STARVATION AND SURVIVAL

By GEORGE F. CAHILL, JR., M. D.* AND (*by invitation*) OLIVER E. OWEN, M. D.

BOSTON

Primitive man faced several unique problems. Survival required the capacity to withstand prolonged periods of deprivation and yet the sparing of as much body protein as possible in order to be able to hunt successfully at the first available opportunity, or, on the other hand, to escape if preyed upon. Another unique problem was the presence of a nervous system which was relatively hypertrophied compared to other animals and which required a constant supply of substrate throughout the period of deprivation. This brief report will described how man solved these two metabolic problems.

Firstly, how long can man survive total starvation? Good statistics are obviously unavailable except for data derived from obese subjects undergong voluntary deprivation for weight loss. Some reports describe periods of three quarters of a year of total caloric restriction with apparent survival.[1] There are numerous experiences of non-obese man surviving 2–3 months, providing he is relatively basal, has an adequate water supply, and is either in a temporate climate or well-clothed. This duration one could calculate, since an average man contains the fuel reserves listed in Table 1.

His basal requirements at the beginning of the fast would be 1500–1800 Calories/day and, as he becomes more decimated, might fall to 1000–1500 Calories/day. On this basis a theoretical survival of 4 months might be expected, but, as stated above, sparing of nitrogen depots with a preferential utilization of fat is obligatory; in addition, adequate substrate for the central nervous system must be provided.

Concerning body nitrogen, Benedict in his classic study of Mr. Levanzin and the latter's 31 day fast, found that body protein catabolism, as evidenced by urinary nitrogen loss, progressively decreased and, toward the end of the fast, the bulk of calories were derived from oxida-

From the Elliott P. Joslin Research Laboratory in the Department of Medicine, Harvard Medical School and the Peter Bent Brigham Hospital and the Diabetes Foundation, Inc., Boston, Massachusetts.

Supported in part by grants from the United States Public Health Service (AM-09584-03; AM-05077-12, and 5-MO1-FR-31-07) and the John A. Hartford Foundation, Inc.

* Investigator, Howard Hughes Medical Institute.

Reprint requests should be sent to Dr. George F. Cahill, Jr. 170 Pilgrim Road Boston, Massachusetts 02215.

TABLE 1

	g	Calories
Fat		
Mainly adipose tissue	15,000	141,000
Protein		
Mainly muscle	6,000	24,000
Carbohydrate		
Liver glycogen	70	280
Muscle glycogen	120	480
Free glucose (extracellular fluid)	20	80
		165,840

tion of fat with but a very small contribution from protein.[2] There was no evidence of net carbohydrate utilization by the body as determined by indirect calorimetry after the 4th or 5th day of fasting. Similar data have been obtained in our studies on both normal[3] and obese subjects.[4] This is not unexpected since Table 1 shows that total stored carbohydrate is approximately 300 grams, a trivial quantity when compared to the daily caloric turnover or particularly to the potential energy in the adipose depot.

Numerous studies have demonstrated that brain consumes 100 to 145 grams of glucose/24 hours, or 400 to 570 Calories/day.[5, 6] Were this glucose to be derived from gluconeogenesis, an absolute minimum of 130 to 145 grams of protein need be catabolized, assuming that all amino acids are glucogenic and that there is 100 per cent efficiency. (Krebs[7] and others have estimated the optimal conversion to be about 57 per cent). Thus urinary nitrogen should amount to 20 or more grams/day instead of the measured 3–6 grams excreted after several weeks of fasting.

Figure 1 shows that the human brain has solved this discrepancy by substituting oxidation of acetoacetate and β-hydroxybutyrate for a major share of the glucose.[8] Thus, by this biochemical adaptation, glucose synthesis is spared, and, *pari passu*, body nitrogen. It can be said that brain, therefore, has, like the rest of the body, also adapted to fat utilization, since these two substrates, acetoacetate and β-hydroxybutyrate, are products of partial oxidation of fatty acids by the liver.

Figure 2 presents some analyses on urinary nitrogen in a subject fasted for several weeks, demonstrating that the primary nitrogenous component in the urine is ammonia, in contrast to urea, the primary component excreted during the fed state. In fact, urea excretion is diminished to several hundred milligrams/day. A total analysis of all urinary constituents has shown that the ammonia is synthesized and excreted to titrate

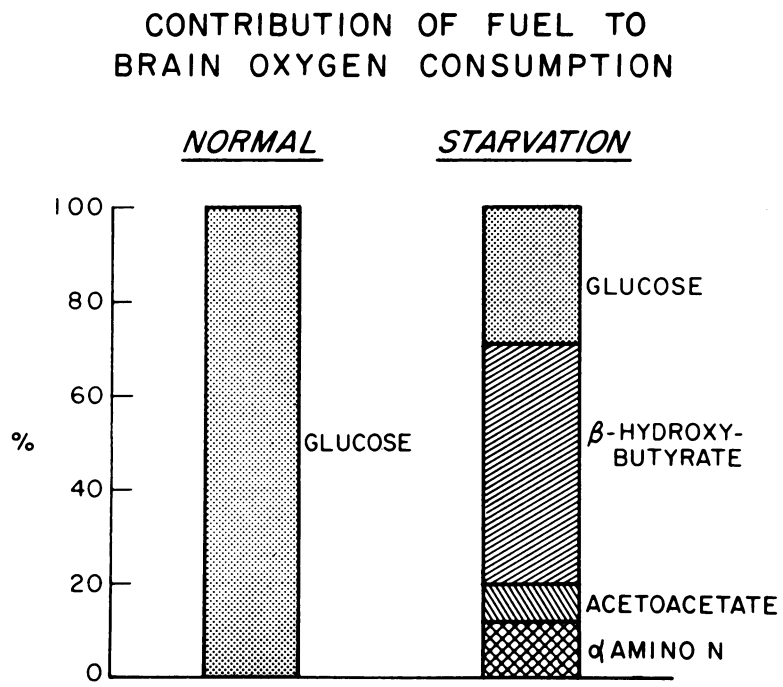

FIG. 1. Contribution of various substrates to cerebral fuel consumption. In the fed state glucose is essentially the sole substrate. In the fasted state, the major fuel becomes the ketoacids.

principally the organic acids, of which approximately 150 meq are acetoacetate and β-hydroxybutyrate. The necessity of this process for survival is obvious, since the urinary loss of ammonia protects the body against progressive acidosis, and more important, negates the need for excretion of sodium and potassium, the cations which are necessary for maintenance of extra- and intracellular spaces respectively. Thus preservation of fluid volumes and acid-base balance appears to take precedence over protection of nitrogen stores, in spite of the metabolic "effort" of the body to conserve nitrogen.

Knowing the exact amount of protein catabolized, one can calculate how much glucose could be synthesized, assuming that the only site of overall glucose utilization were brain. Certain other tissues also use glucose, of which the major quantitative component is the red cell mass. Less important in this respect are the renal medulla, bone marrow, and leucocytes, to name a few, but all of these, and the red cell mass included, metabolize glucose only to lactate and pyruvate, which substances are readily available to be resynthesized back into glucose by liver and kid-

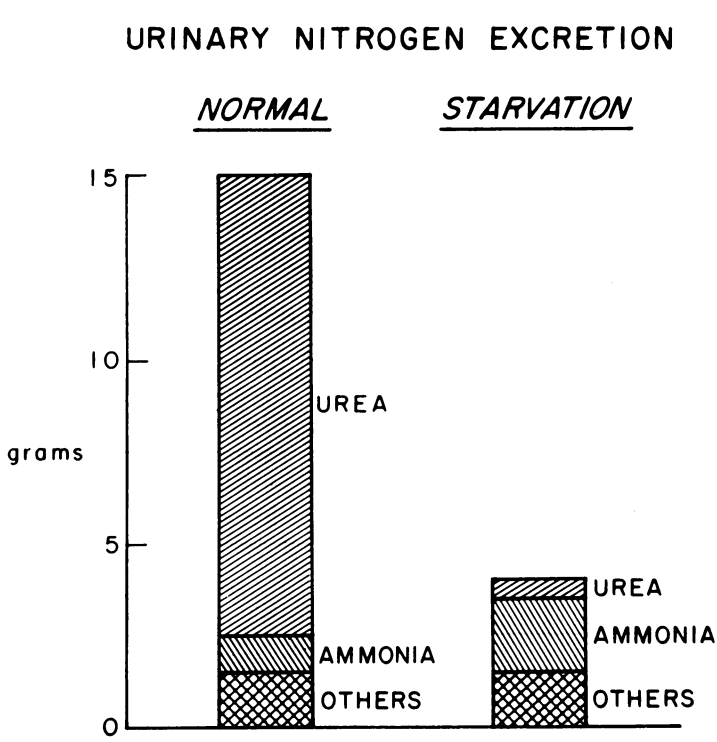

FIG. 2. Analysis of excreted urinary nitrogen of a human subject after an overnight fast or after a period of 5 to 6 weeks of fasting, showing the marked reduction in urea and the predominance of ammonia.

ney. An estimated 40 grams of glucose/day is recycled via this process, but the important point is that there is no terminal loss of the glucose carbon, sparing the need for breakdown of other substrate, notably protein. The energy for this conversion of lactate and pyruvate to glucose is derived from fat oxidation; thus this cycle (the Cori cycle) serves to permit these obligatory glycolytic tissues to derive their energy indirectly from fat, the glucose-to-lactate-to-glucose system serving as an energy shuttle from fat metabolism in liver and kidney to glycolytic-derived metabolism in these tissues.

What about all the other tissues, i.e., viscera, muscle, heart? These utilize solely fatty and ketoacids and totally exclude glucose. In fact, if glucose is given, there is an inability to accelerate its removal from the blood for over an hour, the minimal fall in blood glucose being primarily a function of glucose loss in the urine.[3]

There is, however, not enough material for glucose synthesis from protein catabolism to satisfy even the diminished cerebral glucose utiliza-

tion, and this deficit is met by inclusion in gluconeogenesis of glycerol released from adipose tissue as the triglycerides are hydrolyzed. The glycerol moiety amounts to about 20 grams/day, which, when added to the theoretical maximum of 20 grams of glucose derived from protein catabolism and gluconeogenesis, adds up to 40 grams, the amount terminally oxidized by brain, as measured directly by arteriovenous differences, so the bookkeeping is reasonably correct.[8]

Lastly, reinspection of Fig. 2 shows that the primary urinary nitrogen component is ammonia. Other studies in our laboratory have correlated renal ammonia production with gluconeogenesis.[9, 10] These data, derived from experimental animals, have suggested that as amino acids are deaminated or deamidated, the residues are used for gluconeogenesis by kidney. If such be true in our fasted man, kidney should be contributing to glucose synthesis, particularly that component derived from catabolism of amino acids. This, indeed, has been found to be true, as shown in Table 2 where the uptake of amino acids, lactate, pyruvate and glycerol account for the renal production of glucose. The latter, when multiplied by renal blood flow, makes the kidney equal to the liver in overall glucose production, and, from that component derived from amino acids, kidney appears to be even more important.

In summary, during fasting, nitrogen conservation is achieved by brain adaptation to ketoacid utilization, thereby sparing the need for glucose oxidation and gluconeogenesis from amino acid. What nitrogen is lost from the body is lost primarily in the form of ammonia, and this is derived mainly from amino acid uptake by kidney and incorporation of the

TABLE 2

Mean Arteriovenous Difference Across the Kidney of 3 Subjects Fasted for Five to Six Weeks

	mM/Liter
Oxygen	1.73
CO_2	−1.35
β-hydroxybutyrate	0.278
Acetoacetate	−0.011
Free fatty acid	0.095
Lactate	0.036
Pyruvate	0.004
Glycerol	0.038
α-amino acid	+0.190
[redacted]	
Theoretical glucose yield	0.268 ÷ 2 = −0.134
Observed glucose yield	−0.125

carbon residues into glucose. Other tissues adapt to this nitrogen-sparing process by excluding glucose from being utilized, except those tissues which metabolize the glucose only to lactate and pyruvate, making these two products available for resynthesis into glucose. Were these processes not operative, primitive man would probably not have survived.

REFERENCES

1. THOMAS, T. J., RUNCIC, J. AND MILLER, V.: Treatment of obesity by total fasting for up to 249 days. *Lancet* **2**: 992, 1966.
2. BENEDICT, F. G.: A study of prolonged fasting. Carnegie Institute of Washington, publication 203, 1915.
3. CAHILL, G. F., JR., HERRERA, M. G., MORGAN, A. P., SOELDNER, J. S., STEINKE, J., LEVY, P. L., REICHARD, G. A., JR. AND KIPNIS, D. M.: Hormone-fuel interrelationships during fasting. *J. Clin. Invest.* **44**: 1751, 1966.
4. OWEN, O. E., MORGAN, A. P. AND CAHILL, G. F., JR.: In preparation.
5. SOKOLOFF, L.: Metabolism of the central nervous system *in vivo*, in Handbook of Physiology, Section I, Neurophysiology, Waverly Press, Baltimore, 1959, p. 1843.
6. REINMUTH, O. M., SCHEINBERG, P. AND BOURNE, B.: Total cerebral blood flow and metabolism. *Arch. Neurology* **12**: 49, 1965.
7. KREBS, H. A.: The metabolic fate of amino acids in Mammalian Protein Metabolism, Vol. 1, Munro, H. N. and ALLISON, J. B. eds, Academic Press, New York and London, 1964, p. 125.
8. OWEN, O. E., MORGAN, A. P., KEMP, H. G., SULLIVAN, J. M., HERRERA, M. G. AND CAHILL, G. F., JR.: Brain metabolism during fasting. *J. Clin. Invest.* **46**: 1589, 1967.
9. GOODMAN, A. D., FUISZ, R. E. AND CAHILL, G. F., JR.: Renal gluconeogenesis in acidosis, alkalosis and potassium deficiency: Its possible role in regulation of renal ammonia production. *J. Clin. Invest.* **45**: 612, 1966.
10. KAMM, D. E., FUISZ, R. E., GOODMAN, A. D. AND CAHILL, G. F., JR.: Acid-base alterations and renal gluconeogenesis: Effect of pH, bicarbonate concentration and pCO_2. *J. Clin. Invest.* **46**: 1172, 1967.

DISCUSSION

DR. FRANCIS D. W. LUKENS (Pittsburgh): Dr. Cahill, you did not discuss the method which you used to determine this utilization of ketone bodies by the brain. I am fascinated on historical grounds and will you please correct me if I recite my lesson improperly: We are told that the brain utilizes glucose as the fuel of choice and that it does this without insulin. You now add new information about the special adaptation of the brain to burn ketones. How did you measure this utilization of ketones? Was it by AV difference?

DR. CAHILL: Yes, it was by arteriovenous difference.

DR. LUKENS: Some years ago Dr. Seymour Kety, in working with the physiology of the brain, tried to measure AV differences of ketoacids in people in diabetic ketoacidosis. He could not measure significant AV differences of ketone bodies under those conditions.

DR. CAHILL: Dr. Kety did fail to find a significant uptake of ketoacids in diabetic ketoacidosis. In our studies, it apparently takes several days. We would love to know how long this adaptation persists. If you re-feed, then starve again, will the brain be immediately adapted and ready to utilize ketones right away? These are studies now planned.

DR. WILLIAM B. BEAN: Here is an analogy that probably has no bearing. If you acclimatize somebody to heat, leave them out of the heat for a month or two, they still retain a degree of adaptation. However, if it goes beyond two months, you have to start all over again. I am sure that has no bearing on the high flights you have given us. You have shown us how important it is not to generalize about fat heads [laughter] because now we know people will need to be able to think with fat as well as with lean. [Laughter]

DR. THOMAS H. HUNTER (Charlottesville): George, I am sure you have speculated, as I have from time to time, about what might be the consequences for man of having evolved under highly selective pressures favoring those able to survive long periods of starvation, only to find himself now with the starvation part of the boom and bust cycle removed. Could it be that periodic starvation is advantageous in some way, or that the lack of it may be getting us in trouble?

My experience has been that the only way to get starved, in our setting at least, is to be so sick that you have to be in a hospital bed, an experience I have had several times lately and have thought about at some length. What about the consequences of not ever starving?

DR. CAHILL: Dr. Hunter's question does raise a fascinating problem. If man was originally adapted to periods of feeding and periods of starvation, by eliminating the latter may we have done harm to his overall well-being. I really don't know.

Being particularly interested in diabetes, I tried to find out if this disease bore any relationship to overall nutrition. We all know the clinical fact that overnutrition brings out diabetes. One must ask, therefore, does diabetes provide a selective advantage in undernutrition. I tried to get some insight by following up survivors of Auschwitz and Buchenwald through an organization for this purpose in New York, but too many variables prevented an adequate study. We do have, however, animal models, for example, the sand rat and the spiny mouse, which develop overt diabetes when well-fed. In their normal existence, they barely make ends meet. Similar data are being collected in man, the Hindus who have emigrated to Africa and certain groups of our own American Indians, who, with overnutrition, have developed clinical diabetes in almost one half of the population.

We have tried to see whether mild diabetes or a predisposition to diabetes does provide some survival advantage. If tissues are better able to exclude glucose, which is part of the diabetes syndrome, then gluconeogenesis and, in turn, body protein, should be spared, providing the renal threshold for glucose is not surpassed. Preliminary studies have suggested that this may be true.

DR. HUNTER: I wonder if this has anything to do with atheroma.

DR. CAHILL: I think it probably does very strongly. I should point out that just at this moment we have one patient who has had major three-vessel occlusion with atheroma (as shown by cinearteriography done by Dr. Gorlin and his group). She is now starving. We are following these atheromas to see if they diminish in parallel to the decrease in total body lipid. The result, whatever be the outcome, will be most interesting. So far she is tolerating this procedure extremely well.

DR. HARVEY C. KNOWLES, JR. (Cincinnati): George, were your blood ketone levels at a three months' period similar to the ones of short term studies you recently published?

DR. CAHILL: Yes, they were.

DR. KNOWLES: And second, have you studied the insulin sensitivity at this time, particularly in relation to ketone levels?

DR. CAHILL: If you give these people intravenous insulin their blood sugar will come down very slowly over three or four hours. They are relatively insulin-re-

sistant. The fascinating part is they don't develop marked symptoms as long as the ketoacids are up. They do not have a major hypoglycemic reaction because they apparently have ketoacids to serve the brain's energy needs.

DR. STEWART WOLF (Oklahoma City): Just to follow up the suggestion made by Dr. Bean and Dr. Hunter, in the old days when people wanted to think particularly big thoughts or solve particularly knotty problems, they would go out in the wilderness and eat nothing for forty days. I wonder if this suggests actually better brain function on ketoacids.

DR. CAHILL: Our psychiatrists have followed these people very closely, including formal psychometric testing, and their patterns change, but in their total intellectual capacity there is no major change at all. There is some evidence by others that it may even be improved. There was a society in 1900, the Metaphysics Society of Malta, where the pursuance of starvation itself was the solution of all problems, evils and ills. I point this out, historically, since this is where Dr. Benedict got his subject, Mr. Levanzin, who was the first well-studied faster—he only went thirty days because he got fed up and went out to California and started some religious cult out there. (Laughter).