Letter to the Editor

Protein glycation after return to normoglycaemia: implications for mild, repetitive hyperglycaemia

Dear Sir,

The effect of chronic hyperglycaemia in glycating body proteins is generally agreed to contribute to the secondary consequences of diabetes mellitus [1, 2]. But it is not widely recognised that even if there is a rapid return to normoglycaemia, the later more damaging stages of the glycation sequence cannot be avoided. In vitro work shows that the initial glucose-protein adduct formed in the presence of excess glucose, is converted to its more reactive and permanent forms (Amadori product and crosslinked aggregates) by internal molecular rearrangements that do not require free glucose [3, 4]. These later glycation products tend to accumulate on proteins with low turnover. So in vivo, even brief hyperglycaemic episodes could lead to cumulative and irreversible damage, particularly if they occur often. Repeated hyperglycaemic episodes are common in poorly controlled diabetic patients and (see below) in kidney patients undergoing regular dialysis.

Our preliminary data indicate that the later stages of glycation are glucose-independent in vivo as well as in vitro. Figure 1 shows the conversion of plasma proteins to their Amadori product, in a ketotic diabetic patient returning to normoglycaemia. The most striking point is that Amadori product levels continue to rise as glucose levels fall. This behaviour would be expected from the published rate constants for in vitro glycation [5] but has not to our knowledge been reported for in vivo glycation. This is probably because observations are seldom made in the critical time period i.e. 20–80 h after a glucose challenge. If the Amadori product continues to form after return to normoglycaemia, this could explain why a tendency to even mild hyperglycaemia can double the risk of stroke and coronary heart disease [6]. In this Whitehall study, subjects with 2 h blood glucose levels of 5.4–11.0 mmol/l (following a 50 g oral glucose intake) came into this risk category. We have found that similar glucose levels can be induced in non-diabetic patients by haemodialysis. We compared pre- and post-dialysis levels of plasma glucose in a random sample of non-diabetic kidney patients undergoing routine dialysis for 6 h periods. The dialysis fluid was 11.1 mmol/l (200 g/l) in glucose. Although diabetic patients were rigorously excluded from the analysis on the basis of clinical history and pre-dialysis glucose levels, we found that in 39% of cases, plasma glu-

cose levels rose during dialysis to 7.4 mmol/l or more ($n=71$). In 14% of cases, post-dialysis levels rose to 9.0 mmol/l or more. There was no correlation between post-dialysis glucose levels and age.

Although this hyperglycaemia is comparatively mild, we may assume that glucose-independent reactions continue after return to normoglycaemia, as shown in Figure 1. So, frequent hyperglycaemic episodes which occur in patients undergoing regular dialysis, having impaired glucose tolerance or poorly controlled diabetes mellitus would be expected to promote the accumulation of glucose-modified proteins.

Yours sincerely,
M. W. Brighton and A. J. Furth

Fig. 1. Levels of glycated plasma protein and plasma glucose in a ketotic diabetic patient returning to normoglycaemia. Amadori product was assayed by the thiobarbituric acid method [7], which gave a value of 0.9 μ mol 5-hydroxymethyl-2-furaldehyde HMF/g of plasma protein on admission (time zero in Figure) —●— Amadori product, —x— Glucose

References

1. Brownlee M, Cerami A, Vlassara H (1988) Advanced products of nonenzymic glycosylation and the pathogenesis of diabetic vascular disease. *Diabetes Metab Rev* 4: 437-451
2. Kennedy L, Lyons TJ (1989) Nonenzymatic glycosylation. *Br Med Bull* 45: 174-190
3. Eble AS, Thorpe SR, Baynes JW (1983) Nonenzymatic glycosylation and glucose-dependent crosslinking of protein. *J Biol Chem* 258: 9406-9412
4. McPherson JD, Shilton BH, Walton DJ (1988) Role of fructose in glycation and crosslinking of proteins. *Biochemistry* 27: 1901-1907
5. Baynes JW, Thorpe SR, Murtiashaw M (1984) Nonenzymic glycosylation of lysine residues in albumin. *Methods Enzymol* 106: 88-98
6. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H (1983) Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. *Br Med J* 287: 867-870
7. Fluckiger R, Gallop PM (1984) Measurement of nonenzymatic protein glycosylation. *Methods Enzymol* 106: 77-87

Dr. A.J. Furth
Oxford Research Unit
The Open University
Boars Hill
Oxford OX1 5HR
UK

Announcements

International Meeting: Amino Acid/Protein Metabolism in Health and Diseases

This meeting will be held 19-20 January 1990 in the "Aula Magna" of the Istituto Scientifico H San Raffaele, Milan, Italy. The meeting is based on invited distinguished speakers presenting the State of the Art of research in the field of amino acid/protein research in man. There will also be poster sessions with selected abstracts which must be submitted before November 10, 1989. Poster sessions will include a 5 minute presentation and 3 slides during the specific sessions. *For further information please contact:* Livio Luzi, M.D., Istituto Scientifico H San Raffaele, Via Olgettina 60, I-20132, Milano, Italy. Tel.: (39) (2) 2170.2330 (2752) (2454) (2757), Telefax: (39) (2) 2170.2482

Annual Meeting of the Artificial Insulin Delivery Systems, Pancreas and Islet Transplantation - Study Group of the European Association for the Study of Diabetes

The meeting will be held from January 28-30, 1990 in Igls, Austria. *Main topics:* Insulin therapy in Type 1 and 2 diabetes; segmental pancreas transplantation and islet transplantation; implantable devices; immunosuppression; bioartificial pancreas. *Deadline for abstract*

presentation: November 15, 1989. *For further information please contact:* Dr. Piero Micossi, Direzione Scientifica, Ospedale San Raffaele, Via Olgettina 60, I-20132 Milano, Italy. Tel.: 2170-2758, 2759, Telefax: 2170-2482

13th National Congress of the Italian Society of Diabetology

This congress will be held from May 13-16, 1990 at the Palazzo dei Congressi, Pisa, Italy. *For further information please contact:* International Congress Organization, Via U Della Faggiola 13, I-56126 Pisa, Italy. Tel.: 050/560909-560936, Telex: 551103 INCOR I, Fax: 050/560418

2nd European Congress of Endocrinology

This conference will be held from July 1-6, 1990 in Ljubljana, Yugoslavia. *For further information please contact:* 2nd European Congress of Endocrinology, Secretariat, Kompas Jugoslavija, Congress Department, Prazakova 4, YU-61000 Ljubljana, Yugoslavia. Tel.: 3861 319-445, Telex: 31209 KOMPAS YU, Telefax: 3861 319 888