THE JEREMIAH METZGER LECTURE

KETOSIS

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BOSTON

The sweet smell of acetone in the breath of patients in diabetic coma has been known for well over a century. In the 1880's German investigators demonstrated that the urine of these individuals contained a large quantity of two organic materials, subsequently identified as acetoacetic and beta hydroxybutyric acid.[1] It was later observed that normal individuals when simply fasted or subsisting on a high fat diet, also excreted significant quantities of these two compounds. By World War I biochemical methods had become sufficiently advanced to show increased levels of these materials in the blood of individuals in diabetic acidosis, and Van Slyke and Fitz[2] found these compounds responsible for the reduced levels of plasma bicarbonate. The pre-insulin diabetologist emphasized the role of the pancreas and some factor or factors elaborated therefrom, which when lacking induced the full-blown state of diabetic ketoacidosis in experimental animals. With the advent of insulin, the dramatic and complete reversal of the diabetic state emphasized this hormone's central role in ketoacid metabolism. However, in the two decades after Banting and Best's contribution, it became clear that other hormones, such as growth hormone and hormones from the adrenal cortex also played modulating roles.

Although the general topic of ketosis is therefore a relatively old one, it continues to remain an enigma to the biochemist, and to date the precise controls of the reactions responsible for ketone-body synthesis and utilization remain to be clearly defined. There have been several reviews of this aspect of ketosis in recent years[3-9] including several by members of this organization; therefore in this brief presentation, we would like to emphasize not so much the biochemistry, but rather the physiological role that

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Supported in part by USPHS Grants from the NIH AM-05077, AM-15191, AM-15272, AM-15729 and FR-31 (Clinical Center Grant to the Peter Bent Brigham Hospital).

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ketone-bodies play in the adaptation of several animals, including man, to changes in his environment.

Ketone-Bodies and the Adaptation of Man to Starvation

The clinician thinks of acetoacetate and beta hydroxybutyrate, and particularly of acetone, as being evil omens and therefore representative of pathology. This is far from the case. For overall perspective, a brief discussion of the different fuels available to man is in order.

The human body has three principal forms of energy storage. One of these, carbohydrate, is stored in depot form as glycogen, a large branching polymer of glucose molecules. Recent studies by several Swedish investigators[10] have confirmed the contention that liver glycogen is sufficient to maintain circulating glucose concentrations for only 12–14 hours. Thus periods of deprivation of dietary carbohydrate beyond an overnight's fast necessitate synthesis of glucose de novo by liver. One can ask why doesn't man store more glycogen. The answer is that this large branched-chain structure is enclosed in an aqueous environment, and for every gram of accumulated glycogen there must also be accumulated one to two grams of intracellular fluid. Therefore, as a means of storing energy, glycogen is extremely inefficient, yielding approximately one to two calories per gram rather than the theoretical four calories per gram were it present as a dry solid. Thus mobile animals accumulate only limited quantities of glycogen for emergency situations, and instead, use as their principal energy depot fat stored in adipose tissue. A normal man of average weight has approximately 20 to 30 pounds of triglyceride on board, a two-month's supply of calories. He also has a large quantity of protein, primarily in muscle, which like glycogen yields only one calorie per gram wet weight of total stored tissue. More significant, however, is the fact that animals do not appear to store nitrogen in muscle or in any other organ as protein simply for storage's sake alone. In other words, every molecule of protein is serving a biological function other than for energy or nitrogen storage. One can think of protein as being the body's machinery, and the more that it can be conserved during catabolic states by drawing on the fat reserves, the greater the survival advantage.

Returning to fasting man, there is a progressive switch in metabolic fuel utilization from carbohydrate to fat and fat-derived products in the transition from the fed to the fasted state. Normally, man eating three meals per day uses ingested carbohydrate as a fuel substrate for tissues in the body; the excess that is not used is first stored as glycogen to keep this emergency depot expanded to an optimal amount, and any excess beyond that is converted into fat and stored as such. After he stops eating, certain tissues such as muscle begin to exclude glucose from their metabolic diet

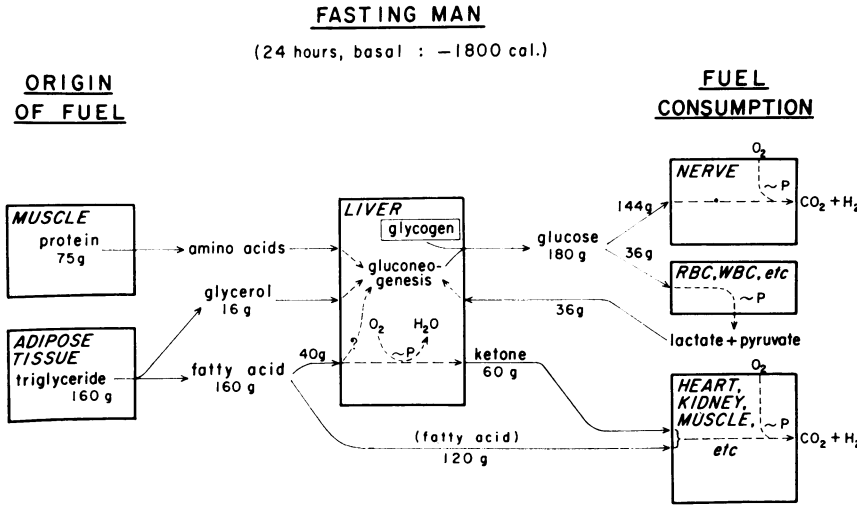

FIG. 1. Overall scheme of fuel flow in a man calculated for a 24-hour period of time after he has already fasted for a day or two. Glucose concentration is maintained by gluconeogenesis with but a small contribution from the remaining liver glycogen. Except for brain, which oxidizes the glucose to CO_2, and certain other tissues such as red cells, which glycolyze the glucose only to lactate and pyruvate, the other tissues exclude glucose from being consumed.

and instead oxidize free fatty acids released from adipose tissue. On the other hand, brain cannot use free fatty acids, since in a mature animal the blood brain barrier prevents their passage. Thus, in the early phases of a fast, the brain will continue to utilize blood glucose as substrate. Initially this glucose is derived from liver glycogen, and as this becomes depleted, it is derived de novo from glucose synthesis in the liver.[11-12] In Figure 1, a metabolic scheme based on directly-determined flow rates and several calculations is presented for a normal man who has fasted a day or two. Brain, as represented by "nerve", is consuming glucose as are several other tissues such as the red cells. These latter tissues, however, metabolize the glucose only to lactate, which is returned to the blood stream, removed by the liver, and resynthesized back to glucose again for another turn of the cycle named for Dr. Cori some forty years ago. The rest of the carcass (heart, muscle, kidney cortex, etc.) excludes glucose from its metabolic diet and therefore is operationally "diabetic". The figure also shows that the glucose that is produced by liver to provide fuel for brain is synthesized at the expense of amino acids derived from muscle protein. To place this in grocery terms, about one half pound of meat and a third pound of oil are consumed daily by fasting man. We need not point out

how clinically discouraging it is to state that totally starving man requires two or three days to lose one single pound of fat!

Why don't muscle and other tissues continue to utilize glucose during a fast? Teleologically the answer is clear, namely that to do so would require continued mobilization of large amounts of stored nitrogen from muscle to be made into glucose. In other words, were the body to utilize only glucose as substrate, survival would be limited to several days to weeks due to the extremely weakened state as a result of the loss of muscle mass.

As also shown in Figure 1, when liver synthesizes glucose from amino acids released from muscle protein, it concomitantly produces ketone-bodies. Dr. John Peters pointed out many years ago that ketone-bodies appear whenever protein assumes the role of carbohydrate as a source of energy. Thus he was the first to point out the close correlation between ketogenesis and gluconeogenesis. Earlier workers such as Benedict and Joslin[13, 14] noted that the degree of glucosuria in the diabetic parallels the capacity to develop ketoacidosis, provided that this glucosuria occurs during starvation or during the consumption of a low carbohydrate diet. In other words if the glucose in the urine is derived from the diet, as occurs in many maturity-onset diabetics, there is not a close correlation between ketogenesis and negative carbohydrate balance. However, if the subject is not eating, this correlation could be made. Atchley, Loeb and their associates withheld insulin from two juvenile diabetics in 1933 and both developed glucosuria.[15] In one, the amount of glucose lost in the urine was less than that consumed daily in the diet and only minimal ketoacidosis developed. In other words this patient was not very different from an individual fasting or consuming small quantities of carbohydrate. The other youngster, however, began to excrete more glucose in his urine than he was consuming, and therefore was in a net negative carbohydrate balance. He progressed into diabetic ketoacidosis. The clinician is only too well aware of this association and the fact that any patient taking in little or no carbohydrate, who is excreting large quantities of glucose in the urine, is going into diabetic ketoacidosis, if he is not already in it. Conversely, spillage of dietary-derived glucose in the urine is not associated with the development of ketoacidosis. To summarize then, the rate of gluconeogenesis is associated with the rate of ketone-body production. This close association is biochemically very advantageous since the oxidation of fatty acids to ketone-bodies provides the energy and reducing equivalents for glucose synthesis at a time when other energy-producing pathways in liver are inhibited. In Figure 2 is a very simplified scheme showing the metabolic pathways which operate in liver in the fed state in

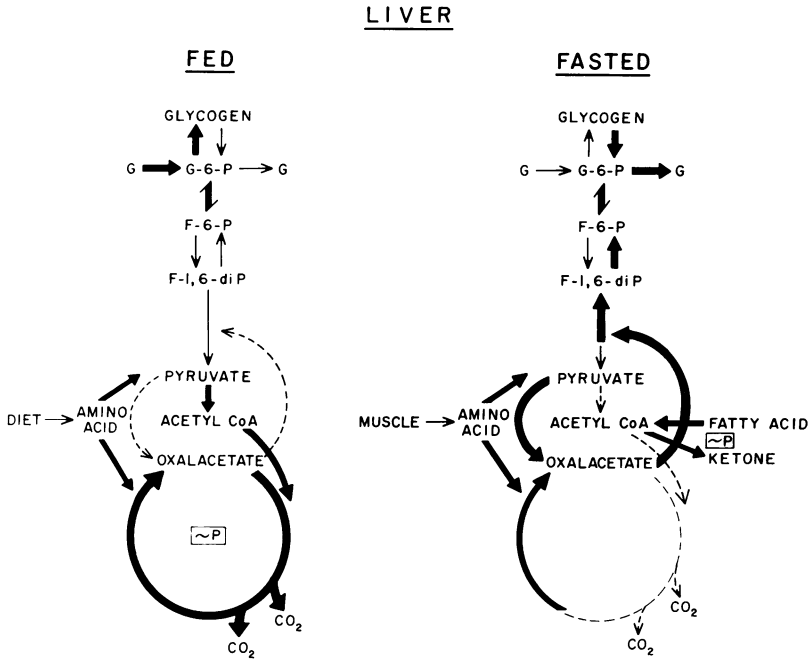

FIG. 2. The two metabolic alternatives for liver are to use glucose in the "fed" state or to make glucose in the "fasted" state. In the former, the energy for liver (high energy phosphate) is derived from the Krebs' oxidative cycle. In the latter, the partial oxidation of fatty acid to ketones provides the energy.

which glucose is consumed and in the fasted state in which glucose and ketoacid are produced.

Without going into the complicated reactions involved in ketone-body production, it is sufficient to point out that the oxidation of a long chain fatty acid to CO_2 occurs essentially in two relatively discrete stages. The first involves partial dehydrogenation and sequential rupture of the fatty acid into two carbon units, acetic acid, or as it exists in the cell in its activated form, acetyl CoA. In Figure 3 it is shown that approximately one-third of the oxygen consumed in the metabolism of long chain fatty acids is used in the formation of acetate; therefore, approximately $\frac{1}{3}$ of the energy available in the fatty acid has been obtained at this point. The next stage or series of reactions involves the oxidation of the acetyl CoA itself to CO_2. This terminal combustion of the original fatty acid results in the availability of the other two thirds of the utilizable energy. In liver, during gluconeogenesis from muscle-derived amino acid, the energy for this and other processes appears to be derived almost exclusively from the initial partial oxidation of the fatty acid to acetyl CoA, and the oxidation

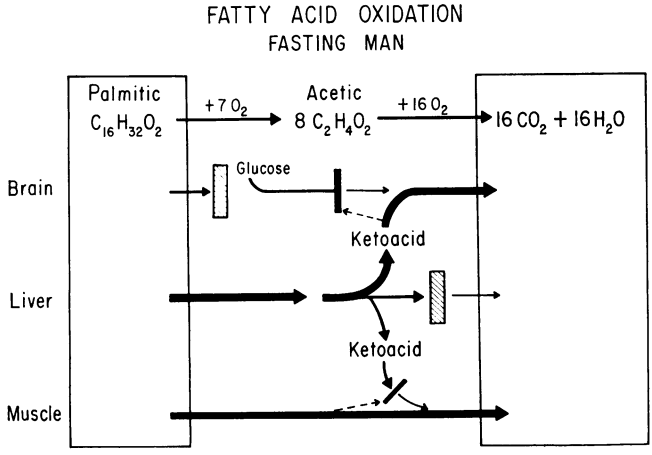

FIG. 3. Oxidation of a typical fatty acid, palmitic acid, first to 8 molecules of acetic acid and the subsequent oxidation of the acetic acids to 16 molecules of CO_2 and water. Muscle is capable of carrying out the entire sequence. Brain excludes fatty acids, and glucose is used as fuel. Ketoacids, however, gradually supplant glucose as fuel for brain in prolonged starvation.

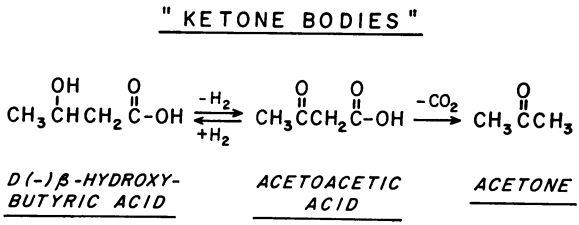

FIG. 4. The "ketone bodies" and acetone. Acetone is primarily a metabolic dead end and is excreted from the body mainly by evaporation loss via the lungs.

of acetyl CoA to CO_2 through the citric acid (Krebs) cycle is markedly diminished. In this situation the liver disposes of acetyl CoA by exporting it, two molecules at a time, in the form of acetoacetate or beta hydroxybutyrate (Fig. 4). Again the precise metabolic control of these reactions, although extensively studied and recently reviewed by several authors,[5, 8] is not clear. The ketone-bodies, beta hydroxybutyrate and acetoacetate, are readily used by peripheral tissues, particularly heart and skeletal muscle. There is evidence that in the two or three day fasted man over 70 to 80% of the oxidative metabolism of his heart is due to ketone-body oxidation!

In fasting man what tells muscle to begin breaking down its stored protein to provide the amino acid as substrate for hepatic gluconeogenesis? Insulin appears to be the primary controller of the entire process. As

glucose levels fall, the beta cell, being as responsive to small changes in glucose concentration in the low or normal range, as in the high range, decreases its rate of insulin secretion. The very short half-life of the hormone, approximately 10 minutes, results in its rapid decrease in tissue fluids. Insulin appears to play a central role both in the promotion of protein synthesis when it is present in high concentration, and in the regulation of protein breakdown when it is present in low concentration. Thus low insulin levels initiate and control muscle proteolysis and the release of amino acid. The low insulin concentration may also be a primary signal to the liver to increase its gluconeogenic capacity as well as its rate of ketone-body production from long chain fatty acid. It may not be the sole signal, however, since recent data suggest that an increase in glucagon, the hormone released from the alpha cells of the pancreas, may also play a very important role in stimulating the gluconeogenic and ketogenic capacities of the liver.[16] Thus the low insulin and high glucagon levels combined provoke the liver to trap amino acids coming to it via the blood stream and to convert these into glucose, with enhanced ketone body production being a concurrent event. It should also be added that it is this low insulin concentration which prevents certain peripheral tissues such as muscle and adipose tissue from utilizing glucose and thereby indirectly spares body protein.

Returning to Figure 1, were the rate of protein breakdown needed to maintain gluconeogenesis in the early phases of fasting to continue for a period of one or more weeks, survival would still be in jeopardy due to loss of muscle protein. Nutrition data suggest that if one third or, at most, one half of muscle protein has been depleted, terminal bronchial pneumonia ensues because of ineffective clearing of the tracheobronchial tree secondary to mobilization of amino acids from protein in the diaphragm and inter-costal musculature. In other words the high demand of man's central nervous system for energy poses a unique problem for him since it requires some form of adaptation to conserve protein if man is to be able to survive starvation for a prolonged period of time. As discussed before this group several years ago, there are several possible solutions to this problem. One of these is that the central nervous system reduces its oxygen consumption; however, this is very improbable inasmuch as even a 10% reduction in cerebral oxygen consumption is incompatible with cerebration. A second possibility is that long chain fatty acids are able to gain access to the central nervous system; to date there are no data which demonstrate that this occurs during starvation. The third possibility, and the one that appears to be the solution, is that the ketone-bodies, fat-derived products, can gain easy access to the central nervous system and are able to provide the necessary calories to maintain brain function, thus

sparing body nitrogen. It appears that ketone-bodies are an extremely important metabolic substrate thanks to their aqueous solubility and their availability to tissues which cannot have access to circulating free fatty acids. Studies by several groups around the world have shown that the adult human brain has the necessary enzymatic machinery to metabolize ketoacids and simply all that is necessary is an adequate concentration in the blood stream in order that a sufficient amount be able to diffuse into the central nervous system to provide fuel.[17-19] The adaptation is therefore not one in brain enzymes, although this has been suggested to be the case, but rather instead, the capacity for the liver and for the periphery to permit the concentrations of ketoacids to rise sufficiently. How and why the presence of a high concentration of ketoacids is able to prevent glucose from being utilized by brain is under current investigation; experiments to date suggest that glycolysis is inhibited in central nervous system cells by the accumulation of metabolic intermediates such as citrate which increase in concentration in association with high rates of ketone-body utilization. Thus in prolonged fasting, the development of ketoacidosis permits man, all the more, to prevent utilization of his muscle nitrogen. In Figure 5 is illustrated the progressive decrease in the rate of nitrogen excretion in a normal man, fasted for several weeks.

In Figure 6 is a clearer representation of the quantitative changes in the principal urinary components during starvation. It can be seen that the excretion of urea is markedly attenuated and that the primary excretory nitrogenous product is ammonia. The teleologic reason for this, of course, is that a moderate amount of organic acid is lost in the urine as beta hydroxybutyric and acetoacetic acids and these need to be excreted with a cation due to their relatively strong acidity. Were sodium or potassium to provide this cation, fluid volume and electrolyte depletion would occur very rapidly, and death would take place in two or three days. The utilization of ammonia for this purpose therefore spares electrolyte and helps maintain intra- and extracellular volume.

Of more interest, however, from a comparative point of view, is that this marked attenuation of urea excretion profoundly diminishes the amount of osmoles excreted per day. Thus obligatory urinary water loss is minimal; in fact, one can make rough calculations that if fasting man were in a cave with a very high humidity and a temperature of about 80°F., thereby minimizing evaporative water loss, the water produced by daily metabolism would almost meet his daily water requirements, and he could go possibly for as long as a week or two without life-threatening dehydration. The survival benefit of this adaptation is obvious. It is interesting that our fasting obese patients if left to themselves will drink only one glass of water a day and will excrete approximately 100 cc of

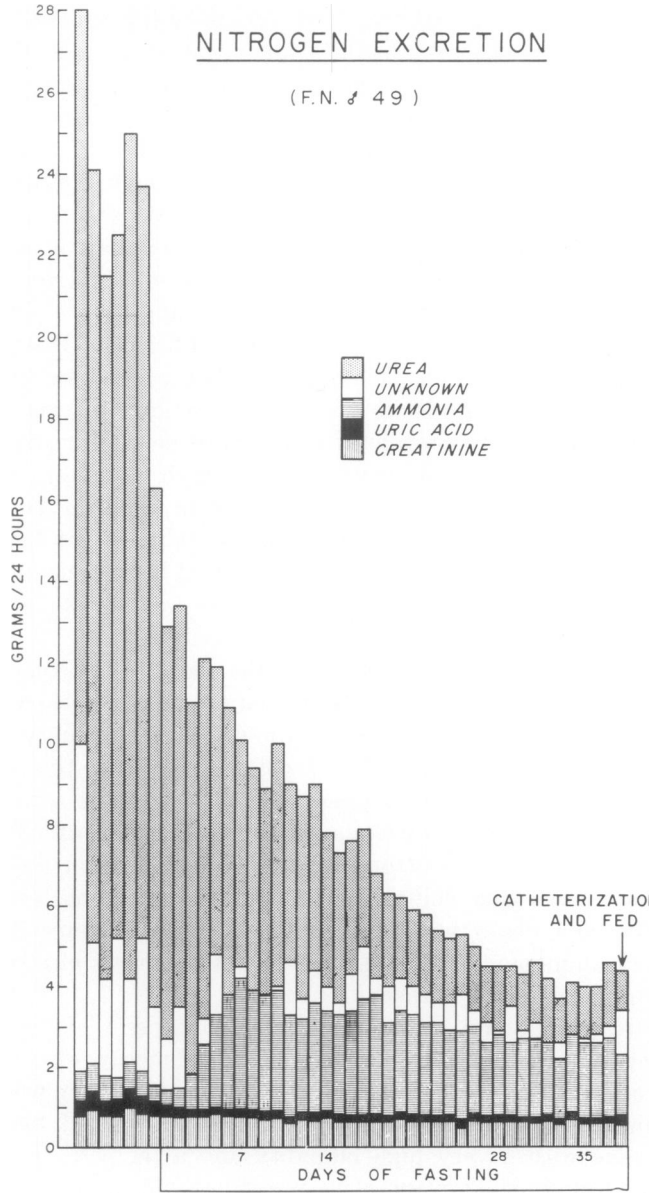

FIG. 5. Nitrogen excretion in a fasting man showing the progressive diminution.

urine. This of course we do not let then do in fear of precipitating uric acid or calcium phosphate in this concentrated urine. It is noteworthy that peripheral tissues other than brain, most notably muscle, participate in

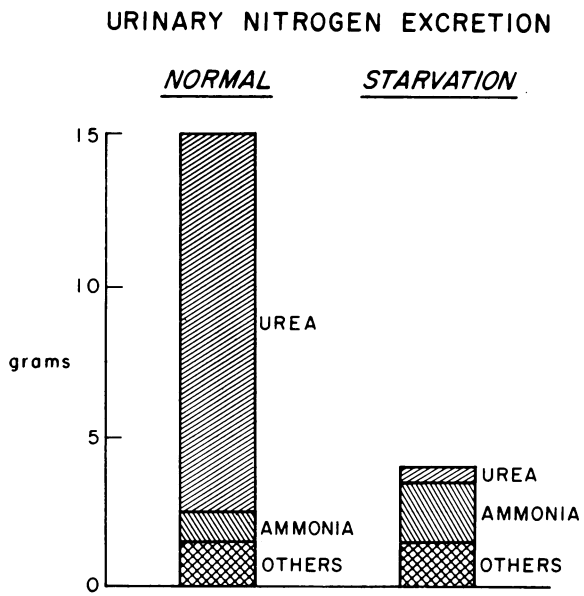

FIG. 6. Urinary nitrogen components in fed and starving man.

ketone-body utilization early in starvation, but later they decrease ketone-body uptake[20] for reasons not yet biochemically clarified. Thus early in starvation peripheral tissues exclude glucose in order to conserve fuel for brain, and later in starvation they exclude ketone-bodies for the same reason (Figure 7). This secondary adaptation by muscle and perhaps other tissues could be of importance for two reasons; first it might be critical for maintaining blood ketone-body levels, if hepatic ketogenesis as well as gluconeogenesis were diminished in prolonged fasting,[11] and second, by causing plasma ketone-body levels to rise, it would increase the magnitude of brain ketone-body utilization.

Diabetic Ketoacidosis

The well-controlled juvenile diabetic is prone to develop ketoacidosis rapidly if insulin is suddenly withdrawn. In this case, there is a rapid increase in fatty acid mobilization from adipose tissue and enhanced ketone production by the liver. In addition, and less well known, peripheral ketone utilization, which also appears to be under insulin control, is depressed.[9, 21-25] Thus, in a severely insulin deficient state, there is decreased muscle uptake of ketoacids, and this markedly enhances the degree of ketoacid elevation in the plasma (Fig. 8). The diabetic, in contrast to the fasting individual, gets into trouble because of the rapidity of these changes in relation to the speed with which his kidney increases ammonia

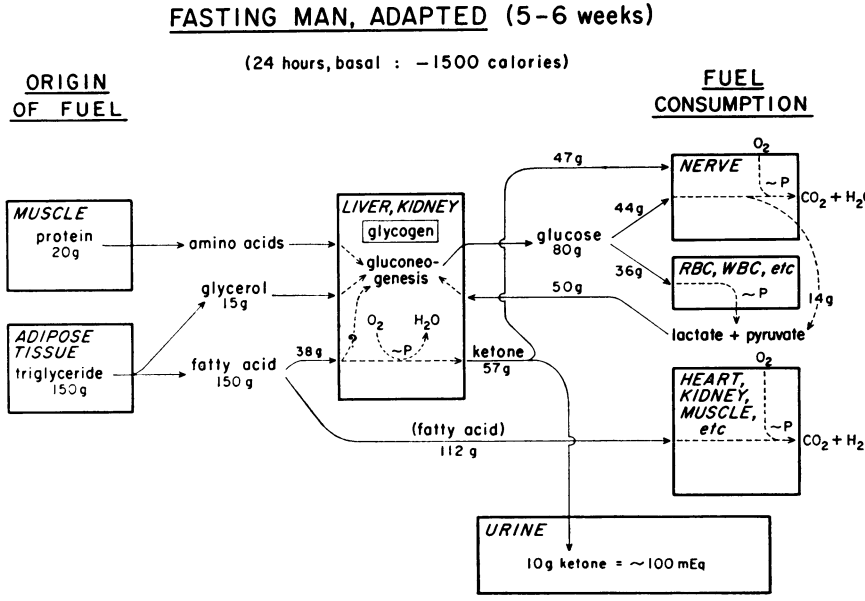

FIG. 7. Metabolic flux of fuels in prolonged fasting man showing displacement of brain glucose consumption by ketones.

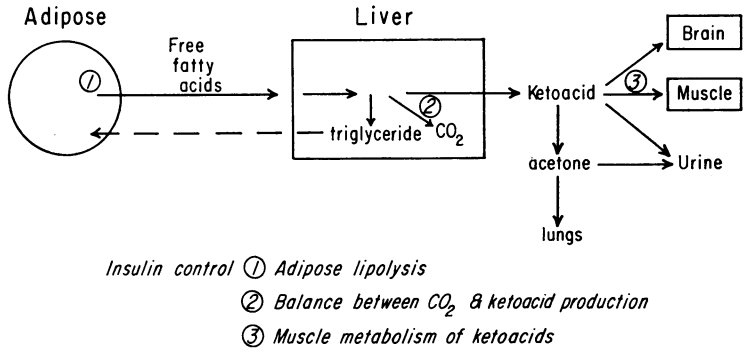

FIG. 8. Sites of insulin control of ketoacid metabolism.

production. It was shown some 30 years ago by Pitts and his group[26] that the capacity for an animal, particularly man, to synthesize and excrete ammonia at high rates takes at least several days. It is interesting that in man the adaptation of the kidney to excrete ammonia precisely parallels

the rate at which he develops ketoacidosis with simple starvation,[11, 12] as if these two processes were programmed together in evolution.

Ketone-Bodies in the Newborn Infant

Are there other occasions in human development when nitrogen conservation is important and where brain may require a water soluble fuel other than glucose? The pediatricians have recently noted that for the first few days after birth, the normal infant is mildly ketoacidotic.[27] The total concentration of ketone-bodies increases to about 1 mMolar, far in excess of what would occur in a normal adult unless he were fasted for one to two days or he was on a high fat diet. Again one may ask is there some reason for the newborn to be ketotic other than to spare gluconeogenesis and thereby conserve nitrogen. There may be two reasons. First, in the transition from the uterine environment into the outside world, the liver has to adapt rapidly to being able to make glucose de novo. This process is apparently limited in the newborn, and he goes through a period of time when his hepatic gluconeogenic capacity is stressed to a maximum, and ketone-bodies might be required as a brain fuel until the liver gluconeogenic system matures. The other reason of course is that the newborn baby is on a mildly high fat diet, since mother's milk contains many more calories in the form of fat then of carbohydrate. Suckling rats go through a very similar metabolic maneuver, and the relatively high fat content in rat milk helps to make the young rats moderately ketoacidotic. In some very elegant studies on ketone-body utilization by rat brain, Krebs and associates[28, 29] have shown that the rate limiting enzyme in acetoacetate metabolism increases shortly after birth, peaks at about 18 days and declines to a lower level thereafter as the rat is weaned. They also showed that the activity of this enzyme paralleled the magnitude of ketone-body uptake by rat brain and that over 50% of brain oxygen consumption in the suckling rat can be provided by ketoacids.[28]

Response to Starvation in Small Animals

If ketoacids are so important for human survival during prolonged starvation one may wonder what other animals behave similarly. If one fasts a laboratory rat, there is only a minimal degree of ketoacidosis, approximately one to two mMolar and after 3 or 4 days of starvation, all the body fat is depleted. The ketosis then decreases and the animal utilizes its muscle mass (Parrilla and Toews, unpublished). Gluconeogenesis, instead of becoming attenuated as in man, progressively increases during starvation in the rat, since the non-obese rat, in contrast to man, has more calories in muscle nitrogen than in his relatively limited adipose tissue.

One wonders how small animals, such as the laboratory rat survive prolonged starvation, and the answer is they don't. If one plots the oxygen consumption per unit weight of small animals and large animals, there is an exponential increase: the smaller the animal the greater its O_2 consumption. Per unit tissue, the mouse and particularly the shrew, need some 10 times or more calories and oxygen per unit weight than do larger animals. Thus even if the small rodent did carry around a moderate fat supply, if he is extremely small, this would yet provide only a minimal extension to the duration of starvation. Small rodents must therefore resort to one of two alternative maneuvers to survive even short periods of starvation. One is to drop body temperature and thereby decrease caloric need, and perhaps equally important is to diminish evaporative water loss. The capacity to drop body temperature (or hibernation) is shared by numerous rodent species and also several insectivores and marsupials.

It is interesting that some very small birds have also been noted to drop their body temperature during times of fasting. This is particularly true of the hummingbird which goes into nocturnal torpor, again to spare both calories and water of evaporation. Laziewski[30] in some very elegant studies on Costa's hummingbird has demonstrated that during activity, oxygen consumption is such that the hummingbird needs to eat and drink water every 20 minutes, otherwise it could not survive for more than several hours. Even if sitting at rest, oxygen consumption of the hummingbird is so great that unless very well fed it cannot survive a night of fasting. To combat this problem it drops its body temperature in order to cut down caloric loss. A second and very obvious and common maneuver of the small animal when challenged with impending deprivation is to hoard food and never truly face the challenge of starvation itself.

Response to Starvation in the Bear

A great deal about our adaptation to fasting may be learned from the study of certain carnivora, which, as part of their annual routine, go into a long winter sleep during which time they are completely starved. The best example of these are North American bears which enter their dens in November or December, depending on how cold is the weather, and only return to the outside world some time in the middle of the Spring.[31, 32] Of particular interest is the female bear who will not only fast but will deliver her cub toward the end of January and then suckle the cub for the next few months prior to leaving the den. Stories by huntsmen have emphasized that these bears are really in a shallow sleep and not in hibernation, since if they are disturbed, they will react immediately with flight or aggression. Studies by several mammologists have shown that these bears drop their body temperature a degree of two, similar to man in

sleep. What is most fascinating about these animals is that they pass little or no urine during their winter sleep.[33] This is also true of the female bear who has delivered her cub and is providing through her milk the fat and protein for the needs of the cub.

That the bear urinates very little, if at all, has been corroborated by animals kept in winter sleep in a captive environment by Drs. Ralph Nelson and his associates at the Mayo Clinic,[34-35] and also by captured or radio-located bears followed by Dr. Ulysses Seal of the Veterans Administration Hospital in Minneapolis.[34-36] There are also other documented observations of bear cubs which have been captured and kept as pets by man and who have gone into their winter sleep under continuous observation.[33] Dr. Ralph Nelson at the Mayo Clinic and his associates have studied nitrogen excretion rates and documented that the bear, like fasting man, excretes only two or three grams of nitrogen per day into his bladder.[35] This would still require occasional urination and Dr. Nelson is currently doing studies to see if the bear bladder is permeable to urea, thereby allowing urea to be reabsorbed and possibly metabolized to ammonia by flora in the gut. In any case, the bear has become remarkably efficient in being able to spare its nitrogen, and, in the case of the female, to export what nitrogen it is expending via the mammary glands to the cub. Since the mother bear has very little if any net amino acid catabolism, one would expect that bear milk would be low in carbohydrate. Indeed, this has been found to be the case by Jenness and associates, again at the University of Minnesota, who in analyses of bear milk have found that it consists of 13% protein, approximately 25% fat and less than 1% carbohydrate.[37] Thus the mother bear is transferring via her milk only protein and fat and by bypassing the need to make carbohydrate she is sparing nitrogen. Again one can ask what is providing substrate for the mother's as well as the cub's brain and the answer again is probably ketone-bodies, which our laboratory has found in significant quantities in the sera of bears studied by Drs. Seal and Nelson.

The relevant part of the bear story to man is the bear's extreme economy in being able to conserve nitrogen. In other words, if the bear can go for several months without urinating, why can't man? Studies currently in progress have shown that insulin is extremely important in supressing muscle protein breakdown. Nevertheless even with high insulin levels, there has to be some turnover and re-synthesis of new protein in muscle which suggests that the bear must possess a mechanism to reutilize just about all of the amino acids hydrolyzed by the initial proteolysis.

To describe this problem in further detail, a brief discussion of amino acid catabolism is in order. Amino acids are catabolized in the body primarily in two tissues, muscle and liver. The three essential branched-

chain amino acids, leucine, isoleucine and valine are almost uniquely catabolized in muscle.[38, 39] All of the other amino acids are primarily catabolized by liver and to a lesser extent by kidney.[40] Thus, as muscle proteolysis takes place, the branched-chain amino acids are normally irreversibly removed and oxidized, and the other amino acids are released into the blood stream for liver and kidney to remove them. These three branched-chain amino acids are essential and cannot be synthesized in any animal tissues. If the oxidation of these three branched-chain amino acids in muscle were to be inhibited, these as well as the other amino acids in muscle would be available for the synthesis of new muscle protein. Thus the control of the oxidation of these 3 amino acids deserves emphasis and exploration.

It is interesting to note also that, unlike many other amino acids, these 3 are not concentrated inside tissues, particularly muscle. Since the enzymes responsible for the transamination and initial decarboxylation of the branched-chain amino acids have low affinities for their substrates,[41, 42] the low levels in tissues would already act as a sparing type of mechanism from metabolism. As the level of leucine, isoleucine and valine in circulating body fluids falls even further during prolonged starvation,[40] both in man and in bear, it is likely that the intracellular levels in muscle fall even further. As shown in Figure 9, these branched-chain amino acids also need co-enzyme A for their initial oxidation. Therefore, in the presence of

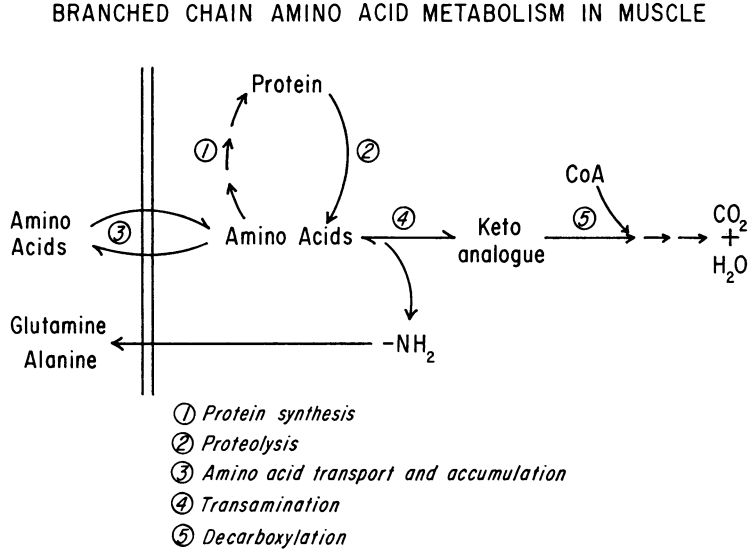

FIG. 9. Branched-chain amino acid metabolism in muscle.

a high rate of fatty acid utilization, when much of the intracellular CoA would be bound to fatty acids and their derivatives, it is possible that the amount of CoA could be rate limiting for branched-chain amino acid oxidation. This too might serve to spare the branched-chain amino acids so that they could be re-utilized for protein synthesis. Currently the possibility that high levels of fatty acids induced by a ketogenic type of diet in man can spare muscle nitrogen and thereby the need for nitrogen excretion is under study.

Brain Function with Ketone-Bodies as a Fuel

Returning to fasting man, how does his brain function when ketoacids instead of glucose are used as the predominant substrate? Our studies have shown that intellectual capacity and performance are unimpaired. There are, however, some hormonal sequelae which originate from the hypothalamus or pituitary. It has been known for years, literally centuries, that the capacity to procreate during starvation is markedly curtailed. Recent studies by many investigators have shown that during starvation the number of ovulatory cycles by the female is markedly diminished. With severe malnutrition not only is ovulation but even the menses themselves are frequently terminated. In a collaborative effort with Drs. Mortimer Lipsett and Lynn Lorieaux at the N.I.H. we have found that the levels of LH remain constant during prolonged starvation, however the levels of FSH diminish dramatically. Thus, the mechanism of anovulation is explained, but the question remains, is this due to the fact that the hypothalamus or pituitary now is utilizing ketoacids instead of glucose? Other interesting sequelae of starvation are the total lack of appetite which occurs in the individual once he has become mildly ketoacidotic. In fact, totally starving individuals frequently become nauseated and have a strong aversion to food. This also suggests that there may be some functional correlates to the substitution of ketoacids for glucose as brain's primary fuel.

That there are electrical correlates that result from altered brain substrate utilization was shown approximately 50 years ago, originally by an osteopathic physician who noted that children with epilepsy frequently improved when placed on total starvation and given repetitive enemas. His hypothesis, that the epilepsy was due to some autointoxication from lymphoid patches in the bowel, was imaginative, but his method of treatment occasionally produced dramatic results.[43] Dr. Russell Wilder[44] at the Mayo Clinic, knowing that a high fat diet would produce a similar degree of ketoacidosis to that of total starvation, placed youngsters with petit mal epilepsy on a high fat diet and again noted the marked improvement in many. The so-called ketogenic diet has had its ups and downs

since, and with the advent of numerous pharmacological agents capable of markedly suppressing epileptic attacks, it fell into disuse as well as disfavor. Recently, however, several investigators[45] including Dr. Peter Huttenlocher and associates at Yale Medical School[46] have placed children with continuous attacks and already on numerous pharmacological agents on the ketogenic diet, and, in certain circumstances, have noted dramatic improvement and occasionally total cessation of epileptic seizures. Dr. Huttenlocher has capitalized on the use of a synthetic triglyceride made of medium chain length fatty acids[47] which are metabolized almost solely by the liver, thereby enhancing the rate of ketoacid production. This is a far more palatable mechanism for producing ketoacids than that which involves feeding a high fat diet, and it is certainly more acceptable and practicable than total starvation. In many of these subjects the electroencephalogram either markedly improved or returned completely to normal. Again one must ask whether it is the utilization of ketoacids that alters the electrical nature of the brain in these young individuals or is it some other factor directly or indirectly related to the mild ketoacidosis. Thus there are some metabolic sequelae resulting from brain utilization of ketoacids including cessation of fertility, production of anorexia, and altered convulsive thresholds.

In summary, ketoacids are probably present in nature to provide a water-soluble, fat-derived substrate to tissues such as brain when carbohydrate and its obligatory precursor, protein, need to be conserved. Insulin appears to be the hormone controlling both the production and utilization of ketoacids.

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