greater degree than it reduces stenosis severity suggest beneficial effects other than plaque regression. To determine if a favorable lipid profile is associated with decreased thrombotic tendency, we determined the relationship between two hemostatic risk factors, fibrinogen and plasminogen activator inhibitor (PAI-1), and LDL cholesterol (LDL-C) in 1,878 subjects free of cardiovascular disease in the Framingham Offspring Study. The subjects studied ranged from those with hypobetalipoproteinemia, a condition characterized by LDL-C $\leq$ 70 mg/dl, and a low incidence of thrombosis and coronary heart disease, to other LDL-C levels grouped by NCEP guidelines.

LDL-C (mg/dl):	<70	70–99	100–129	>130	*p-value
Number subjects:	41	389	653	795	
Fibrinogen (mg/dl)	264 ± 54	287 ± 59	297 ± 57	303 ± 55	<0.0001
PAI-1 antigen (ng/ml)	14 ± 9	21 ± 18	22 ± 17	23 ± 16	<0.0001

*p-value for linear effect of LDL-C

These findings were similar in men and women. Multivariate adjustment for age, gender, body mass index, diabetes, smoking, alcohol intake, and use of antihypertensive medication did not alter the results.

Conclusion: Decreasing LDL-C levels are associated with decreasing levels of hemostatic risk factors. These findings support the hypothesis that lipid lowering therapy may reduce clinical events by reducing thrombotic tendency.

917-96 In Vitro Inhibition of Smooth Muscle Cell Proliferation by Sterol 27-Hydroxylase Metabolites

B.M. Steinberg, E.A. Grossi, J. Greenberg, C. Bizekis, W.J. O'Connor, A. Reiss, A.C. Galloway, N.B. Javitt. *New York University Medical Center, New York, NY*

Sterol 27-hydroxylase controls side chain oxidation of bile acids and is found in vascular endothelial cells. Two metabolites of this oxidation are 27-hydroxycholesterol (27-OH), which inhibits smooth muscle cell (SMC) proliferation in vivo, and 3β-hydroxy-5-cholestenoic acid (C27). We quantified the inhibitory capacity of both these compounds in vitro using a rabbit aortic SMC preparation. Early passage SMC were grown to confluence, plated at a density of 5,000 cells/well, and synchronized for 24 hrs. The cells were then grown in the presence of Dulbecco's modified Eagle's medium with 5% delipidated fetal calf serum alone (control), in increasing concentrations (10, 20, 30 μM) of 27-OH and C27 dissolved in 2-hydroxypropyl-β-cyclodextrin (HPBCD), in an equivalent amount of HPBCD alone (control), and in colchicine (1 mg/dl). Cell proliferation at 24 hrs was measured via formazans formation from the tetrazolium salt MTS by absorbance at OD 490 nm. There was no significant difference in absorbance between the control and the HPBCD (absorbance 0.402 ± 0.037 vs 0.400 ± 0.057) or 10 μM concentration 27-OH (0.383 ± 0.056) or C27 (0.374 ± 0.022) groups. However, concentrations of 20 and 30 μM of 27-OH produced a significant growth inhibition (0.362 ± 0.030 and 0.350 ± 0.021, $p < 0.01$) compared to controls, as did C27 at 20 and 30 μM (0.357 ± 0.22 and 0.344 ± 0.28, $p < 0.01$), while the colchicine group exhibit the greatest inhibition (0.125 ± 0.021). Thus 27-OH and C27 demonstrated a dose response growth inhibition of SMC, and endothelial sterol 27-hydroxylase may play an important role in modulation of myointimal hyperplasia during the atherosclerotic process.

917-97 Decreased Resistance Against Oxidation of LDL from Patients with Homozigous Familial Hypercholesterolemia

Claudio Napoli, Alfredo Postiglione [1], Giuseppe Palumbo [2], Antonio Ruocco [1], Giuseppe Ambrosio, Mario Condorelli, Mario Mancini [1], Massimo Chiariello. *Div. of Cardiology, "Federico II" School of Medicine, University of Naples, Italy; [1] Inst. of Internal Medicine and Metabolic Diseases, "Federico II" School of Medicine, University of Naples, Italy; [2] Dept. of Molecular Pathology, "Federico II" School of Medicine, University of Naples, Italy*

Familial hypercholesterolemia (FH) was the first genetic disorder recognized to cause myocardial infarction. Homozigotes (H) inherit two mutant genes at the low density lipoprotein (LDL) receptor locus, and as a result of the increased levels and prolonged residence time of LDL in plasma, there is a strong tendency toward accumulation of LDL in the arterial wall, causing early atherogenesis. It has been shown that LDL might undergo oxidation before it can be taken up by macrophages and it become foam cells. Thus, one additional explanation for atherogenesis in FH may be the extent to which LDL is susceptible to oxidation. We selected 8 homozigous FH pts (mean total-cholesterol 825 ± 70 mg/dl) matched with 8 healthy subjects to investigate the LDL oxidizability. Skin fibroblast cultures showed that one patient was receptor negative, while others were receptor-defective. LDL were isolated from serum by ultracentrifugations in KBr. Purified LDL was exposed to oxygen radicals generated by the xanthine/xanthine oxidase reaction (2 mM and 100 mU, respectively for 18 hs at 37° C). Malonildihaldehyde (MDA) content was evaluated by the thiobarbiturate method. LDL analysis was carried on polyacrylamide (PAGE; 5 to 16% gradient) and agarose gel electrophoresis (0.8% in Tris-HCL buffer). No significant increase was observed in the basal concentration of MDA between LDL from H and controls (0.8 ± 0.12 and 0.9 ± 0.15 nmoles of MDA/mg of protein, respectively). Instead, after oxidation MDA was 35.1 ± 4.5* nmoles/mg of protein LDL from H, and 23.5±4.1 in controls (*$p < 0.05$). PAGE confirmed the purity of LDL, present as an intact apolipoprotein B_{100}(apo-B_{100}). When oxidized LDL was run on PAGE an extensive apo-B_{100} fragmentation, replaced by lower fragments ranging from 97.400 to 205.000 m.w., was only observed in LDL from H but not in controls in our experimental conditions. MDA content after oxidation of LDL correlated well with the loss of intact apo-B_{100}. Finally, the relative LDL mobility on agarose gel was evaluated. This assay allows to detect changes in electric charge induced by oxidation. Basal LDL from H and controls migrated as homogeneous bands to 1.2 + 0.2 and 1.1 ± 0.2 cm from the origin. In contrast, oxidized LDL from H migrated to 2.1 ± 0.3* cm from the origin while those of controls migrated to 1.5 ± 0.2 (*$p < 0.05$). Thus, in FH LDL appear to be more susceptible to oxidationin vitro; the indices for LDL oxidizability were all significantly different from those of controls. This phenomenon may be an important additional mechanism of atherogenesis in homozigous FH.

917-98 Regulation of Glucose Utilization by L-Carnitine in Cardiac Myocytes

Salah Abdel-aleem, Mohamed Sayed-Ahmed, Steven Hendrickson, James St. Louis, Mark P. Anstadt, James E. Lowe. *Duke University Medical Center, Durham, North Carolina, 27710*

L-Carnitine has been shown to protect the myocardium from ischemic injury, and also improves cardiac function in cardiomyopathies associated with carnitine deficiency and diabetes. However, the exact mechanism whereby carnitine exerts its effect is not fully understood. The present study was designed to investigate the effect of carnitine on the regulation of glucose utilization in the heart. These studies were performed by determining the effect of L-carnitine (5 mM) on the $^{14}CO_2$ release from [1-^{14}C]pyruvate (an index of pyruvate dehydrogenase complex, PDH), [2-^{14}C]pyruvate (an index of acetyl-CoA flux through Kreb's cycle), and [6-^{14}C]glucose (an index of the oxidative utilization of glucose), in rat myocytes.

Substrate	Rate of Oxidation (nmol/mg protein/30 min)	
	Control	L-Carnitine
[1-^{14}C]pyruvate	141.80 ± 8.50	212 ± 28.80*
[2-^{14}C]6436pyruvate	39.40 ± 7.90	21.1 ± 4.40*
[6-^{14}C]glucose	1.56 ± 0.05	0.95 ± 0.05*

Values are presented as the mean ± SD of at least three different experiments. Asterisks represent a $p < 0.05$ of the effect of carnitine vs control. These data show that L-carnitine stimulates PDH activity by 50%. However, the flux of acetyl-CoA and glucose through Kreb's cycle was significantly decreased by this compound. These results suggest that L-carnitine enhances the removal of acetyl-CoA produced from glucose metabolism out of the mitochondrial matrix, thereby, activating the PDH complex.

917-99 Fibrinogen and Lp(a) in Ischemic Heart Disease. The Québec Cardiovascular Study

Bernard Cantin, Sital Moorjani, Jean-Pierre Després, Paul-J. Lupien, Gilles R. Dagenais. *Lipid Research Center, Laval University, Québec, Canada; Department of Medicine, University of Montreal, Montréal, Canada*

In an ongoing ischemic heart disease (IHD) risk factor study, plasma lipid, Lp(a) and fibrinogen measurements were performed in 2125 men aged 45–75 years in 1985. The subjects were followed until September 1st 1990. During that period, 116 first IHD events were documented (myocardial infarction, angina and IHD death). Subjects with IHD were older (59 ± 8 vs 56 ± 7 years; $p < 0.001$), had higher systolic pressure (137 ± 17 vs 130 ± 17 mmHg; $p < 0.001$), a higher frequency of smoking $\geq$20 cig/d (32 vs 23%; $p = 0.027$) and a higher prevalence of diabetes (16 vs 4%; $p < 0.001$). Total cholesterol (235 ± 41 vs 221 ± 39 mg/dL; $p < 0.001$), LDL-cholesterol (162 ± 37 vs 149 ± 35 mg/dL; $p < 0.001$), Lp(a) (41.0 ± 45.9 vs 32.7 ± 34.9 mg/dL; $p = 0.014$) and fibrinogen (3.89 ± 0.81 vs 3.55 ± 0.75 g/L; $p < 0.001$) levels were higher in IHD while HDL-cholesterol was lower (37 ± 9 vs 40 ± 10 mg/dL; $p = 0.005$). Adjusted risk ratios were significantly increased in the third fibrinogen tertile (2.4 ± 0.3; $p < 0.001$) but not in the second fibrinogen nor in any Lp(a) tertile. In order to further ascertain the role of fibrinogen and Lp(a), subjects were assigned to one of four groups according to fibrinogen and Lp(a) levels. The cutoff point for fibrinogen was the median of the distribution (3.52 g/L) and 25 mg/dl for Lp(a).

Group 1: fibrinogen <3.52 g/L and Lp(a) <25 mg/dL;
Group 2: fibrinogen <3.52 g/L and Lp(a) $\geq$25 mg/dL;
Group 3: fibrinogen $\geq$3.52 g/L and Lp(a) <25 mg/dL;
Group 4: fibrinogen $\geq$3.52 g/L and Lp(a) $\geq$25 mg/dL.