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Detecting Themes and Variations: The Use of Cases in Developmental Biology

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This article unpacks a particular use of ‘cases’ within developmental biology, namely as a means of describing the typical or canonical patterns of phenomena. The article explores how certain cases have come to be established within the field and argues that although they were initially selected for reasons of convenience or ease of experimental manipulation, these cases come to serve as key reference points within the field because of the epistemological structures imposed on them by the scientists using them and, hence, become usable in a wider variety of circumstances including future theory development.

1. Introduction. Reasoning based on or with cases is often viewed as a second-rate epistemological move, perhaps necessary in ‘soft science’ domains in which phenomena are not as regular as in more ‘traditional’ scientific fields thought to have fundamental laws underlying them or when our abilities to derive generalizations are more limited due to features of the domain under examination.[1] Use of cases is ubiquitous within the social sciences; however, although they are well recognized by practitioners in

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1. This caricature of the physical sciences has been undermined by various seminal works, notably Cartwright (1983); the distinction invoked here between types of science is nonetheless maintained in discussions of the role of and need for cases in the social sciences (and their status as a ‘poor stepsister’ to ‘more rigorous’ forms of scientific reasoning). It also should be noted that issues discussed in this article also relate to the move to recognize the heterogeneous range of scientific practices, many of which are not theory driven, and recognition that theory-driven scientific practice is in fact quite atypical (thanks to Alan Love for helping me clarify this point), but I do not have space to investigate the relationship between cases and scientific practice here.

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those fields as an epistemic form, there is little consensus even among them on what constitutes a case, how it is typically used, what reasoning processes underlie its use, and what gives its use warrant.[2]

Paying close attention to the formative stages of a field that later can become invisible (especially to those unaware of the field's history) allows us to identify critical epistemic structures in the nonsocial sciences that appear to share at least a family resemblance with cases in the social sciences.[3] These also are often labeled as 'cases' (or 'case studies') by their scientific users but have had limited conceptual or philosophical attention paid to them, either by scientific practitioners or scholars within the history and philosophy of science.[4] Hence, as part of a broader investigation of how reasoning with cases functions within the biological/biomedical sciences, this article unpacks a particular use of cases within developmental biology, namely, as a means of describing the typical or canonical patterns of phenomena. Why choose developmental biology for this exploration of cases? Cases seem to have strong resonance in those scientific domains in which variation is rife, or at least is relevant to the research questions under examination and is of interest to practitioners, and developmental biology clearly fits this description.

The article thus explores how certain cases have come to be established as central or critical within developmental biology.[5] They involve in-depth, often extremely descriptive studies of some type of delimited unit (usually a particular strain of a species) with the goal of eventually elucidating norms or baseline patterns against which newly observed yet similar phenomena (e.g., in other species) can be compared.[6] I argue that although these cases were initially selected for reasons of convenience or ease of experimental manipulation (among other reasons that might be viewed as nonsystematic or even nonscientific), they come to serve as key reference points within the field because of the epistemological structures imposed on them by the scientists

2. Compare, e.g., Ragin and Becker (1992), Yin (1994), Gerring (2004), and George and Bennett (2005), to name but a few standard sources within the voluminous literature.

3. In my view, 'theory development' is given too high a status as the imprimatur of scientific maturity more generally, but examination of these issues is beyond the scope of this article.

4. On the distinction between cases and case studies, see Morgan (2012). Discussions of cases in other areas of science but not development biology in particular include Forrester (1996), Ankeny (2005, 2011), Creager, Lunbeck, and Wise (2007), and Gabbani (2010), and in history and philosophy of science, Burian (2001) and Lennox (2011). For a related discussion on 'types' in developmental biology, see DiTeresi (2010).

5. The examples have been selected to raise a diversity of issues relating to the use of cases and are not intended to be historically representative of the field in any sense.

6. Note the similarity of this description to Gerring's definition of a case study in political science: "in-depth study of a single unit (a relatively bounded phenomenon) where the scholar's aim is to elucidate features of a larger class of similar phenomena" (2004, 341).

who discover or propose them and, hence, become usable in a wider variety of circumstances including future theory development.[7] In some instances, a case becomes recognized as such because of its typicality, and other examples show that atypical examples sometimes come to be established (and maintained by practitioners within the field) as cases.

But why bother to analyze these reasoning structures in terms of cases? Are these not just Kuhn's well-worn 'exemplars' in a different guise? When Kuhn introduced this concept in his postscript to the second edition of *Structure* (1970), he stressed that in substituting it for 'paradigm', he meant it to refer to "the concrete problem-solutions that students encounter from the start of their scientific education, whether in laboratories, on examinations, or at the ends of chapters in science texts" (187). Hence, there are two obvious differences between the developmental biology cases that I propose to examine and Kuhnian 'exemplars': first, I have not selected these examples because of their retrospective, pedagogical significance, although they may indeed later serve this purpose; however, even in these cases they simultaneously provide a baseline or norm for both nonexpert users such as students and professionals in the field pursuing further lines of research.[8] More importantly, although cases in developmental biology are concrete (perhaps in a wetter and more visceral way than Kuhn imagined in his examples of inclined planes and calorimeters), they cannot be easily viewed as 'problem-solutions', not in the least part because they are often not proposed in response to a specific puzzle or problem of the type envisioned by Kuhn. Instead, as will be shown, cases in developmental biology are often highly detailed and descriptive, establishing themes (as it were) that can be used as the basis for articulating variations and, hence, are ampliative in intent.[9]

2. The Chicken as a (Classic) Case of Developmental Anatomy. The chicken (*Gallus gallus*) has been used as the basis for studying development from ancient times. The so-called laws or principles put forward by Karl Ernst von Baer in the late 1820s (1828–37), which are probably more appro-

7. This line of argument is similar to that made with regard to the use of organisms as 'model organisms' in twentieth-century biology (on developmental biology, the key reference is Bolker [1995]; see also Gest 1995); see Ankeny and Leonelli (2011) for a philosophically oriented analysis.

8. Both for simplicity and to document that these are indeed shared cases as recognized by practitioners in the field, I sometimes use examples taken from the most recent editions of textbooks typically viewed as the standards within the field (e.g., Gilbert 2010; Wolpert et al. 2011) as well as contemporary review articles in the scholarly research literature of the field, at the same time as providing historical context for the origins of these cases.

9. I am grateful to Eli Gerson for this term; for a related discussion on the use of 'descriptive' models in biology, see Ankeny (2000).

priately considered to be generalizations about developmental patterns, were initially derived from chick development in comparison with other vertebrates: for instance, early embryos have more similar structures and features early in development, as general features tend to appear first, and then divergence occurs as development progresses and more specialized features develop. These patterns (few would still call them 'laws') continue to be presented as in some sense 'elements of the truth' (e.g., Arthur 2002, 757), but it has been shown that they hold more precisely for comparisons made among organisms with approximately the same level of phenotypic complexity, such as different vertebrate classes. However, by examining a wider range of vertebrate species, it also has been shown that there is much more variation in these developmental patterns than previously recognized or described.[10]

Of course this finding should not come as a surprise, given that the chicken was clearly selected for convenience and ease of experimentation (e.g., embryonic observations can be made by making a window in the eggshell, and chick embryos are robust even when surgically manipulated) rather than any indication that its development was 'typical' in any sense. From a strictly biological point of view, the chick easily could be argued to be marginal to tracing evolution of development, which illustrates a more general trend: "modern textbooks [in developmental biology] rarely consider species other than the common laboratory animals. . . . Developmental biologists use just a small number of laboratory species as model systems, and are therefore unfamiliar with the diversity of embryonic form in vertebrates" (Richardson et al. 1997, 93, 95; cf. Bolker 1995).

Nonetheless the chicken has served (and continues to serve) as a key case or anchor point for much ongoing developmental research into the variations on developmental themes: even (and especially) those investigations that seek to refute or complicate von Baer's principles go back to the chicken as part of any extensive comparative examination. In addition, due in part to the inclusion of the chicken genome in large-scale sequencing projects, it has become a modern 'model organism' that continues to be used in research on general vertebrate development.[11] Along with perhaps lancelets (*amphioxus*), sea urchins, and the frog (see below), the chicken remains a key case in developmental biology, in large part due to its historical importance in the processes of articulating principles of development.

10. See, e.g., Richardson et al. (1997); on the chicken in particular in comparison to other vertebrates, see table 3, 103.

11. Use of chicken models is more limited than some other model organisms for various biological and technical reasons; for a review of one type of developmental research using chickens, and the rationalization of it as a model for vertebrates, see, e.g., Tickle (2004).

3. The Frog as a Case of the Life Cycle. One of the centerpieces of developmental biology has been the articulation of the processes by which a fertilized zygote develops into an adult organism, and these processes are typically articulated by division into a temporal series of what are sometimes termed 'fundamental' events or transitions in the life cycle: fertilization, cleavage, gastrulation, organogenesis, metamorphosis, and gametogenesis.[12] These events occur in some form in all members of a species and indeed can be projected beyond a particular species to others, although the ways in which the development events occur might differ considerably.[13]

The articulation of the developmental stages of 'the frog' (by which is usually meant the African clawed frog *Xenopus laevis*) is often presented in textbooks as the classic case of the life cycle within descriptive embryology, involving the six main processes outlined above. The frog often is claimed to provide an example of a 'representative' life cycle that can be generalized to other species of frog and even to other taxa. Then on the basis of this standard case or instance, variations are detailed, so, for instance, gametogenesis begins at different times during development, depending on the species; fertilization methods differ (in some species fertilization occurs externally rather than internally); and so on.

Metamorphosis also is often illustrated using a 'generic' frog; the abstract description of this life stage typically makes note of the status of frogs as one of the classic cases providing the baseline or the typical features in comparison to which the variant forms that this process takes can be articulated. As a multiauthored article investigating the concept in its comparative context noted, metamorphosis is "[a] biological process generally attributed to a subset of animals: most famously insects and amphibians . . . (think caterpillar to butterfly)" (Bishop et al. 2006, 655). Since metamorphosis is a process shared across these types of organisms, the specific species is not important to define when talking about the generic case.

However, beyond very widespread consensus about these classic cases of metamorphosis, there has been limited agreement on how to understand the range of variations of the process, for instance, whether the term 'metamorphosis' can rightly be applied to nonanimals such as fungi, flowering plants, and marine algae (Bishop et al. 2006, 655). The obvious response is that it depends on how 'metamorphosis' is defined, but this debate is not

12. In some species, these stages are given numbers or other designators, as in the standardized stages of development of the chick embryo dating back to, e.g., Hamburger and Hamilton (1951), but the basic processes remain the same, which is the key point necessary for my argument.

13. For a survey of these issues and their philosophical implications, see Love (2008).

directly relevant for this article.[14] What is critical is that several species of frog are repeatedly invoked as the classic example of metamorphosis (along with sea urchins, butterflies, and *Drosophila*) and are used as the basis for seeking 'deep mechanistic similarities' among independently evolved life cycle transitions.

A second key point to note is that although articulation of various developmental stages obviously involves judgments about typicality (i.e., what makes something a case of metamorphosis), in contrast the details of the processes of metamorphosis sometimes provide cases of atypicality. So during metamorphosis in *Xenopus*, the eyes move to the front of the head from their previous location on the side, and new neuronal pathways are formed, allowing input from both eyes to reach the same area of the brain, a process that is typical in frogs (Cannatella and de Sa 1993). These pathways involve not just the remodeling of existing neurons but formation of new neurons that differentiate in response to thyroid hormones. This finding can be used as the basis for investigations about these processes in other organisms, so mammals have the same proteins in the optic chiasm (but fish and birds do not). This latter variation does not in any sense invalidate the use of *Xenopus* or even the generic frog as a classic case of metamorphosis but instead provides a structure for understanding what is critical or essential to terming some life stage 'metamorphosis' and what can be deemed a 'variation on the theme'.[15]

4. The Insect as a Case of Diapause. Diapause involves the suspension of development for some time period (a sort of developmental hibernation or 'suspended animation'), and in insects it can occur in the embryonic, larval, pupal, or adult stage, depending on the species. Examples include the overwintering of eggs by hickory aphids in early development, by the silkworm moth (*Bombyx mori*) as an embryo, or by the gypsy moth (*Lymantria dispar*) as a larva.[16] These dramatic developmental delays typically are not physio-

14. See Bishop et al. (2006) for one set of answers from practitioners about the key elements of metamorphosis, noting the range of arguments and understandings among even this small (but diverse) group of scientists. These biologists work on a range of organisms, which in turn influences their understandings of the concept and what is held to be the underlying 'generic' case, particularly because of critical differences between organisms that change their body plan organization, such as insects and those that do not (e.g., many marine invertebrates). I am grateful to Alan Love for raising this point, but I do not have space to explore this issue here.

15. As noted previously, what counts as the classic case and what then becomes a variation have been decisions loaded with historical contingency: for implications of this point for developmental biology, see esp. Bolker (1995).

16. A classic article is Andrewartha (1952); for general background, see review articles by Tauber and Tauber (1976), Kostal (2006), and Denlinger (2008).

logical responses but are induced by stimuli or early cues that come in advance of environmental changes. They allow the organism to survive episodic harsh conditions to cope with seasonally fluctuating resources and are common among species in habitats that undergo severe winters. Diapause is facultative in some species, occurring only when induced by environmental conditions, while the diapause period has become an obligatory part of the life cycles in other species.

Cases of diapause in insects allowed articulation of the general concepts now associated with diapause: (1) it is a dynamic, not static, state; (2) length of daylight and temperature are the major environmental factors that help to maintain diapauses; (3) although these factors are regulatory, few species require specific stimuli to break diapauses; (4) interspecies variation occurs with regard to the specifics of the processes; and (5) within species, there is considerable interpopulation and intrapopulation variation in the duration of diapause. Over 100 mammalian species undergo diapause in different forms, with common strategies including delayed fertilization with storage of sperm for later use and delayed implantation of the blastocyst.[17] Diapause in mammals is induced and broken with the specific control mechanisms varying widely from lactational to seasonal cues, various sorts of hormones, or changes in length of day or nutrition. Even though the mechanisms differ, the basic format is the same: the gestation period is lengthened, and offspring are born at more appropriate times (in the case of marsupials, e.g., when there is not a newborn still nursing), in more hospitable seasons, or when resources or conditions otherwise improve.

Several points can be made about the way in which insects have served as the key case for understanding the category of diverse events grouped under 'diapause'. First, the term clearly has been extended from insects to describe a very wide range of loosely related phenomena that in short are instances of dramatic developmental delays, but of course embryonic diapauses of the types that occur in mammals do not occur in insects. In addition, diapause has evolved independently in a number of different species (Renfree and Shaw 2000). Hence in this example, insects as 'cases' of diapause likely are not pointing to shared underlying genetic mechanisms but instead to other sorts of physiological patterns in relation to ecological and environmental facts.

Second, the classic cases of diapause in insects that have been well studied are not associated with the typical model organisms, notably *Drosophila*, which does not undergo very impressive diapause (it requires quite low temperatures near the developmental threshold for diapause to occur; see Saunders, Henrich, and Gilbert 1989). However, more recently, it might be argued

17. A useful review article on diapauses in mammals is Renfree and Shaw (2000).

that the traditional focus on insects has been displaced by the study of diapause in the dauer larval stage of the nematode *Caenorhabiditis elegans* (Cassada and Russell 1975), especially because its genetic mechanisms can be characterized much more easily and because of its status as a model organism.[18] For our purposes, the key point is that what serves as a baseline or case in a particular context is often dictated by a range of historical and biological contingencies and differs depending on the question or developmental theme of interest.[19]

5. The Nematode as a Case of Programmed Cell Death. 'Cell suicide', or more formally programmed cell death (PCD) or apoptosis, is a normal developmental process required to maintain the appropriate number of cells: it is responsible for 'pruning' unnecessary structures such as the tails of frogs or mammary tissue in males), the formation of complex organs (e.g., fingers where interdigital cell death allows their separation), and more generally controlling the number of cells present in particular tissue types (e.g., the nervous system in vertebrates).[20] One of the pathways for apoptosis was first described in the nematode *C. elegans*. It was demonstrated that 131 cells die reproducibly (and 959 somatic cells come from the egg), and the process is controlled by a unique set of genes (Moyed Ellis and Horvitz 1986). These findings allowed related genes with similar functions in *Drosophila* and humans to be identified; although the apoptotic pathway is much more complex in mammals, it uses the same basic components, and one of the signaling pathways is evolutionarily well conserved even in the plant kingdom (see Solomon et al. 1999).

In the example of *C. elegans* as a case of PCD, again experimental simplicity (in this case particularly the small number of cells, their ease of visualization, and their invariant lineage) and historical contingency (De Chadarevian 1998; Ankeny 2001) were critical features that allowed it to become established and canonical. It is the centerpiece of nearly all textbook discussions and most research papers on PCD that provide any historical background before presentation of their findings, regardless of whether an explicit comparison within the research is being made to findings in *C. elegans*.

18. I am grateful to Alan Love for emphasizing this.

19. However, some researchers have noted that the lack of use of insect model organisms has hindered progress in the field, particularly for articulating underlying genetic or molecular mechanisms of diapause (e.g., Denlinger 2008).

20. The best general text on the topic is Green (2011); for early use of the term 'programmed cell death', see Lockshin and Williams (1964); and from a clinical point of view, see Hotchkiss et al. (2009).

6. Discussion and Conclusion. So what is a case in developmental biology, and what purposes does it serve? The (admittedly extremely limited) examples clearly illustrate that many cases come to be identified as such because of their historic primacy or importance, and often the data or information that were generated from these cases resulted from the ease of experimental tractability, manipulability, or similarity provided by the organism in question in relation to the process or issue under examination. This point highlights a fundamental difference between these cases and model organisms more generally: not all of the cases discussed above are used for wider-scale examinations into developmental or genetic processes, as is the basis for modern model organism research.[21] Oftentimes they serve as a focal point within the field (a baseline 'theme') against which additional examples ('variations') can be articulated but only with regard to a narrowly defined topic of interest, such as a particular developmental stage or phenomenon. These cases, hence, are similar to what social scientists call 'critical cases', which allow generalizations and projection to other instances involving the same or similar phenomena. They provide a key part of the solution to the practical and coordinative problem of 'taming variation' (DiTeresi 2010) in the phenomena of interest.

Second, the cases explored above show that important trade-offs exist between typical and atypical cases. Most of the examples discussed were initially used in the field as 'typical cases' (if only by default because more information was available about them than other examples) and hence served as touchstones for the field as it continued to develop. However, as research progressed on similar phenomena in different species, it became clear that some of these cases were in fact atypical, extreme, or marginal in some way, but yet the original cases continued to provide critical information because they permitted investigation of variations in phenomena or processes that had been identified or even defined by use of the case in the first instance.[22]

What is the epistemological 'payoff' of thinking in cases in this domain? Here, returning to the literature on cases in the social sciences is again useful: Gerring notes that "the case study method is correctly understood as a particular way of defining cases, not a way of analyzing cases or a way of modeling causal relations" (2004, 341). As we have seen in the examples above, there is no one way in which the cases are analyzed, nor are there uniform causal models underlying them (indeed, they are relatively devoid of claims

21. See Ankeny and Leonelli (2011) for an expansion of this point with regard to the distinction between experimental organisms and model organisms.

22. Because of space limitations, I do not explore the implications of these issues in terms of the philosophical literature on the uses (and limits) of idealization and abstraction; some important issues are raised relating to idealization in this domain by Love (2009, 2010) among others.

about causal relations, at least in the earliest stages of their use). Instead, as this article has attempted to show, these cases exist at a fairly early stage (not temporally, but in terms of a chain of reasoning) in the practices of developmental biology, and a critical move occurs each time one of them is explicitly defined or implicitly used as a case.

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