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Neo-Lamarckian medicine

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Summary Darwinian medicine is the treatment of disease based on evolution. The underlying assumption of Darwinian medicine is that traits are coded by genes, which are often assumed to be sequences of DNA nucleotides. The quantitative genetic ramification of this perspective is that traits, including disease susceptibility, are either caused by genes or by the environment, with genotype-by-environment interactions usually considered statistical artefacts. I emphasize also examining those epigenetic signals that can be altered by environmental perturbations and then transmitted to subsequent generations. Although seldom studied, environmentally-alterable meiotically-heritable epigenetic signals exist and provide a mechanism underlying genotype-by-environment interactions. Environment of a parent can affect its descendants by heritably altering epigenetic signals. Neo-Lamarckian medicine is the application of these evolutionary epigenetic notions to diseases and could have enormous public health and environmental policy implications. If industrial contaminants adversely affect organisms by meiotically-heritably altering their epigenetic signals, then cleaning up these contaminants will not remedy the problem. Once contaminants have adversely altered an individual's epigenetic signals, this harm will be transmitted to future generations even if they are not exposed to the contaminant. Exposure to environmental shocks such as free radicals or other carcinogens can alter cytosine methylation patterns on regulatory genes. This can cause cancer by up-regulating genes for cell division or by down-regulating tumour suppressor genes. Environmentally-alterable meiotically-heritable epigenetic signals could also underlie other diseases, such as diabetes, Prader–Willi syndrome, and many complex diseases. If environmentally-altered meiotically-heritable epigenetic effects are widespread – which is an important open empirical question – they have the potential to alter paradigmatic views of evolutionary medicine and the putative dichotomy of nature versus nurture. Neo-Lamarckian medicine would thereby shift emphasis from cure to prevention of diseases.

Introduction

Darwinian medicine has captured the imagination of medical researchers and evolutionary biologists [1,2]. It is defined as the use of "an evolutionary perspective to understand why the body is not better designed and why, therefore, diseases exist at all" [3, p. 358]. The term 'Darwinian' is used to distinguish neo-Darwinian views of evolution from other, often older, views of evolution. In particular, Darwinian evolution is often contrasted with Lamarckian notions of evolution of acquired characters, which are clearly wrong. However, there are portions of cells other than DNA that are faithfully transmitted from one generation to the next, and some of these can be heritably altered by the environment [4]. These signals provide a mode by which the environment in one generation can affect the evolutionary trajectory of subsequent generations. Jablonka and Lamb have discussed many such evolutionary applications, but none in medicine [4–6]. I fill in this gap by introducing such epigenetic effects into evolutionary medicine, calling them neo-Lamarckian medicine.

Neo-Lamarckian medicine is driven by epigenetic signals that are inherited across generations, but are more fluid than DNA nucleotides. Unfortunately, no term exists for such signals, hence I begin by naming these 'meiotically-heritable

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epigenetic' signals to distinguish them from epigenetic that are only transmitted via mitosis.

What are meiotically-heritable epigenetic signals?

The term epigenetic was originally used to describe all factors controlling gene expression and cell differentiation. Waddington [7] used the term epigenetic, amalgamating epigenesis and genetics, where epigenesis refers to the gradual and progressive development of new structures [8]. It was not until Waddington was writing his seminal book that biologists realized that DNA is contained in chromosomes ([9] citing [10]). Genetic phenomena, like epigenetic ones, were originally considered to be of unknown molecular cause. Only genetic and epigenetic effects were known. Fisher defined additive genetic variance as the proportion of phenotypic effects that get transmitted from one generation to the next [11]. Note that this is a population level definition of genetic effects because it requires one to examine average effects and variances. In contrast, Waddington used the term epigenetic to refer to any phenomena that affected development *within an individual* and, therefore implicitly, *within a generation*.

The meaning of the term genetic changed with the introduction of the central dogma and sequence hypothesis [12]. They provided a one-way path from DNA nucleotide sequences, to messenger RNA (transcription), to protein synthesis (translation). Because of this paradigm, molecular biologists effectively re-defined the term genetic to mean DNA nucleotide sequences; a definition that many quantitative geneticists would admittedly find repugnant.

Use of the term epigenetics also changed in the 1970s as molecular biologists began proposing mechanisms, especially cytosine methylation, by which development and gene regulation could be controlled [13,14]. Many of these molecular signatures gradually change irreversibly as cells and tissues differentiate and age. Therefore, whichever molecular mechanisms control development must be reset each generation. "This suggests a supplementary definition of epigenetics to include transmission from one generation to the next, other than the DNA sequence itself" [15, p. 454]. Holliday thereby switched the focus of epigenetics from strictly intra-generational to both intra- and inter-generational (also see [16]). Therefore, I use the terms 'mitotically-heritable' and 'meiotically-heritable' to distinguish the two different contemporary meanings of the term epigenetic. Meiotically-heritable epigenetic signals include cytosine methylation, chromatin structure, and histone acetylation and undoubtedly also include other molecular signals, such as those mediating RNA editing.

Do environmentally-altered meiotically-heritable epigenetic signals exist?

There are several impediments to providing a definitive answer as to whether there exist environmentally-alterable meiotically-heritable e-pigenetic signals. First, most work on heritability of epigenetic signals has focused on faithful transmission of epigenetic signals through mitosis, not meiosis. Second, although it is clear that some epigenetic signals — such as the cytosine methylation signatures of genomic imprinting and heterochromatin — are meiotically-heritable, nobody has quantified their degree of meiotic heritability (i.e. narrow-sense heritability). Third, methods for estimating these environmentally-altered epigenetic components of heritability have not been developed. To remedy this third difficulty, I provide a sketch for an estimation methodology below (details contained in [17]). Neo-Lamarckian medicine can only exist if environmentally-altered meiotically heritable epigenetic signals exist.

At least six labs have independently reported environmentally-altered meiotically-heritable epigenetic signals, two of which work with cytosine methylation in mice. At some loci, amount of gene product is proportional to amount of methylation on the promoter [18]. At one mouse locus, methylation levels and resulting phenotypic effects were both meiotically-heritable and could be altered by feeding maternal parents methyl-rich diets [19]. Similar results were found at another mouse locus [20], but here epigenetic signals were meiotically-heritable and could be altered through either maternal or paternal parents. Chemical alteration of cytosine methylation patterns is also known to be meiotically-heritable in plants [21,22]. Environmentally-alterable meiotically-heritable epigenetic signals are not limited to cytosine methylation. They has also been found in fission yeast [23] and *Drosophila* [24], which are two of the few lineages that has independently lost all or most of their cytosine methylation [25]. We cannot know how common or important these phenomena are until researchers become more cognizant of and systematically search for environmentally-altered meiotically-heritable epigenetic signals [6].

Quantitative genetics of environmentally-altered meiotically-heritable epigenetics

It is surprising that meiotically-heritable phenotypic traits are usually exclusively attributed to genetic and environmental causes, and not also to epigenetic causes. There has been a constant epigenetic thread running through evolutionary biology since the discovery of position effect variegation in the 1920s [26], transposons in the 1940s [27], genomic imprinting in the 1960s [28], and the regulatory roles of cytosine methylation in the 1970s [14]. Each of these phenomena should have injected an epigenetic element into quantitative genetic paradigms, but somehow failed to do so. Thus far, work has been exclusively confined to using quantitative genetics to estimate developmental epigenetics [29,30].

Quantitative genetics considers genetic effects to be any portion of variation that cannot be explained by environmental variation. Parent-offspring models are linear regressions,where offspring phenotype is the dependent variable and the independent variables are the offspring's environment and their parents' phenotypes. The regression coefficient on parents' phenotype equals heritability. With environmentally-altered meiotically-heritable epigenetic signals, we need to add a new independent variable to the regression: the environment of the parents [17]. Its regression coefficient equals the component of narrow-sense heritability due to environmentally-altered meiotically-heritable epigenetic signals.

If environment of the parents is omitted from the above parent—offspring regression, as is traditionally the case, then environmentally-altered meiotically-heritable epigenetic effects will be erroneously ascribed to other regression coefficients, especially genotype-by-environment interactions [17]. Sib analysis, which is the other standard quantitative genetic method, is not available for environmentally-alterable meiotically-heritable epigenetic signals because it does not provide a method for including environment of the parents.

Ramifications for neo-Lamarckian medicine

The above procedure for estimating meiotically-heritable epigenetic signals places neo-Lamarckian evolution on firm theoretical ground. Neo-Lamarckian evolution describes environmental variables altering heritable signals, an idea that even Darwin espoused [31,32]. Meiotically-heritable epigenetics corroborates this notion, albeit in a more random and less directed fashion than Lamarck had proposed [33,34]. Yet, despite neo-Lamarckian effects having first been identified long ago [26,35], neo-Lamarckian evolution is usually caricatured as a mode of evolution that was completely debunked in the mid 1800s (however, see [6]). Greater theoretical and empirical understanding of environmentally-altered meiotically-heritable epigenetic signals will help in correctly ascribing components of heritability. This is essential in so much of medicine, where there is great emphasis on discerning whether diseases are caused by genetics or the environment. Environmentally-altered meiotically-transmitted epigenetic effects show that this is a false dichotomy. In neo-Lamarckian medicine, the environment can heritably alter the epigenome.

Neo-Lamarckian medicine could have enormous public health and environmental policy implications. If industrial contaminants adversely affect organisms (including humans) by meiotically-heritably altering their epigenetic signals, then cleaning up these contaminants will not necessarily remove the problem. Once contaminants have adversely altered an organism's epigenetic signals, this harm will be transmitted to future generations even if subsequent generations are not exposed to the contaminant. Such effects have been documented for carcinogens acting by altering epigenetic signals [36,37]. This provides much greater impetus on preventing and correcting environmental contamination than currently exists. Neo-Lamarckian medicine changes the focus from cure to prevention [38].

The role of meiotically-heritable epigenetic signals in preventing and triggering cancers is intuitively plausible. Epigenetic signals, especially cytosine methylation, are known to regulate gene activity [14]. In particular, methylation of promoter genes almost always suppresses transcription of their structural gene. For many loci, downregulation of the gene is directly proportional to the amount of cytosine methylation on the promoter [18]. Environmental shocks are known to alter epigenetic signals, e.g. demethylate a locus (see [39]; in many of these instances, maintenance methylation following mitosis is precluded, rather than methylation being stripped away). Exposure to environmental shocks such as free radicals or other carcinogens generally alter cytosine methylation patterns on regulatory genes. If enough methylation is removed (including from mitotically produced daughter cells), gene activity can

become highly upregulated [40]. Because cell differentiation is largely the differential suppression of various gene functions, cells with substantial gene upregulation can become dedifferentiated and begin rapidly proliferating. This provides a potential route by which cancers could be triggered [41].

An alternative hypothesis is that tumour suppressor genes can be inactivated by too much methylation [41—43]. That is, methylation suppresses (downregulates) production of substances that preclude tumour growth, such as proteins that mop up free radicals. This alternative hypothesis is consistent with the observation that cancer cell telomeres are highly methylated [44]. Too much methylation is also associated with specific loci in certain tumours and these methylation levels can be environmentally-altered [45]. However, it is not known whether these specific epigenetic signals are meiotically-heritable.

Although I have focused on cancers, other diseases are believed to be of epigenetic origin, usually caused by aberrant levels of cytosine methylation. There is evidence that some forms of diabetes are caused by meiotically-heritable epigenetic effects [46]. Complex diseases are usually believed (and sometimes defined) to be caused by multiple genes and multiple environmental factors [47]. But complex diseases could just as readily be caused by a single gene on which is attached a variety of possible meiotically-heritable epigenetic signals at a single genetic locus [48], i.e. one locus with several epialleles. This is particularly plausible because there are usually multiple epigenetic layers on top of a single nucleotide locus (e.g. cytosine methylation, heterochromatin, histone acetylation). Although there does not yet appear to be any definitive evidence linking meiotically-heritable epigenetic signals with complex diseases, their strong genotype-by-environment interactions [49] makes them ripe for being studied in light of neo-Lamarckian medicine.

There have been a few attempts at applying Darwinian medicine to diseases caused by molecular epigenetic defects, such as cytosine methylation errors in Prader—Willi syndrome patients [50]. But this disease is probably caused by a meiotically-heritable epigenetic defect, rather than a genetic defect [51]. In fact, there does not appear to be any literature on evolutionary medicine being applied to diseases with meiotically-heritable epigenetic aetiology. My hope in introducing this conceptual foundation for neo-Lamarckian medicine is that those working in human medical genetics will begin considering meiotically-heritable epigenetic effects as possible causes for disease. If such diseases are found to be triggered by environmental perturbations, such as carcinogens, then there need to be concerted efforts made to prevent such diseases before subsequent generations are adversely affected.

Conclusion

Environment in one generation can affect subsequent generations by altering epigenetic signatures. If environmentally-altered meiotically-heritable epigenetic effects are widespread (which is an important open empirical question), they have the potential to alter paradigmatic views of evolutionary medicine, including abjuring the nature versus nurture dichotomy that pervades so much of modern medicine. With these effects, we may find the molecular basis for genotype-by-environment interactions. Their application in evolutionary medicine, called neo-Lamarckian medicine, could shift emphasis from cure to prevention of diseases.

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