenuated in succeeding cultures.

In summary, in certain convalescents from dysentery I have shown that the disappearance of the dysentery bacilli is coincident with the appearance of an invisible microbe endowed with antagonistic properties against the pathogen. This microbe, really a microbe of immunity, is an obligate bacteriophage. Its parasitism is strictly specific, but if it is restricted to a certain species, it is gradually able to acquire activity against various germs. It seems therefore that in the dysentery bacillus, as well as a homologous immunity coming directly from the person infected, there exists a heterologous immunity coming from an antagonistic microbe. It is probable that this phenomenon is not restricted to dysentery, but that it is of general significance, because I have been able to observe a similar situation, even though weaker, in two cases of paratyphoid fever.

Comment

This discovery of bacteriophages, or bacterial viruses, was actually first made by Twort in 1905. But his work is not too clear and was not followed up, so that I have included here the paper by d'Herelle, which was really responsible for the beginning of extensive scientific work on these interesting organisms.

Most species of bacteria that have been studied have been shown to be hosts for bacterial viruses. As d'Herelle suspected, the phenomenon is widespread. But his early hopes that bacterial viruses would be useful in treating bacterial infections or in conferring immunity have not been fulfilled. d'Herelle had little understanding of the word "immunity" as we use it, since the injection of a bacterial virus could not be expected to induce antibody formation against a bacterium. The bacterial viruses have remained essentially laboratory curiosities. They have been used as model systems for the study of viral reproduction and have made great impact on molecular genetics. They have also been used in diagnostic laboratories in the typing of certain widely occurring pathogens, such as *Salmonella typhosa* and *Staphylococcus aureus*. But all trials of their use as therapeutants have been unsuccessful.