Workshop Summary

Report on the Workshop on Diabetes and Mechanisms of Atherogenesis

September 17th and 18th, 1992, Bethesda, Maryland

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This workshop is a joint endeavor of the National Heart, Lung, and Blood Institute and the National Institutes of Diabetes and Digestive and Kidney Diseases to discuss the scientific advances that may help to explain why atherosclerosis and its consequences are a major cause of disability and death in diabetics. Our knowledge of the pathogenesis of atherosclerosis is rapidly expanding, reflecting advances in vascular biology, lipoprotein metabolism, and other areas. Much of this knowledge remains to be applied to the study of the diabetic lesion. The workshop set out to describe the present understanding of the basic mechanisms that lead to increased atherosclerosis in diabetics by bringing together experts in the relevant disciplines.

The workshop was presented in seven sessions devoted to the current status of knowledge about diabetes and atherogenesis, dyslipidemia in diabetics, diabetes and vascular disease, animals models of diabetes and atherosclerosis, diabetes and atherothrombosis, and diabetics and immunology.

Current Status of Knowledge of Diabetes

Dr. Michael Stern, University of Texas, San Antonio, provided an epidemiological overview, indicating that at equivalent conventional risk levels, e.g., equivalent total serum cholesterol, there is four to five times the mortality from vascular disease in diabetics. There is also persuasive evidence that elevated triglyceride is a substantial risk factor in diabetics. Glycemic control appears to influence primarily microvascular disease. Glycemic control in many type II diabetics is not necessarily paralleled by control of lipid abnormalities. The conventional risk factors for atherosclerosis in the general population also operate for macrovascular disease in type II diabetics. Endogenous hyperinsulinism has also recently received attention as a possible cardiovascular risk factor. He pointed out that many of the lipid-lowering pharmacological strategies may need to be carefully reviewed for diabetics because of potential effects on glycemic control.

Dr. Ken Polonsky, University of Chicago, reviewed the pathophysiology of type I and type II diabetes. Type I diabetes is an autoimmune disease with early selective destruction of beta cells occurring particularly in individuals bearing Dw3 and Dw4 HLA types and non-aspartic acid residues at position 57 of the DQB chain. Islet cell antibodies are usually present at the time of diagnosis. Insulin secretory defect is usually complete in the full-blown syndrome. In type II diabetics, genetic factors play a very important role, as evidenced by a concordance rate in identical twins approaching 100%. Although in most patients the specific genetic changes are not known, mutations in insulin and the insulin receptor have been identified.

Early onset of type II diabetes is associated with a gene polymorphism on human chromosome 20q, in linkage with the adenosine deaminase gene or with mutations in the glucokinase gene. Dr. Polonsky also described the insulin secretory abnormalities in non-insulin-dependent diabetes. These include reduction in first-phase insulin secretion, delayed and blunted insulin secretory peaks after meals, elevations of proinsulin, and abnormalities in oscillatory insulin secretion. Finally, he reviewed syndrome X, which is accompanied by glucose intolerance, hyperinsulinism, insulin resistance, increased very low density lipoprotein (VLDL) triglyceride, decreased high density lipoprotein (HDL) cholesterol, and upper body obesity—all factors that predispose to diabetes and appear to enhance atherogenesis.

Dr. Jeffrey Flier, Beth Israel Hospital, Boston, presented a masterful review of the insulin receptor and its emerging signaling pathways in response to insulin binding, involving, among other intermediates, phosphotyrosines, phosphatidylinositol-3-kinase, microtubule-associated protein kinase and kinase kinase, ras, GTPase-activating protein, raf and S6 kinase, etc. Several insulin receptor mutations have been described that lead to insulin resistance. There are a number of nonclassical targets of insulin action, e.g., the kidney, ovary, skin, vascular tissue, and brain. The signaling pathways may differ from the prototype in these tissues. Of particular relevance is vascular cell responsiveness.

Current State of Knowledge of Atherogenesis

The second session was devoted to the current state of knowledge of atherogenesis. Dr. Joseph Witzum, University of California at San Diego, discussed the metabolism of low density lipoprotein (LDL) in nondiabetic and diabetic subjects. He reviewed the role of LDL oxidation in atherogenesis and discussed how LDL oxidation may trigger many metabolic responses in the vascular wall, including the chemotaxis of blood monocytes, the stimulation of the expression of a number of vascular cell genes, and the evolution of foam cells.
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arising from the uptake of oxidized LDL by macrophages. Oxidized LDL epitopes are found in the atherosclerotic plaque. The nonenzymatic glycosylation of LDL in the presence of hyperglycemia may delay the LDL receptor–dependent clearance of LDL, thus prolonging the extracellular residence time of LDL and thereby increasing its likelihood of undergoing oxidation. Dr. Witztum indicated that poor diabetic control may be associated with triglyceride enrichment of LDL, which can cause reduced receptor-dependent LDL uptake. Improved diabetic control reduces LDL levels even in individuals with normal LDL cholesterol levels. He also noted that aminoguanidine, which is being used to inhibit advanced glycosylation end product (AGE) formation, may have the additional benefits of reducing lipid (i.e., LDL) oxidation.

Dr. Peter Libby, Brigham and Women’s Hospital, Boston, reviewed the roles for growth factors in atherogenesis. Smooth muscle cell proliferation and matrix synthesis are hallmarks of hyperplastic vascular disease, including atherosclerosis and other vascular complications of diabetes mellitus. Growth control of cells in vivo probably reflects a dynamic balance between stimulatory and inhibitory signals from families of growth factors under tight regulation. Growth factors can beget other growth factors, as well as their own inhibitors. Their action depends on receptor expression and post-receptor mechanisms that vary in different target cells. Like cell growth, the response of matrix, e.g., collagen synthesis is controlled by a balance between stimulatory and inhibitory cytokines. Although most attention has been devoted to smooth muscle cell proliferation, macrophage replication is probably as great. Genes particularly expressed in macrophages like apoprotein E, c-fms, and the scavenger receptor increase profoundly with the evolution of the atherosclerotic plaque.

Dr. Thomas Wight, University of Washington, Seattle, reviewed studies on the vascular matrix, which affects the viscoelastic properties of vascular tissue and influences such vascular events as local lipid metabolism, local effectiveness of growth factors, calcification, and thrombosis. He reviewed our current understanding of proteoglycans, many of which are synthesized by vascular endothelial and smooth muscle cells. Such growth modulators as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) are also potent “effectors” of proteoglycan synthesis by these cells. Both of these molecules lengthen the glycosaminoglycan chains. PDGF increases the ratio of chondroitin-6-sulfate to chondroitin-4-sulfate, but TGF-β does not. Chondroitin-6-sulfate may increase the susceptibility of LDL to oxidation, perhaps by sequestering LDL.

Dr. Alan Fogelman, University of California at Los Angeles, reviewed the events associated with the early stages of a developing atherosclerotic plaque, which are probably induced by mildly oxidized LDL and attenuated by HDL. The early events of fatty streak development include lipoprotein transport, retention, and modification within the subendothelial space and monocyte adherence to the endothelium followed by their migration into the subendothelial layer, where they differentiate to macrophages that become foam cells. The modification of LDL in the subendothelial space that can be attenuated by HDL involves limited oxidation, so that LDL retains recognizability by the LDL receptor. Such minimally modified LDL (MM-LDL) promotes monocyte but not neutrophil binding to endothelial cells, which produce monocyte chemotactic factor (MCP-1) and colony stimulating factors. Injection of MM-LDL into mice induces expression of these genes, as well as that of serum amyloid protein, by hepatocytes, especially in atherosclerosis-susceptible mice (C57BL/6). Nuclear factor kappa B (NFκB) transactivation factor is also more notably induced in susceptible than resistant mice (C3H). MM-LDL can be formed in a cell-free system by the combined action of phospholipase A2 and lipoxygenase. Dr. Fogelman also presented evidence that cyclic AMP and protein kinase A may be important mediators of the MM-LDL effects on vascular gene expression.

The dyslipidemia found in diabetic subjects was reviewed by Dr. John Brunzell, University of Washington, Seattle. Treated non–insulin-dependent diabetics often have mild hypertriglyceridemia, which is associated in general with increments in small VLDL, intermediate density lipoprotein, and small, dense LDL as well as a decline in buoyant HDL (HDL₃), consisting of apo A-1 without apo A-2). In these patients, the dyslipidemia is associated with a central obesity syndrome (visceral obesity, hypertension, and insulin resistance). This syndrome is associated with increased hepatic lipase, which may in turn account for the observed changes in LDL and HDL. These defects seem to be independent of glucose control. This lipoprotein profile is similar to that described as pattern B, seen in some patients with familial combined hyperlipidemia. It remains to be established whether the diabetic dyslipidemia is, like pattern B, influenced by genes at the chromosome 19 level (perhaps the LDL receptor or insulin receptor).

**Diabetes and Vascular Disease**

The next session of the workshop was devoted to diabetes and vascular diseases. Dr. Alan Chait, University of Washington, Seattle, began with an overview of the way that diabetes may modify established risk factors. Lipoprotein oxidation appears to be increased in diabetes, attributable to the effects of glucose on LDL oxidation, increased monocyte superoxide generation, perhaps a decrease in antioxidant defense (e.g., vitamin C), and an increased susceptibility of LDL to oxidation. The uptake of LDL by the LDL receptor is sensitive to its triglyceride content. Triglyceride-enriched LDL is not readily taken up, so that its residence time in the artery wall may be prolonged, allowing it to be oxidized in situ. Also, the action of local arterial lipoprotein lipase on such triglyceride-rich LDL may generate a triglyceride-depleted particle that is readily taken up by receptors on smooth muscle cells or macrophages. Nonenzymatic glycation of key proteins in the vessel wall may alter their function, e.g., by modulating growth factor and cytokine expression, so as to favor atherogenesis. Hyperinsulinemia may be proatherogenic by modulating lipoprotein receptors and smooth muscle cell migration and proliferation, by increasing local cholesterol synthesis, or by decreasing cholesterol efflux. The diabetic state increases the tendency to thrombosis, perhaps caused by enhancing platelet aggregability and increasing such clotting factors as factor VIII, factor X, and plasminogen activator inhibitor. Elevated
plasma triglyceride and lipoprotein(a) (Lp[a]) may also play a role in the prothrombotic state.

Dr. Jonathan Diamond, Hershey Medical Center, Hershey, presented his interesting studies emphasizing how hypercholesterolemia may augment macrophage infiltration into the glomerular mesangium with increased matrix production and glomerulosclerosis. Rats treated with the nephrotoxin puromycin aminonucleoside developed albuminuria and nephrosis. After an initial decline, there is increased expression of TGF-β and fibronectin. Cholesterol feeding may, on its own, produce similar changes in gene expression or may augment that produced by aminonucleoside administration. Infiltrating macrophages appear to be responsible for the cytokine production and are correlated with the appearance of albuminuria. Fibronectin gene expression is TGF-β dependent. These changes may constitute the early phases of the later mesangial matrix expansion and glomerulosclerosis.

Dr. Helen Vlassara of the Picower Institute for Medical Research, Manhasset, N.Y., reviewed the potential role of AGEs and their receptors in diabetic vascular pathology. The discovery of this pathway represents a critical potential link between hyperglycemia and diabetic vascular disease. These products result from a nonenzymatic interaction between glucose and the amino groups of proteins. Amino lipids can also react. AGE may cross-link proteins, causing several alterations such as collagen cross-linking, basement membrane thickening, and irreversible protein trapping, and may react with NO, thereby preventing its vasodilatory effect. The cross-linking of AGEs can be inhibited with aminoguanidine. AGEs may also induce a series of biological responses, that are mediated by their interaction with specific receptors on the surfaces of macrophages, T cells, endothelial and smooth muscle cells, and fibroblasts. A monococyte/macrophage receptor system may facilitate removal by binding and endocytosis of damaged proteins and cells. The interaction of AGEs with their receptors on macrophages may trigger release of cytokines (interleukin-1β and tumor necrosis factor-α [TNF-α]) and growth factors (PDGF and insulin-like growth factor-1α) with the potential of growth enhancement in the vascular wall. The AGE receptors appear to be under hormonal (insulin) and cytokine (TNF-α) control, at least in culture. T lymphocytes also express AGE receptors, which in the presence of a costimulus may produce interferon gamma (IFN-γ), which primes the macrophages. Thus, these modified proteins may enhance a number of responses relevant to vasculopathy. In vivo, the injection of exogenous AGE peptides resulted in increased permeability, transendothelial migration, glomerulosclerosis, and reduced vasodilation (NO inactivation), all of which could be prevented by the simultaneous administration of aminoguanidine.

Dr. Mark Creager, Brigham and Womens’ Hospital, Boston, detailed his studies of vascular dysfunction in human subjects with insulin-dependent diabetes. Major influences on vasoactivity are endothelium-derived relaxing factor (EDRF) and prostanooids. The study of human forearm vascular responses (venus occlusion plethysmography) to methacholine chloride (endothelium dependent) and nitroprusside (endothelium independent) revealed that endothelium-dependent vasodilation is impaired in diabetic subjects. Aspirin was administered to eliminate the influences of vascular prostanoids. Diabetes may inactivate EDRF, impair its signaling mechanisms, or reduce the concentration of substrate for its production. It is not clear whether the impairment in vasodilation and EDRF function reported in this study is related to hyperglycemia, hyperinsulinism, or both.

Animal Models

Thorough molecular approaches to the study of diabetes in atherosclerosis require suitable animal models. Dr. Ake Lernmark, University of Washington, Seattle, reviewed the available animal models for diabetes and insulin-resistant syndromes. Several obese and insulin-resistant rodents are available. However, Dr. Lernmark focused on two models of type I diabetes, mice (nonobese diabetic [NOD] mice) and rats (diabetes-prone BB rats). In both of these inbred models, the incidence of diabetes is higher in specific pathogen-free and virus antibody–free animals. Type I diabetes develops after complete specific destruction of pancreatic beta cells, which is thought to be immunologically mediated. In the NOD mouse, the diabetes is associated with the H-2 I-A major histocompatibility (MHC) allele. Crosses of inbred NOD mice with other characterized strains followed by genetic probing revealed type 1 diabetes associations of loci on five different chromosomes in addition to that carrying MHC. In the case of the BB rat, similar approaches indicated the association of at least three different loci with the development of diabetes, one of which is on rat chromosome 4 (in close linkage with neonatal T lymphopenia) and another of which is on rat chromosome 20 (MHC). Breeding studies based on these genetic markers may be useful in the development of animal models with both diabetes and a genetically defined atherosclerosis propensity.

Dr. Henry McGill, Southwest Foundation, San Antonio, reviewed the animal models in use for the study of atherosclerosis. A variety of animals develop hypercholesterolemia and atherosclerosis when fed cholesterol- and fat-enriched diets. Susceptibility to diet varies among species, from the highly susceptible hypercholesterolemic rabbit to the resistant rats and mice, with many primates, including humans, exhibiting intermediate susceptibility. Susceptibility to diet varies among individuals within each species and is heritable. Selective breeding has produced lines of rabbits, pigeons, cynomolgus monkeys, and baboons that are either resistant or responsive to dietary fat and cholesterol. Watanabe heritable hypercholesterolemic rabbits carrying an LDL receptor mutation are widely used for the study of hypercholesterolemia and atherosclerosis. An LDL receptor–deficient rhesus monkey has also recently been described. Inbred nonhuman primates are used to study the genetics of dyslipoproteinemias. Transgenic mice have the potential to determine the mechanisms of action of candidate genes for atherosclerosis. Rabbits have been used to study the interaction of diabetes and atherosclerosis. Alloxan treatment of cholesterol-fed rabbits protects against diet-induced atherosclerosis, probably because they accumulate large triglyceride-rich lipoproteins that do not permeate the vascular wall. Useful models that simulate the interac-
tion of diabetes and atherosclerosis are quite poorly developed and yet much needed.

Dr. Nora Sarvetnick, Scripps Research Institute, La Jolla, summarized some of her studies on transgenic models of type I diabetes. No model is a phenocopy of the human disease. In these models, the insulin promoter has been used to drive the expression of potential effector molecules in the pancreatic beta cell. Among these are lymphokines or cytokines. Dr. Sarvetnick has studied the expression of IFN-γ in the beta cells of transgenic animals. This induced diabetes is associated with the destruction of islet cells that occurs with an influx of inflammatory cells. A cross of such interferon-transgenic animals with severe combined immunodeficient mice showed that in progeny lacking mature lymphocytes, islets were not destroyed. Lymphocytes from transgenic animals but not those from nontransgenic animals were cytotoxic to normal islets. These results suggest that the destruction of islets in interferon-transgenic mice is attributable to the function of interferon as a costimulator of lymphocytes that attack the islet cells. This presentation emphasized the potential power of transgenic animals that possess only one transgene, or gene replacement, in developing models for studying the vascular complications of diabetes. During the discussion of this paper, Dr. J. Flier reported that he has produced a transgenic animal that had some of the features of type II diabetes. Using the thermogenic promoter of brown adipose tissue to drive diphtheria toxin expression in brown adipose tissue resulted in brown adipose tissue destruction, severe obesity, hyperphagia, glucose intolerance, insulin resistance, and hypertriglyceridemia.

Diabetes and Thrombosis

There followed a session on the relation between diabetes and thrombosis. Dr. Ralph Nachman, Cornell Medical College, New York, discussed the potential effect of Lp(a) on plasmin formation. The endothelial cell membrane contains a 40-kD receptor that has two binding sites, one of which binds plasminogen and the other, tissue plasminogen activator. Plasminogen bound to this surface, where it was able to be converted to plasmin. Lp(a) competes for the binding of GLU plasminogen to its binding site, thus inhibiting cell-surface plasmin formation. It has little effect on fluid-phase plasmin formation. Dr. Nachman also reported that in their experiments, Lp(a) increased the expression of plasminogen activator inhibitor. He also reviewed strategies for reducing Lp(a). Omega-3 fatty acids, large doses of niacin, gemfibrozil, N-acetylsleutene, estrogen, and ethanol all lower Lp(a) levels; however, it is not clear that these approaches are clinically useful.

Dr. David Stern, Columbia University, New York, presented a detailed view of his recent isolation of the receptor for AGE. It is the operator molecule that responds to AGE accumulation in diabetes and so influences vascular responses. This receptor is a member of the immunoglobulin superfamily; it is a transmembrane protein that binds AGE and also a lactoferrin-like polypeptide. The receptor is widely distributed on endothelial cells, macrophages, and neurons, the latter suggesting a role for the receptor outside the vascular system. This localization is confirmed by immunohistochemistry. The cloning of the receptor for AGE allowed Dr. Stern to generate antibodies to the receptor, as well as soluble receptors that lack their transmembrane domains. He has developed a competitive assay for AGE that uses purified receptor and radiolabeled AGE albumin. AGE albumin is cleared rapidly from the plasma by the receptor, since the clearance is inhibited by the soluble receptor. Infusion of AGE leads to expression of PDGF-A chain, especially in the kidney, a phenomenon blocked by the soluble receptor. AGE also activates macrophages by a process that apparently involves NFkB. Their effect is probably attributable to interaction with the AGE receptor, based on the influence of antireceptor antibody and soluble receptor analogues. These tools should improve our understanding of the role of AGE in the vascular complications of diabetes.

Immunology and Diabetes

The final thematic session concerned the relation of immunology and diabetes. Dr. Ake Lernmark discussed the immune factors in the pathogenesis of diabetes. Type I diabetes is an autoimmune disease, reaction involving almost total loss of pancreatic islet cells. Most patients express islet cell antibodies, insulin autoantibodies, and antibodies against glutamic acid decarboxylase (GAD), of which there are two isofoms, GAD 65 and GAD 67. Seventy-five percent of patients have antibodies to GAD 65, which is expressed in the islets, compared with only 8% of patients who have antibodies to GAD 67. The predicted value of GAD 65 antibodies may be higher than that for islet cell or insulin antibodies. However, since the prevalence of these antibodies exceeds the prevalence of the disease by a factor of about 10 and these antibodies may be present regardless of HLA alleles (they may be expressed even in persons who have HLA alleles negatively associated with type I diabetes), it is likely that other markers that are more specifically predictive of diabetes are yet to be discovered. In several family members who type positive for the available immunological markers, there may nevertheless be no progression to clinical diabetes. At the moment, the most useful immunological index involves a combined assessment of autoantibodies to islet cells, insulin, and GAD 65, together with the HLA alleles (DR3 and 4, DQA, and DQB).

The final talk was given by Dr. Garrison Fathman, Stanford University, Stanford, on the pathogenesis and immunotherapy of insulin-dependent diabetes. The fact that type I diabetes is an autoimmune disease raises the possibility of immunotherapy. The interval between the expression of islet autoantibodies and the loss of sufficient insulin reserve to produce frank diabetes may be quite long, allowing for the possibility of therapy at a time when sufficient beta cell mass is preserved. A number of immunotherapeutic approaches have been and are being used, ranging from nonspecific treatment such as monoclonal antibodies directed at CD4 helper/inducer T cells to specific peptide tolerization schemes, one of which was described by Dr. Fathman. This takes advantage of the recent surprising observation that partial peptides representing the antigen recognized by the responding T cell can prevent the specific autoimmune response. Soluble peptides without adjuvant should be able to tolerize NOD mice and prevent progression to the full expression of type I diabetes.
This represents a hopeful approach to intervention before full-blown type I diabetes is developed.

**Summation**

The workshop concluded with a summation session in which each of the individual session chairs identified important areas for future research.

Clearly there needs to be a better understanding of the basis for the accentuated atherosclerotic heart disease in diabetes at constant conventional risk factor levels (cholesterol, hypertension, etc.). Does this operate at subtle lipoprotein influences, other plasma factors such as antioxidant levels, or procoagulant activity, or does it operate at the vessel wall level?

**Promotion of Atherogenesis by Diabetes**

The fundamental cell and molecular biological study of both atherogenesis and diabetes needs to proceed with dispatch. There is a need to use modern techniques of gene mapping to locate and characterize the marker and candidate genes involved in diabetes and atherogenesis. This will also require the study of large families in which candidate genes are likely to be segregating. New techniques of quantitative trait analysis should yield much new information on both diabetes and atherogenesis.

**Animal Models**

Both diabetes and atherosclerosis are multifactorial diseases, a characteristic that makes their study difficult. There is a need for well-characterized genetic models of each, so that the interaction of diabetes and atherosclerosis can be investigated on more defined terms. It was evident in this workshop that no ideal or even satisfactory animal model currently exists for such studies. An ideal model should have hyperglycemia, insulin resistance, dyslipidemia, and increased predisposition to atherosclerosis. Such an animal model would allow the use of the newest cellular and molecular techniques to study important pathophysiological mechanisms related to the role of diabetes in atherosclerosis. However, the newly described transgenic and gene knock-out models for atherosclerosis or diabetes present the possibilities of beginning investigations on candidate genes.

**The Role of Hyperinsulinism**

A particular feature of type II diabetes, obesity, and other insulin-resistant states is hyperinsulinism. Does hyperinsulinism promote atherogenesis? If so, is there a difference between endogenous and exogenous insulin? What effect does insulin and hyperglycemia have on the vascular wall? Are the signaling pathways used by insulin in vascular tissue similar to the prototype described in other cells? Do vascular beds, e.g., microvascular and macrovascular beds, differ in their response to insulin and/or hyperglycemia? There is a known heterogeneity in the distribution and associations of microvascular and macrovascular disease.

**Prediabetic State**

There is a need to define the prediabetic state and to characterize vascular responses in this state, not only to physiological regulators but also to potentially atherogenic influences. It is in the prediabetic state in partic-ular that the interaction of atherogenic stimuli and diabetes is likely to be best studied.

**Vascular Biology**

In vitro studies have led to many recent advances in understanding of the general process of atherogenesis. Much less, however, is known about the potential role of factors specifically relevant to diabetes in the regulation of most of these events. Thus, there is clearly a requirement to extend basic studies to determine how those factors that are unique to or grossly exaggerated in diabetes influence these events at a cellular and molecular level. Factors relevant to diabetes include not only hyperglycemia and hyperinsulinemia but also the formation of AGEs, increased lipoprotein oxidation, and an increased prevalence of the atherogenic dyslipidemia phenotype. There has been almost no modern work on the problem of fibrinolysis or coagulation in diabetes. This situation should be rectified.

One of the intriguing recurrent themes highlighted in the workshop was the similarity in the regulation of growth factor and cytokine expression by mildly oxidized LDL and AGE proteins. Lipoprotein oxidation and formation of AGE proteins are expected to be increased in both insulin- and non-insulin-dependent diabetes, thereby contributing to accelerated atherosclerosis. Confirmation that mildly oxidized LDL and AGE proteins play a role in accelerated atherogenesis in diabetes should be a high priority. However, to determine the real relevance of these factors to the pathogenesis of atherosclerosis in diabetes, research will have to be extended to the in vivo situation. Studies to determine whether lipoprotein oxidation or AGE protein formation is increased in diabetes will not be easy. However, novel ways to assess these processes in vivo should be pursued, since useful information is likely to be gathered. Specific work on the diabetic lesion in humans would be valuable. Does it simply represent a rapidly progressing atherosclerotic lesion, or does it have a different composition and a difference in the pattern of cellular responses and gene expression, e.g., in macrophages and macrophage products?

There has been much exciting work on the immunology of type I diabetes. Atherosclerosis is an inflammatory-like lesion, containing as much as 20% T cells. Some have been activated by IFN-γ. MHC class II antigens are expressed on macrophages, smooth muscle cells, and endothelial cells. There are autoantibodies in the arterial wall. Basic research in the immunological aspects of atherosclerosis along with the influence in diabetes should be investigated.

**Lipoproteins of Diabetes**

Diabetic dyslipidemia resembles the lipoprotein pattern B described by Krauss. This dyslipidemia requires further characterization. The ability of lipoproteins from diabetic plasma to modify cholesterol homeostasis and/or cytokine or growth factor expression in vascular cells should be studied, as should other functional characteristics of these particles. The relation between intra-abdominal obesity and the genesis of diabetic dyslipidemia requires much additional investigation.
Clinical Studies

The study of atherogenesis in diabetes has been impeded in the past by the frequent practice of excluding diabetic subjects from studies of atherosclerosis, its evolution, and treatment. While this has probably been appropriate, it may now be timely to study atherosclerosis in diabetic subjects. For such studies there is a great need, as there is in the study of human atherosclerosis generally, for better methods of noninvasive imaging and quantification of atherosclerotic lesions.

The role of lipoprotein oxidation should be studied in diabetic subjects. Since oxidant stress appears to be increased and antioxidant levels decreased in the diabetic state, this may be an ideal context in which to test the oxidation hypothesis of atherosclerosis, e.g., by performing a clinical trial of antioxidants.

The Effect of Glycemic Control on Macrovascular Endpoints in Non–Insulin-Dependent Diabetes Should Be Studied

- The role of AGEs in the atherogenesis of diabetes should be studied. A trial of aminoguanidine should be considered after preliminary studies in a suitable animal model.

- Obesity so often accompanies non–insulin-dependent diabetes and its concomitant dyslipidemia that a more concerted effort to better understand appetite and body weight regulation would benefit the large atherosclerotic diabetic population.

In summary, this workshop has highlighted the need to proceed with fundamental cell and molecular studies of both atherosclerosis and diabetes and to apply these studies to the development of a suitable animal model for more refined investigations of the mechanisms that underlie the accelerated atherosclerosis in diabetes. There is a need to explore the role of hyperinsulinism in diabetes to characterize and study the prediabetic state, especially in animals where the unique influences of diabetes on vascular responses can be explored, and to undertake clinical studies on the role of oxidation, AGEs, obesity, and glycemic control on the evolution of atherosclerosis and its treatment.
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