Perspectives

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The Murky Origin of Snow White and Her T-Even Dwarfs

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> That two distinct kinds of substances—the d'Hérelle substances and the genes—should both possess this most remarkable property of heritable variation or "mutability," each working by a totally different mechanism, is quite conceivable, considering the complexity of protoplasm, yet it would seem a curious coincidence indeed. It would open up the possibility of two totally different kinds of life, working by different mechanisms. On the other hand, if these d'Hérelle bodies were really genes, fundamentally like our chromosome genes, they would give us an utterly new angle from which to attack the gene problem. They are filterable, to some extent isolable, can be handled in test-tubes, and their properties, as shown by their effects on the bacteria, can then be studied after treatment. It would be very rash to call these bodies genes, and yet at present we must confess that there is no distinction known between the genes and them. Hence we cannot categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists, and physicists, simultaneously with being zoologists and botanists? Let us hope so.
>
> H. J. Muller (1922, pp. 48–49)

THE T-even bacteriophages—T2, T4, and T6—represent facile experimental systems that are both relatively complex and meticulously well defined. They played essential roles in the birth and early nurturing of the field of molecular genetics and could serve similarly as model organisms for ecology. Identification of the source habitat from which these phages were isolated would be satisfying from an ecological as well as historical perspective. Here I infer, mostly from published materials, the habitats from which these three phages were isolated, plus I delve into the history of their host, *Escherichia coli* B.

Bacteriophages (phages) are viruses whose hosts are bacteria. We employ the term bacterio*phage* rather than bacterio*virus* because phages were initially characterized by their ability to lyse cultures of bacteria. On macroscopic scales, phage growth can occur as though an invisible creature were eating a culture's bacteria. Consequently, the Greek verb *phage* (φαγειν), to eat or devour, was applied to this process in 1917 by Felix d'Hérelle, the French-Canadian co-independent-discoverer and popularizer of bacteriophages (d'Hérelle 1917). It was only after years of controversy, however, that phages were broadly accepted for what we now understand them to be, the viruses of bacteria.

The utility of phages nevertheless was immediately obvious to d'Hérelle. Phages kill bacteria. Bacteria cause disease. Therefore phages may be harnessed to combat disease. Phage therapy as a treatment of disease, however, has a controversial history (Burnet 1934; Stent 1992; Summers 1999). This controversy has a number of interacting bases including (i) the difficulties of doing clinical trials, under primitive conditions, with poorly defined and heterogeneous antimicrobials; (ii) the primitive state exhibited by the science of bacteriophagy in its early years (Stent 1963); (iii) a lack of emphasis on fundamental research (Delbrück 1946a); and (iv) of no minor consequence, the often dogmatically abrasive style (Duckworth 1976; Summers 1999) that "caused other workers only to redouble their efforts to show d'Hérelle to be wrong" (Stent 1963, p. 11).

During the early 1940s bacteriophagy's disarray was brought under control and then reversed through the efforts of Max Delbrück and colleagues, making up the Phage Group (Delbrück 1946b; Edgar 1982; Stent 1982, 1992; Cairns *et al.* 1992; see also Stent 1963, 1982, for an overview of F. M. Burnet's and M. Schlesinger's earlier contributions). Ironically, Delbrück championed d'Hérelle's "heterodoxical," nonbiochemical approach to phage biology (Stent 1982; Summers 1993; Judson 1996), although not d'Hérelle's interest in

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phage therapy (Delbrück 1946b). More or less simultaneously, the 1940s saw a decline in the fortunes of phage therapy coinciding with the dramatic rise in prominence of chemical antibacterials such as penicillin (Stent 1963). However, as the efficacy of antibiotics today declines, phage therapy may be achieving something of a scientific as well as a popular comeback (Lederberg 1996; Levin and Bull 1996; Radetsky 1996; Barrow and Soothill 1997; Alisky *et al.* 1998; Barrow *et al.* 1998; Holzman 1998; Koerner 1998).

Bacteriophages are useful for more than just killing bacteria. They also serve as easy-to-work-with model organisms, some of whose physiology, genetics, etc., borrows from or mimics the physiology, genetics, etc., of their host or of other organisms, including the viruses of plants and of animals (*e.g.*, Boyd 1956; Ellis 1992). Ultimately the genius of the Phage Group was the successful implementation of the idea—expressed by Muller (1922) in the quote introducing this *Perspectives* (and again, without reference to Muller, by Delbrück 1942)—that bacteriophages may be used as tools for understanding the basic principles of life (Edgar 1982; Stent 1982; Cairns *et al.* 1992; Cairns 1997). Phages thus served as workhorses in the development of the field of molecular genetics (Watson 1991; Stent 1992), achieving absolute triumph with the publication of the structure of DNA by Watson and Crick (1953). Watson, literally, was a student of the Phage Group (Watson 1992), investigating phage T2 in particular (Watson 1950). Crick, in turn, would go on to help define the details of the genetic code, using T4 bacteriophages (Crick *et al.* 1961). The ultimate spawn of these efforts was molecular biology, which, with the power of cloning and DNA sequencing, all but defines modern genetics as well as much of modern biochemistry.

This study attempts, through a scrutinizing of available literature, to clarify the very early scientific histories of three phages, the so-called T-even phages, T2, T4, and T6. These phages served as three of the original seven coliphages popularized by the phage group (Demerec and Fano 1945; Delbrück 1946a). It may never prove possible to identify, with high confidence, the time, place, and source material for the original isolation of phages T2, T4, and T6. Nevertheless, a better understanding of from where the T-even phages originated has historical significance and is of scientific consequence to those of us interested in the ecology of these organisms.

THE T PHAGES

Anderson (1992, p. 73) provides an overview of the founding of the "T-set" (*T* for *type*; Hershey 1946) of lytic bacteriophages of *E. coli* B:

> In the summer of 1944 the phage workers under the influence of Delbrück made an important decision. Previously, almost every investigator who worked with bacteriophages had his own private collection of phages and host bacteria. It was therefore almost futile to compare results of different workers, or even to gather a satisfying amount of information about one system. Delbrück insisted that we concentrate our attention on the activity of a set of seven phages on the same host, the now famous *E. coli* strain B and its mutants, in nutrient broth at 37°C. . . . The set of approved phages had been collected by Demerec and Fano (1945) for their studies of the patterns of mutation of strain B to resistance to the phages.

Public description of this group of phages occurred at least by November of 1944, in a paper by Anderson, Delbrück, and Demerec presented in Chicago to the Electron Microscope Society of America (Hedén 1951; see Anderson 1945 for the full reference). Publication occurred in March of 1945, with the manuscript received August 8, 1944 (Demerec and Fano 1945). "Of the seven, the so-called T-even strains (T2, T4, and T6), which are similar structurally, antigenically, and genetically, proved the most useful for biochemical and genetic studies" (Champe 1963, p. 87).

From a biological as well as historical perspective, it is likely (and humbling) that phages T2, T4, and T6 were all isolated either from fecal material or from feces-containing sewage. First, the relevant literature, reviewed throughout this study, is most consistent with the isolation of these phages from either of these two possible sources. Second, the biology of these phages is consistent with T-even phages, like their *E. coli* hosts (*e.g.*, Savageau 1983), doing the majority of their growing within the colons of animals (Abedon 1989, 1990a,b; Kutter *et al.* 1994). Third, T-even-like phages are typically isolated either from feces or from sewage (Kutter *et al.* 1994). Fourth, as noted by Boyd (1956, p. 84), "Although no specific statement to this effect can be found in the literature, there is little doubt that, like the others [*i.e.*, T_3, T_4, T_5, and T_6], T_1, T_2 and T_7 were isolated from sewage or faeces."

MURKY ORIGIN OF PHAGES T4 AND T6

Demerec and Fano (1945, pp. 119–120 and 135) acknowledge the isolation of phages T4 and T6 as follows (absence of "T3" from the second half of quote is as published):

> The materials used in our experiments consisted of the same bacterial strain—*E. coli* **B**—previously used by Luria and Delbrück (1943). . . . The phage strains were indicated as type I to type 7 (TI to T7). TI and T2, with which Dr. Luria supplied us, are the alpha and gamma strains of Delbrück and Luria (1942) and are identical with the P28 and PC strains of Dr. J. Bronfenbrenner (Kalmanson and Bronfenbrenner 1939); T_3, T_4, T_5, and T6 were isolated from a mixture of phages supplied by Dr. Tony L. Rakieten; T_7 was isolated from the standard anti-coliphage mixture prepared by Dr. W. J. MacNeal. . . . We are grateful to Dr. S. E. Luria for cultures of **B** bacteria and of TI and T2 phages; to Dr. Tony L. Rakieten, of The Long Island College of Medicine, for a culture of mixed phages from which T_4, T_5, and T6 were isolated.

Delbrück (1946a, p. 30) similarly described phages T3 through T6 as having been derived "from mixed virus preparations." From what or where might Rakieten have obtained this mixture of phages?

The evidence suggests that Tony L. Rakieten and her frequent co-author (and husband) Morris L. Rakieten considered sewage to be "an excellent source of bacteriophage of the coli-typhoid group" (Rakieten 1932, p. 808). Indeed, I found no reference to their isolation of phages from feces, but many instances of their phage isolation from sewage (*e.g.*, Rakieten and Rakieten 1938, 1943; Rakieten *et al.* 1940; Rakieten and Bornstein 1941). Thus, odds are that, when Tony Rakieten supplied Demerec and Fano with "a mixture of phages," that mixture consisted of raw sewage or of a phage lysate originally inoculated with raw sewage (Rakieten *et al.* 1940) and grown, perhaps, by using an *E. coli* B host. Consistently, as noted by Boyd (1956, p. 84), phages "T_3, T_4, T_5, and T_6 were from a series collected by Rakieten, who isolated his [sic?] phages from sewage."

MURKY ORIGIN OF PHAGE T2

Tracing phage T2 back to 1927: The history of phage T2 is complicated by its many pre-Demerec and Fano (1945) name changes. In brief, phage T2 was obtained from Salvador Luria who, for reasons we consider below, called this phage γ. Again as documented below, in the early 1940s Luria obtained phage γ from Jacques Bronfenbrenner, who described this phage by using various permutations of the letters PC. The pre-1940s history of phage T2 consequently is of a phage PC, particularly in the hands of Bronfenbrenner.

Bronfenbrenner, for whom Alfred D. Hershey worked in various capacities at Washington University, St. Louis (Summers 1993; Cairns 1997; Stahl 1998), employed many phages and hosts over the course of his career (*e.g.*, Hetler and Bronfenbrenner 1932; Varney and Bronfenbrenner 1932; also Bronfenbrenner 1927). Unfortunately, Bronfenbrenner was not always careful to name phages or describe phage isolations in his publications. Consequently, tracing Bronfenbrenner's use and ultimately his isolation of phage T2 [a.k.a. PC] is not a simple task. An important clue, however, is presented by Bronfenbrenner (1933, p. 730), where phage P.C. is described as "one of the coli-phages in our collection, used in the various experiments in our laboratory for nearly 6 years and invariably found to be pure according to all accepted criteria. . . ." The publication is dated February 8, 1933. That places phage P.C. in the Bronfenbrenner laboratory on or about February 1927. A possible corroboration of this date comes from Kalmanson and Bronfenbrenner (1939), who twice mention 1927 as the year Bronfenbrenner performed unpublished experiments that were repeated in 1939 with phage P.C. The next year, 1928, Bronfenbrenner moved from the Rockefeller Institute in New York to Washington University (http://www.microbiology.wustl.edu/dept/history/#early).

The oldest Bronfenbrenner reference to a phage PC/P.C. apparently was in 1932 (Bronfenbrenner 1932). The oldest reference I could find to a phage P.C., however, comes from a pair of 1928 papers (Muckenfuss 1928a,b) by Bronfenbrenner's frequent collaborator, Ralph S. Muckenfuss (Bronfenbrenner *et al.* 1926, 1927; Bronfenbrenner and Muckenfuss 1926, 1927a,b). No indication is made in these or later studies by Bronfenbrenner and Muckenfuss from where or from what phage P.C. was obtained. From what, then, might we infer that Bronfenbrenner isolated his coliphages? Fortunately, Bronfenbrenner supplied us with clues. For example (Bronfenbrenner 1928, p. 390), "In order to obtain a new strain of bacteriophage, one usually introduces into a culture of bacteria some material contaminated more or less directly with intestinal contents of higher animals." Burnet (1934, p. 332) echoes this philosophy. Bronfenbrenner supplied some specific descriptions of phage isolations; although few in number, in all cases these were from feces (Bronfenbrenner and Korb 1924b, 1925a,b; Bronfenbrenner *et al.* 1926). Hershey and Bronfenbrenner (1935, p. 453) additionally describe *E. coli* isolation from "unselected human fecal specimens."

Significantly, I found no reference in a Bronfenbrenner study to the isolation of phages from sewage. Thus, Bronfenbrenner and his co-workers showed a bias toward isolating phages from feces. This tendency is not too surprising, given the great precedent of Felix d'Hérelle's fecal phage isolation (d'Hérelle 1917; Bronfenbrenner 1928; Duckworth 1976; Summers 1999) and a series of papers (I–XII) published by Bronfenbrenner and colleagues, whose titles began with, "Studies on the bacteriophage of d'Hérelle. . . " (Bronfenbrenner and Kalmanson 1925; Bronfenbrenner and Korb 1925a,b,c, 1926; Bronfenbrenner *et al.* 1926; Bronfenbrenner 1927; Bronfenbrenner and Muckenfuss 1927b; Hetler and Bronfenbrenner 1928; Muckenfuss and Korb 1928; Muckenfuss 1928a,b) plus two others whose titles include d'Hérelle's name (Bronfenbrenner and Korb 1924a,b). If phage PC was isolated by Bronfenbrenner, then it is likely that this isolation was made from fecal material rather than from sewage.

Deciphering "P.C.": Bronfenbrenner and others appear to have used the strain designations "P.C." and "PC" interchangeably (*e.g.*, Bronfenbrenner 1932, 1933; Kalmanson and Bronfenbrenner 1942). The origin of these initials is not mentioned by Kalmanson and Bronfenbrenner (1939), however, nor by any other publication accessible to me. Perhaps P.C. was a person's initials. In 1946, a text called *The Bacteriophage: A Historical and Critical Survey of 25 Years Research*, authored by Dr. *P. C.* Flu (1946), was published posthumously. Flu cites Muckenfuss (1928b), which is one of

the earliest references to a phage P.C., but there is no indication in either reference that Flu collaborated with Bronfenbrenner's group. Alternatively, P.C. might have possessed functional meaning, abbreviating, for example, phage coli [*e.g.*, "P.C. phage (coli)"; Bronfenbrenner 1933] or polyvalent-phage coli or phage coli-shiga. Indeed, Kalmanson and Bronfenbrenner (1943) refer at one point to phage PC as coliphage "PC" and at another to PC as coli PC bacteriophage. Bronfenbrenner and Sulkin (1937) also use the term coli (P.C.) phage, and Muckenfuss (1928a) uses the designation P.C. coliphage, despite the polyvalent nature of the phage (see also Hershey 1946). I speculate on additional possibilities below.

MURKY ORIGIN OF *E. COLI* B

***"Bacterium coli"* P.C.:** Kalmanson and Bronfenbrenner (1939) utilized a "*B. coli*" P.C. This strain is of historical significance for two reasons in addition to sharing its name with phage P.C. First, *B. coli* P.C., according to Anderson (1945), is the "strain PC of Kalmanson and Bronfenbrenner, '39, and called "B" by Luria and Delbrück, '42." Second, Schaechter and Neidhardt (1987) trace the early popularity of *E. coli* as a model experimental system in part to Bronfenbrenner. Assuming that Anderson is correct, then *B. coli* P.C./*E. coli* B is the most famous *E. coli* strain associated with Bronfenbrenner. Unfortunately, I could find no mention from where Bronfenbrenner obtained *B. coli* P.C. (but see my speculation below). In addition, there appears to be no reference to this strain in any of the earlier Bronfenbrenner, Kalmanson, or Muckenfuss studies. Kalmanson and Bronfenbrenner (1939, p. 206), however, note, "The culture used throughout the work was a strain of colon bacillus (*B. coli* P.C.) which was known to be free of spontaneous lytic activity over a period of 15 years," thus placing *B. coli* P.C.'s isolation on or before 1924. Although not by Bronfenbrenner, *E. coli* K12 was isolated from a stool sample in 1922 (Bachmann 1996).

"Coli Bordet": At the Paris Institute Pasteur, Elie Wollman worked with an *E. coli* strain called coli Bordet that was considered identical, in terms of phage susceptibility at least, to the *E. coli* B strain of Luria and Delbrück (E. Wollman, personal communication). This Paris strain is named for Jules Bordet, who discovered complement and was the winner of the 1919 Nobel Prize in Medicine; founded the Pasteur Institute of Brussels, Belgium; and has the bacterial genus Bordetella named after him. André Gratia is a possible connection between Bordet and Bronfenbrenner. Gratia, a student of Bordet's, had moved to the Rockefeller Institute before 1924 (Summers 1999), the presumptive date of Bronfenbrenner's acquisition of *B. coli* P.C. (above), as well as the date that Bronfenbrenner moved to Rockefeller (http://www.microbiology.wustl.edu/dept/history/#early). Thus, it is possible that coli Bordet and *B. coli* P.C. are clonally related. Might P.C. therefore stand for Pasteur-coli or for Paris-coli? As I discuss below, however, it is probably unlikely that Luria and Delbrück had Bordet in mind when *B. coli* PC was renamed *E. coli* B.

If *E. coli* B is coli Bordet, then this leads to a bit of irony. Gratia and Bordet played notorious roles as d'Hérelle's nemeses. They denied d'Hérelle's viral explanation for bacteriophages and discovered a codiscoverer of bacteriophages, F. W. Twort (1915). Thus, d'Hérelle's bacteriophages became widely known as the Twort-d'Hérelle phenomenon (Stent 1963; Duckworth 1976; Summers 1999). Tony and Morris Rakieten, on the other hand, were post-doctoral fellows in d'Hérelle's Yale laboratory between 1928 and 1933, even inheriting d'Hérelle's Yale phage collection when d'Hérelle left (Kutter *et al.* 1994; W. C. Summers, personal communication). Through Tony Rakieten, then, phages T4 and T6 (plus T3 and T5) at the very least might claim "academic" descent from the laboratory of Felix d'Hérelle. Thus, metaphorically at least, quite possibly we reenact the historical rivalry between d'Hérelle and Bordet whenever we add phages T3, T4, T5, or T6 to a culture of *E. coli* B/Bordet.

***E. coli* B:** Delbrück and Luria apparently employed strain-naming conventions with little concern for strain histories. Luria (1992, p. 173), for example, describes the naming of phages T1, T2, and *E. coli* B as follows:

> Delbrück and I adjourned to New York for a 48-hour bout of experimentation in my laboratory at the College of Physicians and Surgeons. I had received from Dr. Bronfenbrenner of St. Louis two *coli* phages active on the same host: P28, later called α, later TI, and PC, later called γ, later T2. The reason for choosing the names α and γ was that my [Olivetti; Luria 1984] typewriter had the signs α, β, and γ; β was left out for reasons of symmetry, the common host being called B for bacterium.

Delbrück, however, began naming his *B. coli* strains "B" as early as 1940 (Delbrück 1940) and by 1942 (Delbrück 1942, p. 11) had collected a number of so-named bacteria (and similarly named phages): "B_1 and P_1 (Ellis and Delbrück 1939)," "B_2 and P_2 (Delbrück 1940)," and "B_3 and two viruses, P_3 and P_4 (Delbrück and Luria 1941)." Delbrück and Luria (1941) is indicated as "to be published," but so far as I can tell does not exist. Delbrück and Luria (1942) does exist, however, and is the first study to employ *E. coli* B, phage α, and phage γ as so named. From the latent periods of phages P_3 and P_4 (Delbrück 1942) I infer that phage P_3 is Delbrück and Luria's (1942) phage α and that phage P_4 is phage γ. If so, then the *B. coli* B_3 of Delbrück (1942) and the *E. coli* B of Delbrück and Luria (1942) are likely synonymous, and T2 apparently was briefly called P_4.

Delbrück and Luria (1942, p. 112, footnote) note that their "choice of [phage and bacterial] names, an adaptation to our experiments, will presently be justi-

fied." Apparently a phage-γ-resistant descendant of their *E. coli* B they called "A" and a phage-α-resistant descendant of their *E. coli* B they called "C." Bacterium A was thus an indicator for only phage α, bacterium C an indicator for only phage γ, with bacterium B an indicator for both. Ultimately, however, Demerec and Fano (1945) revived Delbrück's letter-number phage-naming method with the letter T replacing Delbrück's previously employed letter P.

CONCLUSION

In approximate order of use (Hershey 1946 and above), strain designations for what today we call phage T2 have included P.C., PC, P_4, γ, and P_9H. P_9H was later called T2H. Demerec and Fano's (1945) phage T2 was the phage γ of Luria, which later would be called phage T2L. Luria's phage γ, in turn, descended from a phage PC stock that later would be called phage T2K (for Kalmanson). The standardization of phages and phage names was an important early step toward the development of the discipline we now call molecular genetics (Anderson 1992, as quoted above). Perhaps we need look little further than this tortured history of phage T2 to understand the genesis of the Delbrück-influenced desire for a simplification of not just what phages people used, but what they called them.

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