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Nutrient-dependent Pheromone-Controlled Ecological Adaptations: From Angstroms to Ecosystems

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Abstract

This angstroms to ecosystems model of ecological adaptation links nutrient energy-dependent epigenetic effects on base pairs and amino acid substitutions to pheromone-controlled changes in the microRNA/messenger RNA balance and chromosomal rearrangements *via* the physiology of reproduction in species from microbes to humans. The nutrient-dependent pheromone-controlled changes are required for the thermodynamic regulation of intracellular signaling, which enables biophysically constrained nutrient-dependent protein folding; experience-dependent receptor-mediated behaviors, and organism-level thermoregulation in ever-changing ecological niches and social niches. Nutrient-dependent ecological, social, neurogenic and socio-cognitive niche construction are manifested in increasing organismal complexity. Species-specific pheromones link quorum-sensing in microbes from chemical ecology to the physiology of reproduction. The reciprocal relationships of species-typical nutrient-dependent morphological and behavioral diversity are enabled by pheromone-controlled reproduction. Ecological variations and biophysically constrained natural selection for codon optimality links nutritional epigenetics to the behaviors that enable ecological adaptations. All biodiversity is an ecologically validated proof-of-concept. Ideas from population genetics, which exclude ecological factors, are integrated with an experimental evidence-based approach that establishes what is currently known. Simply put, olfactory/pheromonal input links food odors and social odors from the epigenetic landscape to the physical landscape of supercoiled DNA in the organized genomes of species from microbes to man during their development.

Keywords Epigenetic; Biophysics; Ecology; Variant; Constraint; Adaptation; Vitamin; Nutrient; Species; Diversity

Introduction

Charles Darwin's detailed observations [1] provided the prescient framework for a biologically plausible and ecologically valid link from the epigenetic landscape to the physical landscape of supercoiled DNA in the organized genomes of species from microbes to man. His 'conditions of life' were then gradually eliminated from consideration, although ideas about population genetics and mutations added little to human understanding of how the basic principles of biology and levels of biological organization led to Natural Selection or to Sexual Selection.

Nutritional epigenetics underlies what is now known about Darwin's genetically predisposed 'conditions of life.' Biophysically constrained nutrient-dependent ecological factors link conditions of healthy longevity to genetically predisposed ecological adaptations and to species diversity *via* conserved molecular mechanisms. Ideas about constraint-breaking mutations [2] can be viewed in the context of an ongoing neo-Darwinian nightmare that nearly eliminated the physiology of reproduction from further consideration in the context of descent with modification [3]. The ideas that others added to Darwin's theory can now be considered in the context of the nutrient-dependent pheromone-controlled physiology of reproduction.

Darwin may have suffered from concerns about the fact that nutrient-dependent systems have a life-sustaining purpose. Indeed, biological facts make it difficult to explain the natural tendencies of increasing organismal complexity in non-teleological terms. However, the level of difficulty does not excuse attempts to explain increasing nutrient-dependent organismal complexity and species diversity in terms that do not make sense.

More than 40 years ago, the claim was made that "*Nothing in Biology Makes Any Sense Except in the Light of Evolution* [4]." If he was alive today, Dobzhansky would probably agree that current perspectives on nutritional epigenetics make sense in the light of what is known about the conserved molecular mechanisms of ecological adaptations.

In the two parts of this review, I will address what is known about the conserved molecular mechanisms of ecological adaptations. I will also address the question of whether or not current ideas about evolution makes sense in the light of what is currently known about biophysically constrained ecological variations and nutrient-dependent, pheromone-controlled, epigenetically-effected, receptor-mediated ecological adaptations.

In Part one, the focus is on energy-dependent links from angstroms to ecosystems *via* natural selection for codon optimality linked to RNA-mediated amino acid substitutions.

In Part Two, the focus will be on examples of links across a continuum of nutrient-dependent, pheromone-controlled, epigenetically-effected, receptor-mediated ecological adaptations *via* energy-dependent changes in the microRNA/messenger RNA balance and fixation of RNA-mediated amino acid substitutions. The changes in the microRNA/messenger RNA balance also link virus-driven energy theft to all pathology.

Amino Acid Substitutions: Biophysics

Conserved molecular mechanisms of biologically-based cause and effect link sensory input from the epigenetic landscape to the physical landscape of DNA in the organized genomes of species from microbes to man. A direct metal ion atomic-level physical link to the genetic underpinnings of conserved molecular mechanisms exemplifies across-kingdom cause and effect that enables human ecological adaptations.

The direct link from nutritional variation to epigenetic effects on genes and ecological adaptations is clearly indicated when ecological information is combined with population genetics data. Simply put, all organisms naturally select what to eat, and food selection causes physiological specializations that result from natural selection of nutrients in the context of codon optimality and energy metabolism. See [5] for review of flies.

Three mammalian gene families [6] link sensory input from invertebrates to critical functions in vertebrates that include cell type-specific, nutrient-dependent, receptor-mediated metal ion-regulated cardiac excitation-contraction coupling, neuronal signaling and excretion of nutrient metabolites [7-10]. Ecological adaptations and physiological specializations in flies are manifested in distributions of some human hemoglobin variants [11]. The hemoglobin variants are associated with endemic malaria and the thalassemias. The hemoglobin S variant of sickle cell disease links ecological variation and endemic malaria to other hemoglobin variants *via* physiological specializations associated with the metabolism of dairy products.

Lactase Persistence is an Ecological Adaptation

Expression of the enzyme lactase throughout life is called lactase persistence (LP). It is reported to be a genetically determined ancestral trait. Lactase is necessary for the digestion of lactose, which is the main carbohydrate in milk. Milk ingestion, which is associated with experience-dependent lactase production, is down-regulated after the weaning period in most humans and in all other mammals studied. However, genetically predisposed LP is an ecological adaptation in human populations in different parts of the world.

Apparently, different populations of modern humans have adapted to metabolize dairy products. However, LP occurs in populations where people have no problems making vitamin D in their skin. Thus, the calcium assimilation hypothesis associated with LP *via* population genetics can be viewed in the context of ecological adaptations. LP appears to be a nutrient-dependent ecological adaptation driven by the advantages of calcium and vitamin D uptake in human populations that live at latitudes with less sunlight if individuals continued to drink milk after weaning [12].

How do Ecological Adaptations Occur?

A nutrient energy-dependent cascade of interactions associated with the metabolism of fermented milk products in mice suggests that fecal micro biota shared among mammalian conspecifics effect starch and sucrose metabolism. The effects of fecal microbiota were demonstrated *via* RNA sequencing of human gut microbes in mice. The experimental evidence revealed that probiotic bacteria in fermented milk products change the expression of gut microbe genes. The gut microbe genes encode key metabolic enzymes, such as those involved in the catabolism of sugars, which are found in many fruits and vegetables. Mass spectrometry measurement of nutrient metabolites in urine, which were metabolically ramped up in probiotic-fed mice, confirmed the alterations found by analyses on gut microbes from human yogurt eaters [13].

When it is linked to the hemoglobin variant in sickle cell disease, the nutrient-dependent fermented milk product advantage is clear in disease carriers where falciparum malaria is commonly reported in the context of population genetics. Carriers survive the parasitic infection and the carriers reproduce. Other studies of candidate genes, which are not strictly associated with monoallelic variants such as the hemoglobin variants, also show the expected role of nutrient selection for energy-dependent codon optimality and epialleles in population genetics. Simply put, natural selection of nutrients is required for enzyme-dependent energy metabolism, sodium homeostasis, and the ability to digest lactose from milk and starch from plants. See for citations [14].

Ecological Niche Construction is Biophysically Constrained by Nutrient Availability

The likelihood that hemoglobin variants are associated with other beneficial nutrient energy-dependent changes in microbiota populations in the gut can be considered in the context of how balanced nutrition, which includes access to endogenous vitamin C in human populations, supports efficient metabolism and ecological niche construction [13].

Nutrient-dependent epigenetic effects on histone modifications and DNA methylation play an important role in stabilizing cell type identity and in orchestrating many developmental processes. For example, vitamin C appears to stimulate histone demethylases, which appear to alter the de novo creation of functional G protein-coupled genes such as olfactory receptor genes [15-19].

Researchers recently rediscovered a nutrient-dependent epigenetic variant that links vitamin C to what is probably a glucose and glucose dehydrogenase-dependent base pair change. The base pair change results in addition of a methyl group to a cytosine base, which takes on a hydroxyl group to form different 5-hydroxymethylcytosines (5hmCs). Different 5hmCs are associated with differences in cell types that have the same genetic backgrounds. Nutrient-dependent epigenetically-marked bases help to explain how hundreds of cell types in the human body and in the brain [20] are differentiated and how they maintain their glucose-dependent and other nutrient-dependent receptor-mediated identities [21].

For example, calcitriol is the active form of vitamin D. Its effects on the microRNA(miRNA)/messenger RNA (mRNA) balance appear to protect against virus-driven energy theft linked from perturbed protein folding to colorectal cancer. MiRNA-627 targets the mRNA that encodes an enzyme linked to histone demethylation and amino acid substitutions that increase stability of hydrogen bonds in DNA, which are important to protein folding [22]. Rarely does a week go by without yet another report that details cause and effect in the context of miRNAs [23]. For example, the potential for therapeutic use of miRNA-126-5p to treat atherosclerosis was reported in time for me to note the importance of miRNAs to cell type differentiation *via* the circulatory system [24]. However, in Part 1 of this reveiw, my focus is on the role of vitamins in nutritional epigenetics. The importance of the biophysically constrained miRNA/mRNA balance to protein folding that enables structural and functional differentiation of cell types is detailed further in the Part Two of this review.

Structure and Function

Nutrient energy-dependent stimulation appears to change the structural integrity and functional significance of epigenetically stabilized hydrogen bonds and cell types *via* amino acid substitutions. This extends the effects of vitamins from the epigenetic landscape to receptor-mediated intracellular interactions and protein folding. The molecular mechanisms that enable this nutrient-dependent epigenetic stimulation appear to be conserved across phyla as diverse as amoeba and mammals [25]. Experimental evidence from studies of amino acid substitutions and cell type differentiation [26] suggests that a cascade of energy-dependent changes in protein structure and function may begin with a single vitamin-dependent base pair change [15].

Base pair changes may be caused by other environmental effects. However, the conserved molecular mechanisms of nutrient-dependent organizing base pair changes are attributed to the epigenetic effects of food odors and the pheromone-controlled physiology of reproduction [27]. Indeed, methylation of the carbon-5 position of cytosine, which results in differences in 5hmCs, may be the most commonly studied type of nutrient-dependent pheromone-controlled structural and functional eukaryotic modification that results from organizing base pair changes.

Because vitamin C and other vitamins appear to epigenetically effect nutrient-dependent methylation at the level of single-base resolution in mammals, it has become more important to determine how base-pair changes alter intracellular interactions in embryonic stem cells or intercellular interactions in other cells that result in cascades of downstream intracellular and intercellular organizing interactions throughout life. Other vitamins, such as vitamin D, and metal ions such as calcium, iron, lead and manganese also appear to epigenetically alter these organizing interactions. Therefore, a biophysically constrained, nutrient-dependent, epigenetically-effected, receptor-mediated recognizable organized pattern of developmental events during life history transitions can be viewed in the context of ecological variations and ecological adaptations.

Pattern Recognition

Nutrient-energy dependent subatomic particle-level changes may determine the nucleotide changes in a specific base pair. The nucleotide changes appear to link nutrient-dependent single nucleotide polymorphisms (SNPs) from the availability of fruits and vegetables or fermented milk products to individual differences and to species differences in the need for certain vitamins. For example, cell type determination and differentiation are associated with the nutrient-dependent 3D distribution of amino acid substitutions as they accumulate during a history of ecological adaptations [28] in flies [5] and in humans [29]. Sex differences in behavior also appear to arise from the single-molecule and single cell levels in flies, which suggests that adaptive changes in behavior can be explained in the context of nutrient-dependent pheromone-controlled genome-environment interactions that alter circuit plasticity *via* amino acid substitutions [30].

Amino acid substitutions in humans are associated with loss of vitamin C synthesis and loss of uricase production at the advent of urate production as a substitute for vitamin C biosynthesis in primates. Increased availability of vitamin D from fermented milk products and increased availability of vitamin C in the diet of primates link ecological variations and ecological adaptations in areas where nutrient-dependent hemoglobin variants also appear to enable variations in reproductive fitness in populations of modern humans who live where malaria is endemic [29].

Nutrient-dependent epigenetic effects of vitamins appear to work in combinations with ions at the level of hydrogen atom transfer in DNA base pairs in solution in ways that have not been fully considered in the context of ecological variables, nutrient metabolism and ecological adaptations. For example, phosphate is also important in ecological terms. In the context of systems biology, it is often a limiting nutrient in environments and its availability may govern the growth rate of organisms [31]. Furthermore, a recent report suggested that metabolites of phospholipids, which are present in cell membranes, may soon link clinical assays to early diagnosis and treatment of Alzheimer's disease [32].

The complexity of conserved molecular mechanisms involved in the atoms to ecosystems rate-limiting epigenetic effects of phosphate ions and elemental phosphorus are perhaps best exemplified when phosphate-contaminated water drains into lakes and causes problems with algal blooms that may reportedly kill dogs and causes illnesses in people [33]. However, the observed pattern suggests nutritional epigenetics is not something to be considered in the context of one nutrient or nutrient uptake in some but not all species. The pattern suggests nutritional epigenetics must be considered in the context of other ecological factors that link the pattern of nutrient uptake and nutrient metabolism across kingdoms.

From Plants to Animals

In the 'peppered moth' example of a rapid response to human-induced ecological change, experimental evidence suggests the estimated displacement was about 2 km per day [34]. The displacement appears to parallel what experimental evidence has showed about the upwind distance some male moths will fly each evening to find a female that is secreting a nutrient-dependent species-specific blend of attractant pheromones. One study reported what is likely to be a change in moth pheromone-production that was linked to a species-specific sex-linked change in the gene for a transcription factor [35].

The likelihood that eating lead and manganese contaminated leaves caused an ecological adaptation in moth larvae that led to a developmental change in morphology from fawn to peppered color in adults was dismissed when a replication attempt failed. Therefore, the displacement of the moths was attributed to predation more than 80 years ago. See for review [36]. At that time, virtually nothing was known about nutrient-dependent pheromone-controlled biophysical constraints on the biochemistry of invertebrate morphology and behavior. Since then, others have learned that morphology includes nutrient-dependent ecologically adapted pigmentation in insects [37]; in birds [38,39], and in humans [40].

What else has changed during the past 80 years?

Across-species comparisons make the role of nutrient-dependent pheromone-controlled reproduction in species diversity clearer since species-specific pheromones appear to control the physiology of reproduction in species from microbes to man. However, there may always be some confusion about cause and effect. For example, one report linked ecological variation and a single gene to fatty acid metabolism, pheromone production and speciation in flies [28]. Less than one month later, two of the co-authors of the article that attested to nutrient-dependent pheromone-controlled ecological adaptations in

flies linked 1000 mutations in a single gene to mimicry and species diversity in butterflies [41].

The molecular mechanisms of speciation are not likely to vary in flies and butterflies [42], but results from experiments still require interpretations, which are not always placed into the context of a model of cause and effect. The tendency remains for some researchers to report findings based on what might somehow occur in the context of population genetics.

Fortunately, some researchers are now taking an energy-dependent angstroms to ecosystems approach to ecological adaptations, which includes experimental evidence of nutrient-dependent biophysical constraints. Experimental evidence has ecologically validated the role of nutrient energy and/or contaminants in ecological adaptations. However, the complexity of biophysical constraints on nutrient-dependent ecological and pheromone-controlled social niche construction in insects and other species often seems to go without mention and is not typically discussed by evolutionary theorists. More experimental evidence of biologically-based cause and effect will almost undoubtedly move discussions about biophysical constraints, ecological variation and ecological adaptations forward -- if only the discussions are based on what is already known. What is known is that nutrient-dependent epigenetic effects of vitamins appear to cause changes to base pairs that differentiate cell types *via* amino acid substitutions during the development of species-specific morphological and behavioral phenotypes. See for review [26].

Complex adaptations that quickly enable ecological niche construction may begin with single nucleotide polymorphisms (SNPs) in base pairs. The contribution of microbiota and bacterial production of vitamins that alter base pairs and alternative splicing of pre-mRNA appears to be exemplified across invertebrate and vertebrate species in the context of nutrient-dependent ecological niche construction. Clearly, researchers are on the verge of extending what has been learned about nutrient sensors in flies [43] to other species. Researchers are also extending what has been learned about metal ion and amino acid transporters as well as synaptic proteins in round worms and in other model organisms to across-species comparisons through a combination of genetic and functional methods that detail the molecular basis of food choice and mate choice imprinting [28,44,45].

After insects, nematodes and mammals have established their energy-dependent ecological niche, they can either ingest amino acids or use gut microbes to produce them. Use of gut microbes frees them to devote their energies to other aspects of nutrient-dependent survival of the species. This links nutrient-dependent pheromone-controlled ecological niche construction and social niche construction in gut bacteria to ecological niche construction associated with amino acid substitutions and cooperation among competing organisms, which is exemplified in species from microbes to man. See for review [26].

Cooperation and competition also appear to lead to greater organismal complexity when nutrient-dependent amino acid substitutions stabilize the genome in the context of synthetic biology in microbes. Researchers have demonstrated that the loss of biosynthetic genes that led to the loss of uricase in primates [29] may enable ecologically stable metabolic interactions. That loss of biosynthetic genes appears to confer a significant fitness advantage to the microbial strains involved [46]. Similar ecological adaptations link dietary change in mammals to the energy-dependent de novo creation of olfactory receptor genes; to the appearance of pseudogenes; and to species diversity [19,47]. For example, frugivorous bats have relatively larger olfactory bulbs than nonfruit eating bats. Adaptation to frugivory also includes evidence of selection for a glucose transporter gene and skull architecture associated with adaptive radiation in bats [48], which may extend evidence from skull architecture and adaptive radiation to nutrient-dependent epigenetic effects in human populations [49].

Attributing too Much to Vitamins?

In the context of population genetics, others have suggested that snake predation might somehow be responsible for differences in the human brain that are associated with skull architecture [50]. However, the magnitude of cause and effect attributed to vitamin D was only recently revealed. Vitamin D-mediated production of serotonin may be critical for the production of serotonergic signals during neurodevelopment. This indirectly links vitamin D to the development of the brain and changes in the brain associated with skull architecture and brain development throughout adulthood because serotonin plays a critical role in regulating a variety of brain functions, which include social behavior. Vitamin-dependent social behavior is not likely to be considered in the context of population genetics.

For example, few people may fully realize that what they call 'vitamin D' circulates in the blood as the steroid hormone calcitriol. Its ability to alter gene expression has important implications for lowering gastrointestinal inflammation, increasing bone mineral density, and controlling autoimmunity. Nutrient-dependent vitamin D availability could also epigenetically effect social functioning *via* the synthesis and response to oxytocin and the response to vasopressin. For a recent review of other epigenetic effects that might be attributed to vitamin D, see Patrick and Ames [51] who note that the complete details of likely benefits of vitamin D are outside the scope of their article.

Attempts to focus on one steroid hormone also limit the broad-based representations of hormone-organized and hormone-activated changes in the brain and behavior described in other reviews. See for example [52]. Thus, the complete details of the likely benefits of natural selection for food or for any specific vitamin or nutrient that epigenetically effects the hormone-organized and hormone-activated development of the brain and behavior is outside the scope of the first part of this review. Others will no doubt continue to detail the cascade of epigenetic effects attributed to micronutrients and macronutrients. Explanations that incorporate the epigenetic effects of vitamins can then be compared to explanations of changes in morphological and behavioral phenotypes that do not incorporate what is known about conserved molecular mechanisms.

Moving forward, the link from nutritional epigenetics to alternative splicing of pre-mRNA in different tissues seems to be clear [53]. Alternative splicings and amino acid substitutions that lead to stable protein folding or to misfolded proteins, which are attributed to destabilizing mutations, are on the verge of being more thoroughly examined in the context of cause and effect relationships [54]. Explanations of how and why epigenetically-effected perturbed networks of proteostasis are associated with diseases and disorders can be compared to how pathology-free conformational states are maintained across species [55]. Nutritional epigenetics and alternative splicing techniques of pre-mRNA will probably continue to become more important considerations in the context of health when alternative splicings are compared to their role in mutations and pathology.

Molecular Epigenetics and Alternative Splicing Techniques of Pre-mRNA

In our review of hormone-organized and hormone-activated behavior [52] we included a section on molecular epigenetics with information on how epigenetic imprinting occurs in species as diverse as yeast, flies, mice, and humans. Imprinting was attributed to small DNA-binding proteins called 'chromo domain' proteins, e.g., polycomb. The polycomb proteins alter chromatin structure, transcription and silencing of various genes. Sexual differentiation in two species also appeared to be altered by small intranuclear proteins that participate in generating alternative splicing techniques of pre-mRNA. "*That similar proteins perform functions in humans suggests the possibility that some human sex differences may arise from alternative splicings of otherwise identical genes* [52]." Our model of hormone-organized and hormone-activated behavior detailed what appeared to be an across-species continuum of molecular epigenetics from yeasts to humans. The model was subsequently extended to hormone-organized and hormone-activated behavior in insects [56] and to the honeybee model of life-history transitions [57].

Neurogenetic analyses in flies have since confirmed that sex differences in behaviors, including courtship behaviors are due to transcription factor genes that determine the development of sexually dimorphic neural circuitries in a sex-specific manner [45]. Experimental evidence and common sense take the concept of transcription factor genes and hormone-organized and hormone-activated behavior a step further in the context of what is known about nutrient-dependent alternative splicings and amino acid substitutions. The amino acid substitutions are associated with gene loss and with the de novo creation of olfactory receptor genes or creation of pseudogenes that facilitate receptor-mediated nutrient uptake and metabolic diversity, which appear to be the driving force of ecological adaptation in species from microbes to man. Thus, olfaction and odor receptors provide a clear trail that can be followed from ecological adaptations in unicellular organisms to ecological adaptations in insects and in humans. See for review [27].

Section Two: The microRNA/Messenger RNA balance

The driving force of ecological adaptation?

Experimental evidence continues to add support for the role of ecological variation and nutrient-dependent epigenetically-effected ecological adaptations that occur *via* amino acid substitutions, which determine the cell types of individuals in all species. More substantial support for epigenetic effects on cell type differentiation comes from what has been learned during the past decade about the role of small non-coding RNA molecules. The small non-coding RNA molecules that were called pre-mRNAs are now called microRNAs (miRNAs). MiRNAs alter intercellular signaling by changing the balance between miRNAs and messenger RNA (mRNA). The changes are linked to health and to pathology [58].

One paragraph of speculation unsupported by experimental evidence

Nutrient-dependent changes in glucose- and glucose dehydrogenase-dependent hydrogen bonds of base pairs might alter the hydrogen bonds of miRNAs. Altered hydrogen bonds in miRNAs could alter the miRNA/mRNA balance. The cascade of nutrient-dependent, epigenetically-effected, pheromone-controlled, receptor-mediated ecological adaptations might result in alternative splicings of RNA and fixation of amino acid substitutions that determine cell types in individuals of different species. Nutrient-dependent pheromone-controlled amino acid substitutions and host specialization probably led to evolutionary divergence *via* reciprocal miRNA/mRNA interactions that differentiate the cell types of individuals in different species.

On the way from one paragraph of speculation to what is supported by more experimental evidence, I now note that it is beyond the scope of this review to prove anything to anyone. However, a single– amino acid change enabled a unicellular pathogen to affect a specific host by disabling an enzyme in the host. The tragic result was the Irish Potato Famine [59]. Although no epigenetic effect of a specific nutrient on a specific base pair that conclusively led to a specific amino acid substitution was demonstrated, nutrient-dependent amino acid differences link algae to cell type differentiation in plants [60]. Thus, the atoms to ecosystems approach continues to be based on some speculation, but it is also based on experimental evidence, which comes from others who also have speculated about biologically-based cause and effect in the context of the miRNA/mRNA balance and amino acid substitutions.

Nutrient-dependent microbe-plant-animal interactions

Experimental evidence suggests that ingested bacteria alter signals from cells in the intestine of nematodes, which enable the organism to respond and consume more of that bacteria [61]. This makes sense in the context of a recent review that clearly differentiated effects of what appear to be nutrient-dependent changes in the miRNA/mRNA balance and amino acid substitutions on gene networks and differences in the morphological and behavioral phenotypes of nematodes without teeth and nematodes with teeth [62,63].

The nematode without teeth is one of several model organisms that exemplify nutrient-dependent pheromone-controlled fixation of amino acid substitutions associated with alternative splicings of pre-mRNA. The alternative splicings of pre-mRNA appear to differentiate the cell types of one nematode from the cell types of the other nematode in the context of pheromone-controlled ecological, social and neurogenic niche construction, which are linked to differences in morphological and behavioral phenotypes. See for review [26].

The nutrient-dependent pheromone-controlled physiology of reproduction in a model of vibrio-squid symbiosis, links the flagellar shaft rotation of the bacteria to beneficial microbe-animal interactions in an aquatic invertebrate. Bioluminescent bacteria in sea water colonize newly hatched Hawaiian bobtail squids. The bacteria get nutrients from the squid. Their nutrient-dependent pheromone-controlled reproduction results in a population-wide 'tipping point,' and they collectively emit light that the squid uses to avoid predation [64].

In a terrestrial invertebrate, amino acids derived from pollen and other ingested chemicals that butterflies eat were liked by theories of population genetics to wing patterns and bird predation based on the chemical appeal of the butterfly [65]. Amino acid substitutions and transposable elements link nutrient-dependent genome diversity within Heliconius butterflies to ecological adaptations and pheromone-controlled genome diversity within moths [37].

In section one, I mentioned the moth larvae that ate leaves contaminated with lead and manganese. Their fawn color changed to a

peppered color [34], which appears to be an example of nutrient-dependent pheromone-controlled plant-animal mutualisms in the context of ecological adaptations and color changes that are controlled by the physiology of reproduction in all animal species [3]. Results from recent studies of insect predation also suggest that ecological factors such as soil nutrient levels; weather; how plants respond to their environment; and intraspecific competition link trophic variations associated with nutritional value, toxin content and visual signals of prey to the specific micronutrients and/or macronutrients found in the tissues of predatory birds [66].

The links from soil nutrients to toxins in insects associated with the color patterns of butterfly wings and to predator aversion exemplifies the complexity of nutrient-dependent pheromone-controlled ecological adaptations across species that may seal the fate of a specific butterfly population. Mathematical models of evolution eliminate this complexity. They incorporate the nutritional content of prey as a variable, which suggests that predators somehow select for up to ~1000 inherited differences in nucleotides [42]. The different inherited nucleotides are supposedly somehow involved in the regulation of a single gene that results in different-colored wing patterns.

By excluding ecological variation and nutrient-dependent pheromone-controlled amino acid substitutions from consideration, neo-Darwinian Natural Selection *via* bird predation in butterflies appears to be determined by two things: 1) whether or not the butterfly had previously ingested chemicals associated with toxicity; and 2) whether or not the predatory bird had previously somehow associated the visual appeal of an ingested look-alike butterfly with its nutrient-dependent toxicity [42]. Thus, theoretically, neo-Darwinian Natural Selection occurs because a predatory bird is less likely to eat - more than once - a butterfly with a wing pattern of color the bird has already associated with the nutrient-dependent toxicity of a mimic.

Simply put, even non-toxic mimics are less likely to be eaten and predatory birds control reproduction of some moths. Darwin insisted that his 'conditions of life' be considered before Natural Selection was considered [67]. Therefore, the nutrient-dependent pheromone-controlled 'conditions of life' of butterflies with wing color patterns that mimic those of butterflies that have eaten substances, which are toxic to predatory birds, have been assigned a secondary priority. In neo-Darwinian Natural Selection, selection occurs long after the nutrient-dependent pheromone-controlled 'conditions of life' have been established *via* conserved molecular mechanisms in species from microbes to butterflies. Neo-Darwinian Natural Selection, in butterflies, suggests that the visual appeal of an organism, which is associated with differences in nucleotides, somehow became the determinant of selection, and that predatory birds, not nutrient-dependent pheromone production, determines the reproductive fitness of these butterflies [42].

Plant spores on materials that hummingbirds use to make nests are essential to synzoochoric mutualism between the hummingbird and one fern species and seven moss species [68]. Other microbe-plant–animal mutualisms are among the key ecological interactions that seem more likely than mimicry to generate and maintain biodiversity across species of invertebrates and vertebrates [69,70]. In a recent report, mimicry in snakes is attributed to conserved pigments but not attributed to mutations or to ecological factors linked to amino acid substitutions [70].

No significant sequence homology has been found between the miRNAs of plants and animals. However, the finding that plant miRNAs are stable in the blood and other tissues of mice and humans [71] establishes what appears to be an across-species causal link from the diversity of microbes such as bacteria and yeasts [72] to nutrient-dependent epigenetically-effected changes in the miRNA/mRNA balance and the diversity of plants and animals [73].

A biological process that is central to life in the plant and animal kingdoms

Posttranscriptional regulation of gene expression by miRNAs is a central biological process in plant kingdom and in animal kingdom. Similarities in co-existing genes in a starlet sea anemone and a species of coral suggest that the function of the genes that are regulated by the miRNA/mRNA balance has diverged over a long time. Divergence is known to occur in insects, when miRNAs are preferentially loaded into two different subfunctional proteins associated with nutrient-dependent amino acid substitutions [74]. Similarly, phylogenetic analysis of amino acid matrices from concatenated protein sequences appears to support the placement of aquatic invertebrates, called comb jellies, as the sister group to all other animals [75]. This includes animals that link the comb jellies to terrestrial invertebrates with nervous systems and to aquatic and terrestrial vertebrates *via* the conserved molecular mechanisms of nutrient-dependent epigenetic effects on conserved molecular mechanisms of pheromone-controlled reproduction. The conserved molecular mechanisms that enable nutrient-dependent amino acid substitutions probably enable ecological adaptations in the cell types of all animals.

For example, species-specific amino acid changes and positively selected genes, which include olfactory receptor genes in minke whales [76] extend the concept of nutrient-dependent pheromone-controlled ecological, social, neurogenic and socio-cognitive niche construction from killer whales [77] to ecologically adapted terrestrial predators. Indeed, the conserved molecular mechanisms of species diversity appear to incorporate dual encoding of amino acid sequences and regulatory information in the organized DNA of all complex genomes [78].

From killer whales to a competent terrrestrial predator

Exogenous plant miRNAs appear to be acquired orally, primarily through food intake in human subjects [71]. Based on what occurs *via* conserved molecular mechanisms in plants and other animals, others have suggested that miRNAs are the bridge between ecological variation in the availability of nutrients and nutrient uptake in different organisms, which is probably essential for differential gene expression and species diversity *via* post-transcriptional silencing of nutrient-dependent miRNA-facilitated mRNA translation in animals [79].

Clearly, gene expression is somehow controlled by epigenetic effects on transcribed small RNAs [2]. Experimental evidence suggests nutrient-dependent epigenetic effects on vitamin-dependent base pair changes lead from changes in the miRNA/mRNA balance to fixation of amino acid substitutions and the differentiation of cell types. That makes it possible to begin with nutrient-dependent changes in base pairs and to tentatively arrive at the morphological and behavioral phenotypes of different species based on what is currently known about the involvement of the miRNA/mRNA balance in species diversity. Simply put, nutrient-dependent pheromone-controlled ecological adaptations *via* fixation of amino acid substitutions [26] appear to require fine-tuning of conserved molecular mechanisms in

species from microbes to man [27]. The nutrient-dependent miRNA/mRNA balance is probably responsible for that fine-tuning in plants and in animals.

Biophysical Constraints on Ecological Adaptations

Experimental evidence suggests that miRNAs act as signaling molecules in intercellular communication. Some miRNAs appear to become long non-coding miRNAs that differentiate tissue-specific cell types associated with physiological aspects of health and pathophysiological aspects of disease. Extracellular miRNAs appear to alter the intercellular thermodynamics of hydrogen bonds in cell types that link cardiovascular biology to atherosclerosis *via* the presence of miRNAs in the circulatory system of mammals [24,80]. Others have suggested that de novo gene creation may occur more frequently than gene duplication [81].

The fact that ecological adaptations in microbes [82] are biophysically constrained by niche construction [83] has led others to consider the likelihood that the nutrient-dependent creation of epialleles is the substrate for ecological adaptations and species diversity. Thus, the role of ecological adaptations can be compared in the context of theories about whatever substrates are loosely associated with actions, such as those of predatory birds on butterflies [42], that might somehow result in species diversity [84].

The presence of miRNAs in the embryonic cerebrospinal fluid [85] and in the circulatory system of mammals links epigenetic effects of nutrients that are manifested in mammalian embryonic development to the apparent ability of miRNAs to alter cell types in the circulatory system, which appears to extend to the ability of miRNAs to alter cell types in the heart, brain and other tissues throughout the life of mammals. However, the complexity of systems biology may be difficult to grasp [86,87].

Nevertheless, it appears that vitamin-induced changes in base pairs and nutrient-dependent changes in the miRNA/mRNA balance, which alter the post-transcriptional silencing of mRNA translation, can also be considered in the context of amino acid substitutions, hemoglobin variants, cardiovascular disease, and differentiation of cell types associated with atherosclerosis and mosaic copy number variation in neurons of the human brain [88]. Indeed, there may be nothing about nutrient-dependent ecological variation that is not somehow linked to biophysically constrained epigenetically-effected ecological adaptations in species from microbes to man.

Experimental evidence suggests that accelerated development of specific areas of the human brain may be shaped by changes in miRNA expression. Analyzing differences in miRNA and mRNA expression in two brain regions of two non-human primates and comparing the differences in macaques, chimpanzees, and humans throughout their lifespan showed that species-specific gene expression divergence, which was independent of age, is comparable between humans and chimpanzees. Accelerated development of the prefrontal cortex (PFC) was associated with differences in miRNA and mRNA expression that differentiated humans and chimpanzees from macaques [89,90].

In the context of nutrient-dependent amino acid substitutions, it may be of interest to note that Dobzhansky was aware that amino acid substitutions might have caused hemoglobin variants, which were linked more than 40 years ago to primate species diversity. What is now suspected about the nutrient-dependent pheromone-controlled miRNA/mRNA balance, supports biological facts reported by Dobzhansky. "*...the so-called alpha chains of hemoglobin have identical sequences of amino acids in man and the chimpanzee, but they differ in a single amino acid (out of 141) in the gorilla* [4]."

During the past 40 years, accumulated experimental evidence shows that conserved molecular mechanisms of nutrient-dependent changes in the miRNA/mRNA balance alter the post-transcriptional silencing of mRNA translation. This does not prove that nutrient-dependent pheromone-controlled epigenetic effects are the mechanism by which our epigenetic landscape alters morphological and behavioral phenotypes [71]. Minimally, however, cause and effect relationships that link nutrient-dependent epigenetic effects of sensory input to the physical landscape of DNA in organized genomes and to morphological and behavioral phenotypes suggest ecological variation in nutrient availability alters the miRNA/mRNA balance. The miRNA/mRNA balance may drive ecological adaptations *via* conserved molecular mechanisms in animals. This may also occur in plants and in every other form of life. Indeed, experimental evidence suggests that the stability of protein folding is conserved *via* the same molecular mechanisms in all genera in all ecologies [91].

The importance of experimental evidence that clarifies the role of conserved molecular mechanisms across species cannot be overstated because it has repeatedly shown that there are biophysical constraints on nutrient-dependent changes in the miRNA/mRNA balance. The biophysical constraints involve hydrogen bonds. The hydrogen bonds may be altered by the epigenetic effects of vitamins, which alter miRNA and protein folding. Thus, it is conceivable, although it has not been shown in all organisms, that nutrient-dependent epigenetically-effected changes in base pairs and in miRNAs modulate the thermodynamic stability of hydrogen bonds and/or the translational efficiency of their target messenger mRNAs that differentiate cell types in individuals of all species *via* biophysically constrained conserved molecular mechanisms of amino acid substitutions. See for review [92].

What Could Possibly Go Wrong?

Evidence from population genetics conflicts with experimental evidence of ecological adaptations. It suggests that species diversity somehow arises from constraint-breaking mutations [2]. It is important to note that evidence from population genetics is not experimental evidence and that no evidence from population genetics indicates what constraints are broken by mutations or how constraint-breaking mutations result in species diversity. Therefore, although it should not be unacceptable to ask questions about an accepted null hypothesis, these questions remain unanswered. Does something unusual happen to base pairs? Does something atypical happen to the miRNA/mRNA balance or to stabilizing amino acid substitutions? Has anyone ever suggested how anything outside the realm of what is currently known about biophysically-constrained conserved molecular mechanisms of ecological adaptation might cause species diversity?

One way to move from these unanswered questions to what is known about species diversity is to compare the evidence from population genetics to experimental evidence of ecological adaptations. The evidence from population genetics appears to suggest that constraint-breaking mutations alter biophysically-constrained nutrient-dependent epigenetically-effected protein biosynthesis and degradation. This puts suggestions based on evidence from population genetics into the context of experimental evidence that has been used to detail how the basic principles of biology and levels of biological

organization link sensory input from the epigenetic effects of food odors and pheromones [27] to morphological and behavioral phenotypes *via* the gene-cell-tissue-organ-organ system pathway [26].

Simply put, biologically plausible and ecologically validated nutrient-dependent epigenetic effects appear to biophysically constrain the conserved molecular mechanisms of species diversity, which are associated with the base pair changes that appear to result in changes in the miRNA/mRNA balance and amino acid substitutions that provide the thermodynamically stable structure of functional proteins. Biophysically constrained amino acid substitutions also appear to establish typical morphological and behavioral phenotypes.

Mutant conspecifics with three eyes are unlikely to arise either from constraint-breaking mutations or from amino acid substitutions. Similarly, constraint-breaking mutations are not likely to result in increased organismal complexity. Instead, perturbations in protein folding are a likely link from mutations to physical diseases and mental disorders associated with nutrient-stress and social stress. Unlike nutrient-dependent epigenetic effects on amino acid substitutions that stabilize the genome, mutations perturb genomic stability. Perhaps that explains the findings from one model organism, a nematode. Apparently, genetic diversity can be maintained indefinitely without one allele or the other ever being fixed in the population [93]. Perhaps evidence from one model organism that suggests mutations are not fixed extends across all organisms *via* conserved molecular mechanisms. It seem metaphorically inappropriate for conserved molecular mechanisms to fix anything that is not broken, or to break something by fixing a mutation in DNA that codes for a dysfunctional protein or that causes dysfunctions in networks of other proteins.

Modeling the role of nutritional epigenetics in ecological cause and effect, and explaining that role in simplistic terms of how nutrient-dependent species diversity arises *via* an amino acid substitution that differentiates morphology and behavior in nematodes [62] may help to clarify the role of mutations in diseases and disorders compared to ecological variation and ecological adaptations. However, some people may want more details on the role of mutations, which is why I will briefly address them before returning to the central theme of nutritional epigenetics. I will only touch on the most basic concerns that differentiate the theory of mutation-driven evolution from a model of nutritional epigenetics and ecological adaptations.

Is mutation-driven evolution a biologically plausible null hypothesis?

The conservation of the sequence and secondary structure of miRNA-451 among vertebrates suggests that biophysical constraints on conserved molecular mechanisms maintain specific miRNA processing pathways, which appear to be involved in ecological adaptations. Experimental evidence shows that mutation-induced differences in several miRNAs appear to be processed in the absence of Dicer, which is believed to be a central processing enzyme in the maturation of small RNAs. A link from miRNA analysis in wild type and in MZdicer and MZago2 mutants also revealed that posttranscriptional regulation of miRNA-451 levels alters erythrocyte maturation in zebrafish.

Alterations in erythrocyte maturation in zebrafish link miRNAs to differences in the 1182 monoallelic human hemoglobin variants that determine the oxygen-carrying capacity of erythrocytes [11]. I mentioned above that the hemoglobin S variant appears to be among other nutrient-dependent hemoglobin variants. If so, hemoglobin variants might be linked *via* a pre-miRNA from conserved molecular mechanisms that biophysically constrain physiologically functional miRNA structure to maintenance of the pre-miRNA to miRNA sequence in the context of different cell types in individuals of species as different as deer mice [94] and hummingbirds [95].

The pre-miRNA to miRNA sequence results in the secondary structure of miRNA-451 across vertebrates. Thus, the molecular origins of the vertebrate miRNA lineage provided a means to genetically dissect the functions of individual vertebrate miRNAs [96]. This likely cause and effect relationship could be examined in more detail by anyone who is unwilling to accept the representations of biophysically constrained cause and effect in this review. For example, preliminary reports link miRNA repression to cancer [58]. Dissecting the functions of individual vertebrate miRNAs could lead to findings that support an unknown role of mutations in species diversity, but that role seems likely to be associated with pathology.

For example, an experimentally-induced mutation blocks the synthesis of a fatty acid, which alters synaptic plasticity, learning and memory in mice. Mutation-induced changes appear to consistently link atypical and detrimental effects on learning and memory from mice to human activity-dependent thought processes *via* conserved molecular mechanisms [97]. However, if not for the human ability to detect fatty acid content in foods [98] and the human ability to detect social odors linked to sickness [99], this review might end here.

Attestations to human olfactory prowess and our ability to sniff out differences in the nutritional value of food and our ability to sniff out differences in the health of conspecifics are required. Otherwise, there is no logical way to link olfactory/pheromonal input [100] to human cognition *via* conserved molecular mechanisms [101], and no way to compare any neuro-psycho-evolutionary ideas about the emergence of the mind, which have been portrayed by others. For example, see *The "Id" Knows More than the "Ego" Admits* [102].

Instead of simply accepting the blow to my ego that has repeatedly been delivered by human pheromone-deniers [103], who seem to think our ability to detect social odors in not comparable to our ability to detect ecological variation in nutrients *via* food odors, I will transition back to the focus on biophysically constrained nutrient-dependent epigenetic effects on hydrogen bonds and amino acid substitutions. Fortunately, the conserved molecular mechanisms that enable us to detect difference in food odors and pheromones can now be viewed in the context of substitution of the achiral amino acid glycine in the gonadotropin releasing hormone (GnRH) decapeptide in vertebrates.

Substitution of glycine

Researchers who have already noted the importance of feedback loops in microbes [104] and mammals [105] will welcome information that appears to link an amino acid substitution to genomic stability. Glycine is the only achiral amino acid and GnRH secretion is a conserved feature of what appears to be vertebrate ecological adaptations [106].

Similarities and differences in epigenetically-effected vertebrate nutrient-dependent pheromone-controlled ecological adaptations suggest the ecological adaptations are biophysically constrained by the substitution of glycine in the GnRH decapeptide of vertebrates. Similarities in the glucose-dependent pheromone-controlled modulation of GnRH pulse frequency and amplitude in mammals [107] might even be one way to recognize differences in the thought processes of vertebrates and invertebrates.

Experimental evidence suggests that humans gained the ability to think about the epigenetic effects of food odors and pheromones on our behavior, although few people are consciously aware of how important those epigenetic effects of input might be [100]. However, some scientists are aware of the importance of GnRH to the biology of nutrient-dependent pheromone-controlled vertebrate behavior.

For example, food odors and pheromones alter the pulsatile secretion of GnRH, which links the conserved molecular mechanisms of nutrient-dependent pheromone-controlled ecological adaptations in yeasts at the advent of sexual reproduction [104] to nutrient-dependent-pheromone-controlled reproduction in mammals [105]. See for review [26,27]. An evolutionary continuum of ecological adaptations indicates that the ancient mechanisms of cell division arose from nutrient-dependent epigenetically-effected intercellular diversity that altered the genome. The intercellular diversity appears to have enabled chromosomal rearrangements that led to sex differences associated with ecological, social, neurogenic and socio-cognitive niche construction, which is manifested in the increasing organismal complexity of species from microbes to man.

The amount of energy as information carried *via* the link from food odors and pheromones to the pulsatile secretion of GnRH in vertebrates, can be compared to what is known about the difference between information carried across systems *via* a series of on/off switches. Metaphorically, pulses of GnRH could be described as "Pulses of information sent along the telegraph that generate a code for letters and as a consequence sentences can be communicated. This converts the same signaling pathway from a simple on/off switch to a device that can transfer, for example, the works of Shakespeare [108]." That concept of information transfer has since been technically represented in the context of simultaneous encoding of amino acid and regulatory information within exons [78].

In the context of secreting, sensing and signaling [109], which links ecological variation from the epigenetic landscape to the physical landscape of DNA in the organized genomes of species from microbes to man *via* feedback on one central signaling pathway, it is not surprising that the Shakespeare metaphor also appears in the context of a recent report that linked de novo creation of miRNAs to expansion of the outer subventricular zone (OSVZ) in primate brains. The following quote from the senior author of a miRNA- OSVZ-primate brain article [110], appeared in a news report."The OSVZ gave rise to primates' expanded brains and to the cells that ultimately brought us Shakespeare [111]." Clearly, there are times when metaphors may help non-scientists to better realize what molecular biologists are saying about ecological adaptations, which enable information transfer from the sensory environment. Metaphorical interpretations may or may not enter our conscious thoughts until we are reminded of something that Shakespeare said, or that we think he might have said about our sense of smell.

Current Evidence that Supports Past Conclusions about the Birds and the Bees

The ability of nutrients to epigenetically effect changes in base pairs and to alter the miRNA/mRNA balance appears to link food odors; cell type-specific alternative splicings of pre-mRNA; de novo gene creation and pseudogene creation; chromosomal rearrangements and the metabolism of nutrients to species-specific pheromones that control the physiology of reproduction in species from microbes to man [26,27,52,100]. The bottom-up epigenetic effects of food odors associated with nutrients and the top-down epigenetic effects of pheromones seem to act within the context of biophysically constrained conserved molecular mechanisms that finely tune the transcriptional output of different alleles.

Ecological variation and the fine-tuning of different alleles [112] appears to enable ecological adaptations and species diversity *via* epigenetic effects on monoallelic gene expression [18,113-118]. The molecular logic and the perceptual logic of the epigenetic effects of olfactory/pheromonal input on ecological, social, neurogenic, and socio-cognitive niche construction was placed into the context of ecological adaptations in a recent review [119].

Examples of niche construction that have not yet have received consideration in the context of any review at the time of this submission include a recent report that links nutrient-dependent pheromone-controlled ecological variation to ecological adaptations in birds. Two fixed differences among 597 amino acids drive a valine to alanine polymorphism that distinguishes morphological and behavioral phenotypes in white throated sparrows. In a clear indicator of what a single amino acid substitution can do, estrogen receptor 1 (ESR1), which is the gene that encodes estrogen receptor alpha (ERa), is most closely associated with what appears to be different nutrient-dependent hormone-organized and hormone-activated adult behavioral phenotypes. Subtle differences in parental feeding behavior appear to lead to transgenerational epigenetic effects on behavior. The difference in biparental feeding compared to single-parent feeding seems to enable the manifestations of chromosomal rearrangements in hormone-organized and hormone-activated ecological adaptations [120] associated with social odors and the physiology of reproduction in birds [121]. Nutrient-dependent effects of vitamin E and fatty acids in birds have also been linked *via* flight exercise to brain development [122]. These nutrient-dependent epigenetic effects can be compared to the nutrient-dependent epigenetic effects of vitamin D [51] on the differentiation of morphological and behavioral phenotypes associated with maternal behavior in mammals [123-125].

Recently, the difference between an epigenetic effect on hormone-organization and hormone-activation and an effect on behavior was clarified [126]. That clarification may make it easier for others to understand how nutrient-dependent pheromone-controlled epigenetic effects on hormones affect behavior. The ability of mutations to somehow positively affect behavior can be considered in the same context.

A more telling recent review is one that links evidence of conserved molecular mechanisms in insects such as honeybees to alternative splicings, which appear to be the "...driving force behind the wide radiation, rapid evolution and evolutionary success of eukaryotic organisms [127].""Nutritional Control of Reproductive Status in Honeybees *via* DNA Methylation" [128]; "Extensive histone post-translational modification in honey bees" [129] and what is known about "DNA methylation dynamics, metabolic fluxes, gene splicing, and alternative phenotypes in honey bees" [130] also link ecological adaptations from invertebrates to vertebrates *via* conserved molecular mechanisms.

Current Evidence Supports Past Conclusions: Mammals

Concentrations of circulating cell-free DNA (cfDNA) between 0 and 100 ng/ml have been reported in people. The conserved molecular mechanisms that enable cfDNA transfer from cells to circulation are

being examined from different theoretical perspectives. For example, apoptosis might cause the DNA in complexes with glycoproteins to be actively released into the bloodstream where it could act as a signaling molecule in different signal transduction pathways. This might link genetic and epigenetic alterations of cfDNA to genometastasis or to genomeepistasis. For example, animal studies suggest that small fragments of nucleic acids may pass to the bloodstream and even get into various tissues. If so, food may be a source of DNA fragments that sometimes avoid total degradation during digestion, which allows them to enter the circulation and get into the tissues of goats, pigs, and mice [131]. The presence of miRNA in circulation may link networks of miRNAs *via* protein biosynthesis and degradation to specific carbohydrate codes *via* the complexities of nutrient-dependent intracellular thermodynamics and organism-level thermoregulation [132].

Complaint department: The complexity of systems biology is overwhelming

No one expected that detailing the conserved molecular mechanisms of ecological adaptations that result from ecological variations would be easy. That may explain the popularity of population genetics and theories that remove geographical and ecological factors from consideration [133]. For comparison, the title of my first presentation to a scientific assembly was "Luteinizing hormone: The link between sex and the sense of smell?" [134]. The question mark was added to the title to indicate there was a lack of conclusive proof, in 1992. Since then, many others have learned what was summarized in a recent report on goats [135]. Simply put, the reproductive center of all vertebrates is the same and so are the conserved molecular mechanisms that enable the epigenetic effects of food odors and pheromones to be manifested in GnRH-directed changes in luteinizing hormone (LH).

The putative human pheromone, androstenol alters LH secretion in human females [136]. Male axillary extracts alter LH secretion and mood in women [137]. Therefore, it seems likely that nutrient-dependent epigenetic changes in circulating miRNAs and epigenetic inheritance in mammals [138] could be measured by subtle changes in LH, which link sex and the sense of smell and that may link pheromones to non-invasive treatments of neurodegenerative disease [139] or atypical social behaviors.

Summary

Do enzymes such as glucose dehydrogenase allow organisms from microbes to man to incorporate nucleotides from other organisms into new structures associated with glucose uptake and amino acid substitutions? There is still a lack of conclusive proof that links DNA uptake among different bacterial species existing in similar environments [140] to nutrient-dependent epigenetic effects on interspecies changes in the physical landscape of DNA and speciation *via* conjugation in bacteria [141-143]. However, there are clear indications that microbial reproduction began with an active nutrient uptake mechanism in heterospecifics and that the mechanism of ecological adaptation led to symbiogenesis in the conspecifics of asexual organisms [144].

In yeasts, nutrient-dependent epigenetic changes might then have led to the creation of novel cell types, which are required at advent of ecological adaptations that led to sexual reproduction [145]. These nutrient-dependent epigenetic changes in the pheromone-controlled physical landscape of DNA in microbes probably occur across a continuum of ecological adaptations that includes both nutrition-dependent reproduction in unicellular organisms and sexual reproduction in mammals. For example, ingested plant miRNAs influence gene expression across kingdoms [146]. In mammals, this epigenetically links what mammals eat to changes in gene expression [13] and to new genes required for the evolutionary development of the mammalian placenta [147] and the human brain [148].

MiRNA-mediated regulation of glucose-dependent biological processes involved in immune system function and embryogenesis also appears to link glucose-dependent receptor-mediated alternative splicings of pre-mRNA and cell type-specific genes. Multiple genes may be concurrently targeted, which suggests that the same miRNA simultaneously controls multiple genes *via* changes in the miRNA/mRNA balance during the development of morphological and behavioral phenotypes. Micronutrients and macronutrients clearly facilitate amino acid substitutions and the de novo creation and differentiation of cell type that could not exist outside a thermodynamically regulated glycosylation network [132] of protein folding, which is required for nutrient-dependent organism-level thermoregulation. Constraint-breaking mutations probably perturb protein folding, which suggests they contribute to pathology and that they are unlikely to contribute to species diversity *via* the conserved molecular mechanisms of nutritional epigenetics that result in the pheromone-controlled physiology of reproduction.

The complexity of systems biology that appears to link the epigenetic landscape to the physical landscape of DNA makes it difficult to conclusively prove that Darwin's 'conditions of life' [1] are nutrient-dependent and pheromone-controlled. Nevertheless, it appears that biophysical constraints and biological laws deserve more consideration than they have been given in the context of how species diversity arises.

Biological Laws

Biophysical constraints and biological laws appear to link ecological variation to ecological adaptations *via* conserved molecular mechanisms in all species. For example, nutrient-dependent ecological niche construction leads to pheromone-controlled social niche construction *via* the nutrient-dependent pheromone-controlled physiology of reproduction. The nutrient-dependent origin of amino acid substitutions in viruses [149-152], which also are manifested in plant and animal interactions, exemplifies a continuum of biological plausibility and ecological validity in the context of Laws of Biology. These Laws of Biology include Kohl's Laws of Biology, which are so-named because the surname of the first author or sole author on each of 7 peer-reviewed publications in the paragraph below is Kohl. The Kohls did not create the Laws of Biology; they merely independently incorporated what is known about them into what appears to be a cohesive series of published works.

Kohl's Laws of Biology

Life is nutrient-dependent. That is a Biological Law. The ecological origin of all biological laws is apparent 1) in the context of systems biology [87]; 2) in the context of the metabolism of nutrients by microbes [153]; and 3) in the context of how the metabolism of nutrients results in species-specific pheromones that control the physiology of reproduction [154]. Taken together, the systems biology of nutrient metabolism to species-specific pheromones, which control

the physiology of reproduction, can be expressed in a summary of Kohl's Laws of Biology: 1) Life is nutrient-dependent. See for review [27,155]. The physiology of reproduction is pheromone-controlled. See for review [26]. In the context of nutrient-dependent epigenetically-effected human reproduction, it is clearer that the epigenetic effects of human pheromones integrate neuroendocrinology and behavior [100], which includes the neuroendocrinology of mammalian behavior associated with the development of sexual preferences [156].

Kohl's Laws help to explain what was missing from Darwin's 'conditions of life.' Darwin knew nothing about genetics, which means he knew nothing about the epigenetic effects of food odors or pheromones. For contrast, the following representation of cause and effect acknowledges what is known today:

"James Kohl, an independent researcher who also markets "human pheromones" to the general public, believes that pheromones may have a primary influence in setting up a person's basic sexual orientation. Other, more consciously perceived aspects of attractiveness, such as facial appearance, are attached to a person's basic orientation through a process of association during early postnatal life, according to Kohl.

This model is attractive in that it solves the "binding problem" of sexual attraction. By that I mean the problem of why all the different features of men or women (visual appearance and feel of face, body, and genitals; voice quality, smell; personality and behavior, etc.) attract people as a more or less coherent package representing one sex, rather than as an arbitrary collage of male and female characteristics. If all these characteristics come to be attractive because they were experienced in association with a male- or female-specific pheromone, then they will naturally go together even in the absence of complex genetically coded instructions."

Still, even in fruit flies, other sensory input besides pheromones -- acoustic, tactile, and visual stimuli play a role in sexual attraction, and sex specific responses to these stimuli appear to be innate rather than learned by association. We simply don't know where the boundary between prespecified attraction and learned association lie in our own species, nor do we have compelling evidence for the primacy of one sense over another [157]."

Compelling evidence of the primacy of olfaction exists in every species. If Darwin had known about pheromones that control the physiology of reproduction, he might have linked the importance of food odors and pheromones to his 'conditions of life.' That might have prevented others from inseminating their ideas about mutations and neo-Darwinian Natural Selection into his theory. It is time to move forward with Darwin's theory by including what is known about ecological variation because it appears to be the driving force of ecological adaptations manifested in species diversity. For comparison, the selective advantage of any mutation or accumulations of mutations must be detailed for such claims of mutation-driven species diversity to be seriously considered. If such claims are to be seriously considered, they should first be compared to what is known about nutritional epigenetics and conserved molecular mechanisms in species from microbes to man, which link the epigenetic landscape to the physical landscape of DNA in organized genomes.

In the context of food odors associated with nutrient stress and pheromones associated with social stress and the controlled physiology of reproduction and species diversity, adaptive evolution seems to be an inappropriate term for what clearly appear to be ecological adaptations in species from microbes to man. In an attempt to promote use of the term 'ecological adaptation' instead of the term 'mutation' in discussions of morphological and behavioral differences manifested in species diversity, I now enlist the aid of others with a quote from two researchers who are familiar with the issues involved in different debates during the past 40 years.

""The evolutionary biologist Theodosius Dobzhansky famously noted that "nothing in biology makes sense except in the light of evolution," but perhaps, too, "nothing in evolution makes sense except in the light of biology." Although the latter might be an exaggeration, an important gap is being filled by molecular understanding of the genesis of variation that confers the ability to evolve [158].""

The genesis of variation is manifested in ecological variation, which confers the ability to adapt *via* nutrient-dependent epigenetically-effected pheromone-controlled ecological, social, neurogenic, and socio-cognitive niche construction. Niche construction is manifested in organismal complexity. Everything about ecological adaptation appears to make sense in the light of what is currently known about molecular biology. What is currently known about the conserved molecular mechanisms that link the epigenetic landscape to the physical landscape of DNA can now be compared to any forthcoming explanations that attempt to make sense of how mutation-driven evolution might occur.

Conclusion

Nutrient-dependent pheromone-controlled ecological adaptations exemplify how sensing nutrients and secreting the metabolites of nutrients accomplishes different tasks. Efficient circuits enable the functional flexibility that is required in ever-changing ecologies that cause species diversity. Biophysical constraints on ecological adaptations are exemplified in physical proof which suggests that Kohl's Laws of Biology (Kohl's Laws) represent what Darwin called 'conditions of life.'

Physical proof of species diversity links ecological variations from nutritional epigenetics to 1) biophysically constrained protein folding *via* 2) atomic level changes in base pairs (i.e., the nucleotides of DNA); 3) amino acid substitutions; 4) changes in the miRNA/mRNA balance; 5) the metabolism of nutrients to species-specific pheromones that 6) control the physiology of reproduction, and 7) chromosomal rearrangements that link the reciprocity of these interactions to the morphological and behavioral phenotypes manifested in species diversity. Across-species examples of biologically plausible ecologically validated cause and effect link the physical proof from conserved molecular mechanisms of DNA uptake that extends these representations of nutrient-dependent epigenetic effects to differences in pheromone-controlled morphological and behavioral human phenotypes.

The plausibility and ecological validity of Kohl's Laws in the context of Darwin's 'conditions of life' can be compared to theories about biologically-based cause and effect in the context of species diversity. In mammals, for example, the explanatory power of a model of ecological variation and biophysically constrained nutrient-dependent pheromone-controlled ecological adaptations became clear with companion papers published in 2013. See for review [26].

The companion papers [159,160] told a new short story of ecological adaptations. In the context of climate change and changes in diet, the story began with what probably was a nutrient-dependent base pair change and a variant epiallele that arose in a human population in what is now central China. Apparently, the effect of the

epiallele was adaptive and it was manifested in the context of an effect on sweat, skin, hair, and teeth. In another mammal, such as the mouse, the effect on sweat, skin, hair, and teeth is probably due to a nutrient-dependent epigenetic effect on hormones responsible for the tweaking of immense gene networks that metabolize nutrients to pheromones. The pheromones appear to control the nutrient-dependent epigenetically-effected hormone-dependent organization and hormone-activation of reproductive sexual behavior in mammals such as mice and humans, but also in invertebrates and in microbes as previously indicated.

The ecological adaptations, which appear to be manifested in the human population are detailed in these two reports [159,160]. The ecological adaptations are likely to be nutrient-dependent and pheromone-controlled. If so, ecological variation probably leads to ecological, social, neurogenic, and socio-cognitive niche construction, which is manifested in increasing organismal complexity and species diversity. If not, there may be something as yet unknown about mutations and evolution that makes sense in the light of what is known about nutritional epigenetics and the molecular biology of species from microbes to man.

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Conflicts of Interest

The author is the founder of Pheromones.com, RNA-mediated.com and Autophagy.pro and other domains, which have been associated with information dissemination about human pheromones and with the marketing of human pheromone-enhanced fragrance products.

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