1. Full Title: Plasma leptin levels as a predictor of cardiovascular-related morbidity
   Abbreviated Title: Leptin and cardiovascular disease

2. Writing Group:
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3. Timeline:
   Measurement of plasma leptin levels in the simultaneous batch his approximately 50% complete and should be finished by November, 1998. A draft manuscript is projected to be distributed for internal circulation by February, 1999.

4. Rationale:
   The leptin gene was identified in late 1994 by Friedman and colleagues using positional cloning techniques and an aggressive strategy of intraspecific and interspecific backcrosses and intercrosses in obese mice with mutations in \textit{lep} (Friedman et al. 1991). A syntenic region on human chromosome 7 was subsequently found to contain the human homologue of the leptin gene (Green et al. 1995). Leptin is expressed almost exclusively in adipose tissue, and it was originally thought to serve primarily as a regulator of stored adipose. Several studies have shown that leptin infusion can attenuate the gross obesity found in mutant mice lacking the protein, by both decreasing feeding responses and increasing basal metabolic rate (Campfield et al. 1995; Halaas et al. 1995; Pellymounter et al. 1995). In humans, expression of LEP mRNA and levels of circulating leptin protein are positively correlated with BMI and percent body fat (Hamilton et al. 1995; Lonnqvist et al. 1995), and additional research in humans has indicated that diet-induced changes in body fat stores result in concomitant changes in the circulating protein (Considine et al. 1995; Maffei et al. 1996). Though these findings support a role for leptin as an indicator of stored energy levels, they also indicate that common forms of human obesity do not appear to be a consequence of leptin deficiency.

   More recent research has indicated that leptin may play a role in blood pressure regulation, and thus may be a contributing factor in the development of cardiovascular disease. Shek et al. (1998) reported that continuous leptin infusion at doses similar to those found in obese individuals produced sustained increases in both blood pressure and heart rate in non-obese rats which was alleviated upon cessation of the leptin infusion. These researchers suggested that leptin may be one factor in the development of obesity-related hypertension. Several mechanisms exist whereby alterations in leptin function might influence blood pressure and hypertension, via:
   1) its interaction with neuropeptide Y and other neurotransmitters within the brain known to control blood pressure, 2) its influence on the sympathetic nervous system enervating the kidney or vasculature, 3) tissue-specific leptin receptor action within the renal system, or 4) its interaction with insulin.

   Several studies have shown that leptin has a direct effect on lipid metabolism via modification of expression of enzymes involved in free fatty acid oxidation (Chen et al. 1996; Halaas et al. 1997; Zhou et al. 1997). These
reports suggest an active role for leptin in the processing of circulating and stored fat. The chronically elevated blood lipids associated with obesity and increased leptin levels are known risk factors for atherosclerosis, myocardial infarction and stroke.

Though several studies have investigated the relationship between circulating leptin and measures of body mass/fat, fasting insulin, fasting glucose, blood lipids, and related measures, few studies to date have investigated the relationship between plasma leptin levels and cardiovascular disease morbidity or hypertension. Two separate studies have indicated that leptin concentration may be one component of an insulin resistance syndrome, independent of BMI (Couillard et al. 1997; Leyva et al. 1998). Leptin levels were significantly correlated with blood pressure in a Japanese subject sample, and a polymorphic marker within the leptin receptor gene was linked to both systolic and diastolic blood pressure in Mexican Americans (Bray et al. 1998). No evidence for linkage was found between hypertension and genetic markers proximal to the leptin gene in African Americans, however (Agata et al. 1997; Rutkowski et al. 1998). Despres and colleagues (1998) reported that baseline leptin levels were not predictive of ischemic heart disease in Canadian men. This proposed study would include determination of 1) the relationship between leptin and cardiovascular disease risk factors in both Caucasians and African Americans, and 2) the ability of leptin levels to predict incident CHD and carotid wall thickness.

5. Main Issues/Hypotheses to be addressed:
   a. Ability of leptin to predict incident CHD and ultrasound case status controlling for other traditional risk factors. Race- and gender-specific effects will also be explored.
   b. Relationship between leptin levels and cardiovascular disease risk factors, including both blood pressure and hypertension status. Race- and gender-specific effects will also be explored.

6. Data:
   Leptin is being measured in the entire simultaneous batch. These assays are currently underway. Proportional hazard regression analyses will be conducted in the incident CHD cases, ultrasound cases and controls, and the cohort random sample. Correlations between leptin and cardiovascular disease risk factors will be conducted in the cohort random sample, the PAD cases, the ultrasound cases, and the supplementary African-American cases and controls, with additional stratification of these samples as recommended by Dr. Chambless.