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The Chemical Characterization of the Gene: Vicissitudes of Evidential Assessment

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ABSTRACT – The chemical characterization of the substance responsible for the phenomenon of "transformation" of pneumococci was presented in the now famous 1944 paper by Avery, MacLeod, and McCarty. Reception of this work was mixed. Although interpreting their results as evidence that deoxyribonucleic acid (DNA) is the molecule responsible for genetic changes was, at the time, controversial, this paper has been retrospectively celebrated as providing such evidence. The mixed and changing assessment of the evidence presented in the paper was due to the work's interpretive flexibility – the evidence was interpreted in various ways, and such interpretations were justified given the neophytic state of molecular biology and methodological limitations of Avery's transformation studies. I argue that the changing context in which the evidence presented by Avery's group was interpreted partly explains the vicissitudes of the assessments of the evidence. Two less compelling explanations of the reception are a myth-making account and an appeal to the wartime historical context of its publication.

KEYWORDS – Oswald Avery, evidence, evidential context, gene, DNA, transforming substance, Avery, MacLeod, McCarty (1944)

Introduction

The chemical characterization of the molecule responsible for the phenomenon known as the "transformation" of pneumococci was presented in 1944 by Avery, MacLeod, and McCarty (hereafter referred to as *AMM1944*). They gave evidence supporting the hypothesis that transformation is caused by a transfer of deoxyribonucleic acid (DNA). Although interpreting their results as evidence that DNA is the primary genetic molecule was, at the time, controversial, their results have been retrospectively celebrated as providing such evidence. Reception of this work at the time was mixed: some immediately saw potential in pursuing nucleic acid research; others maintained an open, albeit skeptical, attitude regarding the role that DNA has in hereditary transmission; still

others rejected outright the possibility that DNA could play a functional role in gene transmission.

This manifold reception was due to the work's interpretive flexibility. The evidence presented in the paper was interpreted in various ways, and such interpretations were justified given the neophytic state of molecular biology and given limitations of methods employed by Avery's research group. There were contemporaneous criticisms of interpreting these results as evidence that genes are functionally composed of DNA. Textbooks of genetics in the years following publication of *AMM1944* were skeptical of its results. Citations to *AMM1944*, though frequent, were intellectually non-committal. In retrospect, many have expressed surprise that Avery was not awarded a Nobel Prize, for neither his important prior achievements in immunology nor his studies on transformation. A close look at the rhetoric of prize committees that did, in fact, honor Avery reflects further skepticism about the importance of *AMM1944* in the ten years following its publication.

Today, the attempt to determine the "chemical characterization of the gene" might seem misguided, since, as Burian (2004) argues, "no exact molecular definition of the gene or molecular criteria for delimiting genes can serve the needs of molecular biology in general, let alone the various disciplines with which molecular biology is allied." This is a view with which I have much sympathy. It is, though, a contemporary view. As Morange (2008) and others have argued, early molecular biologists investigated biological phenomena using epistemological principles of physics as a model, with the aim of discovering simple rules and principles. Moreover, Avery and his contemporaries were committed to explaining basic biological phenomena with tools from physical chemistry (Deichmann 2008). Transformation – a phenomenon at least resembling a transfer of genetic material – was a prime candidate for such investigations.

The protracted period of mixed reception and critical assessment of *AMM1944* later came to be cause for regret, and beginning about fifteen years after its publication the work began to be widely lauded. Many scientists have, in retrospect, described this paper as definitively showing that DNA is the genetic material and thus have praised this paper as a legendary landmark of molecular biology. In the second section, I describe the evidence presented in *AMM1944*, followed by a description of the diverse reception of *AMM1944* during the years immediately after its publication. In the fourth part of the paper, I argue that the changing evidential context in the ten to fifteen years after its publication partially explains the vicissitudes of the assessment of *AMM1944*. Two other potential explanations for the changed reception of the paper – a myth-making account and an appeal to the wartime context of its

publication – are explored in the last section, and I argue that although these explanations are moderately compelling, they are not as compelling as the appeal to the changing evidential context.

Transformation

In 1928, Fred Griffith published his work on the transformation of pneumococcal types. He had injected heat-killed, virulent, "smooth" (S) Type I pneumococci and live, non-virulent, "rough" (R) Type II pneumococci into mice. The mice died and from their blood Griffith isolated live S form Type I pneumococci. This was a surprising result. The live bacteria had changed virulence (R to S) and type (II to I); in other words, they had "transformed." Transformation was soon replicated at the Koch Institute in Berlin (Neufeld et al. 1928). Oswald Avery was at first skeptical of Griffith's results. "For many months, Avery refused to accept the validity of this claim [transformation] and was inclined to regard the finding as due to inadequate experimental controls" (Dubos 1956).[1]

Soon after, though, Avery's own colleagues at the Rockefeller Institute replicated Griffith's results, first following Griffith's original protocol and then, after isolating the transforming substance, they achieved transformation *in vitro* (Dawson 1928, 1930; Alloway 1932). Alloway (1933) provided an early clue to the chemical identity of the "transforming substance": when he added the transforming substance to alcohol, "a thick syrupy precipitate formed." Commenting on this alcohol precipitate in 1936, Avery said that "the transforming agent could hardly be carbohydrate, did not match very well with protein," and so Avery is reported to have "wistfully suggested that it might be a nucleic acid" (Hotchkiss 1965). There is, however, no indication that Avery's group entertained a genetic interpretation of transformation during this early phase of research on the phenomenon. In an internal report, Dawson wrote of "the possible significance of these adoptive changes in the course of infection and in the epidemiology of disease."[2] These early experiments on transformation were exploratory.[3]

By late 1940, Avery and Colin MacLeod were attempting to improve

[1] Amsterdamska (1993) suggests that Avery's hesitation to accept Griffith's findings was due to his commitment to the stability of pneumococcus types.

[2] Report of the Board of Scientific Directors of the Rockefeller Institute for Medical Research, April 1929, p. 212. The National Library of Medicine (NLM) in the United States has made available some archival material related to Avery and his work, including extracts from laboratory notebooks, reports to the Rockefeller Institute Board of Directors, personal letters, speeches, and published manuscripts. In this paper I refer to primary sources directly, but some of the material was accessed through the NLM collection at http://profiles.nlm.nih.gov/CC/

[3] For a recent discussion of exploratory experimentation in this journal, see Burian (2007), Elliott (2007), and O'Malley (2007).

the isolation and preservation of the transforming substance in order to begin the chemical characterization of the substance and in 1941 they had begun enzymatic tests to that end.[4] Their manuscript was submitted in November 1943 to the Rockefeller Institute's in-house journal, the *Journal of Experimental Medicine*. According to Olby (1974) the manuscript was not evaluated by peer review. It appeared in print in February 1944, about fifteen years after Avery's laboratory had begun experiments on transformation.

Their evidence showing that the transforming substance is DNA was multimodal; a variety of evidence of different kinds was concordant for the hypothesis that the transforming substance was DNA.[5] Elementary chemical analysis of the transforming substance showed that the amounts of carbon, hydrogen, nitrogen, and phosphorous were close to the theoretical values for DNA. Trypsin, chymotrypsin, and ribonuclease (which are protein and ribonucleic acid degrading enzymes) had no effect on the transforming substance, whereas a DNA-degrading enzyme was capable of inactivating it. Ultraviolet absorption, electrophoretic movement, and the large molecular weight of the transforming substance were characteristic of DNA. Qualitative chemical tests for DNA were positive and qualitative chemical tests for RNA and protein were negative. The final sentence of the discussion in *AMM1944* read: "If the results of the present study on the chemical nature of the transforming principle are confirmed, then nucleic acids must be regarded as possessing biological specificity the chemical basis of which is as yet undetermined." In his oft-cited 1943 letter to his brother, Avery asked, "Who could have guessed it?"

Reception

Despite the retrospective applause given to *AMM1944* (discussed below), praising the work for providing "conclusive" evidence that genes are composed of DNA, at the time of its publication and in the decade following many scientists were skeptical of interpreting the results as evidence that genes are composed of DNA. The strongest contemporaneous critic of such an interpretation was Alfred Mirsky, Avery's colleague at the Rockefeller Institute. Mirsky's main experimental concern was that the transforming substance used by Avery, MacLeod, and McCarty was impure and could have had trace amounts of protein in it that caused the transformation (this methodological criticism is described in further

[4] According to their laboratory notes; see MacLeod et al. (1940) and MacLeod et al. (1941).
[5] On multimodal evidence, see Stegenga (2009).

detail in the fourth section). McCarty (1985) claims that this criticism was voiced by Mirsky "frequently in personal conversations with interested individuals." Moreover, Mirsky put this criticism into print: "[…] it is not yet known which the transforming agent is – a nucleic acid or a nucleoprotein. To claim more, would be going beyond the experimental evidence" (Mirsky et al. 1946).

But *AMM1944* did not claim more. The final paragraph of *AMM1944* reads:

> It is, of course, possible that the biological activity of the substance described is not an inherent property of the nucleic acid but is due to minute amounts of some other substance absorbed to it or so intimately associated with it as to escape detection.

The last three sentences begin with "If ," "Assuming […]," and, again, "If." This cautious rhetoric was typical of Avery in print and serves to show that in 1944, publicly at least, Avery, MacLeod, and McCarty were not "going beyond the experimental evidence."[6] Avery knew that it would be difficult to show conclusively that genes were composed of DNA. He wrote his brother that "[…] it takes a lot of well documented evidence to convince anyone that the sodium salt of desoxyribose nucleic acid, protein-free, could possibly be endowed with such biologically active and specific properties and this evidence we are now trying to get" (1943). Avery's own assessment of the evidence, then, was hesitant.[7]

The reception of *AMM1944* was not completely critical. The paper was a stimulus for Erwin Chargaff who, in retrospect, wrote, "This [*AMM1944*] was really the decisive influence, as far as I was concerned,

[6] Some have suggested that his quiet manner, hesitation to attend conferences and to publish widely, and self-critical stance may have contributed to what later came to be seen by many as a slow recognition of the importance of *AMM1944*. For instance, Stanley (1970) suggested that "instead of a timid and unusually cautious presentation the authors might have set forth their conclusions with greater firmness and confidence and this would have fostered ready acceptance." What *AMM1944* needed, claimed Stanley, was "not only a vigorous presentation but also a vigorous and continuing promotion for acceptance." There is perhaps some truth to this; elsewhere in his letter to his brother Avery wrote "It's lots of fun to blow bubbles – but it's wiser to prick them yourself before someone else tries to" (1943). However, I argue that what was needed was not necessarily a vigorous and confident promotion of *AMM1944*, but rather an altered evidential context to consider its evidence properly as a general genetic phenomenon. See also Morange (1998) for a discussion of Avery's cautious personality.

[7] More accurately, Avery was publicly cautious in his interpretation of the evidence in *AMM1944*. Privately he wrote, "If we are right and of course that is not yet proven, then it means that nucleic acids are not merely structially [sic] important but functionally active substances in determining the biochemical activities and specific characteristics of cells and that by means of a known chemical substance it is possible to induce predictable and hereditary changes in cells. This is something that has long been the dream of geneticists [...]. Sounds like a virus - may be a gene. But with mechanisms I am not now concerned" (Avery 1943).

to devote our laboratory almost completely to the chemistry of nucleic acids […]."[8] Chargaff's claim about the significance of *AMM1944* was made long after the paper appeared, though he did begin his work on DNA base-pair compositions immediately after its publication.

Nevertheless, it has been suggested that *AMM1944* was neglected. Wyatt argued that it was less well known than it ought to have been (1972). McCarty himself wrote that one of the main reasons *AMM1944* was not broadly recognized was that "the *Journal* [*of Experimental Medicine*] was not one that was read by geneticists and general biologists" (1985, 214). Horace Judson, in a popular history of molecular biology, also suggested that *AMM1944* was relatively ignored (1979). However, recent historiography has shown that the work did not go unnoticed (Morange 1998; Deichman 2004). Simply examining the citations to *AMM1944* ought to dispel the notion that the work went unnoticed: it was cited over 300 times between 1945 and 1954.[9] Dubos, Hotchkiss, McCarty, Zamenhoff, and Chargaff accounted for many of the direct citations to *AMM1944* in the years immediately following its publication, each citing the paper several times; although with the exception of Chargaff, each of those scientists were personally involved with the transformation studies.[10]

Thus, *AMM1944* was not neglected. Lederberg (1972) suggested that, to the contrary, *AMM1944* became so well known that it almost achieved "brand name" status. There was no need to refer to the work directly because the knowledge had become common lore: "Evidently the pneumococcus work was so well known that it did not even require an explicit bibliographic reference!" Thus the citations to Avery's work could very well underrepresent the notice that the work received. As Lederberg (1972) further noted:

> The Rockefeller group's work was so well entrenched in the general discourse of genetics that I used the 1944 paper throughout my own teaching of genetics

[8] Quoted in Olby (1974, 211). However, in the Chargaff Papers at the American Philosophical Society, in a massive collection of correspondence with hundreds of scientists and a similarly huge collection of works by other scientists, there is no correspondence with Avery, MacLeod, or McCarty, nor does the collection contain any publications by the group.

[9] Institute for Scientific Information. Citations to publications by "Avery," "Avery O.T.," and "McCarty M" in the Science Citation Index, 1945-1954. Institute for Scientific Information, 1989. For a recent detailed application of citation analysis to assessing the impact of Watson and Crick's seminal 1953 paper, see Gingras (2010). Gingras makes a similar case for Watson and Crick's paper as I have made for *AMM1944*: despite the claims of some historians that Watson and Crick's work had a "quiet debut," it was the highest cited paper published in *Nature* in the decade after its publication.

[10] Institute for Scientific Information. Although Hershey and Chase did not cite *AMM1944* in their 1952 paper (more about this later), Hershey did cite it in 1946. Luria and Monod both cited it twice, once each in 1946 and 1947. Watson and Crick did not cite it in their famous letter to *Nature* (1953).

> at Wisconsin. […] the 1944 work was also cited in many reviews; or else a later updating article by one of Avery's colleagues might be a more efficient reference. The "pneumococcus transformation" was so well known that it was often cited, or Avery's name used, without a specific reference.

That *AMM1944* became well-known soon after its publication is not surprising, considering that Avery had published much of his life's work in *The Journal of Experimental Medicine*, was already a widely accomplished scientist, worked in a prestigious institute, and many of his students and post-docs had gone on to hold important academic positions throughout the United States.[11]

In a close historical study, Deichmann (2004) argued that the fact that *AMM1944* was cited so often is evidence that the paper was well-received: "These citations show an immediate appreciation of Avery's paper across disciplinary boundaries, including the recognition that Avery might have isolated a gene." However, being a well-known work does not imply that most scientists at the time interpreted it in the same way and certainly few contemporaries of Avery would have agreed with the interpretation of *AMM1944* as evidence for the isolation of a gene. Mirsky's criticisms are a clear example. But more frequent than direct criticisms of the type that Mirsky voiced were references to *AMM1944* that were intellectually vague and non-committal.

Max Delbrück, the German former physicist turned geneticist, later claimed that it "came as a total shock and surprise when Avery and his associates discovered that the transforming principle was DNA" (1978). However, it is not at all clear that, at the time of its publication, Delbrück and his students and close colleagues were either shocked or surprised, nor did they interpret *AMM1944* as showing that "the transforming principle was DNA." Transformation was a hot topic at the 1946 Cold Spring Harbor Symposium (titled "Heredity and Variation in Microorgansims"), which was organized by Delbrück and attended by Delbrück's students and colleagues. The interpretations of the evidence presented in *AMM1944* were non-committal. One author at the symposium wrote: "The pneumococcus transforming principle [… is] difficult if not impossible to distinguish from viruses" (Anderson 1946). When referring to *AMM1944*, Alfred Hershey, one of Delbrück's close colleagues and co-founder of the Phage Group, defined the process of transformation as "transmission of genetic material," without specifying the mol-

[11] Olby also questioned the thesis that geneticists were unaware of Avery's work: "Luria, Dobzhansky and Burnet visited Avery personally in the 1940s" (1972). In an interview, Delbrück said: "Avery made his great discovery in 1943, but we knew about his working on this problem for at least a couple of years before then" (1978).

ecule responsible as either DNA or protein (1946).[12] Another member of the Phage Group referred to the "classical investigations of Avery and McCarty on pneumococcus transformation … with a nucleoprotein" (Spiegelman 1946). The term "nucleoprotein" seemed to be the most appropriate for the transforming substance, given the general concerns regarding potential contamination of the transforming substance with protein. However, in the two years following publication of *AMM1944*, Avery's group had become more confident in their identification of the molecule: "accumulated evidence … has established beyond reasonable doubt that the active substance responsible for transformation is a specific nucleic acid of the desoxyribose type" (McCarty 1946).

Theodosius Dobzhansky, when commenting on transformation studies in the 2nd edition of *Genetics and the Origin of Species* (1941), claimed that transformation was not a transmission of hereditary material, but rather a transmission of a substance that could induce a specific mutation. His interpretation of transformation was as follows: "If this transformation is described as a genetic mutation – and it is difficult to avoid so describing it – we are dealing with authentic cases of induction of specific mutations by specific treatments – a feat which geneticists have vainly tried to accomplish in higher organisms" (Dobzhansky 1941, 49).[13] Genetics textbooks in general reflected the hesitation towards interpreting *AMM1944* as proof that genes are composed of DNA. In a study of genetics textbooks from the 1950s, Gaster (1990) showed that even after many studies had provided corroborating evidence for *AMM1944*, the results of the paper were not incorporated into undergraduate education. Even into the late 1950s and early 1960s, leading textbooks were referring to genes as proteins or nucleoproteins.

One might think that the reception or assessment of a scientific work can be gauged by the prizes awarded to the scientist associated with the work. A more nuanced gauge, though, is to examine the awarding group's rationale for the prize. In his biography of Avery, René Dubos lists several prizes won by Avery after 1944: the Copley Medal (1945, Royal Society of London), the Kober Medal (1946, Association of American Physicians), the Charles Mickle Fellowship (1946, Univer-

[12] The Phage Group was formed in 1941 by Delbrück and the Italian Salvador Luria. Hershey became the third key member of the group in 1943. Because Delbrück and Luria were citizens of enemy countries, they were not given war-related responsibilities. They started a "phage course" at Cold Spring Harbor and many young geneticists and molecular biologists were students there. All were required to be graduate students or post-doctoral fellows, and many were trained in physics. There was a strong emphasis on quantification, evident for example in the title of their symposium publication, *Cold Spring Harbor Symposium on Quantitative Biology*.

[13] On the interpretation of transformation as induced mutation, see also Beadle (1948) and Boivin (1947).

sity of Toronto), and the Lasker Award (1947, American Public Health Foundation). This is an impressive list and, at first glance, suggests that the transformation work was lauded in subsequent years. However, an examination of the reasons cited for these awards further supports the argument above: the reception of *AMM1944* in the decade after its publication remained muted.

The Lasker Award is limited to achievements in medicine and public health, and is awarded to more than one individual annually (five individuals and two groups were given the award in 1947 besides Avery). Cited as reasons for this award were Avery's contributions to understanding the immunological and pathogenic properties of the pneumococcus; no mention at all was made of the work presented in *AMM1944*. The Copley Prize, awarded by the Royal Society of London and considered one of the most prestigious prizes in science, was given to Avery in 1945.[14] Avery was considered for it in 1943, but rejected. He was considered for it again in 1944, and again rejected. Finally, in 1945, it was awarded to him for "recognition of his success in introducing chemical methods in the study of immunity against infective diseases."[15] This was a reference to the immunological research to which Avery had dedicated most of his life. The Royal Society has been commended for recognizing the importance of Avery's work. However, no mention was made of transformation, DNA, or *AMM1944* among the reasons cited for the award – twenty-one months after the publication of *AMM1944*. This omission was retrospectively corrected by a memorandum to Sir Henry Dale (President of the Society) late in 1945, which Dale included later in a public address, enunciating the importance of "this new peak of discovery."

Avery also won the 1944 Gold Medal of the New York Academy of Medicine. Founded in 1847, the New York Academy of Medicine has primarily been concerned with public health, "with a particular emphasis on disadvantaged urban populations."[16] The medal was awarded to Avery because he had "isolated the 'transforming principle' as a thymonucleic acid. This discovery has far-reaching implications for the general science of biology"(Anonymous 1944, 328-329). How transformation

[14] Among others it has been awarded to Benjamin Franklin (1753), Joseph Priestley (1772), Charles Darwin (1864), Ivan Pavlov (1915), Albert Einstein (1925), and James Watson (1993).

[15] For discussion of Avery's Copley Prize see Bearn (1996). Bearn relates the following anecdote: Avery disliked travel and meetings, and so did not attend the ceremony to receive his prize. The Secretary of the Society then tried, for one year, to transfer the £35 prize to Avery. Finally Avery asked that the money be "transferred to some British fund devoted to the advancement of research in the field of medicine and related science" as an anonymous gift.

[16] http://www.nyam.org/about/

was related to disadvantaged urban populations is unclear. Regardless, this prize was obscure enough for McCarty not to know that Avery had won it (according to his 1985 memoir). The one prize that McCarty knew Avery had *not* won was the Nobel Prize.[17]

In sum, despite receiving many citations, being discussed at a major conference, and generally being a well-known paper, *AMM1944* was assessed in a cautious, critical, and intellectually vague manner. It was a stimulus for further research, including several other transformation studies and Chargaff's research on base-pair composition. However, due to its interpretative flexibility, in the years after its publication few scientists considered the evidence in *AMM1944* as evidence that genes are composed of DNA. Although it was highly celebrated decades later, it was not celebrated at the time. Why then has *AMM1944* been so strongly lauded in retrospect? In the following section I argue that in the 15 years after the publication of *AMM1944*, its evidential context changed, thereby changing its interpretation.

Evidential Context

There were theoretical and methodological reasons why Avery's contemporaries were opposed to the interpretation of the evidence presented in *AMM1944* as showing that genes are comprised of DNA. However, its evidential context changed in the ten years following the paper's publication, enabling scientists to assess and interpret *AMM1944* differently.[18]

The principle methodological criticism was that the chemical tests available to Avery were not sensitive enough to detect the presence of up to 5% protein, and the enzymatic degradation of protein using trypsin and chymotrypsin could have been ineffective in degrading active protein, especially if it was covered by structural nucleic acids. Even

[17] Dubos, in his obituary of Avery for the *Biographical Memoirs of the Royal Society*, wrote that it "remains to this day, a matter of painful surprise that Avery was not awarded a Nobel Prize" (1956), and in *Nature*'s 50th anniversary of Watson and Crick's famous letter describing the structure of DNA, the editor wrote "the fact that McCarty, Avery, and MacLeod were not awarded the Nobel Prize is an oversight that, to this day, still puzzles." Avery had already been nominated for the Nobel Prize in the late 1930s, in recognition of his immunological studies. The Nobel Foundation discussed *AMM1944* as follows: "The discovery, because of its far-reaching implications, aroused much interest, and Avery was proposed for a Nobel Prize. But doubts were also expressed, and the Nobel Committee found it desirable to postpone an award. Actually, Avery's finding was not accepted in all quarters until A. D. Hershey … and M. Chase, in 1952, demonstrated that bacteriophage-DNA carries the viral genetic information from parent to progeny" (Quoted in McCarty 1985, 219). In the fourth part of the paper, I argue that the method used by Hershey and Chase was just as liable to protein contamination as Avery's method.

[18] On the notion of evidential context, see Pinch (1985).

if the transforming substance was 99.99% pure DNA, one microgram of contaminating protein in the transforming substance could have had millions of protein particles (given Avogadro's number). This potential for systematic error in the methods of Avery's group was the target of Mirsky's criticisms.

Beyond technical criticisms of the possibility of systematic error, according to Dubos, "certain members of the 'phage group' regarded the orthodox chemical approach to the understanding of biological phenomena as pedestrian, too slow, and not revolutionary enough for their intellectual ambition...they did not seem able to do much with or build on [Avery's experiment]" (cited in Deichmann 2004).

Theoretical considerations were also important when assessing and interpreting *AMM1944*. For years, it had been assumed that proteins were the hereditary molecule and DNA was, at best, a structural molecule supporting the transmission of protein in genetic change. Commenting on *AMM1944* in retrospect, Stanley (1970) stated, "Perhaps of major importance was the fact that the discovery was quite contrary to the dominant thinking of many years." This was partly the legacy of one of Avery's colleagues at the Rockefeller Institute, Phoebus Levene, who had proposed the tetranucleotide hypothesis for the structure of nucleotides. This hypothesis claimed that nucleotides have a highly regular, repetitive structure, like collagen (Levene 1921; Levene et al. 1929). Given Levene's views, it was assumed that DNA was not structurally diverse enough to have the required functional complexity of genes. In other words, the assumed simplicity of the structure of DNA was thought to be insufficient to explain the complexity of genetic phenomena. In contrast, many assumed that genes were functionally constituted by proteins, because proteins were known to be highly diverse in structure and function.

Moreover, to consider the evidence presented in *AMM1944* as relevant to a hypothesis about a more general genetic phenomenon, it was clearly necessary that the pneumococcus have genes. However, it was not obvious that the pneumococcus did. Many geneticists "did not consider the bacteria, with their simple life cycles, presumably devoid of any element of sexual reproduction, as suitable for genetic study" (McCarty 1985, 215). Morange (1998) puts this worry as follows: "the pneumococcus was poorly understood in terms of both its make-up and its biochemical nature. Prior to Avery's work, the only nucleic acid that had been characterized in this bacterium was RNA. The existence of genes in bacteria was not universally accepted" (Morange 1998, 33-34).

Thus, at the time of its publication, there were methodological and theoretical reasons that can explain the hesitant reception of *AMM1944*.

But the evidential context of *AMM1944* shifted throughout the 1940s and 1950s, and assessments of the significance of AMM1944 concomitantly changed.

In the years soon after its publication, different types of experiments were performed which provided corroborating evidence for *AMM1944*. Results of experiments by Avery's group with DNase (DNA-degrading enzyme), presented in two papers after *AMM1944*, strengthened the interpretation that DNA was the transforming substance (McCarty 1945; McCarty et al. 1946). Transformation studies were also performed on different organisms. For example, the transformation of bacillus by Boivin (1947) provided further confirmation.[19] Transformation was shown on genetic markers other than those used in *AMM1944* (Hotchkiss 1951; Alexander et al. 1953).

Independent evidence was provided to support the background assumptions necessary to interpret transformation as a genetic phenomenon. Genetic recombination in bacteria was demonstrated in 1946 by Lederberg and Tatum – thereby proving that bacteria had genes, which supported the interpretation of *AMM1944* as providing evidence that the pneumococcus transforming substance was a gene. By 1951, Chargaff had overturned the tetranucleotide hypothesis of the structure of DNA by showing differences between species in base composition and demonstrating A:T and C:G ratios, making it at least conceivable that DNA could have the variability required of genes (1950; 1951). The evidence in *AMM1944* could then be interpreted in the context of other evidence generated with a variety of methodological approaches, showing consistent patterns of results and based on new considerations of assumptions auxiliary to the transformation studies (bacterial genetics, DNA structure). In short, by 1951 the evidential context of *AMM1944* had significantly changed, thus becoming more compelling to consider its evidence as showing that genes were functionally comprised of DNA.

The most striking independent confirmation came with the 1952 paper by Hershey and Chase, which reached the same conclusion as *AMM1944* using a completely different method. Hershey and Chase labeled bacteriophages with S^{35} (which labeled only protein) and P^{32} (which labeled only DNA), and found that when the bacteriophage infected bacteria, P^{32} entered the bacteria while most of the S^{35} remained outside the cell. Given that bacteriophages use host bacteria to replicate

[19] This work was presented to the Cold Spring Harbor meeting at which Mirsky was present. Mirsky stood up during the discussion period of Boivin's paper and reiterated his skepticism, to which Boivin responded by saying that the burden of proof now rested on those who wished to maintain that proteins were the transforming substance (discussed in McCarty 1985).

and since only DNA entered the host bacteria, this was evidence that DNA is the molecule responsible for hereditary changes. However, the primary criticism that could have been directed at Hershey and Chase's method was exactly the same methodological criticism that was in fact directed at *AMM1944*.[20] That is, the potential for protein contamination in the portion of the virus that entered the cell in Hershey and Chase's experiments was as great as the potential for protein contamination in Avery's transforming substance; further, the inability to detect such protein contamination was equally problematic for both sets of experiments.

Despite the potential for systematic error in Hershey and Chase's method, the fact that a completely different method provided evidence for the hypothesis that the molecule responsible for hereditary phenomena was DNA, favorably shifted the evidential context of *AMM1944*. Philosophers often claim that the convergence of multiple lines of evidence is an epistemic virtue; this is sometimes called "robustness."[21] Once Hershey and Chase's evidence was available, a robustness argument could be made for the hypothesis that genes are functionally composed of DNA by appealing to the convergence of their evidence with the evidence in *AMM1944*.

As the scientific context of *AMM1944* changed, its assessment changed. Mirsky himself, once the strongest critic of interpreting *AMM1944* as providing evidence that genes are DNA, exemplified this change. In the mid-1950s, after the shift in evidential context of *AMM1944* (and one year after Avery had died), Mirsky wrote: "that intact nucleic acids have a high degree of specificity in biological systems is evident both from the role of DNA in bacterial transformation (Avery et al. 1944) […]" (1956). Ten years after this, Mirsky was even more forthright: "25 years ago [that is, in 1944], [DNA] was conclusively shown to be the genetic material" (1968). Conclusively, perhaps, but only in the evidential context established by the mid-1950s.[22]

[20] About Hershey and Chase's method, Olby wrote: "Their evidence was not all that convincing, certainly their chemical data was inferior to that of Avery, MacLeod, and McCarty" (1974). At the time of Hershey and Chase's publication, such criticisms were not as pronounced as they had been against *AMM1944* – the evidence presented by Hershey and Chase was rapidly accepted, and Hershey went on to win a Nobel Prize in 1969.

[21] Several synonyms have been used for robustness: "multiple derivability" (Nederbragt 2003), "more varied data" (Kruse 1997), "argument from coincidence" (Cartwright 1991), "triangulation" (Leigh Star 1989), and perhaps most famously "consilience of inductions" (Whewell 1837).

[22] Cresto (2008) gives a formal analysis which purports to show that both Avery's group and critics such as Mirsky can be thought of as rational despite disagreeing over the interpretation of the evidence provided by the transforming studies. My discussion lends support to Cresto's analysis. The evidential context of *AMM1944* was changing throughout the decade after its publication, and the disputants had different degrees of confidence in the quality of Avery's methods, and thus such disagreement was reasonable.

One of the strongest retrospective supporters of *AMM1944*, Joshua Lederberg, also changed his assessment of *AMM1944* after the evidential context of *AMM1944* had shifted. Lederberg used vague, cautious language when discussing Avery's work on the transforming substance in the mid-1950s. He claimed the active material in transformation is only "intimately connected with the stuff of heredity" – intimately, perhaps structurally, but not necessarily causally or functionally connected (1956). Until transformation studies were "broadened about 1951 with experiments on drug resistance and other markers, a variety of opinions were forwarded (mostly on a purely speculative level) on the biological interpretation of Griffith's findings."[23] In this and another genetics review published around the same time, Lederberg warned the reader to take note of the valid criticisms, by Mirsky and others, against overinterpreting transformation studies. However, in Lederberg's Nobel speech of 1958, we read:

> By 1943, Avery and his colleagues had shown that this inherited trait was transmitted from one pneumococcal strain to another by DNA. The general transmission of other traits by the same mechanism can only mean that DNA comprises the genes. To reinforce this conclusion, Hershey and Chase proved that the genetic element of a bacterial virus is also DNA.

Here we again observe a change in the assessment of the evidence presented in *AMM1944* concomitant with a change in its evidential context. Lederberg's claims in this passage – that the conclusion of *AMM1944* was "reinforced" by the work of Hershey and Chase, and that the evidence in *AMM1944* can "only mean" that genes are functionally comprised of DNA – were only stated with such conviction after the evidential context had favorably changed to support such an interpretation of *AMM1944*. And decades later, in a letter to McCarty, Lederberg wrote: "2/1/44 was an important day in my life …" (cited in McCarty 1985, 234).

Thus by the mid-1950s the evidential context of *AMM1944* had favorably shifted, allowing many to interpret *AMM1944* as showing that genes are composed of DNA. By the late-1950s and through the 1960s those early critics of *AMM1944* came to describe it as an important discovery. Decades later it had become common to heap praise on the paper. Lederberg claimed that it was "the pivotal discovery of 20th-century biology" (1994). Peter Medawar called the transformation work by Avery's group "the most interesting and portentous biological experiment of the 20th century" (quoted in Lederberg 1994). In 1972, H.V. Wyatt

[23] "Griffith's findings" being synonymous with the transformation studies by Avery and colleagues.

wrote, "It is generally accepted that molecular biology began with the paper by Avery, MacLeod and McCarty in 1944." During an interview in 1978 Max Delbrück called it a "great discovery." Textbooks of molecular biology today often refer to *AMM1944* as foundational.

In sum, I have argued that the disparity between the reception of *AMM1944* in the 15 years after its publication compared with its celebration in subsequent decades can be understood by the dynamic evidential context in which its evidence was interpreted. Thus far I have ignored two common historiographical strategies used to explain such a disparity: the thesis of later scientists creating a founding myth and the appeal to the broader socio-economic context to explain shifts in the assessment of a scientific work.

Myths and War

One might think that the vicissitudes of the reception of *AMM1944* can be understood as the product of a founding myth, similar to the founding myth and neglect story associated with Mendel: an interesting scientific work is apparently neglected for years; it is later celebrated as a revolutionary discovery; its original neglect is bemoaned (see, e.g., Abir-Am 1985). If such an historical account is compelling, then there is little mystery regarding the disparity between the original hesitant reception of *AMM1944* and its later celebration: this disparity is readily explained by the fact that scientists tend to create founding myths, in which their founder was not recognized in his own time. But as historians, we stand outside the myth-making framework and, thus, should not be surprised to observe retrospective myth-making celebrations and concomitant neglect stories. An assumption of this kind of historical explanation is that the later celebrations of the scientific work are less compelling if the scientific work is properly assessed in its historical and evidential context.

A myth-making historical explanation of the vicissitudes of the reception of *AMM1944* is at least partially correct. As we have seen, when *AMM1944* was first published it was not quickly recognized as providing evidence of an important discovery, and this muted assessment continued for roughly ten years, but later much praise was heaped on Avery and *AMM1944*.[24] The disparity between the early muted reception and later celebration suggests that the scientists giving retrospective praise

[24] Sometimes such myths claim that the original work was 'ahead of its time'. Stent (1972), for instance, claimed that *AMM1944* "had little impact on geneticists. The reason for the delay was not that Avery's work was unknown to or mistrusted by geneticists but that it was 'premature' … The significance of Avery's discovery was not appreciated by molecular geneticists until 1952."

were indeed creating a founding myth. However, I hope to have made the case that the component of neglect in myth-making accounts was missing in the case of the reception of *AMM1944* – the work was well-known – and I hope to have made the case in the previous section that the critical assessment of the evidence in *AMM1944* was, at the time, justified based on its evidential context. This ought to render a myth-making explanation for the changing assessment of *AMM1944* less compelling.[25]

Another consideration one might think explains the vicissitudes of the reception of *AMM1944* is the broader historical context during the time of the paper's publication and the years immediately following. The year was 1944, the world was enmeshed in tragedy; this was no time to appreciate novel scientific findings. The hesitant reception of *AMM1944*, one might think, can be understood by taking into account the war-time context in which it was published. There is, *prima facie*, some plausibility in such a consideration.

Pirie (1972), for example, appealed to the wartime context when he suggested that since "scientific communication and publication did not get properly restarted until 1947," it was reasonable that *AMM1944* did not have rapid impact: "Avery's explanation of the 'Griffith phenomenon' was incorporated into the general picture about as quickly as could have been expected."

Prior to the publication of *AMM1944* there had been little work on transformation. Although in retrospect the chemical identity of the transforming substance would seem to be an exciting and fruitful research program, there was a break in research on transformation in Avery's lab from 1937 to 1940 and a hiatus in publication on transformation from 1933 to 1944. Commenting on the apparent hiatus in research on the transforming substance, Lederberg wrote:

> More remarkable than the neglect which is imputed (in my view incorrectly) to Avery's work since 1944, is the failure of other microbiologists and geneticists to explore the Griffith phenomenon between 1928 and World War II. More undisciplined or better informed speculation might have encouraged experiments with a wider variety of genetic markers; these studies were technically possible at least 20 yr before they were attempted [sic]. (Lederberg 1972)

In short, little research was done on transformation during the 1930s and early 1940s, and one possible reason for this was the economic and

[25] The myth-making historical explanation has an element of arrogance on the part of the historian. It suggests that historians are clever enough to identify when retrospective scientific praise is justified, but scientists themselves are not.

political climate of the late 1930s and early 1940s.[26] It is also plausible that little work was done on transformation in part due to the war-related work that occupied Avery's lab. Besides Avery's immunological research, after 1941 he and his research team had been enlisted to provide education and research for the war effort. In 1942 another report of the Rockefeller Institute reads: "With the outbreak of the war Dr. Avery and Dr. Horsfall secured an OSRD contract for the investigation of atypical pneumonia. Since March of this year a major portion of their time has been devoted to the problem."[27] In a 1940 report of the Rockefeller Institute describing Avery's work in moderate detail, there is no mention of research on the transforming substance or on DNA and in the spring of 1942 there was still no mention of work on the transforming substance in the Rockefeller Institute reports.[28] In his 1943 letter to his brother, Avery explains his research on transformation and its background, as if Roy did not at the time know what Avery was working on: "It is the problem of the transformation of pneumococcal types. You will recall that Griffith, in London, some 15 years ago […]." It almost seems that transformation was a new topic for Avery. He then tells his brother: "For the past two years, first with MacLeod and now with Dr. McCarty, I have been trying to find out what is the chemical nature of the substance in the bacterial extracts which induces this specific change." In other words, they had been working on the chemical nature of the transforming substance since 1941. Avery was close to his brother – after retirement from the Rockefeller Institute, he moved to Nashville to live with him. His letter suggests that the chemical identity of the transforming substance was for him a recent research topic.[29]

The wartime context of its publication may have played a role in the

[26] In his biography of Avery, Dubos (1976) wrote that "the countless experiments performed between 1934 and 1940 to extend Alloway's findings did not lead at first to a systematic program, simply because the results were not reproducible." However, this claim (that "countless experiments [on transformation] had been performed between 1934 and 1940") is difficult to verify with either published or archival documents. At a conference in 1939 Pirie asked Landsteiner if any work was being done on the "Griffith phenomenon" at the Rockefeller Institute, to which Landsteiner answered in the negative (Pirie 1972).

[27] Report of the Director of the Institute to the Corporation of the Rockefeller Institute for Medical Research, (1942), pp 16.

[28] Report of the Director of the Hospital to the Corporation of the Rockefeller Institute for Medical Research, pp 128-153.

[29] Despite the several papers published before 1933 extending the "Griffith phenomenon," Dubos suggests several factors that brought a temporary end to published research on transformation: active research on other topics, time spent treating patients with respiratory diseases, technical difficulties isolating the transforming substance and culturing a "competent" R strain. Dubos further suggests that after the introduction of sulfa drugs, patient-care demands were eased, and at the same time technical advances made work on the transforming substance more consistent.

hesitant assessment of *AMM1944* in the 1940s. But surely by the late 1940s and early 1950s, the influence of the wartime context on the reception of the work was waning, and to the extent that the wartime context was still an important factor in its assessment, presumably it would have been important for the reception of other scientific works as well. Appealing to the wartime context of its publication would be irrelevant to the question of whether or not *AMM1944* was known or discussed, since I have argued that many scientists at the time were aware of it, and it was widely discussed. Moreover, one ought to be able to apply such socioeconomic considerations symmetrically – that is, if the wartime context muted a positive reception then it should also have muted a negative reception – but there are enough examples of criticism of *AMM1944* immediately after its publication (canvassed in the third section) to suggest that, in fact, the immediate post-war period had ample opportunity for both scientific criticism and praise.[30]

Conclusion

The reception of *AMM1944* was a complex affair. For some scientists it was a stimulus to develop research programmes on nucleic acids. However, although it was a well-known scientific work, in the decades after its publication relatively few scientists interpreted *AMM1944* as providing evidence that genes are functionally comprised of DNA. Despite having some plausibility as an explanation for the disparity between the initial hesitant reception and the later retrospective celebration of *AMM1944*, a founding-myth account, and an appeal to its wartime publication, are less compelling than the primary explanation argued in this paper. The evidential context of *AMM1944* changed by the mid-1950s, making it more plausible to interpret *AMM1944* as evidence that genes are composed of DNA. Auxiliary hypotheses were strengthened, transformation studies were continued with a variety of methodological parameters, and independent evidence of an altogether different kind was presented which was concordant with that of *AMM1944*. The vicissitudes of the reception of *AMM1944* can be, at least in part, explained by the changing evidential context in which its evidence was assessed and interpreted.

[30] Olby (1972) notes that "In war-torn Europe conditions were not conducive to the public discussion of Avery's work, yet in Paris André Lwoff and Boris Ephrussi held a colloquium with support from the Rockefeller Foundation at which the new work which had had its genesis in Avery's discovery was reported."

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