Chapter 13

Explaining the Ontogeny of Form: Philosophical Issues

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The aim of this article is to survey philosophical issues that arise in offering scientific explanations of the ontogeny of form. Section 1 presents a conceptual framework from which to understand these explanations as responses to many distinct but related questions in developmental research. The second section identifies and describes the biological content of these questions, both in terms of the phenomena to be explained and current preferences for molecular genetic approaches. Each subsequent section focuses on an area of epistemology relevant to explaining the ontogeny of form (representation, explanation, and methodology). Topics discussed include typology, individuation, model systems, reduction, and research heuristics. In closing, I draw attention to several metaphysical topics that deserve further scrutiny.

1. The Old Problem (Agenda) of the Ontogeny of Form

Explaining the ontogeny of form, that is, discerning the processes and causes that generate the different shapes, size, and structural features of an organism as it develops from embryo to adult, is an old problem domain in the life sciences. The basic issues surrounding these explanations go back to ancient Greece. Aristotle rejected purely "efficient" causal explanations for the developmental origination of morphological features. "Formal" and "final" causation were necessary to adequately explain the ontogeny of form. A clear lesson from Aristotle is that philosophical commitments about scientific explanation permeate questions about what is required to explain how macroscopic complex "form" features of organisms emerge from seemingly simpler features of the embryo (Lennox, 2001).

One of the most persistent dichotomies in explanatory projects directed at these questions is epigenesis versus preformation (Maienschein, 2005). Epigenesis is the claim that heterogeneous, complex features of form emerge from homogeneous, less complex embryonic structures through interactive processes. Thus an explanation of the ontogeny of these form features requires attention to how these interactions occur. Preformation is a claim to the contrary that complex form preexists in the embryo and "unfolds" via ordinary growth processes. An adequate explanation involves detailing how growth occurs. Although preformation has a lighter explanatory burden in accounting for how form emerges during ontogeny (on the assumption that growth is

easier to explain than process interactions), it must also address how the starting point of the next generation is formed with the requisite heterogeneous complex features. This was sometimes accomplished by embedding smaller and smaller miniatures *ad infinitum* inside the organism. Though nothing prevents mixing these two outlooks in explaining different aspects of the ontogeny of form, polarization into dichotomous positions has occurred frequently (Maienschein, 2005; Roe, 1981; Smith, 2006).

Attending to only preformation and epigenesis is a drastic oversimplification of the historical dimensions of explaining the ontogeny of form (see, e.g., Lenoir, 1989; Oppenheimer, 1967). For many of the issues discussed here, one key aspect of recent history is the molecularization of experimental (as opposed to comparative) embryology (Fraser & Harland, 2000), with the concomitant stress on the explanatory power of genes. Although the emphasis on genes has been controversial among developmental biologists (Berrill, 1961), one point of commonality is that explaining the ontogeny of form consists of many interrelated questions rather than a single problem. These questions have been manifested with differing frequency and vigor through history. The ability to answer any of them, as well as the nature of the questions themselves, is contingent on different research strategies and methodologies.

We can observe this multiplicity of questions in philosophical commentary on the problem of explaining development. For example, Sober refers to just two questions of interest on the agenda of problems surrounding ontogeny. "There are problems in biology that remain unsolved. The area of development (ontogeny) is full of unanswered questions. How can a single-celled embryo produce an organism in which there are different specialized cell types? How do these cell types organize themselves into organ systems?" (Sober, 2000, p.24). Moss claims that "the real question concerning metazoan ontogeny is just how a single cell gives rise to the requisite number of differentiated cell lineages with all the right inductive developmental interactions required to reproduce the form of the mature organism" (Moss, 2003, p.97). There are clearly *many* questions lurking in Moss's description of "*the* real question," including but not limited to features of cellular differentiation and inductive interactions.[1] The central *problem* of development is actually composed of *many* different but related scientific questions, each of which can be seen as requiring answers to obtain an adequate explanatory framework.[2] Claims that developmental research has shown a lack of "erotetic progress" because of an inability to decompose its central question are unsubstantiated,[3] which will become clear as these questions are identified and characterized in detail (Section 2).

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1 Other descriptions are susceptible to a similar analysis. "The central problem of developmental biology is to understand how a relatively simple and homogeneous cellular mass can differentiate into a relatively complex and heterogeneous organism closely resembling its progenitor(s) in relevant aspects" (Robert, 2004, p.1).

2 This can be observed among biologists as well. "Vertebrate mesoderm induction is *one* of the classical problem*s* in developmental biology" (Kimelman, 2006, p.360, emphasis mine). In his textbook, Gilbert speaks of the "general problems of developmental biology" (Gilbert, 1997, p.2) or "general questions scrutinized by developmental biologists" (Gilbert, 2003, p.4).

3 "In contemporary developmental biology, there is . . . uncertainty about how to focus the big, vague question, How do organisms develop?" (Kitcher, 1993, p.115).

Although there are a number of independent reasons for preferring an analytical strategy in philosophy of science focused on problems rather than theories, it is more profitable to move directly to the idea of a "problem agenda" before using it to interpret attempts to explain the ontogeny of form. "Problem agenda" refers to any distinguishable set of related phenomena that pose a suite of intertwined research questions. These questions are investigated with the aim of providing a satisfactory explanatory framework capable of addressing all of the component phenomena. *Problem* highlights the emphasis on that which is unknown, uncertain, or perplexing – questions rather than answers. *Agenda* denotes the multifaceted nature of the unit. What is unknown is not one thing, but many, a sort of "list of things to be done" by a group of scientific researchers. Researchers address the problem agenda through the ongoing development of a satisfactory explanatory framework, as well as articulating new questions and reframing old ones. Problem agendas are larger units of analysis than individual empirical or theoretical problems and can be thought of as "big" questions (abstractly framed) concerning a particular domain of inquiry. Most individual researchers focus their attention on concrete *research questions* ("empirical problems") within the context of specific biological systems, tackling them theoretically or experimentally using a variety of different formal and laboratory techniques. Answering research questions contributes to a greater understanding of the problem agenda phenomena. Problem agendas are a combination of domains of phenomena with the cognitive activity of asking questions about these domains (cf. Bechtel, 1986). Formally, they can be seen as analogous to individual questions in philosophical discussions of scientific explanation (e.g., van Fraassen, 1980, ch. 5)

This necessarily truncated discussion generates several indicators for teasing apart what is involved in the project of explaining the ontogeny of form. We can expect to isolate and characterize problem agenda features such as the phenomena to explained, interrelated questions about those phenomena (with particular presuppositions), proposed explanations of phenomena, and implicit or explicit reasons for seeing specific explanations as adequate answers to member questions of the problem agenda.[4]

2. Explaining the Ontogeny of Form

Although there are many questions in the problem agenda of the ontogeny of form, philosophers of biology have turned to development over the past decade because of its promise to provide help in rethinking evolutionary theory (e.g., developmental systems theory; Oyama, Griffiths, & Gray, 2001) and deflate overstated claims about the causal power of genes (Keller, 2002; Neumann-Held & Rehmann-Sutter, 2006). Seemingly, many biologists have given up explaining *development* in favor of explaining *the role of genes in development*, while tacitly maintaining that the latter task is equivalent to the former (Robert, 2004). Whether this is in fact true needs to be investigated because it would imply a reduction in the number of research questions associated with the

4 There is no implicit commitment that the interrelated questions of problem agendas must exhibit hierarchical relationships, as others have argued for with respect to structural relationships among questions in a domain of inquiry (e.g., Kitcher, 1993, ch. 4).

ontogeny of form, as well as a negative evaluation of alternative, non-genetic explanations. Contemporary textbooks are a natural place to begin. "Developmental biology is at the core of all biology. It deals with the process by which the genes in the fertilized egg control cell behavior in the embryo and so determine its pattern, its form, and much of its behavior" (Wolpert et al., 1998, p.v). Besides the central role of genes offered, this description highlights that there is more to developmental biology than explaining the origin of form.[5] Wolpert distinguishes pattern and behavior, although it is natural to include pattern *form*ation in the category of "form." This conceptual slipperiness arises from the fact that "form" is not so straightforwardly characterized.

Some have cast form in terms of the production of "shape" (Davies, 2005), where the key process of "morphogenesis" is flagged etymologically ("morph" ≈ form; "genesis" ≈ coming to be). This excludes differentiation and signaling, which are often included in discussions of morphogenesis because cellular differentiation can lead to changes in cell *shape* (Minelli, 2003, ch. 6) and cell death (apoptosis) can sculpt morphology (Lohmann et al., 2002). A broader account can be culled from morphological investigation where form has been defined in terms of the material composition and arrangement, shape, or appearance of organic materials (Bock & Wahlert, 1965). Understanding form in this way recovers Wolpert's distinguishing of behavior from other aspects of development. The ontogeny of function, at all levels of organization, is a critical component for understanding ontogeny, but it is often bracketed because of the visibility (both past and present) of questions surrounding the ontogeny of form.

Most textbooks (e.g., Gilbert, 2003; Slack, 2006; Wolpert et al., 1998) describe a canonical set of events that occur in metazoan ontogeny. The first of these is *fertilization* (in sexually reproducing species), where an already structured egg (upper surface, animal pole; lower region, vegetal pole) is penetrated by sperm followed by the fusion of the nuclei to generate the appropriate complement of genetic material. Second, the fertilized egg undergoes several rounds of *cleavage*, which are mitotic divisions without cell growth that subdivide the zygote into many distinct cells. After a number of rounds of cleavage this spherical conglomerate of cells (now called a *blastula*) begins to exhibit some specification of the germ layers (endoderm, mesoderm,[6] and ectoderm), and then proceeds to invaginate at the vegetal pole, a process referred to as *gastrulation*, eventually generating a through-gut. (All three germ layers become established during or shortly after gastrulation is complete.) *Organogenesis* refers to the production of tissues and organs through the interaction and rearrangement of cell groups. Events confined to distinct taxonomic groups include *neurulation* in chordates, whereas others correlate with mode of development (*metamorphosis* from a larval to adult stage).

Several key processes underlie these distinct developmental events and the resulting features of form that emerge (the *through-gut* formed subsequent to gastrulation or the *heart* formed during organogenesis). These processes are critical to the ontogeny of form

5 Other textbooks see development primarily in terms of form: "Developmental biology is the science that seeks to explain how the structure of organisms changes with time. Structure, which may also be called morphology or anatomy, encompasses the arrangement of parts, the number of parts, and the different types of parts" (Slack, 2006, p.6).

6 Cnidarians (such as jellyfish and coral) do not have a mesodermal germ layer. They are sometimes referred to as "diploblastic" in contrast to metazoans with three germ layers ("triploblasts").

and mediate the types of research questions posed in the problem agenda. First, cellular shapes change during ontogeny. This is largely a function of cellular differentiation whereby cells adopt specific fates that include shape transformations.[7] Second, regions of cells in the embryo are designated through arrangement and composition alterations to generate different axes (dorsal–ventral, anterior–posterior, left–right, and proximal–distal). The successive establishment of these regions[8] is referred to as pattern formation. Third, cells translocate and aggregate into layers (e.g., endoderm and ectoderm, followed by the mesoderm in many lineages) and later tissues (aggregations of differentiated cell types). Fourth, cells and tissues migrate and interact to generate new arrangements and shapes composed of multiple tissue layers with novel functions (i.e., organs). These last two sets of processes are usually termed morphogenesis (Davies, 2005; Hogan, 1999) and include many distinct mechanisms (Figure 13.1). Fifth, there is growth in the size of different form features in the individual, remarkably obvious when comparing zygote to adult, although proportional changes between different forms (termed *allometry*) are often of primary interest (Richtsmeier, 2003).

None of these processes occur in isolation and explanations of particular form features usually draw on all of them simultaneously, often presuming form features that originated earlier in ontogeny by different instantiations and combinations of the processes. These core processes capture the broad contours of what kinds of questions are asked about "form" arising during development: how do various iterations and combinations of these processes generate form features during ontogeny? There is a shared presupposition that the phenomena (e.g., shape of the heart) are in need of explanation and not artifacts. A related presupposition is that these processes are routinely involved in the ontogeny of form.

A particular case of form origination illustrates the multiplicity of research questions in the problem agenda. How does the vertebrate heart, with its internal and external shape and structure (as well as location) originate during ontogeny (Harvey, 2002; Harvey & Rosenthal, 1999)? This particular phenomenon poses a number of interrelated questions related to the core processes. How does the heart come to exhibit left/right asymmetry in the body cavity, and be in that particular location? How do muscle cells migrate to, aggregate in, and differentiate at this location? How does the interior of the heart adopt a particular tubular structure with various chambers (that differ among vertebrate species)? How does the heart grow at a particular rate and achieve a specific size? How do different tissues interact to progressively generate the form of the heart? Answers to these questions entail characterizing the operation of the core processes. But cellular differentiation alone does not explain why the heart has particular cell types rather than others. Solutions relevant to explaining the ontogeny of form characterize causal factors that drive these core processes, especially the *specificity* of their outcomes. What causes cells to adopt a *muscle* cell fate? What causes certain tissues to interact in the prospective location of the heart? What causes the *arrangement* of the internal tubular shape of the heart? What causes growth in size to occur in the

7 "Totipotent" cells can adopt any fate whereas "pluripotent" cells are able to adopt many but not all fates.

8 Metaphorically termed "embryo geography" (Carroll, 2005) or "compartment maps" (Kirschner & Gerhart, 2005).

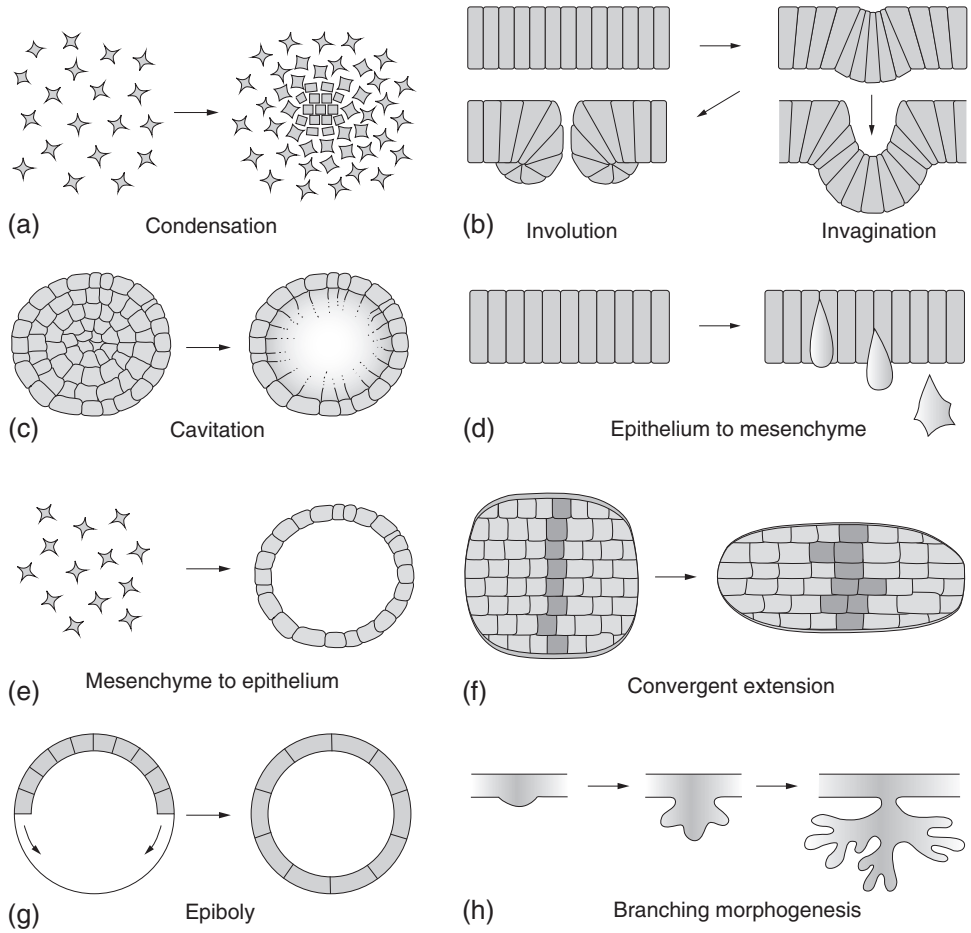

Figure 13.1 Different mechanisms of morphogenesis (Slack 2006, 17)

heart? Proposed solutions to the problem agenda of the ontogeny of form must appeal to causal factors relevant to questions such as these that pertain to the nature of the core processes.

It is no secret that the primary candidates for causal factors involved in answers to these questions are *genes*.[9] One primary rationale for this privileging (in the sense of holding genetic explanations more adequate than alternatives) is that the specificity of outcomes produced by the core processes is thought to lie in genetic "information" [See BIOLOGICAL INFORMATION]. This encourages the use of "blueprint," "program," and other linguistic metaphors in developmental investigations (Keller, 2002; Moss, 2003):

9 In fact, spatiotemporally regulated gene expression is taken as a complete solution to the origin of form by some researchers: "We now understand how complexity is constructed from a single cell into a whole animal" (Carroll, 2005, p.10). Many would evaluate this sentiment as premature.

"How is Form Encoded in the Genome?" (Carroll, 2005, p.34). Robert identifies a "consensus" around these metaphors that underwrites a blending of preformation and epigenesis themes according to three core theses: *genetic informationism* ("genes contain the entirety of the preformed, species-specific developmental 'information'"), *genetic animism* ("a genetic programme in the zygotic DNA controlling the development of an organism"), and *genetic primacy* ("the gene is the unit of heredity, the ontogenetic prime mover, and the primary supplier and organizer of material resources for development, such that the phenotype is the secondary unfolding of what is largely determined by the genes") (Robert, 2004, 39). This consensus is a mixture of themes from preformation and epigenesis because a preformed genetic program (passed along by inheritance) contains all the information determining the epigenetic outcomes observed during ontogeny.

However, there are reasons for thinking there might not be a consensus on development. Take an incriminating textbook example.

> How are the organizing principles of development embedded within the egg and in particular within the genetic material – DNA? . . . Genes control development mainly by determining which proteins are made in which cells and when. . . . The differences between cells must therefore be generated by differences in gene activity. Turning the correct genes on or off in the correct cells at the correct time becomes the central issue in development. All the information for embryonic development is contained within the fertilized egg. (Wolpert et al., 1998, pp.1, 13)

These loaded statements are often redacted or qualified.[10] For present purposes we only need evaluate the prospects of gene privileging for explanations of the ontogeny of form, not its actual distribution among current researchers. Robert argues against the privileging of genes by illustrating that they do not have the favored status attributed to them, either causally during ontogeny or transgenerationally via inheritance (Robert, 2004). The role of genes in development is only a subset of what is required to explain the reliable causal production of phenotypic features from generation to generation. This conclusion is synthesized from a variety of arguments offered by philosophers of biology to demonstrate that genetic informationism, genetic animism, and genetic primacy are all problematic (Jablonka & Lamb, 2005; Keller, 2002; Moss 2003; Oyama et al., 2001; Sarkar, 2000).

Instead of rehearsing these arguments, we can observe the abstract conclusion against privileging genetic explanations by returning to vertebrate cardiogenesis. Are there problems with claiming that genes contain all of the developmental "information" to form vertebrate hearts? Is there a genetic program in the DNA controlling heart development? Are genes the primary supplier and organizer of material resources for heart development, largely determining the phenotypic outcome? Existing studies of

10 "As all the key steps in development reflect changes in gene activity, one might be tempted to think of development simply in terms of mechanisms for controlling gene expression. But this would be highly misleading. For gene expression is only the first step in a cascade of cellular processes that change cell behavior and so direct the course of embryonic development. To think only in terms of genes is to ignore crucial aspects of cell biology, such as change in cell shape, . . ." (Wolpert et al., 1998, p.15).

heart development have identified a role for fluid forces in specifying the internal form of the heart (Hove et al., 2003) and its left/right asymmetry (Nonaka et al., 2002). Additionally, biochemical gradients of extracellular calcium are responsible for activating the asymmetric expression of the regulatory gene *Nodal* (Raya et al., 2004) and inhibition of voltage gradients scrambles normal asymmetry establishment (Levin et al., 2002). A number of genes are also critical to these processes (Hamada et al., 2002) but the conclusion seems to be that genes do not carry all the "information" needed to generate form features of the heart. And if there is a genetic program for these features, it is difficult to assign it "control" since an extragenetic feature is the initial cue for asymmetric spatiotemporal gene expression (Raya et al., 2004; cf. Farge, 2003). Also, genes do not "determine" the outcome because the experimental manipulation of fluid forces causes severe phenotypic malformations in the heart (Hove et al., 2003).[11]

Another pivotal reason for being wary of gene privileging is "phenotypic plasticity," the phenomenon of phenotypic differences arising from variation in development due to environmental factors (Hall, Pearson, & Müller, 2004; Pigliucci, 2001; Schlichting & Pigliucci, 1998; West-Eberhard, 2003) [See Phenotypic Plasticity and Reaction Norms]. If the same set of genetic resources produces very different phenotypic outcomes due to diversity in the environmental factors present, then the specificity of form features originates from more than gene expression. Relevant "information" or determining causes required to explain the ontogeny of form reside "outside" of the organism. Intrinsic "environment" dynamics are also relevant, such as developmental selection (Kirschner & Gerhart, 2005), whereby competition among components (e.g., neurons) leads to the preferential preservation of one array of components rather than others.

It may be unsurprising that a concrete example reveals many of the difficulties identified by others regarding the privileging of genetic explanations in development. Claims about the "hardwiring of development" (Arnone & Davidson, 1997) lack support on several fronts but should be treated as philosophically interesting in their own right. Continued attempts to privilege genes in explanations of the ontogeny of form are clues to epistemological issues. For example, *modeling* genetic regulatory interactions in terms of input/output network wiring diagrams encourages the "hardwiring" metaphor analogous to the control attributed to an electronic circuit board (cf. Keller, 2002). Part of the rationale is an increased generalization of the explanatory apparatus purchased through abstraction. Abstract "network" models are applicable to very diverse phenomena (Shiffrin & Börner, 2003). Having jumped ahead to some of these philosophical concerns in looking at the emphasis on genetic explanations, it is now time to cast our net more widely.

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11 Similar comments can be observed from researchers working on different form features, such as avian feathers. "The genetic control provides transcription and translational control of molecules. Specific sets of cell surface molecules and intra-cellular signaling are produced for particular cell types. The molecular information endows cells and their micro-environment with particular properties. Based on these properties, cells interact in accordance to physical-chemical rules, and there are competition, equilibrium, randomness, and stochastic events, at this cellular level. Epigenetic events appear to play important roles at the cellular level. The integument pattern we observe is the sum of these cell behaviors" (Jiang et al., 2004, pp.131–2).

3. Epistemological Issues: Representation

The first representational decision made in explaining the ontogeny of form concerns what constitutes the system of investigation ("intrinsic") and what is the outside or environment ("extrinsic"). In most cases this is implicitly determined by the intuitive inside/outside epithelial boundary exhibited by organisms studied in the laboratory. This does not prevent appeals to "extrinsic" causal factors in explanations but distinguishes the labeling ("representation") of those factors as either intrinsic (e.g., gene expression) or extrinsic (e.g., nutrition) to the organism. As with intuitive conceptions of biological individuality, a number of reasons can be marshaled to question a privileged circumscribing of developmental systems (cf. Keller, 2001).

A second key epistemological issue is how continuous ontogenetic trajectories are to be discretely represented. Often ontogenies are partitioned into developmental "stages" consisting of a numbered sequence. For example, chick ontogeny is divided up into 45 stages (Bellairs & Osmond, 1998), which were originally established over fifty years ago (Hamburger & Hamilton, 1951). The practice of dividing ontogeny into stages has only recently begun to be systematically investigated historically (Hopwood, 2005). There is agreement that "chronological age" is of little use, in part because of variability despite homogeneous environments; the same stage in the same system under identical control conditions is reached at different "ages." But how exactly these representational decisions are made is largely unique to each model system (because it involves discernible characters as indices) and is a function of several factors including the ability to communicate results among researchers unambiguously, replicate experimental results, and coordinate stages with other taxa. These decisions are contingent on the historical period in which the stages were set forward. Closely connected with the determination of stages are fate maps meant to show features of later stages prospectively in an earlier stage embryo (e.g., cleavage), such as where heart cells will originate prior to their migration and differentiation.

Decisions about how to stage development naturally provoke questions about how time itself is represented for ontogeny, especially since stages do not straightforwardly correlate with hours (or days). The changes that occur in ontogeny are all physically continuous and thus the measures of time utilized must connect the "stages" represented. Several basic distinctions about time can be recognized (Reiss, 2003; cf. Minelli, 2003, ch. 4). The first is between sequence and duration. Sequence concerns event ordering, such as gastrulation occurring prior to organogenesis, whereas duration concerns a succession of defined intervals, which may or may not map onto sequences of events. For any sequence we can ask about the relative duration of the events (for interval definition *d*, *A* to *B* occurs over 3*d* in one species whereas in another species it occurs over 4*d*), and whether they exhibit reliable transformation ordinality (*A* always precedes *B*; *B* always precedes *C*: or, *A* always precedes *B*; *B* sometimes precedes *C*). Relative timing of one set of sequences to another can also be assessed using an "intrinsic" interval definition. For two event sequences ($A \rightarrow B \rightarrow C$; $D \rightarrow E \rightarrow F$), the timing of $D \rightarrow E \rightarrow F$ can be measured with respect to the interval occurrences defined by $A \rightarrow B \rightarrow C$. Alternatively, one or more event sequences or intervals can be measured according to extrinsic time measures. ("The transition from event *A* to event *B* occurs

in 2–3 hours.") These choices are usually relative to explanatory aims but not necessarily explicitly justified.

Another critical issue is the recognition of sameness for units and similarity of mechanisms in different species. This is a necessary prerequisite for making generalizations outside of the model used for laboratory investigation. It is a manifestation of the problem of homology and is unavoidable in answering questions pertaining to representation of units across taxa.[12] In the attempt to assess whether a particular explanation of form origination in one species can be generalized to another, an assessment of the sameness of causal factors and phenomena in other taxa must be presumed (if not established). Thus, to claim that factor *x* (protein) causally explains the form feature *y* (heart shape) that occurs in the event *E* (organogenesis of the heart) in vertebrates requires that *x*-type factors, *y*-type form features, and *E*-type events are instantiated in vertebrate taxa. We can exemplify this as a research question: are genes, cardiac cells, and "hearts" of *Drosophila* relevantly homologous (Bodmer & Venkatesh, 1998)? Homology judgments concerning the individuation and sameness of these different aspects of ontogeny must be made prior to assessments of generalization, such as the behavior of particular genes in heart development or what counts as a segment (Minelli, 2003, ch. 9). Representational issues surrounding time and stage are directly pertinent to this question.

The factor of time alongside homology allows us to see another issue in a different light: typology. Although typological thinking and its ignoring of variation have a history of being disparaged because of *metaphysical* incompatibility with population thinking in evolutionary theory (Mayr, 1976),[13] type concepts may be necessary for explanatory purposes (Amundson, 1998, 2005). Variations of "typological thinking" are manifested in explaining the ontogeny of form as a consequence of conceptualizing continuous ontogenies in terms of discrete partitions and generalizing processes (morphogenesis), events (organogenesis), and form features (heart) across all of the instances within an organism kind, as well as to other developmental systems. These explanatory practices require that particular kinds of variations be disregarded. This is not to say that they are unbiased, as is the case for all representational decisions made in scientific investigation, and developmental generalizations are fraught with difficulty (Alberch, 1985; Minelli, 2003, ch. 4). Developmental stages can be questioned with respect to what counts as "typical" ontogeny.[14] But the reasons why researchers adopt different

12 Formally, homology concerns sameness ("correspondence") rather than similarity but representational claims about similarity of mechanisms are usually predicated on sameness of mechanism components and their activities.

13 "Population thinking" usually refers to the ontological claim that only individual organisms are real as a consequence of the variations they exhibit and any statistical terms used to describe them collectively are abstractions and not objective features of the world. "Typological thinking" is supposed to represent a contrary (metaphysical) position, whereby the "types" used to collectively describe organisms are objectively real (often equated with "essences") and, in some sense, downplay the reality of variations exhibited by individuals.

14 For example, in the original paper establishing stages for the chick embryo, the authors claim "we have tried to establish average or 'standard' types by comparing a considerable number of embryos in each stage, and we have selected for illustrations those embryos which appeared typical" (Hamburger & Hamilton, 1951, p.52).

kinds of typology should be sought in the epistemic context of explaining the ontogeny of form, not by way of contrast with a metaphysical essentialism that is in conflict with population thinking in evolutionary biology.

4. Epistemological Issues: Explanation

Causal explanations of the ontogeny of form can be distilled out of our earlier discussion of questions in the problem agenda. For example, within the domain of organogenesis, questions can be asked about what causal factors active in the core processes of development produce the specific form features of organs, such as the heart. Researchers are seeking to isolate and identify developmental causes that bring about specific form feature "effects." But not all explanations appeal to material causal factors, such as particular proteins. We can distinguish another related set of explanations that identify *structural* aspects of causal explanations, such as mathematical relations between features of developing organisms due to physical rules or constraints. Two historically famous examples are Thompson's use of geometrical shape transformations to show that specific form features arise solely from proportional changes in the growth of parts (Thompson, 1992 [1942]), and Turing's use of gradient equations to show how the diffusion of molecules can produce patterns (Turing, 1952; cf. Keller, 2002). These approaches causally explained the ontogeny of form without the invocation of specific genes. Structural and material explanatory strategies need not be in competition but, as in the case with epigenesis and preformation, there has been a widespread perception of mutual exclusivity.

More recent instantiations of these approaches include shape analysis of form features during ontogeny using geometric morphometrics (Zelditch et al., 2004) and "embryo physics" (Forgacs & Newman, 2005). Physical rules (e.g., surface area to volume ratios) are often used to generate models of core processes such as morphogenesis (Takaki, 2005) and specific events such as gastrulation or neurulation (Schiffman, 2005). Often there are several material explanations that could fit within the structural constraints (Davidson et al., 1995). This is taken by some as a motivation for the prioritization of material explanatory strategies because the structural aspects are necessary but not sufficient for the specification of form during ontogeny. But a number of researchers have argued that explanations appealing to physical features of biological "matter" are sufficient to explain specific form features, especially early in evolutionary history (Newman, 1994; Newman & Müller, 2000). Segments, tubes, hollow spheres, and layers of cells are generic structures attributable to biomechanical forces (Minelli, 2003, ch. 3) and can be multiply realized by different material components (e.g., proteins or cells). Related phenomena include the wrinkling of an elastic sheet under tension (Sharon et al., 2002) or the elasticity of biological gels (Storm et al., 2005). Studying these mechanical properties of biological materials that are responsive to stress and strains experienced during development is a strategy for explaining the ontogeny of form that utilizes a different set of causal factors. A philosophical motivation for this approach is that generalizations based on physical principles have a wider scope in the sense of operating in all ontogenies, whereas appeals to particular material factors may not be instantiated widely. Explanatory trade-offs are also conditional upon

the degree to which structural explanatory strategies can account for the origination of specific forms as adequately as material-based strategies.

4.1. Model systems and generalizations

Explanations of form's ontogeny focus on form feature *types* (kinds) rather than form feature *tokens* (instances). Although some authors have stressed the explanatory value of token reductionism in developmental biology (Delehanty, 2005; Weber, 2005, chs. 1, 8), a central feature of current research is the search for generalizations across organism instances and different species relevant to the origination of form. These generalizations can be assessed along at least three dimensions: abstraction (how much a generalization is able to ignore particular details or variation), stability (how resilient the generalization is to changes in causal structures and relations), and strength (how frequently the generalization holds) (Mitchell, 2000). In general, strength and stability are the focus of developmental biologists utilizing material explanatory modes, whereas abstraction is also critical to structural ones.

One of the most significant features affecting these different properties of generalizations is the use of model organisms. The National Institutes of Health (NIH) primarily sponsor developmental research on a small number of animal models: round worms (*C. elegans*), fruitflies (*Drosophila*), zebrafish, frogs (*Xenopus*), and mice (http://www.nih.gov/science/models/). Most observations and analyses of core developmental processes are made in these systems, as well as in the historically important chicken (*Gallus*) (cf. Slack, 2006, section 2). Many explanations of the ontogeny of form are predicated on the assumption that these species can serve as models for the developmental processes extant (and extinct) in the diversity of life. There are many reasons to question this assumption because the models were chosen for *non*-representative reasons: small body size, rapid embryonic development/short gestation period, early sexual maturation (shorter generation time), optical translucency of the embryo, and ease of laboratory cultivation (Ankeny, 2001; Burian, 1993; Bolker, 1995; Schaffner, 1998). These are largely aspects of highly derived (and therefore "atypical") ontogenies (Hedges, 2002).

One explanation for the optimism of developmental researchers and pessimism of evolutionary researchers can be seen through the lens of different hierarchical levels of developmental organization (such as protein, cell, tissue, organ, etc.). Some developmental researchers are confident in the generalization potential of model systems because characters at lower levels (such as gene network components) are widely instantiated across a diversity of taxa.[15] This has led to unprecedented experimental manipulation, such as the expression of fruit-fly genes in mice. But alongside this success has been a growing body of evidence indicating that higher levels of organization (tissues, organs, and anatomical parts) can be multiply realized by different lower-

15 "The mechanisms of development are very similar for all animals, including humans. This fact has only been known since it has become possible to examine the *molecular basis* of developmental processes" (Slack 2006: 3, emphasis mine). The expectation underwrites the motivation for studying model systems, as in this *Drosophila* paper: "We expect that similar mechanisms may specify pattern formation in vertebrate developmental systems that involve intercellular communication" (Flores et al., 2000, p.75).

level constituents. In part this is because these higher levels emerge from combinations of compositional and procedural hierarchies during ontogeny not widely instantiated in other species; molecular level generality is *not* transitive (McShea, 2001; Salthe, 1985). A generalization that holds across model organisms ("gene *x* plays the same causal role during cardiogenesis in *Drosophila* and vertebrates") does not necessarily yield a generalization about higher levels of organization ("epithelial–mesenchymal interactions, in which gene *x* is expressed, play the same causal role during cardiogenesis in *Drosophila* and vertebrates"). Evidence for this non-transitivity includes the dissociation of homologous gene expression from homologous structures (Wray, 1999), co-option and convergence of gene expression (True & Carroll, 2002), self-organization dynamics (Camazine et al., 2001), and epigenetic interactions occurring during ontogeny (Müller, 2003). Cardiogenesis in vertebrates involves neural crest cells, which are not present in *Drosophila*. But many of the same genes are expressed during cardiogenesis in both organisms. Strong and stable molecular-level generalizations that hold across many species do not translate into generalizations that obtain at all hierarchical levels for those species.[16]

This empirical situation serves as another plank in the argument against gene privileging: a *solitary* explanatory strategy of decomposition and localization of developmental components (genes) and their interactions (gene networks) is insufficient for explaining the ontogeny of form apart from further, distinct evidential support (cf. Bechtel & Richardson, 1993). A model organism may represent a lower hierarchical level in other taxa quite accurately while simultaneously being a poor model for other (higher) levels. Caution is necessary when explanations of form origination gleaned from one level of biological organization are applied to another level in different species. Studies of cellular differentiation in bacteria (Iber et al., 2006) are relevant but insufficient for comprehending higher-level form feature origination.

4.2. Reductionism

Model systems and the non-transitivity of molecular generalizations also raise problems related to reductionism. A tendentious discussion in recent philosophy of biology comes from Rosenberg (Rosenberg, 1997; see REDUCTIONISM), where he sets out two different principles putatively at work in antireductionist approaches to developmental phenomena:

Principle of Autonomous Reality: The levels, units, kinds identified in functional biology are real and irreducible because they reflect the existence of objective explanatory generalizations that are autonomous from those of molecular biology.

Principle of Explanatory Primacy: At least sometimes, processes at the functional level provide the best explanation for processes at the molecular level.

16 A related issue is making generalizations across different anatomy *within* the same model, such as developmental mechanisms underlying the establishment of nerve and blood vessels (Carmeliet & Tessier-Lavigne, 2005). These generalizations are motivated by the exhibition of shared form features, such as stereotypical branching.

Rosenberg takes a dim view of both principles, holding that molecular developmental biology rejects them: "there are no explanatory generalizations at higher levels of organization" (Rosenberg, 1997, p.447). Many have challenged his account. Keller is concerned that Rosenberg misreads contemporary developmental biology (Keller, 1999), especially its metaphors, whereas Wagner and Laubichler claim he is not sufficiently sensitive to the many–many relations between developmental outcomes and molecular constituents (Laubichler & Wagner, 2001; cf. Frost-Arnold, 2004), highlighted above in terms of the non-transitivity of molecular-level generality and the role of biomechanical forces in the origin of specific form features.

An important aspect of this discussion is that what is meant by reductionism varies tremendously (Sarkar, 1998, chs. 2–3). "Reductionism" is rejected by some *cell* biologists,[17] which should at least lead us to pause about "reductionism" in developmental biology. One distinction of crucial importance is the difference between genetic and physical reductionism (Sarkar, 1998). Genetic reductionism is the project of explaining the phenotype in terms of abstract genes in an abstract (non-spatial) hierarchical relationship between genotype and phenotype. Physical reductionism is the explanation of biological phenomena using the physical properties of constituent molecules and macromolecules, usually conceptualized in a spatial hierarchy. Considerations of spatial hierarchy highlight the relevance of part/whole relations (Hüttemann, 2004; Sarkar, 1998, ch. 3; Wimsatt, 1976). Rosenberg's position is a conflation of genetic and physical reductionism that prefers certain kinds of macromolecules (DNA, RNA, proteins) to explain the ontogeny of form features in a presumed spatial hierarchy. Some difficulties with this position include an inability to defend a preferential treatment of particular macromolecules, especially since others (phospholipids, fatty acids, cholesterols, and carbohydrates) play key developmental roles (e.g., Hsu et al., 2006), and not having a explicit articulation of the hierarchical relationships involved. Developmental phenomena are heterogeneous and "developmental biology" is multidisciplinary as a consequence. Ignoring this diversity of research programs facilitates missing the heterogeneity of explanatory aims directed at different core processes in ontogeny and their characterization at multiple levels of organization (cf. Keller, 2002). Generalizations relevant to explaining the ontogeny of form are diverse and higher-level generalizations in particular can be objectively identified (cf. Gilbert & Sarkar, 2000).

One feature not routinely recognized for reductionism concerning part–whole relations is *temporality*. Supervenience is an atemporal notion, capturing relations of dependence at a particular time (Rueger, 2000; Sober, 1999). But causation is inherently diachronic, which is especially applicable to ontogeny. Given the representational dimension of time and the focus on causal explanation, understanding "reductionism" along a temporal axis is critical. Are higher-level form features (such as hearts) causally produced by the activity of their component parts (e.g., proteins) at earlier times? Further work is required to turn any synchronic realizations into diachronic dependencies between parts and wholes in biological hierarchies. Temporality opens up a broader space of alternatives for explanations of the ontogeny of form not captured by

17 E.g., "Our results suggest that the cellular responses . . . may be an emergent property that cannot be understood fully considering only the sum of individual . . . interactions" (Kung et al., 2005, p.3587).

synchronic ideas of reduction. This can be seen through attention to explanatory norms.

One norm for causal explanations is that more fine-grained explanations are preferable (ceteris paribus) (Jackson & Petit, 1992). But "fine-grain" can mean either "small grain" (prefer micro to macro causal information) or "close grain" (prefer proximate to distal causal information). Almost all discussion surrounding reduction in philosophy of biology has concerned "small grain." Consider an argument for the "small grain" preference.

(1) To explain is to provide information on the causal history of the *explanandum* phenomena.
(2) Better causal information is obtained at the micro-level ("small grain").
(3) Therefore, micro-level explanations are better.

A parallel argument is obtained by substituting "close grain" for "small grain" with the conclusion that proximate causal information is preferable. But the "small grain" preference is problematic because the second premise is not supported; there are times to prefer "large grain" because better causal information is available (Jackson & Petit, 1992). Since the close grain premise is similarly problematic, especially in embryogenesis where distal causal factors are sometimes highly relevant, a form of explanatory pluralism seems warranted even when temporality is emphasized.

But what are the consequences of preferring proximate causal information in developmental explanations? One possibility is that proximate causes constrain or channel earlier causal factors. Another is that wholes may "bring about" other wholes or parts (temporally), both of which are composed of (and maybe even "reducible" to) parts (spatially). Biologists have recognized something akin to this: "The unidirectional flow from genes to shape is being modified to include cell movements that cause 'physical stress' in neighbouring cells inducing specific gene expression. This causal chain, from a molecular event to physical stress inducing the next molecular event appears as an emergent acting as a downward cause" (Soto & Sonnenschein, 2005, p.115). Diachronic considerations are largely orthogonal to most discussions of reductionism (e.g., Rosenberg, 1997). Proximate factors may include entities favored by both "reductionism" and "antireductionism" because the main issue concerns relative location of the processes in a temporal sequence regardless of their level of organization. The close-grain preference allows higher levels of organization to causally explain lower levels of organization even if synchronic supervenience holds (Sober, 1999). Candidates for these kinds of explanations include the role of mechanical loading of muscle in shaping the form of bones (Rot-Nikcevic et al., 2006), cellular and tissue mechanosensation from compression leading to gene expression (Farge, 2003; Tschumperlin et al., 2004), and fluid forces in proper cardiac development or vascular remodeling (Hove et al., 2003; Tzima et al., 2005).

All of this bears on Rosenberg's two principles. It is patently false that "in developmental molecular biology there is no room for downward explanation, in which some regularity at the level of cell physiology plays a role in illuminating the molecular processes that subserve development" (Rosenberg, 1997, p.455) once the temporality of developmental processes is absorbed into the explanatory project of understanding the

ontogeny of form. Generalizations about higher levels of organization compose the *explanans* of developmental biology, not just a halfway house of *explananda*, and no implicit teleological claims are involved.[18]

Even if we set aside the issue of temporality, difficulties remain. On the assumption that a particular lower level of explanation is preferred, there are questions about types of entities at that level and how many of them are explanatorily relevant. Physical reductionism does not inherently decide between macromolecular types. Much of the excitement in recent developmental biology arose from the discovery of conserved transcription factors and signaling proteins (from "regulatory" genes) that spatiotemporally modulate transcriptional activity during ontogeny (Carroll, 2005; Davidson, 2001). But structural genes also play a critical role in producing form features (Sakai, Larsen, & Yamada, 2003). How does one evaluate the contribution of genes, spontaneous electrical activity, fatty acids, and competition (*inter alia*) to neuronal morphology arising during ontogeny? There is no accepted currency for comparing these different causal factors to establish their relative role in the ontogeny of a form feature, either in term of causal contribution or difference making (Sober, 1988). This also holds for the structural aspects derived from physical rules. Answers to these questions have an impact on the kinds of generalizations available, which are not solved even if one accepts a physical reductionism that favors molecular explanations.

5. Epistemological Issues: Methodology

Many of the methodological questions that emerge in the problem agenda for the ontogeny of form can be extracted from our earlier discussion. Why choose a particular staging of an organism's ontogeny? Why preferentially investigate factors deemed intrinsic to the system versus extrinsic variables? Instead of teasing each of these out, it is useful to turn to research heuristics (or simplifying assumptions) utilized in explanations of the ontogeny of form. Following earlier analyses on the role of research heuristics in scientific investigation (Wimsatt, 1980, 1986), Robert has reconstructed an argument for a (genetic) reductionist research heuristic that explains development (and thus the ontogeny of form) in terms of the role of gene activity during ontogeny (Robert, 2004).

(1) Simplifying strategies and assumptions, as such, are absolutely necessary in biological science.
(2) Simplifying the context of a system is advantageous if we want to learn about intrasystemic causal factors.
(3) Genes by themselves are not causally efficacious, as genes and environments (at many scales) interact (differentially, over time) in the generation of any phenotypic trait.

18 Rosenberg raises this specter: "Cellular structures only come into existence through molecular processes that precede them. There is . . . no scope for claims about the indispensable role of cellular structures in these molecular processes. The future cannot cause the past" (Rosenberg, 1997, p.455).

(4) We decide to focus on the causal agency of genes against a constant background of other factors, for pragmatic or heuristic reasons.
(5) A trait *x* is caused by a gene *y* only against a constant background of supporting factors (conditions), without which *x* would not be present (even if *y* is present).
(6) Therefore, organismal development is a matter of gene action and activation, as particular alleles have their specific phenotypic effects against standard environmental background conditions.

The second premise is subject to two alternate readings according to Robert. The first pragmatically ignores the biases, such as a tendency to concentrate on lower-level intrasystemic factors or underestimate the impact of intersystemic factors (Wimsatt, 1980, 1986) and generates the hedgeless hedge heuristic (HHH).[19] HHH encourages proceeding *as if* genes are sufficient to explain developmental processes. When objections arise one admits their insufficiency for explaining the ontogeny of form while continuing to prosecute a gene-focused methodology. But the isolation of a genetic causal factor against a fixed background shows that this gene activity is a *relevant* factor, not the only or most important causal factor (or type of factor). Because the HHH does not experimentally explore the role of any extragenetic factors, using it alone involves researchers in a methodological fallacy.

From a second reading of premise (2) Robert generates a different strategy, the constant factor principle heuristic (CFPH): "Against standard background conditions, aspects of organismal development may be partially a matter of gene action and activation, and it remains to be determined whether (and how) extragenetic factors make a specific causal contribution to ontogenesis" (Robert, 2004, p.17). CFPH prevents an unlicensed inference from pragmatic choices about methodology to claims about gene activity as the best explanation. If we return to the study of fluid forces in cardiogenesis, something similar to the CFPH seems to have motivated the investigative strategy.

> The formation of a functional heart is regulated by the coordinated interplay between a genetic programme, fluid mechanical stimuli, and the inter- and intracellular processes that link them. While the genetics of cardiogenesis are being analysed intensely, studies of the influence of epigenetic factors such as blood flow on heart development have advanced more slowly owing to the difficulty of mapping intracardiac flow in vivo. (Hove et al., 2003, p.172)

The authors readily admit that genetic factors have received the most scrutiny for practical reasons and that technical difficulties were a major hurdle.

But CFPH leaves a key question unanswered: what heuristic do we use to isolate and characterize "standard background conditions" and the causal role of extragenetic factors during ontogeny? CFPH protects us from drawing illicit inferences about development from the role of genes in development but it does not guide us toward experiments that identify extragenetic factors in ontogeny. Even if CFPH produces a compulsion to execute different experiments, it does not by itself tell us what *kind* of experiments

19 Hedge$_{df}$ = a word or phrase used to allow for additional possibilities or to avoid overly precise commitment. Thus, the HHH seemingly recognizes additional possibilities but in fact does not.

these are or how to establish appropriate simplifying assumptions. To isolate causes relevant to explaining the ontogeny of form in terms of something other than genes, new positive research heuristics need to be articulated that are responsible to the conceptual arguments made against privileging genetic explanations of development.

One strategy for analyzing "standard background conditions" involves comparing the ontogeny of form in a model system with a closely related non-model system. For example, developmental stage 10 for *Xenopus* used to have dorsal mesoderm originating only from the deep mesenchymal layer. Two studies of a related anuran (*Hymenochirus boettgeri*) alongside *Xenopus* demonstrated that dorsal mesoderm also originated from surface cells in both species (Minsuk & Keller, 1996, 1997). Any gene that was expressed in the surface cells would not have been considered as a mesodermal contributor prior to this reevaluation. Basic descriptive and manipulative embryology evaluating "standard background conditions" is still required in order to interpret gene expression patterns. Another result of these investigations was that the contribution of surface cells to mesoderm varies between spawnings for *Xenopus*, ranging from nearly absent to almost ubiquitous, and that surface epithelial cells invade the notochord and somites via a novel developmental mechanism not previously described. The standardized background conditions presumed for the model system were problematic and required revision.

The seeds of one alternative positive heuristic are available in our discussion of temporality and a latent aspect of the previously discussed example of left/right asymmetry in cardiogenesis. How did researchers identify crucial extragenetic causal factors if they were focusing on the role of genes in left/right asymmetry origination *as a substitute* for left/right asymmetry origination? A glance at the investigative motivations show that they were driven to find the symmetry breaking event that initiates asymmetrical gene expression (Raya et al., 2004). They were led to extracellular Ca^{2+} because of prior work identifying a voltage gradient across the midline (Levin et al., 2002). The reasoning takes the form of following a causal chain backwards, seeking earlier and earlier antecedent causal factors in the ontogenetic trajectory. This suggests a different kind of heuristic strategy, one not fundamentally focused on reductionism. Following a causal chain involves seeking the next most proximate cause in a temporally extended causal sequence. A proximate cause heuristic (PCH) makes a simplifying assumption that focuses on the causal agency of proximate factors against a constant background of distal factors (for pragmatic or heuristic reasons), despite the recognition that distal causes play important roles in producing form features during ontogeny. PCH illustrates a potential *method* for finding higher-level explanatory generalizations, even under strong commitments favoring reductionism. The proximate cause of a particular form feature can be a higher-level entity without having to deny that gene expression and cellular dynamics are critical for generating the entity in the first place.

The application of PCH will be methodologically complex because of different conceptualizations of developmental time. What counts as proximate and distal will be relative to the sequences or durations specified. PCH also naturally transgresses the intrinsic/extrinsic boundary in searching for causal factors (Gilbert, 2001; Van der Weele, 1999). Whereas reductionist research heuristics are biased toward localization of causal factors within a system as opposed to its environment (Wimsatt, 1980), tracing causal chains and looking for proximal (or distal) causes are not. Following a sequence of events in time might lead to extrinsic causal factors that are relevant to

particular processes underlying form origination, such as limitations on growth from precocious hatching due to vibrational cues from predators (Warkentin, 2005) or diet induced transformations of morphology (Greene, 1996).

6. Unexplored Issues and Summary

Though we have ranged widely over a variety of issues pertinent to explaining the ontogeny of form, we have left many untouched. One worth mentioning is the experimental utilization of developmental trajectories conceived of in terms of fertilized egg to adult from sexually reproducing species. Prior to molecularization, embryological studies concerned with form origination often concentrated on asexually reproducing species, specifically choosing asexual budding to understand the ontogeny of form (Berrill, 1961; cf. Minelli, 2003). Regenerative developmental phenomena have also received less attention (Alvarado, 2003). This nexus of issues touches directly on representational preferences, the scope of generalizations, and methodological biases.

Metaphysical issues have also been largely ignored here, in part to keep the focus on explanations. Some points of contact include: (a) reduction, emergence, physicalism, and concepts of supervenience, especially once temporality is included (Rueger, 2000); (b) causation, both in terms of concepts relevant to preformation and epigenesis such as "production" and "propagation" (Salmon, 1998) and whether *probabilistic* causation (Hitchcock, 2002) is useful for articulating a common currency to assess multiple causal contributions during ontogeny in the production of form features; and (c) dispositional properties, especially as they bear on transient "potentiality" in development and whether causal powers are intrinsically located (cf. Love, 2003). Questions about individuation and identity through time are also salient. Canonical events in form origination (such as gastrulation or organogenesis) direct us to consider the status of events in relation to other entities (Macdonald, 2005), especially whether "event" or "aspect" is more appropriate for developmental causes (Paul, 2000).

The idea of a problem agenda set forth earlier can also be applied to philosophical questions. Investigations of epistemological and metaphysical issues attending the attempt to causally explain the developmental origin of the material composition, arrangement, shape, and appearance of organismal features are interpretable as part of a *philosophical* problem agenda. It should be transparent that this agenda of philosophical issues affiliated with the ontogeny of form contains more than its fair share of outstanding questions, many of them distinct from evolutionary theory and the causal power of genes. Developmental phenomena have been persistent provocateurs of intellectual reflection for two millennia. In addition to constituting a multifaceted problem agenda for ongoing empirical research in developmental biology, the associated philosophical questions warrant increased scrutiny from philosophers of biology.

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