Meeting Summary

The 12th Annual European Conference on Vascular Biology

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The 12th annual scientific meeting of the European Vascular Biology Association was held in Gilleleje, Denmark, from April 27 to May 1, 1991, in collaboration with the Scandinavian Society for Atherosclerosis Research. The sessions of the meeting covered two major fields: hyperlipidemias relating to the genetic variability of apolipoprotein B-100 and transendothelial flow of macromolecules.

The first session covered several aspects of familial combined hyperlipidemia (FCH). All speakers agreed on the heterogeneous nature of this disease, which appears to include several different metabolic disorders, each with a separate genetic background. Support for one possible candidate gene was found in the studies by James Scott (United Kingdom), showing an association with the restriction fragment length polymorphisms of the A-I–C-III–A-IV gene cluster. Among the underlying mechanisms for FCH, Ronald Krauss (Berkeley, Calif.) mentioned the possibilities of associations between FCH and heterozygous lipoprotein lipase deficiency, cholesterol hydrolase deficiency, and an upregulation of apolipoprotein B expression in liver cells. One of the characteristics of FCH is related to the low density lipoprotein (LDL) particle size distribution. FCH is often associated with the so-called type B LDL pattern, which is characterized by small, probably more atherogenic LDL particles. The type B LDL pattern appears at least in part to be genetically determined. Patients with FCH have not only small LDL particles but also frequently elevated very low density lipoprotein and intermediate density lipoprotein. A role for these lipoproteins in atherogenesis was suggested from the studies by Börge Nordestgaard (Denmark) on the uptake and deposition of lipoproteins in the rabbit aorta. His data suggest that the rate of efflux is closely and negatively related to particle size, with much lower rates of efflux for larger particles. Thus, although the influx of larger particles is also lower, a net accumulation of the larger particles, i.e., very low density lipoprotein and intermediate density lipoprotein, would follow.

If the genetic background of FCH is largely unknown, the genetics of familial defective apolipoprotein B-100 (FDB) is fairly well known. Actually, in this case the identification of the mutation preceded the clinical characterization of the disease. All cases studied so far seem to be descended from one ancestor with the characteristic mutation of amino acid 3,500. The metabolic consequences of this mutation were described by Thomas Innerarity (San Francisco, Calif.). He also discussed how the lipoproteins from patients with this disorder might be used in metabolic studies. His investigations show poor receptor binding and delayed clearance of LDL particles with the mutated apolipoprotein B-100. Subjects with FDB could also be studied for the analysis of lipoprotein(a) catabolism. These data strongly suggest that the lipoprotein(a) particle is not cleared by receptor-dependent mechanisms as efficiently as the LDL particle. Studies of FDB in Europeans, presented by Anne Tybjaerg-Hansen (Denmark) and Steve Humphries (United Kingdom), suggest a frequency for FDB of between one in 500 and one in 1,000. Ongoing screening studies will give more reliable estimates of the frequency of the disease in the population. The clinical features of patients affected by FDB are now becoming clearer. There is a high frequency of coronary artery disease in these patients. Some cases are presented as patients with the classical familial hypercholesterolemia with xanthomas and severe hypercholesterolemia, but there are also less severe cases with mild hypercholesterolemia or serum cholesterol levels within the so-called normal range.

Several aspects of the transendothelial transport of macromolecules were presented. The role of transendothelial pores and vesicles for this transport was discussed by Jörgen Frökljär-Jensen (Denmark), based on his studies of endothelial cells with serial sections and electron microscopy. His data did not support the idea of a major role for either pores or channels in the transport of macromolecules. With this technique, however, the possibility of the presence of occasional pores and vesicles cannot be excluded. The paracellular pores, on the other hand, have been rather well characterized, as in the studies by J.A. Firth (United Kingdom). The nature of ridge-formed tight junctions could be visualized, as well as the pores formed in these junctions. These junctions are not static but instead constitute a dynamic system of interconnecting ridges, thus allowing solutes to circumvene the ridges or pass through discontinuities in the tight junctions, as described by Magnus Bundgaard (Denmark). The dynamics of these junctions is also well described by the reversible changes induced by inflammatory agents.

The flexibility of the endothelial barrier was also supported by in vitro studies of endothelial monolayers by Victor van Hinsbergh (The Netherlands) and Jeremy Pearson (United Kingdom). The complexity of molecular transport across the endothelium can to some extent be explained by the two-size pore model de-
scribed by Bengt Rippe (Sweden). This model assumes the presence of small and large pores in the capillary endothelium. The observed molecular flow across the endothelium can be mathematically explained by assuming a bidirectional flow across the endothelium. The relevance of this model had been tested in humans by studying patients undergoing intermittent peritoneal dialysis.

Whether increased endothelial permeability precedes atherosclerosis is a classical question. Dawn Schwenke (Winston-Salem, N.C.) suggested that the initiation of the atherosclerotic plaque is related to subendothelial structures rather than to a primary change in endothelial permeability. Thus, her data gave no indication of increased permeability in atherosclerosis-prone areas of the aorta. Along the same lines she found no increased endothelial permeability in either atherosclerosis-prone strains of pigeons or the early phase of cholesterol feeding in rabbits.

Although the importance of lipoprotein influx into tissue was supported by Steen Stender (Denmark), he suggested that the retention of lipoproteins in the subendothelial structures is also very important. In particular, his studies of aortic transplants suggest that very low density lipoprotein and intermediate density lipoprotein may be more readily retained in the arterial intima than LDL. A local variation in LDL influx into arterial tissue that is related to endothelial structure and subendothelial characteristics was also suggested by the data reported by John Lever (United Kingdom) and Lars Nielsen (Denmark). In addition, hydrostatic pressure influences the uptake of macromolecules by arterial tissue, as shown in studies by Donald Fry (Columbus, Ohio).

That genetic influences may contribute to variation in endothelial integrity was shown by data from a study of endothelial injury in rabbit siblings presented by Harriet Björk (Sweden).

Other than the studies mentioned in this summary, several shorter presentations and posters on the themes of the meeting were presented. The conference highlighted the frontiers of these scientific fields and gave a very strong impression of the diversity and the high quality of the ongoing research within these areas.
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doi: 10.1161/01.ATV.12.5.645
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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