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Scott F. Gilbert

1 Development and the Baldwin Effect

Developmental biology is not often called upon to relate mind and body. However, the Baldwin effect almost demands that it be considered. The Baldwin effect (Baldwin 1896) was formulated to explain how psychological characteristics that made an individual more fit in a particular environment could be fixed in the genome. One way of restating this (see Marcos 2000) is to say that the greater the ability of an individual to adapt to external conditions, the greater its fitness (i.e., the production of progeny). This ability, which was originally a physiological response to particular conditions, will eventually be inherited even if the original initiating conditions are no longer present. Whereas Baldwin believed that a single mutation could transfer the inducing signal from the environment to the genotype, Ivan Schmalhausen and Conrad Waddington found that the transfer of competence from an environmental inducer to an internal inducer could also arise through the cryptic variation already present in the population. Waddington (1953, 1956) called this transfer "genetic assimilation."

The first tenet of the Baldwin effect and genetic assimilation is phenotypic plasticity. This idea that environment can induce phenotypic variation is now very well established. Reaction norms, dietary polyphenisms, seasonal polyphenisms, and predator-induced polyphenisms have become more familiar to biologists, especially as life history strategies research has begun to enter developmental biology (Gilbert 1997, 2001; Schlicting and Pigliucci 1998; Tollrian and Harvell 1998). Moreover, environmentally regulated gene expression has now been demonstrated. Physical stress, for instance, has been known to effect bone density, both positively and negatively. It is

now known that physical load activates certain osteoblast genes involved in increasing bone mass (Sato et al. 1999; Nomura and Takano-Yamamoto 2000; Zaman et al. 2000), and weightlessness downregulates the genes involved in maintaining bone density (Hammond et al. 2000; Wassersug 2000). Similarly, genes for erythropoietin and angiogenetic factors (which generate more blood cells and blood vessels) are activated by low oxygen pressure (Brunn et al. 1998; Wenger et al. 1998).

The second tenet of the Baldwin effect and genetic assimilation—that environmental stimuli can become replaced by embryological inducers—is now being shown on a molecular level as well. This has been demonstrated experimentally by numerous researchers including Waddington (1953, 1956, 1957), Ho et al. (1983), and Matsuda (1982, 1987). Waddington (1953), for instance, found that in certain strains of wild-type *Drosophila melanogaster,* heat shock of 40˚C during the pupal period caused disruptions in the posterior wing crossvein. Two selection regimens were followed, one where the aberrant flies were bred to one another, and another where the non-aberrant flies were bred to one another. By generation 14, in the crossveinless-selection line, some crossveinless individuals were found even if they did not treat the pupae. More were found in each succeeding generation. A response (and not necessarily an adaptive one) induced by the environment could be assimilated into the genotype. A similar situation was seen when ether shock caused a phenocopy of the bithorax mutation. Waddington's studies on bithorax phenocopy were confirmed and extended in 1996 by Gibson and Hogness. Ether exposure caused numerous flies to have the bithorax phenotype. Selection procedures then generated flies whose bithorax phenotypes were independent of ether exposure. Using polymerase chain reactions, they found that a large percentage of these phenotypes were due to at least four polymorphisms in the *Ultrabithorax* gene, the gene that naturally regulates the bithorax phenotype. Moreover, this example of genetic assimilation can be simulated by computer (Behera and Nanjundiah 1997). Genetic assimilation definitely can occur in the laboratory.

However, the idea that genetic assimilation occurs in nature remained controversial until Rutherford and Lindquist (1998) demonstrated a possible molecular mechanism for it. The abnormalities that they observed when the *Hsp83* was mutated, or the Hsp90 protein (the product of the

Hsp83 gene) inactivated, did not show simple Mendelian inheritance, but were the outcome of the interactions of several gene products. Selective breeding of the flies with the abnormalities led over a few generations to populations where 80–90 percent of the progeny had the mutant phenotype. Moreover, these mutants did not keep the *Hsp83* mutation. In other words, once the mutation in *Hsp83* allowed the cryptic mutants to become expressed, selective matings could retain the abnormal phenotype even in the absence of abnormal Hsp90. Hsp90 appears to be responsible for allowing mutations to accumulate but keeping them from being expressed until the environment changes. Each individual mutation might not change the phenotype, and mating would allow these mutations to be "collected" by members of the population. An environmental change (anything that might stress the cells) would thereby release the hidden phenotypic possibilities of a population. In other words, transient decreases in Hsp90 (resulting from its aiding stress-damaged proteins) would uncover preexisting genetic interactions that would produce morphological variations. Most of these morphological variations would probably be deleterious, but some might be selected for in the new environment. Continued selection will enable the fixation of adaptive physiological responses to the environment.

2   Predator-Induced Polyphenism and the Immune System

Baldwin's "new factor for evolution" was, of course, polyphenism. But Baldwin was more interested in the behavioral than in the physical phenotypes. Recent studies suggest that the two may not be all that different when we look at a particular type of developmental change that is induced by the external environment, predator-induced polyphenism. Predator-induced polyphenism is the ability of the developing organism to respond to the presence of a predator by changing its morphology and behavior in such a way as to make it less susceptible to predation. To demonstrate predator-induced polyphenisms, one has to show that the phenotypic change is caused by the predator (usually from kairomones, soluble chemicals released by the predator), and that the induced phenotypic modification increases the fitness of its bearers when the predator is present. For instance, juvenile *Daphnia* and other invertebrate species will alter their morphology when they develop in pond water in which their predators have been

cultured. The water in which the predatory larvae of the dipteran *Chaoborus* have been cultured can induce a "neck spine" or a "helmet" during *Daphnia* development. These allow the *Daphnia* to escape from their predator more effectively. The induced *Daphnia* suffer lower mortality from these predators (Tollrian and Dodson 1999; Agrawal et al. 1999). This induction is even transferred to the parthenogenetic offspring of these *Daphnia*. Those *Daphnia* whose mothers had been exposed to predation cues were born with large helmets, even if the mothers had been transferred to water that lacked the caged predators. Thus, progeny born in a precarious environment (i.e., an environment where the kairomone concentration is high enough to induce helmet growth in their mothers) are thereby born with a defense against predation.

Predator-induced polyphenism has been documented throughout the animal kingdom, and it is seen in vertebrates, as well as in invertebrates. There are usually trade-offs that prevent the fixation of one phenotype as the best in all environments. Usually, in a predator-induced polyphenism, the induced phenotype can better survive the predator, but the phenotype may be less adaptive in other ways. In *Daphnia,* the production of helmets appears to lessen the amount of resources that can provision eggs (Riessen et al. 1984, 1992). If the induced phenotype were not only more successful in avoiding predators but also had no significant trade-offs, one might expect that it would become the dominant morph of the population. To have this happen, the more fit phenotype would have to be formed even in the absence of the environmental inducer. In other words, the same phenotype would be induced by internal rather than external factors. This replacement of external inducers by internal inducers would cause the Baldwin effect or genetic assimilation. However, what is usually inherited is the potential to respond if predation abounds.

In vertebrates, structural predator-induced polyphenisms are often accompanied by behavioral polyphenisms as well (Relyea 2001a,b). This has been documented in amphibians, where tadpoles exposed to the water in which predators have been swimming show not only different morphologies than they would have in predator-free water, but also show different predator-avoidance behaviors that go with these new structures. Interestingly, the behavioral phenotypes seem as plastic as the structural phenotypes, and different sets of behavioral and structural phenoypes are

inherited together. It seems that Baldwin's prediction of behavioral plasticity was correct. What may have been a learned response for predator avoidance is now part of the genetic repertoire of the amphibian species.

Human predator-induced polyphenism is on a scale unimaginable in invertebrates. Our major predators, of course, are microbes, and our mechanism for predator-induced polyphenism is called the immune system. We respond to microbial predators through an immune system based on the clonal selection of lymphocytes that recognize specific predators and their products. Our immune system recognizes a particular microbe such as a cholera bacterium or a poliovirus by expanding precisely those lymphocytes that can defend the body against them. When a B-cell binds its foreign substance (the antigen), it enters a pathway that causes that B-cell to divide repeatedly and to differentiate into an antibody-secreting cell that secretes the same antibody that originally bound the antigen. Moreover, some of the descendants of that stimulated B-cell remain in the body as sentinels against further infection by the same microorganism. Thus, identical twins are not identical with respect to their immune systems. Their phenotypes (in this case, the lymphocytes in their lymph nodes and their ability to respond against an infectious microorganism) have been altered by the environment. Our immune system also provides transgenerational immunity against common predators. The IgG antibodies produced by our mothers during pregnancy can cross the placenta and give us passive immunity when we are born. In birds, a similar antibody is placed into the eggs. The cells of our respective immune systems are not specified solely by our genetic endowment. (Even the genes for the antibodies and T-cell receptors aren't present in the zygote.) Rather, experience is added to endowment. The environment, in this case, antigens, directs the development of our lymphocytes.

The immune network is a remarkable semiotic system wherein each molecular shape outside the body has a molecular image within the body (see Chernyak and Tauber 1992). Interestingly, the only things we are unable to recognize through the immune system is the body, itself. In order to recognize something as foreign (i.e., as an antigen), we must see this foreignness in the context of a self-protein. The protein receptors on our T-lymphocytes do not recognize foreignness out of context. Only when a foreign substance is bound to a particular class of self-proteins can it be recognized as being

something from outside the body. Our immune systems recognized "altered self" better than "nonself."

Moreover, according to Matzinger (1994; 1998), the immune system has evolved not to discriminate self from nonself, but to recognize "danger" from "nondanger." This view looks less at the specificity of the immune response and more at inflammation and the context of antigen presentation, wherein a substance provided in one context elicits an immune response, while the same substance presented in a less dangerous context does not. It builds on the antigen presenting cell (which does not distinguish self from nonself) as the arbiter of the immune reaction, and Matzinger links this phylogenetically to the origins of the immune system in avoiding danger. This model has been seen as central for the re-evaluation of the evolutionary role of the immune system (Tauber 2000).

So humans have the ability to respond to predation by having evolved an immune system that is constantly in the state of developing. It has the capacity to change the population of lymphocytes based on which microbes are present in its environment; and this immune system may have arisen as a mechanism of predator-induced polyphenism to escape dangerous situations. This has important implications when we look at the body's other sensory network, the nervous system.

3   The Plastic Nervous System

So far, we have looked at the immune system as having evolved as a way of evading predators by changing development. I now wish to look at the nervous system in a similar light—as a system that monitors the external environment and that can adaptively alter its development in response to that environment. The plasticity of the nervous system has long been appreciated by behavioral biologists, and the relationship between neural plasticity and behavior has been the foundation of evolutionary hypotheses by Baldwin (1896; 1902) and more recently by Dennett (1991), and Gottlieb (1992). Molecular analyses have confirmed many of their intuitions.

There is extensive evidence that experience does create more neurons and neuronal connections. The cerebral cortices of young rats reared in stimulating environments are packed with more neurons, synapses, and dendrites than are found in rats reared in isolation (Turner and Greenough

1983). Even the adult brain is developing in response to new experiences. When adult rats learn to keep their balance on dowels, their cerebellar Purkinje cell neurons develop new synapses (Black et al. 1990). Studies on rats and mice indicate that environmental stimulation can increase the number of new neurons in the dentate gyrus (Kemperman et al. 1997; Gould et al. 1999; Praag et al. 1999), and it appears that these neurons formed in the adult rat hippocampus are associated with memory (Shors et al. 2001). Several thousands of these neurons are produced each day, and experience appears to protect them from apoptosis. These neurons appear to integrate into the adult brain where they respond to regionally specific cues and differentiate into site-specific types of neurons (Gage et al. 1995; Suhonen et al. 1996). Behavior can even modify the neuroanatomy, as shown by Breedlove's experiments (Breedlove 1997) on the SNB region of the spinal cord. Here, a specific behavior (copulation) altered the morphology of a particular region of the central nervous system.

Neuronal plasticity appears to be an extremely significant part of the human phenotype. If there is any important developmental trait that distinguishes us from the rest of the animal kingdom, it is the retention of the fetal neural growth rate. During early postnatal development, we add approximately 250,000 neurons per minute (Purves and Lichtman 1985). Apes' brains have a high rate of growth before birth. After birth, this rate slows greatly. In contrast, humans have rapid brain growth both before birth and for years thereafter (Martin 1990). By the time humans are adults, they are literally off the chart. The ratio of brain weight to body weight is similar for great apes and humans at birth. However, at adulthood, the human ratio is 3.5 that of apes (Bogin 1997). It is in this early postnatal stage that intervention can raise IQ (reviewed in Wickelgren 1999). This age also sees much of the maturation of the neural circuitry as determined by axon diameter and myelination.

The retention of the fetal neural growth rate gives us a remarkable number of new neurons, and we can only speculate that these will be utilized in ways that allow us to think and act. It is thought that this increase in neurons may (1) generate new modules (addressable sites) that can acquire new functions, (2) store new memories for use in thinking and forecasting possible scenarios, and (3) learn by interconnecting among themselves and with prenatally generated neurons. It should provide a new level of

plasticity, one that adds experience to endowment; for the nervous system, like the other sensory network, the immune system, can develop according to environmental needs. Its repertoire is enormous, and we can each learn different skills and have different memories. Indeed, it is during this childhood stage that we learn how to learn. As Childs (1999) has concluded:

Extended exposure of a gradually maturing nervous system to experiences of a variable environment, together with the mental resiliency to continue to learn at all ages, is a recipe for the adaptive agility that has enabled human beings to live in all latitudes and so to exploit the earth's resources to construct civilizations and to be aesthetically creative.

We retain our plasticity into adulthood. Cortical reorganization is still possible in adults, and the "phantom limb" syndrome appears to be due to such "rewiring" of the nervous system (Flor et al. 1995; Davis et al. 1998; Montoya et al. 1998). Thus, the human brain is not an anatomical fait accompli at birth (or even after childhood). Like the immune system making new lymphocytes from its stem cells, so the nervous system keeps making new neurons. Purves and Lichtman (1985) have concluded, "The interaction of individual animals and their world continues to shape the nervous system throughout life in ways that could never have been programmed. Modification of the nervous system by experience is thus the last and most subtle developmental strategy."

4   The Nervous System and the Immune System

The immune system monitors the outside environment. It has the ability to recognize all possible shapes in the external world. It has memory such that once it has been exposed to an antigen, it "recalls" seeing it and can react to it more rapidly and efficiently. The same features, of course, are seen in the nervous system. I will propose (as others have before me) that the immune system and the nervous system are actually different components of an integrated sensory network. Hoffmeyer (1995) has seen the immune system as metaphor for the nervous system, taking the nervous system into the body. There is now evidence that the connections between the immune system and neural system are quite real.

First, classical "neuromodulators" of the nervous system also affect the immune system, while classical "cytokines" of the immune system also af-

fect the nervous system. Several cytokines can function in the nervous system. Interleukin-2, the prototypical T-cell growth factor and immunoregulatory cytokine, can function as a neurotrophic factor (Petitto et al. 1999). The hypothalamus is rich in IL-2 receptors, and mice having genetic defects of IL-2 synthesis have reductions in hippocampal mossy fiber length and in spatial learning and memory (as assayed by the Morris water maze). Interleukin-1 receptors are also present in the hypothalamus, and IL-1 is able to produce several CNS effects, including fever and lethargy. IL-1 has also been implicated in the hippocampus, where it appears to play an inhibitory role in long-term potentiation (O'Connor and Coogan 1999; Hammond et al. 1999).

Conversely, several neuromodulators have important effects in the immune system. Since the 1980s, we have known that stress has important effects on the CNS. Physiological stress reduces lymphocyte number and function, and both ACTH and alpha-endorphins severely reduced T-cell-dependent immune responses (Keller et al. 1981; Johnson et al. 1982). Beta-endorphins appear to enhance the T-cell response (Gilman et al. 1982). These interactions between the neural and immune systems have given rise to new scientific disciplines (such as neuropsychopharmacology) as well as a burgeoning popular literature on how to stay healthy (as in Bernie and Siegel 1992). T-cells respond to serotonin by proliferating (Sibella-Arguelles 2001), and even nerve growth factor (NGF) appears to be involved as a cytokine (Solomon et al. 1998; Turrini et al. 2001). Eosinophils have NGF receptors and they make and store NGF. NGF can induce eosinophils to selectively release peroxidase (but not IL-6).

One remarkable phenomenon showing the integration of the immune and neural systems is the ability to use Pavlovian operant conditioning to induce allergies by odors. When paired with an audiovisual or odor cue, the injection of an allergen can induce an allergic immune response in rodents. After several paired trials of allergen and sensory cue, the allergic response can be triggered solely by the audiovisual or odor cue. The entire immune response has become regulated by the nervous system. The actual allergen is no longer needed (Metalnikov and Chorine 1926; Russell et al. 1984; Palermo-Neto and Guimaraes 2000).

Even the expression of major histocompatability genes can be regulated by neural activity. Carla Shatz's laboratory has shown that in the murine

lateral geniculate nucleus, the genes encoding class I major histocompatibility complex (MHC) proteins were significantly repressed upon neural stimulation (Cooriveau et al. 1998; Huh et al. 2000; Boulanger et al. 2001). While class I MHC proteins are the critical molecules used to display certain antigens, these proteins also appear to be necessary for developmental plasticity and synaptic modification. If these brain neurons fail to synthesize MCH class I proteins, several memory functions are impaired or enhanced. One of the papers concluded, "These observations indicate that class I MHC molecules, classically thought to mediate cell-cell interactions exclusively in immune function, may play a novel role in neuronal signaling and activity-dependent changes in synaptic connectivity." Another classic set of immune molecules, the immunoglobulins, may also play roles in the nervous system. Immunoglobulin synthesis has been detected in the mammalian brain cortex (Upender et al. 1997; Weiner and Chun 1997), and Upender and Naegele (1999) provide evidence that neural immunoglobulin may be involved in regulating phagocytosis in the CNS.

There is even an "immune synapse" between T-lymphocytes and B-lymphocytes. While this term was originally used as a metaphor, suggesting that the contact points between T lymphocytes and antigen-presenting B cells were like the neuromuscular junction, research by Khan and colleagues (2001) has shown that the neuromuscular junction organizing protein, agrin, is also found in these "immune synapses," and it is important for the restructuring of the membranes and signaling proteins of this region, just as it is in the neuromuscular junction. Trautmann and Vivier (2001) speculate that just as agrin appears to be important for the establishment of neural memories, it might also be critical for the establishment of immune memory.

Last, another possible, though not as mechanistically grounded, area where the immune system and nervous system can be seen to interact may be in the pathogenesis of autism. Studies looking at the relationships between autoimmune diseases and mental health suggest that in some families, immune dysfunction may be interacting with other environmental factors to play a role in the development of autism (van Gent et al. 1997; Comi et al. 1999).

Therefore, it is misleading to consider the immune system as something distinct from the neural system. There is as much an immunoneural system

as there is a neuroendocrine system. But as the neuroendocrine system monitors the internal milieu, the immunoneural system is a sensory network that monitors the external environment, remembers what it has perceived, and can react upon that memory when it perceives the outside signal again. These are not merely metaphorical terms. As has been shown with operant conditioning of allergic responses, histamine release from mast cells can be taken from immune function to neural function; monitoring the external environment can give you the same result through either pathway. One cannot make an antibody to an idea; but the ability to mount an immune response to a noise or an odor perception indicates a remarkable synergy between the immune and neural sensory networks. Both these networks have the capacity for simple learning and memory. Their synergism might lead to the emergence of unexpected properties.

5   *Quid significat?*

So far, we have shown that predator-induced polyphenism is prevalent in the animal kingdom, and that the immune system can be viewed as an elaboration of this ability to defend oneself against predators by changing cellular development. We have shown that, like the immune system, the nervous system retains its plasticity throughout development. We have also shown that the immune system and the nervous system are so tightly integrated that molecules active in the signaling of one system are also active in signaling in the other system. Moreover, these cross-signaling properties are physiologically relevant. There exists an immunoneural sensory network.

   What does it all mean? Most all hypotheses concerning the evolution of cognition describe the evolution of the nervous system. Thus, nervous system-specific phenotypes such as language acquisition or childhood have been foregrounded as being essential to becoming human. But if the entire sensory network (not just the nervous system) is involved with plasticity and cognition, perhaps other phenotypes were equally important. Let me leave the data for the moment and enjoy some speculation. I'll suggest as a hypothesis that a major role of the sensory network (ie., the immunoneural system) was that of predator defense. In other words, the neural portion of the sensory network was (and is) also involved in what the immune portion was doing. How does the neural portion of the sensory network help us

avoid predators? There are two ways. The first is the obvious way of seeing, smelling, tasting, touching, and hearing. These we share with any other preyed-upon species. But I had always learned (indeed, since elementary school) that humans were weak animals, and that it was our brains that allowed us to prevail in nature. So our brains are involved in particularly human ways of escaping from predation. There are two ways this could be done. One way is the manufacture of weapons. The other way is more primary. It is to fantasize that which isn't there or even possible. Humans can imagine alternatives and fantasize what would happen if one follows them. Our brain can fantasize how we would feel in different situations, and then we could choose, having imagined ourselves in these alternatives scenarios. This ability to fantasize may be critical in our becoming human, for humans are those animals who can visualize alternatives and make plans to enhance the odds of certain alternatives happening.

In our most basic metaphor of choosing, we envision two paths diverging from where we stand. Which path do we follow? This is perhaps the key to fantasy, for the roads will rarely be equal. We must imagine what lies beyond the horizon on each path. Here is where our mind must act to avoid predators. While our immune system acts to avoid the micropredators, the brain acts to avoid the lions, tigers, and bears. We are not good fighters or runners. As any martial arts instructor will tell us, the first rule of self-defense is to avoid the confrontation. We must fantasize which path is the safest. And then we must choose, based on these fantasies. Paul Tillich and other existentialist philosophers have also located the essence of humans in their ability to choose between alternatives. To choose is an act of will. But in order to choose, we must first be able to visualize the consequences of our choices before making the decisions. In other words, we have to be able to fantasize the counterfactual, the not-yet-brought-into-being. Fantasy becomes a prerequisite for our humanness.

The next step is to take an active part in realizing what one has only imagined. In the above metaphor, humans are the choosers, but the diverging paths lie before us, already made. But what if there is but one path, and one can imagine it going into a place fraught with danger. One can imagine oneself being chased, mutilated, or eaten there. One can imagine making another, safer, path. One can envision a better destination, and make plans for reaching it. One, literally as well as metaphorically, can make one's own

path. This means that humans can plan. In this model of the sensory network as a predator-avoidance system, the first step is to fantasize, the second step is to choose, and the third step is to plan. They are not far apart, and one event might lead quickly into the others. As the philosopher A. J. Heschel (1965) has noted, we are event-planning animals. We can avoid danger by imagining what would happen if we pursued certain paths; and we can attempt to manipulate events such that certain outcomes become more probable than others. The immune function and the neural function are combined in this critical act of cognition.

The ability to fantasize is incredibly well developed in humans. We can be lying on a sofa, a loved one or a pizza by our side, while watching an action movie on television. When the hero is in peril, we undergo all the flight-or-fight responses—even though we are in a safe, even loving, environment. Our sympathetic nervous system is pumping hormones into our blood to give us strength to run away from the perilous situation. The mind has the ability to fool itself. Perhaps given the enormous responsibilities of life, the mind needs to fool itself if only to allow us to continue our daily existence. Denial is also a fundamental fact of human cognition, and it is a consequence of our ability to fantasize the counterfactual. Indeed, the ability to avoid reality may be both prerequisite and perquisite of being human. The ability to fantasize is probably selected, and other animals probably share it with us in rudimentary form. Dreaming and erotic fantasy certainly show that the mind can fool itself (and the body), and other mammals also seem to be able to partake in both these types of exercise. Rabbits and other easy prey make their burrows with several escape routes. Perhaps they can imagine a time when they will be needed; and those that did not have probably been eliminated by natural selection.

It may be possible that cognition and mind originated in the context of predator-induced polyphenism, the ability of the organism to alter development in a manner that would increase its fitness. Baldwin would have certainly understood this. The ability to avoid predators by sensing them immunologically and neurally emerged early during evolution. What forms a cognitive mind would be the combination of these elements to form a joint immune and neural sensory network that interacted in such a manner that one part of the system would synergistically aid the other. Both the human immune system and the human nervous system are able to continue

growth for a long duration. Unlike all other primates, the human nervous system grows significantly after birth. It is in this period of childhood that fantasy is learned. And it may be that fantasy, as much as or even more so than language, is what makes us human.

Acknowledgments

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