

Oberholzer V G, Levin B, Burgess E A & Young W F. Methylmalonic aciduria.
Arch. Dis. Child. 42:492-504, 1967.
[Queen Elizabeth Hospital for Children, London, UK]

Large amounts of methylmalonic acid were detected in the urine of a child with persistent metabolic acidosis. Two cases are described and evidence presented indicating a new syndrome resulting from a block in the conversion of methylmalonyl coenzyme A to succinyl CoA. [The SCI® indicates that this paper has been cited in over 180 publications since 1967.]

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January 17, 1984

"Following World War II, the Queen Elizabeth Hospital servicing the children in the East End of London became a centre for paediatric teaching of undergraduates. Among the number of gifted members on the staff, the consultant pathologist Barnett Levin (now retired) was responsible for creating and developing the clinical biochemistry section. As part of the general pathology department, this was housed in a series of basement rooms partly below ground. Despite the overcrowded conditions, important contributions to inherited disorders of metabolism were made. In 1962, we reported the first cases of ornithine transcarbamylase deficiency, an inherited disorder of urea synthesis.¹

"One of the patients at this time was a girl believed to have a form of renal tubular acidosis. She had been successfully managed since birth through many severe acidotic episodes and is now 24 years old and physically and mentally well. During one of her hospital admissions at the end of 1965, the resident medical officer, M.N. Buchanan, who must be given credit for first challenging the diagnosis, asked me to explain why this child

under controlled treatment with alkalis was producing an acid urine. Somewhat puzzled, I said I'd see what I could find in the urine. Screening for organic acids was not then a routine procedure. My initial guess from chemical and chromatographic evidence as to the identity of the organic acid found in the urine fortunately was soon confirmed by an adaptation of a newly described colour reaction for the measurement of methylmalonic acid in pernicious anaemia.² The appearance of the specific emerald green colour was the high point of my investigation. In methylmalonic aciduria, the term we used for this condition, apart from ketone bodies, large amounts of only one organic acid are excreted. This undoubtedly made it easier to identify. The survival of our patient allowed us to study her disorder in detail.

"Winifred Young had remembered a previous patient with a similar history of recurrent acidosis and ketosis who had died in 1959. Luckily, a small amount of this child's plasma had been kept. The discovery that it contained a high level of methylmalonic acid was another exciting moment.

"A reward for all the research work done by the hospital has been the new Research Building, following the launch of our research appeal at the end of 1965. It was officially honored by the Queen in 1972, and I was given the honour of showing Her Majesty around the spacious biochemistry department.

"The frequent citation of this paper is most likely due to its being a first report of a new disorder and one that has been found to have the highest frequency of occurrence among the organic acidurias.

"More recent studies in the synthesis of the vitamin B12 cofactor, 5' deoxyadenosyl cobalamin, necessary for the conversion of methylmalonyl CoA to succinyl CoA, widened the field of interest and has led to a better understanding of the biochemical heterogeneity of the inherited defects in methylmalonic acid metabolism. An excellent review has recently been published."³

1. Russell A, Levin B, Oberholzer V G & Sinclair L. Hyperammonaemia: a new instance of an inborn enzymatic defect of the biosynthesis of urea. *Lancet* 2:699-700, 1962. (Cited 120 times.)
2. Giorgio A J & Plant G W E. A method for the colorimetric determination of urinary methylmalonic acid in pernicious anemia. *J. Lab. Clin. Med.* 66:667-76, 1965. (Cited 100 times.)
3. Matsuji S M, Mahoney M J & Rosenberg L E. The natural history of the inherited methylmalonic acidemias. *N. Engl. J. Med.* 308:857-61, 1983.