

# Developmental Disorders and Evolutionary Expectations: Mechanisms of Resilience

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Every living organism can trace its lineage back to the unicellular organisms that first populated Earth. We are thus the descendants of creatures who have not only survived but have successfully reproduced in the face of gross atmospheric shifts, blasts of ionizing radiation, the impacts of comets, ice ages, global warming, earthquakes and hurricanes, plagues of any number of viral and bacterial forms, predation, starvation and drought, the toxins of plants and animals, parasites, competing tribes, jealous fathers, indifferent mothers, and everyday accidents of all kinds. Any survivor of this wildly improbable lineage is made of tough stuff. The point of this chapter is to turn the usual discussion of developmental vulnerability on its head and, rather than discuss the effects of an "environmental insult(s)" on a fragile infant, examine the design features of the tough stuff of which we are made. We argue that only in this evolutionary context will the disorders of development that sometimes do emerge make mechanistic sense.

## EVOLUTIONARY DRIVES

### Catastrophe

Conservation of the building blocks of the embryo across the invertebrate and vertebrate lineages and the resilience of that embryo have been part of a general rethinking of the character of the evolutionary process to which our ancestors were subjected, along with greater awareness of the effects of periodic global catastrophes on the nature of the genome (Gerhart and Kirschner, 1997). Struggle for success among individuals in an evolutionary landscape of potential niches and their associated fitness peaks, *success* defined by better adaptation resulting in greater reproduction, is the essential Darwinian view. The kinds of adaptations highlighted by this process are both increasingly subtle organism and environment fits and enhancements important in sexual selection, a central aspect of evolutionary change.

Catastrophe, local or global, provides a force in which all organisms, across radiations and species, are

subjected to a severe filter; success arises from survival in suddenly changed environments (Alvarez et al., 1980; Albritton, 1989). Variation in gene transmission during catastrophe can arise from individual competition as well, but whole radiations may be lost. The best-known example, of course, is the extinction of the dinosaurs and survival of mammals in the late Cretaceous period. Selection will favor the robust and adaptable organism, able to weather disaster, to relocate or create its favored niche or get by in a new one, and to reproduce as much as possible. Our genomes carry the history of both types of change. Moreover, the nature of genetic change appears to make it likely that this history is not overwritten in such a way that it is inaccessible, but rather added to, as we will elaborate later.

#### Evolvability

"Evolvability" is a related, but distinct idea that carries import for how a genome can respond to challenge. This idea has been used in two distinct ways in the allied fields of evolutionary biology and artificial intelligence and robotics by means of genetic algorithms. The first, and somewhat stricter, sense of this concept arose from the hypothesis and later demonstration (in bacteria) that in times of extreme stress and crisis, "deliberate" additional variation and mutation would arise as an adaptive mechanism, suppressed in favored environments (Gerhart and Kirschner, 1997; Radman et al., 1999). The second, more general, sense is the observation that some types of genomic or informational structures more readily produce usable adaptive changes and the potential for evolution than others (Lipson and Pollack, 2000; Nolfi and Floreano, 2002; Baum, 2004). Everything else equal, the "evolvable" organism is more likely to be with us today. Both the strict and the general sense of evolvability will be important in understanding the response of organisms to developmental challenge.

#### Adaptive Response Or Pathology?

The third conceptual thread to be woven into the argument for evolutionary change is the recasting of some states usually viewed as illness or pathology as adaptations by the emerging field of evolutionary medicine (Nesse and Williams, 1996). A virus co-opting our genome for its own purposes is a bad thing. Consequently, an immune response disables

the virus at the cellular level (antibodies), makes its environment inhospitable (fever), and expels it (all the various miseries of flu). Each of these symptoms can be viewed as adaptive responses, not as pathology. Of course, not every response to disease or trauma is adaptation, and the urge to tell such "just-so" stories must be strictly policed. For example, exsanguination when an artery is severed might cleanse the wound and quickly lessen metabolic load, but obviously it is not an adaptive response. Conceptual clarity in this domain gets particularly muddled when organisms are in close competition. For example, it would appear that the enterprising rhinovirus has co-opted the expulsion component of the immune response for its own adaptive purpose of spreading itself around the environment—whose adaptation is the sneeze?

Evolutionary medicine becomes particularly relevant to the developmental response to shortages and pathogens when the normal, tactical nature of the response of the adult organism to challenges is considered and applied to development (Bateson et al., 2004; Gluckman and Hanson, 2004). The best and most elaborated example in physiology is the balancing of requirements for short- and long-term survival in the hypothalamic-pituitary-adrenal axis in response to acute and chronic environmental stressors (Sapolsky et al., 1986). In order to survive an immediate threat, energy is mobilized by metabolic changes that, if they persist long-term, will damage the animal. Alterations in nervous systems and behavior in response to early environmental challenges, particularly commonly encountered ones, might also be tactical adaptations and should not automatically be construed as pathology. For example, perhaps it is a good bet to alter interest in food compared to general exploration in perpetuity if early experience shows food to be in unusually short supply (Smart and Dobbing, 1977; Levitsky, 1979; Bateson et al., 2004; Gluckman and Hanson, 2004).

#### Environmental Expectation

The fourth thread is environmental expectation. This is usually raised in the context of predictable environments and a genome predisposed to learn (Greenough and Black, 1992): if information about the future structure of visual information in the world is well predicted by present structure, and there is time to learn it, why waste genome specifying it? Considering one of the classic cases of ethology, if mother is

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the first large, moving thing any duck likely to survive sees, then learning the qualities of the first large, moving object is an efficient way to get the information. On the other hand, the physiological armamentarium available indicates that we also expect trauma, infection, and poor nutrition of all kinds. There is no reason to assume that the brain is not similarly prepared. Recent comparison of the genome of the chimpanzee and of the human, showing rather more changes in genes involved in food metabolism and immune response than in the brain-related genes, has underlined that genetic response to often-encountered challenges may be fairly rapid, and “diet and pathogens are dominant selective forces for all species” (Olson and Varki, 2004). Relevant to this chapter is the cultural history of alcohol. As alcohol has served as a common source of nutrition and food preservation in Western Europe, those populations (compared to Asian ones) have become equipped to metabolize alcohol, and there is some evidence that the incidence of alcoholism falls the longer fermented products have been used in a particular culture (Goedde et al., 1992; Whitfield, 1997). To understand a developmental response to an environmental challenge, it will make a great deal of difference whether the challenge is “expected,” such as alcohol, or unprecedented—for example, a designer drug such as thalidomide that may mimic the form of an early regulatory gene.

#### A Warning and a Road Map

In the following section, we first examine a few central cases of the developmental consequences of alcohol and other substance abuse, and turn the usual style of presentation upside down to show the outrageous situations in which the typical embryo can survive. A strong caveat is necessary here: at no point should a demonstration that the “typical” infant can be born without defect—for example, following a persistent bath of alcohol—be mistaken as an argument endorsing alcoholism in pregnant mothers. A substantial percentage of infants exposed to ethanol do have defects, a probability no prospective parent should ignore. Nor are we in any way attempting to minimize the value of locating and ameliorating those defects caused by developmental insults described in many of the other chapters of this volume. Rather, our point is that if we fail to appreciate the robust nature of the developing embryo and consistently mislabel

deviations as pathology instead of adaptations (or just deviations), we will be in an explanatory realm that makes no sense if we try to understand the pathologies of development that can and do occur.

Next, we will turn to some general design features of development that are stable in the face of challenge, and consider some particular cases of nervous system development that show those principles. Overall, the guiding principal in this discussion is one that is true for all life sciences but is often ignored in medicine: “nothing in biology makes sense except in the light of evolution.” (Dobzhansky, 1973)

#### CONTEXTUALIZING THE DEVELOPMENTAL EFFECTS OF ALCOHOL, NICOTINE, AND THALIDOMIDE

##### Alcohol

The human body has a variety of mechanisms for the screening and disposal of toxins. Alcohol is no exception. The presence of alcohol in our evolutionary and developmental environment has led to specific enzymes responsible for its metabolism: alcohol dehydrogenase and acetaldehyde dehydrogenase. Ethanol is naturally encountered in fermentation in fruit, and also is a direct result of fermentation of starches in the gut. In many human cultures, alcohol is sought not only for the obvious psychoactive consequences but also because it serves a useful role as a preservative and secondarily as a source of calories (Goedde et al., 1992; Whitfield, 1997; Dudley, 2000, 2002). Alcohol can thus be considered not simply a completely alien disruptive element but also a normal part of the developmental environment. This is not to downplay the dangers of ethanol to a developing organism but to place it in the context of a regulating system. We note in passing that this evolutionary history may have a significant impact on the relevance of animal models to human development, where frugivores and omnivores might be considerably better models than carnivores.

With the assumption of the robustness of the developmental system in mind, we turn to a recent study from Martinez-Frias and colleagues (2004) on the relationship between alcohol consumption during pregnancy and congenital anomalies, paying specific attention to those anomalies indicative of fetal

alcohol syndrome (FAS). From a corpus of data collected over 24 years, Martinez-Frias and colleagues drew a group of 4705 malformed infants and a comparable group of 4329 normal infants whose mothers reported alcohol consumption during pregnancy. These infants were examined in the first 3 days of life for a variety of congenital anomalies, including various nervous system defects and a set of craniofacial anomalies. These facial anomalies, including a hypoplastic nose, are indicative of several cognitive impairments (Swillen et al., 1999; Donnai and Karmiloff-Smith, 2000). In particular, they are typical of FAS and, in conjunction with maternal alcohol consumption, are considered reliable predictors of the condition (Astley and Clarren, 1997; Coles et al., 2000; Streissguth and O'Malley, 2000; Sood et al., 2001).

Subjects can be grouped by maternal alcohol consumption into five categories, ranging from group 1, who experienced low, sporadic exposure through a range of daily doses, to group 5, who were exposed to over 92 g of absolute alcohol per day throughout gestation, including several glasses of distilled spirits. Group 5 also included the offspring of those who self-identified as alcoholics. An odds ratio was calculated for each birth defect to indicate the effect of alcohol consumption on the risk of developing that defect.

To begin with the worst-case scenario, we should expect infants of group 5 mothers to show severe deficits. In adults this level of alcohol consumption is associated with anoxia, the pathological deficiency of oxygen, as well as renal failure and severe nutritional deficiencies. As a result, it would be expected that this level of exposure would cause a variety of deficits in a developing organism. Among 87 infants exposed to this amount of ethanol, 67 had at least one physical defect. Thus, only 23% were normal at birth. Looking to the nervous system, however, 79% of the infants showed no central nervous system (CNS) defects under standard infant neurological examinations. Given a level of alcohol exposure known for its damaging effects on the physiology of adults, this is remarkable resilience. Because the neurological component of the suite of FAS-associated symptoms is not consistently detectable at this age, facial phenotypes alone are used as a proxy for FAS (Astley and Clarren, 1997); fully 60% of the infants in group 5 had a normal facial phenotype. Although 40% damage is a tragic statistic, even in this extreme case of shockingly irresponsible alcohol consumption, more than one-half of the infants show evidence of being quite normal.

Normality dominates the rest of the groups. In group 4 (the second-highest group), the offspring of mothers who consumed between 56 and 88 g ethanol per day, 95% of the infants showed normal facial phenotypes. According to the odds ratio, children of these mothers were twice as likely to develop the typical FAS characteristics, but the difference was not statistically significant. Only group 3, with low daily consumption, showed a statistically significant relationship between alcohol consumption and this phenotype. At this consumption level, 97% of the infants showed the normal phenotype. In the sporadic alcohol consumption groups (1 and 2), not only were FAS-predictive anomalies present in only 3% and 2% of the infants, respectively, but the odds ratios suggested that alcohol consumption decreased the risk of anomalies, although these differences were not statistically significant.

An important consideration in this study, and generally in the field, is that of socioeconomic factors. Children of mothers of lower socioeconomic status are at greater risk, for a variety of reasons. These mothers are more likely to be exposed to other risk factors, including lead (Malcoe et al., 2002; Morello-Frosch et al., 2002), chemical solvents (Cordier et al., 1992), and illegal drugs (Hans, 1999). These risk factors are also associated with cognitive impairments. Hence, it is difficult to separate alcohol from other potential causative factors. Additionally, even given equivalent alcohol and drug exposure, children of higher socioeconomic status are more likely to be normal. A substantial review of neurobehavioral studies of alcohol-exposed children (Mattson and Riley, 1998) confirms the prevalence of low scores on cognitive tests in groups of low socioeconomic status, but also includes startling examples of children who perform at normal levels and even above on cognitive tests (Streissguth et al., 1980; Fried and Watkinson, 1988, 1990; Fried et al., 1992). Indeed, the term *low-risk group* is used synonymously with higher socioeconomic status in these studies. Notably, given low to moderate consumption and a high level of maternal education, IQ and other cognitive scores fall well within the normal range, and occasionally with mean scores a full standard deviation above normal. Although these scores were lower than those achieved by children in the same socioeconomic level without fetal alcohol exposure, it is clear that multiple factors in the developmental environment beyond alcohol consumption are at work in children who show substantial deficits.

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Further, studies of the effects of exposure to low (Forrest et al., 1991; Greene et al., 1991; Fried et al., 1992) or even moderate (Mau, 1980) amounts of alcohol fail to find a cognitive deficit. Although these studies focus on exposure to lower amounts of ethanol, they are significant in light of conventional wisdom that any and all alcohol consumption during pregnancy is an unacceptable risk. Rather than being a silver bullet capable of derailing normal neurological development, alcohol exposure at low levels has effects that are hard to demonstrate, which makes sense in terms of the long-term presence of alcohol in our ancestry. Even at pathologically high levels it does not have 100% penetrance.

### Nicotine

Nicotine is certainly less common than alcohol in our evolutionary history. Indeed, consumption of any significant amount of nicotine is a recent development in human history. The suite of developmental effects caused by smoking (the most typical way of using nicotine) is complex, involving respiration and oxygen availability directly, peripheral vasoactive effects, and action on central neurotransmitter systems. Still, a number of its effects fall within a well-developed evolutionary context in development, that of reduced resource availability. Although we cannot review this context and its effects fully here, it is well established that the developmental program shows significant flexibility with regard to nutrient availability. Within limits, growth can be scaled back or delayed in times of poor nutrition, favoring the brain whose generation is largely prenatal, and caught up when conditions are favorable (Lucas and Campbell, 2000).

Tobacco exposure restricts the availability of nutrients to the developing fetus (Lambers and Clark, 1996). Carbon monoxide from tobacco smoke binds with hemoglobin, the oxygen-carrying molecule in blood, to form a stable carboxyhemoglobin, limiting oxygen transport in the mother and thereby depriving the fetus of oxygen as well. Nicotine increases heart rate and causes vasoconstriction, increasing blood pressure in the mother, reducing uterine blood flow, and therefore decreasing a fetus's access to all nutrients. Hypoxia, malnutrition, and the ensuing metabolic challenges force the fetus to make do with inadequate resources. As such, it is not surprising that the most common effect of nicotine exposure is low

birth weight (Ellard et al., 1996; Lambers and Clark, 1996). Low birth weight is independently associated with cognitive deficits (Chaudhari et al., 2004; Corbett and Drewett, 2004; Viggedal et al., 2004), regardless of the causative agent. Indeed, as a systematic problem, it is generally associated with growth deficits throughout the body, including osteopathic effects (Nelson et al., 1999), yielding a generally underdeveloped organism. As such, it is difficult to determine whether any cognitive deficits can be directly attributed to nicotine or tobacco or if they secondarily stem from anoxia and generally decreased resources.

The direct effects of nicotine on neurological development are controversial, and in a way that is reminiscent of the complex interactions of postnatal environment with prenatal malnutrition. A variety of studies indicate no cognitive deficits in infants and young children (Streissguth et al., 1980; Forrest et al., 1991), and there is some evidence of a transitive effect, with scores on the Bayley Scales of Development (BSID) that are low at 12 months coming up to normal levels by 24 months (Fried and Watkinson, 1988). Often tests that do indicate an effect in children of heavy smokers fail to separate it from postnatal exposure (Richardson et al., 1995), which has more reliably been associated with decreased scores on cognitive tests (DiFranza et al., 2004). Even so, this effect on BSID test scores is typically small when compared to other factors, including number of toys in the household, socioeconomic status, number of infant illnesses, and even the identity of the examiner. Essentially, the data indicate that one would be better off spending the cigarette money on toys, as a deficiency of toys in the child's home is a more reliable predictor of decreased cognitive scores than nicotine and tobacco exposure.

### Embryological Silver Bullets

In contrast to our relatively robust developmental defense against alcohol, for which we have evolved specific mechanisms dedicated to its detoxification and metabolism, and against nicotine, which may be subsumed under mechanisms already available to buffer resource limitations, there stands a new class of potential teratogens: designer drugs. These drugs are often evolutionarily novel, based on molecules never encountered by our ancestors in the natural environment. Or they can be similar to or even based on molecules naturally produced by the human body,

potentially bypassing protective mechanisms, to manipulate the developmental process directly.

Though hardly typical of modern entries into the category, thalidomide is certainly the most infamous example of a designer drug. Introduced in 1957 as a sedative and anti-nausea agent, it was considered so safe as to be regularly prescribed to combat morning sickness and insomnia in pregnant women. Withdrawn from the market in 1961, in less than 4 years thalidomide had caused a worldwide epidemic of birth defects. While no accurate census was ever taken, it is estimated that between 10,000 and 20,000 babies were born disabled as a result of thalidomide (Knightley et al., 1979; see <http://www.thalidomide.ca>, [http://www.marchofdimess.com/professional/681\\_1172.asp](http://www.marchofdimess.com/professional/681_1172.asp)). Completely unknown is the rate of embryonic rejection in the face of this drug. Thus it is difficult to estimate the penetration of the teratogenic effects of thalidomide.

The methods of action responsible for the teratogenic effects of thalidomide are still under investigation nearly 50 years after its introduction. Indeed, study has increased drastically in recent years as new applications for the drug have been found in treatments for leprosy, lupus, rheumatoid arthritis, and other disorders. As a result, at least 30 different mechanisms have been proposed for the teratogenic effects (Stephens and Fillmore, 2000). Some have been discredited, others are contradictory, whereas others can coexist handily.

An affinity for DNA sequences rich in guanine has been established, such as those in the GC-box, a hexanucleotide promoter in the human genome (GGGCCG). Thalidomide can insert into such sequences, interfering with their function (Jonsson, 1972). Approximately 9% of the human genome uses G-rich promoters to the exclusion of other common promoters such as TATA and CCAAT boxes (Bucher, 1990). Additionally, thalidomide has been linked to the fibroblast growth factor (FGF) family of transcription factors. Wolpert (1976, 1999) champions the idea that thalidomide inhibits FGF-8, an initiator of sonic hedgehog (*shh*). Stephens (1988) implicated it in the insulin-like growth factor (IGF) I/FGF-2/angiogenesis pathway. A follow-up to this work (Stephens and Fillmore, 2000) details the interrupted pathway and its promoter sequences, effectively tying together the leading theories on thalidomide embryopathy to make a strong case for intersecting vulnerabilities in certain systems.

Within the thalidomide-affected population, certain trends in the abnormalities are relevant to our discussion. Some defects are much more common in children that survived to birth. Limb outgrowth deficiencies are far and away the most common, present in approximately 90% of the group. Ear and eye defects are the second most common pathologies, affecting approximately 60% of the group (Yang et al., 1977; Quibell, 1981; Lenz, 1985).

In the developing limb, the IGF-I/FGF-2/angiogenesis pathway is necessary for normal outgrowth. Of 10 genes in the pathway, 9 rely on GC-box promoters lacking TATA or CCAAT promoter sequences. This pathway is particularly vulnerable to intercalation by thalidomide. A similar situation exists for the vascular endothelial growth factor-integrin pathway, which has been implicated in deformities of the ear. Regardless of which or how many of these mechanisms are eventually implicated in developmental disorders, it is notable that the explanations, as a class, directly implicate developmental control mechanisms.

#### FEATURES OF EVOLUTION AND DEVELOPMENT THAT MAXIMIZE STABILITY

The prior examples show that we have a phenomenon to account for developmental stability of most infants in the face of what would appear to be severe challenges, particularly in the case of "expected" challenges. Most of the other chapters in this volume give accounts of abnormality; here we make some argument for forces for normality.

A list of the features of the genome and development that produce "evolvability" and the list of those that produce stable solutions to developmental challenges are quite similar. Both problems have the defining feature of producing a functional consequence in the event of a deviation. In the case of evolution, the deviation to be assimilated comes from the genome; in the developmental cases we are discussing here, the deviation is introduced from the environment. The principal difference is that evolution lacks the tactical nature of some developmental solutions. Evolution has no plans for the future, and in the genome and life histories of current organisms we see the direct evidence of what is evolvable. Development, however, most certainly has intention

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and tactics, as they have been selected and written into the genome. No developmental program has as its end point a perfect, nonreproductive infant. Trade-offs and faults can be gambled on to produce an imperfect, reproductive adult.

### Duplicate and Vary

An overall quantitative feature of evolution is that as organisms become more complex, from prokaryotes to eukaryotes and to plants and animals, they have more DNA and more genes (Lynch and Conery, 2003). That an increase in complexity should be partnered with an increase in genes at first seems reasonable on its face, until the amount of conservatism in basic metabolic pathways is confronted and the actual history of genetic change is investigated (Szathmáry et al., 2001). It is not clear that increasing the number of gene products per se should necessarily lead to fancier animals—if Shakespeare had had a few more letters of the alphabet to work with, few would argue that the plays would thereby be deeper.

The historical record of the genome as viewed in current animals does not show linear increases of genetic material consistent with the notion of progressive addition of complexity. Rather, duplications occur many times over, gene duplication followed by variation of one of the duplicated genes, both at the level of the individual gene and at the level of the whole genome, as well as at various intermediate steps (Lynch and Conery, 2000). We give a few examples. The trichromatic color vision of primates has arisen three separate times, by duplication of the “yellow” opsin followed by one or two minor amino acid changes in one of the genes producing a slight change in wavelength selectivity (Jacobs, 1998). A whole-genome duplication occurs at the chordate-vertebrate boundary, implicated particularly in the subsequent elaboration of the cranium, jaw, and forebrain (Northcutt, 1996).

The regulatory genes controlling body plan, which are conserved across vertebrates and invertebrates, show evidence of multiple replications in evolutionary history (Gerhart and Kirschner, 1997). The use of this strategy is clear—one gene can continue its essential roles, while a second can be free to vary, assume new functions, or be produced in different contexts. The ability to duplicate and vary “semantic” aspects of the genome—that is, aspects of the genome that relate to meaningful components of

the organisms—is a feature that allows evolvability, and has been employed to advantage in “genetic algorithms” in computer science (Lipson and Pollack, 2000; Nolfi and Floreano, 2002; Baum, 2004).

Duplicate-and-vary by its nature makes development responsive to local genetic accident. One frustrating aspect of early genetic work (to geneticists) is that when it became possible to “knock out” single genes (in the case of nonlethal omissions), the usual effect was often nil, largely because of the massive redundancy of gene copies. It should be emphasized that extra or slightly altered gene copies did not evolve in anticipation of future accident. Once in place, however, creatures with the duplications have had a developmental edge. Many other versions of the duplicate-and-vary strategy can be seen in addition to gene and variation. For example, the segmental structure of the vertebrate and invertebrate brain and body plan is another version of duplicate-and-vary, at a higher level of complexity.

Large neural structures, such as the cortex and cerebellum, may also be cases of duplicate-and-vary (or multiply-and-vary), regardless of whether the unit duplicated is a cell assembly, a “cortical column,” a region, or a cortical area. Cortical areas have the analogous strategic features of conserved structure throughout, such that cortical areas may be functionally substituted for each other, as shown from myriad examples of plasticity either early or late in life, but particular cortical areas, such as visual or somatosensory cortex, appear to have functionally relevant local features “wired in” (reviewed in Kingsbury and Finlay, 2001; Pallas, 2001). Finally, it is possible that some of the peculiar features of our bilateral body (and brain) plan might be placed in this context. The exact caloric requirements of each body part appear to be very tightly regulated. For example, the brain size and gut length (two metabolically expensive organs) co-vary negatively with each other very precisely in primates with the result of keeping basal metabolic rate unchanged (Aiello and Wheeler, 1995). Yet the amount of each organ we possess seems to be far from the bare minimum required, or even the amount required for everyday function. Jared Diamond calculates from various successful surgeries in humans that we can get by with one kidney, half of one lung, a third of a liver, half the cerebral cortex, and so on (Diamond, 1994). It has now been acknowledged that creative use of brain lateralization, in the duplicate-and-vary version, can be found throughout the invertebrate

and vertebrate lineage, in fruit fly, fish, birds, and many arthropods, and, of course, ourselves (Vallortigara and Rogers, 2005). Humans do quite peculiarly well with early, full hemispheric deletions.

### Convergent Redundancy

Frank duplication and variation of identifiable developmental mechanisms seem to have occurred numerous times; as can be seen in the many isoforms and other variants of cell recognition molecules, signaling molecules, and trophic molecules. An absolute hallmark of development, however, is redundancy of a different type, where multiple distinct mechanisms are all directed toward the same outcome. The retinotectal system, in which the two-dimensional layout of cells in the retina is faithfully transferred to the two-dimensional surface of the tectum for the organization of eye and body movements, has served as a "model system" for the investigation of axon guidance, synaptogenesis, and topographic map formation since Roger Sperry first investigated it half a century ago (Sperry, 1963). This model system provides the clearest instance of mechanistic redundancy. Each proposed mechanism has had its researcher-champion, until the realization dawned that evolution had taken no vow of mechanistic parsimony.

There are a number of logical possibilities of mapping an array A-B-C-D onto a second array A\*-B\*-C\*-D\*, each of which alone can solve the developmental puzzle. A could recognize A\*; B recognize B\*, and so on, which is called "chemoaffinity," Sperry's first hypothesis (Sperry, 1963). Alternative to attraction, A could be repelled by D\*, and less by C\* (Bonhoeffer and Huf, 1992). Or, A might stick to B better than to C, preserving intrinsic order in the fiber array, and then have some rule about how to position itself relative to A\*-D\* (Fraser, 1980). Or, temporal order in development might be exploited, having A and A\* mature first, then B and B\*, and so on (Reese, 1996). Or, the elements in both arrays could be produced in excess, connected at random, and errors removed by some second rule, as cell death is a major component of brain development (Oppenheim, 1991). Or, the map could self-organize by a Hebbian rule, using the feature that the contrast level of neighboring elements in the visual world is more highly correlated than distant elements (Schmidt, 1985; Wong, 1999). The answer is, of course, that every single one

of these logically separate mechanisms cooperate to produce orderly maps. During development, it is possible to disable one or more of these mechanisms altogether, yet still preserve topographic map order, much as in gene knockout experiments, as residual mechanisms rescue the map.

These two separate forms of redundancy, duplicate-and-vary and convergent redundancy, contribute to a massively parallel, semimodular architecture of developmental mechanisms living beneath the surface of an organism maturing over time. Starting from scratch to build a complex organism, one might be predisposed to a sequential, assembly-line mechanism, producing one part at a time, and connecting it up, but the relatively greater vulnerability of such a system to loss of any component is obvious. It is interesting to observe the present-day parallel evolution of manufacturing systems from the strictly serial Ford assembly line to current, multiple-component "just-in-time" manufacturing systems. The fact that evolution *must* tinker with existing systems rather than design from scratch is often given as an argument for the unique, redundant nature of biological construction, but it is possible evolution has come upon solutions for efficient biological construction that we may not yet be able to recognize.

### Catastrophe Curves

It will not do to make a large fraction of an organism: it is a waste of energy for the parents and certainly no good for the offspring. Restated, partial solutions are no good in development—if uncorrectable defects are detected, no more energy should be spent on the embryo to compound the metabolic loss. For this reason, bailing out is perhaps the most common response to developmental defect. For many species, particularly "r-selected" animals who are specialized for rapid reproduction in challenging environments, embryos may be resorbed until late developmental stages in response to very small changes in environmental stress, or the fetuses may be aborted and cannibalized, as any researcher attempting to study the etiology of developmental disorders in rodents knows. Even for primates, who spend much energy on the growth and care of one or two infants, a large proportion of conceptions are aborted and resorbed in the first trimester; the common figure given in medical advisories about pregnancy is "up to 50%," although it is hard to locate the empirical basis of this claim.



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Even if the number is much lower, the recognition of developmental disorder and termination of development, particularly in early stages, are as much an important facet of development as constructive mechanisms.

If a commitment to the offspring is unavoidable—for example, if it is the only chance at reproduction, or a life-threatening metabolic commitment has already been made—then every subsequent choice to preserve the offspring should be made as is physically possible. Particularly in shortage situations, clearly strategic choices are made—for example, to preserve the brain of the infant, which is generated only early in development, over and against the musculoskeletal system, whose growth can be delayed, or to favor the infant's nutritional needs over the caloric requirements of the mother (Martyn et al., 1996; Lucas and Campbell, 2000). One "difficulty" in research on developmental disorders, which may not be entirely obvious to those working in well-established paradigms, is to be able to find just those regimes that lie on the cusp between the plateaus of embryonic rejection and death, and full normality.

Analogous strategic similarities can be seen in various developmental mechanisms in the nervous system, for example, a certain number of neurons, a certain convergence ratio between neurons, or a feature of physiology. Central mechanisms can gird the system against environmental stressors, but at a critical value, this defense will suddenly and catastrophically collapse. For example, if the number of neurons in the cortex is progressively depleted by the mitotic inhibitor methylazoxymethanol during early development, the thalamus projecting to that cortex will show no loss of neurons until more than 70%–80% of its target is gone, and then collapse itself (Woo et al., 1996). Similar events may be at play with the anti-mitogen ethanol. Prenatal exposure to ethanol causes a <35% reduction in the number of cortical neurons (Miller and Potempa, 1990) and no loss of thalamic neurons (Mooney and Miller, 2000). Unfortunately, no studies have generated fetal damage sufficient to cause catastrophic loss of cortical neurons. If the convergence ratio in the retinotectal system is challenged, synaptic organization will reconfirm to simultaneously produce normal single-neuron response properties and normal gross topography, and at a critical point, both aspects of organization fail together (Xiong and Finlay, 1996).

The belief that developing organisms should pro-

duce a linear response in degree of malfunction to linear increases in environmental stressors is written very deeply into our experimental paradigms, and at best is a hypothesis to be demonstrated. The nature of malfunction-functions will depend on the evolutionary expectations and consequent strategic developmental choices of each separate species.

### Self-Initiate, Self-Terminate

The nature of control and monitoring regimes to move animals through developmental stages should be evaluated routinely for developmental robustness. In the following sections, we will examine some aspects of early neural development, particularly neurogenesis, neuron type specification, critical periods, and the features these periods appear to have to stabilize developmental outcomes. The bottom line is that most developmental mechanisms contain numerous (and redundant) logical checkpoints to determine if the correct complement of cells is being produced. Feedback-free, "I Love Lucy" assembly lines are virtually nonexistent.

Developmental mechanisms are initiated when multiple conditions for initiation are satisfied, and are terminated when the process initiated is completed, not with respect to arbitrary clocks. In evolution of mammals, in which the time taken to produce a brain scales by a factor well over 10, mechanisms like these simply allow graceful scaling (Clancy et al., 2001). As brains enlarge during evolution, investigators begin to observe "waiting periods" in the development of certain properties, as a set of cells or axon terminals go quiescent until appropriate environmental conjunctions appear to be reached. In the case of developmental challenges, the same ability to pause or delay may be employed to amass enough material or wait for the right conditions to occur to proceed.

### ROBUSTNESS AND VULNERABILITIES IN FUNDAMENTAL DEVELOPMENTAL PROCESSES

Having introduced several features of development through which evolution and development produce stability, we now examine in detail instantiations of these principles at various developmental stages in the vertebrate nervous system.

### Neurogenesis and the Process of Cell Type Specification

*Neurogenesis* comprises the production of neurons and glia that will reside in a structure; this is analogous to *organogenesis*, which is the production of cells that will constitute an organ. Thus, neurogenesis includes the proliferation of neural precursors, the fate decision, the migration, differentiation, and sometimes death of the cells. Most neuronal precursor cells are generated in the proliferative zones that line the inner surface of the neural tube (see Chapters 2, 11, and 12). In these zones, precursor cells undergo mitosis, with “symmetric” divisions, producing more precursors. Eventually, some precursors begin “asymmetric” divisions, with one daughter cell exiting the cell cycle and the proliferative zone, and then beginning the transformation into particular types of neurons or glia (Caviness et al., 1995; Ohnuma and Harris, 2003). The original size of the progenitor pool combined with the duration of neurogenesis of any given part of the brain predicts its size (Finlay and Darlington, 1995; Finlay et al., 2001).

Not every precursor cell in the nervous system differentiates. In some regions of the brain, stem cells remain undifferentiated throughout the life of the animal, and recent work suggests that these cells can be pressed into service to effect repairs for damaged neural circuits even in the adult brain (e.g., Alvarez-Buylla and Garcia-Verdugo, 2002; Gage, 2002; Picard-Riera et al., 2004). That is, neuronal stem cells may provide a substrate for compensatory plasticity in some systems of the brains of adults.

We concentrate here on the mechanisms that control the assignment of cell identity, with particular attention paid to how the process may regulate itself if disturbances occur. Researchers first framed the question of cell specification in terms of where cell specification occurs. Conceivably, this decision is (a) intrinsic, such that specific precursor populations give rise to particular subpopulations of cells only; (b) determined by a clock producing a certain cell type after a required number of precursor cell subdivisions or with regard to some externally specified stage; or (c) extrinsic, defined by the external milieu of the precursor cells, in either the proliferative zones or their eventual destination. The answer that may vary from one brain region to another is likely the usual developmental answer: all of the above. We give a few specific examples, and consider the implications of

hybrid mechanisms for producing normal structures in response to challenge.

In vivo and in vitro experiments demonstrate that the order of neurogenesis and cell type are correlated. For example, in the vertebrate nervous system, most glia are produced after the completion of neuronal generation (Ohnuma and Harris, 2003). In the retina, the six types of cells are produced in order, although in all cases, the production of cell types overlaps (Polley et al., 1989). Evidence suggests that a combination of clock-like initiation of specification of particular cell types and feedback processes that assess how many cells of a class has been produced. One of these, p27<sup>Kip1</sup>, a cell cycle inhibitor, gradually increases in progenitors until a critical level is reached, whereupon cells designated as oligodendrocytes exit the cell cycle and differentiate (Freeman, 2000; Dyer and Cepko, 2001; Ohnuma and Harris, 2003). Thus, the gradual accrual of p27<sup>Kip1</sup> is a negative feedback mechanism that tells precursor cells when to start differentiating into glia as opposed to neurons.

Injury is capable of resetting the neurogenetic mechanism. In frogs and fishes, for example, Muller glia can re-enter the cell cycle in response to retinal injury, and can produce progeny that differentiate into neurons (Reh and Levine, 1998). In mature glia, p27<sup>Kip1</sup> is expressed at high levels. Following retinal injury, however, p27<sup>Kip1</sup> is down-regulated in cells that re-enter the cell cycle, allowing for the generation of new neurons. Regulation of specification of cell classes has also been shown to occur at a more detailed level—for example, if the retina is depleted of a particular class of amacrine cells while retinogenesis is ongoing, the subsequent production of that cell type is up-regulated (Reh, 1987).

Negative feedback control of the rate of histogenesis provides flexibility and robustness in the developing organism relative to more rigid developmental schemes that might plausibly have evolved. For instance, suppose that only glia are produced on a set day following the onset of neuronogenesis, or that glia are produced only after a certain number of cell cycles with no feedback regulation. In either of these cases, if anything interferes with cell production at a certain time point, an essential cell group might never be generated. On the other hand, if progression through cell classes is regulated only by feedback, in the case of low resource availability, neurogenesis could stall at an early point and never produce late-generated cell groups. Intrinsic clocks, overlapping

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distributions of cell production, and feedback regulation of the amount of each cell type in concert together virtually guarantee that some members of each cell class are generated, and their normal ratios defended.

### Cell Migration

The migration of developing neurons to their adult positions in the brain is a critical step in the development of the nervous system. Several distinct developmental mechanisms, such as radial and tangential migration and cellular adhesion molecules, are thought to govern this process (Rosenweig et al., 1999; Corbin et al., 2001). This is a process that can go wrong, and “ectopia,” cell groups lying elsewhere than their normal terminal site, is one of the principal morphological deviations associated with retardation (Evrard et al., 1989a, 1989b). Even if migration abnormalities result in misplaced cells, however, all is not lost.

One of the most striking demonstrations of developmental robustness comes from one model system of perturbed cell migration, in *reeler* mice. Reelin is a protein secreted by several neuronal populations during development, and is vital for allowing neurons to complete migration and adopt their ultimate positions in a number of laminar structures in the CNS (Rakic and Caviness, 1995; Rice and Curran, 2001). Mice lacking reelin (*reeler* mice, so named for their staggering gait, which results primarily from a cerebellar anomaly) show abnormal patterns of cerebral cortical lamination. The arrangement of the six layers of the cerebral cortex is inverted, so that the earliest-generated cells form the most superficial layers of the cortex and late-generated neurons tend to be distributed in deep cortex. Despite this perturbation, afferent projections to the visual, somatosensory, olfactory, and motor cortices find their correct target cells. In addition, the overall organization of major systems and the physiological responses of individual neurons in *reeler* mice are comparable to those in the normal brain. *Reeler* mice have other anatomical abnormalities relative to wild-type mice. These include changes in synaptic density, distribution, and topology that are present in a number of brain structures including the hippocampus, piriform cortex, and cerebellum. Nevertheless, although morphology is grossly abnormal, function is spared. This result suggests caution in any assumption that disturbed morphology has negative functional consequences.

*Reeler* mice provide an additional demonstration of the robustness of the “duplicate-and-vary” strategy. Only mice homozygous for the mutant *reelin* allele show the neuronal abnormalities listed above. Studies of mice heterozygous for *reelin* have neuronal and behavioral phenotypes virtually indistinguishable from those of wild-type mice (Salinger et al., 2003).

### Maturation of Cell Types during Later Development

The maturation of neuronal morphology provides an example of convergent redundancy. In vitro experiments show that granule and Purkinje cells isolated from their normal connections grow in a typical manner (Seil et al., 1974). This finding implies that signals intrinsic to cells can regulate aspects of neuronal differentiation. The neural environment of developing cells, however, also influences cell morphology and connectivity. For instance, some spinal cells are directed to become motor neurons under the influence of cells ventral to the notochord (Roelink et al., 1994). If a second length of notochord is inserted above the spinal cord, cells begin to differentiate as motor neurons on either side of the notochord. Cell–cell interactions of this sort, in which cells influence the fates of adjacent precursor cells, are referred to as *induction*, and have been documented extensively in the vertebrate brain (Rosenweig et al., 1999). The ability of extrinsic cell–cell interactions to regulate cell fate is not restricted to precursor cells. Cortical transplant studies consistently show that sensory and motor cortex cells grafted onto distant cortical regions can assume morphological, connective, and functional properties appropriate to that region. For instance, fetal visual cortex of rats transplanted into rat neonatal somatosensory cortex develops the barrel-like whisker representations characteristic of primary somatosensory cortex (Schlaggar and O’Leary, 1991), and the expression of the limbic system-associated membrane protein that marks specific functional regions of the cerebral cortex can be regulated by environmental stimuli (Levitt et al., 1997).

Patterned sensory activity can alter cell fate. Cross-modal rewiring of retinal axons into ferret auditory thalamus provides visually patterned activity to the auditory cortex (Pallas et al., 1999). Primary auditory cortex provided with early visual input resembles visual cortex topographically (Roe et al., 1990), physiologically (Roe et al., 1992), and perceptually (von Melchner et al., 2000). Neurons in this altered auditory

cortex not only assume the functional properties and arrangement of neurons in the visual cortex but also are capable of mediating visually guided behavior (von Melchner et al., 2000).

Hence, intrinsic factors such as gene expression and extrinsic factors such as induction, neuron-neuron interactions, and patterned activity are all capable of regulating cell fate at various (and sometimes overlapping) points in development. Not all of these mechanisms are necessarily invoked or even necessary during the production of any given neuron.

#### Postnatal Development and Critical Periods

*Critical periods* are time windows in postnatal development during which neurons and circuitry are particularly receptive to acquiring certain kinds of information critical for normal development (Hensch, 2004). Critical periods have been extensively documented for sensory systems, motor systems, and multimodal functions such as imprinting, birdsong learning, sound localization, and human language learning. How are critical periods useful for ensuring normal development, when it seems that the unlucky absence of a particular experience at a particular time might permanently derail normal development? The answer is that the critical-period onset, duration, and termination is not regulated simply by age, but rather by experience. If appropriate neural activation is not provided at all, then developing circuits often remain in a waiting state until such input is available. For instance, the segregation of ocular dominance columns depends on visual experience. If all visual experience is denied, the representation of the two eyes does not begin its segregation and the special neurotransmitters and receptors that are responsible for this structural change are held in their initial state (Kirkwood et al., 1995). Within certain constraints, when experience is reinstated, anatomical, pharmacological, and physiological events then progress as they would have independent of the age of the animals. A similar phenomenon has also been observed in birds that learn their songs from tutors—for the unfortunate nestlings born too late in the season to hear any of the spring songs that establish territory, the critical period is held over until next spring, when singing begins again (Doupe and Kuhl, 1999). Critical periods have vulnerabilities. If activation is only partial, it may initiate the progression of the critical period, stabilizing an

abnormal state, as has been seen in the production of ocular dominance columns: if both eyes are closed, the critical period is delayed. On the other hand, if just one eye is closed, the critical period proceeds, dedicating all resources to the open eye (Katz and Shatz, 1996).

#### ETHANOL AND THE DEVELOPING NERVOUS SYSTEM: EVOLUTIONARY CONSIDERATIONS

Here we look at a few of the cases in which the effects of ethanol on developing systems have been investigated and consider them in the context of self-regulation. The effects of ethanol on the nervous system—at any stage of development—are known to be numerous and varied (see Chapters 11–18). For instance, ethanol can both inhibit and stimulate neuron proliferation, depending on the physical location of the cells, and the concentration and even timing (day or night) of exposure (Luo and Miller, 1998; see Chapter 11).

Given that the effects of ethanol on the developing nervous system are numerous, complex, and contingent upon many factors, can we be sure that all these effects are malignant? To be sure, some are unambiguously deleterious. Ethanol can induce neuronal death *in vitro* and *in vivo*, oxidative stress, and excitotoxicity (Chapters 15 and 16); interfere with glucose transport and uptake; and reduce the expression and adhesive properties of cell adhesion molecules (Chapter 13). Other effects of ethanol, however, may not necessarily be maladaptive. For instance, in addition to causing neuronal death in developing cerebellum (Li et al., 2002) and cortex (Jacobs and Miller, 2001), ethanol can slow the production of developing cerebellar (Li et al., 2002) and cortical (Miller and Nowakowski, 1991; Miller, 2003) neurons, and it can increase the time during which postmitotic cortical neurons remain in the proliferative zone before commencing their migration while also decreasing the rate of neuronal migration (Miller, 1993). Given that development is dynamically regulated and sensitive to environmental cues, it is not implausible that these delays might be an adaptive response to a hostile developmental environment (high concentrations of ethanol) in which cell production and migration are retarded until a more favorable environment becomes available. This interpretation generates testable predictions. If cell-cycle and migration

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delays are a response to a hostile environment, then we should expect to see a restoration of these activities to normal (or even above-normal) rates once the normal developmental environment is restored. In practice, we might expect to see resumption of neuron proliferation and migration after transient exposure to ethanol (after the restoration of normal cellular environment). Certainly, research has demonstrated that the nervous system can and does recover from ethanol-related developmental insults (Anders and Persaud, 1980; Riley, 1990; Popova, 1997) but the precise mechanisms mediating recovery are poorly characterized. We suggest that some of the observed ethanol-induced changes in the developing nervous system may not be disorders, but remnants of processes that have mediated recovery.

## SUMMARY AND CONCLUSIONS

Development can go wrong. One need only consider the appearance of a poorly placed or underfertilized garden plant compared to its well-nourished siblings to counteract the rosy glow that this chapter, with its relentless underscoring of mechanisms designed for developmental stability, may have produced. Nevertheless, there are many reasons for taking a view of pathology that begins with evolution, rather than with human development in isolation.

First, although due caution should be employed in advising pregnant mothers, communicating the wild improbability of gross developmental disorders from tiny infractions in alcohol consumption during pregnancy would relieve unnecessary anxiety.

Second, animal "models" should be examined for their appropriateness to understanding human pathology. Vertebrate nervous systems are quite conservative in structure; current work comparing the genomes of different species suggests that their defensive packaging is quite different, depending on such factors as "r" and "k" selection and the dietary and pathogen exposure in the evolutionary history of the species. The kind of modeling of development we do must change and is, in fact, in the process of change—from the assumption of linear dose-response curves to pathogens and teratogens, to multicomponent chaotic systems in which "normalcy" is the strongest attractor, or in which several attractors, each representing a developmentally stable strategy, may exist.

Finally, we need to establish better causal links in developmental models that go from fundamental physiology to morphology to behavior, in order to discriminate pathological change from compensatory change and from simple deviation. Evolutionary models can provide scaffolding for such understanding that pathology-based research can never provide.

## Abbreviations

BSID	Bayley Scales of Development
CNS	central nervous system
FAS	fetal alcohol syndrome
FGF	fibroblast growth factor
IGF	insulin-like growth factor

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