/COMMENTARY
by Bernard Dixon

NEW HOPES FOR BACTERIOPHAGE THERAPY

Do you mean to say you think you've discovered an infectious disease of bacteria, and you haven't told me about it?" the chief asks young Martin Arrowsmith in Sinclair Lewis's masterly, microbiological novel of that name. "My dear boy, I don't believe you quite realise you may have hit on the supreme way to kill pathogenic bacteria."

For some time after Frederick Twort and Félix-Hubert d'Herelle revealed the existence of bacterial viruses—bacteriophages—in the second decade of this century, there were high hopes of using them as potent weapons against human and animal infections. What could be more tempting than to administer appropriate phages as a means of demolishing virulent populations of bacteria? Alas, as in Sinclair Lewis's fictional world, it soon became obvious that the dramatic effects of bacteriophages on bacteria living in laboratory glassware were not reliably duplicated in sick patients. So today's microbiologists do not value these submicroscopic agents for their therapeutic significance. They think of them instead for their historic role, allied to Max Delbruck's genius, in triggering the dawn of molecular biology. Since genetic engineering came to fame, phages have of course been much exploited as vectors for gene transfer via transduction.

One contemporary researcher who has not been content to leave phage therapy on the scrap heap of history is Dr. H. Williams Smith, who works at Houghton Poultry Research Station near Huntingdon in England. A few years ago, mindful of the conflicting and eventually negative results achieved earlier this century against maladies like cholera and dysentery, he began wondering whether our modern, infinitely more detailed knowledge of bacteriophages could now be harnessed to turn them into really effective magic bullets. Might phages provide a way around drug resistance and other problems that still bedevil antibiotic therapy?

Judging by two papers Willie Smith has published recently with his colleague Dr. M. B. Huggins, the answer seems to be yes. Bacteriophages *can* be administered to control intestinal and other infections. They *do* lack the drawbacks associated with antimicrobial drugs and have several unique additional features that make them much more attractive to clinicians and veterinarians than the antibiotics now deployed on such a wide scale. In short, the Houghton work may mark a watershed as significant as those caused by the successive discoveries of sulphonamides, penicillin, and streptomycin.

Smith and Huggins's first efforts, last year, centered on a pathogenic strain of *Escherichia coli* that had caused meningitis in a baby. They were able to show that an appropriate phage was more effective in combatting the cerebral and generalized infections caused by this organism in mice, than were most of the antibiotics they used for comparison. Unlike those dismal failures of the distant past, the phage's performance *in vivo* mirrored its activity *in vitro*. Furthermore, the few resistant mutants to emerge during treatment were of very low virulence—unlike the situation that often occurs during antibiotic therapy.

The next stage was to explore the vulnerability of other potential targets to their corresponding phages. For this purpose Willie Smith and his associate chose enteropathogenic strains of *E. coli* which, as causes of intestinal diseases in calves, piglets, and lambs, are a source of considerable economic loss to the farming community. The results of these studies, reported recently in the *Journal of General Microbiology* (1983, **129:**2659), are so exciting as to prompt a new dimension of optimism about the future extension of bacteriophage treatment in animal and human medicine.

In one series of experiments, calves were protected against a potentially lethal oral infection if they received a mixture of two phages before, but not after, the onset of diarrhea. The phages simply prevented the pathogenic bacteria from establishing themselves in sufficient numbers in the small intestine—even in animals deprived of the antibodies they would normally have derived from their mother's colostrum. In contrast to past work, too, one of the phages seemed to be much more virulent when inoculated than when studied in the test tube. When the second was replaced by a third phage, the mixture remained effective even after the calves had developed diarrhea.

Next, Smith and Huggins found that one phage by itself was capable of curing diarrhea in piglets caused by another enteropathogenic variety of *E. coli*. In contrast to the calf studies, resistant mutants did not pose a problem, so there was no need to incorporate a second phage as a means of curbing their proliferation. The outcome in lambs was somewhat less dramatic, though here again a single bacteriophage interrupted the course of infection.

Aside from their sense of history revisited and revised, these investigations reveal an anti-microbial strategy superior in several respects to today's orthodoxy. Most obviously, phages need to be given in just a single dose. Instead of being continuously diluted, like antibiotics, they proliferate and actually increase in concentration at the site of infection—until, that is, the battle is won. Second, resistant mutants that emerge during therapy seem to be very much less virulent than their parent strains. Third, cross-infection of animals with feces from infected animals treated with phage poses no problem.

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loan is not paid back in full, partial payment would be preferable to the current alternative granting system that gives money without expectation that it will be repaid.

Government loans for university research should never be a substitute for the existing granting system; grants must continue to provide money for excellent basic research where no immediate technological implications are envisioned. The research loan would be an additional mechanism for universities to fund advanced research without locking themselves into exclusive corporate arrangements. It would also provide another method for the government to assist indirectly in technological development with the opportunity for funding agencies to return money to the tax-based federal coffers.

—Christopher G. Edwards

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Quite the reverse: calves, piglets, and lambs can actually acquire phages in this way and thus become protected against disease.

Back in 1944, one of Hitler's bombs destroyed the Brown Institution laboratories, attached to London University, where Frederick Twort was pursuing a dogged dream of exploiting his discovery that bacteria themselves are plagued by parasites. Forty years later, it seems that those studies—never again pursued amid postwar austerity—are on the verge of being fulfilled.

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research by identifying projects for preferential tax status. Tax forgiveness should be available to businesses that are developed from investments in research and technological areas that the government wishes to stimulate and encourage. This forgiveness would act as an endstage grant to support the development of new technology, but only in proportion to the commercial success of the proposed development. Such incentives would make research investment more valuable to financial underwriters and this sort of investment in new technology would be even more appealing. For this purpose, a national center for industrial policy might help focus government objectives.

In the United States, the private sector has demonstrated increasing interest in new technologies, and with increasing amounts of money going into tax-sheltered R&D limited partnerships, private sources may account for a greater share of the financial interest in biotechnology than large industry. This growth of new investors will require mechanisms that can serve the needs of all participants, allow for access to worthy projects, and provide the means and standards by which these projects can be evaluated.

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