# INTRODUCTION

Clinical and experimental studies suggest hyperinsulinemia could be a risk factor for atherosclerotic vascular disease. An early observation prompted to hypothesize that high levels of circulating insulin are related to the pathogenesis of atherosclerosis *(Stout and Vallance-Owen; 1969)*. They pointed out that most of the patients with ischemic heart disease had elevated insulin responses to glucose regardless of fasting insulin levels. These abnormalities were even found to be in non-obese patients who had experienced a myocardial infarction *(Stout and Vallance-Owen;1699)* .In contrast, the South African Bantu, who have an extremely low incidence of ischemic heart disease, have 50 % of the insulin response to an oral glucose load that is normally reported for white subjects *(Rubenstien et al; 1969)*. The best evidence linking hyperinsulinemia and atherosclerotic vascular disease comes from prospective epidemiological studies of ischemic heart disease conducted in Helsinki *(Pyorala,1979)*. Paris *(Ducimentiere et al; 1980)*, and Busselton,Western Australia These studies found a significant association between insulin concentrations and the development of ischemic heart disease independent of other risk factors including lipids, blood pressure, and smoking*(Stout,1987)*. Additional studies have found a striking relationship between high insulin concentrations and cardiovascular disease in normal individuals and patients with non-insulin dependent diabetes mellitus (NIDDM). Patients with NIDDM controlled by diet

and oral hypoglycemics were also found to have a significant correlation between the incidence of coronary heart disease and C-peptide levels. However, NIDDM patients treated with insulin experienced the highest incidence of cardiovascular disease while having the lowest C-peptide levels *(Standl and Janka,1985)*. Although mechanisms explaining the association of atherosclerosis with hyperinsulinemia are incompletely understood, several possibilities have been proposed. First, a high insulin level may directly promote the formation of the atheroma in the arterial wall through its effects on several cellular and metabolic processes *(Stout,1977)*. Second, hyperinsulinemia is associated with high blood pressure levels *(Laakso and Barrett-connor,1989)*, low HDL cholesterol, and high VLDL triglyceride concentrations *(Laakso and Barrett-connor,1989)*. Third, insulin resistance could be the primary abnormality related to atherosclerosis, with hyperinsulinemia as only a secondary compensatory mechanism *(Zavaroni et al; 1989)*. This third hypothesis is supported by the recent observation that asymptomatic atherosclerosis is associated with insulin resistance characterized by reduced whole - body and nonoxidative glucose uptake *(Zavaroni et al; 1989)*.

The overall objective of this study is to determine the effect of hyperinsulinemia as an independent risk factor for atherosclerotic arterial disease. This objective will be accomplished by rendering non-diabetic dogs hyperinslinemic by selective diversion of pancreatic venous outflow and then inducing atherosclerotic lesions. Progress of the atherosclerotic lesions will be compared in normal controls, hyperinsulinemic animals. In all animals native vessel lesions and

atheromatous changes in venous interposition grafts will be studied by surgical histology.

# AIM OF THE WORK

This study is designed to examine the effects of hyperinsulinemia and insulin resistance in a non diabetic canine model on the progression of atherosclerotic vascular disease. Thus, the specific aims are:

1. To test the effects of hyperinsulinemia on vascular intimal regeneration and the development of atherosclerotic lesions.
2. To test the effects of hyperinsulinemia on myointimal hyperplasia of vein grafts