Introduction

Diseases of postsynthetic protein modification mediated through nonenzymatic reactions are becoming increasingly recognized.[1] Aspirin donates an acetyl moiety to the reactive site of prostaglandin synthetase and may precipitate a hypocoagulable state in susceptible individuals.[2] Cyanate, when administered orally[3] or when present in excessive amounts as a breakdown product of urea in uremic individuals,[4] can lead to a demyelinating segmental peripheral sensorimotor neuropathy[5,6] and posterior subcapsular cataract formation[7,8] concomitant with carbamylation of the tissues at risk. Acetaldehyde, the primary metabolite of ethanol metabolism, is a highly reactive biologic aldehyde. Acetaldehyde has been shown to form stable adducts with proteins, participate in nonenzymatic browning reactions, and has been hypothesized as a potential mediator of certain sequelae of alcoholism.[9,10]

As early as 1912, Maillard suggested that the chemical reactions that now bear his name might play a role in the secondary sequelae of diabetes.[11] The food industry expressed the greatest interest in these types of reactions due to the recognized changes in food quality and properties following nonenzymatic interaction with carbohydrates. Although chemists concerned with agricultural implications of nonenzymatic glycosylation reactions have characterized a number of these processes, a great deal of the basic chemistry as well as the biologic and toxicologic implications of these reactions remain to be defined.

While workers familiar with food technology are well aware of the chemical reactions associated with browning reactions, the potential for in vivo glycosylation and browning was largely ignored. The biomedical sciences have recently become familiar with in vivo nonenzymatic glycosylation reactions and the Amadori rearrangement,[12] but the subsequent rearrangements with resultant late Maillard or browning reactions and their pathologic implications have been neglected.

The present symposium brought together two groups of investigators. One group tended to have a background in food technology and chemistry while another was concerned primarily with nonenzymatic glycosylation reactions and their relevance to diabetes mellitus. As is detailed in the symposium, nonenzymatic glycosylation of proteins with resultant structural and functional changes has been implicated in a number of pathologic sequelae of diabetes including cataract formation, neuropathy, connective tissue pathology, and early aging.

The glycosylation of erythrocyte and serum proteins has generated considerable clinical interest. The reaction of hemoglobin with glucose is especially interesting since this molecule is exposed to glucose in the internal milieu for the life-span of the erythrocyte (120 days). Therefore, glycosylation with hemoglobin A_{1c} formation provides not only a biochemical model for glycosylation resulting in structural and functional changes in proteins[12] but also a useful marker for monitoring blood glucose concentration over time. Other serum proteins may be useful as clinical markers over a shorter time period as well. Serum proteins and hemoglobin are also conceptually important as indicators of which proteins in the organism are vulnerable to glycosylation. Proteins such as serum proteins will be constantly vulnerable to the changes in circulating glucose levels but must themselves circulate for an appropriate period of time for glycosylation to take place. Intracellular proteins such as hemoglobin must reside in cells that are not totally dependent on insulin concentrations for the development of excess glucose or biologically reactive aldehydes in their internal milieu. The fact that glucose is one of the least reactive of the aldohexoses may be of evolutionary significance.[13]

The use of glycosylated proteins as markers for hyperglycemia has permitted a more accurate assessment of ambient glucose levels over time. These measurements have in turn stimulated investigators to readdress the question of the relationship of glucose "control" to the pathology of diabetes mellitus.[14] These latter studies have in turn stimulated increasing interest in means by which improved glucose levels can be achieved in hyperglycemic individuals.[15]

Those present at the symposium became convinced that

they were meeting on the tip of an iceberg. The chemistry of glycosylation was much broader in its implications than had been appreciated by those in the biomedical sciences, and the in vivo potential for reactions that had formerly been considered only in in vitro systems was exhilarating to those involved in organic and food chemistry.

Diabetes mellitus does appear to be, in part, a disease of postsynthetic protein modification. The extent to which nonenzymatic processes contribute to the protean sequelae of the disease will be increasingly defined over the next decade. Of special interest to clinicians is the concept that other biologically active aldehydes may play similar roles. The studies of glycosylation reactions in diabetes have implications of potential import to the clinical syndromes of uremia and alcohol abuse as well.

An interdisciplinary symposium of this nature is difficult to initiate and translate into reality. The Kroc Foundation provided the support, facilities, and spirit of collegiality that erased the barriers of individual scientific disciplines. Perhaps the most notable manifestation of appreciation by the participants was their relative inability to terminate, as many began to look forward to "Nonenzymatic Glycosylation and Browning II."

The following persons attended the conference:

Wendy J. Fantl, Rockefeller University, New York, New York

Paul-André Finot, Nestlé Research Department, La Tour-de-Peilz, Switzerland

Mendel Friedman, U.S. Department of Agriculture, Berkeley, California

David E. Goldstein, University of Missouri, Columbia, Missouri

Thomas Huff, University of Georgia, Athens, Georgia

Laurence Kennedy, Royal Victoria Hospital, Belfast, Northern Ireland

Robert R. Kohn, Case Western Reserve University, Cleveland, Ohio

Tung-Ching Lee, University of Rhode Island, Kingston, Rhode Island

Donald E. McMillan, Sansum Medical Research Foundation, Santa Barbara, California

Gary E. Means, Ohio State University, Columbus, Ohio

Vincent M. Monnier, Rockefeller University, New York, New York

Charles M. Peterson, Rockefeller University, New York, New York

Miriam Saltmarch, Virginia Polytechnic Institute and State University, Blacksburg, Virginia

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