require coordinate effects of direct forces acting on the cell, endothelium. This will be contrasted with the generation of concentrations of potent chemicals at the cell membrane, an endothelium, particularly studies conducted on the surface features of endothelial cells as they pertain to the external load will be considered within the realm of direct generated forces such as those associated with blood flow is related to endothelial biomechanical properties. I will review a useful paradigm for mechanical stress mechanisms in cells the concepts of flow-mediated mechanotransduction in its goals.

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 CLINICIANS 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 be 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 affect 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 CARdio­VASCULAR 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 (PGI₂) 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-I (ET1), thromboxane A₂ and prostaglandin H₂. ET1 activates ETA- and ETg-receptors on vascular smooth muscle to cause contraction and endothelial ETg-receptors cause vasodilatation (by NO and PGI₂). 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

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

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, contrast with the conclusions reached with isolated animal tissues. In addition to relaxing factors, the endothelial cells can produce contracting substances (endothelium-derived contracting factors; EDCF) which include superoxide anions, endoperoxide, thromboxane A₂ and the potent vasoconstrictor peptide endothelin. To judge from animal studies, the propensity to release EDCF to that of EDCFs may play a crucial role in the vascular hyperreactivity seen in hypertension.