PRESIDENT'S ADDRESS

STARVATION

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The greater efficiency (calories/gram) of storage of energy as fat instead of protein or carbohydrate is crucial to animals in whom mobility plays an important role, particularly for those who must struggle against gravity. Even in plants, lipid is the optimal form of stored energy when mobility is a factor, as in the nuts and other seeds, the coconut and avocado being prime examples. Thus for man who once survived as a hunter and gatherer and in whom mobility certainly was critical in his competition with other creatures, storage of energy as triglyceride in adipose tissue was mandatory for survival. As man eats, his first priority is to provide fuel for immediate metabolic requirements, displacing endogenous fuels. When small amounts of carbohydrate are taken in, either orally or parenterally, hepatic glucose production to provide glucose as fuel for the brain is suppressed by just the amount consumed. Man's second priority is to expand his modest glycogen reserves in liver and muscle and also to replace the amount of protein broken down in various tissues since the last meal, particularly in muscle. The third priority is to convert the excess ingested calories, whether the originally-ingested energy is in the form of carbohydrate or protein or fat, into triglyceride, and then to store this energy in his adipose tissue.

In fasting, the priorities are reversed. The body undergoes a series of hormonal and metabolic changes to draw selectively on its extensive supply of energy in adipose tissue, and thereby to spare the breakdown of vitally-needed proteins, such as contractile protein in muscle or as enzymes in critical structures like heart or liver, or, even more precious, proteins involved in nervous tissues, particularly brain, which appear totally conserved and not mobilized at all during starvation.

First, an overall accounting of calories in various forms and tissues is necessary to provide perspective to fuel economy and mobilization in man. A normal adult uses 4–5 kJ (1–1.2 Cals)/minute to maintain basal energy needs, or 6–7.5 MJ (1500–1800 Cals)/day. With standard physical activity or in a cold environment without insulation, this is doubled, and with strong physical activity, daily expenditure may increase to 20–25 MJ (5,000–6,000 Cals)/day. Thus the 400–600 MJ (100,000–150,000 Cals) in the 12–16 kilograms of triglyceride in fat provides 1–3 months of survival-fuel depending on physical activity, again, assuming that the supply of energy is the rate-limiting factor for survival. In a very fat human,

survival would be for much longer, and total starvation of a year has been documented in some very obese subjects under carefully observed conditions in which cheating would be most difficult.

Phases of Starvation

In the transition from the fed to the fasted state in man, a sequence of metabolic alterations occurs to provide calories for survival and are listed as follows with their approximate duration:

1) Gastrointestinal absorption of substrate	1–8 hours
2) Glycogenolysis (liver and muscle)	1–2 days
3) Gluconeogenesis (liver)	first week
4) Ketosis	3–4 days onward
5) Diminishing gluconeogenesis and increasing cerebral ketone consumption	second week onward

Gastrointestinal Phase

Although this is beyond the general scope of this brief essay, a few words on the disposition of a meal are appropriate, especially concerning the variations in energy content and the distribution in carbohydrate, protein and fat. With a large meal, mainly carbohydrate, the entire body oxidizes glucose. This is a result of two phenomena, both involving insulin. Liver actively removes glucose from the blood due to the elevation in insulin levels, as well as a lowering of the glucagon concentration. The glucose is incorporated into glycogen and is also glycolysed to pyruvate and lactate. The pyruvate is subsequently oxidized to acetyl CoA which is used for both liver's energy needs via the tricarboxylic acid cycle and for fatty acid synthesis. Subsequently fatty acid is incorporated into triglyceride and is then exported to adipose tissue as very low density lipoprotein (VLDL). Brain continues to use glucose for fuel, as it did before the meal, and this process does not requrie insulin. Again because of elevated insulin levels, muscle preferentially utilizes glucose to replenish its previously depleted glycogen reserves, as well as to use glucose as fuel for energy. This preferential glucose metabolism in muscle is also a function of low levels of free fatty acids, a result of insulin's effect on adipose tissue. In adipose tissue, insulin also stimulates glucose uptake and the conversion of glucose to fatty acid and subsequent incorporation into the triglyceride vacuole in the center of the adipocyte. Triglyceride hydrolysis (lipolysis) of the stored triglyceride is inhibited by insulin resulting in a decreased release of free fatty acid, and in lower circulating levels of free fatty acids. The larger the meal, the more rapid the rate of glucose uptake by these various tissues; this is in response again to the

higher levels of circulating insulin. Thus in adipose tissue insulin increases fat synthesis and decreases its mobilization.

The ingested fats from the meal enter into the blood stream as chylomicrons via the lymphatics, and the simple sugars and amino acids from the meal are absorbed into the portal circulation going to the liver. The glucogenic amino acids, for the main part, as well as certain essential amino acids like trytophan, are removed and metabolized by liver. The three branched chain amino acids, leucine, isoleucine, and valine, which will be discussed in further detail later, are mainly removed by muscle and adipose tissue. Because of the availability of insulin and the increase in amino acid levels, peripheral protein, particularly in muscle, is replenished. The chylomicrons serve to transport absorbed fat directly to adipose tissue where the fatty acids are released, and then incorporated as a new triglyceride molecule and stored inside the triglyceride vacuole in the center of the adipocyte along with the newly synthesized fatty acids.

Should the meal be low in carbohydrate, so that the rate of carbohydrate entry into the blood stream is less than that needed by brain and other obligatory glucose users, insulin is still released at a greater rate than basal. This greater rate allows the initiation of peripheral protein synthesis, especially in muscles and also the stimulation of some lipogenesis in adipose tissue from amino acids (particularly the branched-chain amino acids), and the uptake of circulating triglyceride into adipose tissue. However, glucose levels must be maintained in the presence of this increased insulin, and thus the liver must be poised toward glucose production in spite of the increased insulin levels. This appears to be the primary biological role of glucagon in mammals (27), whose release is stimulated by both the increase in blood levels of amino acids themselves, particularly arginine, as well as sensitization of the alpha cells to release more glucagon per change in substrate level. This latter sensitization may be mediated by pancreozymin, which appears to be the "gut" hormone which stimulates not only exocrine pancreatic activity during a meal, but also the endocrine alpha and Beta cells, the former to release glucagon and the latter to release insulin, especially after protein ingestion.

Thus in meals containing little or no carbohydrate, by initiating increased insulin activity as well as that of glucagon, the non-hepatic tissues receive the "fed" signal to take up circulating fuels, but the liver remains in the "fasting" mode in order to maintain blood glucose concentration by continuing to produce glucose, and this it does as a result of the increase in glucagon levels. Thus, whether the liver at a given time is glucogenic or glycogenic-glycolytic is a function of the ratio of the two hormones, insulin and glucagon, as originally postulated by Unger and subsequently corroborated by a number of investigators. If the meal

contains sufficient carbohydrate to be able to displace the need for hepatic glucose production, in other words, enough carbohydrate to enter into blood at a rate of over 100–200 mg/minute, then the slight rise in glucose concentration is sufficient to increase Beta cell insulin release and to suppress completely the alpha cell from releasing glucagon, and as a result, hepatic glucose production is suppressed. In addition, this slight increase in glucose level markedly synergizes the Beta cells to produce even more insulin as a response to the increase in amino acids, so the glucagon/insulin ratio is even more altered.

In summary, the gastrointestinal phase of starvation varies as a function of the fuel ingested, and if deficient in carbohydrate, the liver is signalled to produce glucose as if no meal had been eaten, probably the principal role of glucagon. Should this type of diet be continued for longer periods of time, experimental animal data have shown that the liver becomes more and more poised toward gluconeogenesis due to the increased activities of the key rate-limiting enzymes involved, and the liver is thus metabolically similar to that in total starvation.

Glycogenolysis Phase

Total body free glucose amounts to only 15 to 20 grams, or about one hour's worth of fuel for basal energy needs (Table 1). If one permits a "physiologic excursion" from the fasting level of 80 mg/100 ml in plasma to 60 mg/100 ml, that would be 15 minutes' fuel for the whole body, or if it was limited to brain's needs, about 45–50 minutes. Thus there must be exquisitely sensitive mechanisms to respond to small changes in glucose concentration which can result in increased or decreased rates of glucose production by liver. Insulin and glucagon play central roles, and there is also evidence that the glucose molecule itself may be important in liver in controlling its own destiny.

First, the liver cell membrane does have a specific glucose transporting mechanism, but its rate (Vmax) is so great that the concentration of glucose inside the liver cell closely approximates that in circulation.

TABLE 1
Body Fuels in Adult Man (70 Kg)

	Kg	Kilocalories
Adipose tissue triglyceride	12	110,000
Muscle protein	6	24,000
Carbohydrate		
glycogen-muscle	0.4	1,600
glycogen-liver	0.07	280
blood glucose	0.02	80
Total		135,960

Second, the kinase in liver responsible for forming glucose-6-phosphate is unique in that it has a low affinity for glucose, one within the physiologic range, meaning the higher the blood glucose level, the more is phosphorylated. This is different from the hexokinase enzyme in muscle and adipose tissue, where the rate-limiting step is glucose entry across the membrane into the cell. But once the glucose molecule has entered, as a result of insulin's effect on the membrane, it is rapidly phosphorylated because of the very high affinity (low Km) that this hexokinase in muscle and adipose tissue has for glucose. Thus, hyperglycemia results in increased glucose phosphorylation in liver and thereby in glucose uptake, this being simply a function of the concentration of glucose. In other tissues, permeability, as controlled by insulin, is rate-limiting.

To return to glucagon and insulin, the ratio of these two hormones plays a central role in controlling the level of cyclic AMP (cAMP) inside the liver cell, and thereby the rate of glucose synthesis and release. It has been suggested that cAMP serves as a generalized signal in evolutionary terms for carbohydrate lack (58), and this seems to be particularly applicable to man and other mammals.

As glucose absorption from the gut decreases at the end of the gastrointestinal phase, insulin levels fall also and the liver gradually stops removing glucose; it then is more or less in a "neutral" state and subsequently begins to produce glucose. About 4–5 hours after a meal, and perhaps longer if it was a very large meal, liver begins to return its stored glycogen as free glucose back into the blood to provide fuel needs, mainly for the central nervous system (Figure 1). The signals are twofold, a lower insulin level and a lower level of portal blood glucose. Whether glucagon, no longer suppressed, increases or not in this brief time is not yet clearly documented. It is the author's guess that the "fine-tuning" is primarily a function of insulin and glucose, and not glucagon. For example, in experiments in fasting humans, doubling the glucagon concentration by infusion has little effect on glucose homeostasis (54). However, suppression of both glucagon and insulin by somatostatin infusion lowers blood glucose (20), suggesting the presence of glucagon to be necessary for hepatic glucose production, but not regulatory.

During this phase of decreasing glucose and insulin levels, peripheral tissues such as muscle and adipose progressively diminish glucose utilization, so that after 8–10 hours, over one half of muscle fuel needs are met by free fatty acid oxidation. Simultaneously the levels of free fatty acids increase as the insulin levels fall, primarily due to increased levels of cAMP stimulating triglyceride lipolysis in adipose tissue. Whereas in liver, insulin is pitted against glucagon in controlling cAMP concentration, in adipose tissue it is insulin versus norepinephrine released locally from sympathetic nerve endings. Knowledge of the contribution of muscle

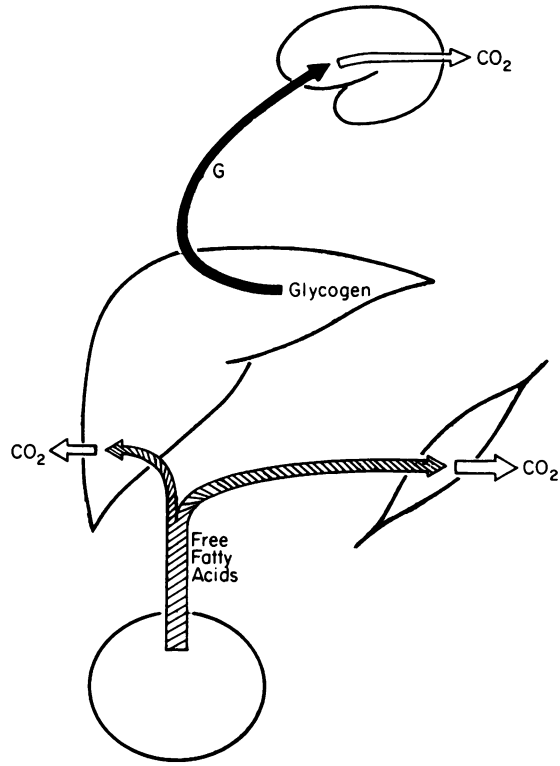

FIG. 1. See text. G means glucose, AA stands for amino acids.

glycogen to fuel utilization as a direct result of fasting without exercise is limited. After a meal the glycogen content of human muscle may be as high as one percent. With exercise it is rapidly diminished, and, if fasting persists it is not replenished. At a glycogen content of one percent, the 30 kg of muscle in a normal man would provide 300 g of glycogen or 5.0 MJ (1200 Cals). This is a nominal supply, possibly explaining the persistence of a higher respiratory quotient in starving man than can be explained solely by release and oxidation of the glucose stored as glycogen in liver.

Gluconeogenesis

Although there are few data concerning liver glycogen levels after a large meal, extrapolating backward from the 4–5 percent glycogen content in liver in the post-absorptive state, the amount may be as much as 10 percent or more. Thus liver glycogen maintains blood glucose for 12–16 hours, and studies in the post-absorptive state show glycogen providing

75 percent of splanchnic glucose output: gluconeogenesis provides the remainder.

As gluconeogenesis is initiated, a number of metabolic changes occur in the liver. These changes result from two processes, the first involves a higher glucagon/insulin ratio due to a significant decrease in insulin, thereby increasing levels of cAMP. In the second process, a higher level of free fatty acids provokes fat oxidation and produces a higher level of fat-derived materials such as acetyl CoA and fatty acyl CoA. As these enzymes and co-factors all change over 12–24 hours, the rate of liver glucose output begins to be controlled by the level of substrate coming to it, and the rate-control is thus transferred from liver to the release of precursors from peripheral tissues (15).

Over the ensuing 2–3 days of starvation, muscle and adipose tissue become progressively more efficient in decreasing their glucose utilization, both by blocking glucose uptake, and as a further check, by preventing glycolysis of the glucose to pyruvate (Figure 2). As a final check, pyruvate is completely prevented from being oxidized to acetyl CoA (pyruvic

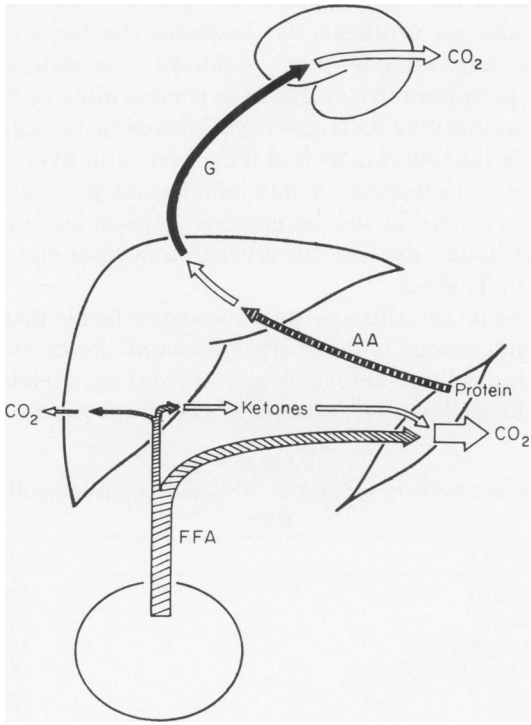

FIG. 2. See text and caption to Figure 1.

dehydrogenase), so what little pyruvate is formed is either exported, or transaminated to alanine and then sent back to the liver for gluconeogenesis. Thus muscle stops using carbohydrate or any of its potential precursors.

Returning to liver, its own energy needs are met by oxidation of free fatty acids, but as starvation progresses, and the oxalacetate is utilized more for gluconeogenesis, less is available for tricarboxylic acid cycle activity. Furthermore, what oxalacetate is available is reduced to malate and the liver is flooded with free fatty acids and with the reducing equivalents resulting from their oxidation. Thus, as the fatty acids are dehydrogenated and split into 2 carbon units of acetyl CoA, the diminished acceptor, oxalacetate, decreases acetyl CoA entry into the cycle and the liver's alternative is to export the acetyl CoA, two at a time, as β-hydroxybutyrate or acetoacetate, the "ketone" bodies. Ketone production thus appears to be the result of two phenomena, the glucagon/insulin ratio being high, increasing the enzymatic machinery for ketone production, and an increase in the delivery of free fatty acids from adipose tissue (21).

Thus, to summarize the gluconeogenic phase, liver enzymes become poised toward glucose synthesis, fat becomes the hepatic fuel, but the fatty acids eventually are only partly oxidized to acetate units, and then exported to the periphery two at a time as acetoacetate or β-OH butyrate. Adipose tissue hydrolyzes its triglyceride to free fatty acids and glycerol (lipolysis), the former serving as fuel for muscle and liver, and the latter, like amino acids from muscle, or like lactate and pyruvate from muscle and other tissues, is used by liver as gluconeogenic substrate. Quantitative estimates for 24-hour substrate turnover in a normal man fasted for 3–4 days are given in Table 2.

Thus brain begins to utilize ketoacids as their levels increase in blood; glucose utilization beings to diminish; splanchnic ketoacid production is maximal and the bulk of ketoacids are utilized by skeletal muscle and heart. In fact, heart has been shown to satisfy 75 percent of its energy

TABLE 2

Quantitative Estimates for 24-hour Substrate Turnover in a Normal Man Fasted for 3–4 Days

Component	Amount g
Brain glucose utilization	100
Brain ketone utilization	50
Splanchnic glucose output (16)	150
Glucose utilization by other tissues	50
Muscle proteolysis (9)	75
Adipose lipolysis	180
Splanchnic ketogenesis (47)	150

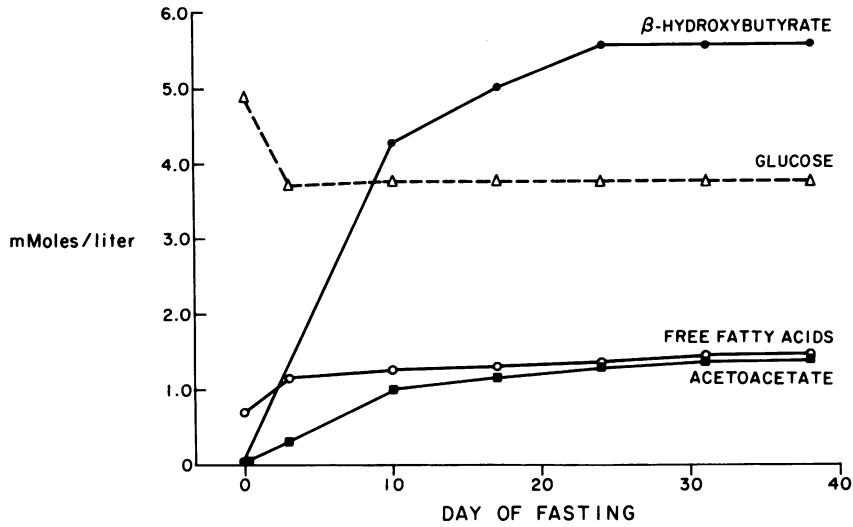

FIG. 3. This chart shows the plateau of blood ketoacid values achieved by the end of the second week of starvation.

needs by ketoacid metabolism in 3-day fasted man. Ketoacid loss in the urine is minimal calorically, but their acidic properties necessitate ammonia production by kidney to prevent loss of sodium or potassium and thus to preserve body fluid volume (51).

Ketosis

By the 3rd day of starvation, ketoacid production by the splanchnic bed is maximal (19) but blood levels continue to increase progressively until the end of the second week when a plateau is achieved (9) (Figure 3). Owen and Reichard (42) have shown that this progressive increase is mainly a function of decreased ketoacid metabolism by muscle as fasting progresses. Thus by the 3rd or 4th day, ketoacid levels are 1–2 mM but by the second week they may be 6–10 mM. Serum bicarbonate levels are reduced accordingly, and there is a mild but compensated metabolic acidosis. The purpose of this ketoacidosis is to provide a sufficient gradient for the facilitated diffusion of these water soluble fat products across the blood brain barrier to satisfy brain's energy needs (41). Again, this production of ketoacid by liver is a result of a high glucagon/insulin ratio and an increase in the levels of free fatty acids released from adipose tissue, another function of low insulin.

The intermediary metabolism of the ketoacids has been reviewed in great detail in several recent articles. Hepatic ketogenesis was well elaborated by McGarry and Foster (32, 33), and the peripheral metabo-

lism of the ketoacids and their effects on other substances was extensively reviewed by Robinson and Williamson (50). Fenselau (17) has just detailed the biochemical reactions involved in ketogenesis and ketoacid metabolism and Liljenquist (30) has just discussed ketoacid regulation in chapters in Brownlee's multivolumed series on diabetes mellitus (6).

The third ketone, acetone, is thought to be the product of a nonenzymatic decarboxylation of acetoacetate (although its production still could be enzymatically catabolized). Therefore, acetone is a function of levels of acetoacetate and the duration of its elevated level. Reichard and colleagues (46) and Owen, et al. (43) have recently shown that a third of the acetoacetate is decarboxylated to acetone, and, surprisingly, about two-thirds of the acetone is recovered in glucose, a novel observation. Thus the old adage that fat cannot be converted into carbohydate in man is not quite true. This route of fatty acid to acetate to acetoacetate to acetone, probably via propanediol, is a long way around, but, as will be discussed, may play a very important role in prolonged fasting in man.

Diminished Gluconeogenesis and Increasing Brain Ketoacid Consumption

The final phase in starvation occurs as ketoacid levels reach a plateau and the brain is preferentially using ketoacids as fuel and diminishing glucose utilization accordingly (Figure 4). The net effect is to decrease the need for gluconeogenesis and thus to spare mobilization of muscle protein. Nitrogen excretion diminishes from 12 g/24 hours to 3–4 g/24 h,

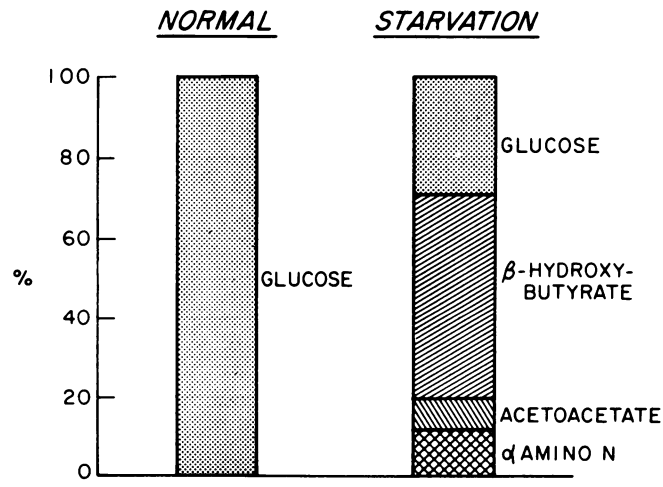

FIG. 4. The brain preferentially uses ketoacids as fuel during starvation; cerebral utilization of glucose falls concomitantly.

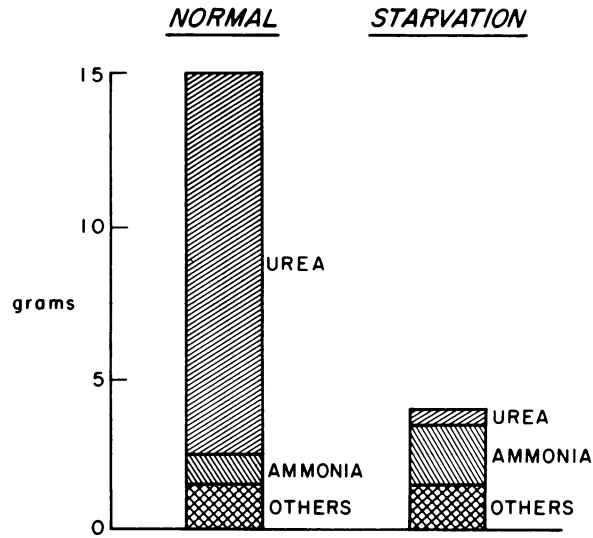

FIG. 5. Nitrogen excretion (in g/24 hours) falls during starvation.

signifying a reduction of protein breakdown from 75 g daily to 12–20 g daily (Figure 5). Thus in starvation the body can continue to utilize the plentiful energy provided by fat while sparing necessary protein. Insulin levels continue to be low, but insulin appears yet to be the controlling signal for integrating the various metabolic processes. Glucagon appears to return to post-absorptive levels, but the glucagon/insulin ratio is still in favor of glucagon so the liver is poised in the direction of gluconeogenesis. Quantitative estimates of 24-hour substrate turnovers are shown in Table 3.

With starvation, as mentioned earlier, the overall rate-control for gluconeogensis is switched from liver to muscle, or in other words, liver becomes substrate-regulated by muscle proteolysis. As shown over 50 years ago by Van Slyke, circulating amino acid levels respond to insulin, and Wool and Cavicchi (60) and others have shown a very important role of insulin in promoting and maintaining the protein synthetic machinery inside muscle. Thus a major effect of increased insulin is to initiate uptake of certain amino acids and their incorporation into protein. A more recently described effect of insulin is also to decrease muscle proteolysis, as shown by several workers including Jefferson et al., (24) and Fulks, Li and Goldberg (18). Thus insulin appears to control the rate of net muscle proteolysis; the lower the insulin, the more rapid the net proteolysis. However, as discussed above, muscle proteolysis diminishes with more prolonged starvation and yet insulin levels are, if anything, even lower; thus we have a paradox needing explanation. Factors other than insulin must be playing a role.

TABLE 3
Quantitative Estimates of 24-hour Substrate Turnovers in Prolonged Starvation

Component	Amount g
Brain glucose utilization	40
Brain ketone utilization (41)	100
Splanchnic glucose output (40)	80
from amino acid	20
from glycerol	20
from returning lactate and pyryvate	40
Muscle proteolysis	20
Adipose lipolysis	180
Splanchnic ketogenesis (47)	150

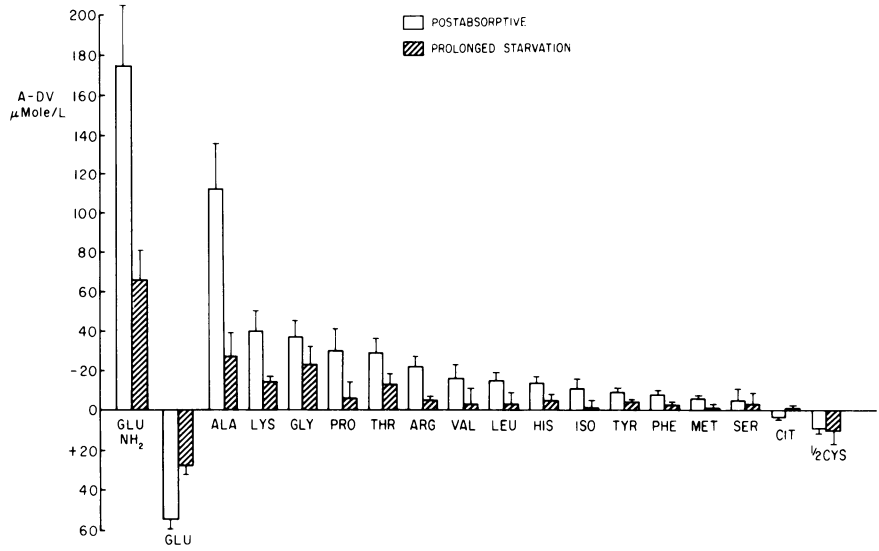

FIG. 6. In the postabsorptive state and in protracted fasting alanine and glutamine (the first and third entries from the left of the abscissa) release exceeds what can be accounted for by their quantities in muscle protein. Ordinate: A-DV means arteriovenous difference.

Much emphasis has been recently directed to the role of amino acids in intermediary metabolism in man. In the post-absorptive state and in prolonged starvation, alanine and glutamine are released in greater quantities than explicable by their contents in muscle protein (31) (Figure 6). Apparently, there is rearrangement of amino acids resulting from proteolysis with the branched chain amino acids transaminating to pyruvate to form alanine or donating ammonia for glutamine synthesis. Other amino acids contribute carbons to form the pyruvate or α-ketoglutarate for the formation of alanine, or glutamate and glutamine. Some of the

glutamate for glutamine formation is taken up from the blood as it courses through muscle. The preferential release of alanine and glutamine is teleologically sound, since alanine is the preferred gluconeogenic substrate for liver and glutamine for kidney. Also, some of the glutamine is made into alanine by the non-hepatic splanchnic bed, so alanine becomes an even greater hepatic gluconeogenic precursor (15).

The explanation for the nitrogen-sparing appears to lie in the unique interrelationships between ketoacids, fatty acids and the metabolism of the branched chain amino acids in muscle mitochondria. As was previously mentioned, early in starvation, ketoacids serve as the predominant muscle fuel, but with more prolonged starvation they are less well used. In fact, as acetoacetate is taken up by the muscle, it is returned back to the blood as β-hydroxybutyrate, signifying a more reduced state of the muscle mitochondria, secondary to free fatty acid utilization. Thus fatty acids appear to take precedence for oxidation and ketoacid oxidation ceases, sparing the ketoacids for brain, a superb overall survival process. But, the excess oxidation of fatty acids also produce a more reduced redox potential in the muscle and a lower rate of amino acid release (1) as well as a diminished ketoacid utilization. A direct effect of ketoacids on amino acid release has also been found both in vivo (55) and in vitro (56) and may be secondary to a decrease in oxidation of the deaminated residues of the three branched-chain amino acids, leucine, isoleucine and valine (2). Thus fat spares oxidation of these amino acids, which appear to play a central role in maintaining muscle protein; this is particularly true for leucine (7, 18).

Thus the "nitrogen-sparing" of prolonged starvation results really from fat being selectively used in muscle. One can show in experimental animals that fat prevents the terminal nitrogen catabolic phase in starvation (12). As will be discussed later, feeding only a small amount of energy as protein is able to replace the nitrogen depletion of otherwise total starvation, and this concept has been capitalized by Blackburn and co-workers (4) in their proposal that endogenous fat, if allowed to be mobilized by not giving carbohydrate, may even be more efficient in sparing nitrogen in patients receiving parenteral alimentation.

Under normal circumstances, kidney in man provides less than 10 percent of glucose production, although the data are scant. In prolonged starvation, as overall gluconeogenesis decreases, the component provided by liver decreases dramatically and that of kidney increases in proportion to the increase in ketoacid loss in urine. This loss necessitates ammonia excretion to prevent loss of cation in urine, and this in turn appears to be coupled with increased glucose synthesis. After several weeks of starvation, kidney provides up to one half of total gluconeogenesis, using the same substrates as liver, but the proportions are different so that amino

acids, primarily glutamine, are used primarily for ammonia synthesis, and in fact, there is more nitrogen in the urine as ammonia than as urea in prolonged starvation. Thus, as far as amino-acid-derived gluconeogenesis is concerned, the kidney is even more important than liver.

During the gluconeogenic phase, up to 500 g of lean flesh may be lost daily in addition to the 150–200 g of fat, the total tissue weight loss being approximately 500–750 g. However, total weight loss is far greater, unless the subject has previously been on a restricted carbohydrate intake. This weight loss is due to a saline diuresis, the precise mechanism of which has yet to be adequately explained. Some evidence suggests that it may be related to an increase in the glucagon/insulin ratio (3, 57). In grossly overweight individuals, this diuresis may result in 5, 10 or even 15 Kg or more of weight loss. In normal, non-obese subjects, 2–2.5 Kg may be lost, particularly in females. Administration of NaCl, or of adrenal mineralocorticoids has essentially no effect (57). This saline diuresis is exquisitely sensitive to the intake of even small amounts of carbohydrate and on refeeding a previously fasted individual, sodium excretion may fall to less than 1 mEq/day. Thus in some subjects, if placed on a liberal salt intake during refeeding, gross edema may occur. Occasionally circulatory stability may be compromised leading to congestive failure in those with heart disease. This has been called "refeeding edema". Later, in total starvation, after the gluconeogenic phase and the saline diuresis, weight loss falls to what one would calculate, 100–200 g of lean tissue and 150–200 g of fat, for a total of approximately 500 g per day.

A frequently asked question is how well the brain functions when using predominantly ketoacids as fuel. Intellectual function appears to remain intact, but emotional alterations are noted, such as depression or lability. Most individuals decrease spontaneous activity, obviously as a mechanism to spare calories, but physical activity can be marked, as in one marathon runner whose pre-race preparation was total calorie abstention for one week! Of much interest is the elevation of the electroconvulsive threshold of the brain utilizing ketoacids as fuel. In the 1920s this was initiated as a form of therapy in children with seizure disorders and has again been resurrected for those children in whom use of multiple pharmacologic anticonvulsive agents is yet ineffective.

The hypothalamic area appears to be significantly altered in the ketosis of prolonged starvation. Appetite is diminished and this may be part of the success of the ketogenic diets used in the treatment of obesity. More dramatically, the desire for fluid intake is diminished, and fasting subjects usually need to be encouraged to drink water. On this point, the markedly decreased urea excretion diminishes the osmotic excretory load, and urine output of 100 to 200 ml/day may be all that is necessary. Again, the survival value is obvious; fasting man need drink very little water, and the 200–300 ml/day produced by metabolism may permit him to survive

water deficits for literally several days to a week or more, providing he is not in a hot, dry, dehydrating climate (10).

Of greater interest, libido is markedly decreased in starvation, and there are significant reductions in the release of pituitary gonadotropins (38) (Newmark, et al., 1976). Thus in the female there is first anovulation and subsequently amenorrhea. In the male there is decreased testicular function. These changes are similar to those noted in subjects with anorexia nervosa by Boyar (5).

With progressive ketosis and the mild metabolic acidosis, there is a gradual and continual excretion of calcium and phosphorus in amounts beyond that lost from the lean tissue being catabolized. Thus bone mineral is gradually being dissolved, similar to that noted in chronic renal acidosis, but to a much lesser degree. This phenomenon has made some clinicians reluctant to use starvation or ketogenic diets in individuals prone to osteoporosis, such as Caucasian females for prolonged periods of time. More significant, as ketosis becomes moderate, the kidney retains uric acid to a greater degree, and serum urate levels rise to 8–10 mg/100 ml, and in some individuals to levels as high as 15–18 mg/100 ml. Amazingly, episodes of gout are rare in spite of this super-saturation, and what attacks have been precipitated have usually been in individuals with previous disease.

A decrease in metabolic rate has been noted in starvation for decades, having been extensively studied by Dubois, Benedict and others. Part of this is explained by the progressively decreasing lean body mass, but the energy decrease appears to be more than accounted for by decreased metabolizable mass. The selective use of fat as fuel, everything else being equal, would be expected to increase oxygen consumption, since it is slightly less efficient than glucose as an energy source, yet, total oxygen consumption is decreased about 10–15 percent.

Recently investigators have noted that the levels of thyroxine remain normal during starvation, but those of triiodothyronine decrease strikingly into the hypothyroid range (45, 59). In contrast, the level of the inactive triiodo form ("reverse T_3" in endocrine jargon) increases (8).

When refed with carbohydrated, fasted man reverses the levels of the two triiodo thyronines and the active form returns to euthyroid levels. Whether the decrease in active T_3 is the sole mediator of the decreased oxygen consumption remains to be demonstrated. In any case, administration of triiodothyronine to fasted subjects not only increases oxygen consumption, but also nitrogen excretion (11); however, feeding a high protein intake is able to maintain nitrogen balance (25).

Protein or Amino Acid Supplementation

Giving totally fasted humans small amounts of protein, as discussed by Folin over 60 years ago, can maintain nitrogen balance and permit

selective utilization of fat calories as fuel. This concept has been used by Blackburn (4) and others (23) as a mode of therapy for subjects unable to eat. This technique has been used in postoperative patients in whom total starvation plus added amino acids maintain better nitrogen balance than total starvation, or by administration of equicaloric amounts of glucose without amino acids.

The mechanism whereby this is achieved appears to lie mainly in the branched-chain amino acids which not only are rate-limiting essential precursors to muscle protein synthesis but also (especially leucine) promote the synthesis of protein and decrease its breakdown directly (7, 18). Proof of their essential role is the ability to use the non-amino carboxylic acid analogues of the branched-chain amino acids in totally fasting man (52, 53), and these result in a significant reduction in daily nitrogen excretion. Thus, it is far more logical to feed small amounts of protein to otherwise fasted man in the basal condition to spare his body nitrogen and yet provide the barest minimum of calories from external sources, than to provide a similar amount of calories in the form of carbohydrates.

In summary, starvation entails a progressive selection of fat as body fuel. Soon after a meal glucose utilization by muscle ceases and fatty acids are used instead. Ketoacid levels in blood become elevated over the first week, and brain preferentially uses these instead of glucose. The net effect is to spare protein even further, as glucose utilization by brain is diminished (Figure 7). Nevertheless there is still net negative nitrogen balance, but this can be nullified by amino acid or protein supplementation. Insulin appears to be the principal regulatory hormone. Recent data suggest that decreased levels of active T_3 may play a role by sparing otherwise obligated calories by decreasing metabolic needs.

Some Other Animals Compared to Man

As discussed above man markedly diminishes his nitrogen excretion with prolonged starvation thanks to ketoacids providing most of the brain fuel. There still is some glucose use by brain, and this is met partly by its formation in liver and kidney from glycerol, partly from some amino acid catabolism and, as shown by Reichard and his group (46), a little from acetone. Why the persistent nitrogen breakdown? With ketoacid loss in the urine, ammonia must be formed to conserve cations, so obviously some nitrogen catabolism must occur. With man's hypertrophied brain, the nitrogen spared by diminishing the need for gluconeogenically-reproduced glucose for brain fuel far outweighs the small amount lost as ammonia to cover ketoacid loss.

Small animals cannot tolerate starvation especially with their increased metabolic rate per unit mass, so they must drop their temperatures, and

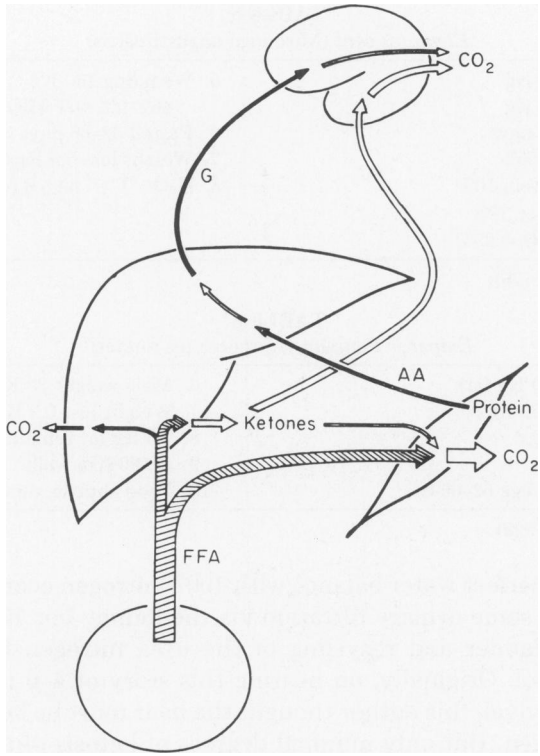

FIG. 7. See text and caption to Figure 1.

TABLE 4
Black bear (Ursus americanus)

1. Dens in October	4. Milk: fat 25%, prot 15%, carb <0.4%
2. Delivers hypomature cub in January	5. Leaves den in April
	6. Total Fast
3. Nurses cub 0.5 Kg → 10 Kg	7. Absent urine and feces

this they do, as found in many rodents, bats, marsupials and insectivores, and even, nocturnally, in the hummingbird. Some larger animals, however, can meet the challenge without much or any drop in metabolic rate, and I will briefly mention three superbly studied examples, the bear, the elephant seal and the emperor penguin.

Black Bear. As studied in detail by Nelson and colleagues over the past decade (Table 4), the black bear in northern climes dens through the winter months with only a minimal fall in body temperature to 32–35°C, and neither eats, drinks, urinates or defecates (3, 34–37). In other

TABLE 5
Elephant seal (Mirounga angustirostris)

1. Adult ♀	600 Kg	5. Weanling 130 Kg	
2. Newborn	34 Kg		40% fat, 40% H_2O
3. Nurses	28 days	6. Fasted 32–68 days	
4. Milk	fat 55%	7. Weight loss 0.5 Kg/d	
	protein 10%	8. H_2O $T_{1/2}$ 53.5 days	
	water 35%		
	CHO <.25%		

From reference (26).

TABLE 6
Emperor Penguin (Aptenodytes forsteri)

1. Adult 40 Kg (20 Kg fat)	6. Male weight 23 Kg
2. Rookery 100–200 Kms	7. Weight loss 0.2 Kg/d
3. Gestation 40–50 d	8. 2.5 Kg fat remains
4. Single egg	9. ≅ 190 Km walk
5. Male incubates egg 62–66 d	10. Food shuttle, 6 mos

From reference (29).

words, it is in perfect water balance with 100% nitrogen economy and this is achieved by some urinary filtration via the kidney but 100% reabsorption by the bladder and recycling of the urea nitrogen back into the amino acid pool. Originally, on hearing this story of 4–6 months deprivation and survival, this author thought the bear must be ketotic in order to spare nitrogen. But only minimal degrees of ketosis of about 1.5 mM β-hydroxybutyrate were found (Aoki, Cahill, unpublished) and in retrospect this should have been predicted. Why? With the bear weighing several hundred pounds, consuming 4,000–5,000 Calories/day of its stored fat, the 50 grams of glycerol should be more than adequate to provide glucose for its brain and nerves. Thus ketoacids are not necessary if one has a low brain/carcass ratio and a large storage of fat (Table 3).

Elephant Seal Pup. Precisely the same phenomenon is found in the elephant seal pup who fasts for 2–3 months after weaning, as shown in the elegant studies of LeBoeuf and his colleagues at the University of California, Santa Cruz (26, 39, 44, 48, 49). Again, the low brain/carcass ratio and the large carcass itself provide this unique capacity to survive prolonged starvation (Table 5).

Emperor Penguin. Continuing along this vein, there is another superb example as studied by several naturalists and physiologists, particularly Dr. Yvon LeMaho of France and his colleagues (14, 22, 28, 29); namely, the nesting male emperor penguin who waddles for almost 100 miles to the nesting site, breeds with the female, awaits two months for her to produce the egg, and then he hatches the egg for two months, awaiting her return to regurgitate a stomach full of anchovies to feed the chick as it hatches on her return (Table 6). One can say this is why the emperor

penguin, who weighs up to 100 pounds, is an "emperor", since he needs enough body mass to carry the fat to provide the glycerol to provide the glucose for his brain. As expected, his ketosis, like that of the elephant seal or the black bear, is minimal, approximately 0.1 mMole for both β-hydroxybutyrate and acetoacetate.

Although these are fascinating biological phenomena, we are left with the question how they achieve 100% nitrogen economy and obviously turn off the catabolism of all essential amino acids, the branched chains in muscle and the remainder in liver (and kidney). The mechanisms have yet to be elucidated, but their importance cannot be sufficiently emphasized, since if this efficiency could be achieved in man, the need for renal transplantation or dialysis programs would be obviated. Hence, the metabolic maneuvers that the emperor penguin, elephant seal and black bear are able to mobilize are critical to be clarified and understood with the possibility that this information may be of help to man and his medical problems.

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