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Studying Physiological Development: Past, Present and Future

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ABSTRACT

The study of physiological development is an old, even ancient, one. Yet, there exists but a scant conceptual framework within which to use modern technology and theory to pursue studies of physiological development. This review paper will explore a variety of concepts, including developmental trajectories, critical windows, variable rates of organ system development, form/function relationships, genetic/maternal effects and animal models for studying physiological development. Consideration of these concepts in future studies of developmental physiology (indeed, all studies of development at the organismal level) will help provide a greater understanding of how animals progress from egg to adult.

Key words: Development, Physiology, Developmental trajectory, Critical window

History and Transition of the Study of Physiological Development

Almost from the beginning of recorded history, philosophers and pioneering scientists have written of physiological changes during development. As but one example, the rate of beating of the pulsating red spot (the heart, of course) that can be seen upon opening a recently laid, fertile chicken egg has been recorded by Aristotle, Socrates, Vesalius and Galileo. However, as we take stock at the beginning of a new millenium, we see that the study of physiological development has been overshadowed by two other major areas of ontogenetic research. One the one hand, there is the long-standing, rich literature on morphological changes during development –i.e., the study of embryology– dominated by the European (and especially German) literature of the nineteenth century. On the other hand, many recent, ongoing studies at the cellular and molecular level have probed how complex organs and organ systems grow from presumptive embryonic tissue, how neurons find their target tissues, how endocrine receptors appear and are modified over time, etc... Ironically, the vital study of physiological development –that is, how developing animals function as independent entities– has lagged far behind structural and molecular studies.

Though physiological developmental studies are relatively few in number, we are beginning to see a distinct transition in this

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burgeoning field. Up until about the end of the 1980's or so, experiments in physiological development consisted primarily of descriptive studies, asking questions such as "*What is the heart rate of a bird embryo on Day 8 of incubation?*", or "*How does the oxygen hemoglobin affinity change during development in the frog tadpole?*". The study of any biological discipline must necessarily begin with a lengthy descriptive phase in which the basic variables and their normal ranges are outlined. Evidence of the maturation of a discipline becomes apparent, however, when what was the publishable experiment of ten years ago becomes merely today's basic preparation necessary prior to carrying out the designed experiment. Indeed, beginning in the late 1980's, there has been an increasing tendency for true experimentation in physiological development, designed to answer a new set of more detailed questions such as "*How does the heart rate of a bird embryo become regulated with growth from Day 5 to Day 10*" and "*By what mechanism is blood oxygen affinity regulated during development of the frog tadpole?*". The questions emerging from physiological studies of development are now being answered by active experimental perturbation of the systems being studied (e.g. pharmacological manipulation, neural stimulation, environmental disturbance, induced activity), rather than by the previous, more passive approach of "simply" instrumenting an embryo or larvae and recording the resultant values. While there is doubtlessly a great deal of important descriptive work to be done on the many unstudied species and organ systems about which we know so little, I predict that the next 10-20 years will see increase use of a true experimental, hypothesis-driven approach to answering the pressing questions in developmental physiology.

The Concept of Developmental Trajectory

The concept of "developmental trajectory" is demonstrating its utility in shaping developmental physiological studies (Burggren and Fritsche, 1997; Burggren, 1999). Let us consider an analogy in which the developing embryo is likened to a missile siting on its launch pad. The flight path of the missile is pre-programmed, taking into account the ballistic properties of the missile. By analogy, the developmental events of the embryo are pre-programmed by instructions for growth and development coded in the genes of the animal's DNA. Once a missile is launched, a number of variables (e.g. prevailing winds, the amount of fuel carried by the missile, atmospheric density) can subtley or profoundly alter its trajectory pre-programmed flight path en route to its target. Similarly, the genetically programmed developmental trajectory of a fertilized animal egg can be altered by a number of factors. These factors can be either abiotic (environmental temperature, oxygenation, pH) or biotic (nutritional reserves, predation, competition). Like the missile deflected to a new landing site away from its targeted landing

site, the developmental trajectory of a growing embryo can be deflected during development, leading to a phenotype that differs from the phenotype predicted strictly from the genotype.

The concept of developmental trajectory can be illustrated more concretely by considering possible trajectories in the transition from egg to adult (Figure 1). In this schematic, three developmental scenarios are shown. In the upper panel, a fertilized egg follows a genetically dictated developmental trajectory (T1) unperturbed by environmental factor, ending with the formation of an adult Phenotype 1. The middle panel depicts a scenario in which the normal T1 trajectory is interrupted by a significant biotic or abiotic environmental perturbation. Two categories of outcome can arise. In the most extreme case, the disturbance disrupts development to the point of causing the death of the embryo. However, a less extreme perturbation will cause embryonic development to proceed along a new trajectory, T2, leading ultimately to an adult Phenotype 2 that differs from that produced by T1. The bottom panel shows yet another scenario, in which the environmental perturbation causes the embryo to move from T1 to T2, but unlike in the previous situation, this scenario shows the possible effects of subsequent removal of the environmental perturbation part way through development. In one case, the organism continues to develop along T2 until the adult Phenotype 2 is reached. In other words, once the embryo is pushed to T2, development continues unalterably along that trajectory. In an alternative situation,

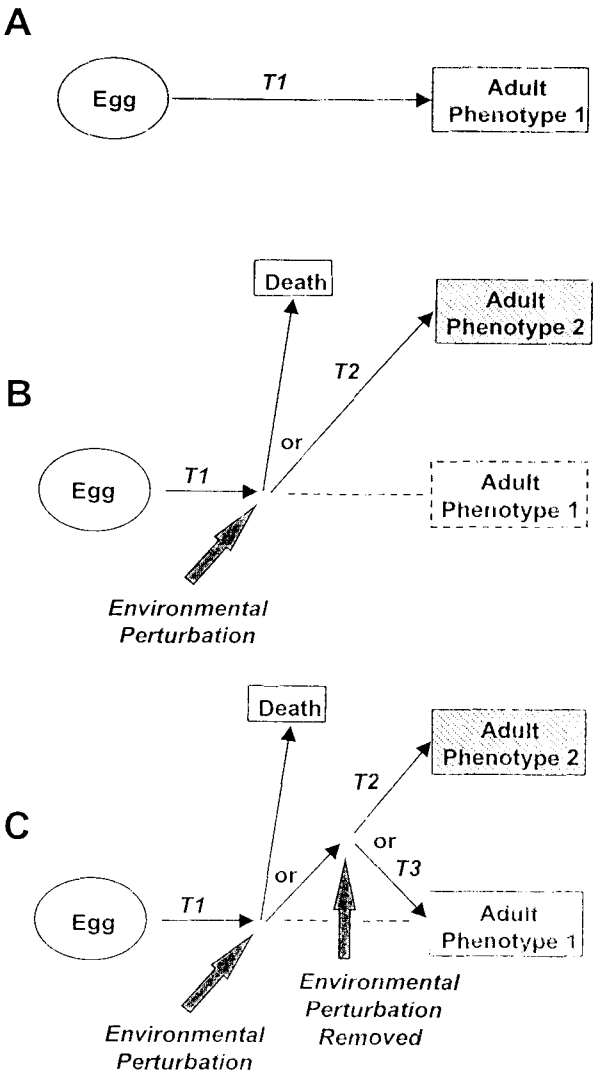

Figure 1. The concept of developmental trajectory and its potential modification by environment. A). The normal (undisturbed) trajectory 1 (*T1*) leading from fertilized egg to adult. B). Possible modifications of trajectory 1 by environmental perturbation leading to death or, in less severe cases, trajectory 2 (*T2*). C) Additional modifications of the scenario depicted in B), in which the environmental perturbation lasts for a discrete time period, after which the animal may remain on *T2*, or revert back to the originally intended adult phenotype via trajectory *T3*. (From Burggren and Fritsche, 1997).

however, removal of the environmental perturbation causes the animal to assume a third trajectory, T3, which reflects a "self-

correction" that results in the formation of the adult Phenotype 1. As described in Burggren and Fritsche (1997), tangible examples of all three scenarios are to be found in respiratory and cardiovascular studies on developing vertebrates. For example, both lung volume and an index of lung surface area increase to enhance gas exchange during chronic hypoxia in developing bullfrog larvae (Burggren and Mwalukoma, 1983; Pinder and Burggren, 1983). These changes persist as long as hypoxia persists, but some of these variables were actually reversed upon return to normoxic conditions (Pinder, 1985). This reversal produced a normal adult phenotype, illustrating the complex developmental pathway of T1 → T2 → T3 → normal phenotype.

In summary, the analogy of the developing embryo as an in-flight missile whose trajectory can be perturbed by environment is useful in providing a conceptual framework that can allows us to understand in rather straight-forward terms how abiotic and biotic factors can influence the developmental trajectories of not just the whole organism, but also individual organ systems.

Multivariate Interactions During Ontogeny

Building upon the concept of environmentally altered developmental trajectories, it is important to recognize that environment can not influence the *trajectory* of a developing organism, but it can also alter the *rate* at which that organism progresses along any given trajectory. That is, there are multivariate interactions between developmental stage, environment and time that influence the adult phenotype and how long it has taken to reach that phenotype. These interactions can greatly confound the developmental process, and our attempts to describe and understand it. To illustrate this, consider the interactions between a variable of interest (e.g. heart rate, lung size, gut architecture, etc.), the developmental stage of an animal, the time it takes to get to that developmental stage, and finally the environmental perturbation (in this case, environmental temperature at which development occurs) (Figure 2). Almost all organisms have a temperature-dependent rate of development. This graph depicts the development of an organism at either a cool or warm temperature. In comparison with being raised in a cool temperature, an organism raised in a warm temperature will develop more rapidly, both in terms of the developmental stage at any given time as well as the amount of time that it took to reach that developmental stage. Additionally, in the warm-reared organism the variable of interest –say, lung size– will be higher at any given point because of the effect of temperature on growth. The net result is that a warm-reared animal demonstrates not only a quite different developmental trajectory, but also a different vector describing the magnitude of the interacting variables.

Examples of multivariate interactions abound in developmental physiology. Illustrating the complex interactions that can arise

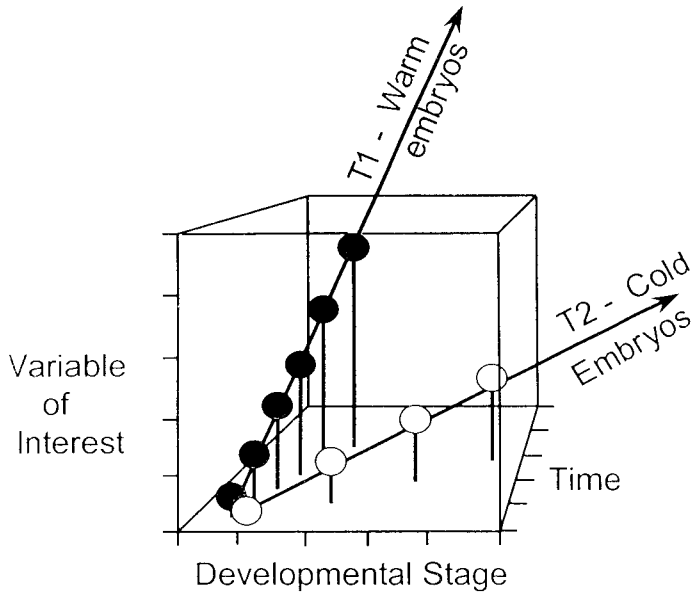

Figure 2. Interactions of temperature, developmental stage, time and growth in a hypothetical organism. Trajectory 1 (T1) indicates the developmental path taken by warm reared embryos, while trajectory 2 (T2) shows that taken for cold reared embryos. For a given period of time, warm embryos typically pass through more stages, and grow larger, than cold acclimated animals.

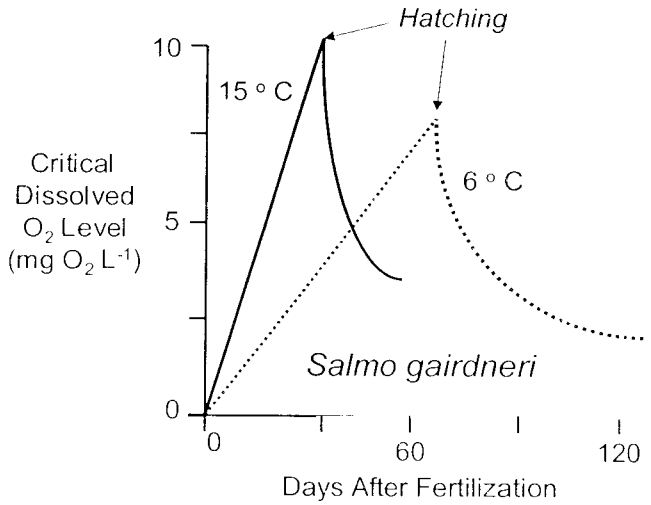

Figure 3. The influence of temperature on the critical oxygen level in the steelhead, *Salmo gairdneri*. (modified from Rombough, 1988).

when both temperature and oxygen are allowed to influence development, consider the interactions development of the steelhead, *Salmo gairdneri*. Figure 3 shows how temperature and oxygen interact to influence the critical oxygen level (the oxygen level at which the embryos become unable to maintain oxygen consumption at normoxic oxygen levels), as well as the rate of development of the embryos (after Rombough, 1988). At 6°C, the critical oxygen level is about 8 mg O_2 l^{-1} at hatching, which takes place at 25-30 days postfertilization. At 12 °C, however, the critical oxygen level rises to 10 mg O_2 l^{-1} at hatching (that is, the embryos are less tolerant of hypoxia), and the time required to develop to the point of hatching has doubled to approximately 60 days postfertilization. The developmental trajectories of these two fish populations have been modified in complex ways that may actually affect their relative fitness. This example, and many others like it, illustrate that multivariate interactions during development can result in profound developmental differences over time that must be either controlled for or carefully documented, but not ignored.

Critical Windows: A Basic Tenet of Development

Implicit in a consideration of developmental trajectories and the influence of environment upon them is the notion that developing embryos and their particular organ systems have developmental phases where they

are more or less sensitive to environmental change. In fact, a basic tenet of developmental biology is that every organ and organ system (and thus, by extension, every organism) has a "critical window" in which it is most susceptible to experiencing unalterable developmental change – that is, most susceptible to being put onto T2 leading to a different adult phenotype (middle panel, Figure 2). Probably most of what we know about critical windows in development comes from correlational studies between changes in embryonic/fetal environment and birth defects in humans. Thus, we know for humans for example, that the critical windows for major morphological abnormalities for the CNS, heart, upper limbs, eyes and teeth are 3-16 weeks, 3.5-6.5 weeks, 4-7 weeks, 4.5-8.5 weeks and 7-9 weeks, respectively. In some cases, the precise causes for abnormalities in these systems are not know. In other cases, however, exposure to a teratogenic factor such as retinoic acid can have such precise and predictable effects that it can be used as an experimental tool in animal models (Gittenberger-de Groot and Poelmann, 1997)

Recognizing the existence of critical windows is one thing, but actually delineating them for a discrete organ system is quite another. While the design of experiments to map out critical windows, say, the influence of hypoxia on heart size at birth in a chicken embryo, are fairly straight forward, practically speaking such experiments are long, tedious, and require dozens if not hundreds of animals. The design of such a "crossover experiment", as we have called them, is indicated in Figure 4A. Three (or more!) populations of developing animals are maintained in normoxia, hyperoxia and hypoxia. At a precise point in development, sub-populations of embryos are switched ("crossed over") from one oxygen condition to the two others. Following development to hatching, each sub-population is sampled to determine if changes in heart mass have occurred during embryonic development. Figure 4A basically shows just one iteration of this experiment which would indicate whether the time in which the crossover occurred actually fell within the critical window for oxygen effects on heart mass. In practice, this experiment has to be replicated so that multiple crossovers occur at regular intervals during development. In Figure 4B, a critical window at interval 3, for example, would only be revealed by showing no effect in the preceding interval 2 and the following interval 4. To try to delineate between one of four critical windows in development, using three environmental conditions, and sampling ten animals at each juncture, would require at least 280 embryos at the outset of the experiment! Consequently, it is hardly surprising that few, if any, such experiments specifically to delineate critical windows have been conducted, particularly in the realm of lower vertebrates and/or physiology. Nonetheless, increased emphasis on the study of critical windows will surely be needed to truly understand the interactions of environment and morphological or physiological development.

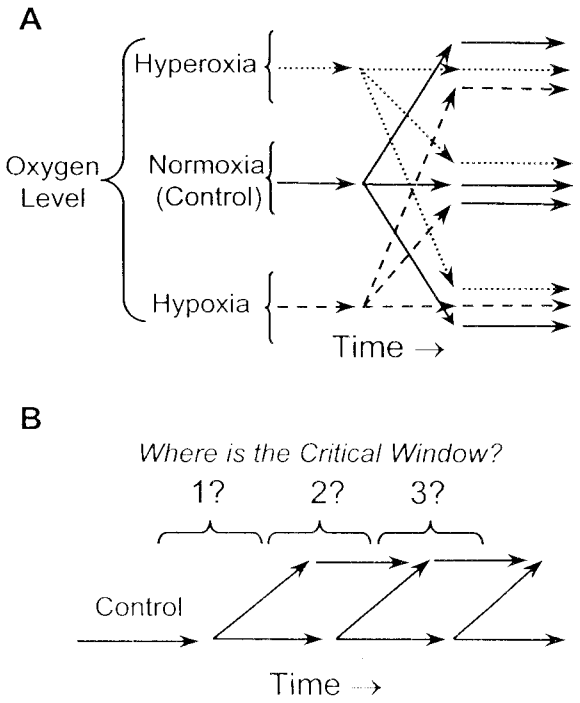

Figure 4. An experimental design for determining the critical window for development of a given physiological or morphological trait. A). This experiment is set up to determine the critical window at which the trait of interest is altered by environmental oxygen levels. Populations that were developing at controlled levels of oxygen are switched ("crossed over") from one oxygen level to another, and their development subsequently monitored to see if the variable of interest was altered by the change in oxygen levels at the indicated time. B). To delineate the critical window(s), a series of crossovers must be carried out at regular time intervals. This figure shows a subset of the necessary crossovers outlined in part A) required to determine the effects on the variable of interest of an increase in oxygenation at various points in development. Full delineation of the critical windows requires numerous crossovers by large numbers of sub-populations drawn from the initial population. See text for additional details.

Accelerated Organ System Development

Evolutionary biologists have long recognized that species diversity arises in part through heterochrony – evolutionary change in the rate of development of tissues, organs and organs systems (Gould, 1977). While the concept of heterochrony was meant to apply to evolutionary change, theoretical aspects drawn from the ideas underlying heterochrony are very useful in viewing how organ system development may change on the time scale of the development of a single individual. Could specific environmental perturbations induce specific organ systems to accelerate in growth and development? We can imagine numerous situations where "heterochronic growth" within an individual's lifespan could convey superior fitness in that individual. Imagine, for example, a bimodal breather such as an air-breathing fish or a typical anuran amphibian that begins life as a strictly water breather but at some point in development makes the transition to breathing air with a specialized aerial gas exchange organ (e.g. lungs). Early in development, severe aquatic hypoxia can represent a serious threat that could affect further growth and lead to altered adult phenotype at best, or could kill the developing animal at worst. However, almost all hypoxic aquatic environments come into contact with O_2-rich air, which represents a potential "escape" from aquatic hypoxia if the animal can use its air breathing organs for gas exchange. Acceleration of the necessary morphology (e.g. lungs) and physiology (e.g. development of pulmonary blood flow) for air breathing in an amphibious animal could provide a trajectory allowing escape from the potentially serious consequence of aquatic hypoxia. Similarly, accelerated development of

the kidneys could aid in combating ionic challenges presented by the environment, while accelerated digestive tract changes could aid in combating inadequate or inappropriate food sources. Indeed, evidence for such "developmental heterochrony" exists in the ambystomid salamander *Ambystoma tigrinum*. A small proportion (<15%) of tiger salamander larvae from a population occupying a deteriorating, increasingly crowded environment characteristic of ephemeral ponds and marshes, for example, will spontaneously turn into cannibalistic morphs complete with larger jaws, enlarged vomerine teeth, and accelerated growth rates (Lannoo and Bachmann, 1984). Assuming metamorphosis is at least in part size-dependent, these cannibalistic larval morphs should be more likely to survive in aquatic habitats that are shrinking and drying out.

Environmentally induced changes in the rate of certain tissues, organs or organ systems may not only contribute to the survivorship of individuals in populations, but it may also lead to developmental mosaics, especially in those species with sharp demarcations between embryonic, larval/fetal and adult morphologies. Returning to our example of an animal with accelerated lungs for escaping aquatic hypoxia, the resulting animal may be a mosaic of adult features (i.e. lungs), and more typical larval features (e.g. immaturity of limb musculature for terrestrial locomotion as opposed to swimming). That is, because only certain organ systems may be stimulated by environment, the animal may show certain organs that are accelerated, others that are on par for normal development, and still others that may be delayed in growth, particularly if the accelerated growth of certain organs occurs at the expense of others.

Unlike the major challenge of documenting critical windows, the task of showing accelerated organ system development should be quite straight forward and, indeed, experiments are underway in our laboratory to test the hypothesis that aquatic larvae can escape aquatic hypoxia by accelerating air breathing capabilities.

Form/Function Relationships

Understanding physiological development of necessity requires a deep exploration of form/function relationships – that is, of how physiological processes derive from anatomical structures. Intriguingly, the perspective of physiologists can differ from that of anatomists on this issue (see Burggren and Bemis, 1990). While anatomists hold fast to the notion that form very strictly dictates function, some physiologists (particular *comparative* physiologists) view form/function interrelationships as much more loosely defined. As just one example, consider the role of the walking legs in the crab *Scopimera inflata* (Maitland, 1986). In typical decapod crustaceans, the limbs are covered in a thick, chitinous exoskeleton that confers rigidity to the legs and, along with the underlying muscular and connective tissue, creates a typical Arthropod organ for

locomotion. In *Scopimera*, the walking legs are still used for locomotion. However, the dorsal surface of the walking legs contains a small oval region where the cuticle is much thinner than at other regions of the exoskeleton. Combined with a rich underlying flow of hemolymph, these structural modifications create a "gas exchange window" across which the majority of oxygen uptake occurs. In answering the question "are form and function tightly related in *Scopimera*"?, one can see that a minor modification of a structure - thinning of the cuticle - creates a major shift in function from solely locomotion -> locomotion + gas exchange! Examples of the loose relationship between form and function abound. To give just two, consider leg feathers of tropical buzzards acting as urine-soaked evaporative coolers, and the thin membranes on the wings of bats carrying out gas exchange.

Understanding how the physiology and anatomy of organ systems interrelates is particularly important in understanding how form/function relationships arise in the developing embryo and, importantly, how these relationships change during subsequent development of the animal. Because form and function may not only be quite loosely related, but also change profoundly during development, developmental physiologists cannot automatically interpolate findings in adults back to early developmental stages. To put it succinctly, embryos are not merely small adults! To illustrate this, consider the role of the heart in the early embryo. Interpolating back from adults, we are inclined to conclude that the heart of embryos beats to create a convective delivery of nutrients and hormones and removal of waste products. However, recent experiments have shown that the convective delivery of oxygen in blood propelled by the heart is not required for oxygen consumption and growth in vertebrates as taxonomically diverse (and representative) as the zebrafish *Danio rerio* (Pelster and Burggren, 1996), the frog *Xenopus laevis* (Burggren and Territo, 1985; Territo and Burggren, 1998), and the chicken *Gallus domesticus* (Warburton *et al.*, 1996). Indeed, an embryo of the salamander *Ambystoma tigrinum* will develop into a freely swimming larva even after surgical removal of its presumptive heart tissue (Mellish *et al.*, 1994)! Why does the heart beat, then? We believe that, in fact, the heart begins to beat to aid in the process of peripheral angiogenesis by providing a "pressure wedge" of blood that both mechanically extends the lumen of peripheral vessels and contributes to endothelial cell proliferation through sheer and strain on the endothelial cells lining forming vessels. These data, showing that the embryonic vertebrate heart is not primarily involved in transport functions, collectively indicate that at least for the form/function relationships of the heart we cannot simply assume that the same physiological processes that spring from embryonic structures will spring from juvenile or adult structures.

Maternal Effects in Developmental Physiology

Recent studies on the cardiovascular physiology of developing birds (Burggren, Tazawa and Thompson, 1994) and amphibians (Burggren, Crossley, Rogowitz and Thompson, 1997) have revealed that the developmental trajectories for heart rate are much more similar in siblings than in non-siblings. This "clutch" or "sibling" effect is most likely explained by assuming that even aspects of physiological development such as heart rate at a specific point in development are genetically regulated. However, an emerging consideration in the interpretation of developmental events in embryos is to what extent observed developmental patterns reflect "maternal effects" rather than, or in addition to, the genetic blueprint for that organism's adult phenotype. Maternal effects are effects on a developing embryo caused by processes or behaviors of the mother that influence the resultant developmental trajectory of her offspring (see Bernardo, 1996, and other articles in American Zoologist, Vol. #, 1996; Burggren, 1999 for additional information on maternal effects). Examples are Fetal Alcohol Syndrome in human infants whose mother consumed alcohol during a critical window for nervous system development, thinning egg shells in birds whose mothers were exposed to DDT, and modification of embryo size by the relative amount of egg yolk deposited in the egg at time of laying. As J. Bernardo (1996) comments, "Maternal effects contribute complexity to phenotypes, as well as to biologists' attempts to analyze phenotypes". In the context of studying physiological development, we are sometimes left to ponder whether an observed pattern of physiological development is the result of genetically dictated trajectories, or are influenced by maternal effects that alter the ultimate adult phenotype (Burggren, Tazawa and Thompson, 1994). Sorting the "nature/nurture" aspects of development is not a trivial task from an experimental design point of view, although the employment of animal models exhibiting polyembryony, for example, may help resolve this important question (Burggren, 1999).

Animal Models for Studies of Physiological Development

Frequently, we can look back over the history of various fields of physiological study and identify quantum leaps that resulted directly from the discovery and utilization of a particular suitable animal model. Is there a "best" animal model for studying physiological development in vertebrates? Certainly, large numbers of studies have focused on the use of the chick embryo, the frog *Xenopus* and, the most recent contender, the zebrafish (see Burggren and Fritsche, 1997; Chen and Fishman, 1997; Keller, 1997; and other chapters in Burggren and Keller, 1997). Comparison of these data sets leads to the rather surprising conclusion that vertebrate embryonic physiology is highly conserved. Indeed, not only qualitatively, but even quantitatively, cardiovascular physiological variables such as cardiac output, systemic

arterial blood pressure, and peripheral resistance are very similar in the early embryos of fish, amphibians and birds. Only after the heart is fully septated do these various cardiovascular systems begin to diverge from a common anatomical and physiological pattern (Figure 5). This suggests that developmental physiologists studying at least early embryonic physiology of vertebrates can be highly entrepreneurial, selecting animals which show the most useful combination of size, transparency, ease of maintenance, etc. To answer the question posed above, there would appear to be no overall "best" vertebrate model, but rather a wide range of vertebrate embryos can potentially assist in the solution of problems in vertebrate physiological development.

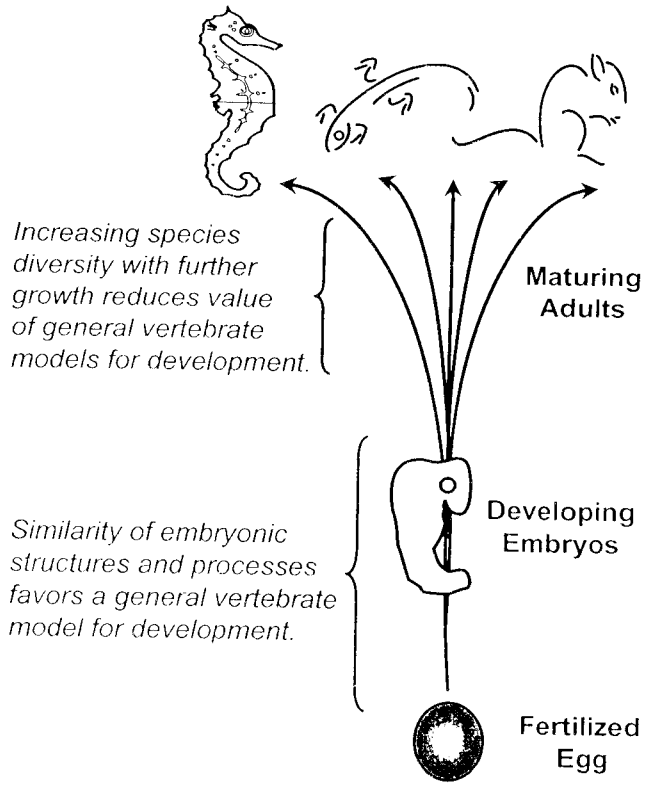

Figure 5. The utility of individual animal models for studying vertebrate cardiovascular development is greatest early in development, where a diverse array of embryos nonetheless show a high degree of qualitative and quantitative similarity. As development proceeds, individual taxa begin to take on characteristic aspects that make them less useful as general vertebrate models for development. (From Burggren and Fritsche, 1997)

The Future of Physiological Development

The study of physiological development is at an exciting juncture in its long history, where the fields of embryology and molecular biology are being knit together under the theme of "how do developing animals and their organs systems function?" Useful concepts in the study of developmental physiology including "developmental trajectory", "multivariate interactions", "critical windows", "accelerated organ system development" and "maternal effects" are being used to expand the field from primarily descriptive studies to include hypothesis-generated experimental work. The burgeoning of microtechniques for physiological investigation (see Burggren and Fritsche, 1995) is bound to lead to physiological studies that probe increasingly deeply into both the origins and maturation of physiological processes. Like Aristotle, we peer into the fertilized chick egg and ponder the processes within. With our advantages of modern techniques and an emerging conceptual framework for understanding our observations, however, we are making advances in achieving

a fundamental understanding of the processes underlying physiological development

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發育生理學的過去、現在與未來

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摘 要

胚胎發育的生理變化雖然很早就已經引起人們的注意，然而概念架構的不足，使得新技術和理論難以更進一部拓展此領域，本評論將介紹一些概念，如發育軌跡、關鍵階段、發育速率、形態功能、遺傳效應以及模式動物等。發育軌跡是指胚胎發育的預定過程，就如同飛彈發射的預設軌跡一樣，兩者都有預設的藍本，但受到進展過程中的許多因素影響，不一定能照預期的到達目的地。關鍵階段在胚胎發育的過程中也是很基本而重要的概念，胚胎發育時，最容易受到外界影響的時期就稱為關鍵階段。胚胎發育的速率也非一成不變，當環境變化時，其速率也會隨著改變，且不同的器官系統受到的影響常不一樣，這樣的改變很可能和其生存適應有密切的相關。特定的形態構造常有特定的功能，但些微的構造改變，可能產生意想不到的生理功能，且相同的構造在不同的發育階段其功能也可能不一樣。不同的遺傳基因也會隨著影響胚胎發育的過程和結果。最後模式動物的獲得和研究，則能使該學門快速發展。若能顧及以上這些概念，將有助於研究動物由受精卵至成體的變化過程。

關鍵詞：發育軌跡、關鍵階段、發育速率、形態功能