STARVATION AND BODY NITROGEN

By GEORGE F. CAHILL, Jr., M.D. and (*by invitation*)
THOMAS T. AOKI, M.D.

BOSTON

As the anatomic and embryologic study of a species may give information concerning its present and former living habits, the examination of its metabolic patterns can provide information about its adaptations to nutritional and other environmental challenges to survival. The recent availability of sensitive and specific immunoassays prompted us to study human starvation and the interrelationships between substrate and hormone levels in blood.[1] Insulin is most important for the proper disposition of ingested fuels into various depots in the fed state. It also appears to occupy a central position in fasting fuel homeostasis where its most sensitive effect seems to be related to nitrogen conservation. In fact, the metabolic manoeuvers used by man to spare nitrogenous compounds suggest that nitrogen conservation may have been more crucial to survival than overall caloric balance. This essay will provide evidence for this speculation.

A few general comments concerning body nitrogen are first in order. Unlike carbohydrate storage as glycogen in liver and muscle, or lipid storage as triglyceride in adipose tissue, nitrogen as protein is not accumulated anywhere in the body for storage purposes alone. Every molecule of protein, as far as we know, is serving some function. It may be an enzyme, or it may serve a structural role such as a molecule of collagen. Other roles include maintenance of osmotic pressure (albumin) or motion (the contractile proteins in muscle). Therefore, any decrease in body nitrogen results in a less effective mechanism, since functioning body tissue (or machinery) must be sacrificed.

Another general comment deals with the interrelationships of nitrogenous compounds with glucose and fat. If the body depots of carbohydrate and protein are optimal, any intake of calories in excess of those expended are converted into and stored as fat. There is a very practical teleologic reason for this metabolic interconversion. Since fat is stored as a droplet

From the Elliott P. Joslin Research Laboratory, Harvard Medical School and The Peter Bent Brigham Hospital, Boston, Mass.

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Address requests for reprints to: George F. Cahill, Jr., M.D., 170 Pilgrim Road, Boston, Mass. 02215.

of almost pure oil inside the fat cell, oxidation of this tissue yields close to the theoretical maximum of 9.4 Cal/gram of pure lipid. In contrast, glycogen and protein are both accumulated in cells in an aqueous environment and provide only 1–2 Cal/gram of tissue instead of the theoretical 4 Cal/gram from pure carbohydrate or protein. Man, therefore, as a forager who relied on mobility for survival, stored extra calories most efficiently as fat.

Normal man has some 100,000–150,000 Calories in his adipose tissue, a 2–3 months' supply. He carries only 200–300 grams of glycogen as emergency fuel for sudden fight or flight situations and in his muscle mass has approximately 25,000 Cal as protein. But the more of this muscle he can retain during starvation, the better his chance for survival.

A final general comment deals with the interconversions of glucose, amino acids and fat. As mentioned above, glucose or other sugars derived from carbohydrate ingestion in excess of immediate energy needs are readily converted into fat and stored as such. Amino acids, likewise, can be converted into fat, either via glucose and then to fat or directly to fat in adipose tissue and stored. This latter process is particularly true in the carnivore. Once long chain fatty acids are formed, however, they are stored for later use or else they can be oxidized for energy; they cannot be converted into carbohydrate or carbohydrate-like compounds or into amino acids. Plants have this capability to form protein and carbohydrates from fatty acids but not animals. This biochemical handicap of animals is especially problematic in man, as will be emphasized.

Normal Brief Starvation

Compiling data from studies measuring total metabolic balance with those derived from regional substrate balances using catheterization of veins such as the hepatic, jugular or deep forearm,[2] one can construct a reasonable flow-sheet for normal fasted man. In a 24 hour period he mobilizes and oxidizes approximately 75 grams of protein, mainly muscle, and 160 grams of fat. His brain and other central nervous system components use approximately 140 grams of glucose. This glucose is mainly derived by gluconeogenesis from muscle amino acids but also from glycerol and from hepatic glycogenolysis. Other tissues such as the red cell mass and bone marrow also oxidize glucose, but only to lactate and not to CO_2. The lactate is reintroduced into the circulation and returned to the liver (and kidney) where it is remade into glucose, the so-called "Cori cycle". The remainder of the carcass, during brief starvation, uses both fatty acids released directly from adipose tissue and ketoacids released by liver from fatty acids originally derived from adipose tissue. It uses little,

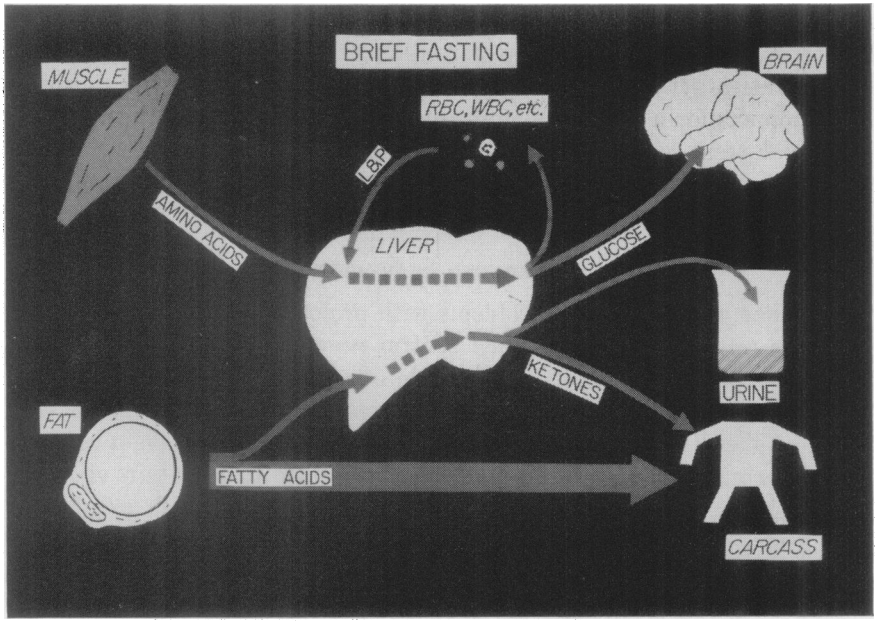

FIG. 1. Schematic view of flux of substrate in man after 1–2 days of starvation. Central nervous system glucose consumption is matched by gluconeogenesis, mainly in liver, from amino acids coming from muscle. Not shown is a small contribution of glycerol released by lipolysis in adipose tissue. Carcass is oxidizing both fatty acids released from adipose tissue directly and fatty acids partially oxidized by liver to ketoacids. A small amount of ketoacids are lost in urine.

if any, glucose and obviates thereby gluconeogenesis from muscle protein. These interrelations are all schematically shown in Fig. 1.

For many years the so-called "nitrogen-sparing" effect of carbohydrate has been known. Gamble in his classical monograph emphasized this point.[3] If one administers glucose to a fasting normal individual, the rate of urinary nitrogen loss decreases markedly. By providing glucose for central nervous system needs, muscle release of amino acid is decreased. This decreased release of amino acids is presumably secondary to the suppression of muscle protein breakdown by insulin. Thus, the provision of even as little as 25–50 grams of glucose is sensed by the body and results in nitrogen-sparing. One can use teleological reasoning to conclude that the body primarily strives to conserve its muscle mass when fasting and that the exquisitively sensitive nitrogen-sparing effect of carbohydrate is in accord with this reasoning.

A small clinical point relevant to the nitrogen-sparing effect is the need

for the continuous administration of glucose (100–200 grams/day) to any patient unable to eat since this permits maximal conservation of muscle mass. Patients with debilitating diseases usually expire with terminal bronchopneumonia resulting fom ineffective clearing of the tracheobronchial tree—a "protein" death due to decreased respiratory muscle mass and function as muscle protein is broken down to fulfill the glucose requirement, via gluconeogenesis, of the brain.

Prolonged Starvation

Man has his own special problems with prolonged starvation stemming from his relatively hypertrophied central nervous system which needs a continuous large supply of fuel capable of crossing the blood-brain barrier. He cannot diminish the energy requirements of his brain and survive, since, as is well known to any clinician, nerve tissue must have a continuous and constant supply of oxygen and substrate to maintain viability. Fig. 2 shows the changing levels of substrate in blood with progressive starvation, and the concentration of β-hydroxybutyrate is seen to rise

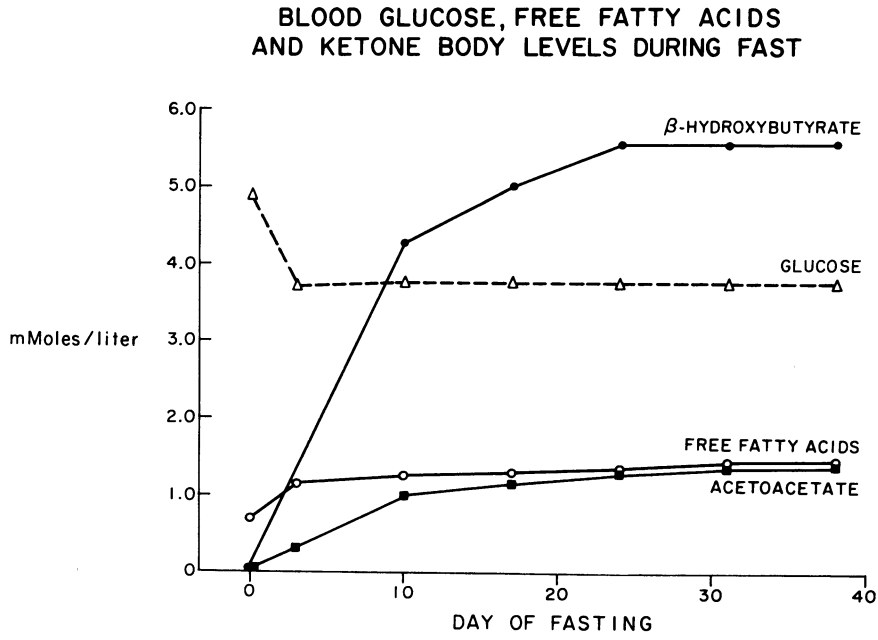

Fig. 2. Levels of water soluble fuels in blood with progressive starvation showing the slight decrease in glucose concentration and the marked increase in ketoacids, particularly β-hydroxybutyrate.

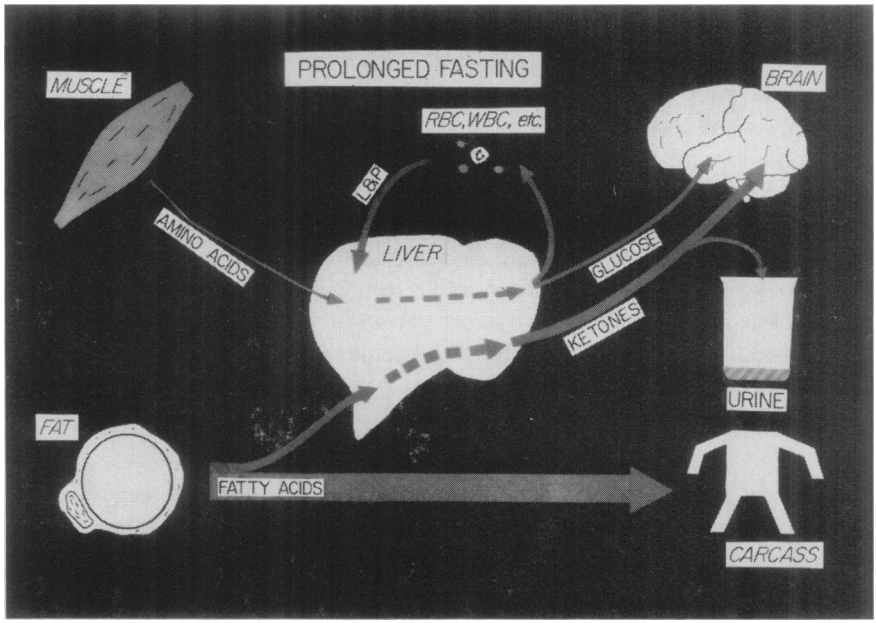

FIG. 3. Schematic view of flux of substrate in man with prolonged fasting showing displacement of brain glucose requirements by ketoacids, sparing, thereby, nitrogen mobilization from muscle.

above that of glucose. Also, and more important, were glucose to continue to be used by brain at the expense of gluconeogenesis, body muscle would be largely depleted in 2–3 weeks, no doubt a major handicap in a primitive society. This problem is met by brain metabolizing β-hydroxybutyrate, and its companion "keto" acid, acetoacetate. Thus brain also begins to metabolize fat, but in an indirect fashion, the fat being partially oxidized and "solubilized" by liver in the form of a ketoacid or "ketone" body (Fig. 3). This simple alteration of brain's energy requirements from glucose to ketoacids permits weeks of survival to be extended to months, matching minimal utilization of the body's nitrogen resources with maximal utilization of its abundant lipid reserve. In fact, one can roughly calculate that a man, moderately well-upholstered with fat, but not obese, with a good supply of muscle nitrogen, would possess the combination of mobility together with good fuel reserves to be the ideal survivor of a primitive world. A small brain would have helped from a fuel point of view, but certainly would have been a disadvantage in a competitive society!

Urinary Nitrogen

Early in fasting, urinary urea is the main nitrogenous component. As brain uses more and more ketoacids, hepatic gluconeogenesis decreases, and urea decreases accordingly to but one to two grams/day. The main nitrogenous component becomes ammonia, excreted to preserve sodium and potassium, which if lost in excess of tissue catabolized, would result in hypovolemia and death. Of great interest to students of metabolic adaptation to environment, the marked decrease in urinary urea excretion diminishes strikingly the number of osmoles needed to be eliminated daily in urine. Thus man, starving for a short period of time, need drink very little water, and, if in a humid cave, not too hot nor too cold, may go for several days without any water intake at all.

Involved Hormones

Early in starvation, insulin appears to be the primary regulator of peripheral amino acid release and, pari passu, hepatic gluconeogenesis. With more prolonged starvation, the precise controls as yet cannot be defined. Insulin levels are relatively decreased and glucagon levels relatively increased,[4] but the physiologic meaning of these levels as they relate to fuel control remains to be defined. How does the muscle know that the brain of fasting man can utilize ketoacids and thus decrease its rate of release of amino acids? Likewise, how does the carcass know that it should now decrease its rate of ketoacid utilization to spare this substrate for brain? These problems are currently being studied.

Trauma

There is one metabolic situation where the body's attempts to spare nitrogen are completely abandoned, and that is when there is major trauma or sepsis or a combination of both. These conditions are associated with a hypercatabolic state of body nitrogen, and, as recently shown by Kinney and colleagues,[5] result in increased glucose synthesis and utilization. Reparative tissues are obligatory glycolyzers, and, again, from a teleologic point of view, it must have been selectively advantageous for primitive man to part with some of his cherished nitrogen to expedite closure of the wound if he were to survive at all. Availability of intravenous dextrose and water was obviously never anticipated. Of extreme interest is the mechanism whereby normal untraumatized muscle perceives that there has been a major insult and responds accordingly with accelerated proteolysis and amino acid release. Recent data have shown that the patterns of amino acid release are similar to those in otherwise uncomplicated starvation, but that the rate of release is increased, as one

might expect.[6] Although adrenal cortical hyperfunction has long been implicated as the mediator of this hypercatabolic response, other factors appear to play a more significant role, perhaps a humoral factor released from damaged tissues.

Summary

Man seems to have developed a series of metabolic manoeuvers designed to spare his body protein. The efficiency of these is rather remarkable, and provides a metabolic basis for survival without food for many weeks to months, with a preferential use of fat as fuel resulting in maintenance of muscle mass.

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DISCUSSION

Dr. Herbert G. Langford (Jackson, Mississippi): Those of us who occasionally starve the fatties think that after several days their ravenous appetite disappears. In your subjects do you find such disappearance of appetite and can you pin it down biochemically?

Dr. Cahill: Yes, but I have no idea at all why the appetite diminishes. My guess is that the brain recognizes high ketoacid levels and the ketoacids may be part of this. We know that there are other metabolic changes. For example, if you fast a normal individual, gonadotropins decrease. Again, teleologically, when times are tough, don't reproduce. But how does the hypothalamus detect that the individual is fasting? Perhaps through the ketone level. The hypothalamus can detect the pattern of substrates coming to it, including amino acids, but precisely what regulates the natural appetite mechanisms, is unknown. It is certainly true that once you fast an overweight individual for two or three days, he dreams about food but doesn't want to eat it.

Dr. Belton A. Burrows (Boston): Did you have potassium balances along with the nitrogen balances in those long term fasting patients? Did they lose more potassium than you'd expect from the usual ratio of 2.7 to 3 mEq of potassium per gram of nitrogen?

DR. CAHILL: It was precisely 3 to 1. In other words it was just as if they were taking a piece of lean meat every day and getting the phosphate, potassium and other ions out of it. It's interesting also that the sodium they lose per day is one-fifth the potassium, which would come from just the extra-cellular fluid in that piece of lean meat. You maintain perfect homeostasis electrolytewise and also vitaminwise. If you don't eat, you don't need vitamins. If you eat a little carbohydrate without vitamins, you get scurvy, beri-beri and all sorts of other problems.

DR. FRANCIS C. WOOD (Philadelphia): Did you try intravenous amino acid feeding in this man with the fractured femur to see if it would help? From watching Jonathan Rhoads and his group it is my impression that people with infection and trauma have something beneficial happen as a result of this therapy.

DR. CAHILL: I'm very familiar with Dr. Dudrick's and Dr. Rhoads' work and have looked at it with great interest. One can totally feed a person parenterally once the acute trauma phase has passed, and can even achieve a markedly positive nitrogen balance. But in looking closely at their data and at those of others who tried by mass action to push nitrogen during the acute stage, the results have been very disappointing. One can get a few extra grams of nitrogen on board but I wonder if this isn't building up the BUN in the blood, etc., instead of making muscle or enzymes.

DR. DONALD W. SELDIN (Dallas): I want to ask your comments about a remarkable clinical paper that was published in 1948 by Chakrabarty on the Bengal famine of 1943 to 1945. He mentioned two fascinating observations. One was the fact that the natives who were profoundly malnourished often came to his office with Folin-Wu blood sugars below 40 mg% without symptoms of hypoglycemia. Presumably some factor other than glucose could function as a substrate in protracted starvation, as you've beautifully shown in previous work. The second phenomenom he mentioned was sudden death, presumably caused by an acute lack of substrate for the brain.

We have also observed patients with profound malnutrition who developed overwhelming, sometimes lethal, hypoglycemia. The hypoglycemia does not appear to be a function of short-term starvation but rather protracted malnutrition. It is not clear what factors are responsible for the severe hypoglycemia. Several possibilities suggest themselves. First, it may be that the level of such counter-regulatory hormones as glucagon, hydrocortisone, growth hormone, and epinephrine falls relative to that of insulin. Second, it is possible that the exhaustion of fat stores in prolonged malnutrition results in a fall in free fatty acids of plasma. As a result, ketone production by the liver would be reduced, rendering the subject critically dependent on glucose. However, the fall in free fatty acids would accelerate the entry of glucose into peripheral tissues, thereby critically reducing the blood sugar. Finally, it is possible that protein depletion results in a limitation in even the small amount of gluconeogenesis required to maintain the blood sugar. I wonder if you have any thoughts as to what mechanism ultimately fails.

DR. CAHILL: My guess, Dr. Seldin, is that he is running out of fat. We have excellent precedents for that because before 1921 the only way we could keep juvenile diabetics alive was to keep them in this marasmic cachectic state with literally no adipose tissue on board. Hence the only fuel they had to rely on was really glucose, which kept their glucose level at or below the renal threshold so they didn't have this continuous predisposition to go into marked acidosis. When one starves a rat or a dog, unlike man, the dog and the rat will utilize their nitrogen freely and don't have to develop as severe a ketosis as does fasting man because they don't have the big brain to feed. My guess is that man, once he runs out of the fat, will have to begin utilizing glucose again which must be made from muscle, and this is incompatible

with survival. We've never really "starved" people. These are all obese individuals with ample calories on board. We've looked for people who have congenital atresia of the gut or similar problems but they are so complicated with attempts at parenteral feeding that one can't get a well-controlled experimental situation, fortunately.

DR. W. TALIAFERRO THOMPSON, JR. (Richmond, Virginia): Several years ago we were using total starvation for certain obese patients and particularly those with cardio-pulmonary problems. We noticed that some of these patients seemed to become delusional or to have ecstacies if not hallucinations. This puts one in mind of the religious fanatics and others who have ecstacies after periods of fasting and it raises a question as to whether this is psychological or whether there is a metabolic factor which prevents the brain from using ketones as well as glucose.

DR. CAHILL: It's true that with starvation a torpor sets in. This is one reason why armies have been using starvation for centuries as a means to subdue the population and prisoners of war. A fasted rat will not move, it will just sit. Once food is offered, it will go like fury after the food. Don't ever put your finger in a cage of a rat that's fasted four or five days. There is torpor; there's a depression of total modalities which does accompany starvation but as far as mental acuity is concerned, it appears to be unaffected. There isn't any more dulling of sensation than with non-fasted controls also placed in the same kind of hospital-confined environment. We've been able to show no specific dulling of I.Q. on any kinds of tests that one cannot explain simply by the environmental deprivation of their being in the hospital ward for long periods of time. Again, teleologically, if man's brain coudn't think on ketoacids after being holed up in a cave for a couple of weeks, you and I wouldn't be here!