In search of the best explanation about the nature of the gene: Avery on pneumococcal transformation

Eleonora Cresto

CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas)
Buenos Aires, Argentina
eleonora.cresto@gmail.com

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Abstract

In this paper I present a model of rational belief change, and I show how to use it to obtain a better insight into the debate about the nature of pneumococcal transformation, genes and DNA that took place in the forties, as a result of Oswald T. Avery's work. The model offers a particular elaboration of the concept of inference to the best explanation, along decision theoretic lines. Within this framework, I distinguish different senses in which Avery's team can be said to have proceeded with caution, thus throwing some light upon a persistent source of disagreement among researchers in the history of genetics. In addition, I explain why we are entitled to say that rival parties such as physicist Maclyn McCarty and biochemist Alfred Mirsky were epistemically rational, in spite of the fact that they reached different conclusions on the basis of the same evidence.

Keywords

Inference to the best explanation; Cognitive decision theory; Bayesianism; Avery; DNA; Pneumococcal transformation

1. Introduction

In this paper I present a model of rational belief change, and I show how to use it to obtain a better insight into the debate about the nature of pneumococcal transformation, genes and DNA that took place in the forties, as a result of Oswald T. Avery's work. In very few words, the model offers a particular elaboration of the concept of inference to the best explanation, along decision theoretic lines. I worked through the details of this approach elsewhere, so here I shall only sketch the main features of the proposal, and focus on its ability to carry out a successful analysis of Avery's case. In particular, I hope to explain why we are entitled to say that rival parties such as Oswald T. Avery and biochemist Alfred Mirsky were both, for the most part, *epistemically rational*, in spite of the fact that they reached different conclusions on the basis of the same evidence. In addition, I hope to show that the proposed framework provides the necessary tools to distinguish different senses in which Avery's team can be said to have proceeded with caution, which has been a persistent source of disagreement among researchers in the history of genetics.

The paper is organized as follows. In Section 2 I state the main controversies and problems that appear in the literature on Avery's research; I describe the basic structure of the model in Section 3, and I apply it to Avery's case in Sections 4-9, with the aim of solving some of the problems mentioned in Section 2. In Section 4 I present a brief historical introduction to bacterial transformation; sections 5 and 6 address Avery's attitude, while Sections 7-9 provide rational reconstructions of competing inferences to the best explanation that might have been carried out by different members of the scientific community in the forties and early fifties. Finally, in Section 10 I offer some conclusions.

2. Avery's case: overview and main problems

Avery and his team are remembered for having stated that the substance capable of transforming pneumococcal types in controlled experiments was DNA, which in turn paved the way for the conjecture that *genes* were made of DNA.[1] Their research crystallized in three successive papers: Avery *et al*. (1959 [1944]), and McCarty & Avery (1946a,b), though the second and third are not as widely read and quoted as the first one.

Compared to other epoch-making cases from the forties and fifties, Avery's is far more complex from an epistemological point of view. Let me mention briefly the main controversies that have arisen in relation to Avery's case; by the end of the section I shall point to those that will be specifically addressed in this paper.

(1) In the first place, the 1944 article is written in a very cautious style, and hence there is room to discuss whether Avery himself had real and living doubts about some of his findings. Indeed, many authors seem to suggest that Avery's style constitutes proof that he was not convinced of what we take now to be the main moral

[1] Strictly speaking, the claim that genes are made of DNA may be said to be a category mistake – for instance, if we argue that "genes" refer to abstract entities. For a nice discussion of this point *cf.* Hotchkiss (1966). In any case, the expression can be taken to be a relatively harmless simplification, and it is indeed a widely used one, so I shall indulge in it without major qualms. Notice that, to some extent, the idea of gene as an abstract, non-physical entity survives in contemporary biology, insofar as there is no privileged way to count segments of DNA. See for instance Kitcher (1992), and Maienschein (1992). For a brief overview of how the concept of gene evolved, see Carlson (1989), pp. 259 ff. A number of philosophical considerations related to such evolution can be found in Kitcher (1982), Burian (1985), and Beurton et al. (2000).

of his research – namely, that genes are made of DNA; by way of illustration, *cf*. Fleming (1968, p. 152); Pollock (1970, p. 14); or Toulmin (1972). For the opposite view, *cf*. Diamond (1982), Russell (1988), and, to some extent, Amsterdamka (1993, p. 34). Related to this, some historians sought to distinguish between Avery's prudent public statements and his private thoughts on the matter (see Olby, 1994, p. 187; or Judson, 1996, p. 21 ff.), while others tried to convey a more complex state of affairs, according to which, even though Avery privately engaged in speculations that went beyond the content of the 1944 paper, he was also persistently worried about the possibility of being wrong (*cf*. McCarty, 1985, especially pp. 163 ff; *cf*. also McCarty, 1994, p. 394).

(2) Secondly, we find discussions concerning the timing of acceptance of the relevant hypotheses of the case by the scientific community. To begin with, we might want to focus on the reactions of other members of Avery's team. Interestingly, different collaborators claim to have been committed to different degrees of caution back then – and, correspondingly, they tend to conceive of such attitudes as the most reasonable ones; *cf*. paradigmatically Hotchkiss (1966), for a defense of a moderately skeptical attitude, and McCarty (1985), for a defense of the reasonability of a bolder approach back in the forties.

The situation is somewhat more complex when we consider the attitude of scientist not directly related to Avery's work. In two well known articles, Wyatt (1972) and Stent (1972) have claimed, respectively, that Avery's 1944 paper was not immediately acknowledged by its peers (it conveyed "information" that did not become "knowledge" until much later) and that its content was not immediately profited by other members of the community (it was a "premature discovery"). Since then, most writers interested in Avery's case have rejected the two statements (*cf.* for example Lederberg, 1972; Dubos, 1976, pp. 157-159; McCarty, 1985, pp. 227 ff.; Russell, 1988, p. 393; Olby, 1994, pp. 202 ff; Deichmann, 2004 to mention a few).

Even granting that Wyatt and Stent's suggestions are ultimately unjustified, there is still room to discuss whether particular researchers accepted the paper's implications sooner or later than others. According to the standard view on this topic (as found, for example, in Dubos (1976, pp. 145, 156); McCarty (1985, Ch. XII); Olby (1994, pp. 190 ff.); Cohen (1998, p. 8) scientists such as geneticist André Boivin or biochemist Erwin Chargaff – to mention two paradigmatic examples – were early enthusiastic supporters of Avery's research, whereas biochemist Alfred Mirsky was a persistent skeptic until much later. This view has been at least partially contested by Mirsky (1972, 1973). On the other hand, in Watson & Berry (2003, p. 39), we find the more general claim that geneticists as a whole were readier than biochemists to acknowledge the consequences of Avery's article; Hotchkiss (1966, p. 183; 1979, p. 325), by contrast, recalls a very different picture, according to which most classical geneticists were actually very reluctant to greet Avery's work with positive eyes.

(3) In the third place, we can find discussions concerning how to assess the overall role of Avery's findings for the advancement of genetics. Consider, for example, the controversy about the legitimacy of the use of the term "revolutionary" (in some sense akin to the one coined by Kuhn (1970 [1962]) to account for Avery's inquiry. In Olby (1990, 1994), for instance, we find an enthusiastic affirmative answer to the question as to whether the term is applicable in this case; Lederberg (2000, p.

194), also refers to Avery's paper as constituting a "scientific revolution"; Pollock (1970) or Judson (1980), (1996) are good examples of negative answers; while Dawes's (2004) paper can be mentioned as an attempt to reach some sort of intermediate ground (he dubs Avery's discovery "a *quiet* revolution").

(4) Consider also the controversy about the exact relationship between Avery's research and molecular biology. Many scientists and historians take Avery's 1944 paper to mark the origins of molecular biology (*cf.* for example Burnet, 1968, p. 81; Wyatt, 1972, p. 86). Other writers, however, while acknowledging the merits of Avery's work, prefer to emphasize the role of Luria & Delbrück's (1943) article on bacterial mutation, or that of Hershey & Chase (1952) (*cf.* for example Judson, 1980) – where all four authors belonged to the so-called Phage Group, which aimed to analyze genetic replication in bacteriophages.[2] Still other voices, such as Olby (1990), contend that molecular biology has several roots, including the research done by Avery's team and the Phage Group, but also including contributions from scientists working on the three-dimensional structure of molecules (the "Structural School"), or on plant viruses.[3]

(5) Finally, we might want to reflect on whether the main characters of the case behaved rationally, given the circumstances. It should be mentioned that there is no explicit historiographical controversy here; still, I think it is important to bring attention to the problem, and take a stance on it. Among other things, it relates to

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[2] For an overview on the Phage research program, *cf.* Olby (1994), chapter 15; for a first-hand account, *cf.* Cairns *et al.* (1966).

[3] For some thoughts on the complex relationship between classical genetics and molecular biology, *cf.* Kitcher (2003 [1984]).

traditional concerns about the extent to which turning points in the history of science favor the occurrence of decisions that cannot be rationally accounted for.

A quick look at the literature shows that, at times, Mirsky's attitude has been suspected to be a by-product of a personal confrontation with Avery's group (see for instance McCarty, 1985, p. 148). Similarly, several discussions of Avery's caution focus on Avery's *personality* (as in Russell, 1988, p. 400; in a somewhat different sense, *cf*. also Fleming, 1968, p. 152). Strictly speaking, references to biographical circumstances of the kind mentioned in Fleming, McCarty or Russell's accounts are not incompatible with the existence of more comprehensive explanations that seek to illuminate whether the relevant agents can be credited with rational epistemic decisions. However, to this day no such comprehensive explanations have been proposed to address specifically Avery's case.

In this paper I shall not attempt to settle contemporary discussions on whether Avery's work generated a scientific revolution, or on Avery's exact contribution to the rise of molecular biology (points (3) and (4) above). Rather, I shall concentrate on some of the controversies mentioned in points (1) and (2), and I shall also seek to explain why we are entitled to say that rival parties in the forties (most clearly, McCarty's and Mirsky's) proceeded rationally, for the most part (point (5)).

Concerning (1) and (2), I shall argue that, in many cases, we find a good deal of confusion as to what the terms of the discussion really are. For instance, it is not always clear in the literature which concept of "caution" is at stake. Thus, different authors that coincide in assessing Avery's attitude as cautious might be trying to convey very different ideas: they might be trying to express that he was *legitimately* prudent (as in Hotchkiss, 1966), or that his procedure revealed *more* skepticism than reasonably needed (as in Toulmin, 1972).

Other confusions are harder to spell out. I shall attempt to clarify them by offering a decision-theoretic model of inquiry that requires the elucidation of sets of questions and potential answers to those questions, whose merits agents are required to assess.

Concerning point (5), I shall rely again on the aforementioned framework in order to explain why it was reasonable for McCarty and Mirsky to arrive at different conclusions, even though they shared the same empirical evidence. I shall also seek to explain very briefly why other well known models of research are not equally able to deal with Avery's case.

A few clarifications are in order. First, it is apparent that *real* agents, as opposed to their ideal counterparts, are never perfectly rational: typically, they engage in sub-optimal ways to gather information (by their own lights), and they fail to acknowledge useful consequences of their prior beliefs, to mention only a couple of salient problems. However, we can still wonder whether a given epistemic attitude, as exhibited by a real agent in the history of science, has *a rational core,* so to speak – namely, whether there is a way of connecting the particular epistemic behavior of the agent with her perception of the *epistemic gain*, or gain in overall understanding, involved in such behavior.

Second, I should mention at the outset that I shall not provide direct evidence for the assumption that the epistemic behavior of rival parties in Avery's case exhibited a rational core, in the sense just stated. I do not think that such a proof can be offered at all – or demanded, for that matter. As I can see it, on reading the relevant papers and reports, none of the characters involved comes across as evidently unreasonable. But, of course, this is not the type of conclusion one can arrive at just by pointing at a particular passage, or page, within an author's overall production at a given period of time. This is not to say that there is nothing we can do to support the assumption. Indeed, we can obtain an indirect defense by providing a detailed explanation of why, and how, this situation was possible in the first place. This line of defense can be reinforced if we show (as I hope to do) that, by engaging in this type of rational reconstruction, we gain a better understanding of Avery's case – a type of understanding that cannot be attained by mere reference to the relevant biographical data.

In the next section I shall proceed with a brief description of the model of inquiry that I favor; I shall return to the details of Avery's research in Section 4.

3. A model of inference to the best explanation

Let me suggest the following model of rational inquiry, within a decision theoretic framework. I shall describe a research process as a series of steps aimed at the acceptance of the best explanation available for the set of perplexities of a given agent at a given time. I shall call it a process of inference to the best explanation, or, for short, an IBE process.

Very roughly, an IBE process goes as follows. At a given time *t*, an agent *X* is assumed to have a set of full beliefs $K_{X,t}$. Then, for an IBE process to begin, researcher *X* should be able to identify a set $Q_{X,t}$ of questions (not necessarily why-questions) that *X* seeks to answer at *t*. (I shall drop the sub-indices when there is no risk of confusion).

A few formal constraints to $Q_{X,t}$ suggest themselves. To begin with, questions typically have presuppositions. Within the context of semantic analyses of questions, the label "presupposition" is usually meant to refer to those propositions an agent *should* take for granted, as a matter of rationality, if the question is to be meaningful for that agent. Thus, for example, questions such as "Why ϕ?," or "How possibly ϕ?," presuppose that ϕ does occur. A question such as "What is it that causes ψ?," presupposes that ψ occurs (or that it may occur – depending on the case) and that there is something that causes ψ, and so forth. I shall say that a question *q* is *legitimate* for an agent *X* at *t*, if and only if (a) all presuppositions of *q* of which *X* is aware at *t* are in $K_{X,t}$, and (b) *q* is not settled for *X* at *t*, that is to say, *X* does not think that some member of $K_{X,t}$ counts as a suitable answer to *q*. Notice that if (a) is false, the question is ill-formulated, as far as *X* is concerned.

Suppose *q* is legitimate for *X* at *t*. Then *X* may, but need not, feel the need to search for an answer to *q* at *t*. She might not be ready to devote time and effort to attempt to settle *q* at that particular time –say, because more urgent matters demand her attention at *t*. In other words, at a given time *t* an agent *X* might only be interested in answering a small subset of her set of legitimate questions, if at all. In addition, even assuming she feels the urge to answer *q* at *t*, it is not certain that she will be able to concoct suitable answers to *q*: *X* might only be able to generate possible answers to a yet smaller subset of the set of legitimate questions that she wants to answer at *t*.

What is in $Q_{X,t}$, then? $Q_{X,t}$ *contains all legitimate questions (for agent X, at t) that X wants to answer at t, and which are able to generate suitable possible answers, as far as X is concerned.* Notice that, so defined, two agents might have identical belief sets, and hence identical sets of legitimate questions, and still hold different question sets at *t*.

As we can see, $Q_{X,t}$ is partly defined by reference to *a set of answers*, which I shall call set $E_{X,t.}$ Each member of $E_{X,t}$ provides an explanatory answer to all questions of $Q_{X,t}$; I shall also require that members of $E_{X,t}$ had already been put to the test, and survived the testing. In addition, I shall demand that all members of $E_{X,t}$ be compatible with the agent's prior set of full beliefs; they should be pairwise incompatible; and the agent should believe that exactly one of them is true.[4] Next, agents may choose to accept some of the hypotheses in $E_{X,t}$, or they may choose to suspend judgment among some, or all of them. In order to make a decision as to which expansion strategy to adopt, the model assumes that agents rely on personal assignments of probabilities and epistemic utilities over the members of $E_{X,t}$, and that they seek to maximize expected

[4] Here I shall not define what an explanatory answer is. As I can see it, a satisfactory theory of explanation should focus on offering objective steps to determine when an agent is entitled to select a *best* explanation (or, eventually, a disjunction of best explanations) out of a previous batch of explanatory elements. By contrast, the theory should not tell an agent which hypotheses she should find explanatory in the first place; this amounts to a non-analyzable, ultimate fact. As I see it, explanatoriness is directly related to the ability the hypothesis has of enhancing the agent's overall understanding, in the sense of promoting a psychologically compelling world picture. And, in this sense, the burden of deciding which statements qualify as explanatory is on particular agents. The resulting position can be described as a pragmatist conception of explanation, by analogy with the general layout of pragmatist epistemology. According to so-called Peircean epistemology, for instance, agents should not seek justification for their prior beliefs, but only for the *changes* that occur in their epistemic states; similarly, according to a pragmatist conception of explanation, agents should not seek justification for finding certain statements explanatory, but for choosing to expand their belief sets with certain explanatory statements. For contemporary elaborations on what I call here Peircean epistemology, *cf*. Levi (1997), p. 4; the Introduction of Fuhrman (1997); Bilgrami (2000), pp. 251-257; or Bilgrami (2004), among others.

epistemic value, in agreement with the recommendations of (some brand of) cognitive decision theory.[5]

I have argued elsewhere that an adequate concept of epistemic utility on members of E should be a function of a measure of the *virtuosity* of the basic hypotheses.[6] I have in mind features such as simplicity, unification power, fertility, testability, economy, or accuracy. Then agents are assumed to be able to perform a trade-off among the many virtues that they deem relevant. Contrary to what seems to be a common presupposition, I believe that the virtues just mentioned do not bear any clear relationship with truth or probability. They are not *truth-tracking*, so to speak – our most virtuous hypotheses can actually bear low personal probability, and can be, as a matter of fact, false. Rather, each virtue fosters, in its own particular way, the construction of a satisfying world-view – and, in this sense, each virtue has its own peculiar way of promoting *understanding*. As we shall see in further sections, the reference to virtues will be crucial at the time of explaining the epistemic behavior of Mirsky's and Avery's parties.

In this paper I shall leave open, for the most part, the exact formulation of the epistemic utility function that I favor (based on the aforementioned concept of theoretical virtues), as well as the exact way to interpret the probabilities that enter into

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[5] The best-known approach to cognitive decision theory is found in Levi (1980); *cf*. also Maher (1993), or van Fraassen (1989, 2002). It could be contended that, insofar as I allow for suspensions of judgment, the set of potential answers for agent A at t is not set $E_{A,t}$, but the set of all Boolean combinations of members of $E_{A,t}$. In this paper I shall not discuss this, or similar, technicalities.

[6] *Cf*. Cresto (2006), chapter 3.

the equation.[7] However, for the sake of simplicity I shall adopt the idea that, when a hypothesis H is *assumed to be false*, its epistemic utility is 0, as no comfort can be obtained from it. Hence $EEU(H) = P(H)f(H)+P(H)0 = P(H)f(H)$; where $P(H)$ is H's probability, $f(H)$ stands for H's epistemic utility, and $EEU(H)$ is H's expected epistemic utility. More complex approaches are of course possible (and perhaps desirable), but they will not make any substantial difference for the purposes of this paper.

Within this model, the overall explanatory force of members of E is identified with their expected epistemic utility. Therefore, whenever there is a single best element in E, it should be interpreted as *the best explanation* for the set of perplexities that prompted the research, as far as the agent is concerned.

What should agents do with best explanations? I shall assume that agents can be credited with specific thresholds, for particular contexts of inquiry; then, the model recommends that the best element from E (or the disjunction of all best elements, in case there is more than one) be added to the agent's set of full beliefs K – but only if its expected epistemic utility is above the chosen threshold. As we can see, within this account the agent's boldness is conceived of as part of the very structure of what we should understand by rational epistemic decisions.[8]

Notice that, according to this framework, agents come to believe best explanations *because agents think that best explanations are worth the risk.* Indeed,

[7] I believe the best way to go is to adopt some form of temperate personalism and demand that priors be sensitive to observed frequencies, when available (*cf.* Shimmony, 1993 [1970], or Levi, 1994). In addition, I believe we should not require that agents possess a single personal probability function, but a convex set of such functions (as in Levi, 1980). But nothing fundamental in this paper depends on the adoption of this or other perspective on probabilities.

[8] Within more complex approaches, caution indices can enter into the composition of the epistemic utility function; *cf.* paradigmatically Levi (1984), chapter 5.

agents risk being wrong – they risk coming to believe a false hypothesis – but taking the risk may be rational if the gain in overall understanding is high enough. As it is clear, this view departs from a common way of conceiving of best explanations, according to which explanatory force is the hallmark of truth. By way of contrast, within the present model, we are entitled to believe best explanations when their explanatory force makes the risk of being wrong worth taking.

4. Avery et al. on bacterial transformation

Let me go back to Avery's case. What did people have in mind, in the thirties and forties, when they talked about "bacterial transformation," or, more specifically, "pneumococcal transformation"? Let me begin by recalling that pneumococci had been found to come in different specific types; in addition, virulent organisms of any type were known to be surrounded by a capsule – the reason for the virulence being precisely that white cells of infected hosts were not able to digest the capsule. Virulent colonies exhibited smooth edges; hence they were commonly referred to as S ("smooth") variants. Attenuated pneumococci, by contrast, were known to be non-encapsulated, and were referred to as R (for "rough") variants, again due to the visual form of the colonies. In the twenties Avery had found this capsule to be a polysaccharide, which was involved in the determination of the pneumococcal type (*cf.* Heidelberg & Avery, 1923; Avery & Heidelberg, 1923). This result constituted the first indication that substances other than proteins could express biological specificity, against the common wisdom of the time.

Frederick Griffith (1928) reported that mice inoculated with heat-killed type I S pneumococci together with a live R II strain died, surprisingly, from a type I S infection; Dawson & Sia (1931) were able to repeat the transformation experiment in a test tube, and soon after that, Lionel Alloway – a younger colleague of Avery's at the Rockefeller Institute – showed how to obtain transformation in the presence of active extracts of the heat-killed pneumococci, rather than using intact, heat-killed cells (Alloway, 1932, 1933).

Griffith had interpreted the transformation phenomenon as an indication that pneumococcal types might change in response to environmental conditions. Against this, Avery's earlier studies on the pneumococcal capsule pointed to the fixity of immunological types – hence Avery was of course intrigued by the chemical nature of the transforming agent. On the other hand, it was hard to imagine back then that it would turn out to be DNA. In (1931) Levene and Bass had proposed that the DNA molecule exhibited a repeating structural unit, represented by the four nucleotides arranged in the same order. In Chargaff's words, it was a well-established *dogma* before his 1950 paper appeared (*cf*. Chargaff, 1950, 1979, pp. 350-351). Thus, DNA was conceived of as devoid of biological specificity, which implied that it could not be the trasnsforming substance. Proteins, by contrast, appeared to be the natural candidates to play this role.

The experiment described by Avery, MacLeod and McCarty in 1944 accounted for the transformation of rough type II pneumococci into smooth, virulent type III. In very few words, the experiment consisted in placing a culture of RII pneumococci in a suitable medium, together with a substance (the "transforming principle") capable of inducing type transformation. Once a change of type was effectively seen to occur, the transforming substance would be analyzed to try to establish what it contained, and what it did not.

As I have already suggested, our understanding of Avery's case can benefit from the application of the model sketched in the previous section. In order to do so, let me begin by considering two main questions that caught the attention of researchers on pneumococci at the Rockefeller in the early forties:

(i) What is the chemical composition of the transforming substance? (For example: Protein? RNA? DNA?)

(ii) How should we interpret the activity of the transforming substance? And, correspondingly, what does the transformation phenomenon really amount to? (For example: Does it reflect the action of a virus? Of a gene?)

Notice that, in the context of discussions on bacterial transformation, in order to assert *that genes are made of DNA* we would need to accept both the claim that the transforming principle reveals the action of genes, and the claim that it is DNA. That is to say, we would need to answer both questions (i) and (ii) in a particular way. But, insofar as (i) and (ii) express two distinct, independent problems, each of which requires a particular set of possible solutions, the timing of acceptance of answers to (i) and (ii) need not coincide. Related to this, considerations about Avery's putative caution should better specify whether we are referring to Avery's attitude to (i), or to (ii), or to both.

In the next section I shall address Avery's research from his own point of view.

5. Avery's question set

Let Q_A be Avery's question set in the thirties, which prompted the research that led to the 1944 paper and its sequels. We can say that the content of Griffith's 1928 report acted as the *surprising fact* that called for an explanation, in Peircean terms.[9] But what was it exactly that Avery sought to explain? We read, for instance:

> [Our] major interest has centered in attempts to isolate the active principle from crude bacterial extracts and to identify if possible its chemical nature or at least to characterize it sufficiently to place in a general group of known chemical substances. (1944, p. 175).

This is no other than question (i) from Section 4. Consider also Avery's well known letter to his brother Roy:

> [A]fter innumerable transfers and without further addition of the inducing agent, the same active and specific transforming substance can be recovered far in excess of the amount originally used to induce the reaction. Sounds like a virus – maybe a gene. *But with mechanisms I am not now concerned* – One step at a time – and the first is, *what is the chemical nature of the transforming principle?* Someone else can work out the rest. (Reproduced in McCarty, 1985, p. 159; my emphasis).

Again, here Avery asserts explicitly that his first preoccupation is to find an answer for (i). Moreover, in this passage he states clearly that at the time he is not concerned with the kind of question that may be answered by claiming that the transforming principle is "a virus – maybe a gene." Hence, question (ii) as stated in the previous section is not in Q_A.

This asymmetry between (i) and (ii) will turn out to be consequential at the time of assessing whether Avery did, or did not, proceed with excessive caution. Let

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[9] In the sense of Peirce (1931-1958), Vol. 5, p. 189.

me devote the remaining part of this section to deal with question (ii); I shall postpone a discussion of Avery's attitude towards the potential answers to (i) until Section 6.

Was Avery too cautious at the time of interpreting the activity of the transforming substance? In the light of the above, being cautious in this respect cannot mean failing to accept a preferred potential answer to (ii) (or, at any rate, a non-trivial disjunction of preferred potential answers), insofar as (ii) was not a question of Q_A. However, someone could complain that, by neglecting (ii), Avery revealed a serious *lack of understanding* of the genetic implications of the case. According to this line of argument, had Avery realized that the transformation process might well have amounted to a genetic change – and had he understood the enormous consequences that this fact had for biology – he would not have refused to take question (ii) seriously, and he would have risked asserting an appropriate answer to it.

At least at first blush, this criticism seems wrongheaded. There are many sources that document that Avery was perfectly aware of the possibility of a connection between his experiments on transformation and regular genetic facts. In addition to the aforementioned letter to his brother Roy, in 1943 he reported:

> The genetic interpretation of [the transformation] phenomenon is supported by the fact that once transformation is induced, thereafter without further addition of the inciting agent both capsule formation and the gene-like substance are reduplicated in the daughter cells. (Avery & Horsfall, 1943, pp. 151-152).

And, in 1947,

> …those of us actively engaged in the work have for the most part left matters of interpretation (of the transformation phenomenon) to others and have chosen rather to devote our time and thought to experimental analysis of the factors involved in the reaction. This is not to say that we are indifferent and have not among ourselves indulged in speculation and discussion of the relation of the problem to other similar phenomena in related fields of biology. (Avery, 1947, p. 127)

In the light of previous reports, by “similar phenomena in related fields in biology” he most certainly meant to include *genetic* phenomena. Incidentally, the quote from 1947 also shows that Avery voluntarily chose to focus exclusively on the attempt to settle (i) – hence reinforcing my previous suggestion that (ii) was not in Q_A.

Still, we owe the potential critics some explanation regarding how it could have been reasonable for Avery to suspect that the transformation process was the action of genes, and yet refuse to address (ii). We can produce the required explanation by recalling that, according to the model presented in section 3, a question may be legitimate for an agent and still not be the type of question that prompts an IBE process, as far as the agent is concerned. But reluctance to perform a particular IBE process at a given time does not show that an agent is ignorant of the potential implications of her current research, or that she is not interested in solving other questions beyond the ones that prompted the original inquiry. In particular, I have suggested that no question set Q can be defined unless the agent is able to identify a suitable set E of pairwise incompatible answers to the members of Q. Indeed, we might well conjecture that (ii) was not in Q_A because Avery did not feel comfortable at building a suitable E_A for a question set that contained both (i) and (ii) – the reason for this being, in turn, that he had not concocted specific experiments to test the various possible responses to (ii) that might have occurred to him in the early forties: he was just too busy searching for the *chemical composition* of the transforming principle. So even though in 1944 Avery and his co-workers did list the several solutions to (ii) that were popular in the literature back then (see Avery et al., 1959 [1944], p. 190), they never gave any indications to the effect that they thought of the aforementioned list of option as exhaustive, or as serious candidates for explanation *by their own lights*. Avery must have felt that he was not in the position to start an IBE process on such bases. Rather, he might have hoped to know more about the chemical composition of the principle (and about the transformation phenomenon as a whole) before embarking in a new IBE. This is not incompatible, however, with his believing that, *were he to ask question (ii) with the goal of an IBE in mind* (and had he conducted prior specific tests to this effect), a genetic answer of some type would probably have been among the favorite ones.

A new counterargument suggests itself: shouldn't the very same research that Avery and his collaborators were conducting, by its very nature, have shed light on all the relevant elements needed to perform a suitable IBE regarding question (ii)? Against this suggestion, I believe Avery's attitude towards (ii) was sensible, given the circumstances; to put it differently, *he was indeed cautious*, *but certainly not overly cautious*. The fact that changes induced by DNA were "predictable, type-specific and heritable" (Avery et al., 1959 [1944], p. 190) strikes our contemporary sensibility as more than sufficient evidence to talk about genes. But relating the pneumococcal transforming principle to genetic activity did not come naturally to anyone back then, as it was not even clear that bacteria had genes. As Hotchkiss put it nicely,

> [Back in 1940], genetists, too, could not get past the objection that one whole bacterial cell took part in making two daughter cells; so they found no sign of the channeling of genetic determinants through such a concentrated stage as a chromosome. It may have seemed to some unfair for them to ask for a mating test to demonstrate the genes in bacteria – but without it, where was the evidence that specific determinants exist which sometimes do, and sometimes do not, manage to gain access to a particular cell? (Hotchkiss, 1966, p. 183)

> [A classical geneticist] might have asked me to show that our bacteria had compound eyes, or two sets of wings (Hotchkiss, 1979, p. 325)

Even if the presence of genes in bacteria were not an issue, the way rough pneumoccocus of type II led to smooth type III was not an obvious example of sexual cross, so it took some time for biologists and geneticists to understand what was going on.[10]

Let me turn now to question (i).

6. Competing hypotheses

How shall we reconstruct the set of basic explanations E_A built as responses to question (i)? As time went by, different hypotheses were suggested, prompted by the need to purify the transforming substance by discarding from the killed type III cells what the transforming principle was probably *not*. As a result of the process of proposing specific conjectures and putting them to a test, Avery and his co-workers ended up with a definite set of options, with specific probabilities attached.[11] The transforming principle was taken to be:

H_1 Capsular protein (a type-specific antigen)

H_2 A polysaccharide

H_3 RNA

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[10] But more about this in Section 7.

[11] Here I adopt the view that tests very seldom *prove* the falsity of given hypotheses – the most they do is make them very unlikely.

H_4 A protein located in the nucleus of the cell (that is, the "protein version of the central dogma" in the theory of the gene, in Olby's terminology)[12]

H_5 DNA plus protein (that is, nucleoprotein – or Mirsky's "chromosin")

H_6 DNA alone

Thus, let $E_A=\{H_1\text{-}H_6\}$. Recall that all members of an agent's set of basic hypotheses should be compatible with the agent's set of full beliefs. I shall leave open the possibility that Avery might have *contracted* at some point his belief set K_A, so as to avoid conflict with H_1-H_6. For example, I shall assume that, had Levene's tetranucleotide hypothesis been in K_A in the thirties, it would have been removed well before putting H_6 to the test, and hence well before building E_A. *Mutatis mutandis* for any other statement incompatible with the members of E_A.

Interestingly, there is no agreement on *when* exactly Avery and his co-workers begun to focus on DNA – not even among the main characters involved.[13] But, in any case, at some point H_6 emerged as the favorite candidate. Did Avery actually *accept* H_6 by the mid-forties? There is no straightforward answer to this question, so let us examine the evidence with some care.

On the one hand, several retrospective accounts suggest that Avery was still skeptical by 1943 (that is, by the time the 1944 paper was submitted for publication):

> I can remember that as we discussed the situation on the way home on the train, Colin asked him with a certain amount of impatience: 'What else do you want, Fess? What more evidence

[12] *Cf*. Olby (1994), Ch. 6.

[13] For instance, compare Hotchkiss (1965), p. 5 – and also Olby (1994) p. 185 – with McCarty (1985), p. 232.

> can we get?' I don't believe that he replied to this, but one answer that he had was to seek still more advice. (McCarty, 1985, p. 163)[14]

> I am afraid that both Colin and I became increasingly impatient with Avery's caution, even though we were not unaware of the importance of being sure of our ground. We were just young enough to become convinced more readily. Avery expressed his doubts repeatedly in his letter to [his brother] Roy [in May 1943] and they were also obvious on almost a daily basis in the laboratory. (McCarty, 1994, p. 394)[15]

On the other hand, it is not clear that we can take *the style* of the 1944 paper – which was undoubtedly Avery's (*cf*. for instance McCarty, 1985, p. 165) – to support the claim that Avery was overly cautious. (Notice that Avery might have indeed been cautious by 1943, as shown by McCarty's memoirs, and still be the case that the paper does not constitute additional proof of this). Surely, the authors never stated that H_6 was actually *true*, but this omission is not self-explanatory. What they *did* say was that the transforming principle consisted "largely, if not exclusively," of DNA, and that the results "strongly suggested" that DNA possessed specificity (1994, p. 188). In another widely commented upon passage near the end of the discussion section, we find:

> 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 adsorbed to it or so intimately associated with it as to escape detection. (Ibid, p. 190)

But soon after that, at the closing paragraph we read, once more:

> The evidence presented supports the belief that a nucleic acid of the desoxyribose type is the fundamental unit of the transforming principle of Pneumococcus Type III. (Ibid, p. 191)

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[14] Compare with McCarty (1994), p. 394, where he states that "the 'else' that [Avery] would have liked to have was a purified DNase to try on the transforming DNA."

[15] Curiously, both Olby (1994) and Judson (1996) take Avery's letter to Roy to support the interpretation that Avery was *publicly cautious, but privately confident* of H_6.

In other words, the available evidence "supported the belief" that H_6 was correct – although they did not say, literally, that it *was* correct. This, however, by itself, is hardly sufficient evidence to conclude that Avery was still unconvinced. The style is not unusual for a scientific article; we can find well known examples in which similar writing styles were deemed adequate – by the relevant portion of the scientific community at the time – to convey particular results loud and clear, and were not perceived as symptoms of excessive prudery.[16] In the light of this, we might wonder whether the perception, in the mid-forties, of Avery *et al*.'s 1944 paper as unusually cautious was not the result of fellow scientists' inadvertently imposing well known facts about Avery's personality to the paper itself. After all, as many writers have pointed out in response to Wyatt's claims, news was transmitted by personal interaction as much as by publications in scientific journals (*cf*. for instance Olby, 1994, p. 202).

In short, there are good reasons to say that Avery still had doubts about the truth of H_6 by 1943, even though such reasons do not include considerations about the style of the 1944 paper. In addition, Avery might have become more confident of H_6 as

[16] Just to mention a couple of cases, in Lederberg and Tatum's famous 1946 paper we read that their experiments "*strongly suggest* the occurrence of a sexual process" in *Escherichia coli* (1946, p. 558; my emphasis) – yet their writing style never prompted any controversies. The style is not peculiar to biology either. For a very well known example drawn from the history of physics, we might recall J. Chadwick's celebrated report in (1932), which is usually understood as an attempt on Chadwick's part to recount the observation of a neutron, even though Chadwick explicitly states that it is not easy to choose between the hypothesis that a neutron has been observed, and a competing hypothesis. [I want to thank Alejandro Cassini for this example]. In general, I am inclined to think that *any* paper that puts forward a particular answer as the favorite candidate to settle a particular question – say, by stating that it is comparatively more supported by the evidence – can be understood as urging the reader to perform a suitable IBE, and (in case the reader holds the appropriate priors and epistemic utilities), accept the hypothesis. The 1944 article by Avery, MacLeod and McCarty satisfies the antecedent of this general maxim: the authors took pains to establish how much the evidence boosted the probability of H_6, whereas they raised no doubts about its epistemic virtuosity. In other words, the paper was clearly structured so as to instill *confidence* in the truth of H_6 – the prior of H_6 being each reader's responsibility. Here I shall not press this line of argument any further.

time went by and he managed to gather more evidence, as he certainly had done by 1946:

> The results of the present investigation show that in order to detect proteolytic activity, it is necessary to use an amount of purified desoxyribonuclease 100,000 times greater than that required to cause rapid and complete destruction of activity of the transforming substance. This evidence, in conjunction with the data previously reported on the chemical and physical properties of the active principle, leaves little doubt that the ability of a pneumococcal extract to induce transformation depends upon the presence of a highly polymerized and specific form of desoxyribonucleic acid, and that this constituent is the fundamental unit of the transforming principle. (McCarty & Avery, 1946a, p. 94)

Let me state briefly what we have obtained so far. It is clear that Avery did not believe that genes were made of DNA by the mid-forties. Can we accuse him of being unduly cautious? I have argued that, in order to address this problem, we need to distinguish between Avery's willingness (or lack thereof) to accept that the transformation phenomenon revealed the action of genes (which counted as a possible answer to (ii)), and his willingness to accept that the transforming principle was DNA (which was meant to answer (i)). We have seen that, regarding (ii), we cannot accuse him of being too prudent because of reluctance to endorse an explicit connection between bacterial transformation and genetics, but, if at all, because of a more fundamental reluctance to conceive of (ii) as a question that could prompt a suitable IBE process in the early forties. But, first, from this fact we should not infer that he was ignorant of the relevance of the problem, or of its potential implications; secondly, I have argued that the caution Avery exhibited by not adopting question (ii) as an IBE-prompting question was perfectly justified at the time. On the other hand, by 1943 Avery seemed not to have fully believed H_6 either, even though he was *explicitly* committed to finding an answer to (i); he most probably became convinced around 1946. As we have seen, the two situations are not comparable: by 1943 we could not have expected him to accept the idea that the transforming principle was linked to genetic activity, although we could have hoped him not still to be a skeptic about H_6. Are we entitled to say that he overly cautious *with respect to* H_6, then? To answer this question, we should assess first whether H_6 carried highest expected epistemic utility, from Avery's own perspective. I shall postpone a discussion of this point until Section 8, where I shall also discuss the epistemic behavior of other members of his team.

7. Accepting that DNA is the "transforming substance"

In this section I want to discuss the timing of acceptance of H_6 by various members of the scientific community; I shall provide suitable explanations for their epistemic behavior in Sections 8 and 9.

We have already seen that Avery might have accepted H_6 by 1946 (although, as a matter of fact, there is no unequivocal first-person account stating so). The situation is less controversial in the case of McCarty, Boivin or Chargaff, to mention a few clear examples. McCarty's commitment to H_6, for instance, can easily be revealed by the content of his lectures right after 1944:

> Certainly, there can be little doubt that desoxyribonucleic acid must be present in its intact, highly polymerized form [for transformation to occur], and when all of the evidence is considered it appears extremely unlikely that small traces of some other specific substance, such as protein, could be responsible for the manifestation of transforming activity. (McCarty 1946; quoted in McCarty, 1985, pp. 206)

and, more emphatically, by the general tone of his memoirs (McCarty, 1985, 1994). Consider also some of Boivin's claims from the 1947 Cold Spring Harbor Symposia, where he presented results of tranformation in *Escherichia coli*:

> In bacteria – and, in all likelihood, in higher organisms as well – each gene has as its specific constituent not a protein but a particular desoxyribonucleic acid which, at least under certain conditions (directed mutations of bacteria), is capable of functioning along as the carrier of hereditary character; therefore, in the last analysis, each gene can be traced back to a macromolecule of a special desoxyribonucleic acid. (Boivin 1947, p. 13)

Notice that by 1947 Boivin appeared to be not only convinced *of* H_6, but of the full-fledged statement that genes were made of DNA, whereas he mistakenly interpreted the transformation phenomenon as "directed mutation of bacteria." A similar attitude can be attributed to Chargaff, who asserted in many occasions that Avery's paper immediately made him change the course of his research to focus on DNA (*cf.* for instance Chargaff 1978, pp. 82 ff.).

In short, several scientists became committed to the truth of H_6 no later than by 1946-47. In McCarty's case, moreover, his "impatience" with Avery's caution prior to 1944 (*cf.* quote on p. 21) point to the fact that acceptance goes back at least to 1943.

Other researchers, by way of contrast, were clearly wary of H_6 during the forties. Most evidently, Mirsky expressed serious concerns on whether all traces of protein had actually been removed:

> There can be little doubt in the mind of anyone who has prepared nucleic acids that traces of protein probably remain in even the best preparations… No experiment has yet been done which permits one to decide whether this much protein [1 or 2 per cent] actually is present in the purified transforming agent and, if so, whether it is essential for its activity; in other words, 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 & Pollister, 1946, pp. 134-135)

Similar claims can be found in Mirsky (1947, p. 16); Mirsky & Ris (1949, p. 667); or Mirsky (1951, p. 133) – hence showing that he was still skeptic around the early fifties. It is worth mentioning here that some of his colleagues considered that his doubts were malicious (*cf*. for example Perutz, 1994), and that they prejudiced part of the scientific community against Avery's research (*cf*. McCarty, 1985, p. 218; *cf*. also Olby, 1994, pp. 192-193). On the other hand, according to Mirsky's own recollection of the situation,

> In 1946 and 1951 I accepted the idea that DNA is part of the transforming material, but asked whether protein is not also necessary. At the time this was an obvious question. It was finally decided by Hotchkiss's work and in 1953 I do not mention the possibility of protein still being there. (Mirsky, 1973).

Interestingly, Mirsky has also stressed that, in his view, it would be definitely unfair to regard him as one of the chief opponents to Avery's conclusions (Mirsky, 1972, 1973). As it turns out, however, what he meant by this is that he had succeeded in understanding *the role of the transforming agent* sooner than people more directly involved with Avery's project – in particular, sooner than Hotchkiss: by 1951 Hotchkiss was still thinking of the transformation phenomenon as the induction of a specific mutation, while Mirsky already considered it "to be essentially a hybridisation." (Mirsky, 1972; *cf*. also Mirsky, 1951, p. 133). In other words, Mirsky can be shown to have been committed early on to the right answer to (ii) – although it should be clear that this, by itself, does not tell us anything relevant about Mirsky's attitude *towards* H_6.

In the next couple of sections I shall seek to offer a rational reconstruction of different epistemic attitudes towards H_6. In particular, I shall attempt to explain McCarty, Avery and Mirsky's behavior, which, as we have seen, amount to cases of early acceptance, early caution, and late skepticism, respectively.

8. In search of a suitable explanation (I): McCarty and Avery

How shall we explain the epistemic behavior of members of Avery's team by 1943? Consider first the probabilities that might have been at stake. It is plausible to say that Avery, MacLeod and McCarty's personal probability functions did not differ too much from one another, insofar as the cumulative effect of the tests reported in the 1944 paper tended to wash priors away. (This would occur even more so as new experiments were conducted in the late forties and early fifties, but the phenomenon was still sufficiently clear before their first paper was published.) Let P_A refer to such probability measure. Indeed, by the time E_A was built, the probability of all elements of E_A had been suitably updated in response to the results of many successive tests: as Avery's research program made progress, the probabilities of H_1, H_2, H_3 and H_4 went down, whereas those of H_5 and H_6 became larger. Moreover, the probability of H_6 augmented more than that of H_5, given that H_6*'s* likelihood could well be taken to be higher than that of H_5 (*i.e.*, $P_i(e_i/H_6) > P_i(e_i/H_5)$), where "$e_i$" refers to the result of test *i*, and "P_i" refers to the personal probability function held by members of Avery's team right before updating by e_i).

Let me focus now on the way Avery, MacLeod or McCarty could have assessed the epistemic virtuosity of the hypotheses at stake. To a large extent, this depends on which statements were in each agent's set of full beliefs at the moment of evaluating virtues; I think it is safe to assume that the relevant portions of Avery, MacLeod or McCarty's belief set (for the present context) did not differ significantly from one another. Consider, first, which elements of E_A might have ranked best at unification power. In principle, many different hypotheses can enhance unification, albeit in very different senses. For example, stating that the transforming principle is a polysaccharide may lead to a picture in which the generating substance and that which is generated (a type-specific capsule in pneumococci) are chemically alike; stating that it is a protein, on the other hand, matches well with the importance attributed to proteins in the early forties. As there is not a clear winner, let me turn to the one which ranks definitely worst. H_5 is a clear candidate for this: it refers to two substances rather than one, it does not take tests at face value (the additional reference to proteins in addition to DNA does not seem to play any explanatory role, as far as Avery, MacLeod or McCarty are concerned) and, in general, it presents a more complex picture of bacterial transformation.[17]

Similar considerations indicate that H_5 ranked worst at testability and economy, from Avery's team's point of view, insofar as it was uncertain how to test the presence of substances that could not be detected by state-of-the-art techniques. As for fertility,

[17] This analysis, however, might not hold for other researchers: my claim that there is no overall unification gain in accepting complex hypotheses such as H_5 might not be true if the prior set of full beliefs were somewhat different, as we shall see.

H_6 was, as a matter of fact, the only hypothesis that led Avery, McCarty and (later) Hotchkiss to design a clear path of future research.

In short, there was at least one virtue at which H_6 did better than any other hypothesis (namely, fertility), and quite a number of other virtues at which its most important rival (to wit, H_5 – Mirsky's favorite candidate) did worse.

Let me show now how to integrate these elements so as to produce a comprehensive explanation of particular epistemic attitudes. Consider first McCarty's behavior. I have suggested that McCarty's personal probability for H_6 was larger than that of its rivals. But notice that, by itself, this fact does not constitute sufficient reason to say that he was justified in believing it. By way of illustration, if all McCarty cared about was to avoid importing error into his belief set, then the best option for him would have been to suspend judgment. However, as a matter of fact, researchers also care about enhancing their understanding of the world – or else no research project would ever get off the ground. In McCarty's case, we can provide a rationale for his epistemic attitude towards H_6 by taking simultaneously into account his evaluation of how probable H_6 was, as well as his assessment of H_6's overall virtuosity (to the best of our knowledge) – in short, by taking into account McCarty's assessment of H_6's overall explanatory force. On the basis of such considerations, it seems reasonable to postulate the existence of an appropriate epistemic utility function $f_A(\text{Virtue}_1(H_i),\ldots, \text{Virtue}_j(H_i))$, such that $EEU(H_i) = P_A(H_i)f_A(H_i)$ was maximum for H_6, and such that $EEU(H_6)$ was above McCarty's particular caution threshold.

How shall we explain *Avery's* epistemic behavior, then? According to the present analysis, it seems reasonable to say that $EEU(H_6)$ was maximum for Avery as well – however, we might also conjecture that his acceptance threshold was just stricter than McCarty's. In what sense – if at all – can we then assert that he was being overly cautious? I take it that such a claim should be understood as conveying a *relative* sense of caution – relative to the speaker's own boldness; in other words, I suggest that, within the present analysis, claims to the effect that Avery was excessively prudent should be taken to mean that, had the speaker been in Avery's shoes – and had the speaker shared Avery's assessment of H_6's expected epistemic utility – she would have had a higher acceptance threshold.[18]

9. In search of a suitable explanation (II): Mirsky's case

As we have seen, it is safe to assume that Mirsky was, at the very least, still skeptic about H_6 by 1952. In addition, we can also assume that Mirsky had already rejected H_1-H_4 by the late forties; recall that, as early as in 1946 he stated explicitly that the two serious options were H_5 and H_6.[19] So let Mirsky's set of basic explanations be $E_M=\{H_5, H_6\}$.

Consider now the IBE process that might have taken place on the basis of E_M. Why did H_5 "survive" for Mirsky by the early fifties, and not for Chargaff, Boivin, or

[18] The problem of whether there is any "objective," or "absolute" sense of caution is indeed an interesting one (can we ever say that some caution indices are just too high to be rationally admissible?) but well beyond the scope of this paper.

[19] "[I]t is not yet known which the transforming agent is – a nucleic acid or a nucleoprotein." (Mirsky & Pollister, 1946, p. 135).

Avery's team, to mention a few? To address this question, let me start by conjecturing Mirsky's personal probability function by that time, or P_M.

Notice that right after 1944 we could expect that Mirsky takes H_5 to be more probable than H_6. Whatever might have been the evidence that led him to endorse Levene's hypothesis in the past (and the lack of specificity of nucleic acids), it could also count as evidence in favor of H_5 and against H_6 – even if Levene's hypothesis were no longer in Mirsky's belief set. To this we should add a possible lack of confidence in Avery's biochemical skills, which might have led him to question the significance of Avery's results.

In the light of the above, we might be tempted to say that acceptance of H_6 occurred as soon as new evidence in favor of H_6 came in. In this sense, we could interpret Mirsky's statements in (1973) (*cf*. page 26 above) as expressing that, once he got acquainted with Hotchkiss's results in (1952), the probability of H_6 became sufficiently high so as to justify acceptance. I believe, however, that this reconstruction is misleading, for it omits part of the story. Let me explain why.

To begin with, recall that by July of 1948 Hotchkiss had already presented the crucial findings that would constitute the core of his (1952) paper – namely, that the ratio of contamination of the transforming principle with protein was less than 0.02% (Hotchkiss, 1952; *cf*. Hotchkiss, 1949). Even assuming that Mirsky had not heard about Hotchkiss's research until 1952 – and even disregarding Boivin's 1947 report at the Cold Spring Harbor Symposium on *Escherichia coli* (which could not be confirmed by other laboratories) – many other relevant results were obtained during those years. Consider, in the first place, McCarty and Avery's papers in 1946

(McCarty & Avery, 1946a,b), which showed that minute amounts of purified DNase inactivated the transforming agent, that a fivefold greater yield of purified transforming agent could be obtained by inhibiting the action of DNase with citrate, and that the transforming substance of types II and IV behaved just as that of type III. We should also count a number of crucial tests on the relation between genes and DNA, such as Boivin et al. (1948), as well as Mirsky's own studies with Hans Ris in (1949, which showed that the amount of DNA in diploids cells doubled that of haploids cells (Mirsky & Ris, 1949). Let me also add to the list Chargaff's (1950) famous paper stating that the amount of DNA varied with the species but always preserving certain base ratios, and, finally, Hershey and Chase's (1952) article showing that only the DNA of phages entered the bacterial cell at the time of infection, whereas the phage coat was left outside.

Notice that, by mere Bayesian updating, the probability that the transforming agent was DNA increased with each of the tests; the probability that it was a combination of DNA plus protein, on the other hand, increased as well, but not as much. Granted, many of the aforementioned findings on genes and DNA did not make explicit connections with prior experiments on bacterial transformation; however, once we couple such results with Mirsky's early understanding of transformation as a type of *genetic* phenomenon – which, as we have seen, he was proud to acknowledge – then the conclusion should be that they boosted H_6's prior more than that of H_5. Thus, $P_M(H_6/e_i)–P_M(H_6) > P_M(H_5/e_i)–P_M(H_5)$, where e_i refers, in each case, to the evidence provided by the successive tests just mentioned. In short, even though we cannot *guarantee* that Mirsky already held $P_M(H_6) > P_M(H_5)$ by the late forties – this might not have been the case if the initial difference between $P_M(H_6)$ and $P_M(H_5)$ had been very large – this is indeed quite a plausible statement. (Of course, the later the time we consider, the more likely that H_6 obtains greater probability.)

Let me turn now to a possible reconstruction of Mirsky's assessment of how virtuous each of the two hypotheses really was, comparatively speaking. Consider first how each of them ranked with respect to unification power. As I have already mentioned, the extent to which a given hypothesis can be seen to enhance the unification of a particular belief corpus depends, among other things, on the prior contents of that corpus. Thus, in the previous section I have contented that, from Avery and McCarty's point of view, H_5 hinted at a more complex picture of bacterial transformation, and hence it should rank worst as far as unification power goes. Clearly, this is not the case for Mirsky. Mirsky had devoted a large portion of his career so far to the study of the behavior of proteins, and, in particular, since the early forties he concentrated on *nucleoproteins* (*cf*. for instance Cohen 1998). If there was somebody convinced of the subtleties proteins were able to display, it was him. Accordingly, we should expect his set of full beliefs K_M to differ from Avery's or McCarty's in many crucial ways. In Mirsky's case, the apparent complication of referring to two substances rather than one (as responsible of the transformation) can be outweighed by the fact that, by doing so, H_5 helped Mirsky make a coherent picture out of the received view on proteins and nucleic acids, together with the new findings. In the light of this, it is reasonable to think that, for Mirsky, only H_5 carried maximum value for unification power.

On the other hand, Mirsky might have taken H_6 to be the most testable and economical, for reasons analogous to those already advanced in connection with McCarty's IBE: namely, that it was uncertain how to test the presence of substances that could not be detected by state-of-the-art techniques. In addition, H_5 and H_6 might have been perceived as equally accurate, in the sense that none of them described the chemical composition of the transformation phenomenon at a substantively greater level of detail.

Based on these considerations, we can conjecture that Mirsky proceeds as if there exists some epistemic utility function f_M, according to which unification power is given more weight than other virtues, and which yields that $EEU(H_i) = P_M(H_i)f_M(H_i)$ is tied for H_5 and H_6 – *even under the assumption that* $P_M(H_6) > P_M(H_5)$.

10. Conclusions

I hope to have shown that the model sketched in Section 3 can be successfully used to clarify a number of misunderstandings about Avery's attitude towards his own research, as well as about the early reaction of the scientific community to the 1944 article. By being sensitive to the structure of questions and explanatory answers presupposed in Avery's case, the model helped us identify in what sense (if any) we can say that Avery was overly cautious, and why. In addition, by being sensitive to the structure of personal probabilities and epistemic virtues of different agents, the model helped us understand why it was rational for both Mirsky and McCarty to proceed the way they did, in spite of the fact that McCarty was an early supporter of the hypothesis that the pneumococcal transforming principle was DNA, whereas Mirsky was reluctant to accept it as late as in the early fifties.

As I can see it, the proposal sketched in this paper has clear advantages over other models of inquiry. To begin with, many rival accounts simply do not apply to our case study. Strict Hypothetico-Deductivism and Falsificationism are not adequate contenders, since all interesting rival hypotheses were actually compatible with the evidence. In addition, as revealed by many of the quotes from McCarty or Boivin (as stated in section 8) agents sometimes do accept, or come to believe, non-tautological statements, in the sense that they become truly convinced that such statements are true.[20] No model of research can properly represent this situation unless it allows that agents "detach" the conclusions of their non-deductive arguments and add them to their epistemic corpora. These considerations count against positions such as radical probabilism, as well as against traditional brands of Bayesianism, according to which we are only entitled to accept evidential statements, but not general hypotheses.

As for other models of IBE, some of them do not construe IBE as an acceptance rule at all, and hence, as with Bayesianism, they are unable to explain why it might have been rational for scientists to fully believe that the transforming principle was DNA. To mention a few well known examples, Day & Kinkaid (1994) conceive of IBE as a highly contextual principle that helps us obtain the relevant priors and likelihoods that feed Bayes's theorem at the time of calculating the posterior

[20] In this paper I have not distinguished between accepting a statement and fully believing it. For well known proposals that trade on this distinction, *cf*. van Fraassen (1989, 2002), Cohen (1992), Maher (1993), or Lehrer (2000). Other interesting suggestions can be found in Tuomela (2000), or Da Costa & French (2003). For an overview of the treatment this subject has received in the literature, see the articles in Engel (2000).

probability of hypotheses, via Bayesian conditionalization (see in particular ibid., pp. 285-286). Similarly, Okasha (2000) urges us to think of IBE as a rule that gives us "a way of determining priors and likelihoods" (ibid., p. 703). Finally, in Lipton's account (as presented in Lipton, 2004) we find once again an ambiguous stance towards the notion of IBE as an ampliative rule. Right after asserting that he takes IBE to deal with hypothesis acceptance, he points out that he will "leave the notion of acceptance to one side" in order to show that IBE and Bayesianism are actually compatible (ibid., p. 113). However, Lipton cannot show that this is indeed the case without betraying his own proposal. Clearly, if an agent ever comes to believe new (non-evidential) hypotheses, her so coming to believe them cannot be the result of conditionalizing on the evidence: a conception of IBE as a tool that puts conditionalization in motion is incompatible with a conception of IBE as an ampliative rule. Independently of this problem, I am not sure whether a Lipton-style approach could give us a fine-grained analysis as to why McCarty and Mirsky were entitled to carry out incompatible IBEs. Within Lipton's proposal, we could point out that the two scientists disagreed on which hypothesis was the "loveliest" – where the loveliest hypothesis, in his jargon, is the one that provides the most understanding (ibid., Ch. 4). But this is less informative than what we intuitively demand from an explanation of the fact that McCarty and Mirsky exhibited strikingly different epistemic attitudes.

As a final comment, let me address two possible sources of concern. In the first place, it could be objected that the present model is strictly individualistic, and hence that it is not sensitive to the way in which different groups of people interacted with each other.[21] Against this objection, it should be pointed out that, within the present framework, the epistemic state of an individual agent is allowed to change as a response to suggestions or evidence provided by her colleagues; hence the fabric of a particular belief state is in itself the result of an interactive process. In other words, the fact that we aim at reconstructing individual perspectives and decisions does not force us to eliminate references to social interaction. It is true, however, that the analysis proposed here did not focus on the evolution of the scientific community *as a whole*. But we can concede this and still claim that the model I favor constitutes exactly the type of proposal we need in order to deal with (1), (2) and (5) from section 2 – to wit, in order to clarify questions about Avery's caution, about the timing of acceptance of H_6 by particular scientists, or about the rationality of incompatible epistemic attitudes.

The second potential concern is related to the fact that the analysis I have just offered *assumed* all along that the attitudes of Avery, McCarty or Mirsk had a rational core. I believe the charitable procedure paid off, in the sense that it enabled us to obtain a richer mental picture of the case, from an epistemic point of view. It is worth stressing, however, that I do not think rational reconstructions are always desirable; I do not think that we should always attempt to provide explanations (for a given pattern of behavior) that grant the rationality of the agents involved. Indeed, nothing prevents us from using the given framework to actually distinguish rational from irrational epistemic attitudes. This is, of course, as it should be. No abstract model should ever force us to violate our basic intuitions as to whether a concrete case in the history of science is an instance of good, or not-so-good, epistemic behavior. Rationality is in the

[21] I want to thank an anonymous referee for putting forward this objection.

eye of the beholder, so to speak. All a model should do is be flexible enough so as to embody and refine our prior intuitions in the best possible terms – as well as tell us how to proceed when no clear intuitions are at stake. And, in this sense, the proposal suggested in Section 3 delivers just what we hoped to obtain.

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References

Alloway, J. L. (1932). The transformation in vitro of R pneumococci into S forms of different specific types by the use of filtered pneumococcus extracts. *Journal of Expermiental Medicine, 55*, 91-99.

Alloway, J. L. (1933). Further observations on the use of pneumococcus extracts in effecting transformation of type in vitro. *Journal of Experimental Medicine, 57*, 265-278.

Amsterdamka, O. (1993). From pneumonia to DNA: the research career of Oswald T. Avery. *Historical Studies in the Physical and Biological Sciences, 24*, 1-40.

Avery, O. T. (1947). Report of Dr. Avery (assisted by Drs. Hotchkiss, McCarty and Taylor). In *Report of the Director of the Hospital to the Corporation of the Rockefeller Institute for Medical Research* (pp. 126–136). 19 April. Sleepy Hollow, NY, Rockefeller Archive Center. (Available at http://profiles.nlm.nih.gov/CC/A/A/N/R/_/ccaanr.pdf)

Avery, O. T., & Heidelberg, M. (1923). Immunological relationships of cell constituents of pneumococcus. *Journal of Experimental Medicine, 38*, 81.

Avery, O. T., & Horsfall, F. L. (1943). Report of Drs. Avery and Horsfall: Study on the chemical nature of the substance inducing transformation of specific types of pneumococcus (Avery and McCarty). *Scientific Report to the Corporation and the Board of Scientific Directors of the Research Institute*, 31 (1942–1943), 143–175. Sleepy Hollow, NY, Rockefeller Archive Center. (Available at http://profiles.nlm.nih.gov/CC/A/A/D/S/_/ccaads.pdf)

Avery, O. T., MacLeod, C. M., & McCarty, M. (1959). Studies on the chemical nature of the substance inducing transformation of pneumococcal types: Induction of transformation by a deoxyribonucleic acid fraction isolated from pneumococcus type III. In J. A. Peters (Ed.), *Classic papers in genetics* (pp. 173–192). Englewood Cliffs, NJ: Prentice Hall. (First published in 1944, *Journal of Experimental Medicine*, 79, 137–158).

Beurton, P. J., Falk, R., & Rheinberger, H.-J. (Eds.). (2000). *The concept of the gene in development and evolution*. Cambridge: Cambridge University Press.

Bilgrami, A. (2000). Is Truth a Goal of Inquiry? Rorty and Davidson on Truth. In R. Brandon (Ed.), *Rorty and his critics* (pp. 242-261). Oxford: Blackwell.

Bilgrami, A. (2004). Skepticism and Pragmatism. In D. McManus (Ed.), *Wittgenstein and scepticism* (pp. 56-75). London: Routledge.

Boivin, A. (1947). Directed mutation in colon bacilli, by an inducing principle of deoxyribonucleic nature: Its meaning for the general biochemistry of heredity. *Cold Spring Harbor Symposium on Quantitative Biology*, 12, 7-17.

Boivin, A., Vendrely, R., & Vendrely, C. (1948). L'acide desoxyribonucleique du noyau cellulaire, depositaire des caractéres hereditaires; arguments d'ordre analytique. *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, 226, 1061-1063.

Burian, R. M. (1985). On conceptual change in biology: the case of the gene. In D. J. Depew, & B. H. Weber (Eds.), *Evolution at a crossroads: the new biology and the new philosophy of science* (pp. 21-42). Cambridge: The MIT Press.

Burnet, F. M. (1968). *Changing patterns: an atypical autobiography*. Melbourne: Heinemann.

Cairns, J., Stent, G., & Watson, J. (Eds.). (1966). *Phage and the origins of molecular biology*. Cold Spring Harbor, Long Island: Cold Spring Harbor Laboratory of Molecular Biology.

Carlson, E. A. (1989). *The gene: a critical history*. Ames, Iowa: Iowa State University Press. (First published 1966)

Chadwick, J. (1932). Possible existence of a neutron. *Nature*, *129*, 312.

Chargaff, E. (1950). Chemical specificity of nucleic acids and mechanism of their enzymatic degradation. *Experientia*, *6*, 201–240.

Chargaff, E. (1978). *Heraclitean fire: sketches from a life before nature.* New York: The Rockefeller University Press.

Chargaff, E. (1979). How genetics got a chemical education. *Annals of the New York Academy of Sciences*, *325*, 345-360.

Cohen, J. (1992). *An essay on belief and acceptance.* Oxford: Clarendon Press.

Cohen, S. S. (1998). Alfred Ezra Mirsky. *Biographical memoirs*. *National Academy of Sciences*, *73*, 322-332.

Cresto, E. (2006). *Inferring to the best explanation: a decision-theoretic approach*. Ph.D. thesis, Columbia University, New York.

Da Costa, N. C. A., & French, S. (2003). *Science and partial truth: A unitary approach to models and scientific reasoning*. New York: Oxford University Press.

Dawes, H. (2004). The quiet revolution. *Current Biology, 14*, R605-R607.

Dawson, M. H., & Sia, R. H. P. (1931). In vitro transformation of pneumococcal types. I. A technique for inducing transformation of pneumococcal types in vitro. *Journal of Experimental Medicine*, *54*, 681-700.

Day, T., & Kincaid, H. (1994). Putting inference to the best explanation in its place. *Synthèse*, *98*, 271-295.

Deichmann, U. (2004). Early responses to Avery *et al.*'s paper on DNA as hereditary material. *Historical Studies in the Physical and Biological Sciences*, *34*, 207-232.

Diamond, A. (1982). Avery's 'neurotic reluctance'. *Perspectives in Biology and Medicine, 26,* 132-136.

Dubos, R. J. (1976). *The Professor, the institute and DNA.* New York: The Rockefeller University Press.

Engel, P. (Ed.) (2000). *Believing and accepting*. Dordrecht: Kluwer.

Fleming, D. (1968). Emigré physicists and the biological revolution. *Perspectives in American History, 2*, 152-189.

Fuhrmann, A. (1997). *An essay on contraction*. Stanford, CA: Center for the Study of Language and Information.

Griffith, F. (1928). The significance of pneumococcal types. *Journal of Hygiene, 27*, 113-159.

Heidelberg, M., & Avery, O. T. (1923). The soluble specific substance of pneumococcus. *Journal of Experimental Medicine, 40*, 301.

Hershey, A. D., & Chase, M. (1952). Independent functions of viral protein and nucleic acid in growth of bacteriophage. *Journal of General Physiology*, 36, 39-56.

Hotchkiss, R. (1949). Études chimiques sur le facteur transformant du pneumocoque. In Centre National de la Recherche Scientifique, *Unités biologiques douées de continuité génétique. Paris, Juin–Juillet 1948* (pp. 57–65). Colloques Internationaux du C. N. R. S., 8. Paris: Centre National de la Recherche Scientifique.

Hotchkiss, R. (1952). The role of desoxyribonucleates in bacterial transformation. In W. D. McElroy, & B. Glass (Eds.), *Phosphorus metabolism. A symposium on the role of phosphorus in the metabolism of plants and animals*, vol. II (pp. 426-439). Baltimore: John Hopkins Press.

Hotchkiss, R. (1965). Oswald T. Avery. *Genetics, 51*, 1-10.

Hotchkiss, R. (1966). Gene, transforming principle and DNA. In J. Cairns, G. S. Stent, & J. D. Watson (Eds.), *Phage and the origins of molecular biology* (pp. 180-200). Cold Spring Harbor, Long Island: Cold Spring Harbor Laboratory of Molecular Biology.

Hotchkiss, R. (1979). The identification of nucleic acid as genetic determinants. *Annals of the New York Academy of Sciences, 325*, 321-342.

Judson, H. (1980). Reflections on the historiography of molecular biology. *Minerva, 18,* 369-421.

Judson, H. (1996). *The eighth day of creation: the makers of the revolution in biology*. New York: Simon & Schuster. (First published 1978)

Kitcher, P. (1982). Genes. *British Journal for the Philosophy of Science, 33*, 337-359.

Kitcher, P. (1984). 1953 and all that: a tale of two sciences. Reprinted in P. Kitcher (2003), *In Mendel’s mirror: philosophical reflections on biology* (pp. 3-30). New York: Oxford University Press.

Kitcher, P. (1992). Gene: current usages. In E. Keller, & E. Lloyd (Eds.), *Keywords in evolutionary biology* (pp. 128-131). Cambridge, Mass.: Harvard University Press.

Kuhn, T. (1962). *The structure of scientific revolutions*. (2nd ed.). Chicago: University of Chicago Press. (First published 1962).

Lederberg, J. (1972). Reply to H.V. Wyatt. *Nature*, 239, 234.

Lederberg, J. (2000). The dawning of molecular genetics. *Trends in microbiology*, 8, 194-5.

Lederberg, J., & Tatum, E. L. (1946). Gene recombination in *Escherichia coli*. *Nature, 158*, 558.

Lehrer, K. (2000). *Theory of knowledge*. Boulder: Westview Press.

Levene, P., & Bass, L. W. (1931). *Nucleic acids*. American Chemical Society Monograph Series. New York: Chemical Catalog Company.

Levi, I. (1980). *The enterprise of knowledge*. Cambridge, Mass: The MIT Press.

Levi, I. (1984). *Decisions and revisions*. Cambridge: Cambridge University Press.

Levi, I. (1994). How to fix a prior. In D. Prawitz, & D. Westerstahl (Eds.), *Logic and philosophy of science in Uppsala* (pp. 185-204). Dordrecht: Kluwer.

Levi, I. (1997). *The covenant of reason*. Cambridge: Cambridge University Press.

Lipton, P. (2004). *Inference to the best explanation* (2nd ed.). London: Routledge. (First published 1991)

Luria, S. E., & Delbrück, M. (1943). Mutations of bacteria from virus sensitivity to virus resistance. *Genetics, 28*, 491-511.

Maher, P. (1993). *Betting on theories*. Cambridge: Cambridge University Press.

Maienschein, J. (1992). Gene: historical perspectives. E. Keller, & E. Lloyd (Eds.), *Keywords in evolutionary biology* (pp. 122-127). Cambridge, Mass.: Harvard University Press.

McCarty, M. (1946). Chemical nature and biological specificity of the substance inducing transformation of pneumococcal types. *Bacteriological Reviews, 10*, 63-71.

McCarty, M. (1985). *The transforming principle: discovering that genes are made of DNA*. New York: Norton.

McCarty, M. (1994). A retrospective look: how we identified the pneumococcal transforming substance as DNA. *Journal of Experimental Medicine*, 179, 381-394.

McCarty, M., & Avery, O. T. (1946a). Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Part II: effect of the desoxyribonuclease on the biological activity of the transforming substance. *Journal of Experimental Medicine*, *83*, 89-96.

McCarty, M., & Avery, O. T. (1946b). Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Part III: an improved method for the isolation of the transforming substance and its application to the pneumoccocus types II, III and VI. *Journal of Experimental Medicine*, *83*, 97-104.

Mirsky, A. (1947). Chemical properties of isolated chromosomes. *Cold Spring Harbor Symposium on Quantitative Biology*, *12*, 143-146.

Mirsky, A. (1951). Some chemical aspects of the cell nucleus. In L. C. Dunn, *Genetics in the 20th century*: *essays on the progress of genetics during its first 50 years*. New York: Macmillan.

Mirsky, A. (1972). Letter to Joshua Lederberg. 31 October. Sleepy Hollow, NY, Rockefeller Archive Center. (Available at http://profiles.nlm.nih.gov/CC/A/A/H/P/_/ccaahp.pdf)

Mirsky, A. (1973). Letter to Jack S. Cohen. 29 June. Sleepy Hollow, NY, Rockefeller Archive Center. (Available at http://profiles.nlm.nih.gov/CC/A/A/H/R/_/ccaahr.pdf).

Mirsky, A., & Pollister, W. (1946). Chromosin, a desosyribose nucleoprotein complex of the cell nucleus. *Journal of General Physiology*, *30*, 117-148.

Mirsky, A., & Ris, H. (1949). Variable and constant components of chromosomes. *Nature*, *163*, 666-667.

Okasha, S. (2000). Van Fraassen's critique of inference to the best explanation. *Studies in History and Philosophy of Science*, *31*, 691-710.

Olby, R. (1990). The molecular revolution in biology. In R. C. Olby, G. N. Cantor, J. R. R. Christie, & M. J. S. Hodge (Eds.). *Companion to the history of modern science* (pp. 503-520). London: Routledge.

Olby, R. (1994). *The path to the double helix: the discovery of DNA* (2nd ed.). New York: Dover. (First published 1974)

Peirce, C. S. (1931-1958). In C. Harstshorne, P. Weiss, & A. Burks (Eds.). *Collected papers of Charles Sanders Peirce* (8 vols.) Cambridge, MA: Harvard University Press.

Perutz, M. (1994). Letter to Joshua Lederberg. 31 March. Sleepy Hollow, NY, Rockefeller Archive Center. (Available at http://profiles.nlm.nih.gov/CC/A/A/I/E/_/ccaaie.pdf)

Peters, J. A. (Ed.). (1959). *Classic papers in genetics*. Englewood Cliffs, N.J.: Prentice-Hall.

Pollock, M. (1970). The discovery of DNA: an ironic tale of chance, prejudice and insight. *Journal of General Microbiology*, *63*, 1-20.

Russell, N. (1988). Oswald Avery and the origin of molecular biology. *British Journal for the History of Science*, *21*, 393-400.

Shimony, A. (1970). Scientific inference. Reprinted in A. Shimony (1993), *Search for a Naturalistic World View. Vol. I: Scientific Method and Epistemology* (pp. 183-273). Cambridge: Cambridge University Press.

Stent, G. S. (1972). Prematurity and uniqueness in scientific discovery. *Scientific American*, *227*, 84-93.

Toulmin, S. (1972). *Human understanding* (Vol. 1). Princeton, N. J.: Princeton University Press.

Tuomela, R. (2000). Belief versus Acceptance. *Philosophical Explorations*, 2, 22-157.

Van Fraassen, B. (1989). *Laws and symmetry*. Oxford: Clarendon Press.

Van Fraassen, B. (2002). *The empirical stance*. New Haven: Yale University Press.

Watson, J., & Berry, A. (2003). *DNA: the secret of life*. New York: Alfred A. Knopf.

Wyatt, V. (1972). When does information become knowledge? *Nature*, *235*, 86-89.