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The "X" Word: Xenohormesis

Xenohormesis is derived from the root word "xeno" (implying foreign) and "hormesis" (relating to control). In essence, xenohormesis means altered cellular function due to exposure to foreign molecules in the food supply, water, or air. Emerging science recognizes xenohormetic substances as molecules that send signals to receptors on various cells, thereby altering their functions—affecting virtually all physiological processes including immunity, inflammation, body-fat retention, appetite, blood fat levels, insulin signaling, and cellular division. The end result is that we are witnessing food being redefined as "information" that alters cellular function in the post-prandial state. REF #1

Chronic stress is an illegitimate signal that may shift body phenotype to suit a more conservative state of energy management. Modern techniques of husbandry and agriculture can produce stress in the food chain, such that the food itself can act as an illegitimate signal of chronic stress. Through xenohormesis, consumers of stressed foods may sense those signals and assume a stressed phenotype. This maladaptive process may promote obesity. REF #2

Theoretically, precise molecular characterization of human disease will allow us to understand the basis for disease susceptibility and environmental influence; to offer an explanation for the different phenotypic manifestations of the same disease; to define disease prognosis with greater accuracy; and to individualize disease treatment for optimal therapeutic efficacy. Contemporary classification of human disease derives from observational correlation between pathological analysis and clinical syndromes. This diagnostic strategy, though time-honored, has significant shortcomings. There is a logical basis for a new approach to classifying human disease that uses conventional reductionism and incorporates the non-reductionist approach of systems biomedicine. REF #3

Homo obesus: A Metabotrophin-Deficient Species

In most countries the prevalence of obesity now exceeds 15%, the figure used by the World Health Organization to define the critical threshold for intervention in nutritional epidemics. In an article recently published in Current Pharmaceutical Design, a group of researchers present and describe *Homo obesus* (man the obese) as a recent phenotypic expression of *Homo sapiens*. They classify *Homo obesus* as a species deficient of metabotrophic factors, including endogenous proteins, which play an essential role in the maintenance of glucose, lipid, energy and vascular homeostasis, and also improve metabolism-related processes such as inflammation and wound healing. REF #4

The Evolution of Taste Preferences
Conventional wisdom says that preferences for particular tastes evolved to ensure an adequate instinctual intake of metabolic resources. In *Medical Hypotheses*, Dr. Anthony Yun and Dr. John Doux advance the hypothesis that taste preferences for sugars, fats, and salt evolved in part to detect stress, thereby augmenting our ability to adapt to ecologic challenges. They suggest that the modern context may have rendered maladaptive the previously valuable link between taste preferences and stress signals. REF #5

A Review of Nutritional Hormesis
Dr. DP Hayes, from the New York Department of Health and Mental Hygiene, has published a review of nutritional hormesis in the *European Journal of Clinical Nutrition*. Hormesis describes the observation that small quantities of some substances have different biochemical and toxicological effects than large quantities. In this review, hormetic and other dose-response relationships are categorized, depicted, and discussed. Evidence for nutritional hormesis is presented for essential vitamin and mineral nutrients, dietary restriction, alcohol (ethanol), natural dietary and some synthetic pesticides, some herbicides, and acrylamide. REF #6

Resveratrol and Sirtuin Functions
Calorie restriction is the most robust and reproducible way to delay age-related diseases and extend lifespan in mammals. Experiments have implicated the sirtuin/Sir2 family of NAD+-dependent deacetylases and mono-ADP-ribosyltransferases as mediators of the physiological effects of calorie restriction. In mammals, seven sirtuin genes have been identified (SIRT1-7). Resveratrol has been shown to extend the lifespan of evolutionarily distant species including *S. cerevisiae*, *C. elegans*, and *D. melanogaster* in a Sir2-dependent manner. In the November, 2006 issue of *Nature*, a group of researchers led by Dr. David Sinclair of Sirtris Pharmaceuticals published a study showing that resveratrol shifts the physiology of middle-aged mice on a high-calorie diet towards that of mice on a standard diet and significantly increases their survival. In the animals, resveratrol produced changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-1), increased AMP-activated protein kinase (AMPK) and peroxisome proliferators-activated receptor-γ coactivator 1α (PCG-1α) activity, increased mitochondrial number, and improved motor function. Parametric analyses of gene set enrichment revealed that resveratrol opposed the effects of the high-calorie diet in 144 out of 153 significantly altered pathways. REF #7

Sirtuins or Sir2 (silent information regulator 2)-related enzymes have originally been defined as a family of nicotinamide adenine dinucleotide (NAD+)-dependent enzymes that deacetylate lysine residue on various proteins. Certain sirtuins also have an ADP-ribosyltransferase activity. The mammalian sirtuins are implicated in a variety of cellular functions ranging from gene silencing, over the control of the cell cycle and apoptosis, to energy homeostasis. The wide range of cellular activities of the sirtuins suggests that they could constitute therapeutic targets to combat metabolic, neurodegenerative, and proliferative diseases. REF #8

Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. A major cause of cell death caused by genotoxic stress is thought to be due to the depletion of NAD+ from the nucleus and the cytoplasm. Researchers (again led by David Sinclair) recently published data in *Cell* showing that NAD+ levels in mitochondria remain at physiological levels following genotoxic stress and can maintain cell viability even when nuclear and cytoplasmic pools of NAD+ are depleted. The sirtuins have emerged as key regulators of cell survival and organismal longevity. REF # 9

Clinician/Researcher of the Month

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Dr. Christoph Westphal is co-founder of Sirtris Pharmaceuticals, a biopharmaceutical company focused on discovering and developing proprietary, orally available, small molecule drugs with the potential to treat diseases associated with aging. He received his MD and PhD from Harvard University and his BA from Columbia University. Dr. Westphal was formerly a consultant with McKinsey and a general partner in a venture capital fund.

Launched just two years ago and the subject of a recent *Fortune* cover story, Sirtris had its beginnings in the lab of Dr. David Sinclair, the Harvard researcher who published the 2003 study suggesting that resveratrol can mimic the effects of calorie restriction in yeast cells and boost lifespan by 70%. The company has been on the fast track and is already clinically testing its first medicine, a resveratrol-based drug to keep diabetic patients' blood sugar under control. Because of the broad therapeutic potential of resveratrol-based drugs, medicines developed by Sirtris—if successful—may retard the onset of age-related diseases while also potentially extending lifespan. Researchers connected to Sirtris are actively publishing their findings, including a 2006 article in *Cell* suggesting resveratrol positively impacts mitochondrial function and metabolic homeostasis. REF #10-11

In Closing: Infection-induced Viscerosensory Signals

The presence of certain bacteria in the gastrointestinal tract influences both behavior and brain function. Little is known regarding the interface of immune sensory signals with brain substrates that mediate changes in behavioral stress. Researchers at the University of Virginia designed an animal study to explore this issue and published their findings in *Brain Behavior and Immunity*. In this study, mice were challenged with either *C. jejuni* or saline and were assessed using the open holeboard by immunohistochemical detection of the protein c-Fos as an activation marker in the brain. The findings implicate the paraventricular nuclei (PVN), amygdale, and bed nucleus of the stria terminals (BST) as

interfaces between gastrointestinal pathogenic challenge and brain regions that mediate behavioral response to stress, and reinforce these nuclei as anatomical substrates by which viscerosensory stimuli can influence behavior. REF #12

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