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Phage therapy

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Following the discovery of phages in 1915 by Twort there was an intensive period of enquiry into their use for the treatment of infections. Although early poorly controlled studies suggested efficacy, properly controlled studies such as that of Boyd and Portnoy, which investigated the use of shigella phages in the control of dysentery in German prisoners of war, produced little if any effect. With the discovery of sulphonamides and antibiotics the investigation into bacteriophage therapy was largely abandoned but its use has continued in the former Soviet Union and Eastern Europe.

Whilst the broad spectrum of antibiotics make them convenient to use, phages do have potential advantages over them, most of which arise from their unique property of replication. Small single doses have been sufficient to treat experimental infection and since phages multiply at the site of infection more will be present where they are needed and less where they are not, thus reducing potential side effects. Most phages are active against only a limited range of strains of bacteria. Although this limits their potential in 'blind' therapy the limited host range means that unlike antibiotics, suppression of, and selection of resistance in a patient's normal flora is likely to be minimal. Phages do have a number of potential disadvantages. They are relatively large and may not penetrate readily to some sites though their multiplication once there may compensate for this. They may carry determinants for antibiotic resistance, or other undesirable features of bacteria, so only phages without such features and without the ability readily to acquire them should be considered for therapeutic use. Phages are larger and more complex than antibiotics, and might be expected to produce allergic or toxic reactions, though no adverse effects were observed when Ochs and his colleagues injected a phage intravenously to healthy volunteers or when Soothill injected phages into the peritoneal cavities of mice or added them to cultures of human epidermal cells.

Although many early controlled experiments in animals were negative, some such as those of Asheshov et al, Ward, and Dubos et al were more encouraging. In the 1980s interesting and encouraging studies of phage therapy were done by Smith and his colleagues on *E coli* infection in mice and then in farm animals. Both prophylaxis and treatment was possible using phage in numbers smaller than those of the inoculated bacteria, indicating rapid phage multiplication *in vivo*. In view of Smith's successes Soothill investigated the effect of phage therapy on infections by antibiotic-resistant bacteria that affect humans, especially infections of burns, where topical phage therapy could be used. He demonstrated that destruction by *P aeruginosa* of small skin grafts to guinea pigs could be prevented by the prophylactic application of phage. Systemic *P aeruginosa* and *Acinetobacter baumanii* infections of burned patients also occur so Soothill investigated phage therapy of generalised infections of mice by those bacteria. A pseudomonas phage protected mice against systemic infection by *P aeruginosa* and as few as 10^2 PFU of an acinetobacter phage protected mice against 5 x LD50 (1×10^8) of a strain of *Acinetobacter baumanii*. Phage was demonstrated to have multiplied in the mice.

Although controlled evidence for the efficacy of phage in the treatment of human infections is lacking, experimental investigations in animals demonstrated efficacy. The rise of antibiotic resistance and the rapid improvement of techniques for the study of genetics has stimulated renewed interest in phage therapy.