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New Products are Now Available from Synthesis by Jeffrey Bland, PhD
Perspectives on Autism – A 4-CD audio collection and featuring commentary by Dr. Bland and expert interviews excerpted from past issues of FMU. Interviews include S. Jill James PhD (University of Arkansas), Martha Herbert, MD, PhD (Massachusetts General Hospital), and Richard Deth, PhD (Northeastern University). In a special bonus interview, Dr. Bland pays tribute to a pioneer in the field of behavioral toxicology, Herbert Needleman, MD (University of Pittsburgh). Set price: $40 plus shipping.

Beyond Metabolic Syndrome – Jeffrey Bland's popular 2007 one-day seminar is now available on audio CD. This 7-CD set features over 5 hours of audio material plus more than 300 slides provided on CD-ROM. Set price: $60 plus shipping.

Understanding Atherogenesis and Exploring New Therapeutic Strategies
In 2002, *Nature Medicine* published a series of review articles that Dr. Bland utilizes to provide context for the primary subject of this month's FMU: Functional Cardiology.

In atherosclerosis, the vascular smooth muscle cell (VSMC) contributes to vessel wall inflammation and lipoprotein retention, as well as to the formation of the fibrous cap that provides stability to the plaque. The VSMC can undergo a proliferative response that underlies the development of in-stent restenosis, bypass graft occlusion, and transplant vasculopathy. Although the benefit/risk of therapeutic inhibition of VSMC proliferation in atherogenesis is unclear, experimental and human evidence strongly suggests the therapeutic potential of antiproliferative therapy for in-stent restenosis, bypass graft failure, and other vascular proliferative disorders. REF #1

Macrophages have evolved specialized functions to protect the body from infection. However, the same mechanisms that enable phagocytosis of pathogens and activation of leukocytes also permit the uptake of lipoproteins and release of reactive oxygen species and immune mediators that collectively contribute to atherosclerosis. New approaches to inhibit lipid accumulation in macrophage foam cells and reduce inflammatory responses may be of therapeutic value in preventing coronary artery disease. REF #2

Traditional risk factors like hypercholesterolemia are important for atherogenesis, but it is now apparent that the immune system also plays an important role. Uncovering the mechanisms by which specific components of the immune system impact atherogenesis will not only provide new insights into the pathogenesis of lesion formation, but could also lead to novel therapeutic approaches that involve immune modulations. REF #3

The participation of platelets in atherogenesis and the subsequent formation of occlusive thrombi depend on platelets' adhesive properties and the inability to respond to stimuli with rapid activation. By understanding the multifaceted mechanisms involved in platelet

interactions with vascular surfaces and aggregation, new approaches can be tailored to selectively inhibit the pathways most relevant to the pathological aspects of atherothrombosis. REF #4

Research points to pivotal roles for lipids in the development of atherosclerotic plaques. Lipid-lowering statins substantially reduce acute coronary events resulting from plaque development, but only modestly reduce arterial stenosis. This apparent paradox has shifted the goal of therapy towards plaque stabilization rather than enlargement of the lumen. More thorough understanding of the biology of atherosclerosis should enable us to manipulate plaque stability, and reduce further the acute complications of atherosclerosis. REF #5

Polyunsaturated Fatty Acids and the Stability of Atherosclerotic Plaques
A randomized controlled trial of patients awaiting carotid endarterectomy was conducted to assess the hypothesis that incorporation of n-3 and n-6 PUFAs into advanced atherosclerotic plaques increases and decreases plaque stability, respectively. Study participants were randomly allocated to control, sunflower oil (n-6), or fish-oil (n-3) capsules until surgery. The finding of this study indicated that atherosclerotic plaques readily incorporate n-3 PUFAs from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of n-6 PUFAs did not affect carotid plaque fatty acid composition or stability over the time course that was studied. REF #6

Hypercholesterolemia and Inflammation: Partners in Crime
In an article included in the *Nature Medicine* series, Dr. Daniel Steinberg reflects on a historical perspective on atherosclerosis and once-controversial hypotheses. Plaque formation was once thought to be dependent upon hypercholesterolemia alone, or solely in response to injury. More recently, inflammatory cascades were thought to be at the root of lesion development. Dr. Steinberg suggests that a more realistic view may be that atherosclerosis is neither exclusively an inflammatory disease nor solely a lipid disorder: it is both. REF #7

Lipoprotein Families: A Novel Classification System
The categorization of discrete lipoprotein families based on apolipoprotein composition instead of size and density provides a new way of describing plasma lipoproteins. There are 2 principal classes of lipoproteins, one of which is characterized by apolipoprotein A (apo A; apo A-I + apo A-II) and the other by apolipoprotein B (apo B) as the major apolipoprotein constituents.

The lipoprotein subclass containing apolipoproteins B and C is considered the most atherogenic (LpB:C). A group of researchers conducted a study to evaluate the acute effects of individual fatty acids on apo B-containing lipoproteins in adults with type 2 diabetes. The results published in the *American Journal of Clinical Nutrition* suggest that unsaturated fatty acids differentially affect concentrations of apo B-containing lipoprotein subclasses. A rise in LpB;C adversely affects endothelial function. Meals containing

MUFA + EPA/DHA attenuated the postprandial rise in LpB:C and the impairment of endothelial function. REF #8

Methylarginine Metabolism and Vascular Homeostasis

Asymmetrical dimethylarginine (ADMA) and monomethyl arginine (L-NMMA) are endogenously produced amino acids that inhibit all three isoforms of nitric oxide synthase (NOS). ADMA accumulates in various disease states, including renal failure, diabetes, and pulmonary hypertension. Its concentration in plasma is strongly predictive of premature cardiovascular disease and death. Both L-NMMA and ADMA are eliminated largely through active metabolism by dimethylarginine dimethylaminohydrolase (DDAH). Thus, DDAH dysfunction may be a crucial unifying feature of increased cardiovascular risk. In a study of 2543 persons with and 695 without coronary artery disease (CAD), ADMA concentration was found to predict all-cause and cardiovascular mortality in individuals with CAD independently of established and emerging cardiovascular risk factors. REF #9-10

C-Reactive Protein May Be an Atherosclerotic Risk Factor Even in Healthy Young Persons

The serum concentration of C-reactive protein (CRP) is known to be an independent risk factor and a predictor for coronary heart disease (CHD). It has been established that atherosclerosis originates early in life, and that its risk factors track to adulthood. A study was undertaken to determine the association of CRP with generalized and abdominal obesity, body fat composition, metabolic syndrome, and oxidative stress marker among young people, aged 10-18 years. The study authors found a significant positive association between CRP and oxidative stress in healthy young people, and concluded that oxidative stress and CRP may interact in the early inflammatory processes of atherosclerosis. REF #11

The Iron-Heart Hypothesis

The Iron-Heart Hypothesis was first put forth by Sullivan in 1981 and suggested that increased body iron stores are a risk factor for coronary heart disease and that iron depletion through phlebotomy or other means could reduce risk. Sullivan formulated this hypothesis to explain the age-related increase in risk of myocardial infarction (MI) in women following menopause. Testing the Iron-Heart Hypothesis in humans has focused on epidemiological associations between biomarkers of body iron status and risk of cardiovascular disease. Serum ferritin, the iron-storage protein for which levels are elevated with iron overload and proportionally reduced with iron depletion, is considered the best biomarker for long-term iron stores. Substantial preclinical and clinical literature supports the contribution of iron-related oxidative stress to the pathogenesis of atherosclerotic cardiovascular disease. However, this concept remains controversial because of differences in findings between clinical studies having variable experimental design. REF #12-13

Cholesterol Ester Transfer Protein (CETP) Inhibitors: A Pharmaceutical Target that is Attractive but Controversial

Limited clinical trials have suggested that an increase in HDL cholesterol levels may reduce the progression of coronary atherosclerosis and decrease cardiovascular morbidity. Cholesterol ester transfer protein (CETP) facilitates the transfer of cholesterol ester from HDL cholesterol to low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol. However, the effectiveness of CETP inhibition as a strategy for antiatherosclerotic therapy has been controversial, most recently as a result of published data from clinical trials of the CETP inhibitor, Torcetrapib. It has been suggested that a lack of efficacy may be related to the mechanism of action of this drug class or to molecule-specific adverse effects. REF #14

Clinician/Researcher of the Month

Roger Newton, PhD
(Preferred contact information pending)

Dr. Roger Newton's research interests for the past thirty years have focused on the nutritional and pharmacological regulation of cholesterol and lipoprotein metabolism as they relate to atherosclerosis and vascular diseases. He has had a long and distinguished career in pharmaceutical and life sciences industries. Dr. Newton co-discovered and was the product champion of what is now the most prescribed cholesterol reducing drug in the world, atorvastatin (Lipitor®).

In 1998, Dr. Newton co-founded Esperion Therapeutics, a biopharmaceutical company dedicated to the discovery and development of pharmaceutical products for the treatment of cardiovascular diseases through the use of a new treatment approach called "HDL Therapy". Esperion was acquired by Pfizer in February 2004 for $1.3 billion. Dr. Newton's most recent position was as Senior Vice President of Pfizer Global Research and Development, and Director of Esperion Therapeutics (a Pfizer Inc. Company).

Dr. Newton has co-authored nearly one hundred peer-reviewed articles and chapters during his research career. He is past Chairman of the Great Lakes Venture Quest, and a former member of the Michigan Life Science Corridor Steering Committee (1999-2003). He is currently Director on BOD (Board of Directors) of Rubicon Genomics, a member of the University of Michigan Cardiovascular Center National Advisory Board, Biotech Business Associates Advisory Board, and the University Musical Society Board. Through his philanthropic interests and the Esperance Family Foundation, Dr. Newton and his family are active supporters of non-profit organizations focusing on human potential, social justice, health and the environment. REF #15

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