Developmental Biology as a Science of Dependent Co-origination

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Between fertilization and birth, the developing organism is known as an embryo, and forming an embryo is the hardest thing you will ever do. To become an embryo, you had to build yourself from a single cell. You had to respire before you had lungs, digest before you had a gut, build bones when you were pulpy, and form orderly arrays of neurons before you knew how to think. One of the critical differences between you and a machine is that a machine is never required to function until after it is built. Every multicellular organism has to function even as it builds itself.

Developmental biologists are those privileged to study the origins and development of the embryo. We get to ask some of the most important questions about life. How does newness come into the world? How does one cell--the fertilized egg--divide to become the trillions of small cells that comprise my body? How does this one fertilized egg cell generate all the different types of cells—blood cells, brain cells, liver cells? How do these cells become organized into functional organs? How is it that I have only two eyes, and they are both in my head? Why do I have only one heart? How do the organs know their correct size? How do organisms make cells that can reproduce? Did other organisms help me come into being? Is the form of the adult somehow present in the egg or does form arise from nothing? These questions have been explored not only by Tsongkhapa and many other Buddhist scholars from the viewpoint Buddhist logic but also by myriads of developmental biologists spanning several centuries using scientific technologies and the empirical method.

As a developmental biologist, I get to tell animal stories, modern jataka tales that not only illustrate the mystery of development but also have the potential to help listeners understand the processes through which form arises. Here, I wish to deliver three scientific stories about animal cells and about the origin of animal body patterns. The first will be a story of *early* development. Indeed, it is a piece from the epic tale of fertilization. The second will be from the *middle* part of development, when organs are forming. It will be the story of the coming-into-being of the eyes. And the third story will be from a *later* stage of development, soon after we are born. It will be a story of blood vessel formation.

I will first provide the stories. Afterward, I will provide some of the scientific data behind these stories. And as a third part, I will suggest that these stories are relevant to thinking of the world in terms of (1) flux, (2) context, and (3) the continuous interdependent-coming-into-being.

Part 1. THREE SMALL STORIES

A. The story of cellular consummation

The human body is composed of trillions of cells that are constantly being born and dying. What we call "life' is actually as much about death. Throughout life, many trillions of cells come and go, yet there is the illusion of stasis. There are blood cells, brain cells, stomach cells, and many others. But one type of cell is very special. These are the germ cells. While in the embryo, the germ cells will migrate into the developing testes, if the embryo is male. And they will become the sperm cells of the adult. If the embryo is female, the germ cells migrate into the developing ovary, and they will become the eggs of the mature adult.

The sperm cells and egg cells are remarkable in many ways. They have only half the genes of normal cells. So when sperm and egg unite, they make complete the normal number of genes, and these genes provide most of the instructions for

normal development. The sperm and the egg are two cells at the verge of death. Both the sperm and the egg will soon perish. Yet, by their interactions, they can make an organism that will lives several decades. Both sperm and egg are remarkable partners. Out of the millions of sperm ejaculated, only about a dozen make the full journey and reach the vicinity of the egg. And out of the millions of eggs originally in the ovary, only about 500 will be ovulated, one per month; and only they have a chance of meeting a sperm.

For the sperm, the race is not necessarily to the quickest. The sperm that fertilizes the egg is one of the sperm that cooperates best with the woman. For the woman's reproductive tract is not a passive tube through which sperm race, and the sperm that are ejaculated are not mature sperm. In fact, they cannot fertilize eggs.

Rather, the sperm that get ejaculated are immature sperm. They have to complete their formation. And this is accomplished by interacting with the oviduct cells of the woman's reproductive tract. The fastest sperm, those getting immediately to the egg, cannot fertilize it. That's because it remained immature. The women's oviduct cells change and mature the sperm, giving it the capacity to find and fertilize the egg. Molecules in these oviduct cells bind to the sperm, slow it down, and change the sperm cell's membrane. After the membrane has changed, the sperm can then bind sperm-activating substances produced by the newly released egg, and this binding makes sperm swim faster, and gives the sperm direction to propel it toward the egg. Only after interacting with the oviduct cells can the sperm find the egg and fuse with it.

And when the sperm meets the egg, it does not bore into it. It does not drill into it; it does not punch a hole in it. Rather, the sperm head leans against the egg, and the egg sends out processes to envelop it. The sperm and egg membranes fuse, causing the two cells to become one.

And now the sperm reciprocates. In the oviduct, the sperm was matured and activated by the egg. Now, the sperm activates and matures the egg. For the human egg is also immature. It has not completed its final division. This completion of egg development happens when the sperm enters. Now, the activation of the egg allows development to begin.

So we have a parable of two immature cells, both at the verge of death. The sperm gets matured and activated in the woman's reproductive tract, allowing it to mature and activate the egg to begin development. This is how our life begins. Not in combat, not in violence, but in reciprocal interacting and partnership.

B. The story of the eye

Imagine the head of an early human embryo. In the early embryo, there are no eyes, ears, nose, tongue; no sound, smell, taste, no realm of seeing-- a starting point that is fundamentally similar to that described in the opening portion of "The Heart Sutra." The head is initially covered with skin. There are not yet holes for the mouth or nose. There are no eyes. If left alone, no eye lenses will form. But something has to tell some of the skin cells to become the lenses of the two eyes. What does this? It is the brain. In a specific region of the developing brain, a pair of bulges appears. They travel out from the brain, and they eventually touch the skin. When these young brain cells touch the embryonic skin, they produce chemicals that instruct these skin cells to turn away from the path of skin development and to enter the path of lens development. The brain tells these skin cells: "You are to become the lens of the eye." And as the lens cells form, the developing lens cells tell the brain cells that formed them: "And you are not going to become brain. You will become the retina of each eye." The developing lens is in conversation with the developing retina. They help form each other. Without the lens, there is no retina. Without the retina, there is no lens. Eventually, the retina will secrete a fluid that fills the chamber of the eye, separating the two. Where the lens and retina remain in contact,

the iris muscles form from the retina, thereby allowing the lens to focus light onto the retina. The stalk connecting the retina to the brain becomes the optic nerve.

This is how human organs form. They do not come into existence independently. They come into existence through the effort of a community of other organs. The cells that become the heart need the head and the gut in order to form properly. The cells that become the bones of the hand need signals from the skin in order to grow.

One of the proteins needed for eye development is BMP4. BMP4 is a chemical that goes from one cell to another cell. But what it does is very different in different parts of the body. In the head, BMP4 is one of the proteins made by the brain cells that instruct the skin cells to start becoming lens cells. But BMP4 in the connective tissue of the body says, "build bones." BMP4 in the very early embryo says, "Become skin". And BMP4 between the bones of our fingers tells the cells to die, thereby separating our digits. Context is everything. There is no essence to BMP4. It does different things in different situations.

So as organs form, the *reciprocity* that we saw in the sperm and egg continues. One sees interdependent co-origination. The retina doesn't form without the lens forming. The lens doesn't form without the retina forming. One also sees that the *context* in which a molecule functions determines the function of that molecule. We also see the eye as an organ in *flux*. It was made by immature cells. The function of the *adult* retina is to receive light. The function of the *embryonic* retina is to induce the formation of the lens.

C. The story of the intestinal capillaries

Our gut contains trillions of bacterial cells. They are not dangerous. Quite the opposite, we need them, and they need us. We acquire these bacteria at birth-- the moment we start coming through the birth canal. Our mother has bacteria

throughout her reproductive tract and gut, and as we pass through the birth canal, these bacteria colonize our bodies. The first thing our bodies do, before even the first breath is taken, is to acquire these bacteria.

And this is good. One can experimentally breed mice that lack such bacteria. These mice are not normal. First, they have an immune deficiency and cannot make the normal amount of antibodies. Second, they lack the necessary blood vessels to take food from the gut. Third, they have behavioral problems. Normal mice and normal people are full of bacteria. And these bacteria help construct our bodies. Bacteria act just as embryonic cells do. Just as the brain cells put forth chemicals that change gene expression in the skin cells to turn them into lenses—so the bacteria also produce the chemicals that activate certain genes in the surrounding tissues, and this gene expression tells the cells what to do. Bacteria activate certain genes in our gut tissues, and they suppress the expression of others genes. These changes in gene expression that are caused by the bacteria are needed to make certain organs. We are told how to develop not only by the cells we acquire from the union of sperm and egg. We also are told how to develop from over 100 species of bacteria that inhabit our young body. We expect the bacteria, and we are born with poorly formed organs if these bacteria are not present.

For instance, the symbiotic bacteria in the gut, especially a genus called *Bacteroides*, actually tells the intestine cells to turn on the genes that make a protein called angiogenin-4. The intestinal cells make angiogenin-4 and secrete it to their neighboring cells. The cells around the intestine bind angiogenin-4, and angiogenin-4 tells these nearby cells to make capillaries.

But angiogenin-4 does more than help produce capillaries. It also kills *Listeria*, a bacteria that is a competitor for *Bacteroides*. *Bacteroides* helps us; we help *Bacteroides*.

So important are these symbiotic bacteria that we have integrated them into our physiology. During the last months of pregnancy, the woman's hormones change the types of bacteria living inside her. These bacteria actually help the pregnant woman maintain the fetus. When the baby is born, it acquires these microbes as the fetus passes through the birth canal. Equally amazing, when the mother feeds the baby, she is giving the baby two sets of nutrients. One type of food feeds the baby. The other type of food feeds the good bacteria. The food from the mother contains sugars that that humans can't digest. However, they selectively permit the growth of certain bacteria—the ones we want in the baby's body. We nourish the sin-boos, and they help construct us.

Such interactions between species is called symbiosis, and we find that symbiosis is not the exception to the rule. Rather, symbiosis is the rule. One sees symbiosis inside our cells, one sees symbiosis in making organs. One sees symbiosis in the production of oxygen and in the nitrogen of our soil. We see it in tidegrass communities and in our bodies. We are not individual bodies. That is an illusion. We are ecosystems of co-dependent processes.

So we do not develop on our own. The fertilized egg does not have within it all the material needed for the completion of development. We literally "become with others." This is one of the great biological discoveries of the 21st century, and one that overturns much of the competitive paradigms of the 19th and 20th century. We need the other species to survive. That's not metaphor. It is reality as science knows it.

Part II. Scientific Explication

In this section I would like to provide some of the scientific details that allow us to tell such stories[1].

A. **FERTILIZATION. The essence of fertilization is the mutual activation of the sperm and egg such that development can be activated in the egg and that the inherited material can be transmitted from one generation to the next. Fertilization is about the *interaction of cells* to transform each other.**

Fertilization is the story of interaction between two cells, the sperm from the male, the egg from the female. Both the sperm and egg are immature cells and have to be activated. And this is done by activating certain proteins within the sperm and egg.

1. **Activation of the sperm: I. Capacitation**. The activation of the mammalian sperm is done in two steps, the capacitation reaction and the acrosome reaction. Both steps alter the membrane of sperm cells to make their next steps possible. Capacitation allows the sperm to find the egg. The acrosome reaction allows the sperm to bind to and enter the egg. During capacitation, the cells of the female's oviducts bind to the sperm and stop the sperm from moving. This cessation of movement allows cholesterol to be removed from the sperm cell membrane. This removal of cholesterol allows calcium ions from the woman's reproductive tract to flow into the sperm, and these calcium ions activate the adenylate cyclase enzyme on the sperm cell membrane. This enzyme is a protein that turns a small molecule, AMP, into another small molecule called cyclic AMP. Cyclic AMP activates tyrosine kinase proteins, and these proteins add phosphate groups onto other proteins. These changes cause the sperm membrane proteins to reorient on the sperm.

[1] All the details can be found in Gilbert and Barresi (2016). The notion that descriptions of development might benefit from Buddhist philosophy is not necessarily new (Rose 1997, p. 34; Barash 2013).

As a result of capacitation, the Izumo protein, which is necessary for sperm-egg binding, migrates into the membrane, where it will be functional in biding to the egg. The proteins that are needed to receive the directional signals from the egg are also activated. Capacitated sperm can now recognize these chemical signals and swim quickly to the egg. The uncapacitated sperm cannot.

2. **Activation of the sperm. II. The acrosome reaction**. Once near the egg, the membrane formed during capacitation is exchanged for another cell membrane, coming from inside the sperm. This change is called the acrosome reaction. As the sperm approach the egg, substances from the egg or from the cells surrounding the egg (the "cumulus" of cells that had been connected to it in the ovary) cause the tip of the sperm cell membrane to disintegrate, while another membrane is put in its place. This new membrane contains the proteins (such as Izumo) that will bind to the egg. This new membrane also has the proteins that bind to outer surface of the egg. After undergoing capacitation and acrosome reactions, the sperm is competent to fertilize the egg.

3. **Sperm-egg binding. I. Zona pellucida**. The binding of sperm and egg also occurs in two steps. First, the sperm binds to the protective layer of the egg, the zona pellucida. In humans, this layer is made of 4 proteins, and it has two functions. First, it only binds active sperm. Second, this protein shell serves a protective function for the embryo developing inside it, preventing the embryo from adhering to the oviduct cells as it travels to and into the uterus. (Once inside the uterus, the embryo digests the zona pellucida and is able to adhere to and enter into the uterus.) The proteins on the sperm bind to proteins, mainly protein ZP2, on this protective outer layer of the egg. Chemicals released by the sperm can then digest a small channel in the zona pellucida, allowing the sperm to reach the egg.

4. **Sperm-egg binding . II. Membrane fusion**. When the sperm reach the egg, they do not bore into it or drill into it. Rather, the sperm head places itself adjacent to the huge egg surface, and the egg cell membrane extends folds that envelop the sperm. The Izumo protein on the sperm membrane recognizes a receptor, Juno, on the egg membrane. If one wants to use metaphors, the egg embraces the sperm. And then, the sperm cell membrane melts into the egg cell membrane, and sperm and egg become one.

5. **Egg activation. I. Re-initiating cell division and development**. The sperm can now reciprocate and activate the egg. A protein from the sperm—PLC-zeta—releases calcium ions from their storage vesicles inside the egg. This is very similar to the use of calcium ions during the capacitation and acrosome reactions in the sperm. The calcium ions activate certain egg proteins that activate other egg proteins. Again, this is very much like what happens in capacitation. The activated egg proteins do several things. First, they change the egg cell membrane such that it cannot bind any more sperm. Only one sperm is permitted to enter the egg. Second, the activated proteins re-start the maturation of the egg. The human egg is stopped in the middle of its second meiotic division. It is still immature. The entry of the sperm allows the egg to mature and complete its second meiotic division to give it half the number of genes. And third, the newly activated enzymes re-start the production of new proteins, the proteins that will allow cell division to take place.

6. **Egg activation. II. The union of genetic materials.** Fertilization has two functions—the initiation of development and the creation of a new genome whose genes are derived half from the mother and half from the father. After the sperm has activated the last cell division of the egg, the egg now has a nucleus with half the number of genes, and the sperm nucleus also has half the number of genes. How do these two nuclei find each other? This feat involves another step of sperm-egg cooperation. The sperm brings in not only a nucleus, but also the centrosome, a set of proteins that make fibers. The

chemicals that make these fibers, the tubulin proteins, come from the mother. The sperm centrosome spins its net of egg proteins, catching the female nucleus. Then, the male and female nuclei move toward each other in this net, and finally come together and fuse. The chromosomal genes of the mother join with the chromosomal genes of the father and cell division occurs. The formation of the new person has begun.

Thus, there are enormous amounts of cooperation taking place during fertilization. The female reproductive tract and egg are not always passive. They mature and activate the sperm. Once activated, the sperm becomes capable of initiating the maturation of the egg. The sperm and the egg are both active and passive, and the sperm and the egg activate each other by similar chemical means. (Interestingly, these mechanisms of activation use many of the same proteins that will later be used in transmitting neural signals.) Moreover, the sperm and the egg bring different elements into the fertilized egg. First, while both sperm and egg bring the same number and type of genes, some genes can only be active if they come from the egg, while other genes are only active if they come from the sperm. Like the Buddhist notions of red matter making some organs and white matter making other organs, the sperm and egg have some complementary functions and are both needed to make a complete body. The sperm brings in the centrosome, which is necessary for cell division. The mother brings all the mitochondria, which provide the energy for such division. So while the sperm and egg are two cells on the verge of death, if they cooperate successfully, the human embryo begins to form.

B. ORGAN FORMATION. The essence of organ formation is the expression of different genes in the cells of different organs.

Vertebrate organ formation is about the *interaction of tissues* to mutually transform each other.

Fertilization gives each of us our genome—the set of genetic instructions that are critical in constructing and maintaining our bodies. As the fertilized egg divides to produce all different the cell types of the body, the genes in each cell replicate as the cell divides, so that every cell has the same number and types of genes. Cloning has shown that the genes of each cell are the same. The genes are the instructions that make proteins, and the proteins do the work of the cell. But each gene is not active in every cell. Quite the contrary; different genes are active in different types of cells, and the proteins made by these different genes are what give the organs their different functions. In the red blood cells, the genes for hemoglobin are active, and this red compound transports oxygen to the cells. The pancreatic beta cells do not make hemoglobin. Rather they activate the genes that make, among other things, insulin, the protein needed for sugar metabolism. The lenses of our eyes are told to activate the genes that make the transparent crystalline proteins, while the genes in the epidermis of our skin are told to makes special keratin proteins that that are water-resistant and elastic.

So the genome has to be told which genes to activate in which cells. How is this done? The agents of differential gene expression are a set of proteins called *transcription factors*. These proteins bind to a certain region of the gene and allow the binding of an enzyme, RNA polymerase II, which starts the processes by which the gene becomes active and makes proteins. Different transcription factors bind to different genes, and the combination of certain transcription factors allow the genes to become active.

Which transcription factors act in a cell depends on where the cell is and what that cell's neighbors are. Context is critical. We are thinking with cells that could have been used for eating, had they been in a different part of the embryo. As the fertilized egg divides to become a ball of cells, different transcription factors are activated in the inside cells than the outer cells. This is the first distinction in the embryo. The outer cells will become the placenta; the inner cells will become the body. These tissues, now different, influence each other to become more tissues (Stephenson et al 2012; Harrison et al 2017) .

One of the best examples of organ formation is that of the eye. The formation of the eye begins when two areas of the developing forebrain brain, each expressing the Rx transcription factor, are instructed (by the proteins activated by this transcription factor) to grow toward the skin. When these brain cells reach the skin, they flatten against it and secrete a group of proteins including BMP4, Fgf8, and Notch. Each of these proteins binds to a specific receptor protein on the surface of the embryonic skin cells. When they are bound to the receptor proteins on the membranes of the neighboring skin cells, the receptors activate certain transcription factors that tell the embryonic skin cells to elongate and to become the transparent cells of the lens. These cells start making the crystalline proteins that characterize the lens cells. One of the transcription factors induced in the developing lens cells activates the gene for another protein that is *secreted from* the elongating lens cell. This protein binds to receptors on the brain cells and tells the brain cells to become the neural retina cells. As the brain cells are telling the skin cells to become lenses, the skin cells reciprocate by telling those particular brain cells to become the retina.

In addition, the physical adhesion of the developing lens cells and the developing retinal cells prevents other cells from migrating into this area. The migrating cells would have been the neural crest cells that form the dermis of the head skin. The neural crest cells also have the ability to block the signals made by the developing

lens and brain. So these antagonistic cells, which would have prevented lens formation, are physically blocked from entering the eye-forming areas.

The FGF8, BMP4, and Notch signals activate transcription factors to activate or repress particular genes. Pax6, Sox2, and L-MAF are transcription factors that are needed to activate many of the crystalline gene of the lenses. Pax6 is in the entire head ectoderm, and it is placed there by earlier inductions involving the heart and gut cells. Sox2 is activated in the lens by BMP4 from the brain tissue, and L-Maf is similarly activated by Fgf8. Pax6, Sox2, and L-Maf bind close to each other on the DNA of certain genes, such as the crystalline genes. And by their interactions, RNA polymerase is allowed to bind to them, and the crystalline gene is activated. Usually, it is a combination of transcription factors that activates genes. And these transcription factors are activated by signaling chemicals originating in the neighbors. The rule of organ formation is that neighbors build neighbors.

Again one sees this co-dependence of embryonic development. The genes are both active and acted upon; the cells are both acted and acted upon. Each group of cells helps determine the fate of the other.

C. The essence of developmental symbiosis is that certain microorganisms signal normal development in the host organism. This type of development involves the interactions between cells of different biological species.

We were never individuals[2] . We are not individuals anatomically, as at least 50% of the cells in our body are microbes. We are not individuals physiologically, as 30% of the soluble material in our blood is derived from these bacteria. Our metabolism is intimately linked to theirs. We are not individuals by developmental criteria, since

[2] Details of these studies can be found in Gilbert et al (2012), McFall-Ngai et al 2013).

bacteria are necessary for our normal development. In fact, none of us are individual animals. For over a decade now, several biologists have been considering animals as holobionts—the organism plus its colonies of persistent microbial symbionts. When you think of a cow, you may think of a slow moving animal that eats grass. Only, it can't eat grass. The genes of the cow encode no proteins that allow her to digest cellulose or any of the woody parts of grass. Those proteins are made by the bacterial symbionts of its stomach. The cow is not a cow without these microorganisms. Similarly, termites can't eat wood. That ability is given to them by their microbes.

The microbes activate normal gene expression just like an embryonic tissue would. The vertebrate gut without its symbionts has a different pattern of gene expression and is like a genetic mutant. In fish, the division of the gut stem cells is induced by the gut bacteria, and without the bacteria certain cells don't form. I wish to give two fascinating examples of the need for microbial involvement in normal development.

First, the bobtail squid feeds in the shallow waters off the Hawaiian islands. However, it is only a big as your palm, and many other creatures find it tasty. When it feeds during the full moon, the light of the moon can cast the squid's shadow on the sea floor, showing it to its predator. To avoid this happening, the squid has evolved an amazing structure—the light organ. On the belly of the squid, there is a pouch that glows softly and can cancel its shadow. This is called the light organ of the squid. However, it is not there at birth. It is made by a single species of bacteria, *Vibrio fischeri*. The squid collects these bacteria in such a high quantity that they start glowing, something they do not do on their own. So the light organ is a piece of anatomy that is made in one organism by another organism for the benefit of both. The squid's development is not complete without the microbe; and the microbe's development is also changed by its being inside this organ, which provides it a safe home.

But let me now talk of some science that would border on science-fiction were not the proper controls done. One large study (Hsaio et al 2013) used viral stress in mothers to induce an autism-like condition in their offspring. These "autistic" mice spend a lot of time self-grooming, lack normal exploratory behaviors, and prefer solitary cages. This study found that the autistic-like mice act more like normal mice when you alter their bacteria. If one adds certain species of *Bacteroides*, this alters the community of the bacterial symbionts, and it increases the integrity of the gut epithelium. This simple procedure stops the leaking of bacterial products into the gut and normalizes several of the autism-like behavioral abnormalities. One of these chemicals, 4EPS, is made by bacteria and causes anxiety-like symptoms in mice. In the "autistic" mice this product is seen in relatively high amounts in the circulation. In the normal (bacteria-containing) mice without these symptoms—and in the "autistic" mice that were treated with the bacteria—4EPS can hardly be detected. This study opens up a new area that investigates cognitive and emotional situations as products of bacterial metabolism (Hsaio et al 2013; Desbonnet et al. 2014). Different microbes may make us different people. Different microbes provide different amounts of resistance to kwashiorkor in humans (Smith et al 2013) and malaria in mice. (Villarino et al 2016).

We are multilineage organisms. The separation of us from our environment is an artificial one, based on visual cues and not on the evidence of anatomy, physiology, or developmental biology. We have numerous ecosystems within us, and we are part of each of these ecosystems (Gilbert 2014).

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III. CODA: Becoming with others

We always tell stories by linking perceptions into a narrative, a plot with a beginning, middle, and an end. However, scientific stories differ from many other

stories because they are severely constrained by data[3] . They are also severely limited by controls, which mean not only that a certain story is possible, but also that other stores are *not* possible.

For the past century, there have been three major biological stories that have failed the test of data. The first has been has been that the story that fertilization is all about male struggles and success. The egg was a passive recipient of the sperm, and the female reproductive tract a passive conduit. That story is wrong. Fertilization is a story about interaction and cooperation. If there is competition, it is usually in the form of which sperm cell cooperates best.

Second, we were often told a story that the creation of an embryo is strictly controlled by our genes. The genes were considered to be our essence; they are who we are. The notion that our DNA is seen as the basis for our autonomous self-hood has been documented by historians and sociologists who studied the rhetoric of DNA in Western society (for instance, Nelkin and Lindee 1985). In Western countries, anti-abortion websites maintain that we are exactly who we are at fertilization; even automobile ads use DNA as metaphor for essence (Gilbert and Howes-Mischel, 2004).

This story has fallen apart. We now know that the environment plays critical roles, and that the environment can also change gene expression. We also know that development (*lus kyi chags tshul*; how the body is made) consists of the making of parts that become different, and that once different, these parts interact with one

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[3] Garrett (2008) has claimed that the stories told about embryology in the Tibetan Buddhist tradition are not scientific stories, as they are stories not about the embryo but about the adept (P. 57, 157). Exoteric Buddhist stories are about gestation being a realm of suffering; exoteric Buddhist stories concern the adept's being reborn into an enlightened body. Garrett (p. 130) claims that the 12 steps of dependent self-origination creates a middle ground between the extremes of eternalism (that there is an eternal essence of each person) and nihilism (that the person is destroyed at death).

another to form organs[4]. Embryonic development is based on specific induction, such as the formation of the lens by brain tissue touching the skin. No other tissue but the brain will turn skin into lens. No other tissue but the developing lens will turn brain into retina. Developmental biology is a science based on the notion of "specific conditionality, *idaṃpratyayatā*," namely, that one part comes into being by interacting with another part. "*This* is because *that* is. This is not because that is not." However, the third postulate of specific conditionality --as *this* ceases to be, so does *that*—is often circumvented by the embryo. When cell A tells cell B to become B', the product of the genes that are activated in B to effect this conversion often activate themselves. The cell becomes B' even after cell A dies or moves to a new location. If the teacher dies or moves, the teaching is still continued.

We are not merely self-manifestations , the "readouts," of our genes. "Self-manifestation," as the third Karmapa, His Holiness Rangjung Dorje(1284-1339), explained in his *Wishing Prayer for the Attainment of the Ultimate Mahamundra*, "has never existed as such, and is erroneously seen as an object." Indeed, according to the Buddhist tradition (as in the *Mahamudra*), attachment to this non-existent self-manifestation is a root of the pernicious duality of "I and other." However, rather than our body having a genome-defined "essence," we are constructed by parts that receive their identity as they are being constructed. This relates directly to the principle of *Pratityasamutpada*, which emphasizes that what appears to be an individual entity comes into existence though interdependent relationships that create one another, in a process of continual arising and ceasing.

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[4] Development finds itself as the integrator between structural biology (anatomy and physiology) and evolution. One achieves evolutionary changes by altering the patterns of development. This is the science of evolutionary developmental biology. One of the fundamental principles of evolutionary developmental biology is that of the "small toolbox." From using the same tools in different contexts, one can generate the diversity of organisms. In Buddhist philosophy, this is the problem of homologous cause and effect (*rgu 'bras bu dang rjes su mthun pa*). According to Garrett (2008), both Kyempa Tsewang and Lodrö Gyelpo asked how an infinite variety of forms can be generated from a small set of causes. This is a central question of evolutionary developmental biology.

Indeed, not only is *interaction* is critical, but so is impermanence. *Impermanence* is seen in the transient organs of the embryo, which exist to make other organs but then perish themselves. The primitive streak and notochord are critical in forming the embryo; but they are not organs of the newborn. Impermanence is also seen in the fundamental metabolism of the cells. We retain our identity solely by changing our component parts, as we eat, drink, and excrete. The world passes through us as we pass through the world (Jonas 1966; Gilbert 1982).

And in developmental biology, *context* is also critical. BMP4 is important in making the lens of the eye. But in another context, the hand, BMP4 tells the cells between our fingers to die. In another context, the early embryo, it tells cells to become the skin and not the nervous system. In another context, it instructs cells to become bone, and in a different context, it instructs cells to become heart. So what this molecule does depends on where and when it is expressed. Specifically, the function of the molecule depends upon the history of the cell receiving it. The same pathways used for activating an egg will be used for neural transmission.

And the third story of the 20th century that doesn't stand the scientific scrutiny of the 21st century is that we are unilineage organisms whose genomes are in competition. In that perspective, life is seen as a continuous struggle of each against all. However, a new story is emerging—that each organism is a collection of species, a holobiont, and that most evolution occurs though interspecies cooperation rather than intraspecies competition. As Margulis and Sagan wrote (1986), "In short, I believe that most evolutionary novelty arose and still arises directly from symbiosis. Life did not take over the world by combat, but by networking." This is still a controversial story; but I think it will be one of the most fundamental changes in the way Western science views nature. One reviewer (Bolker 2016) recently reported—"The claim that 'all development is co-development' …sounds a little new age in the context of current individual-based paradigms for thinking about development, but I

suspect that within the next decade, we will take our status as holobionts for granted."

We are seeing life as "becoming with the other." This is a new scientific story that may make the competition story either untenable as a mechanism for change or a fine-tuning mechanism that may work within a species. As Lama Tsong Khapa noted, one's view of nature changes when one realizes the co-dependent origins of all parts. "Just seeing that interdependence never fails brings realization that destroys how you hold to objects, and then your analysis with view is complete."

One finds context, interdependence, and impermanence as normal in animal development. One can meditate on an embryo as one can on a mandala. Indeed, in his book on the emergence of order in development, Johannes Holtfreter (1968, p. xi), one of the most important biologists of the Twentieth Century, wrote

> We managed more or less successfully to keep our work undisturbed by humanity's strife and struggle around us and proceeded to study the plants and animals, and particularly, the secrets of amphibian development. Here, at least, in the realm of undespoiled Nature, everything seemed peaceful and in perfect order. It was from our growing intimacy with the inner harmony, the meaningfulness, the integration, and the interdependence of the structures and functions as we observed them in dumb creatures that we derived our own philosophy of life. It has served us well in this continuously troublesome world.

This meditation on the embryo reflects that of Lama Tsongkhapa. For Holtfreter the experience of the embryo instilled faith, banished negativity, and stabilized his otherwise chaotic mind. The interdependence of structures is not being imposed from without. It is being discovered and appreciated by the scientists. Similarly, one

of the world's best fertilization researchers, Edward E. Just (1939, p. 368), wrote explicitly,

> Whether we study atoms or stars or that form of matter, known as living, always must we reckon with inter-relations.

And in my science textbook on *Ecological Developmental Biology*, I cite Nagarjuna as someone who saw interdependent creation as the basis of the world. Developmental biologists do, as Lama Tsongkhapa (cited in Hixon, 1993) suggested, "listen to the harmonious symphony of interdependence."

Embryology is always replete with moral and political categories (BGSG 1988; Martin 1991; Garrett 2008, p. 17). The story of our development is an origin story, and such stories are instructive as well as descriptive. So we must be careful and judge such stories against a cultural framework. Are these scientific stories or are these stories that merely repeat on a microscopic level the values that society is expected to give men and women? Is the scientific narrative being used to reinforce capitalist values, democratic values, authoritarian values, compassionate values? And if so, is there any justification to it?

There is a story, not confirmable by science, that before his birth, The Buddha gave sermons from his mother's womb (Garrett 2008, p. 102). Perhaps by looking at the embryo, though, we are indeed taught that all things are impermanent, that context is critical, and that our coming into existence is based interdependent becomings with others. This co-dependent origination, *Pratityasamutpada*, appears to be the rule of nature, whether it is on the cellular or ecological level. It is probably most easily seen in development, which is about the formation of bodies. Developmental biology is a science of becoming, context, and transience. Of the Twelve Linked Stages of Interdependent Causation, eleven occur before or during birth (Samyutta Nikaya; Hopkins 1983; Garrett 2008).

Biologically speaking, we are not and have never been individuals. As expressed by anatman, we are not apart from nature. We must become used to seeing life as a web where changes in one process can cause changes in all. As Rev. Martin Luther King, Jr, (1963) noted about human relations, "We are caught in an inescapable network of mutuality, tied in a single garment of destiny. Whatever affects one directly, affects all indirectly."

Or as Lama Tsongkhapa has written (quoted in Thurman 2014) p. 178:

Whatever depends on conditions
Is empty of intrinsic reality
What excellent instruction could there be
More amazing than this discovery?

So I will finish by showing something amazing--a photograph taken by developmental biologist and Buddhist monk Willliam Bates, who was an instructor in the Science for Monks program in 2006 and 2007.

To a biologist, it's obvious what these are. They are frog eggs in a pond. But when you see the context of the photograph, one realizes that this is not a pond. It is an

elephant's footprint. Who would have thought that these frogs have an existence that depends on elephants, and that the elephant has become part of the life cycle of the toad? Maybe these are not merely frog eggs; maybe they are Indra's pearls.

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