The inactivation of NO by advanced glycation endproducts (AGEs), which accumulate on tissue proteins as a function of age and hyperglycemia, focused attention on the role of these ubiquitous posttranslational modifications in acquired impairments of vascular reactivity and other signaling processes. This observation occurred during a watershed period of basic and translational research in glycation that encompassed new pathologic phenomena and novel intervention strategies. How has the AGE paradigm for the tissue complications of aging and diabetes fared since the identification of the link between these glycation products and NO inactivation, and what lessons may be offered for future investigations?

A serendipitous discovery
The discovery of NO as the active constituent of endothelium-derived relaxing factor prompted new lines of investigations into cardiopulmonary physiology, innate immunity, neuroscience, and metabolism (1). The 1991 report published by my team in the JCI that revealed protein glycation adducts, which accumulate with age on long-lived proteins and in greater amounts in diabetes, react with and inactivate NO developed serendipitously (2). During my internal medicine training, Eugene Braunwald taught residents (at the bedside) the variants of anginal syndromes, including those mediated not by luminal obstruction but by an imbalance in vasoactive factors. Following residency, I conducted research with Anthony Cerami in glycation biochemistry that set the stage for considering how the interposition of glycation adducts, which result from the rearrangement of the glucose-derived Amadori reaction on long-lived proteins, could functionally impede NO-mediated vasodilatation. Glycation-mediated protein crosslinking was thought to account for senile cataracts and for age- and diabetes-related decreases in vascular wall compliance and glomerular basement membrane function, and ultimately, it was hypothesized to contribute to a host of age-related phenomena, including systolic hypertension, diastolic cardiac dysfunc-

Targeting AGE-mediated damage
Views of the biologic consequences of glucose-related macromolecular damage expanded substantially in the ensuing years to encompass genotoxic DNA damage (4), aminolipid glycation and oxidation (5), amyloid deposition (6), and intracellular glycation and redox stress (7). The molecules participating in glycation damage also expanded beyond endogenous reducing sugars and their metabolites to include tobacco smoke (8) and diet (9), with each observation lending further support to an overarching AGE hypothesis for the seque-

What lies ahead?
Despite the conceptual promise, why have AGE-directed therapies been disappointing? The financial exigencies of drug development often force clinical testing of the first, but not necessarily the “best,” drug candidate. Better knowledge of the targeted chemical moieties and in vivo pathways for AGE formation and removal is criti-

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such as calcium channel blockers. Despite the availability of quantitative immunoassays and more sensitive and robust liquid chromatography mass spectrometry methodologies, straightforward methods to monitor important AGE intermediates and their progression to macromolecular damage are lacking, especially in living biologic systems. Information about tissue damage remains very dependent on in vitro and in vivo model studies, but even the study of experimental disease may be limited due to evidence that the tissue damage and cross-linking signatures in experimental animals differ from those in long-lived humans (15). Given the explosion of information in medical genetics and genetic modifiers of disease, it could be useful to investigate more closely whether certain individuals are predisposed to rapid or slow progression of AGE damage and whether pharmacologic intervention confers greater benefit in a particular subgroup of individuals. That the many sequelae of aging may be unified in their pathogenesis by glycation, nevertheless, remains highly attractive conceptually and deserves the convergence of continued multidisciplinary investigations. Much remains to be done.

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