The Controversy Concerning Counterregulatory Hormone Secretion

A Hypothesis for the Prevention of Diabetic Ketoacidosis?

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SUMMARY

Diabetic ketoacidosis is characterized by an excess secretion of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Experimental evidence obtained in both diabetic man and animals suggests that elevation of the plasma concentration of these hormones is necessary to initiate excess hepatic production of ketone bodies. This increase in hepatic ketogenesis in concert with the inability of peripheral tissues to completely utilize ketone bodies results in clinical ketoacidosis. This hypothesis would suggest that pharmacologic control of excess counterregulatory hormone secretion would be a rational therapeutic modality to prevent diabetic ketoacidosis. DIABETES *26*:596-601, June, 1977.

HYPOTHESIS

The development of diabetic ketoacidosis has classically been attributed to absolute insulin deficiency.[1] This etiologic approach has been reinforced by the clinical observation that insulin administration with adequate fluid and electrolyte replacement results in correction of the ketoacidotic state[2] provided any underlying infection or other "stress condition" is simultaneously treated. However, recent studies in ketosis-prone insulin-dependent diabetics now suggest that insulin deficiency per se may not alone cause ketoacidosis and that excess exposure to at least one counterregulatory hormone is the initial event preceding the development of excess hepatic ketoacid production (figure 1). This hypothesis suggests the possibility that pharmacologic control of counterregulatory hormone secretion in insulin-dependent diabetic man may be a rational therapeutic approach to the prevention of diabetic ketoacidosis.

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EVIDENCE

There are five lines of evidence to support the hypothesis that excess counterregulatory hormone secretion may be an obligatory hormonal defect, in association with relative insulin deficiency, in the development of ketoacidosis (defined as a plasma concentration of total ketoacids in excess of 2.0 mmol/L.[3]). First, counterregulatory hormone-deficient diabetic animals do not develop ketoacidosis. In 1937, C. Long demonstrated that diabetic ketoacidosis could be prevented in the pancreatectomized diabetic cat by either adrenalectomy or hypophysectomy.[4] In 1942, these observations were extended to the dog,[5] and in 1953 Campbell and co-workers demonstrated that the active pituitary ketogenic hormone in this animal was growth hormone.[6] In the rat, Scow et al. later demonstrated that either hypophysectomy or adrenalectomy prevented the development of ketoacidosis in pancreatectomized diabetic rats.[7] When these rats were administered glucocorticoid, death from ketoacidosis occurred in all animals within 24 hours. Each of the above-cited studies suggests that participation of counterregulatory hormones is essential to the development of diabetic ketoacidosis.

The second line of evidence emphasizing the ketogenic role of counterregulatory hormone secretion is derived from examination of the precipitating causes of ketoacidosis in man. In a detailed investigation of the cause of ketoacidosis in 26 patients, Muller et al.[8] were able to identify some type of stress (infection, surgery, etc.) in 24. A similar positive correlation between stress and the development of ketoacidosis has been recognized by other investigators.[2,9-11] Since excess secretion of counterregulatory hormones characterizes all major forms of stress,[12,13] it would be expected that the concentration of these hormones would be elevated in

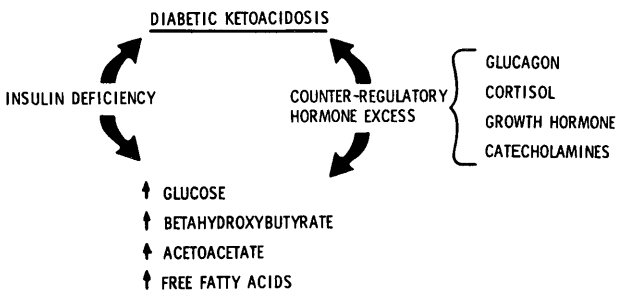

FIG. 1. The development of diabetic ketoacidosis is characterized by a combination of relative insulin deficiency and counterregulatory hormone excess. Recent studies in insulin-dependent diabetic man would suggest that counterregulatory hormone excess is a necessary prerequisite for inducing hepatic keto-acid production and the resultant development of ketoacidosis.

ketoacidosis. In fact, at least one counterregulatory hormone is elevated in every reported case of diabetic ketoacidosis in which each of these hormones has been measured (figure 2). Plasma catecholamines (particularly norepinephrine) are characteristically elevated in diabetic ketoacidosis, and the magnitude of the elevation is directly proportional to the degree of metabolic derangement.[14] Plasma glucagon concentration is also characteristically elevated in diabetic ketoacidosis,[8] and the elevation of this hormone is reported to parallel the development of diabetic ketoacidosis.[15] In a similar fashion, both plasma cortisol and growth hormone concentration are frequently elevated in diabetic

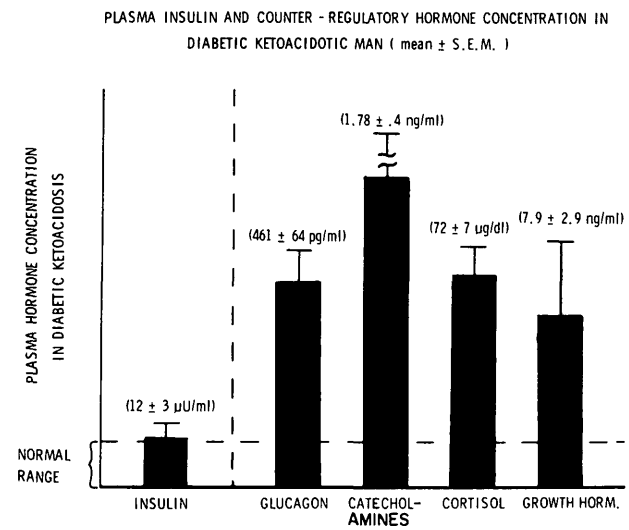

FIG. 2. Diabetic ketoacidosis is characterized by counterregulatory hormone excess. Plasma insulin concentration may be within the normal range observed in nondiabetic subjects after an overnight fast[27] but is low relative to the decompensated metabolic state of the diabetic. Data for this figure were obtained from references 2, 8, 14, 16, and 28.

ketoacidosis and return to normal concentration with therapy of the diabetic state.[2,16,17] The above reported studies indicate that counterregulatory hormone excess is characteristic of the "stress conditions" that usually precipitate the metabolic decompensation of diabetic ketoacidosis.

The third line of evidence supporting counterregulatory hormone excess in the development of diabetic ketoacidosis relates to the consequences of insulin withdrawal in diabetic man. In 1975, Gerich and co-workers withdrew insulin therapy from juvenile-onset diabetic patients and simultaneously infused somatostatin to block endogenous glucagon and growth hormone secretion.[15] Ketoacidosis was delayed in these diabetic subjects until exogenous glucagon or growth hormone was administered.[18] The association between a rise in plasma glucagon and the development of ketoacidosis in insulin-withdrawn diabetic subjects has been confirmed by Alberti and co-workers.[19]

The fourth line of evidence that implicates counterregulatory hormone secretion in inducing ketoacidosis is derived from investigation of counterregulatory hormone administration to insulin-dependent diabetic subjects. Infusions of physiologic concentrations of glucagon into insulin-dependent diabetic man have demonstrated that this hormone is markedly ketogenic.[20] Similarly, both norepinephrine and epinephrine possess ketogenic activity, including a direct stimulatory effect on hepatic ketogenesis.[21,22] In man, cortisol possesses lipolytic activity, thus supplying substrate for ketogenesis.[23] Administration of physiologic concentrations of glucocorticoids to insulin-deficient diabetic man results in ketoacidosis.[24] The ketogenic activity of growth hormone has recently been demonstrated in diabetic man[18] to be quantitatively comparable to that of glucagon, although qualitatively growth hormone-induced ketosis is of delayed onset and of prolonged duration.[25] Thus, each counterregulatory hormone possesses sufficient ketogenic activity when elevated to high physiologic concentrations in diabetic man to induce ketoacidosis when, simultaneously, a relative deficiency of insulin exists.

The fifth line of evidence supporting a direct etiologic role of counterregulatory hormones in ketoacidosis is based on pharmacologic blockade of counterregulatory hormone secretion. Attempts to reduce the frequency of diabetic ketoacidosis with counterregulatory hormone blockade were first reported by Baker et al. in two brittle-diabetic patients.[26] Utilizing β blockage to inhibit catecholamine activity,

these authors significantly reduced the clinical occurrence of spontaneous ketoacidosis during a two-year observation period. In an experimental setting, Gerich and co-workers[15] demonstrated that the somatostatin suppression of both glucagon and growth hormone significantly delayed the rise in plasma ketone body concentration following withdrawal of insulin therapy in diabetic subjects. More recent studies[27] have demonstrated that suppression of endogenous cortisol secretion by metyrapone in ketosis-prone diabetic subjects significantly reduced basal ketone body concentration. These studies emphasize that pharmacologic blockage of an individual counterregulatory hormone results in amelioration of hyperketonemia in diabetic man.

The above-cited evidence supports the hypothesis that excess counterregulatory hormone secretion is an essential prerequisite to the development of diabetic ketoacidosis. A simultaneous relative insulin deficiency is probably necessary to allow the ketogenic activity of counterregulatory hormones to be expressed. These data suggest that the prevention of the development of ketoacidosis may rationally require pharmacologic control of excess counterregulatory hormone secretion in addition to the traditional replacement therapy with insulin.

ACKNOWLEDGMENTS

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ABSTRACTS

(All are verbatim summaries)

Scow, Robert O.; Chernick, Sidney S.; and Guarco, Barbara A. (Lab. of Nutr. and Endocrinol., NIAMDD, PHS, U.S. Dept. of HEW, Bethesda, Md.): KETOGENIC ACTION OF PITUITARY AND ADRENAL HORMONES IN PANCREATECTOMIZED RATS. Diabetes *8*:132, 1959.

Severe diabetes with marked alterations of fat metabolism develops in several species following total extirpation of the pancreas. The classical experiments of Houssay and of Long and Lukens clearly demonstrated that the anterior pituitary and adrenal glands are necessary for the development of diabetes in such animals. There have been few studies, however, to determine which hormones are involved in this process, especially in the development of ketosis and accumulation of fat in the blood, liver and kidneys. It was recently demonstrated that severe diabetes culminating in coma and death develops in well-nourished rats when they are deprived of 99.5 per cent of the pancreas. This preparation has been used in the present experiments to study the ketogenic and adipokinetic action of the pituitary and adrenal hormones in diabetes.

Muller, Walter A.; Faloona, Gerald R.; and Unger, Roger H. (Dept. of Intern. Med., Univ. of Texas (Southwestern) Med. Sch. and the VA Hosp., Dallas): HYPERGLUCAGONEMIA IN DIABETIC KETOACIDOSIS. Am. J. Med. *54*:52, 1973.

The prevalence of hyperglucagonemia was studied in twenty-six consecutive patients admitted to Dallas hospitals in diabetic ketoacidosis. Plasma glucagon averaged 390 pg/ml, ranging from 120 to 1,290 pg/ml, significantly greater than the fasting level of 118 pg/ml in diabetic subjects without ketoacidosis. Absolute hyperglucagonemia, i.e., levels over 240 pg/ml, was present in sixteen; all had "relative hyperglucagonemia." Glucagon levels declined after four hours of therapy and were normal at discharge. The plasma glucagon level was significantly correlated with the blood glucose level, respiratory rate and hours of insulin therapy required to correct the ketonemia. Patients with absolute hyperglucagonemia required significantly more insulin than patients without absolute hyperglucagonemia.

The results indicate that glucagon excess is present in most patients hospitalized with diabetic ketoacidosis and are compatible with the view that glucagon, an insulin-opposing hormone, may increase the severity of the disease and its insulin requirements.

Garber, Alan J.; Cryer, Philip E.; Santiago, Julio V.; Haymond, Morey W.; Pagliara, Anthony S.; and Kipnis, David M. (Metab. Div., Depts. of Med. and Pediatr., Washington Univ. Sch. of Med., St. Louis, Mo., and the Div. of Endocrinol. and Metab., Depts. of Med. and Cell Biol., Baylor Coll. of Med., Houston, Tex.): THE ROLE OF ADRENERGIC MECHANISMS IN THE SUBSTRATE AND HORMONAL RESPONSE TO INSULIN-INDUCED HYPOGLYCEMIA IN MAN. J. Clin. Invest. *58*:7, 1976.

Sequential determinations of glucose outflow and inflow, and rates of gluconeogenesis from alanine, before, during and after insulin-induced hypoglycemia were obtained in relation to alterations in circulating epinephrine, norepinephrine, glucagon, cortisol, and growth hormone in six normal subjects. Insulin decreased the mean (±SEM) plasma glucose from 89±3 to 39±2 mg/dl 25 min after injection, but this decline ceased despite serum insulin levels of 153±22 μU/ml. Before insulin, glucose inflow and outflow were constant, averaging 125.3±7.1 mg/kg per h. 15 min after insulin, mean glucose outflow increased threefold, but then decreased at 25 min, reaching a rate 15% less than the preinsulin rate. Glucose inflow decreased 80% 15 min after insulin, but increased at 25 min, reaching a maximum of twice the basal rate. Gluconeogenesis from alanine decreased 68% 15 min after insulin, but returned to preinsulin rates at 25 min, and remained constant for the next 25 min, after which it increased linearly. A fourfold increase in mean plasma epinephrine was found 20 min after insulin, with maximal levels 50 times basal. Plasma norepinephrine concentrations first increased significantly at 25 min after insulin, whereas significantly increased levels of cortisol and glucagon occurred at 30 min, and growth hormone at 40 min after insulin.

Thus, insulin-induced hypoglycemia in man results from both a decrease in glucose production and an increase in glucose utilization. Accelerated glycogenolysis produced much of the initial, posthypoglycemic increment in glucose production. The contribution of glycogenolysis decreased with time, while that of gluconeogenesis from alanine increased. Of the hormones studied, only the increments in plasma catecholamines preceded or coincided with the measured increase in glucose production after hypoglycemia. It therefore seems probable that adrenergic mechanisms play a major role in the initiation of counterregulatory responses to insulin-induced hypoglycemia in man.

Christensen, Niels Juel (2nd Clin. of Intern. Med., Kommunehospitalet, Aarhus, Denmark): PLASMA NOREPINEPHRINE AND EPINEPHRINE IN UNTREATED DIABETICS DURING FASTING AND AFTER INSULIN ADMINISTRATION. Diabetes *23*:1, 1974.

Employing a precise and sensitive double-isotope derivative technic, plasma norepinephrine and epinephrine were measured in twenty-three normal subjects and fourteen diabetics during various metabolic conditions. Patients with poorly controlled diabetes showed a rise in norepinephrine, which correlated with the degree of metabolic derangement, during resting conditions. High epinephrine values were seen only in patients with moderate to severe ketoacidosis. During exercise, diabetic patients with ketosis demonstrated large increments in plasma catecholamines as compared to normals. During insulin treatment, when good control had been achieved, plasma catecholamine levels were similar to those in normal subjects.

During prolonged fasting, plasma norepinephrine rose from 0.18 to 0.40 ng. per milliliter in four normal nonobese subjects. No change was observed in plasma epinephrine.

During insulin hypoglycemia, high plasma epinephrine levels were seen only in subjects in whom the blood glucose concentration declined to values below 20 mg. per 100 ml. Plasma

norepinephrine rose as blood glucose concentrations decreased even in diabetics in whom values had not reached hypoglycemic levels. No correlation was observed between plasma epinephrine and increase in pulse rate during hypoglycemia.

Gerich, John E.; *Lorenzi, Mara*; *Bier, Dennis M.*; *Schneider, Victor*; *Tsalikian, Eva*; *Karam, John H.*; *and Forsham, Peter H.* (Metab. Res. Unit and Depts. of Med. and Pediatr., Univ. of Cal., San Francisco): PREVENTION OF HUMAN DIABETIC KETOACIDOSIS BY SOMATOSTATIN: EVIDENCE FOR AN ESSENTIAL ROLE OF GLUCAGON. N. Engl. J. Med. *292*:985, 1975.

To evaluate the role of glucagon in the pathogenesis of diabetic ketoacidosis in man, we studied the effect of suppression of glucagon secretion by somatostatin on changes in plasma β-hydroxybutyrate and glucose concentrations (as well as changes in their precursors) after acute withdrawal of insulin from seven patients with juvenile-type diabetes.

Suppression of glucagon secretion prevented the development of ketoacidosis for 18 hours after acute insulin withdrawal, whereas in control studies mild ketoacidosis occurred 10 hours after insulin was stopped. Plasma β-hydroxybutyrate, glucose, free fatty acid, and glycerol levels were all markedly lower during suppression of glucagon secretion ($p<0.001$), whereas plasma alanine levels were higher ($p<0.001$).

These studies indicate that insulin lack per se does not lead to fulminant diabetic ketoacidosis in man and that glucagon, by means of it gluconeogenic, ketogenic, and lipolytic actions, is a prerequisite to the development of this condition.

Gerich, John E.; *Martin, Malcolm M.*; *and Recant, Lillian* (Dept. of Med., Georgetown Serv., District of Columbia Hosp., Georgetown Univ., Dept. of Pediatr. VA Hosp., Washington, D.C.): CLINICAL AND METABOLIC CHARACTERISTICS OF HYPEROSMOLAR NONKETOTIC COMA. Diabetes *20*:228, 1971.

Clinical and metabolic data of twenty patients with hyperosmolar nonketotic come (HNC) and ten patients in ketoacidosis (DA) are compared. HNC patients were older; fewer were previously known diabetics; more had multiple chronic diseases. Common precipitating factors in HNC included infection, dehydration and administration of diabetogenic drugs. Blood glucose and urea nitrogen, plasma sodium, bicarbonate and osmolarity were significantly higher in HNC. Plasma potassium and chloride levels were similar in both groups. Patients with HNC had significantly lower plasma levels of free fatty acids, cortisol and growth hormone.

Plasma insulin levels in HNC were low and not significantly different from those observed in KA. Patients with HNC required more fluids and less insulin therapy. Mortality was 20 per cent in HNC, lower than that generally observed in this condition, but higher that that of KA, 0 per cent.

On the basis of the above findings, it is suggested that dehydration and hyperosmolarity may play significant roles in the etiology of HNC, and that therapy should, therefore, be directed at restoration of normal osmolarity and correction of water deficits with 0.45 per cent saline and moderate amounts of insulin.

Gerich, John E.; *Lorenzi, Mara*; *Bier, Dennis M.*; *Tsalikian, Eva*; *Schneider, Victor*; *Karam, John H.*; *and Forsham, Peter H.* (Metab. Res. Unit, and Depts. of Med. and Pediatr., Univ. of Cal., San Francisco): EFFECTS OF PHYSIOLOGIC LEVELS OF GLUCAGON AND GROWTH HORMONE ON HUMAN CARBOHYDRATE AND LIPID METABOLISM. J. Clin. Invest. 57:875, 1976

To study the individual effects of glucagon and growth hormone on human carbohydrate and lipid metabolism, endogenous secretion of both hormones was simultaneously suppressed with somatostatin and physiologic circulating levels of one of the other hormone were reproduced by exogenous infusion. The interaction of these hormones with insulin was evaluated by performing these studies in juvenile-onset, insulin-deficient diabetic subjects both during infusion of insulin and after its withdrawal.

Infusion of glucagon (1 ng/kg · min) during suppression of its endogenous secretion with somatostatin produced circulating hormone levels of approximately 200 pg/ml. When glucagon was infused along with insulin, plasma glucose levels rose from 94±8 to 126±12 mg/100 ml over 1 h ($P<0.01$); growth hormone, β-hydroxybutyrate, alanine, FFA, and glycerol levels did not change. When insulin was withdrawn, plasma glucose, β-hydroxybutyrate, FFA, and glycerol all rose to higher levels ($P<0.01$) than those observed under similar conditions when somatostatin alone had been infused to suppress glucagon secretion. Thus, under appropriate conditions, physiologic levels of glucagon can stimulate lipolysis and cause hyperketonemia and hyperglycemia in man; insulin antagonizes the lipolytic and ketogenic effects of glucagon more effectively than the hyperglycemic effect.

Infusion of growth hormone (1μg/kg·h) during suppression of its endogenous secretion with somatostatin produced circulating hormone levels of approximately 6 ng/ml. When growth hormone was administered along with insulin, no effects were observed. After insulin was withdrawn, plasma β-hydroxybutyrate, glycerol, and FFA all rose to higher levels ($P<0.01$) than those observed during infusion of somatostatin alone when growth hormone secretion was suppressed; no difference in plasma glucose, alanine, and glucagon levels was evident. Thus, under appropriate conditions, physiologic levels of growth hormone can augment lipolysis and ketonemia in man, but these actions are ordinarily not apparent in the presence of physiologic levels of insulin.

Schade, David S.; *and Eaton, R. Philip* (Dept. of Med., Univ. of New Mexico Sch. of Med., Albuquerque, N.M.): GLUCAGON REGULATION OF PLASMA KETONE BODY CONCENTRATION IN HUMAN DIABETES. J. Clin. Invest. *56*:1340, 1975.

The present study was designed to test the hypothesis that physiological concentrations of glucagon may increase plasma ketone body concentration when sufficient free fatty acid substrate is available to support hepatic ketogenesis. Physiological elevations of plasma glucagon concentration were produced by a constant infusion of hormone, and increased plasma-free fatty acid availability was produced by simultaneous heparin injection to induce intravascular lipolysis. In the five insulin-dependent diabetic subjects studied, when plasma glucagon concentration remained at the normal basal level of 72±14 pg/ml during control saline infusion, the heparin-induced increase in free fatty acid availability resulted in approximately a 20% increase in plasma ketone body concentration. In contrast, when plasma glucagon concentration was elevated by hormone infusion to the physiological level of 215±35 pg/ml, the heparin-induced increases in free fatty acid availability resulted in approximately an 80% increase in plasma ketone body concentration. These results suggest that physiological elevations in plasma glucagon concentration may augment ketonemia in diabetic man when simultaneous elevations in plasms-free fatty acid are present.

Willms, B.; *Böttcher, M.*; *Wolters, V.*; *Sakamoto, N.*; *and Soling, H.*

D. (Medizinische Universitätsklinik Göttingen): RELATIONSHIP BETWEEN FAT AND KETONE BODY METABOLISM IN OBESE AND NON-OBESE DIABETICS AND NON-DIABETICS DURING NOREPINEPHRINE INFUSION. Diabetologia 5:88, 1969.

The effects of an intravenous infusion of norepinephrine, 0.08 μg/kg·min on lipolysis (as measured by an increase of free glycerol and nonesterified fatty acids (NEFA)), on the blood concentration of ketone bodies and on the serum concentrations of immunoreactive insulin (IRI) and insulin-like activity (ILA) were studied in normal weight and obese nondiabetics and diabetics. Normal weight diabetics and nondiabetics showed the same increase in lipolysis. A significantly higher rate of lipolysis occurred in obese persons, irrespective of whether they were diabetic or not. Even the maximum absolute concentrations of free glycerol and NEFA during the infusion were higher in obese persons than in insulin-dependent diabetics, who showed the highest values before the beginning of the infusion.–In obese subjects, the infusion of norepinephrine according to the theoretical normal weight was still sufficient to produce a higher rate of lipolysis than in normal weight subjects. This probably reflects the greater mass of adipose tissue in obese subjects.–In diabetic and nondiabetic obese persons, the concentration of ketone bodies rose higher than in control subjects, which is in agreement with the higher rate of lipolysis in the obese groups. On the other hand, the normal weight insulin-dependent diabetics showed a significantly higher increase in the concentration of ketone bodies than the obese persons. This demonstrates that the degree of ketonaemia in man is not exclusively determined by the plasma level of NEFA.–The higher increase in the β-hydroxybutyrate/acetoacetate ratio in insulin-dependent diabetics points to a higher rate of oxidation of fatty acids in the liver.–ILA and IRI responded in a different way to norepinephrine infusion, demonstrating again, that changes in ILA can, but may not always reflect changes in immunoreactive insulin. According to these results, changes in the rate of lipolysis and in ketonaemia in obese diabetics are determined by the factor "obesity", wheras changes in these parameters in insulin-dependent diabetics are determined by the factor "insulin deficiency".

Baker, Lester; *Barcai, Avner*; *Kaye, Robert*; *and Haque, Nasir* (Div. of Metab., the Children's Hosp. of Philadelphia, the Philadelphia Child Guidance Clinic, and Depts. of Pediatr. and Psychiatry, the Univ. of Pennsylvania): BETA ADRENERGIC BLOCKADE AND JUVENILE DIABETES: ACUTE STUDIES AND LONG-TERM THERAPEUTIC TRIAL. J. Pediatr. 75:19, 1969.

In comparison with normal children, the diabetic child has a significantly more rapid increase of blood ketones following injection of epinephrine. Beta adrenergic blockade with MJ 1999 removes this ketone responsiveness, presumably by interfering with free fatty acid release from adipose tissue triglyceride, and perhaps from hepatic, stores. Two diabetic preadolescent girls, who were virtually incapacitated because of repeated hospitalizations for severe diabetic ketoacidosis, were studied. A specific stress interview with one child produced marked changes in blood glucose and plasma free fatty acid concentrations, associated with significant increases in plasma concentrations of corticoids and growth hormone as well as in urinary excretion of epinephrine. Beta adrenergic blockade prior to a repeat stress interview blocked the metabolic changes without interfering with the hormonal response to stress. During a therapeutic trial with MJ 1999 for the past 12 months, the need for hospitalization for each of these children has been markedly decreased.
