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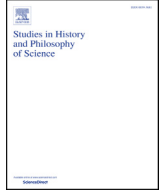
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Heritable changeability: Epimutation and the legacy of negative definition in epigenetic concepts



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ABSTRACT

Epigenetic concepts are fundamentally shaped by a legacy of negative definition, often understood by what they are not. Yet the function and implication of negative definition for scientific discourse has thus far received scant attention. Using the term *epimutation* as exemplar, we analyze the paradoxical like-but-unlike structure of a term that must simultaneously connect with but depart from genetic concepts. We assess the historical forces structuring the use of epimutation and like terms such as paramutation. This analysis highlights the positive characteristics defining epimutation: the regularity, oxymoronic temporality, and materiality of stable processes. Integrating historical work, ethnographic observation, and insights from philosophical practice-oriented conceptual analysis, we detail the distinctive epistemic goals the epimutation concept fulfills in medicine, plant biology and toxicology. Epimutation and allied epigenetic terms have succeeded by being mutation-like and recognizable, yet have failed to consolidate for exactly the same reason: they are tied simultaneously by likeness and opposition to nouns that describe things that are assumed to persist unchanged over space and time. Moreover, negative definition casts the genetic-epigenetic relationship as an either/or binary, overshadowing continuities and connections. This analysis is intended to assist practitioners and observers of genetics and epigenetics in recognizing and moving beyond the conceptual legacies of negative definition.

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Much has changed in the world of epigenetic research over the last two decades, but the base definition of molecular epigenetic phenomena has remained largely the same, some version of the following: *the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence*. In this definition the epigenetic is simultaneously negatively characterized as not-DNA and yet remains like it, concerning heritability and gene function. Instead of brushing past this obligatory and by now rather rote definition of epigenetics, this paper

stops to examine the paradoxical character of negative definition in this domain of discourse, and its fundamental role in shaping the field. No other arena in the history of modern biology is so limned by being like and yet not-something; not only is its core definition framed as change that is non-genetic or not based in sequence, epigenetic discourse is populated by a range of other terms conceptualized in negative and oppositional frameworks, from the non-coding and the non-Mendelian, to the rogue, the paramutation, and the loss-of-imprinting defect. We argue that negative definition, with its twin demands of bridging to genetics while departing from it, has been formative for epigenetic terms but has also left a legacy of enduring conceptual instability.

Rather than taking on all epigenetic concepts at once, or retreading the much-visited ground of the word *epigenetics* itself,

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we focus this analysis of negative definition through the lens of one particular term, the *epimutation*.¹ From observational notes and interview transcripts generated by ethnographic field work in research settings in germ stem cell biology, chromatin biology, and epigenetic toxicology, we have selected epimutation as a representative case for the broader phenomena of negative definition and its effects, including the difficulties of positive definition in the face of being not-something, and a damaging legacy of binary polarization produced by constantly framing epigenetic *versus* genetic phenomena.² We supplement these empirical observations of contemporary discourse with insights from both the history of biology literature and philosophical practice-oriented conceptual analysis (Brigandt, 2010; Cusimano & Sterner, 2019; Sapp, 1987).

Epimutation was originally coined in the mid-1980s by Robin Holliday to refer to “changes in gene activity based on DNA methylation,” in order to “distinguish them from classical mutants, which are due to changes in DNA base sequences” (Jeggio & Holliday, 1986, p. 2948). Significantly, Holliday later commented that the term arose due to the “terminological problem” posed by referring to particular experimental phenomena – cultured cells showing a phenotype consistent with a mutation in the absence of a change in DNA sequence (Holliday, 1990, p. 331). There were no extant words for this like-but-not-mutation. As will be discussed in further detail below, epimutation exemplifies the paradox of consistent utility with persistent lack of consensus around definition characteristic of much epigenetic language, subject to enduring arguments as to both its reality and significance as it continues to be deployed nonetheless.

Representative rather than remarkable, epimutation here allows us to analyze key features of epigenetic terms coined in contrast or opposition to genetics: a fundamentally ambivalent like-but-unlike formation that results from a structural demand to simultaneously bridge with and depart from established genetic concepts in order to survive being completely dismissed, or, alternatively, being entirely assimilated. Our cross-disciplinary study provides new context in which to understand a growing number of semantic studies of epigenetic metaphors (Raz et al., 2019; Stelmach & Nerlich, 2015), ethnographic studies of epigenetic laboratory practice and discourse that continually encounter the epigenetic-genetic relation (Lappé, 2018; Müller et al., 2017), and historical and philosophical work on epigenetic concepts and practices (Buklijas, 2018; Griesemer, 2002; Nicoglou & Merlin, 2017; Stotz & Griffiths, 2016).

In what follows, we offer a brief history of the emergence of epimutation, situating it in a family of past and present neologisms for mutation-like but non-Mendelian, non-coding, or otherwise deemed atypical inheritance phenomena that have arisen over the twentieth century, each shaped by negative definition. Going

beyond lack as a unifying feature, we argue that this idiosyncratic family occupies an “epistemic space” adjacent to the more classic mutation, but nonetheless exhibits distinctive positive material and temporal features aside from being non-DNA-sequence or non-permanent (Müller-Wille & Rheinberger, 2012). We then turn to a close examination of formal written and informal discursive deployments of epimutation in medicine, plant biology and toxicology, in order to understand its epistemic utility in these settings.

Finally, we return to the question of the contemporary limitations of epimutation and like terms in epigenetics as a legacy of their origins. We suggest that these terms have succeeded by being mutation-like and recognizable, yet failed to consolidate for exactly the same reason: they mirror, and thus are bound in an unforgiving binary with nouns that describe *things* presumed to persist unchanged over space and time. Such terms came into existence in an effort to describe and explain the regularity, oxymoronic temporality, and molecular dynamics of stable *processes*, and therefore are poorly served by remaining yoked to the language of classical genetics (Nicholson & Dupré, 2018).

1. The rather short history of epimutation

Epimutation has been increasingly evident in the scientific literature since its coining in the mid-1980s presence in the literature, as shown in Fig. 1. Very similar to mutation, its meaning derives originally from an epigenetic/genetic opposition. It is both manifestly useful and yet experienced as difficult to define, or defined differently by everyone. Our aim here is not to pin down the definition of epimutation once and for all, nor to take sides in the notably polarized terms of debate found in transgenerational epigenetics, but to use this specific example to diagnose the more general role of negative definition in the generation of sides in the first place. We first situate epimutation in the brief and rather scattered history of its use, understanding its genesis in the context of a larger family of neologisms that arose over the twentieth century to describe experimentally detected and elaborated changes in biological continuity heritable over organismal generations, changes that were apparently akin to mutations but lacked some key property of a what a mutation was understood to be. We then turn to its contemporary uses.

1.1. Epimutation as material and temporal distinction

Epimutation was coined by Robin Holliday in the context of research on DNA repair and cancer (Buklijas, 2018, p. 177; Holliday, 1985). He defined epimutations as “aberrant patterns of DNA methylation that cause the silencing of a normally expressed gene,” or the “ectopic expression” of a previously silent or only selectively expressed gene (Holliday, 1990, p. 331). It is worth understanding the experimental ground that contoured this use, as it illuminates the material and temporal distinctions being made in this act of naming.

In recounting Robin Holliday’s work on the causes of aging, historian Lijing Jiang writes that the British geneticist spent much of the 1960s and 70s promoting a relational and integrative approach to aging and disease distinct from the dominant mode of searching for single genes or macromolecules (Jiang, 2014). Initially these arguments about the cause of aging were framed in terms of cytoplasmic inheritance, “a slightly stigmatized concept in the 1960s” (ibid., p. 563). Then his experimental trajectory and theoretical attention shifted toward methylation, or more importantly, methylases, the enzymes that modify DNA by adding a methyl group primarily to cytosine (Buklijas, 2018).

Theories of aging based in notions of accumulated somatic mutations came together with the biology of methylation in

¹ Many authors have commented on and analysed the definition(s) of “epigenetics,” including historian Michel Morange, who writes that “Epigenetics cannot be defined *per se*, but only as an evolving opposition to the piecemeal, reductionist approach of genetics” (2002, p. 50). A more positive and comprehensive attempt to pin down a definition is found in Adrian Bird’s “Perceptions of Epigenetics” (2007). Histories of the term provide useful context to its polysemy (Buklijas, 2018; Felsenfeld, 2014; Haig, 2004; Morange, 2013), while philosophical interrogations of epigenetics also touch on definitional concerns (Griesemer, 2002; Stotz & Griffiths, 2016). While there have been many efforts to call for consensus definitions or restrictions in usage in an effort to discipline its use, these seem to have made little impact on how the term epigenetics is used in publications or everyday discourse today (Deans & Maggert, 2015; Henikoff & Greally, 2016; Ptashne, 2007).

² Ethnographic field work was conducted between April 2018 and December 2019 in two academic epigenetics laboratories in the United States, at professional meetings in the United States and Europe on topics of toxicology, gene regulation, and transgenerational epigenetics, and by 20 semi-structured interviews of scientists working in the domains of molecular epigenetics, stem cell biology, and environmental mutagenesis.

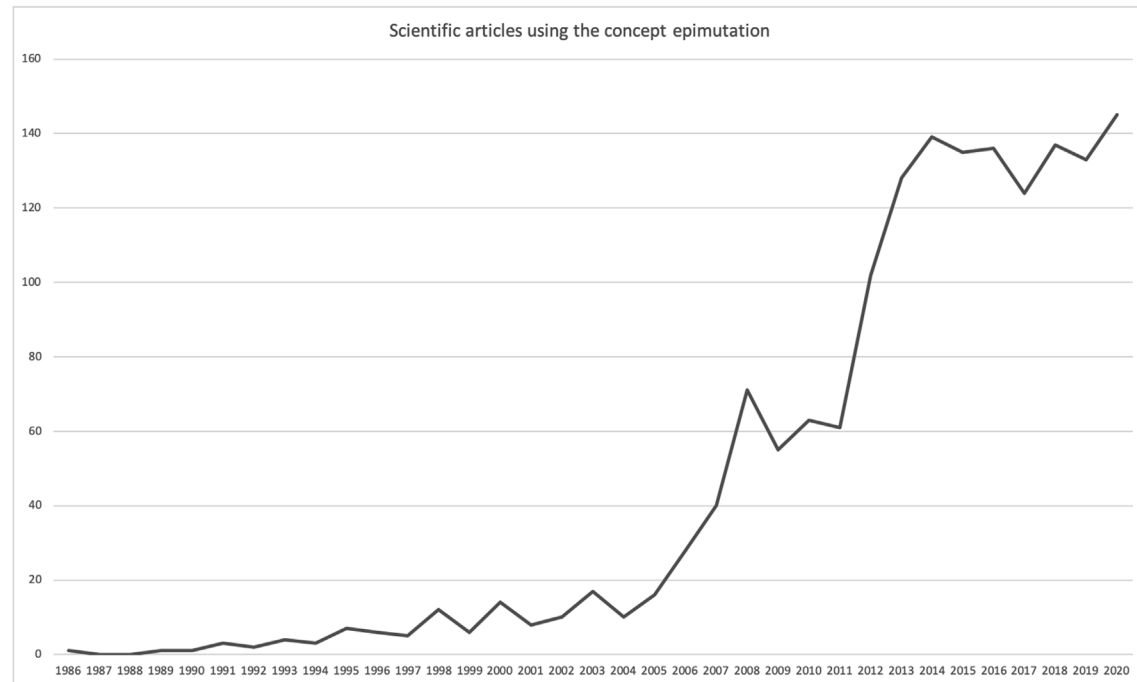


Fig. 1. Number of scientific articles using the concept epimutation (Source: PubMed and PMC up to Dec. 31, 2020).

cultured diploid somatic cells used to study mechanisms of DNA repair after 1963 (Setlow & Carrier, 1964). The use of cultured cells in mutation screens on the model of bacterial genetics was much in vogue during this brief heyday of somatic cell genetics (Landecker, 2007), and Holliday used the Chinese Hamster Ovary (CHO) cell line exposed to the mutagen ethyl methanesulfonate (EMS) in an effort to generate cells with mutations in genes active in DNA repair. A small fraction of cells surviving EMS treatment were indeed unable to repair DNA damage upon subsequent exposure to x-rays, and thus it seemed that “bonafide mutants” had been generated (Holliday, 1991). Yet further treatment with 5-azacytidine, a DNA methyltransferase inhibitor, restored DNA repair activity in these seeming-mutants.

What could be behind this anti-intuitive finding of a mutation whose permanence lay not in the change itself but in the perpetual nature of its potential for reversibility? A mutation was by this time understood to be caused by a permanent change to the DNA sequence, particularly in a cell in which DNA repair was non-functional. Holliday showed that when the cells were initially treated with EMS, at least one allele of the DNA repair gene in question was protected from mutagen damage by methylation. With one allele mutated by EMS and the other silenced by methylation, the phenotype was deficiency in DNA repair – the genetic heterozygote was phenotypically equivalent to a disabling mutation in both alleles in this case. Inhibition of methylation with the second agent opened out the previously-silenced allele, restoring at least partial gene activity and the ability of the cell to respond to x-ray induced DNA damage (Jeggo & Holliday, 1986, p. 2947). The apparently-mutant phenotype was both experimentally and “naturally” reversible, in that after many passages in culture, the allele in question would be silenced by methylation again if 5-azacytidine was not applied; this was subsequently shown to also be the case for other epimutations in other genes and cell lines (Holliday, 1991).

The distinction drawn by epimutation was between changes in methylation and the changes in DNA sequence that one would

expect with a “classical mutation” (Holliday, 1990). A second contrast was implicitly drawn by the focus on DNA excision repair, initially conceived in terms of reversibility of DNA damage caused by radiation (Yi, 2007). Because Holliday was interested in the accumulation of DNA damage and its prevention or amelioration in aging and cancer, he was on the lookout for reversals. But DNA repair is a simple change and return that does not repeat: it is prompted by random damage in the cell and involves directed change to the pre-damage state. Although some areas of the genome are more predictably vulnerable to damage than others, there is no expectation that a site of DNA repair will be a future site of switching between states. Where DNA repair is a one-time change followed by restoration, the reversion characteristic of the epimutation is an ongoing vacillation – the continuous possibility, as with the cells multiply passed over time in culture, of one state or the other.

Thus the epimutation drew both obvious and more subtle distinctions, while relying on accepted meanings of mutation for recognition and acceptance. The material substrate was methyl groups not DNA sequence, and the temporal status was also like but unlike: a heritable change that nonetheless was permanently changeable. The distinction between normal and abnormal relied fully on the connotations which came with mutation, and indeed the initial goal of this terminology was to distinguish heritable epigenetic states involved in pathological phenotypes from mutations that looked phenotypically identical. This successful rhetorical strategy came at a certain cost, because the invocation of mutation also carried with it the idea of the epimutation as a thing – a material change in space and time – rather than a process, downplaying the dynamic dimension of epigenetic processes that Holliday himself had highlighted: “a continual interaction between cytoplasmic enzymes and DNA sequences is an essential part of the model to be presented” (Holliday & Pugh, 1975; quoted in; Jiang, 2014, p. 575).

Table 1
The Epimutation Family. Neologisms for experimental phenomena that were like-but-unlike mutations, with their original definition and reasons for coinage.

Name	First occurrence	Definition
Dauermodification	Jollos, 1913, ciliates (<i>Paramecium</i>)	"The absence of influence on the hereditary disposition, particularly evident during the conjugation experiments, sets the cases at hand fundamentally apart from mutations; they must therefore be appraised as modifications. But because on the other hand ... they are also sharply distinguishable from habitual modifications through their long-lasting constancy when returned to the original life conditions – in the case of B1, constancy was maintained over 600 divisions – it is therefore quite necessary to create a new concept for this kind of phenomena. We describe them therefore as 'dauermodifications' [<i>Dauermodifikationen</i>]." (pp. 232–233, our translation)
Mutable locus ^a	McClintock, 1950, maize (<i>Zea mays</i>)	"[T]he changed phenotypic expressions of such loci are related to changes in a chromatin element other than composing the genes themselves ... [M]utable loci arise when such chromatin is inserted adjacent to the genes that are showing the variegated expression. The events occurring to this inserted chromatin are reflected in a changed expression of the neighboring genes, or sometimes in a loss of these genes. It is the inserted material that is undergoing the 'mutational' events." (p. 347)
Paramutation	Brink, 1956, maize (<i>Zea mays</i>)	"The invariable occurrence of heritable change in <i>Rr</i> in certain heterozygotes and the corresponding regularity of partial reversion in other combinations forbids application of the term mutation to these events ... A new name is needed for the present phenomenon, therefore, which gives effect, among other things, to the invariability of occurrence of the heritable changes in question." (Brink, 1958, p. 379, p. 379)
Imprinting/Loss of imprinting	Crouse, 1960, gnat (<i>Sciara</i>)	"[A] chromosome which passes through the male germ line acquires an 'imprint' which will result in behavior exactly opposite to the 'imprint' conferred on the same chromosome by the female germ line. In other words, the 'imprint' a chromosome bears is unrelated to the genetic constitution of the chromosome and is determined only by the sex of the germ line through which the chromosome has been inherited." (p. 1442)
Transposon ^a	Hedges & Jacob, 1974, bacterium (<i>E. coli</i>)	"We designate DNA sequences with transposition potential as transposons (units of transposition) ..." (p. 38)
Epiallele	Kermicle, 1978, maize (<i>Zea mays</i>)	"It is convenient to replace the phrase 'the relation between maternally and paternally imprinted forms of a gene' with a single word. I use <i>epiallelic</i> in this connection and refer to the individual gene forms as <i>epialleles</i> ." (p. 358) "Epiallele: An allele that can stably exist in more than one epigenetic state, resulting in different phenotypes. The DNA sequence of different epialleles of a particular gene is unchanged; for example, classic parentally imprinted genes." (Rakyan et al., 2002, p. 348, p. 348)
Epimutation	Holliday, 1985, mammals	"[T]he heritable changes based on DNA modification should be designated epimutations to distinguish them from classical mutations, which are changes in DNA sequence." (Holliday, 1987, p. 168)
Metastable epiallele	Rakyan et al., 2002, mammals	"For more than half a century, geneticists have been fascinated by mammalian alleles that are VARIABLELY EXPRESSED , even in the absence of genetic heterogeneity ... It is now clear that the variable expressivity arises because the activity of these alleles is dependent on their epigenetic state ... We propose that mammalian genes that display these unusual properties should be referred to as METASTABLE EPIALLELES , which will reflect their true nature." (p. 348)

^a Mutable locus and transposon (as well as its variant transposable element) refer to the same biological event.

1.2. The epimutation neologism family

The coining and definition of epimutation depended on an assumed shared understanding of basic key characteristics of a genetic mutation – regular Mendelian heritability ratios, permanence over time, and underlying changes in genes – in order to generate a new category of entity that was like but unlike mutation. As such, it joined a growing twentieth-century family of neologisms, depicted in Table 1, each answering the need for a means to name and conceptualize phenomena that were “distinct from, but not wholly unlike, mutation” (Brink, 1958, p. 379). It did not matter particularly that mutation itself was far from a given, agreed-upon entity for much of the twentieth century, as has been extensively discussed in the historical literature.³ The family resemblance between these like-but-unlike mutation terms makes it clear that it was not an exact unified definition of mutation that was essential to these neologisms, but rather they are similar in a flexible strategy of *adjacency*, of opposition conjoined with likeness to a dominant category.

Unsurprisingly, “unorthodoxies” (Crouse, 1960, p. 1442) or “seeming exception[s]” (Brink, 1956, p. 872) have consistently cropped up in biological research on mutations and heredity throughout the history of genetics. Even William Bateson, who

confidently predicted that plant breeding using Mendelian principles of the segregation of unit characters would finally free farmers from the “rogue” bearded wheat and spindly peas that afflicted their fields, essentially abandoned the unresolved subject of rogue peas after being unable to find a reason why commercially valuable large-leaved plants sporadically gave rise to “thin, weed-like” offspring that themselves only bred more rogues (Bateson & Pellew, 1915, p. 16; Radick, 2013). Bateson and his student Caroline Pellew wrote of the inheritance pattern of rogues in field peas, it is “evidently quite unlike anything with which we are familiar in ordinary Mendelian inheritance” (Bateson & Pellew, 1915, p. 30). For them, this discrepancy amounted to a theoretical impasse: “The gametes capable of producing rogues are given off sporadically and not in accordance with any system that we can perceive.” (Bateson & Pellew, 1915, p. 31). It was not until Alexander Brink in the 1950s coined the term “paramutation” to describe the ability of one allele to convert another to a new heritable expression state that the rogue was pulled back out of the dustbin of the inexplicable (Chandler & Stam, 2004; Santo et al., 2017).

Jan Sapp’s important history of cytoplasmic inheritance demonstrates the twin fates of assimilation or dismissal of initially puzzling unorthodox inheritance phenomena that arose in the course of experiments (1987). Sapp catalogs a cascade of rhetorical strategies employed by American geneticists reacting to apparent exceptions, ranging from assumptions that genic control was “masked in some way,” to dismissal on grounds that these were phenomena confined to (strange) plants (quoted in Sapp, 1987, p. 82; Sinnott & Dunn, 1939, p. 251). Many were eventually successfully subsumed under Mendelian laws, for example instances of co-dominance or incomplete dominance. It was in this vein that Theodosius Dobzhansky castigated the “defeatist attitude” of “some writers” who in his view renounced

³ Space does not allow a long exposition of the history of the mutation concept, which has been the subject of extensive scholarship by historians of genetics (Carlson, 2011; Kay, 1993; Kohler, 1994), and historians of evolutionary biology (Beatty, 2016, 2019; Stoltzfus & Cable, 2014). Historians and sociologists have emphasized the economic and social milieu history of mutation concepts (Gausemeier et al., 2013; Müller-Wille & Brandt, 2016), particularly in relation to medicine and genotoxic exposure (Lindee, 1997; Navon, 2019).

the possibility of understanding continuous variation in “genic” terms because of the technical difficulty and laborious experimentation involved, and instead alleged certain phenomena “to be non-Mendelian and to be due to some vague principle which assiduously escapes all attempts to define it more clearly” (Dobzhansky, 1982, p. 57; quoted in; Sapp, 1987, p. 85).

Epimutation, as with the other terms in Table 1, took the narrow path of adjacency that lay between the Scylla of assimilation and the Charybdis of dismissal. It came into being by harnessing the category of mutation, while holding the newly named phenomenon apart by opposition. It might well have gone the way of the countless neologisms that arise in biology to describe an observation or experimental phenomenon that quietly perish after a few instances, except that its material and temporal distinctions – a non-DNA substrate underlying a stable-but-reversible heritable change – proved useful in other domains. The term quickly migrated from its original context of use into botany, exactly because it was delineating a kindred epistemic space to terms such as transposon and paramutation in the context of plant genetics, and in particular maize genetics. In order to describe “stable mutations with identical phenotypes [that] can arise by two markedly different types of molecular events, one of which alters the element’s nucleotide sequence and the other of which does not,” Nina Fedoroff and colleagues explicitly drew on Jeggo and Holliday’s articulation of epimutation to describe the transposable Suppressor-mutator element (Spm) in maize (Fedoroff et al., 1989, p. 139). As we describe in the section below on epimutation’s epistemic utility in contemporary discourse, this borrowing of epimutation set the stage for describing the frequent trans-generational epigenetic variation prevalent in plants.

1.3. An oxymoronic temporality

At first sight, the negative definition intrinsic to epimutation – a heritable change not in DNA – seems fairly straightforward. Yet the short history of the designation of epimutations in plants shows a greater depth to the concept, one that is about anticipation, the contradiction of expectation, the act of unveiling, and a distinctively oxymoronic temporality. The invocation of the cultural two-sided figure of Superman/Clark Kent to name an epimutation illustrates this conceptual complexity. The *Superman* (*SUP*) gene in the model organism *Arabidopsis thaliana* was first named in 1992 in reference to the properties of its apparent mutants, which induced more stamen formation than normal (Bowman et al., 1992). This would remain but one more example of dubious sexual humor in genetics, except that the story did not go as anticipated.

Arabidopsis had become popular as a model organism by the 1990s precisely because of its small genome and high mutation rate, making it a “botanical *Drosophila*” for the study of the molecular processes underpinning things such as floral development (Leonelli, 2007). A screen for further mutations in flower development by applying mutagens or transferred-DNA insertional mutagenesis turned up a series of seven mutants “with phenotypes similar to but weaker than that of the known *sup* mutants”; these were accordingly called *clark kent* (*clk*) 1 through 7 (Jacobsen & Meyerowitz, 1997, p. 1100). The progeny of these apparently mutant lines behaved “like a real mutation, except that they revert to the wild type allele at low frequency,” about 3% per generation (Kakutani, 2002, p. 1107). While at first it seemed that the mutant screen had turned up another gene, *CLK*, involved in the same process as *SUP*, sequencing revealed no nucleic acid sequence changes compared to wild-type plants. Bisulfite sequencing revealed that in these cases *SUP* was extensively methylated. This led to the conclusion that the *clark kent* “mutants” were in fact epimutants: epigenetically suppressed *Superman* alleles, the same

in essence but with different powers according to the mode of dress.

The *clark kent* epimutants were generally stable but could revert, and revertants could in turn give rise to the epimutated progeny. In other words, they exhibited the distinctively oxymoronic temporality of an epimutation: “the genetic instability that is characteristic of many other epigenetic phenomena,” that is paradoxically a recurrent tendency (Jacobsen & Meyerowitz, 1997, p. 1101). What we see in this example is also identifiable in many others: while epimutation has been described as a heritable *change* in gene activity, following the definition of mutation, it would actually be more accurate to call it a heritable *changeability* in gene activity. An oxymoron is the conjugation of apparently contradictory terms and in the case of epimutation it is the stable instability, the consistently mutable. “Intrinsic epimutability” is considered difficult to grasp in part because evolutionary frameworks have not previously made room for a category of biological things that permanently vacillate; it does not fit demands for what is understood as stability (Loison, 2018, p. 29).

The surprise generated by the foiled anticipation of a conventional mutation points to considerable epistemological obstacles to discovery and description of epimutations. Epistemological obstacles not only limit what is theoretically conceivable, they are entrenched in the material and institutional contours of scientific practices (Bachelard, 2002; Müller-Wille, 2005). The experimental systems set up to study the nature of mutation were centered around genic DNA-sequence alterations. Having been led to the supposed origin point of the mutation and finding no sequence change there, it was only the combination of a distinctive temporal manifestation and the identification of an alternative substrate that defined the new entity. Once named, the oddity ceases to be idiosyncratic noise, nor can it be exactly domesticated as a new version of the already known. New concepts with new terms designate them as a subject of scientific inquiry in their own right.

2. Epimutation in contemporary discourse

Despite this apparently unified story of the historical genesis of epimutation, today the term remains mired in debates about its meaning and appropriate usage, particularly in the context of transgenerational epigenetics (Oey & Whitelaw, 2014). Indeed, epimutation first came to our attention not as a historical object but as a site of argument that typified features of epigenetic discourse observed in field work and interviews: ongoing complaint about the “loose” use of language and the lack of consensus about what words mean, a domain corseted by binaries, and repetitive legitimacy debates.⁴ As many of our interlocutors noted, the lack of agreement on technical and definitional criteria for epimutation reflects the larger debate around definitions of epigenetics.

In this section we turn first to the paradox of consistent utility with persistent lack of consensus found in both our ethnographic data and the literature. On the one hand, the concept possesses a fundamental vagueness. On the other, there are many situations when it is called for, even necessary, to describe instances of experimental work in grants, presentations and abstracts, to explain phenotypic outcomes, or to communicate to non-specialist

⁴ Other social scientific studies of the field of epigenetics have previously noted these features in both the United States, the United Kingdom, and Europe, see for example Kasia Tolwinski’s sorting of interview subjects into champions, skeptics, and middle-ground figures (Tolwinski, 2013), and Martyn Pickersgill’s analysis of the language of contestation and uncertainty prevalent in his interviews with UK researchers about epigenetics and its public communication (Pickersgill, 2016).

audiences—in short, to achieve certain epistemic goals. We therefore track the epistemic utility of epimutation by analyzing the inferential roles it plays in modes of explanation in disease, toxicology, and plant biology—how it is experimentally identified, followed, and used in analyses—and the epistemic goals it fulfills driven by certain research questions (Brigandt, 2010).

2.1. “You can hear many people say epigenetic modification or epigenetic mutation”

When asked their understanding of the term, practicing scientists who work in the domain of molecular epigenetics tended to pause markedly before attempting to define epimutation, and responded in a wide variety of ways, often rather incoherently compared to other parts of the interview, such as in the following exchange:

AL (interviewer): About the concept of epimutation ... I saw that you used it a couple of times in your slides in your presentation. Is it a concept that is useful for you?

PRE (interviewee, postdoctoral researcher in epigenetics): I think it's actually a good concept and it could help more, because it is just faster than to say *epigenetic mutations* and it's really specific: *epimutation*, it really tells everything. To be honest, I haven't heard it so much in the general scientific community. So, I don't know if it will take over and will start to be more common.

AL: And how would you define it?

PRE: Epimutation?

AL: Yes.

PRE: A modification of the epigenetics (*pause*) of (*pause*)—well, I think you can just define it as a mutation of epigenetics, and that will be okay. Then you can have a broader—try to explain mutation—a modification of the epigenetics of a (*pause*) of a cell, or something like that. The problem is that there is also some debate—I think that's already gone but—of actually if epigenetic *modification* is epigenetic *mutation*. Because how we understood mutation from the beginning was a change in the genome. Then I think it's more or less accepted now that we also call *that* mutations. But then you can hear many people say epigenetic modification or epigenetic mutation. And the concept is the same as epimutation. It just is all the same. People use different concepts but it's the same.

Here our interlocutor, who had just used the term epimutation in a formal presentation of experimental results during a meeting without commenting overtly on its use or definition, moves seamlessly from stating that it is a good term that is quick to say and “really tells everything,” to struggling to define it, to commenting that the term is debated because it might be more accurate to say epigenetic modification, to saying that “many people” use different terms to refer to the same thing.

The definitions we were offered by interviewees varied significantly: epimutation is understood to be a form of “epigenetic modification” that is “heritable”; a change that refers to “an interesting inheritance pattern”⁵; or it is an aberrant change—“a sequence should be methylated and is not methylated”.⁶ Scientists also expressed skepticism about the applicability of strong criteria of stability, sometimes turning the question back to the interviewer: “Do people think it is permanent?”⁷ During an informal discussion of research on brain cancer, a debate arose between a

postdoctoral cancer biologist and a senior stem cell scientist about whether the term epimutation necessarily denotes abnormality: while the former stated that an epimutation would be the “difference between tumor tissue and adjacent normal tissue,” the latter reacted: “I have a problem with that. Epigenetic states may differ from one tissue to the other ... It can be a normal difference.”

We also noted many instances in which the original distinction drawn by the definition of epimutation was becoming more difficult with the expansion in molecular epigenetics. While originally the negatively defined non-DNA-sequence change had only one opposite possibility, change in DNA methylation status, today *non-DNA* in molecular epigenetics could refer to a change in DNA methylation, histone tail modification, non-coding RNA, or some combination of these. A range of positive definitions opens out that is experienced by insiders as uncomfortably variable and lacking in rigor because of the uncertainty around explicit criteria. Interlocutors both within and outside of epigenetics research communities complained that the term was used “loosely” or “too casually” in the literature, sometimes in order to denote *any* form of moderately stable epigenetic modification, and often without specific metrics: does a differentially methylated region count as an epimutation? Does histone retention? Which are the appropriate readouts that could identify an epimutation? Would anyone use the term epimutation to describe a change in non-coding RNA expression or location?

The second aspect of negative definition that initially worked well with epimutation but is becoming more complicated by further research is the opposition between permanent and reversible. Our interviews and observations of lab meetings and conferences revealed the temporal properties of epimutation to be an open question. A senior plant epigeneticist highlighted the “continuum” of stability among epimutations found in experimental studies of *Arabidopsis*, ranging from “stable epimutations” or “epialleles” that “segregate according to Mendel's laws” to “unstable epimutations” that “progressively revert in 3–5 generations.” Another mid-career scientist, working in invertebrate biology rather than plants, preferred to talk in terms of memory that could persist and then fade rather than stability or instability, while reflecting on findings he had just heard over three days at a *C. elegans* meeting - for example that nematodes experienced a persistent but not open-ended multigenerational transmission of learned avoidance of pathogenic bacteria (Moore et al., 2019). Other interlocutors simply refused the term epimutation altogether, choosing instead to use the more recent *metastable epiallele*, because the phenomena showed no “persistency in a simple way” (see Table 1).⁸

Taken together, our interview data points to unease with exactly what mental reference either in terms of material basis or time to call upon when speaking about the significance or the technical basis of epimutation discovery and elaboration. Many practitioners would discuss epimutation and comment on how “people” use the term—but then say that they themselves do not use it *in their own work*. A cancer epigeneticist said that they were “not currently, but potentially” using it, and the PI of an epigenetics lab noted that they did not call the relevant epigenetic changes they observed in the lab epimutation, but found it useful for the introduction section of one of their papers. This frequent act of pointing to a language “out there,” without committing to personal ownership is one sign of how these terms remain in a state of only partial acceptance, used in need (such as in grant applications and abstracts) because there seem to be no other adequate words, yet with some doubt.

⁵ Postdoctoral researcher, cancer epigenetics.

⁶ Junior scientist, working in the field of developmental epigenetics.

⁷ Senior scientist, working in the field of developmental epigenetics.

⁸ Senior scientist, working in the field of molecular epigenetics.

Given this ambivalence, it seems necessary to ask what keeps epimutation in play as these doubts swirl. Philosopher Ingo Brigandt has usefully distinguished between three kinds of components that make up any scientific concept: its reference, its inferential role, and “the epistemic goal pursued by the concept’s use,” such as “confirming particular claims, explaining certain phenomena, or making discoveries of a certain kind” (Brigandt, 2010, 2012, p. 76). We have mostly discussed what epimutation represents, and how that representation works to infer meaning via adjacency with mutation; here we turn to the third element that Brigandt highlights as critical to understanding how scientific concepts function in investigative practice: their epistemic value—“what scientists attempt to achieve when using a concept” (2012, p. 76). Here we turn to the question of what epimutation is *good for* in contemporary discourse, and how it operates across a variety of domains and audiences.

2.2. Epimutation in disease: distinguishing between normal and pathological

“Just as mutations alter DNA, epimutations alter DNA methylation or chromatin patterns” (Reik & Walter, 2001). In the context of biomedical research, mutation occupies a central role in the ontology and understanding of disease. The use of epimutation in this context therefore hews closely to—and in fact often joins ranks with—the way mutation is “mobilized,” to use sociologist Daniel Navon’s term, to understand and explain disease, and organize research (Navon, 2019). Imprinting disorders are a good example: imprinted genes follow a fixed pattern of expression determined by the parental origin of each allele (see Table 1). At imprinted loci, rather than both maternal and paternal alleles being expressed, only one allele is typically expressed, while the other is silenced by DNA methylation and histone modifications. Loss of imprinting, that is ectopic expression of imprinted genes (either both alleles or the wrong parental allele) results in serious developmental disorders and tumor development (Monk et al., 2019; Tucci et al., 2019). Like mutation, loss-of-imprinting is an aberrant change that occurs in a specific locus in the genome; because it occurs in germ cells, it affects an organism’s entire development, in a permanent way, and may be seen as “constitutional epimutation” (Hitchins, 2015). Unlike a genetic mutation, however, it is not faithfully passed on to the next generation, since imprinting occurs anew in each generation.

More generally, epimutations have become important in explanatory paradigms in cancer research, in particular when referring to the hypermethylation of promoters of tumor-suppressor and mismatch repair genes that silence these key genes. In denoting a much larger domain, often filling in where conventional mutation explanation alone falls short, as a “second hit,” or playing the role of “missing” heritability, the concept has moved away from a strict parallel with the concept of mutation (Evans et al., 2018). A recent study reported an epimutation as one of the main causes of an inborn error of vitamin B₁₂ metabolism (Guéant et al., 2018). What is denoted by *epimutation* in this work is not a single discrete epigenetic event but the combination of various changes: DNA hypermethylation and accumulation of histone marks that silence the promoter of the *MMACHC* gene important to vitamin B₁₂ metabolism. This group of changes was tracked in the blood, tissues, and sperm of a proband and two other generations in the same family, and within the cells of the individual, and thus was seen as a single event. Here the concept of epimutation unifies different changes into a functional role, namely an abnormality conducive of pathology. The concept is significantly emancipated from the strict definition of epigenetic changes as independent from genetic events. This epimutation is fully interdependent with genetic changes: while the epimutation silences

the promoter of *MMACHC* gene, it is itself “secondary” (Horsthemke, 2006) to mutations in the *PRDX1* gene, which encodes an antioxidant enzyme; the physiological outcome results from heterozygosity for the genetic mutation and the promoter epimutation.

In the midst of significant extension, the concept of epimutation continues to be relied upon in practice to make a distinction between normal and abnormal epigenetic states – even though in principle not enough is known about epigenetic variance across tissues to be able to always designate normal and abnormal states. In the context of disease, the use of epimutation to denote an abnormality that is potentially reversible is central, while the distinction from genetics appears to be non-essential. Its proximity to mutation allows it to efficiently convey meaning not only in basic research but also in the clinic for both physicians and patients. Researchers have called for screening for epimutations in patients with complex undiagnosed diseases when genetic analysis did not reveal any relevant mutation (Hitchins, 2015; Horsthemke, 2006). Epimutations have been considered as targets for future targeted therapies for precision medicine (Werner et al., 2017). As epigenetics enters the clinic, epimutation is often used in communication materials for patients, seen as part of “ordinary” language compared to more technical terms such as DNA methylation or histone modification that require a certain level of scientific literacy.

Sometimes epimutation fails to be sufficiently like mutation: while heritability through mitosis is a key feature of the concept of epimutation, heritability through meiosis remains contested. For example, when a research team proposed to use the term germline epimutation to describe a “soma-wide, allele-specific and mosaic hypermethylation of the DNA mismatch repair gene *MLH1*” identified in the tissues of two individuals and the sperm of one of them (Suter et al., 2004), commentators contested the term on the ground that the study did not demonstrate that the mark *itself* had been inherited through the germline: it could well have been reinstated in the new generation following on genetic events (Chong et al., 2007; Horsthemke, 2007). Later, one author of the original study partly dissented from the results, showing that the epimutation could not be detected in additional tests of the proband’s sperm (Hitchins & Ward, 2007).

The objection to using *germline epimutation* here rests on the claim that it must be demonstrably directly passed through the gametes, rather than reinstated following on a genetic mutation in each new generation. Yet, as the authors of the original study point out, this seems to hold the research to an impossible standard: without isogenic subjects, epigenetic events cannot in humans be separated from genetic events with certainty (Suter & Martin, 2007). Even if monozygotic twins could be used, that would restrict the applicability of the concept to such an extent as to undermine its usefulness. Here, the demand to exactly parallel the mutation concept – to be unlike and yet demonstrate exactly the same kind of material continuity – strains the experimental framework of epigenetics to the point of rendering the concept of epimutation hardly applicable.

2.3. Epimutation in plant biology: conceptualizing adaptation

Such a limit was not encountered with plants. While the term epimutation was proposed in the context of cancer research, it saw enthusiastic uptake in botany, where it was—and is still—often used closely with epiallele (Jorgensen, 1993). Researchers have noted that inbred lines of *Arabidopsis thaliana* show a “frequency of single base variation of DNA methylation ... much higher than genetic mutation” (Borges & Martienssen, 2013). Epigenetic reprogramming, although it exists in plants, is less extensive than in

animals. The absence of early separation between germline and soma in plants allows epigenetic features to pass more easily to progeny than is the case in animals. These factors facilitated a rather seamless introduction of the concept of epimutation in continuity with mutation.

Even as Holliday is consistently hailed as originator of the term, usage of epimutation in this domain differs appreciably. Here, epistemic goals involve describing variants that may well be neutral or adaptive, while pathology recedes. Instead, stable transmission of a character over generations is key, while allowing reference to stability that differs from that of the mutation. Epimutants predictably revert at some frequency after a number of generations, yet are not random. Such emphasis on stable variation means that epimutations figure prominently in ideas of plant phenotypic diversity, adaptation, and evolution. Unlike the domain of medicine, these changes are not necessarily seen as deleterious, and therefore one sees greater interchangeability between *epimutant* and *epiallele* in usage, depending on context. Indeed, limited stability allows for better correlation with environmental changes and confers functional advantage (Kinoshita & Jacobsen, 2012, p. 764). These uses in turn make the epimutation an object of empirical inquiry in experimental approaches to evolution. For instance, a study uses “mutation accumulation lines” with methylation changes to obtain estimates of “forward and backward epimutation rates” (Graaf et al., 2015). The concept of epimutation promotes the transfer of experimental designs and analytic concepts in evolution from genetics to epigenetics.

Epimutations are made materially tangible and re-described in the course of efforts to generate or control them for experimental or industrial use. The sensitivity of plant epialleles to the environment, combined with their relative stability, has generated interest in their use as agricultural technologies for increasing resistance of crops to environmental changes (Mirouze et al., 2018). Epigenetic tools are expected to complement the core tool of mutation for breeding, allowing for productivity gains in established elite strains; some well-described epimutations occur in economically important crops, such as the Epi-dwarf allele in rice (Quadrana & Colot, 2016). As one of our interviewees, a senior scientist in the field of plant epigenetics, noted, directed epimutation can produce results in a much shorter timespan than traditional genetic breeding “with no risk of losing the strain” since the DNA sequence is left unaffected. The same geneticist remarked that a lack of permanent stability, while detrimental at first sight, could become a commercial advantage in the current economic system, allowing producers of epigenetically modified strains to periodically sell new seeds to farmers. Epimutations thus offer a new kind of tool for breeding: limited in amplitude and duration but also relatively flexible.

2.4. Epimutations imply epimutagens: toxicology, awareness and regulation

Genetic toxicology developed around environmentally-induced mutation as its core concept (Frickel, 2004; Muller, 1927). Mutagenesis assays have come to constitute the foundation of regulatory regimes around chemicals as health hazards, in particular carcinogens, both in the United States and in Europe (Creager, 2014, 2015; Schwerin, 2010). However, not all toxicants that cause disease are overtly mutagenic, and the language of the “epimutagen” as agent and “epimutation” as outcome are key to toxicology’s ability to account for cases in which long-term outcomes from low-dose exposures do not adhere to the classic models of and tests for carcinogenicity and mutagenicity.

Research into the impact of arsenic on health provides an interesting example of the need epimutation/epimutagen is answering in the realm of toxicology. Not coincidentally, the early term *dauermodification* (Table 1) was coined in 1913 in an effort to conceptualize a mutation-like effect of arsenic exposure on paramecia, phenotypic changes which could last hundreds of generations but would then revert (Brandt & Schloegel, 2016; Sapp, 1987). For much of the twentieth century, despite growing epidemiological evidence of adverse consequences of arsenic exposure, scientists were unable to produce an animal model of arsenic carcinogenesis (Parascandola, 2012). Arsenic is not a point mutagen. It is now being reframed as an epigenetic toxicant, impacting DNA methylation (Bailey & Fry, 2014; Bustaffa et al., 2014), but also interfering directly with microRNAs, enzymes that modify chromatin, and DNA repair enzymes (Björklund et al., 2018). The “double capacity” of arsenic to indirectly induce DNA damage and epimutations may be the main cause of arsenic-induced carcinogenesis (Bustaffa et al., 2014, p. 1043). In addition, low-dose exposures are increasingly seen as relevant to non-cancer health outcomes such as diabetes and male infertility, and prenatal exposure has been linked to fetal growth restriction, fetal death, infant mortality, and neurodevelopmental defects in both animal models and human epidemiological studies (Farzan et al., 2013).

In the specific case of arsenic, and in the broader scene of other twenty-first century pollutants from bisphenol-A (BPA) to air pollution, the epistemic goal is to account for the disease outcomes of low-dose chronic exposures instead of acute high dose exposures, and, importantly, to give an alternate *in vitro* and epidemiological means for detecting harms distinct from the traditional frame of toxicological testing (Martin & Fry, 2018). Through the language of epimutation and epitoxicant, a new form of toxicity closely tied to our historical moment becomes immediately recognizable both to the lay public and regulators, as something that fits criteria as a candidate for regulation. However, the apparent transparency of the language of “epimutation” also conceals the specific challenges it entails for risk assessment (Chung & Hecceg, 2020). It is still unclear which epigenetic event could serve as a testable endpoint. Epigenetic states and changes, because they are often unstable and tissue-specific, are difficult to assay. Exactly because they concern long time spans at low doses, new modes of measurement and accountability must be developed. Rather than simply being a double of mutations, epimutations open onto new temporalities, calling for new forms of regulation (Angrish et al., 2018).

In sum, this analysis of the various mobilizations of epimutation shows that it has become established by being useful in distinct explanatory contexts. Its meaning is strongly context-dependent, relying on different aspects of its similarity and dissimilarity to mutation. Such pluralism allows the concept to be a useful explanatory tool in different experimental contexts. Contrary to the idea that the term is rendered weaker by having multiple definitions or different uses in different contexts, our brief analysis has shown that different uses in these very different fields tend to inform one another, according with how philosophers Samuel Cosimano and Beckett Sterner analyze pluralism in scientific concepts (Cosimano & Sterner, 2019). They write that an “an epistemically virtuous coherence” may arise from differing uses in which “the set of definitions” may be considered “as a whole worth more than the sum of its parts” (2019, p. 24).

3. Beyond mutation: bridges that end mid-air

We opened this article with the question of how negative definition has left a legacy of conceptual instability in epigenetic terminology. In the case of epimutation, we see that being *like*-mutation has been central to making a range of mitotically and/or meiotically heritable epigenetic changes legible to scientific investigation or medical and regulatory intervention. At the same time, the negative definition—being fundamentally *unlike* mutation—remains central, if the phenomenon is to remain its own kind of thing, and not completely subsumed to a genetic framework nor dismissed as a fringe case. Now that we have carefully unpacked the paradoxical existence of these entities, we may better understand that their means of attaining legibility or autonomy as epistemic things can also explain the ongoing nature of their relative weakness and definitional instability (Rheinberger, 1997). We see several ways in which the bridges built outward from genetic concepts could be said to end in mid-air, successfully taking users only so far until the logical structure fails to account for, or adequately describe, what is being investigated.

First are the consequences of being like-mutation. As noted above, the experimental systems built to find genetic mutations sometimes caught phenomena that were like mutations at first pass but then diverged in some way. Such likeness is very useful in terms of establishing legitimacy or recognition, but the parallels between mutation and epimutation have become more tenuous as the work expands beyond the organism or experimental system of its first discovery, and the molecular basis of epigenetic processes expands beyond DNA methylation. For example, tracking epimutations in plants is quite straightforward compared to their study in the context of human disease. Epimutation screens may seem analogous to mutation screens, but the lability of epimutations across time, their variability across cells and tissues, and the variety of epigenetic marks complicate matters considerably (Hitchins, 2015; Horsthemke, 2006).

Second are the consequences of being negatively defined (non-DNA, non-genetic, non-Mendelian). This sets up a separation between genetic and epigenetic phenomena and an enduring expectation of binary categories. To maintain epistemic autonomy—to be its own thing—epigenetic phenomena must be an opposite pair to the base genetic term, defined by it but not it. Frequent demarcations of “*bona fide*,” “true,” or “pure” epigenetic phenomena as instances in which genetic or intergenerational/intrauterine influences have been rigorously excluded by experimental design characterize explanations of the relationship between genetic and epigenetic inheritance. Implied in this search for purity are assumptions that any discovered genetic influence disqualifies an epigenetic event as significant, and that there is a true-or-false component to any finding of epigenetic inheritance. After all, the opposite of pure is impure; of *bona fide* is unauthentic. Rather than bring the continuum of genetic-epigenetic relations or their physical coexistence into view, researchers are constantly pushed to take sides in a debate cast in terms of binary formulations: primary/secondary, leader/follower, soft/hard, freakish/tip-of-the-iceberg (Gouil & Baulcombe, 2018; Heard & Martienssen, 2014; McCarrey, 2014; Oey & Whitelaw, 2014).

Third, the linguistic and technical lexicon of mutation was and is built through genic DNA, reflecting the long arm of the double helix and the central dogma. The inertia that comes with established instrumentation therefore initially oriented analysis toward DNA methylation, with a much slower development of means to account for chromatin and RNA biologies as other modes for the persistence of change over cellular or organismal generations. Persistence of a changed phenotype over time may be supported by a set of interlinked processes, in which there is an initiating change in one

molecular medium that is then propagated over time through a different one, in which case the mental referent of a one-time permanently altered single substrate is misleading (Schaefer & Nadeau, 2015). Can this genic language be stretched to accommodate the many other entities now being described in the domain of inheritance: non-coding RNAs and their transport between cells and organismal generations by exosomes, the increasingly complicated world of circulating DNA and circular DNA, and the importance of metabolites as both material substrates and informational cues in both epigenetic and genetic processes? (Donohoe & Bultman, 2012; Ryan & Kuzawa, 2020).

Finally, these ways of defining epigenetic inheritance phenomena in relation to genetics have had the paradoxical effect of making them legible while tying them conceptually to nouns that are presumed to describe *things* that persist unchanged over space and time. This invocation of things downplays the metabolic fluxes, genome-epigenome interactions, or other processual elements that could as well be referents for the term. Epimutation, as well as dauermodification, transposon, paramutation, imprinting, and metastable epiallele, all represented different strategies to tell “a new story, against the grain of the language available to tell it in” (Beer, 2009). It is clear from their origins that what scientific workers were reaching for, in this effort to bridge the territory “on the border between the known and the unknown,” was a lexicon to capture temporal processes with characteristic regularity but not fixity, changeable stability, and dynamic materiality (Rheinberger, 2015, pp. 168–169). McClintock held that transposition brought “[t]he long-held dogma of genome stability ... under attack, demanding readjustment of concepts” (McClintock, 1987, p. 617). Holliday was working to find new language in order to bring into view the constant interaction of enzymes and DNA sequences and therefore to refocus on processes such as methylation as a permanently ongoing constitution of genetic states rather than a permanent thing encoded in a sequence. The adjective ‘metastable’ was adjoined to epiallele in order to “emphasize the labile nature of the epigenetic state of these particular alleles” (Rakyan et al., 2002, p. 350). This has left epigenetic terms to a certain push-me-pull-you existence, necessary but often ill-fitting.

4. Conclusion

We offer this analysis of the short career of the epimutation as a kind of reflexivity tool, to enable practitioners and commentators to better understand the origins and implications of epigenetic terms and concepts. Recognizing the tensions or uncertainties of definition residing within these terms does not imply they should be abandoned; as Beurton and colleagues observed in writing about the concept of the gene, it is the task of the epistemologist to understand “how and why fuzzy concepts” work the way they do, and, “instead of trying to codify precision of meaning, we need an epistemology of the vague and exuberant” (Beurton et al., 2000, p. 222). Here we have shown that epimutation has maintained at least a brief window of epistemic utility across a range of biological and medical subdomains of the life sciences through a strategy of adjacency to mutation concepts, and this accounts paradoxically for both its success and its limitations.

Recognizing the historical contingency by which the field of epigenetics has been fundamentally shaped by negative definition should make us better able to recognize and therefore work around assumptions of the separateness and presumed hierarchical relations between genome and epigenome. Rather than bemoaning the polysemy of epigenetic terms, our aim is to further understanding of what purposes they serve, and the scientific, medical and regulatory situations in which traditional genetic concepts have proved inadequate to the task of description and explanation

of persistent change over time. Binary formulations in which phenomena are either pure or impure, important or inconsequential, mechanisms or myths are an unhelpful legacy of oppositional definition that obscure possibilities for rethinking the relations between our historical depth of knowledge of genetic phenomena and the novel RNA, protein, and non-genic DNA entities now emerging in our instruments and concepts.

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