special report

2nd International Symposium on Reverse Cholesterol Transport: Report on a Meeting

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The 2nd International Symposium on Reverse Cholesterol Transport and Coronary Heart Disease was held on November 14–15, 1992 in Fort Worth, TX, sponsored jointly by the Texas College of Osteopathic Medicine and the University of British Columbia. The meeting was attended by 110 participants including 33 from outside the United States. The selection of the topics and the speakers was carried out in consultation with the Organizing Committee composed of Drs. Philip Barter, Christopher J. Fielding. Henry Ginsberg, Andras G. Lacko, Norman Miller, P. Haydn Pritchard, and Paul S. Roheim.

A substantial amount of novel and unpublished information was presented under four major topics: 1) Extravascular aspects, 2) Intravascular aspects, 3) Metabolism of HDL, and 4) Clinical aspects of reverse cholesterol transport. In addition, new insights were developed on a number of aspects of reverse cholesterol transport. The concluding summary by Dr. John Dietchy was particularly enlightening as he analyzed the task of reverse cholesterol transport in a number of systems.

EXTRAVASCULAR ASPECTS (CHAIRMAN: RICHARD WEINBERG)

Cholesterol transport between cells and HDL (Michael C. Phillips)

Dr. Phillips described cell culture systems as tools for studying the mechanisms of cholesterol clearance from cells mediated by HDL. Two aspects of this initial step in reverse cholesterol transport were considered. First, the efflux of cholesterol from specific intracellular pools. Second, the role of HDL structure in this process. HDL particles induce a bidirectional flux of unesterified cholesterol between HDL and the plasma membrane. Cholesterol molecules diffuse through the intervening aqueous layer, while the direction of net cholesterol flux is determined by the cholesterol concentration gradient between the membrane and the HDL surfaces. The rate of cholesterol efflux from cells is not influenced by the binding of HDL to the cell surface. The efflux of cholesterol from the plasma membrane and lysozomal compartments exhibits similar kinetics except for an initial 40-min lag period for the latter pool; cholesterol molecules move from lysozomes to the plasma membrane during this period. To determine the role of HDL subspecies in reverse cholesterol transport, the efflux of cellular cholesterol to various reconstituted HDL particles has been investigated. Unidirectional efflux of cholesterol from cells occurs to small unilamellar phospholipid vesicles but the rate is greatly enhanced if the same concentration of phospholipid is present as that of discoidal apolipoprotein/phospholipid complexes. Studies with human apolipoproteins and synthetic, amphipathic, α-helical peptides indicate that the structure of apolipoproteins can have a significant effect on the rate of cholesterol release from cells.

HDL receptors and cholesterol efflux (John F. Oram)

Clearance of excess cholesterol from cells is facilitated by the interaction of HDL apolipoproteins with cell-surface binding sites or receptors. This receptor interaction appears to activate a signaling pathway that stimulates transport of excess intracellular cholesterol to the plasma membrane for excretion from the cell. A plasma membrane HDL binding protein has been cloned that has several features predicted for an HDL receptor. Studies are in progress to define the biological function of this protein and its role in atherogenesis.

Cholesterol esterase: structure and gene regulation (David Y. Hui)

Previous evidence from other laboratories has suggested an important role for the cholesterol esterase in intestinal absorption of dietary fat and cholesterol. Previous work has also shown that the liver is capable of synthesizing a similar protein. Structural analysis of the pancreatic cholesterol esterase has revealed similarities to other serine esterases, such as acetylcholinesterase and butyrylcholinesterase. The catalytic triad forming the active site domains of the cholesterol esterase was identified by site-directed mutagenesis. The data revealed the importance of Ser^{194}, His^{435}, and Asp^{320} in the charge relay system re-

quired for catalyzing cholesteryl ester hydrolysis.

Studies on the regulation of the cholesterol esterase gene expression in the rat pancreatoma cell line AR42J showed that incubation of these cells with cholecystokinin and secretin resulted in a 2- to 3-fold increase of cholesterol esterase secretion. The increased secretion was due to increased secretion was to increased synthesis of cholesterol esterase but not to increase in its mRNA. Furthermore, inhibition of RNA biosynthesis by actinomycin D failed to inhibit the hormone-induced cholesterol esterase biosynthesis and secretion, indicating post-transcriptional activation of cholesterol esterase biosynthesis.

Additional studies have shown that the liver was also capable of synthesizing bile salt-stimulated cholesterol esterase. Using two different hepatoma cell lines (HepG2 and McA-RH7777), significant bile salt-activated cholesteryl ester hydrolytic activity was demonstrated in the conditioned medium of these cells. The structural relationship between that of the liver-secreted and pancreatic cholesterol esterases was verified by hybridization of liver RNA with the pancreatic cholesterol esterase cDNA, and by immunoreactivity of the secreted liver enzyme with anti-pancreatic cholesterol esterase.

HDL cholesterol delivery in hepatoma cell; evidence for an extra lysosomal pathway (John DeLamatre)

Rat hepatoma cells, Fu5AH, were studied as a model for the delivery of apoE-free HDL cholesterol to a cell. The net delivery of HDL cholesterol to the cell was demonstrated by several different types of experiments: decreased media cholesterol concentration, decreased cellular cholesterol synthesis, and increased cellular cholesteryl ester synthesis. Evidence was found for the existence of an HDL retroendocytosis pathway in this cell. Data were consistent with extralysosomal hydrolysis of HDL cholesteryl ester. Further experiments indicate that a neutral cholesteryl ester hydrolase probably accounts for the hydrolysis of HDL cholesteryl ester and that the enzyme is active either on the plasma membrane or in an endocytotic compartment.

Role of interstitial lipoproteins in reverse cholesterol transport (Paul S. Roheim)

In his presentation, Dr. Roheim compared the composition of plasma and prenodal peripheral lymph (an accepted model of interstitial fluid). In addition, he reviewed recent in vitro data comparing peripheral lymph and plasma cholesterol flux from peripheral cells, and the mechanism of decreased LCAT activity in the interstitial fluid. Significant emphasis was placed on the characterization of HDL subpopulations in plasma and peripheral lymph using two-dimensional electrophoresis. Evidence was also presented demonstrating changes in HDL subpopulations during incubation of plasma, suggesting that HDL is a metastable lipoprotein continuously undergoing remodeling (in vivo). The physiological and pathophysiological roles and/or modes of action are likely to be influenced by the metabolic state of the respective HDL particles.

Regulation of apoE expression in cholesterol-loaded macrophages (Ladislav Dory)

A number of factors are involved in the posttranscriptional regulation of apoE expression in macrophages. Positive and negative effectors, acting through the cAMP and protein kinase C pathways, respectively, were discussed. Evidence was presented for the profound inhibition of apoE expression at the level of translation by mediators acting through the protein kinase C pathway, including phorbol ester, phospholipase C, and endotoxin. The effects and site of action of HDL_3 and cAMP on apoE expression were also discussed. Finally, the regulation of apoE expression was discussed in the context of cellular cholesterol metabolism.

ApoD expression of cholesterol transport (Eric Rassart)

ApoD is a glycoprotein of approximately 30 kDa that shares a high degree of homology with members of the lipocalin family of proteins, and therefore it is likely to be the transporter of small hydrophobic ligand(s). In the rabbit, apoD is expressed in all tissues but at different levels. In situ hybridization showed that apoD is expressed primarily in fibroblast-like cells and in glial cells. In cultured human fibroblasts, apoD gene expression is observed in confluent and in serum-starved cultures, suggesting that its production/secretion coincides with growth arrest. Dr. Rassart reported on the sequencing of a 1.2 kbp region of the human apoD gene promoter that showed consensus with transcriptional regulatory elements such as acute phase and steroid hormone regulatory elements. The role of apoD is still poorly understood, although cholesterol, steroid hormones, and heme-related compounds have been proposed as physiological ligands. On the basis of the present knowledge, Dr. Rassart proposed that apoD may be a multi-ligand, multi-functional protein.

INTRAVASCULAR ASPECTS (CHAIRMAN: GEORGE MELCHIOR)

Structure/function of LCAT (Omar Francone)

Dr. Francone reviewed the results of a series of experiments involving the site-directed mutagenesis of putative active site components of LCAT. The serine residues at positions 181 and 216 of the human enzyme were replaced with alanine, glycine, or threonine. All substitutions at position 181 eliminated enzyme activity but did not affect secretion. By contrast, substitutions at position 216 gave

rise to normally secreted active products; however, the magnitude of activity differed depending on the characteristics of the replaced amino acid. These data strongly suggest that the serine at position 181 forms part of the active site of human LCAT. The putative catalytic role of the free cysteines in LCAT was also investigated by replacing cysteine-31 and cysteine-184 with glycine. The results of these studies suggested that these residues were not required for cholesterol esterification and that the inhibition of LCAT activity by sulfhydryl inhibitors may result from steric hindrance.

Site-directed mutagenesis was performed to replace amino acid residues at each of four N-glycosylation sites to prevent the attachment of carbohydrate. Mutants at three of the four sites retained significant phospholipase and acyltransferase activities. However, the elimination of the N-glycosylation site at asparagine-272 resulted in the loss of acyltransferase activity but a retention of the ability to generate fatty acids. It was suggested that the carbohydrate present at this site may have a role in determining the substrate specificity of LCAT.

Re-creation, expression and functional assessment of natural mutations of lecithin:cholesterol acyltransferase (P. Haydn Pritchard)

Familial LCAT deficiency (LCATd) and fish eye disease (FED) are rare genetic disorders of the plasma enzyme LCAT. To elucidate the molecular mechanism resulting in the distinct biochemical presentation of FED compared to LCATd, we have used site-directed mutagenesis of an LCAT cDNA to introduce natural mutations that cause these disorders. The mutant cDNAs were cloned into an expression vector and transfected into COS cells. The FED mutations resulted in the secretion of significant amounts of LCAT that were incapable of esterifying cholesterol in HDL or proteoliposomes. However, they retained the ability to esterify cholesterol in plasma and LDL at near normal levels. These results support the hypothesis that LCAT in FED plasma has lost the ability to esterify cholesterol in HDL but retains esterification activity toward other lipoproteins. By contrast, mutations causing LCATd resulted in the lack of secretion of active or immunologically detectable LCAT.

Intravascular cholesterol pools in reverse cholesterol transport (Christopher J. Fielding)

Dr. Fielding reported on the relationship between concentration of prebeta-HDL and the rate of free cholesterol transfer from cell membranes to plasma components. Incubation of plasma in the absence of cells rapidly reduces the prebeta-HDL level but this change is inhibited either when peripheral cell membranes are present or when plasma LCAT activity is blocked. Red cell membranes were found to have no protective effect, and protection by nucleated peripheral cells was lost after protease treatment. When the concentration of prebeta-HDL was systematically varied, and the rate of cholesterol efflux was determined, a linear correlation was observed. Approximately 60% of total efflux was prebeta-HDL-dependent. The balance of "nonspecific" efflux probably represents a diffusion component of total transfer.

Expression of the human CETP gene in transgenic mice (Lou B. Agellon)

Dr. Agellon reported on recent studies on the regulation of the human CETP gene. Transgenic mice were developed using a human CETP minigene linked to various amounts of its natural flanking sequences. In transgenic mice containing a transgene linked to 3.2 kb of upstream and 2.0 kb of downstream sequences, the CETP mRNA was found in tissue sites similar to that in humans. In addition, transgene expression was increased by a high fat and high cholesterol diet. This effect can also be reproduced by a diet high in cholesterol but low in fat. In transgenic mice containing the CETP minigene under the control of the metallothionein promoter, the same diets had no effect on CETP mRNA abundance. Characterization of the human CETP gene promoter was also described. The expression of the human CETP transgene in mouse hepatocytes decreased rapidly after isolation from the liver. The decrease in the CETP mRNA was concomitant with the decrease in the level of mRNA encoding the transcription factor known as C/EBPa. High levels of this transcription factor are normally found in the liver where it is thought to activate the expression of an array of genes. Detailed characterization of the human CETP gene promoter revealed the existence of a binding site for C/EBPa. Transfection studies done on HepG2 cells indicate that the CETP gene promoter is transactivated by C/EBPa, indicating that the site is functional.

CETP as a factor in atherosclerosis (K. R. Marotti)

CETP mice fed a high fat, high cholesterol diet have a significantly altered lipoprotein profile. The change in the lipoprotein profile is characterized by a reduction in both the size and quantity of the plasma HDL and an increase in both size and quantity of the plasma LDL. Two groups of mice (CETP transgenic and C57BL/6) were used to compare the extent of the development of atherosclerosis in the animals on a high fat/high cholesterol diet. The expression of CETP produced a lipoprotein profile with higher LDL and VLDL and thus more atherogenic compared to the controls. The animals with increased CETP levels exhibited increased severity and more extensive atherosclerotic lesions. Based on these findings, Dr. Marotti suggested that the enhancement of the atherosclerotic process was largely due to the higher levels of CETP and the subsequent alterations of the lipoprotein profile in transgenic mice.

Modulating atherogenesis by manipulating apolipoprotein genes in mice (Edward Rubin)

Dr. Rubin described studies on the suitability of the mouse as a model system for assessing the genetic determinants of atherosclerosis in humans. Mice with overexpressed human genes involved in lipid transport (apoA-I, apoE, and apoA-II) were investigated for the progress of atherogenesis. Although in humans high plasma levels of apoA-I are associated with decreased atherosclerosis, whether this is a direct or an indirect association has been difficult to test. High levels of human apoA-I dramatically decrease murine atherogenesis, supporting a direct role for apoA-I in preventing atherosclerosis. The role of apolipoprotein E in atherogenesis was assessed by comparing the extent of preatherosclerotic lesion formation in transgenic mice expressing human apoE at various levels. Increasing levels of human apoE were associated with decreased diet-induced atherogenesis in the apoE transgenic compared to control animals.

The relationship between human apoA-II and atherosclerosis was also investigated. Plasma HDL with both apoA-I and apoA-II (A-I w A-II) and HDL containing only apoA-I (A-I w/o A-II) were used. Two lines of transgenic mice with similar levels of HDL but with different apolipoprotein composition were developed. One group of animal's HDL contained primarily human apoA-I while the second group of animal's HDL contained both human apoA-I and human apoA-II. The HDL containing apoA-II has significantly less antiatherogenic properties than HDL free of apoA-II, providing the first direct in vivo demonstration that the apolipoprotein composition of HDL determines its antiatherogenic properties.

METABOLISM OF HDL (CHAIRMAN: WALDO FISHER)

Multicompartmental analysis of reverse cholesterol transport (Charles C. Schwartz)

A multicompartmental model of free cholesterol and esterified cholesterol in VLDL, IDL, LDL, and HDL has been developed to quantitate pathways of cholesterol movement between lipoproteins and tissues. Human subjects were injected with HDL (or LDL) labeled with isotopic free cholesterol, esterified cholesterol, and mevalonic acid. The kinetic analysis revealed that over 70% of plasma esterified cholesterol synthesis occurred in HDL from HDL free cholesterol and the remainder was synthesized in apoB-containing particles. There was net transport of esterified cholesterol from HDL to VLDL-LDL. Most of the transport of esterified cholesterol from plasma to tissues was via LDL and IDL, about 3 mmol/min. By contrast, HDL esterified cholesterol transfer to tissues was <0.3 mmol/min. The vast majority of plasma cholesteryl ester transport to tissues was from LDL/IDL to a compartment that had many kinetic features of the liver. In addition, extrahepatic tissues and liver exchanged free cholesterol extensively with HDL; there was net movement of free cholesterol (over the background of exchange) from extrahepatic tissues to HDL and from HDL to the putative liver compartment. The magnitude of HDL free cholesterol net transport to the liver was comparable to LDL/IDL cholesterol ester transport to the liver.

Regulation of HDL apoA-I catabolism (Henry N. Ginsberg)

The presentation covered recent work related to the regulation of fractional catabolic rates of apoA-I in humans. The role of HDL composition and/or size as a determinant of apoA-I binding to HDL particles and the role of the kidney in apoA-I catabolism were discussed in addition to recent data on HDL cholesteryl ester transfer to TG-rich lipoproteins (mediated by CETP). Overall, the presentation was based on the hypothesis that accelerated HDL CE exchange for VLDL (IDL) TG results in the formation of a modified, TG-rich HDL particle from which apoA-I can dissociate and be cleared by the kidney. Accelerated exchange of HDL-CE for VLDL-TG may result from both increased VLDL-TG levels or increased numbers of normal VLDL particles.

Abnormal HDL apolipoprotein metabolism in patients with HDL disorders (Daniel J. Rader)

Dr. Rader reported on the investigation of the in vivo kinetics of apoA-I and apoA-II in a series of patients with severe hypoalphalipoproteinemia, including patients with: *1)* classic (complete) LCAT deficiency (LCAT-D), *2)* fish-eye disease (FED), or *3)* patients with HDL-C <20 mg/dl who do not belong to either of these two categories. In patients with classic LCAT-D, the fractional catabolic rate of apoA-I was increased, but the FCR of apoA-II was markedly faster than that of normal. In patients with FED, who have an incomplete deficiency of LCAT, the kinetics of apoA-I and apoA-II were similar to those in LCAT deficiency, with rapid catabolism of apoA-I and especially of apoA-II. These findings were confirmed using endogenous labeling of apoA-I and apoA-II with an infusion of a stable isotope-labeled amino acid. In all LCAT-D and FED patients studied, the catabolism of apoA-I on LpA-I:A-II was faster than that on LpA-I, the opposite of normal, in which apoA-I on LpA-I is more rapidly catabolized. Finally, in a series of patients with HDL-C $<$ 20 mg/dl but not LCAT-D or FED, the FCRs of apoA-I and apoA-II were also faster than normal, and highly correlated with the plasma concentrations of apoA-I and apoA-II. None of the patients studied had evidence of delayed synthesis of apoA-I or apoA-II as the primary cause of the low levels of HDL. Hence, despite low steady state levels of HDL-C, the transport or "flux" of apoA-I is

normal and net reverse cholesterol transport may not be substantially impaired in these patients.

Additional studies reported by Dr. Rader included investigation of the HDL apolipoprotein kinetics in two homozygous cholesteryl ester transfer protein-deficient (CETP-D) patients using a similar approach of paired radiotracer and stable isotope techniques. The catabolism of both apoA-I and apoA-II is markedly delayed in CETP-D, resulting in high plasma concentrations of HDL-C and apoA-I. These findings suggest that the rate of reverse cholesterol transport may actually be delayed in these patients.

Regulation of CETP and HDL-C levels by changes in dietary cholesterol (Ruth McPherson)

Plasma CETP concentration is strongly correlated with the abundance of CETP mRNA in both liver (in cynomolgus monkeys) and adipose tissue (in hamsters), suggesting that the variable synthesis in these organs accounts for a major part of the variation in plasma CETP concentration. In animals, an increase in dietary cholesterol leads to an increase in CETP mRNA abundance in both liver and adipose tissue in association with increased plasma CETP concentrations. In addition, cultured macrophages secrete more transfer activity after cholesterol loading. Thus, the CETP gene appears to be responsive to changes in cellular cholesterol, and it is possible that the effect of dietary cholesterol on plasma levels of CETP is mediated by an effect on regulatory cholesterol pools in tissues such as liver and adipose. Evidence was presented that dietary cholesterol also increases plasma concentrations of CETP and adipose tissue CETP mRNA levels in 30 normal male subjects. The plasma CETP response to cholesterol feeding differed amongst the three apoE genotype groups tested (E 3/2, +37%; E 3/3, +18%; E 4/3, +9%; $P < 0.05$) as did the HDL-C response (E 3/2, no change; E 3/3, +4%; E 4/3, +12%; $P < 0.05$). Although, across the apoE genotype groups, the mean changes in CETP and the mean changes in HDL-C were inversely related, linear regression analysis of the individual values showed that the change in CETP and the change in HDL-C were not correlated. The two variables, apoE genotype and the change in plasma CETP explained 40% of the observed variation in HDL-C change in response to dietary cholesterol. ApoE genotype has significant and opposite effects on plasma CETP and HDL-C responses to dietary cholesterol in man.

Remodeling of HDL (P. J. Barter)

Dr. Barter presented a model based on in vitro incubation studies of human plasma carried out for 3–8 h. Several changes were observed in the components of HDL including the dissociation of a portion of apoA-I from HDL. With prolongation of the incubation beyond 3 h, the dissociated apoA-I progressively returns to the HDL fraction, coinciding with the appearance of discoidal HDL particles. This phenomenon is likely to involve complexing of apoA-I with phospholipids that are released from VLDL undergoing lipolysis. Most of the discoidal HDL are subsequently converted to spheroidal HDL, presumably as a result of LCAT activity. After 8 h incubation, all of the apoA-I has been returned to the HDL fraction which now comprises mainly spheroidal particles. These studies are consistent with the existence of a cyclical process in which apoA-I dissociates from HDL and subsequently complexes with phospholipids to form discoidal HDL. These discoidal particles are then available to incorporate unesterified cholesterol from other lipoprotein fractions or from cell membranes. Subsequent esterification of this cholesterol by LCAT converts the discs into spheroidal HDL, thus completing a cycle in which unesterified cholesterol in lipoproteins or cell membranes is used to expand the cholesteryl ester core of HDL particles. The findings of this study suggest that cholesteryl ester transfer protein (CETP), hepatic lipase (HL), and VLDL interact synergistically to reduce the core lipid content and the particle size of HDL.

Effects of intravenous infusion on human lipoprotein metabolism (Norman E. Miller)

Dr. Miller presented preliminary findings on the effects of intravenous infusion of apoA-I on the cardiovascular risk profile of human subjects. This approach has been made possible because of the large amounts of apolipoprotein A-I (apoA-I) prepared by the Central Laboratory of the Swiss Red Cross. The isolation procedure involves a multi-stage precipitation, followed by sterilization and lyophilization. The initial phase of these studies has been performed to assess the effects of intravenous infusion of human apoA-I on plasma lipoproteins and lipid transport in subjects with low initial HDL cholesterol and apoA-I concentrations. In addition, data is being collected on toxicity, antibody response, and urinary excretion of apoA-I.

Metabolic consequences of deleting HDL apolipoprotein genes (Nobuyo Maeda)

Dr. Maeda reported on studies with mice carrying mutations in various lipid metabolism-related genes. Mice lacking apoA-I have markedly reduced plasma cholesterol and HDL, but have no obvious atherogenic problems. Mice that can produce apoB-48 but not apoB-100 model hypobetalipoproteinemia and show problems associated with fat-soluble vitamin deficiencies. Mice lacking apoE have spontaneous hypercholesterolemia, and develop atherosclerotic lesions as early as 3 months old, even on normal low-fat mouse chow.

CLINICAL ASPECTS OF REVERSE CHOLESTEROL TRANSPORT (CHAIRMAN: MICHAEL CLEARFIELD)

Triglyceride turnover and HDL-C particles in hypertriglyceridemic patients (Elliot Brinton)

Studies of HDL turnover in human subjects have demonstrated that the fractional catabolic rate (FCR) of apoA-I is inversely proportional to the average size of HDL particles. These forms of HDL may be rapidly catabolized by the kidney, suggesting that the association of HDL size and its removal from the plasma may be associated with the formation of very small apoA-I-containing particles from HDL. Dr. Brinton has presented evidence for the existence of these particles in vivo by gel filtration column chromatography, native polyacrylamide gel electrophoresis, and agarose electrophoresis. He has also presented a preliminary description of the characteristics of these circulating small forms of HDL.

Postprandial lipemia (Wolfgang Patsch)

Fasting triglycerides (TG) are considered a secondary risk factor of coronary artery disease (CAD). In multivariate analyses, TG tend to be eliminated by high density lipoprotein (HDL) cholesterol. However, studies in the postprandial state have shown that the metabolism of TG-rich lipoproteins influences the concentration of HDL-C in plasma. The role of TG metabolism in CAD was evaluated in postprandial lipemia, to elucidate the paths of TG-metabolism in patients with CAD. In 61 male subjects with severe CAD, the magnitude of postprandial lipemia was greater than in 40 control subjects without CAD as verified by angiography. Single postprandial TG levels 6 and 8 h after the meal were highly discriminatory ($P < 0.001$), and displayed an accuracy of 68% in predicting the presence of absence of CAD. This level of accuracy was similar to that of HDL_2-cholesterol (64%) and apoB (68%). The most accurate multivariate model contained postprandial TG in addition to HDL_2-cholesterol, apoB, and age, and classified 82% of subjects correctly. This study supports the concept that plasma TG-transport is an independent predictor of CAD when ascertained in the postprandial state.

Additional studies based on apoE phenotyping and receptor binding studies suggest that impaired removal of intestinally derived lipoproteins is not the primary determinant of atherosclerosis; rather, impaired metabolism of TG-rich lipoproteins, irrespective of origin, underlies the association between elevated postprandial lipemia and CAD.

Diagnosis of hypoalphalipoproteinemia (J. J. Frohlich)

Dr. Frohlich discussed the diagnosis and treatment of hypoalphalipoproteinemia (HA) both for patients with well-defined genetic deficiencies and for those with low HDL of unknown etiology. He summarized the current views on the interplay of environmental and genetic factors in the development of HA. He noted that while genetic diseases such as Tangier disease and LCAT deficiency are accompanied by clinical hallmark symptoms, no such manifestations are found in patients with HA of unknown origin. Isolated low HDL-cholesterol, or primary isolated hypoalphalipoproteinemia, is relatively uncommon and likely to be associated with the group of disorders currently termed familial combined hyperlipoproteinemia.

Dietary or drug treatment of HA is often difficult and its indication is dependent on the overall cardiovascular risk profile. Currently there is no evidence to show that treatment of isolated HA prevents coronary heart disease.

Concluding remarks (J. Dietchy)

Dr. Dietchy, drawing on his vast research experience in cholesterol metabolism, presented a unique, quantitative assessment of the cholesterol load that is a challenge to reverse cholesterol transport. His theoretical calculations yielded surprisingly close estimates to those presented by Dr. Schwarz based on model studies.

SUMMARY

The purpose of this symposium was to provide a forum for presenting recent findings and for exchange of ideas concerning reverse cholesterol transport. Because the mechanism involving HDL in the prevention and/or reversal of atherosclerosis is still unknown, this area is of intense interest. Although reverse cholesterol transport as an essential physiological mechanism has been validated, the clinical significance of this pathway remains unclear. Key elements of knowledge are lacking that would allow the linking of cholesterol efflux from cells and tissues with specific events in HDL metabolism, particularly those that are relevant to the prevention and/or reversal of atherosclerosis. Because of the intricate nature of the interaction between the components of reverse cholesterol transport, this second conference involving the leading investigators proved particularly valuable for presentation and extensive discussion of unpublished and occasionally controversial findings. Following this conference, an agreement was reached between the organizers and Dr. Norman E. Miller to combine this symposium with the previously held International Symposia on High Density Lipoproteins in Atherosclerosis (organized by Dr. Miller).

We are grateful to Ms. Jan Sharp for her assistance with the organization and local arrangements. Support for this meeting was provided by the National Institutes of Health, The Amon Carter Foundation, The Osteopathic Medical Center of Texas, Warner Lambert/Parke Davis, Warner Lambert/Parke Davis of Canada Inc., Sandoz Pharmaceuticals, The Upjohn Company, Upjohn Research Laboratories, Marion/Merrell Dow Inc., Merck Sharp and Dohme, the Texas Osteopathic Medical Association, and The Burroughs Wellcome Fund.