**Presume It Not: True Causes in the Search for the Basis of Heredity**

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**Abstract**

Kyle Stanford has recently given substance to the problem of unconceived alternatives, which challenges the reliability of inference to the best explanation (IBE) in remote domains of nature. Conjoined with the view that IBE is the central inferential tool at our disposal in investigating these domains, the problem of unconceived alternatives leads to scientific anti-realism. We argue that, at least within the biological community, scientists are now and have long been aware of the dangers of IBE. We re-analyze the nineteenth-century study of inheritance and development (Stanford's case study) and extend it into the twentieth century, focusing in particular on both classical Mendelian genetics and the studies by Avery et al. on the chemical nature of the hereditary substance. Our extended case studies show the preference of the biological community for a different methodological standard: the *vera causa* ideal, which requires that purported causes be shown on non-explanatory grounds to exist and be competent to produce their effects. On this basis, we defend a prospective realism about the biological sciences.

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My subject's
still the wind still
difficult to
present
being invisible:
nevertheless should I
presume it not
I'd be compelled
to say
how the honeysuckle bushlimbs
wave themselves:
difficult
beyond presumption

– *A. R. Ammons*

**1. Introduction**

The most bracing recent challenge to scientific realism is Kyle Stanford's ([2006]) problem of unconceived alternatives. Stanford argues that many scientific inferences are eliminative, that eliminative inferences are reliable only when all competing hypotheses have been considered, and that we have good reason to believe that there exist unconceived alternatives to our best current theories. Thus we should not accept our best current theories as true.

Stanford and his critics agree that eliminative inference, especially in the form of inference to the best explanation (IBE), is 'the central inferential tool of scientific inquiry' (Stanford [2006], p. 30). His critics try to save eliminative inference from the problem of unconceived alternatives. For instance, they argue that features of present-day scientific communities reduce the chance that serious alternatives will go unconsidered (Godfrey-Smith [2008]; Ruhmkorff [2011]; Dellsén [2016]). Both parties resemble Ammons in our epigraph: concerned that IBE is presumptuous, convinced that it is ineluctable.

We proceed differently. Stanford's criticisms of IBE are compelling. However, the biological community has long recognized that IBE is problematic and has adopted a different standard of reasoning (the '*vera causa* ideal') that mitigates the problem of unconceived alternatives. On this basis, we defend a form of scientific realism about the biological sciences. This realism is

prospective (realism's 'holy grail'; Vickers [2013]): it identifies which scientific claims are worthy of realist commitment without relying on hindsight.

We defend these views by weaving together reconsideration and extension of Stanford's analysis of theories of heredity (Sections 3 and 5) with more abstract discussion of the *vera causa* ideal and its implications for scientific realism (Sections 2, 4, 6 and 7).

**2. Stanford on Unconceived Alternatives**

For Stanford, the history of science reveals a pattern of *recurrent transient underdetermination*. Underdetermination: the evidence available at a given time supports multiple hypotheses roughly equally well. Transient: the competing hypotheses are not empirically equivalent; further evidence may favor one over the other. Recurrent: transient underdetermination besets each member of a succession of theories within a domain. We add: unrecognized. In the cases Stanford considers, scientists relied on eliminative inference to favor a hypothesis without recognizing that they were subject to underdetermination, because they failed to conceive of the relevant alternatives.

The problem of unconceived alternatives is an historically substantiated version of the 'argument from the bad lot' (van Fraassen [1989]). IBE proceeds in three steps: scientists develop a set of hypotheses, rank them by their explanatory power, then infer the likely truth of the highest-ranked hypothesis (Lipton [2004]). For IBE to lead to the acceptance of an approximately true hypothesis, such an hypothesis must be in the set initially considered. If superior, unconceived alternatives exist, IBE will select the best of a bad lot. Stanford shows on historical grounds that scientists frequently fail to consider alternative hypotheses that could account for the evidence available at a given time. If eliminative inference is rampant in science, this leads to a widely applicable anti-realism.

Stanford takes the problem of unconceived alternatives to be most acute when dealing with 'remote or inaccessible domains of nature' ([2006], p. 32). Remoteness for him is relative to human perceptual capabilities. Domains may be remote because they contain entities that are too small,

or processes that occur too quickly or slowly, or that are too far away, and so forth. Remoteness comes in degrees: an amoeba is less remote than a quark, a dinosaur less remote than a pre-Cambrian metazoan. The remoter the domain, the more vulnerable we are to the problem of unconceived alternatives.

Unlike the pessimistic meta-induction, which uses the failure of past successful theories to induce doubt about our current theories, Stanford's argument concerns the cognitive capacities of theorists. Though current theories are more successful than past theories, current theorists are as limited as past theorists. Moreover, present-day scientists continue to rely on eliminative inferences to support theories about remote domains. Our current theories are thus vulnerable to the problem of unconceived alternatives, and so we should be anti-realists.

Rather than defend IBE, we aim to show that, at least in biology, IBE is as problematic as Stanford suggests—*and biological practice respects this*. Where possible, biologists avoid IBE. Where impossible, they are modest in their claims. Such, at least, is the ideal, however imperfectly it is realized in any given case (see Section 7).

**3. Pangenesis: A Re-Analysis**

According to Stanford ([2006], ch. 3), Darwin's hypothesis of pangenesis was accepted because of its explanatory power, even though there existed superior but unconceived alternatives. However, while Darwin may have accepted pangenesis, this is not true for the broader biological community. The reaction to pangenesis was negative, even among those who supported Darwin's evolutionary theory. A recurring theme of critics was that the *vera causa* ideal had not been met.

Darwin proposed his 'provisional hypothesis of pangenesis' at the end of the second volume of *The Variation of Animal and Plants under Domestication* ([1875], ch. 27). On this hypothesis, each cell of the body throws off gemmules, which circulate through the body and multiply by division. They aggregate in the sexual elements, where they are transmitted to offspring in a dormant state. In the offspring, activated gemmules direct orderly growth. Pangenesis accounted for the

phenomena of heredity that Darwin considered most important: the transmission of gemmules explains parent-offspring resemblance; their circulation and aggregation explains the inheritance of acquired characters; their attraction to the site of amputation explains the re-growth of limbs; and their ability to remain dormant for multiple generations explains reversion to ancestral states.

However, Darwin failed to conceive of 'common cause' alternatives to pangenesis. In 'linear' theories like pangenesis, the somatic cells and tissues of one generation cause (by some intermediate mechanism) the properties of the somatic cells and tissues of the next generation. In common cause theories (including modern genetics), characteristics shared between the generations are due to shared genetic material. Darwin failed to grasp that common cause alternatives were serious contenders with explanatory power equal to that of linear pangenesis, even when Francis Galton presented such a theory.

Despite publicly calling pangenesis a mere 'provisional hypothesis,' Darwin maintained great private confidence in it. His correspondence reveals his commitment to the theory's truth:

> You will think me very self-sufficient, when I declare that I feel sure if Pangenesis is now stillborn it will, thank God, at some future time reappear, begotten by some other father, and christened by some other name. (Darwin to Hooker, 23 February 1868)[2]

Stanford's evidence that Darwin was convinced of his hypothesis is compelling, and he is right that Darwin failed to recognize the threat of unconceived alternatives. But the key question for the realism debate is not whether individual scientists are fallible, but whether the community as a whole fails to recognize problematic hypotheses. We argue that the biological community adheres to a standard (the *vera causa* ideal) that mitigates the problem of unconceived

[2] See also Darwin to Hooker, 28 February 1868, and Darwin to Ogle, 28 February 1868.

alternatives.[3] Darwin's contemporaries quickly recognized that pangenesis did not meet that standard.

Darwin's reference to the 'stillbirth' of his theory attests to his contemporaries' dissatisfaction. Because its primary support was its explanatory power, they were unwilling to take it as anything more than a how-possibly account of the mechanism of heredity.

A representative author is George Henry Lewes, who made 'many good criticisms in a perfectly fair spirit' (Darwin [1875], p. 350). Following a largely positive discussion of Darwin's various theories, especially natural selection, Lewes ([1868]) ended with a critique of pangenesis. He granted the theory's power to explain the phenomena of heredity and development:

> [Pangenesis] is advanced only as a provisional conception grouping together a multitude of facts, and, as such, it will be generally admitted to surpass all previous attempts in the same direction. (p. 503)

However, Lewes argued that explanatory power is insufficient confirmation of a hypothesis. Whereas natural selection was a 'true cause' (p. 372) and 'simply the introduction of one inference in a series of facts' (p. 507), pangenesis was 'hypothetical throughout' (p. 507). For Lewes, natural selection was based on demonstrable facts about variation and the struggle for existence. Explanatory power only entered when Darwin argued that selection is responsible for most transformations in evolutionary history—that was the 'one inference.'

Pangenesis rested on less secure foundations.[4] '[A]ll its elements are inferences,' wrote Lewes, 'not one of them can be admitted as proven' (p. 507). There was no evidence that gemmules

[3] This is distinct from the argument that the structure of contemporary scientific communities mitigates the problem of unconceived alternatives (cf. Godfrey-Smith [2008]; Ruhmkorff [2011]; Dellsén [2016]; see Stanford [2015] for a rejoinder). That argument is compatible with ours: where both arguments apply, communities will be double-buffered against Stanford's problem.

[4] Was Darwin's methodological thinking consistent? His arguments for evolution by natural selection adhere to the *vera causa* ideal, while in the case of pangenesis he relied on explanatory power. Ruse ([1975]) argued that this reflects a shift in Darwin's thinking: over time he began to consider explanatory power sufficient warrant for an hypothesis. Hodge ([2008], XI, especially footnote 21) has objected that the tension

existed or that they had the many specific properties required for the overall hypothesis to work. Gemmules needed to be shed by all the parts of cells, to circulate without decomposition, and to multiply by self-division. Lewes saw no problem in framing hypotheses: in view of its explanatory power, pangenesis was potentially a 'clue to great discoveries' (p. 508). However, he warned against the danger of forgetting the 'real nature' of the hypothesis, 'when instead of using it as a provisional mode of grouping together unexplained facts, we use it as an explanation' (p. 508).

The Italian botanist Federico Delpino voiced similar concerns (Delpino [1869a], [1869b]). In his critique, which Darwin described as the best he had seen (Darwin [1875], p. 350), Delpino was less charitable than Lewes with pangenesis as a how-possibly explanation. But his overall methodological worries matched Lewes' perfectly: he questioned whether the entities assumed by pangenesis had received non-explanatory support for their existence and causal properties. Darwin's attempts to provide such support by analogy left Delpino unconvinced. For instance, Darwin argued for the ability of gemmules to multiply by drawing an analogy to bacteria. Delpino found this 'repugnant to all analogy' (Delpino [1869b], p. 392), because it assigned to lifeless particles the same multiplicative capacity shown by living bacteria.

In concluding his critique, Delpino reiterated his criticism that 'everything proceeds by force of unknown elements':

> The existence of the gemmules is a first unknown element; the propagative affinity of the gemmules is a second; their germinative affinity a third; their multiplication by fission is a fourth — and what an unknown element! (p. 408)

is only apparent. Darwin used both *vera causa* and explanatory reasoning throughout, always taking explanatory reasoning to be the more tentative. We cannot here adjudicate this debate. We are content to note that, even in the case of pangenesis, Darwin (a) explicitly divided his explanatory from his non-explanatory reasoning and (b) presented pangenesis as a mere 'provisional' hypothesis. Whatever his private beliefs, he recognized the sway the ideal held among his peers.

This quote reveals methodological agreement across the chasm between nineteenth-century physicalists (Lewes) and vitalists (Delpino). Both believed that explanatory power provides insufficient warrant for claims concerning the existence or the properties of the entities invoked by a hypothesis. This is the negative aspect of the *vera causa* ideal (Section 4). Together with its positive aspect (Sections 5–6), the *vera causa* ideal constitutes an important methodological standard in biological science. We submit that it has been widely influential in the thinking of life scientists in both the nineteenth and twentieth centuries. Where operative, it has powerful implications for the debate about scientific realism (Section 7).

## 4. The *Vera Causa* Ideal I: Negative Aspect

In the case of pangenesis, we saw the biological community's reticence to accept a hypothesis supported only by its hypothetical explanatory power. Critics expected Darwin to show on independent grounds the reality of gemmules and of the properties he ascribed to them. Darwin failed to do so.

The expectation that one should establish the reality of one's posits on non-explanatory grounds is the heart of the *vera causa* ideal. The ideal traces back to Newton, was philosophically popularized by Thomas Reid in the eighteenth century, and was broadly influential in nineteenth-century science (Laudan [1981], ch. 7). M. J. S. Hodge ([1992]; 2008: IX), interpreting Herschel ([1831]), characterizes the *vera causa* ideal in terms of three epistemic tasks. Satisfying the ideal requires showing that a purported cause exists (*existence*), that it is competent to produce the relevant phenomena (*competence*), and that it is responsible for causing particular instances of those phenomena (*responsibility*).[5]

The *vera causa* ideal is a methodological standard concerning the evidence required to complete these tasks. However, we are not beholden to any particular historical articulation of

[5] This need not suggest a fixed temporal order of inquiry. Existence claims are often investigated only after a hypothetical entity has been proposed to be responsible for producing some phenomena.

the ideal. Our aim is to extract, from the methodological practice of biologists, a general form of the ideal, both true to the spirit of this tradition and relevant to contemporary science.

The *vera causa* ideal has positive and negative components. The negative component is the skepticism of IBE that Lewes and Delpino shared. An explanation invokes a *vera causa* only when there is non-explanatory support for the existence of the purported cause and its purported causal properties. If our only justification for believing that some cause exists is its hypothetical explanatory power, it is not a true cause. From our reanalysis of the case of pangenesis, we have revealed a shared commitment to the negative component of the ideal. This leaves open what can establish the existence, competence and responsibility of an entity or process. An answer to that question constitutes the positive side of the ideal, which will come into focus later (Sections 5–6).

The *vera causa* ideal demands that existence and competence claims be supported by non-explanatory reasoning. However, once the existence and competence of a particular cause is established, explanatory considerations may license inferring that it is *responsible* for causing some particular phenomenon. What the *vera causa* ideal forbids is reliance on IBE to establish the cause's existence and competence in the first place. Existence and competence claims supported by IBE should be treated as provisional (pursuit-worthy but not belief-worthy)—just as Lewes treated pangenesis.

The negative component of the *vera causa* ideal cannot be assimilated into an IBE framework. One might read Lewes and Delpino as criticizing pangenesis for reliance on *ad hoc* hypotheses (each causal power of gemmules was invoked to explain one particular hereditary phenomenon) and for being disunified (each causal power of gemmules could exist or fail to exist independently of the others). These are traditionally considered explanatory vices, so perhaps Lewes and Delpino were merely complaining that pangenesis was a bad explanation.

This interpretation mischaracterizes both our proposal and Lewes' and Delpino's criticism. Though the *vera causa* ideal shares with IBE an aversion to *ad hoc* hypotheses, it does not consider reliance on such hypotheses an *explanatory* vice. Lewes and Delpino criticized pangenesis because its assumptions lacked support beyond their explanatory power. If such support for Darwin's

assumptions could be provided, gemmules would simply be accepted to exist and to have those causal powers that could be demonstrated, without relying on IBE at all. Similarly, the disunity of these causal powers, once gemmules had been shown to possess them, would provide no barrier to invoking them in explaining heredity. Disunity is not intrinsically problematic.

The negative component of the *vera causa* ideal limits the scope of Stanford's challenge to scientific realism. Though IBE really is unreliable in the way that he isolates, fewer theories than commonly assumed are supported by IBE. Thus the extent of the anti-realism supported by Stanford's arguments may be roughly coextensive with the class of biological hypotheses toward which biologists are already anti-realist. Note: we do not take the descriptive fact that biological practice adheres to the negative aspect of the *vera causa* ideal to justify the normative claim that it is good to do so. What makes it good to adhere to this ideal is precisely the vulnerability of IBE to unconceived alternatives.

This response to Stanford is only partial. It undermines his argument for anti-realism without thereby supporting a realist alternative. Biologists' standards for accepting claims, although different from IBE, may nonetheless be vulnerable to the problem of unconceived alternatives. To defend realism, we must show that the positive aspect of the *vera causa* ideal allows biologists to mitigate the problem of unconceived alternatives. We now turn to that task, looking first at a concrete case (Section 5), then characterizing the positive aspect more abstractly (Section 6).

**5. Rendering Heredity Accessible**

Here, we trace theorizing on heredity into the twentieth century, showing how the speculative hypotheses of the nineteenth century were succeeded by hypotheses that increasingly met the *vera causa* ideal. After the rediscovery of Mendel's rules, geneticists established that independently assorting germinal differences caused hereditary differences. They then localized these germinal differences to chromosomes. Finally, biochemical research decomposed chromosome components, demonstrating that heritable traits were transmitted by nucleic acids.

Like Lewes and Delpino, classical geneticists condemned late nineteenth century theories of heredity on methodological grounds. Here, for instance, is Arend Hagedoorn criticizing August Weismann's theory of the germ plasm:

> The hypothesis that these hereditary things are vital units, composed of protoplasm and capable of assimilation and growth, certainly fits the facts. But we ask more of a theory of heredity and evolution. A working-hypothesis, to be of any use as an instrument of research, must explain the facts in terms of what is already known. It is inadmissable [*sic*] to try to explain the facts of evolution and inheritance by the behaviour of living particles which have been invented simply to admit of this explanation. ([1911], p. 23)

By demanding that one 'explain the facts in terms of what is already known,' Hagedoorn rejects inferences to the existence or the properties of hypothetical entities based on their explanatory power. Entities invoked in an explanation must be known beforehand: explanatory power plays no role in establishing them.[6]

Thomas Hunt Morgan shared Hagedoorn's assessment. In *The Physical Basis of Heredity* ([1919]), he worried that theories of representative particles can account for anything 'if the theorizer is allowed to endow the particles with any and all the attributes that he wished to use in his explanation' (p. 235). Because nineteenth century theoreticians assigned arbitrary attributes to hereditary particles 'these views appear to-day highly speculative' (p. 235), even 'metaphysical' (Morgan [1934]).

Hagedoorn lucidly discussed the more reliable Mendelian reasoning. If we wish to understand the influence of two different sets of causes on a phenomenon, then '[o]nly if either one varies, the other remaining constant, can we get to know them separately' (p. 23). Such

[6] Hagedoorn appears to forbid all hypotheses that invoke unknown entities, in contrast to Lewes' praise of pangenesis as a fruitful working hypothesis. We side with Lewes.

difference-making information, which relates changes in a cause to changes in an effect against constant background conditions, meets a key part of the *vera causa* ideal: it demonstrates a cause's competence to produce an effect (cf. Woodward [2003]; and see Section 6).

Mendelian breeding experiments show how this standard can be approximated in practice. Hagedoorn considered the example of a breed of rabbits with long hair and white color. How can we infer that there exist separate germinal differences in these rabbits that cause long hair and white color, respectively, and that these are independently distributed to offspring? Why not assume that something about the overall physico-chemical constitution of the germ causes a breed to be simultaneously longhaired and white? Crossing experiments allowed the relevant causal factors to be teased apart in two steps. In the first step, the longhaired white rabbits are crossed with shorthaired colored ones, yielding a new generation which is shorthaired and colored. This enables an inference to the existence of a dominant germinal difference found only in the shorthaired and colors type (Hagedoorn [1911], p. 3).

In a second step, the offspring's hybrid germ cells must be examined further. However, no method existed for directly examining genetic factors: 'As yet, we can only recognize the presence of the inherited factor necessary for the production of a quality by the production of this quality. It is as yet impossible to find these things in the germcells themselves' (p. 3). We can, however, test the hybrid generation's germ cells against a known genetic background, one 'whose gametes are certainly void of that which produces colour and short hair, in this case to a long-haired white animal' (pp. 3–4). On mating the hybrids from the first crossing with the parental stock, we find that half the progeny is white and the other half is colored; that half the progeny is longhaired and the other half is shorthaired; and that these two traits are assorted independently of each other. Hagedoorn concluded:

> Through this analysis we get to know positively that for each of the two conditions, shorthairedness and colour, there must be inherited a separate causating [*sic*] agent, capable of independent transmission. (p. 4)

This marks an advance over the speculative mode of model-building. Mendelian geneticists detected germinal differences and demonstrated their effects in known genetic contexts. They were beginning to satisfy the *vera causa* ideal by providing direct evidence for the *existence* of independently transmitted germinal differences and their *competence* to produce particular phenotypic traits.

Crossing experiments were, however, known to be limited: germinal constituents were detected on the basis of expressed traits, and the effects of these constituents could only be tested in crossing experiments rather than by more surgical intervention. As Morgan put it, they licensed inferring the existence of independently segregating elements (genes), but not of 'any further attributes or localizations' ([1919], p. 237). In particular, they could not localize genes to chromosomes, or say anything about their chemical nature.

In the early twentieth century, microscopic observations suggested a parallel between the segregation of Mendelian factors and the segregation of chromosomes during meiosis. W. S. Sutton ([1902]) was able to identify and trace distinct pairs of chromosomes across successive cell divisions in the grasshopper *Brachystola magna*. Based on this work, Sutton ([1903]) proposed explanations for several salient Mendelian phenomena. Pairing and separation of maternal and paternal chromosomes during maturation divisions could explain the separation of maternal and paternal traits. Random distribution of maternal and paternal chromosomes to gametes could explain independent assortment.[7] Physical linkage of Mendelian factors on chromosomes could explain linked inheritance of traits. In retrospect, the explanatory power of the proposal seems overwhelming.

However, the chromosome theory was not accepted until many years later. In 1910, Morgan raised two pressing difficulties for the theory (pp. 466ff.). First, microscopic observations did not settle the question of whether chromosomes remained intact during meiotic alignment. If they

[7] Direct microscopic evidence for this assumption came with the work of Eleanor Carothers ([1913]; [1917]).

mixed, then how did the original genetic elements separate cleanly afterwards? Second, if the chromosomal theory was correct, one had to assume that many traits 'Mendelized' together. While some traits were correlated, Morgan saw no evidence that the groups of traits that Mendelized together were 'commensurate with the number of chromosomes' (p. 468).

Morgan began to take the chromosome theory more seriously after Janssens ([1909]) published his observations of what we now call crossing-over: the exchange of segments between aligned homologous chromosomes.[8] Crossing-over could explain why genes co-localized on a chromosome were not always inherited together. It could also explain why sex-linked traits could be disassociated in the female gametes (where two X-chromosomes align during meiosis) but not in male gametes (whose X-chromosome lacks a homologue).

Despite its explanatory power, Morgan did not accept the chromosome theory outright. In 1915, in the preface to *The Mechanism of Mendelian Heredity*, though Morgan stressed that 'the chromosomes furnish exactly the kind of mechanism that the Mendelian laws call for' (Morgan et al. [1915], p. viii), he nevertheless conceded that '[e]xception may perhaps be taken' (p. viii) to the book's emphasis on chromosomes as the physical basis of heredity. In his view, the evidence was not yet definitive.

By this time, however, the Morgan group was publishing the clinching evidence for the chromosomal location of at least some Mendelian factors. This work, led by Calvin Bridges, concerned the phenomenon of non-disjunction. Ordinarily, sex-linked traits can show a criss-cross inheritance pattern (Morgan [1911]). Assume a locus on the X chromosome with two alleles: recessive *a* for white eyes and dominant *A* for red eyes. A homozygous *aa* female will have white eyes, while an *A* type male will have red eyes. If these are crossed, the next generation will normally consist of *Aa* females with red eyes and *a* males with white eyes. However, anomalies exist: the first offspring generation also contains a small proportion of white-eyed females and red-eyed males.

[8] On Morgan's 'conversion,' see Lederman ([1989]).

Bridges ([1913]) proposed the hypothesis of non-disjunction to explain these anomalies. He suggested that, during the maturation of germ cells, the female's X-chromosomes will occasionally fail to separate, producing one gamete with two X-chromosomes and one with none. Some offspring will thus receive two maternal and no paternal X-chromosomes, which results in a white-eyed female. Other offspring will receive only a paternal X-chromosome, which produces a red-eyed male. Thus non-disjunction can explain the deviations from the expected pattern of criss-cross inheritance.

The work on non-disjunction played an important role in convincing geneticists of the chromosome theory. In a thorough study of the theory's reception, Brush ([2002]) concluded that many cytologists and geneticists of the period cited non-disjunction as its 'most definitive proof' (p. 473). However, the importance of non-disjunction is puzzling on an IBE view. Why should the explanation of yet another phenomenon be exceptionally compelling? Brush considered whether non-disjunction convinced the community in virtue of being a successful novel prediction of the chromosome theory, but he found this inadequate. Although the prediction that cytological study would find XXY genotypes (two female X-chromosome and a male Y) was confirmed, contemporary practitioners were not especially swayed by this (Brush [2002], p. 517).

The *vera causa* approach, by contrast, illuminates why non-disjunction was treated as uniquely conclusive. Bridges saw non-disjunction as proof of the chromosomal theory:

> The genetic and cytological evidence in the case of non-disjunction *leaves no escape from the conclusion* that the X chromosomes are the carriers of the genes for the sex-linked characters. (Bridges [1916], p. 161, our emphasis)

While Bridges did not articulate the *vera causa* ideal explicitly, his discussion parallels the requirements of that standard. First, cytological observations allowed Bridges to detect the non-disjunctive distribution of chromosomes, establishing the *existence* of the putative cause. He found that gametes with two X-chromosomes existed, and that female exceptions from criss-cross

inheritance invariably had the XXY-genotype (see especially Bridges [1916], pp. 107–11). Bridges concluded:

> The distribution of sex-linked genes (as tested by experimental breeding methods) has been demonstrated to be identical […] with the distribution of the X chromosomes (as tested by direct cytological examination). (p. 161)

Thus, the microscope permitted the detection of the postulated cause.

Second, the work on non-disjunction demonstrated the *competence* of chromosomes to cause the expression of traits. Previous observations concerning the role of chromosomes in heredity had been plagued by the possibility of confounding. Microscopic studies seemed to show that the sperm contributed mainly the nuclear chromosomes in fertilization, but perhaps cytoplasmic factors were delivered as well (cf. Morgan et al. [1915], ch. 5). In non-disjunction, however, such confounders were under control. Bridges explained:

> The argument that the cell as a whole possesses the tendency to develop certain characters is completely nullified by the fact that in these cases the cells that produce exceptions are of exactly the same parentage as those which do not produce exceptions, *the only difference* being the parentage of a particular chromosome, the X. ([1916], p. 161, our emphasis)

Thus, the work on non-disjunction was unique in providing unconfounded difference-making data. Bridges described in detail the relevant contrasts:

> Those eggs which have lost nothing but the X chromosome have completely lost therewith the ability to produce any of the maternal sex-linked characters, and with the introduction of an X from the father these eggs have developed all of the

> sex-linked characters of the father. Conversely, those eggs which have retained both X's of the mother and have received no X from the father show all of the sex-linked characters of the mother and none from the father. (p. 161)

In effect, non-disjunction created a natural experiment. It produced fertilized zygotes which differed only in the presence or absence of particular X-chromosomes. Differences in chromosomes could thus be inferred to cause differences in expressed phenotypic traits.

With evidence of both existence and competence in place, non-disjunction demonstrated that chromosomes were *veræ causæ* of heritable traits. This demonstration did not rest on IBE. This fits with previous scholarship that de-emphasizes the role of explanatory reasoning in classical genetics. Waters ([2004]) argued against the view that classical geneticists aimed to extend the explanatory scope of a unifying theory of transmission genetics. Instead, geneticists were interested in investigating a broad range of biological phenomena for which they used transmission genetics as a tool. But expanding the core theory's explanatory scope was not a driving concern. Waters ([2004], p. 794) left it open whether individual experiments in genetics were best understood as IBEs. Later, Waters ([2007]) treated causation in classical genetics in terms of Woodward's ([2003]) interventionism, arguing that classical genetics was focused on finding *actual difference makers* in populations. This complements our *vera causa* account.

Despite the establishment of chromosomal variations as causes of phenotypic variations, the chemical composition of genes remained unknown. In his Nobel lecture, Morgan ([1934]) himself stressed that the findings of classical genetics were secure: genes could be localized to stretches of chromosomes. Different experimental techniques were required to uncover the genes' chemical nature.

To address this question, the development of a novel experimental system was crucial. Frederick Griffith, a British pathologist, reported in 1928 a series of experiments on pneumococci (today *Streptococcus pneumoniae*), a bacterial cause of pneumonia (Griffith [1928]). The bacterium occurs in both S (smooth) and R (rough) forms. The S form produces a polysaccharide capsule

which renders it pathogenic, whereas the R form does not produce a capsule and is harmless. Griffith reported in the *Journal of Hygiene* that he could transform the R into the S form by inoculating the live R form in mice, together with heat-killed bacteria of the S type. He speculated that the transformation occurred because of the transmission of a protein from the killed S to the live R form (p. 151).

Contrary to that expectation, Oswald T. Avery and collaborators published a report in 1944 identifying a desoxyribonucleic acid (DNA) fraction as the 'transforming principle': when isolated from the S form, it seemed competent to induce a heritable capsule in the R form (Avery, MacLeod and McCarty [1944]). But the results of the Avery group met with skepticism. Most researchers suspected that proteins were more likely to have the complexity necessary to determine hereditary traits.

The resulting uncertainty stimulated biologists to make their methodological standards explicit. One informative discussion is in a symposium contribution by Daniel Mazia ([1952]). In 1939, Mazia and Lucena Jaeger had shown that chromosome structure is preserved when treated with nucleases but not when treated with protein-digesting trypsin. This appeared to support the hypothesis that proteins were the key components of chromosomes. By 1952, however, Mazia favored the DNA hypothesis and proposed a criterion for its assessment:

> [W]e may set as the ultimate test the possibility of transferring [the genetic material] from one cell to another and obtaining the same results as when genes are introduced by genetic techniques. ([1952], p. 111)

As we would expect on the *vera causa* account, Mazia's 'ultimate test' asked for difference-making evidence for the competence of the suspected cause. The Avery group's data strongly suggested that the transforming principle was either DNA 'or so intimately associated with DNA that it cannot be separated from it by procedures considered to yield pure DNA' (p. 117). But Mazia ended on a cautious note:

> If we recall how poorly characterized are the chemical constituents of the nucleus and their associations, we will admit that we are scarcely in a position to formulate the alternatives, much less to propose that one of the known fractions is the genetic fraction. (pp. 117–8)

Mazia rightly feared unconceived alternatives. Much of the debate from the mid-1940s onward was concerned with showing that DNA had been purified sufficiently for its causal competence to be demonstrated and for such alternatives to be excluded.

Avery et al. had focused heavily on the details of DNA extraction. Was their DNA sufficiently pure, or were their results confounded by a protein contaminant? They addressed this concern in several ways. In 1946, McCarty and Avery showed that the transforming activity of the extract could be inactivated by desoxyribonuclease, which was known to destroy DNA but not protein (McCarty and Avery [1946a]). They effectively reversed the structure of the difference-making evidence: while completely pure DNA was unavailable, the extract's effects vanished when it was treated with an agent known to *destroy* DNA. The group moreover developed an improved extraction technique which gave higher yields (McCarty and Avery [1946b]). DNA extracts eventually contained no more than 0.02% of protein (Hotchkiss [1955]) while retaining the ability to transform pneumococci.

The follow-up work has broader conceptual significance. Technical improvements that increase purification or manipulability are central to advances in the life sciences because they permit the *vera causa* ideal to be approximated more closely. In particular, the demonstration of causal competence requires a putative cause to be changed surgically in order to avoid confounding (see Section 6).

Although many biologists were convinced by the 1950s, skeptics remained. These holdouts worried that even 0.02% of protein might suffice to transform bacteria. At a 1954 symposium, Rollin Hotchkiss, a member of Avery's lab, presented. In the subsequent discussion, Cooper

offered an ingenious alternative explanation of their results: perhaps the nucleic acids protect the proteins (Hotchkiss [1955], p. 18). Then, exposed to nuclease, the proteins lose their protection and are degraded.

Hotchkiss' response accused Cooper of philosophical skepticism, for similar objections could apply even to robustly established facts, such as the protein nature of enzymes:

> It has never been shown that there are not small amounts of unknown, undetected materials in enzymes that go along with the crystallizable proteins and are inactivated when the protein is damaged. (Hotchkiss [1955], p. 20)

Moreover, Hotchkiss argued that Cooper's hypothesis required an unusual protein that could be active in small amounts, but stable to heat and other disturbing factors—that is, an unknown type of entity with previously undocumented causal properties.

It may now seem as though we have gained nothing: even on the *vera causa* approach, unconceived alternatives remain. The real cause may not be DNA, but a substance closely associated with DNA; and DNA may not be the hereditary material, but merely protect it against degradation. However, although the problem of unconceived alternatives has not vanished, the remaining alternatives are much more narrowly circumscribed than before. They concern confounders and mediating mechanisms, which can be investigated further. A confounder would have to be localized in proximity to chromosomes and would have to parallel their movement. As discussed below, biologists quickly suggested novel methods for tracking down such alternatives. And although the determination of a causal relationship leaves open the question of its mediating mechanism, the causal relationship itself can be expected to remain stable even as our mechanistic ideas change. Extracted samples of DNA would still cause pneumococcal transformation even if the operative mediating mechanism were entirely beyond our ability to conceive. Thus, while the unconceived does not go away, in the *vera causa* account it is either methodologically tractable (since finding confounders is a routine part of scientific practice), or it

does not yield genuine alternatives (since multiple mechanisms are compatible with an established causal relationship).

In the course of inquiry, the remaining alternatives must be tested experimentally. Given the results presented by Hotchkiss and the worries expressed by Cooper, Sol Spiegelman suggested an experiment by which DNA could be further purified. In order to avoid spurious effects by trace amounts of protein, a radioactive tracer could be used to accurately detect the presence of protein and to isolate the putative cause more cleanly.[9] Explanatory considerations are valuable: postulating previously unknown kinds of proteins, as Cooper had done, does make an explanation worse. But to achieve justified beliefs, techniques needed to be refined until DNA's causal competencies could be demonstrated.

In sum, establishing DNA as a physical basis of heredity required more than elaborating increasingly powerful explanatory models. The crucial improvements lay in experimental work that rendered remote entities, such as chromosomes and DNA, accessible to demonstrations of their causal competence.

## 6. The *Vera Causa* Ideal II: Positive Aspect

In the biological community's reaction to Darwin's hypothesis of pangenesis, we saw that biologists reject IBE as sufficient confirmation for existence and competence claims. This leaves open the question of what does suffice to render such claims worthy of acceptance. Our study of twentieth-century genetics illuminates the positive aspect of the *vera causa* ideal.

Geneticists did not rely on IBE to argue for Mendelian inheritance. Instead, they took themselves to be *detecting* the existence of particular genetic differences (germinal, chromosomal, then molecular) and to determine their causal *competencies* (in breeding studies, cytological observations, and biochemical experiments). Key strategies included the *isolation* and *intervention*

[9] Experiments by Hershey and Chase ([1952]) used radioactive isotopes to separately label DNA and protein. They showed that bacteriophages, in order to replicate themselves, insert DNA but not protein into cells.

on the relevant difference, as well as the observation of the effects of surgical changes induced in them by natural processes. Over time, geneticists increasingly met the *vera causa* ideal for their key claims.

Scientific work was continually shaped by the requirements of the *vera causa* ideal. The limits of classical genetics were set by the fact that germinal differences could only be detected via phenotypes, and that their effects could only be determined via crossing experiments. Before germinal differences could be localized to chromosomes, cytologists needed to learn to detect individual chromosomes by microscope. Their effects could only be determined when the Morgan group found a natural process—non-disjunction—which produced insightful differences in the distribution of the X-chromosome. In order to assign genetic effects to the DNA fraction of the chromosome, biochemists learned to detect and isolate DNA, RNA and protein, and to test their causal competencies in an appropriate model system. Long debates about the reliability of the techniques for detection and isolation ensued before biologists were confident in affirming DNA competent to produce hereditary effects.

We suggest that this combination of detection, isolation, and intervention is characteristic of the type of evidence that biologists require in support of existence and competence claims, and that claims established in this way are less vulnerable (though not invulnerable) to unconceived alternatives than those supported by IBE.[10] Moreover, we have sketched how new domains of the world are rendered accessible by the development of novel experimental techniques and experimental systems. In the nineteenth century, the positive component of the *vera causa* ideal simply could not be met by students of heredity. IBE was the best Darwin and his contemporaries had, and it was not good enough. Only with the advances of the twentieth century were the true causes of heredity elucidated.

Both the negative and the positive ideal we describe are in the spirit of the *vera causa* tradition. We do not consider this tradition to be monolithic or unchanging. Rather, we understand it as an

[10] Most of our examples involve manipulation, but this is not required: see the discussion of Bridges' work on non-disjunction in Section 5, where a natural experiment was crucial.

evolving family of methodological proposals. As scientists have learned how best to study the world, the *vera causa* ideal has been productively modified. A historical epistemology of the ideal, elucidating how a succession of methodologists have understood and advanced it, remains to be written. We present a crude sketch here.

We see a commitment to the negative aspect of the ideal as broadly shared within the tradition. One way to read Newton's 'hypotheses non fingo' is as skepticism about hypotheses supported only by their observable consequences (Cohen [1962]; Smith [2002]). We find this same skepticism continued in Herschel, Lewes, Morgan, etc., up to biologists of the present day. This negative aspect, however, is inherently compatible with any number of positive standards for acceptance.

The tradition thus includes numerous attempts (of varying plausibility) to specify a positive standard for establishing existence, competence and responsibility. Nineteenth century proponents such as Herschel, Lyell, and Mill said little about establishing the existence of unobservable causes, but this became of acute practical interest to scientists in the second half of the nineteenth century with the advent of new detection techniques (for example, in microscopy). Meanwhile, ideas about demonstrating a cause's competence litter the works of the ideal's early proponents. Between Herschel ([1831]) and Mill ([1843], III.VIII), the understanding of key experimental methods (difference, agreement, concomitant variation) was considerably refined. But that was a mere beginning. In the period between ca. 1850 and 1950, our understanding of difference-making experiments grew tremendously. Methodologists such as Claude Bernard, Robert Koch, R. A. Fisher and Austin Bradford Hill studied how to control for confounders more reliably, how to infer causality in populations, and how to discern subtle differences in an effect with the help of statistical methods. These developments have contributed to the ongoing articulation of the *vera causa* ideal, which continues to the present day.

## 7. Implications for Scientific Realism

We have argued that biologists strive to adhere to the *vera causa* ideal. They are sensitive to the unreliability of IBE (negative component) and use other methods to support existence and competence claims (positive component). On this basis, we defend a form of realism about the biological sciences. Our realism may be simply expressed: once a given entity or process is established as a *vera causa*, it can confidently be said to exist. Similarly, controlled experiments permit us to determine an entity's causal properties (its competence) under at least some background conditions. While these conditions could turn out to be rarely realized, it would remain true that the entity has the causal property ascribed to it. As with any plausible realism, ours is fallibilist. We argue only that it is unlikely that claims that meet the standard will be overturned, not that it is impossible.

In contrast to existence and competence claims, generalized claims about the responsibility of previously characterized entities or processes are less stable, because such claims are vulnerable to a version of the problem of unconceived alternatives: alternative causal pathways, unknown or unconsidered, may produce the same effects. Our realism is thus at once bold (we believe that some facts are firmly established) and modest (we learn about the world in a piecemeal and partial fashion).

Each of the three stages of our case study shows biologists establishing causal knowledge about the basis of heredity. The transmission genetic methods of Hagedoorn and Morgan established the existence of independently assorting germinal differences competent to produce phenotypic differences. The work of Bridges on non-disjunction established that many of these differences can be localized to the chromosomes. Finally, the Avery et al. experiments (and follow-up work) localized these differences more precisely to DNA. Though these were quite profound achievements, in the end we are left with the fairly modest claim that DNA is competent to produce at least some hereditary effects. This leaves open just how much of heredity can be ascribed to DNA. Subsequent research revealed DNA's thoroughgoing role in heredity, to the point where, for some time, the presumption was that DNA was not just a basis of heredity, but

its sole basis. Recent work suggests that some aspects of heredity are explained by epigenetic marks. This research challenges DNA's exclusive responsibility for hereditary effects. However, it challenges neither the existence of DNA nor its competence to produce those hereditary effects.

We thus see cumulative growth in the established causes and mechanisms of heredity, even as beliefs about the relative significance of these mechanisms and processes fluctuate in a non-cumulative manner. On the *vera causa* account, knowledge of what causes exist and what they are adequate to explain grows fairly cumulatively. Claims that meet the ideal are established on non-explanatory grounds in a manner that mitigates the problem of unconceived alternatives. By contrast, views about the responsibility of such causes are vulnerable to the discovery of new, unconceived alternatives. Not all are equally vulnerable, however. Claims will be more vulnerable to modification the more they (a) slide from competence to responsibility without adducing additional evidence and (b) deny prematurely the existence of other causes competent to produce similar effects.

The *vera causa* ideal provides a template for realism: be a realist about those claims whose support meets this standard. Our historical case study illustrates the viability of this template, showing how the development of novel experimental systems and techniques allowed the biological community to mitigate the problem of unconceived alternatives. In the nineteenth century, the study of heredity was repeatedly frustrated by the problem of unconceived alternatives, as Stanford ([2006]) argues. As we have shown, however, the nineteenth century biological community was duly skeptical of speculative but explanatorily powerful hypotheses. Community level skepticism about the physical basis of heredity only began to evaporate in the first half of the twentieth century, when the *vera causa* ideal was increasingly met by the Morgan group's work on non-disjunction and the work by Avery's group on the causal role of DNA.

Establishing a viable template for realism leaves open the possibility that it cannot be applied very widely. We believe that the *vera causa* standard is widely accepted in other areas of the biological sciences as well, but an individual case study such as ours is only suggestive in this regard. Precisely defining the scope of our realism remains a task for future work.

Stanford ([2010], [2011]) has defended a form of realism that is somewhat similar to ours. Stanford argues, and we agree, that what matters to realism is not the (un)observability of the cause under consideration, but rather the type of reasoning supporting our claims. He distinguishes between 'consequentialist' and 'projective' reasoning. Consequentialist reasoning (including IBE) confirms a hypothesis by confirming its empirically testable consequences. By contrast, projection involves taking a cause known to exist and to be competent to produce certain phenomena and invoking it as responsible for producing other phenomena of the same kind. Whereas consequentialist reasoning is vulnerable to the problem of unconceived alternatives, Stanford argues that projection is not. He even links projection to the nineteenth-century 'demand for a *vera causa*' ([2011], p. 895).

Stanford's realism and our realism are compatible in principle. Establishing a cause as a *vera causa* occurs before one engages in projective inference. Projective inference then establishes responsibility: that the cause is not only competent to produce some effect but has in fact produced it in a given case or range of cases. Our realism concerns existence and competence claims, while Stanford's concerns responsibility claims.

In fact, however, we conflict with Stanford on both points. While Stanford says little about how existence and competence claims are established, his examples are illuminating. They suggest that he implicitly accepts a version of the observable/unobservable distinction, despite explicitly renouncing it. Stanford's examples of established causes include taphonomic processes that can be experimentally recreated in the lab (Stanford [2010], [2011]) and entities seen through a microscope (Stanford [2006], p. 33). To our knowledge, entities visible through a microscope are the only unobservable entities about which Stanford has endorsed belief in existence claims. He does so because microscopes can be checked directly against very small but still observable entities. If such direct checks are the only way to extend our knowledge into 'remote' domains, then Stanford's notion of remoteness ends up being a version of the observable/unobservable distinction congenial to the constructive empiricist (cf. van Fraassen [2008], pp. 109–11; Frost-Arnold [2016], Section 5.2). In contrast, we have argued that remoteness is relative to our methods

of investigation, and that we can firmly establish existence and competence claims well beyond the bounds of the observable.

As for responsibility claims, we are not convinced that projective inferences escape the problem of unconceived alternatives. They simply suffer from a special form of it. As is often the case in the biological sciences, multiple causes can produce indistinguishable effects. That a cause is known to exist and to be competent to produce some effect does not entail that it actually is responsible for any particular token of that effect. Projective inference does not *merely* involve taking a known cause and projecting it into unknown cases. It also involves eliminating other possible causes competent to produce the same effect, and in that regard it is vulnerable to the problem of unconceived alternatives. Perhaps the problem can be mitigated under the right conditions, but relying on projection rather than consequentialist reasoning is not by itself sufficient.

Our realism has several virtues. First, our realism is prospective, that is, it tells us which specific elements of contemporary biology fall under its umbrella. Because *vera causa* realism turns on a methodological standard of biologists, we can decide what to be realist about by looking to what biologists see as meeting the ideal. This will not be infallible, but no realism can aspire to infallibility. Nor is our proposal that we should blindly follow the authority of the biological community: we are merely taking their judgments as a proxy for direct assessments of what meets the standard.

Precisely because the biological community is fallible, there will be cases where biologists have collectively accepted existence and competence claims without satisfying the standard. This points to the second virtue of our realism: it does not leave everything as it is. On our view, anti-realism must be *critical*: anti-realism about some hypothesis widely accepted by the biological community implies a critique of the grounds on which the community accepts that hypothesis. This contrasts with anti-realist views that offer an anti-realist interpretation of scientific acceptance of claims without criticizing that acceptance (for example, constructive empiricism).

This critical aspect to our realism reflects our view that there is no question of realism about some hypothesis over and above the question of how well that hypothesis is supported by the evidence.

Third, our realism is not a form of convergent realism. It does not say anything about a succession of theories each of which is a better approximation to the truth than the last. Stanford ([2006], ch. 6) rightly condemns as 'pyrrhic victories' those forms of realism that, in order to salvage the approximate truth of past theories, attenuate the acceptance we should grant to our best current theories. Our realism does not require us to preserve the approximate truth of past theories in this way. Thus we may bypass this standard realist strategy and all the problems it carries with it, including the problem of pinning down how theories 'approximate' truth. On our view, existence and competence claims are simply true. However, there is an important sense in which these truths are partial: they are but small parts of complex puzzles. Causes are rarely or never individually sufficient to produce an effect, such that the background conditions under which the cause operates must be investigated; we will usually wish to decompose causal connections into their mediating mechanisms; and often there are entire alternative causal pathways to explore as well. Our case study of twentieth-century genetics suggests just such dynamics: partial truths get established with a fair amount of certainty, but this leaves open, and indeed defines, many questions for further investigation. Thus, on our view biological knowledge does not converge on the truth by producing ever closer but unstable approximations. Instead, a long series of stable but partial truths are uncovered and integrated with each other.

The notion of partial truth helps to show how our account fits with current controversies in the philosophy of genetics. As our understanding of heredity has expanded, identifying any one material unit as 'the' basis of heredity has become increasingly untenable, and the 'gene' concept has fragmented into multiple distinct, mutually irreducible concepts (Griffiths and Stotz [2013]). Nonetheless, the causal knowledge established during the period of our case study has remained stable. Germinal differences, as identified by crossing experiments, are competent to produce phenotypic differences. Many of these germinal differences associate with chromosomes and, more specifically, are differences affecting DNA. The competence of differences in DNA to

produce heritable differences remains unchallenged. Likewise, the 'Mendelian gene' remains as needed now as in the early 1900s, because the transmission genetic techniques on which it is based remain in use (Griffiths and Stotz [2013], ch. 2). The source of the current controversies is not that previously established claims were in error, but that they are only a part of picture that has proven to be much more complex than initially expected.

Fourth, our account meshes well with the philosophy of biological mechanisms (Machamer, Darden and Craver [2000]; Bechtel and Abrahamsen [2005]). Providing evidence of mechanisms requires showing that parts exist and are competent to engage in relevant causal interactions (Bechtel [2006]; Craver and Darden [2013], ch. 8). Mechanistic knowledge grows in a piecemeal fashion, since we usually understand individual entities and interactions before we understand whole mechanisms. Furthermore, although the existence of particular mechanisms can be firmly established, ascriptions of responsibility for individual effects may fluctuate over time.

Fifth, our realism enables a response to the fact that Stanford's new induction runs over the cognitive capacities of theorists and not over the empirical success of theories. Theorists today are as limited in conceiving alternatives as ever, but they have better tools (instruments, experimental techniques, etc.) for rendering previously inaccessible domains accessible. Once accessible, domains of nature that are remote from perception can be explored without reliance on IBE. So the cognitive limitations of individual scientists are irrelevant.

Sixth, our view explains the importance of relative significance disputes in biology (Beatty [1995]). These are the natural result of the fact that knowledge of entities and competencies grows cumulatively, while ascriptions of responsibility fluctuate with the discovery of new entities and processes. Further, for many cases of interest, multiple known causes may be competent to produce similar effects, leaving room for debate concerning both (a) what cause was responsible in any given case and (b) what cause is generally more important. Our view suggests that much theoretical change in biology involves overreaching extensions of established causal processes to unknown cases, often on the basis of explanatory power. Subsequent discoveries then require us

to cull back these extensions. Underlying this change, however, is the growth of body of stable existence and competence claims.

The final virtue of our view is that we do not misdescribe scientific reasoning. It has become the received view that IBE is the dominant inferential tool scientists use to reason about the unobservable. Stanford's argument for anti-realism takes this for granted, as do many defenses of realism (for example, Psillos [1999]). The view has even found its way to philosophical discussion more generally, where it is cited as an established truth about scientific reasoning (for example, Hawley [2006]; Paul [2012]; Williamson *forthcoming*; see Novick [2016] for critique). Even for those who do not accept our conclusions concerning scientific realism, we hope that our arguments will contribute to the ongoing reevaluation of IBE's putative centrality to scientific reasoning (Roche and Sober [2013]; McCain and Poston [2014]; Scholl [2015]; Sober [2015]; Climenhaga [2017]; Khalifa, Millson, and Risjord [forthcoming]; Norton [unpublished (a)]; Norton [unpublished (b)]).

**8. Conclusion**

In his famous deductions, Sherlock Holmes' aim was not to make scientific discoveries, and his inferential tools were not suited to such an aim. Take for instance *A Study in Scarlet* (Doyle [1888], ch. 7), in which Holmes describes how he inferred forcible poisoning as the cause of a particular death:

> Having sniffed the dead man's lips I detected a slightly sour smell, and I came to the conclusion that he had had poison forced upon him. Again, I argued that it had been forced upon him from the hatred and fear expressed upon his face. By the method of exclusion, I had arrived at this result, for no other hypothesis would meet the facts.

The 'method of exclusion' does not establish new processes, but simply chooses the best supported of a number of antecedently known alternatives, as Holmes is quick to point out:

> Do not imagine that it was a very unheard of idea. The forcible administration of poison is by no means a new thing in criminal annals. The cases of Dolsky in Odessa, and of Leturier in Montpellier, will occur at once to any toxicologist.

Holmes relied on causes known to exist: he merely inferred their responsibility in a particular case. He was, in short, constrained to reason within those domains of nature that had already been rendered accessible by scientific inquiry. And so we should expect, for he was merely inferring to the best explanation. He could go no further.

Our contention is that biologists have long appreciated these limitations of IBE as a method of induction, and that this fact points the way to a defensible scientific realism about biology. We have shown that, though Stanford's problem of unconceived alternatives is a genuine problem for IBE, IBE is not as widely used as is commonly thought. Biologists instead adhere to the *vera causa* ideal: they display exactly the mistrust of IBE that the problem of unconceived alternatives warrants. To be invoked in explanations, entities must first be shown, on non-explanatory grounds, to exist and to be competent to produce particular effects. The growth of experimental techniques continually renders new domains accessible to non-explanatory reasoning, and thus mitigates the problem of unconceived alternatives.

On this basis, we have defended scientific realism about biology. The key feature of this realism is that we should expect a fairly cumulative growth in our knowledge of those entities and processes established as *veræ causæ*. By contrast, large-scale generalizations about these entities and processes, especially about their responsibility for causing biological phenomena, should fluctuate more, for the attempt to explain new phenomena by known mechanisms is vulnerable to unconceived alternatives in a manner in which our knowledge of those mechanisms is not. It is always possible that an as yet undiscovered mechanism exists in the new domain.

A core virtue of *vera causa* realism about biology is that it does not rest on a mistaken view of scientific inference. It recognizes that many inferences in biology are not IBEs and are therefore not susceptible to the problem of unconceived alternatives as traditionally presented. Because this form of realism is linked to criteria addressed by standard scientific methodology, it is prospective: scientists can plausibly tell in advance which claims will be stable. Moreover, if IBEs are rarer in biological practice than the received view suggests, our realism is wide-ranging. Finally, the proposed realism is testable. As we show in the present paper, historical sources can speak for or against the claim that the *vera causa* ideal is operative at a given time and that judgments made on its basis are stable in the long-run.

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