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The Importance of Patient-Centered Care

Most systems that support clinicians would benefit from redesign that aligns care more completely with patients' needs and interests. This topic was the subject of a recent editorial published in the *Journal of the American Medical Association*. Clinical trials have demonstrated that desired outcomes can be affected by system changes. The chronic care model is an example of an evidence-based system approach that includes self-management support and care coordination as key components. The authors of the editorial discuss numerous options, including open access, use of technology, and use of tools such as agenda cards (an application developed in the United Kingdom). Asking clinicians to work harder or presuming that lack of patient centeredness is due to a lack of knowledge or training is not the answer to the complaint that the United States lags behind other countries in meeting patients' needs and expectations. Well-designed support and delivery systems are essential in allowing physicians to build the kind of relationships with patients that directly address patients' needs and priorities. REF #1

Translational Medicine is here to Stay

Translational medicine is an amalgam of pharmacogenomics and other tools designed to bring research advances to the patient in the form of better medicine and diagnostics. For public-sector scientists, this means paying attention to clinical applications of research even during the basic stages. Some believe that the slow pace of clinical impact is necessitating this approach. With major investments from both NIH and pharmaceutical companies, the clinical world has seen some early successes. On January 2005, the Institute for Translational Medicine and Therapeutics (ITMAT) opened in Pennsylvania. Strategic planning at the University of Pennsylvania School of Medicine led to the establishment of the institute, as well as one key observation: the need for more investigators versed in model systems, mechanism-based clinical investigations, and human pharmacology. ITMAT has plans to launch centers in translational research, personalized medicine, imaging, bioinformatics in translation, and chemical biology. REF #2-3

Vitamin D and Multiple Sclerosis Risk

In its hormonal form, vitamin D can prevent experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Although evidence remains inconclusive, a protective effect of vitamin D on MS is supported by the reduced MS risk associated with sun exposure and use of vitamin D supplements. Dr. Bland discusses a study recently published in the Journal of the American Medical Association. The results of this study suggest that high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis. REF #4

Chronic Fatigue Syndrome: How Far Have We Come?

Nearly 20 years after being named as a clinical entity, the root causes of chronic fatigue syndrome (CFS) have still not been identified; however, researchers have had some success in uncovering potential triggers and treatments. A valuable source of information has proven to be data from the Wichita CFS Surveillance Study, a program launched by the Centers for Disease Control and Prevention (CDC) in 1997. The study includes the following findings: the disease may be associated with genetic and environmental determinants; some cases may be linked to stress and childhood trauma (emotional, physical, and sexual abuse, and emotional and physical neglect); and higher emotional instability and self-reported stress are associated with increased risk. In addition, impairments in metabolism and dysfunction of the immune and nervous systems are underlying biological abnormalities that are suspected of playing a role in the etiology of the disease. Current therapies for CFS includes symptom management, coping strategies, cognitive behavioral therapies, and exercise in addition to standardized treatments that help manage pain, sleep problems, and severe fatigue. REF #5-8

In a recent issue of the Journal of the Royal Society of Medicine, a substantive systematic review of clinical data was published. The purpose of the review was to determine whether any particular intervention or combination of interventions is effective in the treatment, management, and rehabilitation of adults and children with a diagnosis of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Randomized (RCTs) clinical trials and non-randomized controlled trials of any intervention or combination of interventions were eligible for inclusion. Studies on behavioral, immunological, pharmacological, complementary therapies, nutritional supplements, and miscellaneous other interventions were identified. Based on evidence from RCTs, graded exercise therapy and cognitive behavior therapy appeared to reduce symptoms and improve function. For most other interventions, evidence of effectiveness was inconclusive. REF #9

Bacteria Infect Mitochondria in Lyme Disease Ticks

The tick species *Ixodes ricinus* is the main vector for Lyme disease. Two years ago, an Australian postdoctoral student working at the University of Milan, Nate Lo, came across a novel 16S rRNA sequence while screening for human pathogens in the tick species. What he and his colleagues eventually found were intracellular microbes—living not in the cytoplasm of the tick ova, but rather within their mitochondria. This is the first known discovery of a bacterium that infects the mitochondria, and could have significant implications. The new genus has been named *Midichloria mitochondrii*. REF #10

Evidence of Oxidative Damage in the Erythrocytes of CFS Patients

It has been hypothesized that a link exists between erythrocyte metabolism and erythrocyte shape. Studies have been conducted to investigate a correlation between erythrocyte morphology and erythrocyte oxidative damage in chronic fatigue syndrome (CFS). Research aimed at confirming earlier results was recently published in an issue of the *Archives of Medical Research*. This research provided further evidence for the role of free radicals in the pathogenesis of CFS and a link between erythrocyte metabolism and erythrocyte shape. There was also an indication that the increase in erythrocyte antioxidant activity is associated with the presence of stomatocytes. REF #11

Oxidative Phosphorylation Disorders
The final steps in the production of adenosine triphosphate (ATP) in mitochondria constitute the oxidative phosphorylation (OXPHOS) system. Genetic defects of OXPHOS are now recognized as important causes of disease. The metabolic consequences of OXPHOS impairment include accumulation of metabolic intermediates, increased generation of reactive oxygen species (ROS), and decreased ATP production. REF #12

AMP-activated protein kinase (AMPK) is a chief regulator of whole-body energy balance that governs the activity and number of mitochondria, which produce energy by oxidizing fatty acids and glucose. An age-related reduction in mitochondrial activity can lead to an accumulation of intracellular fat in muscle and liver cells, which can lead to insulin resistance and type 2 diabetes. Howard Hughes Medical Institute investigator Dr. Gerald I. Shulman and colleagues at Yale University have conducted an animal study that examined the effects of aging on the activity of AMPK. The results of the study suggest that aging-associated reductions in AMPK activity are likely important factors contributing to the observed reductions in mitochondrial function and increases in triglycerides inside muscle cells associated with aging. This decline in AMPK activity and mitochondrial biogenesis predisposes older adults to insulin resistance and type 2 diabetes. Related studies in human subjects are planned. REF #13

In another animal study (this one published in *Science Magazine*), a group of investigators showed that mice expressing a proofreading-deficient version of the mitochondrial DNA polymerase γ (POLG) accumulate mtDNA mutations and display features of accelerated aging. Accumulation of mtDNA mutations was not associated with increased markers of oxidative stress or a defect in cellular proliferation, but was correlated with the induction of apoptotic markers, particularly in tissues characterized by rapid cellular turnover. REF #14

Aging is the greatest risk factor for neurodegenerative diseases. Since mutations in mitochondrial DNA and oxidative stress both contribute to aging, evidence has suggested that mitochondria have a central role in the pathogenesis of neurodegenerative diseases. The propensity of mitochondrial disorders to affect the brain and muscles has thus far been explained by the different tissue requirements for mitochondrial function. In an article published in *Nature*, a group of researchers speculated that mitochondrial differences between different cell types might be at least as important in this selectivity, if not more so. REF #15

An interesting animal study related to OXPHOS was published in Free Radical Biology & Medicine in 2004. This study examined the effect of long-term dietary treatment with N-acetylcysteine. It documented the marked tissue specificity of the decline of bioenergetic functions in isolated mitochondria from aged rats by revealing an age-related decrease in respiratory fluxes in the brain but not in heart mitochondria. REF #16

Dietary Fatty Acid Intakes and Infertility

Specific dietary fatty acids can affect peroxisome proliferators-activated receptor gamma (PPAR-gamma) activity. Because pharmacologic activation of PPAR-gamma improves ovulatory function in women, a study was recently conducted to assess whether the intakes of total fat, cholesterol, and major types of fatty acids affect the risk of ovulatory infertility. This was a prospective cohort study of 18,555 married, premenopausal women without a history of infertility who attempted a pregnancy or became pregnant between 1991 and 1999. Using logistic regression analyses, it was determined that obtaining 2% of energy from trans fats rather than from monounsaturated fats was associated with a more than doubled risk of ovulatory infertility. REF #17-18

Endocrine Disruptors and Male Fertility

Transgenerational effects of environmental toxins require either a chromosomal or an epigenetic alteration in the germ line. Vinclozolin is a fungicide used in the wine industry. Research into reproductive biology at Washington State University has shown that vinclozolin blocks cell receptors that are normally activated by the hormone androgen. Vinclozolin and another endocrine disruptor, methoxychlor (a pesticide), have been shown to cause fertility defects in male rats that are passed down to nearly every male in subsequent generations. The ability of an environmental factor to reprogram the germ line to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology. REF #19-20

Clinician/Researcher of the Month

Paul Cheney, MD, PhD
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For over 20 years, Dr. Paul Cheney has been a pioneering researcher in the field of chronic fatigue syndrome (CFS). Profiled in the book, *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic*, Dr. Cheney is an internationally recognized authority on this subject. He was a founding director of the American Association of Chronic Fatigue Syndrome (now IACFS). Since 1990, Dr. Cheney has headed the Cheney Clinic, the site of several FDA-approved pharmaceutical drug trials on CFS patients. No other single clinic has drawn as many CFS patients from as many states and foreign countries. REF #21

Dr. Cheney was a guest on *Functional Medicine Update* for the first time in 1994. He and Dr. Bland discuss what has transpired in the field of chronic fatigue syndrome research in the years that have passed since their first interview. In his own words, Dr. Cheney also describes his own illness—a sudden onset of idiopathic cardiomyopathy that eventually led to a heart transplant in 2003 after a steady decline over a 3-year period.

Believing that CFS was tied to a deep-seated energy problem somewhere at the cellular level, Dr. Cheney began to study a link between low cardiac output and chronic fatigue syndrome upon his return to clinical practice. After conducting research using impedence

cardiograph and echocardiograph machines, Dr. Cheney found a common thread among CFS patients he tested: diastolic dysfunction. Diastolic dysfunction is a state in which the heart does not have energy at the cellular level. He also found that some of these patients had elevated pulmonary pressure and left atrial cavitation, and about 90% had patent foramen ovale (PFO). These observations could point to a relationship between chronic fatigue syndrome and a defect in the handling systems for oxygen.

In this wide-ranging and informative discussion, Dr. Bland and Dr. Cheney discuss the techniques of cognitive behavioral therapy and graded exercise therapy. Dr. Cheney expresses his concerns about these treatments when applied to all patients with considering individual uniqueness, and the technique of rebreathing is also discussed.

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