

# 13 **Hammond's Law: A Mechanism Governing the Development and Evolution of Form in Domesticated Organisms**

Richard Gawne and Kenneth Z. McKenna

The entire process of the development of living forms is guided by [the Malthusian] principle. The struggle for existence . . . for food and propagation, takes place at all the stages of life between all orders of living units from . . . the elements that are accessible to direct observation, to the cells, and still higher up, to individuals and colonies.

—August Weismann (1896)

I call the balancing between the volume of organic masses, and by shorthand the balancing of organs, [the fourth] law of living nature, by virtue of which a normal or pathological organ never acquires extraordinary prosperity in such a way that another of its system or its relations does not suffer as a result.

—Geoffroy Saint-Hilaire (1822)

As other chapters in this volume have indicated (chapters 1, 2, and 14), agriculture appears to constitute a striking example of evolutionary convergence. Several distantly related lineages of animals, including hominids (Smith 1998; Rindos 1984), insects (Mueller et al. 2005), and snails (Silliman and Newell 2003), have evolved a life-history strategy that involves the farming of other organisms for food. Although the agricultural lifestyle is not universally fitness-enhancing (Mueller et al. 2005; Mummert et al. 2011), there are many contexts in which it has significant advantages over hunting and gathering. As a consequence, it is hardly surprising that a number of different animals have become farmers. Somewhat more counterintuitive is the fact that entering into an agricultural arrangement can be beneficial to the organism being tended (chapter 5, this volume). Over large time scales, plants, animals, and fungi that become domesticates can outnumber their wild ancestors by orders of magnitude (Razifard et al. 2020). However, entering into an agricultural relationship is certainly not a risk-free life-history strategy. Artificial selection often produces “improvements” in crops and livestock that reduce their fitness in natural habitats, thereby making them increasingly dependent upon the services provided by their farmers.

The specific modifications exhibited by a domesticated lineage are likely determined by a complex array of factors that include internal developmental constraints (Alberch 1982; Smith 1998), local environmental conditions (Hammond 1936), and the precise artificially applied selective pressures it experiences (Gregory 2009). However, looking across species, it is possible to identify general patterns of morphological change that seem to recur over and over again, even in widely diverged organisms (Wilkins, Wrangham,

and Fitch 2014; Zeder 2006, 2015). Among other things, there is a tendency for domesticates to exhibit extreme enlargements of body parts that are deemed valuable to their farmers (Smith 1998; Fuller et al. 2014). These traits are ecologically and evolutionarily noteworthy because they have the potential to make a domesticate's relationship with its farmer obligate, but their importance does not end there. The highly derived morphologies of domesticates are also of significant interest from a developmental point of view. If a particular body part or the overall form of a domesticated organism differs in some way from that of its known wild ancestor, this gives us two populations with quantifiable morphological variation and immediately invites the question of what developmental mechanisms are responsible for producing the observed differences.

Numerous approaches have been used to address questions of this type. Some researchers have looked for genomic signatures of selective sweeps (Tian, Stevens, and Buckler 2009), while others have focused on the enrichment of proposed candidate genes (Domyan et al. 2016) or attempted to locate hormonal differences between the populations (Haase and Donham 1980), and so on. These studies have undeniably provided important insight into the processes that are responsible for generating domesticated morphologies. Yet, they are limited in the sense that the developmental differences identified between the ancestral and domesticated populations are almost always necessary, rather than sufficient, for generating the observed variation in form (Domyan et al. 2016; Domyan and Shapiro 2017). Jointly, these studies tend to yield an ever-increasing list of causally relevant factors that play a role in shaping the morphologies of the focal character(s), but provide little understanding of their relative significance, and no obvious insight into how they interact.

This emphasis on list-making and lineage-specific pathway minutiae rather than the "big picture" is increasingly being recognized as a significant flaw in the way that developmental biology is practiced (Gawne, McKenna, and Nijhout 2018; Nicholson and Dupré 2018; Bizzarri et al. 2019; DiFrisco and Jaeger 2019, 2020). Contrast the state of affairs in development to those of closely related fields such as ecology and evolution. In the latter, nearly all aspects of research are driven by generalized theoretical hypotheses that apply across both taxa and time. Even when a particular study is narrowly focused on a specific organism, the results are often used to test and refine large-scale theories that matter to the larger community. This back-and-forth dialogue between theory and data is largely absent in developmental biology, in part because the conceptual foundations of the field remain in a somewhat primitive state (Woodger 1929; Minelli and Pradeu 2014). Development clearly lacks a universally applicable theory that is analogous in scope to Darwinian evolution, but to make matters worse, it also has remarkably few context-specific hypotheses that would be similar in breadth to, for example, inclusive fitness theory (West, Griffin, and Gardner 2007), Batesian mimicry (Ruxton et al. 2019), the neutral theory of ecology (Hubbell 2001), or sexual selection (Andersson 1994). This translates to an open opportunity for future research dedicated to the construction of developmental theories.

It is well known that early evolutionary biologists were able to formulate sweeping generalizations about the nature of natural selection by studying how artificial selection alters the morphology of domesticates (Evans 1984; Gregory 2009). There is nothing stopping developmental biologists from taking a page from this playbook and using the same basic dataset to identify the ontogenetic principles that help to facilitate these phe-

notypic changes. Indeed, that is precisely what this chapter aims to do. In the sections that follow, we reintroduce and refine a developmental theory formulated by the British agricultural scientist John Hammond (1889–1964), which predicts how, when, and why an organism's form can be quantitatively modified to suit the needs of farmers. We refer to this hypothesis as “Hammond's law” and show that it (1) has the potential to explain how past selection on physiological mechanisms helped to produce the exaggerated morphologies observed in certain domesticates and (2) provides insight into the conditions under which the phenotypes of tended plants, animals, and fungi can be further altered to increase their productivity. In short, Hammond's law provides a generalized account of the processes that facilitate and constrain an organism's ability to move through morphospace in response to artificial selection. More importantly, perhaps, we predict that the theory is equally applicable to wild organisms that are subjected to naturally occurring selective pressures, making it a rare instance of a truly broad-brush developmental hypothesis.

### Developmental Constraints on Organismal Form

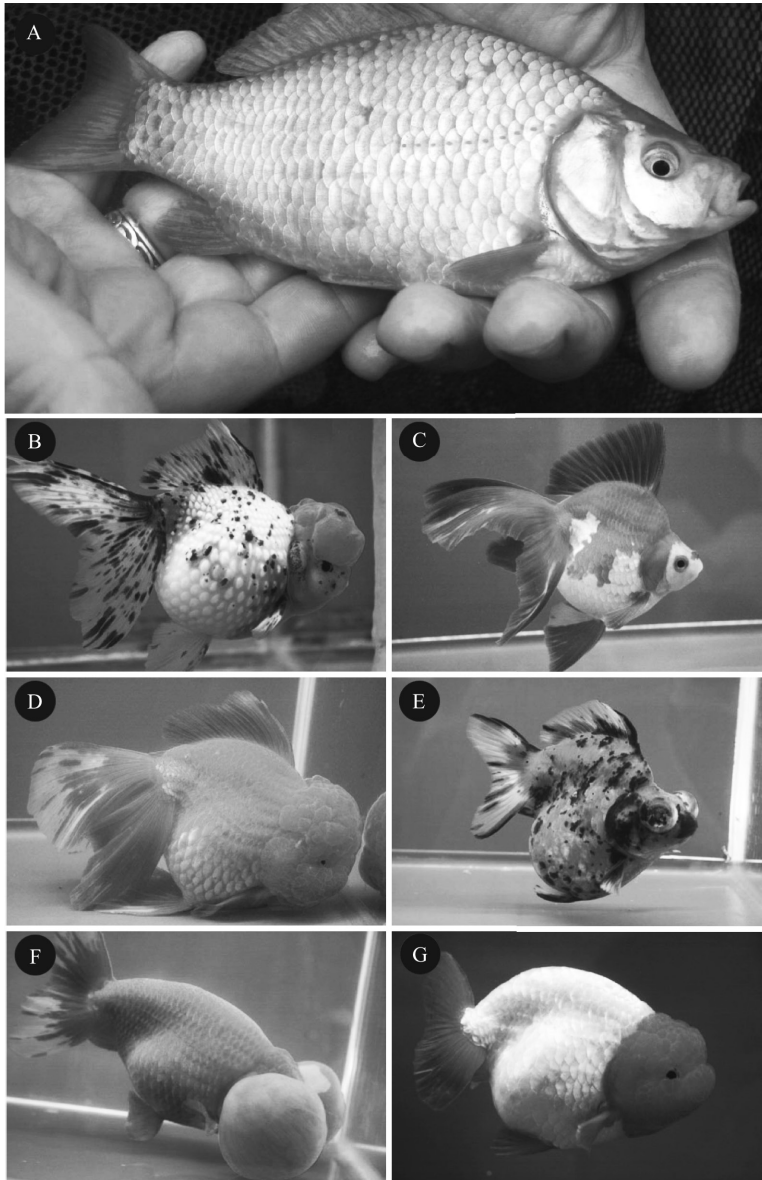
The domesticated organisms that fill our fields and refrigerators often bear only a vague resemblance to their wild ancestors. Many fruits and vegetables, for example, have undergone monstrous changes of proportion (figure 13.1) and, in some cases, these alterations have taken place in a remarkably short amount of time (Meyer, DuVal, and Jensen 2012). This is shown from scientific data, including findings from the archaeological record (Zeder 2006; Zeder et al. 2006; chapter 10, this volume), as well as human cultural artifacts such as paintings (Zoltán et al. 2007) and descriptions found in ancient texts (Andrews 1949). Dramatic phenotypic changes have also been produced in pet animals (Drake and Klingenberg 2010; Komiyama et al. 2009) (figure 13.2) and prey species such as cattle (Bovine HapMap Consortium 2009) and sheep (Hammond 1932). Surveying the vast array of quantitative morphological change that has been induced in these organisms, it is easy to start thinking of domesticates as being almost infinitely labile. If the need arises, and we initiate the right artificial selection regime, it seems that the phenotypes of these plants and animals can effectively be altered at will.

There is a long history of conceiving of domesticated organisms in this way. Darwin commented on this fact in the *Origin of Species*, noting that “breeders habitually speak of an animal's organisation as something quite plastic, which they can model almost as they please” (Darwin 1859, 31). To support this point, he quotes the agriculturalist/politician John Sebright, who once boasted that with pigeons, he could “produce any given feather in three years” but would need “six years to obtain head and beak” (Darwin 1859, 31). In some ways, this optimism is warranted—just look at all the previous success we've had in reshaping the morphology of our domesticates. More importantly, think about how organisms evolve in the wild. Given enough time and the right sort of variation to work with, natural selection can produce absolutely stunning morphological changes. Artificial selection is not fundamentally different from natural selection, so it seems logical that we should be able to accomplish something similar—and presumably in a much shorter amount of time—using selective pressures that we apply ourselves.



**Figure 13.1**

Domesticated organisms exhibiting exaggerated morphological traits. Over time, artificial selection by humans has produced significant changes in the anatomical features of domesticates. (A) The fruits of the modern domesticated pumpkin *Cucurbita pepo* are significantly larger than those of its wild ancestor, and their sizes have continued to increase in recent years. Left: a “large” pumpkin photographed in 1928. Right: a large pumpkin by current standards. The weight of this particular fruit is not documented, but specimens are known to exceed 2,000 lbs. (B) Left: Like the ancestors of other domesticated fruits, wild strawberries (*Fragaria sp.*) tend to be small in size. Right: Modern domesticated varieties (*Fragaria sp.*) are often larger by several orders of magnitude. (C) Left: The domesticated chicken is descended from the red jungle fowl (*Gallus gallus*). Artificial selection has dramatically increased the body size of domesticated breeds, with some such as the Brahma (right) weighing in at over 15 lbs. All photographs shown are courtesy of Wikimedia Commons and have been edited by the authors to produce the final figure. (For author and license credits, see Acknowledgments.)



**Figure 13.2**

Morphological change produced by artificial selection in the domesticated goldfish (*Carassius auratus*). When attempting to highlight the extreme morphological changes humans have produced through artificial selection, researchers often appeal to case studies involving food plants such as maize. However, equally impressive (and more rapid) changes have been elicited in companion domesticates such as the goldfish. *C. auratus* is thought to be descended from the crucian carp (*Carassius sp.*), shown at the top of the figure (A). The following domesticated varieties are displayed below: (B) crowned pearlscale, (C) ryukin, (D) oranda, (E) telescope cross ryukin, (F) bubble eye, and (G) ranchu. Many phenotypic alterations, including changes in the patterns of pigmentation, head and tail morphology, scaling of the abdomen, and the complete loss of the dorsal fin can be observed. These morphologies might be favored in the tightly controlled environments provided by humans, but would almost certainly carry significant fitness costs in the wild. All photos are courtesy of Wikimedia Commons and have been edited by the authors to produce the final figure. (For author and license credits, see Acknowledgments.)

It certainly would be nice if our crops and livestock were this malleable. There is always an incentive to improve the health of our domesticates, increase yields, and, in general, provide the highest nutritional returns at the lowest possible financial cost (Timmusk et al. 2017; Tubiello et al. 2008). However, despite having ample motivation, improving established domesticates is often extremely difficult, even with modern techniques (Sinclair, Purcell, and Sneller 2004; Denison 2012). This could be because we have not found the right candidate genes or have been prevented by ethical panels from doing the appropriate trans-species knock-ins. It could also be that we just have not been diligent enough in our application of artificial selection. A more pessimistic possibility is that none of these techniques will yield the sort of aggressive morphological changes we would like to see because the phenotypic flexibility of domesticated organisms has already been more or less exhausted.

To understand what is being suggested here, consider the effects of natural selection acting on wild populations. Selection is an incredibly powerful creative force, yet there are countless morphological forms that have not been produced in the past 3.7 billion years even though they would likely be fitness enhancing. This is partly because various features of an organism's development can limit the efficacy of selection. These "developmental constraints" (Alberch 1982; Smith 1998) have an important role in determining which regions of morphospace a species can and cannot occupy (McGhee 2015; chapter 1, this volume). Since the mid-1900s (Woodger 1945), discussion of internal constraints has become increasingly common, and they are widely acknowledged to exist in principle. Nevertheless, it remains unclear what they actually are empirically. Even something as simple as deciding when and where to start looking for constraints is a challenge. Using data from free-living populations, it is often unclear what we should infer from the absence of a particular morphology. When a certain form does not occur, this could be due to checks imposed by internal constraints, but it is also possible that the appropriate selective pressures have never been applied. This makes it extremely difficult to identify the areas of morphospace that are truly "off limits" developmentally, and under such circumstances trying to identify constraint-inducing processes is destined to be an exercise in futility.

The study of domesticated organisms can help us get through this quagmire because we can be confident that various selective pressures have been applied but have not been completely successful (Denison 2012; Zeder 2018). Under such circumstances, it is reasonable to infer that some sort of internal developmental constraints really are at work. The next step is identifying the specific morphogenetic processes that are imposing these restrictions on the focal species' form. This is what Hammond's law does.

## Hammond's Law

In simple terms, Hammond's law is a hypothesis that specifies how the availability and subsequent use of growth factors during ontogeny produces variation in adult phenotypes (Hammond 1947; Hammond and Zuckerman 1950). Hammond developed his ideas over the course of several decades, with many of the relevant studies being completed from the 1940s to the 1960s. His original papers contain a wealth of data and verifiable predictions that we cannot hope to fully summarize in a single book chapter. Our aim in this section is to provide a broad overview of Hammond's ideas, sacrificing some depth for breadth

in order to make his work accessible to a wide scientific audience. We begin by trimming his logic down to a pair of core principles and then selectively focus on a small number of supporting case studies.

### ***Principle 1: Body Parts Compete for Resources during Development***

The idea that growth is energetically costly lies at the heart of Hammond's theory. Over the course of development, the majority of the body's parts increase in size. This growth is generally brought about by mitotic divisions that require metabolically combustible "fuels" such as amino acids, lipids, and other circulating macronutrients (Masumura et al. 2000; Géminard, Rulifson, and Léopold 2009; McCue 2010; Koyama, Mendes, and Mirth 2013). These internal developmental resources are often acquired or indirectly synthesized from dietary factors that are sequestered from the local environment (Koyama, Mendes, and Mirth 2013; Koyama, Syropyatova, and Riddiford 2008; Nijhout and McKenna 2018). The fact that the availability of growth factors is linked to diet is important because it implies that external environmental conditions can dictate how much an animal is able to grow over the course of its development. By the 1920s and 1930s, it was widely known that organisms reared under optimal nutritional conditions generally grow to a larger final size than those that experience nutritional stress (Hammond 1936). Hammond's contribution was recognizing that even in times of abundance, the growth of certain body parts can be constrained through a type of developmental interaction that is now referred to as "character-character competition" (Gawne, McKenna, and Levin 2020). These competitive interactions are intensified when nutrition is suboptimal, sometimes leading to significant changes in the organism's overall form.

Competition between characters takes place when multiple body parts rely on the same limited supply of metabolic fuel to drive their growth. Consider a situation in which two body parts concurrently grow in a nonisometric manner, meaning that one of the traits ( $A$ ) increases in size more rapidly than some other trait ( $B$ ). All else being equal,  $A$  will achieve a larger final size than  $B$  due to its higher relative growth rate. The differential growth rate of  $A$  and  $B$  translates into a nonidentical rate of resource consumption. To be more specific, we would expect  $A$  to consume more fuel than  $B$  due to its relatively higher rate of growth. If the resource usage differential between  $A$  and  $B$  is especially high, or internal growth factors are in unusually short supply due to poor dietary conditions, the growth of character  $A$  can actively constrain the growth of  $B$  by depleting a disproportional percentage of the available resources. The idea that body parts can compete in this way during morphogenesis is implicit in much of Hammond's work on character-specific growth rates in domesticated (Hammond 1947; Hammond and Zuckerman 1950), and recent studies have confirmed that these interactions regularly occur in both domesticated and free-living organisms (Nijhout and Emlen 1998; Klingenberg and Nijhout 1998; Denison 2012; Gawne, McKenna, and Levin 2020).

### ***Principle 2: Resource Availability and the Timing/Rate of Growth Lead to Character-Character Competition***

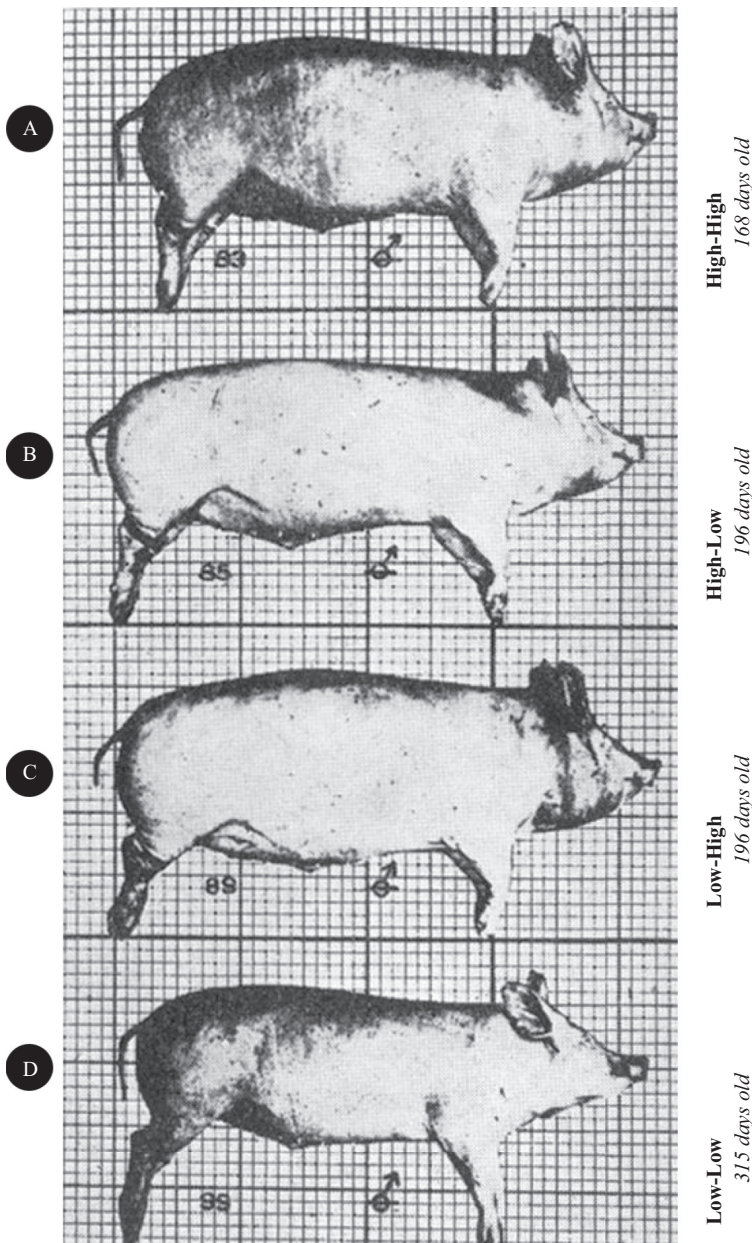
The experimental studies Hammond conducted on domesticated farm animals revealed that body parts tend to reach their maximal growth rate in a highly stereotyped sequence.

Early in development, (1) the bones, cranium, and gut fat attain their maximal rate of growth, followed by (2) the major muscle groups and subcutaneous fat, and (3) the intramuscular fat and muscle tissue around the vertebrae (McMeekan 1940; Hammond 1947; Hammond and Zuckerman 1950). This temporal partitioning of maximal growth rates plays a crucial role in the establishment of organismal form, especially when nutritional intake is varied over the course of ontogeny. For example, Hammond found that pigs will obtain different body proportions—not just sizes—when they are fed a low-nutrient versus a high-nutrient diet during development, and something similar was documented when the nutritional treatments were switched before the animals reached maturity (figures 13.3 and 13.4). Pigs that received a high-nutrient diet throughout ontogeny tended to develop large frames and a substantial amount of body fat. However, Hammond discovered that if the animals were initially fed a high-nutrient diet and were later switched to a low-nutrient diet, they often failed to produce adipose tissue. Conversely, he found that pigs that were fed a low-nutrient diet immediately after birth displayed stunted skeletal growth and possessed little fat, yet if the animals were switched to a high-nutrient diet later in ontogeny, they eventually produced relatively large quantities of fat (McMeekan 1940; Hammond 1947; Hammond and Zuckerman 1950). These seemingly mundane observations are important because they indicate that developing organisms are able to alter the way growth factors are partitioned in response to dietary intake, leading to changes in form. To put it another way, a developing animal makes “decisions” about when and where to allocate internal resources, and different body parts are prioritized when the nutritional regime is altered.

Hammond suggested that the allocation of internal resources during development is determined by two factors: (1) the timing of growth, or the order in which body parts attain their maximum growth rate, and (2) character metabolic rate, understood as the speed at which a body part increases in size due to an underlying rate of resource consumption. He hypothesized that the brain and peripheral nervous system are given priority early in development and achieve their maximal rate of growth before other parts of the body. In addition, Hammond inferred that these tissues must be especially costly to construct and maintain compared with other characters. The fact that the nervous system begins to grow early and is energetically expensive to produce means that it will sequester the greatest proportion of the internal growth factors that the animal has available. Ultimately, this entails that the body parts that reach their maximal rate of growth later in development will be vying for a reduced supply of metabolically combustible fuels, especially when dietary conditions are suboptimal.

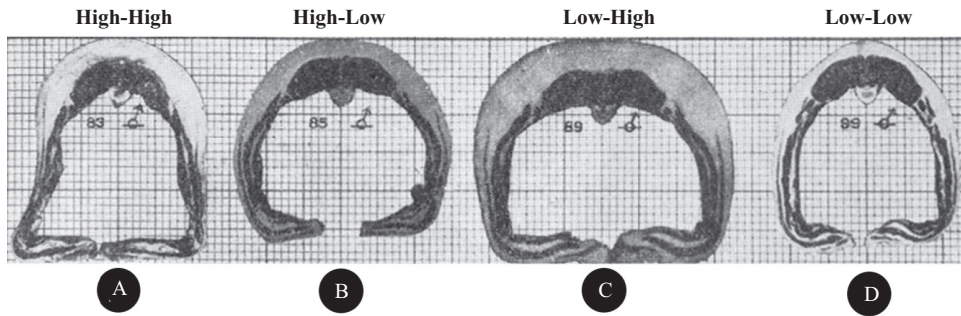
After the nervous system, the growth of the bones is prioritized. These characters represent the next most significant energetic investment during development, followed by muscle and fat tissue (figure 13.5). In pregnant females that are themselves still growing, the situation becomes slightly more complicated because the mammary glands and unborn fetus sequester resources that the mother could otherwise use to construct her own bones, fat, and muscle. Describing his version of the diagram depicted in figure 13.4, which illustrates high-priority structures with multiple arrows and low-priority structures with fewer arrows (depicted, respectively, as thicker and thinner arrows, in figure 13.4), Hammond summarized the situation as follows:





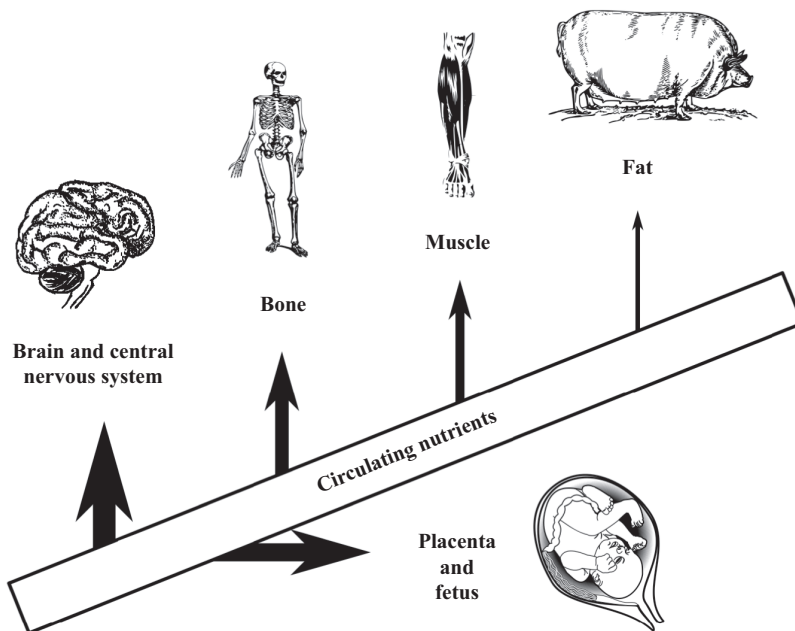
**Figure 13.3**

Differences in the body proportions of pigs of the same relative age obtained by changing nutrition during postembryonic development. The pigs are scaled to the same shoulder height. Each animal is a representative sample from the dietary treatment group described on the right-hand side of the figure. The pig shown in (A) was fed on a high-nutrition diet throughout development (high-high). These animals grew larger and reached their final adult size more quickly (168 days) than those in other treatments. The pig shown in (B) belongs to a treatment group that began development on a high-nutrition diet, but was switched to a lower plane of nutrition at 16 weeks of age (high-low). Prior to the change in diet, pigs in the high-low treatment group grew rapidly. When transferred to the poor-nutrient diet, growth slowed substantially, and the animals attained their final adult size at approximately 196 days. (C) When pigs were initially fed a low-nutrient diet and switched to a high-nutrient diet at 16 weeks of age (low-high) an effect opposite of that observed in high-low group was documented. Growth was initially slow, but ramped up significantly following the transition to a diet with optimal nutrition. Pigs in this treatment reached their final size at approximately 196 days, similar to what was observed in the high-low treatment. However, although they shared similarities in the timing of their development, the body proportions of the high-low and low-high groups differ. (D) Pigs that were fed on a low plane of nutrition throughout ontogeny grew the slowest and reached a smaller final size than those in the other experimental treatments. These pigs took 315 days to reach adulthood and developed almost no fat deposits in their bodies. The results described are noteworthy because they indicate that character-specific growth rates are altered in response to nutritional intake. Figure adapted from Hammond (1950) with permission from the publisher.



**Figure 13.4**

The proportion of muscle and fat in the experimental treatment groups of pigs described in figure 13.3. Temporal variation in nutrition has a strong influence on the partitioning of nutrients during postembryonic development. (A) The high-high treatment produced pigs with a large frame and substantial amounts of muscle and fat. (B) Pigs reared on the high-low dietary regime developed a large frame, but failed to grow fat. (C) Conversely, on the low-high regime, skeletal growth was reduced. However, optimal nutrition later in development facilitated the deposition of large quantities of fat on this small frame. (D) Pigs fed on a poor diet throughout development displayed stunted skeletal growth and almost no fat deposition. The differences between (B) and (C) are especially noteworthy. These pigs are the same age and similar in weight, yet they show considerable differences in body composition. This suggests that the timing of nutritional uptake, and not just the quality of the materials ingested, is an important determinant of organismal form in some domesticated organisms. Figure adapted from Hammond (1950) with permission from the publisher.



**Figure 13.5**

A visual representation of Hammond's theory of nutrient partitioning during development. Hammond believed that the nutrients circulating in the bloodstream during development (i.e., growth factors) are allocated in a controlled manner over the course of ontogeny. The thickness of the arrows is proportional to the amount of nutrients each part of the body sequesters, and their order from left to right represents the order in which they are prioritized under nutritional stress (left: high priority; right: low priority). In developing vertebrates, the brain and nervous system consume most of the available growth factors, followed by the placenta and fetus in pregnant females. Skeletal components are the next most costly bodily components, followed by muscle and fat. Reading this figure from right to left, one sees the order in which various features of the body will be diminished in size under suboptimal nutritional conditions. This figure is based on an illustration from Hammond (1950).

If nutrition is on a very high plane all tissues are served to their maximum requirements. When the plane of nutrition is lowered one arrow is deducted from each, so that fat ceases to be put on, but the other tissues continue growing but at a slower rate. When the plane of nutrition is lowered still further and two arrows are taken from each, brain and bone still continue to grow but at a much slower rate, muscle ceases to grow and fat is withdrawn to supply energy for growth of the brain etc. (Hammond 1952, 222)

To reiterate a point made earlier, this means that if a character grows later in development, or grows at a time when many other body parts are also rapidly increasing in size, it will have less fuel at its disposal and, as a consequence, could be reduced in size. In addition, this implies that if a costly structure grows early in ontogeny, its resource consumption patterns could inhibit the maturation of later-developing body parts.

Developing characters might be modular in the sense that distinct batteries of genes could be expressed in their tissues (Arnone and Davidson 1997; Raff and Sly 2000; Wagner 2018), but when the type of interactions described by Hammond occur, their growth can still be tightly correlated. Many classically trained embryologists were aware that developing body parts sometimes compete for internal resources (Roux 1881; Weismann 1896; Saint-Hilaire 1822). However, because these interactions are fundamentally physiological in nature, they cannot be identified or studied from the genetically based reductionist perspective that has dominated developmental biology since the 1950s. This is a case where modern “advances” have impeded scientific progress by causing researchers to forget something that was formerly known to the community.

### **Putting It All Together: Formalization, Predictions, and Evidence for Hammond's Law**

Hammond's law can be more formally stated as follows: (1) all growth is energetically costly, (2) many body parts rely on the same finite supply of internal resources, and, therefore, (3) the growth of one body part can constrain the growth of others. This implies that (4) the overall availability of internal resources, in conjunction with the timing and rate at which body parts grow, can be an important determinant of the organism's final adult form. Hammond suggested that previous work on pigs (McMeekan 1940) and sheep (Verges 1939) supported his hypothesis, but it was also validated by his own work on milk production in cattle.

First, Hammond showed that pregnant cows grow to different weights based on their plane of nutrition (Hammond, 1936, 1947; Hammond, 1952). The nutritional intake of female cattle also influenced their ability to develop mammary glands and subsequently produce milk. More specifically, cows fed on a low plane of nutrition were unable to produce the same quantity of milk as siblings reared under more nutrient-rich control conditions (Wallace 1944; Hammond 1947). Hammond followed this study with a historical account of selection for milk production in zebu cattle (Hammond 1947). For several generations, farmers in India selected for improved milk yields in their cows but saw no increases in output until the government adopted more regimented feeding practices that were used in other countries. This change in the rearing environment was crucial because it eliminated variation in diet across the population and allowed the farmers to select for increased milk production under a single environmental condition. In 1912, cows could produce an average daily yield of 5.8 pounds of milk. By 1922, this had nearly doubled

to 10.8 pounds and, roughly a decade later, the cattle produced approximately 18.5 pounds of milk per day on average (Hammond 1947).

From the farmers' perspective, the exaggeration of the udder is often highly desirable when nutrition is ample; however, selection for enlarged udders under a high plane of nutrition can also come at a significant cost. Over time, artificially selecting for enlarged udders under optimal dietary conditions sometimes results in organs that are so monstrously outsized (see, e.g., figure 13.6) that they reduce the viability of the animals when they are reared on a lower-quality diet. The udders are prioritized during development, and when animals are reared under nutrient-poor conditions, they sequester a substantial proportion of the body's internal supply of nutrients, which would otherwise be allocated elsewhere. As a consequence, cows that experience nutritional stress can exhibit a host of undesirable defects, including a higher susceptibility to disease (Caeneiro and Rhoad 1936; van der Waaij 2004). The consequences of this unwanted character-character competition are so serious that agriculturalists now select for increased milk production under less-than-optimal nutritional conditions (van der Waaij 2004). As farmers themselves have occasionally put it, this ensures that females will not "milk the flesh off [their] bones" (Hammond 1947, 199) due to the intense character-character competition that an extremely enlarged udder initiates.



**Figure 13.6**

Artificial selection for increased milk production in cattle breaks the wild-type scaling relationship between the udders and other body parts. The udders of domesticated cattle are sometimes so monstrously enlarged that they hinder the animal's movement and must be supported by a harness in order to prevent injury. Increased udder size improves milk yields, but as Hammond (1947) noted, the enlargement of this body part can lead to unwanted character-character competition during development. In particular, the udder can consume growth factors that are normally allocated to the bones and other body parts, leading to a feeble animal with low fitness, even in the highly controlled agricultural environment. The photograph shown is courtesy of Wikimedia Commons and has been edited by the authors to produce the final figure. (For author and license credits, see Acknowledgments.)

## Nutritional Variation and Character-Specific Reaction Norms: Adaptation to Controlled Agricultural Environments Breaks Functional Constraints on Development

One of the things that makes agricultural niches unique is the fact that environmental variables tend to be tightly controlled in order to promote an optimal level of growth in the domesticate. The fact that external conditions are stabilized in this way means that selection on phenotypic traits tends to occur in a more-or-less homogenous environment, wherein phenotypic variation is almost entirely the result of underlying genetic variation. These conditions differ substantially from those experienced in the wild, where temperature, photoperiod, and nutrition are always in flux. The fact that environmental conditions are seldom constant in natural settings means that the development of most organisms is adapted to respond to a wide range of external variables. When a feature of the environment varies continuously, it often produces an associated range of phenotypic outcomes (Shingleton et al. 2007). One of the first researchers to document this trend was the German biologist Richard Woltreck (1909; Nanjundiah 2020), who noted that quantitative traits are generally tightly distributed around a mean in any given environment. Crucially, Woltreck also noted that the value of the mean tends to differ significantly from environment to environment, and he found that when nutrition varies continuously, certain quantitative characters vary in an analogous manner. He referred to the range of phenotypic variance produced under these circumstances as a “reaction norm” and, in coining this term, was the first of many biologists to realize that a single genotype can give rise to a host of different phenotypic outcomes.

Woltreck hypothesized that the mean phenotypic value obtained for any given environmental condition results from the fact that organisms in a population rely on common regulatory mechanisms to control their development. Variance around the mean was then attributed to individual genetic variation that determines how an organism responds to changes in the focal environmental condition(s) (Woltreck 1909). Conceived in this way, the particular norm of reaction an organism exhibits is specific to its genotype. Woltreck's studies are important for our purposes because they suggest that phenotypic plasticity—that is, the ability to produce a range of phenotypic outcomes in response to changes in environmental variables—has a genetic basis and can itself be an adaptation if a single, nonplastic phenotype would have different fitness coefficients in different environments.

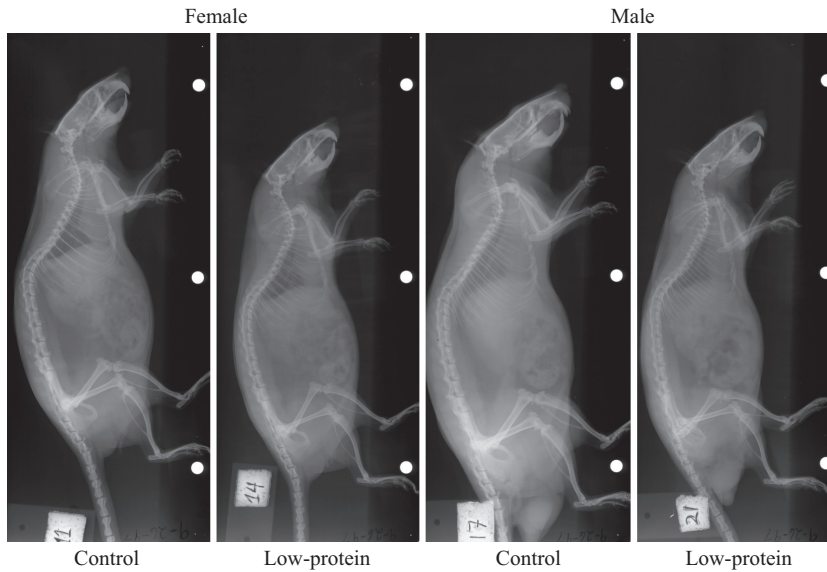
In recent years, reaction norms and developmental plasticity have been widely studied (Shingleton et al. 2007; Koyama, Mendes, and Mirth 2013; Thompson 2019; Frankino et al. 2019; Suzuki, McKenna, and Nijhout 2020), but much of this research overlooks the fact that each character in the organism has a unique norm of reaction that results from internal developmental mechanisms that function specifically to control growth. One of the best examples of character-specific reaction norms comes from the literature on *Drosophila melanogaster*. In these animals, nutritional variation affects growth rate via insulin-like peptides (ILPs). The concentration of ILPs is directly correlated with nutritional intake (Géminard, Rulifson, and Léopold 2009), meaning that, all else being equal, organisms that develop under optimal dietary conditions will have more ILPs circulating in their bodies than those that experience nutritional stress. This is important because, in

most insects, the availability of ILPs helps to determine the final sizes of the body's various parts (Koyama, Syropyatova, and Riddiford 2008; Nijhout and McKenna 2018). The wings and legs, for example, exhibit dramatically reduced growth when ILP concentrations drop, but organs such as the gonads maintain a similar rate of growth across all ILP concentrations (Tang et al. 2011). These findings suggest that each organ or appendage has a unique dose-response curve for ILPs that determines the norm of reaction it will exhibit when it is exposed to different nutritional regimes.

Numerous studies have shown that character-specific scaling of growth in *Drosophila* is facilitated by differential expression of intracellular components involved in the insulin/TOR cascade, which transduces the ILP signal and thereby produces cellular proliferation. In the gonads, this intracellular cascade is set up in a way that ensures these tissues are always attempting to grow, regardless of the ILP availability. This makes the reproductive organs ultrasensitive to the insulin signal at all concentrations (Tang et al. 2011). In contrast, the wings and legs respond to the presence of ILPs in a concentration-dependent manner, meaning their growth rate increases and decreases according to ILP availability (Tang et al. 2011). The fact that the characters in question respond differently to the ILP signal is noteworthy because it demonstrates that the scaling of growth in response to environmental variation can be controlled on a character-by-character basis throughout the organism. Perhaps even more importantly, the work in question suggests that the range of phenotypes produced must be heritable because genetic factors play a role in determining how the signal transduction network in any given body part responds to ILP concentration.

The fact that the scaling of growth is partially controlled by genetic interactions that are modularly tuned within each body part is what allows the reaction norms of characters to vary independently of one another. Support for this hypothesis can be found in a series of studies examining how nutritional status affects patterns of correlated growth in the limb bones of the common rat (*Rattus norvegicus*) (Miller and German 1999). Male rats reared on a protein-deficient diet tend to grow more slowly and reach a significantly smaller final size than littermates fed a protein-rich control diet. In addition, the growth of long bones in animals reared under the low-protein condition displays a strong signature of integration, or correlated growth, that is not present in the control treatment (Zelditch 1988; Miller and German 1999; Reichling and German 2000; Hallgrímsson et al. 2004) (figure 13.7). This suggests that the genetic variation in the developmental mechanisms associated with each body part can manifest differently across nutritional environments. More specifically, the growth kinetics of bones tend to be nonidentical when protein is abundant, but when nutrition is restricted, this variation collapses, and the characters begin to grow more or less isometrically.

For our purposes, the above findings are of interest because they add further emphasis to the point that farmers wishing to induce directional changes in the morphology of domesticates need to be conscious of the conditions under which artificial selective pressures are applied. With the zebu cattle mentioned by Hammond, rearing animals under optimal nutrition allowed for selection on the genetic variants that produced a maximal udder size. However, a selective regime of this type can turn out to be problematic when no consideration is given to how the enlarged udder will scale with the rest of the body under suboptimal dietary conditions. As discussed above, when developing cattle experience nutritional stress, their udders often continue to grow at a maximal rate, which further

**Figure 13.7**

Adult male and female rats fed on different dietary regimes during development. The images shown above are of littermates that received either an optimal diet or a low-protein diet. Animals that were fed the low-protein diet stopped growing at substantially smaller body sizes than littermates from the control group. All images were taken once growth had ceased and the scaling is constant across the four treatments. Similar to what Hammond observed in domesticated farm animals (figures 13.3 and 13.4), this suggests that organismal form is highly sensitive to nutritional status. Images were graciously provided by Rebecca German and Fred Nijhout.

decreases the amount of resources available for use in the development of other body parts and leads to health problems. In this case, a reaction norm that is clearly deleterious under suboptimal environmental conditions might not be selected against in the agricultural setting, as it likely would be in the wild. Under natural conditions, nutritional availability frequently oscillates over the lifetimes of individuals and across generations, which means that reaction norms and their associated genotypes are consistently subjected to purifying selection.

Most exaggerated characters produced by natural processes, including sexually selected body parts in insects and vertebrates, display hyperallometric (slope  $>1$ ) reaction norms, wherein the focal character is exaggerated in large males and more normally sized in smaller males (O'Brien et al. 2018; Rodríguez and Eberhard 2019). Males with larger body sizes are generally able to sequester more resources from the local environment than smaller males (Emlen and Nijhout 2000; Emlen et al. 2012), which means that there will likely be enough internal resources available for all body parts to reach their maximal genetically prescribed size. Under these circumstances, selection can favor the enlargement of certain body parts, because the development of other characters will not be significantly affected. Conversely, in males that fail to attain their maximal size, selection for extreme enlargement of a particular character can be deleterious. This is because smaller males sequester comparatively fewer resources from the local environment and thus have a more limited supply of internal macronutrients available to fuel their growth. With smaller individuals, enlargement of, say, a horn could constrain the development of

other important characters, leading to decreases in fitness. For this reason, in animals with smaller body sizes selection would be expected to favor the maintenance of existing body proportions.

The idea that there is little selection against reaction norms in agricultural environments may have been first stated by Helen Spurway (Spurway 1955; Nanjundiah 2020). In an interesting 1955 paper that has been almost completely lost to history, she suggested that, prior to human intervention, domesticates experienced more uniform selective pressures that eliminated genotypes that disproportionately affect the way developmental events are patterned. The agricultural environments created by humans destabilize the selective pressures that normally act on developmental processes because these niches are tightly controlled, thereby removing organisms from many of the environmental factors they would experience in the wild. In this respect, domesticated organisms are of interest to basic research because they allow us to see certain potentials of developmental systems that are generally hidden/suppressed by natural selection. The fact that numerous organisms have been domesticated and are readily obtainable provides biologists with an opportunity to study how internal resources are allocated during development.

### **Potential Applications of Hammond's Law to Insect Agricultural Systems**

In terms of our more immediate task of identifying parallels between the evolution of agriculture in humans and insects, if Hammond is correct and competitive interactions between characters have shaped the morphologies of our domesticates, it is possible that they could do the same in organisms farmed by insects. For example, several recent studies have shown that defensive compounds are costly for plants to produce and tend to come at the expense of somatic tissue growth (Huot et al. 2014). Many of the plants domesticated by humans exhibit decreased levels of protective secondary metabolites in their tissues, which is thought to create a surplus of internal resources that allows other features of the organism to increase in size (Rosenthal and Dirzo 1997; Massei and Hartley 2000; Moreira et al. 2018). Extending this logic to nonhuman agricultural systems, it would be interesting to determine whether the loss of ancestral chemical defenses in insect-tended fungi or plants has facilitated an analogous upregulation in growth. The fact that the lower- and higher-attine fungi are cultivated on different substrates and have different morphological features (chapters 8 and 14, this volume) is also of interest from the perspective of developmental energetics. The nutrient-dense gongyliidia present in the fungi of the higher-attine ants (chapters 8 and 14, this volume) are likely metabolically costly to produce (Henrik, Boomsma, and Tunlid 2014). If the fungal substrate is reduced in quality, it would be worth examining whether the gongyliidia decrease in size/nutritional quality, or remain more or less unaffected (Masiulionis et al. 2014). The former would indicate that the development of these structures is nutrition-sensitive, while the latter would be indicative of developmental prioritization, similar to what Hammond documented in the udders of cattle.

The principles identified by Hammond could also potentially help us to make sense of the growth dynamics of the fungal mycelium in insect agricultural systems. Ant-tended fungi tend to remain in a vegetative, mycelial state as they grow and rarely produce the fruiting bodies that are needed for sexual reproduction (Mueller et al. 2001). The fact that



the fungi exist in this vegetative form is sometimes attributed to the activities of their ant farmers, which are constantly dividing and pruning the mycelial connections (Fisher, Stradling, and Pegler 1994a, 1994b; Mueller 2002). It is also possible, however, that the constant supply of high-quality nutritional substrate provided by the ants encourages the fungus to grow asexually, in its mycelial state. The basic idea is that when resources are abundant, and/or the ratio of proteins to carbohydrates in the substrate is optimized (Shik et al. 2016), the fungus will take advantage of this situation as long as possible by increasing in size, rather than attempting to reproduce sexually. There is, in fact, some evidence to suggest that life history progression in wild leucocoprineaceous fungi is tied to nutrition in this manner (Vellinga 2004), at least in tropical, wet-forest species. This finding is intriguing because it provides insight into how insects might have first been able to domesticate their fungal cultivars. If the fungi had an ancestral tendency to stay in their asexual state when the nutritional environment was conducive to growth, insect farmers could have exploited this fact by providing fungi brought to the nest with a surplus of decomposable resources. This would serve the dual function of ensuring that edible mycelium is continually produced, while also preventing the fungus from “escaping” by entering the sexual stage of its life cycle. Under this scenario, the ants could effectively force fungi into becoming their crops by exploiting their existing developmental tendencies. Once the fungi reach a certain size, environmental factors such as rainfall and temperature would be predicted to promote fruiting, even when nutrition is abundant. At this stage, the hypothesis would be that active pruning of mycelial connections would then become the dominant means by which ants deter sexual reproduction in their crops.

These are just a handful of examples of how taking a developmental-energetics point of view could be of use in understanding nonhuman agricultural systems. If the evolution of agriculture in humans and insects is truly a case of convergent evolution, it seems plausible that Hammond's law will be broadly applicable to all domesticated organisms, regardless of what species takes on the role of the farmer.

### **Hammond's Law as a Generalized Developmental Theory**

Development has long been regarded as one of the least understood and poorly synthesized branches of biology (Woodger 1929; von Bertalanffy 1933). Not even a century ago, a handful of embryologists were still speculating that it might be an impenetrable subject, which is either mostly or entirely screened off from scientific understanding. When confronted with laboratory results that were difficult to explain, vitalists such as Hans Driesch (1867–1941) turned tail and retreated to mystical explanations involving immaterial forces (Driesch 1908). Emboldened by the molecular revolution of the 1950s, researchers eventually stopped running from the problems of development and, instead, began to ignore them entirely. Given its simplicity and seemingly unparalleled explanatory power, an implicit form of genetic determinism has slowly but surely become the guiding principle of developmental biology. Indeed, reading the contemporary literature, one can easily get the impression that morphogenesis is nothing more than a complex series of interactions that are both initiated by, and completely reducible to, the activities of gene products (Nijhout 1990; Larsen 2005; Gawne, McKenna, and Nijhout 2018).

Part of the allure of genetic determinism is the fact that it allows us to get a lot done experimentally. Environmental influences on phenotypes are backgrounded, and physiological processes that are difficult to control are treated as inconsequential downstream events or dismissed outright as a type of developmental noise. This leaves researchers free to focus on things such as candidate genes and other genetic factors that are readily identifiable and easy to manipulate in the lab. Although it has utility in certain contexts, it is important to recognize that the stripped-down form of genetic determinism that dominates modern developmental biology is not a true predictive theory. Instead, it is a sort of baseline assumption that provides a methodological script for doing experimental work. For any given aspect of character formation, we are assured that there are primitive genetic causes and, as biologists, we are told that it is our job to identify these factors.

Over the years, research born out of this tradition has generated an enormous amount of genetic, genomic, and transcriptomic data for nearly every phenotype imaginable. The assumption seems to be that if we keep our heads down and continue to amass more and more empirical data, theoreticians will eventually be able to construct some sort of generalized hypothesis that will “effectively enable one to compute the adult organism from the genetic information in the egg” (Wolpert and Lewis 1975, 21). If future generations of scientists can pull something like this off, it would certainly be an astonishing intellectual achievement. But of course, there is no guarantee that this day will ever come. And more importantly, we do not need big-picture developmental theories 50, 100, or 1,000 years in the future. We need them right now. The idea that we should continue to hoard genetic data simply because there is a chance that someone might eventually be able to use it to construct large-scale predictive models is little more than a procrastinator’s excuse that allows us to avoid doing the messy theoretical work ourselves.

If we hope to formulate a developmental theory with wide applicability, it is necessary to abandon genetic predetermination and acknowledge the fact that organisms are hierarchically arranged systems whose final adult phenotypes are produced and maintained by nonlinear causal interactions (Gawne, McKenna, and Nijhout 2018; DiFrisco and Jaeger 2020; Suzuki, McKenna, and Nijhout 2020). The second thing we need to do is reorient our understanding of what developmental biology is ultimately trying to accomplish. The chief objective of the field is not necessarily the identification of one-to-one causal mappings between molecular processes and specific phenotypic characters, as the genetic paradigm suggests. Prior to the mid-twentieth century, classically trained embryologists tended to regard developmental biology as the science of form (Holmes 1904; Zuckerman 1950; Medawar and Zuckerman 1950). Accordingly, their goal was to determine how scaling relationships and the overall shape of organisms arise over the course of ontogeny (Huxley 1932; Huxley and Teissier 1936; Thompson 1942). The form of a plant or animal is the sum total of the sizes and shapes of all its individual body parts, and as a consequence it cannot be explained by simple causes such as a mutation, single nucleotide polymorphism, or duplication event.

Understanding how form is produced requires that we shift our attention to the higher-level interactions that take place between developing body parts. As Hammond recognized nearly a century ago, the development of organs, appendages, and other characters is seldom fully independent or “modular” (Hammond 1947; Gawne, McKenna, and Levin 2020). The growth rate and final size of most traits can be affected by morphogenetic

events that take place in other parts of the body. Hammond identified one of the primary means by which these interactions take place—namely, character-character competition. In modern terms, Hammond's law is valuable because it helps to explain the proximate causes that constrain organismal form: when the growth of body parts is driven by the same macronutrients, increases in the size of one part often restricts the development of others. Growth rate is correlated with metabolic rate, and, if structures are growing at the same time, those with a higher rate of growth that grow earlier than others will consume a disproportionate percentage of the body's internal resources. When this occurs, the traits that are competing will exhibit correlated growth and their final scaling relationship will be allometric, because the larger, more mitotically active body parts constrain the growth of their smaller counterparts that grow more slowly.

Hammond's law explains how scaling relationships can be produced, making it a theory of organismal form. It is a generalized theory of form because the predictions it makes are not taxon-specific. Any organism that undergoes size increases through mitotic divisions has the potential to experience the type of character-character competition his hypothesis describes. More work must be done to determine how often character-character competition occurs and what body parts are affected, but, in principle, Hammond's law has an extraordinarily wide domain of applicability. When developmental biologists attempt to construct theoretical hypotheses, there is a tendency to reach for mathematical tools that describe the phenomena in technical terms that only a small fraction of the field can understand, let alone critique. However, there is no reason to think that every generalized hypothesis needs to be chromed-out with flashy formulas, especially when it is first conceived. Indeed, anyone who opens *The Origin of Species* will find persuasive evidence to the contrary. Like Darwin, Hammond supported his hypothesis using careful observations of common domesticated animals. This approach might seem "unsophisticated" to developmental biologists trained in the molecular era, but as more supporting studies are conducted and the theoretical predictions of Hammond's law are further refined, it could very well be transformed into the sort of truly generalized developmental theory that modern methods have systematically failed to produce.

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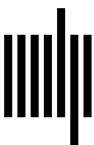
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