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This Week's Citation Classic™

Haemmerli U P, Kistler H, Ammann R, Marthaler T, Semenza G, Auricchio S & Prader A. Acquired milk intolerance in the adult caused by lactose malabsorption due to a selective deficiency of intestinal lactase activity. *Amer. J. Med.* 38:7-30, 1965. [Depts. Med. and Medical Out-Patient Dept., Kantonsspital, and Dept. Biochem. and Children's Hosp., Univ. Zürich, Switzerland]

Acquired selective intestinal lactase deficiency with lactose malabsorption was demonstrated in nine patients with a history of intolerance to the ingestion of milk by means of carbohydrate tolerance tests with lactose, maltose, and a combination of glucose and galactose, as well as by measurements of the intestinal disaccharidases lactase, maltase, isomaltase, and sucrase in peroral jejunal biopsies. Results were compared with 12 normals and three patients with celiac sprue. [The *SCI*® indicates that this paper has been cited in over 190 publications since 1965.]

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"During my training as assistant resident in medicine at Mount Sinai Hospital in New York (1957-1959), the Sippy regimen was still used for ulcer patients. Not infrequently, we observed that individuals receiving milk every two hours developed colicky abdominal pains and diarrhea. The symptoms disappeared when milk was replaced by a normal diet. In 1959, I heard the Dutch pediatricians Weijers and van de Kamer talk on their recent discovery of a syndrome of congenital lactose intolerance in infants, which was published a year later.[1] The description was based on a selective malabsorption of one disaccharide among many tested. Intestinal enzymes could not be determined at that time.

"I suddenly wondered whether our ulcer patients on a Sippy regimen did not have a similar, but acquired, lactase deficiency. During 1960-1962, Dahlqvist, at the department of physiological chemistry in Lund, Sweden, developed a method to determine human intestinal disaccharidases in intestinal mucosa.[2] In 1962, he started to work at the department of pediatrics at the University of Zürich and taught his method to biochemists Auricchio and Semenza. Meanwhile, I had returned from New York to the department of medicine at the University of Zürich, bringing along the method of peroral jejunal biopsy which pediatricians there were not yet using.

"Combining the different facilities, Kistler and I started examining patients recruited from the outpatient department of medicine at Kantonsspital with intolerance to the ingestion of milk. Among many cranks and neurotics (which were really the hardest part of the study!), we discovered nine patients with the expected syndrome: we could demonstrate an isolated intestinal lactase deficiency combined with a flat blood glucose curve after lactose ingestion. The other disaccharides tested were absorbed normally. We postulated an acquired syndrome, because we knew that in the congenital variety observed in infancy the symptoms disappear as the patients grow older. Intolerance to milk was also present in the three sprue patients examined, but of course all intestinal disaccharidases were deficient.

"Meanwhile, Dahlqvist had gone to the VA Hospital in Hines near Chicago with his method, and Armand Littman's group published the same syndrome in a preliminary report of three patients in 1963,[2] a few months after we had reported our first four patients in Bern before the Swiss Society for Internal Medicine on May 12, 1963.

"The nearly simultaneous discovery of the syndrome in Switzerland and the US produced an avalanche of papers in the literature. The entity is now contained in every standard textbook of medicine, and has recently been treated in a monograph.[3] Our own paper has been cited widely because it was the first description in detail of a new, but quite common, clinical syndrome.

"However, nothing is new in science. Among veterinarians, lactose had long been used as a laxative, as all mammals lose their intestinal lactase after the suckling period, and of course fowls never have any lactase in their gut. The California sea lion became a favorite object of study because it has no lactose in its milk.

"The first patient with documented lactase deficiency may well have been the German physician M. Traube, who in 1881 reported the successful treatment of his own chronic constipation with lactose.[4]

"Our paper was awarded the Biennial Prize of the Swiss Society for Gastroenterology. It later led us to create our own 'artificial' disaccharide malabsorption syndrome: in 1966 we introduced successfully the synthetic disaccharide lactulose for the treatment of chronic hepatic coma.[5] Man has no intestinal enzyme to digest lactulose. Lactulose is—as unabsorbed lactose—fermented by bacteria in the colon to organic acids. Acidification of fecal contents prevents ammonia formation and lowers elevated blood ammonia levels in hepatic coma."

1. **Weijers H A, van de Kamer J H, Mossel D A A & Dicke W K.** Diarrhoea caused by deficiency of sugar-splitting enzymes. *Lancet* 2:296-7, 1960. (Cited 75 times.)
2. **Dahlqvist A, Hammond J B, Crane R K, Dunphy J V & Littman A.** Intestinal lactase deficiency and lactose intolerance in adults. Preliminary report. *Gastroenterology* 45:488-91, 1963. (Cited 120 times.)
3. **Paige D M & Bayless T M, eds.** *Lactose digestion: clinical and nutritional implications.* Baltimore, MD: Johns Hopkins University Press, 1981. 280 p.
4. **Traube M.** Ueber den Milchzucker als Medikament. *Deut. Med. Wochenschr.* 7:113-14, 1881.
5. **Bircher J, Mueller J, Guggenheim P & Haemmerli U P.** Treatment of chronic portal-systematic encephalopathy with lactulose. *Lancet* 1:890-3, 1966.