Friday, 5/19, Trianon Ballroom, 1:30 pm–3:30 pm Theme III: ASH/Government/Academic/Industry Symposium: Pharmacoeconomics in the Management of Hypertension

OUTCOMES RESEARCH - A CLINICIAN'S PERSPECTIVE

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Outcomes research (OR) proposes to study the appropriateness of health care services in order to identify the manner by which diseases can be most *effectively* prevented, diagnosed and treated. Proponents of OR claim that this methodology will do this better than the randomized clinical trial (RCT), which we have traditionally used as the gold standard to obtain answers to many of the same questions. OR, like RCTs, uses the tools of epidemiology and biostatistics but OR studies the factors involved in the process of care in existing large data bases, not in specifically recruited and highly selected cohorts. Contrary to what some critics of RCTs have said, both methods try to understand what is responsible for better clinical outcomes but OR concentrates more on patient satisfaction and the cost-effective use of health care resources. RCTs, which have been called "efficacy" studies, have actually provided us with considerable data on outcomes and much valuable guidance for therapy. These efficacy studies, however, have been widely criticized for not reflecting the "real world" of medical care and for creating artificial outcomes which can not replicated in the usual clinical setting. This presentation will review clinical trial methodology, discuss RCTs which are designed to be "effectiveness" studies (large simple trials) and compare to RCTs to OR. I will suggest that unless OR finds a way to control bias and identify the innumerable confounders that can effect the therapeutic process, it will not be able to accomplish its goals.

Friday, 5/19, Mercury Ballroom, 5:00 pm–7:00 pm Theme I: Endothelial and Physical Factors in Hypertension

ENDOTHELIAL FACTORS IN THE CARDIO-VASCULAR SYSTEM

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The cardiovascular system is regulated by neuronal influences, circulating hormones as well as paracrine and autocrine mechanisms in the blood vessel wall. Endothelial factors play a primary role by releasing substances which can regulate vascular tone and structure as well as adhesion of circulating blood cells. Prostacyclin (PGI_2) activates cAMP and is a vasodilator and platelet inhibitor function. Nitric oxide (NO) formed from L-arginine via the activity of endothelial NO synthase (eNOS). Platelets also express eNOS. eNOS is increased in its expression by shear stress and estrogen and possibly other factors. The L-arginine nitric oxide pathway also is stimulated by shear stress as well as receptor-operated mechanisms (i.e. acetylcholine, histamine, bradykinin, substance P, ATP/ADP and thrombin). NO acts as a vasodilator and platelet inhibitor via cGMP. Furthermore, endothelial cells produce constricting factors such as endothelin-1 (ET1), thromboxane A_2 and prostaglandin H_2. ET1 activates ET_A- and ET_B-receptors on vascular smooth muscle to cause contraction and endothelial ET_B-receptors cause vasodilation (by NO and PGI_2). In vascular smooth muscle cells, NO is an inhibitor and ET1 a stimulator of migration and proliferation.

The endothelium is a target and mediator of cardiovascular disease and may exhibit profound dysfunction as cardiovascular disease progresses.

Key Words:
Hypertension, Hyperlipidemia, vascular disease

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CELLULAR RESPONSES TO MECHANICAL STRESS

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Virtually all cells accommodate or respond to the mechanical environment. The responses of endothelium to externally-generated forces such as those associated with blood flow is a useful paradigm for mechanical stress mechanisms in cells in general. In the case of the endothelium there are important physiological and pathological cardiovascular consequences related to endothelial biomechanical properties. I will review the concepts of flow-mediated mechanotransduction in endothelium, particularly studies conducted *in vitro*. The concept of intrinsic cell tension and its modification by an external load will be considered within the realm of direct displacement of a mechanical sensing system in endothelium. This will be contrasted with the generation of flow-mediated responses by changes in the local concentrations of potent chemicals at the cell membrane, an indirect mechanism of flow signalling that may or may not require coordinate effects of direct forces acting on the cell, such as shear stress. State-of-the-art techniques to measure the surface features of endothelial cells as they pertain to the distribution of flow forces will be presented.

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ENDOTHELIUM-DERIVED VASOACTIVE FACTORS IN HYPERTENSION

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The endothelium plays a pivotal role in a number of responses (relaxations or contractions) of isolated arteries and veins from animals and humans. The endothelium-dependent relaxations are due to the release by the endothelial cells of potent nonprostanoid vasodilator substances. Among these, the best characterized is endothelium-derived relaxing factor (EDRF) which most likely is nitric oxide (NO). Nitric oxide is formed by the metabolism of l-arginine by the enzyme NO synthase in the endothelial cells. In arterial smooth muscle, the relaxations evoked by EDRF are explained best by the stimulation by NO of soluble guanylate cyclase that leads to the accumulation of cyclic GMP. In a number of animal blood vessels, the endothelial cells release a substance that causes hyperpolarization of the cell membrane (endothelium-derived hyperpolarizing factor, EDHF). In blood vessels from hypertensive animals, endothelium-dependent relaxation usually are reduced. A decreased release of EDRF and/or a reduced sensitivity of vascular smooth muscle to NO can contribute to the reduction. The limited information available on isolated human blood vessels, or obtained in situ in human limbs, concur with the conclusions reached with isolated animal tissues. In addition to relaxing factors, the endothelial cells can produce contracting substances (endothelium-derived contracting factors; EDCFs) which include superoxide anions, endoperoxide, thromboxane A2 and the potent vasoconstrictor peptide endothelin. To judge from animal studies, the propensity to release EDCFs is maintained or even augmented in diseased blood vessels. This is particularly the case in arteries taken from spontaneously hypertensive animals, where the release of endothelium-derived endoperoxide(s) is increased, and the sensitivity of the vascular smooth muscle to the EDCF is augmented. The switch from a normally predominant release of EDRF to that of EDCFs may play a crucial role in the vascular hyperreactivity seen in hypertension.