**THE CORNER TREASURY OF ARCANE AND NEGLECTED PHILOSOPHICAL GEMS (OF MY OWN MAKING)**

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Gem #5: '(EPI)GENETIC' CONTROL OF DEVELOPMENT IN HUMANS AND OTHER SENTIENT BEINGS, WITH SPECIAL REFERENCE TO 'IDENTICAL' TWINNING.

As a 'card-carrying' (sic) experimental embryology old-timer (PhD 1962, Columbia University), I feel impelled to register a correction to the otherwise fascinating article on 'TWINS' in the Jan-2012 issue of National Geographic Magazine (NGM). "Epigenetics", namely, is not at all a "new third force" in developmental biology but, rather, the all-pervasive instructive link between environmental and genetic factors (both of which are only permissive in nature). The 'epigenetic landscape' is a more than 70 year old metaphor coined by CH Waddington to describe the progressive determination of the fate of each developing cell in multi-cellular organisms. Given the identity of the genome in all of the cells of any given individual, in progressively activating biochemical processes within the cytoplasm (cell sap) that, in turn, selectively activate subsets of the genome (DNA) at the proper time in the right cells. The activated genes then initiate the process of generating the raw materials (proteins eventually) required for the full development and maintenance of each cell in its specialized mature form. (In vertebrates, cytoplasmic differentiation among cells is initiated by the heterogeneous physico-chemical conditions at different sites within the embryo, whereas in many invertebrates 'morphogenetic' chemical factors are already dispersed within the fertilized egg cell, and become parceled out non-equally with each successive cell cleavage).

I used the term 'epigenesis' myself in print two decades ago, and in a more rigorous form two years later, in connection with the relatively late realization of researchers that intrinsically generated electrical activity of the nervous system is also an important factor in development. The musical keyboard analogy mentioned in the NGM 'TWINS' article proved to be a valuable metaphor for explaining the fundamentals of how genes work, fundamentals which are often forgotten, leading even many specialists to embrace fallacious notions of 'genetic determinism'. I used this metaphor informally on many later occasions, but have always taken pains to point out that it's not (as claimed in the article) an animal's "traits", or even its constituent cell types, but only individual protein molecules that are the ultimate 'downstream' products of activation of the genetic 'keys'. When I was still a graduate student, the "one gene, one enzyme" principle had already been established, and with the discovery of the double helix and the triplet code this became generalized to "one gene, one protein". Since a variety of proteins contributes to even the simplest phenotypic characteristics, and most proteins participate in more than one cellular `trait', it should be readily apparent that the genetic 'keyboard' cannot be the repository of 'scores' for generating any of the 'music' played upon it. The genome is thus no more – or less - a 'book of life' than a dictionary is a compendium of all the works of literature written in a given language, or a LEGO catalog constitutes an instruction manual for building everything that can be made using the available blocks.

In the absence of either 'morphogenetic fields' acting upon the organism from the outside, or 'genetic programs' directing its growth and maintenance from inside, where does the information for biological pattern formation come from? The powerful modern concept of 'self-organization' gives body to the classical idea of epigenesis: dynamic molecular networks within the cytoplasm integrate environmental stimuli and, on that basis, 'place orders' from the nucleus (genome) for just those proteins that the differentiating cell in question seems to be in need of. Whether or not those proteins are actually synthesized and, if so, how they become structurally and functionally incorporated into the cell is determined downstream from genetic influences. Even further 'downstream' from the genes are the interactions among differented cells so as to form, by selective adhesion, repulsion, migration and growth, the distinctive organs and tissues making up the body as a whole.

Epigenesis is thus an umbrella term embracing the entire operation of the complicated developmental programs and molecular 'machinery' that create adaptively ordered patterns at the cellular, system and organismic levels of life. The common misconception of the genome as 'software', and the rest of the cell as hardware thus gets the story pretty much backwards: the range of proteins and their combinations that are theoretically possible under suitable intracellular conditions are literally astronomical. When, for instance, fertilized fish nuclei (thus containing the entire genome) were injected into enucleated egg cells from a related species, the larvae developed traits of the latter and not those of the gene donors.... so much for 'Jurassic Park'! Rather than discovering a "radically new third force", as the authors of the 'TWINS' article proclaim, modern developmental biology has rediscovered an unjustly neglected general unifying principle.

So, if neither NATURE (one's genetic constitution, ignoring for simplicity's sake that a fertilized egg cell is much more than just a genome!) nor NURTURE (one's history of environmental experiences) provide instructions for becoming who we are, how to explain the popular misconception that heredity and environment sum up to determine one's finished Self? The answer to this conundrum lies in the erroneous application to developmental mechanisms of the formula used in population genetics to quantify the sources of individual differences within a population. Thus, when identical seeds, for instance, are nurtured under varying conditions, differences among the resulting plants can be said to be for 100% environmental in origin. When, on the other hand, genetically different strains are cultivated under identical conditions, the differences will be 100% genetically 'determined', and when neither genes nor environment are identical, the source of individual differences can be calculated as an addition of "so much due to environmental differences, and so much to genetic differences". [Note that if the word

"factors" is substituted for "differences", as is far too often the case, the root cause of the ensuing confusion immediately becomes clear]. As causal factors, however, both heredity and environment are always 'epigenetically' involved for 100%.

With respect to twinning, finally, the assertion in the target article that "differences between identical twins must be due to environmental factors" is simply not true. Besides what is known as 'genetic drift', there is always the possibility of unequal cleavage of the egg cell cytoplasm which, as we have seen, could in itself lead to differential genetic activation patterns within the two "halves' of the zygote. Even if the initial cleavages are equal, however, yet another epigenetic factor is often at play. Cleavage of the developing embryo, namely, can occur relatively late, leading to 'Siamese' twinning if separation is incomplete, or to mirror-image development of one or more body features. In the case of the brain, this most frequently involves a left-handed and a right-handed twin (right and left brain motor dominance, respectively), but can also produce a 'Narcissus and Goldmund' dyad involving complementary cognitive characteristics such as a propensity for one twin to be scientifically oriented (left brain cognitive dominance) and/or ascetically inclined (Apollonian) and the other to be artistically gifted (right brain dominance) and or inclined to a 'Bohemian' lifestyle (Dionysian).

Presumably, in such cases, the normal developmental trend towards certain bodily asymmetries has already been initiated at the time that the primitive embryo splits in half, and this left-right bias does not become completely reversed when each daughter zygote 'regulates' to form a whole rather than half a body. Intrinsic 'epigenetic' growth processes can thus lead to striking differences between twins even in the absence of hereditary (whether genetic or cytoplasmic) or intra- and/or post-uterine environmental differences between them. After a half-century of being misled by the `molecular biology mafia', let's never again forget that cellular differentiation begins in the cytoplasm, not the nucleus, and that genome merely delivers – but only 'on order' – the raw material appropriate for a particular cell at a particular time in development. Except for cell types that require a protein not coded for by the organism's DNA, there appears to be no limit to what can be made using an identical set of genes. And since all living organisms are based on the same biochemical mechanisms, there is no mystery to why so much DNA is shared from protozoa to humans.

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