

Reno-cerebral oxalosis induced by xylitol

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Summary. A 20-year-old man suffering from Crohn's disease developed coma and generalized seizures following ileocecal resection. During postoperative parenteral feeding he received xylitol in an unusually high concentration. CT examinations a few days before death showed intense hypodensity and swelling of brainstem and basal ganglia and increasing triventricular dilatation. Autopsy revealed, mainly in the brainstem and cerebellum, a destruction of intracerebral, intracerebellar and leptomeningeal vessel walls by birefringent crystals (probably calcium oxalate), an early inflammatory reaction and severe brain edema with final tonsillar herniation. The same crystalloid deposits were found in the kidneys.

Key words: Xylitol-infusions – calcium oxalate crystals in reno-cerebral vessel walls – perivascular inflammatory reactions and brain edema – computed tomography

Intravenously infused xylitol may be used for supplying the organism with carbohydrates when the metabolism of glucose is disordered e. g. after trauma or surgery [21].

In 1970 Australian authors reported severe complications following the administration of high doses of xylitol even with fatal outcome in some cases [24]. At autopsy, marked calcium oxalate precipitations were found in the renal tubules. Such deposits could also be seen in the walls of small intracerebral vessels.

Because of these findings, xylitol has been withdrawn in Australia and in the United States.

At the same time, an inquiry performed by the Pharmaceutic Committee of the German Medical Association did not reveal any similar observations.

In 1972 similar autopsy findings had first been reported in Germany [4]. In all these cases, intravenous infusions containing high doses of xylitol had been administered to the patients.

These alarming results led to the recommendation to limit the quotidian dose of xylitol to a maximum of 1.5 g/kg body weight [1].

Meanwhile some further reports on the toxic effects of xylitol have been published, especially in Germany, where xylitol is still used [7, 17, 19], the effects occurring when xylitol is administered in high doses or frequently within a short time. Clinically, the patients show neurological or psychopathological signs of various degrees.

We report the case of a 20-year-old male patient with striking cerebral changes on CT, whose autopsy revealed a reno-cerebral oxalosis induced by xylitol [13].

Case report

The patient suffered from Crohn's disease with stenosis of the terminal ileum. Repeatedly treated with azulfidine and corticosteroids, the patient's condition was satisfactory for some years. Later, unilateral hydronephrosis caused by an inflammatory conglomerate compressing the ureter led to deterioration. An ileocecal resection was therefore performed.

During 9 postoperative days of parenteral nutrition the patient whose body weight was 50 kg was treated with a quotidian dose of 150 g xylitol, that is double the maximal amount recommended by the Pharmaceutic Committee. The postoperative course was uneventful, but after one week septic fever occurred. Twelve hours later, after several seizures, the patient lost consciousness. A severe metabolic acidosis, disorder of the electrolyte balance and acute renal failure developed.

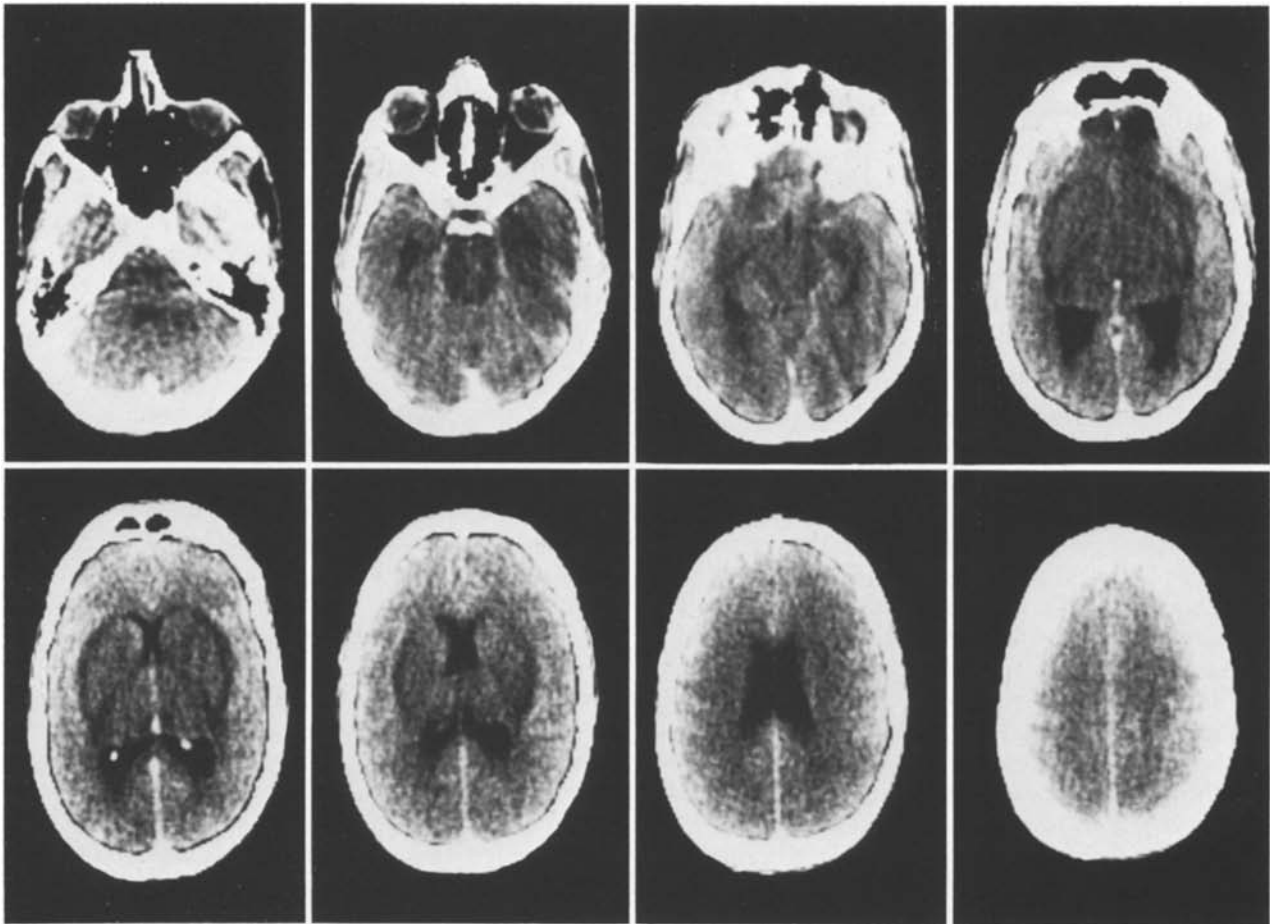


Fig. 1. Postcontrast CT on the 7th postoperative day: hypodensity and swelling of brainstem and deep grey nuclei without pathological enhancement, bilateral edema of the internal and external capsules, partial compression of the supratentorial ventricles and subarachnoid spaces

CT was performed on the 7th postoperative day (Fig. 1): There was hypodensity and swelling of the brainstem, the basal ganglia and the thalami with edema of the internal and external capsules on both sides. The 3rd ventricle and the frontal horns of the lateral ventricles were narrow, the temporal and occipital horns slightly enlarged, the sulci ill-defined. The quadrigeminal cistern was narrow, the 4th ventricle normal. Pathological enhancement was not seen.

Plain CT performed on the following day (Fig. 2) showed that the cisterns surrounding the brainstem were almost obliterated. The lateral ventricles were dilated, especially the occipital horns, and their outlines were ill-defined. The supratentorial hypodense area had increased in size, reaching the cortex.

At this time the patient's condition further deteriorated. He became anuric on the next day and his respiration ceased. Two days later EEG was isoelec-

tric and death occurred on the 11th postoperative day.

Autopsy revealed marked signs of elevated intracranial pressure with tonsillar herniation. Microscopically severe lesions of intracerebral, intracerebellar and leptomeningeal vessels with deposits of birefringent crystals were found. These crystals were morphologically identical with calcium oxalate crystals (Fig. 3). The pathologic changes of the vessel walls, with perivascular inflammatory reactions and brain edema were particularly pronounced in the brainstem and cerebellum. Crystalloid concretions were also found in the renal tubules (Fig. 4).

Discussion

The localization of these pathological changes and their exclusive distribution in the kidneys and the

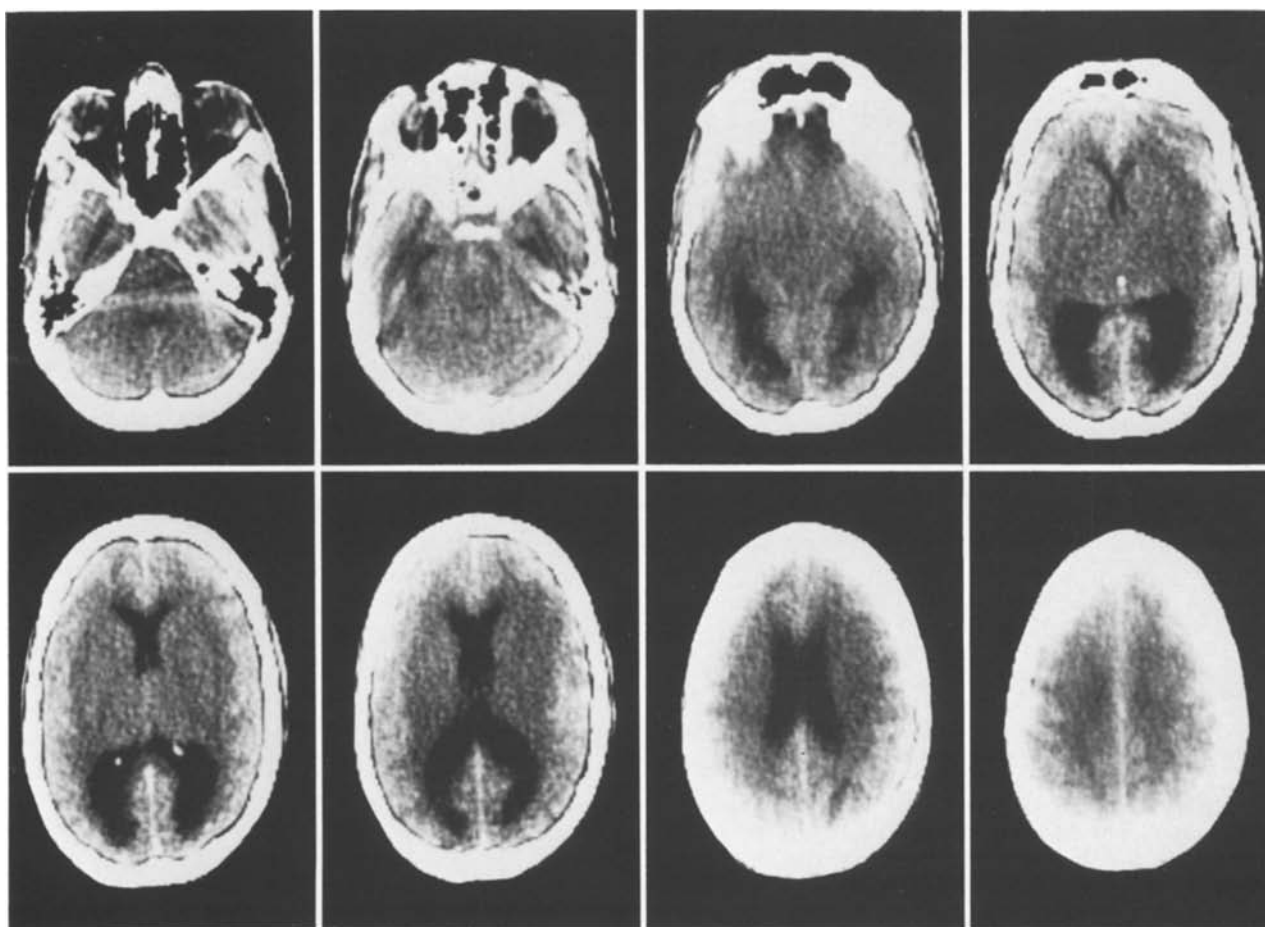


Fig. 2. Precontrast CT on the 8th postoperative day (3 days before death): progression of the hypodense and space-occupying changes, dilation of the lateral ventricles

brain characteristically demonstrate the type of oxalosis, which can be induced by xylitol [8, 25].

In *primary* oxalosis, however, caused by congenital enzyme defects, only scanty cerebral oxalate deposits inconstantly occur, despite massive oxalate precipitations in all other organs [11, 15].

The same can be assumed for most of the *secondary* oxaloses [2] which are defined by disturbances of the oxalic acid metabolism. The latter develops either *endogenously* e.g. in renal insufficiency [26] or *exogenously*, dependent on intoxications, for instance caused by oxalic acid [27], ethylene glycol [18, 23] or the anaesthetic methoxyfluran [9]. Hyperoxalemia occurring as well in primary as in secondary oxaloses does not lead to severe cerebral changes because the blood brain barrier remains undamaged [20].

In xylitol-induced oxalosis, however, the insoluble and therefore inert calcium-oxalate in the cere-

bral vessel walls is probably just the final product of a series of reactions, which can not yet be biochemically entirely clarified [10, 12].

Intoxication caused by the anti-freeze ethylene glycol induces the same renal and cerebral damage as xylitol [4, 18, 19]. In a lethal case of ethylene glycol intoxication we were also able to find at autopsy the same birefringent deposits of calcium oxalate in cerebral, cerebellar and leptomeningeal vessels as well as in renal tubules. Therefore a common biochemical pathway can be supposed [16, 20, 22].

Indeed, Maier recently reported a case of sublethal intoxication with ethylene glycol showing a reversible density decrease of the brainstem, the basal ganglia and the thalami in CT [14].

In an overdose of xylitol as well as in intoxication with ethylene glycol, the precursors of oxalic acid, developing in the liver, especially glycolic acid, are probably the real toxic substances. The inflam-

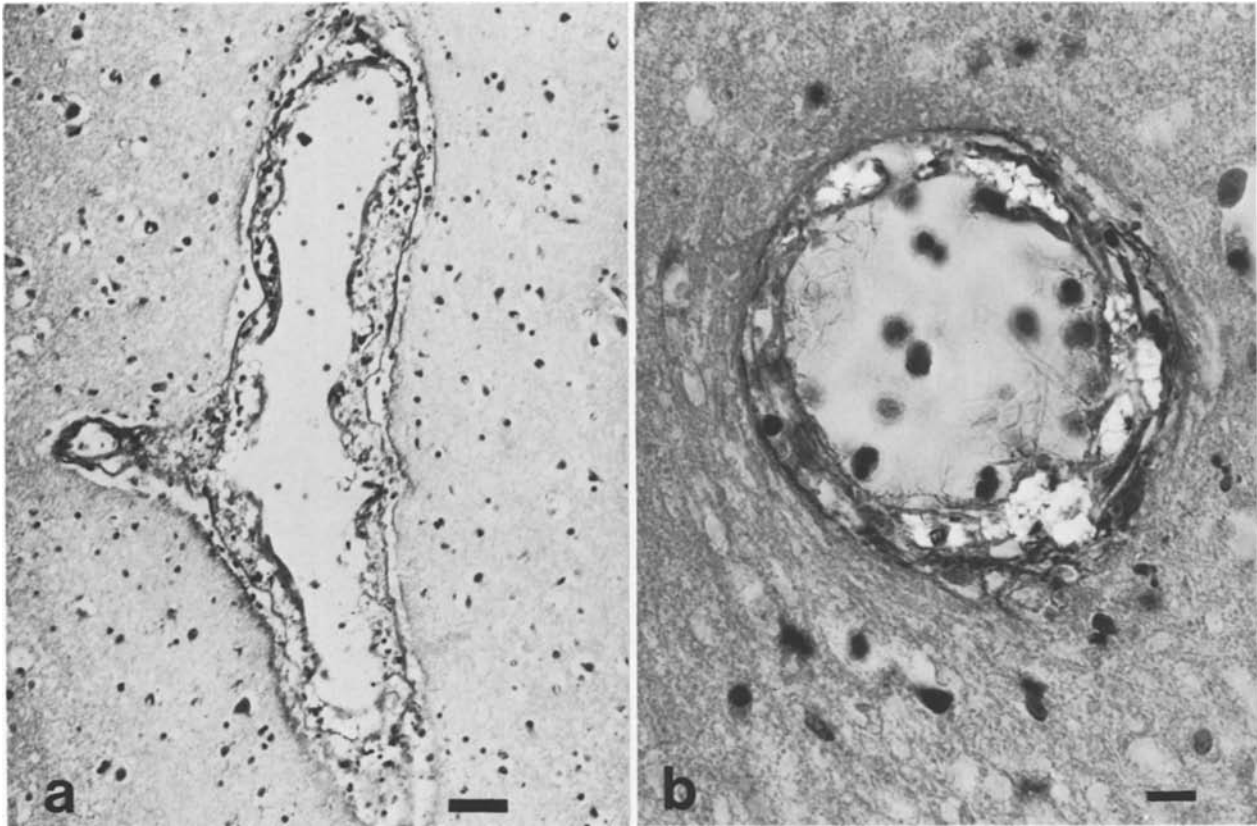


Fig. 3 a and b. **a** Intracerebral blood vessels with acute inflammatory reactions in the vessel wall (scale bar 50 μ) **b** Localized deposits of a birefringent crystalline material (probably calcium oxalate) in a blood vessel wall at a higher magnification and with closed polarizing filters (scale bar 10 μ). Paraffin embedding, HE staining

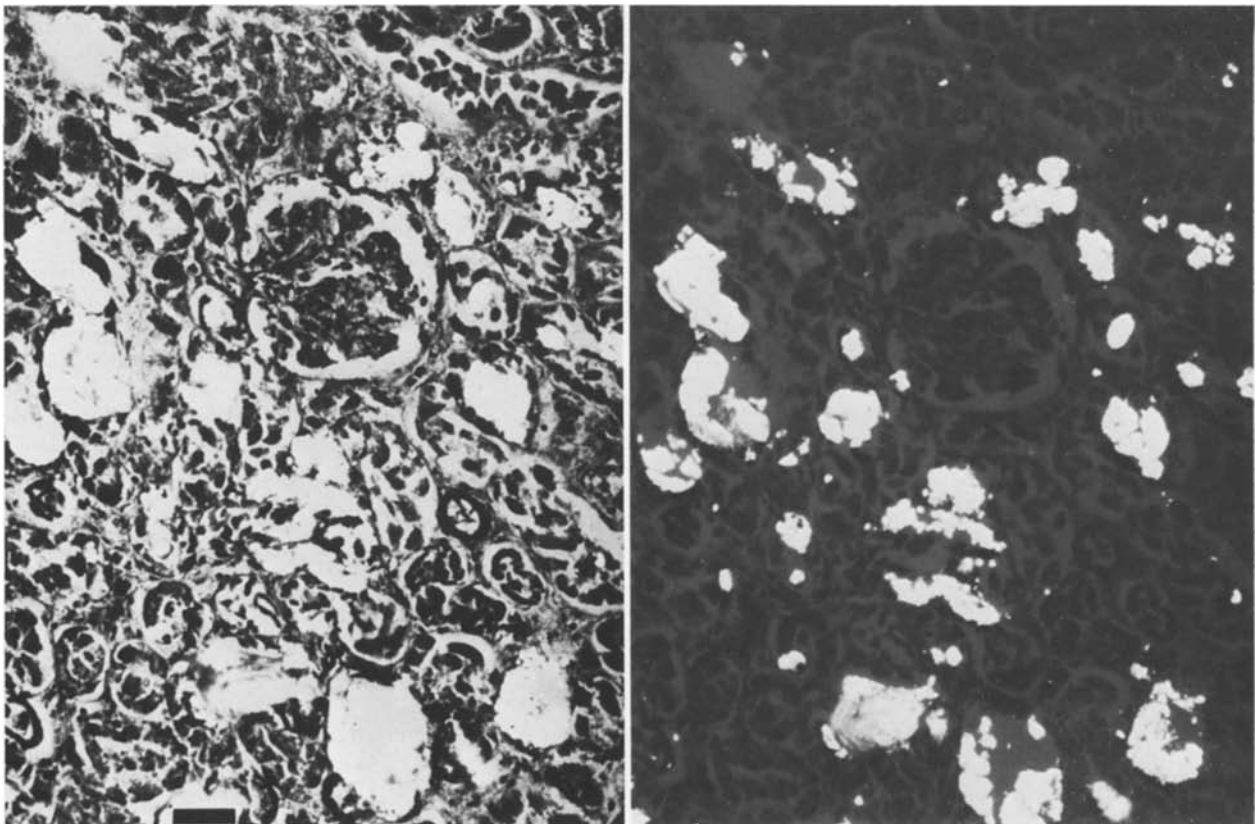


Fig. 4. Renal cortex with circumscribed deposits of a birefringent crystalline material (probably calcium oxalate) inside the renal tubules. The polarizing filters are more open on the left and more closed on the right side (scale bar 50 μ). Paraffin embedding, HE staining

matory cerebral changes and the metabolic acidosis, occurring in both intoxications, had been attributed to these substances too [5, 6].

It is questionable whether there is any connection with Crohn's disease or the ileocecal resection in this patient, even when, because of a disturbance of the oxalic acid resorption, an enterogenous hyperoxaluria or hyperoxalemia may develop under these circumstances [12]. In some reported cases of cerebral oxalosis appearing after ileocecal resection [3] the cerebral changes might have been caused by infusions of xylitol too [20].

References

1. Arzneimittelkommission der Deutschen Ärzteschaft (1972) Dosierungsgrenzen bei der Infusion von Zuckeraustauschstoffen beachten! *Dtsch Ärztebl* 69: 3399
2. Bednar B, Jirasek A, Stejskal J, Chytil M (1961) Die sekundäre urämische Oxalose. *Zentralbl Allg Pathol* 102: 289–297
3. Beppu T, Mori S, Omoto R, Nishi T, Oya G (1975) Secondary oxalosis after ileocecal resection. Report of two autopsy cases and review of the literature. *Nippon Shokakibyō Gakkai Zasshi* 72: 520–521
4. Büngener W (1973) Kalziumoxalatausfällung in Niere und Gehirn nach hochdosierter Xylitinfusion. *Zentralbl Allg Pathol* 117: 204
5. Chou JY, Richardson KE (1978) The effect of pyrazole on ethylene glycol toxicity and metabolism in the rat. *Toxicol Appl Pharmacol* 43: 33–44
6. Clay KL, Murphy RC (1977) On the metabolic acidosis of ethylene glycol intoxication. *Toxicol Appl Pharmacol* 39: 39–49
7. Dölp R, Paulini K (1976) Oxalatbildung nach parenteraler Ernährung mit Aminosäuren und Xylit bei einem polytraumatisierten Patienten. *Int J Vitam Nutr Res [Suppl]* 15: 228–233
8. Evans GW, Phillips G, Mukherjee TM, Snow MR, Lawrence JR, Thomas DW (1973) Identification of crystals deposited in brain and kidney after xylitol administration by biochemical, histochemical and electron diffraction methods. *J Clin Pathol* 26: 32–36
9. Frascino JA, Vanamee P, Rosen PP (1970) Renal oxalosis and azotemia after methoxyflurane anesthesia. *N Engl J Med* 283: 679–684
10. Gambardella RL, Richardson KE (1978) The formation of oxalate from hydroxypyruvate, serine, glycolate, and glyoxylate in the rat. *Biochim Biophys Acta* 544: 315–328
11. Haqqani MT (1977) Crystals in brain and meninges in primary hyperoxaluria and oxalosis. *J Clin Pathol* 30: 16–18
12. Hodgkinson A (1977) *Oxalic acid in biology and medicine*. Academic Press, London New York San Francisco
13. Ludwig B, Schindler E, Bohl J, Pfeiffer J, Kremer G (1982) Xylit-induzierte reno-cerebrale Oxalose. 18. Jahrestagung der Deutschen Gesellschaft für Neuroradiologie, Hamburg
14. Maier W (1983) Cerebral computed tomography of ethylene glycol intoxication. *Neuroradiology* 24: 175–177
15. Nissen P, Jester HG, Gille J, Kluge R (1973) Primär endogene Oxalose mit klinisch manifestem Gefäßbefall. *Dtsch Med Wochenschr* 98: 1714–1715
16. Parry MF, Wallach R (1974) Ethylene glycol poisoning. *Am J Med* 57: 143–150
17. Peiffer J (1979) Komplikationen bei Infusionsbehandlung. *Zentralbl Allg Pathol* 123: 145–147
18. Pons AC, Custer PR (1946) Acute ethylene glycol poisoning: a clinico-pathologic report of eighteen fatal cases. *Ann J Med Sci* 211: 544–552
19. Schröder R, Féaux de Lacroix W, Franzen U, Klein PJ, Müller W (1974) Therapie-bedingte Form einer reno-cerebralen Oxalose? *Acta Neuropathol (Berl)* 27: 181–184
20. Schröder R (1980) Störungen im Oxalsäurestoffwechsel bei parenteraler Ernährung mit Xylit. *Dtsch Med Wochenschr* 105: 997–1001
21. Schultis K (1971) Xylit als Glucoseaustauschstoff bei der gestörten Glucoseassimilation im Postaggressionssyndrom. Eine Übersicht über tierexperimentelle und klinische Studien. *Z Ernährungswiss [Suppl]* 11: 87–96
22. Scully RF, Galdabini JJ, McNeely BU (1979) Case records of the Massachusetts General Hospital, case 38-1979. *N Engl J Med* 301: 650–657
23. Terlinsky AS, Grochowski J, Geoly KL, Stauch BS, Hefter L (1981) Identification of atypical calcium oxalate crystalluria following ethylene glycol ingestion. *Am J Clin Pathol* 76: 223–226
24. Thomas DW, Edwards JB, Edwards RG (1970) Examination of xylitol. *N Engl J Med* 283: 437–445
25. Thomas DW, Edwards JB, Gilligan JE, Lawrence JR, Edwards RG (1972) Complications following intravenous administration of solutions containing xylitol. *Med J Aust* 1: 1238–1246
26. Zaremski PM, Hodgkinson A, Parsons FM (1966) Elevation of the concentration of plasma oxalic acid in renal failure. *Nature* 212: 511–512
27. Zaremski PM, Hodgkinson A (1967) Plasma oxalic acid and calcium levels in oxalate poisoning. *J Clin Pathol* 20: 283–285

Received: 12 December 1983

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