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This Week's Citation Classic®

Cahill G F. Starvation in man. *N. Engl. J. Med.* 282:668-75, 1970.
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This review article summarized a number of studies on fasting man, showing insulin to be the primary hormone controlling fuel mobilization, the brain's use of ketoacids as fuel, the role of glutamine and alanine release from muscle, and the quantification of the various roles of the principal organs in substrate metabolism. [The *SCI*® indicates that this paper has been cited in more than 575 publications.]

A Review of Starvation

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More than 30 years ago, as a fledgling biomedical investigator, I became interested in how fat was synthesized and stored during feeding and, conversely, mobilized during fasting. My late, slightly older colleague, mentor, and dear friend, Albert Renold, had opened up a new area of study in endocrine/metabolic research using isolate rat adipose tissue as the model system. Immunoassays also had become available. A third component was a very simple approach to marked obesity resurrected for therapy of refractory patients—starvation. Obviously, it had been around for millennia, but it again came into vogue in many clinics in the 1960s.

The classic study done 50 years earlier by F.G. Benedict on starving man[1] needed repeating with modern techniques, so we studied the metabolism of fasted obese subjects at the Clinical Research Center at the Peter Bent Brigham Hospital. Insulin appeared to be the primary regulator of fuel release: glucose from the liver, amino acids from muscle, and free fatty acids from adipose tissue. The first study on six normal volunteers who fasted for eight days was published[2] and became a *Citation Classic*®.

Next, a very simple question arose—one that I had discussed several years earlier with Rachmiel Levine. What keeps the brain going in fasting, using one-fifth of the body's oxygen consumption, especially after glycogen stores are depleted and muscle amino acid release becomes too small to provide substrates for gluconeogenesis in the liver and kidneys? After Oliver E. Owen joined the group as a fellow, the answer was found to be brain consumption of the ketoacids beta-hydroxybutyrate and acetoacetate,[3] a paper which was to become another *Citation Classic*. Next, another fellow, Philip Felig, studied the release of muscle amino acids and their control. Alanine was the primary amino acid released,[4] and this paper, too, became a *Citation Classic*. Later, Errol B. Marliss observed glutamine[5] to be equally as important. Alanine was used by the liver for gluconeogenesis and glutamine by the kidneys for gluco- and ammoniogenesis to maintain acid-base homeostasis and cation conservation, allowing prolonged survival during times of caloric abstinence.

Thus, the revisitation to Benedict brought the science up to date. When asked to summarize the topic for a seminar in medicine at Boston's Beth Israel Hospital and for the *New England Journal of Medicine*, I assembled this review article. It made a rather nice story, especially for teaching medical and graduate students, and the illustrations and tables from the aforementioned papers have appeared in a number of reviews and textbooks. Formal and informal discussions and collaborations as to how other animals cope with starvation ensued, as well as some political and financial problems dealing with human population starvation. A practical fallout has been the modification of nutritional and hormonal therapy in traumatized or otherwise-ill humans.

Even more gratifying was the use of *Homo sapiens* to unravel some of the fundamental questions of metabolism and their endocrine controls. It is not easy to study man, and it is growing even more difficult. There are legal, ethical, emotional, and financial issues that complicate things.

1. Benedict F G. *A study of prolonged fasting*. Washington, DC: Carnegie Institution, 1915. 416 p. Publ. No. 203. (Cited 280 times since 1945.)
2. Cahill G F, Herrera M G, Morgan A P, Soeldner J S, Steinke J, Levy P L, Reichard G A & Kipnis D M. Hormone-fuel interrelationships during fasting. *J. Clin. Invest.* 45:1751-69, 1966. (Cited 795 times.) [See also: Cahill G F. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press, 1986. p. 249.]
3. 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. (Cited 570 times.) [See also: Owen O E. Citation Classic. *Current Contents/Life Sciences* 30(41):19, 12 October 1987.]
4. Felig P, Owen O E, Wahren J & Cahill G F. Amino acid metabolism during prolonged starvation. *J. Clin. Invest.* 48:584-94, 1969. (Cited 545 times.) [See also: Felig P. Citation Classic. *Current Contents/Clinical Medicine* 15(41):18, 12 October 1987 and *CC/Life Sciences* 30(41):18, 12 October 1987.]
5. Marliss E B, Aoki T T, Pozefsky T, Most A S & Cahill G F. Muscle and splanchnic glutamine and glutamate metabolism in postabsorptive and starved man. *J. Clin. Invest.* 50:814-7, 1971. (Cited 210 times.)

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