The Pleiotropy Problem for Evolution

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Abstract

Pleiotropy is the effect resulting from an interconnected genetic system in which a single gene influences many different biological systems in positive or negative ways. Pleiotropy occurs because multiple phenotypic effects usually arise from each expressed gene. The adverse effects of pleiotropy on the effectiveness of natural selection is reviewed in this paper. It is concluded that pleiotropy creates a major problem for evolutionary theory because the accumulation of mutations, even beneficial mutations, often has unintended negative effects.

Introduction

Pleiotropy—from *pleio*, meaning "many," and *tropo*, meaning "changes"—is defined as the situation in which a single genetic variant is responsible for a number of distinct and often unrelated phenotypic effects (King and Stansfield, 1997, p. 264). Genes never operate alone, but are part of a highly interrelated biological system (Wagner et al., 2008). Therefore, even if a mutation is positive for one trait, negative effects frequently result as well, creating what is termed a "fitness cost." In humans the result is obvious when a single mutation causes a disease that produces many unrelated symptoms (Dudley et al., 2005).

The best-known example of pleiotropy is the multiple effects resulting from the damage to one gene in sickle-cell anemia, a disease that results from a single mutation in the hemoglobin gene. Besides anemia, other physical complications include leg ulcers, bone problems, blood clots, anoxia caused by the abnormal blood cells that lack the ability to flow properly, spleen damage, strokes, and hemolysis. Bacteria also frequently utilize a type of pleiotropy as part of their adaptive capabilities (Anderson and Purdom, 2008).

Pleiotropy, Mutations, and Evolution

The pleiotropy pitfall must be thoroughly addressed because mutations are considered the major source of genetic variety selected to achieve evolutionary change. Pleiotropy is "frequently observed" in the natural world and poses clear "evolutionary disadvantages for an organism, including limiting the rate of adaptation for some traits in response to selection for others" (Dudley et al., 2005, p. E8). The disadvantage for evolution by mutations is: If a particular phenotype is the result of a mutation that produces the loss or alteration of a single function, it may also cause the loss of other functions that are required by disrupting part of a branching pathway.

This impediment to evolutionary progress is called "the cost of complexity" (Orr, 2000, p. 13). Another obstruction is that loss of function for one gene may affect several phenotypic traits adversely, and difficulties may result if a protein that is encoded by one gene serves several functions (see Dudley et al., 2005).

Pleiotropy is a consequence of the fact that most genes in eukaryotic cells are controlled by ten or more regulatory proteins, and each gene is in turn regulated by a dozen or more sites where the regulatory proteins bind. These gene regulation sites are usually upstream in close proximity to the gene being regulated, but they may be located some distance away, even on another chromo-

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some. For this reason one mutation can have multiple phenotypic effects, often on different organs and even different organ systems (Hodgkin, 1998).

An entire class of genes called *homeotic genes* all contain a sequence called a *homeobox* that produces Hox proteins. Hox proteins are master regulators of developmental programs involved in the coordinated construction of entire structures, such as wings or limbs. Mutations in Hox genes can cause a whole series of major phenotypic changes, such as development of an extra set of nonfunctional wings. Often mutations in Hox genes produce a cascade of ultimately lethal changes.

Just as construction of a modern office complex requires the coordination of hundreds or thousands of workers, by analogy, so does the construction of cells, wings, and organs such as lungs, hearts, and kidneys. A building will not function properly if the mechanical, electrical, or structural aspects are not properly designed or are improperly assembled and/or not integrated correctly. So too, if the parts of an organ or structure are not assembled correctly or have design flaws, the living organism will be unfit for life.

Types of Pleiotropy

Genes are classified into two basic gene types relative to their pleiotropic effects: the highly pleiotropic genes called *major pleiotropic genes*, those that have a large effect; and the non- or limited pleiotropic genes called the *minor pleiotropic genes*, those that have a small effect because they apparently act independently (Albert *et. al.*, 2007). This classification is limited because even though some genes are major and others are minor, many manifest a pleiotropic effect on the phenotype for other reasons.

Hodgkin (1998) proposed a classification system that divides the pleiotropic effect into seven distinct types according to its cause. This classification system documents how extensively interconnected genes are at the phenotypic level and, also, the many ways that genes can be interconnected. His classification system is as follows.

1. *Artefactual pleiotropy*, in which adjacent but functionally unrelated genes are affected by a single mutation, such as when two genes are located next to each other on a chromosome and a mutation in one affects the other. Hodgkin claimed that organisms with "compact, gene-dense genomes will be especially susceptible to artefactual pleiotropies" (1998, p. 502). This observation indicates that pleiotropy may be more of an impediment in simpler and more primitive organisms. An example is the Drosophila claret-nondisjunction mutation that causes both eye color abnormalities and meiosis nondisjunction.
2. *Secondary pleiotropy*, or "relational pleiotropy," involves a single mutation causing biochemical alterations that produce changes affecting many structural changes. An example is a mutation causing phenylketonurea, a defect in a liver enzyme (phenylalanine hydroxylase) that causes a deficiency in axon myelination. It leads to numerous health defects, including mental retardation (Hodgkin, 1998, p. 502). Secondary pleiotropy is especially common in complex, long-lived organisms, and consequently presents a major problem for the evolution of "higher" creatures.
3. *Adoptive*, or *exaptational pleiotropy*, is the situation whereby one gene product is used for very different biochemical reactions in different tissues. An example Hodgkin gave is crystalline protein that is not only the most abundant protein in the eye lens but also is used for structural roles in other tissues such as smooth muscle.
4. *Parsimonious pleiotropy* is the case in which one enzyme is used to catalyze the same chemical reaction in many different tissues and organ systems or is used in different biochemical pathways. An example is that the same enzymes are used in very different branches of a biochemical pathway that synthesizes isoleucine and valine.
5. *Opportunistic pleiotropy* is an event whereby one regulatory protein serves an important role with other cell or tissue types in addition to its main functions. The example Hodgkin used is the control elements *sisB* and *runt* on the x chromosome that cause problems early in development and which genes are also used in later stages of growth, such as during secondary sexual development.
6. *Combinatorial pleiotropy* is a case of one gene product interacting with different proteins in different cell types and being used in several different ways that result in distinct variations. A large number of examples exist, including most transcription factors, which cause a very different biochemical activity, depending on where they interact with the genome. As a result, mutations affecting this protein "have multiple and often very diverse effects on a wide variety of tissues" (Hodgkin, 1998, p. 503).
7. *Unifying pleiotropy* is a phenomenon whereby one gene or cluster of adjacent genes encodes multiple proteins that have common or related biologi-

cal functions. Examples include various structural components, binding domains and enzymes. As a result, mutations in genes in this category "have complex physiological consequences, which may be hard to explain if the underlying biology is not understood" (Hodgkin, 1998, p. 503).

In all seven of these types of pleiotropy, the mutations (even if beneficial) can cause negative or even lethal effects elsewhere. This list illustrates the many ways in which all systems are interconnected. It also illustrates how one genetic change can cause adverse modifications in the system directly affected, and in very different systems or even in later developmental stages. This fact causes a critical difficulty for evolution, because any mutation, even if beneficial, will likely have some or many negative effects.

Antagonistic Pleiotropy

Antagonistic pleiotropy occurs when a single gene produces multiple *competing* effects so that its beneficial effects are offset by deleterious consequences produced by the same gene. Some genes, for example, can increase fitness when a person is young but decrease fitness later in life. A case in point is the testosterone hormone gene, which increases reproductive fitness in an adolescent but can contribute to prostate cancer in an older adult.

Functions of Pleiotropy in Biology

Pleiotropy is necessary in order to coordinate body growth and development. For example, a normal healthy small woman has close to the same proportion of body parts, such as limbs, heart, lungs, and other internal organs, as does a normal healthy large man. A tall man has longer limbs than a short woman, but each leg is normally close to the same proportion in each person. Pleiotropy is likewise a major means of coordinating a variety of body functions such as metabolism.

One reason genetics influences phenotypic correlations is because genes control the quantity of hormones secreted, and hormones often influence many separate functions. An example is the growth hormone secreted by the pituitary gland, which increases not only height and size of hand and foot, but also controls the entire body size. Many genes have well-known pleiotropic effects, including one important gene called p53 and all heat-shock genes that are part of the genetic systems responding to temperature fluctuations (e.g., Meyers, 1995, p. 281–285). The heat-shock response activates a number of genes that protect the cell from thermal damage. This complex response to heat damage is both rapid and reversible.

Another example of the results of pleiotropy is cytokine networks. The cytokines are hormone-like polypeptides produced transiently by a wide variety of cells. They usually act locally to alter cellular physiology by binding to cell surface receptors in order to activate certain genes. The effects of cytokines are *redundant* (meaning different cytokines may have the same effect) and yet can have multiple effects on the same cell in different circumstances.

This fact again illustrates that single mutations, although beneficial, often have a wide variety of results, some quite negative, on other systems. A single cytokine can have different effects on different cells and different cytokines also may interact either synergistically or antagonistically, or even in an additive way (Meyers, 1995). Since the origin of new genetic information upon which evolution selects is mutations, pleiotropy demonstrates that positive mutations usually also add to the "cost of complexity," by bringing more harm then benefit.

Examples of Pleiotropy from Medicine

All drugs affect the body's biochemistry, and all medicines have side effects due to pleiotropy. The reason is that all medicine attenuates or activates certain aspects of the body's biochemistry, medically impacting the entire interconnected biochemical system it affects. Common side effects of many drugs include tiredness, nausea, dry mouth, reduced alertness, stomach problems, and allergies. Aspirin interferes with the prostaglandin biochemical pathway that not only blocks pain, but also interferes with the body's ability to protect the stomach from the corrosive effects of HCl stomach acid.

A disease-causing mutation that damages one gene often can result in many different, and at times unrelated, symptoms. A mutation that damages the phenylalanine hydroxylase gene, which makes an enzyme that converts the amino acid phenylalanine into the amino acid tyrosine, can increase phenylalanine concentrations to toxic levels. This metabolic disease known as phenylketonuria (PKU) if not treated causes a variety of symptoms including mental retardation, hair growth reduction, blue eyes, and light skin color from skin pigmentation reductions (Hodgkin, 1998).

These examples all illustrate the extent of biochemical connectedness of human physiology and how attempts to alter it to benefit the patient often result in undesirable effects. Likewise, a beneficial mutation, even if very helpful, also can cause numerous undesirable side effects. The cost of complexity can be great, and for this reason evolution by the accumulation of mutations is seriously problematic. Instead, these examples of pleiotropy argue for creation *ex nihilo*.

Examples of Pleiotropy from Animal Breeding

Pleiotropy is a significant obstacle to successful animal breeding. The negative

effects that result from animal breeding illustrate why evolution by the accumulation of mutations is not a realistic mechanism. When breeding for a single desired trait, undesirable consequences almost always result (Grandin and Johnson, 2005). Chicken breeders select hens and roosters that are fast growing, bulky, and well muscled. Grandin and Johnson (2005) claimed that a gain in one of these traits *invariably* results in a loss in other traits. For example, fast-growing hens and roosters usually end up with fertility problems, a side effect also found with Belgian Blue cattle and certain other animals.

When a trait that allows faster growth in chickens was selected, the resultant chickens had weak hearts. Death from heart failure then became more common. Attempts to breed chickens with larger breasts resulted in chickens with deformed, bent, and swollen legs. Attempting to solve these problems, breeders worked on creating chickens with both larger breasts and stronger hearts. They eventually produced what appeared to be a dream chicken—a strong chicken with larger breasts, heavy legs, and strong hearts—but they soon discovered severe behavioral problems, such as a tendency for the roosters to kill the hens in part because the breeding led to the inadvertent elimination of the rooster's courtship dance. In the absence of the courtship dance, the hens would not cooperate sexually with roosters. The problem of breeding for one trait and losing others is universal. Grandin and Johnson (2005, p. 72) concluded this adversity happens "all the time when breeders over-select for a single trait. You get warped evolution."

Yet, Grandin and Johnson (2005, p. 72-73) claimed that what artificial selection cannot achieve, natural selection can. In their section heading titled "Selection Pressure," they discussed the evolution of color vision in primates, which they claimed natural selection produced in primates without intelligence. The implication is that artificial breeders usually create genetic problems when they try to select for single traits, but the blind forces of nature can do the job just fine. However, they provide no support for that claim.

Negative selection repercussions can typically be avoided by selecting only for minor improvement; i.e., instead of the largest chicken possible, select for larger chickens that, although they compromise the other traits, do not compromise them to the degree that the problems that result are insurmountable or even serious. As is well known, breeding always carries limits, and, as we reach these limits, complications always eventually arise because of pleiotropy. Likewise, this illustrates why macroevolution by the accumulation of mutations is very unlikely—one step forward invariably results in several steps backward due to the effects of pleiotropy.

Epistasis

The concept of pleiotropy is related to the concept of epistasis. Both refer to interactions that influence phenotypic traits. Epistasis refers to the complex interactions that exist between different genes, often when one gene is modified by other genes, called **modifier genes.** *Synergistic* epistasis is a positive interaction resulting in a higher expression of a trait; *antagonistic* epistasis is a negative interaction resulting in lower expression of the trait.

Epistasis often refers to normal gene control and regulation, while pleiotropy refers to both normal and abnormal gene interaction. But both systems can create major difficulties for Darwinian evolution by the accumulation of mutations. If one gene in an epistatic system is altered, it can effect other genes. Evolutionists argue that synergistic epistasis gives natural selection a powerful means to remove deleterious mutations, preventing their accumulation. They reason that if a mutation in one gene effects the proper operation of other genes, a non-lethal mutation can become lethal or adversely affect the survival of the organism. Thus, the organism possessing the mutation is more likely to be negatively selected by natural selection, reducing the overall mutation load of the organism.

While this effect may work, at least in theory, it can also cause many normally non-lethal neutral mutations (including those that are potentially beneficial mutations) to become lethal or be negatively selected as a result of the epistatic interactions. Consequently, the synergistic effect removes not only many deleterious mutations, but also most of the potentially beneficial ones. The net effect is mutations, both negative and positive, are removed, producing a conserving effect that resists genetic change. As a consequence, for beneficial mutations to increase and become fixed within the population there is an increased cost of selection (ReMine, 2006). It is unlikely that most populations could accommodate this increased cost.

Molecular Mechanisms for Pleiotropy

One important reason for pleiotropy is that molecules must constantly interact with one another in a living organism, and to function they must bind to some and not bind with others. Most often a molecule interacts with many other molecules in the cell within what is referred to as a "noisy biochemical environment" (Savir and Tlusty, 2007, p. e468). Mutations often change the conformation (shape) and even the binding properties of molecules, which can affect their interaction with other molecules.

This result is important because "practically all biological systems rely on the ability of biomolecules to specifically recognize each other," and a change may mean that they do not recognize the molecules that are required and, consequently, react with some they should not, both conditions causing problems

(Savir and Tlusty, 2007, p. e468). Some common examples include antibody-antigen recognition, binding of regulatory proteins to DNA, and enzyme-substrate interactions required in body chemistry.

Overlapping Genes

Overlapping genes occur where one or more genes actually exist within another gene, or two genes overlap so that one gene is part of another gene next to it. Evidence now exists that there can be up to 12 or more overlapping codes in one gene. Changing one nucleotide can thus affect multiple information systems, indicating that almost all mutations will have pleiotropic effects (Trifonov, 1989; 1997). The recent ENCODE project has documented that a typical nucleotide is part of multiple overlapping messages, and this shows that most mutations should have pleiotropic effects (Kapranov et. al., 2007). Sanford introduced the concept of "poly-functional DNA," which means many functional units of DNA are "poly-constrained" such that a mutation improving one message will often damage the overlapping messages (Sanford, 2008).

How Common Is Pleiotropy?

The study of many life-forms, including yeasts, demonstrates that "a large number of pleiotropic genes" exist (Dudley et al., 2005). Much research indicates that most, and possibly all, genes have a pleiotropic effect. It is at least clear that a majority of genes have pleiotropic effects. For instance, promoter regions alone are regulated by nearly a dozen to several dozen transcription-factor binding sites (Stone and Wray, 2001). One study of the number of traits affected by each mutation using quantitative trait loci (QTL) analysis of skeletal traits in mice found half of QTLs affected up to six traits and one set of QTLs affected as many as 25 to 30 different traits (Wagner et al., 2008, p. 471).

Another QLT study looked at the number of major and minor pleiotropic effect genes for the body shape of two stickleback species. Their findings indicate that about half were minor pleiotropic effect genes and several had "large and possibly widespread effects" (Albert et al., 2007, p. 76). More studies are needed to determine the level of pleiotropic effects of other genes. The effect likely is probably much greater than this study indicates.

Hox genes and other transcription factors are known to influence and regulate the development of body morphology (Coyne, 2005). Hodgkin (1998, p. 501) argued that pleiotropy "may well be the rule rather then the exception in higher organisms." He showed that recent evidence supports this conclusion, demonstrating its importance in higher organisms. Jaroslav Flegr has proposed that pleiotropy limits the plasticity of a species (Hall, 2009). High plasticity life-forms, such as dogs, are able to produce many morphological variations, and plastic species have a greater proportion of their traits coded by a single gene. Thus they show fewer gene-gene interactions, while frozen species have a greater proportion of their traits coded by a larger number of genes and show enhanced genetic interactions (Hall, 2009).

Summary

Pleiotropy not only creates a major genetic barrier to both micro- and macroevolution, but it also even sets limits on animal and plant breeding because of the biochemical interconnectivity existing in cells, tissues, organs, and organ systems. This fact is well known among plant and animal breeders, as well as those persons who fancy purebred dogs, horses, and other animals. As Hodgkin (1998, p. 501) admitted, "In complex eukaryotes, pleiotropy may lead to major constraints on possible mutational avenues" that might allow evolution to occur. As stated earlier, the evidence of pleiotropy favors special creation (Tinkle, 1975).

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Book Review

The Ultimate Proof of Creation: Resolving the Origins Debate

by Jason Lisle

Master Books, Green Forest, AZ, 2009, 254 pages, $14.00.

This book by Jason Lisle is devoted to apologetics and the defense of the Biblical worldview. It focuses on defending the Biblical understanding of creation and the creation account in Genesis. Dr. Lisle explains the importance our worldview plays in determining how we both understand and interpret scientific evidence (as well as life in general). His main argument, the "ultimate proof" of the title, is that only the Biblical worldview embracing the accuracy of the entire Bible provides a consistent basis for knowledge. This is so because, though we rely on our sense to perceive the world around us, we have no guarantee that our senses are reliable unless the Bible is true in declaring that there is a Creator. Dr. Lisle also discusses logic, both formal and informal, and the role of evidence in our understanding of the world. He gives many examples of emails and letters he has received and guides the reader through analyzing them and applying what has been learned. The book is an excellent introduction to logic and apologetics for the layperson, and is helpful for learning to spot errors in logic.

One drawback to the book is the lack of an index and glossary, both of which would be helpful resources for the reader. Overall the book is an excellent apologetics resource and is a great addition to any Christian library.

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