Mini-Series: Paths to Discovery

Ketone Bodies as a Fuel for the Brain during Starvation

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THE STATUS OF OUR KNOWLEDGE OF STARVATION AND BRAIN METABOLISM IN HUMANS WHEN I BEGAN MY RESEARCH

This story begins in the early 1960s when the general level of knowledge about whole-body metabolism during human starvation was grossly deficient. This was partly caused by a lack of accurate and specific methods for measuring hormones and fuels in biological fluids, which became available about 1965.[1] Rigidly designed protocols for studying human volunteers or obese patients, who underwent semi- or total starvation for prolonged periods of time, were not widely employed, and much of the published data regarding metabolic events during starvation were not readily accessible. To complicate matters further, a great deal of the available data was confusing because much of the supposition regarding mechanisms used by the body to survive prolonged periods of starvation was based upon information that was obtained from nonstandardized and often erroneous procedures for studying metabolism. For example, the rate of urinary nitrogen excretion during starvation was sometimes confounded by the consumption of carbohydrate during the studies. Today, students of biochemistry take for granted the fact that tissues of the human body have a hierarchy of fuel usage. They know that the brain, an organ devoted to using glucose, can switch to use ketone bodies during prolonged starvation (2–3 days), thus sparing glucose for other tissues (*i.e.* red blood cells must use glucose as a fuel; without mitochondria, they have no choice!). However, this fundamental insight into human metabolism was not recognized in the early 1960s, when my research in this area began. How this simple but fundamental fact that ketone bodies provide critical fuels for the brain was discovered and its implication for energy metabolism in the human is the subject of this article.

DIABETES AND WHAT IT HAS TAUGHT US ABOUT HUMAN METABOLISM

The pathway to knowledge on the nature and regulation of human fuel metabolism has taken a long and circuitous route. It is easy to understand how physician-scientists initially formulated erroneous concepts regarding the requirements of the brain and other tissues for fuels such as glucose. Ironically, studies of diabetics and patients with insulin-induced hypoglycemia complicated (rather than clarified) the understanding of the normal metabolism of the brain. The treatment for diabetes became available with the discovery of insulin at the University of Toronto in 1921–22. This scientific breakthrough was one of the most dramatic events for the management of any disease. By lowering the level of blood glucose, insulin's impact on a diabetic patient was sensational and seemingly miraculous.[2] However, initial research of brain metabolism was hindered by the widespread yet erroneous hypothesis that developed as a consequence of treating diabetic patients with insulin.[3]

Early insulin therapy was not perfect; insulin saved the lives of experimental animals and subsequently humans, but researchers initially had no way of knowing how much to administer or how to best administer it. They recognized that in the absence of insulin the concentration of blood glucose rose to high levels and death occurred. Also, injecting too much insulin lowered the blood glucose to a

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[1] In 1962, the work of Williamson, Mellanby, and Krebs resulted in a major advance in the understanding of ketone body metabolism. Work performed in their Oxford Laboratory in the United Kingdom laid forth a method for rapid and accurate measurement of β-hydroxybutyrate and acetoacetate in biological fluids. The availability of these convenient procedures for measuring ketone bodies did much to widen the field of study. For years researchers and scientists had viewed ketone bodies as metabolic intermediates of disease (as in the case of diabetes mellitus). It was not until good methods for measuring these compounds in urine and blood became available that the importance of ketone bodies as useful fuels for metabolism was recognized.

[2] "Late in 1923 the Nobel Prize was awarded for the discovery of insulin. It was awarded to Banting and J. J. R. Macleod. This raises what seems to be the single really controversial point about the discovery: why should Macleod have shared a Nobel Prize for work done in his lab while he was on holiday? It is fairly well known that Banting was dissatisfied with the Nobel Committee's decision. He immediately announced that he was sharing his half of the award with his colleague C. H. Best. Macleod announced that he would share his half with J. B. Collip, a biochemist who had joined the team late in 1921 and worked on the development of the extract." (Taken from *The Discovery of Insulin* by Michael Bliss, The University of Chicago Press, 1982.)

[3] The most severe form of diabetes mellitus is manifested during diabetic ketoacidosis; it is a state of catastrophic tissue breakdown, in which all the fuels used by the body for energy production are simultaneously dumped into the bloodstream. This diseased state floods the blood with an overabundance of mostly usable fuel. Thirst develops and profuse urination occurs even as the body becomes progressively more dehydrated. The body literally melts away and is drained out of the body in the urine as glucose and ketone bodies. Fortunately, insulin reverses this devastating tissue breakdown.

point where a "peculiar" behavior occurred; animals and humans began frothing at the mouth, became unconscious, developed convulsions, and died. Eating carbohydrate-rich foods (*i.e.* orange juice or candy) or receiving intravenous glucose reversed these adverse effects. Glucose was clearly the key fuel metabolized by the brain; the possibility that other fuels, such as ketone bodies, were also metabolized by this organ was completely ignored. The presence of ketone bodies in the blood and urine of insulin-deficient diabetic patients was recognized in the 1880s and was associated with severe disease states. In the 1920s, it became evident that insulin lowered the content of glucose in the blood and urine of diabetic humans, and it also removed ketone bodies. Nonetheless, the idea that insulin controlled only glucose metabolism and that too little glucose in the blood led to brain dysfunction led to the widely held concept that glucose was the only fuel used by the brain. In the 1950–60s, researchers learned that insulin lowered not only the concentration of glucose and ketone bodies in the blood and urine but also a host of other fuels, including free fatty acids and amino acids. Unfortunately, these isolated discoveries did not correct the widely held misconception that ketone bodies were unhealthy and that glucose was the only source of fuel for the brain.

Between 1959 and 1965, numerous human studies, which were performed when the blood glucose concentration was normal and blood ketone body concentrations were low, demonstrated that the brain consumed glucose at an estimated rate of 100–145 g per day. Catheterization of the blood vessels leading to the brains of patients during diabetic ketoacidosis showed that the central nervous system could not extract measurable quantities of acetone. At that time, β-hydroxybutyrate and acetoacetate were subjected to strong acids that converted them into acetone, and the acetone concentrations in the arterial and venous blood draining the brain were measured. These studies showed that the brain extracted only a negligible quantity of acetone from the blood during diabetic ketoacidosis. This was the current state of understanding of the sources of metabolic fuel for the brain when I began my studies in 1965.

STUDIES ON HUMAN STARVATION

There were several classic studies on starvation before 1965 that measured O_2 consumption and CO_2 production coupled with urinary nitrogen excretion to determine human energy requirements. However, there were no studies that coupled the exchange rates of fuels across various organ beds with urinary nitrogen excretion rates and the exchange rates of respiratory gases in humans during prolonged starvation. Accurate, rapid, and financially feasible methods for measuring fuels (glucose, β-hydroxybutyrate, acetoacetate, lactate, pyruvate, glycerol, free fatty acids, and amino acids) and hormones (insulin) had all been developed by the mid-1960s.

As an example of the problems that plagued the field of starvation research, a highly touted study performed at Johns Hopkins Hospital in 1963–64 [4] was contaminated by the consumption of small quantities of carbohydrate-containing beverages during the fasting period. I was one of the medical residents in training at Johns Hopkins Hospital that oversaw the health status of a morbidly obese man who underwent about 14 months of starvation and semi-starvation for weight reduction. However, I did not recognize (nor did anybody else) the impact that drinking a small quantity of carbohydrate-containing beverages had on this patient's urinary nitrogen excretion. I recall the patient saying something like, "I need to drink a cola because my brain needs sugar." It wasn't until 1972 that Daniel G. Sapir *et al.* [1] demonstrated the exquisite sensitivity of urinary nitrogen excretion rates to ingestion of small quantities of carbohydrates.

Basic studies on the pathways of metabolism in mammals, including humans, had established that glucose is synthesized from lactate, pyruvate, amino acids, and from the glycerol released during lypolysis but not from fatty acids (other than propionate and acetone). Quantitatively, amino acids are the major source of carbon for gluconeogenesis and can be oxidized to CO_2 and H_2O during starvation [2]. When the carbon skeletons of the amino acids are converted to glucose in the liver, the amino nitrogen is used for the synthesis of urea via the urea cycle and is excreted in the urine. In the early 1960s, there was considerable confusion regarding the amount of urinary nitrogen excreted daily to the point that the ratio of nitrogen excretion to glucose production in humans was questioned by prominent investigators.[5] However, information was available indicating that 3 g of glucose were synthesized for each gram of nitrogen excreted [2, 3]. In addition, the nature of the urinary nitrogenous products was not clearly characterized. Very few clinical investigators at that time recognized the possible paradox between urinary nitrogen excretion and the requirements of the brain for glucose. The time was ripe for the research of George F. Cahill, Jr., and me to totally change the way we think about human metabolism.

THE CAHILL ERA

George F. Cahill, Jr., then an associate professor of Medicine at Harvard Medical School and director of the Joslin Research Laboratory, was one of a very few clinical investigators who thought that the metabolism of starving humans should be reinvestigated in detail. In 1965, I was afforded a fellowship position in metabolism under the tutelage of Dr. Cahill, who in conjunction with his other academic appointments served on the professional staff of the Peter Bent Brigham Hospital. He was a creative and colorful medical director who had assembled a vibrant, cohesive research laboratory that was staffed by outstanding junior faculty, fellows, and proud, hard working, bright technicians who strove for exactness. The Peter Bent Brigham Hospital had a National Institutes of Health-supported clinical research center where patients could be housed and continuously observed during experimental protocols. A classical study by Cahill and colleagues was published in 1966 in *The Journal of Clinical Investigation*

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[4] Presentations by the late G. W. Walker, Sr., formerly of Johns Hopkins University School of Medicine, at Medical Grand Rounds and at local and national meetings (approx. 1963–65).

[5] Personal communication from the late Dr. Rachmiel Levine (approx. 1966).

[4], which reported the hormone-fuel interrelationships during a 1-week fast (subjects consumed only water, salt, and vitamins during their starvation period) in six healthy subjects and two patients with type 2 diabetes mellitus. This article laid some of the groundwork for subsequent studies of prolonged starvation in obese humans.

When we began studying the energy requirements of adult humans and determining the organ or regional metabolism in these individuals, there were considerable gaps in our knowledge. It was probable that 1 g of urinary nitrogen could be equated to hepatic synthesis of about 3 g of glucose, that glucose synthesis occurred primarily from protein but not from fat, and that the brain used about 125 g of glucose daily to meet its energy requirements. In addition, the quantity of glucose stored as glycogen in the body was limited to approximately 1 day's supply. It was also known that only one-half of the body nitrogen (protein mass) could be mobilized during starvation, before death occurred. An average adult has about l,000–1,200 g of nitrogen (mainly as muscle protein), but only 500–600 g can be mobilized before death occurs. This suggests that only 1,500–1,800 (500–600 $\times$ 3) g of glucose could be synthesized in the body during that period. If the brain continued to oxidize 100–145 g of glucose daily during starvation, survival would be limited to a minimum of 10 (1,500/145) and to a maximum of 18 (1,800/100) days. These calculations did not match the facts known at that time. First, obese humans consuming only water could usually live about 2 months. Second, to synthesize 100–145 g of glucose daily, the urinary excretion rate of nitrogen would have to be about 33 (100/3) to 48 (145/3) g; the quantities of urinary nitrogen that were excreted during starvation were much less than these estimates.

We recognized the discrepancy between the requirement of the brain for glucose and the quantity of nitrogen excreted during starvation [2]. However, the quantity of nitrogen and the complete nature of the nitrogenous compounds excreted in the urine had not been clearly defined at that time. Furthermore, there was a verbal controversy regarding the ratio of urinary nitrogen and glucose production, and the sites of glucose production in the body during starvation had not been definitively established. Nonetheless, the quantity of glucose that can be totally oxidized to CO_2 and water is considerably less than the 100–145 g/day required by the nervous system. Therefore, some fuel other than glucose must be providing the energy for the brain during starvation. When we began studying metabolic adaptations during starvation in humans, we did not know how long a person could fast and what fuels would be used by specific tissues. Once new insight began to accumulate, the energy requirements of all organs and the body as a whole had to be reevaluated.

STUDIES WITH OBESE PATIENTS

When I arrived at Harvard, Dr. Cahill was "on the speakers' circuit." He frequently traveled to various cities to address medical audiences regarding his metabolic research with humans. Dr. V. K. Vance of Buffalo, NY, became aware of his interest in starvation and referred an obese nurse who had recurring chest pain to him for evaluation and for possible prolonged fasting for weight loss. The patient, Ms. B., was motivated by fear of having a heart attack; her father had died from a myocardial infarction, and her mother had suffered several heart attacks. Physical examination revealed a large-framed woman whose height was 5 feet 8 inches, with a body weight of 280 pounds and blood pressure of 140/90. Her total plasma cholesterol was 360 mg/dl, and her fasting blood glucose was 112 mg/dl. Other routine laboratory tests were normal. Her resting electrocardiograms did not suggest that she had inadequate cardiac circulation, but from her medical history we suspected that she had insufficient blood flow through her heart. The most definitive test for determining cardiac blood flow was coronary angiography with left ventriculography. These tests required placing catheters into a peripheral artery in the thigh or forearm and threading the catheter into the coronary arteries and into the major chambers of the heart and filling these sites with contrast dye that could be seen on x-rays.

None of us realized at the time Ms. B. was hospitalized on the Peter Bent Brigham Clinical Research Center that she was a godsend for our research.[6] She understood the research starvation protocol and the catheterization studies that were planned in addition to her diagnostic heart studies, and she admired and trusted Dr. Cahill and his staff. Ms. B. knew how 24-h urinary collections were performed and was compulsive in voiding urine and collecting her specimens accurately. Later, other volunteer-patients followed the pattern she and our research team developed. The length of time selected for our starvation study of Ms. B. was 6 weeks. When someone asked me why we chose the 6-week period, I replied that "Jesus fasted forty days and forty nights; and afterward he hungered" (St. Matthew 4:2).

We began our study by putting Ms. B. on a balanced diet of proteins, fat, and carbohydrates, and after a few days on the diet, we initiated an approved starvation protocol. She received water, salt tablets, and vitamins. Our research team made daily recordings of her weight, blood pressure, body temperature, and pulse and also measured her total body energy requirements using indirect calorimetry. Urine was collected daily to determine the rate of excretion of nitrogenous waste compounds, and blood was sampled periodically for the routine analysis of metabolites. After Ms. B. had fasted for ~41 days, we inserted multiple catheters into her blood vessels to measure the exchange rate of metabolic materials between the brain and liver. Although our team at the cardiac catheterization laboratory had provided for every safety precaution, we were concerned about the inherent risks of ob-

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[6] Dr. Cahill and I had another blessing on the Peter Bent Brigham's Clinical Research Center. There was a very motivated hospital orderly who wanted to go to medical school but did not have the financial means to do so. While he was helping us oversee the health of the obese volunteers and collect the specimens for analysis, he received a 6-year scholarship to a medical school in the United Kingdom. He was a key figure in executing the early obesity and starvation experiments. We learned a great deal from the studies with this first obese patient that underwent prolonged starvation, and subsequent studies were largely based on the information gathered from the data obtained from Ms. B.
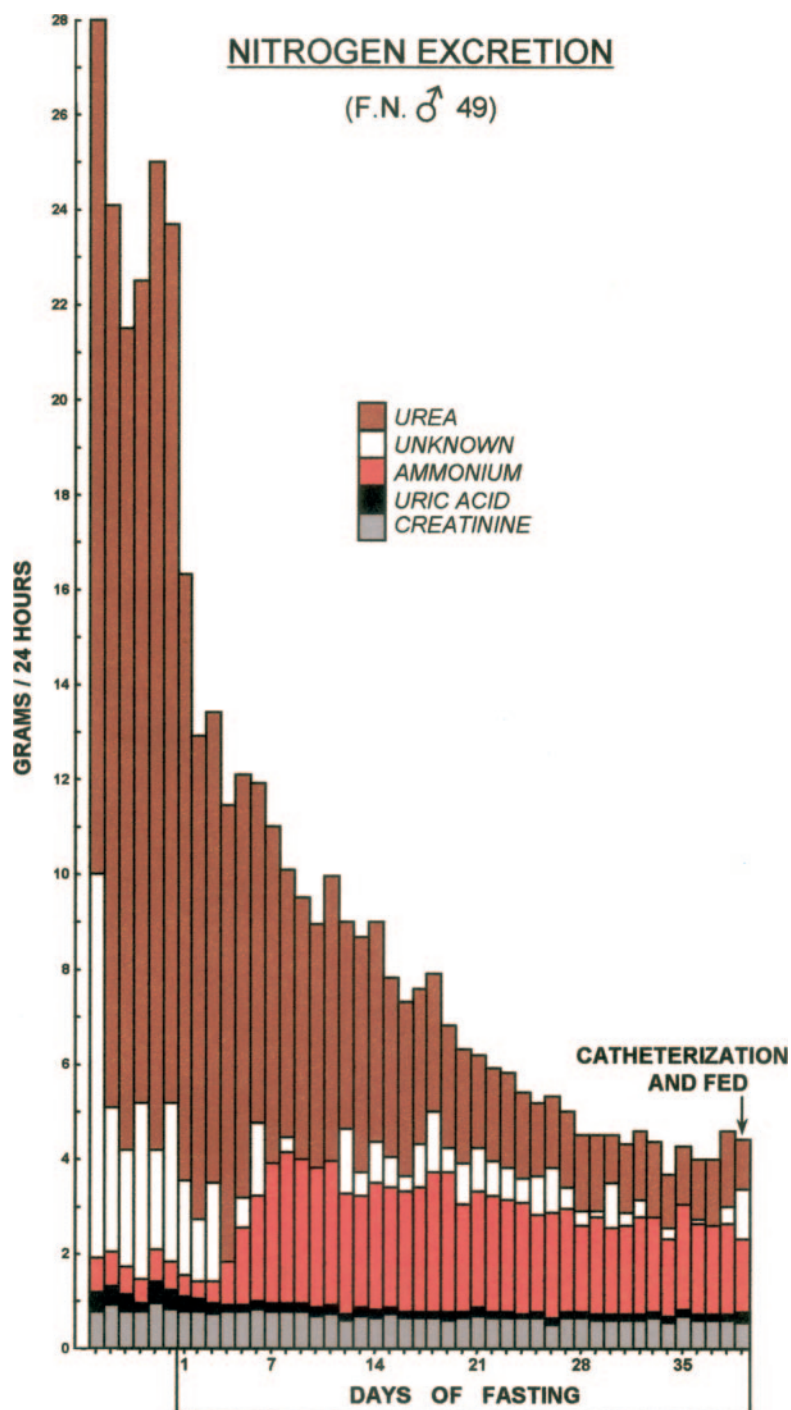
NITROGEN EXCRETION
(F.N. ♂ 49)

UREA
UNKNOWN
AMMONIUM
URIC ACID
CREATININE

GRAMS / 24 HOURS

CATHETERIZATION
AND FED

DAYS OF FASTING

FIG. 1. **Daily urinary nitrogen excretion in Mr. N., who fasted for 38 days.** There was wide fluctuation in urinary nitrogen excretion during the baseline period and a dramatic decrease in total nitrogen excretion during prolonged starvation with ammonium becoming the primary excretory product.

taining multiple artery and venous blood samples from a patient who had not eaten for 41 days. Simultaneous arterial and venous blood samples were obtained over a 10-s timed period from around Ms. B.'s brain and liver, and the level of metabolites was determined. We were thrilled to learn Ms. B.'s brain had survived this long period of starvation by metabolizing ketone bodies and greatly diminishing the use of glucose. The fact that the brain could derive energy from substrates other than glucose was of monumental importance for understanding human survival during starvation. Our findings explained why humans can survive 60 or more days without food; the brain obtained most of its energy requirements from ketone bodies, a fuel derived from fatty acids. This finding resulted in a total

reappraisal of the hierarchy of fuels used by different tissues of humans.[7]

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[7] An average human of ~75 kg (165 pounds) has roughly 15 kg (33 pounds) of fat stored in 16 kg (35.2 pounds) of adipose tissue and ~12 kg (26 pounds) of protein suspended in 60 kg (132 pounds) of lean body mass, mostly muscle. Practically all of the body fat is expendable without serious adverse effects. In contrast, only one-half of the body's protein can be mobilized and used as fuel before death occurs. The conversion of 6 kg of protein to glucose results in the formation of only 3.4 kg of glucose. If the brain oxidizes 100–145 g of glucose daily, the average human could starve for only 23–34 days. The fact that the brain can derive two-thirds of its energy from ketone bodies, synthesized mostly from fat, allows humans to survive total starvation for 60–90 days.

THE ROLE OF THE KIDNEY DURING STARVATION

As is often the case in medical research, our preliminary data raised as many questions as they answered. According to our findings, Ms. B.'s liver produced less glucose than was extracted by her brain. It was known from previous studies that after 3 days of starvation the concentration of glucose in the blood stabilizes, indicating a balance between the rate of production and rate of utilization of glucose. Although Ms. B.'s brain was extracting only a small amount of glucose, it was more than the liver was producing, and yet the concentration of glucose in her blood remained constant. We thus set out to determine the cause of this imbalance with the idea that there must be another source of blood glucose.

A few days later, we received the results of Ms. B.'s urine samples (collected over each of the 24-h periods) and began to suspect that both the kidney and the liver were synthesizing glucose during prolonged starvation. The conventional wisdom at this time was that urea produced by the liver constituted the principal source of excreted nitrogen throughout starvation. Hepatic glucose production is linked to the synthesis of urea to dispose of the nitrogen generated from the amino acids that provide the carbon used for gluconeogenesis. However, during prolonged starvation, the body relies more on ammonium ion production and excretion by the kidneys than it does on urea excretion to dispose of the nitrogen generated in the synthesis of glucose. Furthermore, kidney production of ammonium is directly coupled to renal gluconeogenesis. There were suggestions of this coupling from biochemical studies on animals. Fuisz, Goodman, and Kamm in Cahill's laboratory [5] reported a link between the generation of ammonium ions and the production of glucose in rat kidney slices. This led me to predict that part of the glucose used by Ms. B.'s brain during prolonged starvation had been generated by her kidneys. Hearing this prediction, Dr. Cahill leapt out of his chair and shouted, "You're right!"

On the basis of our initial findings with Ms. B., we extended our research to include an assessment of the role of renal gluconeogenesis in human metabolism during prolonged starvation. Our next patient, Mr. N., was a 49-year-old man who, at 5 feet 11 inches, weighed 300 pounds and had most of his body fat concentrated in the regions of his chest and abdomen. He had an impaired glucose tolerance, and we suspected problems with his kidneys after detecting traces of protein in his urine. Mr. N. also suffered from high blood pressure (180/110 mm Hg); small bouts of exercise left him fatigued and short of breath. An electrocardiogram indicated the presence of left ventricular hypertrophy. He lost 55 pounds during starvation and was most satisfied with this accomplishment. His daily urinary nitrogen excretion rates are representative of well hydrated, obese people undergoing prolonged starvation (Fig. 1). His blood glucose and blood pressure became normal. He underwent brain, liver, and kidney catheterization studies before a refeeding period of a low caloric diet.

The third patient-volunteer, Ms. L., was a 26-year-old woman who weighed 324 pounds. She had chaotic menstrual irregularities (known to occur with morbid obesity)
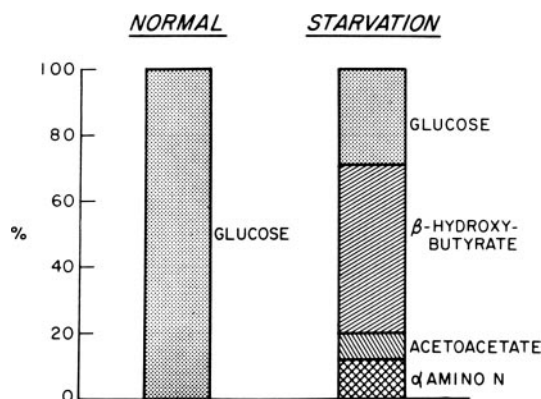

FIG. 2. **After an overnight fast in normal individuals, glucose consumption by the brain can account for all of the oxygen consumed.** During starvation, glucose consumption is suppressed to one-third, and ketone body consumption to two-thirds, of the oxygen uptake. The error in measuring α amino nitrogen was too great to show a significant uptake.
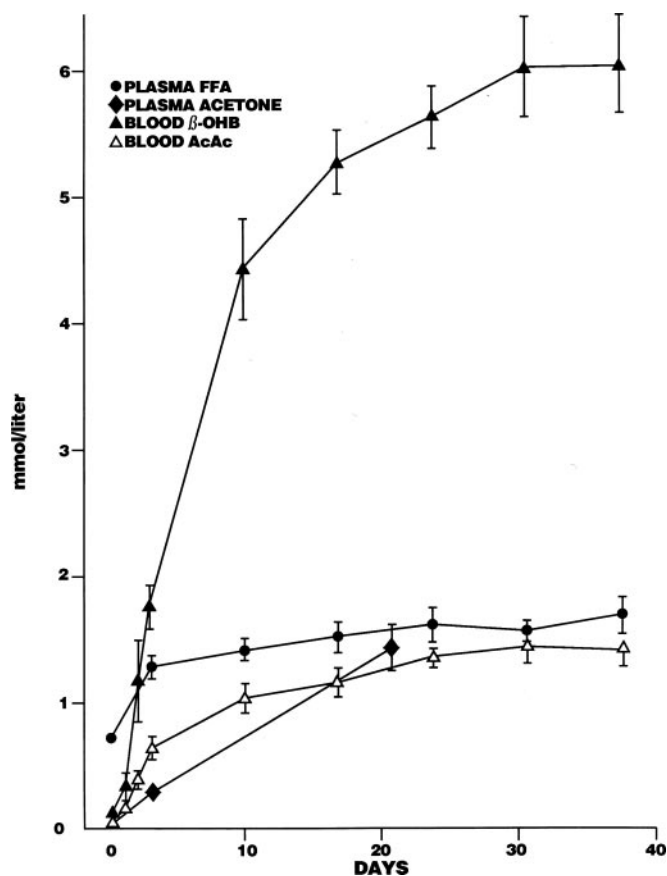

FIG. 3. **Concentrations of ketone bodies and free fatty acids during starvation in humans.** Values are shown as the means ± S.E. Ketone bodies undergo the greatest changes of all fuels during total starvation.

and at times heavy vaginal bleeding every 3–4 months that required surgical treatment (dilatation and curettage) and hormonal therapy. Laboratory screening indicated no diabetes mellitus or thyroid, liver, or kidney disease. She fasted for 39 days, tolerated the food deprivation surprisingly well, and lost 51 pounds. She underwent brain, liver, and kidney catheterization studies. She tolerated these procedures easily and returned to the care of her regular physician.

Retesting our theory on Mr. N. and Ms. L. confirmed our initial results: during prolonged starvation, the brain extracts significant quantities of acetoacetate and β-hydroxybutyrate from the blood, thus sparing the metabolism of glucose. We grasped immediately that the metabolism of ketone bodies rather than glucose was the predominant source of energy, sparing muscle protein and insuring survival during starvation (Fig. 2). Equally important, we again noted that during prolonged starvation glucose production was shared between the liver and the kidney.

In 1967, the results of these studies were published in *The Journal of Clinical Investigation*; this article, entitled "Brain metabolism during fasting," went on to become a Citation Classic [6]. The work focused on "Liver and kidney metabolism during prolonged starvation" was published in 1969 in *The Journal of Clinical Investigation* [7]. It also met the criteria to be a Citation Classic.

SUMMING IT UP

All of us who worked in the Cahill laboratory have been gratified by the impact that our studies have had on an understanding of human metabolism. The concept of "protein (nitrogen) sparing," which is so fundamental of an integrated view of human metabolism, arose directly from this research. Fuel storage depots, like subcutaneous and abdominal adipose tissue, have a high calorie:weight ratio and are capable of meeting the energy requirements directly or indirectly (lactate and pyruvate powered by free fatty acid oxidation) for most tissues, without adverse effects. As we demonstrated, survival during prolonged starvation depends upon the ability of the body to spare the oxidation of vital proteins in the liver, muscle, heart, kidney, etc. Of special importance in this regard is the metabolic role of ketone bodies. Because of their association with diabetes, ketone bodies were long held to reflect a disease state; our research totally changed this view. Ketone bodies are synthesized from the acetyl CoA generated by the oxidation of fatty acids in the liver. The fact that a significant portion of the fatty acids mobilized from adipose tissue is converted to ketone bodies for brain metabolism during starvation is significant. Fatty acids themselves are not metabolized by the brain, so that ketone bodies (which do cross the blood-brain barrier) are the fuel of choice during starvation. Finally, it is interesting to note the changes in blood ketone body concentrations during starvation. The magnitude of their changes is among the greatest that occur in biological systems. Starvation causes an exponential rise in acetoacetate and β-hydroxybutyrate (Fig. 3). These fuels plateau after about 18 days of total starvation. During prolonged starvation, the concentrations of acetoacetate plus β-hydroxybutyrate increase from barely detectable levels immediately after a meal containing carbohydrate to 6–8 mM. The concentration of acetone slowly drifts upward to about 1–2 mM. The fall in blood glucose reaches a nadir after 3 days of starvation and is paralleled by a decrease in serum insulin.

Our work on ketone body metabolism by the human brain demonstrated how human beings survive and maintain mental function during physiologic hypoglycemia and hyperketonemia of prolonged starvation. Ketone body consumption by the brain has an essential role in preserving life.

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