FUNCTIONAL MEDICINE UPDATE
MARCH 2009
ISSN 1092-1761
Vol. 29, No. 3

New Therapeutics are Dependent on Information Being Developed at the Cellular Level

Dr. Bland opens this issue with a discussion of an article co-authored by Dr. Kevin Morris that appeared in *Science* magazine in 2004 titled "Small Interfering RNA-Induced Transcriptional Silencing in Human Cells." Dr. Morris is the featured researcher of the month for this issue, and Dr. Bland lays the groundwork for how the work of Dr. Morris and others is playing a central role in the eventual development of new therapies that will be applied clinically. Small interfering RNA (siRNA) and microRNA silence genes at the transcriptional, posttranscriptional, and/or translational level. In this particular article, Dr. Morris and his colleagues investigated whether siRNA-induced transcriptional gene silencing occurs in human cells. REF #1

More Studies are Being Published on the Role of Low-Level Chemical Exposure

In the first issue of 2009, the journal Human Reproduction featured an article titled "Maternal Levels of Perfluorinated Chemicals and Subfecundity." This study was an international effort among several research groups that examined whether exposure to perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), ubiquitous man-made compounds that are possible hormone disruptors, decreased fecundity in humans. Data was collected from 1240 women from the Danish National Birth Cohort recruited from 1996 to 2002. Plasma levels of PFOS and PFOA were measured at 4-14 weeks of pregnancy. The findings of the study suggest that PFOA and PFOS exposure at plasma levels seen in the general population may reduce fecundity. Such exposure levels are common in developed countries. REF #2

Managing Early-Stage Symptoms of Cognitive Decline

In a previous issue of *Functional Medicine Update*, Dr. Bland discussed at length the work of Mattson, et al, on the beneficial roles of dietary phytochemicals in protecting against chronic disorders such as cancer, and inflammatory and cardiovascular diseases. Emerging findings suggest that several dietary phytochemicals also benefit the nervous system and, when consumed regularly, may reduce the risk of disorders such as Alzheimer's and Parkinson's diseases. REF #3

In a February 2009 article published in the *Archives of Neurology*, researchers from Columbia University investigated the association between the Mediterranean diet and mild cognitive impairment (MCI). This was a multiethnic community study in New York using Cox proportional hazards. All of the models were adjusted for cohort, age, sex, ethnicity, education, APOE genotype, caloric intake, body mass index, and duration between baseline dietary assessment and baseline diagnosis. Mean follow-up was 4.5 years. The conclusions of this study were that higher adherence to the Mediterranean diet is associated with a trend for reduced risk of developing MCI and with reduced risk of

MCI conversion to Alzheimer's disease. This study was a follow-up to a 2006 study published by the same group which reflected similar results. REF #4-5

Related to this discussion of cognitive decline is an interesting paper that was recently published in the *Journal of Alzheimer's Disease* by a research team from Finland and Sweden. This study is titled "Midlife Coffee and Tea Drinking and the Risk of Late-Life Dementia: A Population-Based CAIDE Study." The aim was to study the association between coffee/tea consumption at midlife and dementia/Alzheimer's disease (AD) risk in late life. Data was gathered from participants of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. The average follow-up was 21 years, and the researchers found that coffee drinkers at midlife had lower risk of dementia and AD later in life compared with those drinking no or only little coffee adjusted for demographic, lifestyle and vascular factors, apolipoprotein E4 allele, and depressive symptoms. The lowest risk (65% decreased) was found in people who drank 3-5 cups per day. REF #6

New Data from the Women's Health Initiative

A large-scale examination of data from the Women's Health Initiative was recently published in the *Archives of Internal Medicine*. This article is titled "Multivitamin Use and Risk of Cancer and Cardiovascular Disease in the Women's Health Initiative Cohorts," and the aim was to examine associations between multivitamin use and risk of cancer, cardiovascular disease (CVD), and mortality in postmenopausal women. This study included 161,808 participants from the Women's Health Initiative clinical trials, and a total of 41.5% of the participants used multivitamins. Median follow-up was 8.0 years in the clinical trial cohort and 7.9 years in the observational study cohort. The study authors state that the data provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women. REF #7

Dr. Bland uses this study as an example to again make the case that supplementary nutrients are not the primary modulators of function, but rather lifestyle, as a variable, needs to be given consideration. The Council for Responsible Nutrition issued a press release in response to the publication of this article, in which they state, "Multivitamins, like all other dietary supplements, are meant to be used as part of an overall healthy lifestyle; they are not meant to be magic bullets that will assure the prevention of chronic diseases, like cancer." REF #8-10

Vitamin D Supplementation: Stories from Past and Present Research

Dr. Bland discusses an article sent to him by an FMU subscriber about Dr. Arthur Alexander Knapp, a respected physician who had a distinguished career at Columbia University doing ophthalmological research. In this article from the late 1970s, Dr. Knapp describes his 40 years of research, and in particular, the positive results he felt he achieved with vitamin D supplementation. REF #11

Dr. Bland discusses two articles published in 2008 that focus on vitamin D, specifically as it relates to the epidemiology of frequent respiratory infections and influenza. Dr. John J. Cannell is a co-author of both articles, one of which addresses the issue of seasonal and

population effects of vitamin D on innate immunity. Dr. Bland also discusses recent report linking vitamin D deficiency and the risk of developing multiple sclerosis in people with a genetic predisposition for the disease. REF #12-14

Clinician/Researcher of the Month

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Dr. Kevin Morris received his PhD in Comparative Pathology Microbiology and Immunology from the University of California, Davis. He was a post-doctoral fellow at the University of California, San Diego, and an assistant research scientist at the Beckman Research Institute at the City of Hope in Duarte, CA. Dr. Morris is currently an associate professor at the Scripps Research Institute.

In 2004, Dr. Morris co-authored an article for *Science* magazine describing transcriptional gene silencing (TGS). TGS differs from post-transcriptional gene silencing in that noncoding RNAs turn off transcription by interacting with a gene's promoter. The observations by Dr. Morris' lab and others have shown that small RNAs can regulate a gene's expression at the transcriptional level. According to his website, "These findings suggest that the once held dogma that RNA functions as an information transfer medium between DNA and protein may not be complete. In fact, it has become apparent that small RNAs can regulate the transcription of a gene via the targeting of silent state epigenetic marks and chromatin remodeling complexes to the gene's promoter." Dr. Morris' lab is interested in determining whether this recently described mechanism is endogenous in human cells or a vestigial mechanism, and specifically if this mechanism can be applied to treat human diseases, such as silencing HIV-1.

Dr. Bland and Dr. Morris discuss his publications and his research, as well as explore the ways this research is relevant to clinical application and potential future therapies. They both share thoughts and visions for the future. Dr. Morris has recently been an awarded an Astor Fellowship at Oxford University, where his research will continue. REF #15-16

In Closing: The Statin/Coenzyme Q10 Relationship
Coenzyme Q10 (ubiquinone) is a vitamin-like substance present in most cells. It helps mitochondria, the powerhouses of the cell, turn sugars and other fuels into energy. Taking a statin lowers coenzyme Q10 because it is carried through the bloodstream in LDL/ Lowering LDL—the main job of a statin—means less coenzyme Q10 in circulation. It has been hypothesized that statins' effects on coenzyme Q10 might account for the muscle aches and pains these drugs sometimes cause. According to Dr. Yiannis Chatzizisis of Harvard University, in the September 2008 *Harvard Heart Letter,* taking a

supplement increases blood levels of coenzyme Q10, but the effect inside muscles is inconsistent—one study showed an increase of coenzyme Q10 after supplementation, another a decrease. The only two trials of coenzyme Q10 for statin-induced muscle problems contradict each other. In one supplementation had no effect on muscle pain, and the other showed a modest benefit. REF #17

Dr. Bland discusses three recent articles on this topic that look at this subject in greater detail. Two reviews summarize the latest information on risk factors associated with statin-induced myopathy. The third article addresses the case for measurement of plasma coenzyme Q10 levels based on the potential to identify individuals most likely to benefit from supplementation therapy. REF #18-20

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