

This Week's Citation Classic

Cahill G F, Jr., Herrera M G, Morgan A P, Soeldner J S, Steinke J, Levy P L,
Reichard G A, Jr. & Kipnis D M. Hormone-fuel interrelationships during fasting. *J.*

Clin. Invest. 45:1751-69, 1966.

[Elliott P. Joslin Research Lab., Depts. Medicine & Surgery, Harvard Medical Sch. and
Peter Bent Brigham Hosp.; and Diabetes Foundation, Inc., Boston, MA]

This paper reports that insulin plays a significant role in glucose homeostasis in fasting as in feeding. It also emphasizes the progressive nitrogen and glucose sparing, with fatty acids and ketones becoming the dominant fuels. Finally, it shows that the brain diminishes glucose utilization during fasting [The SOI[®] indicates that this paper has been cited in over 650 publications since 1966.]

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"Since Berson and Yalow had introduced the immunoassay for insulin to the research community, and since one of us (J. Soeldner) had developed a very sensitive and accurate low-range insulin assay, a study on insulin levels in fasting man seemed warranted, particularly since it hadn't been done. Totally insulin-deprived animals and man develop fatal ketoacidosis, so we knew that even low levels of insulin must play some physiological role. Also, growth hormone had been suggested as a major lipid mobilizer and another of us (D. Kipnis) had a good immunoassay going in St. Louis thanks to colleagues W. Daughaday and C. Parker.

"Who could we get to volunteer to fast for a week while enduring C¹⁴-glucose turnover sampling, twice-daily Douglas bag breathing, blood sampling, precise water intake and urine sampling, and minimal bed-chair activity? It would be impossible to do it on ourselves like the previous one-day studies on insulin effects, exercise, utilization of various sugars as altered by insulin, and many other variables. This was a decade before the present regulations on self-experimentation or soliciting students for research. Nevertheless, we found the ideal, dependable, honest, motivated, and financially limited volunteers at the Harvard Divinity School who needed the money (\$300 for the week) to go home for Christmas. There were

one Baptist, four Congregationalists, and one Episcopalian (his glucose values were always highest!).

"I felt the paper to be a straightforward, not-too-imaginative piece of biomedical reporting, but it led to our subsequent studies showing that the brain uses ketoacids during starvation,¹ that alanine² and glutamine³ were preferentially released from muscle, that insulin directly inhibited amino acid release *in situ* in forearm muscle,⁴ and a number of others that were summarized.^{5,6} Glucagon, growth hormone, and glucocorticoids were also studied, both by determinations and by infusion into obese subjects undergoing prolonged starvation for weight reduction, and found to have some interesting and yet unexplained effects, but their roles in controlling fuel flux and patterns were vastly subordinate to that of insulin. For this overall work, especially for the initial paper (the *Citation Classic*) I received recognition including the Goldberger Award in Nutrition, the Gairdner International Award of Canada, and the Banting Medal of the American Diabetes Association. My younger colleagues in these studies — Soeldner, Owen, Felig, Marliss, and Aoki, to name several — have all continued to provide significant contributions in the area.

"Perhaps most important, the quantitative schemes we generated for fuel flux in man in fasting, feeding, diabetes, and trauma have appeared as the standards in many physiological and biochemical texts. Also, the studies have served as a basis for the recently developed discipline of parenteral alimentation and hyperalimentation since they involved interorgan substrate and energy exchange. The most enjoyable part of the series, however, was the pleasure of doing straightforward, fundamental physiological biochemistry in man and having the results be directly applicable to clinical problems and human disease. They also led to a number of formal and informal collaborations and correspondence with scientists around the world interested in starvation in other species as well as man."

1. Owen O E, Morgan A P, Kemp H G, Sullivan I M, Herrera M G & Cahill G F, Jr. Brain metabolism during fasting. *J Clin. Invest.* 46:1589-95, 1967. (Cited 425 times.)
2. Felig P, Owen O E, Wahren J & Cahill G F, Jr. Amino acid metabolism during prolonged starvation. *J. Clin. Invest.* 48:584-94, 1969. (Cited 435 times.)
3. Marliss F. B, Aoki T T, Pozcisky T, Most A S & Cahill G F, Jr. Muscle and splanchnic glutamine and glutamate metabolism in postabsorptive and starved man. *J Clin. Invest.* 50:814-17, 1971. (Cited 145 times.)
4. Pozcisky T, Felig P, Tobin J D, Soeldner J S & Cahill G F, Jr. Amino acid balance across tissues of the forearm in postabsorptive man. Effects of insulin at two dose levels. *J. Clin. Invest.* 48:2273-82, 1969. (Cited 285 times.)
5. Cahill G F, Jr. Starvation in man. *N. Engl. J. Med.* 282:668-75, 1970. (Cited 365 times.)
6. The Banting Memorial Lecture 1971). Physiology of insulin in man. *Diabetes* 20:785-99, 1971. (Cited 215 times.)