A new perspective on chronic disease

Microcompetition with Foreign DNA and the Origin of Chronic Disease. (2003). Hanan Polansky. Cambridge International Science Publishing Co. ISBN: 0-9740463-0-2. Price: $69.95 (£36)

Reviewed by
Yvonne R. Thorstenson
Stanford Genome Technology Center
855 California Avenue
Palo Alto CA 94304

Biomedical scientists are at a distinct disadvantage in this post-genome era. As a group of professionals, we have successfully characterized the gene to the molecular level, developed safe and efficacious vaccines for many diseases, and developed robust animal and cell models of human disease. But, as individuals, we still have only one brain, and two sets of fingers. No single person can hope to understand it all. So we each break off our small piece and try to make sense of it within our chosen disciplines, and it works really well. Except when the missing pieces for a complex puzzle are stuck between the cracks of the existing dogma.

The origin of chronic disease is one of the most important and vexing questions in biomedical research today. Hope for ameliorating human suffering caused by these diseases is a strong motivator for government funding agencies. Yet, it is difficult to point to a breakthrough concept, though many have been trumpeted. We have been tempted with explanations for chronic disease: one day it is environmental toxins in the air or in our food, the next day it is inflammation or infection. All of these are important lines of investigation, and it is reasonable to trust that the cumulative bits of evidence from all different areas will eventually reveal a satisfying answer. But what if we are missing a critical piece? Isn't it worthwhile to occasionally pause from our frenetic trajectory to consider possible alternative explanations? Maybe there is a path across the terrain that we didn't notice before.

Hanan Polansky's book offers just such a thought-provoking, mind-stretching opportunity. He provides a radically different perspective on the biomedical literature by applying a whole-system approach with mathematical models based on economic probability theory. Reading Polansky's book was like a mini-sabbatical. It allowed me to step away from my narrow viewpoint, examine my biases, and emerge with an unmanageable number of new ideas to think about.

There are two complementary, but independent ideas presented in the book. The two ideas can be linked, but the failure of one does not negate the other. The first idea is that competition for limited transcription factors (''microcompetition'' in his lexicon) can affect gene expression in cells, and that foreign DNA can be a robust competitor. To illustrate this point, Polansky offers numerous examples of disease states that could be explained by microcompetition. One implication of the theory is that the oncogenic effect of some viral infections could be DNA-based rather than protein-based. A further implication is that any event leading to altered DNA or RNA copy number should be scrutinized for unexpected effects on gene regulation.

The second, more profound idea in the book is an exhaustive description of the quantitative, step-by-step process whereby changes in gene expression could be manifested to the disease phenotype. Furthermore, the resulting perturbations can be subtle, but still have dramatic effects when they reach a critical threshold. Polansky sells this idea by proposing a testable model for relevant cellular changes in diverse chronic human disease states. The example of atherosclerosis elegantly illustrates how gene expression changes might alter the accumulation of LDL-containing cells in blood vessels in the early stages of the disease. Specifically, the direction of cell movement across the intimal space of the blood vessel depends on a subtle balance between the concentration of different ligands and the affinity of cells binding to it. In the forward direction, cell movement is powered by binding of CD18 receptors to a gradient of ICAM ligand, and in the reverse direction by an opposing affinity of TF receptors for the fibronectin ligand. In this scenario, altered expression of either the ligands or ligand receptors would leave cells and their LDL cargo trapped in the intimal space, eventually causing atherosclerosis. It is easy to extrapolate this model to other types of changes in cell motility, such as in metastatic cancer.

Of course, any newcomer with a radical idea about how to approach a difficult problem is not necessarily right. As with any departure from convention, it is human nature to want to simplify the meaning in order to easily dismiss it. Although Polansky uses specific examples to illustrate his ideas, they are just a starting point for discussion. What I hope readers will take away from the book is that we can improve on our current models of chronic disease by using Polansky's mathematical relationships to explore the effect of biochemical reactions on a higher-order scale.

One criticism is that the tone of the book is overly cautious and the extensive explanatory notes make it difficult to read in one sitting. However, the careful reader will be rewarded, and will admire the author's completeness in establishing a credible link between the theory and the published experimental observations. I particularly recommend taking time to study the chapters with the definitions of microcompetition and cell motility. These two chapters explain the author's unique mathematical notation, and help translate a few new terms for familiar concepts, such as ''shape'' instead of ''conformation'' and ''remoteness'' instead of ''distance traveled.''

BioEssays 27:230–231, © 2005 Wiley Periodicals, Inc.

This book has the potential to change the way that we think about complex systems, and help us connect the dots from genotype to phenotype. Although more philosophical than pragmatic, it is definitely worth the effort to see if the grand unifying vision can be realized in practice. I heartily recommend the book to any serious scientist who is looking for a fresh perspective or needs some traction to restart a stalled research project.

DOI 10.1002/bies.20185
Published online in Wiley InterScience (www.interscience.wiley.com).