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 SCOPUS indicator indicates that this paper has been cited in over 520 publications.]


Antecedent to his work, Cahill pioneered the study of ketone body metabolism in fasting and gluconeogenic mechanisms in the liver. He was recognized for his contributions to carbohydrate metabolism, particularly in relation to ketone body metabolism.

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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 glycogen derived from lipolysis. The amount of nitrogen excreted in the urine reflects amino acid catabolism. During starvation the brain will excrete far less nitrogen than it requires for gluconeogenesis to supply the central nervous system (CNS) with glucose as the only fuel source.

Cahill and colleagues recognized the paradox between the absolute requirement of glucose for the brain and the quantity of nitrogen excreted in the CNS during starvation.

A 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 diseases states of diabetes and obesity. 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.