7. Xylitol in dietetics and medicine

7.1 Discovery of enzymes of xylitol metabolism in mammals

The detection of L-xylulose in the urine of non-pentosuric humans [250–252], guinea-pigs [251] and rats [252] indicated that this ketopentose may be a normal metabolite in mammals. This idea was supported by the discovery of a very active enzyme system for the reduction of L-xylulose to xylitol [253]. It was also found that D-xylulose 5-phosphate, rather than D-ribulose 5-phosphate, is the ketopentose substrate of transketolase in the 6-phosphogluconate pathway [254, 255]. Simultaneously, new mitochondrial enzymes linking metabolically the two enantiomorphic forms of xylulose were studied in guinea-pig liver [249].

In these and subsequent studies, carried out largely by Touster and Hollmann, it was further established that guinea-pig liver mitochondria catalyze the reduction of L-xylulose to xylitol. Reversibility of the reaction xylitol<->ketopentose was confirmed [253]. The enzyme responsible for this reaction was located in the insoluble part of mitochondria. The reaction required pyridine nucleotides. The specificity of the enzyme was very high, because no activity toward several ketoses and polyols tested, except for xylulose and xylitol, did occur [253]. This high specificity thus differentiated the enzyme from other enzymes known at that time to catalyze the interconversion of ketoses and polyols. The ‘L-xylulose-xylitol enzyme’ of guinea-pig mitochondria was found to need NADP and its high specificity was confirmed [256]. In addition to the involvement of this type of highly specific enzymes, Hollmann and Touster [256] emphasized the multiplicity of NAD-dependent liver polyol dehydrogenases. These dehydrogenases catalyze the interconversion of several polyols and ketoses. It is likely that the use of guinea-pig as one of the first test objects was a fortunate choice and to a certain extent speeded up the understanding of xylitol metabolism in man, because both species require α-ascorbate in the diet. On the other hand, xylitol and ascorbate are closely related to each other through the glucuronate-gulonate pathway, or glucuronate-xylulose cycle, established subsequently [257, 258]. In liver perfusion tests the utilization of L-xylulose was slower with hamster, rat and monkey than with guinea-pig.

Hollmann [259] purified satisfactorily two enzymes in guinea-pig liver mitochondria: a NADP-xylitol(L-xylulose) dehydrogenase and a NAD-xyliol-
tol(D-xylulose) dehydrogenase. The NADP-dependent enzyme catalyzed the reactions xylitol ⇌ L-xylulose. The NAD-dependent enzyme was a Zn-containing SH-enzyme, capable of oxidizing the following polyols: L-iditol, D-sorbitol, xylitol, D-glycero-D-glucoheptitol, ribitol, allitol and L-threitol. Thus the required configuration was that of a D-erythro-l,2,4-polyol. Of all substrates xylitol had the lowest value of $K_m$ ($5.96 \times 10^{-4}$ M) [259], indicating a high affinity for the enzyme among the polyols tested.

A recent study [597] suggested that the L- and D-xylulose reductase catalyzing the reversible NAD-linked reduction of D-xylulose and the NADP-linked oxidation of xylitol proceed with opposite chirality of hydrogen transfer to the coenzyme. This is an important suggestion as this type of enzymes have so far been found to catalyze hydrogen transfer from and to the coenzyme invariably with the same chirality.

The above and certain other studies, referred to later, have resulted in the availability of information about xylitol metabolism, which has up to now been summarized and discussed at several symposia of which three main are as follows:

1. 'Metabolism, Physiology, and Clinical Use of Pentoses and Pentitols', Hakone, Japan, August, 1967 (published by Springer-Verlag, New York, in 1969) [290].

A recent symposium in Würzburg (Symposium II über Zuckeraustauschstoffe; Dtsch. zahnärztl. Z. 32, Suppl. 1) mostly dealt with sugar substitutes in the prevention of dental caries. The first symposium revealed, for example, the following findings:
- Xylitol was shown to be less lipogenic than sucrose.
- Intravenously administered xylitol was considered effective and safe in young and old human subjects, both with regular metabolism as well as with diabetes, liver disease and after surgery.
- Xylitol augmented adrenal steroidogenesis, preventing suppression under steroid treatment.
- Xylitol was considered useful in suppressing ketosis resulting from amino acid diets in pediatrics.
- Xylitol had a favourable effect in reducing bilirubin levels in infantile jaundice.
- The above findings could be largely explained by the fact that xylitol was found to be rapidly oxidized in animal and human tissues, including red blood cells in which it prevented hemolysis. Xylitol is oxidized to xylulose in entering the pentose phosphate pathway.
- Xylitol was found to restore glycolysis in diabetic rat liver slices without the use of insulin.