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Continuing the Discussion on Xenohormesis

Dr. Konrad Howitz and Dr. David Sinclair have published an essay in *Cell* titled “Xenohormesis: Sensing the Chemical Cues of Other Species.” The authors point out that one-third of the current top 20 drugs on the market are plant-derived, but despite the success of plant molecules as drugs, they are losing favor among drug developers due to issues such as patentability. At present, it is not fully understood why many plant molecules are safe and beneficial to human health. Are biochemical interactions merely a remnant of what existed in the common ancestor of plants and animals, or is selection maintaining interactions between the molecules of plants and animals? In the article, Howitz and Sinclair discuss what they call the “Xenohormesis Hypothesis.” REF #1

Focus on Cancer

Earlier this year, *The New England Journal of Medicine* launched a series of reviews on the molecular origins of cancer to highlight advances in the biology of cancer. Over the past decade, insights into the origins and behaviors of human cancers have reshaped our understanding of these diseases and have generated advances in clinical care. REF #2

Cancer is a disease of extreme heterogeneity. Dr. Bland discusses a recent article published in the *Yale Journal of Biology and Medicine* titled “Mechanisms of Oncogenic Cooperation in Cancer Initiation” that addresses this. He also refers to a 2006 article published in *Theoretical Biology & Medical Modelling* that describes the complex dynamic process of human carcinogenesis as “one of the most intricate phenomena in biology.” REF #2-3

With a focus on possible endogenous origins of cancer initiation, Dr. Bland turns to the work of Dr. Eleanor Rogan and her colleagues at the University of Nebraska. Experiments on the metabolism of estrogens, formation of depurinating adducts, carcinogenicity, mutagenicity, and cellular transformation have lead Dr. Rogan’s team to the hypothesis that certain metabolites of endogenous estrogens—in particular, estradiol(estrone)-3,4-quinones—can react with DNA to form depurinating adducts, which can generate critical mutations, possibly initiating cancer and other diseases. REF #5

The hypothesis of fetal origins of adult disease posits that early developmental exposures involve epigenetic modifications, such as DNA methylation, that influence adult disease susceptibility. A group of researchers led by Dr. Randy Jirtle at the Department of Radiation Oncology and University Genetics and Genomics at Duke University recently published an important study on neonatal exposure to bisphenol A (BPA), a chemical used in the manufacture of polycarbonate plastic. This animal study demonstrated that epigenetic patterning during early stem cell development is sensitive to BPA exposure, and moreover, that maternal dietary supplementation, with either methyl donors like folic

acid or the phytoestrogen genistein, negated the DNA hypomethylating effect of BPA.
REF #6

Much of today's research into the origins of cancer can be tracked to the important pioneering work of individuals such as Dr. Bruce Ames. Dr. Ames published a landmark article in *Science* in 1983 titled "Dietary Carcinogens and Anticarcinogens: Oxygen Radicals and Degenerative Diseases" in which he discussed how the dietary intake of natural antioxidants could be an important aspect of the body's defense mechanism against cancer, heart disease, and aging. Dr. Bland also pays tribute to Dr. Judah Folkman, a path-breaking cancer researcher who faced years of skepticism before his ideas led to successful treatments. Dr. Folkman passed away in January at the age of 74.
REF #7

Clinician/Researcher of the Month

Devra Lee Davis, PhD, MPH
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Dr. Devra Davis heads up the world's first Center for Environmental Oncology at the University of Pittsburgh Cancer Institute. The multidisciplinary center includes experts who develop cutting-edge studies to identify the causes of cancer and propose policies to reduce the risks of the disease. As a former Senior Advisor to the Assistant Secretary for Health in the Department of Health and Human Services, Dr. Davis counseled leading officials in the United States, the United Nations, the World Health Organization, and the World Bank. President Clinton appointed Dr. Davis to the newly established Chemical Safety and Hazard Investigation Board (1994-1999), an independent executive branch agency that investigates, prevents, and mitigates chemical accidents.

A member of both the American Colleges of Toxicology and of Epidemiology, Dr. Davis is also Visiting Professor in the Department of Environmental and Occupational Medicine at Mt. Sinai Medical Center in New York City. In addition, she is a Visiting Scientist of the Strang Cornell Cancer Prevention Center of the Rockefeller University and Scientific Advisor to the Women's Environment and Development Organization. She also founded the International Breast Cancer Prevention Collaborative Research Group, an organization dedicated to exploring the causes of breast cancer. She currently serves on the Boards of the Climate Institute, the Coalition of Organizations on the Environment and Jewish Life, and the Earthfire Institute.

Dr. Bland and Dr. Davis discuss her research, including an important article she published with collaborator Dr. Leon Bradlow in *Scientific American* in 1995. Dr. Davis is the author of two best-selling books, *When Smoke Ran Like Water* (2002), and more recently, *The Secret History of the War on Cancer* (2007). REF #8

In Closing: The Anti-Cancer Effects of Polyphenols

Evidence suggests that edible small and soft-fleshed berry fruits may have beneficial effects against several types of human cancers. The anticancer potential of berries has been related, at least in part, to a multitude of bioactive phytochemicals that these colorful fruits contain, including polyphenols (flavonoids, proanthocyanidins, ellagitannins, gallotannins, phenolic acids), stilbenoids, lignans, and triterpenoids. Studies show that the anticancer effects of berry bioactives are partially mediated through their abilities to counteract, reduce, and also repair damage resulting from oxidative stress and inflammation. Dr. Bland finishes this interview with a review of recent articles on this subject. REF #9-15

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