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FUEL METABOLISM IN STARVATION

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■ **Abstract** This article, which is partly biographical and partly scientific, summarizes a life in academic medicine. It relates my progress from benchside to bedside and then to academic and research administration, and concludes with the teaching of human biology to college undergraduates. My experience as an intern (anno 1953) treating a youngster in diabetic ketoacidosis underscored our ignorance of the controls in human fuel metabolism. Circulating free fatty acids were then unknown, insulin could not be measured in biologic fluids, and β -hydroxybutyric acid, which was difficult to measure, was considered by many a metabolic poison. The central role of insulin and the metabolism of free fatty acids, glycerol, glucose, lactate, and pyruvate, combined with indirect calorimetry, needed characterization in a near-steady state, namely prolonged starvation. This is the main topic of this chapter. Due to its use by brain, D- β -hydroxybutyric acid not only has permitted man to survive prolonged starvation, but also may have therapeutic potential owing to its greater efficiency in providing cellular energy in ischemic states such as stroke, myocardial insufficiency, neonatal stress, genetic mitochondrial problems, and physical fatigue.

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THE EARLY YEARS

The Cahill grandparents came from the west of Ireland, County Clare, in about 1870. Near the same time, my maternal grandparents, the Wagners, came from Schwaben, Germany. Both grandfathers died in their nineties after working during World War II into their late seventies in factories in New Haven, Connecticut. My father went to Hillhouse High in New Haven, and at age 16 was taken into the class of 1911 at Yale Medical School. He supported himself as a night railroad express agent several blocks from New Haven Hospital. He did well academically and was accepted as an intern in the postgraduate surgical section at New York's Bellevue Hospital. George Sr. married in 1916, went to France in 1917, and ended up as commanding officer of Field Hospital #8, a hospital originally operated by the French but taken over by Americans after we officially entered the fray. After his return to Bellevue, he joined the Urologic Service of J. Bentley Squier at Columbia College of Physicians and Surgeons, where he continued to work until his death in 1959 due to complications from a perforated duodenal ulcer.

The relevant role of George Sr. and the above personal information illustrates a classic self-made, newly privileged, second-generation American family. Those in our home on Park Avenue in New York City had a strong work ethic, particularly in academics. I was born in the city on July 7, 1927. My first three years of educational instruction were given partly in German by a *Fräulein*, who lived with us, until one evening when my father said there would be no more German talk, thanks to Hitler. The most significant figure in my life was my father, who after his Sunday rounds at the Columbia/Presbyterian Hospital frequently took me to the Natural History or Metropolitan museums, to the Aquarium or the Bronx Zoo, or to the home of one of his Columbia colleagues. He succeeded Dr. Squier as head of Urology at Columbia and became one of New York's best-known urologists, with a large number of patients from the business, academic, theatrical, and political arenas. He eventually served and presided at the major national and international urologic organizations. The bottom line is that our life was very active, both physically and intellectually.

I was shipped off to the Hotchkiss School in Connecticut at age 12, the youngest and second smallest in the ninth grade, and sang soprano through my second year! Biology, chemistry, and mathematics were my love, and I ended up chairing the Chem-Physics club at the school; however, my youth and smaller size limited my athletic career until my senior year. I entered Yale in 1944, age 16, and was then finally able to compete athletically. I enlisted in the Navy as Hospital Corpsman Second Class at age 17. After I completed boot camp in Sampson, New York, and then Corps School in San Diego, the bomb saved me from joining a Marine platoon in Camp Pendleton to invade Japan. Instead, I was sent for more than a year to the Oakland, California, Naval Hospital, which was full of the Okinawa wounded. I returned to Yale as a premed student and then went to Columbia College of Physicians and Surgeons (P&S). I graduated in 1953. My wife, Sally, and I married in 1949 and began to have children, eventually six in all.

Columbia P&S was a turning point. Yale was one party with a few academics thrown in. I had a grand time—including fraternities, athletics, and many

permanent friendships—but not much intellectual growth in comparison with my experience at Hotchkiss. My first two years at Columbia P&S were interesting but not very challenging. In my third year, I responded to an invitation for students who were interested in research to meet with Dr. Robert Loeb, chairman of Medicine. I was assigned to work with an English research fellow, Dr. Oliver Garrod, nephew of geneticist Sir Archibald Garrod. With another student, we characterized the acute effects of glucocorticoids on renal function in adrenalectomized dogs (25). This led me into reading about the adrenal. I already had some exposure from my father, who operated on adrenal tumors and hyperplasias with endocrine abnormalities. He was also the first on the East Coast to successfully remove a pheochromocytoma. But I can thank prostate surgery for financially supporting my early education and family life! The GI Bill helped me meet the Yale and P&S expenses.

ENDOCRINOLOGY AND METABOLISM VIA BIOCHEMISTRY

The name Thorn kept appearing in the endocrine literature and, because I had grown up in New York as well as attended medical school there, I applied to the Peter Bent Brigham Hospital in Boston, where George W. Thorn, the Hersey Professor of the Theory and Practice of Physic, was Physician-in-Chief. So off we went to Boston with our two kids. One of my first patients as an intern (“Medical House Officer”) in Medicine was a Peruvian physician who had a kidney implanted into his right groin by Dr. David Hume. It produced urine for six months, long before immunosuppression was in use (74, p. 57). The Brigham was an exciting hotbed of medical research into areas including renal dialysis, renal transplantation, heart valve repair, and endocrinology, particularly of the adrenal. Every patient was discussed in depth, with an emphasis on pathophysiology and biochemistry. The medical students were plentiful, eager, and brilliant.

My senior resident was a German Swiss, Albert Renold, and one night, while on Emergency Ward duty, we took care of a moribund, unconscious young lad brought in by the Boston Police. He was hyperventilating, hypotensive, and had dry skin with poor turgor: classical diabetic coma, particularly with the sweet smell of acetone. He awakened after we administered appropriate fluids and intravenous insulin, and he was discharged a few days later. Renold and I discussed the how and why of ketosis through the night. The lad, an Irish American from the Mission Hill District of Boston, was a high school dropout who lived in poverty with an alcoholic family. I befriended him and saw him on numerous occasions for about ten years. He served as a volunteer for a number of studies on insulin/glucose relationships. We found that establishing a fixed insulin level to maintain a normal fasting glucose concentration was inadequate to allow the body to handle a glucose load. And, more interestingly, the higher insulin level needed to be achieved rapidly, meaning the physiologic response is not only a function of insulin level but also the rate at which the level is achieved, namely d_{insulin}/dt . One of our former fellows,

Thomas Aoki, many years later studied in depth this approach in the treatment of very labile type 1 diabetics and found that very rapid intravenous pulses of insulin markedly improve glucose homeostasis for days to weeks (1).

Renold had spent two years in the Department of Biological Chemistry with Prof. A. Baird Hastings prior to his Brigham senior residency, studying carbohydrate metabolism using C^{14} in liver slices from normal and alloxan diabetic rats. Fructose uptake was similar; however, labeled glucose conversion into glycogen, fat, and CO_2 were all diminished in the diabetic. Insulin therapy corrected the deficiency. After a second clinical year, I joined the Hastings laboratory, and found glucose metabolism to have an overall K_m about 5 mM. The finding that this was not due to cell permeability suggested the presence of a specific hepatic "glucokinase" that was controlled by insulin (10). In contrast to muscle, glucose permeated the liver cell wall equally in normal and diabetic patients (9). The enzyme, glucokinase, and its decrease in diabetes were soon characterized by Sidney Weinhouse in Philadelphia and Alberto Sols in Madrid, Spain. Also, with James Ashmore, another fellow in the lab at the time, we found a reciprocal increase in glucose-6-phosphatase activity in the diabetic liver (3). This was just the time that Eugene Knox demonstrated the adaptability of hepatic tryptophan oxidase to dietary tryptophan levels. Prior to this time, enzyme activities were thought to be relatively stable, an erroneous concept emphasized at Harvard by Professor Otto Folin, who had preceded Professor Hastings as chairman of Biological Chemistry.

ADIPOSE TISSUE

After two years in the Hastings lab, I returned to the Brigham for another clinical year and then joined Renold, who had moved several blocks to the Baker (later the Joslin) laboratories at the New England Deaconess Hospital. He had a small group of fellows, many from Europe (particularly Switzerland), and the major effort at the time was devoted to studies on adipose tissue using the rat epididymal fat pad, a preparation originally characterized by E. Wertheimer and colleagues in Israel and F. Hausberger at Philadelphia. The exquisite sensitivity of the pad to insulin, as quantified by increased glucose oxidation to CO_2 , was used by Renold and colleagues as an assay for circulating insulin in biological fluids, including human serum. Renold and I assembled what was then known about adipose tissue in the *Handbook of Physiology* for the American Physiological Society. It covered the adipose literature up to 1966 and contained more than 4300 references (56).

Many small points were clarified regarding adipose tissue, such as the release of free glycerol with the fatty acids mobilized during fasting or epinephrine stimulation (42). But all of these studies suggested that the role of insulin in fasting is very important, perhaps as important as its role in the fed state. By the early 1960s, I was in charge of the Brigham Endocrine-Metabolic Unit in addition to my research efforts with Renold at the Baker lab, which, by the way, was and continues today to be a part of the Joslin Foundation, but academically under the aegis of Harvard Medical School via Dr. Thorn's Department of Medicine. The Brigham had and

continues to have a Clinical Research Center supported by National Institutes of Health (NIH) funds. By then, immunoassays had been devised for many hormones, insulin, glucagon, and growth hormone in particular. The Baker lab has grown into the prestigious Joslin Research Laboratories, now headed by C. Ronald Kahn, with an annual budget of well over \$20 million. Renold had returned to Geneva in 1962 and founded a major research team focused on all aspects of diabetes, leaving me in charge of the Joslin labs.

THE BRIGHAM

The Department of Surgery at the Brigham, under the direction of Francis D. (Franny) Moore, focused on the metabolic alterations in surgery and trauma. He was a world leader, and thanks to the small size of the Brigham, the medical and surgical staffs were closely intertwined. There were only 6 surgical and 12 medical interns, and more than once I helped sew up patients in the ER when the surgeons were too busy and, likewise, when we medical types were overloaded, we had help. Also, the medical house officers attended and even participated in some of the major surgical procedures, particularly cardiovascular surgeries. Part of this collegiality was generated at Friday's Grand Rounds. The first half hour was pure surgery, the next full hour was devoted to combined medical/surgical, and the final half hour to medical alone, although many surgeons, junior and senior, would stay over. We frequently also came early to hear the surgical cases. I should add that my original plan was to spend a year in medicine and then to move on to Dr. Moore's Department of Surgery. The Renold tutelage, the diabetic youngster, and the two years in biochemistry took care of any future surgical career, except for many collaborative activities with the Brigham surgeons.

STUDIES ON STARVATION

In 1965, we enlisted six divinity students to fast for eight days and studied the levels of every metabolic substrate and hormone that we could measure (11). The central role of insulin in controlling the fed state had been well characterized, and its role in fasting needed clarification. Essentially, we repeated and expanded the 1911 classical study of starvation by Benedict, who fasted a Maltese, Mr. Levanzin, for 30 days and nights (4). We also fasted two type 2 diabetics, who differed from the normals by better nitrogen conservation. They were slightly more efficient, in keeping with the concept of James Neel (at Michigan) that type 2 diabetes may have been an evolutionary selective advantage in a starving population. Stuart Soeldner (69) at the Baker laboratory devised an exquisitely accurate and sensitive double-antibody immunoassay for insulin, and this allowed us to characterize the central role that low levels of insulin play in controlling fuel metabolism in starvation. Likewise, an accurate enzymatic analysis of the ketoacids was designed by Derek Williamson in Sir Hans Krebs's lab (59, 82), which also helped greatly.

Therapeutic fasting of obese subjects was in vogue in the 1950s and 1960s. In an informal conversation with Rachmiel Levine, who knew of our fasting work, it became evident that the fuel substrate for brain could not continue to be glucose since gluconeogenesis from protein would consume so much muscle that long-term viability would be dramatically decreased (6). At about the same time, a very bright and industrious Hopkins Medical Resident, Oliver Owen (29, 48), joined our team and launched a series of studies lasting the next five years or so at the Brigham. Dr. Owen continued his studies after his move to Temple (24, 51, 55). The first question related to brain substrate utilization. Three very intelligent obese subjects were selected for a five- to six-week starvation study (Figures 1 and 2). Urinary nitrogen excretion fell to 4–5 grams/day, and catheterization of the jugular, as we expected, showed some two thirds of brain fuel consumption to be D- β -hydroxybutyrate and acetoacetate, markedly diminishing the need for muscle proteolysis to provide gluconeogenic precursors (Figure 3). Thus, a normal adult human could survive two months of starvation; an obese person could survive much longer. Were it not for the β -hydroxybutyrate and acetoacetate providing brain fuel, we *Homo sapiens* might not be here!

Oliver Owen's data on brain (50), then on liver and kidney (49), and Thomas Pozefsky's on muscle (53), along with many succeeding fellows, particularly Philip Felig, allowed us to piece together the interplay of hormones and substrates in starvation. The team also included Errol Marliss, Thomas Aoki, Guillermo Herrera, Neil Ruderman, Aldo Rossini, and several from the surgical staff (Fred Morgan and Murray Brennan, to name two). There were also collaborations with other groups, such as George Reichard's team at the Lankenau Institute in Philadelphia (55). Many other fellows helped fill out the overall scheme in complementary metabolic studies in tissues in vitro and in rodents and dogs. However, the human studies quantifying the flux of numerous metabolites through various organs during starvation summarize in simple form these interrelationships (Figure 4). High points are the significant metabolism of β -hydroxybutyrate and acetoacetate by brain and their production in liver. About two fifths of fatty acid metabolism in the whole body is via hepatic ketogenesis, some 100 to 150 grams/day. Yet there is still significant brain metabolism of glucose (Figure 3). Hepatic glycogen contribution to blood glucose is essentially zero by the second or third day of starvation. Total splanchnic glucose production in several weeks' starvation amounts to approximately 80 grams daily. About 10–11 grams/day come from glucose synthesis from ketone bodies, 35–40 grams from recycled lactate and pyruvate, 20 grams from fat-derived glycerol, and the remaining 15–20 grams from protein-derived amino acids, mainly alanine (Figures 4 and 5).

The next question to be answered is how the levels of the above substrates are controlled. One has to turn first to the major nitrogen pool, namely muscle. Muscle nitrogen is probably the determinant of long-term survival in man, particularly in a primitive environment. The branched-chain amino acids, leucine, isoleucine, and valine, are metabolized in situ in muscle and the nitrogen released into the bloodstream primarily as glutamine (44) and alanine (15–18). The

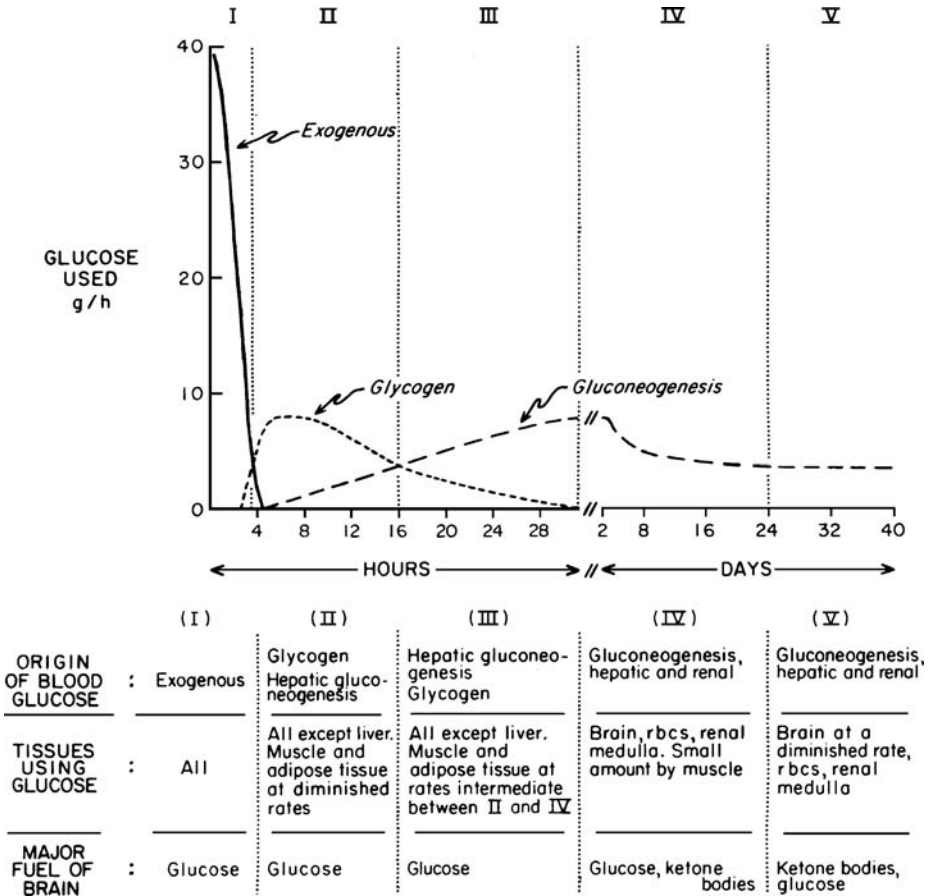


Figure 1 The five metabolic stages between the postabsorptive state and the near-steady state of prolonged starvation (62).

glutamine is mainly metabolized by kidney to produce ammonium ions and the remaining carbon goes to glucose via the gluconeogenic pathway (27, 35) (Figure 5). The kidneys in starvation produce about two fifths of new glucose. The remaining three fifths is made by liver from (a) alanine coming from muscle and the nonhepatic splanchnic bed; (b) recycled lactate and pyruvate (the Cori cycle), e.g., from red blood cells and renal medulla; (c) glycerol from adipose lipolysis; and finally, as mentioned above, (d) a small amount from β -hydroxybutyrate to acetoacetate to acetone to propanediol to pyruvate to glucose, as in Figure 5. The urinary ammonium ion is excreted with β -hydroxybutyrate and acetoacetate to maintain acid-base homeostasis and cations, mainly sodium, to maintain extracellular volume. It should also be pointed out that ammonia excretion saves calories

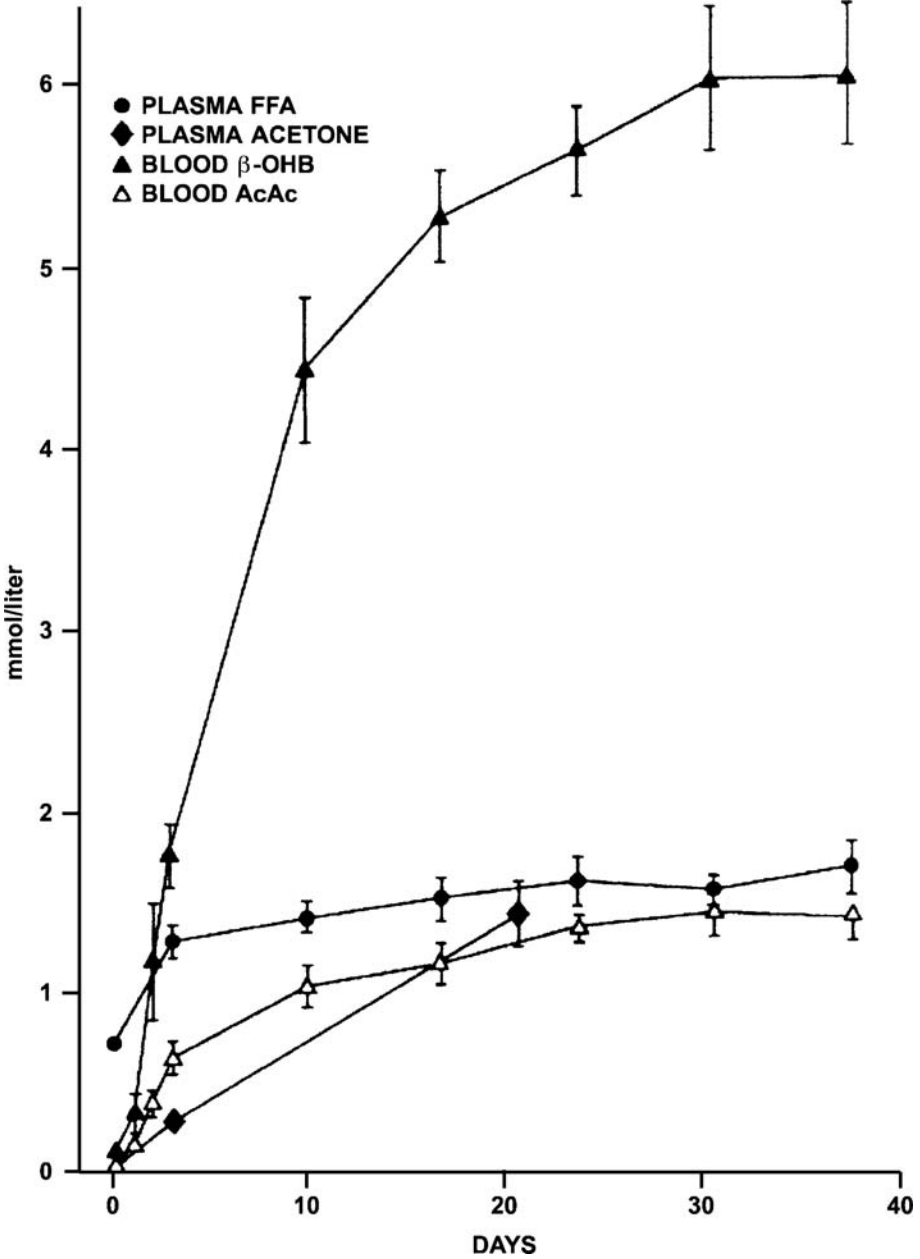


Figure 2 Concentrations of ketone bodies and plasma free fatty acids (FFA) in transition from the postabsorptive state to 4–6 weeks of starvation in a large number of subjects, male and female. Note the more than three orders of magnitude change in β -hydroxybutyrate and the doubling of FFA. Data courtesy of Dr. O. E. Owen.

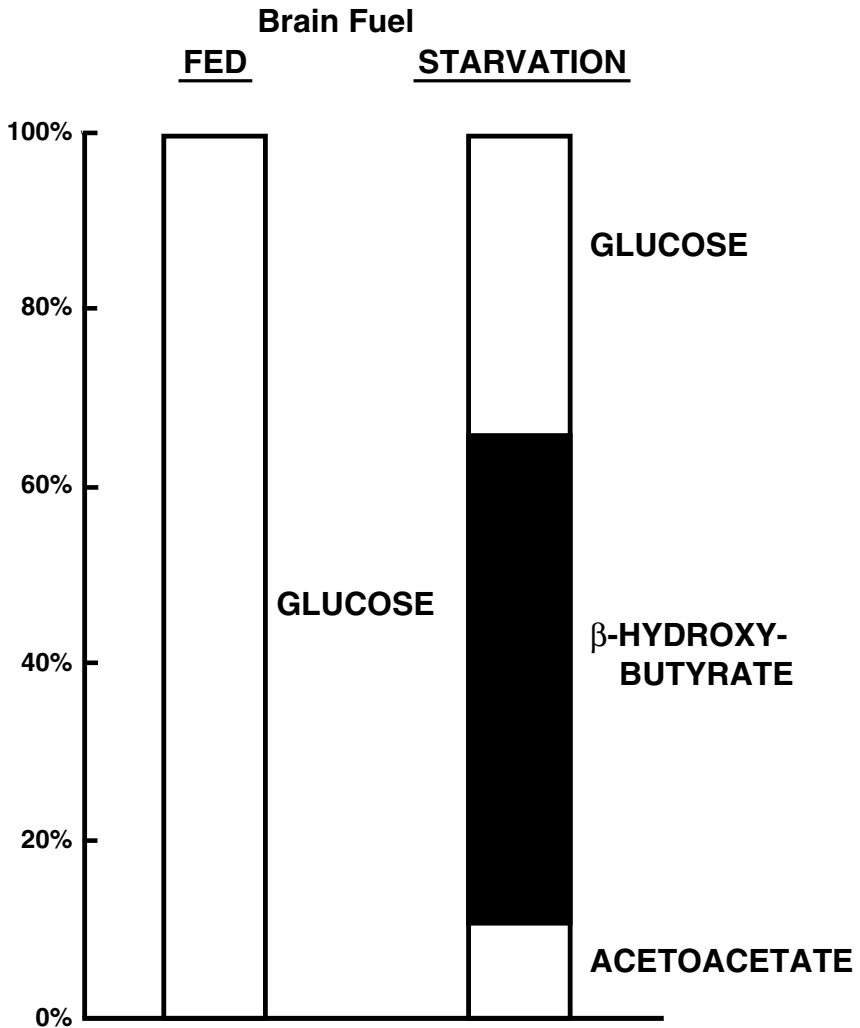


Figure 3 Brain substrate utilization in three fasting obese volunteers after several weeks of starvation (48, 49). Many studies suggest human brain cells can survive with little to no glucose, but proving the point is difficult as well as experimentally difficult and ethically questionable.

otherwise needed for hepatic urea synthesis, i.e., two high-energy phosphates per urea nitrogen.

What controls glutamine levels? Acid-base homeostasis has been shown by administration of sodium bicarbonate to diminish urinary ammonium and total nitrogen excretion accordingly in fasting subjects (28, 51). Conversely, trapping

glutamine by administration of phenylacetate to fasting subjects increased urinary nitrogen excretion by the amount excreted as phenylacetylglutamine (51), which suggests a fine homeostatic control of blood glutamine levels.

Next, I turn to the question of what controls hepatic glucose production. It appears simply to be the rate of release of alanine from muscle as reflected by its blood concentration (18). As originally championed by Felig (16), the liver in starvation is wide open, so to speak. Both in the lab and in the clinic, administration of alanine results in a rapidly increased glucose synthesis. Also, the syndrome of hypoketonemic hypoglycemia in children is associated with low levels of circulating alanine and is corrected by alanine administration (31, 52). It thus appears that the blood glucose level in starvation is controlled by muscle proteolysis, the regulator being insulin concentration and its subsequent metabolic effect (8) (Figure 4). On the other hand, renal glucose production appears to surpass that which can be explained by glutamine consumption alone.

What controls ketogenesis? First, the accelerated adipose tissue lipolysis produces increased fatty acids and glycerol, the latter being quantitatively incorporated into glucose by the liver. J. P. Flatt (21) has suggested that mitochondrial adenosine triphosphate (ATP) produced by the partial oxidation of fatty acids to β -hydroxybutyrate and acetoacetate provides the major energy for liver metabolism and thereby reaches an upper limit approximating that achieved in diabetic ketoacidosis (40). Elevated levels of β -hydroxybutyrate inhibit adipose release of free fatty acids (73, 81), but insulin is necessary for this effect.

How does the brain function using mainly β -hydroxybutyrate and acetoacetate? Intellect-wise it is indistinguishable from glucose. Many studies have shown reversal of hypoglycemic signs and symptoms by ketone bodies. However, some changes do occur. Gonadotrophins decrease, but these also decrease in other caloric deficits without elevated ketone levels, as in patients with anorexia nervosa who eat some 100 grams or less of carbohydrate daily (23). Yet, there are metabolic alterations, as is well known in the world of epilepsy. As popularized by the Hopkins group of John Freeman and Ellen Vining and associates (22, 26), about one third of the children with multidrug-resistant epilepsy improve dramatically on a strict ketogenic diet, another one third improve to some extent, and the remainder experience little or no effect. The problem is that the diet has poor palatability, and patients may experience gastrointestinal problems as well as a degree of osteoporosis, delayed growth, delayed puberty, and some changes in potentially atherogenic blood lipids, although this last point is not accepted by all. Adherence to the diet is clinically difficult (61).

β -HYDROXYBUTYRATE AND ENERGY PRODUCTION

In 1995, my colleague Richard (Bud) Veech, MD, PhD, and his associates at the NIH, Kashiwaya et al. (35) and Sato et al. (66), reported that the working perfused rat heart showed an increase in work output and a decrease—yes, a *decrease*—

in oxygen consumption when β -hydroxybutyrate was added to the glucose in the medium. This observation stemmed from an immense amount of laboratory work to measure numerous metabolic intermediates. The data demonstrated that the increased efficiency was the result of the widening mitochondrial substrate ratio of NADH and NAD^+ between complex 1 and complex 2. The net effect is a greater potential for ATP production. Richard Strohmman used the work of Veech and colleagues (35, 66, 79, 80) to illustrate the essentiality of determining numerous substrate concentrations involved in enzymatic reactions controlled by thermodynamic principles to understand fluxes in complex metabolic pathways. Strohmman has applied the term "strength control" to this science (71). Measuring enzyme activities is only a small component of the picture, and stepping back a little, so are the genetic controls of the enzymes. One can talk of the genome, the transcriptome, and the proteome, but the control is in the metabolome, the basis of metabolic homeostasis. Small changes in transcription and translation in enzyme protein synthesis and thus in enzyme levels may be functionally unimportant in overall metabolic control. A recent book by E.D. Schneider and D. Sagan (68) has underscored the fundamental role of nonequilibrium thermodynamics in living systems.

This brings us to the evolutionary history of β -hydroxybutyrate (β OHB) and the role of various energy sources required for life. Most bacteria use poly- β -hydroxybutyrate as an energy store; coliforms are an exception. In some protozoans, up to 90% of dry weight is poly- β OHB. Even archaea use it for energy storage, which suggests it has been around for well over 2–3 billion years. It is possible that its selection was aided by the periods of low environmental oxygen that occurred during the Archaean, Proterozoic, and Palaeozoic eras. Poly- β OHB is stored as several large granules in the cytoplasm, therefore having very little osmotic effect. This is in contrast to the two other fundamental archaeal energy stores, polypyrophosphate (38) and various polysaccharides (14). Both of these require much hydration, with 2–4 grams of water stored in cells along with each gram of glycogen (19). Polypyrophosphate for energy storage disappeared with the prokaryotes. However, we have retained poly- β OHB, but apparently not for energy. It is a component of cell walls and, in one case, a component of a Ca^{2+} channel (57). This is the only example of a nonprotein ion channel so far reported. It is also present in low concentrations in blood serum, and altered levels have been reported in diabetic animals (58). I should point out that I have been unable to find evidence of triglyceride in prokaryotes!

Returning to fasting man, brain use of β OHB, by displacing glucose as its major fuel, has allowed man to survive lengthy periods of starvation. But more importantly, it has permitted brain to become the most significant component in human evolution. Other secondary adaptations had to be made, particularly in reproduction. The mega brain of *H. sapiens* and the recent antecedents such as *neanderthalensis*, *erectus*, and *habilis* posed a problem in getting the big head through the pelvic canal, particularly with bipedalism, as the hominoids became hominids, some 7 mya. Bipedalism necessitated narrowing of the pelvic canal

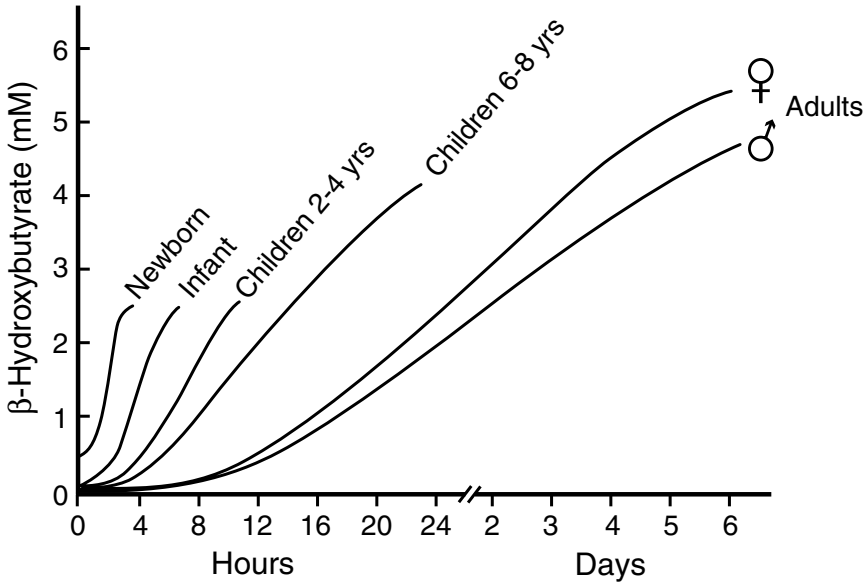


Figure 6 Levels of β -hydroxybutyrate in starving subjects of different ages (5, 13, 30, 54, 59, 66). Not shown is the accelerated ketosis in fasting pregnant or lactating women or in any subject with marked renal glucosuria requiring increased gluconeogenesis, e.g., when the renal threshold is surpassed, as in type 1 diabetes (40), or with genetic renal glucosuria or chemical inhibition of tubular reabsorption of glucose (phlorizin administration).

for optimal mobility. Speed necessitates limbs close together, whereas limbs far apart result in waddling, i.e., greyhounds versus bulldogs, deer versus turtles, pheasants versus ducks. We are the only primate born facing backward and, more importantly, born obese. Obstetric problems in primates other than humans are essentially unknown (60).

Not well known, however, is the metabolism of the human newborn, which is essentially ketotic. Blood glucose levels fall strikingly in the neonate, and concentrations of β OHB may rise to 2–3 mM. The newborn human brain consumes 60%–70% of total metabolism at birth, nearly half via β -hydroxybutyrate. Fitting in with this pattern is maternal colostrum. It contains much triglyceride and protein, but little lactose, starting man's entry into society on an Atkins diet (Figure 6)! Lactose gradually increases during the first two to three days of lactation (46), during which time ketosis disappears. Also, humans are born a few months premature compared with our primate cousins. And, again, we are the only primate born fat, probably to furnish the caloric bank for our big brains. We are also the only primate with significant neonatal brain injury (20) due to extreme sensitivity to hypoxia/ischemia (78). Again, this is a penalty for having a big brain!

Several reports have noted that infants raised on the breast from birth are brighter than those placed on formula (43). This energy importance of colostrum is supplemented by its immunoglobulins, but it is not as important as in some of our domesticated animals, particularly the newborn foal, where the immune defense provided by colostrum is critically important for survival.

To summarize where we are so far, β OHB plays a central role in prolonged starvation in man. How about other long-term starvers? Recently our bird feeder was destroyed, as it is every year, by a local black bear that had emerged from its den after a 4- to 5-month winter sleep. Was the bear ketotic during that period? No. Ralph Nelson at the University of Illinois has studied renal function in the black bear in winter sleep and has found that the level of β OHB remains below 0.5 mM while the bear is starving in its den (70). The reason is that glycerol from adipose lipolysis is more than adequate to provide glucogenic substrate for hepatic gluconeogenesis. Any animal whose brain accounts for less than 5% of total metabolism need not and does not get ketotic during starvation (ruminants are an exception, *vide infra*). This includes several cetaceans with 20- to 40-pound brains and multiton bodies that eat annually for a period of only several weeks and yet have ample glucose for brain owing to a plentiful supply of glycerol from their adipose tissue. Except for some small rodents that can achieve β OHB levels of 2–3 mM on starvation, most rodents have levels that remain at less than 1 mM, and only humans, as far as we know, achieve levels over 5 mM, the adult average being between 4 mM and 7 mM after two weeks fasting. Although I have no data, the ideal candidate for long-term starvation survival would seem to be a sumo wrestler or an overweight six-foot-tall Polynesian male or female in whom brain would be some 10% of total metabolism. The increased glycerol from adipose lipolysis would increase hepatic gluconeogenesis and spare muscle nitrogen accordingly, similar to eating small amounts of carbohydrate. Apparently, the brain size of adult *H. sapiens* is poorly, if at all, related to the size of the remainder of the body!

There are several exceptions to the genesis of ketosis in man described above. Levels of 5 mM or higher can be achieved in children in two to three days of starvation (Figure 5). The larger the brain/body ratio, the more rapidly the ketosis develops, as in the newborn. The same holds true for the pregnant woman, since the conceptus, calorically speaking, is just another glucose-consuming tissue like brain. In the same vein, lactation necessitates increased gluconeogenesis, and nursing mothers who are fasting experience increased ketosis. However, prolonged severe ketosis in a starving female may terminate pregnancy, which tragically can occur in prolonged population starving or more rapidly in diabetic ketoacidosis. The blockade of tubular reabsorption of glucose in the kidney by phlorizin, producing marked glucosuria, similarly induces ketosis in both man and experimental animals. This same concept holds in the ruminant, already on a ketogenic diet from its rumen. Any extra demand for glucose synthesis augments hepatic gluconeogenesis, and *pari passu*, ketogenesis. The farmer finds his best milk-producer staggering in the pasture, hyperventilating, and, if determined, suffering from

hypoglycemia. Therapy is a bolus of 50% glucose, but more practical is simply a molasses "lick." Also, twinning in sheep by adding the glucose needs for two concepts to the otherwise small glucose need by brain necessitates increased gluconeogenesis and concomitant increased ketosis.

In vitro studies using brain slices show the priority of CNS usage of β OHB over glucose (33, 63). It appears that one can roughly use the relative molar concentrations of β OHB and glucose to know the relative brain metabolism of the two. With 7.0 mM β OHB and 3.5 mM glucose, two thirds of brain's metabolic substrate is β OHB. An approximation for clinical use is that if a diet contains over 100 grams carbohydrate, there is no ketosis (<0.1 mM). As one decreases dietary carbohydrate, ketogenesis begins. Glucose intake ("carbs") of 20–40 grams is associated with β OHB of approximately 1 mM, but wide variations exist between people. Glucose administration to fasting normals reverses starvation metabolism rapidly, particularly nitrogen loss (Figures 7a and 7b). Even a small amount such as 7.5 grams decreases ketoacid and ammonia nitrogen excretion (65). An anthropologic extrapolation would suggest that a few berries or a carbohydrate-containing

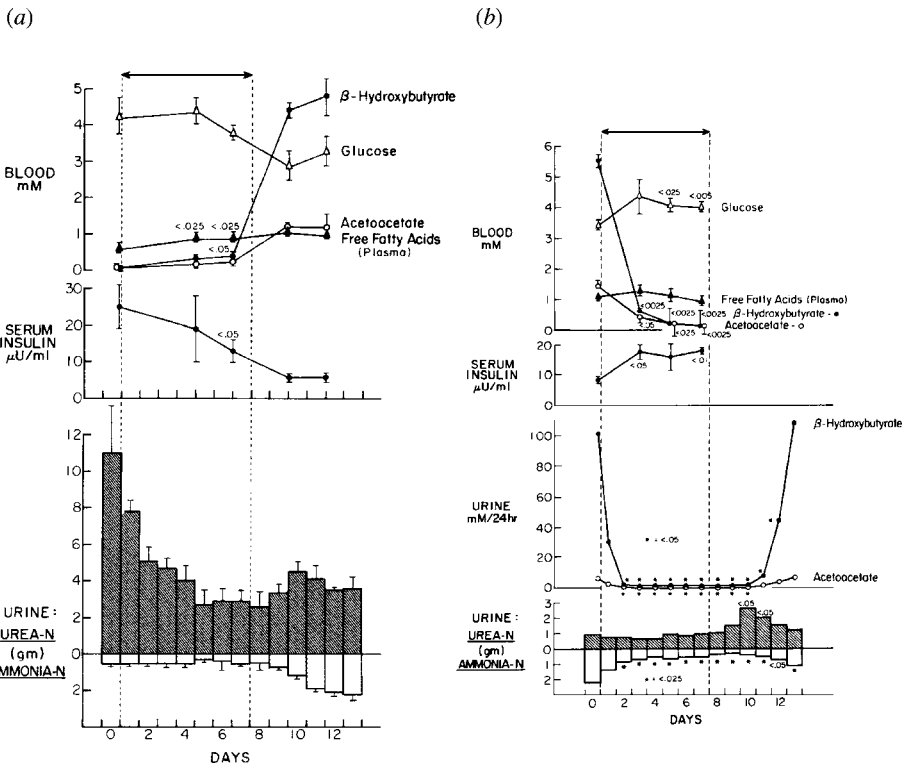


Figure 7 Inhibition of starvation metabolism by administration of 150 grams of glucose daily for seven days either before a fast (Figure 7a) or following three weeks of starvation (Figure 7b) (horizontal line at top of each figure is glucose infusion) (2).

TABLE 1 Metabolic fuels*

Substrate	Kcal/g
Free fatty acids	9.31
β -hydroxybutyric acid	4.69
Glucose	3.72
Acetic acid	3.48
Pyruvic acid	3.17

*National Bureau of Standards.

root nibbled intermittently by a cruising hunter-gatherer might be critical for long-term survival.

Absent carbohydrate is similar to total starvation. However, protein intake plays a very large role. One can consider 1 gram of protein to produce about a half gram of glucose, and this certainly is a very significant component in the treatment of children with epilepsy by the ketogenic diet. High protein, as well as carbohydrate, has to be avoided. Also, the degree of ketosis in man on a high-protein, high-fat diet, namely the diet of the Inuit, is intermediate thanks to the protein (32). However, caloric homeostasis in a 70-kg man on protein alone is incompatible with life since the maximum rate of urea synthesis is insufficient to provide even basal calories, about 1000–1300 Kcal/day, or 250–325 grams of protein (64). The Arctic explorer Stefansson as well as others eating pure meat without the blubber learned this only too well. Protein poisoning in Arctic explorers is well described by McKinlay in his report on an Arctic tragedy (45, p. 101).

β -HYDROXYBUTYRATE: THE MOST EFFICIENT FUEL

Veech and colleagues discovered that administering β -hydroxybutyrate to the perfused rat heart in place of glucose increased work output but decreased oxygen consumption (35). Henry Lardy (41), in the 1940s, showed that bull sperm motility was increased in vitro by β -hydroxybutyrate as compared with 15 other substrates but with a *decrease* in oxygen consumption, similar to the perfused heart. One then has to consider β -hydroxybutyrate as a unique nutritional compound (Table 1).¹ It has equally balanced hydrophilic and hydrophobic characteristics, and therefore is neither fat nor carbohydrate. Again, it is an archaic molecule. Does it have any therapeutic value as either a nutraceutical or a pharmaceutical agent?

Veech et al. addressed this question in 2001 (80) and again more recently in 2004 (79). A more simplistic paper for physicians was also published (12). One

¹R.L. Veech has summarized in a recent publication (79) the biochemical mechanisms whereby β -hydroxybutyric acid is the most efficient fuel per molecule of oxygen consumed when compared to glucose, to pyruvate, and particularly to free fatty acids (39). The biochemical and biophysical discussion is beyond the scope of this paper.

can posit a number of uses, including in obstetrical problems whereby the infant might be supported by β OHB during difficult labor, the agent being infused into the mother. It readily crosses the placenta. Next, the fact that nature delayed the synthesis of adequate lactose for the first day or so suggests β OHB might be of help in any newborn, particularly if small for gestational age. It has already been used in children with congenital disorders in fat oxidation or ketone production with some dramatic success (54, 75). As mentioned above, its use in drug-resistant childhood epilepsy to displace the ketogenic diet awaits the availability of orally absorbable esters. The sodium salt has been given to children without apparent problems, but the amount needed to get the blood level into the therapeutic range for epileptic children challenges the capacity to excrete alkaline urine as well as deal with the sodium overload.

Essentially, any cell challenged by low oxygen availability or by a toxin interfering with mitochondrial function should benefit by utilizing β -hydroxybutyrate in preference to any other substrate, including glucose, lactate, pyruvate, or fatty acids. In a very simple experiment, mice given β -hydroxybutyrate exposed to 4% oxygen survived longer (37, 72). Likewise, neurons in models of Alzheimer's and Parkinson's disease survive better with β -hydroxybutyrate in the system (36). Recent studies have shown that rats fatigued on an exercise wheel perform better after β OHB addition to the diet and, more interestingly, subsequently are able to improve in psychological tests (R.L. Veech and K. Clarke, personal communication).

This brings up a number of possibilities for its potential therapeutic uses. Ketosis, as described above, has a major role in drug-resistant epilepsy, and the ketogenic diet, though effective, is unpalatable and has some metabolic adversities. If it takes 125–150 grams/day of β OHB to bring an adult to 5 mM, 75 grams or so is required for a child. If given as the sodium salt, it causes metabolic alkalosis. However, infants with hereditary deficiencies in fat metabolism given much smaller amounts appear to tolerate the excess alkali, and most importantly, may have a dramatic reversal of their nervous system problems and, in some (75), improvement of cardiac function. But if β OHB increases the capacity of oxygen-deprived or otherwise ATP-deficient states as in mitochondrial deficiencies, hereditary or acquired, it could have numerous applications. A significant clinical improvement has been shown in patients with Parkinson's disease placed on a severely carbohydrate-deficient diet (76, 77). As of this writing, attempts are being made to synthesize esters of β -hydroxybutyrate that are orally acceptable and metabolizable to provide sufficient therapeutic levels in the circulation. A major current medical problem is the cognitive impairment of subjects undergoing cardiac surgery, particularly those put on a bypass pump machine. Professor Stanton Newman of London (47) has reviewed the clinical and pathologic data, which show numerous microemboli in brain cortex. Experimental animal data indicate increased survival of brain cells is a high probability with 5 mM β -hydroxybutyrate in the circulation.

RESEARCH, EDUCATION, AND THE BIOMEDICAL COMMUNITY

My first work in the lab of Dr. Hastings, interrupted by clinical training and then by work on the adipose tissue, brought me some recognition in the research world: I was given the Young Investigator Award of both the Endocrine Society and the American Diabetes Association. I subsequently became extremely busy serving with a number of governmental agencies, bio-research institutes, scientific advisory boards (i.e., chairman of Merck's), the National Diabetes Commission, the Nutritional Advisory Board of NASA, and others. I was offered several chairs of medicine and deanships, but my disregard for administrative minutiae persuaded me to remain a free agent. However, I did take on one major role, namely with the Howard Hughes Medical Institute (HHMI).

Going back to 1960, Dr. George Thorn (7), my major mentor, who was research director of HHMI and one of its three founding officers, offered me a position as an investigator. HHMI was an institute without walls, its investigators scattered at biomedical research centers around the country. I was then one of Harvard's six or eight located at the Brigham Hospital. The investigatorship covered salary and fringe benefits and eventually research support. HHMI was not then and is not today a foundation. After I finished my six-year HHMI term, I was promoted to associate professor of Medicine with tenure at Harvard.

In 1972, I joined the HHMI Scientific Advisory Board, which was in control of candidate selection, as well as 3–5-year reviews of investigator performance. I had been promoted to professor of Medicine, Harvard, in 1970. The Institute then had three programs: Endocrine-Metabolic, Immunologic, and Genetic. Currently it has six programs: (a) Cell and Developmental Biology, (b) Genetics and Molecular Biology, (c) Immunology and Microbiology, (d) Mathematical Biology and Epidemiology, (e) Neuroscience and Physiology, and (f) Structural Biology and Biochemistry. A number of "experts" in the field serve on a Scientific Review Committee for each program. Many other activities on college campuses, as well as some in high schools and museums, are supported by HHMI, with a current total budget of about \$500 million/annum. Dr. Thorn became president in 1978, and I replaced him as director of research in charge of the scientific review committees and candidate selection as well as salaries, budgets, and investigator reviews. I won't go any further except to note that I had to learn much basic science in the six disciplines. The annual meeting for each group was an education, and without mentioning any names, every gathering had one or more Nobelists either on an advisory board or as an investigator in the Institute. No one could ask for a more exciting and educational job. I was also responsible for the NIH Cloister Program in which medical students spent one or two years at the NIH with one of the NIH staff members as his/her preceptor. James Wyngaarden, the director of the NIH at that time, awarded me the Director's Medal for the program's success.

Other activities included the setting up of the Human Gene Organization (HUGO) with Hopkins Professor Victor McKusick as its founding president. As its secretary/treasurer, I arranged the first meeting, held in Building 10 at the NIH, which was attended by 150 of the world's leading human geneticists and chaired by Sir Walter Bodmer of the Imperial Cancer Institute. The NIH soon got going and appointed James Watson to head their unit. At the time, Francis Collins, now its director, was a Hughes investigator at the University of Michigan. The Institute funded HUGO with a \$1 million grant. Some called the organization "Victor's Hugo"! The journal *Genomics* is its current product, among many other activities. George Thorn was made president and chairman of the board of HHMI; Donald Fredrickson subsequently became President, followed by Purnell Choppin. The present president is biochemist (and Nobelist) Thomas R. Cech.

UNDERGRADUATE TEACHING

The aforementioned was not good for family life. We had an apartment in Bethesda, one in Newton, Massachusetts, and our anchor was a small house built in 1834 in Stoddard, New Hampshire. I was elevated to a vice presidency of HHMI but appreciatively resigned in 1989. However, the Institute had reviewed a grant request from Dartmouth College to support their biology programs. Since Stoddard is 50 miles from Hanover, I considered doing some teaching and met with James Friedman, then president. I was given the title of Professor of Biological Sciences. I spoke to a number of the biology faculty members and put together a proposed course on biology centered on humans and their diseases. Some faculty members were very much in favor and some were very opposed to this MD outsider competing for student attention. Anyway, the course was started in a classroom that held about 100 students. Within a few days, we had to move to a larger auditorium, then yet again to a major facility that held more than 400 students. I taught the course for seven years, and loved it. So, I gather, did the students. The course continues to be taught by Professor Lee Witters and it remains a favorite. I had known Lee since his research efforts at Massachusetts General Hospital, and we became reacquainted soon after my start at Dartmouth. My broad experience at HHMI in multiple areas of biology also led Dean Andrew Wallace to appoint me to the Board of Overseers of the school. I also joined the MD/PhD Committee.

RETIREMENT

Biomedical science has been a great pleasure. I peruse the *New York Times*, *New England Journal of Medicine*, *Science*, *Nature*, *Lancet*, and for life in general, the *Economist*. Keeping our forest trails open, plowing roads in winter, and mowing fields in the summer, assisted several decades ago by our six children, has kept me physically in reasonable shape. But behind all of the aforementioned and

continuing today is my wife and colleague of almost 56 years, Sally. She has tolerated much and has been a major factor in both my private and professional lives. This is in addition to her social grace and numerous charitable activities involving hospice, our little village of Stoddard, church, her alma mater (Miss Porter's School), handgun control, 14 grandchildren, etc. She continues to be a very busy lady and an outstanding companion.

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*I was informed that this review should be partly biographical and accordingly want to state that the references quoted are mainly those of myself and my colleagues. I do not want to lose my remaining endocrine-metabolic friends!

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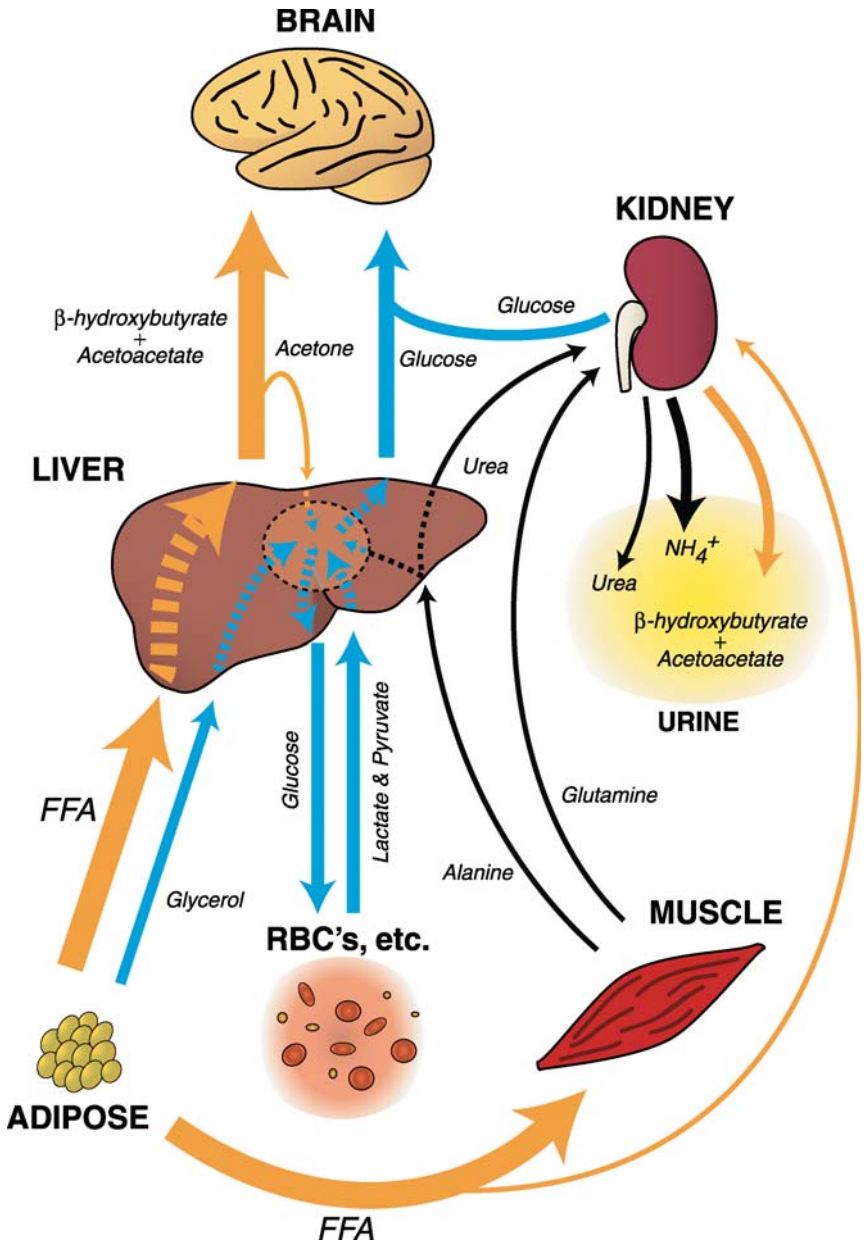


Figure 4 Overall scheme of starvation fuel metabolism. Liver derives its major energy by partial oxidation of FFA to β -hydroxybutyrate and acetoacetate; muscle and kidney by complete oxidation of FFA to CO_2 and H_2O . Brain utilizes both β -hydroxybutyrate and acetoacetate and glucose. FFA, free fatty acids; RBCs, red blood cells.

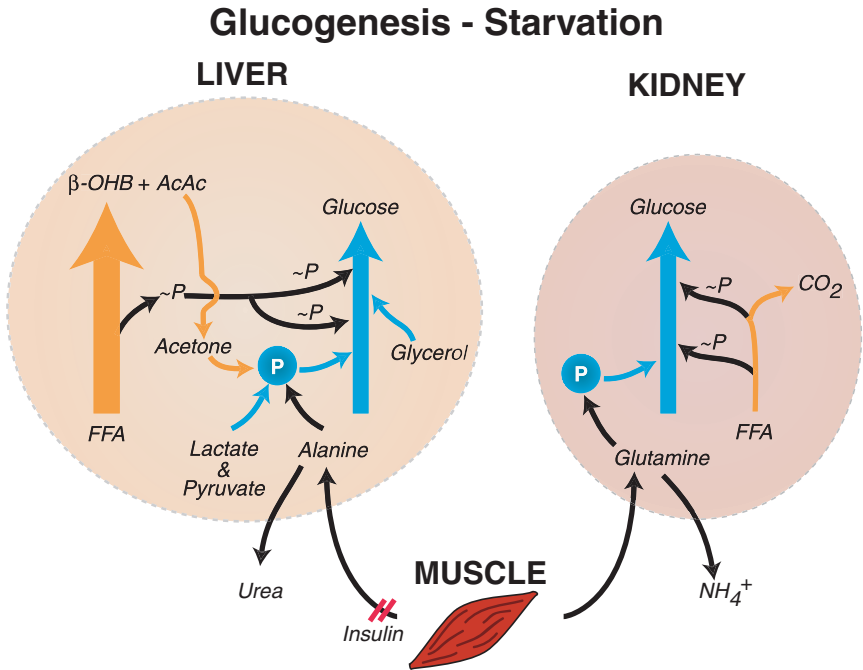


Figure 5 Glucogenesis in starvation in liver and kidney. Precursors in liver via mitochondrial pyruvate carboxylation (white "P" in blue circle) are acetone, recycling lactate and pyruvate, and pyruvate from deaminated alanine from muscle. Glycerol from adipose tissue enters the glucogenic pathway at triose phosphate. Precursors in kidney are from deamidated and deaminated glutamine with the alpha-ketoglutarate residue made into glucose via the classical mitochondrial and glucogenic intermediates. The energy ($\sim P$) in kidney is derived from free fatty acids (FFA) to CO_2 and H_2O . In liver, it is mainly from ketogenesis. Nitrogen is returned to blood by liver urea synthesis for renal excretion and in kidney by synthesis and excretion of NH_4^+ . The latter titrates the renal loss of acetoacetate and β -hydroxybutyrate.

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ERRATA

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