About 45 years ago George Lyman Duff, together with Gardner McMillan, presented a paper called “The Effect of Alloxan Diabetes on Experimental Cholesterol Atherosclerosis in the Rabbit” at the Second Annual Meeting of the American Society for the Study of Arteriosclerosis, and two papers describing that work were subsequently published in the Journal of Experimental Medicine in 1949. Since the initiation of the George Lyman Duff Memorial Lecture 35 years ago, this is the first one devoted to atherosclerosis and diabetes, a subject obviously close to Dr. Duff’s interest.

The importance of atherosclerosis in diabetes is clear. Since the beginning of the insulin era, the proportion of total deaths from coronary heart disease (CHD) in diabetes has progressively increased to the point where now almost three fourths of deaths among diabetics are attributable to CHD. Recent data from the Joslin Clinic indicate that by age 50, fully one third of male and female individuals with insulin-dependent diabetes mellitus (IDDM) have already died from CHD, a proportion far exceeding that observed in an age-matched non-diabetic cohort. Although CHD mortality cannot be directly equated with atherogenesis, such data are compelling nevertheless.

Of the risk factors for atherosclerosis in the general population, most of the potentially reversible ones are more prevalent among the diabetic population (Table 1). However, an epidemiological analysis suggests that the contribution of all of the commonly measured risk factors together can account for no more than about 25% of the excess CHD in diabetics. Recent data from the Multiple Risk Factor Intervention Trial, which included more than 5,000 middle-aged diabetic men among the more than 350,000 participants, indicate that while the mortality rate for CHD increases exponentially as a function of serum cholesterol levels in diabetics just as it does in nondiabetics, for every cholesterol level diabetics have threefold to fivefold higher CHD mortality rates (Figure 1). This phenomenon now also has been recorded in women. The Nurses’ Health Study contains almost 1,500 diabetic women among the approximately 115,000 participants. In that study also, diabetic women had about a fivefold increase in CHD incidence rate whether cholesterol levels were low or high. This phenomenon is not restricted to cholesterol levels as the differential in CHD mortality rate between diabetics and nondiabetics is seen whether one considers one, two, or three of the common risk factors (cholesterol level, cigarette smoking, and hypertension). Thus, there is a “black box” that must include features unique to diabetes, not measurable by assessment of the traditional risk factors, that contribute to the differential in CHD. In an attempt to shine some light into this black box, I first would like to examine changes in the traditionally measured risk factors that might be occurring in diabetes, other than their increased prevalence.

**Dyslipidemia**

With regard to plasma lipid and lipoprotein levels, it is clear that high plasma triglyceride levels, usually increased in persons treated for diabetes (both IDDM and non-insulin-dependent diabetes mellitus [NIDDM]), have been consistently shown to be a risk factor for CHD among diabetic individuals in cross-sectional studies. This is in contrast to the controversy over the role of hypertriglyceridemia as a CHD risk factor in nondiabetic populations. There is now an 11-year prospective study from Paris indicating that higher triglyceride levels among diabetics increase their risk of developing CHD. Hypertriglyceridemia in diabetes can be associated with a variety of changes in circulating lipoproteins (Table 2).

Chylomicronemia may be seen in poorly controlled diabetics, but from the work of Nordestgaard et al, it appears that chylomicrons are too large to enter the arterial wall and hence need not be considered atherogenic per se. This may explain the phenomenon, originally observed by Duff and McMillan, that the induction of alloxan diabetes (which produces very large particles) in cholesterol-fed rabbits ameliorates the production of atheroma. Presumably this phenomenon is associated with insulin deficiency-related impairment of lipoprotein lipase. However, very low density lipoprotein (VLDL) and remnants of VLDL and chylomicron catabolism have been associated with deposition of cholesterol ester in arterial wall cells and hence can be considered potentially atherogenic.

We have shown that when equal particle numbers of chylomicron remnants and low density lipoprotein (LDL) are incubated with human arterial smooth muscle cells, remnants are at least as effective as LDL in increasing cholesterol esterification and producing cholesterol ester accumulation (Figure 2). In other studies, VLDL obtained from diabetic donors, whether
hypothesis that hypertriglyceridemic or normotriglyceridemic, appears to be more avidly bound and degraded by mouse peritoneal macrophages than VLDL obtained from normal donors. These in vitro findings indicate that the increased VLDL and remnant concentrations seen in diabetics are potentially capable of increasing cholesterol ester deposition in arterial wall cells.

Last year, we presented results of a study in which the effects of remnant-rich lipoprotein fractions (d<1.019 g/ml) obtained before and after a high-fat meal from normal and diabetic donors on cholesterol ester synthesis in human monocyte-derived macrophages were compared. The remnant-rich lipoproteins from donors with NIDDM, compared with those from controls, significantly increased the incorporation of [14C]oleate into cholesterol esters in both the fasted state and in samples obtained up to 8 hours after the high-fat meal. This was not due to differences in medium cholesterol concentration in the added lipoprotein fractions as the concentrations were comparable in NIDDM and control incubations. However, apolipoprotein (apo) E concentrations were significantly increased in all medium samples from donors with NIDDM. Further, the apo E-to-apo B ratio in the plasma triglyceride-rich lipoprotein fractions from donors with NIDDM was significantly increased before and at all times after eating. Density gradient ultracentrifugation indicated that the increased apo E concentration seen in d<1.019 g/ml lipoproteins from diabetic donors was distributed across all the lipoproteins in that density range. The [14C]oleate incorporated into cholesterol esters was significantly correlated with medium apo E concentrations in all incubations containing lipoproteins from normal and diabetic donors (R=0.48, p<0.001, n=65). Thus, increased cholesterol ester deposition in macrophages incubated with triglyceride-rich lipoproteins from donors with NIDDM may be partly explained by the increased concentration of apo E. Thus, remnants and VLDL may be particularly atherogenic in diabetes, largely due to increased apo E content of the particles. This proposed mechanism remains speculative, however, and requires further investigation.

LDL and high density lipoprotein (HDL) can become triglyceride rich as a direct function of hypertriglyceridemia. Hiramatsu et al have shown that the LDL triglyceride-to-cholesterol ester ratio is increased in hypertriglyceridemia, whether or not diabetes is present. Diabetes without hypertriglyceridemia is not associated with triglyceride enrichment of LDL. These triglyceride-rich LDLs have an altered interaction with cultured fibroblasts, demonstrating decreased binding and a reduced ability to internalize cholesterol, as reflected by their impaired ability to downregulate cholesterol synthesis. The degree of triglyceride enrichment of HDL is also a direct function of plasma triglyceride, whether the fractions are from nondiabetic or diabetic donors. The functional significance of triglyceride enrichment of HDL has yet to be fully elucidated.

With regard to LDL, Brunzell has shown by density gradient ultracentrifugation that lipoprotein fractions obtained from persons with NIDDM lose their typical sharp LDL peak and instead have a broad diffuse LDL band (which Fisher had earlier termed "polydisperse LDL"), which when dissected appears to represent an increase in the intermediate density lipoprotein (IDL) concentration, a loss of the normal LDL peak, and an increase in the amount of dense LDL. While small dense LDL particles have been associated with CHD in the general population, no studies of this association in diabetes have been reported.

More than 20 years ago Bagdade, Porte, and I reported a syndrome that we called diabetic lipemia, characterized by an increased concentration of chylomicrons in the circulation associated with an acquired deficiency of postheparin lipoprotein lipase activity in plasma in the untreated, insulin-deficient diabetic. We can now characterize the diabetic dyslipidemia syndrome in the treated NIDDM patient (Table 3), consisting of increased plasma VLDL and remnant levels, an increase in the apo E concentration in VLDL and remnants, an increase in the amount of small dense LDL, and an altered HDL particle distribution. The
latter has been characterized by Cheung and Wolf\textsuperscript{22} using gradient gel electrophoresis, which separates apo A-I–containing particles into those without apo A-II (Lp AI) and those that also contain apo A-II (Lp AI/All). The patterns obtained from donors with NIDDM show a decrease in larger lipoprotein particles in the Lp AI fraction (consistent with a decrease in HDL\textsubscript{2b} seen after ultracentrifugation) and a shift to smaller particles in both Lp AI and Lp AI/All (M. Cheung, unpublished observations; Figure 3). These changes appear to be unique and not simply consequences of hypertriglyceridemia. Thus, the first entry in the black box (Figure 4) could be abnormalities of apolipoprotein and lipoprotein particle distribution (diabetic dyslipidemia).

Although there can be marked differences in lipoprotein changes seen in IDDM and NIDDM, both are associated with accelerated atherosclerosis. Therefore, other factors, perhaps common to both types of diabetes, need to be explored in detail.

**Procoagulant State**

While considering altered lipoproteins in diabetes, it should be noted that hypertriglyceridemia is associated with an increase in the clotting activities of thrombogenic factors, such as factor VII and factor X, and a decrease in the concentration of the inhibitor of tissue plasminogen activator (PAI-1) (Table 4).\textsuperscript{23} These changes, in association with the well-known increased platelet aggregation in vitro,\textsuperscript{24} would contribute to a procoagulant state in diabetes.

Lipoprotein(a) [Lp(a)] may play a role in atherogenesis in diabetes via its contribution to a procoagulant state. Because Lp(a) shares considerable sequence homology with plasminogen, but not its thrombolytic effect, Lp(a) may block plasminogen's action in stimulating clot lysis. During the past year there have been a plethora of reports that Lp(a) concentrations are increased in diabetic patients with proteinuria. For example, in data from Takegoshi and colleagues,\textsuperscript{25} Lp(a) concentrations increased progressively with the degree of albuminuria, ranging from microalbuminuria, to marked proteinuria, to frank chronic renal failure. Half of their diabetics with proteinuria had Lp(a) levels in excess of 30 mg/dl. Such levels are strongly associated with CHD in nondiabetic populations. The relevant in vitro actions of Lp(a) include the inhibition of plasminogen binding and activity and the stimulation of PAI-1 gene expression.\textsuperscript{26} If these effects occur in vivo, they would potentially contribute to the procoagulant state in diabetes (Figure 4). More information concerning the role of Lp(a) in atherogenesis in diabetes appears to be essential.
Atherogenesis In Diabetes: The "BLACK BOX"

- Abnormalities of apoprotein and lipoprotein particle distribution ("diabetic dyslipidemia")
- Procoagulant state
- Insulin resistance and hyperinsulinemia
- Glycation and advanced glycation of proteins in plasma and arterial wall
- "Glycoxidation" and oxidation
- Hormone, growth factor, and cytokine enhanced smooth muscle cell proliferation and foam cell formation

Hyperinsulinemia

Hyperinsulinemia now can be considered a potent risk factor for CHD. In three large population studies from around the world (Helsinki, Paris, and Busselton, Australia) high insulin levels have been shown to be associated with increased incidence and mortality rates of CHD.27-29 The Paris Prospective Study now has a 15-year follow-up of approximately 6,900 healthy men, showing that the annual CHD mortality rate is significantly higher in those healthy individuals who had fasting plasma insulin levels in the highest quintile.29

A question therefore emerges from these population studies: Is insulin atherogenic? This is a particularly relevant question for diabetic patients in whom endogenous insulin levels are usually increased (NIDDM) or peripheral circulating insulin levels are elevated as a result of intermittent injections of large amounts of exogenous insulin (IDDM). Cross-sectional studies of diabetic populations show a phenomenon similar to that observed in the general population. Whether fasting levels of insulin or of connecting peptide (C-peptide, the cleavage product of proinsulin during insulin secretion) are measured, those diabetics with CHD have higher levels than those diabetics without CHD.30-32

Hyperinsulinemia in both normal persons and those with NIDDM appears to be related to obesity. More than 20 years ago we showed that insulin levels, both in the fasted state and after a glucose load, are elevated in obese individuals, whether normal or diabetic, as a function of the degree of obesity.33 Therefore, hyperinsulinemia takes its place among the many risk factors for CHD associated with obesity (Table 5), and we now appreciate that insulin plays a role in modulating all of these obesity-related risk factors. It has recently become apparent that the adverse metabolic consequences of obesity, including hyperinsulinemia, are related to the regional distribution of body fat. Visceral abdominal obesity (rather than subcutaneous or lower-body obesity) appears to be a determinant of these consequences.34,35 The dyslipidemia associated with abdominal adiposity appears to be similar to the dyslipidemia seen in the treated diabetic, i.e., increased concentrations of small VLDL and IDL, presence of small dense LDL particles, and decreased concentrations of HDL2.36 In subjects with both obesity and diabetes, LDL particle size is independently correlated with plasma triglyceride and with insulin levels.37 Thus, the degree of adiposity and the concomitant insulin resistance with hyperinsulinemia are associated with small dense LDL, independent of hypertriglyceridermia, which is also associated with small dense LDL.

Thus, insulin resistance and hyperinsulinemia appear to play a central role in the pathogenesis of atherosclerosis in diabetes (Figure 5). Increased visceral abdominal adiposity is associated with insulin resistance and compensatory hyperinsulinemia. How intraportal adipose accumulation produces insulin resistance in liver and muscle is the subject of current intense investigation and speculation. Nonetheless, in those individuals who are genetically prone to develop NIDDM, this need for increased insulin production to overcome insulin resistance could unmask a genetic defect producing clinical NIDDM. It has also been proposed that NIDDM is associated with insulin resistance and hyperinsulinemia independent of an increase in abdominal fat.38 Hyperinsulinemia in turn is associated with dyslipidemia (increased VLDL, decreased and altered HDL, and small dense LDL) and with hypertension.
both potent risk factors for atherosclerosis. This array of abnormalities and disorders can best be termed the insulin resistance syndrome (rather than syndrome A, Z, or X), a syndrome that has been described and redescribed since the original observations of Vague and Albrink and Meigs more than 25 years ago.

Insulin resistance syndrome itself can affect the arterial wall directly, producing changes that are compatible with enhanced atherogenesis. Direct effects of insulin on the arterial wall potentially include the promotion of both arterial smooth muscle cell proliferation and cholesterol ester accumulation. Insulin in physiological concentrations can stimulate proliferation of human and nonhuman primate arterial smooth muscle cells. Insulin also increases LDL receptor activity in vitro, which could lead to delivery of more plasma cholesterol to cells despite having the potential to lower circulating LDL concentrations. These actions of insulin in cell culture do have in vivo significance, since monocytes freshly isolated from subjects before and after a 4-hour hyperinsulinemic euglycemic clamp show enhanced LDL degradation and since both endogenous and exogenous insulin can accelerate the removal of injected LDL. Therefore, insulin, along with other growth factors, can potentially increase intracellular cholesterol stores by decreasing HDL receptor-mediated cholesterol efflux (Figure 6). Thus, glycated HDL may be functionally abnormal. Being immunogenic, glycated LDL accumulates in plasma and may enhance cholesterol ester accumulation in macrophages. We have recently shown that glycation of HDL impairs its functional ability to bind to the HDL receptor binding site on cells and to promote intracellular cholesterol efflux (Figure 7). Thus, glycated HDL may be another factor potentially contributing to arterial cell cholesterol ester accumulation. However, the concentration of circulating glycated lipoproteins is relatively small, and their role in the arterial wall in vivo needs to be elucidated.

Glycation of lipoproteins and other proteins involves nonenzymatic formation of Amadori products. As a result of the browning (Maillard) reaction, these products can be further processed with the formation of cross-links to advanced glycosylation end products (AGEs). A particular cross-link involving pentosidine has been described by Sell and Monnier, cross-linking arginine to lysine on proteins yielding fluorescent products. Other AGEs such as carboxymethyllysine can be formed by oxidation, and because Amadori adducts are a ready source of superoxide, it appears that glycation of protein enhances its potential for oxidative damage.

| Table 6. Lipoprotein Modifications in Diabetes Affecting Cell Interactions |
|--------------------------|--------------------------|
| Glycosylation            | Oxidation                |
| Chemical modification    | Alterations in lipid composition |
|                         | Core                     |
|                         | Increased triglyceride   |
|                         | Decreased cholesterol ester |
|                         | Surface                  |
|                         | Increased free cholesterol |
|                         | Alterations in apolipoprotein composition |
Collagen subjected to advanced glycosylation will avidly bind LDL as a function of the degree of glycosylation. Vlassara and colleagues have described in a series of studies the multiplicity of ways in which AGEs could be involved in atherogenesis (Table 7). One of the more exciting possibilities is that aminoguanidine, which blocks formation of cross-links in AGE proteins, can markedly inhibit the development of experimental atheroma in rabbits, as reported in a recent abstract. Therefore, glycation and advanced glycation of protein in plasma and the arterial wall deserves to take its place among the factors that are potentially involved in atherogenesis in diabetes (Figure 4). Although the concentration of AGE proteins normally increases with age in skin collagen, their formation is markedly accelerated in diabetes. A recent report documents an increase in the concentration of AGE proteins in the arterial wall of diabetics compared with matched nondiabetics.

![FIGURE 7. Plot of effect of control (○) and glycosylated (●) high density lipoprotein subfraction 3 (HDL3) on cholesterol esterification by human skin fibroblasts. Thirty-eight percent of free lysine residues on HDL3 were glycosylated. [14C]oleate esterification into cholesteryl ester was quantified after cells were pulse-labeled with [14C]oleate for 1 hour at 37°C, giving an indirect assessment of changes in the size of the intracellular pools of cholesterol that are in equilibrium with substrate for acyl coenzyme A cholesterol transferase. Data from Duell et al.52 *p<0.001 versus control HDL3; **p<0.003 versus no HDL3.](http://atvb.ahajournals.org/)

### TABLE 7. Potential Role of AGE in Atherogenesis

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE accumulation in artery wall: Low density lipoprotein trapping</td>
</tr>
<tr>
<td>Endothelial cell changes</td>
</tr>
<tr>
<td>Permeability</td>
</tr>
<tr>
<td>Cell adhesion</td>
</tr>
<tr>
<td>Procoagulant state</td>
</tr>
<tr>
<td>Monocytes/macrophages</td>
</tr>
<tr>
<td>Chemotaxis and activation</td>
</tr>
<tr>
<td>Cholesterol ester accumulation</td>
</tr>
<tr>
<td>Cytokine/growth factor secretion</td>
</tr>
<tr>
<td>Smooth muscle cell proliferation</td>
</tr>
<tr>
<td>Prevention of experimental atheroma by aminoguanidine</td>
</tr>
<tr>
<td>Hyperinsulinemia: Decreased AGE receptor sites</td>
</tr>
</tbody>
</table>

AGE, advanced glycosylated end products.

### TABLE 8. Factors Promoting Lipoprotein Oxidation in Diabetes

- Auto-oxidative glycosylation (glycoxidation)
- Production of free radicals
- Reduced antioxidant defense systems

### Lipoprotein Oxidation

There are a number of factors that promote lipoprotein oxidation in diabetes (Table 8). Auto-oxidative glycosylation, or glycoxidation, are terms describing the proposed role of reducing sugars as catalysts for the oxidative modification and cross-linking of protein. This process is expected to be enhanced in the presence of high glucose concentrations. A role for increased production of free radicals and lipid peroxidation also has been proposed. Coupled with a pro-oxidative potential is a decrease in antioxidant defense systems, since it is well known that concentrations of ascorbate, for example, are uniformly decreased among diabetics. In preliminary studies we have shown that in contrast to LDL obtained from normal subjects, in samples obtained from subjects with NIDDM, LDL susceptibility to oxidation is dependent on the vitamin E concentration in plasma. This is presumably due to the very low levels of ascorbate, since ascorbate protects against the consumption of vitamin E and renders lipoproteins less susceptible to oxidation. In concert with the idea that lipoprotein oxidation is enhanced in diabetes, Morel and Chisolm reported that VLDL and LDL obtained from rats with streptozotocin-induced diabetes had markedly increased thiobarbituric acid–reactive substances and that these lipoproteins were cytotoxic. These lipoprotein changes could be prevented by treatment of the animals with the antioxidants probucol or vitamin E. In preliminary studies (S. Zambon, J. Oram, and E.L. Bierman, unpublished) we have shown that HDL can be oxidized and that this alteration produces functional changes, including an apparent inability of HDL to lower the cholesterol ester content of cholesterol-loaded macrophages. Similar observations have recently been reported. Thus, oxidation of lipoprotein is enhanced in diabetes and can potentially contribute to atherogenesis.

### Other Lipoprotein Modifications

Alterations in core lipid and apolipoprotein compositions have been addressed earlier (Table 6). Increased concentrations of free cholesterol on lipoprotein particles in diabetes have consistently been observed, perhaps related to abnormalities in cholesteryl ester transfer. The plasma free cholesterol-to-lecithin ratio, an impressive index of CHD risk, is typically increased in both IDDM and NIDDM due to changes in all lipoprotein classes. These compositional changes might affect lipoprotein interaction with artery wall cells by either enhancing delivery of free cholesterol to cells or altering reverse cholesterol transport.

### Cell Biology

Finally, a review of the cell biology of atherosclerosis indicates the multiplicity of roles of hormones, growth factors, cytokines, and oxidized LDL on enhanced smooth muscle cell proliferation and macrophage foam cell formation (Figure 8). Diabetes can play a role in
FIGURE 8. Simplified view of the cell biology of atherogenesis. Possible sequence of events is indicated by arrows depicting lipoprotein–cell and cell–cell interactions in the arterial intima (above the dashed line). ASMC, arterial smooth muscle cell; GF, growth factors; CSFs, colony stimulation factors; MCP, monocyte chemotactic protein; LDL, low density lipoprotein; HDL, high density lipoprotein; PDGF, platelet-derived growth factor.

Many steps along this pathway (Figure 9), including enhanced susceptibility to endothelial injury and less efficient endothelial cell repair mechanisms; propensity to oxidation of LDL; and low density lipoprotein–cell and monocyte recruitment; accumulation of AGE proteins, contributing to cytokine production and monocyte recruitment; formation of lipoprotein–immune complexes, contributing to cholesterol ester formation in macrophages; other lipoprotein modifications in diabetes that can produce cholesterol ester accumulation; and last but not least, impairment of receptor-mediated cholesterol efflux from arterial smooth muscle cells and macrophages by insulin and/or growth factor effects and by glycation and/or oxidation of HDL. Thus, enhanced proliferation of arterial smooth muscle cells and foam cell formation in macrophages produced by hormones, growth factors, and cytokines deserve to be included in the black box (Figure 4).

Overview

This list is undoubtedly incomplete. Atherosclerosis in diabetes is clearly multifactorial, but several potential mechanisms stand out and are in need of further focus. Foremost would be the unique effects of hyperglycemia mediated through the mechanisms of protein glycation and glycoxidation. There has not been an adequate clinical trial of glucose lowering and atherosclerosis outcomes. The current Diabetes Control and Complications Trial in subjects with IDDM is not designed to focus on atherosclerosis end points, although some risk factor information will be forthcoming. A focused trial of intensive glucose lowering in NIDDM using quantitative angiography is feasible and should be a high priority.

Comparably, the unique dyslipidemia of NIDDM is likely to be a significant factor and is subject to manipulation. For example, lipid-lowering agents that reduce triglyceride levels, increase lipoprotein particle size, and reduce apo B and E levels should be considered in pilot trials. Antihypertensive drugs that improve diabetic dyslipidemia (a-adrenergic blockers) or reduce microalbuminuria (angiotensin converting enzyme inhibitors) might prove valuable adjuncts in preventing atherosclerosis. As drugs are developed that can lower the Lp(a) level, they should be tested in diabetics with high Lp(a) levels and progressing proteinuria, since such individuals are highly prone to develop CHD.

Evidence continues to accumulate supporting the role of oxidized lipoproteins in atherogenesis. Because oxidant stress is high in diabetes and antioxidant protection (e.g., ascorbate concentration) appears to be reduced, a possible trial of antioxidant treatment of diabetes could be evaluated.

I have not addressed the relation of diabetes to the various stages of atherogenesis (i.e., fatty streak forma-
tion, conversion to fibrous plaques, plaque complications) and to CHD mortality related to changes in the myocardium. Relatively little is yet known in these areas that would warrant more than speculation.

Thus, in this review I have tried to open a window on this black box. Much more enlightenment is needed. Taking my cue from the popular software “Windows” environment (Figure 10), the atheroma icon can be focused at will at any of the proposed mechanisms for further study. The file can be used for untenable hypotheses, and perhaps some usable ones can be retrieved. I have suggested that the list is incomplete and that many more options for explaining accelerated atherogenesis in diabetes exist. More windows will shed more light. Help

**Figure 9.** Schematic presentation of potential effects of diabetes on multiple steps in atherogenesis. Asterisks indicate sites that can be modified in diabetes. AGE, advanced glycosylated end products; ASMC, arterial smooth muscle cell; CSFs, colony stimulation factors; GF, growth factors; HDL, high density lipoprotein; LDL, low density lipoprotein; MCP, monocyte chemotactic protein; PDGF, platelet-derived growth factor.

**Figure 10.** “Windows” version of black box.
from investigators in a variety of disciplines is needed to further explain the process, with the ultimate aim of preventing or reversing the remarkably excessive toll from CHD in diabetes mellitus.

Acknowledgments

Several centuries ago, the poet John Donne wrote that “no man is an island...” This famous phrase is now no more applicable than it is to biomedical science today. The author has been blessed over the years with a group of stimulating and productive research fellows and outstanding colleagues and collaborators. Without their contributions, much of this work would not have been possible. Particular mention is made of the individuals who have contributed to the more recent work cited in this lecture, including J. Brunzell, A. Chait, M. Cheung, J. Oram, R. Braag, E. Brinton, P. Dubb, M. Eto, C.-H. Flórez, K. Hirama, A. Mendez, M. Oppenheimer, J.P. Slotts, and S. Zambon.

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E L Bierman


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