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The Biology of Pleiotropies

Understanding Gene Effects, Vertically and Horizontally

Gene effects (as well as environmental effects) have their beginnings in microscopic events of physiology and morphology. For most of us, these beginnings and early stages in some large part remain unknown or unnoticed. Involved in lengthy sequences of cryptic events and changes in our developing bodies, sometimes with cumulative effects across decades of life, gene effects emerge as participants in all of the aspects of an organism that we call its traits. Some traits, like attached or unattached ear lobes in humans, are features that ordinary people are able to see, measure, and think about; others, like the still unknown physiological and developmental underpinnings of ear lobe differences, may remain cryptic forever.

Early in Mendelian (or "transmission") genetics the label "pleiotropic" was applied to genes known to have multiple effects on the body or its functions -- for example, a gene (or allele) known to affect the expression of two different traits. A gene can also be responsible for differing consequences to its "host" organism merely by being active (or inactive) -- i.e., having the same effect -- in different times and places within the organism. Few things an organism might do are likely to be equally beneficial at all times during its life, or in all parts of its body at any one time in its life.

As an example, at age 17, I may have gained from an inclination to play touch football in front of the girls at recess; at 72, I am fairly certain I would not. Any gene effect that contributed to the tendency to join such physical competitions across all of life -- or at both of these ages -- could therefore be beneficial at one time, deleterious at another.

Pleiotropic effects eventually came to mean any gene effect incidental to the particular effect(s) believed responsible for the gene's persistence. Effects, or traits, known to be beneficial are often referred to as *evolved functions* -- especially if they are also known to involve multiple genes, or for other reasons are believed to have a long history and to occur in combinations that are highly unlikely except as a result of persisting selection.

Incidental or pleiotropic effects of a gene can be either good or bad for the organism. Good gene effects aid the future of the gene responsible by aiding the organismís reproduction, and are likely to be regarded as (to become) part of the evolved function of the gene (or of a trait in which the gene is known to participate); bad ones persist only when they are inevitable side effects of such reproductive or evolved functions. As we shall see, the persistence of incidental bad gene effects becomes the essential why of the senescence that determines the lifetimes of those who happen to survive the prematurity of accidental death.

All of this may seem puzzling, partly because changes in environments alone can lead to changes in features or actions in the organism, tempting us to see such features or actions as merely effects of environment. In fact, the environment cannot have its effects, changing or not, without gene actions underlying them. In this sense gene actions can even be quite particular in their influence on traits without our knowing about them, because we so often interpret traits only in terms of aspects of the environment that are to us more obviously associated with them.

Consider a philosophical construction, or any contribution to literature. We are inclined to talk about such things without even thinking about genes, and we find it difficult to comprehend how genes could be involved in their existence or expressions. But there is no alternative, because such things as philosophy and literature come only from the human form of life, and organisms such as humans cannot exist without genes. In such a "vertical" (developmental or life-course) view of the organism, genes and environment both contribute to every trait in every organism, and in that sense it is futile to think about assessing which is more important in determining any trait.

There is a potential confusion, however, because of the way we try to get at this problem. Both genes and environment differ among different individual organisms. We tend to investigate the *horizontal* question of how much known genetic or environmental *differences* contribute to *differences* in trait expressions in *different individuals.* Thus, if a trait variation correlates with a genetic variation, we say the difference in the two expressions of the traits is heritable. If a trait change can be induced without genetic changes, it is not heritable. It is owing not to genetic differences but to environmental differences. We emphasize this horizontal way of thinking about gene effects because it was for so long our only way of detecting and measuring gene effects. We only knew about those gene effects in which different versions of a gene yielded differences in traits. Such "versions" of genes, called alleles, are homologues (results of mutational divergences) that may occur in different individual organisms in a population, or on the two different members of the paired chromosomes that we receive from our two parents.

But, as already suggested, the parallel cannot be extended to include *how much* any trait, in its entirety, is affected by each of the two necessary variables involved in each case (genes and environment). This question peers *vertically* across the organism's development or lifetime. Asking how much a trait is affected by genes and how much by environment across all of development or life would be like asking how much the area of a rectangle is owing to its length and how much to its width. In this perspective genes and environment both inevitably must contribute to the expression of the trait, whether or not *change* in one or the other fails to influence a particular *change* in the trait. All we can yet say about the entire picture is that genes and environment somehow work together, via development, to produce the organism and its every trait.

Genes cannot survive except in environments, and they can be turned on and off in different environments. As a result their ultimate consequences in determining the traits of organisms can be diverse. Organisms have internal environments as well as external environments, and both affect gene actions. We should keep in our minds that among the more important players in the environment of a gene are the effects of all the copies of all the other genes in the same organism. Every body cell of an organism contains a duplicate copy of its genome, meaning a complete set of the organism's genes.

We should not be too put off because most of the time we still have no clue how to think about the precise contributions of genes to our abilities or inclinations to do certain things. Once we are aware there are such inevitable genetic contributions (gene effects) we can usually ignore them. If we are not aware that they exist, however, we cannot ignore them, but only fail to consider them, even as a whole; and so we will make needless and possibly expensive mistakes from time to time.

Theodosius Dobzhansky, in 1961, summarized nearly all that is said above with the mind-spinning proposition that, in effect, all genes necessarily are pleiotropic (and also epistatic, meaning they also affect one another's effects) because development (or ontogeny) -- the process whereby organisms generate and pursue their lifetimes, beginning from the original fertilized egg -- is unitary!

Heredity is particulate but development is unitary. Everything in the organism is the result of the interactions of all genes, subject to the environment to which they are exposed. What genes determine are not characters, but rather the ways in which the developing organism responds to the environment it encounters.

In the broad sense "development" of the organism encompasses all of its internal processes, not merely across the early parts of its life -- say, as an embryo -- but across its entire lifetime. By present counts the human organism begins as mostly some 40,000 genes (some biologists think significantly more), which can be shuffled separately, or in groups, during mitosis and meiosis. The wonder of the organism is the essentially complete cooperativeness of those thousands of genes, which have generated Dobzhansky's unity of development only because they were able to evolve equal chances of finding themselves in the reproductive propagules of their parent organism, that chance being their sole opportunity to persist.

In evolving the phenomenon known as the organism, genes have thus carried reproductive-opportunity-leveling to the most astonishing extreme represented in the living world, and necessarily concentrated differential reproduction at the level of their groups (genomes, organisms) rather than at the gene level. Genes die out not, because their copies disappear from the groups (genomes) within which they live, but because their presence in the genome reduces or eliminates the opportunity of the genome to reproduce its parts. Sexual reproduction causes the different copies of genes to live in many different combinations by scrambling genomes every generation when the sperm and eggs are generated. One effect is that no gene is stuck with having all its descendant copies grouped permanently with any particular set of associates.

Equal likelihoods of alternative genes getting into the next generation via eggs or sperm is an extreme that has never been duplicated at a higher level, such as that of the family or tribe or nation, even though slight trends in that direction are discernible in the vast majority of life forms, and considerable or dramatic trends in a smaller number. How such a tradeoff between harmony and the stir and flurry of continuing within-group competition will be viewed eventually, by humans increasingly able to use conscious deliberation to influence their own social trends, remains to be seen. In any case, within-group harmony does not itself foster between-group harmony, in either groups of genes or social groups of individuals. It may lead to ever-larger groups, through failures to fission, formation of alliances, and evangelism. But within-group amity has long been seen as one of the engines of between-group enmity, and we can expect this relationship within every species unless the species generates, in terms of reproductive equality, but a single social group across the planet. This possibly idyllic social situation has never been approached in any species. It is one of the great melancholy facts of life that we must doubt whether, even if achieved, it could long be maintained; and one of the great hopes of existence that our species may be able to generate attitudes that eventually will overcome such impasses.

Anyone can understand that the complex cooperativeness of the genes means that the ultimately multi-trillion-celled *unitary* human organism may experience many times 40,000 physiological, morphological, and behavioral events within its body and its mind, *perhaps during any split second of its 90-100-year lifetime!*

Dobzhansky's proposition thus informs us of the likelihood that the lifetimes of organisms, and that of the human organism *a fortiori,* because of the incredible activity of its unique and massive brain (requiring something like one-third of all the calories a human consumes), are by orders of magnitude the most profoundly complex events so far identifiable in the known universe. This possibility defines the massive task before molecular biologists as they work to elaborate a view of life that includes all of ontogeny, beginning from an ultimately reductionist position and utilizing a primarily inductive method.

It is the awesome human lifetime, and its meaning to ourselves, that we set out here to ponder, relish, and modify according to our likings, even should all such thoughts and acts themselves be mere pleiotropies.