Homeostasis: A Legacy of Biological Evolution

Homeostasis is an abiding principle of living systems; it is defined as that "relatively stable state of equilibrium or tendency toward such a state between the different but interdependent elements and subsystems of an organism" (Webster); accordingly, metrical trait values (e.g., blood pressure and plasma glucose concentration) are maintained within limits. Whereas Claude Bernard had only observed constancy of the "milieu interieur" (extracellular fluid), homeostasis actually extends to intracellular and subcellular environments and components. Because of biological individuality, each individual will have a particular location within the larger distribution of quantitative values that describe the parameter in the population; the private homeostatic value may then be seen to be displaced because the individual's system is undermined (by mutation perhaps) or overwhelmed by experience. A displaced value is likely to be disadaptive because evolution of biological diversity by natural selection was the process by which the optimal range of homeostatic values was obtained.

Why Mutations Are Likely to Be "Recessive"

The genomic nucleotide sequence may be a book of life but it is also "an intricate community" with "intergenic wildernesses" and "social collectives where genes play intricate divisions of labor and functional collaborations" (Avise, 2001). Accordingly, the genome signifies complexity in the background against which Mendelian mutant phenotypes act out their roles.

Fisher, when arguing that mutation is essential for biological evolution, proposed that the "successful" allele should become the wildtype, meaning it would become dominant. [See Scriver (2001) for citation of Fisher and Sewall Wright, and for additional discussion.] Hence, by invoking evolution through natural selection, Fisher thought he could explain dominance of the wildtype allele. Wright, a contemporary of Fisher, in recognition of the prevalence of recessive mutant alleles, approached the problem from a different point of view--for example, in metabolism. The network or chain of events linking genotype to phenotype would involve fluxes of molecules in the fluid state of living systems. If several unsaturated enzymes with equivalent activities mediated the flux through the system, there would be a hyperbolic relationship between enzyme activity and the rate of flux. Wright argued that half-normal activity in a single enzyme,
reflecting mutation at a single locus, would be likely to have only a minor effect on flux through a complex network comprising multiple enzymes and pathways.

Wright's argument was revisited (Kacser, Burns, 1981) to show the predicted effect of null-type mutation in systems comprising one or multiple enzyme catalysts; the effect of a mutant allele would always be recessive, with only minor effect on the measured phenotype, in a complex system. As anticipated, the "metabolome" (Scrimer, 2001) has complex behavior; its phenotypes are quantitative traits and they will reflect the allelic variation in the population. So-called monogenic metabolic disorders are variant phenomena located beyond some arbitrary point on the normal spectrum of its corresponding homeostatic parameter.

Mutations Are Buffered in Complex Systems

Homeostasis involves a matrix of catalysts and components that, in the living state, operate at far from chemical equilibrium. Buffering mechanisms exist to offset the effects of phenotype-modifying alleles. When they focus on a single process or pathway and recognize compartmentation in the organism, they represent intrinsic buffering; when the buffering relationship involves independent circuits, the term extrinsic buffering is useful (Hartman et al, 2001).

Three basic mechanisms for buffering are proposed (Hartman et al, 2001): (1) redundancy in the human genome, which is diploid with paired homologous alleles, and redundancy in duplicated genes with overlapping functions; (2) reduction in specificity: interdependency and number of molecular and cellular events committed to a particular homeostatic parameter--a mechanism that is enhanced by increasing the flexibility and versatility of the proteins involved; and (3) negative feedback regulation. Buffering always acts within systems of self-assembly of proteins and of self-organization in cells and organisms. They are the heretofore mysterious features of systems with an "emergent property" in which the whole is greater than the sum of its parts (Kirschner et al, 2000). They confer complexity to the links between genotype and phenotype, thereby endowing robustness and health or, in the presence of allelic variation, the risk of vulnerability and disease (Dipple et al, 2001).

Whereas the aforementioned arguments of Wright and Kacser shed insight on why a disadaptive mutant (metabolic) phenotype is likely to be homozygous for recessive allele(s), a dominantly expressed phenotype begs explanation. Dominance would have to involve one of the following possibilities: (1) the pathway or phenotype would be a one-catalyst event or protein--for example, the relationship between a membrane receptor and its ligand; (2) there is a condition of haploinsufficiency; (3) the allele would produce a dominant negative effect on a homomultimeric structure; or (4) the allele would produce gain of function. Thus the extreme Mendelian phenotypes or diseases, of which there must be several thousand, either recognized or still unclassified, identify gene products and processes that are least well buffered to the effects of mutation.
Of the 923 Mendelian disorders that can be considered in this manner, each highlights a component of pathophysiology beginning at the level of proteins (Jimenez-Sanchez et al, 2001).

Evidence for Complexity in a "Monogenic" Metabolic Disease

Phenylketonuria (PKU)-causing alleles (mutations) at the corresponding locus (gene symbol, PAH) altering function of phenylalanine hydroxylase enzyme are far removed from the mechanisms promoting the clinical disease phenotype (impaired cognitive development). Accordingly, it is no surprise that PAH genotypes are not rigorous and consistent predictors of the clinical and metabolic phenotypes in affected persons--a fact anticipated long ago (Penrose, 1946/1998). In the case of PKU, three levels of organismal assembly and function in the path linking a mutant PAH nucleotide sequence and the associated phenotype contribute to the complexity of the deviant phenotype.

Mutation in the PAH gene, now assigned to chromosome locus 12q23.2 (IHGSC, 2000) is sufficient to explain impaired function of the enzymic phenotype [phenylalanine hydroxylase (monooxygenase), E.C. 1.14.16.1]; the attendant metabolic phenotype is hyperphenylalaninemia; the associated clinical phenotype is impaired cognitive development, apparently a consequence of the hyperphenylalaninemia. During meta-analyses of PAH genotype-metabolic/clinical phenotype correlations (Guldberg et al, 1998; Kayaalp et al, 1997), multiple cases were observed where genotype was not associated with the predicted metabolic or cognitive phenotype. Accordingly, features of a complex trait in PKU can be identified at the three above-mentioned phenotypic levels (Scriven, Waters, 1999):

Enzymic level. Many of the missense mutations do not directly alter the enzymic reaction but affect it secondarily by interfering with anything that would modify flux of the misfolded protein through the nonproductive proteolysis pathway (e.g., chaperone "allelism") and could further modulate the residual enzyme activity.

Metabolic level. The rate of catabolic outflow of phenylalanine overall has been analyzed; it is clearly a complex relationship at its various enzyme-dependent steps (Kaufman, 1999). How interindividual variation in the transaminase-dependent pathway might serve disposal of phenylalanine and modulate phenylalanine pool size--and thus the tolerance for diet phenylalanine--has been analyzed in PKU siblings with identical mutant PAH genotypes (Treacy et al, 1996). Transaminases are often polymorphic and formation of phenylpyruvic acid from phenylalanine has long been known to show quantitative variation in the PKU patient population (Knox, 1970).

Cognitive development. Impairment is not categorically related to genotype (Ramus et al, 1993), but is apparently related to phenylalanine concentration in the brain compartment. Rates of influx of phenylalanine on a transporter across the blood brain barrier show wide variation from normal in some patients with PKU, suggesting that this physiologic parameter can be a modifier of the clinical (cognitive) phenotype associated with hyperphenylalaninemia [see Weglage et al (1998); Moller et al (1998)].

Most "Monogenic" Metabolic Diseases Show Some Degree of Complexity
Awareness that many so-called monogenic diseases do not show consistent relationships between mutant genotype and phenotype has emerged recently (Dipple, McCabe, 2000a; Dipple, McCabe, 2000b; Summers, 1996). Should we be surprised by the apparent discordances? Probably not; "genomes speak biochemistry, not phenotype" (Plasterk, 1999). What goes on in complex metabolic networks, cycles, and pathways, and how the effect of a mutant allele is buffered, is a topic of intense renewed interest (Barkai, Leiber, 1997; Hartman et al, 2001; Hartwell et al, 1999; Jeong et al, 2000), appropriately so in the emerging era of "functional genomics" and proteomics. Whereas there is robustness in biochemical networks that have experienced selection at levels of molecular or modular cell biology, it is the redundancies in alleles, genes, and feedback in regulatory pathways that both randomize and co-opt organization of large-scale metabolic networks. Metabolic homeostasis is actually a "noisy business" (McAdams, Arkin, 1999). Homeostasis of phenylalanine pool size and the relationship between mutant PAH genotypes and phenotypes effectively illustrate the theme.

References


