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KETOACIDS? GOOD MEDICINE?

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ABSTRACT

D-β-hydroxybutyrate, the principal "ketone" body in starving man, displaces glucose as the predominating fuel for brain, decreasing the need for glucose synthesis in liver (and kidney) and accordingly spares its precursor, muscle-derived amino acids. Thus normal 70 kg. man survives 2–3 months of starvation instead of several weeks, and obese man many months to over a year. Without this metabolic adaptation, *H. sapiens* could not have evolved such a large brain. Recent studies have shown that D-β-hydroxybutyrate, the principal "ketone", is not just a fuel, but a "superfuel" more efficiently producing ATP energy than glucose or fatty acid. In a perfused rat heart preparation, it increased contractility and decreased oxygen consumption. It has also protected neuronal cells in tissue culture against exposure to toxins associated with Alzheimer's or Parkinson's. In a rodent model it decreased the death of lung cells induced by hemorrhagic shock. Also, mice exposed to hypoxia survived longer. These and other data suggest a potential use of β-hydroxybutyrate in a number of medical and non-medical conditions where oxygen supply or substrate utilization may be limited. Efforts are underway to prepare esters of β-hydroxybutyrate which can be taken orally or parenterally to study its potential therapeutic applications.

INTRODUCTION

D-β-hydroxybutyrate (R-3-hydroxybutyrate), abbreviated βOHB, is the principal "ketone" body in fasting man (1–3) as well as in the "superfasted" state, namely diabetic ketoacidosis (4). Historically, the association with diabetes and starvation have given "ketones" a morbid connotation. This brief review emphasizes the crucial role played by βOHB in human evolutionary survival during periods of deprivation by providing fat-derived calories to an expanding cerebral cortex (5–7). More significant to modern times, it may be a better fuel than glucose

or fatty acids for reasons other than simply displacing glucose as brain fuel, namely by providing more cellular energy per unit oxygen consumed (8). This brief paper sketches the recent history of βOHB and some potential therapeutic uses already studied in animals and tissue culture models.

STARVATION-KETOSIS AND THE EXPANDING HUMAN CEREBRAL CORTEX

In Figure 1 are shown the three classical "ketone" bodies: βOHB, its dehydrogenated counterpart, acetoacetate, and the decarboxylated-acetoacetate, acetone. In the normal individual, βOHB and acetoacetate are less than 0.1 millimolar and acetone essentially unmeasurable. In the starving human adult, βOHB (Fig. 2) is 5–8 millimolar, acetoacetate 1–2 millimolar and acetone approximately the same as acetoacetate (9). In diabetic ketoacidosis, βOHB may rise to 10–20 millimolar or even higher; acetoacetate to $\frac{1}{4}^{th}$ that amount. Depending on the duration of the ketoacidosis, acetone levels may rise to 10 millimolar from the spontaneous non-enzymatic decarboxylation of acetoacetate. Thanks to its volatility, acetone can be detected by its sweet odor in skin, breath and urine, of diagnostic significance even today.

βOHB and acetoacetate are produced in the liver from long chain fatty acids and released into the blood where they are energy substrates for extrahepatic organs. A low insulin level not only enhances both free fatty acid release from adipocytes and hepatic gluconeogenesis. The lower the insulin the greater the rate of fatty acid release and gluconeogenesis (9).

The adult brain consumes some 20% of basal metabolism, namely

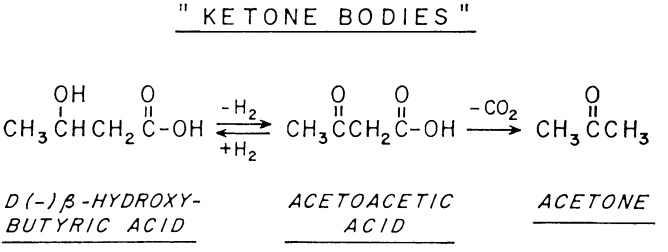

FIG. 1. The 3 "Ketone bodies". D-β-hydroxybutyric acid (βOHB), although properly not a ketone, is interchangeable with acetoacetic acid via βOHB dehydrogenase. Its equilibrium is a function of the NADH/NAD^+ ratio. Acetoacetic acid is slowly and irreversibly decarboxylated to acetone which is mainly lost to the environment through skin, lungs and urine.

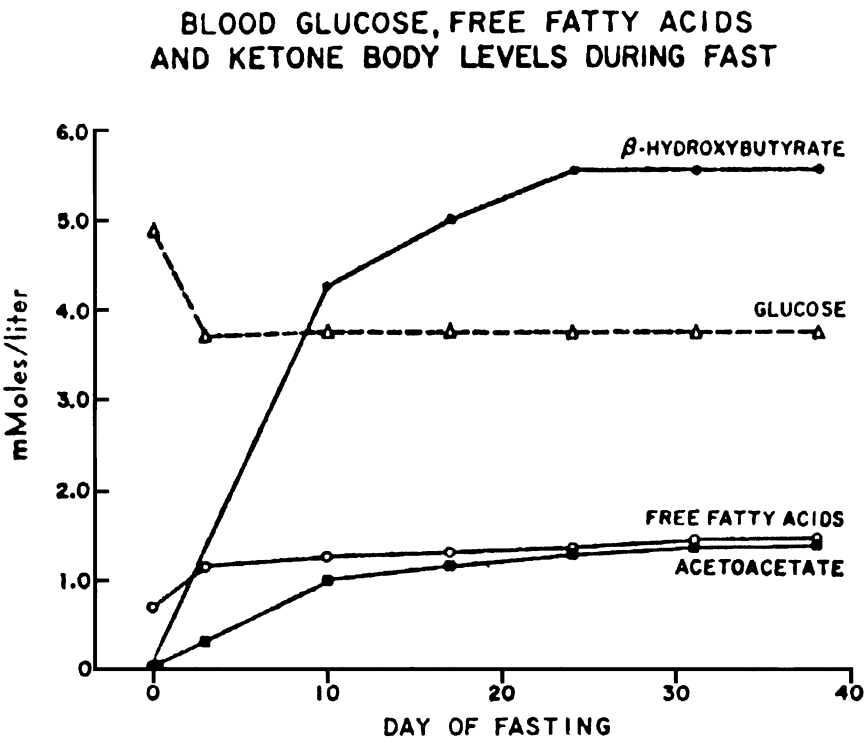

FIG. 2. Circulating concentrations of βOHB, glucose, free fatty acids and acetoacetate in obese but otherwise normal man fasting for 40 days (9).

100–120 grams of glucose/24 hours (5). In the child this may be some 40–50% of the basal, and ketosis accordingly develops more rapidly and more severely in children, hours instead of days (3,10). The same is true for the pregnant human since the conceptus is simply a second metabolic brain consuming near term some 100 grams of glucose daily. Lactation does similarly due to synthesis of lactose from blood glucose. Finally, in the middle of the last century, phloridzin was used experimentally to block renal reabsorption of glucose, and the level of ketosis was linearly related to the degree of glucosuria (11).

Table 1 summarizes body fuels in a normal 70 kilogram man and emphasizes the dominance of his adipose tissue triglyceride for fuel storage. Man stores no protein for storage purposes alone, each molecule serving some physiologic need: myosin, albumin, antibody, all being typical examples. Liver and muscle glycogen reserves are very limited, and glucose in body fluids even more so. In contrast, triglyceride in adipose tissue and protein in muscle are the principal determinants of length of survival during starvation, the former as fuel

TABLE 1
Body Fuels, Adult Man (70 kg)

	Kg.	Kilocalories
Adipose tissue triglyceride	12	110,000
Muscle protein glycogen	6	24,000
	0.4	1,600
Liver glycogen	0.1	400
Glucose (extracellular fluid)	0.014	56
Total		136,056

and the latter, the "machinery". In a simple phrase, fat spares the machinery!

In overnight fasted man (Fig. 3), hepatic glycogen provides glucose for brain, and thanks to the relatively low insulin level, muscle and adipose tissue cease removing glucose. Free fatty acids liberated from adipose tissue provide the bulk of body fuel. After several days of starvation, brain glucose is derived from hepatic gluconeogenesis from muscle derived amino acids. However, the level of ketone bodies in the circulation gradually rises. So after a week or longer, levels of circulating amino acids released from muscle diminish, hepatic gluconeogenesis decreases, and brain metabolism is supplied mainly by the principal ketone body, β-hydroxybutyrate (Fig. 4). It should be emphasized again that the level of insulin appears to be in control by its regulation of amino acid release from muscle. In the super-fasted state (the diabetic) where even basal insulin levels are inadequate, excessive amino acids are released from muscle, hepatic gluconeogenesis and ketogenesis increase and levels of glucose and ketones rise. These result in progressive hyperglycemia, hyperketosis and glucosuria and ketonuria (4). This is the syndrome of diabetic ketoacidosis, with acidosis, severe hypovolemia, hypotension and death unless interrupted by exogenous salt-containing fluids to correct volume and insulin to correct the underlying dys-metabolism. Simple starvation and/or the ketogenic diet produce a mild but closely regulated metabolic acidosis, compatible with normal life as evidenced by Inuit survival before polluted by our American culture!

Brain is unable to use the free fatty acids released from adipose tissue due to their tight binding to albumin and other serum proteins and also to the blood/brain barrier. On the other hand there is a glucose transporter, Glut1, which permits glucose to enter the CNS providing glucose concentration in serum is adequate (12–14). Amino acids likewise have specific transporter mechanisms maintaining their concentrations at very low levels, glutamine being the main exception. This

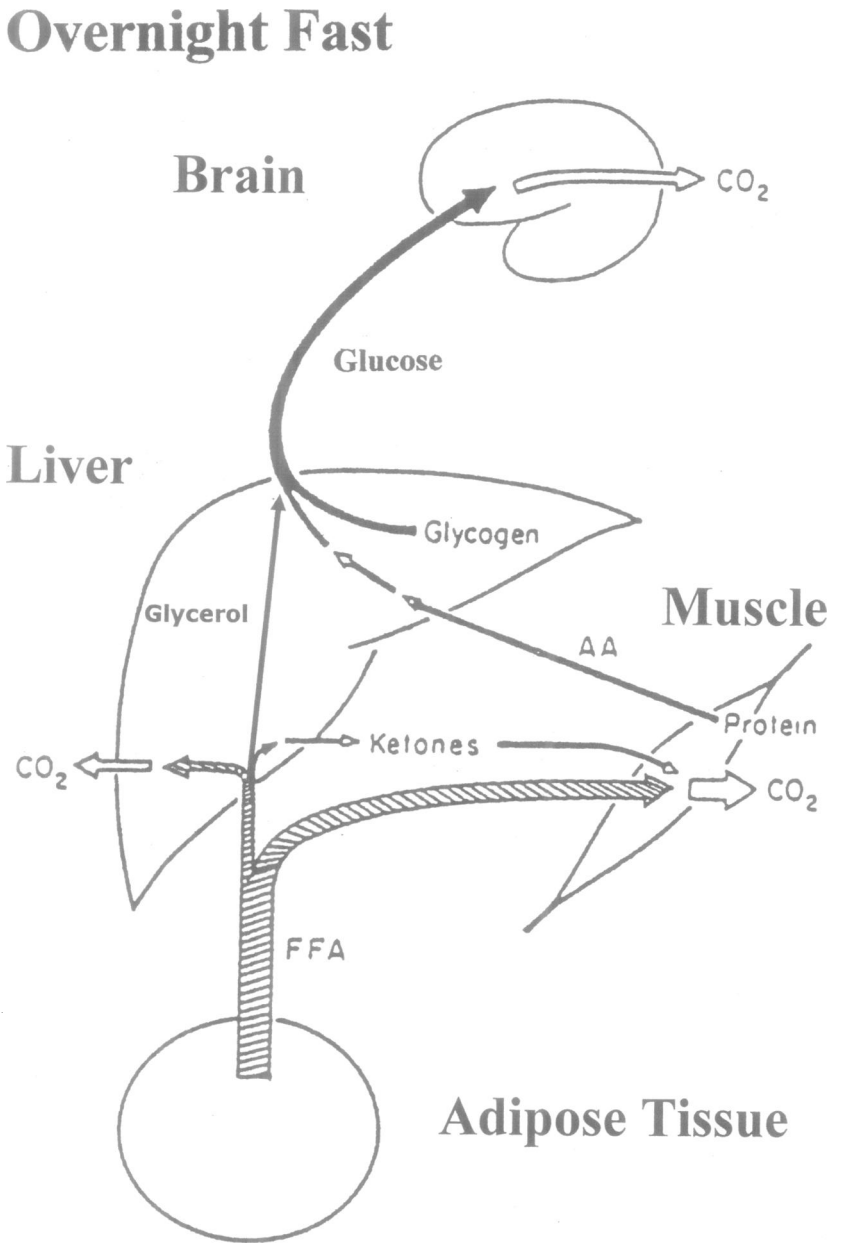

FIG. 3. Fuel metabolism in overnight fasted man. Brain fuel (glucose) is provided mainly by liver glycogen but gluconeogenesis is beginning to take over using amino acids released from muscle protein. Free fatty acids from adipose tissue provide the major portion of body fuel (9).

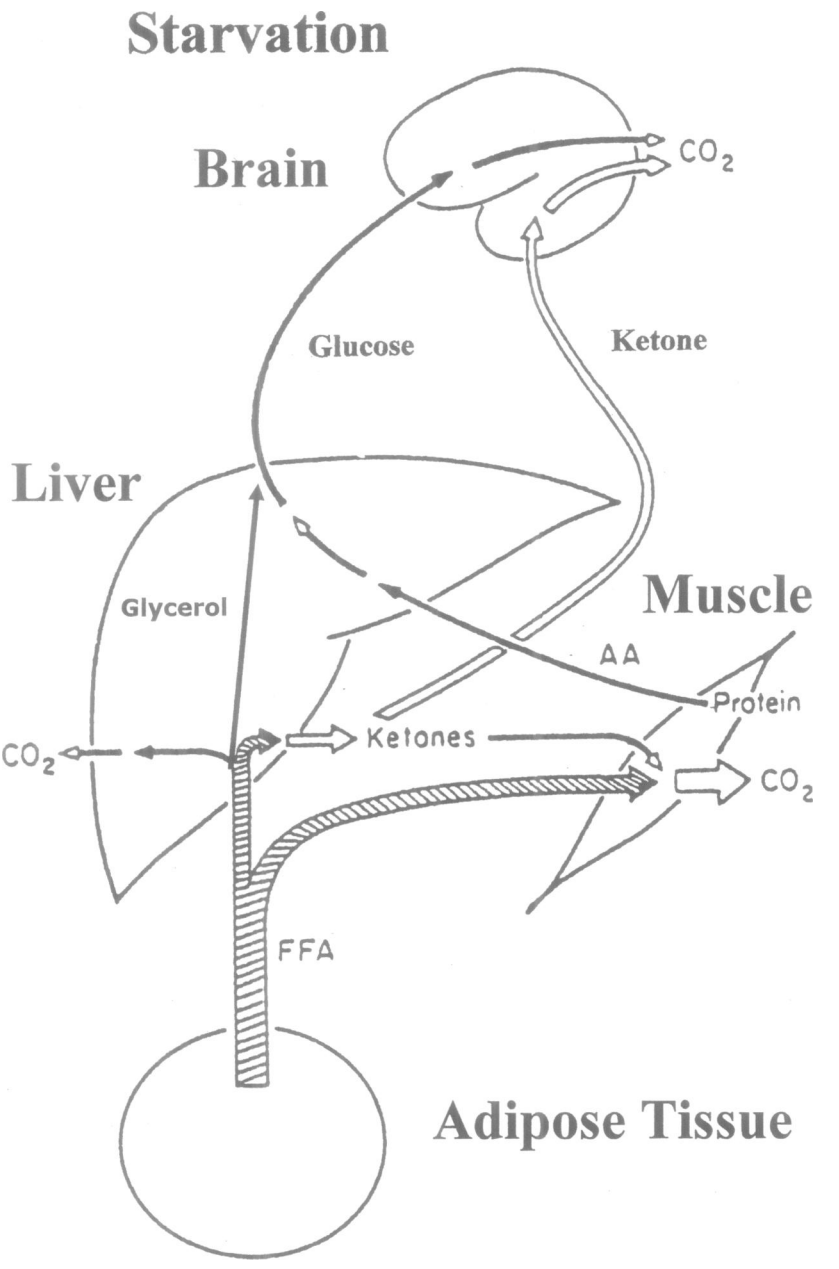

FIG. 4. Fuel metabolism in prolonged-fasted man. βOHB, the principal "ketone body" is the major fuel for brain, displacing glucose utilization. Gluconeogenesis is diminished, sparing the breakdown of muscle protein to amino acids. Thus survival is dramatically prolonged (2,5).

permits a rapid rise and fall of neurotransmitters at synapses, particularly glutamic acid which is in micromolar concentrations in spinal fluid. βOHB is also transported into cerebro-spinal fluid with a Km of 2–4 mM, approximating its level in the fasted human (15). A number of investigators have shown βOHB displacing glucose utilization in brain preparations and the same has been shown to occur in man (5,16,17). This illustrates the concept introduced by Sir Philip Randle that fat and fat-derived products like acetate and βOHB take precedent over carbohydrate and its products such as pyruvate (18).

THERAPEUTIC USE OF KETONE BODIES IN EPILEPSY, THE KETOGENIC DIET

Pierre Marie, the French neurologist of the late 19th century, proposed fasting for the treatment of epilepsy. This approach was resurrected by Hugh Conklin in the 1920's and was replaced by the more acceptable very-low (ketogenic) carbohydrate diet by Russell Wilder of the Mayo Clinic. Today, the use of this diet in patients refractory to multiple anti-convulsive agents has been very successful, eliminating seizures in about ⅓rd and decreasing seizures in the majority of the remainder. John Freeman of Johns Hopkins is the leading figure in this country with a number of publications (19–21). There are problems with the diet, however, and about ½ of children placed on the diet discontinue it in the first 6 months. Any carbohydrate ingested, in even small amounts, decreases the level of βOHB, and seizures rapidly return or increase. This failure in compliance is not unexpected with a diet of whipping cream, fatty meats and cheese!

Recently, a commercial preparation* has become available. It contains a complete array of vitamins and minerals with hydrogenated soy bean fat and milk protein and essentially no carbohydrate. Another approach, dietary medium-chain triglyceride which is metabolized by liver to ketones, has been used with some success in these drug resistant patients (22). This synthetic nutrient permits the testing of children for a brief period to see if their frequency of seizures decreases without the need of educating the parents about a ketogenic diet. The therapeutic level of βOHB in serum is 3–5 mM and this could easily be achieved by oral administration of a βOHB-containing ester several times daily, obviating the need for the diet completely. Such a nutraceutical approach is now being examined.

* "KetoCal," SHS International, Gaithersburg, MD.

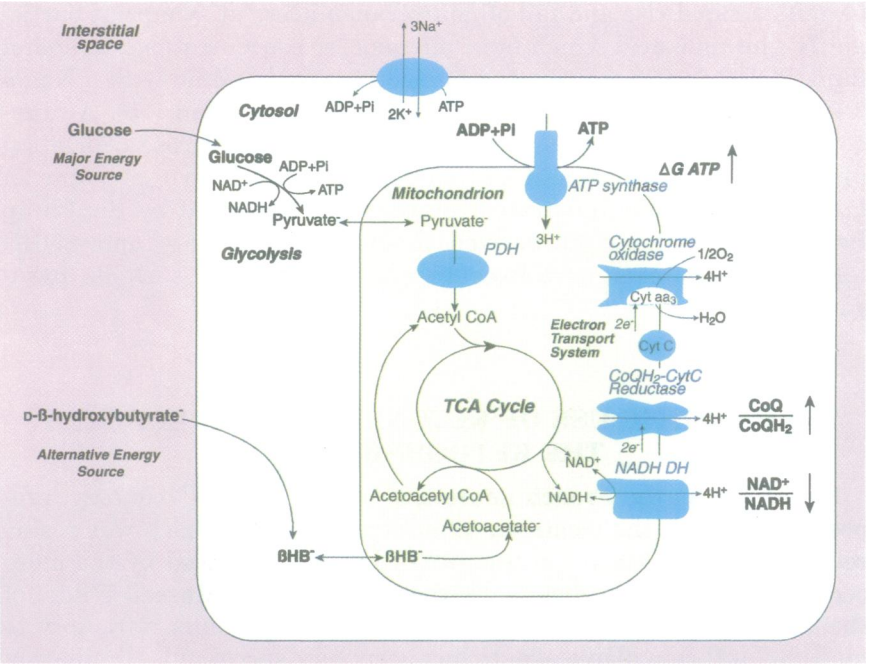

FIG. 5. Biochemical processes within cardiac muscle cytoplasm (white background) and mitochondria (yellow background) in a perfused heart preparation (8,24). With βOHB as substrate, NADH increases relative to NAD^+ and CoQ increases relative to $CoQH_2$ widening the energetic span between the two in the NADH dehydrogenase reaction. This provides an increase in energy for ATP synthesis as compared to that in the heart using glucose.

β-HYDROXYBUTYRATE, NOT ONLY A FUEL, BUT A MORE EFFICIENT FUEL

In an extremely complex perfused rat heart preparation in which mechanical activity, substrate and oxygen uptakes and, subsequently, the determination of the concentration of numerous intermediary metpabolic molecules were determined in the heart itself, it was found that βOHB increased contractility, and, surprisingly, oxygen consumption decreased (23). The explanation was rather simple in overall scope; at two steps in the mitochondrial synthesis of high energy phosphate (ATP), the reactants in one step, (NADH/NAD+), become more reduced, and the next step (Coenzyme Q/Coenzyme QH_2), becomes more oxidized, thus widening the energetic gap between the two, and this increased energy is trapped, presumably, in a greater ATP production.

This process is explained in more detail in a recent extensive publication (8). In addition, thermodynamic tables of the heat of combustion of βOHB per 2-carbon moiety, show more energy than glucose or pyruvate, and as expected, less than long chain fatty acid, which, however, is not preserved due to fatty acid donating ½ of its reducing power to flavoprotein, bypassing the NAD+/NADH step of electron transport. Thus it appears that βOHB is a superior fuel per unit oxygen, at least in the perfused heart preparation (Fig. 5). This opens numerous possibilities for therapeutic approaches.

USE OF β-HYDROXYBUTYRATE IN SOME EXPERIMENTAL SITUATIONS

Theoretically, any cell dependent on oxidative processes should benefit from βOHB when oxygen delivery becomes limiting. Cells die when their energy source is impeded, and this can be either acutely, namely in minutes to hours, or, alternatively, days later due to a programmed, complex cell death, namely the process of apoptosis. The biochemical mechanisms of both of these routes are under intensive study in a large number of laboratories. Further discussion is beyond the scope of this report. Nevertheless, the following is a list with references to a small number of experimental settings where βOHB has been reported to exert significant effects in addition to its well-documented effects in epilepsy in humans and experimental animal models.

Henry Lardy some 60 years ago found sperm motility to increase in the presence of βOHB with a decrease in oxygen consumption (24). The hormonal response to hypoglycemia in dogs is suppressed by βOHB (25,26), and the cerebral symptoms of hypoglycemia in man are prevented (27). Also βOHB diminishes amino acid levels and nitrogen excretion in man (28,29). Cerebral function in anoxic rats and mice is improved and survival prolonged (30,31). Apoptosis in the lung in shocked rodents is diminished (32). Improvement in post-traumatic metabolism in man has been reported (33). It should also be pointed out that the altered ratio of NAD+ to NADH should reduce free radical formation (8,34), and βOHB has been shown to increase viability in neuronal cells in tissue culture exposed to the toxins associated with Alzheimer's and Parkinson's diseases (35).

βOHB AND MAN'S SURVIVAL

As briefly reviewed (8), a ketoacid level of 5–8 mM in starvation is relatively unique to man. In general, mammals with brain consuming less than 5% of basal metabolism need not become ketotic since glyc-

erol released from adipose tissue triglyceride provides sufficient glucogenic precursor for brain's glucose needs. For example, βOHB levels in the black bear in its 4 month or so of winter sleep remain below 1 mm (36).

When did primates cross this 5% line? Certainly well before *Homo habilis* and *H. ergaster* (1–2 myr bp) but after primate bipedalism (7–8 myr bp). A reasonable guess is before the earliest stone age (Oldowan Period of the Lower Paleolithic, 2.5–3 myr bp) (6,7). Brain size then reached a plateau of approximately 1200 cc which increased very slowly over two million years to our present 1400 cc. But brain size is probably just part of the story, and perhaps a small part. Clumsy, uncultured, uncivilized *H. neanderthalensis* had a brain of 1500–1600 cc, probably related to a larger body size. Neanderthals in Europe were wiped out in just a few thousand years between 40,000 and 30,000 yrs bp, by far more clever *H. sapiens sapiens* with his slightly smaller brain.

But is brain size in man very relevant to the intellectual explosion over the past 20,000 years? Clearly not, and we know that brain size and function are poorly related. Compare the great dane to the miniature poodle or the humming bird with a brain orders of magnitude smaller than that of the ostrich! True, much of the larger brain in the larger animal relates to increased innervation to a larger body mass. A 7.5 kg brain in a 40,000 kg whale consumes 5.25 mmole oxygen per minute, a miniscule portion of its basal metabolism (37,38). The 1.5 kg brain in a 70 kg man consumes 2.24 mmole oxygen/minute. Unfortunately paleoanthropologists can only measure the size of the brain cavity with no indication of cellularity such as anatomic cell count or potassium or DNA content.

So something happened recently to man independent of brain size. The anthropologists, Klein and Edgar (7), suggested that prior to *H. sapiens* departure from Africa some 100,000 years ago, and then his spreading both northwestward into Europe and eastward into Asia, a dramatic mutation occurred. This "6^{th} sense" was a sudden expansion in communication meaning language and cognition. One could call this an intellectual gene permitting adaptation and anticipation. Supporting their speculation is the report by British geneticists of an inheritable syndrome caused by a mutation in a fork-headed domain gene resulting in a phenotype of severe deficiency not only in speech itself but also in understanding speech, but with other-wise normal or near normal cognition (39). This would support the concept of the late Steven J. Gould (40) that evolution occurs in long stable periods (equilibrium) interrupted by brief and rapid changes (punctuation). This could not have happened without βOHB supporting survival during

the frequent famines caused by natural catastrophies as well as those caused by man himself during hostilities and migrations.

FUTURE USES OF βOHB

Use of βOHB formed by the ketogenic diet in the treatment of drug-resistant epilepsy is now widespread, but its mode of action remains unexplained (41,42). It has also been shown to be effective in similar entities such as infantile spasms (43). Needed, of course, are mechanisms to produce blood levels of 3–5 mM without the difficult to maintain ketogenic diet. In addition, the diet itself increases serum cholesterol, is associated with renal stones and is very intolerable to many. Only a small proportion are able to continue it over a year.

As an organic acid, βOHB is soluble as the sodium salt. A fasting adult produces about 150 grams daily to achieve a blood level of 5–8 mM. If this amount of βOHB were administered as the sodium salt, a large residual excess of alkali would remain as the βOHB is metabolized. Obviously preparations must be made which can produce this amount of βOHB if taken either orally or parenterally. What are the potential uses of βOHB in addition to pediatric epilepsy? Theoretically, any condition wherein oxygen supply to cells may be limited is an avenue for investigation. The list would encompass almost every disease state. Also, environmental or occupational conditions, where oxygen availability is potentially limited, need be examined. Finally, in many situations where pathogenesis is still not clear, particularly syndromes like Alzheimer's or Parkinson's which remain essentially untreatable or minimally treatable, are candidates. The in vitro studies mentioned above of Kashiwaya et al. (35) showing protection of neuronal cells in tissue culture against proven toxins in these two states illustrate the need to study βOHB in many other models of degenerative diseases.

The challenge now is to make available preparations of βOHB for both clinical, animal and in vitro investigation of disease processes and their therapy (8). Finally a chemical agent, βOHB, that has played such a major role in man's survival may be expected to have actions other than simply calories. When nature has a beneficial substance, it may become pleiotropic through evolution with other survival advantages. Insulin and thyroid hormones are excellent hormonal examples. Butyrate and retinoic acid are examples of substrates recently found to have transcriptional activities as well. Glutamate is an example par excellence with a central role in both protein structure and in neurotransmission. βOHB may also have other metabolic effects than simply

a fuel. Its role in diminishing muscle protein catabolism directly in fasting man and animals. is one example needing biochemical examination.

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DISCUSSION

Neilson, Nashville: A very interesting thought that you provided us. My recollection is that ketoacids are a pretty good appetite suppressant, and I wonder if some of these oral compounds that you mention might also enhance satiety and be an effective way to manage some of the secondary obesity. There may be some literature.

Cahill, Stoddard: Yes, it is on the list. People who starve for three or four days usually lose their appetite. And there are other metabolic changes. FSH levels fall. That is why the amenorrhea of the starving female or with anorexia nervosa. There are other effects, but by and large they are generally benign, surprisingly. The reason the ketones have a morbid connotation is due to their relationship to diabetic ketoacidosis. In this potentially fatal condition, they may rise to 10 to 20 millimolar, displacing levels of bicarbonate to 10 millimolar or so, with a low ph of 6.8–7.0. In starvation, ketones rarely go above 10 millimolar.

Kahn, Boston: George, as you know, there's a tremendous interest in ketogenic diets, and high fats versus high carb diets. So what happens to normal or modestly overweight people when they are put on a high fat, and how much does that change the balance of ketogenesis. Do your studies have some with respect to the dietary approaches?

Cahill: It produces a very mild ketosis with levels of ketones of 1–3 millimolar when measured. The smallest bit of carbohydrate in the diet, say 50 or so grams, halves the level of ketones that would occur in a pure fat/protein diet. A pure fat/protein diet simply dispaces the need to utilize the body's own fat and protein as occurs in simple starvation. Those of you who are pediatricians are very familiar with the use of the ketogenic diet in children with epilepsy resistant to anti-convulsive agents. There are now some 28 agents in clinical use. The diet is difficult, namely cream, cheese, butter, salami, eggs, etc., essentially no or very little carbohydrate. About ⅓rd have no or rare episodes, another ⅓rd a significant reduction and the remainder little or no effect. Interestingly, some children whose fits are prevented by the diet may not have any subsequent fits after a year or so on the diet. A number of investigators have tried to find out the biochemical basis of the diet's effect. Is it simply energy or some unique effect of the structure of the molecule? There is appearing experimental evidence that simple molecules such as retinoic or butyric acid may alter metabolism at the level of DNA transcription and translation.

Thorner, Charlottesville: That was a wonderful presentation. When patients are sick in the ICU setting, we do all sorts of things, but one thing that we do is we affect their nutrition. We reverse the changes that you have shown occurs with starvation. Do you think this is a protective mechanism to raise the beta hydroxybutyrate, and are we actually doing harm by our parental nutrition and so on?

Cahill: I honestly don't know. All of us have looked at ketones as being bad. We therefore administer carbohydrate and, if needed, insulin. On another topic, Ron Kahn introduced it in his superb Gordon Wilson Lecture. Probably the most significant component to man's evolution was to use language, meaning communication, and his superior intellect permitting him to anticipate and adapt to environment. The Polynesian, before boarding his canoe for the voyage of several months, buttered up at the luau and, perhaps as important, performed vigorous dances and war-games to increase muscle mass. There was no sofa and television, our post-prandial practice. Man's brain has taken over the caloric control of lower forms as closely regulated by day/night ratios, environmental temperature, availability of certain foodstuffs, etc. We don't procreate seasonally, nor fatten up in the fall and thin down in the spring! However, the hunter in certain primitive societies today maintains his body fat at 5–10% so he can jog after and tire the gazelle. Anorexia nervosa is his life style. His family depends on it. I already

mentioned the induced adiposity in the Polynesian and probably also in many societies anticipating lengthy periods of food deprivation. Leptin may be essential for rats and mice, and probably is. But I don't want to belittle Jeff Friedman's discovery; other roles are beginning to be found for this unique molecule. A genetic deficiency resulting in marked obesity in childhood has been found, however, and successfully treated with administered leptin. Leptin has little or no effect in standard obesity.