A central theme of our research has been the renal-body fluid feedback control system in which the kidneys play a dominant role in the long-term regulation of body fluid volumes and arterial pressure. A common defect that has been found in all forms of hypertension examined to date is a hypertensive shift in the pressure natriuresis relationship (1-3).

The overall objective of our current work is to determine pathophysiological mechanisms whereby obesity alters endothelial factors, renal hemodynamcis, pressure natriuresis, and blood pressure regulation in a rat models of pregnancy-induced hypertension (PIH),produced by chronic reductions in uterine perfusion pressure or chronic sFlt-1 excess. While recent studies have demonstrated adverse effects of obesity on placental function, the effects of obesity and metabolic factors such as leptin on the pathways that link placental ischemia, endothelial dysfunction, and maternal blood pressure are unknown (7-9). Based on our data and the work of others, we are testing the *central hypothesis that obesity and metabolic factors such as leptin enhance the blood pressure responses to placental ischemia in pregnant rats by enhancing placental and adipose tissue production of sFlt-1. In addition, we propose that obesity and metabolic factors such as leptin exacerbates the blood pressure responses to placental ischemia or chronic sFLt-1 excess by exacerbating TNFα and AT1-AA induced endothelial cell production of ET-1. We also propose that high fat diet induced obesity reduces placental perfusion by attenuating cytotrophoblast*proliferation/*migration and spiral artery remodeling during pregnancy by suppressing the Notch-2/JAG1 pathway.*

To test this hypothesis, arterial pressure is examined in conscious,chronically instrumented rat models of preeclampsia produced by long-term reductions in uterine perfusion pressure (RUPP model) or by chronic sFlt-1 excess. We examine the effects of obesity utilizing a genetic model of obesity which has a Mc4r mutation ($MC4R^{+/-}$). In addition to animal models, in vitro placental explant cultures are used to examine the effect of obesity on hypoxia-induced sFlt-1 production, and endothelial cell culture models to examine the effects of obesity on TNFα and AT1-AA-induced ET-1 production by endothelial cells. Cultured cytotrophoblasts, micro-CT, and Doppler velocimetry are also utilized to assess how obesity affects cytotrophoblast proliferation/migration, spiral artery remodeling and uterine artery resistance index. Thus, a wide range of molecular,biochemical, pharmacological, physiological, and imaging techniques derived as well as in vitro and in vivo models derived from various departmental Cores are used to test our central hypothesis.