

Felig P, Owen O E, Wahren J & Cahill G F. Amino acid metabolism during prolonged starvation. *J. Clin. Invest.* 48:584-94, 1969.

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Alanine is extracted by the splanchnic bed to a greater extent than all other amino acids combined. Marked hypoalaninemia and reduced splanchnic uptake of alanine in the face of unchanged fractional extraction occur after prolonged starvation, indicating that decreased substrate availability is a key regulatory mechanism limiting gluconeogenesis in starvation. [The SCI® indicates that this paper has been cited in over 510 publications, making it the most-cited publication for this journal.]

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In 1976, upon completion of my clinical training in internal medicine at Yale, I joined the laboratory of George F. Cahill as a postdoctoral research fellow. Cahill had completed studies that showed the progressive reduction in protein metabolism which accompanies prolonged starvation and, with Oliver E. Owen, had demonstrated that ketones replace glucose as the major oxidative fuel for brain metabolism in prolonged fasting.

Cahill suggested that I examine amino acid metabolism in subjects undergoing prolonged starvation in an effort to determine the factors regulating gluconeogenesis. Through the cooperation and support of Richard Gorlin, I had the opportunity to work with John Wahren, a postdoctoral fellow in the Cardiovascular Unit, who performed hepatic and renal vein catheterizations permitting an examination of splanchnic and renal exchange of amino acids.

The research involved markedly obese volunteers who underwent prolonged starvation as a method of weight reduction. My initial laboratory experience consisted of setting up and calibrating a newly purchased amino acid analyzer. While our data demonstrated a variety of patterns of changes in circulating ami-

no acids during the course of starvation, the first inkling that our studies were yielding interesting results was a chromatogram from a fasted subject (run on the analyzer on Thanksgiving Eve, 1967) that demonstrated a very low alanine concentration. The splanchnic-bed studies revealed that alanine was quantitatively the most important amino acid extracted by the liver after overnight, 36- to 48-hour, and five- to six-week fasts. Alanine uptake by the splanchnic circulation rose after a 36- to 48-hour fast but fell markedly after a five- to six-week fast. Furthermore, in prolonged starvation, plasma alanine levels fell to a greater extent than all other amino acids, and the hypoalaninemia, rather than a change in splanchnic fractional extraction of alanine, accounted for the marked reduction in splanchnic alanine uptake observed during prolonged starvation.

The paper has been highly cited because these observations not only identified alanine as a major gluconeogenic substrate but also demonstrated that substrate availability was a key rate-limiting factor in the regulation of gluconeogenesis in humans. In subsequent studies alanine was shown to be the key gluconeogenic amino acid released by resting and exercising skeletal muscle¹ and by myocardium, where its metabolism is altered by ischemia.² Furthermore, alanine deficiency has been identified as contributing to hypoglycemia in a variety of conditions such as pregnancy, ketotic hypoglycemia of infancy, maple syrup urine disease, and chronic renal insufficiency.^{3,4} Interestingly, the latter condition has recently been identified as the most common cause of hypoglycemia in hospitalized, noninsulin-treated subjects.⁵

Perhaps the most important outgrowth of this work for me personally is that it led to an ongoing research collaboration with Wahren that has continued for about 20 years,⁶ as well as to enduring friendships with Cahill and Owen.

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