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PERSPECTIVE

A striking example of developmental bias in an evolutionary process: The "domestication syndrome"

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Abstract

The question of whether "developmental bias" can influence evolution is still controversial, despite much circumstantial evidence and a good theoretical argument. Here, I will argue that the domestication of mammalian species, which took place independently more than two dozen times, provides a particularly convincing example of developmental bias in evolution. The singular finding that underlies this claim is the repeated occurrence in domesticated mammals of a set of distinctive traits, none of which were deliberately selected. This phenomenon has been termed "the domestication syndrome". In this article, I will: (a) describe the properties of the domestication syndrome; (b) show how it can be explained in terms of the operation of a specific genetic regulatory network, that which governs neural crest cell development; and (c) discuss Dmitry Belyaev's idea of "destabilizing selection," which holds that selecting for a new behavior often entails neuroendocrine alterations that alter many aspects of development. Finally, I will argue for the potential general significance of such destabilizing selection, in combination with developmental bias, in animal evolution.

KEYWORDS

destabilizing selection, developmental bias, domestication syndrome

1 | INTRODUCTION

The term "developmental bias" lacks a standard textbook definition but will be used here to denote the tendency of developing complex organisms to pursue a limited number of characteristic pathways when perturbed, either by environmental factors or genetic alterations. Its essential property is that the limited number of trajectories and outcomes reflect the properties of the developmental system rather than the specific agents that cause the perturbation. There is much evidence that developmental bias is a general, and probably universal, feature of developmental systems (Alberch, 1982, 1989; Wake, 1991).

The question of whether it contributes significantly to evolutionary change, however, remains a matter of controversy and active debate. The traditional view is that it is not a major influence and that natural selection has the ultimate power to shape evolutionary outcomes (Charlesworth, Barton, & Charlesworth, 2017; Futuyma, 2015). In this view, developmental biases may initially limit the range possibilities of change but, in the end, natural selection can determine a huge variety of different outcomes, whatever the initial starting points of change. Darwin himself would probably have endorsed this sentiment, given his emphasis on the efficacy of selection, both natural and artificial, to create enormously different living forms (Darwin, 1859, Chapter 1). In recent years, however, another view, based on observations from many different sources, has been emerging. It accords developmental bias a significant role in the shaping of evolutionary trajectories (Laland

et al., 2015; Uller, Moczek, Watson, Brakefield, & Laland, 2018). This interpretation does not deny the crucial role of natural selection in evolution but emphasizes the properties of development that limit both the initial divergences and, ultimately, the endpoints of evolutionary change.

There is also a good theoretical argument for the occurrence of developmental bias in evolution. Since all morphological features are the end-products of developmental processes and because these are underlain by genetic regulatory networks (GRNs; Davidson, 2006; Wilkins, 2002, 2005, 2007), it follows that the patterns of evolutionary change in morphological features must reflect underlying genetic changes in those GRNs. Those mutations produce a discrete set of altered GRNs, whose hierarchical structure must produce a finite, relatively limited, set of morphological changes. In effect, the structure of each GRN constrains the range of action of its variants and their final outcomes (Uller et al., 2018; Wilkins, 2005, 2007). The same point has also been argued from a different, computational perspective (Borenstein & Krakauer, 2008).

The very fact of the independent occurrence of similar morphological changes in related lineages that have evolved independently (Alberch and Gale, 1985; Wake, 1991) might seem initially to indicate the existence of developmental bias. Such outcomes, however, can always be argued to be the product of similar selective pressures. To make a strong argument for the role of developmental bias, therefore, it would help to have examples where repeated similar changes involving traits of little or no selective value were produced in different lineages. In this article, I will look at just this phenomenon, as seen specifically in the domestication of animals, the so-called "domestication syndrome" (Wilkins, Wrangham, & Fitch, 2014; Zeder, 2012). In this phenomenon, new phenotypic traits recur repeatedly in independently domesticated lineages but have no obvious functional connection to the selected trait in domestication, namely tameness. In mammals, these traits include several aspects of facial shape, brain size, coat color changes, ear and tail shapes, various endocrinal changes, and altered female sexual cycles.

In this article, I will first describe the domestication syndrome as an example of developmental bias and argue that it reflects perturbations of a well-characterized GRN, specifically the GRN governing neural crest cells (NCCs) formation and development. The focus will then shift to how selection for a new behavior might, via the postulated process of "destabilizing selection," lead to many physiological and developmental changes, as seen in the domestication syndrome, and how these changes might be converted into a hereditary state. The article will conclude with a discussion of why the combination of destabilizing selection and developmental bias might be significant factors in evolution whenever there is a long-term selection for new behavior.

2 | THE DOMESTICATION OF ANIMALS AND THE "DOMESTICATION SYNDROME"

Before getting into the details of animal domestication, a critical question should be addressed first: Is domestication a valid example of an evolutionary process? The involvement of humans in actively guiding domestication, of both plants and animals, has seemed to some scholars to invalidate it as a model for natural evolutionary processes. Domestication, however, can occur by several distinct routes, of which the promotion of specific traits by selective breeding is only one (Larson et al., 2014; Zeder, 2012, 2017). In particular, domestication can also begin via naturally occurring commensal relationships or as a consequence of herding of animals without any special attempts at shaping the progeny over many generations. Crucially, the first steps in all domestication events almost certainly did not involve selective breeding, which came later in some, but not all, lines. Furthermore, domestication involves the signature characteristic of evolution—long-term genetic changes in the population of organisms involved. These population alterations are inevitably accompanied by ecological consequences, a further concomitant of evolutionary change. By these criteria, domestication is certainly an evolutionary process (Zeder, 2017, 2018). This position is hardly new: indeed, Charles Darwin began *The Origin of Species* with a discussion of domestication as a model of the evolutionary process (Darwin, 1859). His viewpoint was intimately tied up with his stress on the power of selection to create stunning morphological changes in animal and plant populations.

In all cases of animal domestication, the process must have been initiated with selection, deliberate or inadvertent, for a degree of tameness not possessed by the ancestral wild stock. "Tameness" denotes the ability of animals to be in close proximity or even to be handled by humans without triggering a fight-or-flight response. Tameness is thus a behavioral change based on a reduced fear-response, which in turn must reflect neurobiological and physiological changes. There is no a priori reason, however, to think that selecting for tameness should always bring in train marked developmental and morphological changes. In principle, tame animals need not look different from their wild progenitors. Yet, strikingly, they often do. The simplest inference is that

animal domestication was accompanied by a suite of developmental and morphological changes, many of which bear a little obvious relationship to the initially selected trait—tameness. There are also, as we will see, measurable physiological changes involving the neuroendocrine and reproductive systems.

The conclusion that animal domestication entails many changes seemingly unrelated to the selected property (tameness) and to each other was first reached by Darwin himself, who had made an intense and broad study of domestication in plants and animals (Darwin, 1875). His strong interest in domestication had two sources. First, as noted above, he was interested in it as a general model for evolutionary change. Second, he saw the records of animal and plant breeders as a crucial source of information for inferring the mechanisms of heredity. Though his resulting theory of the basis of heredity—his theory of "pangenesis"—was a failure, his inadvertent discovery of the domestication syndrome has been amply confirmed. As indicated above, the traits that make up the domestication syndrome in mammals include such features as smaller jaws and teeth, wider heads, floppy ears, altered coat colors, smaller brains, reduced corticosteroid stress responses, and more frequent female sexual cycles than occur in the wild progenitors. Variant but related domestication syndromes are seen in domesticated birds and fishes, indicating that it is a vertebrate-wide phenomenon.

It is now appreciated that there are differences in the exact set of altered traits between different domesticated mammalian species and often amongst their different breeds (Sánchez-Villagra, Geiger, & Schneider, 2016). Nevertheless, many of the same altered traits show up across many of the 26 or so domesticated mammalian species (Francis, 2015; Sánchez-Villagra et al., 2016). Some authors have referred to this generic set of changes as the "domesticated phenotype." However, given the differences in the domestication-associated traits amongst the different domesticated animals, and the variability of phenotypic expression within many individual breeds, the term "domestication syndrome," with its connotations of a generic condition with variable manifestations, is preferable. This usage was first coined more than three decades ago to describe a set of changes shared amongst domesticated plants, relative to their wild relatives (Hammer, 1984) but was later applied to animals (Wilkins et al., 2014; Larson et al., 2014).

It is the existence of the domestication syndrome that indicates the involvement of developmental bias in the creation of the domesticated state in animals. It is, of course, conceivable that the morphological and physiological traits characteristic of the "syndrome" all developed independently and well after the initial domestication steps in the different animal lines. Some strong evidence, however, indicates that they arise as part of the domestication process itself. These results come from the experimental domestication of foxes (reviewed in Trut, 1999 and Trut, Oskina, & Kharlamova, 2009) and chickens (Agnvall, Belteky, Katajama, & Jensen, 2018), in which the domestication syndrome makes an early appearance following selection of animals solely for reduced fear of humans, the prerequisite condition for domestication. The unavoidable conclusion is that the domestication syndrome, as seen in mammals and birds, reflects developmental biases that come into play when the domesticated state is initiated.

3 | THE TAXONOMY OF THE "DOMESTICATION SYNDROME" AS A CLUE TO ITS POSSIBLE UNDERLYING BASIS

The detailed different phenotypes associated with the domestication of 26 species of mammals have been scored by Sánchez-Villagra et al. (2016) and the results summarized in their figure 1. A summary is given here (Tables 1a and 1b).

As can be seen from the table, the only universally shared trait amongst domesticated mammals is tameness. Tameness is essential for close contact between humans and their animals and having some degree of tameness was almost certainly a prerequisite for domestication. All of the other traits show some differences in terms of which species and breeds display them. In the original figure, and in the table here, the domestication-associated traits are divided into those characteristics of the species (Table 1a) and those showing differences amongst breeds of the same species (Table 1b). This distinction might be thought to reflect, respectively, early changes, associated with the first steps of domestication, and later events, associated with subsequent breeding of different lines. That interpretation, however, should be treated with caution. All of the domesticated mammals have had a long history as domesticates, ranging from several centuries to many millennia (Francis, 2015; Larson et al., 2014). Given the basic underlying developmental and physiological commonalities of mammals, it is entirely possible that some of the seemingly breed-specific traits seen in different species arose both late and independently, postdomestication, in those species. It is equally likely, however, that early domestication-associated treats were modified and lost in certain breeds. Hence, whether or not a particular domestication-associated trait is found in all or only some breeds of a species is not a certain indicator as to its time of origin.

TABLE 1a Numbers of domesticated animal species where all individuals and breeds show the indicated change, out of a total of 26

Tame Tameness	Decreased brain size	Decreased heart size	Shorter muzzle	Reduced tooth Size	Vertebrae variabilityNaN	Caudal vertebrae change	More frequent estrous cycles
26	19 (1)	9	8	3	3	3	6

Note: Adapted and simplified from Sánchez-Villagra et al. (2016). Numbers in parentheses indicate numbers of species where the change is uncertain. The species examined were: the dog, silver fox, ferret, mink, cat, donkey, horse, buffalo, cattle, zebu, yak, goat, sheep, reindeer, pig, camel, dromedary, llama, alpaca, rabbit, guinea pig, chinchilla, hamster, mouse, rat, gerbil. For details, see their figure 1.
[a]Thoracic and lumbar vertebrae.

(Another caution is that some of the apparent absences recorded by Sánchez-Villagra et al. probably reflect gaps in the data rather than absence of those traits in particular species or breeds.)

In connection with early-versus-late appearance, one particular trait that deserves special attention because of its ubiquity amongst domesticates is "depigmentation," namely the presence of unusual brown or white patches on the animal coats, where these are never seen in their wild forebears or related wild species. These coat color variations are found in essentially all domesticated species but not all breeds of each such species. Given its universality amongst domesticated species, it is almost certainly an early-developing trait and one closely associated with the onset of domestication. Indeed, depigmentation was one of the first traits to increase markedly in the fox-domestication experiments (Belyaev, 1979; Trut, 1999; Trut et al., 2009). It also appears in commensal house mice (Geiger, Sánchez-Villagra, & Lindholm, 2018) and in captive white-backed munias (a wild finch), the latter bred in captivity for 250 years but not subjected to any specific breeding regime (Suzuki, Ikebuchi, Bischof, & Okanoya, 2014). Thus, the fact that not all breeds of all domesticated mammalian species show white patches indicates that selective breeding can eliminate it in some lines, presumably through a selection of modifier alleles.

The two essential points here, however, are that: (a) many traits appear in connection with domestication and apparently as a concomitant of selection for tameness and (b) the "domestication syndrome" should be considered a generic state, with many variants, the particular traits seen in any case being a function of the species, breed, and particular domestication history.

How can one account for both the multiplicity of traits affected and the differences in phenotype-sets amongst the different domesticated animals? Presumably, once tameness began to be selected in the different lineages that went on to become domesticated, there were mutations involved, whether pre-existing in those stocks or arising de novo. Yet, if multiple traits were affected by these mutations, then these were pleiotropic mutations, by definition. The simplest way to view the situation is that a GRN, affecting all these traits, is involved and that mutations in relatively upstream elements in this GRN account for many of the traits, an explanation first offered in print by Trut, Plyusnina, and Oskina (2004). Differences in the sets of phenotypic traits between different domesticated mammals could reflect differences in the particular genes mutated within the GRN in the different species. The question that this explanation immediately provokes is: what GRN might this be?

4 | RETHINKING THE GENETICS OF DOMESTICATION IN TERMS OF THE GENETICS OF NCC DEVELOPMENT

Wilkins et al. (2014) proposed that the genetic roots of domestication in vertebrates might lie in the genes that underlie the formation and differentiation of the neural crest. The neural crest consists of pluripotent embryonic cells, derived initially from the dorsal-most region of the neural tube in the early embryo. After delimitation and specification, NCCs migrate ventrally in groups in the cranial and trunk regions to specific sites. At those destinations, they give rise to multiple and highly different cell types, ranging from neuroendocrine cells to melanocytes to gut neurons to, in the cranium, connective-tissue cells that eventually develop into the bones of the face. The idea, which is now designated the "neural crest/domestication syndrome" (NCDS) hypothesis was based on a

TABLE 1b Numbers of species in which only some of the domesticated breeds show the trait, out of 26 species listed

Floppy ears	Curly tail	Extra toes	Dwarfism	Coat color change	Skin folds	Hairlessness	Wool	Curly hair
11 (1)	4	5	8	21 (5)	7	9	7	8

Note: Again, numbers in parentheses indicate species in which there is some doubt about the change. Adapted and simplified from Sánchez-Villagra et al. (2016). The species examined were those listed in Table 1a. Again, for details, see figure 1 of Sánchez-Villagra et al. (2016).

large set of observations that show phenotypic similarities between the main traits of the domestication syndrome and the phenotypes produced by strong loss-of-function mutations in various NCC genes. Many of the latter are so-called haplo-insuffiicient mutations, in which a strong loss-of-function alteration in one copy of a diploid pair of genes creates a dominant effect. That result reflects the fact that for some genes, in particular, transcriptional regulatory genes, one wild-type gene copy is insufficient to give the full wild-type phenotype (Veitia, 2002). The basis of the NCDS hypothesis is the similarity in traits affected in domestication and those known to be affected by loss-of-function mutations in different genes essential for NCCs or their derivatives.

Given this information and the abundant evidence that the genetic basis of domestication is polygenic (Larson et al., 2014; Carneiro et al., 2014), Wilkins et al. (2014) proposed specifically that the domestication syndrome reflects the presence in the genome of multiple mild (partial) or "hypomorphic" loss-of-function mutations in genes that specify the neural crest. Such mutations have more residual activity than the kind of complete or near-complete loss-of-function mutations that give the haploinsufficient phenotype but, under the hypothesis, would generate their effects cumulatively—on NCC production or migration—to produce the visible effects. In principle, this idea helps explain the variety of different domestication syndromes. One only need to posit that mild loss-of-function mutations in different, though probably partially overlapping, sets of NCC genes are involved in establishing the variant domestication syndromes of different mammalian species or breeds. "Domestication" would be the shared outcome even though the underlying sets of affected NCC genes were not identical in different species.

Dozens of genes that play crucial roles in NCC biology have been identified and the GRN that contains them and which underlies NCC formation and development has been worked out to a high degree (Simoes-Costa & Bronner, 2015). The network can be seen as a multitiered structure of genes and genetic interactions within and between distinct modules. Its operation begins with a module that helps delimit the neural crest region from the rest of the neural tube, which is followed successively by the operation of modules that, respectively, govern the specification of the NCCs, their migration, and finally their differentiation in situ into the different cell types that are the ultimate developmental product of NCCs. A schematic diagram of the NCC GRN is shown in Figure 1.

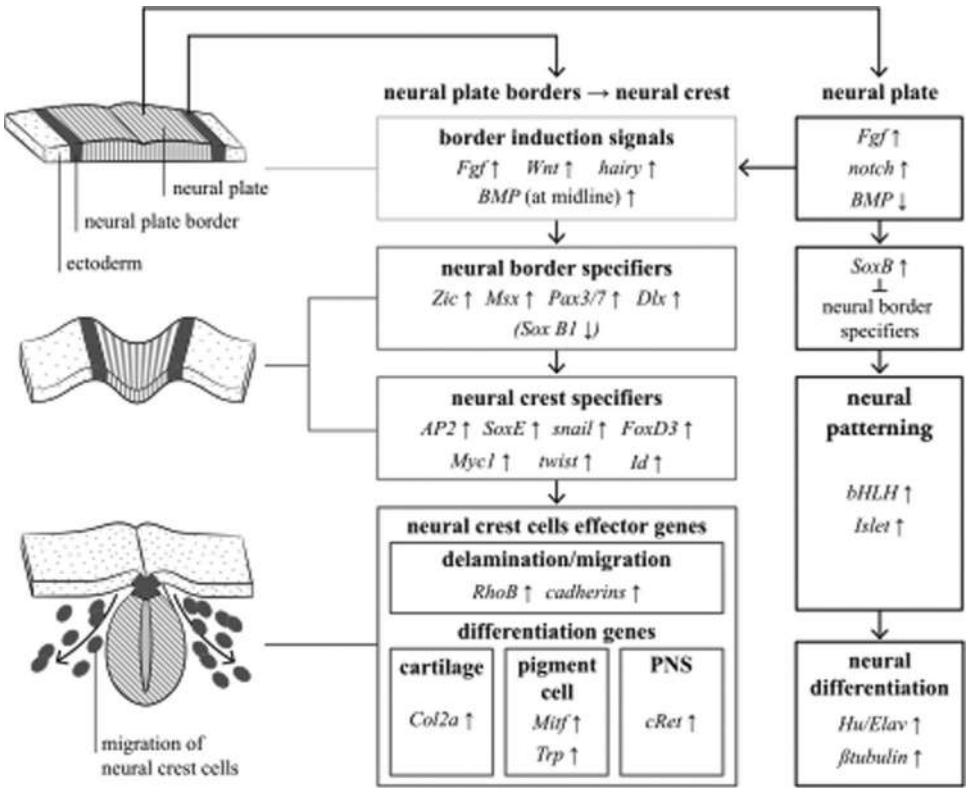

FIGURE 1 A schematic diagram of the genetic regulatory network for neural crest cell development, indicating, on the left, the main stages of development involving the neural crest and its derivative cells, and, on the right, the main modules and some of the key genes that are either up- or downregulated within each. (The detailed genetic interactions within modules are not shown.) Reproduced from Wilkins (2017b)

The NCDS hypothesis predicts that genomes of domesticated breeds will have mutations in NCC genes not seen in the progenitor strains or comparable wild breeds. When a number of mammalian species' genomes are compared in this way, that is exactly what has been found (Wilkins, 2017a). In contrast, an earlier hypothesis, that domestication is based on changes in thyroid hormone physiology (Crockford, 2002), predicts an enrichment in domesticated breeds of mutations in genes in thyroid metabolism; genomic studies, however, have produced much less support for this idea (Wilkins, 2017a).

Confirmation of the NCDS should be regarded as tentative, however, since the genomic studies have largely neglected regulatory mutations in *cis*-control elements and these would be expected to play a major part in any reductions in NCC populations within the developing embryos of domesticated species. Nevertheless, it provides a provisional explanation for the developmental bias toward a set of domestication syndromes and for many of the specific phenotypes observed, and the variety of conditions observed. Some of the phenotypes listed in Table 1a,b do not have an obvious connection to NCCs but may reflect indirect developmental effects from altered NCC biology and this possibility requires further exploration. Furthermore, the NCDS does not, at first glance, supply an obvious explanation to the link between tameness, the root condition of domestication, and the traits of the domestication syndrome. For that, one has to look more deeply at what selecting for a novel behavior might entail.

5 | THE CONSEQUENCES OF SELECTING FOR TAMENESS: "DESTABILIZING SELECTION"

The idea that the domestication syndrome is, in some way, a direct consequence of selecting for tameness is suggested by its general presence in all domesticated mammals, whose roots as domesticates must all trace to an initial selection for some degree of tameness. It follows even more directly, however, from the work of Belyaev and his colleagues, who found that the individual phenotypic traits of the domestication syndrome began appearing in their foxes selected solely for relative lack of fear and consequent tameness, from early in the selection process and then increasing in number as progressively more tame animals appeared.

In attempting to explain the association, Belyaev focused at first on the general question rather than on the specific changes seen in his foxes. That question is: Why might many developmental changes ensue from a selected change in behavior? His answer was that many behavioral responses, especially those involving fear or reduction in fear, are mediated by neuroendocrine responses, and the hormones involved might have profound associated developmental effects. He first proposed the idea in two early articles (Belyaev, 1969, 1974), and then in a more extended form in a special lecture, delivered at the 14th International Congress of Genetics, held in Moscow in 1978, and published the following year, 1979 (Belyaev, 1979) There, he begins his explanation with the following statement: "*What is peculiar and special in selecting for tame domesticated behavior? A close relationship exists between the nervous and endocrine systems. Selection for behavior can intrinsically change the nervous and endocrine systems. Selection for behavior can intrinsically change the hormonal status of the breed and this can also have consequences in the ontogenetic development of the animals. One should bear in mind that the neurohormonal system in all higher vertebrates, especially in mammals, plays a large role in the control of ontogeny. Hormones are important regulators of gene function with all the consequences for enzyme synthesis and biochemical activity during development*" (Belyaev, 1979, p. 306).

In effect, he was proposing that multiple developmental changes would be concomitants of the hormonal changes necessary for the selected behavioral changes, in this case those involved in "tameness." Specifically, this would have involved, at minimum, the corticosteroids produced by the adrenal glands that are intimately involved in stress and fear reactions. Most of the proposed developmental changes would have become visible postnatally, in the juvenile stage, and the behavioral changes during or after the first exploratory behaviors of the young animals. While ideas about gene regulation were still fairly vague in the late 1970s, especially in complex organisms, Belyaev directly related the changes he was proposing to alterations in gene regulation: "*In a genetic and biochemical sense, what may be selected for are changes in the regulation of genes—that is, in the timing and the amount of gene expression rather than changes in individual structural genes*" (Belyaev, 1979, p. 307). Because the process he was hypothesizing involved the disruption or, at least, alteration of normal developmental ("ontogenetic") processes, he named the process "destabilizing selection." (The title of his article was "Destabilizing selection as a factor in domestication.") This term might seem oxymoronic, because selection normally leads to one preferred and stable outcome while destabilization by definition tends to lead to variable states. Nevertheless, it makes sense: the selection is for one behavioral state but the process by

which it is achieved has the consequence of destabilizing features of normal development, with consequential variability of outcome in traits produced by those developmental processes.

A critical question, of course, is whether selection for domestication does involve hereditary, stable changes in the neuroendocrine control of any animal behaviors. The answer is "yes" and was known to be so at the time that Belyaev was proposing the idea. These include not only reductions in the corticosteroids, leading to less fearful animals, but increases in brain serotonin and reductions in brain monoamine oxidase, the latter changes known to be associated with lowered fear and aggressive responses (see reviews by Trut, 1999 and Trut et al., 2009). Altogether, many of the changes in behavior associated with domestication are associated with operation of the hypothalamus-pituitary-adrenal or HPA "axis," which regulates amongst other behaviors, fear, and aggression, as well as being involved in developmental changes at various sites and functions, in particular, those of female reproductive cycles and of pigmentation. The hypothalamus and pituitary also regulate the thyroid gland, which regulates growth and, thereby, many developmental processes.

6 | CONVERTING ONTOGENETIC DESTABILIZATION INTO A HEREDITARY PROPERTY AND AN EVOLUTIONARY CHANGE

Nevertheless, Belyaev's idea was incomplete. The idea, as he framed it, was a hypothesis about the *immediate* physiological and developmental effects of the postulated hormonal changes. As he said about the changes in reproductive capacity specifically, "*These changes reflect a destabilization of normal reproductive patterns that developed and were stabilized in the process of evolution*." He did not address, however, what the later "stabilization" would have involved. He was also skeptical that conventional mutational change was initially involved in the phenotypic changes that accompanied the selection for increasing tameness. The particular finding that was the basis of his skepticism was the high frequency of the appearance of the *Star* phenotype—named for the patch of white on the forehead of domesticated foxes that started increasing greatly in frequency early in the selection process. (There was a low rate of occurrence of this trait in the preselected farm-bred foxes [Trut, 1999].) This new frequency was in the range of 10^{-2}–10^{-3}, hence orders of magnitude greater than a standard forward mutation rate. The back-mutation rate of *Star* was also in this range, again values far too high to be consistent with a normal mutational process. This looks like the kind of change associated with what would now be termed "epigenetic" mechanisms, though the term did not exist in that sense at that time. Nevertheless, many of the features of the domestication syndrome are hereditarily stable, as indicated by domesticated animals that have gone feral and reproduced in the wild (Darwin, 1875; Kruska & Sidorovich, 2003).

If "destabilizing selection" is to join the pantheon of selective processes known to shape evolution—namely, directional selection, purifying selection, balancing selection, frequency-dependent selection, and stabilizing selection—something more is needed. In effect, if the changes induced by "destabilizing selection" are to become evolutionary changes, they have to become hereditarily fixed. For that, inherited mutations must be involved, replacing the initial and nonpermanent regulatory state changes hypothesized by Belyaev to produce the physiological and developmental changes. There are two known processes that could perform this function: "genetic assimilation" and "genetic accommodation."

"Genetic assimilation" denotes the process by which mutations stabilize a particular flexible or "plastic" developmental state induced as a response to an environmental change. Though the idea had late 19th century ancestry, it was first explored in detail and named by the British paleontologist and developmental biologist, C. H. Waddington (Waddington, 1953). He demonstrated several examples in his experimental work on the fruit fly *Drosophila melanogaster*. One was the induction at low frequency of flies with two sets of wings, the so-called "bithorax phenotype" (which refers to the fact that the flies' wings normally develop only on the mesothorax but in the mutant both on the meso- and metathorax), when embryos are exposed to a pulse of ether. Waddington found that by selecting those flies that showed this phenotype and breeding them, he could generate a line of flies that produced the bithorax phenotype spontaneously, namely without exposure to ether in early development. He showed that this phenomenon could be repeated with two other phenotypes, one involving an aspect of wing morphology, the other the size of the anal excretory papillae. He, thus, showed that genetic assimilation was a general phenomenon. Waddington's explanation was that, with the experimenter supplying the selection pressure, mutations could produce the selected phenotype more easily and perhaps more completely than a plastic developmental response would.

"Genetic accommodation" looks subtly different from genetic assimilation though both involve an environmental stimulus evoking an altered response. Starting with some prior genetic alteration, exposure to some new

environmental variable allows previously cryptic genetic variations to reveal themselves via new phenotypes (West-Eberhard, 2003). Subsequent selection for those phenotypes could then fix them, creating a new lineage with those properties. It is possible, however, that genetic assimilation involves a similar process, the induced expression of background "modifiers" that causes the new phenotype to appear with high frequency. With multiple modifiers brought together in the same genotype, the threshold for expression of the phenotype might be lowered.

Whether either of these phenomena has been a major source of "new" phenotypes in the adaptive evolution of complex organisms remains both a matter of debate and difficult to either prove or disprove (Moczek, 2007; Wilkins, 2003). Nevertheless, both are supported by experimental evidence and provide routes by which an initially transient developmental response, appearing in response to an external selection pressure can become a stable, hereditary property of a selected lineage. Hence, they are conceivable ways in which Belyaev's destabilizing selection could have yielded hereditarily stable (evolved) domesticated states.

A distinct though related question is whether the initial changes in domestication involve epigenetic changes, albeit ones with potential for transgenerational inheritance. This was apparently Belyaev's belief, based on his discovery of the *Star* "mutation" (Belyaev, Ruvinsky, & Trut, 1981). As noted above, its inheritance pattern is highly suggestive of an epigenetic state with quasi-heritability. Recently, evidence for stable epimutations in the early stages of domestication of sea bass that affect various developmental genes, including those for neural crest, has been found (Anastasiadi & Piferrer, 2019). More information, however, is still needed on the transgenerational inheritance of epigenetic states and whether they can be converted to true hereditary states by something akin to genetic assimilation or genetic accommodation (Jablonka, 2017; Wilkins, 2011).

7 | CONNECTING THE DOTS: FROM SELECTING FOR TAMENESS VIA DESTABILIZING SELECTION AND DEVELOPMENTAL BIAS TO THE DOMESTICATION SYNDROME AND DOMESTICATION ITSELF

With this background, one can begin to put together a plausible scenario for what takes place when domesticated behavior is selected in mammals and birds. The initial selection would be for some degree of tameness in the animals, whether they were captured and then deliberately bred in captivity or whether they started living in proximity to humans without management by the latter or herded together initially in controlled spaces but not handled or otherwise managed. The selection in all cases would have been for less fearful behavior, in effect a less readily activated fight-or-flight response. This would probably have involved a less reactive HPA axis in the young especially, before the end of their juvenile exploratory period when the fight-or-flight response would not have fully matured (see Wilkins et al., 2014, pp. 802–803). The altered hormonal responses of the HPA axis could have created changes in behavior, reproductive physiology, and developmental processes, via "destabilizing selection."

Over many generations, there would have been the selection for mutations that would have fixed these neuroendocrine responses and their developmental consequences. Because of the crucial role of NCC in generating the cells that carry out so much of this hormonal physiology, this could have involved mutations in the GRN for NCC. Continued multigenerational selection would have worked to select mild loss-of-function mutations in genes responsible for either NCC formation or for NCC specification or for NCC migration. A partial reduction in any of these processes would produce partial deficits in various precursor cells of many of the structures and tissues that ultimately derive from NCC. The consequence would have been the creation of developmental bias toward the set of multiphene conditions known as the "domestication syndrome." The specific features seen in any species or breed would be a function of the particular NCC genes that had been mutated and selected and, of course, the degree of loss-of-function of the mutations involved.

This proposal is still just a speculative scenario and an incomplete one, at that. In principle, the HPA axis and the parts of it involved in fear responses should be subject to mutations affecting parts well downstream of the NCC. Why the genes that promote the development of those cells should be the primary targets, as posited in the NCDS hypothesis, is unclear. Perhaps it is a matter of "target size," namely the number of those genes that can mutate and the postulated cumulative effect of reductions in NCC from multiple hypomorphic mutations in those genes. If the NCDS hypothesis continues to receive experimental support, this question will need further investigation.

The general idea, however, accords with and makes sense of many of the observations. Furthermore, and significantly, it is testable, at least in principle, as discussed in Wilkins et al. (2014). In particular, one potentially highly informative test would involve making combinations of mild hypomorphic mutations in NCC

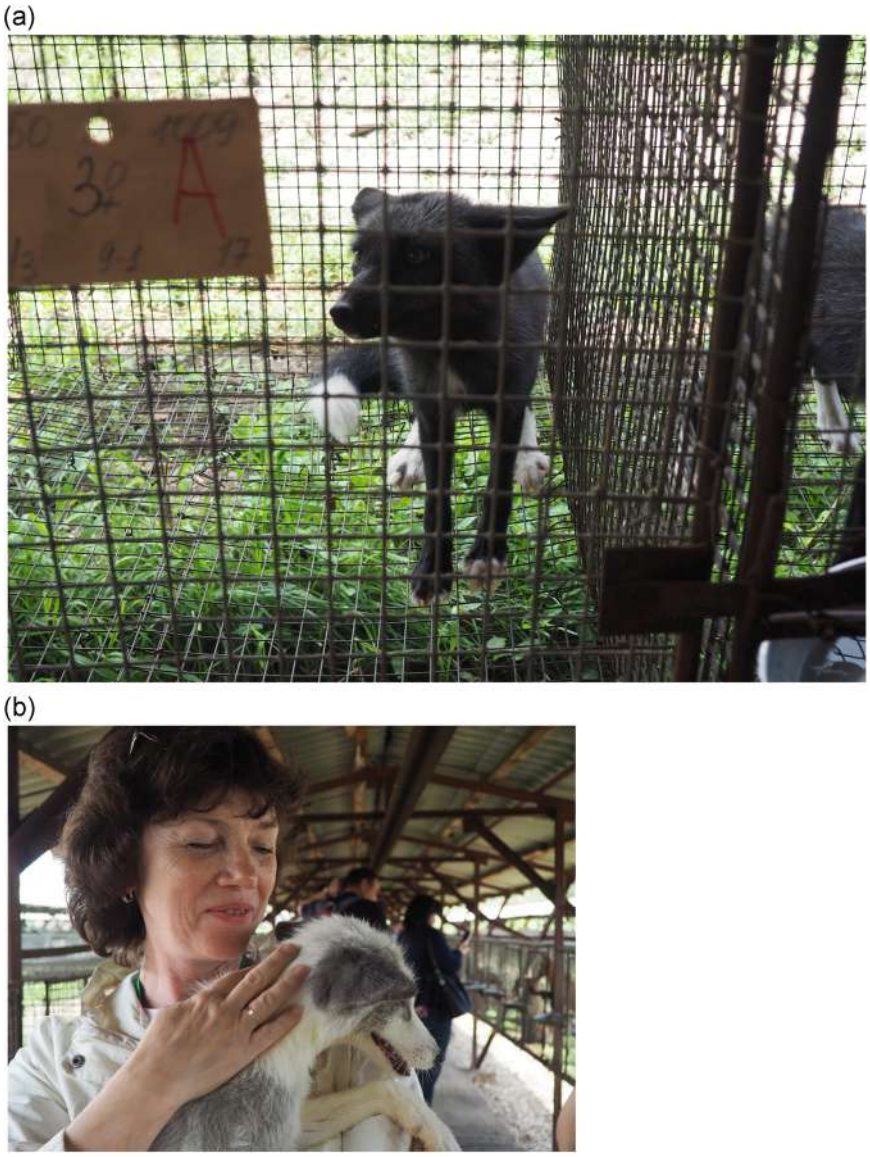

FIGURE 2 (a) A fox from the line selected for greater aggressivity at the Novosibirsk research station (August 2017). Note the white paws, tail tip, and chest patch features also seen in the foxes bred for the opposite behavior, tameness. On the sign, the red letter "A" stands for "aggressive". (b) Highly tame fox at the Novosibirsk experimental research farm (August 2017). Note the extensive areas of white coat color, as well as the floppy ears, another trait of the domestication syndrome [Color figure can be viewed at wileyonlinelibrary.com]

genes, via CRISPR or other techniques of genetic modification, in an animal where this would be permitted, such as mice, rats, guinea pigs—and observing the effects, at the developmental, hormonal, and behavioral levels. The prediction is that this would produce lines with the signature features of domestication. In addition, if comparative studies of NCC numbers and behaviors in the embryos of domestic versus their related wild species were carried out, this could also be very useful for testing the hypothesis.

8 | AND THE LARGER IMPLICATIONS….

Belyaev's idea of "destabilizing selection" was proposed to explain what takes place when one selects specifically for tameness and "domesticated" behavior. Yet he felt that selection for *any* behaviors that involved hormonal systems might have multiple phenotypic effects. If this thinking is correct, then there might be evolutionary consequences and implications going far beyond domestication. In particular, there might be wide-spread connections between selection for many altered behaviors and newly-appearing developmental/morphological traits.

Alterations in the HPA system itself could be the source of both new behaviors and new physical traits. Beyond regulation of fear and aggression and tameness, the HPA is involved in the regulation of memory consolidation and retrieval (via effects on the hippocampus), responses to rewards, vigilance, and, of course, movements in response to many of these stimuli. What, if any, correlated effects there might be on development and morphology would depend on which GRNs the hormones of the HPA effect, the

magnitude of the hormonal responses, the sensitivity of those GRNs, the specific genes affected, and so forth. Nevertheless, and not discounting the complexity of the HPA and its targets, one would expect that the recurrent involvement of certain hormones would tend to produce some repeated effects via the developmental biases inherent in the structure of the HPA and the target GRNs.

There is already some evidence that this is so and it too comes from the experimental fox farm in Siberia. Belyaev and his associates not only selected exceptionally tame or "elite" domesticated foxes but also generated a line of foxes that showed increased aggression. (The selection might have been for lower thresholds of fear in the triggering of aggressive responses, rather than directly for more aggressiveness, but the net result would be the same, namely more readily aggressive animals.) Strikingly, many of these show the white patches seen in the highly tame animals. An example is shown in Figure 2a, where one can see the white feet and white chest spot of this animal. The animals selected for exaggerated aggression do not show the extremes of white pigmentation seen in some of the tamest foxes (Figure 2b), perhaps reflecting lower degrees of selection for aggressiveness, but the crucial fact is that white patches appear at much higher frequencies than seen in the control nondomesticated farm-bred foxes. The simplest explanation is that destabilizing selection in response to higher glucocorticoid levels in these animals produces the development of these depigmented patches via developmental bias.

The idea that selection for altered behaviors can provoke new pathways of developmental-morphological change is not new. Indeed, it goes back to Lamarck, whose views on behavioral change and evolution were more sophisticated than normally portrayed (Burckhardt, 2013). In more recent times, the idea has been championed by, amongst others, the late Allan Wilson and his colleagues (Wyles, Kunkel, & Wilson, 1983). Yet, Belyaev's idea of destabilizing selection, in connection with ideas about the structuring effects of GRNs and developmental bias, enrich and expand these ideas further. Just as "evo-devo" has grown in the past decade or so with the addition of concepts about ecological effects, to create the new field of "eco-evo-devo" (Gilbert & Epel, 2009), it is perhaps not premature to envision that behavior will soon be added to that mix, as well. With a further fusion of genetic and population genetic ideas to that conceptual framework, we can look forward to a new and far more complete evolutionary theory than the classic modern synthesis of the mid-20th century (Laland et al., 2015; Uller et al., 2018; Zeder, 2017, 2018).

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CONFLICT OF INTERESTS

The author declares that there are no conflict of interests.

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