BACERIOPHAGE
A NEW WEAPON AGAINST INFECTION
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IN HIS researches upon rabies or hydrophobia, Louis Pasteur, the founder of bacteriology, was unable to demonstrate under the microscope the causative organism of the disease. The clinical evidence, however, led him to believe the disease in question was a germ disease, but after the most diligent search the organism could not be demonstrated. These researches were started in 1880 and were continued for several years. Although Pasteur proved the infectious and contagious nature of the disease, also a means of control or prevention by vaccination, now known as the Pasteur treatment for rabies, his failure to demonstrate the causative organism led him to suggest that the causative organism was an invisible one, too small to be seen under the microscope.

Today it is well recognized that a number of diseases are caused by organisms which are too small to be seen under the microscope. Such germs are termed, therefore, ultramicroscopic organisms. The first of such cases to be definitely established was foot and mouth disease in which Leoffler and Frosch in 1892 demonstrated the virus of this disease was not only ultramicroscopic, but that it was capable of passing through the pores of a porcelain filter which would retain all visible microscopic organisms. This work led to another designation for the ultramicroscopic germs; namely, filterable viruses, because of their ability to pass through the pores of these very fine filters.

The use of porcelain filters thus became a valuable part of bacteriological technic, making it possible to discover the causes of the diseases now known as the filterable virus diseases. Working with such filters, d'Herelle in

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1916 discovered a filterable virus which was capable of attacking and destroying the germ which causes human dysentery. This was an entirely new view of the filterable virus question, one which possessed tremendous possibilities for study and investigation, and of possible use to mankind in the destruction of disease-producing germs invading the human body. Dr. d’Herelle, being a brilliant investigator, at once recognized the tremendous possibilities for the practical application of this discovery. His reasearches were now pushed in this direction, and it was not long until many new facts came to light regarding the filterable substance capable of destroying bacteria. He called this filterable substance a bacteriophage (“bacteria-devourer”).

Bacteriophages, like bacteria themselves, are ubiquitous in nature. They are strictly parasitic and live only upon bacteria. This state of parasitism may be of mutual helpfulness or tolerance, and it is now known that many bacteria in nature carry bacteriophages, there being developed eventually a state of true symbiosis. Recently it has been discovered that a bacteriophage living in a state of symbiosis with a bacterium may cause changes in the biological properties of the bacterium giving rise to a new bacterial strain or type, which facts give the key to natural evolution among bacteria and the formation of new strains. But not always is a state of symbiosis realized. The union or association may result in the destruction of the bacterium by the bacteriophage or the bacterium may destroy the bacteriophage.

As some bacteriophages are capable of destroying certain bacteria, efforts have been made to find bacteriophages capable of destroying the bacteria which are responsible for certain types of infections in man. To accomplish this the destructive bacteriophage must be brought into contact with the infecting organism. The recovery from natural infections is sometimes due to the patient developing a potent bacteriophage against the infection. Once finding in nature a bacteriophage capable of destroying a definite type or kind of infecting organism,
it is possible by appropriate laboratory technic to step up or enhance the destructive power of the particular bacteriophage for that particular bacterium. Such a bacteriophage to be highly potent for therapeutic work must be able to destroy all of the organisms in a culture of the specific infecting organism within a period of four to six hours. Bacteriophages requiring a longer time are of doubtful therapeutic value.

These destructive bacteriophages are very specific in their action; that is, they will destroy one kind or one strain of bacterium and be harmless to other bacteria. As bacterial infections in man and animals are caused by a wide variety of bacterial types and strains, this specific nature of bacteriophage is a very important factor from a practical therapeutic standpoint. This was shown to be true in calves stricken with a fatal septicemia. In this infection the calves at the time of birth were normal, vigorous, and apparently in normal health. When a few days of age, they developed an acute septicemia which terminated fatally, in all cases, within a few hours. The bacteriological diagnosis revealed the cause of death was a very powerful strain of bacterium known as Escherichia coli. This was proved to be the cause of the disease by injecting the organism obtained from the dead calves into healthy calves, reproducing the disease, and recovering the organism from the artificially infected animals. All attempts to control this infection by sanitation and by the use of commercial antisera failed. Giving the new-born calves large doses of their dam’s blood was only partly successful in controlling the disease. Drug therapy failed entirely. A potent bacteriophage was produced for the organism causing this infection and when administered hypodermically and by way of the mouth to the new-born calves the infection was checked and the calves survived; whereas untreated calves used as checks died when a few days of age. These good results with the bacteriophage continued for several months, during which time a number of new calves had been born in the herd and were being raised successfully. It developed, however, that eventually a calf which had received the bacteriophage at the
time of birth developed the disease and died when a few days of age. From this dead calf the organism Escherichia coli was isolated, but when this strain of the organism was tested against the Escherichia coli bacteriophage being used in this herd, the organism was not destroyed. The next step, of course, was to develop a bacteriophage which would destroy the new strain, and when this was done, it was mixed with the original bacteriophage, the mixture proving successful in controlling the disease.

Sinus infections which are so annoying, painful, and difficult to treat in man are responding to treatment with bacteriophage. The bacteriological examination of the discharges from infected sinuses usually reveals a hemolytic Staphylococcus. Very often this is the only organism found, although it may be associated with other organisms, and, occasionally, an entirely different organism is found. When a Staphylococcus is found, either alone or associated with another organism, to be the cause of the sinus malady, a few treatments with a potent bacteriophage for the particular strain of Staphylococcus usually brings prompt relief to the patient. The bacteriophage is injected into the sinuses after first irrigating the sinuses with sterile water to remove mechanically the pus and nasal discharge. Antiseptics should not be used for this purpose as enough of the antiseptic solution will remain within the sinus to destroy the bacteriophage when it is introduced. Bacteriophages, although not toxic or poisonous themselves for man, may, when introduced into an infected sinus, give rise to a mild reaction. This is a good indication, however, as it demonstrates that the bacteriophage is potent and highly destructive for the specific organism; the absorption of the lytic bacterial products induce the reaction. When a potent bacteriophage, specific for the particular infecting organism, is employed, excellent results will be obtained in these sinus cases, unless the case is of long standing with extensive tissue changes, in which cases the bacteriophage usually brings marked improvement, if not complete recovery.

Bacteriophages which are capable of destroying bacteria do so by a process of lysis (dissolving) in which the
bacteriophage produces an enzyme which dissolves the bacteria, or it may cause the organism first to swell and then to break up into many tiny particles. This may be demonstrated by growing the bacterium in a test tube containing suitable food for the organism, such as broth. When the bacteria are introduced into the broth, the solution is clear, but after standing for a few hours in an incubator, the broth becomes cloudy, due to the growth of great numbers of the bacteria. If, at the time of introducing the bacteria into the broth, a few drops of bacteriophage destructive for that particular bacterium is introduced and the mixture placed in the incubator, the bacteria will multiply and the broth soon becomes cloudy, but the bacteriophage, which is also multiplying upon the bacteria, soon reaches a point of great numbers and suddenly dissolves all of the bacteria. This dissolving of the bacteria causes the broth to change from cloudy to clear.

Wild bacteriophages exist abundantly in nature wherever bacteria are found. It was observed by d’Herelle that in one of the rivers in India the water in which the natives bathed contained large numbers of the bacteria, many disease producing, which were present upon the bodies of the bathers, but a short distance down stream from the place of bathing the water was free of these dangerous bacteria. In the water which was free of the dangerous bacteria of human origin, bacteriophages were present which were capable of destroying these bacteria. Today bacteriologists recover these wild bacteriophages from material containing the bacteria of human infections. As sewage contains the bacteria of many human infections, this material is usually rich in the wild bacteriophages. This material is first passed through a porcelain filter which takes out all of the bacteria present, but permits the bacteriophages to pass through. The filtered product, rich in bacteriophage, is then tested against the bacteria which were isolated from a given infection to determine if it contains a bacteriophage specific for that particular infection. Following such a procedure, it is sometimes found that while the wild bacteriophage will destroy the infecting bacterium, it may require many hours or days to
do so, but by filtering this material and again recovering the bacteriophage and running it against another fresh culture of the bacterium, the time required for destroying the bacterium will be shortened. By repeating this process a number of times the wild bacteriophage is gradually built up to a highly specialized bacteriophage capable of destroying the infecting bacteria within a few hours time. It is now ready for therapeutic use upon the patient. By growing the bacteriophage upon the organism and filtering to separate the two, any desired quantities of bacteriophage may be produced.

The very specific nature of bacteriophages has mitigated against their general use in medical practice. It explains many of the failures which have been charged against them in the past. Before this fact was well understood, some commercial biological firms produced bacteriophages which obviously failed to be of any value in the treatment of many of the infections for which they were intended. These failures have very naturally caused an unfavorable reaction to their use.

Being a living organism (some workers claim it is an enzyme) bacteriophages are readily inactivated by antiseptics. They should, therefore, not be used in conjunction with any chemical substance which destroys them. In the early attempts of biological firms to manufacture bacteriophages for the medical profession, bacteriophages to which chemicals were added to prevent spoilage were distributed to Physicians. In many biological preparations such preservatives may be added without in any way destroying the usefulness of the product, but not so in the case of bacteriophages. Here other methods of handling must be employed; namely, producing the bacteriophage under strict aseptic conditions and maintaining such conditions from the time it is produced until administered to the patient. This error, like failure to recognize the specific action of bacteriophages, has been responsible for numerous failures.

This new weapon for fighting man’s most destructive enemy, bacterial infections, has been delayed in being
incorporated into medical practice because attempts were made to use the weapon in practical warfare upon disease before the weapon itself was properly understood. Dr. d'Herelle has employed the weapon with remarkable success, but others who have tried to duplicate his work, and who failed because of faulty technic or because they did not understand its limitations, have not hesitated to condemn the weapon in toto. There are potent signs, however, that bacteriophage therapy is now passing from the stage of a scientific curiosity to a therapeutic agent of real value. Today in a number of laboratories and hospitals potent bacteriophages are being produced and employed with excellent results in certain types of infections which heretofore have proven very difficult to treat. This weapon does not lend itself to mass production, but must be produced specifically for each type and individual case of infection, and its potency determined for the individual case before it is used upon the patient. To be effective its specific nature must be kept constantly in mind; it must be kept free of foreign substances which may destroy it; it must be produced only by skilled bacteriologists and used only by skilled clinicians. Each infection must be studied carefully in the laboratory, the type of invading organism isolated, and a bacteriophage destructive to this particular strain of the infecting organism produced if good results are to be expected. Without such measures, this weapon will probably fail more often than it will succeed.