

Ketosis and the Optimal Carbohydrate

Diet: A Basic Factor in Orthomolecular Psychiatry

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The response of 73 psychiatric outpatients to manipulation of their dietary intake of carbohydrate was studied with respect to symptoms of anxiety, depression, and dys-perception. In particular these symptoms were evaluated in three conditions: in ketosis, at the transition point from ketosis to non-ketosis, which I regard as an "Optimum Carbohydrate Level" (OCL), and at a higher carbohydrate intake, above 120 g per day.

Ketosis was associated with improvement in 28 percent; the OCL was associated with improvement in 68 percent; and carbohydrate intake over 120 g per day was associated with improvement in 12 percent. Over all, 82 percent of the patients reported improvement when combined results of both ketosis and OCL are considered. On the other hand, 60 percent reported some adverse effects, such as fatigue, nausea, weakness, headache, and a few episodes of palpitations. These were all transient, and most were improved after administration of potassium salts.

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The history and biochemistry of the ketogenic diet and its use in medicine, particularly in the treatment of epilepsy and also obesity, is discussed.

The ketosis method of determining optimal carbohydrate intake appears to be a valuable addition to the practice of Orthomolecular psychiatry.

Ketosis is an altered state of metabolism in which larger than usual quantities of ketone bodies, e.g., aceto-acetic acid, beta-hydroxybutyric acid, and acetone are present in the blood and excreted in the breath and urine. In the breath they are detectable by their characteristic odor, and in the urine their presence can be qualitatively measured by means of a commercially available reagent test strip, the Ames Ketostix.

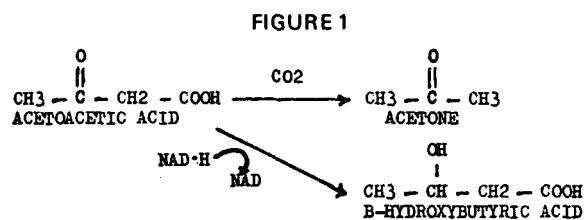
Normally the excretion of ketones is less than 1 mg per 24 hours. In ketosis due to carbohydrate restriction it is often as high as 10 mg per 24 hours, and in starvation up to 20 mg per 24 hours has been measured. Since the caloric value of ketones in metabolism is about 4.5

Kcal per gram, this could account for about 100 Kcal of wasted calories per day. This is not sufficient to account for the accelerated weight loss that is supposed to occur with high-fat, low-carbohydrate, ketogenic diets (Reichard et al., 1974; Hoffman, 1970).

Ketosis occurs as a result of increased oxidation of fatty acids, and the most common cause is starvation. It occurs also in diabetes where lack of insulin interferes with utilization of glucose, but permits the mobilization of free fatty acids, lipolysis, in the adipose cells. However the actual production of ketones hinges not on insulin lack but on the active influence of glucagon, which acts in the liver cells to promote gluconeogenesis from amino acids and ketogenesis from fatty acids (Gerich, 1975).

Ketosis also occurs after high dietary fat intake, becoming especially likely when fats make up over two-thirds of the calories consumed, in which case ketone production is actually greater than with total starvation. That this is due to the ease of lipolysis of triglyceride as compared with already stored tissue fat is suggested by the fact that ketosis has recently been induced by using preparations of medium chain triglycerides (MCT) in place of dietary fat. Since MCT are tasteless they provide a clinically convenient adjunct to induce ketosis.

Whenever lipolysis exceeds lipo-genesis, fatty acids are liberated, oxidized to acetyl-coenzyme A and acyl-coenzyme A and then condensed to beta-hydroxy, beta-methylglutaryl coenzyme A (HMG-CoA), generating finally acetoacetate. Cholesterol is a by-product of HMG production since HMG is a step on the pathway to cholesterol through mevalonate and squalene. Acetoacetate meanwhile yields acetone and beta-hydroxybutyric acid as charted in Figure



B-hydroxybutyrate is important due to its known feedback inhibition of glucose utilization, lipolysis, and insulin release (Senior and Loridan, 1968). Acetoacetate is known to be a strong sedative and in part responsible for the anticonvulsant effect of ketosis. Both acetoacetate and B-hydroxybutyrate are now known to be utilized as fuel by neurons in the brain (Owen et al., 1967).

Ketosis, in the form of fasting, has been known in the treatment of epilepsy for at least two thousand years. In the Bible (St. Mark 9:14-29) Jesus is asked by a father to heal his son, "which hath a dumb spirit ... he teareth him: and he foameth, and he gnasheth with his teeth, and pineth away." "And when they brought him unto Him and when he saw Him, straightaway the spirit tare him; and he fell to the ground, and wallowed foaming." "When Jesus saw that the people came running together, he rebuked the foul spirit, saying unto him, Thou dumb and deaf spirit, I charge thee, come out of him, and enter no more into him."

The results of exorcism were not successful, however, for further on in the narrative His disciples asked Him privately: "Why could not we cast him out?" And He said unto them: "This kind can come forth by nothing but by prayer and fasting."

In the early part of this century ketosis was commonly used in urology for treatment of urinary tract infections because certain strains of bacteria cannot thrive in an acid urine. This usage has been superseded by other acidifiers, such as mandelic acid, methenamine, and acetazolamide, and by antibiotic therapy.

Also early in this century ketosis came into vogue in Europe as an effective method to deal with epilepsy through fasting. Wilder introduced the ketogenic diet for treatment of epilepsy at the Mayo Clinic in 1921, and Peterman, Helmholz, Talbot, Wilkins, Keith, and Bridge all confirmed the beneficial effect of ketosis in controlling epilepsy (Keith, 1963). Many of their cases were followed for long periods of time in ketosis, some over 25 years with important benefits and

without serious adverse effects. More recently Livingston (pp. 378-405, 1972), Gibbs (1958), and Lennox (pp. 733-737, 1960) have all written favorably about this mode of treatment.

The low-carbohydrate, high-fat diet has also been known in the field of general medicine, particularly with regard to weight reduction, for over a hundred years. William Harvey, an English surgeon, treated an obese patient with a diet of meat and ale, but no sweet or starchy foods. The patient, William Banting, published his famous "Letter on Corpulence, addressed to the public" in 1863.

Since then the ketogenic diet has never dropped out of sight for long. In the past 20 years it has reappeared as the Pennington Diet in 1953, the Air Force Diet in 1960, Taller's "Calories Don't Count" diet in 1961, The Drinking Man's Diet in 1964, the Stillman Diet in 1967, and the Atkins "Diet Revolution" in 1972.

Somehow this most recent publication by Atkins has generated an unprecedented backlash of rebuke from the medical establishment. The diet has been criticized as both unscientific and unsafe by medical authorities from the AMA on down to local medical societies throughout the country. A complete rebuttal to Atkins' theories was presented in the JAMA with particular emphasis on the dangers of high-fat intake, particularly regarding atherosclerosis, coronary artery disease, uric acid elevation, and kidney disorders. The upshot of it is: "Physicians should counsel their patients as to the potentially harmful results that might occur because of adherence to the ketogenic diet" (White, 1973).

Because of my interest in clinical nutrition and because some of my patients claimed that the Atkins diet had been quite helpful to them in their efforts at weight reduction, I made it a point to read **Dr. Atkins Diet Revolution** (1972). I am glad that I did because I believe that it makes two new and important contributions to clinical nutrition. In the first place the Ketostix method of monitoring ketone bodies in the urine provides an alternative mode of behavioral reinforcement and reward for obese patients who otherwise must depend on the vagaries of weighing their progress with the bath-

room scale. The measurement of body weight is an inconsistent and frequently inaccurate reflection of food intake because of the confusing effects of fluid intake and retention. The measurement of ketone bodies, on the other hand, is a more consistent and precise measure of dietary carbohydrate restriction and therefore a more effective behavioral reinforcer. This introduces a new and helpful motivational gambit into the difficult practice of bariatrics.

Of equal importance is Atkins' emphasis on the Critical Carbohydrate Level, the point at which the Ketostix cease to develop a purple tinge on being dipped in the urine sample. Atkins used this technique to show his patients their carbohydrate requirements: theoretically a positive reaction of the Ketostix implies weight loss due to ketosis; a negative reaction implies interruption of the progress of weight loss and can be used as an index of a proper maintenance dietary carbohydrate level.

As I combined the reading of Atkins' book with my clinical thinking about Orthomolecular psychiatry, it dawned on me that while medicine is beginning to appreciate the importance to health of optimum quantities and concentrations of the essential vitamins and minerals, the concept of optimum carbohydrate, surely of equal importance, has been used only in a crude manner, i.e., either high, medium, or low.

It seemed plausible that Atkins' Critical Carbohydrate Level could be construed as an Optimal Carbohydrate Level: sufficient to avoid the alleged risks and energy waste of ketosis, while at the same time not so much as to overload the hormonal regulators of metabolism; hence likely to protect against both diabetes and hypoglycemia. Furthermore, since this index of dietary carbohydrate need is determined empirically by dietary titration, it offers precise information that is specific to the individual patient.

I proceeded with caution and hesitation due to the heated controversy raging on about Dr. Atkins and the ketogenic

diet that he had re-introduced. This necessary caution reduced the number of patients in this study because at first I hesitated to try it. From late in 1973 to early in 1975, 73 of my patients

completed the Keto Diet Optimal Carbohydrate Program according to the instruction sheet. This has been reproduced as Figure 2.

FIGURE 2

Ketosis Method - Optimal Carbohydrate Level (OCL)

Name Date

1. Purchase Ketostix at any pharmacy. Test your urine before breakfast and at bedtime.
2. Follow a zero carbohydrate diet until you get a "large" reaction as described on the box of Ketostix; or if that fails to occur, go on to step 3 after five days. Until then eat only foods in the following list of noncarbohydrate foods:
 - MEAT: all types ad lib except NO processed meats, hot dogs, sausages or breaded meats.
 - FISH: all types except NO oysters, clams, scallops, pickled or breaded fish.
 - FOWL: all types except NO stuffing.
 - EGGS: any style ad lib.
 - CHEESE: all types, four ounces a day, except NO cottage cheese or cheese spreads.
 - SALAD: two per day, one cup each: greens, parsley, watercress, mushrooms, asparagus, celery, broccoli, peppers, zucchini, cucumber, radish, eggplant, green olive, pimiento, sprouts.
 - FATS: margarine, butter, oils, shortening.
 - JUICE: of one lemon per day on salad.
 - CONDIMENTS: any type except sugar, honey, sorbitol or catsup.
 - DRINKS: water, mineral water, Calso, club soda, tea, sanko or decaf, bouillon.
 - CREAM: up to four teaspoons per day. No milk or yogurt.
 - SUPPLEMENTS: Kaon (Potassium), 1 or 2 tablets, 3x/day in Ketosis, for lethargy. Also take calcium, magnesium, vitamins C, E, B Complex, 2-3x/day.

3. Then add carbohydrate foods, 5 grams limit per meal, increasing by 10 to 15 grams per day. Observe when the Ketostix remain neutral, indicating the optimal carbohydrate level: sufficient so that fats need not be burned for energy but without excess of carbohydrate to stress the hormonal mechanisms.

The following is a brief tabulation of carbohydrate content of foods:

One quarter cantaloupe	= 7 grams	twelve nuts	= 5 grams
half cup berries	= 6 grams	one tbsp. brewer's yeast	= 4 grams
lettuce-tomato salad	= 6 grams	one tbsp. wheat germ	= 6 grams
half cup carrots or peas	= 10 grams	half cup milk	= 6 grams
half fruit, medium size	= 10 grams	one cup cottage cheese	= 6 grams
half potato, medium size	= 10 grams	one slice bread	= 12 grams
half cup cooked rice	= 20 grams	one cup tomato juice	= 10 grams
four tbsp. bran	= 20 grams	one cup orange juice	= 25 grams

4. Drink six glasses of water per day.
5. Salt food to taste.
6. Increase carbohydrate by 30 grams per day after OCL and observe effects up to 200 grams/day.
7. Keep a diary of foods eaten, feelings and Ketostix reactions as follows:

(Figure 2 continued on next page)

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Date:	Diet	Ketostix		Date:	Diet	Ketostix
	Include everything you eat.	A.M.				A.M.
Breakfast		How Feel				How Feel
Lunch						
Supper						
		P.M.				P.M.

RAK form KDOC 1/10/76

This brief set of instructions has proved effective in guiding my patients through a few days of zero-carbohydrate ingestion until they develop a positive Ketostix reaction, at which point they tediously resume carbohydrates at about 5 g per meal, increasing this by 5 g per meal more each day until the Ketostix no longer show a positive reaction. By keeping a diary of their diet, Ketostix reactions, and perceptual responses the patients develop a more realistic understanding of their symptoms and a more effective motivation to cooperate with the treatment program. In addition they learn something practical about nutrition, such as how to recognize relative values of carbohydrates, proteins, and fats.

The range of dietary carbohydrate amongst these patients prior to treatment was 22 to 730 g per day with a median of 200 g and a mean of 198 g. By contrast the optimum carbohydrate level ranged from 3 to 150 g with a mean of 52 g per day. For almost all of the patients, adhering to the Optimum Carbohydrate Level (OCL) as a guide to carbohydrate intake meant a substantial reduction in dietary carbohydrate intake. Do the results justify such an inconvenience?

Table 1 summarizes the frequency of occurrence of positive and negative responses at three levels of

carbohydrate intake: ketosis (usually almost zero carbohydrate), Optimum Carbohydrate Level (OCL), and upon resuming a high-carbohydrate intake, over 120 g per day in most cases.

TABLE 1

OCL*		120GmCHO	Ketosis
Improved	68%	12%	28%
Worse	14%	81%	53%
Unchanged	14%	7%	19%

* Three patients (4%) did not determine exact OCL.

Three of the 73 cases did not determine the OCL, two of these because they had an unpleasant experience in ketosis and simply reverted to their former diet, and one because he felt so well in ketosis that he didn't bother to raise his carbohydrate intake systematically to determine the OCL.

There was a positive response at the OCL in 48 of 70 cases (68 percent), the patients reporting increased energy,

improved mood, and relief of anxiety and dysperception. On the other hand, 11 of 70 cases (14 percent) were worse, and an equal number were unchanged at the OCL.

Of the 11 patients who reported aggravation of symptoms at the OCL, 8 (73 percent) had a positive response in ketosis and lost this in coming out of ketosis. Three of the patients (27 percent) didn't feel better until ingesting over 120 g of carbohydrate. I cannot explain this, but the fact that some patients relapsed as they came out of ketosis is consistent with the observation of Lennox (p. 727, 1960) that this transition is associated with a compensatory alkalosis and increase in seizure activity.

In contrast to the high percentage of patients who reported improvement at the OCL, the figures were reversed at the higher carbohydrate intake, over 120 g per day. Sixty of the patients (82 percent) suffered recurrence of symptoms and loss of the well-being that they experienced at the OCL. Four patients could detect no difference at the higher level (two of these were obese females and two were chronically anxious males unimproved by Orthomolecular therapy). Only nine patients (13 percent) reported improvement at the high-carbohydrate intake and of these five (56 percent) had a high OCL, over 90 g. Two of them did not go into ketosis at all, even at zero-carbohydrate intake. Of the remaining two patients, one was a middle-aged, chronic depressive, addicted to amphetamine, and the other was a recurrent schizophrenic youth with an abnormal EEG, showing hyperventilation-augmented, non-focal slowing. His was the only such case I observed, the others with abnormal EEG activity all preferred ketosis, or a low-carbohydrate intake.

Ketosis was helpful in 20 of these 73 cases (28 percent) exerting a sedative action in most cases although in others the patients reported increased energy and well-being, or relief from depression or dysperception. It is possible that ketosis was beneficial in some subjects by switching from inadequate or inefficient metabolism of carbohydrate to more satisfactory metabolism of ketone bodies which are known to be actively

utilized, not only in muscle, kidney, and pancreas, but also in brain cells (Owen et al., 1967; Page and Williamson, 1971). The brain is not totally dependent on carbohydrate, as had been believed, but can utilize ketone bodies as an energy source even without a period of fasting adaptation (Flatt et al., 1974).

The fact that ketosis is known to be an effective anticonvulsant suggests that, in those patients who feel better in ketosis, there might be an underlying cerebral dysrhythmia. If so, the ketogenic diet could be used as a clinical test to pick up organic dysfunction.

Unfortunately an electroencephalogram was performed in only eight of the 20 patients who improved in ketosis. Of these, five (62 percent) were abnormal. I am sure that this is a much higher figure than in my practice at large or in the rest of the patients in this series. I conclude that, in some cases, a positive response to ketosis is in fact due to the anticonvulsant action of the ketosis. Nell-haus (1971) has demonstrated normalization of the EEG in ketosis. Perhaps this accounts for the improvement in dysperception in some of my patients.

The actual mechanism of the anticonvulsant action of ketosis is not known. It has been associated in particular with the presence of aceto-acetate; however Lennox (p. 737, 1960) showed a graphic correlation between relief of petit mal seizures and decrease in bicarbonate level in ketosis, and Gamble suggested that the anticonvulsant effect is due to acidosis secondary to the removal of sodium (Gamble et al., 1923). The fact that other states of acidosis also have anticonvulsant properties confirms this: Diamox (acetazola-mide), ammonium chloride, and calcium chloride also reduce seizure activity, as do ascorbic acid and even vinegar. In fact, simply holding one's breath in apnea or breathing into a bag to increase blood CO₂ levels, respiratory acidosis, has significant anticonvulsant and anti-anxiety effects, as any emergency room physician knows.

Of the remaining 12 of the 20 patients who responded well to ketosis, seven (58

percent) were either overweight or had been grossly obese in the past. Actually none of the eight with abnormal EEGs were obese so that the seven obese cases represent a 35 percent overall incidence of obesity amongst the 20 patients in this series who responded well in ketosis. Of the 14 patients who were unchanged in ketosis, five (36 percent) were obese. The similarity of this statistic suggests a common mechanism.

On the other hand notice that over half of the patients found ketosis disagreeable, 39 of them (53 percent) reporting symptoms such as weakness, lethargy, nausea, anorexia, constipation, light-headedness, and headache. Of these only four (10 percent) were obese. This supports the notion that lean patients tolerate ketosis less well than do the obese.

At first I speculated that obese patients may be endowed with a greater capacity to perform gluconeogenesis and thus a lesser vulnerability to ketosis. However the four obese patients in this series required an average of 51 g of carbohydrate to bring them out of ketosis and this is almost identical with the group mean OCL of 52 g for the 73 patients in this series. Furthermore, recent data indicate that hepatic gluconeogenesis and ketogenesis are stimulated by the same hormone, glucagon (Gerich et al., 1975). This means that one is not likely to be synthesizing greater amounts of glucose without at the same time manufacturing greater quantities of ketones—except in the presence of insulin, which inhibits lipolysis and hence limits the availability of free fatty acids from which ketones are made. Since hyperinsulinism is fairly commonplace in obese patients, this is a not implausible factor.

An equally plausible explanation for the greater tolerance of ketosis observed in obese subjects is the possibility that the obese select greater amounts of protein instead of fat in their diet. Since 58 percent of the protein molecule is available for gluconeogenesis, if these obese subjects were ingesting greater quantities of protein rather than fat, of which only 10 percent, the glycerol fraction, can be interconverted to glucose, this would forestall ketosis or at least provide a greater

Total Carbohydrate Potential (TCP). The TCP is calculated as the sum of dietary carbohydrate plus dietary protein times 0.58 and dietary fat times 0.10.

It is often the case that a narrow range of carbohydrate must be maintained for optimum function. DeVivo (1973) reported a well-documented case of epilepsy and ketotic hypoglycemia in a 39-month-old child that was maintained seizure- and hypoglycemia-free at a TCP between 43 and 70 g per day. Below that range hypoglycemia intervened; above that range seizures recurred.

I have observed a similar narrow range of therapeutic control or benefit in some of my patients and with a recurrence of symptoms when the carbohydrate intake approached within about 10 g of the OCL for those who responded better in ketosis and when it exceeded the OCL by 20 to 30 g for those who were better at the OCL.

In reviewing the literature on ketosis in medicine, neurology, urology, and bariatrics, I have been impressed with the relative absence of reports about serious adverse effects of the ketogenic diet. Livingston (p. 402, 1972) reported five cases of nephrolithiasis amongst a thousand children treated with the ketogenic diet for epilepsy. It is noteworthy that magnesium supplementation was not practiced at that time to offset the increased calcium excretion expected with such a diet.

Keith (1963) reported his experience with the ketogenic diet in the treatment of epilepsy, some of his patients being in ketosis over 20 years. No harm to the heart or blood vessels was observed. In my own cases, the most severe adverse effect was the occurrence of a frightening episode of tachycardia and palpitations in a lean patient, who had a preexisting susceptibility to tachycardia. She misunderstood my verbal directions and went on with zero-carbohydrate intake for over a week despite increasing weakness, malaise, and depression, and without calling in for advice.

Since then I always issue written instructions to set a five-day limit on the zero-carbohydrate phase of the OCL determination. I am especially cautious with patients who are lean or underweight. I have seen no adverse effects in any of my overweight patients other than weakness, lethargy, and lightheadedness of a mild to moderate degree. The administration of potassium supplements relieves these adverse symptoms, this in spite of the fact that measurements of minerals in blood and urine do not indicate significant loss of potassium in ketosis. In fact, sodium losses are greater (Bloom and Azar, 1963; Benoit et al., 1965); therefore I instruct the patients to salt their food to their taste at the same time.

In most of my early cases, before and after measurements of cholesterol, uric acid and triglycerides were done. As expected, most patients did show an increase in their cholesterol and uric acid levels, about 10 percent higher. A surprising number showed a significant reduction in cholesterol. Triglyceride was significantly reduced in all cases. I believe there is no convincing evidence that ketosis-induced increase in serum cholesterol increases the risk of coronary artery disease, certainly not for the short-term duration of ketosis incurred in the process of determining the OCL.

The advantages of the Keto-Diet Optimum Carbohydrate Program are summarized as a total of 82 percent reporting improvement, when the combined results of both ketosis and OCL are considered. On the other hand, 60 percent reported some adverse effect, mild and transient as a rule, to these two conditions. The improvement in well-being and mood more than outweighed the short-term inconvenience, for eight out of 10 patients gained a significant degree of mastery over their symptoms of anxiety, depression, neurasthenia, and dysperception.

An additional advantage of this Program is that it enlists the active participation and responsibility of the patient to perform the procedures and keep daily notes. Such an exercise in science is not only

educational but also has the effect of impressing on the patient a more objective attitude about himself and his symptoms. Rapport between doctor and patient is strained by the rigors of the procedure and the temporary adverse responses, but the ultimate effect has been a strengthening of rapport in almost every case. Even where the degree of symptomatic improvement has not been great, the emotional and educational benefits have been substantial.

Another advantage of the OCL method is that it offers a convenient way to test for the possibility of food allergy and intolerance at the same time that the carbohydrate effects are being evaluated. At zero carbohydrate there is no exposure to milk, wheat, or fruits, the most common food sources of cerebral allergy.

I have not been testing for food allergies in my practice routinely so far, but I think it is obvious that, since most of my patients improved after they resumed their carbohydrate intake, and most of them also felt worse when they were in ketosis and at the zero-carbohydrate part of the Program, the dietary avoidance of wheat, milk, and fruits did not play a crucial role in their symptoms.

In conclusion, let me call attention to the clinical observation of Dr. Samuel Livingston (p. 402, 1972), who reviewed the ketogenic diet in his book on epilepsy: "In addition to its excellent anticonvulsant value, the ketogenic diet also favorably affects the hyperactivity, increased restlessness and irritability which one encounters so often in young children with epilepsy. It does not dull mental functioning, as anticonvulsant drugs so frequently do. Many of our patients were described by their parents before the institution of the ketogenic diet, as: 'wild as a little Indian'; and after the diet was started, as: 'calm as a lamb.' It is of interest to note that several of the parents were reluctant to discontinue the diet, in spite of a poor control of seizures, because their children's behavior and disposition were so much better while on the ketogenic regimen than when they were being treated with antiepileptic drugs."

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It is surprising, after so much clinical experience spanning a period of two thousand years, that this paper is the first by a psychiatrist describing the applications of the ketogenic diet in the treatment of anxiety, depression, and dysperception. Meanwhile, throughout this most advanced society of ours, in every modern psychiatric facility patients are exposed to an overdose of carbohydrates. The probable harm thereto is compounded by the additional overexposure to coffee, a well-known aggravator of anxiety, and tobacco, a potent vitamin depletor and mood depressant. It is time that the application of available knowledge in this field should be the rule rather than the exception. Ignorance and fear of controversy are no longer an excuse to withhold this basic and physiologically-oriented treatment from our patients.

ADDENDUM

Muller et al. (1971) have documented the influence of antecedent diet upon glucagon and insulin secretion. A week of carbohydrate restriction lowered fasting insulin from 18 to 11 microunits per milliliter, whereas fasting glucagon rose from 100 to 136 picograms per milliliter. In their carbohydrate-depleted subjects, plasma glucose rose an average of 12 mg per deciliter after a beef meal. Normally, on a free diet, plasma glucose does not rise after a protein meal. Thus, we observe a gluconeogenic effect and hyperglycemia after carbohydrate deprivation.

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