symptomatic CFS patients. We found elevated levels of both metabolites as shown in Table 1. Though preliminary, these findings support the abnormally early intracellular acidosis reported in other CFS patients during exercise[3 4] and now specifically identifies elevated levels of pyruvate and lactate.

References

1. Buist RA: New Light on Chronic Fatigue Syndrome. /. *Orthomol. Med.* 3(3) 146-149 (1988).
2. Mukherjee TM, Smith K, Maros K: Abnormal Red-Blood-Cell Morphology in Myalgic Encephalomyelitis. *Lancet 2,* 328-329 (1987).
3. Arnold DI, Radda GK, Bore PJ, Styles P, Taylor DJ. Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion/fatigue syndrome. *Lancet* 1, 1367-1368 (1984).
4. Behan PO, Behan WMH, Bell E J: The post-viral syndrome — an analysis of findings in 50 cases. /. *Infections* 10, 211-222 (1985).

Glycosylation: A New Cross-Linking Process

Dr. G. E. Schuitemaker[1]

1989 will be a very important year for health care in The Netherlands, especially in relation to cancer. The Dutch Cancer Society has begun to accept free radical pathology as one of the important underlying mechanisms for the development of cancer and other degenerative diseases. Directly connected with this is the increasing concern in Europe for the environmental problems. As in other parts of the world, the environment is the issue for the nineties. The Dutch Cancer Society is now initiating research to study the influence of pollutants on health with free radicals as intermediates. The recommendation of the Dutch Cancer Society to add antioxidants such as beta-carotene, vitamins C and E, and selenium to foods is revolutionary. I believe that within three years the free radical pathology will be generally known and accepted by Dutch health professionals (i.e. physicians and pharmacists). This may be a new era in respect to the viewpoints of professionals towards health and disease, and may even lead to the introduction of nutrients in prevention and therapy of degenerative diseases.

Advanced Glycosylation Endproducts (AGEs)

Free radical pathology has been accepted in Orthomolecular medicine for years. It has been known that free radical reactions underlie the cross-linking process. More evidence reveals that there is also another mechanism which is involved in cross-linking reactions, known as glycosylation.[1 23] Glycosylation is a non-enzymatic conversion in the body of glucose and protein molecules into AGEs. In organic chemistry this is known as the Maillard reaction: an aldehyde (like glucose) and protein produce a Schiff base, which is a rather unstable molecule and reacts again with glucose to form the so called Amadori products. The Amadori products are able to cross-link to form yellow-brownish substances, the AGEs. Not only proteins seem to be susceptible to glucose, but nucleic acid molecules can also be involved in this reaction, which may have consequences for the functioning of the immune system.[4]

Diabetic Cataract

The interesting point is that yellow-brownish substances have been found in cataract eyes. These substances have been confirmed to be AGEs by fluorescence spectrometry. Cataracts, a troubling of the eye lens, is a typical consequence of cross-linking. Diabetics are at higher risk in developing cataracts. This has been attributed to sorbitol, which is formed when the glucose concentration is too high.

1. European Institute for Orthomolecular Science, P.O. Box 420, 3740 AK Baarn, The Netherlands.

Sorbitol then precipitates in the lens. But the glycosylation process might be a second mechanism in the development of cataracts. Because the glycosylation reaction is dependent on the concentration of glucose, we can understand why diabetes predisposes for cataracts, but we can take preventive measures. It is of utmost importance to keep blood glucose on a constant level within the normal ranges. High values give a greater chance for the formation of AGEs.

Other Complications

There are other places in the body where glucose comes in contact with protein so that AGEs might be formed. Glomerulopathy of the kidneys is also a complication of diabetes. Obduction shows us that diabetic glomerulopathy is histologically seen as a thickening on the cellular level. Connective tissue is formed, very probably as a consequence of glycosylation and thus giving cross-linking. Blood vessel walls are involved in a third complication of diabetes, micro-angiopathy.

Blood Circulation

The glycosylation mechanism has very important consequences for health. In the blood stream, glucose as well as all kinds of proteins circulate freely, not only the lipoproteins, which transport cholesterol and other fatty substances (linked to the genesis of atherosclerosis), but also proteins which have a function in the immune system, such as super-oxide dismutase. It has been shown that SOD of erythrocytes react with glucose.[5] This glycosylated SOD, which has a lower activity than free SOD, has been found in significantly greater quantities in erythrocytes of diabetics than in non-diabetics. The substrate of SOD is the super-oxide anion and a number of studies has shown that the super-oxide anion concentration was higher in the case of diabetes.[2] Also other substances which have a free radical scavenging activity are connected to diabetes. The concentration of vitamin E in blood platelets was decreased 66% in diabetes induced rats. This process was reversible by supplementation. Experiments with mice have shown that macrophages have a high affinity for AGEs. AGEs were bound to the protein
membranes of red blood cells and it was seen that these blood cells were eliminated more rapidly than normal cells.[4] Perhaps AGEs are involved in a 'recognition mechanism' for cleaning up old cells by macrophages. It has been shown that the number of receptors for AGEs on macrophages decreased with age.

Conclusion

It seems glycosylation is a second very important pathologic mechanism, underlying degeneration, especially in relation to circulation disorders and diseases such as diabetes. Next to the free radical pathology, knowledge of the glycosylation mechanism gives us a further clue to disease. The pharmaceutical industry has started to research these mechanisms. Needless to say, the industry will try to find patentable drugs which scavenge free radicals and which prevent the formation of AGEs. This new research seems to be more in accordance with basic health principles than was the research of the past thirty years, in which the suppression of symptoms was the most important aim. The 4th International Symposium on the Maillard reaction: relevance to food processing, nutrition and physiology, will be held September 5-8,1989 in Lausanne, Switzerland.

References

1. Adrian J: La reaction de Maillard. Le phe-nomene chimique et le phenomene biolo-gique. *Dietetique et Medecine,* 14, 1987, nr. l,p.3.
2. Lestradet H: La glycosylation non enzyma-tique. Biologie - Pathologic *Dietetique et Medecine,* 14, 1987, nr. 1, p. 17.
3. Brownlee M, et al: Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N. Engl. J.* Med., 318(1988), p. 1487.
4. Cerami A, Vlassara H, Brownlee M: Glucose and ageing. *Scientific American,* May 1987.
5. Oberly LW: Free radicals and diabetes. *Free Radical ir Biological Medicine,* 5 (1988), nr. 2, p. 113.