

3-20-2008

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## Recommended Citation

Scott F. Gilbert. (2008). "All I Really Needed To Know I Learned During Gastrulation". *CBE Life Sciences Education*. Volume 7, Issue 1. 12-13.

<http://works.swarthmore.edu/fac-biology/237>

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# All I Really Needed to Know I Learned during Gastrulation

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## Note from the Editor

This list of key principles in animal development was presented as “life lessons” at the Society for Developmental Biology national meeting in 2005, and it has been edited somewhat for inclusion here. For the video presentation, visit <http://sdbonline.org/fly/gilbert/gilbert01.htm>.

Are there principles of development that can be derived from specific examples? Alexander Kowalevsky predicted that such principles would be found, and his motto became “*In specialibus generalia quaerimus*” (“We seek the general in the specifics”). I think that we may have enough specifics about animal development so that some generalities can be made. In the United States, there was a best-selling book by Robert Fulghum, entitled *All I Really Need to Know I Learned in Kindergarten* (Fulghum, 1988). I would postulate that kindergarten is actually a late stage of education and that “All I Really Need to Know I Learned during Gastrulation.” So, here is my list of developmental principles.

1. One’s fate is determined by how much one listens to mother versus how much one listens to neighbors (Bard, 1997). Thus, as philosopher W.V.O. Quine said, “To be is to be a value of a variable.” A cell is given pluripotency. Its interactions and heritage determine its destiny.
2. You don’t have to be fully differentiated to influence your neighbors. You can make a difference while you are still young. The optic cup cells influence the outer ectoderm to become lens before the optic cup tissue is retina. The myotome cells of the somite tell the dorsal-most layer of the sclerotome to become tendon cells before the myotome cells differentiate into muscle. The embryo is created by “immature” cells.
3. In such interactions, competence is as important as signaling. The ability to respond to signals is itself a specialized state and can be achieved through prior inductions or by maternal specification. This is why the chick epiblast cannot respond to bone morphogenetic protein (BMP) antagonists until it has been exposed to fibroblast growth factors. (A similar operating principle explains why 15-yr-old boys should not be forced to read Jane Austin, whereas 15-yr-old girls can understand the humor of social relations.)
4. “The smallest unit of analysis is the relationship.” (Haraway, 1976). This principle is found at all levels: enhancer–transcription factor interactions, cell–cell interactions, and organism–organism interactions. It means that what an entity is becomes a property of its relationships. It does not exist alone. Waddington and

Weiss were two of the principal expounders of this view.

5. Context matters. It matters a lot and determines the outcome of relationships between components of an embryo. As one example, BMP4 causes bone formation at some times and places. It causes apoptosis at other times and places, and it specifies the epidermis at still other times and places. Whether an action is helpful or not depends on where and when it is done.
6. The preceding leads to “the three fundamental rules of development”:
  - A. Timing is everything.
  - B. The three determinants of value are “location, location, and location.”
  - C. Both of the above-mentioned statements are true.
7. Build in small pieces. Embryos use cassettes, or modules, to carry out many functions. Such modules are critical, such that if one does not work, the entire system is not thrown out of kilter. Such modules allow for impressive compensatory development.
8. The units of construction are not necessarily the units of the adult. Rhombomeres, compartments, heart fields, and the medial rib are modules that do not exist in the adult, but they are important units of construction.
9. Think globally, but use local contractors in embryonic construction projects. The transcription factors that *Drosophila* embryos use to form their second *even-skipped* transcription stripe are not the same transcription factors used to make the first or third stripes. The fourth mammary glands in mice do not form the same way as glands 1, 2, 3, and 5.
10. No one influence controls the entire project. Multiple inducers are needed for successful differentiation in many cases. “You can get a lot done if you don’t care who gets the credit” (George Marshall). The anterior endoderm and heart deserve some credit in forming the lens, even though the optic cup gets most of the glory.
11. There have to be pushes and pulls. The signal to become A must be paired with the signal *not* to become B. Thus, one cell will tell another cell, “Become ectoderm and not mesoderm”, and one field will say to another, “Become female, and don’t become male.”
12. Reciprocal induction is the rule. All entities are both active and passive; actors and acted-upons. “All that you change changes you.” (Butler, 1998). This is the way that complex organs can form.
13. Two negatives equal a positive. Activation is usually the repression of a repressor. Repression is often the

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- repression of the repressor of a repressor. The enemy of my enemy is my friend.
14. The wisdom of the tadpole is paramount: Don't digest your tail until you've built your hindlimbs.
  15. Powerful entities must be powerfully regulated. "Master regulatory genes must be masterfully regulated." It's difficult to get MyoD expressed, and that's the way it should be!
  16. Redundancy is important. We have six sets of Hox10 genes, and this prevents our skeleton from being deformed if one of them goes awry. The same principle is true in daily life: Many of us have our presentations on USB keys and CDs.
  17. There is strength in community . . . and often one needs community to be effective. In other instances, one must migrate as an individual.
  16. Redundancy is important. We have six sets of Hox10 genes, and this prevents our skeleton from being deformed if one of them goes awry. The same principle is true in daily life: Many of us have our presentations on USB keys and CDs.
  18. The whole is greater than the sum of its parts; every part of an organism has a definition only in the context of the entire interacting system of which it is a part.
  19. "Homology" means appreciating both differences and similarities. Whether one emphasizes the similarities or differences between a forelimb and a hindlimb is a matter of context.
  20. Function changes with time. When considering the life history of an organism, have respect for those playing lesser roles as adults, for they once may have been vigorous and important. Those intervertebral discs used to be the notochord, and the anus used to be Hensen's node, itself. Some, like the hypoblast and chorion, killed themselves so that we can be here today. They were important and deserve our study, even though we do not retain them as functional units.

21. There are multiple paths to the same end. Think of the neural tube, which can form in two ways in vertebrates.
22. As Ian Wilmut (2001) said, "Life is messy, and science is a slice of life." If you seek perfection, go into math. Evolution and embryology make do with what they got, and "good enough" is indeed good enough.

With these principles as a starting point, perhaps the most important principle of all was stated by Viktor Hamburger, who affirmed that "Our real teacher has been and still is the embryo—who is, incidentally, the only teacher who is always right" (see Holtfreter, 1968). Gastrulation is the point at which nearly all developmental principles get tested. It's the quality control point to find out if all systems are "go." Anyone who gets past gastrulation and middle school must be respected as a survivor. So at gastrulation, one can see highlighted nearly everything one needs to know about the essential principles of development, and a lot of what you need to get you through life.

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# The Missing Dimension in Developmental Biology Education

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## FOUR-DIMENSIONAL THINKING: AN INHERENT CHALLENGE IN DEVELOPMENTAL BIOLOGY

I arrived at the University of Wisconsin–Madison as a young assistant professor in 1991. In those days, teaching a modern course in developmental biology was an excit-

ing proposition. Modern discoveries at the molecular level due to work in invertebrate model organisms were just beginning to be synthesized into coherent "nuggets" that could be passed on to undergraduates, and the pursuit of the molecular basis of the Spemann-Mangold organizer was hot and heavy. Those were heady days indeed. As time passed, however, the challenges of teaching modern developmental biology changed. How could one convey the fruits of the explosion in molecular detail to the modern student (see the accompanying POV by Wood

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