

Owen O E, Morgan A P, Kemp H G, Sullivan J M, Herrera M G & Cahill G F.

Brain metabolism during fasting. *J. Clin. Invest.* 46:1589-95, 1967.

[Elliott P. Joslin Res. Lab.; Depts. Medicine and Surgery, Harvard Med. Sch.; Cardiovascular Unit, Peter Bent Brigham Hosp.; and Diabetes Foundation, Inc., Boston, MA]

Arteriovenous concentration differences coupled with regional blood-flow rates determined that β -hydroxybutyrate and acetoacetate replace glucose as the dominant fuel for brain metabolism during fasting. [The SCI® indicates that this paper has been cited in over 520 publications.]

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Previous studies on brain metabolism showed that the only energy-yielding substrate consistently extracted from the blood by the human brain was glucose. The quantity of carbohydrate stored in the human body is limited and can supply organs dependent upon glucose for only a few days. During starvation the liver produces glucose for terminal oxidation from amino acids derived from proteolysis and from glycerol derived from lipolysis. The amount of nitrogen excreted in the urine reflects amino acid catabolism. During starvation humans excrete far less nitrogen than is required for gluconeogenesis to supply the central nervous system (CNS) with glucose as the only fuel source.

George F. Cahill, at the Elliott P. Joslin Research Laboratories, recognized the paradox between the absolute requirement of glucose for the brain and the quantity of nitrogen excreted from the body during prolonged starvation. He suggested that it was likely that fuels (ketone bodies) other than glucose were oxidized by the CNS during starvation.¹

Cahill is a creative, colorful man who had developed vibrant, cohesive research laboratories staffed by junior faculty, fellows, and proud, hardworking technicians who strove for exactness, and a new, accurate, and specific enzymatic technique for measuring blood concentrations of ketone bodies (acetoacetate and β -hydroxybutyrate) became available.

I arrived in Boston in July 1965, while the Cahill family was on vacation. Cahill generously permitted my family to temporarily live in their home, with its serene surroundings and a richly endowed library. After returning from vacation, Cahill became my

mentor, and research efforts were initiated under his tutelage. In addition, his collaborators and staff provided me with the guidance and opportunity necessary to investigate the nature and quantities of fuels utilized by the brain during prolonged starvation.

After a 40- to 42-day fast, three obese volunteers underwent catheterization studies, partly to measure the exchange rates of ketone bodies, glucose, free fatty acids, amino acids, O_2 , CO_2 , and other substrates in blood across the brain and liver. This study showed that during prolonged starvation, β -hydroxybutyrate and acetoacetate replace glucose as the predominant fuel for brain metabolism. The results in this report were new and solved the paradox between nitrogen conservation and fuel consumption by the brain during prolonged starvation. It was my first peer-reviewed publication, and fortunately it became a *Citation Classic*. It also led to a second *Citation Classic* written by my cherished friend, Philip Felig.²

Other questions were raised by the initial study. Hepatic glucose released after prolonged starvation was insufficient to supply the quantity of glucose extracted by the brain plus the known quantity needed by other tissues dependent upon glycolysis for energy. Other fellows in Cahill's research laboratories showed a relationship between renal ammoniogenesis and gluconeogenesis, and we learned that during starvation NH_4^+ production increased and replaced urea as the principal excreted nitrogenous product. A group of obese individuals undergoing therapeutic starvation agreed to hepatic and renal catheterization studies. The results showed that the kidneys shared the role of gluconeogenesis with the liver after prolonged starvation.³ This study also revealed that the hepatic production rates of ketone bodies were increased but limited during starvation. Subsequent studies showed that late in starvation there was a paradoxical decrease in muscle utilization of ketone bodies in spite of heightened ketonemia⁴ and that no renal tubular maximal transport rates existed for acetoacetate and β -hydroxybutyrate.⁵ Thus, the kidney conserved these valuable fuels during starvation.

The fundamental knowledge of brain metabolism during fasting was the seminal force that influenced my research efforts for the subsequent two decades pertaining to fuel homeostasis not only during nutritional deprivation but also during diseased states of diabetic ketoacidosis⁶ and alcoholic hepatic cirrhosis.⁷ Simple mathematics and logic were used in a methodical approach to delineate the physiology of fuel homeostasis. Regardless of why the work on brain metabolism during fasting became a *Citation Classic*, recognition of this report brings me joy.

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3. Owen O E, Felig P, Morgan A P, Wahren J & Cahill G F. Liver and kidney metabolism during prolonged starvation. *J. Clin. Invest.* 48:574-83, 1969. (Cited 405 times.)

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