

cranial tension. Pains and aches all over the body and neuralgiform-like attacks occur. Sexual neurasthenics, particularly young males, are legion. Young women are often conscious of abnormal sensations in their breasts or in the region of the ovaries. It would be possible to continue indefinitely enumerating the various manifestations of neurasthenia, psychasthenia or hypochondriasis.

Treatment of the milder forms of these psychogenic disorders is a satisfactory and absorbing problem. If the physician will only take time to analyze the everyday life of such a patient, the irritating factor can often be discerned and discovered and, while it is often not possible to do away with it, methods may at least be suggested which will mitigate the frequency and the severity of the stimuli. When this is done the general rules of hygiene should be laid down and the patient should be given plenty of both mental and physical rest. In the obstinate and exaggerated cases a thorough Weir-Mitchell rest cure may be indicated, but in the milder forms daily rest in the middle of the day will often suffice. Other rules of hygiene as suggested in the treatment of the constitutionally strong should be employed. In these more severe forms where the patient is constitutionally substandard, tact, thoughtfulness and kindness will do much to aid the patient. The discerning physician often becomes the safety valve for emotional outlet. The mere recital of the trouble and the confiding in one who has sympathy acts as a stabilizer, for a time at least, to the individual who is suppressing or repressing certain emotions. The physician can do much for these people. That he can do more than he is now doing is shown by the host who flock under the protecting wing of every cult that offers a shelter. I would plead for these individuals that they be treated as friends and fellows and that they be considered as sick, as ill, and as diseased as he who has a true organic disease.

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## THE BACTERIOPHAGE AS A THERAPEUTIC AGENT\*

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### INTRODUCTION

SCARCELY more than a decade has elapsed since d'Herelle<sup>1</sup> published his first observations on the strange phenomenon which we have come to associate with his name. Something like a thousand scientific papers now point to the interest which his discovery has commanded. D'Herelle's basic observations have been repeatedly confirmed and considerably extended. Indeed, present-day knowledge of the extent of the phenomenon among bacteria of all sorts, pathogenic and nonpathogenic, cannot help causing one to wonder why a phenomenon so striking in its manifestations, and of such general occurrence managed to escape detection so completely during

a half-century of active bacteriological investigation. While many of the studies have centered around the interesting question of the nature of the agent responsible for the phenomenon of transmissible bacterial lysis, as well as around other questions of more academic interest, some investigations have dealt with the possible application of the bacteriophage to the prevention and treatment of infectious diseases. Naturally a substance which even in minute quantities is capable of killing and dissolving bacteria in cultures, and which at the same time is known to be entirely harmless to animal tissues, deserves investigation as a potential therapeutic agent. That the hopes which prompted the inquiries in this direction have not been altogether unfounded, may be gathered from the general trend of some forty reports now in the literature. Time does not permit me to review these in detail. I shall only be able to indicate the general trend of these results and point out the conditions which unfortunately tend to limit the application of this form of therapy.

### REVIEW OF 'PHAGE THERAPY

D'Herelle<sup>2,3</sup> was apparently the first to apply the bacteriophage therapeutically. He administered it to seven cases of *Shiga dysentery*, and noted prompt recoveries in all of the cases treated. Da Costa Cruz<sup>4</sup> in South America claims to have supplied more than ten thousand ampoules of 'phage to physicians and hospitals in Brazil, where, I understand, this form of therapy is now routinely employed in the treatment of bacillary dysentery. According to da Costa Cruz, the results of 'phage therapy have been uniformly good. A potent 'phage is said to bring the bloody stools to a stop, as a rule, within twenty-four hours, and to launch the patients upon an immediate convalescence. I have in my possession a letter received by Doctor d'Herelle from a medical officer in the Sudan to whom 'phage suspensions were supplied while I was with d'Herelle in Egypt several years ago. It reads in part as follows: "The results of treatment of bacillary dysentery with it (the bacteriophage) have been little short of miraculous. . . . In every case, with the solitary exception of a child who was practically moribund when brought to the hospital, the bacillary dysentery has cleared up within twenty-four hours." The value of the bacteriophage as a therapeutic agent in bacillary dysentery has also been confirmed by other investigators (Pereira,<sup>5</sup> Spence and McKinley,<sup>6</sup> Munter and Boenheim<sup>7</sup>). It is of interest that only two, and these are early papers, deny its therapeutic value in dysentery (Otto and Munter,<sup>8</sup> Davison<sup>9</sup>).

Encouraging results have also been reported in *typhoid fever* by a number of investigators (Beckerich and Hauduroy,<sup>10,11</sup> Philibert and Hauduroy,<sup>12</sup> Hauduroy and Arsimoles,<sup>13</sup> Alessandrini and Doria,<sup>14</sup> Smith,<sup>15</sup> Richet, Azerad and Delarne<sup>16</sup>). The results obtained in typhoid, however, lack the high degree of uniformity which mark those recorded for bacillary dysentery. In the treatment of typhoid fever it appears that while some of the cases may make spectacular recoveries, others show themselves entirely

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uninfluenced. This at least has been the experience of most of those who have reported on a number of cases. Only one report (Herderschee and Wolff<sup>17</sup>) has appeared in which the results have been entirely negative.

Favorable results have also been recorded by a considerable number of investigators who have tried 'phage therapy in *colon infections* of the urinary tract (Courcoux, Philibert and Corday,<sup>18</sup> Beckerich and Hauduroy,<sup>19</sup> Alphonsi,<sup>20</sup> Arloing, Dufour, Bouvier and Sempé,<sup>21</sup> Philibert,<sup>22</sup> Lehndorff,<sup>23</sup> Pereira,<sup>5</sup> Winans,<sup>24</sup> Frisch,<sup>25</sup> Zdandky,<sup>26 27 28</sup> d'Herelle,<sup>3</sup> Larkum,<sup>29</sup> Ravina,<sup>30</sup> Dalsace,<sup>31</sup> Cowie,<sup>32</sup> Krueger, Faber and Schultz<sup>33</sup>). While one must be impressed by the striking manner in which some of the cases seem to have responded to this form of therapy, it is, nevertheless, true that not a few failed entirely to respond to the treatments. Here also there seem to be factors operative within the host which tend to influence greatly the results in individual cases. Whether these disturbing influences may eventually be brought under control remains to be seen.

More uniform results seem to follow 'phage therapy of *staphylococcus infections*. Bruynoghe and Maisin<sup>34</sup> as early as 1921 injected 'phage near the base of furuncles and carbuncles of six patients and noted in all of them marked improvement within forty-eight hours. Gratia<sup>35 36</sup> soon after reported excellent results in something like fifty cases of staphylococcus infections, including furunculosis, carbuncles and subcutaneous abscesses. Encouraging results have also been reported following the use of staphylococcus 'phage in the treatment of sycosis (Gougerot and Peyre,<sup>37 38</sup>); of staphylococcus cystitis (Nelson Barbosa<sup>39</sup>); and of staphylococcus wound infections (McKinley<sup>40</sup>). Recently Larkum,<sup>41</sup> of the Michigan State Board of Health, has reported favorable results in sixty-five out of sixty-six cases of furunculosis. In a subsequent paper<sup>42</sup> he states that the series has been extended to "three hundred cases of furunculosis, more than fifty cases of acne,\* eight or ten cases of styes, and several cases of osteomyelitis." According to Larkum, the results have been "sufficiently striking to cause reputable physicians, men of years of experience in practice, men usually cautious in their reaction to therapeutic agents, in submitting their reports, to use such adjectives as 'wonderful,' 'striking,' 'remarkable.'"

This summarizes the diseases around which most of the studies on the therapeutic value of the bacteriophage have thus far centered. You will note that these reports are confined to bacillary dysentery, typhoid and paratyphoid fever, colon infections of the urinary tract and to staphylococcus infections. A few isolated ones have also appeared on its use in the treatment of certain other infectious diseases. Thus McKinley<sup>40</sup> claims to have realized a rapid recovery in a case of *streptococcus abscess of the lung*, treated

by the instillation of 'phage into the infected cavity. Le Louet<sup>43</sup> of Indo-China has reported rapid improvement and recoveries in water buffaloes stricken down with *hemorrhagic septicemia* (Barbone). D'Herelle<sup>44</sup> claims to have observed rapid recoveries in a small number of *plague* cases treated in Egypt, and more recently<sup>45</sup> has reported some very striking results in the treatment of *cholera* in India.

A careful examination of the literature tends to leave one in no doubt as to the potential therapeutic value of properly selected bacteriophages. At the same time it is perfectly clear that the application of this form of therapy presents certain well-defined limitations. It is to these limitations, some of which may not be altogether insurmountable, that I wish to devote most of my paper.

#### FACTORS WHICH TEND TO LIMIT THE APPLICATION OF 'PHAGE THERAPY

Attention has been called to the fact that in bacillary dysentery the results, when a good 'phage is employed, tend to be strikingly uniform, while those in typhoid and paratyphoid fever, in colon infections of the urinary tract and in other infections mentioned, have a tendency to be exceedingly irregular. One may observe in the latter group spectacular recoveries in part of the cases, while others in the same series remain entirely uninfluenced. The question which naturally arises in one's mind is this: Why do the results in bacillary dysentery tend to be so much more uniform than those in other infections? There are probably several reasons for this. The question may possibly be answered in part on the basis of well-established laboratory observations. It is not only known that individual races of bacteriophage may differ widely from each other in their range of action and in the intensity with which they may attack different organisms, but it is well recognized that one may observe marked differences in the uniformity with which the individual strains of given bacterial species may yield themselves to the action of one and the same 'phage. Bacteria may on this basis be divided into two general classes. In the first we find those species in which the individual strains behave in a more or less homologous manner with reference to a particular 'phage. A 'phage which, for example, happens to be active for one strain of such a species is likely to be equally active on all other strains of the species. Typical examples of such *homologous species* are *B. dysenteriae* and *B. pestis*. Were the strains of all pathogenic bacteria as uniformly susceptible as dysentery bacilli, the problem of determining the therapeutic value of the 'phage in any disease would probably be greatly simplified. From the laboratory standpoint it would then become merely a matter of supplying the clinician with a race of bacteriophage possessing marked virulence for the particular bacterial species concerned. Unfortunately, however, most of the pathogenic bacteria belong to that larger group in which the individual strains of a species often differ widely in their susceptibility to 'phage

\* It is of interest that successful results have also been reported by other investigators (d'Herelle, 1928) in cases of acne treated with polyvalent staphylococcus bacteriophage, though the agent of this disease is held by some to be *B. acne*, an anaerobic diptheroid.

action. *B. typhosus* may be cited as an example. An antityphoid 'phage, highly active on one or two strains of *B. typhosus*, may not be at all active on other strains of this species. Another antityphoid 'phage may leave these particular strains entirely untouched, and in turn lyse one or more other strains of the species. The situation which this *heterologous* behavior gives rise to in a therapeutic study of this sort becomes obvious at once.

There is another type of bacterial resistance to 'phage action which should be considered. It is the resistance which an otherwise susceptible bacterium may acquire as the result of exposure to a weakly or only moderately active 'phage. This type of resistance, which one may picture as an acquired immunity on the part of the bacterium, may be induced either *in vitro* or *in vivo*. *In vitro* one sees it in the form of secondary cultures appearing after the acme of lysis. *In vivo*, it may be acquired as the result of a spontaneous invasion of a weak or moderately active 'phage, or as the result of the therapeutic administration of a 'phage of insufficient virulence to complete the eradication of the causal organism. Resistance as the result of a spontaneous invasion of a bacteriophage is not infrequently met with in chronic *B. coli* infections of the urinary tract. Sickenga,<sup>46</sup> for example, found 'phages constantly present in the urine of four cases of pyelitis, and occasionally present in the urine of twelve other cases. Larkum,<sup>29</sup> who has studied this question carefully, found a 'phage present in one or more specimens of urine in about 36 per cent of the cases examined. He also noted that, whereas strains of *B. coli* isolated from the urine in acute cases are practically always susceptible to stock bacteriophages, those isolated from the urine in chronic cases are almost always resistant. Doctor Krueger, in collaboration with Doctor Faber and myself (Krueger, Faber and Schultz<sup>33</sup>), recently made similar observations on a number of urinary cases. Krueger recovered weak to moderately active 'phages from the urines of 70 per cent of the chronic cases, in contradiction to only 8 per cent of the acute cases. Along with this he also noted a much greater incidence of 'phage-resistant organisms in the chronic cases. It does not necessarily follow, however, that all of the 'phages which naturally invade the infected urinary tract, remain of weak activity. The virulence may ascend rapidly and tend to precipitate an immediate spontaneous recovery, both from a clinical and bacteriological standpoint, as Krueger has been able to show in several cases which he followed carefully. Not infrequently, however—and this for reasons that are not clear—a balance is established between the causal microbe and the bacteriophage, and thereafter the two may coexist in the environment. In treating these particular infections the problem, therefore, becomes one of finding a 'phage of unusually marked virulence for the organism. This is not always an

easy matter, but can at times be successfully accomplished.

The bearing which these facts have on the therapeutic application of the bacteriophage cannot easily escape one's notice. An improperly chosen bacteriophage, administered therapeutically, may do no more than lead to the formation of secondary, resistant forms, for which it may in turn become much more difficult, if not impossible, to find a suitable 'phage. Not only is the possibility of gaining an immediate therapeutic result lost, but it is at the same time made more remote. One cannot, therefore, exercise too much care in choosing the bacteriophage which is to serve the therapeutic needs in a given case.

From what I have said, it must not be assumed that all that is necessary for the realization of a therapeutic result is to choose, or have chosen for you, a 'phage possessing maximum virulence for the organisms responsible for the infection. While this undoubtedly fulfills an important theoretical requirement, it is certain that not all cases respond to treatment even when this requirement is fulfilled. There are undoubtedly other factors which may at times influence the results. One of these factors may have to do with the constant variation of microorganisms in their susceptibility to 'phage action. Another may perchance have to do with the antigenic action which the bacteriophage itself is capable of exercising. Let me enlarge on this a little. It is well established (Bordet and Ciuca,<sup>47</sup> and others) that specific antiphagic antibodies can be easily demonstrated in blood of experimental animals having received bacteriophage suspensions parenterally over a brief period of time. Recently Sonnenschein,<sup>48</sup> Katsu,<sup>49</sup> and d'Herelle<sup>45</sup> have called attention to the fact that antiphagic antibodies may appear naturally in the blood of patients suffering from certain infectious diseases. If we stop to consider the frequency with which natural 'phage may be recovered, for example, from the urine of patients suffering with chronic urinary infections, we can begin to see how under certain conditions antiphagic antibodies, capable of inactivating at least certain 'phages, might be caused to make their appearance. These might conceivably neutralize the action of some stock 'phages, otherwise possessing the properties requisite for a successful therapeutic result.

There are undoubtedly still other factors which may influence individual therapeutic results. Inaccessible and sparsely scattered organisms may not be reached by the 'phage before it is itself eliminated from the body. One must remember that while the 'phage increases in concentration at the expense of bacteria which it dissolves, it is promptly eliminated from the body when no further organisms are within its reach, at the expense of which it may regenerate. Marcuse<sup>50</sup> for this reason is inclined to attribute some of the failures in typhoid to incomplete contact between bacteriophage and organisms in the body, and he therefore recommends intravenous injection in addition to ingestion of the 'phage. On the other hand, Hauduroy<sup>51</sup> has found that bile inter-

feres with bacteriophagy *in vitro*. It may, therefore, be possible that some of the failures in typhoid are directly referable to the inaccessibility of bacteria in the gall bladder. Analogous conditions may influence the results in other infections. The 'phage may, for example, become adsorbed to the colloidal matter of an inflammatory exudate and so thrown out of action. It may, moreover, be actually taken up by the leukocytes (Bruynoghe and Maisin<sup>52</sup>). Then again, the reaction of the environment may not always be altogether suitable for bacteriophagy, a slightly alkaline medium being required. In urinary infections an acid urine must therefore undoubtedly influence the results. While there probably are still other factors which may in individual cases contribute to failure, those mentioned will probably suffice to indicate the complexity of the problem.

#### THE PROPER PROCEDURE IN 'PHAGE THERAPY

Despite the fact that there are factors which tend at times to restrict its successful application in the treatment of disease, we must not forget that when *properly chosen* the 'phage may prove an exceedingly helpful therapeutic agent. The proper selection of a bacteriophage for therapeutic purposes is undoubtedly of paramount importance. Such a 'phage must not only be capable of lysing the causal organisms *in vitro*, but must *possess this property to an exceptionally high degree*. Not only must the 'phage be capable of inducing complete clarification of cultures under set conditions, but it should also tend to *keep down the appearance of secondary cultures*. We must keep in mind that in employing the 'phage therapeutically we are endeavoring to effect complete sterilization of the infected region. Whenever a 'phage is employed which is of insufficient virulence to accomplish this with one sweeping stroke,\* the effect is likely to be only a temporary reduction of the flora, with a subsequent ascendancy of secondary, and this time 'phage-resistant forms.

I have called your attention to the fact that individual strains of most bacterial species may differ widely in their susceptibility to bacteriophages active for bacterial species in general. For this reason it is quite impossible to say whether any particular stock 'phage actually possesses the virulence theoretically necessary for a satisfactory therapeutic experiment. *This must always be first determined by preliminary tests in the laboratory.*

Let me indicate the procedure which should properly be followed. The first step is naturally to get the causal organism out in *pure* culture. Whenever possible the material being cultured should be seeded directly on solid media. If this is not immediately possible or desirable, it should be plated out as soon as possible. Even though the plated cultures appear unmixed, one should select five or six representative colonies and transfer these to as many agar slants. Suitable young

broth cultures should then be prepared from each of these agar slants and tested against the various 'phages at one's disposal.† Only those tubes should be filtered for therapeutic use which show complete clarification and in which secondary cultures tend to be suppressed.

#### THE THERAPEUTIC ADMINISTRATION OF THE 'PHAGE

Possibly I should say a few words regarding the methods commonly employed in administering the bacteriophage therapeutically. This is a question which is frequently put to me by physicians interested in giving it a trial. In *dysentery* the practice is to administer the bacteriophage exclusively by mouth. A dose of two or three cubic centimeters of the lytic filtrate is generally given in a half glass of water. This treatment may be repeated in twenty-four hours. While there are no harmful results following the continued administration of the 'phage by mouth, nothing is gained by doing so. If a definite response does not immediately follow two or three doses of the 'phage, no therapeutic effects are likely to be realized. In *typhoid fever* the best results seem to follow a combination of oral and subcutaneous administration, two cubic centimeters being administered simultaneously by each route. Here again the treatment may be repeated in twenty-four hours, but should not be extended beyond this period. This applies particularly to the subcutaneous injections. In *colon infections of the urinary tract* the treatment generally recommended is to instil about ten cubic centimeters of the bacteriophage suspension, diluted with about five volumes of physiological saline, into the bladder, and in the event there is an associated pyelitis, introducing at the same time some of the liquid into the pelvis of the kidney. *These treatments should be preceded and accompanied by alkalization of the urine*, since an alkaline medium is essential for bacteriophagy. They should also be accompanied by two or three subcutaneous injections of undiluted bacteriophage, administered in doses of about two cubic centimeters each, given twenty-four hours apart. All other medication should be withdrawn for the time being. In *staphylococcus infections*, the practice is to give two or three subcutaneous injections of two cubic centimeters each at intervals of twenty-four hours. For carbuncles, about one cubic centimeter should be injected in small quantities of 0.1 to 0.2 cubic centimeters in the immediate region of the lesion. *Wounds*, in addition to such regional subcutaneous injection should be dressed with gauze well moistened with undiluted bacteriophage suspension.

There appear to be no contraindications to

\* It is for this reason that the bacteriological as well as clinical results of 'phage therapy should be read if possible within seventy-two hours after the treatments are begun and the question of its actual sterilizing action answered.

† Because of the increasing number of requests which have come to us from physicians for bacteriophage suspensions, we have recently undertaken to provide a special service (Bacteriophage Research Laboratory, Stanford University, California), open to a limited number of physicians desiring to investigate the therapeutic value of the bacteriophage. Physicians may send us through their clinical laboratories pure cultures of the organisms on which they desire the so-called 'phage-susceptibility test carried out. In the event the organisms are fully lysed, we send them suitable 'phage suspensions for therapeutic trial. Physicians using this service are expected to furnish us reports on all cases treated.

the use of the bacteriophage therapeutically. No harmful effects from its use have been reported. I must, however, caution against the use of turbid suspensions. The filtrates naturally contain no preservatives. Ampoules which are not perfectly clear should be discarded.

#### THE THERAPEUTIC ACTION OF THE 'PHAGE

A few remarks are in order relative to the ways in which 'phage suspensions may be considered to operate as therapeutic agents. Theoretically at least, the bacteriophage exercises no direct effect on either the damaged or normal tissues of the host. Its immediate action, when it does operate effectively is comparable to the action of a specific chemotherapeutic agent, or to the action of an antitoxin acting on a toxin. In other words, its more direct action is on the agent of the disease. It probably contributes only indirectly toward whatever immunity may follow the infection. It certainly exercises no corrective influence on the anatomic conditions which may have predisposed to or followed the original infection. Cases have been reported to me in which unquestionable improvement immediately followed the administration of the 'phage, but in which the improvement was only of short duration. Instances of this type are probably most often noted in urinary infections, in which disturbing anatomic conditions exist. These anatomic conditions we have no right to expect the bacteriophage to overcome, nor have we necessarily any right to expect a durable immunity immediately following the administration of a 'phage. We must keep in mind that even though we administer a highly active bacteriophage, its residence in the body may only be temporary. It is rapidly eliminated from the body in the absence of susceptible organisms. One should moreover keep in mind that whatever transient immunity may be acquired due to the presence of the 'phage itself, this immunity is directed only toward certain specific organisms, *sometimes only against given strains of an organism*. With this we should also associate the fact that in certain infections, as for example urinary infections, the bacterial flora may at times shift to new strains and even new species. It seems to me that all these facts have an important bearing on when, in a given case, the results of 'phage therapy should be read. If we keep in mind that we expect the 'phage to act primarily as a sterilizing agent, there can be no question that the time to begin to make readings of the results is immediately after the 'phage has been given sufficient opportunity to accomplish the task at which it is set to work. The interval of time which may be allowed should probably not exceed forty-eight hours. What are the clinical conditions and the bacteriological findings at the end of this time, and what are the findings at short intervals thereafter? On this hinges the question of whether a bacteriophage actually possesses sterilizing properties. One is naturally always interested in the permanence of the results, but this is in reality not the question immediately before us. In urinary as well as other infections this

may depend in part on associated anatomic conditions; upon the opportunities for immediate reinfection; and upon the speed with which the bodily defense mechanism asserts itself. In evaluating the results of 'phage therapy, one should keep the distinction between therapeutic effect and immunizing action in mind. They are not necessarily synonymous. Immunity may be associated with or immediately follow recovery, but not invariably so, as we all know.

I have stressed the immediate lytic action of the bacteriophage as the mechanism of primary importance in freeing the tissues of invading organisms. This is seemingly, however, not the only way in which a 'phage may contribute to recovery. In certain infections the bacteriophage may come to the aid of the natural defense mechanism of the body. I refer particularly to the rôle which it may play in enhancing phagocytosis. It has been shown by a number of investigators (d'Herelle,<sup>2</sup> Weiss and Arnold,<sup>53</sup> Nelson,<sup>54</sup> Smith,<sup>55</sup> and others) that its presence greatly facilitates phagocytosis of 'phage-susceptible bacteria. Evidence of this may be noted at times clinically. In carbuncles, for example, I have noted more than the usual degree of purulency following a rapid regression of the signs of intense inflammation. There seems little doubt that in pyogenic infections phagocytosis is facilitated by the presence of a suitable bacteriophage.

While the immediate rôle the 'phage may play in freeing the organisms from the tissues should probably be considered the most important in the attainment of a successful therapeutic result, this probably does not entirely sum up the effects of this form of therapy. I allude this time to the antigenic action of the bacterial proteins carried in the filtrate, plus those arising from the bacterial dissolution within the body. While bacterial lysis may be regarded as contributing in a direct way to recovery, the products of this lysis probably serve to stimulate the formation of such immunity as may naturally follow a given infection. The latter does not necessarily follow closely on the heels of the former. Time, as we know, is an important factor in the formation of any sort of acquired active immunity. The relative importance of the two factors is well brought out by some experiments which d'Herelle<sup>8</sup> carried out on the prevention of hemorrhagic septicemia in the water buffaloes of Indo-China. He noted on administering the bacteriophage prophylactically in these animals two refractory periods, separated by an interval during which the animals were fully susceptible to experimental inoculation. The first refractory period, only of forty-eight hours' duration, could be directly attributed to the presence of the injected bacteriophage. With the elimination of the latter from the body the animals again became fully susceptible. This fully susceptible period was followed in due time by a second and much more lasting refractory period. Since the second refractory period could also be induced by filtrates in which the 'phage itself had been in-

activated, it is necessary to conclude that in the production of this more lasting immunity the products of 'phage lysis, rather than the 'phage itself, played the important rôle.

#### CONCLUDING REMARKS

I hope that this brief review serves to indicate somewhat the complexity of the problem at hand. While there undoubtedly is something to support the view that the bacteriophage possesses therapeutic properties, it is at the same time clear that its usefulness tends to be limited by factors which may or may not eventually be brought under control. The time has certainly not yet arrived when the wholesale marketing of stock-bacteriophages, with therapeutic claims, can be scientifically justified. Before this can be justified it will become necessary to probe much more deeply into the question of its therapeutic merits. Larger collections of highly active bacteriophages will have to be brought under our command; standards will have to be determined for 'phage products; the best method of carrying out the treatments will have to be learned; and other questions of a similar nature will have to be settled before commercial distribution can be properly undertaken. It may, indeed, never be possible to justify its commercial production. Its usefulness at best may prove restricted. Only a careful and open-minded inquiry can reveal to us the real merits of this new form of therapy.

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