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DEVELOPMENT AND PROGRESSION OF ATHEROSCLEROTIC LESIONS

4.P.1 Serum levels of lipoproteins in different kinds of rabbits in experimental atherosclerosis

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Serum levels of lipoproteins in two different kinds of rabbits (NZB and chinchilla) with experimental atherosclerosis, were determined. Experimental atherosclerosis was provoked by a 2% cholesterol diet (8 mg/kg) during 12 weeks. Serum levels of triglycerides, total cholesterol, HDL and LDL were measured. A higher increase of lipoproteins was found in NZB rabbits, who are genetically more sensitive to the development of atherosclerosis compared to chinchilla rabbits. The concentration of cholesterol was increased – 320%, of triglycerides – 130%, of HDL – 83% and of LDL – 565% in NZB rabbits. The concentration of cholesterol was increased – 125%, of triglycerides – 120%, of HDL – 89% and of LDL – 141% in chinchilla rabbits. The largest percent of increase was in LDL concentration in NZB rabbits.

4.P.2 Pravastatin reduces carotid intima-media thickness progression also in patients showing an unsatisfactory response in terms of LDL-C reduction. The CAIUS study

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The Carotid Atherosclerosis Italian Ultrasound study (CAIUS) is a multicenter, parallel group, double-blind clinical trial, performed in 305 asymptomatic, moderately hypercholesterolemic patients, which demonstrated the beneficial effect of pravastatin on the carotid intima-media thickness progression. We took advantage of the data-base of the study to investigate whether pravastatin is effective in reducing carotid atherosclerosis progression also in patients showing unsatisfactory reduction of LDL-C. Among the 151 patients treated with pravastatin, 122 showed a reduction of LDL-C higher than 10% and were considered "responders". 16 patients did not respond or showed an unsatisfactory response (LDL-C reduction $\leq 10\%$) and were classified as "non-responders". The responders were further stratified according to the time of maintenance of response to treatment. Patients, who maintained the response for the entire follow-up period were classified as "non response losers" (n = 109) while those that after 18 months tended to lose response were classified as "response losers" (n = 13). In contrast to what observed in the placebo group, that showed a positive rate of IMT progression, all groups treated with pravastatin, independent of the response in terms of LDL-C reduction, showed negative IMT changes. No significant difference was found between responders and non-responders, as well as between response losers and non response losers. We conclude that the effect of pravastatin on IMT progression is apparently independent of its hypolipidemic effect.

4.P.3 The relationship between lipid levels and the severity of early coronary disease

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Objective: To determine whether the different lipoprotein levels have a relationship with the number of significantly stenosed coronary arteries in subjects with early onset of coronary disease.

Material and Methods: A prospective study was made of 109 males less than 50 years of age (25–49) having coronary disease (myocardial infarction or unstable angina showing ischaemic signs in the electrocardiogram) and who had undergone cardiac catheterization. Coronary lesions with $>50\%$ luminal stenosis were considered as significantly. None of the patients were undergoing hypolipidaemic drugs. Total cholesterol (TChol), HDLChol, Triglycerides (TG), apolipoprotein AI (Apo AI), apolipoprotein B (Apo B), and Lp(a) were measured in the same laboratory after 12 hours of fasting. Total corrected

cholesterol (TCC) was calculated using the formula $TCC = TChol - Lp(a)/3$. LDL cholesterol was calculated employing the Friedwald formula as and when TG did not exceed 300 mg/dl. ANOVA was used for the parametric variables and Kruskal-Wallis for the non-parametric ones.

Results: Significant differences were found in the levels of TChol ($p < 0.03$), LDLChol ($p < 0.05$), Apo B ($p < 0.03$), TG ($p < 0.02$) and Lp(a) ($p < 0.005$) according to the number of vessels showing significant stenosis. No significant differences were obtained in the levels of HDLChol, TChol/HDL ratio, Apo AI and TCC.

Conclusions: In our study of young coronary patients significant differences were found in the levels of TG, LDLChol, Apo B and Lp(a) according to the number of vessels showing significant lesions. In spite of also finding differences in TChol levels these disappeared once the levels were corrected.

4.P.4 Hypoxia is present within the arterial wall *in vivo*

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The deeper situated parts of the arterial wall depend upon diffusion to satisfy the need of oxygen and nutrients and to get rid of waste products. During the development of atherosclerotic lesions the energy demand increases and the diffusion capacity decreases. Hypoxia or even frank anoxia may occur locally and metabolic disturbances ensue. Such derangements may decrease the capacity of the arterial wall to heal atherosclerotic lesions or even lead to progression. A vicious cycle may be visualized. On this basis, the *Anoxemia theory of atherosclerosis* has been formulated. However, to validate this theory it is crucial to demonstrate that hypoxia actually exists within the arterial wall, *in vivo*. To address this issue we have developed a method to assess arterial wall hypoxia *in vivo* by using a hypoxia marker, NITP, which may be demonstrated within the tissue by immunohistochemistry.

With this method, NITP has been demonstrated within the aortic arch in rabbits with experimental atherosclerosis. Furthermore, the hypoxia marker has also been demonstrated in the deeper parts of the media in selected areas of the aortic arch close to the branching point of the subclavian artery in healthy domestic swine. The cut off PO_2 for the hypoxia marker in the arterial tissue is within the range of a few mm Hg. We have thus demonstrated that areas with marked hypoxia actually exist in arterial tissue *in vivo*. This observation makes it even likely that areas with a less pronounced degree of hypoxia may be more widespread. These results lend support for the *Anoxemia theory of atherosclerosis*.

4.P.5 Two-year follow-up study of the carotid arteries status in 52 diabetic patients

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Aim of the Study: To evaluate the outcome of carotid arteries status in middle-aged diabetic patients having no clinical signs of cerebrovascular or coronary disease.

Patients and Methods: the study consisted of 18 insulin-dependent diabetes mellitus and 34 non-insulin-dependent diabetes mellitus patients. There were 22 women and 30 males, with a mean age of 54 (range 41–65). Every patient had at least one cardiovascular risk factor associated with diabetes mellitus. Physical examination and resting electrocardiogram were negative for macrovascular disease. Ultrasonography study of carotid arteries (USCA) was done by the same operator with a color doppler (Acuson 128XP10). The 52 patients were classified into 3 groups according to the results of the USCA: absence of vascular abnormalities (group A, n = 30), intima-media thickness (IMT) ≥ 1 mm and/or presence of atheromatous deposits without stenosis (group B, n = 11), presence of carotid stenosis (CS) including CS $< 60\%$ in 8 patients and asymptomatic CS $\geq 60\%$ in 3 patients (group C, n = 11). Clinical evaluation and USCA were repeated 6 months later in the patients who had CS $\geq 60\%$, and 2 years later in the other patients.

Results: Three patients with CS $\geq 60\%$ progressed to 80% after 6 months and an endarterectomy was performed. In the 49 other patients, a progression was noted in 6 (12%). Three patients progressed from group A to group B, 1