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EVOLUTIONARY BIOLOGY TODAY, AND THE CALL FOR AN EXTENDED SYNTHESIS

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ABSTRACT

Evolutionary theory has been extended almost continually since the Evolutionary Synthesis (ES), but except for the much greater importance afforded genetic drift, the principal tenets of the Synthesis have been strongly supported. Adaptations are attributable to the sorting of genetic variation by natural selection, which remains the only known cause of increase in fitness. Mutations are not adaptively directed, but as principal authors of the ES recognized, the material (structural) bases of biochemistry and development affect the variety of phenotypic variations that arise by mutation and recombination. Against this historical background, I analyze major propositions in the movement for an "Extended Evolutionary Synthesis". "Niche construction" is a new label for a wide variety of well known phenomena, many of which have been extensively studied, but (as with every topic in evolutionary biology) some aspects may have been understudied. There is no reason to consider it a neglected "process" of evolution. The proposition that phenotypic plasticity may engender new adaptive phenotypes that are later genetically assimilated or accommodated is theoretically plausible; it may be most likely when the new phenotype is not truly novel, but is instead a slight extension of a reaction norm already shaped by natural selection in similar environments. However, evolution in new environments often compensates for maladaptive plastic phenotypic responses. The union of population genetic theory with mechanistic understanding of developmental processes enables more complete understanding by joining ultimate and proximate causation; but the latter does not replace or invalidate the former. Newly discovered molecular phenomena have been easily accommodated in the past by elaborating orthodox evolutionary theory, and it appears that the same holds today for phenomena such as epigenetic inheritance. In several of these areas, empirical evidence is needed to evaluate enthusiastic speculation. Evolutionary theory will continue to be extended, but there is no sign that it requires emendation.

The current framework of evolutionary theory grew out of the evolutionary synthesis (ES), or the Modern Synthesis, as Huxley (1942) called it. In any discussion of extending or revising current theory, some understanding of the history of the Synthesis and the subsequent development of the subject will be useful. My impression of the history of biology, and of evolutionary biology in particular, is one of generally gradual, rather than paradigm-shaking, development that builds successively on previous accomplishments. For example, soon after the discovery and canonization of Mendel's "laws" in the earliest twentieth century, the "law" of independent assortment had to be modified to account for linkage. The "gene" went from a particulate "factor" to a trinity of recon, muton, and cistron (unit of recombination or mutation or function), thence to a protein-signifying code, and recently to an increasingly ambiguous functional part of a genome. Nevertheless, genetics has not cast out the old to accommodate the revolutionary new. Quite the opposite: classical Mendelian segregation, meiosis, linkage mapping, and mutation are still important foundations of today's immensely more complex genetics.

The same holds for the evolutionary theory that has developed since the late 1920's. The Evolutionary Synthesis (Mayr and Provine 1980) remains, *mutatis mutandis*, the core of modern evolutionary biology. The ES included both the formulation of population genetic theory by Fisher (1930), Haldane (1932), and Wright (1931 et seq.), and the interpretation of variation within species (e.g., Dobzhansky 1937) and of diverse information in zoology (Mayr 1942, Rensch 1947, 1959), botany (Stebbins 1950), and paleontology (Simpson 1944).

Since the 1930's and 1940's, there has been a steady incorporation of new information, ranging from phylogeny and field studies of natural selection to evolutionary genomics and the panoply of genetic phenomena that could not have been imagined in the 1940s or even the 1960s – information that has informed (and sometimes been predicted by) a steady expansion of theory. Modern evolutionary biology recognizes and studies transposable elements, exon shuffling and chimeric genes, gene duplication and gene families, whole-genome duplication, *de novo* genes, gene regulatory networks, intragenomic conflict, kin selection, multilevel selection, phenotypic plasticity, maternal effects, morphological integration, evolvability, coevolution, and more – some of these being phenomena and concepts unknown or dimly perceived a few decades ago.

 Almost all of this amplification of evolutionary biology has been built on the core concepts of the Evolutionary Synthesis (ES), which have held fast with only modest modification. The most important tenets of the ES, I think, are these:

- The basic process of biological evolution is a population-level, not an individual-level, process that entails change not of the individual organism, but of the frequency of heritable variations within populations, from generation to generation. Dobzhansky defined evolution as change of allele frequencies, but some organism-focused evolutionary biologists, such as Rensch, Simpson, and Mayr, had a more comprehensive conception of evolution, including phenotypic evolution, speciation, and differential proliferation of clades, while recognizing that phenotypic evolution and speciation occur by changes in allele frequencies. When Rensch wrote of "Evolution Above the Species Level" and Simpson wrote about "Tempo and Mode in Evolution," they were not talking about allele frequencies –although they recognized this as the elementary, generation by generation process of change.
- Heredity is based on "genes," now understood to be DNA or RNA. DNA sequences transmitted in eukaryotes' gametes are not affected by an individual organism's experiences. Cultural

inheritance has long been recognized, but insofar as it affects biological evolution, it does so by affecting natural selection. Some authors prefer to limit the term "inheritance' to genetic transmission. For the sake of using a common language in this discourse, I will use the term "inclusive inheritance" to include several forms of nongenetic "inheritance," recognizing that this terminology may be disputed.

■ Inherited variation arises by individually infrequent mutations; they are random in that their phenotypic effects, if any, are not directed toward "need". "Random" should always be qualified by "with respect to"; randomness of mutation has never meant that all possible alterations are equally likely, or that all genes mutate at the same rate, or that rates of mutation are immune from environmental factors (such as radiation and mutagens). Claims of "directed mutation" have been shown to be groundless (Maisnier-Patin and Roth 2015). The great majority of mutations that affect fitness are deleterious (Eyre-Walker and Keightley 2007). Likewise, the direct effects of novel environments are more often harmful than beneficial: that is why they engender natural selection and adaptive change. These facts imply that we should be skeptical of the view that organisms are so constructed as to have well integrated, functional responses to mutations or novel environments (as proposed by Laland et al 2015, p.2). Without question, organisms have diverse homeostatic properties that buffer fitness against many environmental or genetic destabilizing events; but the maintenance of function depends on stabilizing or purifying natural selection.

■ The frequencies of hereditary variants are altered by mutation (very slightly), gene flow, genetic drift, and natural selection. Directional or positive natural selection is the only known cause of adaptive change. Natural selection is not an agent, but a name for a consistent (biased, nonrandom) difference in the production of offspring by different classes of reproducing entities. The entities that were the focus of the ES were mostly phenotypically different individual organisms, but they can also be genes (as already recognized by Fisher, Haldane, and Wright), populations, or species.

■ Species of sexually reproducing organisms are reproductively isolated groups of populations that arise by evolutionary divergence of geographically isolated (allopatric) populations. Species evolve gradually, so not all populations can be classified into discrete species. Nonallopatric speciation is now recognized as possible, although its frequency is unknown.

■ Large phenotypic changes of the kind that distinguish higher taxa and occur over long periods of time evolve gradually, as Darwin proposed, i.e. by the cumulation of relatively small incremental changes.

It is important to recognize that in population genetics theory, "mutation" means any new alteration of the hereditary material that is stably transmitted across generations. The discovery of the molecular basis of heredity after the ES led to a greatly amplified understanding of evolutionary process and history, but the core theory of population genetics remained intact. For example, the core theory does not specify whether a mutation is a single base pair substitution, an insertion of a transposable element in a regulatory sequence, a gene duplication, or a doubling of the entire genome. The framework of population genetics has incorporated new kinds of mutations, such as transposable elements, as they have been discovered.

Natural selection commonly was, and often still is, thought of as stemming from the ecological environment, but the forgers of the ES were well aware that selection had a far broader basis. Fisher described the evolution by selection of sex ratio, selfing, and outcrossing, and he provided a genetic interpretation of Darwin's idea of sexual selection; Wright (who influenced Dobzhansky, who influenced Mayr) emphasized epistasis for fitness, in which prevalent alleles at one locus affect the selective value of alleles at another locus. Schmalhausen described "internal selection;" mutations can have environment-

independent effects on the function of physiological and developmental processes, and in turn on viability and reproduction. A causal account of any instance of selection requires different kinds of data – molecular, behavioral, ecological, or other – but showing the existence of selection on a gene locus or a trait requires only data on components of fitness, such as rates of survival, fecundity, or mating success.

Thus, the broad concepts of mutation and natural selection lack material content, in the sense that empirical data are needed to describe real instances of evolution, by identifying the agents of selection and the molecular and developmental basis of phenotypic variants. The conception of causes of evolution embodied in the Synthetic Theory, i.e. allele frequency change, differs from the "structuralist" view of the causes of differences in morphology, physiology, or behavior that are commonly envisioned by mechanistic developmental biologists, physiologists, or neurobiologists (cf. Amundson 2005). A "structuralist" approach to biology is cast in terms of the physical and chemical features of organisms, such as cell types and organs, and a "structuralist" explanation of a morphological difference among species would be expressed in terms of signaling cascades, gene regulation, and assembly of proteins into features that distinguish cell types (see Wagner 2014, pp. 7-38). A complete account of any evolutionary change in phenotype would combine the two kinds of information: population genetic processes (causes of allele frequency change) together with the specific agents of selection and the structural and developmental basis of the altered phenotype. Part of the great power of the population genetic theory of evolutionary change lies in its generalization across diverse kinds of mutations, selective causes, and phenotypic structures.

The leaders of the ES affirmed Darwin's gradualist view of long-term evolution, and rejected the saltationism of Schindewolf, Goldschmidt, and others who supposed that higher taxa evolve by macromutations. Still, what might qualify as a "large" mutational change was and is difficult to specify. Certainly some species differences and polymorphisms map to single loci wth discretely different effects; phenomena such as neoteny (e.g., paedomorphic salamanders) were recognized, and nobody seemed to worry that partially paedomorphic salamanders were unknown and functionally unlikely. The "instantaneous" origin of reproductively isolated species by polyploidy was likewise well known, especially in plants – but the species produced by polyploidy closely resemble the parent species: they are not new higher taxa.

EXTENSIONS OF THE EVOLUTIONARY SYNTHESIS

Evolutionary research in the 1950's and 1960's greatly increased information on genetic variation in natural populations, the seeming ubiquity of natural selection, and speciation. In the 1960's, efforts to synthesize ecology with evolutionary biology were renewed as "population biology" (e.g., Lewontin 1968, Levins 1968), the beginning of a flourishing field of evolutionary ecology (e.g, Hendry 2016). The development of kin selection theory and the distinction between individual selection and group selection gave rise to fields such as behavioral ecology and life history theory. The abundant evidence of natural selection and the development of optimality models for characters that almost unquestionably affect fitness may have led to a broadly held view of selection as an almost exclusive factor of evolution. But the all-important role of selection was challenged by interpretations of molecular polymorphism and evolution in neutralist terms (King and Jukes 1969, Kimura 1968, 1983), and the "neutralist-selectionist" debate ultimately resolved itself into rendering unto Kimura and unto Darwin those provinces of variation that each best explains. In the 1980's and 1990's, the field of molecular evolution grew so massively as to warrant its own society and journal. This expansion was accompanied by the maturation of phylogenetic analysis and its long-deferred integration with the study of evolutionary processes (Cavalli-Sforza and

Edwards 1963, Felsenstein 1973, 2004). Thus, evolutionary theory has undergone enormous expansion since the Evolutionary Synthesis (Gavrilets 2010, Callebaut 2010), with the neutral theory of molecular evolution its most radical extension.

Nevertheless, there have been undercurrents of discontent with the Synthetic Theory ever since the ES (Welch 2017). For example, *Beyond Neo-Darwinism* (Ho and Saunders, 1984) was a diverse collection of essays by developmental biologists, systematists, ecologists and others whose common characteristic seemed to be only an animus against the prevailing paradigm. Stephen Jay Gould's (1980, 1982) calls for extension of the ES had rather more impact. Gould played a significant role in reviving development as a factor in the evolution of form (Gould 1977), as well as the role of developmental or genetic constraints. Although Gould flirted with Goldschmidtian saltation, there is still no evidence that single mutations are responsible for the multiple character differences that typify most genera or other higher taxa. However, population geneticists found that many character differences between closely related species appear to be based on fewer gene differences, of larger effect, than previously supposed (Gottlieb 1984, Orr and Coyne 1992). (Nonetheless, even the effects of a single gene can sometimes be ascribed to complementary effects of several mutations [Stern 2011].) The model of punctuated equilibria introduced by Eldredge and Gould (1972) was a different challenge to gradualism. They claimed that most fossil lineages display rapid shifts (punctuations) between one long-lasting, virtually constant (static) phenotype and another. Following Mayr (1954, 1963) in large part, they postulated that populations cannot readily respond to natural selection because of genetic constraints that may be loosened when a population undergoes a bottleneck associated with founder-effect speciation. This model has been almost universally rejected, but Eldredge and Gould called attention to the important and still not fully explained pattern of stasis, and raised a possible role for speciation in fostering long-term character evolution, which is a topic of ongoing research (Futuyma 2010,Venditti and Pagel 2010, Mattila and Bokma 2008, Magnuson-Ford and Otto 2012). The controversy unleashed by Eldredge and Gould (1972) also contributed to a renaissance of paleontology, in the form of paleobiology. Possibly the current calls for an extended synthesis will similarly have some positive effects.

PROPOSED EXTENSIONS OF THE EVOLUTIONARY SYNTHESIS

Against this background, I will consider the major themes of the proposed Extended Evolutionary Synthesis (EES), drawing largely on the position paper by Laland et al. (2015) and the oral presentations at the discussion meeting sponsored by the Royal Society and the British Academy (November 2016). I will consider niche construction, phenotypic plasticity, inclusive inheritance, and the role of development in the evolution of form.

Niche Construction

The concept of niche construction emphasizes ways in which organisms actively modify their environment, such as burrowing by gophers and dam-building by beavers, but the broadest expression of the idea of niche construction is simply, as Lewontin (1983, p. 280) wrote, that "organisms determine what is relevant." The core idea is that the evolved properties of organisms make some aspects of the environment relevant sources of natural selection, and screen off others, thereby helping to shape and constrain likely paths of the population's evolution. Thus (although Lewontin did not explicate this point), properties of the organism that we think of as proximate mechanisms (e.g., biochemcal capabilities, tolerances, habitat selection, other behaviors of animals) can determine or even constitute Mayr's "ultimate" (i.e., selective) causes of organisms' characteristics. The proponents of niche

construction (Odling-Smee et al. 2003) take this broad view, even if they stress examples in which species (especially of animals such as beavers) actively modify their environment – a theme that has also been developed by Dawkins (1982).

I have been a naturalist since boyhood. I think I recognized niche construction even then, because Lewontin's principle is blindingly obvious to any naturalist. Even if a species does not literally construct its environment, like a beaver, it determines its environment by its behavior and physiology. What is relevant to the life of an aerially foraging swift , to a foliage-gleaning warbler, and to a fish-eating loon (diver) is obviously very different. To a eucalyptus-feeding koala or a larval monarch butterfly that eats only milkweed (*Asclepias*), the defensive compounds of these few plants are highly relevant, but those of hundreds of other plant species in their habitat are not. Likewise, an understory herb experiences a very different environment from an epiphytic bromeliad in the same tropical forest. This principle was obvious to ES figures such as Mayr (1960), who emphasized that behavior (such as habitat choice) often frames selection on morphology and physiology. Jakob von Uexküll's (1921) concept of an animal's *Umwelt* – its species-specific perceptual environment – has long been familiar to students of animal behavior.

In my own research area, the evolution of herbivore-plant associations, the coevolution of behavior and physiology has been a major topic for modeling and empirical study (e.g., Futuyma 1983, Rausher 1984, Castillo-Chávez et al. 1988). In simple two-locus models, one locus affects which species of plant an insect chooses; this affects allele frequency dynamics at a second locus that determines fitness on these plants (and vice versa). The evolution of host choice will influence the subsequent evolution of other features, such as coloration that makes the insect cryptic by resembling part of the plant. This coevolution of habitat preference and other features is one of a rather long list of well studied topics that Odling-Smee et al. include under niche construction, which seems to embrace much of behavioral ecology, evolutionary ecology, and (by virtue of the many effects of niche construction) community ecology. So the phenomena gathered under the label "niche construction" are unquestionably important, and have long been the subjects of research, But the inclusiveness of the term "niche construction" has been cited as "precisely what weakens the value of the idea," for "organismal influences on the environment with profoundly different evolutionary impacts are lumped together" (Brodie 2005).

The related notion of "ecological inheritance" can likewise be criticized because of its imprecision and excessive breadth. Odling-Smee et al. (2003, p. 45) define ecological inheritance as "any case in which organisms encounter a modified feature-factor relationship between themselves and their environment where the change in the selective pressures is a consequence of the prior niche construction by parents or other ancestral organisms," including "the ancestors of other species in their communities"! Their examples include offspring inheritance of their parent's environment (e.g., burrow), occupation of an environment constructed by antecedent generations without reference to kinship, and simple parental care. (For example, because many insects lay eggs on a food plant or other food resource, the offspring "inherit from their mother the legacy of an appropriate source of larval food" (p. 65).

"Ecological inheritance" must differ profoundly from genetic inheritance if it is not transmitted down ancestor-descendant lineages. The critical distinction is whether or not there is covariance between niche-constructing behavior and offspring fitness (Brodie 2005, Gupta et al. 2017). The literature of quantitative genetics has long recognized genotype-environment covariance (e.g., Falconer 1960). Situations in which this is the case, including maternal effects and gene-culture coevolution, have been described by models based in traditional population genetics (e.g., Feldman and Cavalli-Sforza 1976, Kirkpatrick and Lande 1989).

Niche construction may prove useful if it prompts questions and generates research on familiar aspects of biology (as has research on phenomena such as stasis and sex ratios). So far, studies that identify themselves with niche construction have been mostly theoretical, and mostly addressed to cultural niche construction, especially by humans. But these themes had already been addressed long before the term "niche construction" was introduced (Gupta et al. 2017), and understudied phenomena are available to anyone who becomes familiar with enough biology (why do haploid chromosome numbers range from one to more than one hundred among insect species?); so associating a study with a term does not in itself show that the term or concept played a critical generative role. A great deal of research, on many topics as I have noted, has long used the concept of niche construction, without using the label.

Odling-Smee et al. (2003, p. 2) proposed that niche construction "should be regarded, after natural selection, as a second major participant in evolution," and indeed as a "core evolutionary process". In a valuable interchange (Scott-Phillips et al. 2013), skeptics point out that niche construction can influence or even cause the evolutionary process of natural selection, but is not itself an evolutionary process, any more than a changing environment is. If niche construction shapes selection, so do the sources of ecological selection, internal selection, and sexual or social selection. The sources of these several forms of selection are not processes. We can identify many evolutionary processes (Red Queen evolution, kin selection, changes in linkage disequilibrium, and more), i.e. ongoing series of events that constitute evolutionary change. Are they "core" evolutionary processes? I do not know what the criterion of a "core" evolutionary process might be, but none of these seems to be as fundamental and comprehensive as mutation, genetic drift, gene flow, and natural selection. Perhaps a taxonomy of processes would be useful.

Professor Laland also suggests that the value of niche construction is that it provides a different point of view. Whether or not that will prove to be so will depend on whether or not it yields theoretical and empirical research that differs from what would otherwise be pursued (Scott-Phillips et al. 2013). What, exactly, as Gupta et al (2017) ask, has been neglected by standard evolutionary theory that niche construction theory proposes to supply? Will "niche construction" be merely a label or "brand" that advertises its advocates' research, or will it be uniquely productive of insight and understanding? So far, no new, general theoretical principles that promise to guide novel empirical research have been articulated by proponents of niche construction.

The role of phenotypic plasticity in evolution

Phenotypic plasticity refers to the expression of different phenotypic states (together forming a norm of reaction) by a single genotype under different environmental conditions. It takes many forms. It can be reversible, as are many behavioral reactions, physiological acclimation, up- or downregulation of an enzyme level, and some morphological states, such as seasonal changes in bird plumages. Or it may be irreversible, as are many alternative morphological phenotypes induced by environmental conditions during development; familiar examples include height in some plants, the solitary versus gregarious phases of plague locusts (*Schistocerca*), and the castes of many eusocial insects. Plastic responses *sensu lato* include many environmentally induced phenotypes that are called developmental defects, such as skeletal aberrations in rickets, but most evolutionary literature is concerned with adaptive plasticity, such as the cases I have cited.

The concept of phenotypic plasticity, if not the term, is about as old as the distinction between genotype and phenotype. I learned about it in an undergraduate genetics course. As a graduate student, I learned

that genotype × environment interaction was a staple in quantitative genetics (Falconer 1960, Mather and Jinks 1971). Clausen et al. (1940) and many other researchers described adaptive plasticity in plants and animals, and the evolution of adaptive reaction norms was a major topic in Schmalhausen's *Factors of Evolution* (1949). Biologists agreed that some plastic responses are adaptive, and that others are harmful effects of environment. There is no doubt that plasticity can extend tolerance to some new environments and help prevent population extinction. By the 1990's, a large body of quantitative genetic theory on the evolution of adaptive phenotypic plasticity had been developed (e.g., Via and Lande 1985, Gavrilets and Scheiner 1993, Scheiner 1993, de Jong 1995), and a large theoretical and empirical literature on the topic has developed since then. For example, young tiger snakes (*Notechis scutatus*) that are fed larger prey develop longer jaws, and the response is enhanced in an island population that normally feeds on larger prey (Aubret et al. 2004). This simply shows that reaction norms can evolve by natural selection. There is also an extensive literature on the benefits and costs of phenotypic plasticity. Thus, the phenomenon of phenotypic plasticity is widespread, is very well known, and is understood to a considerable degree (Pigliucci 2001, de Jong 2005).

Under some conditions, the optimal reaction norm is "flat," i.e. a constitutive (constant) expression of the same phenotype in all normally encountered environments. The evolution of a constant (constitutive) phenotype from an ancestrally more plastic reaction norm often exemplifies what I will refer to as genetic assimilation, following Waddington (1953). Waddington observed that a phenotype that was induced by an environmental stimulus could become constitutive, and be expressed in the normal environment in the absence of the stimulus, after several generations of selection for individuals most prone to exhibit the phenotype when stimulated. He rightly postulated that selection had increased the frequency of alleles that enhanced the reliability and consistency of the new phenotype. Strong evidence for this hypothesis was provided by experiments in which selection yielded no genetic assimilation in inbred stocks that lacked genetic variation (Scharloo 1991).

Genetic assimilation of a character state in a plastic reaction norm underlies a controversial hypothesis by Mary Jane West-Eberhard (2003) that she calls genetic accommodation because it includes more genetic shaping of characters than in simple genetic assimilation – which, however, is the core of her hypothesis. West-Eberhard proposed that adaptation to a novel environment often proceeds first by inducing a phenotypic response that increases fitness (phenotypic plasticity), followed by allele frequency changes that assimilate and perhaps fine-tune the new character state, so that it becomes a novel, species-typical trait. She stated, provocatively, that "most phenotypic evolution begins with environmentally initiated phenotypic change… The leading event is a phenotypic change with particular, sometimes extensive, effects on development. Gene-frequency change follows, as a response to the developmental change. In this framework, most adaptive evolution is accommodation of developmental-phenotypic change. Genes are followers, not necessarily leaders, in phenotypic evolution" (pp. 157-158) The hypothesis has drawn some favorable attention as an important contribution of development to evolution (e.g., Gilbert and Epel 2015).

West-Eberhard's hypothesis is very similar to what Simpson (1953) called the Baldwin effect. Simpson said that the idea does not violate the standard theory of evolution by natural section. Indeed, Lande (2009; also Chevin et al. 2010) has modeled the role of plasticity and genetic assimilation in adaptation to environmental change, using orthodox quantitative genetics. But Simpson noted that there were few real examples, and doubted they would prove to be common. Should his assessment be revised? Not greatly, at least based on currently available evidence.

West-Eberhard cites many cases in which a species constitutively exhibits a character state that is part of a more variable reaction norm in a related species. In almost none of these examples is there phylogenetic or fossil evidence on the direction of the change, so these tell us only that reaction norms can evolve, an issue not in doubt. Information on the direction of evolution (from plastic to constitutive) has been recognized as an important criterion for testing the hypothesis, and such information is available in a few recent cases which show that genetic assimilation can happen in natural populations (Schlichting and Wund 2014, Levis and Pfennig 2016). For example, montane populations of *Daphnia*, recently faced wth introduced fish that more easily detect melanized individuals, have lost a melanization reaction to ultraviolet light (Scoville and Pfrender 2010). Anadromous marine sticklebacks (*Gasterosteus aculeatus*), when reared under lake-like conditions, display changes in body form that slightly resemble those that have evolved in derived lake-dwelling populations (Wund et al. 2012). However, there is a long history of bidirectional gene flow between freshwater and marine populations (Bell and Aguirre 2013), and the possibility cannot be ruled out that the reaction norm of the marine fishes is affected by alleles derived from freshwater populations. The experimental marine fishes do not show a plastic response of other characters, such as gill raker number, that have also evolved in freshwater populations.

More importantly, the genetically variable reaction norms in a population may or may not be oriented toward the character state that is optimal in the altered environment (Ghalambor et al. 2007). If it is directed toward the optimum, evolution toward and possible genetic fixation of the optimal character state may occur; but as Pigliucci (2010, p. 369) (who is sympathetic to West-Eberhard's hypothesis) has noted, the novel environment "will often not be novel at all, but will be some variant of the sort of environment that has been common in the history of the species." In this case, the reaction norm has previously been shaped by natural selection acting on genetic variation; genes are "followers" only to the extent that genetic assimilation or accommodation "fine-tunes" an adaptation that had already evolved by selection and genetic variation.

Therefore, phenotypic plasticity could be said to truly play a leading role (with genes as followers) if an advantageous phenotype were to be triggered by an environment that really is novel for the species lineage, an environment that its recent ancestors did not experience and which therefore had not exerted natural selection. Of course it is possible that a novel environment – a new pesticide, for example – could evoke a developmental effect that happens to improve fitness, just as it is possible that a random DNA mutation improves fitness. But no theory leads us to expect such an effect to be especially likely. On the empirical front, a few candidate instances have been described. Terrestrial tiger snakes that were raised in water for several months swam faster than land-reared siblings (Aubret et al. 2007); but how does this differ from the performance of trained human athletes? Aside from the lack of inheritance of this phenotypic change, how would one show that this response played a role in the evolution of aquatic species, such as the confamilial sea snakes? Perhaps the best example I have found that fits the Baldwin effect or genetic accommodation is the study by Ledón-Rettig et al. (2010) of the tadpoles of spadefoot toads in the genus *Spea*. Their diet is commonly algae and detritus, but if tadpoles eat animal prey when young, they develop into a carnivorous morph with very large jaw muscles and a shorter gut. Another genus, *Scaphiopus*, in which the carnivorous morph has never been recorded, feeds entirely on algae and detritus. This is almost surely the ancestral diet, so animal prey is a novel environmental stimulus. Young *Scaphiopus* tadpoles, experimentally fed shrimp, developed a shorter than normal gut (as in *Spea*), a point in favor of West-Eberhard's hypothesis. However, they did not develop the most conspicuous features of *Spea*'s carnivorous morph, the greatly enlarged jaw muscles. The critical evidence, induction of an

adaptive plastic response by a truly novel environment (to say nothing of subsequent genetic assimilation and accommodation) is supported by only tenuous evidence at this time.

Moreover, phenotypically plastic reactions to novel environments are often wholly or partly *counteradaptive*. In the well known phenomenon of countergradient adaptation (Conover and Schultz 1995), genetic differences between populations are precisely opposite to the maladaptive direct effects of the different environments the populations inhabit, and compensate for the maladaptive plastic effect (Grether 2014). Human acclimation to high altitude improves performance, but at the cost of increased hematocrit, decreased affinity of hemoglobin for oxygen, and hypertensive pulmonary vessels – all features that differ from genetically adapted highland populations (Storz et al. 2010). A guppy (*Poecilia reticulata*) population exhibited evidently maladaptive plastic changes in expression of many genes when reared in a novel environment (one that lacked predatory fish); descendants of this population adapted to a predator-free environment by precisely opposite evolutionary changes in gene regulation (Ghalambor et al. 2015). Deleterious phenotypic plasticity may be at least as effective in triggering adaptive genetic change as plasticity that enhances fitness (Grether 2005).

I conclude that the evidence so far does not warrant much enthusiasm for the proposition that plasticity often paves the way for adaptation to novel selection pressures, much less for novel morphological or physiological adaptations. Abundant traditional theory, based in population genetics, describes how reaction norms evolve by selection on genetic variation, and there is abundant evidence of adaptation by natural selection on standing genetic variation (Barrett and Schluter 2008, Hendry 2017). Some conditions favor plasticity, some a fixed phenotype. The implication that development has inherent properties that are usually likely to generate new, adaptively directed phenotypes lacks any theoretical – or material, as far I can tell – foundation.

Inclusive Inheritance

Several bases for nongenetic inheritance (meaning here inheritance that is not based on DNA sequence) have long been recognized, including culture, behavioral imprinting, parental environment including some maternal effects, and parental transmission of nucleic acids and diverse chemical compounds. Some, but by no means all, cases of niche construction also qualify (Bonduriansky and Day 2009). As noted earlier, many of these phenomena have been modeled and empirically studied by evolutionary biologists for several decades (e.g., Cavalli-Sforza and Feldman 1981, Kirkpatrick and Lande 1989, Wolf et al. 1998, Mousseau and Fox 1998), and it is not clear that the EES brings anything new to the topic.

 More recently, novel molecular mechanisms of inheritance have proven to be widespread, such as inherited DNA methylation and other epigenetic "marks." Some authors have placed a provocative Lamarckian interpretation on certain of these phenomena (e.g., Jablonka and Lamb 2010, 2014), while others have urged that they be viewed as "interpretive machinery" that can influence gene expression and development, and are inherited along with DNA (Day and Bonduriansky 2011).   These mechanisms can and should be studied, like other organismal and genomic features, in order to determine their evolutionary dynamics and their evolutionary effects. For example, some of these mechanisms can cause traits to continue to evolve after selection has ceased, and can even evolve in a direction opposite to selection (Kirkpatrick and Lande 1989). Day and Bonduriansky (2011) have developed a general model that they claim applies broadly across the various kinds of nongenetic inheritance, in which a key feature is that phenotypic change across generations can be decoupled from genetic change. Depending on the

mechanism, nongenetic inheritance may be more transient (lasting for few generations) or more persistent, but in some cases, even transient inheritance can infuence the direction of genetic evolution.

Some inherited epigenetic effects are influenced by environment, and have been described as vindicating Lamarckian inheritance. I think Haig (2007) and Dickins and Rahman (2012) are likely to be right: they do nothing of the kind. Transgenerational epigenetic inheritance does not intrinsically produce advantageous environmentally-induced phenotypes. Epigenetic imprinting, whether inherited or not, can have both benefits and costs, which provide fuel for theoretical and empirical research (Holman and Kokko 2014). Many epigenetic effects are deleterious (Day and Bonduriansky 2009), so population-typical advantageous instances are best interpreted as the result of natural selection of those genetic variants with epigenetic modification that enhance fitness. The capacity of DNA sites to be marked is genetically variable, and epigenetic variation responds to selection (Day and Bonduriansky 2009, Dickins and Rahman 2012, Verhoeven et al. 2016). Therefore, most instances of adaptive epigenetic variation are best viewed as transgenerationally transmitted adaptive phenotypic plasticity (Jablonka et al. 1995, Uller 2008) that has evolved by mutation and natural selection (Furrow and Feldman 2014).

That is not to deny the possible importance of such effects in evolution, but the importance has yet to be determined. In contrast to a century's accumulated evidence that variation within and among species is based on genes, there is little evidence, so far, that ecologically adaptive features of whole populations or species have an epigenetic basis (Bossdorf et al. 2008). The frequency of certain methylated sites differs among some populations of both plants and animals, and in some instances suggests a correlation with environment (e.g., Herrera et al. 2016, Smith et al. 2016), although in only a few cases have population samples been reared in a common environment, in order to exclude direct environmental induction (Keller et al. 2016). In contrast, a massive literature provides evidence that character differences between species are based on DNA sequence differences in genes (Coyne and Orr 2004). Epigenetic transmission seems to last for at most a few dozen generations, and usually much less.The *peloria* variant of the toadflax *Linaria vulgaris* that Linnaeus described (an epigenetically based reversion from a bilaterally symmetrical to a radially symmetrical flower) can be found in populations today, but there is no reason to think there has been transmission of a mutant lineage since the 18th century. At this time, "empirical evidence for epigenetic effects on adaptation has remained elusive" (Verhoeven et al. 2016). Charlesworth et al. (2017), reviewing epigenetic and other sources of inherited variation, conclude that initially puzzling data have been consistent with standard evolutionary theory, and do not provide evidence for directed mutation or the inheritance of acquired characters.

Perhaps epigenetic inheritance will prove to have important effects in evolution, affecting the dynamics and direction of genetic adaptation (Day and Bonduriansky 2009). However, just as evolutionary biology embraced the discovery of introns, transposable elements, and highly repetitive DNA, and easily adapted traditional population genetic models to describe their evolutionary behavior, so it will be, I suspect, with epigenetic and other nongenetic inheritance. The basic framework of orthodox evolutionary theory has served well in evolutionary genomics thus far, and will almost certainly do so in this context, too. Evolutionary theory will be extended, just as it has been by other discoveries about genomes, but there is no sign that any of its components will have to be discarded.

Development and Evolution

During and since the Evolutionary Synthesis, relationships between developmental biologists and evolutionary biologists have at times been not entirely comfortable. It is sometimes said that development

was excluded from the ES, but there is little ground for this accusation (Smocovitis 1996, Amundson 2005, Love 2009). In the early twentieth century, experimental embryologists divorced themselves from what they viewed as a descriptive, speculative tradition of evolutionary embryology. The developmental biologist Viktor Hamburger (1980) noted that during the period of the ES, books on experimental embryology did not treat evolution; Mayr (1993) claimed that developmental biologists "were not left out of the synthesis…they simply did not want to join." The split between genetics and embryology, initiated by T. H. Morgan, probably affected the content of the synthetic theory, which built more on genetic than developmental foundations (Love 2005). Nonetheless, development was not entirely ignored, as I note below. (My treatment of this topic draws on a rather lengthy essay on macroevolution [Futuyma 2015] that at this time can be downloaded without cost at http://www.springer.com/us/book/9783319150444.)

Whatever the reasons may have been, development was not as effectively assimilated into the ES as it might have been; as many authors have noted, the ES lacked a theory of the origin of phenotypic variation, and especially of phenotypic novelty. One may well wonder what kind of theory could have been developed when the mechanisms of development, and even the molecular nature of genes, were entirely unknown. Experimental embryologists used phenomenological descriptors such as induction and prepattern, just as comparative embryologists had descriptors such as heterochrony and allometry. Kirschner and Gerhardt (2010, p. 276) write that the "Modern Synthesis did not and could not incorporate any understanding of how the phenotype is generated."

Certainly some evolutionary biologists were sensitive to the significance of development. Huxley contributed an analysis of allometry to the ES, and speculated that it provided a nonadaptive (we might now say pleiotropic) explanation for some exaggerated features. Rensch (1947, 1959) discussed allometry and other developmental phenomena at length, and speculated that parallel evolution, as in the wing patterns of Lepidoptera, may arise from similar genetic and developmental factors. Wright (1934) provided a polygenic model for threshold traits (and Lande [1978; Chevin and Lande 2013] later modeled how such traits evolve under natural selection). The idea that development can influence the direction of evolution was fully congenial to the architects of the ES. Mayr (1963, pp. 607-610) wrote, in a passage on "Evolutionary potential and predisposition," that "Every group of animals is 'predisposed' to vary in certain of its structures, and to be amazingly stable in others," and that this is reflected in parallel evolution: "Only part of these differences can be explained by the differences in selection pressures to which the organisms are exposed; the remainder are due to the developmental and evolutionary limitation set by the organisms' genotype and its epigenetic[1] system…The epigenotype sets severe limits to the phenotypic expression of …mutations; it restricts the phenotypic potential." Stebbins (1950) wrote about evolutionary trends in plants, such as the repeated evolution of fused petals, which he analyzed in terms of development: "while the process of 'fusion' is begun by the initiation of a new type of growth center, the degree of union, like that of reduction, is determined chiefly by allometry." Stebbins (1950, 1974) noted that the evolution of different floral structures constrained the way in which seed number might evolve; for example, by increasing the number of ovules per carpel in lilies (Liliaceae), by the number of carpels per flower in buttercups (Ranunculaceae), and by the number of flowers (florets) in the flowerheads of sunflowers (Asteraceae).

[Footnote] [1]Mayr, like Waddington and other biologists until recently, used "epigenetic" to refer simply to developmental processes, not in its modern molecular sense.

The first steps toward modern developmental biology, such as the Jacob and Monod (1961) and the Britten-Davidson (1971) models of gene regulation, were featured in textbooks by Dobzhansky et al. (1977) and myself (Futuyma 1979), both of which emphasized that evolutionary changes in gene regulation could underlie morphological evolution. The second edition of my textbook (Futuyma 1986) included 14 pages on development and evolution, including discussions of prepatterns, the Turing model of pattern formation, the genetics of segment identity in *Drosophila*, developmental constraints, and developmental integration. Today's leading textbooks of evolutionary biology all cover evolutionary developmental biology (e.g., Barton et al. 2007, Freeman and Herron 2014, Futuyma and Kirkpatrick 2017, Zimmer and Emlen 2016). There are now journals that integrate developmental and evolutionary perspectves. Development is now well integrated into evolutionary thinking.

The rise of modern EDB (evolutionary developmental biology) is a valuable maturation of a dimension of evolutionary biology that has been present all along. It represents a structuralist approach that adds material mechanisms to the theory of allele frequency change (Amundson 2005). It is part of a broader union of the theory of evolutionary dynamics with mechanistic biology – a conjunction of Mayr's (1961) "ultimate" (evolutionary) explanation with "proximate" explanation at the level of organisms' structure and function.

These are complementary, not alternative explanations. For instance, one role of EDB may be to demonstrate and clarify the importance of developmental constraints on evolution (Maynard Smith et al. 1985, Brakefield 2006). For example, Brakefield's research group showed that the colors of two spots on the wing of a butterfly species could not be decoupled by artificial selection (Allen et al. 2008). This well known phenomenon is usually referred to as genetic correlation, which is typically ascribed to pleiotropic effects of genes that affect both characters, and is understood to act as a potential constraint on the direction of evolution (e.g., Lande 1982, Walsh and Blows 2009, Futuyma 2010). Genetic constraints become developmental constraints when the mechanisms underlying genetic patterns are understood.

Developmental (or genetic) constraints of this kind clearly influence the direction of evolution, just as the direction of my travel is influenced when the police close a road. As the passages I cited from Mayr and Stebbins show, the idea that genetic or developmental "potential" biases variation and evolution is neither new nor a challenge to traditional theory. Where EDB can provide insight is by identifying mechanistic causes. The demonstration, early in the twentieth century, that some salamanders are paedomorphic because of reduced thyroxin production provided a mechanistic complement to an evolutionary explanation (Gould 1977). Alberch and Gale's (1985) famous experiment provided a mechanistic understanding of the evolutionary sequence of digit loss in amphibians, following a long history of developmental and genetic studies of the mechanisms and evolution of the reduction and loss of limbs in tetrapods (see Lande 1978). Likewise, Turing's model provided a possible mechanism for patterns (e.g., the distribution of hairs or colored spots on an animal [Murray 1981]), but it did not explain why an animal would evolve spots. If spots do evolve, there must be a physical mechanism for their production and distribution. This proximate mechanism should not be confused with the ultimate explanation.

EDB helps to explain some enigmatic evolutionary changes. For example, the pectoral girdle of turtles lies below the ribs, but above the ribs in all other tetrapods. Recent descriptions of development, together with a key fossil turtle, show how changes in the development of the rib primordia and in the antero-

posterior orientation of the ribs enabled this remarkable change (Li et al. 2008, Kuratani et al. 2011). EDB addresses interesting and important questions, such as coordinated evolutionary changes in functionally integrated characters (Kirshner and Gerhardt 2005) and the origin of truly novel characters (Wagner 2014). But the argument for the importance of EDB need not be weakened by unnecessary claims and speculations. Müller (2010) provides a very interesting treatment of morphological evolutionary novelties, such as the turtle carapace and the mammalian patella (knee cap). He describes models of developmental mechanisms that produce changes that result from "activation-inhibition thresholds in geometrically confined spaces." That may well be, but he goes on to postulate that the innovation may be produced as a phenotypically plastic effect that is later genetically assimilated. Thus "genetic evolution, while facilitating innovation, serves a consolidating role rather than a generative one, capturing and routinizing morphogenetic templates."

I view this as an unnecessary concatenation of speculations. Why is so complex and unsupported a hypothesis needed to explain the origin of the patella, which is formed by existing cellular and molecular processes of osteogenesis in a phylogenetically novel location in the body? Changes in gene regulation are known to trigger expression of entire developmental pathways at different times in development (heterochrony) or different sites in the body (heterotopy). Why not simply suppose genetic variation in sites of gene expression, and natural selection for those particular sites in which novel sesamoid bones prove advantageous? The patella is one of many heterotopic bones (e.g., osteoderms of armadillos) that have clear selective value. There have undoubtedly been many disadvantageous mutations that produced heterotopic bones in places that were decidedly wrong. Simpler explanations are generally preferred over more complex (and vague) hypotheses, unless these are supported by evidence.

The EDB described by some adherents to an EES is oddly different from the research literature that has made the most substantial progress in evolutionary developmental biology. That literature is largely concerned with evolutionary changes in gene regulation, and identifying the nature and causes of changes in cis-regulatory regions and trans-regulatory factors (e.g., Carroll 2005, Lynch et al. 2015, Mallarino and Abzhanov 2012). To be sure, much of this literature describes what might be called genetic blueprints or algorithms for making organisms, and not the final molecular processes by which tissues and organs are produced. But models of developmental fields and activation thresholds generally do not achieve this level of mechanism either. Some developmental biologists have been downright anti-genetical in the past (e.g. Goodwin 1984). A disjunction of developmental process from the genetic-*cum*-environmental specification of development seems unlikely to enhance our understanding of evolution.

CORE ASSUMPTIONS

Laland et al. (2015) list 6 "core assumptions" that they say differ between the ES and the EES. I will comment on them only briefly, as the preceding discussion addresses most of these points.

The ES assumes preeminence of natural selection, the EES "reciprocal causation" owing to developmental bias and niche construction. No; advocates of the ES have long recognized (as did Darwin himself) that organisms determine to a considerable extent the environmental sources of selection, including by modifying their environment, and they recognized a role for developmental (or genetic) biases and constraints that can affect the directions of evoplutionary change. But natural selection remains the only process that increases fitness and shapes adaptive characteristics.

The ES assumes random genetic variation, the EES nonrandom variation. No; it has always been recognized that some phenotypic variants are more likely to arise by mutation (expressed via

development) than others. The fact that most mutations that affect fitness are deleterious, and that most novel environments reduce fitness, contradicts the EES claim that "*developmental systems facilitate well-integrated, functional phenotypic responses to mutation or environmental induction*."

The ES assumes gradualism, the EES variable rates of change. Of course, advocates of the ES, beginning with Simpson (1944) and Rensch (1947), have recognized that rates of evolution are highly variable; evolutionary rates at both the phenotypic and genomic levels have been a focus of extensive research. This passage from Laland et al. (2015) refers to the supposition in the EES that saltations are possible, and that the ES does not entertain saltations. I have explained that advocates of the ES have always accepted certain kinds of "large effect" mutations, as in paedomorphosis and polyploidy. There is little or no evidence that saltations occur in evolution via mutations in gene regulation.

The ES has a gene-centred perspective, the EES an organism-centred perspective. A reading of the seminal works of the ES will show that most of the authors had a deep interest in and knowledge of organisms – considerably greater, I venture, than many or even most practicing evolutionary biologists today. I have illustrated this with examples concerning niche construction, developmental processes and constraints. But the founders of the ES recognized that these and other properties of organisms evolve only if they are inherited across generations. Like Darwin, they recognized the common elements of a truly general theory of the evolution of phenotypes – including the phenotypic states that influence subsequent evolution – in variation, inheritance, and natural selection. (We would add genetic drift today.)

The ES assumes genetic inheritance, the EES inclusive inheritance. Of course, the ES has always recognized cultural inheritance, but largely ignored it because it was considered taxonomically very restricted. As the prevalence of several widespread molecular mechanisms of inheritance other than by DNA sequence has come to light, evolutionary biology is provided with new phenomena to study and explain. Interesting theory is being developed as a consequence, and it is largely grounded in traditional population genetics. Documenting the frequency and distribution of nongenetic inheritance in natural populations, and its importance for evolved differences among populations and species, will be a task for empirical research.

Macroevolution: ES explains by microevolutionary processes, the EES by additional processes such as developmental bias and ecological inheritance. I have noted that developmental bias is not a new idea, and no evolutionary biologist who studies macroevolution would deny it. The role of ecological inheritance in macroevolution is speculative and unnecessary until shown otherwise.

CONCLUSIONS

Laland et al. (2015) add that in the EES, evolution is "redefined as a transgenerational change in the distribution of heritable traits of a population." That sounds equivalent to one traditional definition of evolution as change in gene frequencies, except that the EES redefinition would include nongenetic inheritance. Definitions are conventions, so does the definition of evolution matter? Perhaps. The philosophers of science Evelyn Fox Keller and Elizabeth Lloyd (1992, pp. 2-3) noted that words "help to hold worldviews together" and that "the effort to 'control and curtail the power of language' remains a significant feature of scientific activity. The very extent to which scientists…aim at a language of fixed and unambiguous meanings constitutes, in itself, one of the most distinctive features of their enterprise.

And even though never quite realizable, this effort to control the vicissitudes of language, like the commitment to objectivity, reaps distinctive cognitive benefits." Definitions, then, should not be altered lightly.

Are advocates of an extended evolutionary synthesis engaged in an "effort to control the vicissitudes of language," and to what end? Some of the emphases in the proposed EES, such as niche construction, the supposed pioneering role of phenotypic plasticity in adaptation, and quasi-Lamarckian interpretations of epigenetic inheritance, are reminiscent of the rise of neo-Lamarckism in the early twentieth century, during the "eclipse of Darwinism." Bowler (1989, p. 258) writes that "Lamarckism allows life itself to be seen as purposeful and creative. Living things are in charge of their own evolution: they choose their response to each environmental challenge and thus direct evolution by their own efforts. With or without any religious implications, this is certainly a more hopeful vision than that derived from Darwinism. Life becomes an active force in nature, no longer merely responding in a passive manner to environmental pressures." Welch (2017) hears echoes of this theme in current critiques of standard evolutionary theory. He quotes neurobiologist Steven Rose (2016) to that effect ("redefining evolution as 'a change of gene frequency in a population' is a reductionism too far, depriving living organisms of playing any part in their own destiny"), and recalls that Gregory Bateson (1958) found in Waddington's genetic assimilation implications "for the battle between non-moral materialism and the more mystical view of the universe." I do not think all advocates of an EES are impelled by emotional distaste for the utter lack of purpose and agency in evolution by natural selection, but it may be useful to ask if our views of evolutionary theory are affected by extrascientific values. As Welch (2017) notes, "we do need to explain why ideas are so often hailed as important before they have done much scientific work."

Some of the emphases in the proposed EES, especially nongenetic inheritance, may prove interesting, if developed both theoretically and empirically. Evolutionary developmental biology is an exciting field that can join a structuralist approach to the traditional emphasis on genetic variation – but it does not diminish the roles of genetic variation and selection. Modern versions of the Baldwin effect will need considerably more evidence before we can conclude that this kind of effect is important, and there are good reasons to doubt that it is. Overall, I have seen little evidential support for challenges to the basic tenets of the Evolutionary Synthesis.

There have now been many essays on why a new, or supposedly new, viewpoint or approach is warranted. If advocates of an EES are to convince many biologists, they will need to provide empirical support. To remain vital, a field of science requires challengers who aim to topple traditional views; but if it is not to be knocked about and smashed by unruly children (I am thinking of current politics in my country), the science also needs traditionalists. John Maynard Smith (1976), one of the most broad-minded of great evolutionary biologists, wrote, "It is in the nature of science that once a position becomes orthodox it should be subjected to criticism…It does not follow that because a position is orthodox, it is wrong."

LITERATURE CITED

Alberch, P., and E. A. Gale. 1985. A developmental analysis of an evolutionary trend: digit reduction in amphibians. Evolution 39:8-23.

Allen, C. E., P. Beldade, B. J. Zwaan, and P. M. Brakefield. 2008. Differences in the selection response of serially repeated color pattern characters: standing variation, development, and evolution. BMC Evol. Biol. 8:94.

Amundson, R. 2005. *The Changing Role of the Embryo in Evolutionary Thought: Roots of Evo-Devo*. Cambridge University Press, New York.

Aubret, F., X. Bonnet, and R. Shine. 2007. The role of adaptive plasticity in a major evolutionary transition: early aquatic experience affects locomotor performance of terrestrial snakes. Func. Ecol. 21:1154-1161.

Aubret, F., R. Shine, and X. Bonnet. 2004. Adaptive developmental plasticity in snakes. Nature 431:261.

Barrett, R. D. H., and D. Schluter. 2008. Adaptation from standing genetic variation. Trends Ecol. Evol. 23:38-44.

Barton, N. H., D. E. G. Briggs, J. A. Eisen, D. B. Goldstein, and N. H. Patel. 2007. *Evolution*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Bateson, G. 1958. The new conceptual frames for behavioral research. Proceedings of the Sixth Annual Conference at the New Jersey Neuro-Psychiatric Institute, pp. 54-71. Princeton, N. J. (Cited by Welch 2017.)

Bell, M. A., and W. E. Aguirre. 2013. Contemporary evolution, allelic recycling, and adaptive radiation of the threespine stickleback. Evol. Ecol. Res. 15:377-411.

Bonduriansky, R., and T. Day. 2009. Nongenetic inheritance and its evolutionary implications. Annu. Rev. Ecol. Evol. Syst. 40:103-125.

Bossdorf, O., C. L. Richards, and M. Pigliucci. 2009. Epigenetics for ecologists. Ecol. Lett. 11:106-115.

Bowler, P. J. 1989. *Evolution: The History of an Idea*. Second ed. University of California Press, Berkeley.

Brakefield, P. M. 2006. Evo-devo and constraints on selection. Trends Ecol. Evol. 21:362-368.

Britten, R. J., and E. H. Davidson. 1971. Repetitive and non-repetitive DNA sequences and a speculation on the origins of evolutionary novelty. Quart. Rev. Biol. 46:111-138.

Brodie, E. D. III. 2005. Caution: niche construction ahead. Evolution 59:249-251.

Callebaut, W. 2010.The dialectics of dis/unity in the evolutionary synthesis and its extensions.. In M. Pigliucci and G,. D. Müller (eds.), *Evolution: The Extended Synthesis*, pp.443-481. MIT Press, Cambridge, Mass.

Carroll, S. B. 2008. Evo-devo and an expanding evolutionary synthesis: a genetic theory of morphological evolution. Cell 134:25-36.

Castillo-Chávez, C., S. A. Levin, and F. Gould. 1988. Physiological and behavioral adaptation to varying environments – a mathematical model. Evolution 42:986-994.

Cavalli-Sforza, L. L., and A. W. F. Edwards. 1967. Phylogenetic analysis: models and estimation procedures. Evolution 21:550-570.

Cavalli-Sforza, L. L., and M. W. Feldman. 1981. *Cultural Transmission and Evolution: A Quantitative Approach*. Princeton University Press, Princeton, N.J.

Charlesworth, D., N. H. Barton and B. Charlesworth. 2017. The sources of adaptive variation. Proc. R. Soc. B 284:20162864, http://dx.doi.org/10.1098/rspb.2016.2864.

Chevin, L. M., and R. Lande. 2013. Evolution of discrete phenotypes from continuous norms of reaction. Am. Nat. 182:13-27

Chevin, L. M., R. Lande, and G. M. Mace. 2010. Adaptation, plasticity, and extinction in a changing environment: towards a predictive theory. PloS Biology 8(4) e1000357. DOI: 10.1371/journal.pbio.1000367.

Clausen, J., D. D. Keck, and W. M. Hiesey. 1940. Experimental studies on the nature of species. I. Effects of varied environments on western North American plants. Carnegie Institute of Washington Publication no. 520:1-452.

Conover, D. O., and E. T. Schultz. 1995. Phenotypic similarity and the evolutionary significance of countergradient variation. Trends Ecol. Evol. 10:248-252.

Coyne, J. A., and H. A. Orr. 2004. *Speciation*. Sinauer, Sunderland, Massachusetts.

Dawkins, R. 1982. *The Extended Phenotype: The Gene as the Unit of Selection*. W. H. Freeman, Oxford.

Day, T., and R. Bonduriansky. 2011. A unified approach to the evolutionary consequences of genetic and nongenetic inheritance. Am. Nat. 178:E18-E36.

de Jong, G. 1995. Phenotypic plasticity as a product of selection in a variable environment. Am. Nat. 145:493-512.

de Jong, G. 2005. Research review: Evolution of phenotypic plasticity: patterns of plasticity and the emergence of ecotypes. New Phytol. 166:101-118.

Dickins, T. E., and Q. Rahman. 2012. The extended evolutionary synthesis and the role of soft inheritance in evolution. Proc. R. Soc. B 279:2913-2921.

Dobzhansky, Th. 1937. *Genetics and the Origin of Species*. Columbia University Press, New York.

Dobzhansky, Th.,, F. J. Ayala, G. L. Stebbins, and J. W. Valentine. 1977. *Evolution*. W. H. Freeman, San Francisco.

Eldredge, N., and S. J. Gould. 1972. Punctuated equilibria: an alternative to phyletic gradualism. In T. J. M. Schopf (ed.), *Models in paleobiology*, pp. 82-115. Freeman, Cooper, San Francisco.

Eyre-Walker, A., and P. D. Keightley. 2007. The distribution of fitness effects of new mutations. Nature Rev. Genet. 8:610-618.

Falconer, D. S. 1960. *Introduction to quantitative genetics*. Oliver and Boyd, London.

Feldman, M. W., and L. L. Cavalli-Sforza. 1976. Cultural and biological evolutionary processes, selection for a trait under complex transmission. Theor. Pop. Biol. 9:238-259.

Felsenstein, J. 1973. Maximum-likelihood and minimum-steps methods for estimating evolutionary trees from data on discrete characters. Syst. Zoool. 22:240-249.

Felsenstein, J. 2004. *Inferring Phylogenies*. Sinauer, Sunderland, Massachysetts.

Fisher, R. A. 1930. *The genetical theory of natural selection*. Clarendon Press, Oxford.

Freeman, S., and J. C. Herron. 2014. *Evolutionary Analysis* (Fifth edition). Pearson, Boston.

Furrow, R. E., and M. W. Feldman. 2014. Genetic variation and the evolution of epigenetic regulation. Evolution 68:673-683.

Futuyma, D. J. 1979. *Evolutionary Biology*. Sinauer, Sunderland, Mass.

Futuyma, D. J. 1983. Selective factors in the evolution of host choice by insects. In S. Ahmad (ed.), *Herbivorous Insects: Host-seeking Behavior and Mechanisms*, pp. 227-244. Academic Press, N. Y.

Futuyma, D. J. 1986. *Evolutionary Biology* (Second edition). Sinauer, Sunderland, Mass.

Futuyma, D. J. 2010. Evolutionary constraint and ecological consequences. Evolution 64:1865-1884.

Futuyma, D. J. 2015. Can modern evolutionary theory explain macroevolution? In E. Serrelli and N. Gontier (eds.), *Macrovolution: Explanation, Interpretation and Evidence*, pp. 29-85. Springer, Heidelberg.

Futuyma, D. J., and M. Kirkpatrick. 2017. *Evolution* (Fourth edition). Sinauer, Sunderland, Mass.

Gavrilets, S. 2010. High-dimensional fitness landscapes and speciation. In M. Pigliucci and G. B. Müller (eds.), *Evolution: The Extended Synthesis*, pp. 45-79. MIT Press, Cambridge, Mass.

Gavrilets, S., and S. M. Scheiner. 1993. The genetics of phenotypic plasticity. V. Evolution of reaction norm shape. J. Evol. Biol. 6:31-38.

Ghalambor, C. K., J. K. McKay, S. P. Carroll, and D. N. Reznick. 2007. Adaptive versus non-adaptive phenotypic plasticity and the potential for contemporary adaptation in new environments. Func. Ecol. 21:394-407.

Ghalambor, C. K., K. L. Hoke, E. W. Ruell, E. K. Fischer, D. N. Reznick, and K. A. Hughes. 2015. Non-adaptive plasticity potentiates rapid adaptive evolution of gene expression in nature. Nature 525:372-375.

Gilbert, S. F., and D. Epel. 2015. *Ecological Developmental Biology* (second edition). Sinauer, Sunderland, Mass.

Goodwin, B. C. 1984. A relational or field theory of reproduction and its evolutionary implications. In M.-W. Ho and P. T. Saunders (eds.), *Beyond Neo-Darwinism: An Introduction to the New Evolutionary Paradigm*, pp. 219-241. Academic Press, London.

Gottlieb, L. D. 1984. Genetics and morphological evolution in plants. Am. Nat. 123:681-709.

Gould, S. J. 1977. *Ontogeny and Phylogeny*. Harvard University Press, Cambridge, Mass.

Gould, S. J. 1980. Is a new and general theory of evolution emerging? Paleobiology 6:119-130.

Gould, S. J. 1982. Darwinism and the expansion of evolutionary theory. Science 216:380-387.

Grether, G. F. 2005. Environmental change, phenotypic plasticity, and genetic compensation. Am. Nat. 166:E115-E123.

Grether, G. F. 2014. Redesigning the genetic architecture of phenotypically plastic traits in a changing environment. Biol. J. Linn. Soc. 112:276-286.

Gupta, M., N. G. Prasad, S. Dey, A. Joshi, and T. N. C. Vidya. 2017. Niche construction in evolutionary theory: the construction of an academic niche? J. Genetics (in press). (Preprint in bioRχiv, doi:http://doi.org/10.1101/109793.)

Haig, D. 2007. Weismann rules! OK? Epigenetics and the Lamarckian temptation. Biology and Philosophy 22:415-428.

Haldane, J. B. S. 1932. *The Causes of Evolution*. Longmans, Green, New York.

Hamburger, V. 1980. Evolutionary theory in Germany: a comment. In E.Mayr and W. B. Provine (eds.), *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, pp. 303-308. Harvard University Press, Cambridge, Mass..

Hendry, A. P. 2016. *Eco-Evolutionary Dynamics*. Princeton University Press, Prineton, N. J.

Herrera, C. M., M. Medrano, and P. Bazaga. 2016. Comparative spatial genetics and epigenetics of plant populations: heuristic value and a proof of concept. Mol. Ecol. 25:1653-1664.

Ho, M.-W., and P. T. Saunders (eds.) 1984. *Beyond Neo-Darwinism: An Introduction to the New Evolutionary Paradigm*. Academic Press, London.

Holman, L., and H. Kokko. 2014. The evolution of genomic imprinting: costs, benefits and long-term consequences. Biol. Rev. 89:568-587.

Huxley, J. 1942. *Evolution, the Modern Synthesis*. Allen and Unwin, London.

Jablonka, E., B. Oborny, I. Molnar, E. Kisdi, J. Hofbauer, and R Czaran. 1995. The adaptive advantage of phenotypic memory in changing environments. Phil. Trans. R. Soc. B 350:133-141.

Jablonka, E., and M. J. Lamb. 2010. Transgenerational epigenetic inheritance. In M. Pigliucci and G. B. Müller (eds.), *Evolution: The Extended Synthesis*, pp. 137-174. MIT Press, Cambridge, Mass.

Jablonka, E., and M. J. Lamb. 2014. *Evolution in Four Dimensions* (second edition). MIT Press, Cambridge, Mass.

Jacob, F., and J. Monod. 1961. Genetic regulatory mechanisms in the synthesis of proteins. J. Mol. Biol. 2:318-356.

Keller, E. F., and E. A. Lloyd. 1992. Introduction. In E. F. Keller and E.A. Lloyd (eds.), *Keywords in Evolutionary Biology*, pp. 1-6. Harvard University Press, Cambridge, Mass.

Keller, T. E., J. R. Lasky, and S. V. Yi. 2016. The multivariate association between genomewide DNA methylation and climate across the range of *Arabidopsis thaliana*. Mol. Ecol. 25:1823-1837.

Kimura, M. 1968. Evolutionary rate at the molecular level. Nature 217:624-626.

Kimura, M. 1983. *The Neutral Theory of Molecular Evolution*. Cambridge University Press, Cambridge.

King, J. L., and T. H. Jukes. 1969. Non-Darwinian evolution. Science 164:788-798.

Kirkpatrick, M., and R. Lande. 1989. The evolution of maternal characters. Evolution 43:485-503.

Kirschner, M., and J. Gerhart. 2005. *The Plausibility of Life*. Yale University Press, New Haven, CT.

Kirschner M. W., and J. C. Gerhart. 2010. Facilitated variation. In M. Pigliucci and G. Müller G. (eds.), *Evolution: The Extended Synthesis*, pp.253-280. MIT Press, Cambridge, Massachusetts.

Kuratani, S., S. Kuraku, and H. Nagashima. 2011. Evolutionary developmental perspective for the origin of turtles: the folding theory for the shell based on the developmental nature of the carapacial ridge. Evol. Devel. 13:1-14.

Laland, K. N., T. Uller, M. W. Feldman, K. Sterelny, G. B. Müller, A. Moczek, E. Jablonka, and J. Odling-Smee. 2015. The extended evolutionary synthesis: its structure, assumptions, and predictions. Proc. R. Soc. B 282:20151019.

Lande, R. 1978. Evolutionary mechanisms of limb loss in tetrapods. Evolution 32:73-92.

Lande, R. 1982. A quantitative genetic theory of life history evolution. Ecology 63:607-615.

Lande, R. 2009. Adaptation to an extraordinary environment by evolution of phenotypic plasticity and genetic assimilation. J. Evol. Biol. 22:1435-1446.

Ledón-Rettig, C. C., D. W. Pfennig, and E. J. Crespi. 2010. Diet and hormonal manipulation reveal cryptic genetic variation: implications for the evolution of novel feeding strategies. Proc. R. Soc. B 277:3569-3578.

Levins, R. 1968. *Evolution in Changing Environments*. Princeton University Press, Princeton, N. J.

Levis, N. A., and D. W. Pfennig. 2016. Evaluating 'plasticity-first' evolution in nature: key criteria and empirical approaches. Trends Ecol. Evol. 31:563-574.

Lewontin, R. C. (ed.) 1968. *Population Biology and Evolution*. Syracuse University Press, Syracuse, N.Y.

Lewontin, R. C. 1983. Gene, organism and environment. In D. S. Bendall (ed.), *Evolution From Molecules to Men*, pp. 275-285. Cambridge University Press, Cambridge.

Li, C., X.-C. Wu, O. Rieppel, L.-T. Wang, and L.-J. Zhao. 2008. An ancestral turtle from the Late Triassic of southwestern China. Nature 456:497-501.

Love, A. C. 2009. Marine invertebrates, model organisms and the modern synthesis: epistemic values, evo-devo, and exclusion. Theor. Biosci. 128:19-42.

Lynch, V. J. et al. 2015. Ancient transposable elements transformed the uterine regulatory landscape and transcriptome during the evolution of mammalian pregnancy. Cell. Rep. 10:551-561.

Magnuson-Ford, K., and S. P. Otto. 2012. Linking the investigations of character evolution and species diversification. Am. Nat. 180:225-245.

Maisnier-Patin, S., and J. R. Roth. 2015. The origin of mutants under selection: how natural selection mimics mutagenesis (adaptive mutation). Cold Spring Harbor Perspectives in Biology 7(7), article a018176.

Mallarino, R., and A. Abzhanov. 2012. Paths less traveled: evo-devo approaches to investigating animal morphological evolution. Annu. Rev. Cell Devel. Biol. 28:743-763.

Mather, K., and J. L. Jinks. 1971. *Biometrical Genetics*. Chapman and Hall, London.

Mattila, T. M., and F. Bokma. 2008. Extant mammal body masses suggest punctuated equilibrium. Proc. R. Soc. B 275:2195-2199.

Maynard Smith, J. 1976. Group selection. Quart. Rev. Biol. 51:277-283.

Maynard Smith, J., R. Burian, S. Kaufman, P. Alberch, J. Campbell, B. Goodwin, R. Lande, D. Raup, and L. Wolpert. 1985. Developmental constraints and evolution. Quart. Rev. Biol. 60:265-287.

Mayr, E. 1942. *Systematics and the Origin of Species*. Columbia University Press, New York.

Mayr, E. 1954. Change of genetic environment and evolution. In J. Huxley, A. C. Hardy, and E. B. Ford (eds.), *Evolution as a process*, pp. 157-180. Allen and Unwin, London.

Mayr, E. 1960. The emergence of evolutionary novelties. In Tax S (ed.), *The Evolution of Life*, pp. 157-180. University of Chicago Press, Chicago.

Mayr, E. 1961. Cause and effect in biology. Science 134:1501-1506.

Mayr, E. 1963. *Animal Species and Evolution*. Harvard University Press, Cambridge, Mass.

Mayr, E. 1993. What was the evolutionary synthesis? Trends Ecol. Evol. 8:31-34.

Mayr, E., and W. B. Provine (eds.), 1980. *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Harvard University Press, Cambridge, Mass.

Mousseau, T. A., and C. W Fox. 1998. The adaptive significance of maternal effects. Trends Ecol. Evol. 13:403-407.

Müller, G. B. 2010. Epigenetic innovation. In M. Pigliucci and G. B. Müller (eds.), *Evolution: The Extended Synthesis*, pp. 307-332. MIT Press, Cambridge, Massachusetts.

Murray, J. D. 1981. A pre-pattern formation mechnism for animal coat markings. J. Theor. Biol. 88:161-199.

Odling-Smee, F. J., K. N. Laland, and M. W. Feldman. 2003. *Niche Construction: The Neglected Process in Evolution*. Princeton University Press, Princeton, N. J.

Orr, H. A., and J. A. Coyne. 1992. The genetics of adaptation revisited. Am. Nat. 140:725-774.

Pigliucci, M. 2001. *Phenotypic Plasticity*. Johns Hopkins University Press, Baltimore.

Pigliucci, M. 2010. Phenotypic plasticity, In M. Pigliucci and G. B. Müller (eds.), *Evolution: The Extended Synthesis*, pp. 355-378. MIT Press, Cambridge, Mass.

Rausher, M. D. 1984. The evolution of habitat selection in subdivided populations. Evolution 38:596-608.

Rensch, B. 1947. *Neuere Probleme der Abstammungslehre*. Enke, Stuttgart.

Rensch, B. 1959. *Evolution Above the Species Level*. John Wiley & Sons, New York.

Rose, S. 2016. How to get another thorax. London Review of Books 38 (17):15-17. (Cited by Welch 2017.)

Scharloo, W. 1991. Canalization: genetic and developmental aspects. Annu. Rev. Ecol. Syst. 22:65-93.

Scheiner, S. M. 1993. Genetics and evolution of phenotypic plasticity. Annu. Rev. Ecol. Syst. 24:35-68.

Schlichting, C. D., and M. A. Wund. 2014. Phenotypic plasticity and epigenetic marking: an assessment of evidence for genetic accommodation. Evolution 68:656-672.

Schmalhausen, I. I. 1949. *Factors of evolution: The theory of stabilizing selection*. Blakiston, Philadelphia.

Scott-Phillips, T. C., K. N. Laland, D. M. Shukar, T. E. Dickins, and S. A. West. 2013. The niche construction perspective: a critical appraisal. Evolution 68:1231-1243.

Scoville, A. G., and M. E. Pfrender. 2010. Phenotypic plasticity facilitates recurrent rapid adaptation to introduced predators. Proc. Nat. Acad. Sci.USA 107:4260-4263.

Simpson, G. G. 1944. *Tempo and Mode in Evolution*. Columbia University Press, New York.

Simpson G. G. 1953. The Baldwin effect. Evolution 7:110-117.

Smith, T. A., M. D. Martin, M. Nguyen, and T. C. Mendelson. 2016. Epigenetic divergence as a potential first step in darter speciation. Mol. Ecol. 25:1882-1894.

Smocovitis, V. B. 1996. *Unifying Biology: The Evolutionary Synthesis and Evolutionary Biology*. Princeton University Press, Princeton.

Stebbins, G. L. 1950. *Variation and Evolution in Plants*. Columbia University Press, New York.

Stebbins, G. L. 1974. *Flowering plants: Evolution above the Species Level*. Harvard University Press, Cambridge, Massachusetts.

Stern, D. L. 2011. *Evolution, Development, and the Predictable Genome*. Roberts and Co., Greenwood Village, Colorado.

Storz, J. F., G. R. Scott, and Z. A. Cheviron. 2010. Phenotypic plasticity and genetic adaptation to high-altitude hypoxia in vertebrates. J. Exp. Biol. 213:4125-4136.

Uller, T. 2008. Developmental plasticity and the evolution of parental effects. Trends Ecol. Evol. 23:432-438.

Venditti, C., and M. Pagel. 2010. Speciation as an active force in promoting genetic evolution. Trends Ecol. Evol. 25:14-20.

Verhoeven, K. J. F., B. M. Vonholdt, and V. L. Sork. 2016. Epigenetics in ecology and evolution: what we know and what we need to know. Mol. Ecol. 25:1631-1638.

Via, S., and R. Lande. 1985. Genotype-environment interaction and the evolution of phenotypic plasticity. Evolution 39:505-522.

von Uexküll, J. 1921. *Umwelt und Innenwelt der Tiere*. Springer, Berlin.

Waddington, C. H. 1953. Genetic assimilation of an acquired character. Evolution 7:118-126.

Wagner, G. P. 2014. *Homology, Genes, and Evolutionary Innovation*. Princeton University Press, Princeton, N. J.

Walsh, B., and M. W. Blows. 2009. Abundant genetic variation + strong selection = multivariate genetic constraints: a geometric view of adaptation. Annu. Rev. Ecol. Evol. Syst. 40:41-59.

Welch, J. J. 2017. What's wrong with evolutionary biology? Biology & Philosophy 32:263-279.

West-Eberhard, M. J. 2003. *Developmental Plasticity and Evolution*. Oxford University Press, Oxford.

Wolf, J. B., E. D. Brodie III, . M. Cheverud, A. J. Moore, and M. J. Wade. 1998. Evolutionary consequences of indirect genetic effects. Trends Ecol. Evol. 13:64-69.

Wright, S. 1931. Evolution in Mendelian populations. Genetics 16:97-159.

Wright, S. 1934. The results of crosses between inbred strains of guinea pigs, differing in number of digits. Genetics 19:537-551.

Wright, S. 1934. An analysis of variability in number of digits in an inbred strain of guinea pigs. Genetics 19:506-536.

Wright, S. 1968. *Evolution and the Genetics of Populations. Volume 1. Genetic and Biometric Foundations*. University of Chicago Press, Chicago.

Wund, M. A., S. Valena, S. Wood, and J. A. Baker. 2012. Ancestral plasticity and allometry in threespine stickleback reveal phenotypes associated with derived, freshwater ecotypes. Biol. J. Linn. Soc. 105:573-583.

Zimmer, C., and D. J. Emlen. 2016. *Evolution: Making Sense of Life*. W. H. Freeman, New York.

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