Nonenzymatic glycation of protein and accumulation of Maillard reaction products, known as advanced glycosylation endproducts (AGEs) (1) or glycoxidation products (2), contribute to the age-dependent chemical modification and cross-linking of tissue proteins. Accelerated modification of long-lived proteins during hyperglycemia is implicated in the pathogenesis of cataracts, nephropathy, and vascular disease in diabetes (1, 2). Miyata et al. (3) also showed recently that AGEs accumulate on β_2-microgloblin (β_2M) in amyloid deposits in patients with hemodialysis-associated amyloidosis (HAA), and proposed that AGE-β_2M elicits the inflammatory response leading to bone/joint destruction in HAA. While most studies on AGE proteins have focused on long-lived, extracellular proteins, Bucala et al. (4) detected AGEs in both the protein and lipid components of plasma low density lipoproteins, and Makita et al. (5) measured AGEs on hemoglobin in red cells. In this issue of *The Journal,* Giardino et al. (6) extend our understanding of the Maillard reaction by showing that AGEs are also formed on intracellular proteins, including bovine fibroblast growth factor (bFGF) isolated from endothelial cells (EC) grown in vitro. The authors demonstrate that AGE-modification of cytosolic proteins increases over 10-fold within one week in EC grown in high (30 mM), compared with normal (5 mM), glucose medium, and that bFGF isolated from EC grown in high glucose has about sixfold more AGEs and 70% lower mitogenic activity than bFGF isolated from cells grown in low glucose. Parallel studies on modification of bFGF by fructose and glyceraldehyde-3-phosphate confirm that AGE-bFGF, prepared in vitro, also has decreased mitogenic activity.

bFGF is described as a "wound hormone for rapidly initiating cell growth required for routine maintenance of tissue integrity and/or repair after injury" (7). Giardino et al. (6) suggest that the intracellular AGEing of bFGF in diabetes yields a protein with decreased mitogenic activity, and that the failure of this AGE-bFGF to support an adequate protective response to the metabolic and chemical stresses associated with diabetes may explain the loss of EC (and pericytes?) from the retinal vasculature, setting the stage for diabetic retinopathy. The rapid increase in AGEs on intracellular proteins of EC grown in high glucose leads the authors to speculate that, instead of glucose, phosphorylated metabolic intermediates, such as glyceraldehyde phosphate, may be the precursors of intracellular AGEs. Smaller sugars and sugar phosphates are more reactive than glucose with protein and, like glucose, their intracellular concentration is increased during hyperglycemia. Dicarbonyl sugars, such as 3-deoxyglucosone and methylglyoxal, which are formed spontaneously from phosphorylated sugars (8, 9), could also be important sources of intracellular AGEs. Interestingly, oxidative stress, induced by hyperglycemia, is implicated in EC dysfunction in diabetes (10) and accelerates the formation of AGEs and glycoxidation products (2). Thus, hyperglycemia and oxidative stress may not only enhance EC injury in diabetes, but, by promoting the AGEing of bFGF, may also limit the EC response to injury, compounding damage to the vascular wall in diabetes.

The studies of Giardino et al. (6) are significant because they focus attention on the role of sugars other than glucose in the AGEing of proteins and the role of AGEing of intracellular proteins in the pathogenesis of diabetic complications. It will be important to confirm the validity of their model by demonstrating that AGE-bFGF is formed in vascular endothelia and that it is significantly increased in patients with vascular disease. Studies on the effects of high glucose medium on the rate of AGE formation in EC from patients differing in susceptibility to retinopathy may also identify critical factors controlling the rate of intracellular AGE formation and development of microvascular disease in diabetes. Identification of the carbohydrate precursors of intracellular AGEs and of critical targets of intracellular AGEing reactions should greatly expand our understanding of the role of the Maillard reaction in the pathogenesis of diabetic complications.

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0021-9738/94/07/0002/01 $2.00
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