A mathematical model of blood glucose regulation during exercise

by

Beverly Ann McCully

A Thesis Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
MASTER OF SCIENCE

Major: Biomedical Engineering

lversity
Ames, Iowa

1981

TABLE OF CONTENTS

NOMENCLATURE

V = volume (liters)

C = concentration (moles)

C' = levels (mass units)

Rij = rate of appearance (from a to b) (mass/liters-min)

k = reaction rate (constant)

K = diffusion constant (1/min)

x = volume ratio

t = time (min)

Bi = rate of infusion of species i

B = rate of absoption of glucose from gut

Vo = oxygen uptake by lungs

mg% = mg/dl

b = plasma

l = liver

1 = glucose

2 = glucose-6-phosphate

3 = glycogen

4 = glucagon

5 = insulin

6 = epinephrine

cns = central nervous system

gneo = gluconeogenesis

gly = glycolysis

m = muscle

o = basal secretion

D = degredation

INTRODUCTION

The maintenance of blood glucose in mammalian organisms is a unique process. Despite large fluctuations in metabolism, food intake, and physical activity, the concentration of glucose in the blood is maintained at a remarkably constant level. The concentration of the other metabolites may vary by several orders of magnitude, whereas the concentration of glucose, except in specific diseases, does not.

Exercise represents the most common stress to which the mammalian organism is exposed. In "flight or fight" situations it is imperative for survival that the rate of mobilization of energy sources should meet the elevated energy demand for as long as possible; otherwise the blood sugar falls and impairs the function of the central nervous system, leading to the premature cessation of work.

Physical exercise causes a variety of alterations in body fuel homeostasis and hormonal regulation. Glucose uptake by the exercising muscle is increased 7 to 40 times above basal levels, in proportion to the duration and intensity of exercise. To meet the increased glucose demand the glucose pool is continuously replenished by a 3 to 5 fold increase in hepatic glucose production.

There are several factors that are responsible for the sustained mobilization of energy sources during prolonged exercise. The blood levels of epinephrine, glucagon, and other hormones are elevated, thus stimulating hepatic glucose production. Simultaneous with the rise in these hormones is the inhibition of insulin secretion. Decreased levels of insulin sensitize the liver to the actions of the other hormones. It is

hypothesised that increases in blood flow and capillary surface area can lead to an increased delivery of insulin to the muscle even when blood levels of insulin are reduced during exercise.

The mechanism of increased muscle utilization of glucose during exercise is not clear and probably depends on the nature, duration, and intensity of the exercise. Exercise of a generalized nature or involving a relatively large muscle mass can lead to an increase in arterial glucose concentration, which may itself alter the rate of glucose utilization, or to an increase in plasma epinephrine, which may influence glucose uptake directly or by inhibiting insulin secretion. A greater understanding of the underlying process is highly desirable.

Since 1960, there have been many attempts to represent glucose metabolism and its control in mathematical terms, spanning a wide range of sophistication and complexity. All models constitute abstraction from the processes they represent. Some information is omitted when building the model, and thus the model represents a simplification of the underlying physiological process. Within the model only certain relevant aspects are included.

In this paper, a mathematical model of blood glucose regulation which will describe behavior during exercise is presented. The model is intended to explain qualitatively the glucoregulatory response of a normal subject to continuous exercise at mild (30% of Vo2 max) workloads for a period of up to two hours. The mathematical description is based on species material balances which include the metabolic and endocrine processes involved in glucoregulation. The model focuses on the short term control of blood glucose levels by the liver. Nonlinear representation is provided,

thereby allowing systems behavior of the metabolic and hormonal processes to be analyzed, including higher levels of control besides autoregulation.

LITERATURE REVIEW

The concentration of glucose in the blood at any instant represents an equilibrium between the rates at which glucose is entering and leaving the vascular system. Glucose enters the blood as the result of absorption from the intestine and production by the liver through glycogenolysis and gluconeogenesis. Under normal conditions the concentration of glucose in human blood is approximately 100 mg% and is maintained within plus or minus 2 mg% (Srinivasan, 1969). The ability of the body to regulate the blood glucose level to this degree results from the complex relationships that exist between carbohdrate, lipid, and protein metabolism, and the various hormones (Fig. 1).

Physical exercise causes a large increase in the fuel requirements of the working muscles. Energy demands may rise 10 to 20 times above resting values, forcing the body to draw upon energy reserves (Wahren, 1979). At rest, the major energy source for muscle is free fatty acids. However, during exercise glucose oxidation contributes substantially to the energy needs.

During exercise, muscle consumption of blood-borne glucose increases 7 to 40 times depending on the intensity and duration of the performed exercise (Wahren, et al., 1971; Ahlborg et al., 1974; Felig and Wahren, 1975). Hypoglycemia fails to occur despite the increases in glucose consumption because there is a simultaneous increase in glucose output from the liver (Wahren, et al., 1971).

Observed hormonal responses to exercise that could account for this mutual regulation are a fall in plasma insulin (Hartley, et al., 1972a, b;

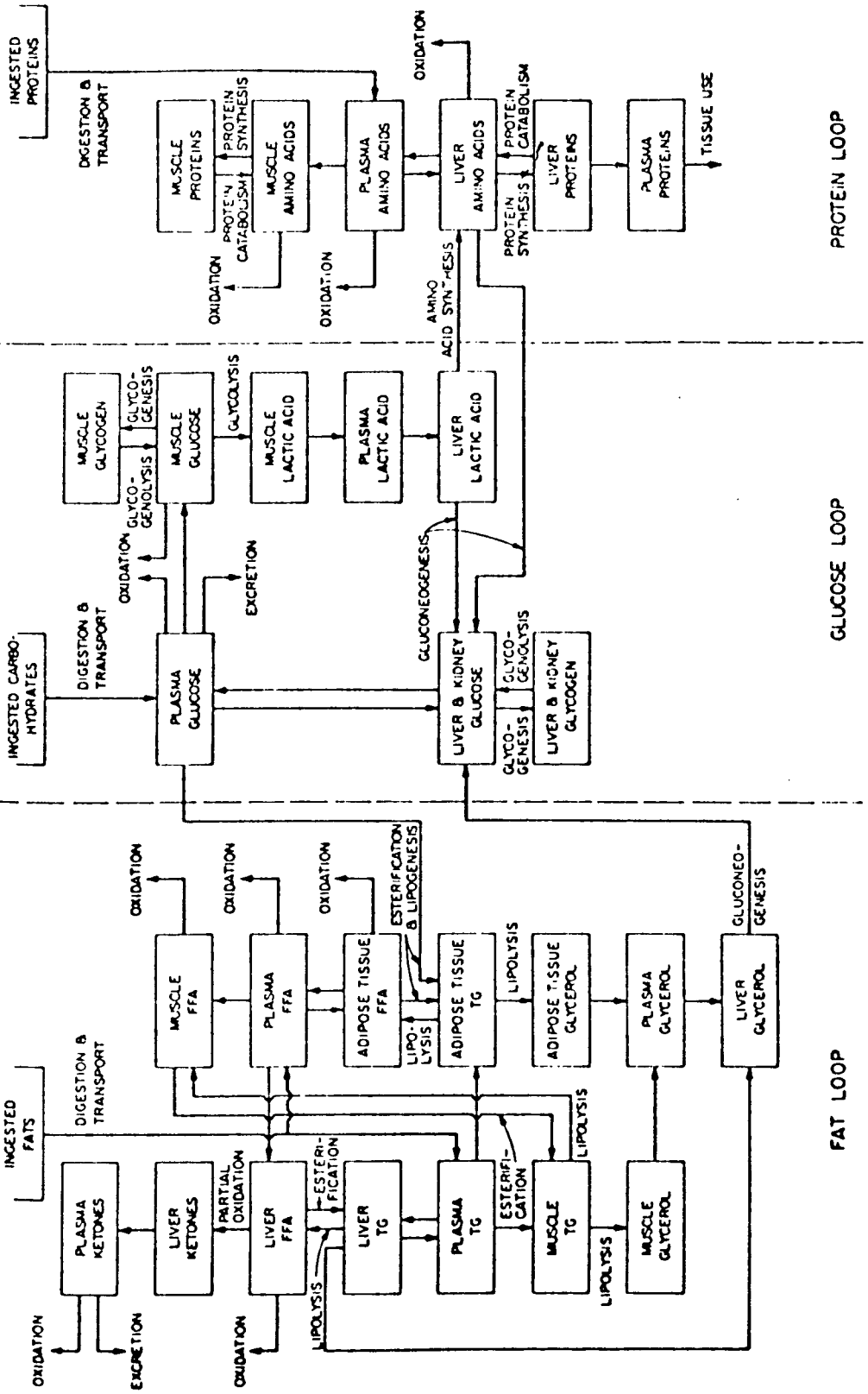


Figure 1. The metabolic plant (from Srinivasan, 1969)

Vranic, et al., 1976), a rise in plasma glucagon (Ahlborg, et al., 1974; Felig, et al., 1972; Galbo, et al., 1975; Vranic, et al., 1976), and elevation in plasma epinephrine (Galbo, et al., 1975; Hartley, et al., 1972a). The relative importance of these various changes has not however been determined.

Carbohydrate Metabolism in Muscle

Glucose metabolism in the muscle is geared to provide storage reserves of glycogen at rest and to utilize these stores and incoming glucose during strenous work (Fig. 2). The basal energy requirements of all muscle types are met chiefly by the oxidation of products derived from the metabolism of fats. In fact, oxidation of fatty acids has been shown to inhibit the utilizaton of glucose, in vitro, in heart and in skeletal muscle (Newsholme, 1976).

Glucose entry into the muscle cells is the primary regulator of muscle glycolysis. Muscle cells are relatively impermeable to glucose and the rate at which glucose becomes available for glycolysis depends on the rate of facilitated diffusion of the glucose across the cell membrane (Goodman, 1974). The glucose transport system is enhanced by either the presence of insulin or by increased muscluar work.

Once it has entered the cell, glucose is trapped by immediate phosphorylation to glucose-6-phosphate (G-6-P). The release of glucose by the muscle cell is prevented by the absence of the enzyme glucose-6-phosphatase which catalyzes the conversion of G-6-P to glucose. The hexokinase catalyzing the phosphorylation reaction is strongly

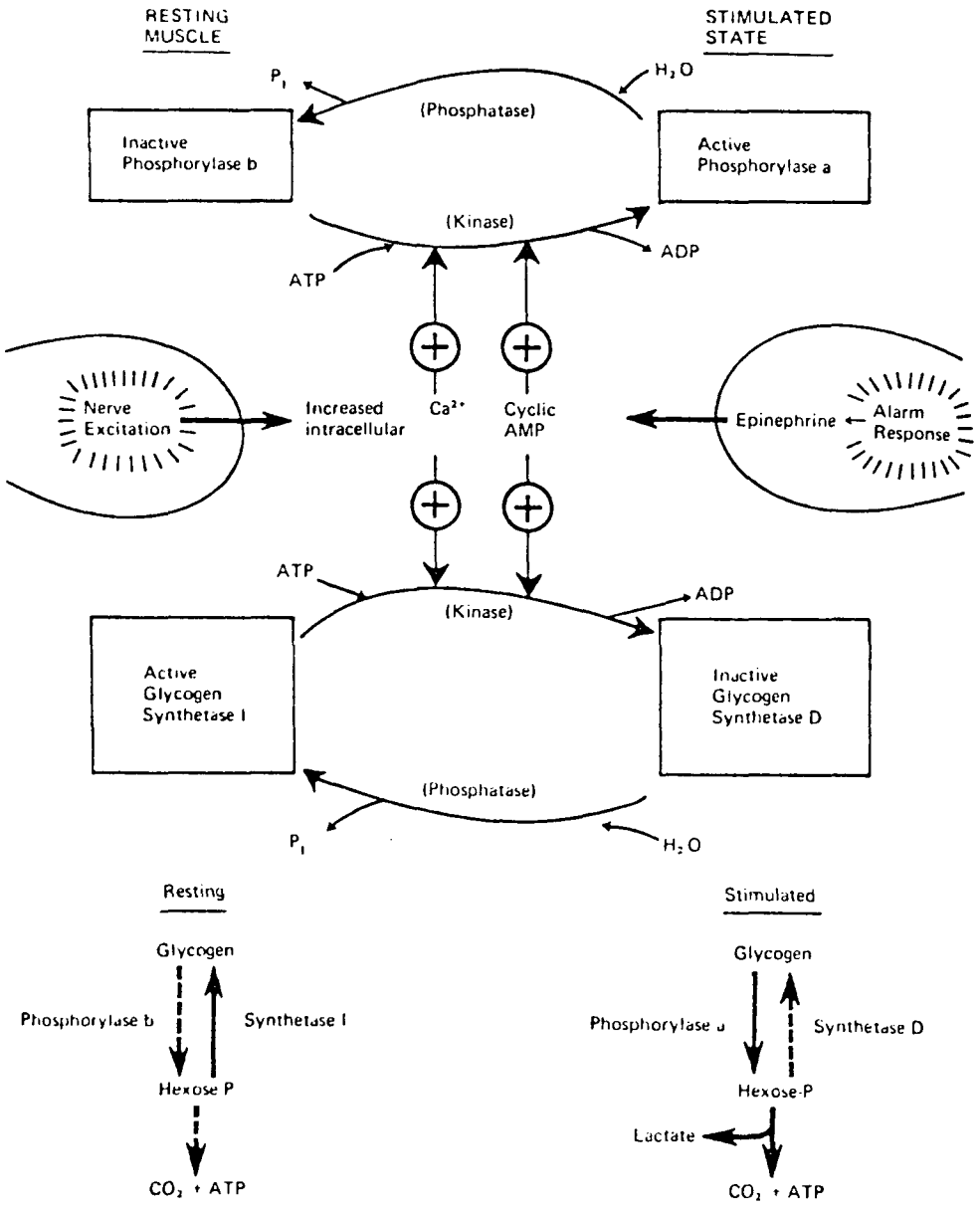


Figure 2. Carbohydrate metabolism in muscle (from McMurray, 1977)

inhibited by increasing concentrations of G-6-P. An increase in the G-6-P inhibits the phosphorylation of glucose and consequently inhibits glucose entry into the glycolytic pathway (Newsholme and Start, 1973). Muscle hexokinase is responsive only to intercellular control and will

phosphorylate glucose only as long as G-6-P can be used in the tissues for glycolysis or glycogen formation (McMurray, 1977).

The fate of G-6-P is determined by the relative activities of the enzymes of glycogen synthesis and glycolysis. In general, the glycolytic enzymes are more abundant so that G-6-P is more likely to follow the glycolytic pathway in muscle (Goodman, 1974).

Exercise increases the average rate of muscle glycogenolysis by more than six times the basal rate, rapidly depleting muscle glycogen stores (Issekutz, 1979). As the glycogen stores are depleted, blood glucose assumes an increasingly important role as a substrate for muscle oxidation. During the first minutes of exercise, while glycogenolysis is the primary energy source, there is only a small net uptake of glucose by the muscle. If exercise continues for 10 to 40 minutes, glucose uptake rises 7 to 40 times the basal level depending on the intensity of the work load performed (Felig and Wahren,1975) (Fig. 3). By 40 minutes of

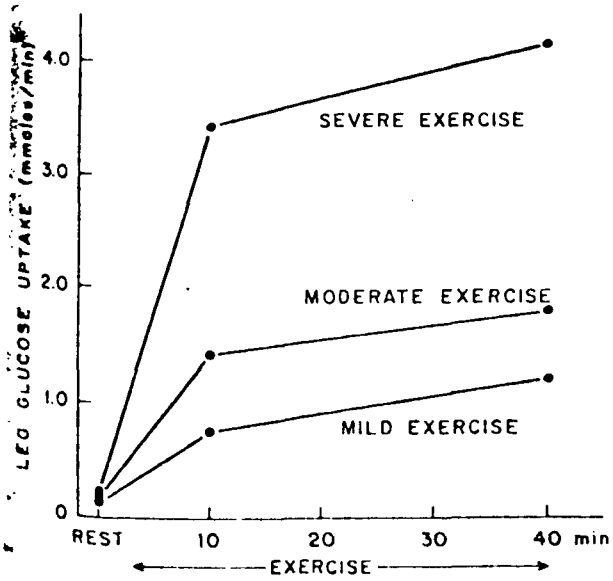


Figure 3. Glucose uptake by the leg muscle during bicycle exercise (from Felig and Wahren, 1975)

exercise, blood glucose is responsible for 75 to 90% of the total carbohydrate consumed. Uptake of the glucose is approximately 35 times the basal level. Beyond 40 minutes of exercise, the rate of glucose utilization increases progressively until it peaks at 90 to 180 minutes and begins to decline (Felig and Wahren, 1975; Wahren, 1979). After about two hours of moderate exercise, free fatty acids again become the major energy yielding substrate (Ahlborg, et al., 1974).

Muscle Glucose Uptake During Exercise

Although the increase of glucose uptake with exercise has been known to occur for approximately 100 years, the mechanism of this increased uptake is only partially understood. Presumably, glucose uptake depends on more than one factor but several mechanisms have been emphasized in recent literature as major potential regulators.

Goldstein (1961) described a muscle activity factor (MAF) released by exercising muscles which stimulated glucose uptake in noncontracting muscle. The existence of MAF has been supported by some observations (Havivi and Wertheimer, 1964) but subsequent studies have not been able to support its existence (Sanders, et al., 1964; Ahlborg, et al., 1975; Berger, et al., 1975).

The simulation of glucose uptake during muscle contraction *in vivo* has been postulated to occur due to increased availability of insulin and glucose to the muscle caused by the multifold increase in blood flow as well as by increases in capillary surface area (Garrat, et al., 1972; Vranic, et al., 1976). However, *in vitro*, the exercise-induced enhancement of muscular glucose uptake does not necessarily depend on changes in blood

flow (Berger, et al., 1975).

In the perfused rat heart marked hypoxia was identified as a potent stimulator of glucose uptake (Randle and Smith, 1958). Studies on the frog sartorius muscle in vitro have revealed different mechanisms of action of hypoxia and contraction (Holloszy and Narahara, 1965) and the glucose uptake stimulated by contraction did not depend on the degree of tissue hypoxia in the isolated perfused skeletal muscle of rats (Berger, et al., 1975).

Initially, the increase in glucose uptake during exercise was thought to occur independently of insulin. However, insulin is now known to play a permissive role in glucose uptake by muscle during exercise. The conclusion that insulin did not affect uptake was based on the observations that exercise can lower glucose concentration in hyperglycemic diabetics who had received an insulin injection 12 or more hours before being sujected to physical activity. The plasma insulin concentration could not be measured in these subjects because of circulating insulin antibodies and was assumed to be zero.

The importance of insulin to the augmented uptake of glucose during exercise was indicated when it was shown, that in depancreatized dogs deprived of insulin for 48 hours prior to exercise, there was no increase in glucose utilization (Vranic and Wrenshall, 1969). Studies of perfused isolated skeletal muscle of diabetic rats also showed a dependence on insulin to produce an exercise-induced augmentation of glucose uptake (Berger, et al., 1975).

The rate at which circulating glucose is utilized by the exercising muscle can also indirectly reflect the interplay of other metabolic

processes. For example, it is believed that elevated glycogenolysis decreases glucose utilization because of the inhibition of G-6-P on hexokinase activity (Newsholme and Start, 1973). Newsholme and Randle (1964) have suggested that fatty acid oxidation can also decrease glucose utilization by the muscle but this interaction could not be demonstrated in perfusion studies (Ruderman, et al.,1979). Although insulin might be a major and possibly the only circulating regulator of muscle glucose uptake during exercise, its effectiveness might depend on the oxidation of free fatty acids and glycogenolysis in the muscle.

Carbohydrate Metabolism in the Liver

The availability of blood-borne glucose to the muscle is regulated by the uptake and release of glucose by the liver, which is dependent on the blood glucose concentration and the actions of the various hormones.

Since the transport of glucose across the liver cell membrane is an equilibrium process the control of glucose uptake by the liver appears to depend on the presence of the enzyme glucokinase. Glucokinase is unique to the liver and catalyzes the phosphorylation of glucose to G-6-P. The dynamics of glucokinase insures that changes in the blood glucose level will regulate glucose uptake by the liver (Cramp and Carson, 1979). Glucokinase is highly specific, having a relatively high affinity for glucose and is not inhibited by G-6-P concentrations. An increase in blood glucose will have a stimulating effect on the activity of glucokinase so that glucose phosphorylation, and consequently glucose uptake by the liver, is increased.

Once G-6-P has been formed one of the possible pathways for its use in the liver is glycogen synthesis (Fig. 4). Glycogen synthesis from G-6-P is regulated by the enzyme glycogen synthetase (UDPG-transferase). The activity of this enzyme is stimulated by increased concentrations of

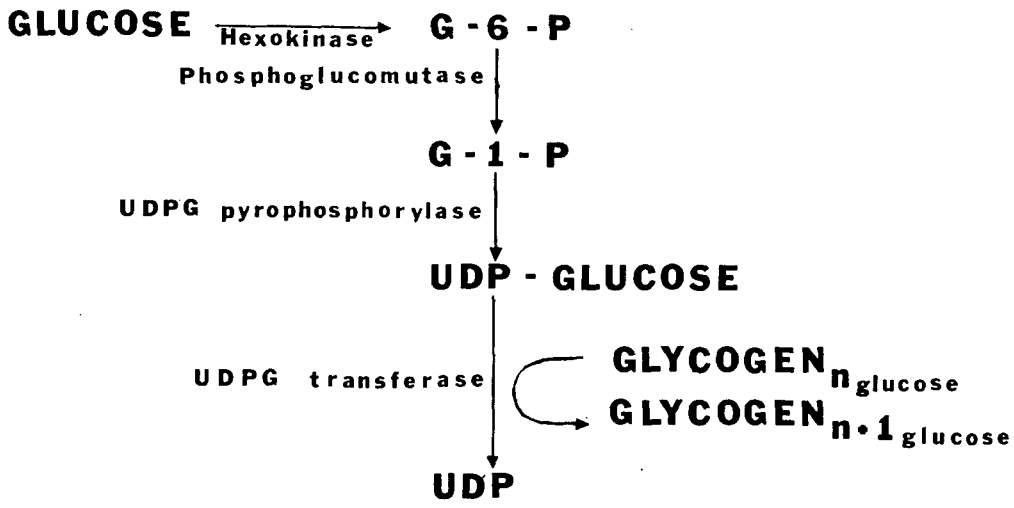


Figure 4. The glycogen synthesis pathway (from Brown, 1978)

glucose and G-6-P, and inhibited by increasing glycogen concentrations (Newsholme and Start, 1973).

Liver glycogen functions as a temporary reserve to maintain blood glucose levels whenever the demand exceeds that available in the blood. In this case, the liver releases glucose into the blood stream by the hydrolysis of G-6-P to glucose, catalyzed by the enzyme glucose-6-phosphatase. The immediate source of G-6-P is the liver glycogen supply (Fig. 5). The rate of glycogenolysis is controlled by the enzyme glycogen phosphorylase, which catalyzes the cleavage of glycogen (Newsholme and Start, 1973).

If glucose needs exceed the supply of glycogen, the liver can produce glucose through gluconeogenesis, the synthesis of glucose from non-carbohydrate sources. The primary control of the gluconeogenic rate is accomplished by variations in substrate presentation. The rate of

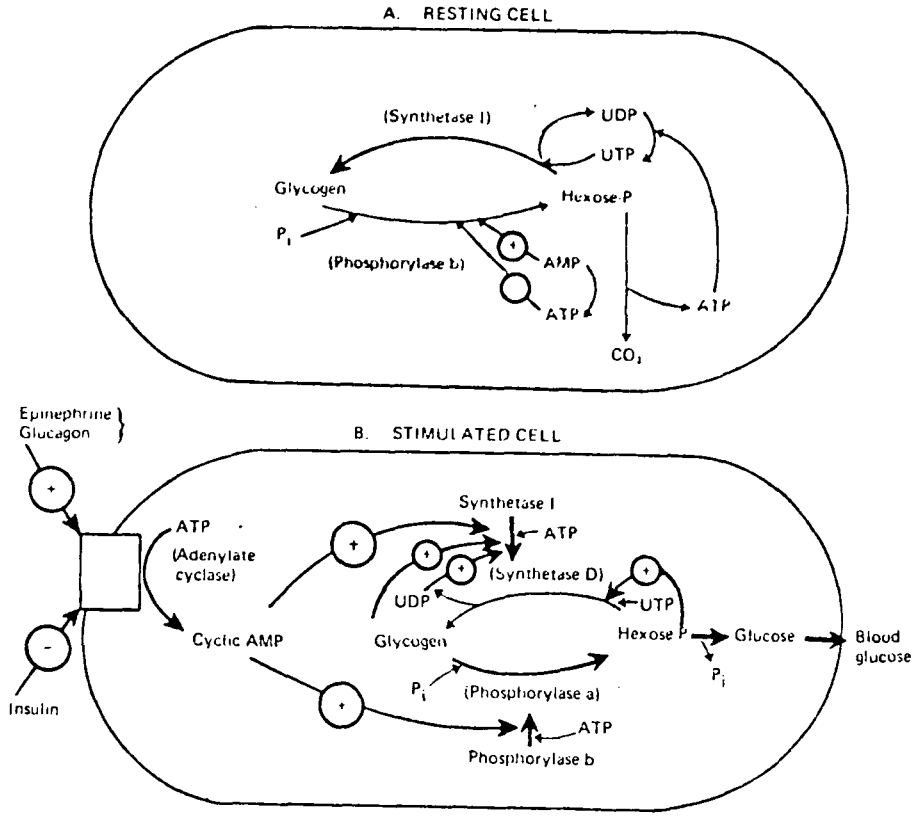


Figure 5. Glycogen metabolism in the liver (from McMurray, 1977)

gluconeogenes is directly proportional to the concentration of gluconeogenic precursors in the hepatic blood and can be altered within seconds of a change in substrate concentration. Changes in precursor concentrations alter the activity of three key enzymes setting the gross limits of the maximum and minimum rates for the saturating concentrations

of the substrates (Cahill et al.,1966).

The most important gluconeogenic precursor is the lactate that originates in other tissues, such as the muscle, and arrives at the liver in the blood stream. During strenuous muscular activity, for example, the production of lactate will exceed the capacity of the muscle for oxidation. The resulting excess of lactate will diffuse into the blood stream and upon reaching the liver provide a carbon source for gluconeogenesis.

Other means of providing substrates for gluconeogenesis include amino acids that are produced by the breakdown of muscle and other tissue proteins, and the mobilization of fat stores from adipose tissue (Goodman, 1974) (Fig. 6).

Liver Glucose Production during Exercise

Under most physiological conditions the rate of glucose utilization is precisely met by an appropriate increase in hepatic glucose production stemming from glycogenolysis and during prolonged activity from gluconeogenesis (Felig and Wahren, 1975; Wahren, et al., 1971; Issekutz, et al., 1967; Vranic, et al., 1976b). In short-term mild to moderate exercise (10 to 30% Vo2 max) the concentration of blood glucose changes little from the basal state but periods of exercise that last longer than 90 minutes can decrease blood glucose by 10 to 40 mg% depending on the severity of the exercise. True hypoglycemia is rare, although it may be observed in marathon runners, patients on low charbohydrate diets, and insulin treated diabetics (Wahren, 1979).

Depending on the work intensity, the output of glucose from the liver

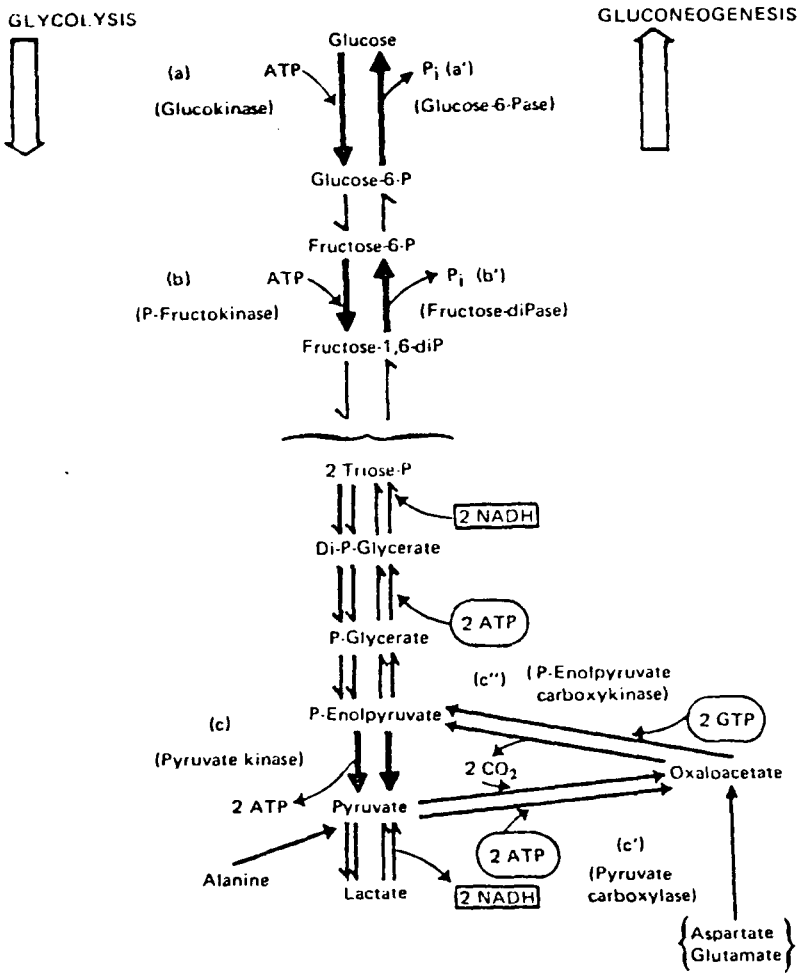


Figure 6. Gluconeogenesis, showing the three irreversible steps of glycolysis at (a), (b), and (c), as well as the reactions (a'), (b'), (c'), and (c'') that circumvent these steps (from McMurray, 1977)

increases 3 to 5 times over basal levels in the first hour of exercise (Felig and Wahren, 1975; Brown, 1978). Approximately 77% of the released glucose is derived from glycogenolysis, the remaining 23% attributed to gluconeogenesis. The initial surge of glycogenolysis probably occurs

because of the high epinephrine output triggered by the sudden demands of exercise (Brown, 1978). The total amount of glucose released from the liver during 40 minutes of heavy work (75% of Vo2 max) is 25% of the total hepatic glycogen stores in the postabsorptive state (Felig and Wahren, 1975). In four hours of exercise 75% of the total hepatic glycogen stores will have been mobilized for energy.

During prolonged mild exercise (10 to 15% Vo2 max) hepatic glucose output doubles in 40 minutes and remains constant for three to four hours (Ahlborg, et al., 1974). Since glucose utilization continues to rise for 90 minutes or more an imbalance between glucose utilization and production occurs resulting in a slight decrease in blood glucose (Felig and Wahren, 1975). The relative contribution of gluconeogenesis to hepatic glucose production increases from 40 minutes of exercise on. If exercise is continued for approximately 240 minutes 100% of the glucose released from the liver is the result of gluconeogenesis. Although the rate of gluconeogenesis may be three times the basal rate, the amount of glucose released from the liver has decreased and approximately 60% of the muscle's energy comes from fatty acid oxidation (Brown, 1978).

Factors that could account for such a marked and sustained stimulation of glucose production are alterations of the levels of hormones during exercise, in addition to plasma glucose levels. When plasma glucose decreases, hypoglycemia may either sensitize the liver directly to the gluconeogenic and glycogenolytic hormones or exert its effect through further stimulation of the release of glucagon and epinephrine.

Hormonal Regulation

Hormones are prime external stimuli that can influence individual tissues to respond metabolically for the benefit of the whole organism rather than the tissue alone (Newsholme and Start, 1973). Hormones augment the regulation of biochemical events at the cellular level by altering enzyme activities and bringing about the intergration of organ systems by means of feedback signals that are elicited from controlled target organs. Hormonal control is responsible for the daily metabolic adjustments necessary to regulate the energy supply of the body.

The integration and control of glucose metabolism is a function of at least six dominant hormones: insulin, glucagon, catecholamines, growth hormones, glucocorticoids and thyroid hormones, that yield a finely regulated blood glucose concentration (Table 1). Insulin, glucagon, and the catecholamine, epinephrine, are the hormones that play a significant role in the immediate response of glucose metabolism to disturbances in glucose homeostasis (De Bodo, et al., 1963). Physical exercise causes a variety of alterations in body fuel homeostasis and hormonal regulation. Table 2 summarizes these exercise effects and the effects of various hormones when they are infused into the resting dog.

The similarities between exercise-induced changes and the various effects of epinephrine infusion in the resting subject are quite striking (Table 2). The only difference is the weak effect of epinephrine on adipose tissue. The effects of hypoglycemia are also similar to exercise effects. The response to hypoglycemia is aimed at maintaining blood

Table 1. Major hormones that control the metabolism of carbohydrate, fat, and protein (from Srinivasan, 1969)

NAME	APPPROXIMATE MOLECULAR WEIGHT	TYPICAL FASTING PLASMA LEVEL OR SECRETION RATE IN NORMAL HUMANS	SOURCE
1. Insulin	6000	15 uU/ml	Beta-cells of pancreas
2. Glucagon	3450	0.4 ng/ml	Alpha-cells of pancreas
3. Catecholamines			
i. epinephrine	183.2	0.1 ng/ml	Adrenal medulla
ii. norepiephrine	170	0.4 ng/ml	Adrenal medulla; Sympathetic nerve endings
4. Growth Hormone	21500	2 ng/ml	Anterior pituitary
5. Glucocorticoids			Adrenal cortex
i. Cortisol	329	20 mg/day	
ii. Corticosterone	346	3 mg/day	
6. Thyroxin	776.9	80 ug/day	Thyroid

PRIMARY STIMULI	IMPORTANT EFFECTS ON METABOLISM OF CARBOHYRATE, FAT, AND PROTEIN
Hyperglycemia	Increased uptake of glucose by liver, muscle and adipose tissue Increased muscle uptake of amino acids and protein synthesis Decreased lipolysis Augmented lipogenesis
Hypoglycemia	Increased hepatic glycogenolysis Increased gluconeogenesis Increased proteolysis Increased insulin secretion
Hypoglycemia; physiologic stress	Increased glycogenolysis in both liver and muscle Increased lipolysis Decreased insulin secretion
Physiologic and emotional stress	Increased lipolysis Decreased insulin secretion
Hypoglycemia	Increased lipolysis Increased protien synthesis
Corticotropin from anterior pituitary	Increased gluconeogenesis Increased proteolysis Increased ketgenesis
Thyrotropin from anterior pituitary	Increased basal metabolic rate Decreased plasma cholesterol levels Increased hepatic glycogenolysis Increased gluconeogenesis Increased proteolysis Actions are interrelated to those of catecholamines

glucose concentration by reducing peripheral glucose uptake and increasing hepatic glucose output. Some of the rise in epinephrine and glucagon release that occurs during exercise has been shown to occur due to hypoglycemia (Galbo, et al., 1977b).

Table 2. Effects of exercise and hormones on substrate mobilization

	Glucose	Epinephrine	Glucagon	Insulin
Exercise	↑	↑	↑	↓
Epinephrine	↑	–	↑	↓
Glucagon	↑	?	↑	↑
Insulin	↓	–	↓↑	↑
Hypoglycemia	↑	↑	↑	↓

The hormonal response to exercise is well documented but it is not clear whether all or some of the hormones are essential or whether some act as compensatory mechanisms. The fact that there are more hormones that directly control utilization lends support to the existence of compensatory mechanisms. When considering the actions of hormones during exercise it is important to account for whether the hormones play regulatory or permissive roles in the maintenance of blood glucose. Hormonal changes that could account for the increased glucose production during exercise are the enhancement of glucagon and epinephrine secretion, and the suppression of insulin secretion (Fig. 7).

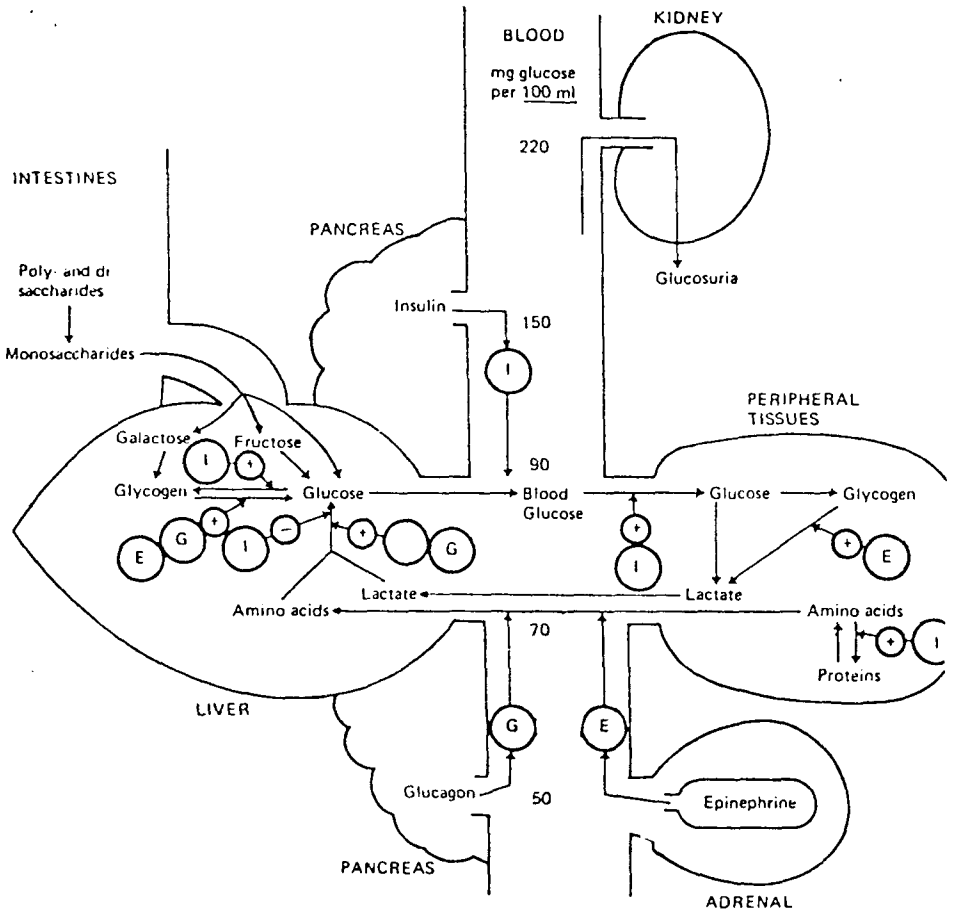


Figure 7. Control of blood sugar levels. Hyperglycemia causes release of insulin (I), while hypoglycemia initiates the release of glucagon (G), and epinephrine (E) (from McMurray, 1977)

Insulin

Insulin is the single most important hormone coordinating the utilization of glucose and other metabolic fuels. Insulin is secreted by the beta cells of the pancreas in response to increasing levels of blood glucose and hyperglycemia. The beta cells secrete between 25 to 50 units of insulin into the hepatic vein each day. The liver removes approximately half of this insulin and the remainder is rapidly metabolized in the peripheral circulation. Insulin's plasma half-life is approximately 1/2 to

1 hour (Sawin, 1969; Brown, 1978) and normal fasting peripheral blood levels range from 7 uU/ml to 20 uU/ml (Sawin, 1969).

Secretion Insulin secretion by the beta cells is controlled primarily by the concentration of blood glucose and the rate of change of this concentration (Srinivasan, et al., 1970). Hyperglycemia is a potent drive that induces a rapid secretion of insulin. A rise in blood glucose above 80-100 mg% acts directly to stimulate insulin secretion. The increased plasma insulin levels lower blood glucose, removing the stimulus to secretion and plasma insulin levels return to pre-stimulus values. The concentration of insulin in the blood has no direct effect on its own secretion (Sawin, 1969).

There are a number of intrinsic factors such as physical activity, and other hormones that modulate the intensity of the beta cell response to glucose. Anything that affects carbohydrate metabolism will affect insulin secretion (Sawin, 1969).

The hormones glucagon and epinephrine can also cause increases in insulin secretion. Glucagon affects insulin secretion by causing a rapid increase in blood glucose as a direct result of glycogen breakdown. Epinephrine causes a rapid rise in blood glucose due to stimulation of glycogenolysis in the liver and inhibition of insulin stimulated uptake of glucose by the muscle. However, epinephrine also acts directly on the beta cells of the pancreas to inhibit insulin release, epinephrine infusions have been shown to virtually stop insulin secretion (Porte, et al., 1966).

The net effect of these factors depends on the state of the organism. If hypoglycemia is present an increase in blood glucose concentration may not affect insulin secretion because the critical blood glucose level of

80-100 mg% has not been exceeded. Removal of any of the factors will lower blood glucose but the change may or may not lower insulin secretion depending on the presence of hypoglycemia.

Decreases in insulin secretion during exercise are probably due to the inhibition of insulin release. Evidence indicates that during exercise alpha adrenergic activity inhibits insulin secretion. Blocking the alpha-receptors during exercise reduced the level of suppression of insulin release (Galbo, et al., 1977b) and in man a diminished rise in plasma catecholamine levels is accompanied by smaller decreases in insulin levels (Hartley et al., 1972a).

Actions Insulin has many different influences within the body and acts directly or indirectly to affect many kinds of biochemical processes. The most important effect of insulin is the regulation of glucose transport across the muscle cell membrane. Insulin increases the velocity of glucose entry into the cell but does not change the affinity of the glucose transport system for glucose. The specific mechanism of insulin action is unknown. The effects of insulin on glucose transport occur instantaneously and are thought to be direct (Goodman, 1974).

The enhancement of glucose transport across the muscle cell membrane leads to an increase in the rate of glycolysis within the cell. Glycolysis is increased primarily by the rise in intracellular glucose, which increases the rate of flux of substrates through the glycolytic pathway (Sawin, 1969).

Insulin increases the incorporation of glucose into muscle glycogen independent of its effect on membrane transport. The conversion of glucose to glycogen is enhanced by the specific increase in the activity of the

regulatory enzyme for glycogen synthesis, UDPG-transferase, that occurs in the presence of insulin (Newsholme and Start, 1973).

Another theory that has been proposed for insulin action is that changes in the circulating levels of insulin may influence glucose utilization by muscle indirectly through changes in the plasma fatty acid concentration. A decrease in plasma insulin will increase the rate of fatty acid mobilization from adipose tissue so that the plasma free fatty acid (FFA) level is elevated and this will in turn inhibit glucose uptake by the muscle. An increase in plasma insulin concentration has the opposite effect. According to this theory, only when excessive carbohydrate is ingested is the level of insulin raised sufficiently to exert a direct effect on glucose uptake by the muscle (Newsholme, 1976).

In the liver, cells are freely permeable to glucose without insulin. Nevertheless, insulin can modify the rates of uptake and release of glucose by the liver through effects on intercellular glucose metabolism (Fig.8).

Glucose uptake by the liver increases due to a specific increase in glucokinase activity. Glucokinase activity appears to be regulated by plasma levels of both glucose and insulin. Insulin may act as a permissive agent allowing glucose to actually induce an increase in enzyme activity. The activity of glucose-6-phosphatase is also altered by insulin but in the opposite direction of glucokinase. The actions of insulin in the liver cell increase the disposition of glucose-6-phosphate and stimulates glycogen synthesis in the same general pattern as in muscle cells (Newsholme and Start, 1973).

Insulin decreases net glucose output by the liver through the

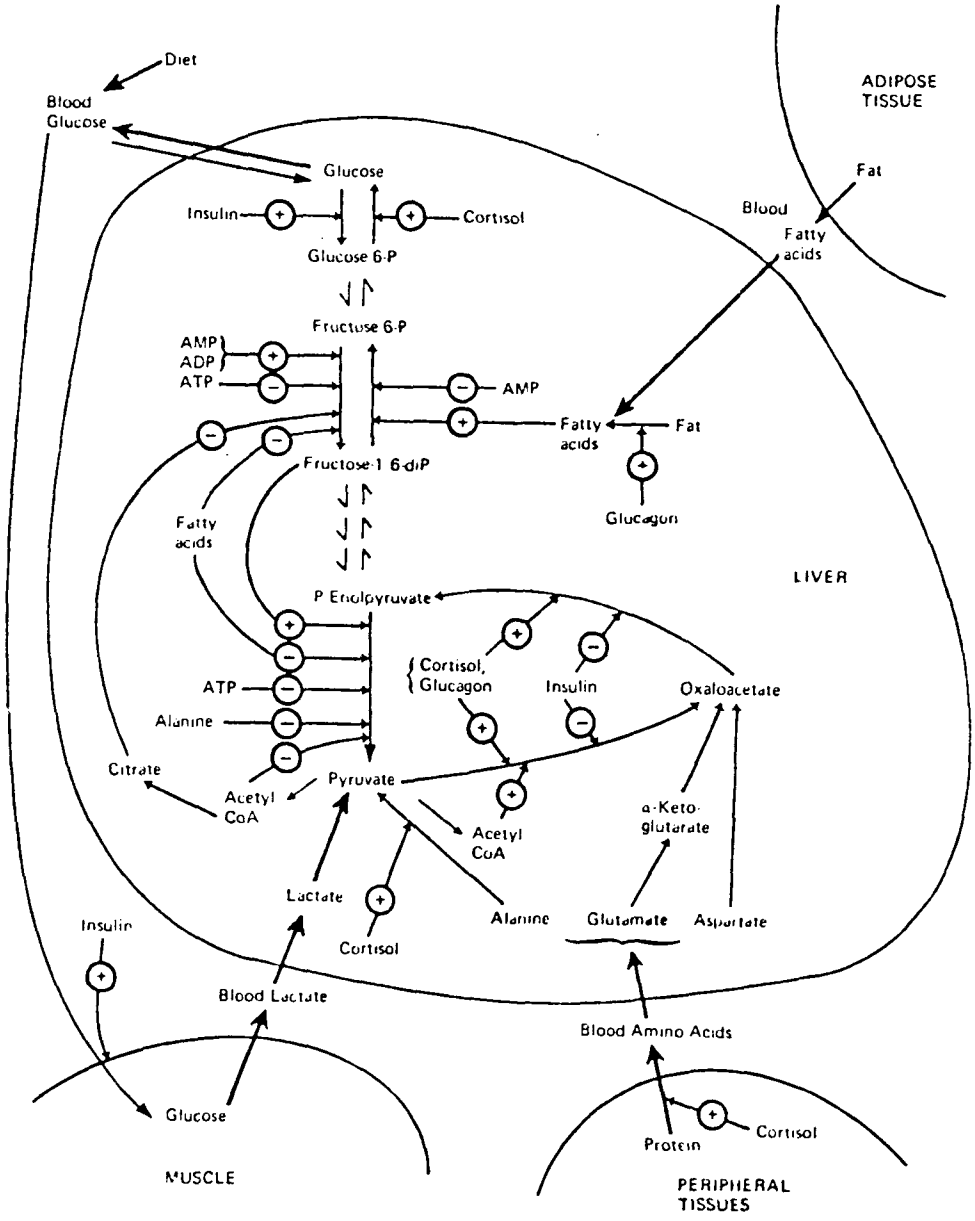


Figure 8. Regulation of glycolysis and gluconeogenesis in the liver; - , reaction is inhibited; + , reaction is stimulated (from McMurray, 1977)

regulation of gluconeogenesis and glycolysis. By inhibiting the release of lactate and amino acids from muscle, and glycerol from adipose tissue, insulin decreases the rate of gluconeogenesis by depriving the liver of substrates. Insulin also causes decreases in the cellular levels of cyclic

AMP that slow the release of glucose from the liver. The decrease in cyclic AMP favors the formation of glycogen and a decrease in the rate of hepatic gluconeogenesis (Newsholme, 1976).

The ultimate effect of insulin is a decrease in the concentration of blood glucose. This occurs through the facilitation of the utilization of glucose by the tissues and the prevention of glycogen breakdown.

Exercise Insulin is essentually the only hormone capable of inhibiting glucose mobilization (Vranic and Kawamori, 1979). Unlike exercise-enhanced glucose disappearance, the hepatic production of glucose is responsive to increases in plasma insulin. Lower levels of insulin are needed to allow for a sufficient increase in glucose production during exercise (Kawamori and Vranic, 1977). The suppression of insulin secretion is important to sensitizing the liver to the actions of gluconeogenic and glycogenolytic hormones (Cherrington, et al., 1976; Vranic, et al., 1976).

Glucagon

Glucagon is secreted by the alpha cells of the pancreas in response to hypoglycemia and decreasing levels of blood glucose. Hypoglycemia stimulates the secretion of large quantities of glucagon that rapidly mobilize glucose from the liver (Guyton, 1976). Glucagon is an extremely potent hormone which is produced in concentrations of pg/ml and an increase in blood concentration of as little as 0.01 ug produces intense glycogenolysis (Tepperman, 1980).

At steady state glucagon is secreted into the portal circulation at an average rate of 50 to 200 ug/hour (Foa, 1972). The concentration of glucagon in the portal blood is considerably higher than in the peripheral

blood. This difference reflects the fact that the liver is the principal site of glucagon inactivation, only 1/3 of the secreted glucagon reaches the peripheral circulation (Tepperman, 1980). In the peripheral circulation glucagon is very short-lived, with a half-life of approximately 1/3 that of insulin, ranging from 5 to 10 minutes (Sawin, 1969).

Secretion The secretion of glucagon responds to changes in the plasma levels of glucose, amino acids, and fatty acids and therefore depends on the metabolism of carbohydrates, proteins, and fats. Anything that affects these metabolic pathways will alter glucagon secretion.

The concentration of glucose in the blood is the most important signal of glucagon secretion. Blood glucose levels below 70 mg% induce large increases in plasma glucagon, while blood glucose levels above 160 mg% cause prompt suppression of glucagon release (Guyton, 1976). The precise signal for glucagon release is unknown, but it appears that glucose must enter the alpha cell to inhibit glucagon secretion (Muller, et al., 1978).

The secretion of glucagon is inhibited by the changes it produces in the concentration of circulating metabolites forming a feedback mechanism for its own regulation. Insulin and epinephrine both stimulate glucagon secretion indirectly through their effects on blood glucose concentrations.

Actions Glucagon has a general catabolic action that is directly antagonistic to the actions of insulin. The secretion of glucagon results in an increased hepatic output of glucose at a rate capable of preventing hypoglycemia (Cherrington, et al., 1978). Glucagon levels oscillate

precisely out of phase with glucose levels, implying that glucagon is important in moment to moment regulation of glucose (Ensink and Williams,1972). Glucagon also increases plasma levels of fatty acids by increasing their mobilization from adipose tissue (Foa, 1972).

The primary site of action of glucagon is the liver. Glucagon increases blood glucose concentrations through its effect on hepatic glucose release by glycogenolytic and gluconeogenic pathways (Ensink and Williams, 1972). Glucagon is presumed to stimulate both glycogenolysis and gluconeogenesis by way of increases in the cyclic AMP concentration in the cells (Tepperman, 1980).

The cyclic AMP formed in response to glucagon is thought to accelerate gluconeogenesis by facilitating the conversion of pyruvate to PEP. This effect combined with the glucagon stimulated increase in blood-borne substrates increases the rate of gluconeogenesis (Goodman, 1974; Foa, 1972). The gluconeogenic effect of glucagon is observed within a minute of the exposure of the liver to increased levels of glucagon (Exton and Park, 1972).

The glycogenolytic action of glucagon results from the activation of glycogen phosphorylase by cyclic AMP and the inactivation of glycogen synthetase (Foa, 1972; Exton and Park, 1972) (Fig. 9). The onset of glycogenolysis is rapid; occurring within 30 seconds of the glucagon stimulated increase of cyclic AMP, and transient, disappearing within one hour after glucagon release (Exton and Park, 1972; Ensink and Williams, 1972).

Glucagon has no direct effect on peripheral tissues, since muscle cell membranes have no glucagon receptors (McMurray, 1977). Glucagon

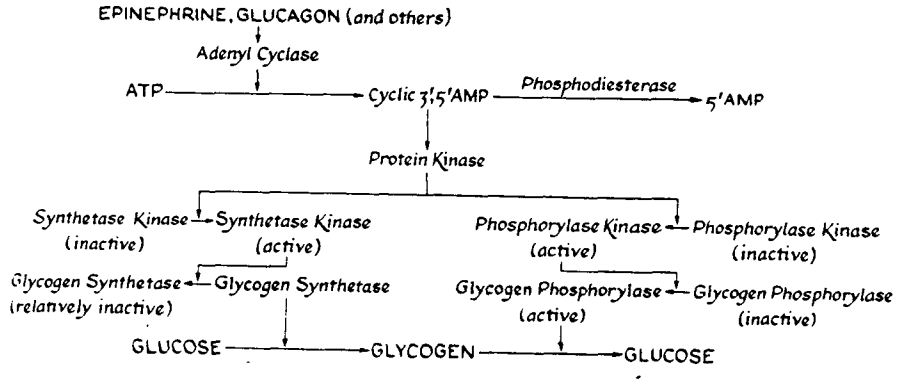


Figure 9. Epinephrine and glucagon effects on glycogen metabolism (Brown, 1978)

induced increases in free fatty acid concentration, however, may decrease glucose uptake, but this would be balanced by the glucagon stimulated secretion of insulin and epinephrine. The insulin secretion that accompanies increased glucagon secretion causes a rise in peripheral glucose utilization of the same magnitude as the increase in production by the liver. This means glucagon can increase glucose turnover without changing the blood glucose concentration (Vranic, et al., 1976a).

Exercise Glucagon is essential in the regulation of glucose production during exercise because suppression of glucagon secretion results in inadequate glucose mobilization. Its role is viewed as permissive because adequate glucose increments are induced even when glucagon levels do not rise (Vranic and Kawamori, 1979). A primary effect of glucagon can be demonstrated on liver glycogenolysis since animals pretreated with glucagon antiserum do not show the large decreases in liver glycogen that usually occur with exercise (Galbo and Holst, 1976).

The stimulus for the increase in plasma glucagon during exercise is

not fully understood. A decrease in plasma glucose level is not needed for glucagon levels to increase (Ahlborg and Felig, 1976) although the increase in glucagon does parallel the decrease in plasma glucose when it is present (Galbo, et al., 1976b). Sympathetic influence could be important since the catecholamines are known to stimulate glucagon release. However, during alpha and beta blockage there is no diminished glucagon response to exercise (Galbo, et al., 1977a). Glucagon secretion during exercise seems to be sensitive to glucose demand in a way not necessarily reflected in glucose levels in the systemic circulation (Terjung, 1979).

The ability of glucagon and epinephrine to maintain glucose during exercise is not fully understood since infusion of glucagon or epinephrine at rest stimulates glucose production only transiently. Suppressed insulin levels during exercise possibly represent an important factor in reversing the transient effect of these glycogenolytic and gluconeogenic hormones (Vranic and Kawamori, 1979).

Epinephrine

The secretion of epinephrine by the adrenal medulla is an important modulator of insulin and glucagon actions (Gerich, et al., 1976). Epinephrine closely links the endocrine and nervous systems; the connection between the two allows psychic influences to modify hormone activity (Srinivasan, 1969).

Under normal conditions epinephrine is secreted at a rate of approximately 0.015 mg/kg body weight/min (Brown, 1978). However, epinephrine is rapidly metabolized in the liver and the circulation and

has a half-life of less than 20 seconds (Tepperman, 1980). The concentration of epinephrine in the blood is usually maintained around 0.06 ug/l (Sawin, 1969).

Secretion The secretion of epinephrine is almost entirely under nervous contol (Sawin, 1969). One stimulus of epinephrine secretion is a decrease in blood glucose concentration. The faster the fall of blood glucose the more pronounced the effect on epinephrine secretion (Shreeve, 1974). Emotional excitement, injury, and exercise also cause augmented release of epinephrine and a consequent rise in blood glucose (Turner and Bagnara, 1976).

The physiologic responses to epinephrine do not inhibit its secretion because epinephrine is controlled by nervous impulses rather than responses of receptors. Another reason there is no inhibition of epinephrine secretion is the transient nature of the response. Secretion ceases after a short time removing epinephrine stimulation.

Actions Epinephrine is one of the most important factors for countering the hypoglycemic action of insulin (Turner and Bagnara,1976). Both epinephrine and glucagon are counter-regulatory hormone to insulin (Fig.10).

Epinephrine exerts its hyperglycemic action by increasing the rate of glycogenolysis in muscle and liver. Under the influence of epinephrine muscle glycogen is converted to G-6-P and channeled through the glycolytic process resulting in the formation of lactic acid. Under certain conditions epinephrine can produce a rise in liver glycogen rather than a fall, especially when liver glycogen was initially low, due to the

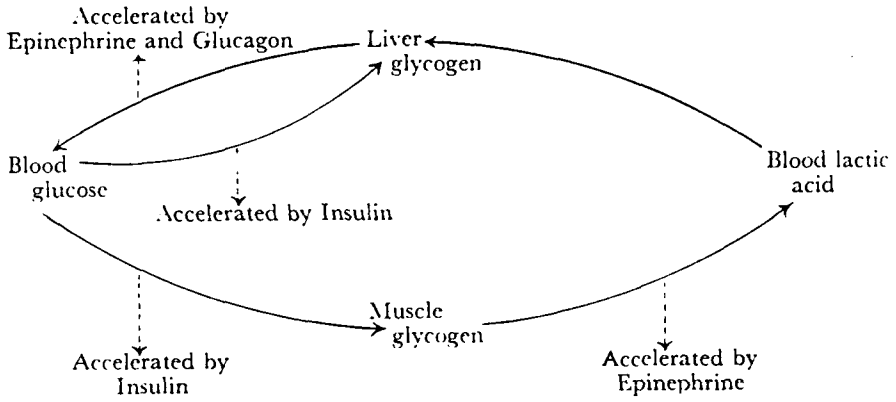


Figure 10. Actions of epinephrine, glucagon, and insulin on carbohydrate metabolism (from Turner and Bagnara, 1976)

formation of liver glycogen from the muscle lactate (Tepperman, 1980).

In muscle, epinephrine interacts with beta adrenergic receptors to activate adenylate cyclase resulting in increased levels of cyclic AMP. Cyclic AMP acts as a "second messenger" whose actions eventually lead to an increased rate of glycogenolysis in muscle (Cohen, et al., 1978; Turner and Bagnara, 1976) (Fig. 11). Stimulation of glycogenolysis in the liver may occur in this manner also but there is evidence that it may occur largely through the interaction of epinephrine with alpha adrenergic receptors. The mechanism of glycogenolytic stimulation in the liver by epinephrine is not fully understood but is known to result in cyclic AMP independent activation of glycogen phosphorylase (Cahen, 1978; Exton, 1972). The concentration of epinephrine required for hepatic glycogenolysis in <u>in vitro</u> studies are 5 to 10 times as high as those needed for the same effect in muscle (Ensink and Williams, 1972).

Epinephrine exerts a direct and immediate effect on the beta cells of the pancreas reducing the secretion of insulin. The physiological

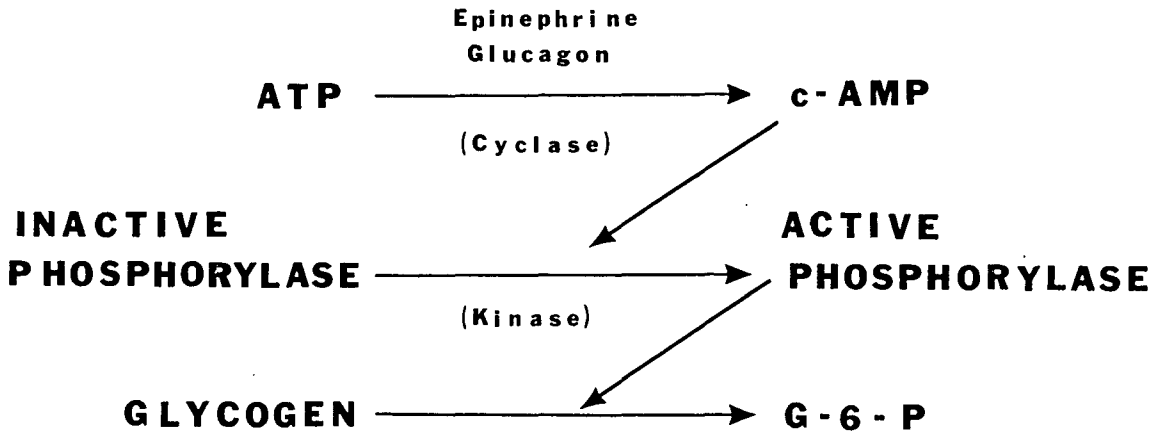


Figure 11. The sites of action of epinephrine in glucose metabolism

significance of this inhibition of insulin release is that under conditions of stress epinephrine would be better able to mobilize glucose from the liver, increasing the readily available supply of fuel to the peripheral tissues.

Epinephrine also stimulates the release of glucagon and the moblization of free fatty acids to some degree. Epinephrine has a biphasic effect on the mobilization of fatty acids that is probably due to its lipotic effect on adipose tissue as well as the antilipotic action of the elevated glucose and lactate levels induced by epinephrine. The effects of epinephrine on glucagon and insulin secretion may mediate as well as strengthen its glycogenolytic effects (Issekutz, 1979). It has been suggested by Ezdindi and Sokai (1966) and more recently by Gerich, et al. (1976) that the effects of epinephrine on glucose production in the liver may be modulated through glucagon. However, other studies have shown

that epinephrine induced hyperglycemia is not mediated through glucagon release. No definite conclusions have been drawn.

Exercise Extensive activation of the sympathetic nervous system occurs prior to and during physical activity (Galbo et al., 1977a). The intensity of the sympathetic discharge is related to the severity of the work preformed.

After an initial pre-exercise rise, changes in circulating epinephrine levels are not generally evident during light to moderate exercise. However, under heavy to intense exercise conditions epinephrine levels increase abruptly near exhaustion (Hartley et al., 1972b). Massive adrenal activation seems to be regulated to more severe work situations.

A similar progression in blood levels of epinephrine can be found during exercise as a function of time. For a submaximal work intensity circulating epinephrine levels can increase 2 to 6 fold with time (Galbo, et al., 1977b; Hartley, et al., 1972a, b). If work intensity is mild enough, epinephrine may not change much initially. However, epinephrine levels increase progressively with prolonged work effort sustained to the point of exhaustion (Galbo, et al., 1976a, b). The time dependent sympathetic response is probably related to the increase in effort experienced in maintaining the work output as fatigue develops.

The increased sympathetic activation during exercise provides an integration function that is essential for normal performance (Fig. 12). Epinephrine exerts its effects through both the alpha and beta andregenic receptor mechanisms. Beta-sympathetic activation promotes both liver and

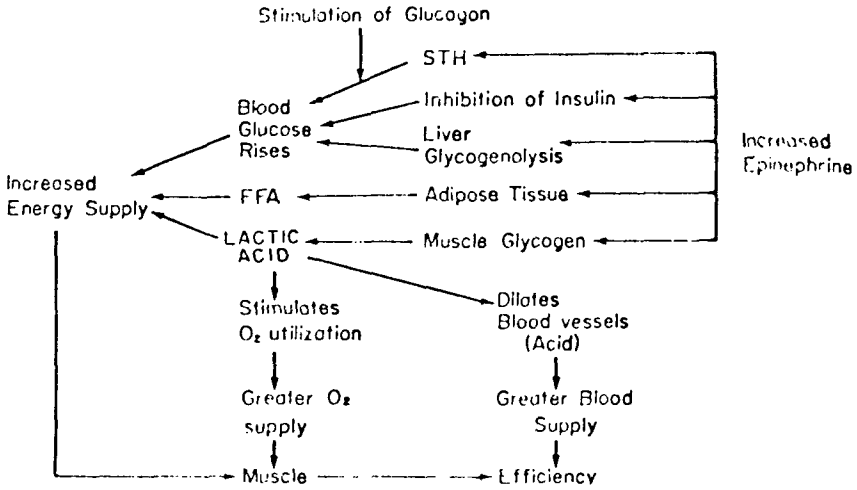


Figure 12. The effects of increased epinephrine secretion under stress (from Brown, 1978)

muscle glycogenolysis and lipolysis. Beta-blockage during exercise increases peripheral glucose uptake indirectly by decreasing muscle glycogenolysis and uptake of fatty acids. However, there is no reduction in glucose production by the liver (Issekutz, 1979). This suggests that the primary role of epinephrine during exercise is not to regulate glucose production by the liver but rather to regulate lipolysis and muscle glycogenolysis (Vranic and Berger, 1979). Alpha-aderegenic activation acts to reduce the secretion of insulin (Issekutz, 1979).

The mechanism of the regulation of epinephrine secretion during exercise is unknown. Glucose administration during exercise in dogs has been shown to markedly reduce epinephrine concentrations (Nazar et al., 1975). An intensified epinephrine response found after alpha-adrenergic blockage along with an increased rate of decline of blood glucose concentration also suggests glucose availablity effects the secretion of epinephrine (Galbo, et al., 1976a).

These findings lead to the hypothesis that during prolonged exercise

glucose sensitive cells in the CNS and pancreas, possibly sensitized by low insulin concetrations, establish a hormonal response that favors glucose production. Consequently, an enhanced hormonal response to exercise would be expected when available glycogen stores are small or hard to mobilize and plasma glucose concentration accordingly declines more rapidly during exercise (Galbo, et al., 1977a). During exercise, glucose sensitive cells respond to changes in blood glucose concentration that do not cause a response at rest (Christensen, et al., 1979).

Models of Carbohydrate Metabolism

Since the first qualitative glucose regulation model was presented by Goldman in 1960, various simulations of the blood glucose regulatory system have been performed. Mathematical models of the system have enabled data reduction, diagnostic classification, hypothesis testing, and design of critical experiments. These mathematical models, which simulate the behavior of the real physiological system, are in turn simulated using various digital and analog computer techniques. Even the simplest of these models has led to a better understanding of glucose metabolic dynamics, under resting conditions. Charette, Kadish, and Sridhar (1969) have written a comprehensive review article of the major models developed through 1969. Since this time, many more models have been developed that emphasize one or more aspects of control or response to perturbations.

Possibly the first nonlinear representations of glucose homeostasis with multihormonal control mechanisms were presented by Charette, et al. (1969), and Srinivasan, et al. (1970). These models were based on a

systems model approach and used current theories of glucose and FFA metabolism. The models gave an adequate view of the overall homeostatic system but the use of the somewhat arbitrary nonlinear mathematical functions for the dynamic processes of the system reduced the amount of physiological insight obtainable from the simulations (Cramp and Carson, 1979).

Campfield (1973) and Foster, et al. (1973) also developed models of glucose homeostasis that included the interactions of glucose and FFA metabolism. These models also failed to give insight into actual physiological processes because model behavior was satisfactory in comparison to the real system even in the absence of a reasonable degree of isomorphism of parameter values to physiological data.

In attempts to simplify the modeling process, models were developed using both linear and nonlinear equations. Vranic, et al. (1973) developed a model that was restricted to the relationships between insulin, glucagon, and the rates of glucose production, utilization, and metabolic clearance. This model represented a systems analysis of the glucoregulatory system based on insulin-glucagon interactions. However, the assumption of linearity for nonlinear reactions reduced the degree to which simulations could mimic actual physiological responses.

Simulations from models of glucose-insulin dynamics agreed reasonably well with physiological data at rest but failed to take into account effects of other hormones than insulin (Lafferty, et al., 1978; Guyton, et al., 1978; Tiran, et al., 1980).

Models of glucose turnover during unsteady state situations include those by Randall (1980), Radziuk, et al. (1978), and Tiran, et al., 1975).

These models are used to simulate specific perturbations such as a glucose tolerance test.

London (1966) developed one of the first models of glucose metabolism making extensive use of enzyme dynamics. The model was concerned with the reactions that interconverted blood glucose and liver glycogen and was based on enzymatic reaction mechanisms and *in vitro* kinetic data. Many subsequent models used London's kinetic data in their development.

Finkelstein, et al., (1975), Bergman and El-Refai (1975), and Bergman (1977) all used modeling approaches similar to that of London. Their models were concerned with determining individual dynamic influences on the liver and integrating them by way of computer simulations of hepatic glycogen metabolism. These simulations lead to specific hypotheses about the biochemical effects of glucose and insulin on the liver.

Cramp and Carson (1979) carried London's approach further and developed a model of the dynamics of blood glucose and its regulating hormones using enzyme dynamics. The model is a nonlinear mathematical representation based on the enzyme dynamics occurring in the liver, and their modulation by substrate and hormone concentrations. Such a model enables the complete systems behavior of the metabolic system and its endocrine control to be analyzed.

The advantages of this model are that the model structure is explicitly based upon current physiological knowledge and incorporates the regulatory dynamics of hormones. It also provides a representation which tends toward isomorphism, so hypotheses concerning relationships between systems structure, parameter values, and various physiological states can be tested.

MODEL DEVELOPMENT

Proposed Model

Starting with the model of glucose homeostasis proposed by Cramp and Carson (1979) shown in Figure 13, a mathematical model of blood glucose

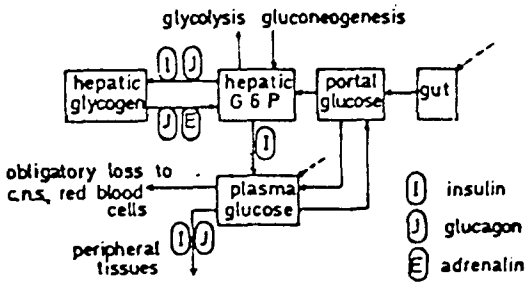


Figure 13. Cramp and Carson's model of liver glucose metabolism and its hormonal control

regulation which will describe behavior during exercise has been constructed. The model is intended to explain qualitatively the glucoregulatory response of a normal subject during continuous exercise at moderate (30% of Vo2 max) work loads for a period of up to two hours. The mathematical description is based on species material balances which include the metabolic and endocrine processes involved in glucoregulation. Some salient features of the model are:

i) it includes the effects of three hormones, insulin, glucagon, and epinephrine

ii) it focuses on the liver glucose system where short term (up to two hours) regulation of glucose metabolism occurs

iii) it incorporates dominant stages of liver enzyme dynamics using data drawn from published enzymological studies

iv) exercise is modeled as an increase in basal epinephrine secretion accompanied by increases in both muscle glucose uptake and muscle blood flow

Assumptions

The following assumptions have been applied to the metabolic control systems for blood glucose in the development of the model presented in this thesis:

1. all compartments are considered to be homogeneous and well-mixed so that the concentration of each species at any time is uniform throughout each compartment.
2. there is relatively rapid equilibriation between the blood plasma and tissue.
3. the central nervous system and the red blood cells impose a constant demand on the metabolic system (Campfield, 1973; Ganong, 1979).
4. the maximum storage capacity of liver glycogen is twice the basal level (Greenbaum, et al., 1971). The rate of glycogenesis is decreased to zero when glycogen stores reach full capacity.
5. glycogenolysis stops when glycogen stores fall below 2 1/2 to 3% of the maximum (Srinivasan, et al., 1970).
6. gluconeogenesis refers to the net difference between glycolysis and movement of carbon to G-6-P from noncarbohydrate precursors.
7. gluconeogenesis in the kidneys is negligible under the conditions considered. It is only important when blood glucose concentration falls

below 0.003 M.

8. the rate of gluconeogenesis is proportional to the concentration of gluconeogenic precursors, mainly lactate, and is altered within seconds of changes in substrate concentration (Walter, 1973; Newsholme and Start, 1973).
9. the dynamic responses of hepatic carbohydrate metabolism to variations in substrate levels result from movement across the cell membrane and from the metabolic consequences once the substrate is inside.
10. epinephrine concentrations in the portal and plasma compartments are assumed to be equal.
11. the effects of epinephrine on carbohydrate metabolism and hormone release occur independently of its circulatory effects (Porte and Robertson, 1973; Sacca, et al., 1979; Dietz, et al., 1980).
12. the concentrations of insulin and glucagon are higher in the portal compartment than in the plasma compartment, reflecting not only a greater dilution in the periphery, but also the fact that considerable amounts of the hormones are destroyed in the liver.
13. norepinephrine has no significant effect on liver glucose metabolism (Ganong, 1979; Sawin, 1969).
14. epinephrine alters insulin and glucagon secretion by acting on the pancreatic alpha and beta cells, possibly altering their sensitivity to blood glucose concentrations (Gerich, et al., 1973; Sawin, 1969; Chideckel, et al., 1977; Galbo, et al., 1977a, b).
15. transport of glucose across the hepatic cell membrane is an equilibrium process.
16. renal excretion of glucose is assumed to be of little importance under

conditions considered. Renal excretion would become a factor if blood glucose exceeded 0.01 M (180 mg%) for an extended period of time (Ganong, 1979).

17. there is no input of glucose from the gut during the conditions considered other than the oral glucose tolerance test.
18. the increased muscle uptake during exercise is due in part to increased blood flow to the muscle and in part to direct stimulation by epinephrine (Vranic, et al., 1976; Vranic and Berger, 1979).
19. skeletal muscles have no glucagon receptors. The inhibition of muscle uptake by glucagon is an indirect effect, resulting from glucagon stimulated increases in FFA motabolism (Exton and Park, 1972).
20. FFA do not play a significant role in hepatic glucose regulation (Newsholme, 1976; Cahill, et al., 1959).
21. uptake of glucose by adipose tissue during the conditions considered is negligible (Newsholme and Start, 1973).
22. insulin acts as a permissive agent to peripheral uptake (Srinivasan, 1969; Cramp and Carson, 1979).
23. the dynamics of the formation and breakdown of the enzyme substrate complexes are so rapid that they do not contribute to the overall dynamics of glucose uptake and production, which are in turn dominated by the much slower velocity of transfer of mass between pools (Bergman and El-Refai, 1975).

Model Structure

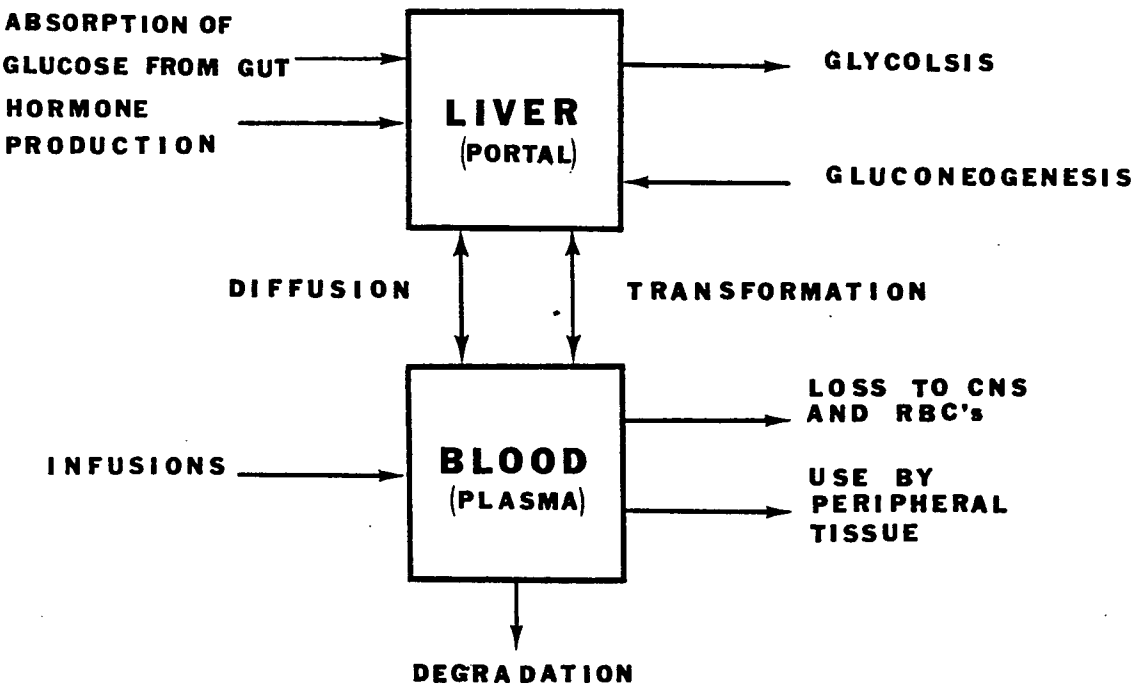
The model of glucose metabolism presented here includes two compartments and six chemical species; glucose, glucose-6-phosphate (G-6-P), glycogen, insulin, glucagon, and epinephrine (Fig.14). Glucose, insulin, glucagon, and epinephrine are found in both the portal and the plasma compartments, G-6-P and glycogen in only the portal compartment.

Assuming the epinephrine concentration in the portal and plasma compartments are equal leads to a mathematical description of the system which includes eight interdependent differential equations. The equation for each species was derived as a function of all sources and sinks affecting its level, following the principle

Rate of accumulation	= input flow rate	- output flow rate	+ Generation or production	- degradation or consumption

The input and output rates for glucose, G-6-P, and glycogen include functions for the rates of mass flux between these species (Appendix b). The enzymes considered to govern these reactions are hexokinase, glucokinase, glycogen synthetase, glycogen phosphorylase, and glucose-6-phophate. These enzymes catalyze the reversible reactions that are believed to be resonsible for the regulation of glucose uptake and release (Newsholme and Start, 1973).

The functions describing the rates of flux between species are in terms of the kinetic reaction mechanisms of the governing enzymes. The kinetic relationships for the enzymes, except glycogen phosphorylase, are expressed as Michaelis-Menten type of order 1 (Fig.15). The more complex



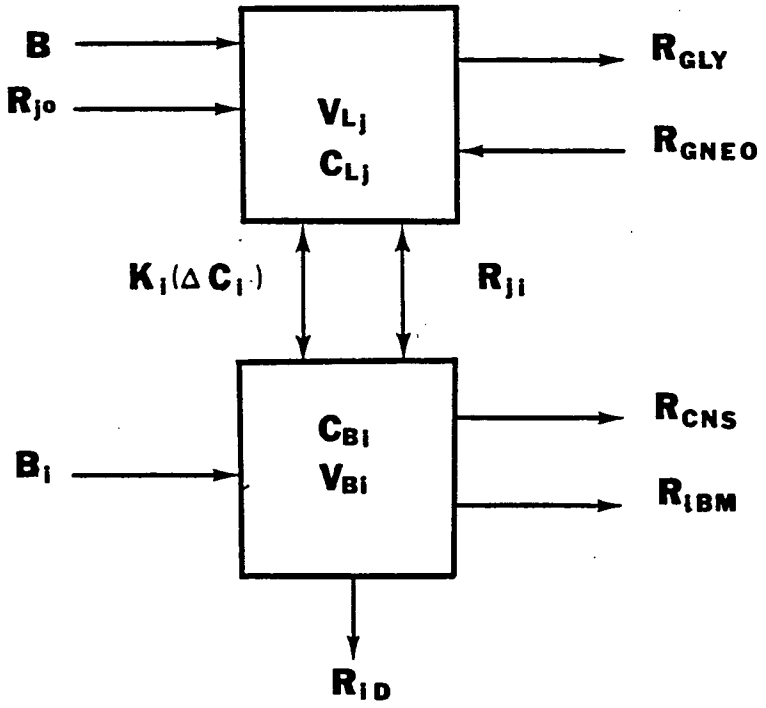


Figure 14. Model configuration

mechanism used for phosphorylase was proposed by London (1966) to account for the dependence of the enzyme's activity on AMP concentrations (Appendix B).

$$d[S]/dt = Vm[S]/([S] + Km)$$

d[S]/dt = rate of unidirectional substrate conversion (m/l^3t)
[S] = substrate concentration (m/l^3)
Vm = maximum reaction velocity ($1/t$)
Km = kinetic constant (m/l^3)

Figure 15. Michaelis-Menten kinetics

The effects of the hormone and substrate concentrations on the reaction mechanisms are included as threshold values for enzyme activity. The threshold values differ in the periphery and the liver because of the different action sites of the hormones.

Systems Equations

The equations used in the simulation are summarized in Appendix B.

The volume of distribution for the hormones and glucose species were assumed to be equal in each compartment (Levine, et al., 1950). The portal compartment includes the liver, hepatic portal vein, pancreas, and the rest of the splanchnic circulation, while the plasma compartment includes the hepatic artery and the remainder of the vascular system. The peripheral tissues include the insulin dependent tissues not included in the portal compartment.

The proposed model equations were written by considering material balances for each species. The equations are similar to those developed by Cramp and Carson (1979) modified to include the effects of epinephrine and exercise on glucoregulation.

Plasma Glucose:

$$Vb[dC1b/dt] = -kcns - K1(C1b-C11) - k1C1b + R21 - R1bm$$

The major pathways by which glucose exits from the plasma compartment are:

1) oxidation by the central nervous system (CNS)

The CNS presents a constant demand on the metabolic system. The rate of glucose utilization by these tissues is constant at approximatly 80 mg/min independent of plasma glucose concentrations (Cahill, et al., 1966).

2) use by the insulin dependent tissues

In the model the uptake of glucose by muscle, adipose tissue, and the other insulin dependent tissues is lumped into one function for peripheral glucose uptake. Insulin acts as a permissive agent with a threshold that must be exceeded before the transport process is initiated. Above this threshold, transport is controlled by enzyme dynamics (Newsholme and Start, 1973; Cramp and Carson, 1979).

At very high levels of insulin the hormone acts as a "multiplier" of glucose concentration, tending to move the reaction towards its maximum velocity. The indirect effect of glucagon is also included as a reduction in the enzymatic reaction gain (Cramp and Carson, 1979).

The stimulatory effect of exercise on muscle uptake was included in the model as a multiplicative factor of uptake and blood flow. Values of

uptake and blood flow from the literature were used to establish the changes that occurred and were then adjusted to fit the model.

3) transfer to the portal compartment

The uptake of glucose by the liver is an equilibrium process dependent on the concentration gradient of glucose. It is affected by the rate of conversion of glucose to G-6-P because the faster the rate the lower the liver glucose concentration.

Portal Glucose:

$$V1[dC11/dt] = k1C1b + K1(C1b-C11) - R12$$

Glucose-6-Phosphate:

$$V1[dC2/dt] = Rgneo - Rgly + R12 - R21 - R23 + R32$$

The glucose that enters the liver is quickly phosphorylated to G-6-P. G-6-P is the major species in the liver compartment, all glucose entering and leaving the liver passes through G-6-P (Newsholme and Start, 1973).

G-6-P is produced from noncarbohydrate precursors through gluconeogenesis. The rate of gluconeogenesis is regulated by portal levels of epinephrine, glucagon, and insulin (Exton, 1976). Near basal levels of glucagon have been shown to stimulate gluconeogenesis when insulin levels are suppressed at or below basal levels (Jennings, et al., 1977). When the hormone threshold conditions are met the rate of gluconeogenesis is modeled as a time dependent linear function that doubles its initial value in approximately one hour (Jennings, et al., 1977).

The glycolytic term in the G-6-P equation reflects the net effect of the glycolytic and oxidative pathways which utilize G-6-P. Basal levels of

glucagon rapidly inhibit glycolysis in the presence of basal levels of insulin (Pilkis, et al., 1976). Insulin levels above basal antagonize the actions of glucagon and epinephrine on glycolysis and gluconeogenesis, but has little effect in the absence of these agents (Claus and Pilkis, 1976; Felui, et al., 1976; Pilkis, et al., 1975).

The reduction in the glycolytic term was adjusted to reflect the inhibition of the glycolytic and not other oxidative pathways when the hormone threshold levels were met.

Glycogen:

$$V12[dC3/dt] = R23 - R32$$

The process of laying down glucose as hepatic glycogen is under both enzymatic and hormonal control. The liver cells, however, have a finite ability to store glycogen and once they are physically replete no further glycogen conversion can occur. This saturation effect results in glucose and its glycolytic products being diverted along other metabolic pathways. This effect is incorporated in the model with the glycogen saturation concentration being set at twice the initial condition (Greenbaum, et al., 1971).

Glucagon also mediates the conversion of glycogen to G-6-P and the reverse reaction. Although this is primarily under the control of insulin, when glucagon is elevated above a threshold value the G-6-P to glycogen conversion is inhibited and the reaction sequence is only restored once glucagon is returned below this critical level (Ross, et al., 1967).

The other effects of hormones on the enzymatic reactions are modeled as switching effects. Both in the liver and in the periphery, insulin and

glucagon act as permissive or inhibitory agents of reactions depending on whether the other threshold values are exceeded.

Plasma Insulin:

$$[dC'5b/dt] = -K5/Vb(C'5b-xC'5l) - R5D$$

Portal Insulin:

$$[dC'5l/dt] = R5o + K5/Vb(C'5b-xC'5l) + R5$$

Plasma Glucagon:

$$[dC'4/dt] = K4/Vb(xC'4l-C'4b) - R4D$$

Portal Glucagon:

$$[dC'4l/dt] = R4o - K4/Vb(xC'4l-C'4b) + R4$$

Epinephrine:

$$[dC'6/dt] = R6o - R6D + R6$$

Insulin and glucagon are secreted by the pancreas into the portal compartment. Both hormones are released in response to the levels of portal glucose, the rate of change of the glucose concentration, and the levels of epinephrine.

Insulin is secreted in response to glucose concentration above basal level and positive rates of change of glucose levels. The sensitivity of insulin secretion to the rates of change of glucose persists regardless of the plasma glucose level (Foster, 1970).

Glucagon is antagonistic to insulin and is secreted in response to

hypoglycemia or negative rates of change of glucose levels. Again the response to the rate of change is present at all glucose levels.

The plasma concentrations of insulin and glucagon reflect the transfer to the blood compartment as well as the degradation that occurs in the liver.

The effects of epinephrine on insulin and glucagon secretion were incorporated into the model as switching effects on glucose dependent secretion. The modulation of hormone secretion by epinephrine was postulated to be affected by the portal glucose level (Gerich, et al., 1973).

The increased secretion of epinephrine during stress is largely under neural control. During physical activity extensive activation of the nervous system occurs (Galbo, 1977a; Hartley, 1975).

The neural stimulation of epinephrine secretion was modeled as an increase in basal secretion rates. Epinephrine was assumed to to be the linking factor between uptake and production. Increases of epinephrine levels prior to the start of exercise, as reported by Hartley, et al.(1972a), and Galbo and Holst (1976) is justifiable as "flight or fight" response priming the system for stress.

Data Used in the Model

In formulating this model the subject was considered to be a normal 70 kg individual with a liver mass of 1.5 kg. The hormonal and glucose distribution volumes were taken as 3.2 l in the plasma compartment and 1.6 l in the portal compartment.

The basal levels for the model are average normal values during fasting (Cramp and Carson, 1979) (Table 3).

Table 3. Steady state values for model variables

SPECIES	VALUE
C1b	0.005 (M)
C1l	0.005 (M)
C2	0.0003 (M)
C3	0.25 (M)
C'4b	0.32 (ug)
C'4l	0.32 (ug)
C'5b	30.0 (mU)
C'5l	30.0 (mU)
C'6	0.16 (ug)

The values for the model parameters were first obtained from results in the literature and were then refined by simulating experiments of glucose, insulin, glucagon and epinephrine IV loads. Threshold values for glucagon, epinephrine, insulin, and glucose were adapted from results from Genuth (1972), Turner, et al. (1971), Sokal (1966), Gerich, et al. (1973), Rizza, et al. (1979), Soman, et al. (1980), Srinivasan, et al. (1970), and Jennings, et al. (1977).

Data for non-linear insulin degradation (Table 4) were taken from Cramp and Carson, 1979).

Factors of blood flow rates for insulin delivery and peripheral uptake (Table 5) were estimated from data published by Wahren et al. (1975). Muscle was assumed to account for approximately 40% of the total insulin dependent peripheral tissues (Srinivasan, 1969). Increased blood flow

Table 4. Nonlinear insulin loss rate (from Cramp and Carson, 1979)

C'5b (mU)	R5D (mU/min)
0.0	4.0
86.0	6.3
112.0	7.3
128.0	15.7
150.4	39.8
176.0	61.3
217.6	93.7
230.6	115.0
272.0	174.0
291.0	227.2

Table 5. Factors for peripheral uptake during exercise at 30% Vo2 max

Duration of exercise (min)	Blood flow factor	Uptake factor
0	1	1
3	6.03	1.63
40	6.33	10.00
90	6.74	17.18
180	6.84	15.00
245	6.77	12.58

during exercise was assumed to reach its new plateau value in three minutes (Falls, 1968).

From the eight interdependent equations and the basal values, the differences of concentrations between time t and t+dt were calculated. Adding the concentration at time t and the difference in concentration between time t and dt gave the concentration at t+dt. The time increment was taken as 0.01 minute.

The program for the model was written in Fortran IV and solved on the VAX-11/780 system.

The data generated by the program were plotted using the Tektronics Graphics AGraph Program. The Fortran computor programs are available from the Biomedical Engineering Program office.

RESULTS AND DISCUSSION

Simulation of Disturbances from Normal Resting Metabolism

The validity of the proposed model has been tested by simulating the effects of various experimental test stimuli on normal metabolism. These simulations were then compared with averaged data from several test subjects reported in the literature. Agreement between the simulated and experimental data was qualitative. No sophisticated curve fitting techniques were employed.

The ability of the model to reproduce responses to different disturbances during resting conditions was used to establish the physiological basis of the model. If the underlying theory is correct, the behavior of the model will approximate empirical behavior.

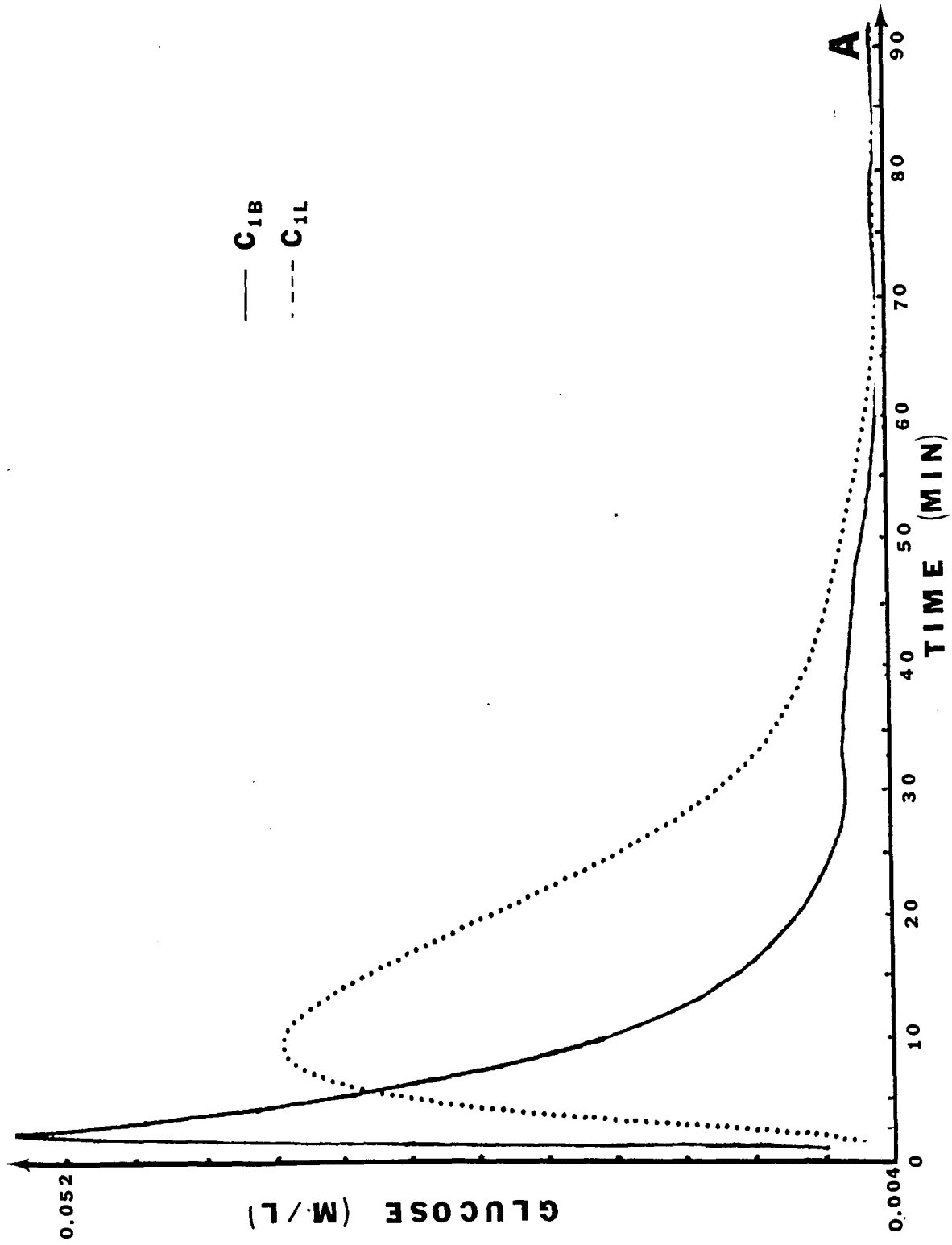
The model has reproduced fairly well the peak values of glucose and the time-to-peak during the different disturbances, although the differences between simulation and experimental results are larger at the end of the response. The results are good considering the preliminary stage of the modeling effort reported here.

The results, shown in figures 16 trough 19, indicate that the model was flexible enough to reproduce clinical observations of glucose, insulin, and glucagon infusions.

Figures 20 and 21 show the simulated responses to a 50 gm oral glucose load resulting from different input functions. Using the input function from Cramp and Carson (1979), that has a maximum rate of absorption through the gut of 0.004 M/min, results in insulin and glucagon levels that compare

Figure 16. Simulation of intravenous glucose injection of 0.5 g/kg bodyweight administered over a two minute period showing plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C), and epinephrine (D) response

Dose rate, B = 0.03 M/min


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.052
0.004
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

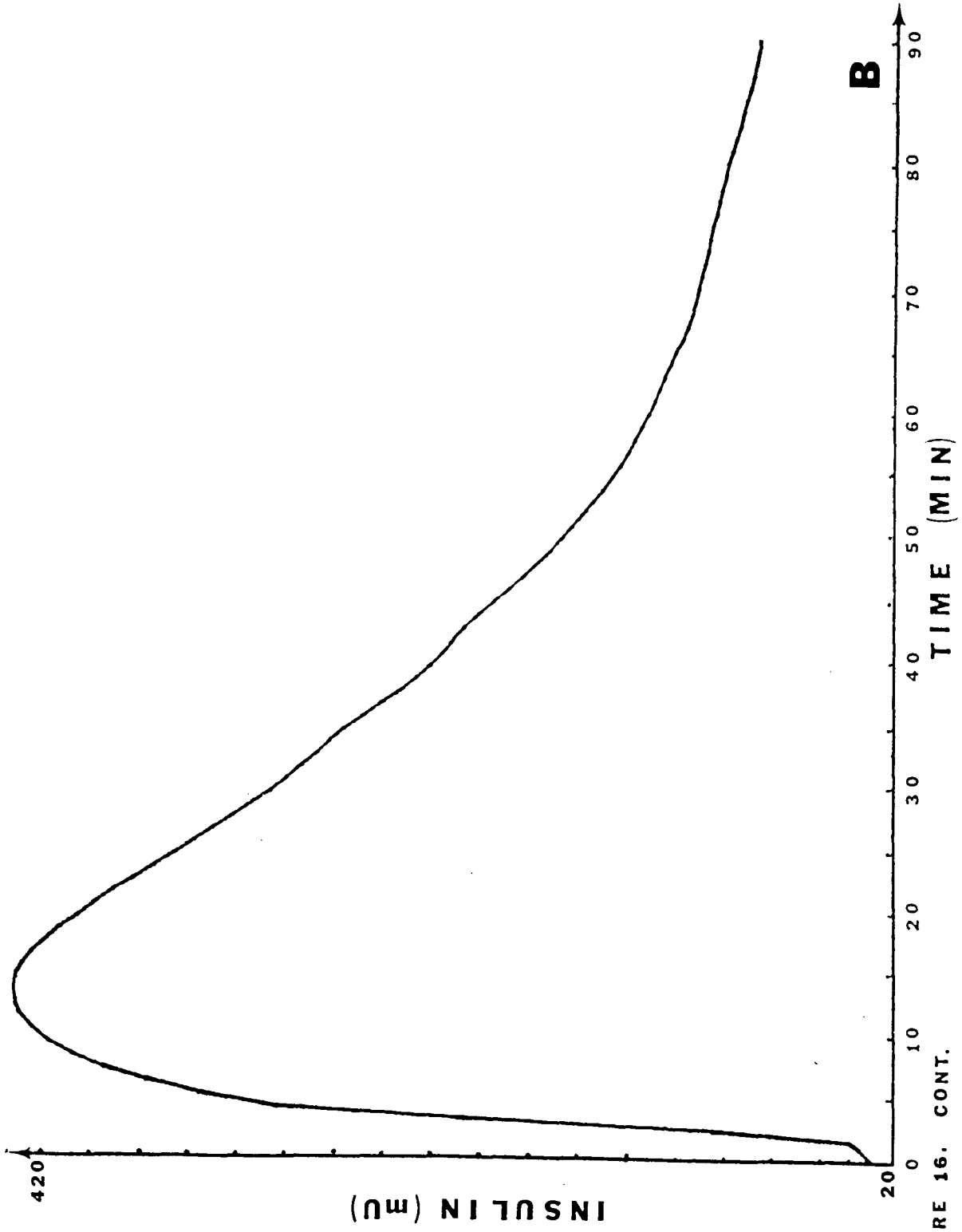


FIGURE 16. CONT.

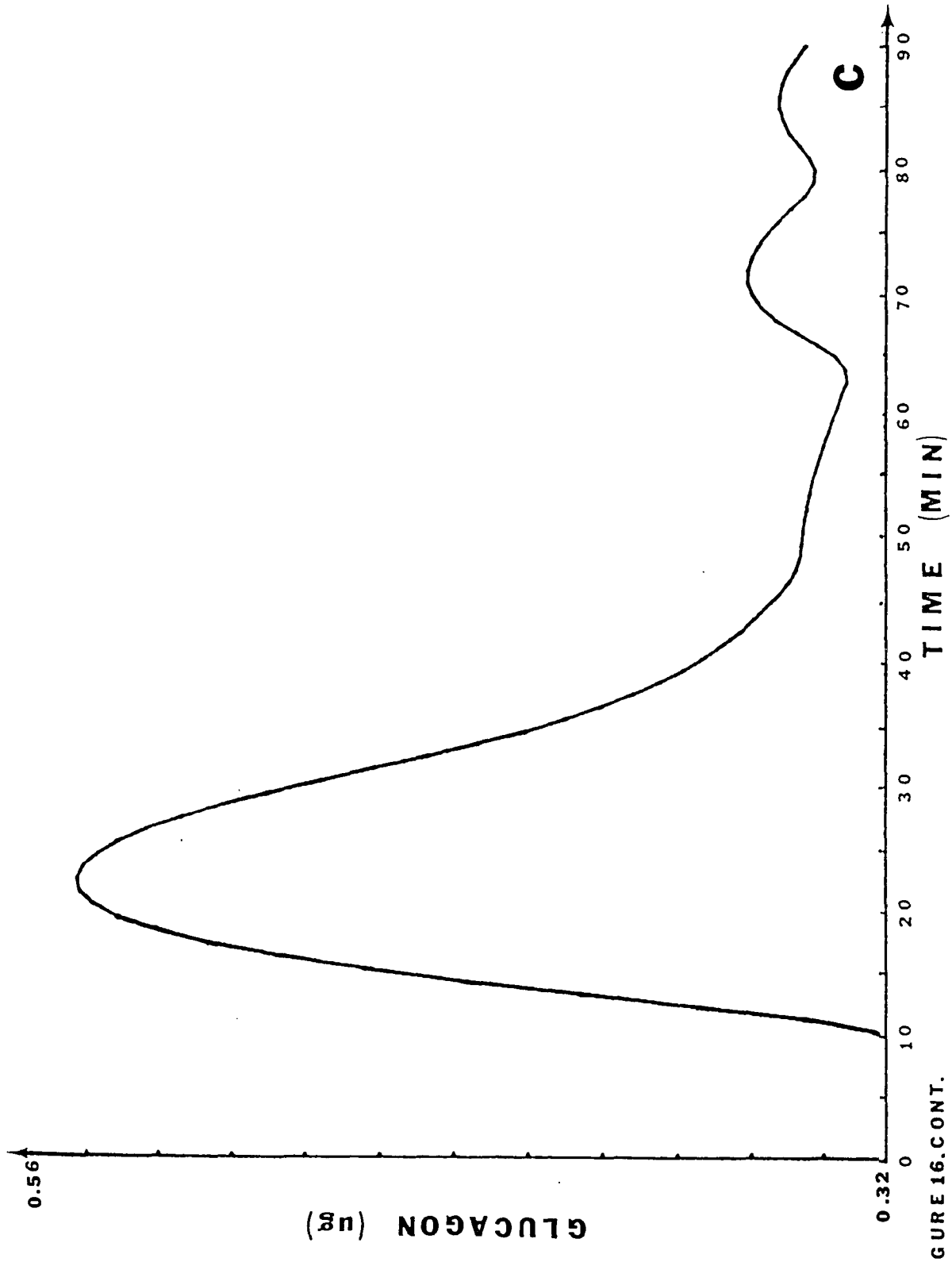


FIGURE 16.CONT.

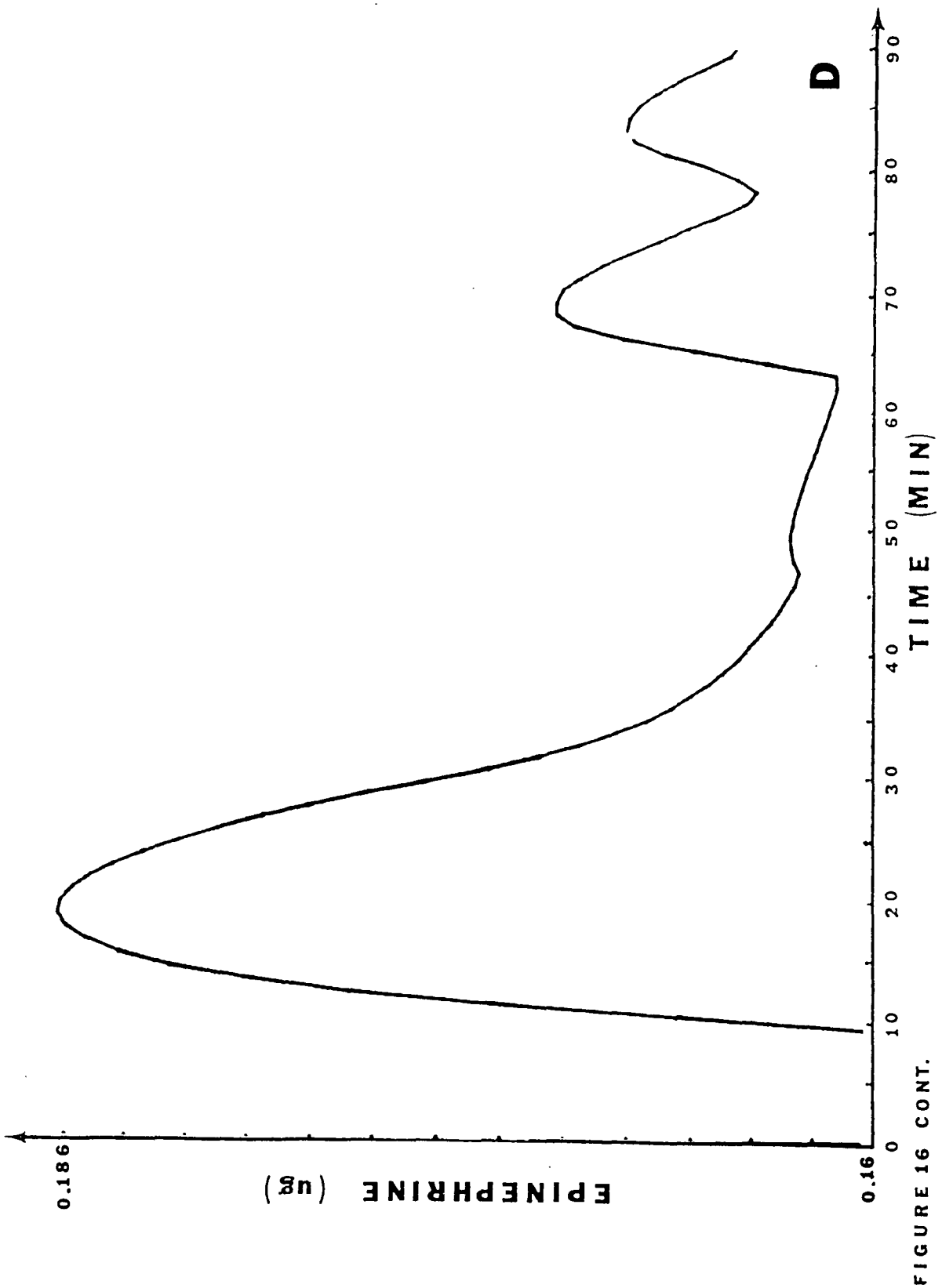
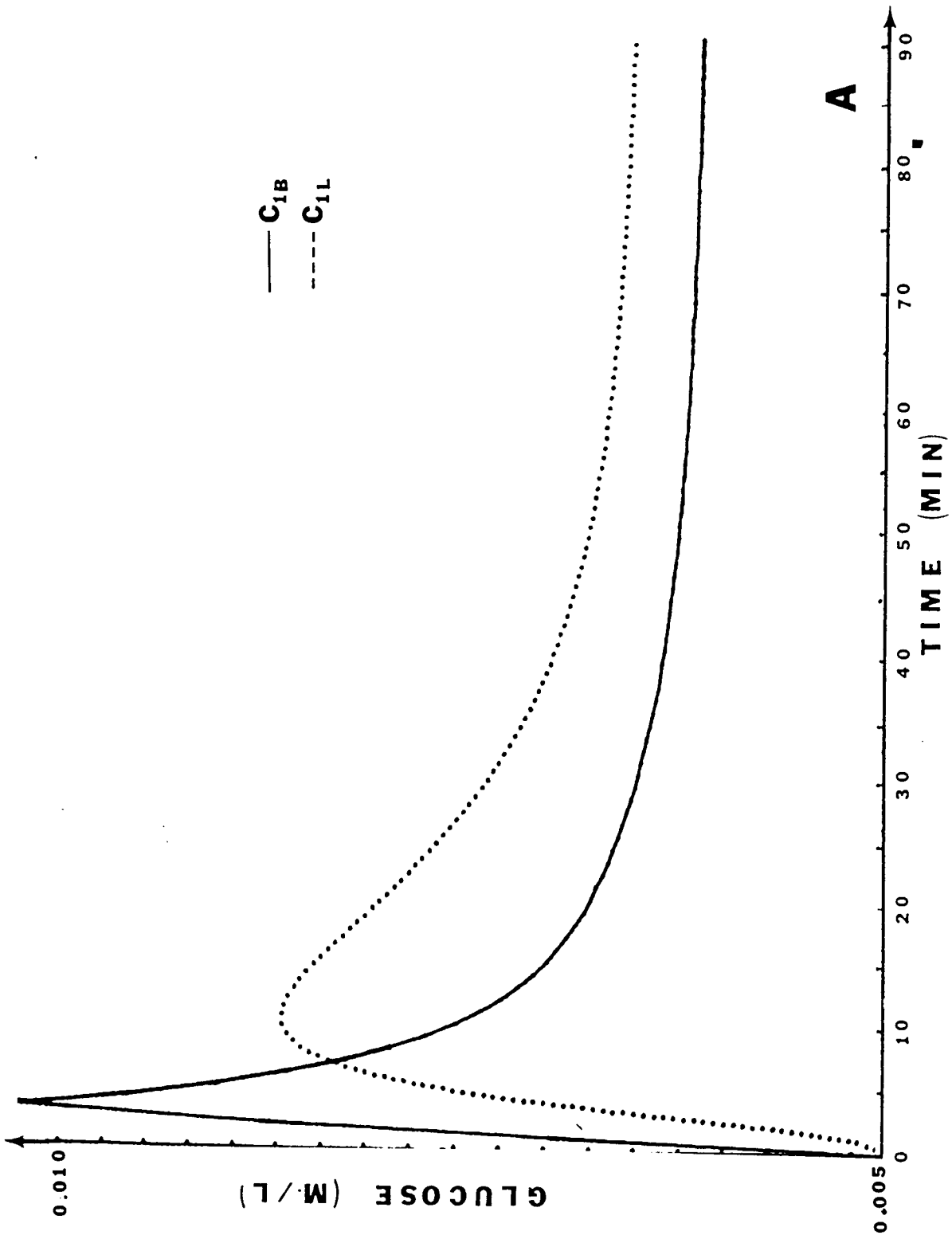


FIGURE 16 CONT.

Figure 17. Simulation of systems response to a primed glucose infusion showing plasma and portal glucose (A), plasma insulin (B), glucagon (C), and epinephrine (D)

$$\text{Dose rate, } B = \frac{0.00434\ t^{3}}{0.00043\ t^{3}} \quad \text{M/min}$$


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.010
0.005
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

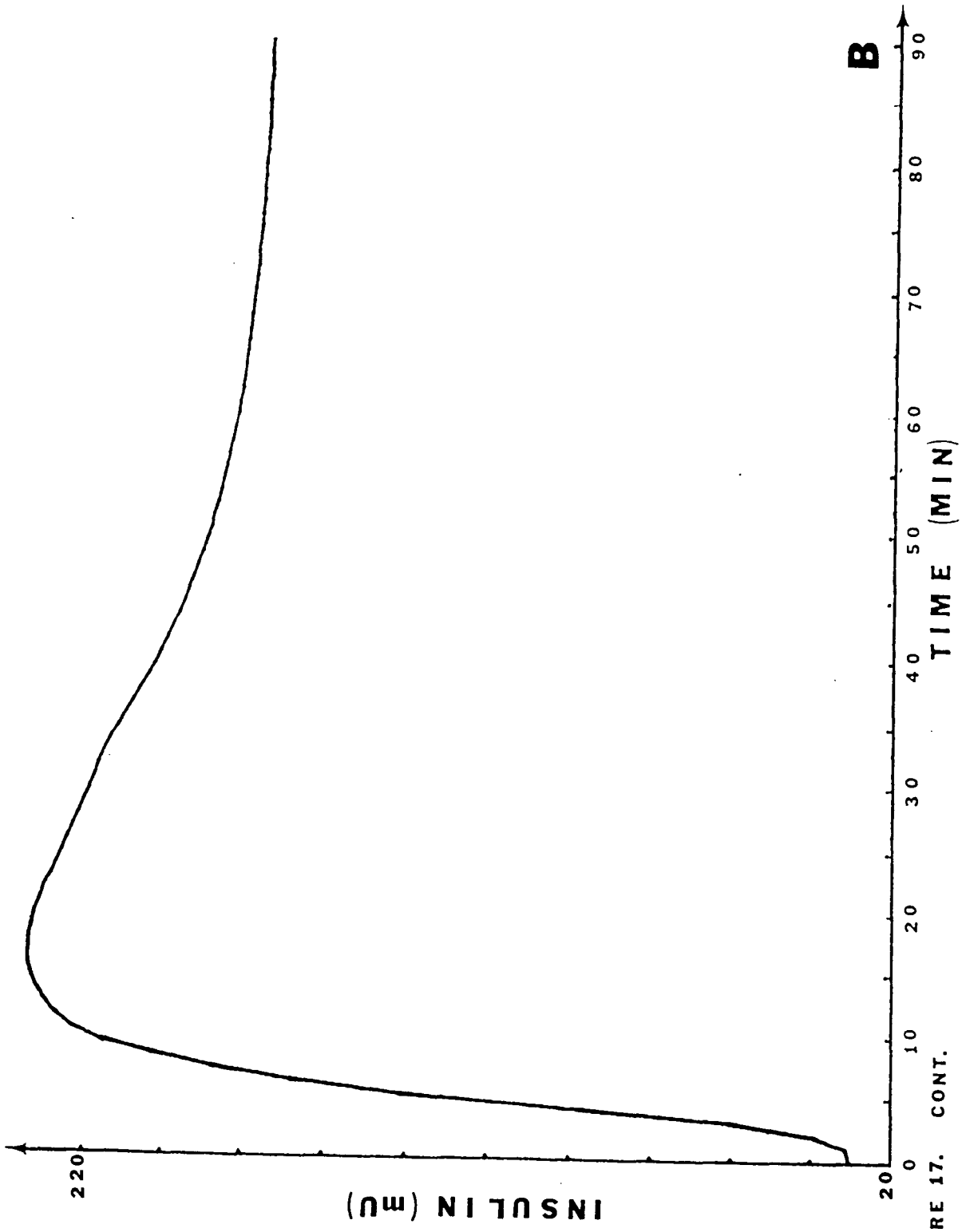


FIGURE 17. CONT.

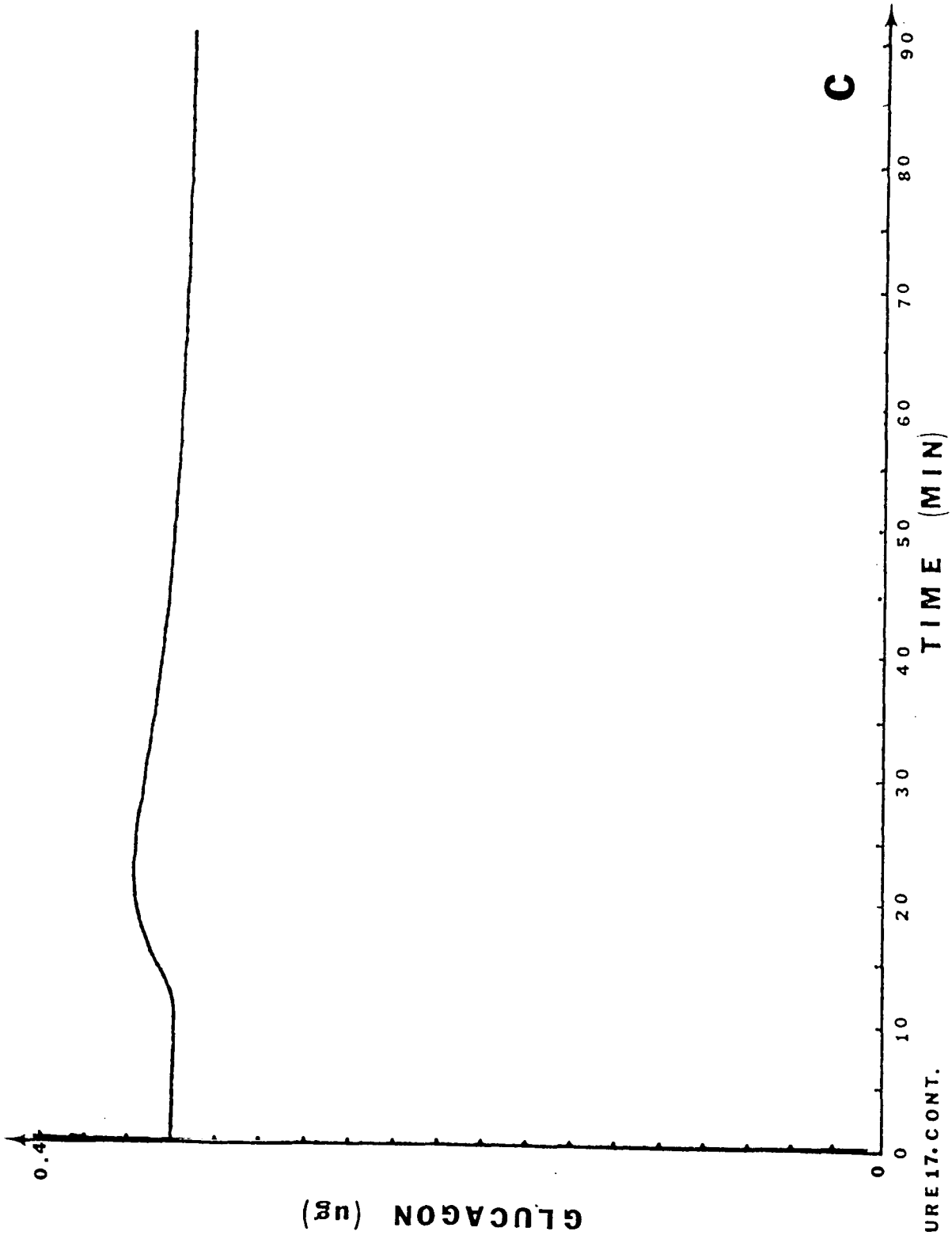


FIGURE 17. CONT.

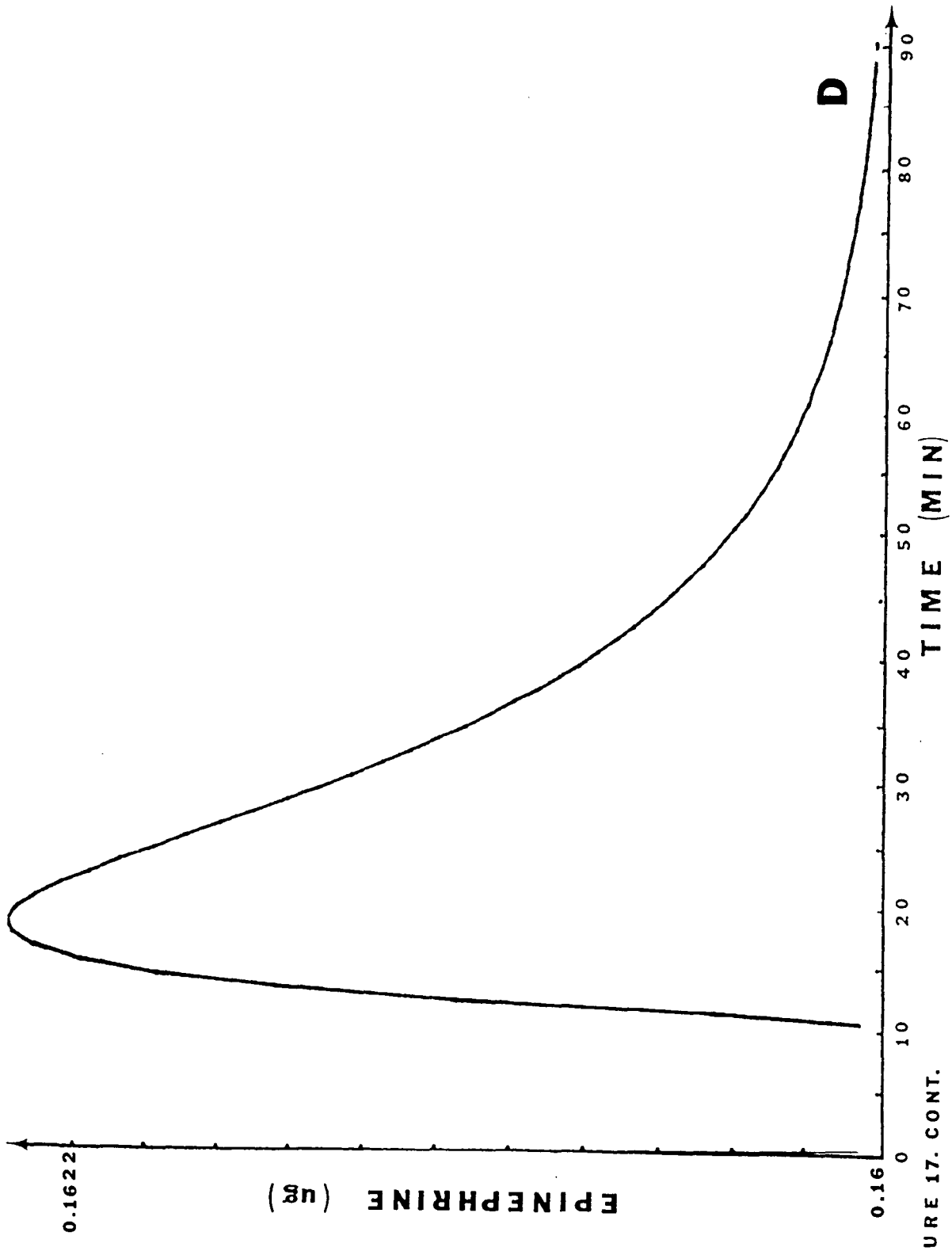
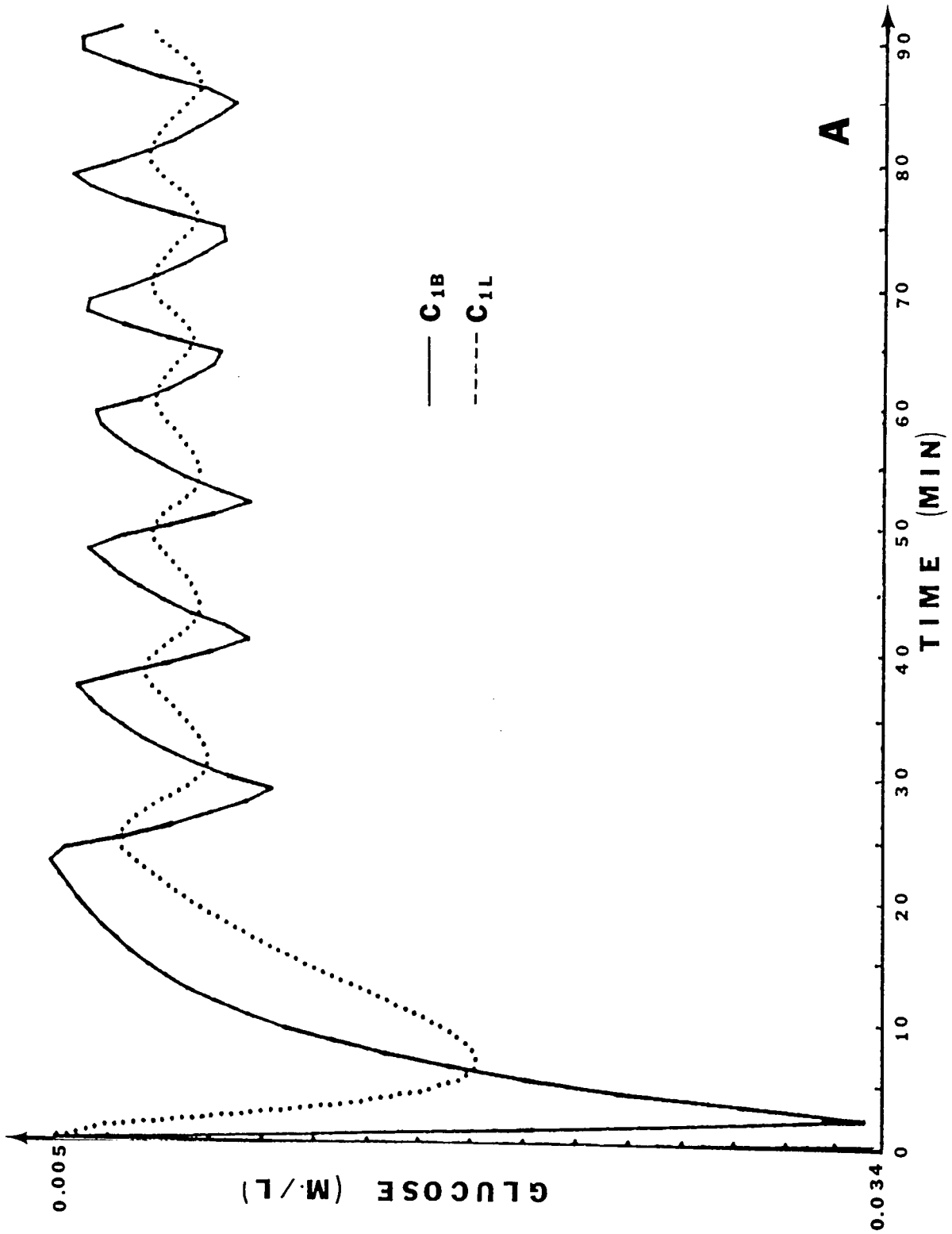


FIGURE 17. CONT.

Figure 18. Simulation of intravenous insulin injection of 0.1 U insulin/kg bodyweight showing plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C), and epinephrine (D) response

Dose rate, B = 7000 mU/min


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.005
0.034
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

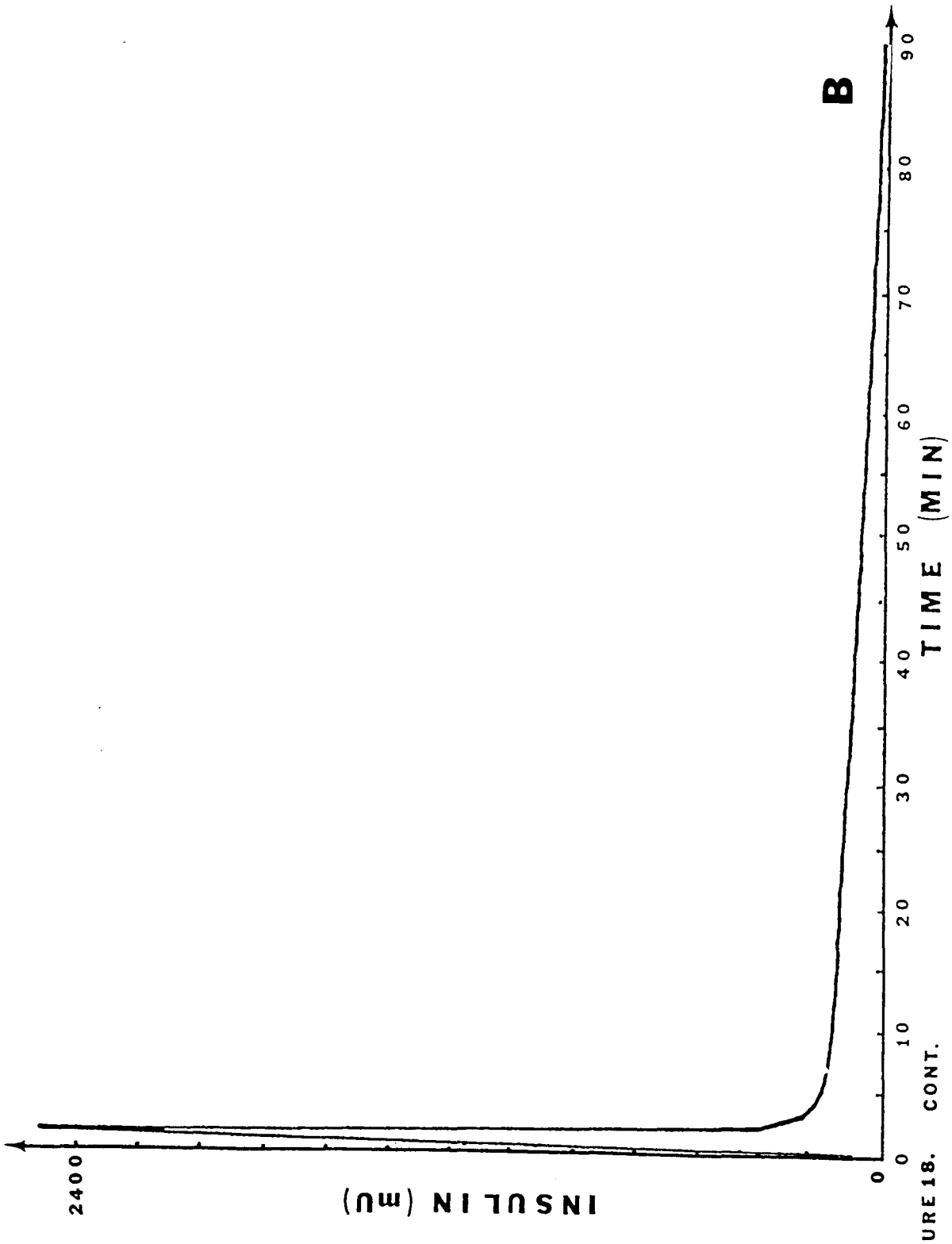


FIGURE 18. CONT.

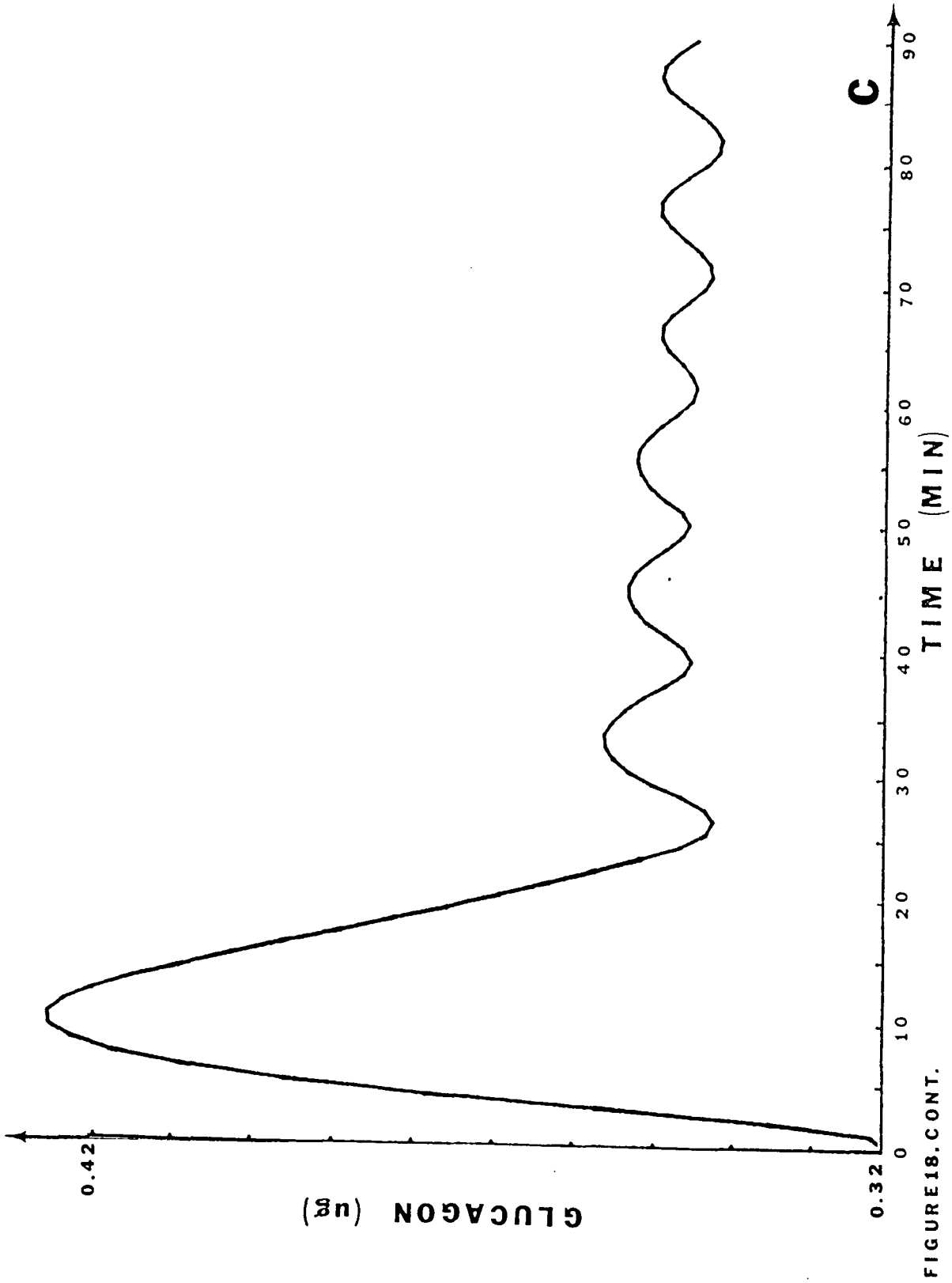


FIGURE18.CONT.

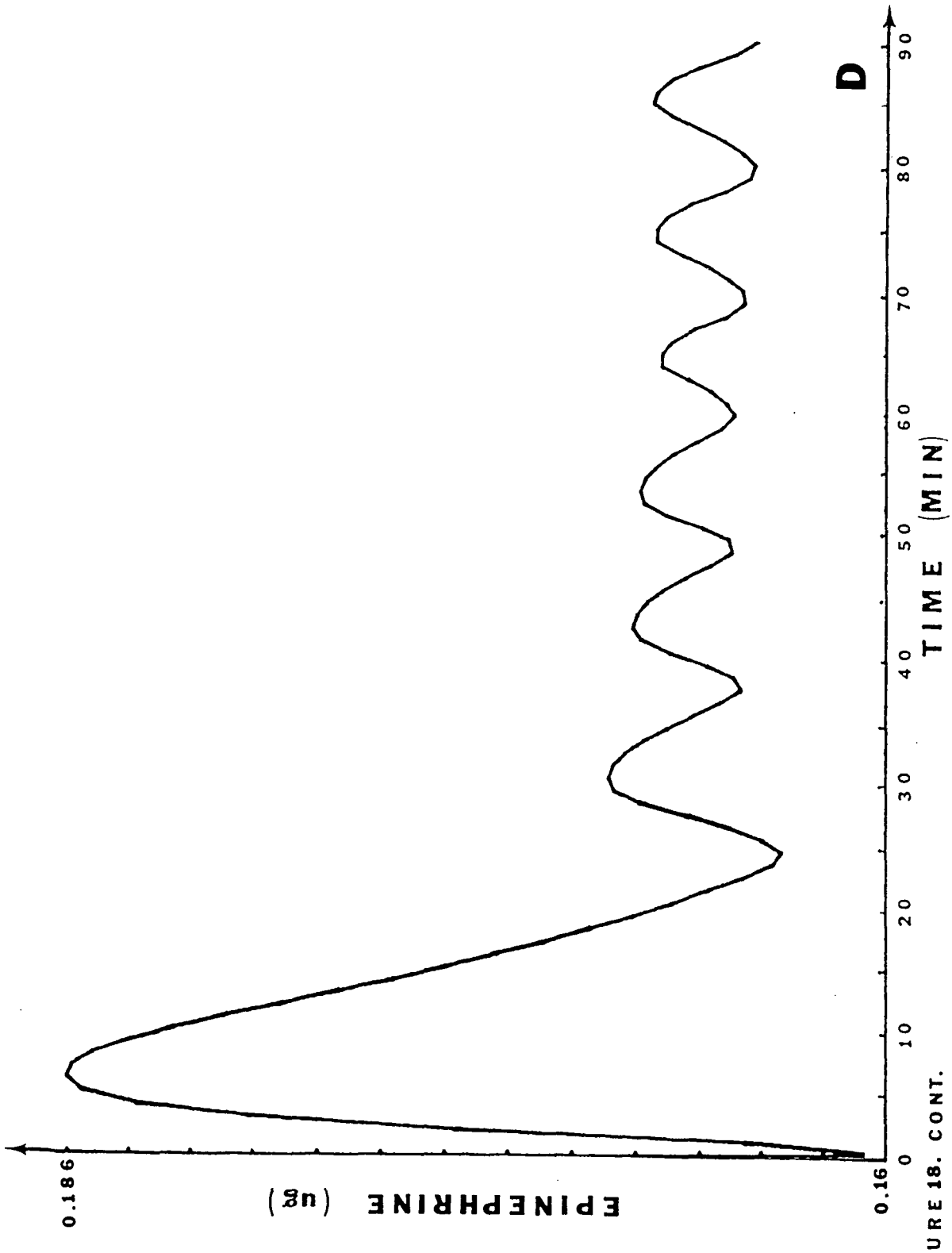
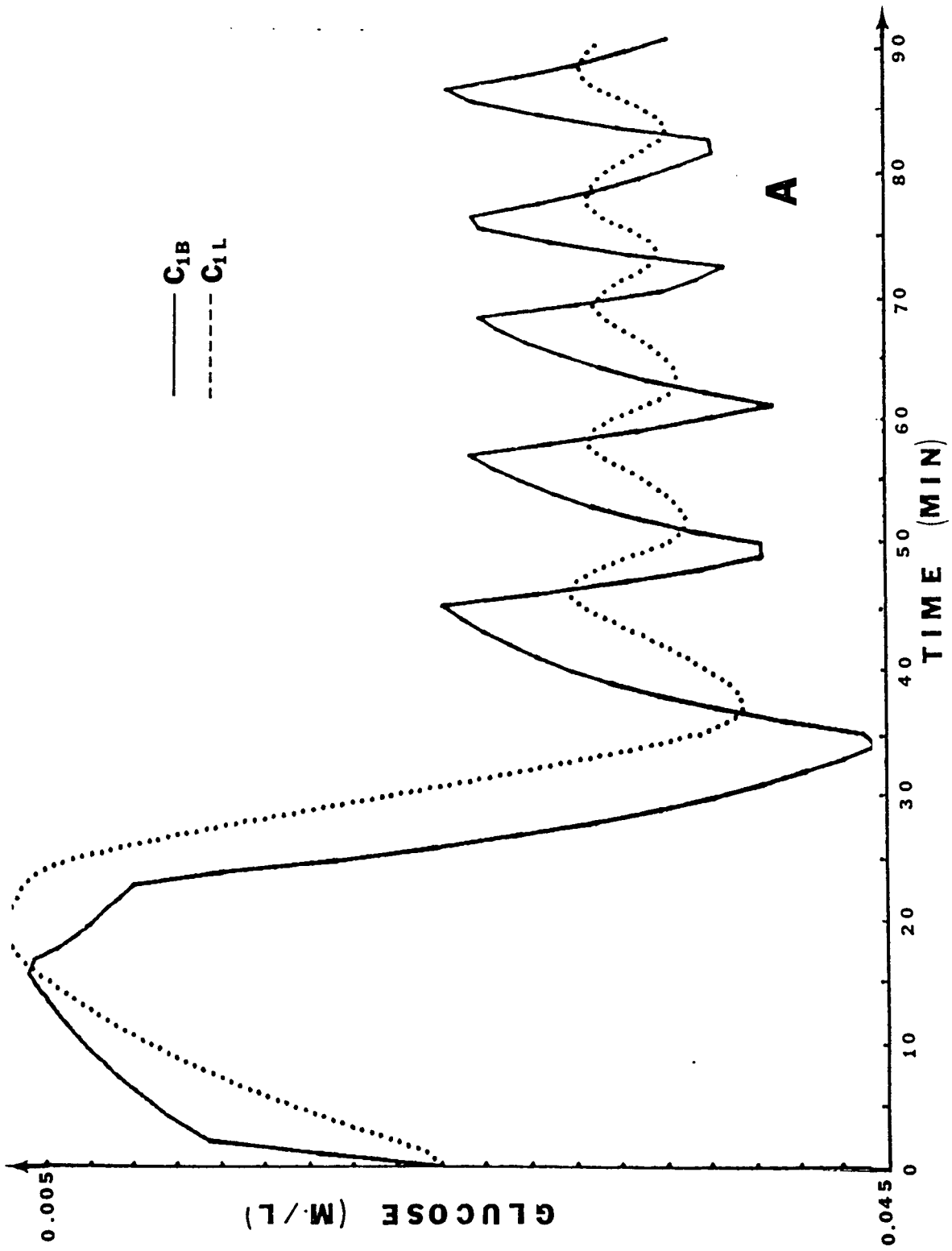


FIGURE 18. CONT.

Figure 19. Response of plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C), and epinephrine (D) during simulation of intravenous glucagon injection of 0.25 mg/min administered over one minute period

Dose rate, B = 250 ug/min


C_{1B}
C_{1L}
A
GLUCOSE (M/L)
0.005
0.045
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

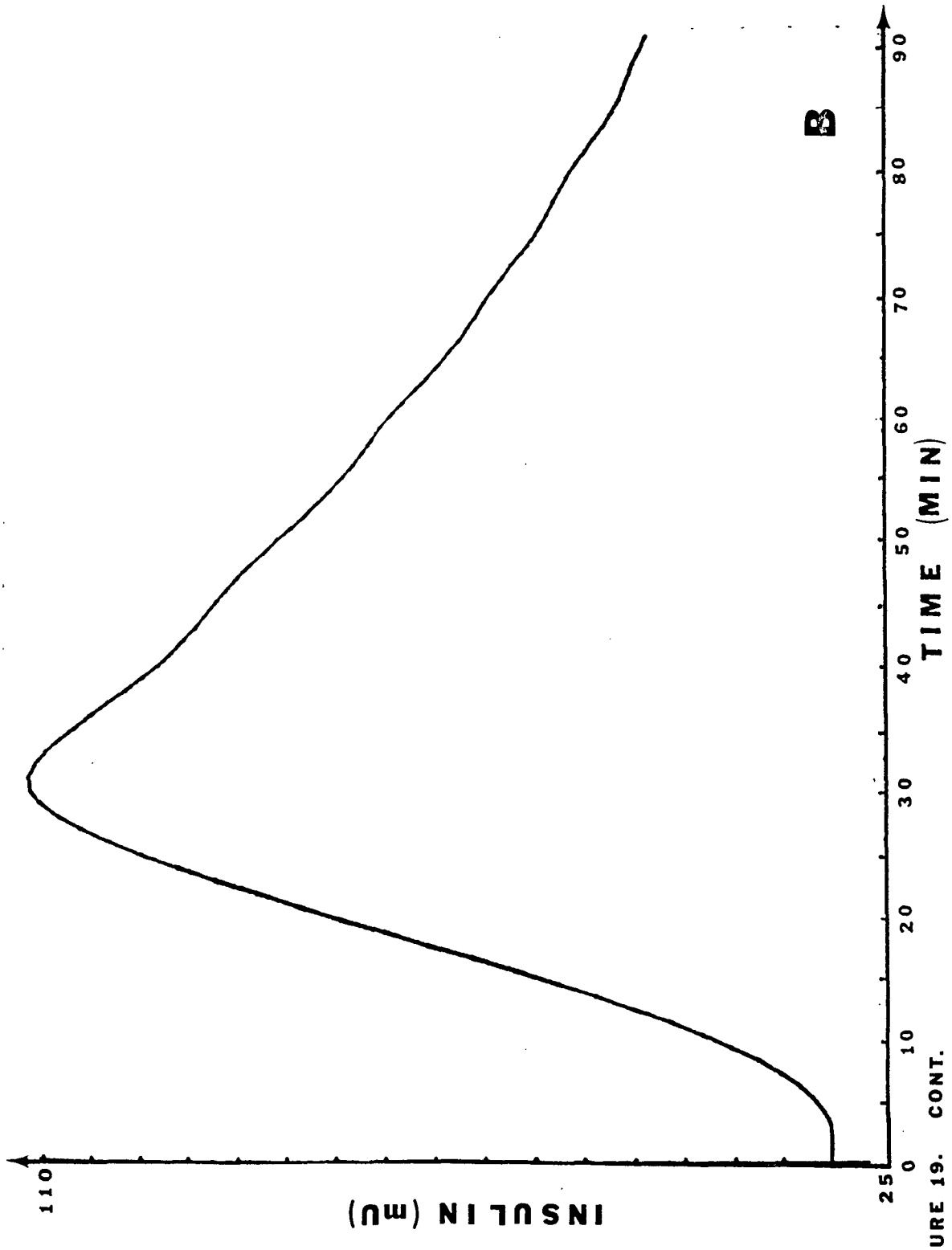


FIGURE 19. CONT.

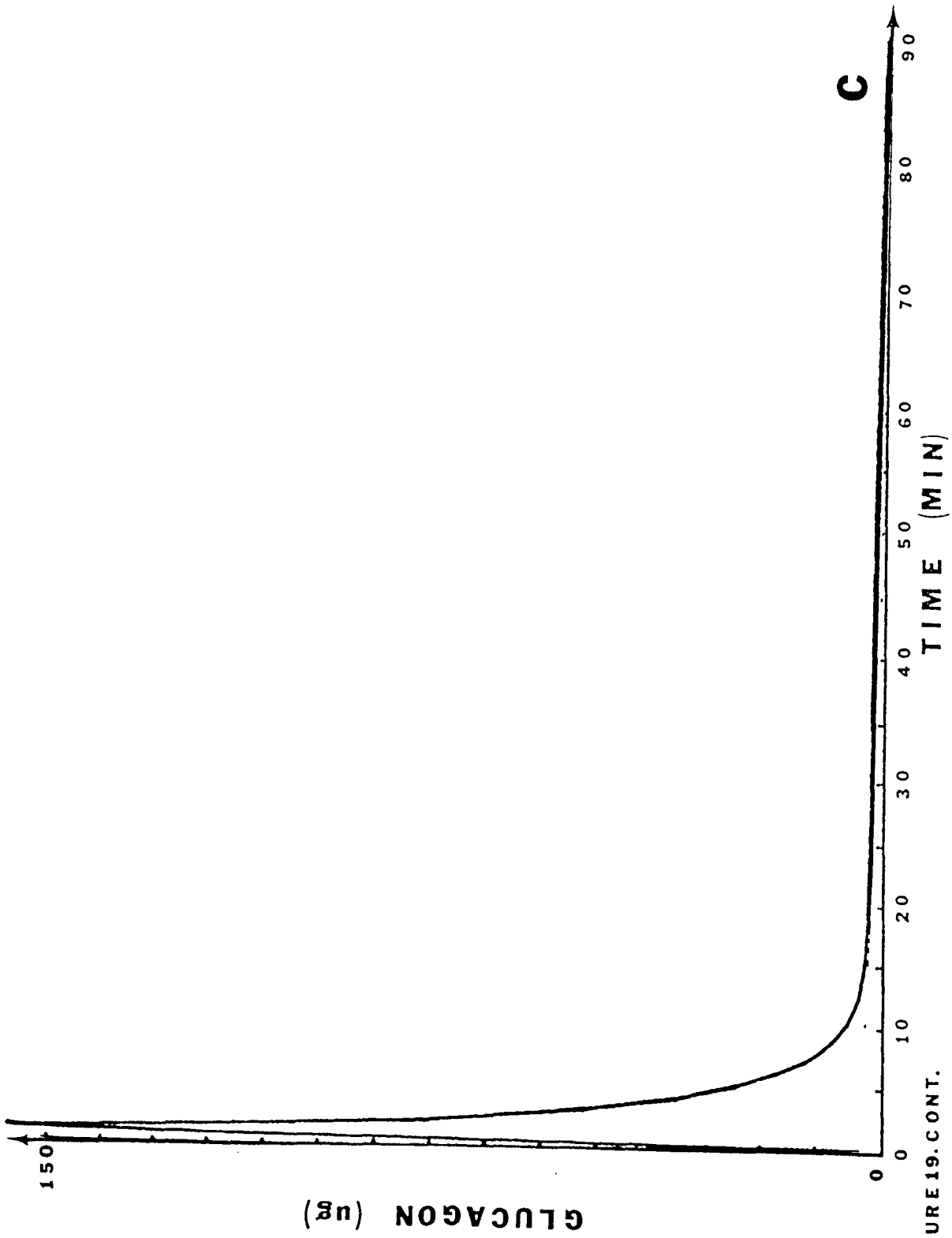


FIGURE 19. CONT.

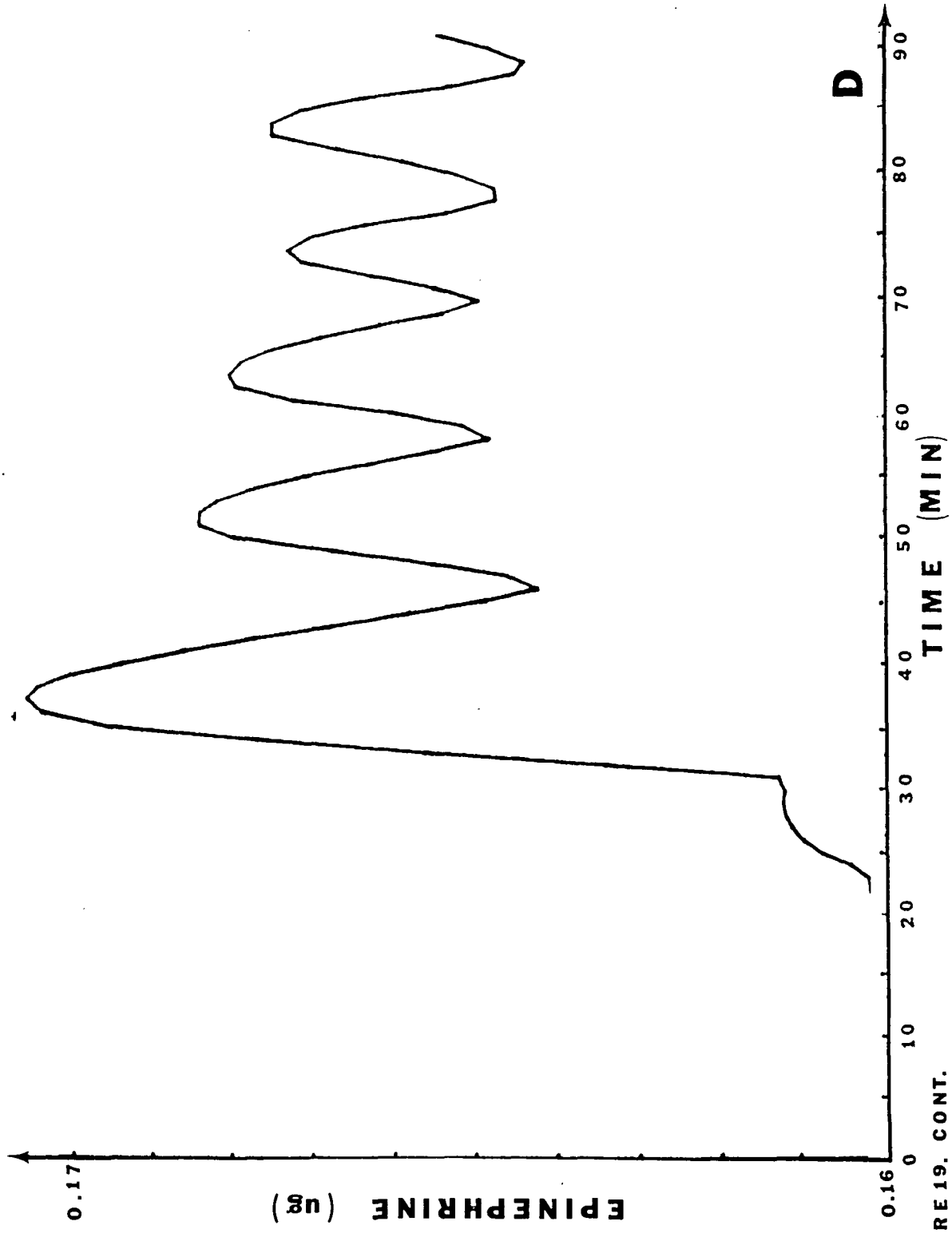


FIGURE 19. CONT.

favorably with the curves reported by Cramp and Carson (1979) and experimental data (Bratusch-Marrain, et al., 1980; National Diabetes Data Group, 1979) (Fig. 20). However, the glucose response at this input level is almost twice that reported by Carson and Cramp but does fit into the physiological ranges reported by Bratusch-Marrain, et al. (1980), the National Diabetes Group (1979), and Sartor, et al. (1980).

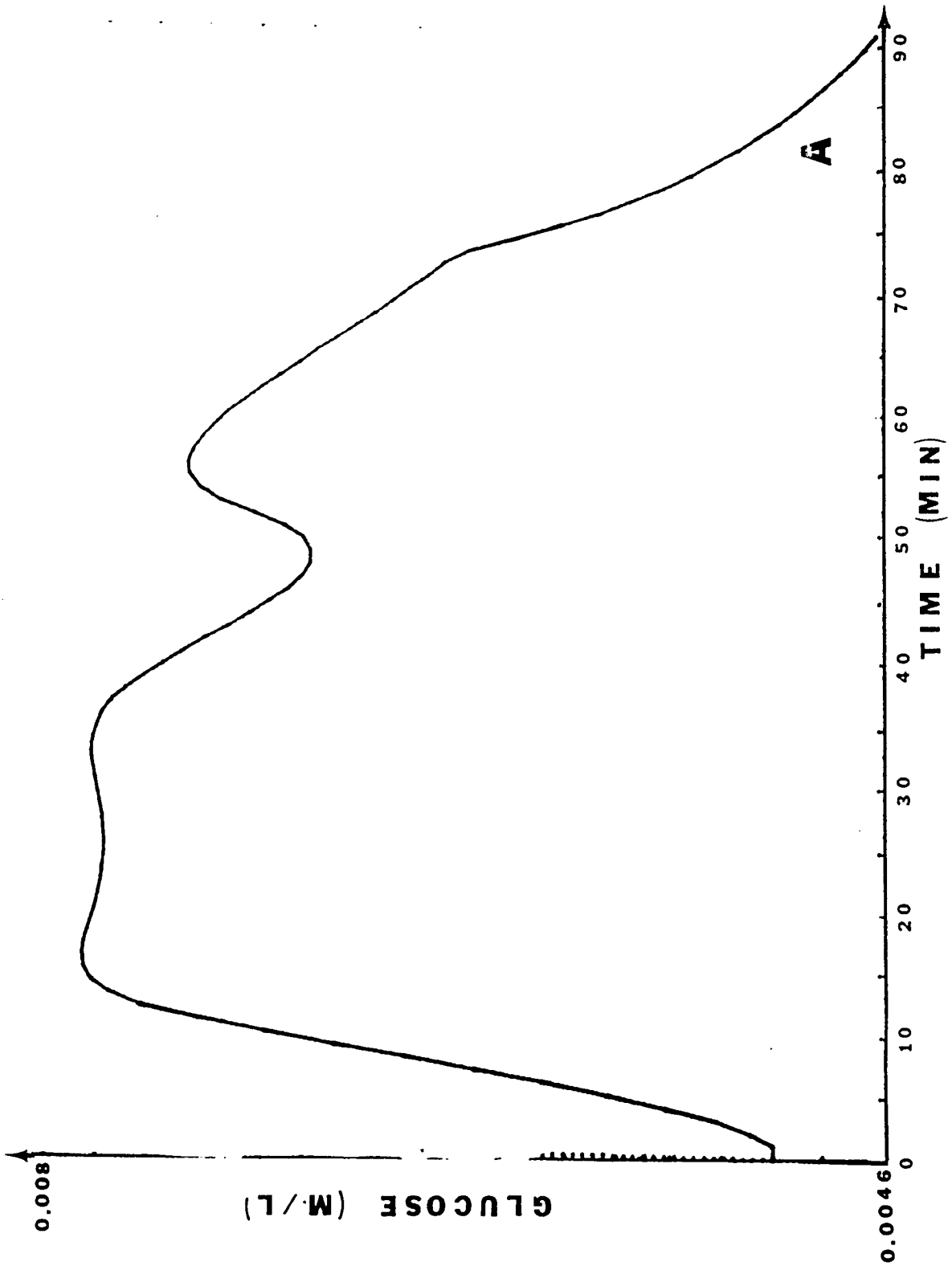
The simulation results from an oral glucose load using a maximum absorption rate of 0.0026 M/min are shown in Figure 21. This input function gives a glucose response that results in a lower level of peak glucose that is similar to that reported by Carson and Cramp (1979) but the time to peak is 15 minutes earlier.

The model's response to the oral load is not as satisfactory as those from the other simulations but much of the problem probably lies with the input function, particularly since the response reported by Carson and Cramp could not be reproduced using their equations and input function. The input function is only an approximation of digestive glucose uptake. A better function for the rate of absorption through the gut may generate a response that is more physiologically accurate. However, the primary reason for the oral glucose simulation was to illustrate that the model could respond fairly well to a variety of different stimuli and not just to any one stimulus in particular.

Figure 22 shows the simulation of a 6 ug/min IV infusion of epinephrine for one hour. The model yields an almost linear increase in glucose concentration in response to the infusion. According to the results reported in the literature the response is not quite linear (Porte, et al., 1966; Altszuler, et al., 1967; Chideckel, et al., 1977; Gerich, et al.,

Figure 20. Simulation of 50 gm oral glucose load where the maximum rate of glucose absorption through the gut is 0.0026 M/min showing response of plasma glucose (A), plasma insulin (B), and plasma glucagon (C)

$$\text{Dose rate, } B = \begin{cases} 0.0026 & t \leq 30 \\ 0.0026 * e^{-0.1(t-30)} & t > 30 \end{cases} \quad \text{M/min}$$


A
GLUCOSE (M/L)
0.008
0.0046
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

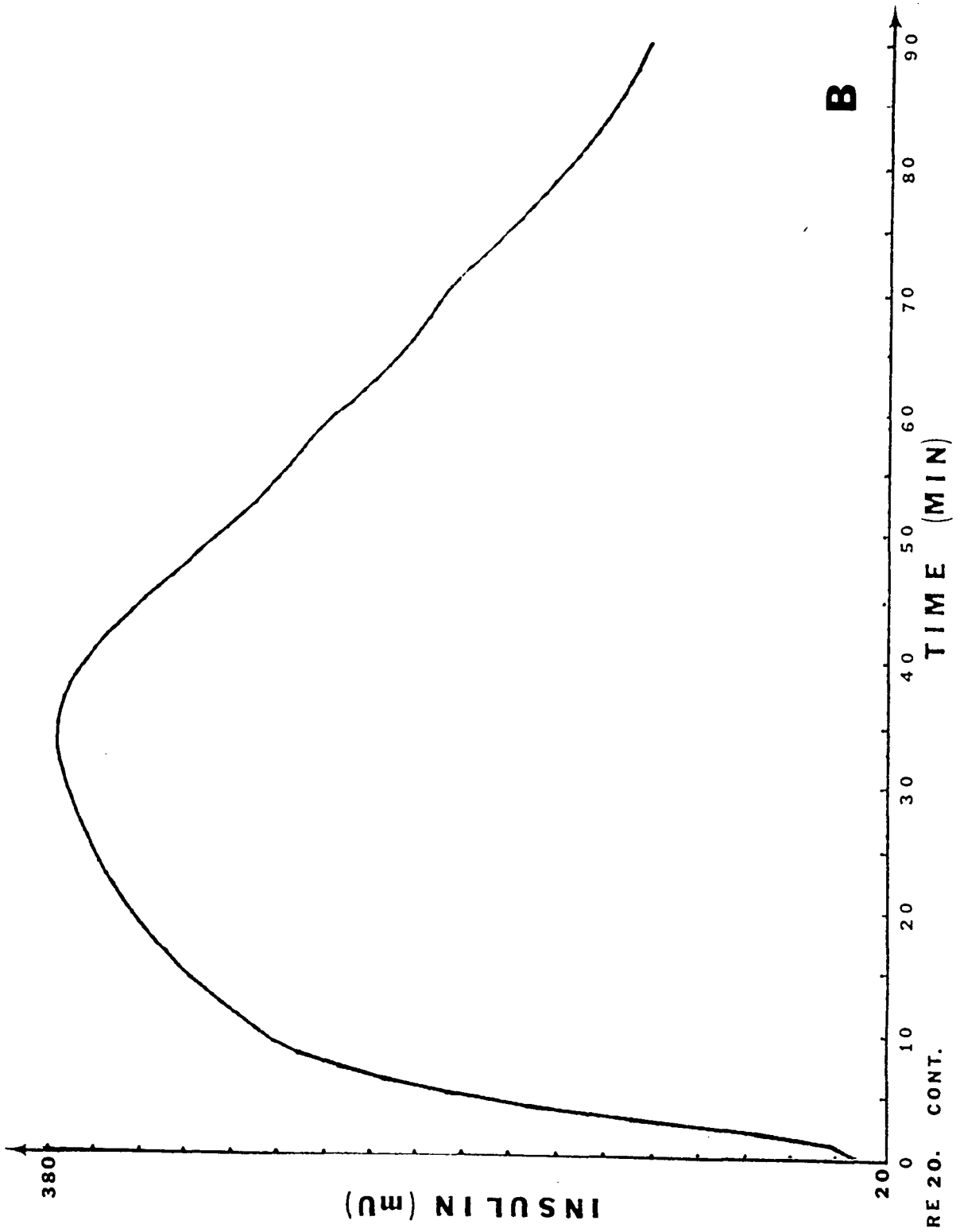


FIGURE 20. CONT.

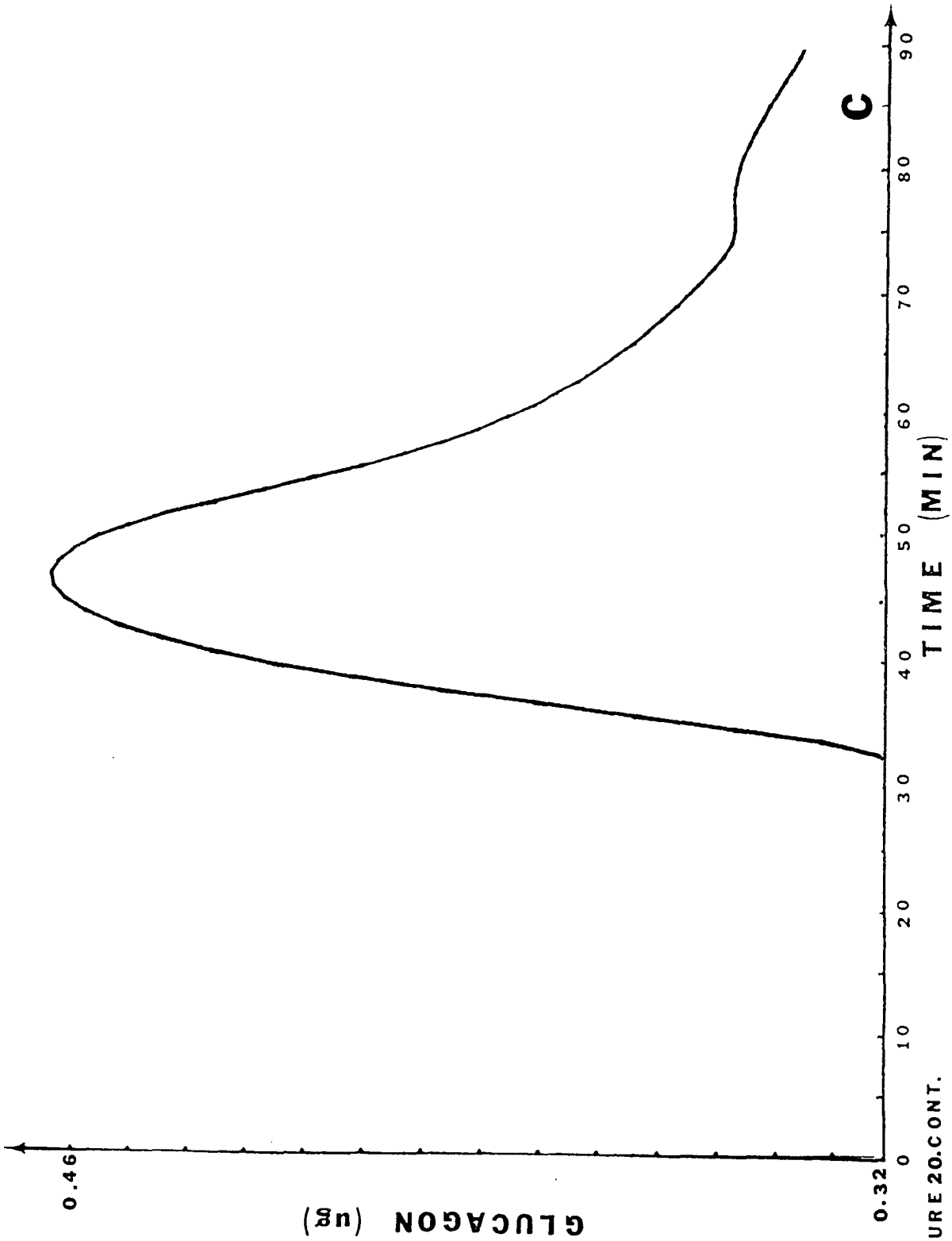
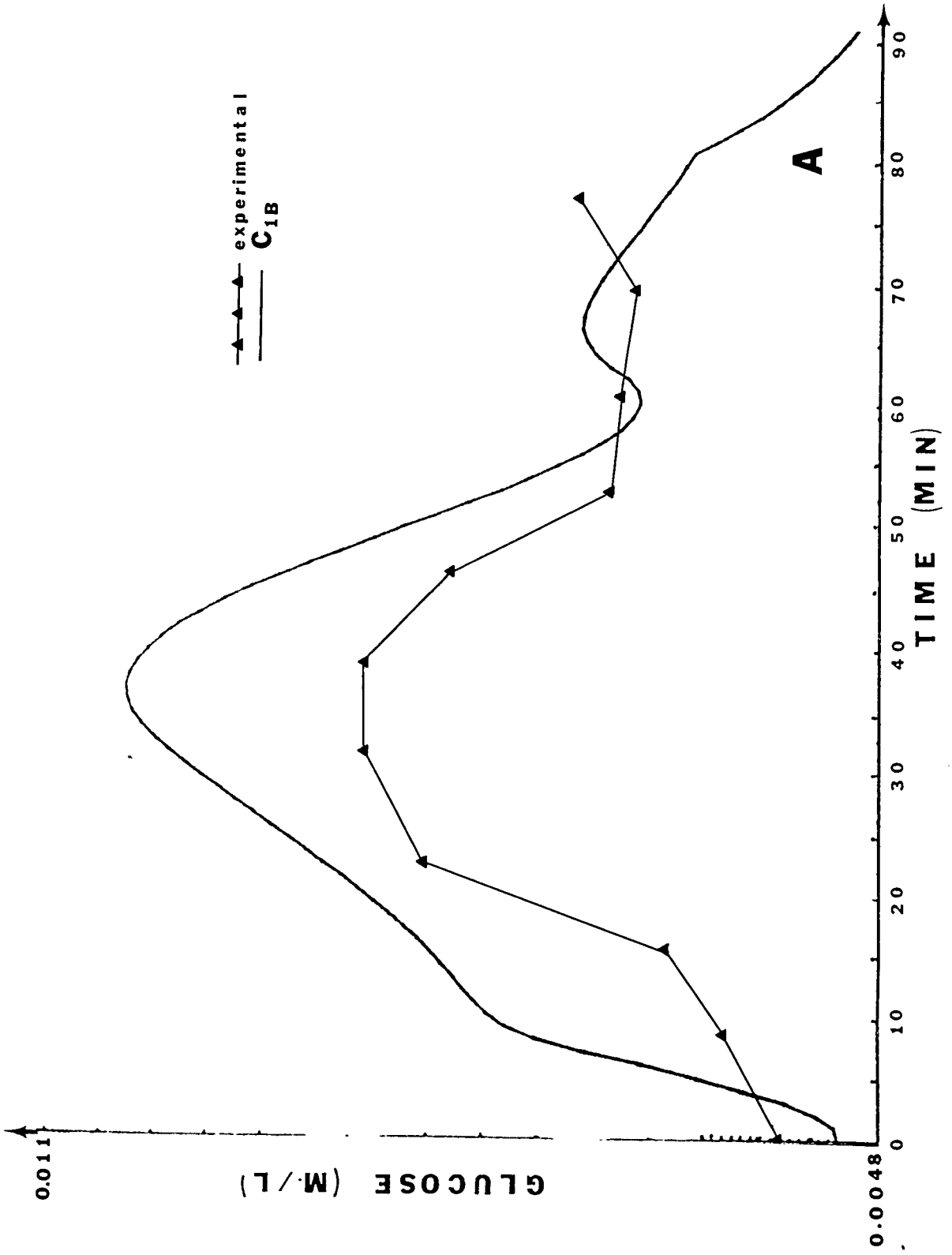


FIGURE 20.CONT.

Figure 21. Simulation of 50 gm oral glucose load where the maximum rate of glucose absorption through the gut is 0.004 M/min showing the response of plasma glucose (A), plasma insulin (B), and plasma glucagon (C)

$$\text{Dose rate, } B = \begin{cases} 0.004 & t \leq 30 \\ 0.004\, e^{-0.1(t-30)} & t > 30 \end{cases} \quad \text{M/min}$$


experimental
C_{1B}
A
GLUCOSE (M/L)
TIME (MIN)
0.011
0.0048
0
10
20
30
40
50
60
70
80
90

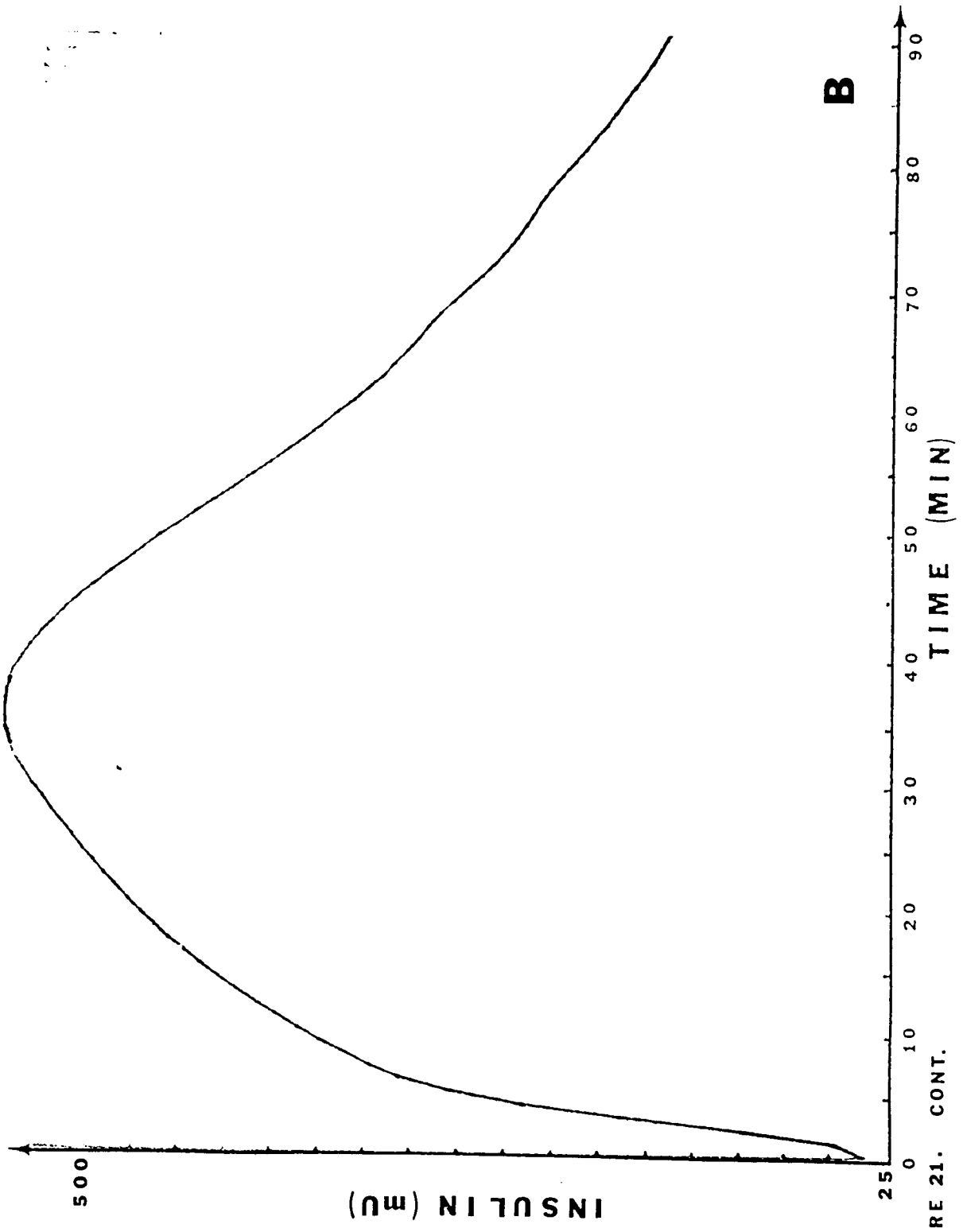


FIGURE 21. CONT.

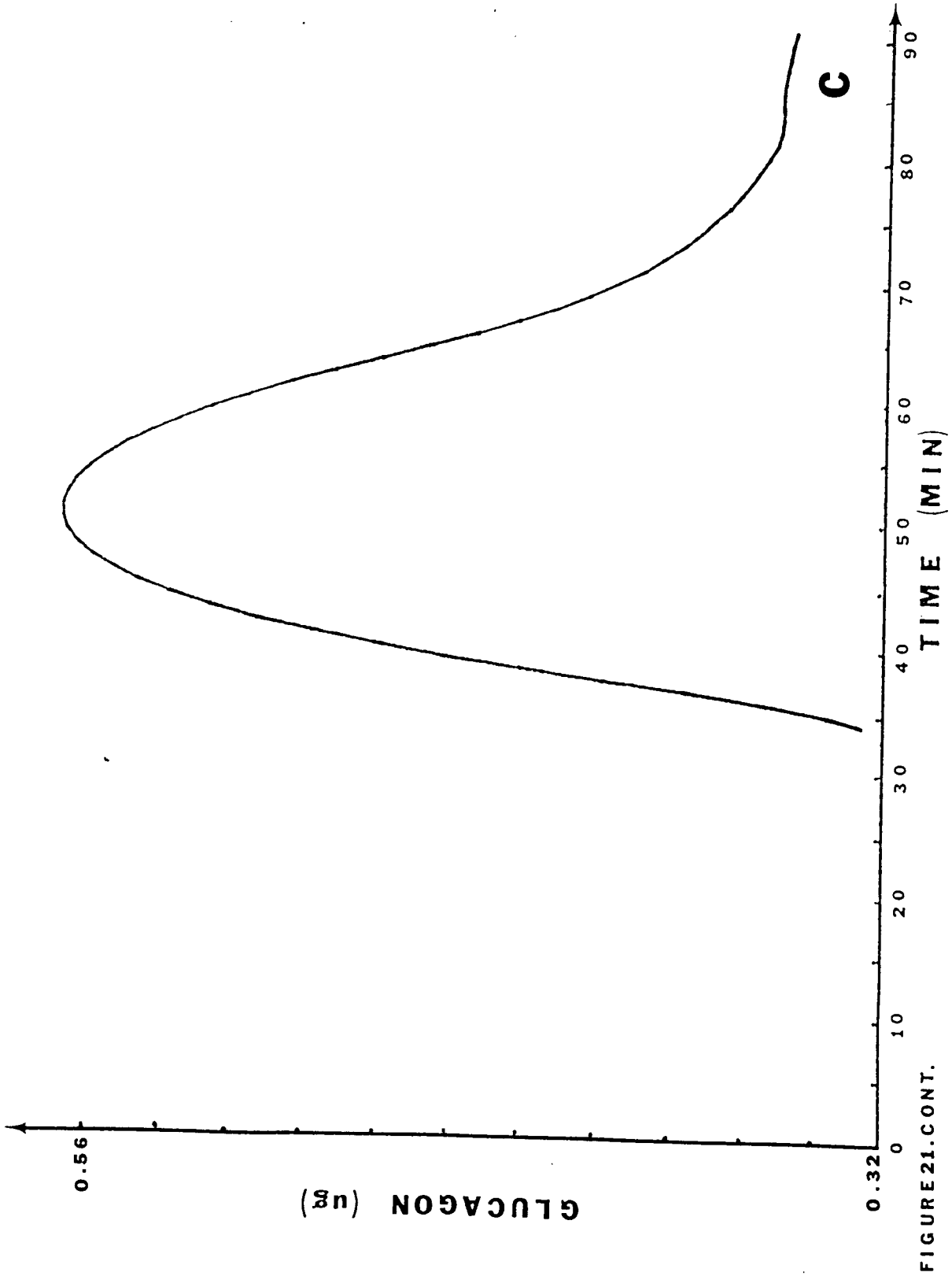


FIGURE21.CONT.

1973; Gerich, et al., 1975). However, the response is fairly accurate considering the functions involved. Requirements of the functions associated with the response of liver glycogenolysis and gluconeogenesis to epinephrine infusion are necessary to better define the response.

Figures 23 and 24 show the simulated data from IV infusions of epinephrine at different doses. Literature results are reproduced fairly accurately. Quantities are within physiological limits although there is some discrepancy as to the shapes of the curves. Again, the response appears more linear in the simulations than expected.

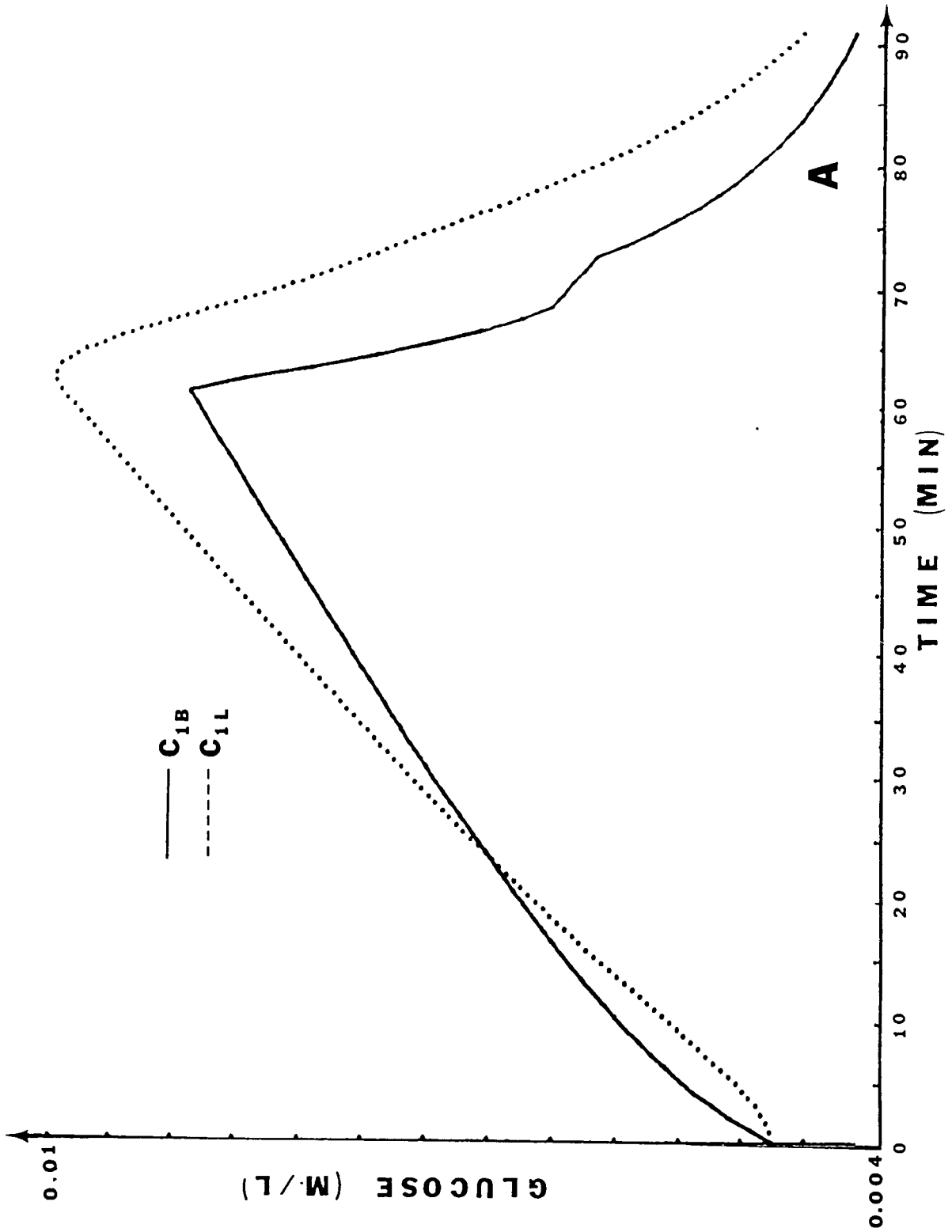
The functions for the increased glucagon secretion in the presence of epinephrine also need refinement as seen from the data from Gerich, et al. (1976) (Fig.22). The glucagon response reflects the linearity of the portal glucose curve. The function for glucagon secretion may be correct; however, a better glucose response is needed to determine if this is the case.

There are not enough data available to model the response of the glucose homeostatic system after epinephrine infusion. Most of the data collected involved the continued infusion of epinephrine past the last data point. The response after epinephrine infusion is probably tied to a better representation of liver glycogenolysis and gluconeogenesis in the model.

There are also other factors not taken into account in the model that could account for the observed differences. The most important of these is the epinephrine effect on the mobilization of fatty acids from adipose tissue. As well as affecting glucose metabolism in other ways, fatty acids will inhibit the release of glucose from the liver, lowering blood glucose levels. Incorporating the effects of free fatty acids on glucose metabolism would probably help create a better simulation response for all cases,

Figure 22. Model response to an intravenous epinephrine infusion administered over 60 minutes showing plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C), and epinephrine (D) responses

Dose rate, B = 6 ug/min


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.01
0.004
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

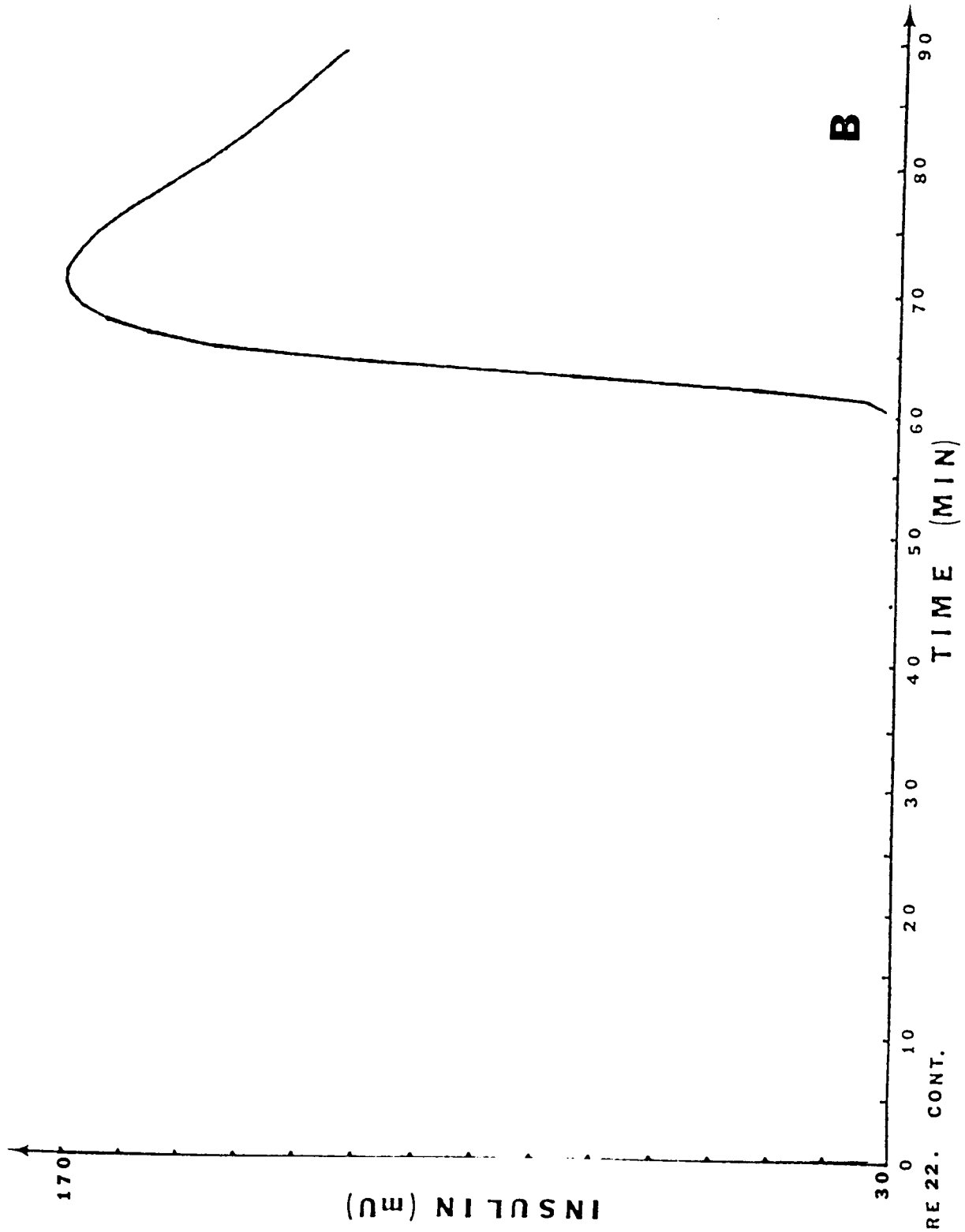


FIGURE 22. CONT.

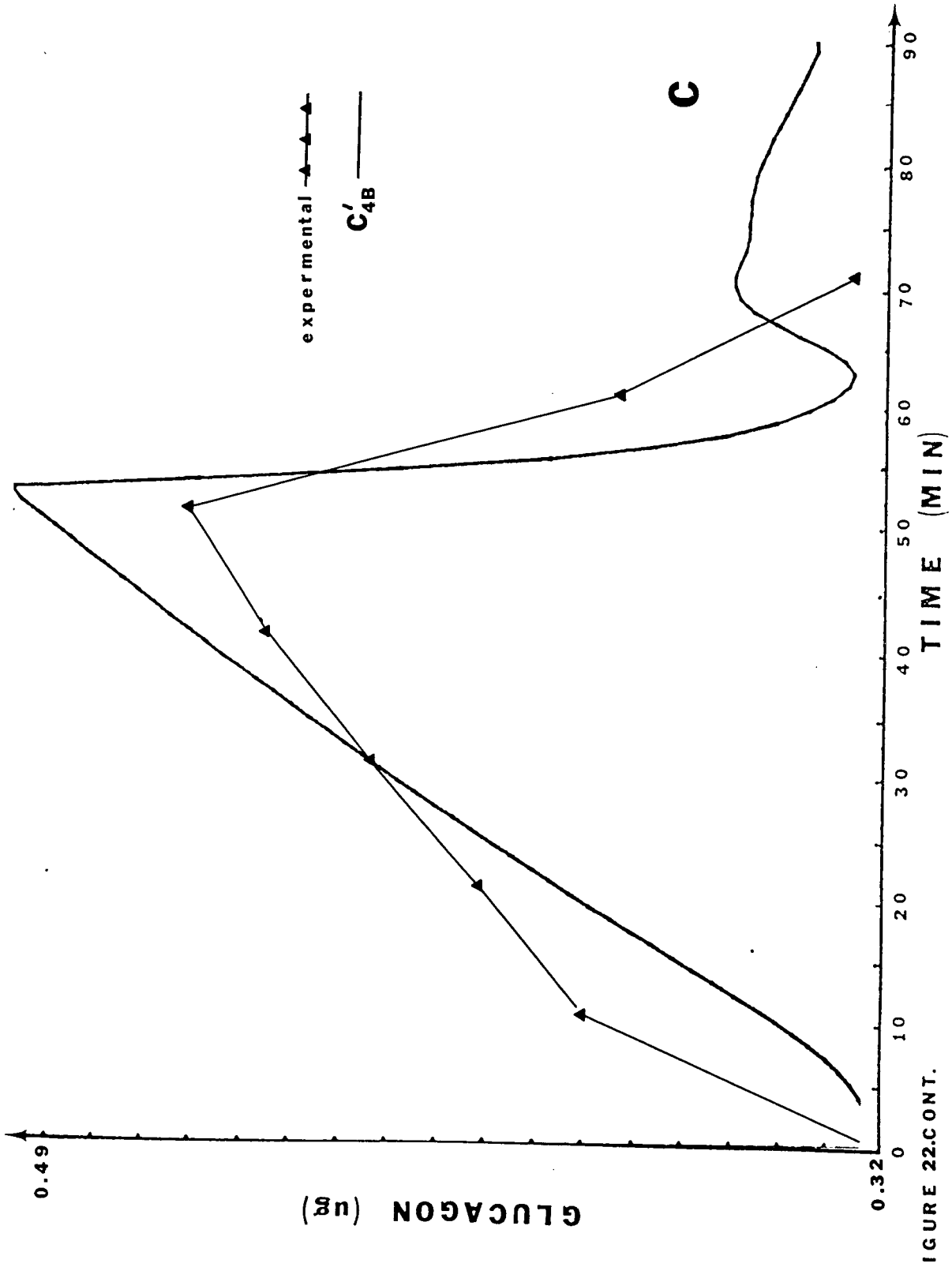


FIGURE 22.CONT.

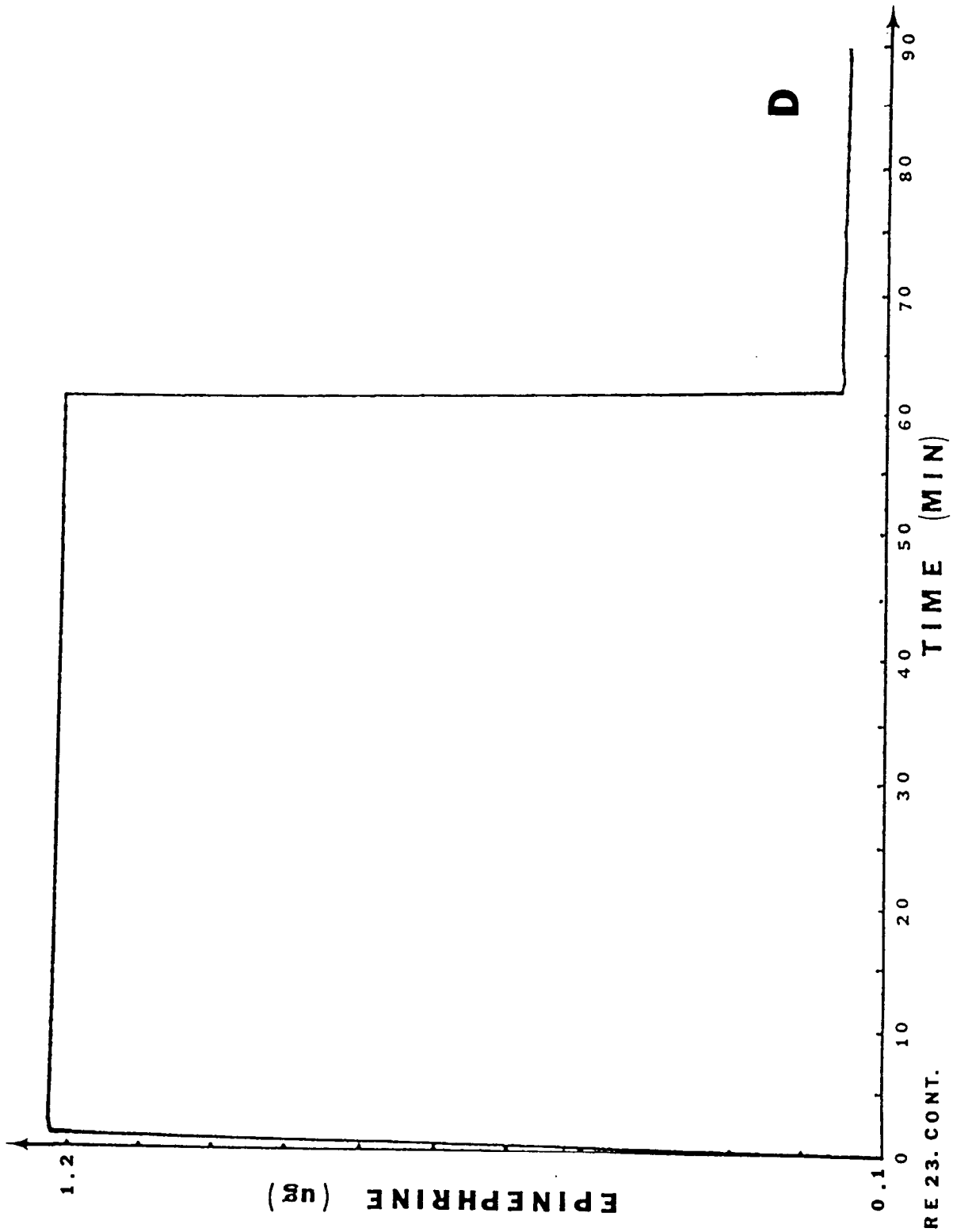
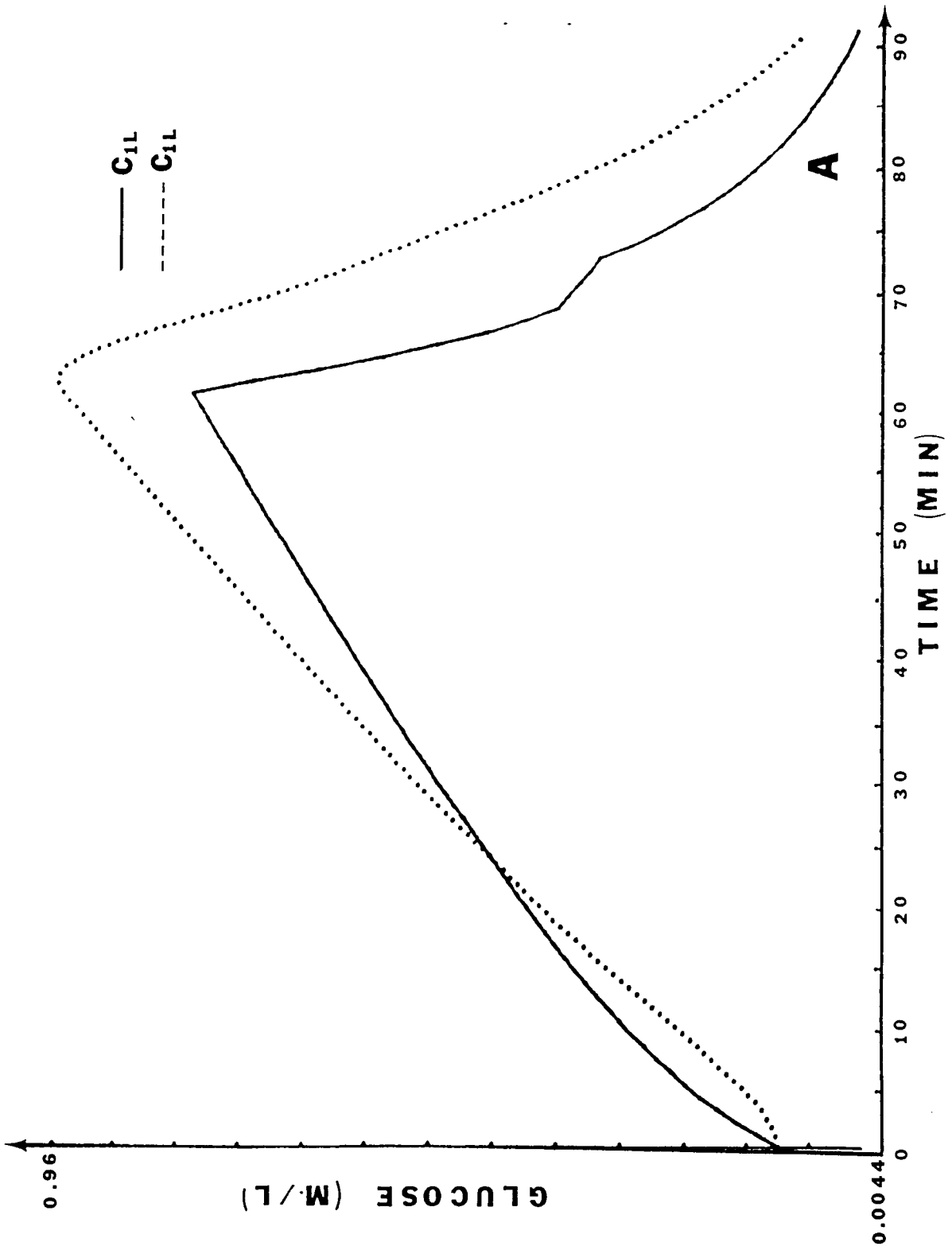


FIGURE 23. CONT.

Figure 23. Simulation of response to 60 minute epinephrine infusion showing plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C) and epinephrine (D)

Dose rate, B = 3.5 ug/min


C_{1L}
C_{1L}
A
GLUCOSE (M/L)
0.96
0.0044
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

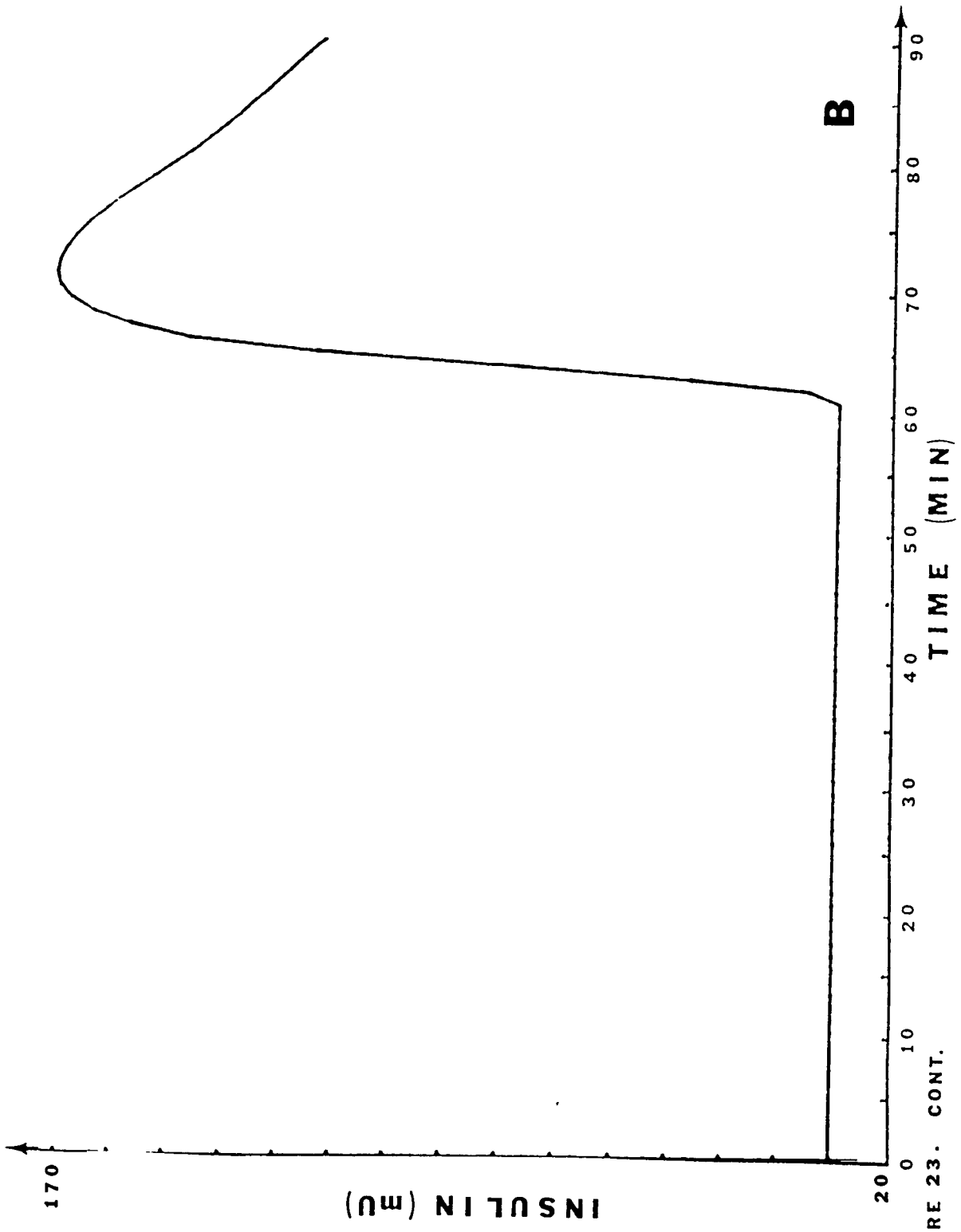


FIGURE 23. CONT.

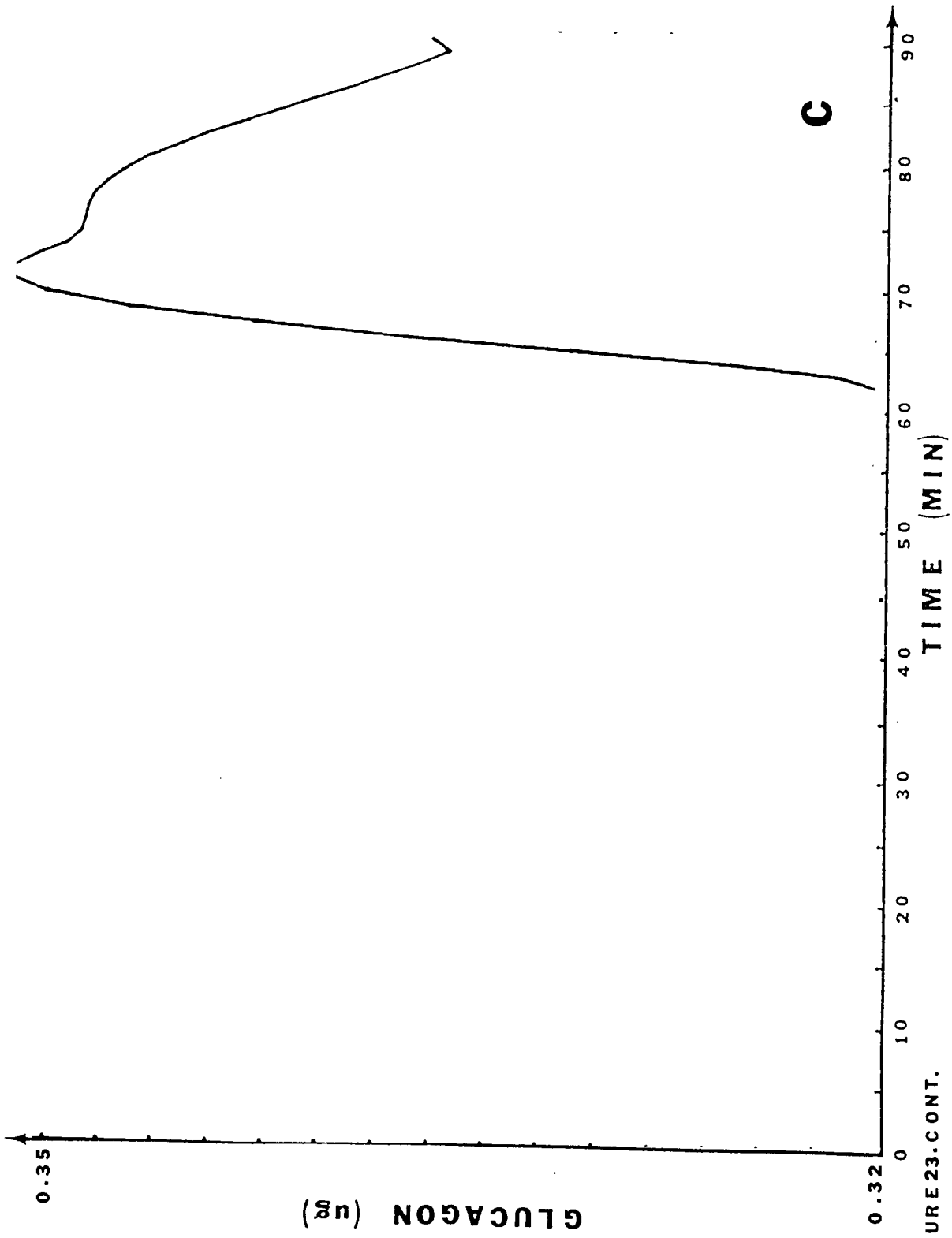


FIGURE23.CONT.

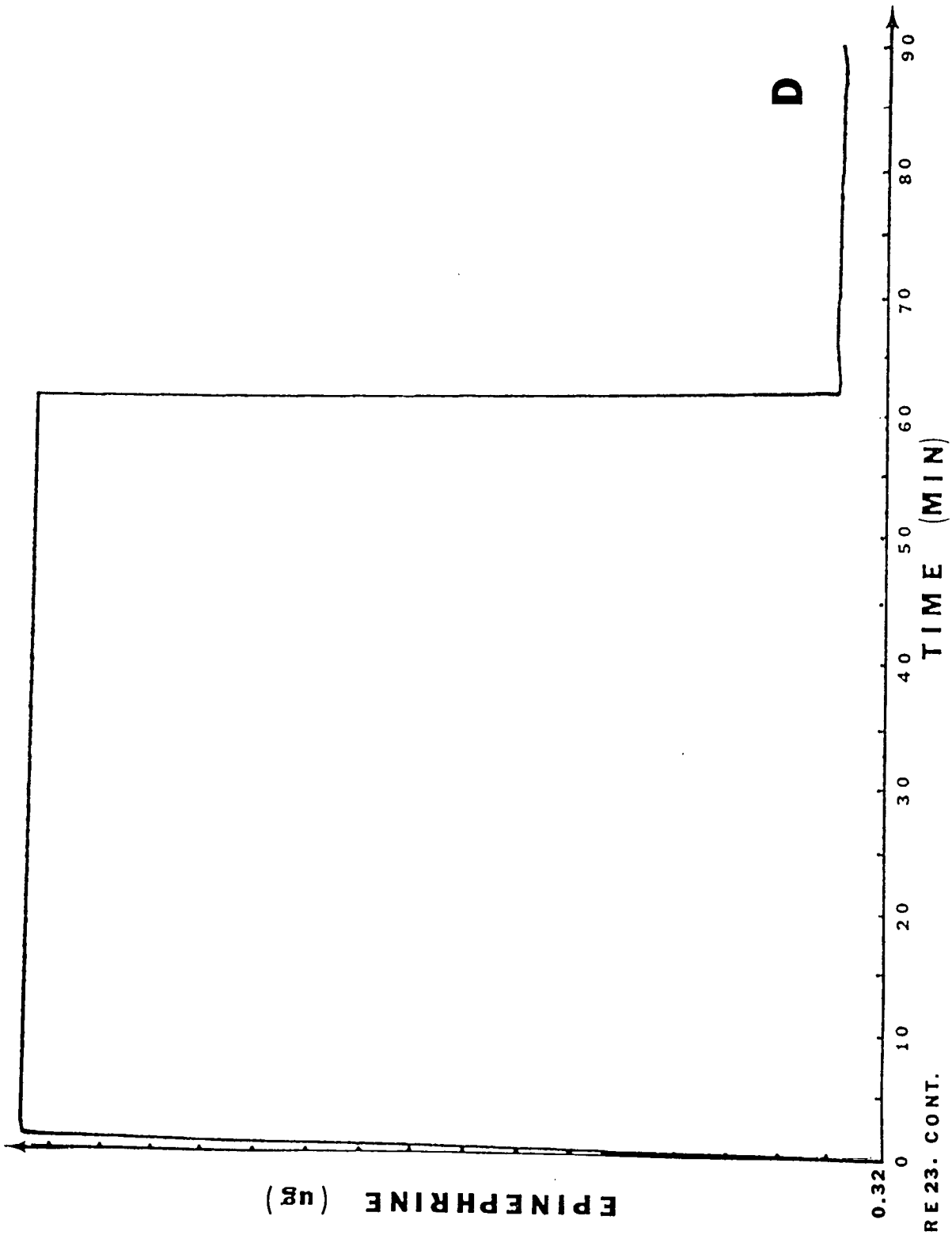
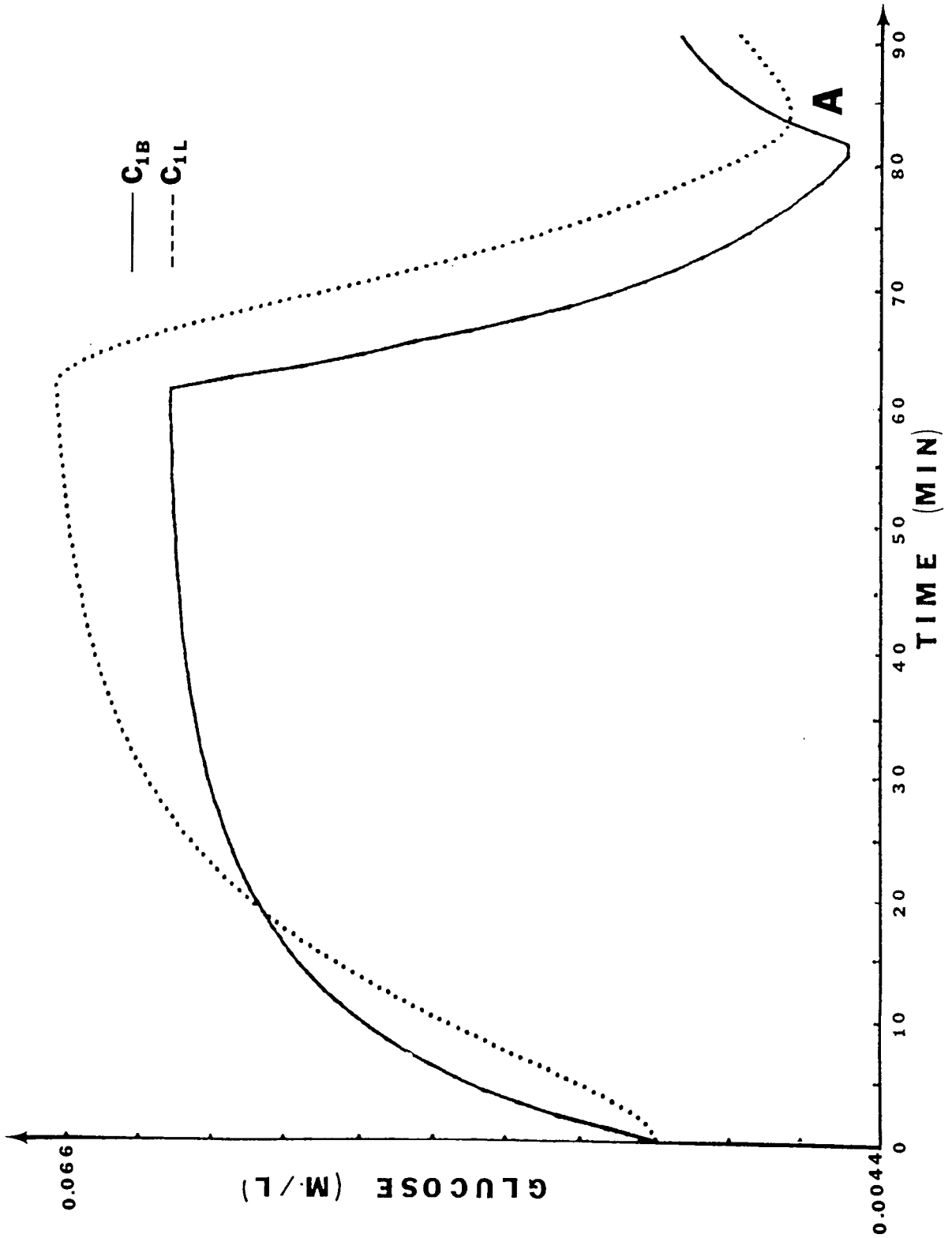


FIGURE 23. CONT.

Figure 24. Simulation of epinephrine infusion at dose rate that prevents critical epinephrine thresholds from being exceeded showing plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C), and epinephrine (D) responses

Dose rate, B = 2.16 ug/min


C_{1B}
C_{1L}
A
GLUCOSE (M/L)
0.066
0.0044
0
10
20
30
40
50
60
70
80
90
TIME (MIN)

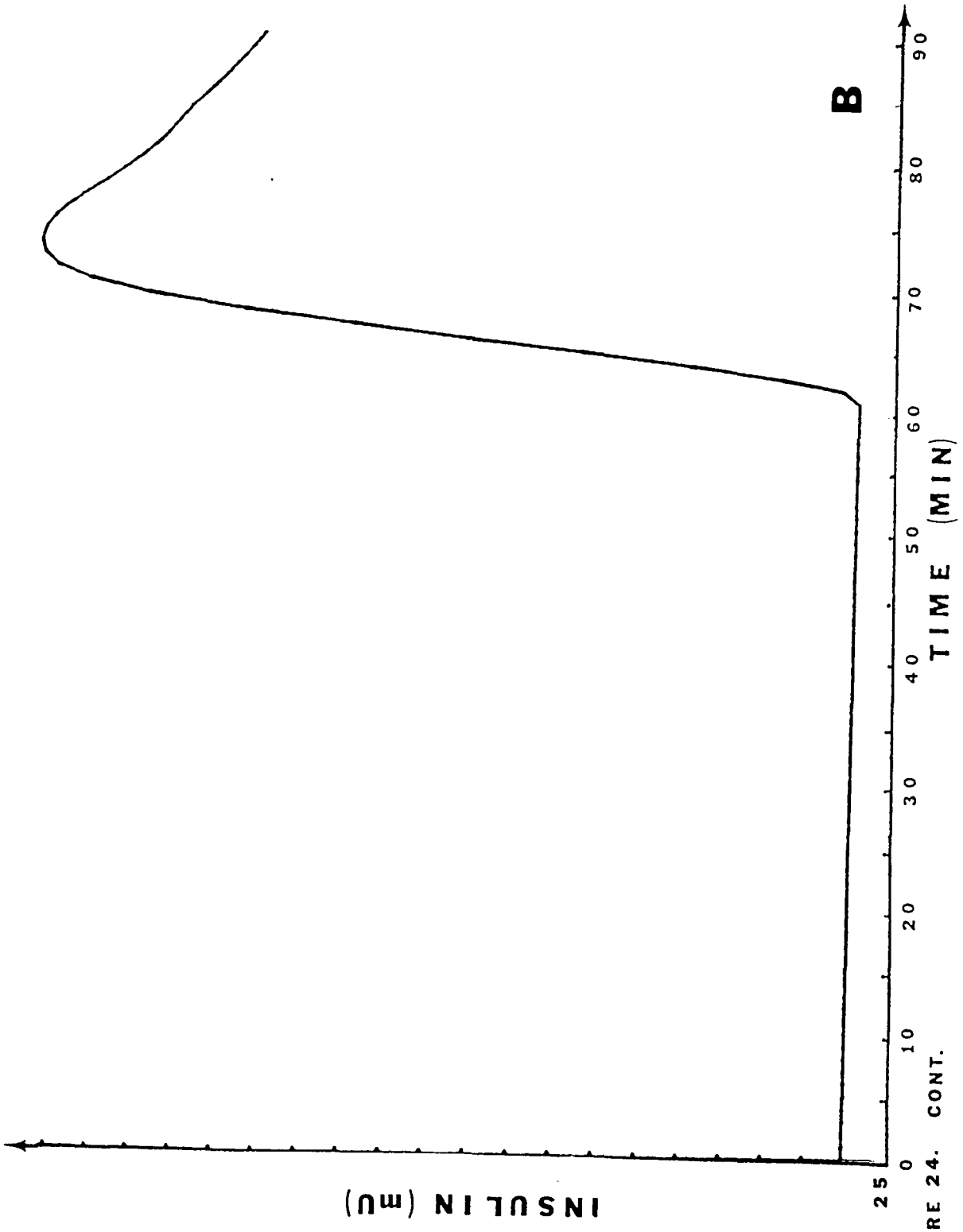


FIGURE 24. CONT.

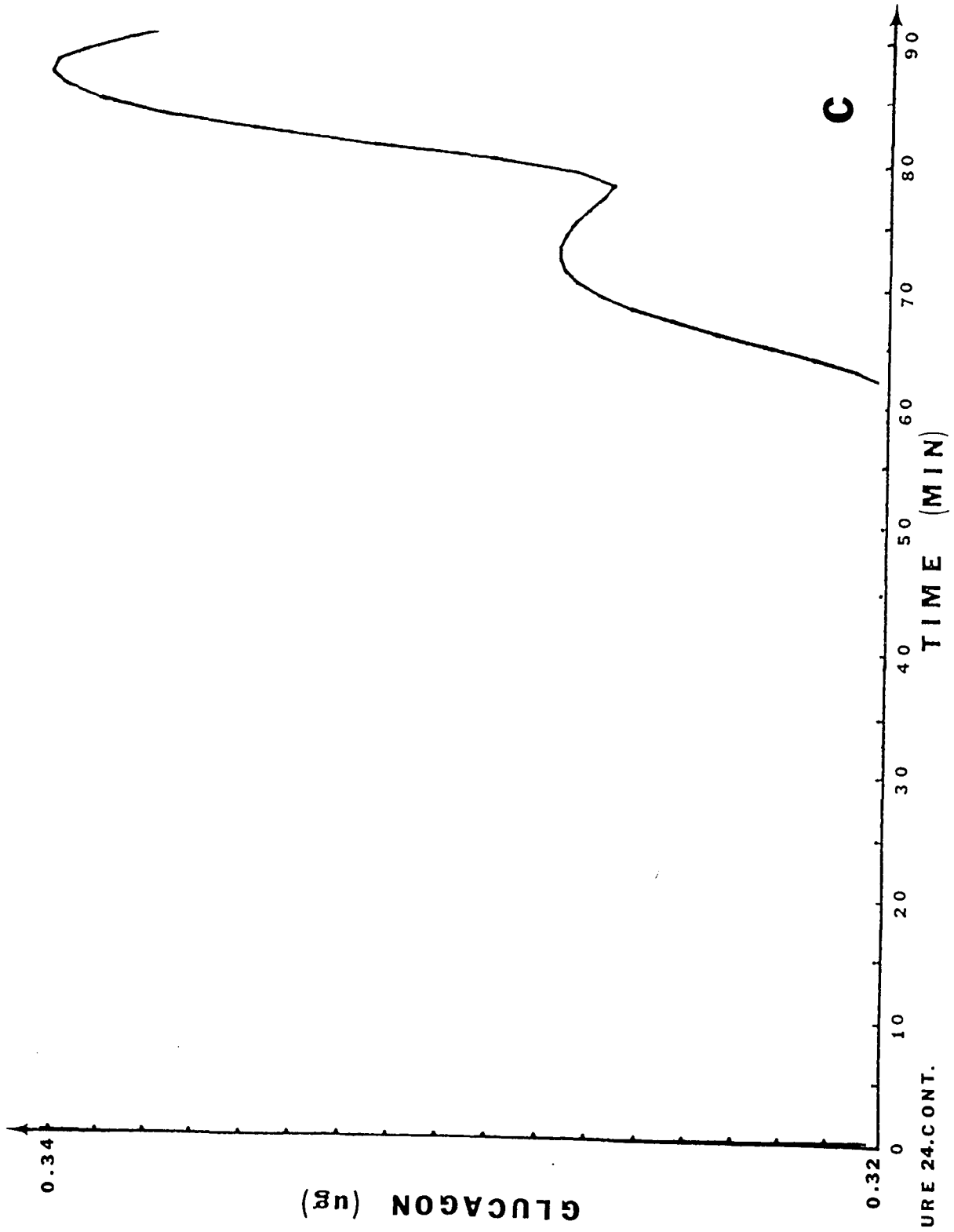


FIGURE 24.CONT.

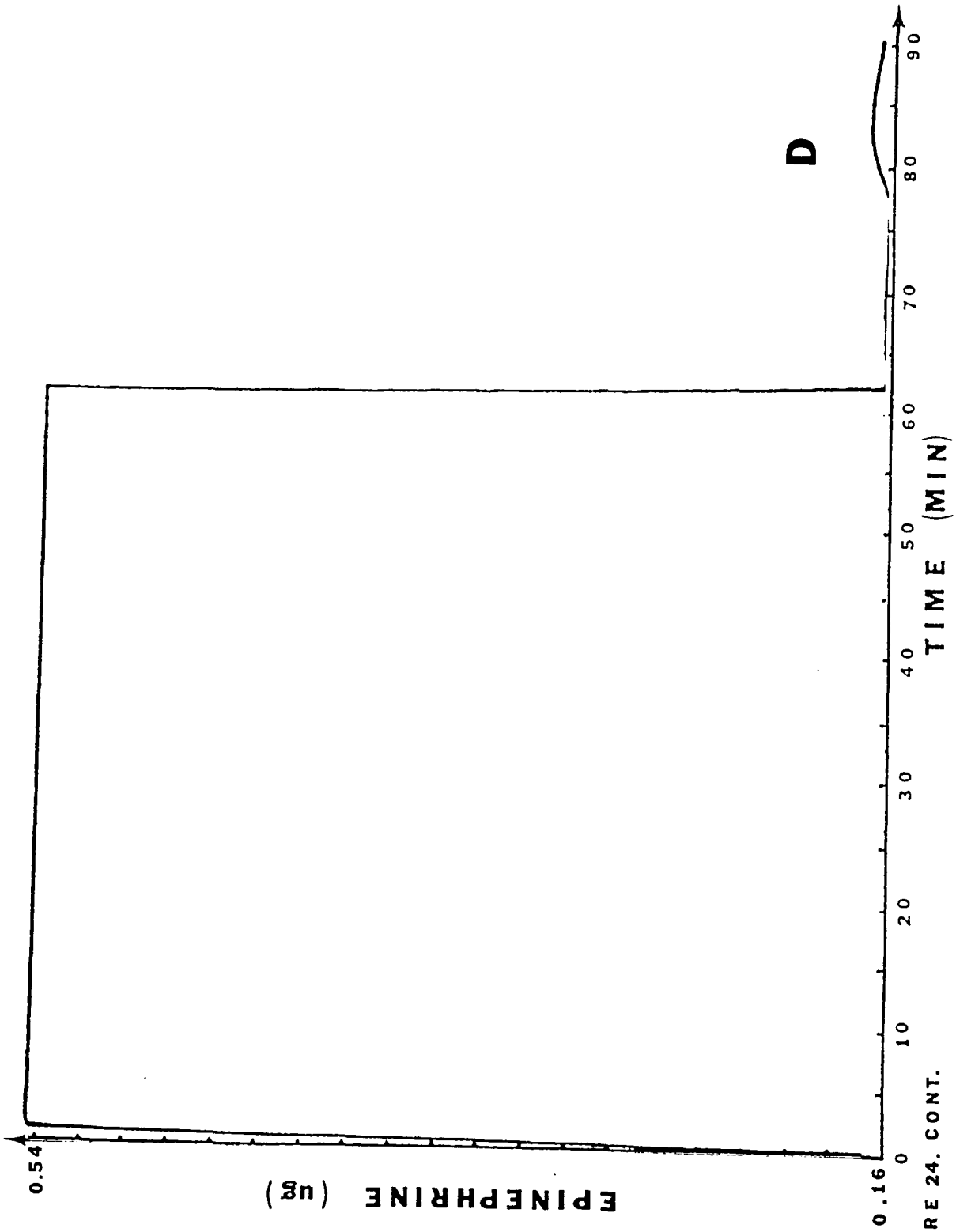


FIGURE 24. CONT.

especially towards the end of the 60 min simulations when FFA effects start to become more important.

Simulation of the Response of Normal Metabolism to Exercise

Prolonged exercise has been defined by Felig and Wahren (1975) as continuous exercise lasting 60 minutes or longer. In the following simulations exercise was considered to have lasted through 170 minutes.

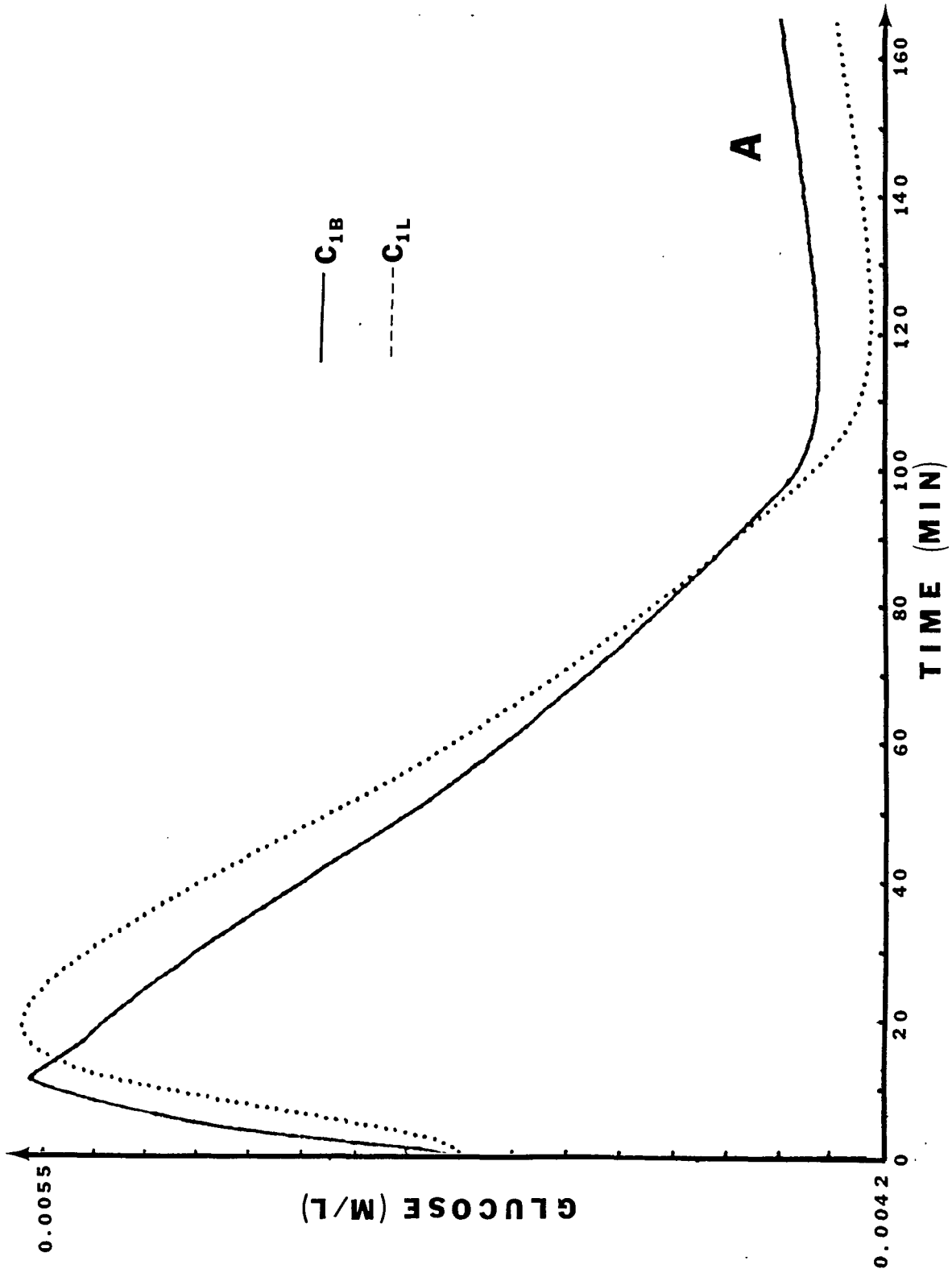
Figures 25 through 29 show the response of the model to various epinephrine levels during an increased muscle glucose uptake that corresponds to a workload of approximately 30% of Vo2 max. The increase in epinephrine levels was modeled as an increase in basal secretion rates that lead to a step increase in blood levels. Levels of epinephrine below the gluconeogenic threshold resulted in the glucose responses shown in figures 25 and 28. The decrease in blood glucose that occurs is the result of the inability of the liver output to meet glucose demands. Hormonal responses seen are due to the decreasing glucose concentrations.

Epinephrine levels that exceed threshold levels for gluconeogenesis result in a steadily increasing glucose concentration (Fig. 26 and 29). Epinephrine levels that exceed thresholds for glucagon control gave same response for glucose but altered the glucagon response (Fig. 27 and 30).

The increase in epinephrine secretion that accompanies exercise was started 10 minutes before exercise began (Fig. 25-27) and at the beginning of exercise (Fig.28-30). A comparison of the results shows that the biggest difference in glucose levels was in the first 40 minutes of exercise when the short term controls considered here are most important. Comparison of

Figure 25. Model response to exercise simulation when basal epinephrine secretion is doubled 10 minutes before the start of physical work conditions showing plasma and portal glucose (A), plasma glucagon (B), and epinephrine (C)

Basal secretion, B = 1.8 ug/min


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.0055
0.0042
0
20
40
60
80
100
120
140
160
TIME (MIN)

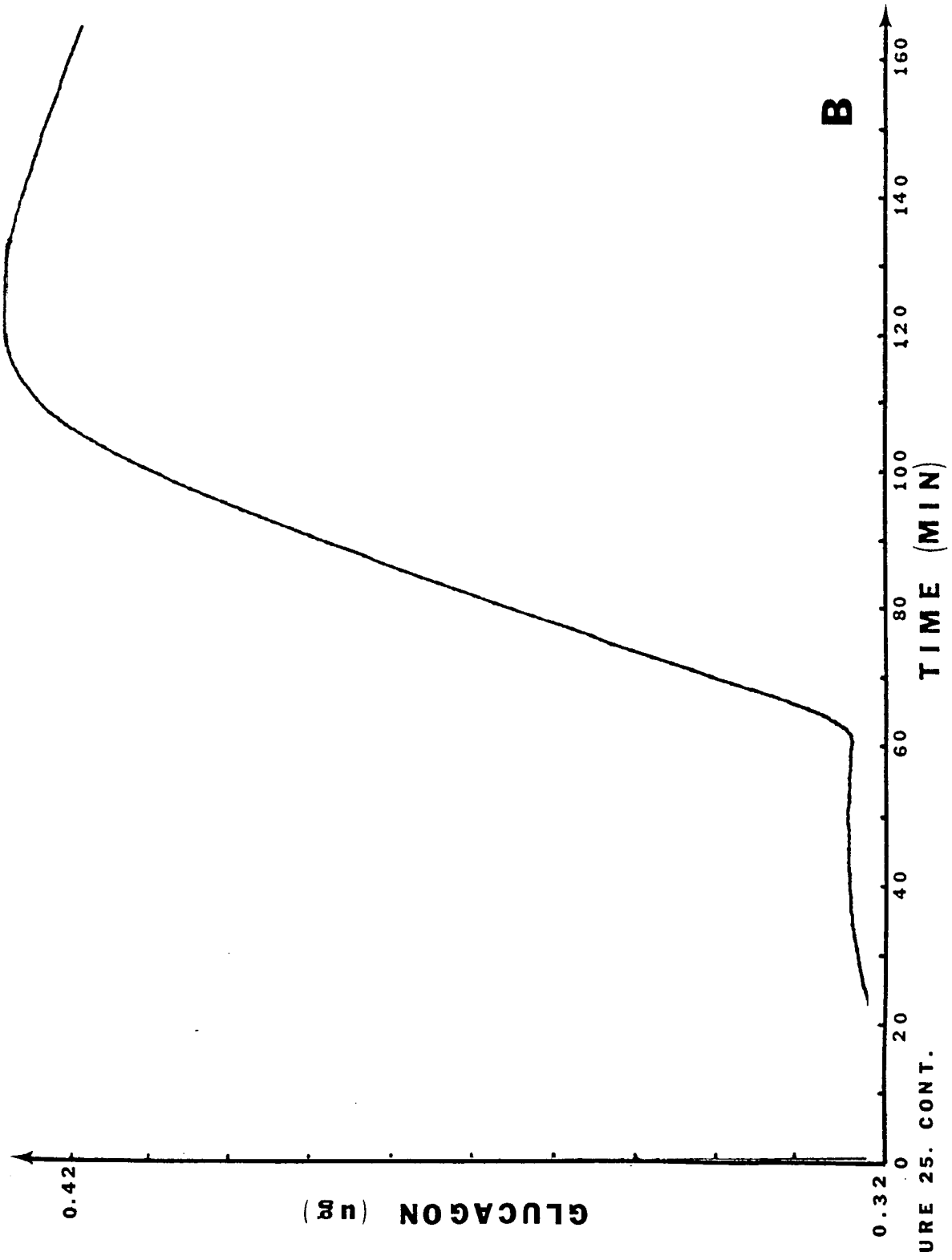


FIGURE 25. CONT.

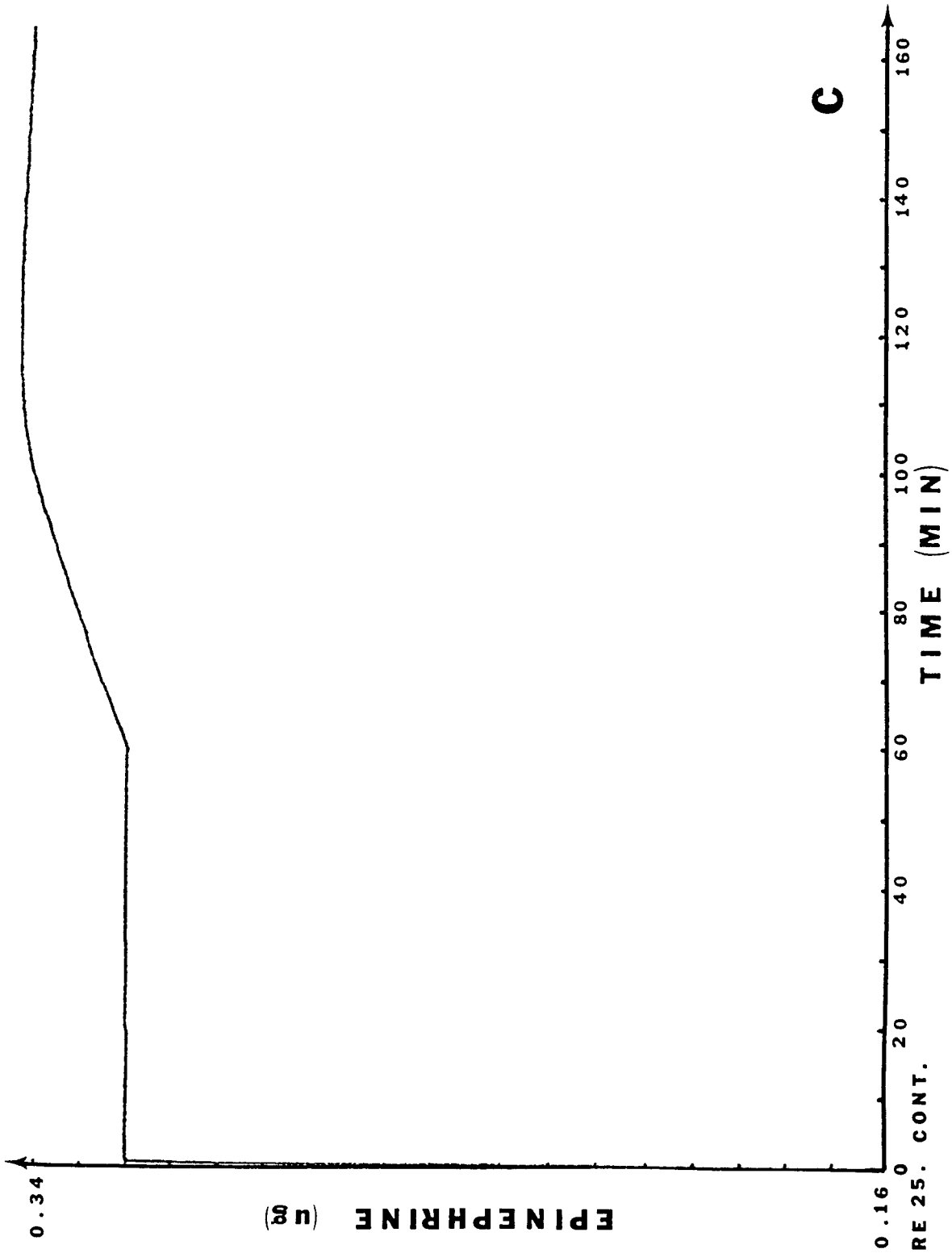
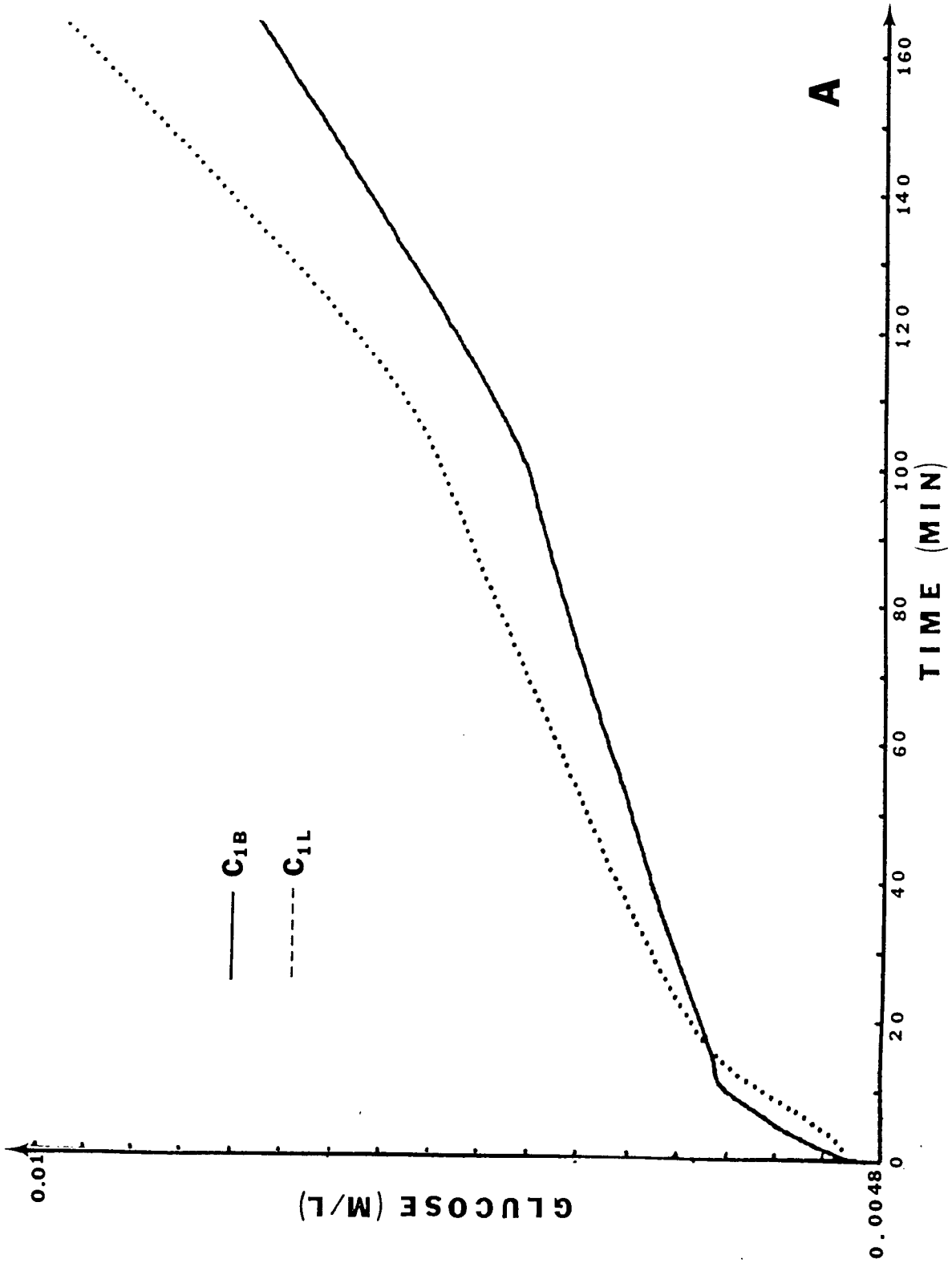


FIGURE 25. CONT.

Figure 26. Model response to exercise simulation when basal epinephrine secretion is increased four times 10 minutes before the start of physical work conditions showing plasma and portal glucose (A), plasma glucagon (B), and epinephrine (C)

Basal secretion, B = 3.6 ug/min


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
TIME (MIN)
0.01
0.0048
0
20
40
60
80
100
120
140
160

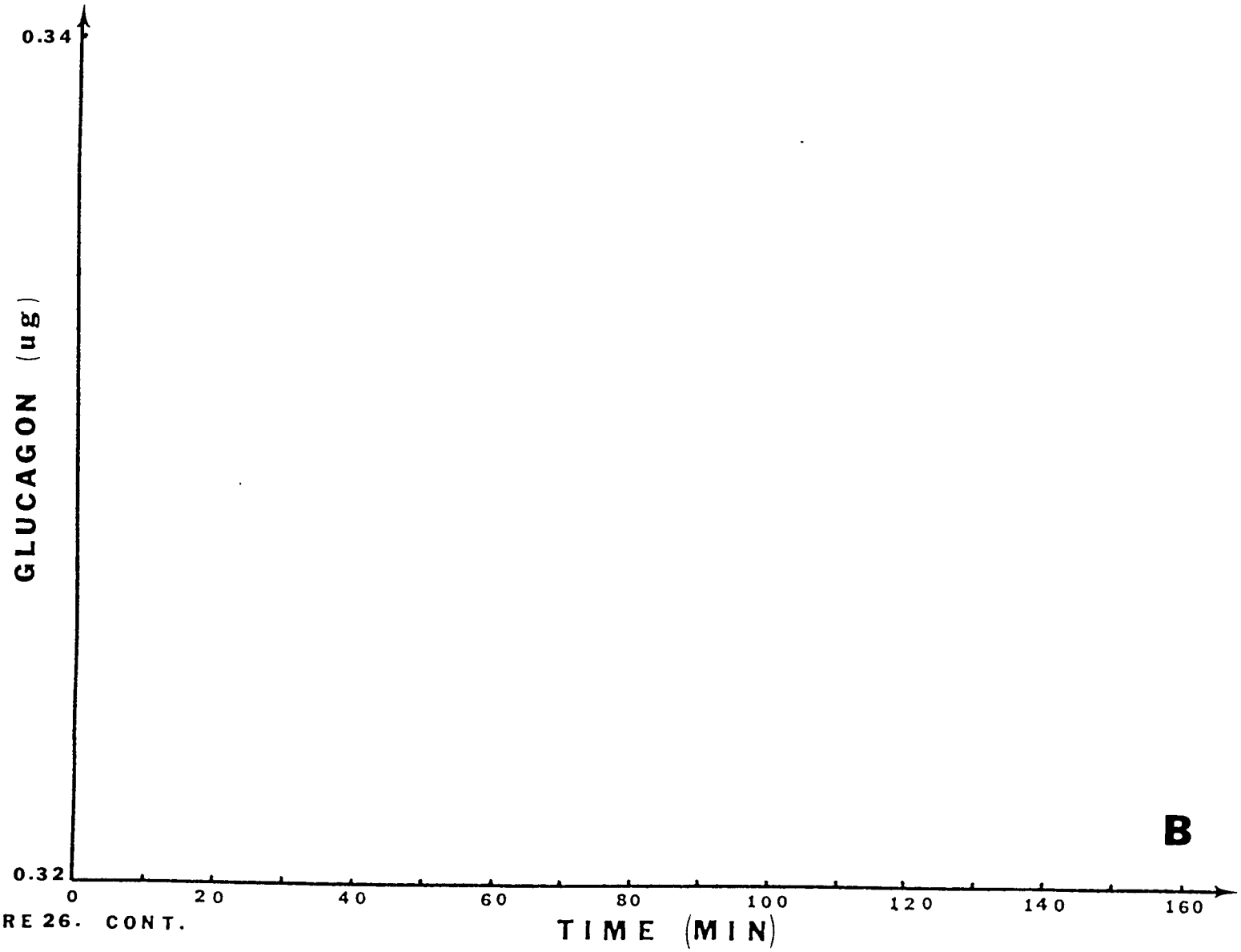


FIGURE 26. CONT.

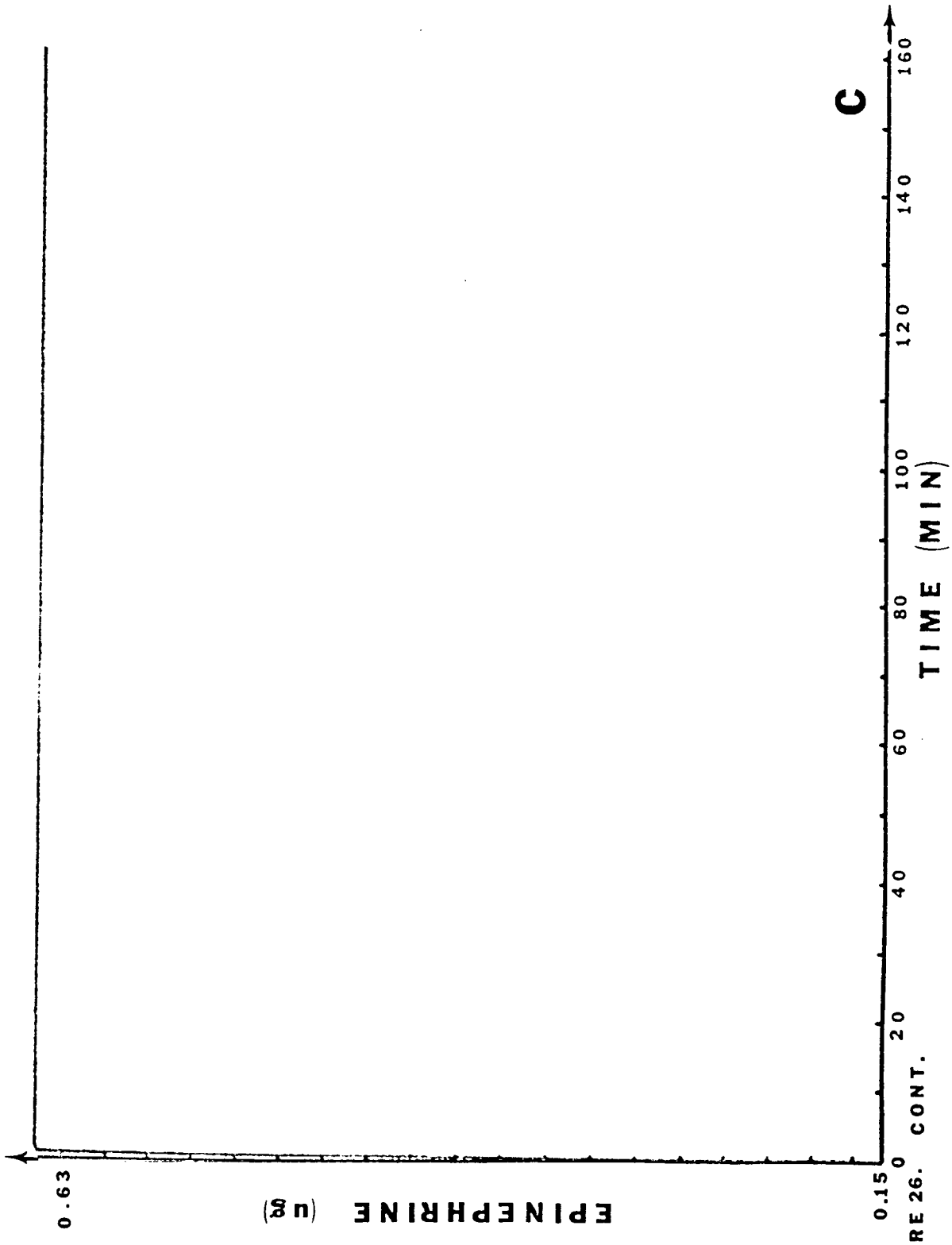
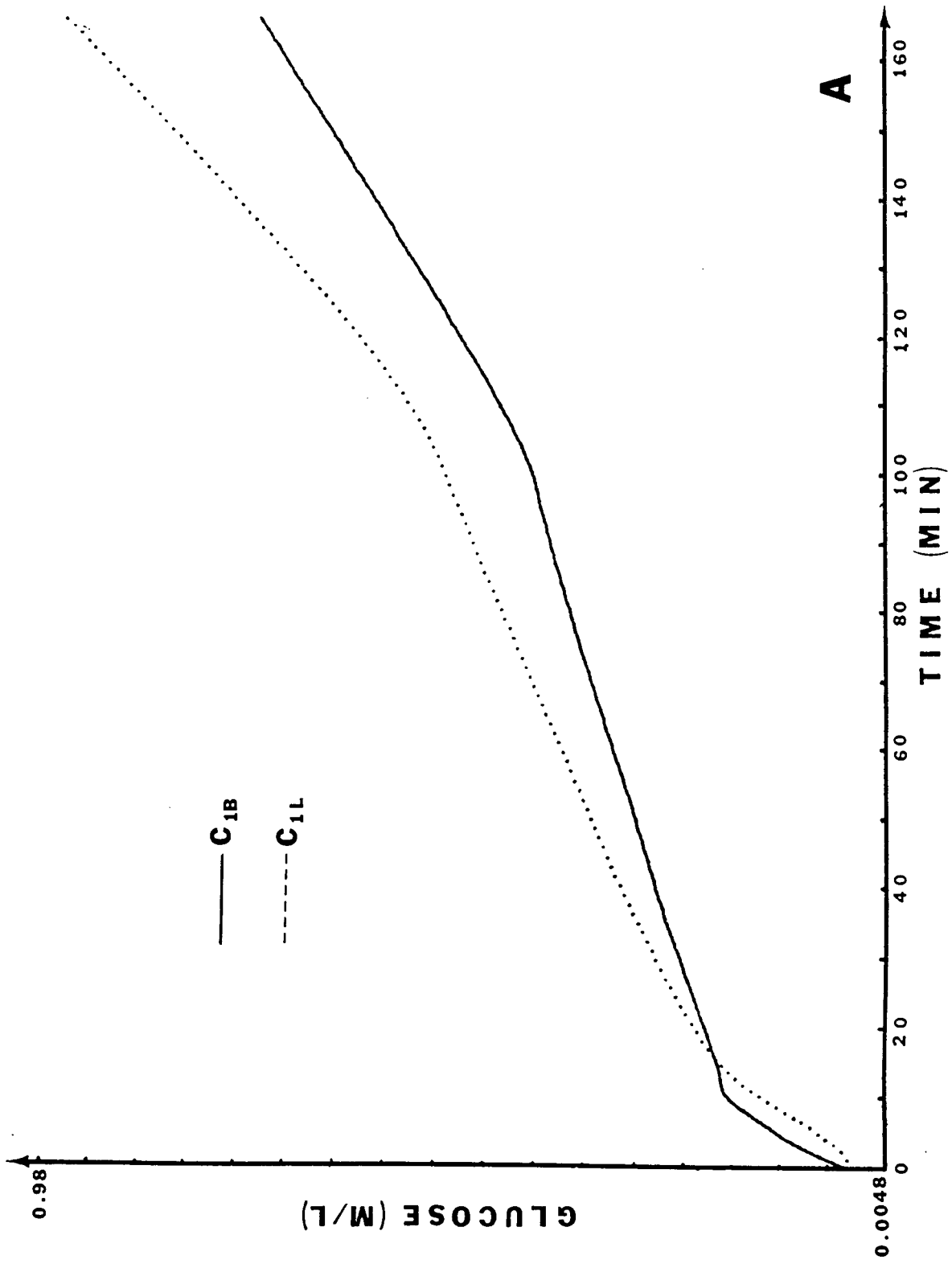


FIGURE 26. CONT.

Figure 27. Model response to exercise simulation when basal secretion of epinephrine is increased 5.5 times 10 minute before the start of exercise showing plasma and portal glucose (A), plasma glucagon (B), and epinephrine (C)

Basal secretion, B = 5.0 ug/min


A
GLUCOSE (M/L)
TIME (MIN)
0.98
0.0048
0
20
40
60
80
100
120
140
160
C_{1B}
C_{1L}

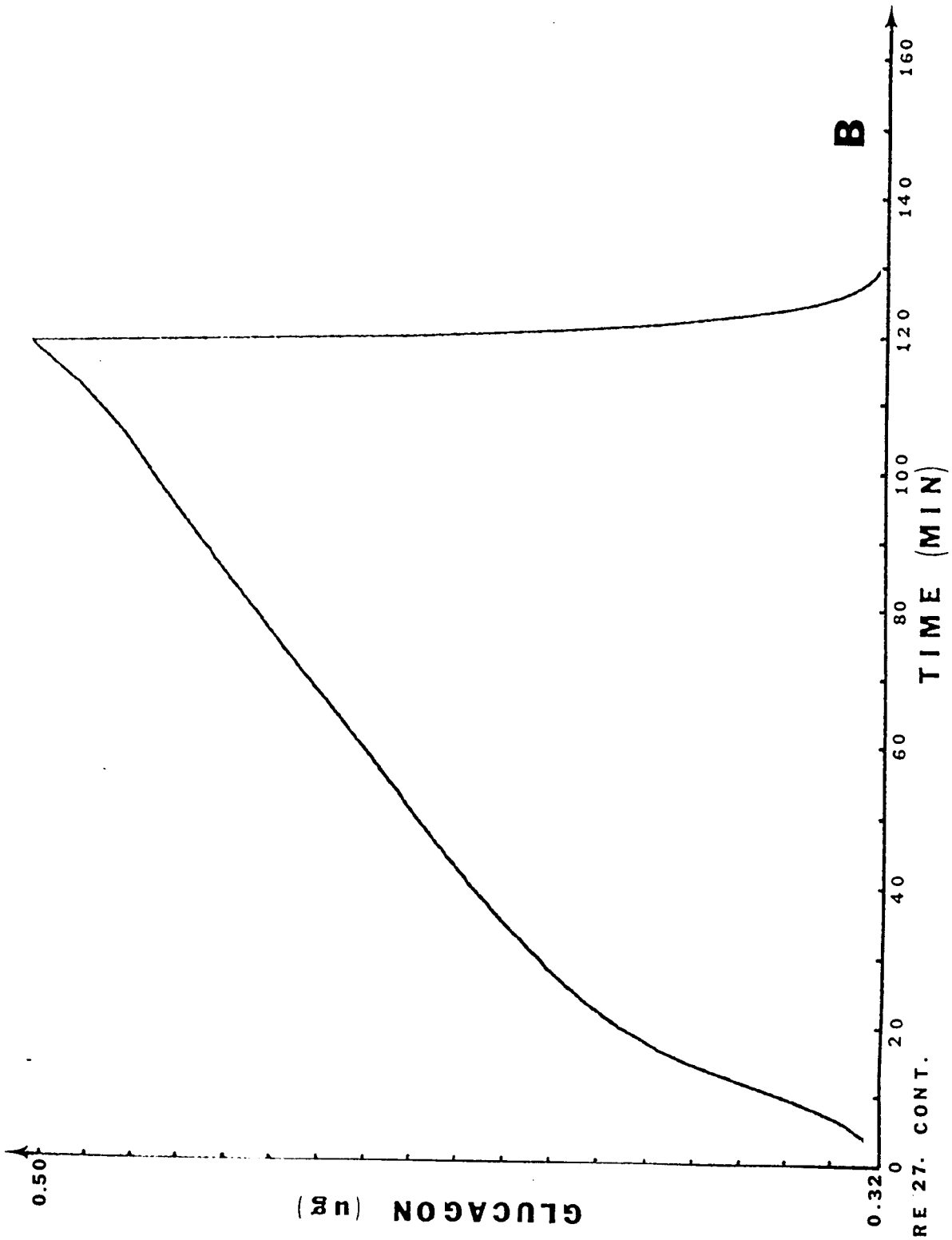


FIGURE 27. CONT.

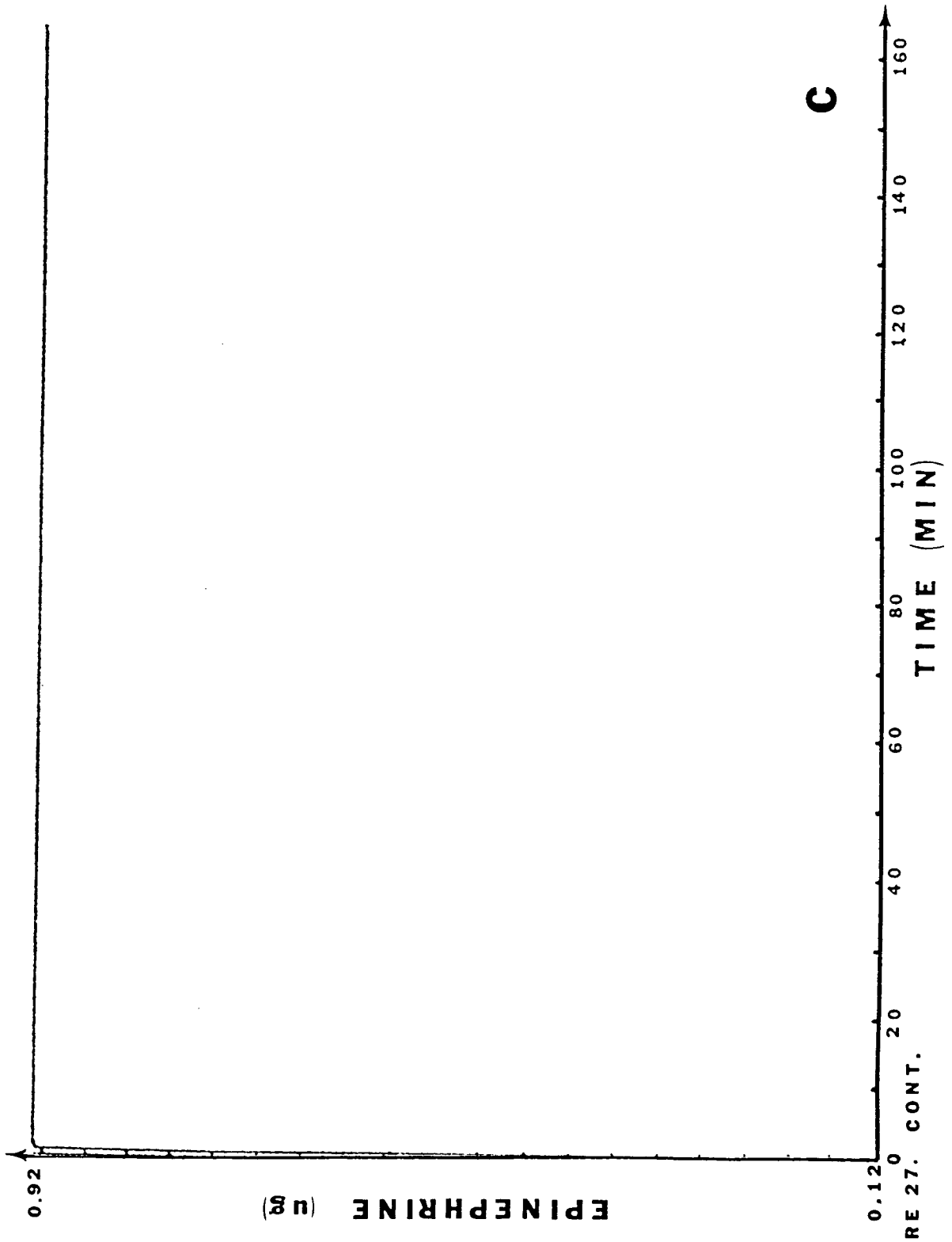
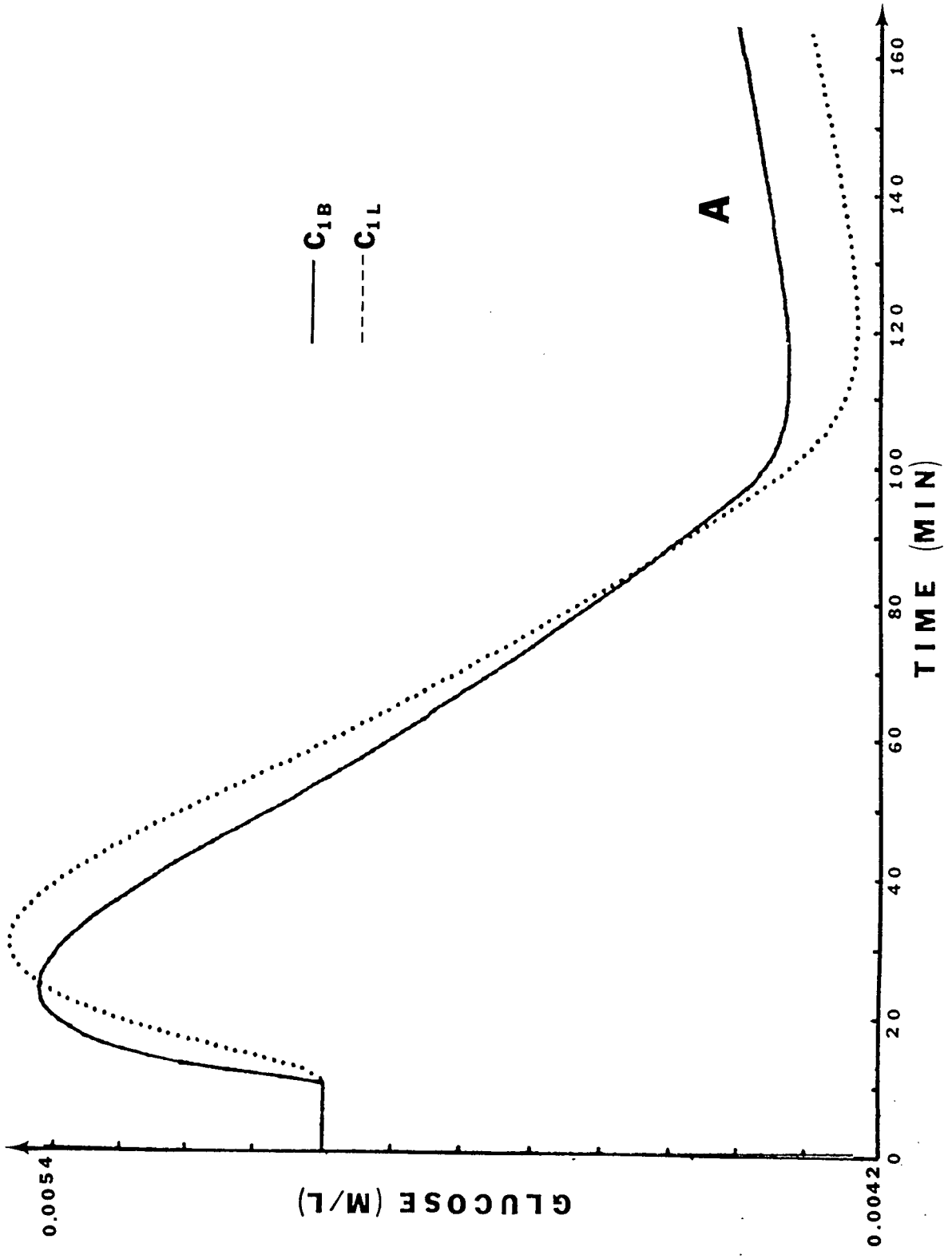


FIGURE 27. CONT.

Figure 28. Response of plasma and portal glucose (A), plasma glucagon (B), and epinephrine (C) during simulation of exercise when basal secretion of epinephrine does not increase until the start of exercise

Basal secretion, B = 1.8 ug/min


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.0054
0.0042
0
20
40
60
80
100
120
140
160
TIME (MIN)

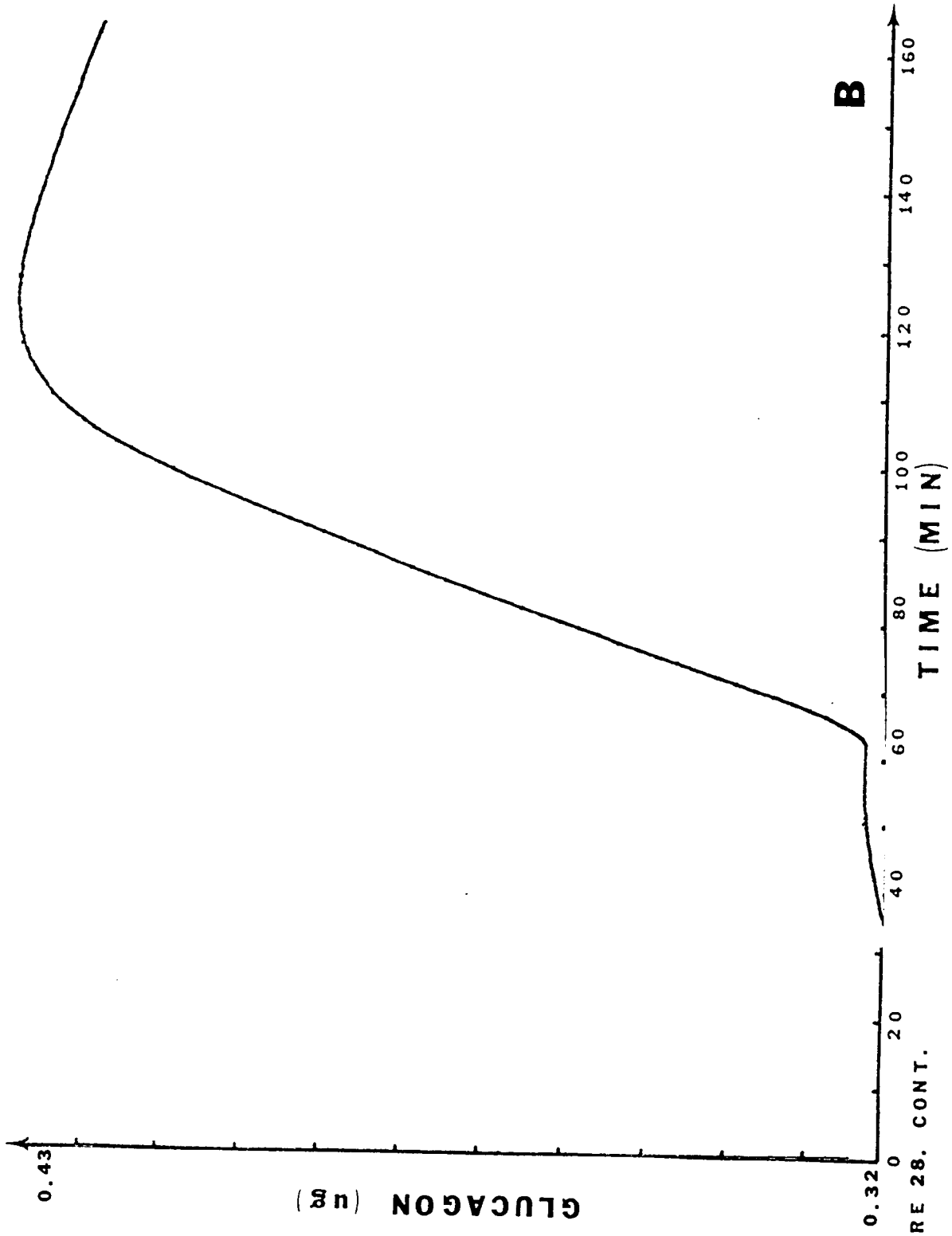


FIGURE 28. CONT.

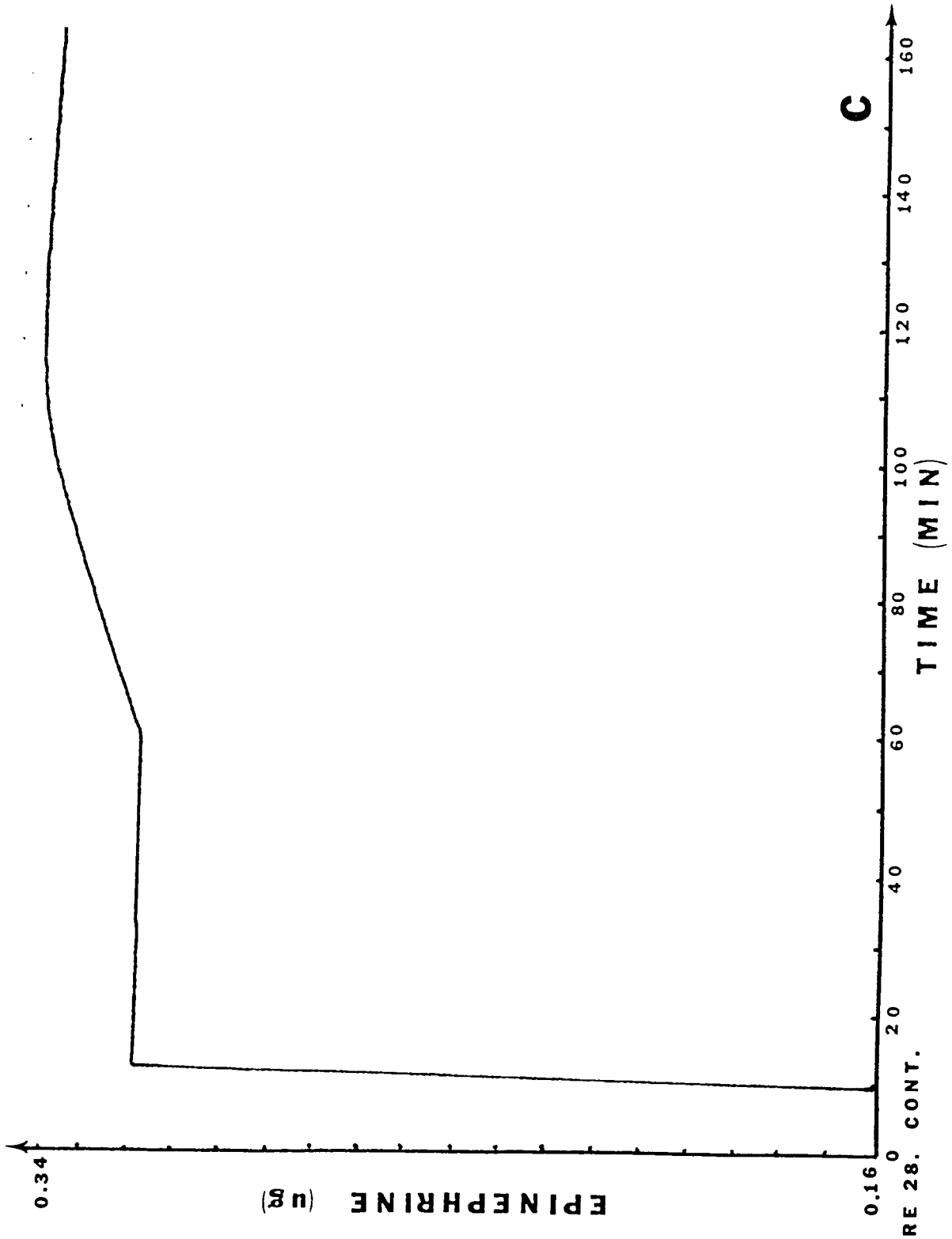
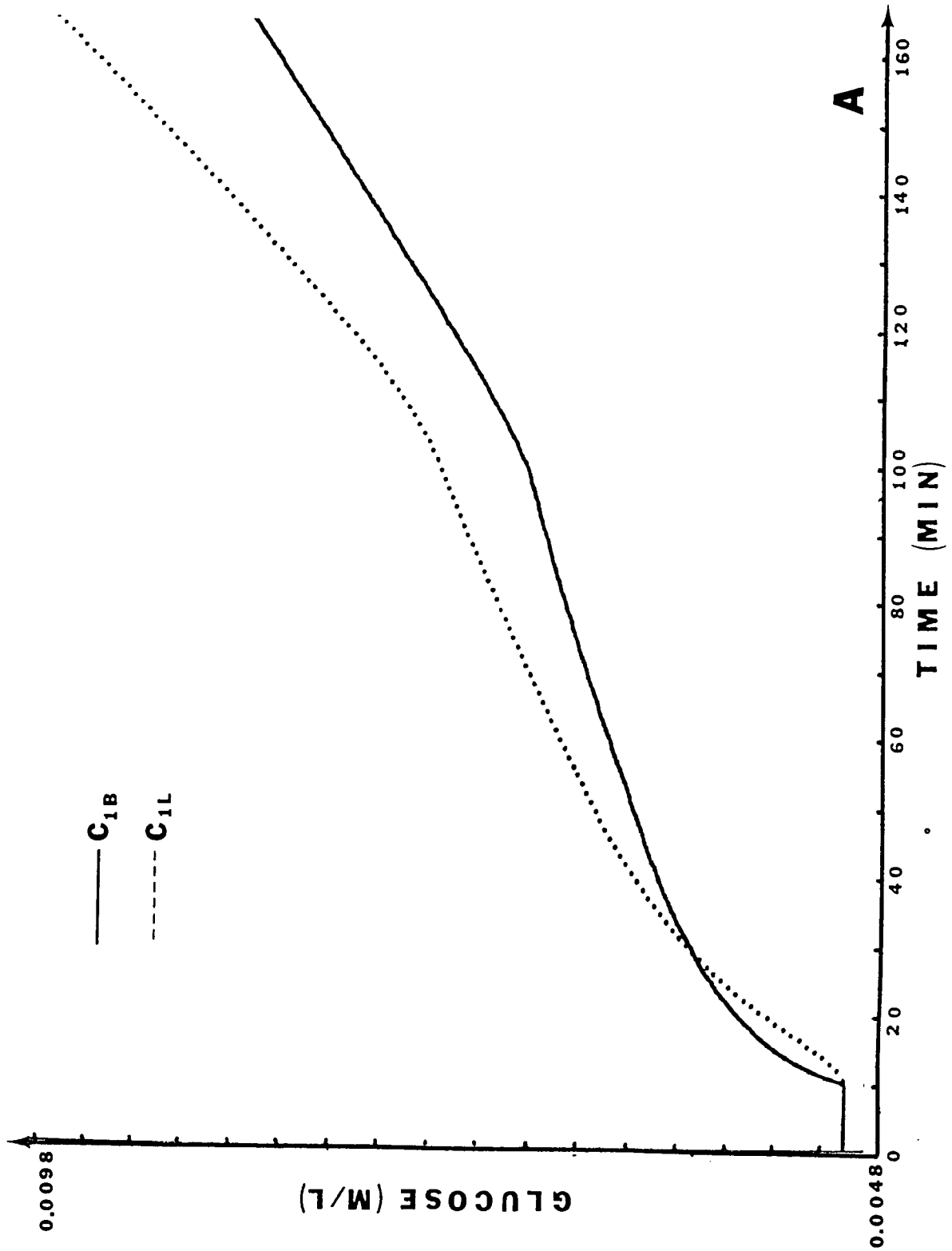


FIGURE 28. CONT.

Figure 29. Plasma and portal glucose (A), plasma glucagon (B), and epinephrine (C) response to exercise simulation when basal secretion of epinephrine is not increased until the start of exercise

Basal secretion, B = 3.6 ug/min


A
GLUCOSE (M/L)
TIME (MIN)
0.0098
0.0048
0
20
40
60
80
100
120
140
160
C_{1B}
C_{1L}

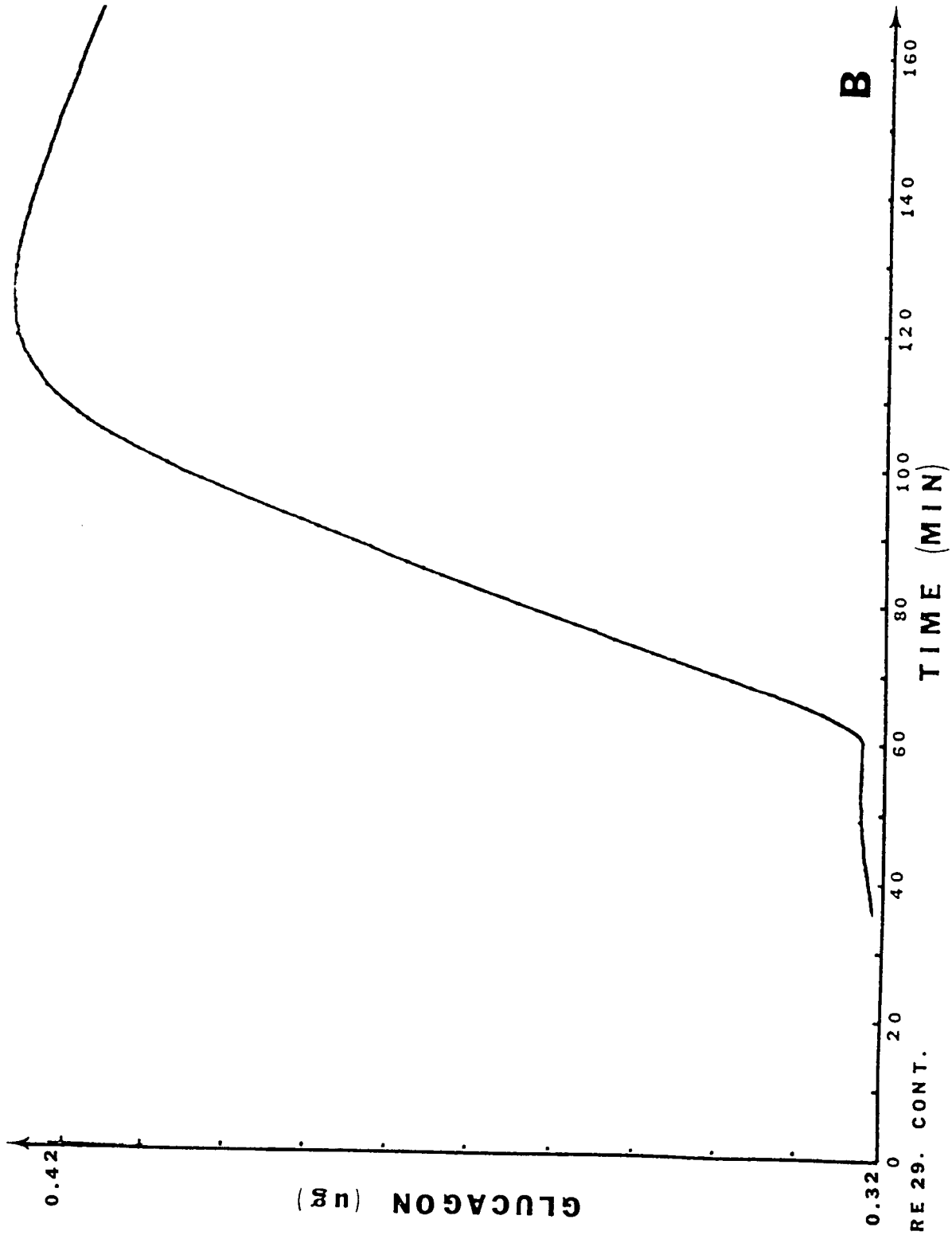


FIGURE 29. CONT.

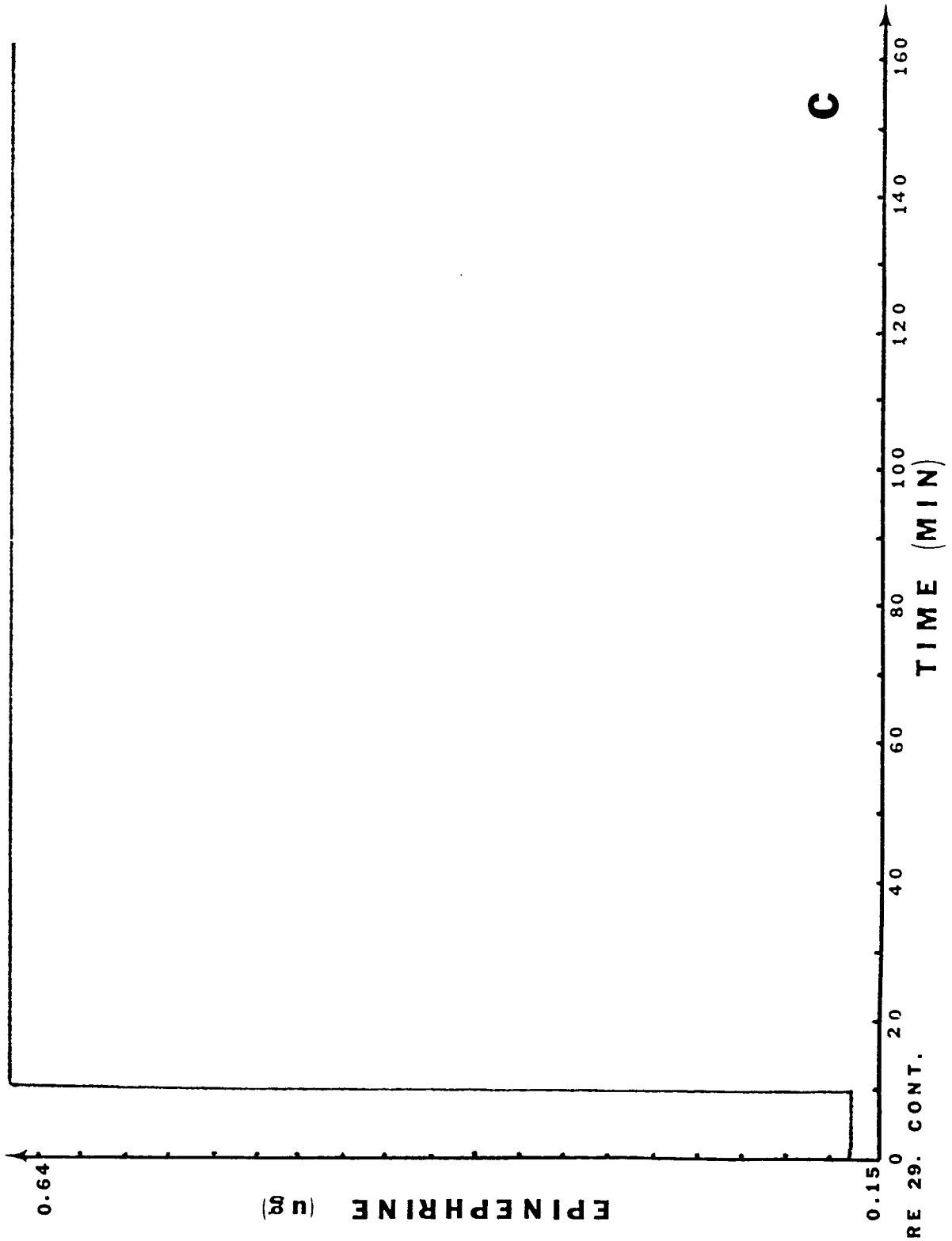


FIGURE 29. CONT.

these situations with actual experimental data from Felig and Wahren (1979) shows that the best fit occurs when the basal secretion rate does not increase until exercise begins. Epinephrine levels that are greater than basal before exercise begins result in glucose levels that are higher than what is expected from actual experiments.

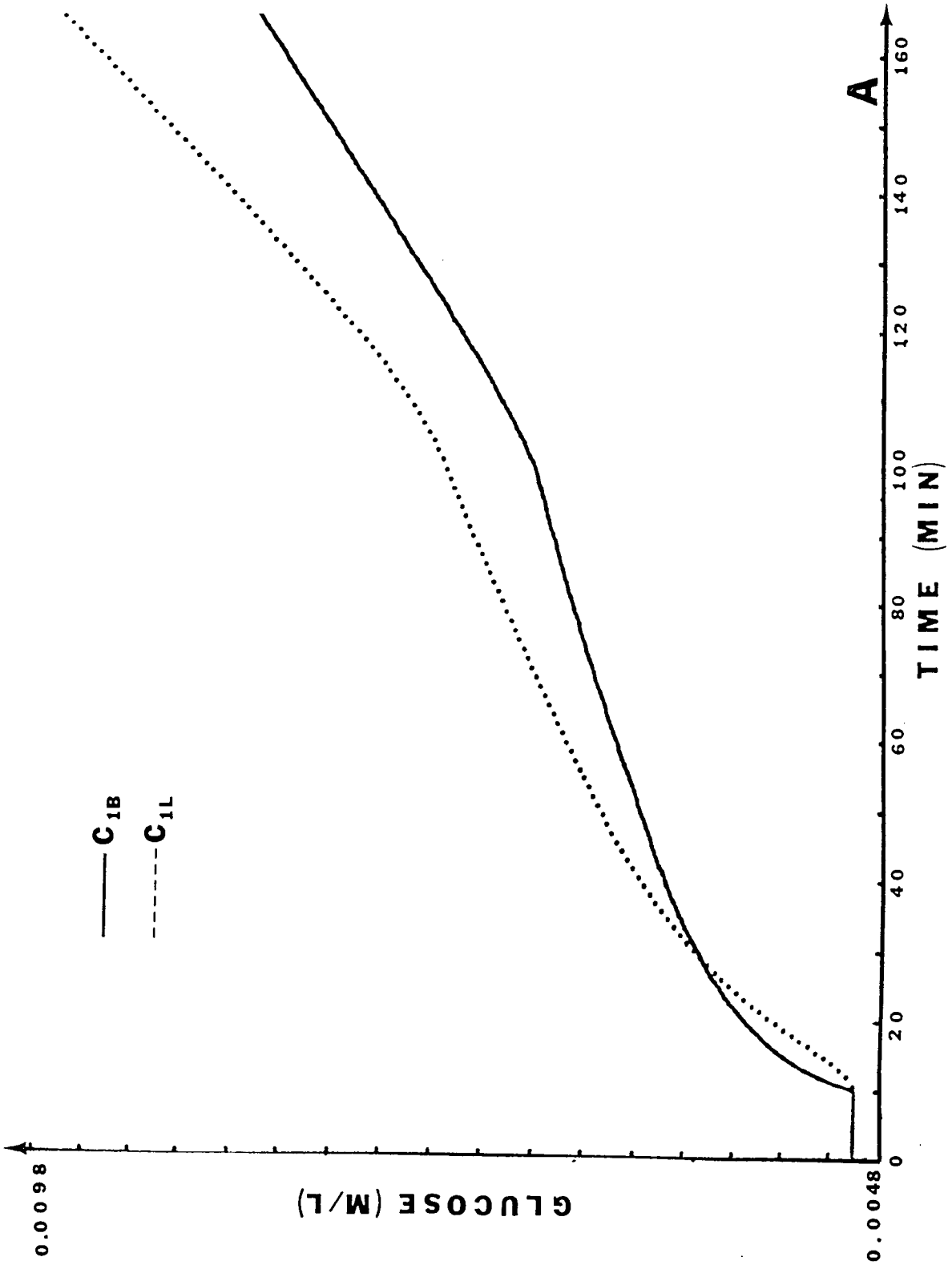
In figures 26-30 a marked change in the rate of glucose increase is seen at 100 minutes. This is at the point where uptake begins to slow and liver output continues to increase because of the time dependent function for gluconeogenesis resulting in the increase in blood glucose levels. The increase in blood glucose levels causes the threshold for glucagon secretion levels to be reached stopping glucagon secretion.

Felig and Wahren (1975) reported that the rate of gluconeogenesis plateaued after approximately 90 minutes of exercise and then showed a steady decline after 180 minutes. The response of the model to a gluconeogenic rate limited at 90 minutes is shown in figures 31 through 35. This still does not result in the expected decrease in blood glucose after 100 minutes. The failure of the blood glucose levels to respond favorably probably results from the fact that after approximately 60 to 100 minutes long term controls such as FFA levels begin to play an important role in glucose homeostasis during exercise and only short term controls are taken into account in this model.

Figure 36 shows the response of the model to exercise situations when the basal level of epinephrine secretion is not increased. This results in severe disturbances of glucose homeostasis during the first 40 minutes of exercise. Larger oscillations are seen in blood glucose levels that are not apparent during even small increases in epinephrine secretion.

Figure 30. Simulation of exercise response of plasma and portal glucose (A), plasma glucagon (B), and epinephrine (C) when basal secretion of epinephrine is increased 5.5 times at the start of exercise

Basal secretion, B = 5.0 ug/min


A
TIME (MIN)
0
20
40
60
80
100
120
140
160
GLUCOSE (M/L)
0.0048
0.0098
C_{1B}
C_{1L}

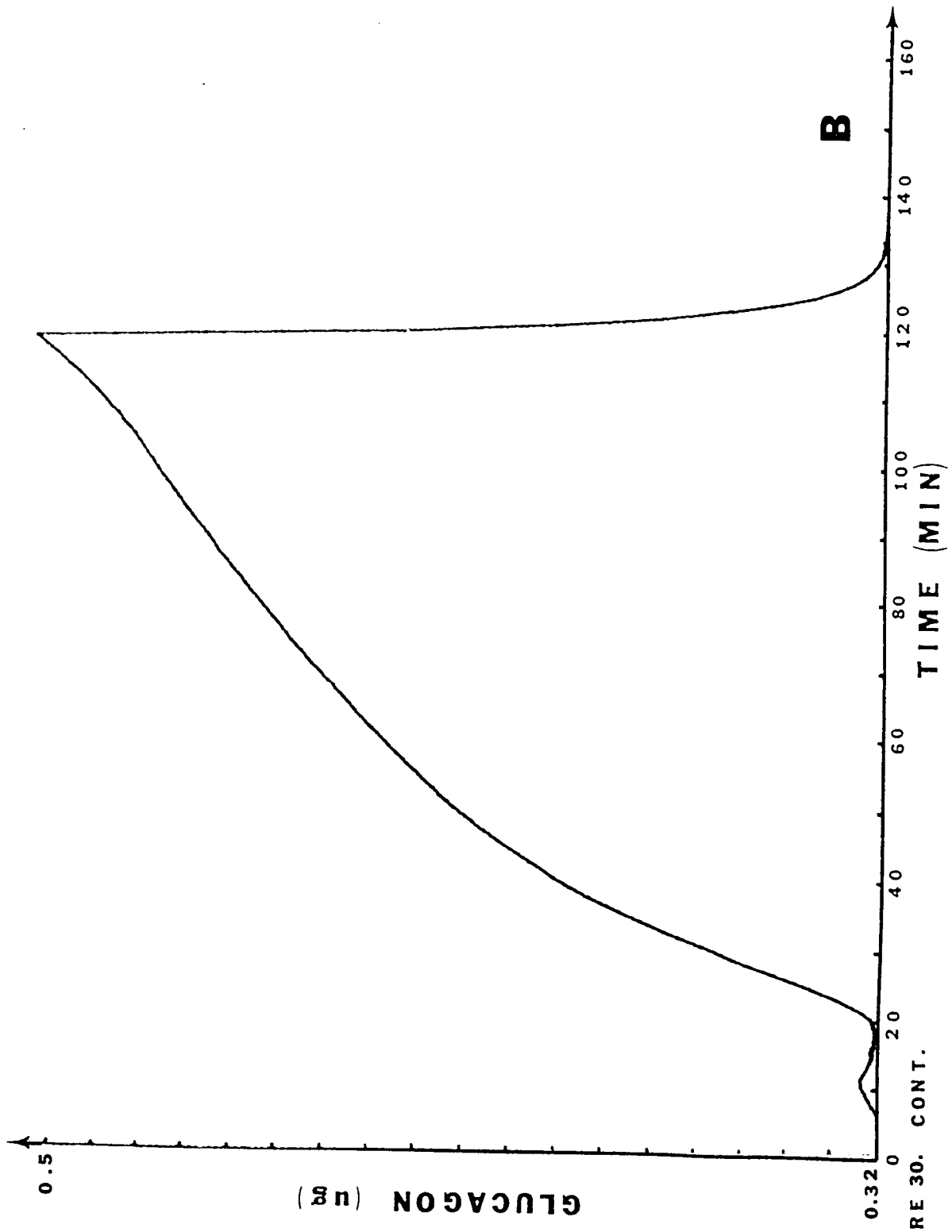


FIGURE 30. CONT.

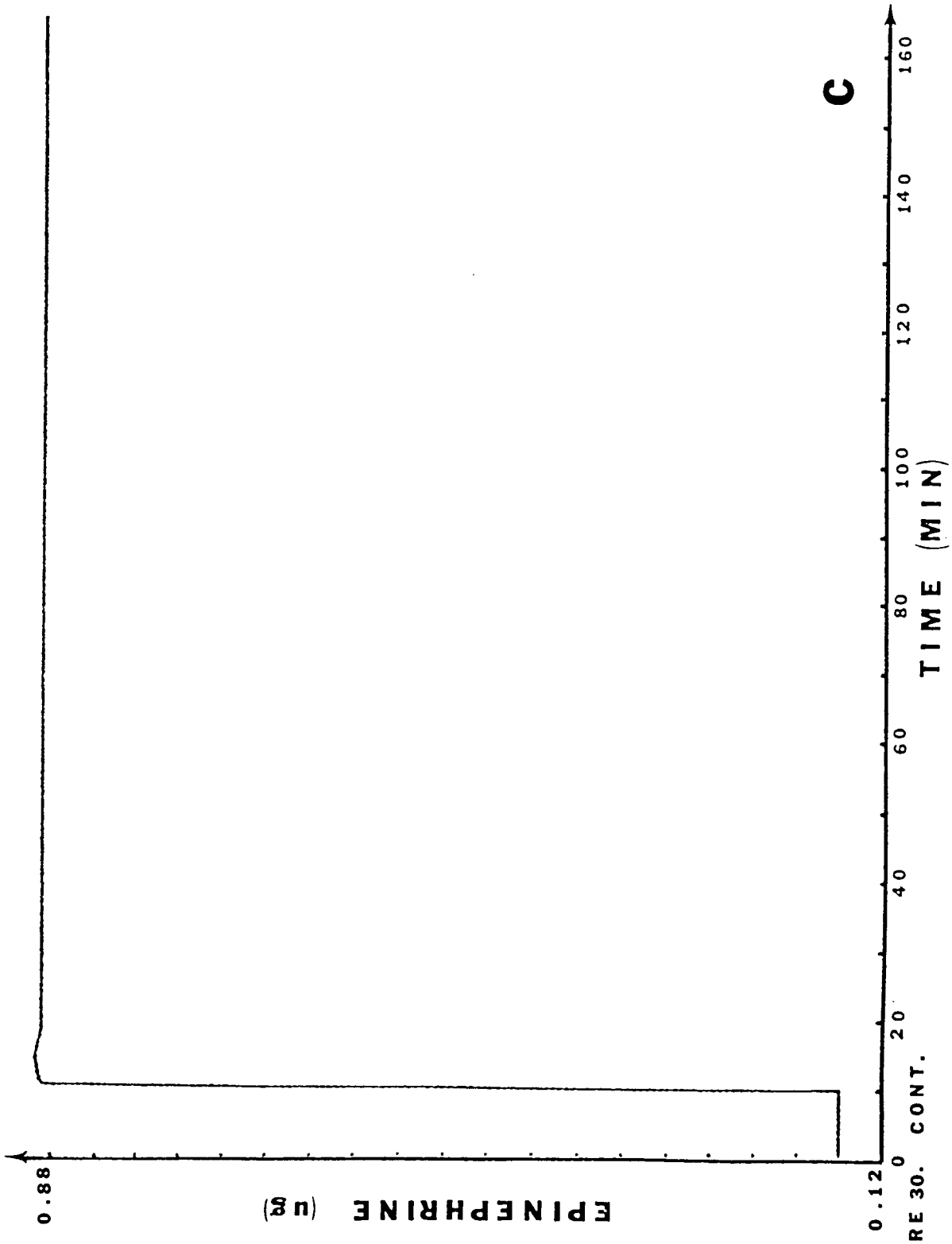


FIGURE 30. CONT.

Figure 31. Comparison of experimental data and model glucose response to exercise when the increase in gluconeogenesis is limited at 90 minutes and basal epinephrine secretion increases four times before the start of exercise

Basal secretion, B = 3.6

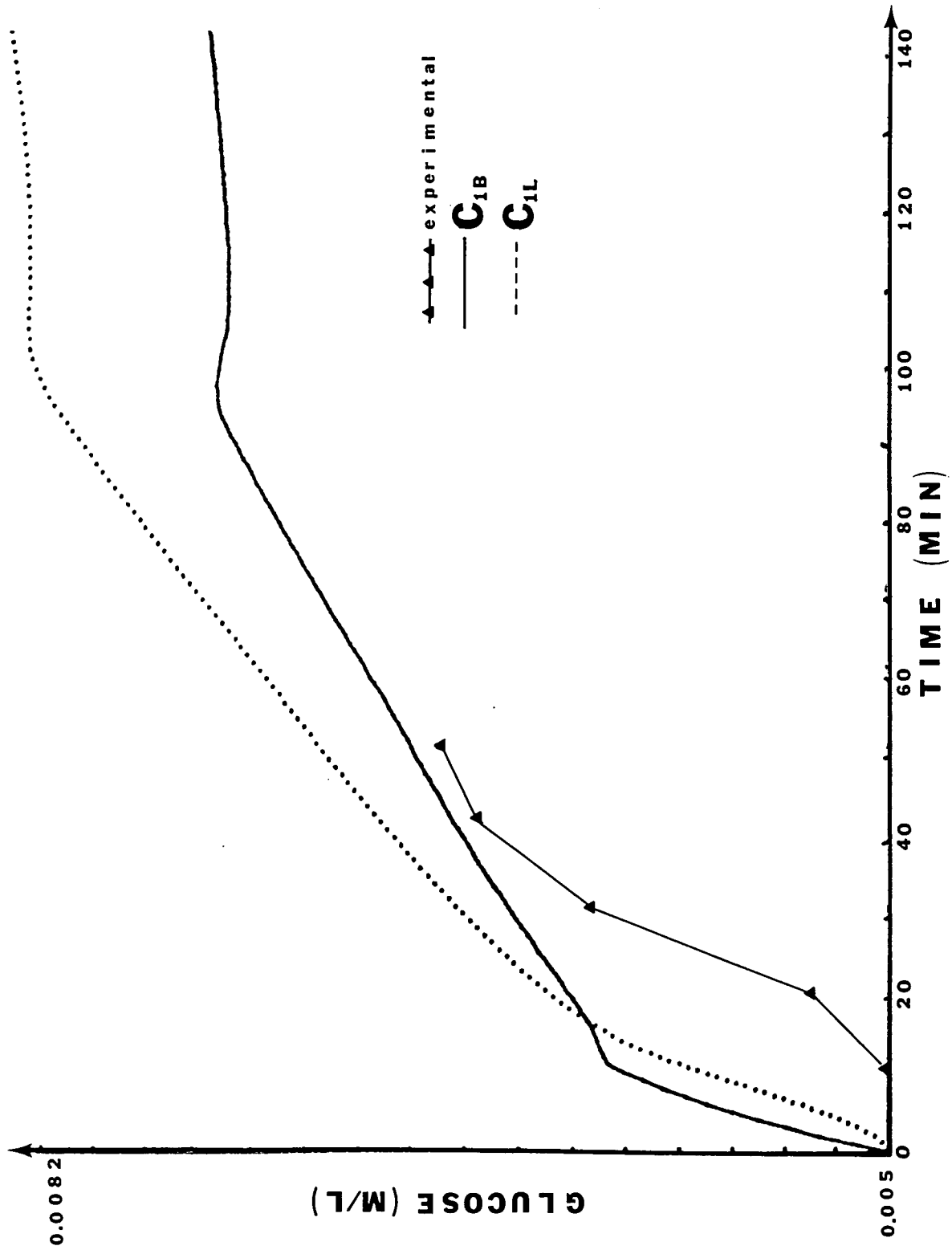

experimental
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.0082
0.005
0
20
40
60
80
100
120
140
TIME (MIN)

Figure 32. Comparison of experimental data and model glucose response to exercise when the increase in gluconeogenesis is limited at 90 minutes and basal secretion of epinephrine does not increase until exercise begins

Basal secretion, B = 3.6

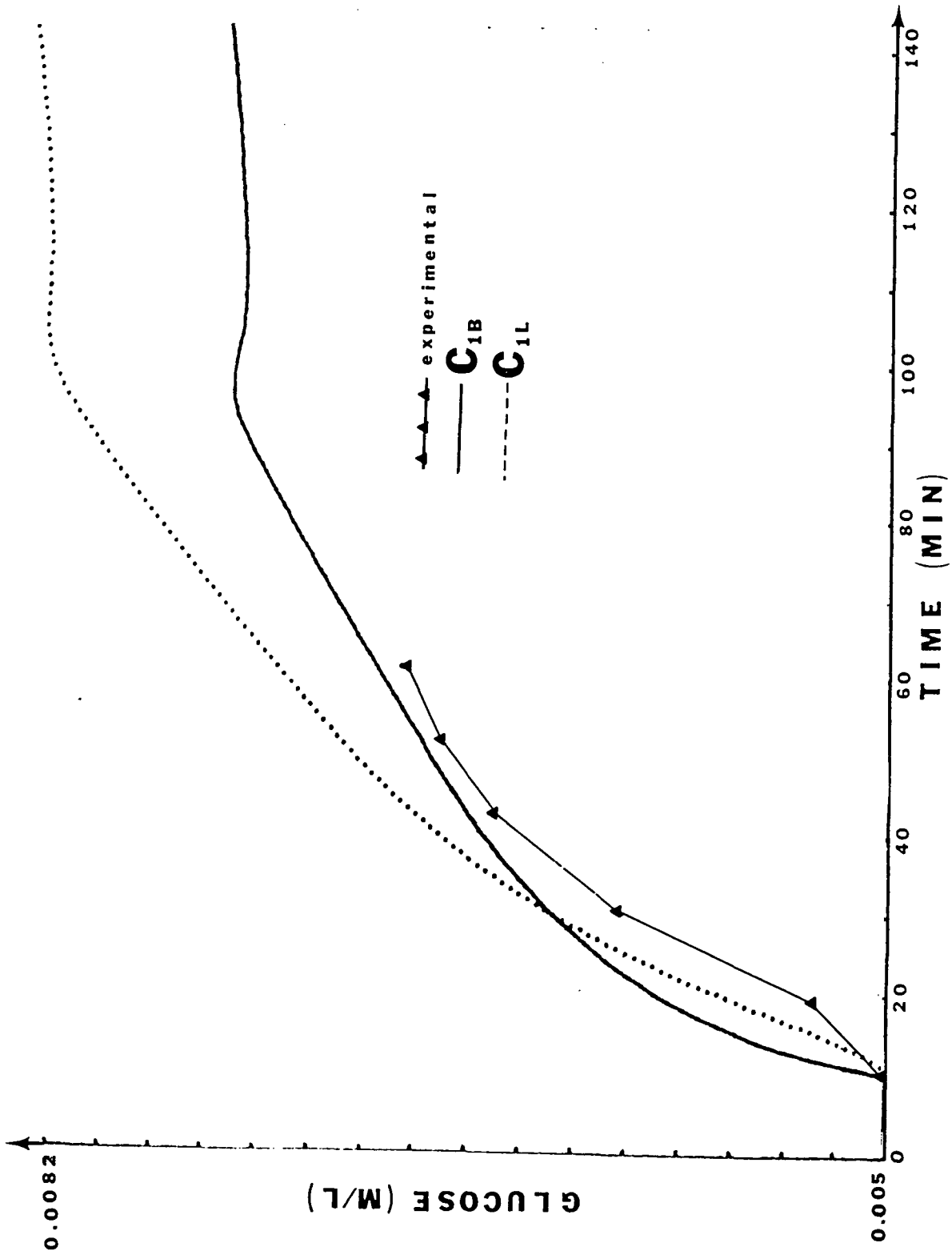
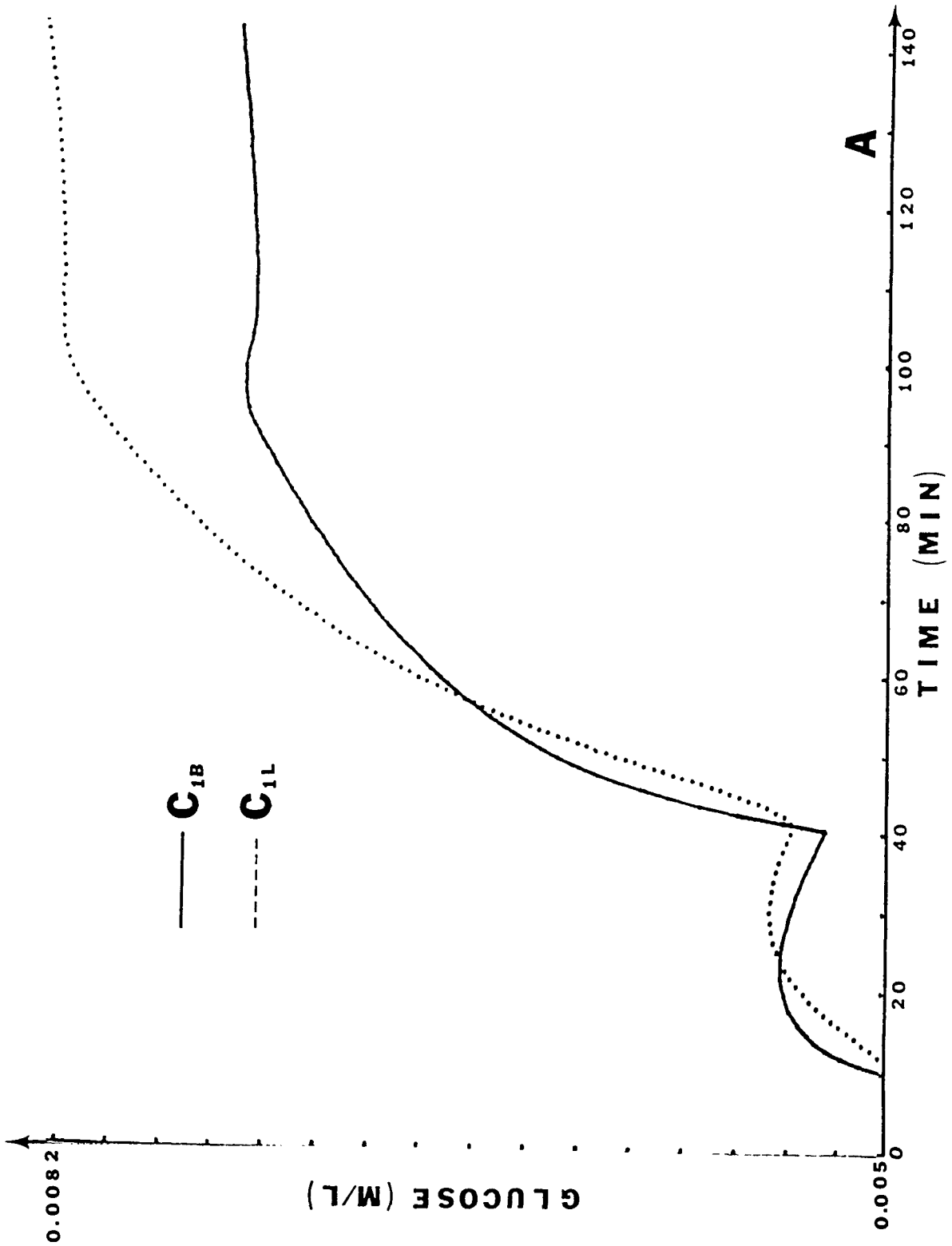

0.0082
0.005
GLUCOSE (M/L)
0
20
40
60
80
100
120
140
TIME (MIN)
experimental
C_{1B}
C_{1L}

Figure 33. Response of plasma and portal glucose (A), and plasma glucagon (B) when basal epinephrine secretion increases with time following the start of exercise

$$\text{Basal secretion, } B = \begin{cases} 2.3 & 10 < t < 40 \\ 4.27 & 40 \leq t < 60 \\ 5.93 & 60 \geq t \end{cases}$$


A
TIME (MIN)
0
20
40
60
80
100
120
140
GLUCOSE (M/L)
0.0082
0.005
C_{1B}
C_{1L}

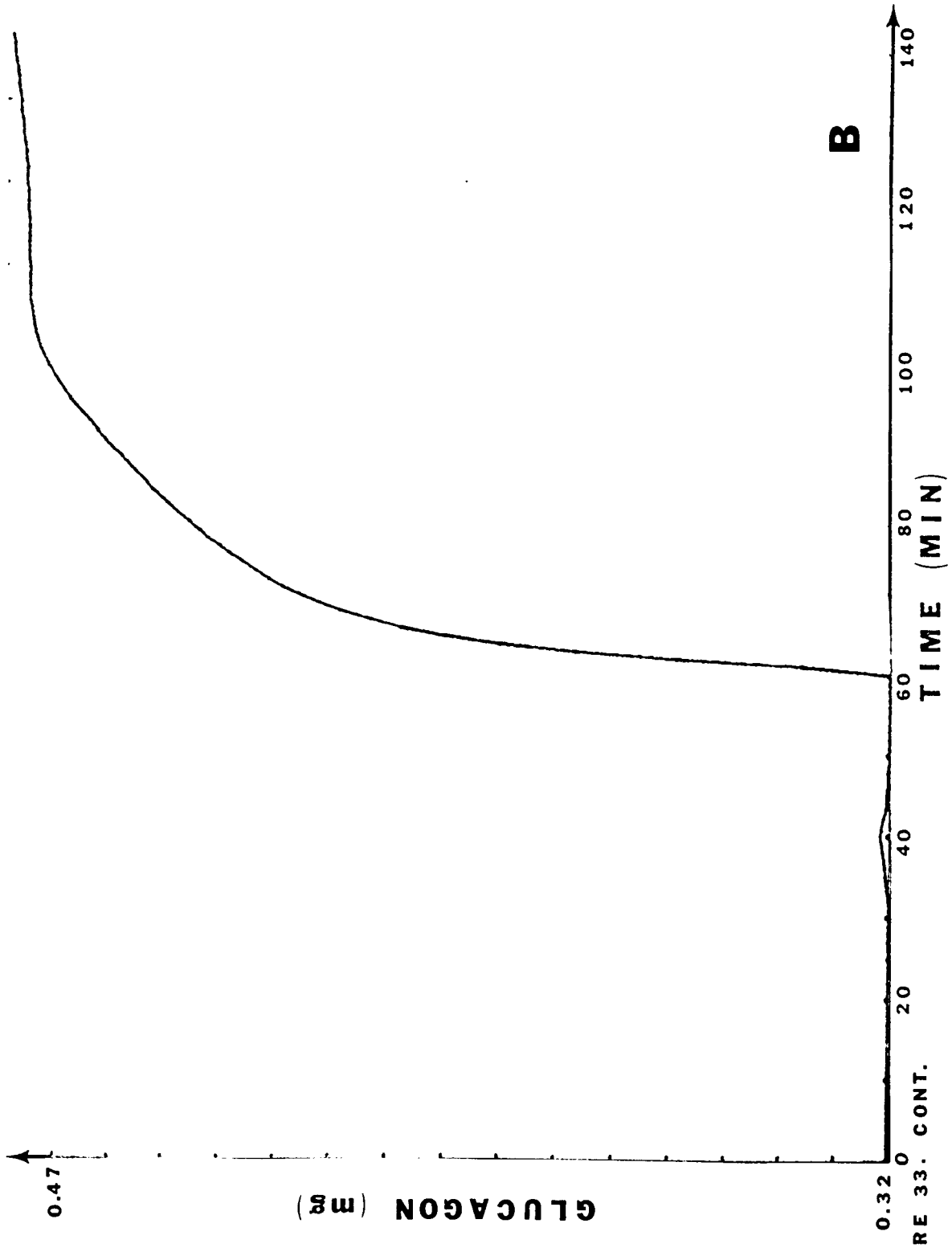
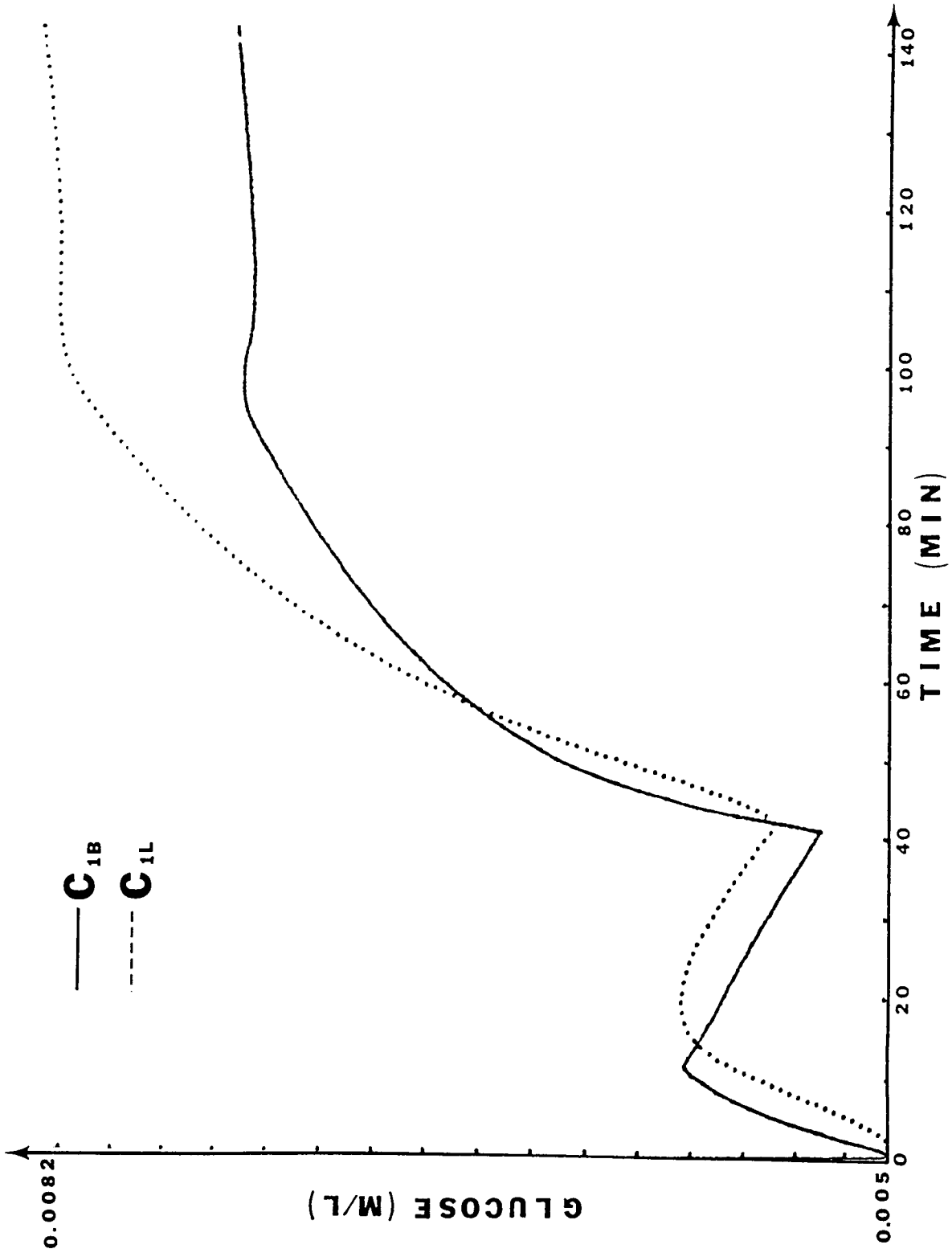


FIGURE 33. CONT.

Figure 34. Response of plasma and portal glucose when basal epinephrine increases 10 minutes before the beginning of exercise and continues to increase over time

$$\text{Basal secretion, } B = \begin{cases} 1.8 & t < 10 \\ 2.3 & 10 \leq t < 40 \\ 4.27 & 40 \leq t < 60 \\ 5.93 & 60 \geq t \end{cases}$$


0.0082
0.005
GLUCOSE (M/L)
0
20
40
60
80
100
120
140
TIME (MIN)
C_{1B}
C_{1L}

Responses to variable levels of epinephrine are shown in Figures 33, 34, and 35. The results from these simulations show that the epinephrine thresholds for glucose output from the liver must be reached in order for increased output to continue.

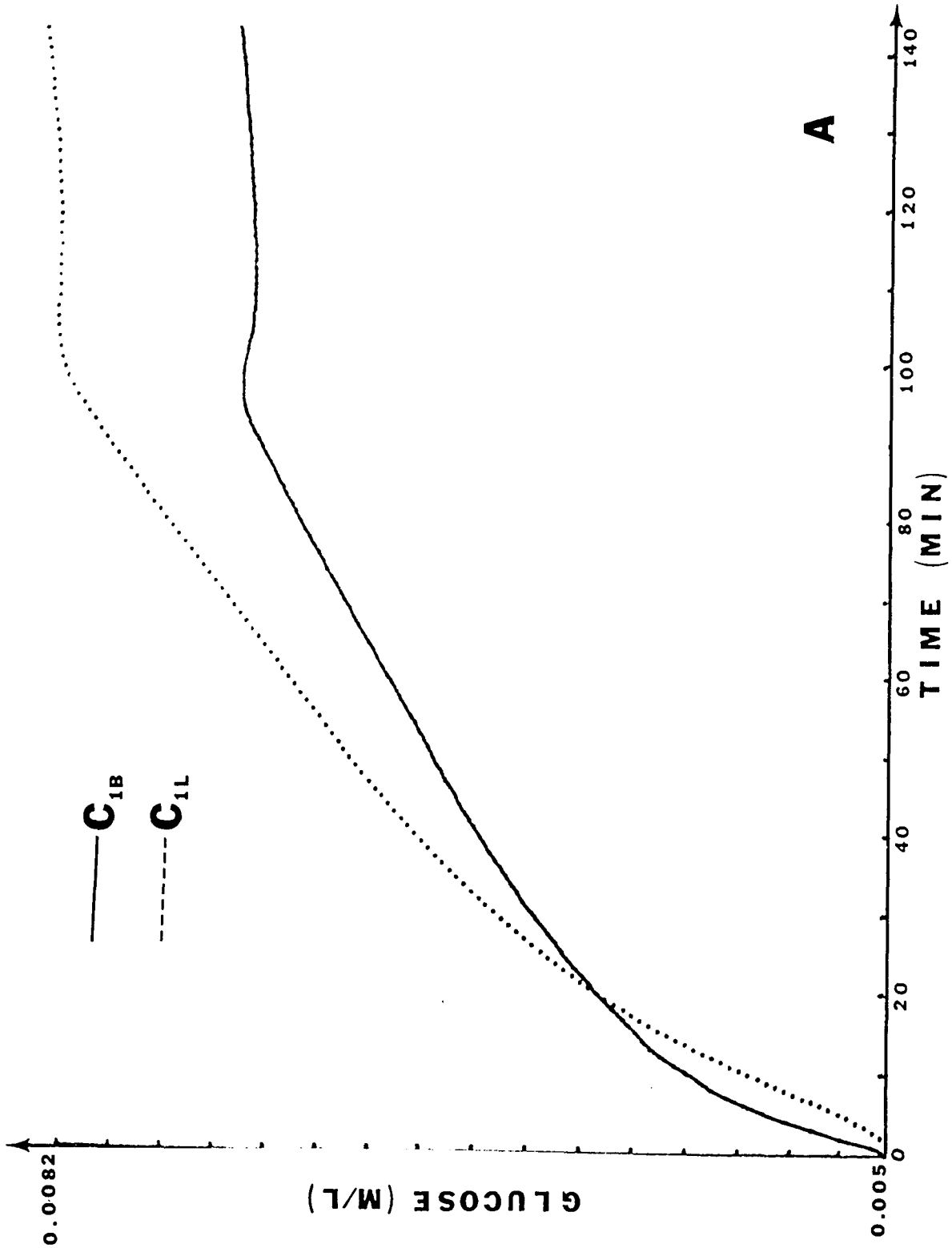
The majority of the data in the literature reported increases in blood glucose levels during the first 40 to 60 minutes of mild to moderate exercise levels. Anywhere from a 15 to 35% increase in blood glucose levels occurred depending on how long it took the subject to reach exhaustion (Felig and Wahren, 1975; Pruett, 1971; Galbo et al., 1975; Bottger et al., 1972; Felig and Wahren, 1979). The simulation results also showed increases in blood glucose levels over the first 40 to 60 minutes, however the levels continue to increase after 60 minutes where experimental data shows decreases in blood glucose levels.

It has been reported that circulating levels of epinephrine do not play a significant role in increased liver output of glucose since <u>in vitro</u> studies have shown that unphysiological concentrations of epinephrine are needed to produce significant changes in glycogenolysis or gluconeogenesis (Exton and Park, 1968; Hutson, et al., 1976; Pilkis, et al., 1975). However, these studies only take into account the direct effect of epinephrine and not the indirect effects of the changes in other hormone levels that occur as a result of increased epinephrine levels.

The simulation results show that epinephrine is important during at least the first 60 minutes of exercise for glucose regulation. When the increase in epinephrine is high enough to exceed the epinephrine thresholds for gluconeogenesis the response of the model to exercise is a good approximation of the glucose curves reported from experimental data. In

Figure 35. Response of plasma and portal glucose (A), and plasma glucagon (B) when basal epinephrine increases 10 minutes before the beginning of exercise and continues to increase over time

$$\text{Basal secretion, } B = \begin{cases} 1.8 & t < 10 \\ 3.2 & 10 \leq t < 40 \\ 4.27 & 40 \leq t < 60 \\ 5.93 & 60 \geq t \end{cases}$$


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.0082
0.005
0
20
40
60
80
100
120
140
TIME (MIN)

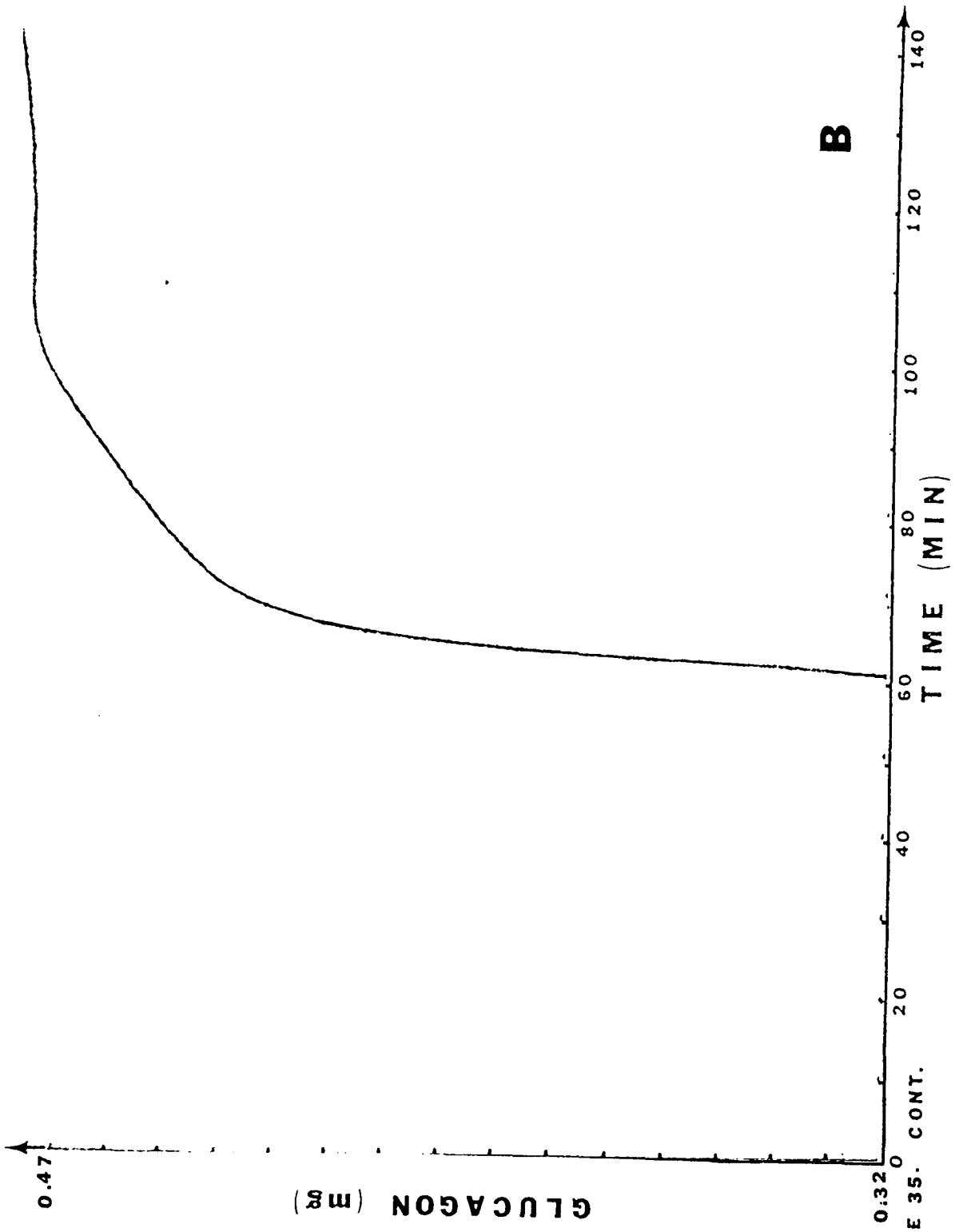
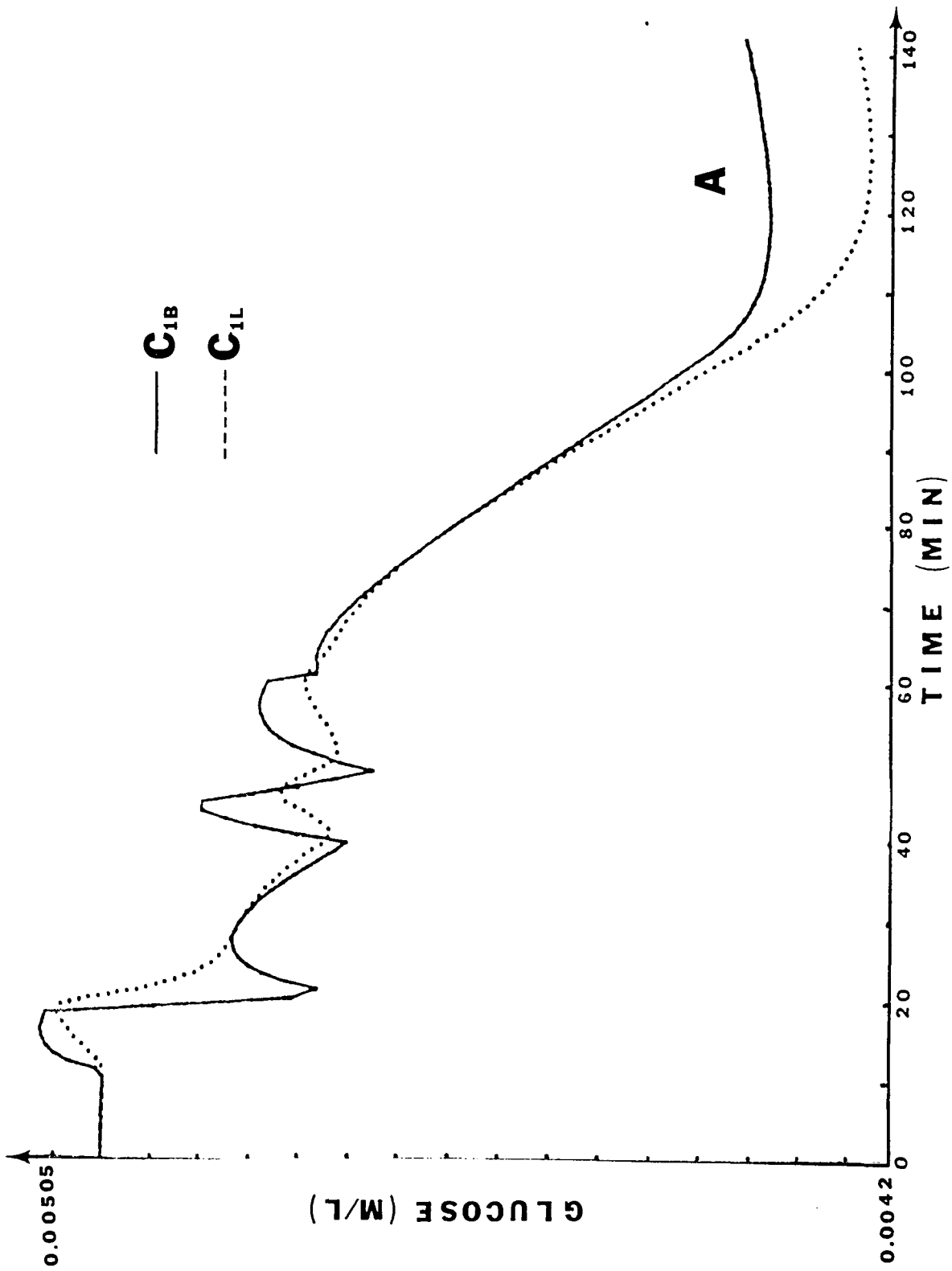


FIGURE 35. CONT.

Figure 36. Model response to exercise conditions when the increase in basal epinephrine secretion is removed showing changes in plasma and portal glucose (A), plasma insulin (B), plasma glucagon (C), and epinephrine (D)


A
C_{1B}
C_{1L}
GLUCOSE (M/L)
0.00505
0.0042
0
20
40
60
80
100
120
140
TIME (MIN)

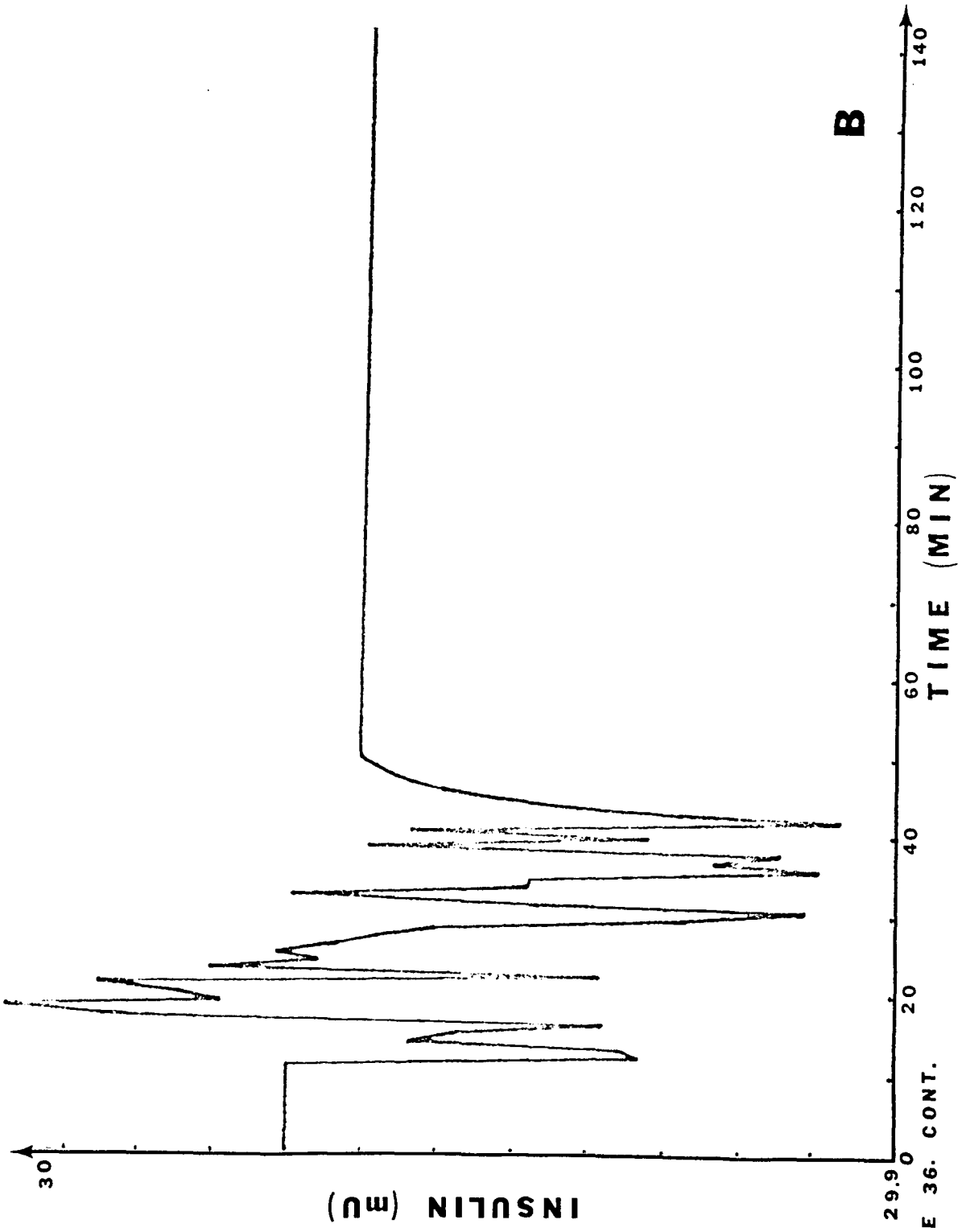


FIGURE 36. CONT.

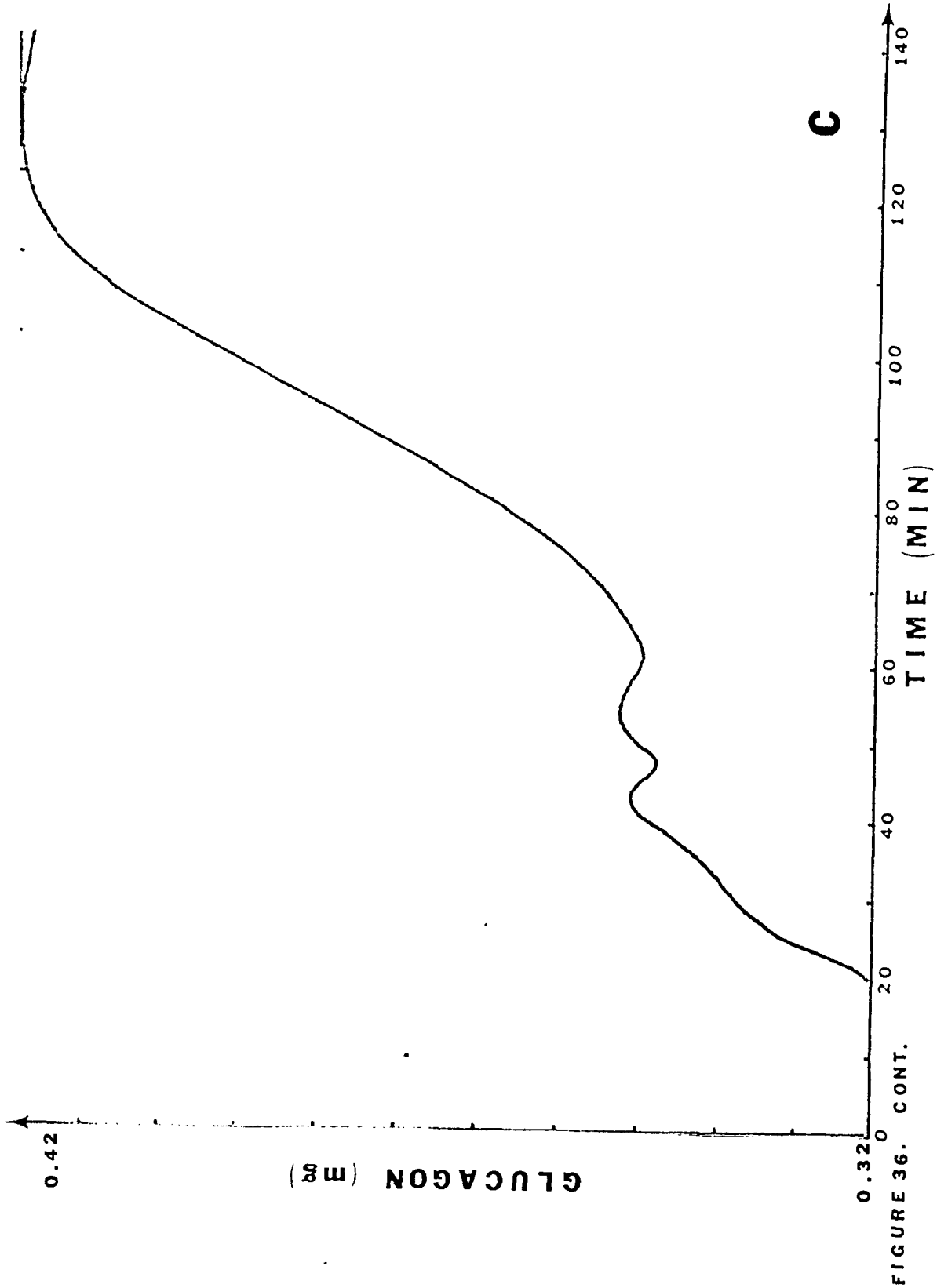


FIGURE 36. CONT.

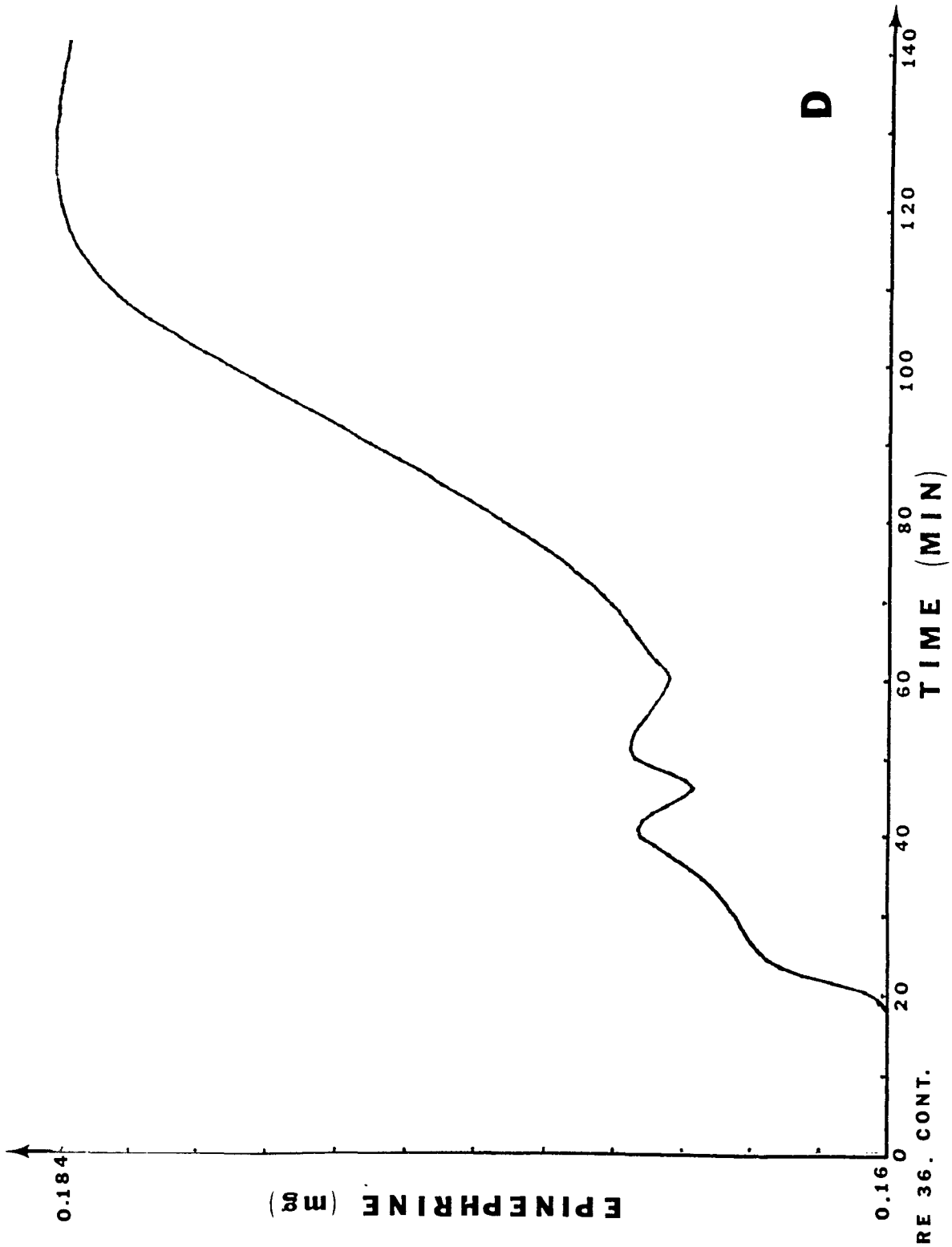


FIGURE 36. CONT.

fact it is remarkable that the curves from this model are so close to that from the data of Felig and Wahren (1979) (Fig. 32) when such rough approximations of the functions for gluconeogenesis and liver glycolysis were used.

CONCLUSIONS AND RECOMMENDATIONS

A mathematical model, employing nonlinear differential equations, was developed to describe the control of blood glucose during exercise. The results from the computer simulations agree reasonably well with data from actual experiments.

The validity of the proposed model was tested by simulating responses of IV infusions of insulin, glucagon, glucose, and epinephrine, and an oral glucose load. Knowing the model responses to stimuli at rest is important in analyzing the responses to exercise, which become quite complex.

Overall, the response of the model to the IV input was good, as well as the oral glucose load. Some refinements are needed, especially of the functions for gluconeogenesis and glycogenolysis, but at this stage of the modeling efforts the simulations yielded accurate approximations of the expected results from experimental data.

During exercise, changes in epinephrine levels act to alter conditions so that the liver can increase its output of glucose. The increased output in the model results from decreases in the utilization of G-6-P in the liver glycolytic pathways and increases in the rate of gluconeogenesis. The increase in gluconeogenesis is important in preventing severe hypoglycemia during exercise.

The exercise results presented showed good correlation up to the first 60 minutes of exercise. After 60 minutes, factors other than those considered here begin to play an important role in the regulation of glucose levels. The only factors considered in this initial model are the short term controls that play a significant role during the first two hours

of a disturbance at rest. These factors apparently do not provide sufficient controls to insure the simulation of actual responses after one hour of moderate exercise. Probably one of the most important factors of glucose regulation during exercise not considered here is the effects of FFA. Fatty acids start to become a major fuel source as exercise continues past one hour and the result is the regulation of glucose metabolism to conserve energy for the glucose dependent tissues. Incorporating these fatty acid effects into the model would give a better understanding of the mechanisms involved in glucose regulation.

Under most physiological conditions, the rates of glucose utilization are matched by similar increments in glucose output by the liver. This precise example of biological engineeering cannot be explained by simple hormonal or metabolic regulation. Such mutual regulation could be accounted for either by signals released by the muscle and the liver and the simultaneous interpretation of the signals by the central nervous system or by circulating signals released by the muscle that would be recieved by the liver. The nature of a central regulation and the existence of muscle messengers has not been thoroughly studied.

From this simulation study, it appears that epinephrine might be a good candidate as an integrating factor for the increased uptake and release of glucose that accompanies exercise. Neural stimulation plays an important part in this theory as it results in the initial increase of glucose output by the liver. The neural response to the increased work-load on the muscles is to increase the secretion of epinephrine. The increased epinephrine levels alter the other hormone levels which act to stimulate the release of glucose from the liver.

However, to get a good idea of how the system works experiments are needed that correlate all the variables at the same time. These are not yet available. When these data do become available the precise scheme of these interactions can be outlined by comparison of the data and computer simulations.

A better model of glucose regulation also needs to be developed. Inclusion of FFA metabolism and refinements of the mathematical relationships, as suggested by studies on specific portions of the model, would undoubtedly yield better results. The most obvious need is for a more precise definition of the functions for gluconeogenesis and liver glycolysis.

BIBLIOGRAPHY

Ahlborg, G., and P. Felig. 1976. Influence of glucose injestion on fuel-hormone response during prolonged exercise. J. Appl. Physiol. 41:683-688.

Ahlborg, G., P. Felig, L. Hagenfeldt, R. Hendler, and J. Wahren. 1974. Substrate turnover during prolonged exercise in man. J. Clin. Invest. 53:1080-1090.

Ahlborg, G., L. Hagenfeldt, and J. Wahren. 1975. Substrate utilization by the inactive leg during one leg or arm exercise. J. Appl. Physiol. 39:718-723.

Altszuler, N., R. Steele, I. Rathgeb, and R. C. DeBodo. 1967. Glucose metabolism and plasma insulin levels during epinephrine infusion in the dog. Am. J. Physiol. 212:677-682.

Berger, M., S. A. Hagg, and N. B. Ruderman. 1975. Glucose metabolism in perfused skeletal muscle. Interaction of insulin and exercise on glucose uptake. Biochem. J. 146:231-238.

Bergman, R. N. 1977. Integrated control of hepatic glucose metabolism. Fed. Proc. 36:265-273.

Bergman, R. N., and M. El-Refai. 1975. Dynamic control of hepatic glucose metabolism: Studies by experimental and computer simulation. Ann. Biomed. Eng. 3:411-432.

Bottger, I., E. M. Schlein, G. R. Faloona, J. P. Knochel, and R. H. Unger. 1972. The effects of exercise on glucagon secretion. J. Clin. Endocrinol. 35:117-125.

Bratusch-Marrain, P. R., W. K. Wadhausl, S. Gasic, A. Korn, and P. Nowotny. 1980. Oral glucose tolerance test: Effect of different glucose loads on splanchnic carbohydrate and substrate metabolism in healthy man. Metabolism 29:289-295.

Brown, J. H. V. 1978. Integration and control of metabolic processes. Van Nostrand Reinhold Co., New York.

Cahill, G. F., Jr., J. Asmore, A. E. Renold, and A. B. Hastings. 1959. Blood glucose and the liver. Am. J. Med. 26:264-282.

Cahill, G. F., Jr., M. G. Herrera, A. P. Morgan, J. S. Soelder, J. Steinke, P. L. Levy, G. A. Reichard, Jr., and D. M. Kipnis. 1966. Hormone-fuel interrelationships during fasting. J. Clin. Invest. 45:1751-1769.

Campfield, L. A. 1973. Application of a mathematical model of glucose and free fatty acid metabolism to the study of hypoglycemia. Pages 484-490 in A. S. Iberall and A. C. Guyton, eds. Proceedings IFAC/APS Symposium on regulation and control in physiological systems. Instrument Society of America, Pittsburgh, Pa.

Charette, W. P., A. H. Kadish, and R. Sridhar. 1969. Modeling and control aspects of glucose homeostasis. Math. Bio-sci. Suppl. 1:115-149.

Cherrington, A. D., J. L. Chiasson, J. E. Liljenquist, A. S. Jennings, K. Keller, and W. W. Lacy. 1976. The role of glucagon in maintaining basal glucose production. J. Clin. Invest. 58:1407-1418.

Cherrington, A. D., P. E. Williams, and M. S. Harris. 1978. Relationships between plasma glucose level and glucose uptake in the conscious dog. Metabolism 27:787-791.

Chideckel, E. W., C. J. Goodner, D. J. Koerker, D. G. Johnson, and J. W. Ensink. 1977. Role of glucagon in mediating metabolic effects of epinephrine. Am. J. Physiol. 232:E464-470.

Christensen, N. J., H. Galbo, J. F. Hansen, B. Hesse, E. A. Richter, and J. Trap-Jensen. 1979. Catecholamines and exercise. Diabetes 28 (Suppl. 1):58-62.

Claus, T. H., and S. J. Pilkis. 1976. Regulation by insulin of gluconeogenesis in isolated rat hepatocytes. Biochim. Biophys. Acta 42:246-262.

Cohen, P., H. G. Nimma, and C. G. Proud. 1978. How does insulin stimulate glycogen synthesis. The Biochem. Soc. Symp. 43:69-97.

Cramp, D. G., and E. R. Carson. 1979. Dynamics of blood glucose and its regulating hormones. Pages 171-201 in D. A. Linkins, ed. Biological systems, modeling and control. Peter Peregrines, Ltd., New York, New York.

DeBodo, R. C., R. Steele, N. Altszuler, A. Dunn, and J. Bishop. 1963. On the hormonal regulation of carbohydrate metabolism studies with C-14 glucose. Recent. Prog. Horm. Res. 19:445-488.

Dietz, M. R., J. L. Chiasson, T. R. Soderling, and J. H. Exton. 1980. Epinephrine regulation of skeletal muscle glycogen metabolism. J. Biol. Chem. 255:2301-2307.

Ensink, J. W., and R. H. Williams. 1972. Hormonal and nonhormonal factors modifying man's response to insulin. Pages 665-684 in D. P. Steiner and N. Frainkel, eds. Handbook of Physiology:Endocrinology Sec. 7, Vol. 1. Am. Phys. Soc., Washington, D. C.

Exton, J. H. 1972. Gluconeogenesis. Metabolism 21:945-990.

Exton, J. H. 1976. Hormonal control of gluconeogenesis. Pages 125-168 in D. M. Klachko, R. R. Anderson, and M. Heimberg, eds. Hormones and energy metabolism. Plenum Press, New York, New York.

Exton, J. H., and C. R. Park. 1968. Control of gluconeogenesis in the liver. J. Biol. Chem. 243:4189-4196.

Exton, J. H., and C. R. Park. 1972. Interaction of insulin and glucagon in control of liver metabolism. Pages 437-456 in D. P. Steiner and N. Frainkel, eds. Handbook of physiology: Endocrinology Sec. 7, Vol. 1. Am. Phys. Soc., Washington, D. C.

Ezdindi, E. Z., and J. E. Sokai. 1966. Comparison of glucagon and epinephrine effects on the dog. Endocrinology 78:47-54.

Falls, H. B. 1968. Exercise Physiology. Academic Press, New York, New York.

Felig, P., and J. Wahren. 1975. Fuel homeostasis during exercise. N. Engl. J. Med. 293:1078-1084.

Felig, P., and J. Wahren. 1979. Role of Insulin and Glucagon in the regulation of hepatic glucose production during exercise. Diabetes 28(Suppl. 1):71-75.

Felig, P., J. Wahren, and R. Hendler. 1976. Influence of physiologic hyperglucagonemia on basal and insulin-inhibited splanchnic glucose output in normal man. J. Clin. Invest. 58:761-765.

Felig, P., J. Wahren, R. Hendler, and G. Ahlborg. 1972. Plasma glucagon levels in exercising man. N. Engl. J. Med. 287:184-185.

Felui, J. E., L. Hue, and H-G. Hers. 1976. Hormonal control of pyruvate kinase activity and of gluconeogenesis in isolated hepatocytes. Proc. Nat. Acad. Sci. 73:2762-2766.

Finkelstein, S. M., M. A. Bleicher, S. Batthang, and J. Tiefenbrum. 1975. *In vivo* modeling for glucose homeostasis. IEEE Trans. Biomed. Eng. 22:47-52.

Foa, P. P. 1972. The secretion of glucagon. Pages 261-279 in D. P. Steiner and N. Frainkel, eds. Handbook of Physiology: Endogrinology Sec. 7, Vol. 1. Am. Physiol. Soc., Washington, D. C.

Foa, P. P., J. S. Bajaj, and N. L. Foa, eds. 1977. Glucagon: Its role in physiology and clinical medicine. Springer-Verlag, New York, New York.

Foster, R. O. 1970. The dynamics of blood sugar regulation. M.S. Thesis. Massachusetts Institute of Technology, Cambridge, Mass.

Foster, R. O., J. S. Soeldner, M. H. Tan, and J. R. Guyton. 1973. Short-term glucose homeostasis in man: A system dynamic model. ASME Trans. (Series G) 95:308-312.

Galbo, H., and J. J. Holst. 1976. The influence of glucagon on hepatic glycogen mobilizationin exercising rats. Pfluegers Archiv. 363:49-53.

Galbo, H., J. J. Holst, and J. Christensen. 1975. Glucagon and plasma catecholamine responses to graded and prolonged exercise in man. J. Appl. Physiol. 38:70-75.

Galbo, H., N. J. Christensen, and J. J. Holst. 1976a. The role of the autonomic innervation in the control of glucagon and insulin responses to prolonged exercise in man. Acta. Physiol. Scand. Suppl. 440:175-190.

Galbo, H., J. J. Holst, N. J. Christensen, and J. Hilsted. 1976b. Glucagon and plasma catecholamines during beta-receptor blockade in exercising man. J. Appl. Physiol. 40:855-863.

Galbo, H., N. J. Christensen, and J. J. Holst. 1977a. Glucose-induced decreases in glucagon and epinephrine responses to exercise in man. J. Appl. Physiol. 42:5225-530.

Galbo, H., E. A. Richter, J. Hilstedt, J. J. Holst, N. J. Christesen, and J. Henricksson. 1977b. Hormonal regulation during prolonged exercise. Ann. N.Y. Acad. Sci. 301:72-80.

Ganong, W. F. 1979. Review of medical physiology. 9th ed. Lange Medical Publications, Los Altos, Calif.

Garrat, C. J., W. J. H. Butterfield, M. E. Abrams, G. Sterky, and M. J. Whichelow. 1972. Effects of exercise on peripheral uptake of 131-I-iodinsulin and glucose in nondiabetics. Metabolism 21:36-49.

Genuth, S. M. 1972. Metabolic clearance of insulin in man. Diabetes 21:1003-1010.

Gerich, J. E., J. H. Karam, and P. H. Forsham. 1973. Stimulation of glucagon secretion by epinephrine in man. J. Clin. Invest. 37:479-481.

Gerich, J. E., M. Lorenzi, S. Hane, G. Gustafson, R. Guillemin, and P. H. Forsham. 1975. Evidence for a physiologic role of pancreatic glucagon in human glucose homeostasis: studies with somatostatin. Metabolism 24:175-182.

Gerich, J. E., M. Lorenzi, E. Tsalikran, and J. H. Karam. 1976. Studies on the mechanism of epinephrine-induced hyperglycemia in man: evidence for participation of pancreatic glucagon secretion. Diabetes 25:65-71.

Goldman, S. 1960. Cybernetic aspects of homeostasis. Pages 61-100 in Mineral Metabolism. Vol. 1A. Academic Press, New York, New York.

Goldstein, M. S. 1961. Humoral nature of the hypoglycemic factor of muscular work. Diabetes 10:232-234.

Goodman, H. M. 1974. Pages 1776-1807 in V. B. Mountcastle, ed. Medical physiology. 13th ed. C. V. Mosby Co., St. Louis, Mo.

Goodman, H. M. 1980. Pages 1638-1676 in V. B. Mountcastle, ed. Medical physiology. 14th ed. C. V. Mosby Co., St. Louis, Mo.

Greenbaum, A. L., K. A. Gumaa, and P. Mclean. 1971. The distribution of hepatic metabolites and the control of the pathways of carbohydrate metabolism in animals of different dietary and hormonal status. Arch. Biochem. Biophys. 143:167-190.

Guyton, A. C. 1976. Textbook of medical physiology. 5th ed. W. B. Saunders Co., Philadelphia, Pa.

Guyton, J. R., R. O. Foster, J. S. Soeldner, M. H. Tan, C. B. Kahn, L. Koncz, R. E. Gleason. 1978. A model of glucose-insulin homeostasis in man that incorperates the fast pool theory of pancreatic insulin release. Diabetes 27:1027-1042.

Hartley, L. H. 1975. Growth hormone and catecholamine response to exercise in relation to physical training. Med. Sci. Sports 7:34-36.

Hartley, L. H., J. W. Mason, R. P. Hogan, L. G. Jones, T. A. Kotchen, E. H. Mougey, L. L. Pennington, and P. T. Ricketts. 1972a. Multiple hormonal responses to graded exercise in relation to physical training. J. Appl. Physiol. 33:602-606.

Hartley, L. H., J. W. Mason, R. P. Morgan, L. G. Jones, T. A. Kotchen. E. H. Mougey, F. E. Wherry, L. L. Pennington, and P. T. Ricketts. 1972b. Multiple hormonal responses to prolonged exercise in relation to physical training. J. Appl. Physiol. 33:607-610.

Havivi, E., and H. E. Wertheimer. 1964. A muscle activity factor increasing sugar uptake by rat diaphragms <u>in vitro</u>. J. Physiol. (London) 172:342-352.

Holloszy, J. O., and H. T. Narahara. 1965. Studies on tissue permeability. X. Changes in permeability to 3-methylglucose associated with contraction of isolated frog muscle. J. Biol. Chem. 240:3493-3500.

Hutson, N. J., F. T. Brumdley, F. D. Assinacopoulos, S. C. Harper, and J. H. Exton. 1976. Studies on the alpha-adrenergic activation of hepatic glucose output. J. Biol. Chem. 251:5200-5208.

Issekutz, B., Jr. 1979. Energy mobilization in exercising dogs. Diabetes 28(Suppl. 1):39-44.

Issekutz, B. Jr., P. Paul, and H. I. Miller. 1967. Metabolism in normal and pancreatectomized dogs during steady-state exercise. Am. J. Physiol. 213:857-862.

Jennings, A. S., A. D. Cherrington, J. E. Liljenguist, U. Keller, W. W. Lacy, and J. L. Chiasson. 1977. The role of insulin and glucagon in the regulation of gluconeogenesis in the postabsorptive dog. Diabetes 26:847-856.

Kawamori, R., and M. Vranic. 1977. Mechanism of exercise induced hypoglycemia in depancreatized dogs maintained on long-acting insulin. J. Clin. Invest. 59:331-337.

Lafferty, H. H., A. E. B. Giddings, and D. Mangnall. 1978. A digital computor model for glucose-insulin dynamics. Comput. Biol. Med. 8:41-55.

Levine, R., M. S. Goldstien, B. Huddlestun, and S. P. Klien. 1950. Action of insulin on the permeability of cells to free hexoses, as studied by its effects on the distribution of galactose. Am. J. Physiol. 163:70-76.

London, W. P. 1966. A theoretical study of hepatic glycogen metabolism. J. Biol. Chem. 241:3008-3022.

McMurray, W. C. 1977. Essentials of human metabolism. Harper and Row, Pub. Inc., Hagerstown, Md.

Muller, W. A., L. Girardier, J. Seydoux, M. Berger, A. E. Renold, and M. Vranic. 1978. Extrahepatic glucagon andglucagon-like immunoreactivity in depancreatized dogs: a quantitative assessment of secretion rates and anatomical delineation of sources. J. Clin. Invest. 62:124-132.

National Diabetes Data Group. 1979. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057.

Nazar, K., Z. Brezezenska, and S. Kozlowski. 1975. Sympathetic activity during prolonged physical activity in dogs: control of energy substrate utilization. Pages 204-210 in H. Howard and J. R. Poortmans, eds. Metabolic Adaptation to prolonged physical exercise. Vol. 7. Brikhauser Verlag, Basel, Switzerland.

Newsholme, E. A. 1976. Carbohydrate metabolism *in vivo*: regulation of blood glucose level. Clin. Endocrinol. Metabol. 5:543-578.

Newsholme, E. A., and P. J. Randle. 1964. Regulation of glucose uptake by the muscle. Biochem. J. 93:641-651.

Newsholme, E. A., and C. Start. 1973. Regulation in metabolism. John Wiley and Sons, New York, New York.

Pilkis, S. J., T. H. Claus, R. A. Johnson, and C. R. Park. 1975. Hormonal control of cyclic 3': 5'-AMP levels and gluconeogenesis in isolated hepatocytes from feed rats. J. Biol. Chem. 250:6328-6336.

Pilkis, S. J., J. P. Riov, and T. H. Claus. 1976. Hormonal control of [14-C] glucose synthesis from [U-14-C] dihydroxyacetone and glycerol in isolated rate hepatocytes. J. Biol. Chem. 251:7841-7852.

Porte, D., Jr., A. L. Graber, T. Kuzuya, and R. H. Williams. 1966. The effect of epinephrine on immunoreactive-insulin levels in man. J. Clin. Invest. 45:228-235.

Porte, D., Jr., and R. P. Robertson. 1973. Control of insulin secretion by catecholamines, stress, and the sympathetic nervous system. Fed. Proc. 32:1792-1796.

Pruett, E. D. R. 1971. Fat and carbohydrate metabolism in exercise and recovery and its dependence upon workload severity. Thesis. Institute of Work Physiology, University of Oslo, Norway.

Radziuk, J., K. Norwich, and M. Vranic. 1978. Experimental validation of measurements of glucose turnover in non-steady state. Am. J. Physiol. 234:E84-93.

Randall, J. F. 1980. The glucose tolerance test. Pages 69-82 in Microcomputors and physiological simulation. Addison-Wesley Pub. Co., New York, New York.

Randle, P. J., and G. H. Smith. 1958. Regulation of glucose uptake by the muscle. I. The effects of insulin, anaerobiosis, and cell poisonson the uptake of glucose and the release of potassium by isolated rat diaphragm. Biochem. J. 70:490-500.

Rizza, R., M. Haymond, P. Cryer, and J. Gerich. 1979. Differential effects of epinephrine on glucose production and disposal in man. Am. J. Physiol. 237:E356

Ross, B. D., R. Hems, and H. A. Krebs. 1967. The rate of gluconeogenesis from various precursors in the perfused rat liver. Biochem. J. 102:942-951.

Ruderman, N. B., M. N. Goodman, C. A. Conover, and M. Berger. 1979. Substrate utilization in perfused skeletal muscle. Diabetes 28 (Suppl. 1):13-17.

Sacca, L., N. Eigler, P. E. Cryer, and R. S.Sherwin. 1979. Insulin antagonistic effects of epinephrine and glucagon in the dog. Am. J. Physiol. 237:E487-492.

Sanders, C. A., G. E. Levonson, W. H. Abelmann, and N. Freinkel. 1964. Effect of exercise on the peripheral utilization on glucose in man. N. Engl. J. Med. 271:220-225.

Sartor, G., B. Schersten, S. Carlstrom, A. Melander, A. Norden, and G. Persson. 1980. Ten year followup of subjects with impaired glucose tolerance. Diabetes 29:41-49.

Sawin, C. T. 1969. The hormones: endocrine physiology. Little Brown and Co., Boston, Ma.

Shreeve, W. W. 1974. Physiological chemistry of carbohydrates in mammels. Saunders, Philadelphia, Pa.

Sokal, J. E. 1966. Effect of glucagon on gluconeogenesis in the isolated perfused rat liver. Endocrinology 78:538-550.

Soman, V. R.,H. Shamoon, and R. S. Sherwin. 1980. Effects of physiological infusions of epinephrine in normal humans: relationship between the metabolic response and beta-adrenergic binding. J. Clin. Endocrinol. Metab. 50:294-297.

Srinivasan, R. 1969. A nonlinear systems model for the control mechanism of free fatty acid-glucose metabolism in normal humans. Ph.D. Thesis, Calif. Inst. Tech., Pasadena, Calif.

Srinivasan, R., A. H. Kadish, and R. Shridhar. 1970. A mathematical model for the control mechanism of FFA-glucose metabolism in normal humans. Comput. Biomed. Res. 3:146-166.

Tepperman, J. 1980. Metabolic and endocrine physiology. Yearbook Medical Pub., Inc. Chicago, Ill.

Terjung, R. 1979. Endocrine response to exercise. Exercise Sports Sci. Rev. 7:153-180.

Tiran, J., H. Broekhuyse, and A. M. Albisser. 1980. Glucose and insulin dynamics in the anaesthetized dog: A mathematical modeling study. Med. Progr. Technol. 7:183-192.

Tiran, J., K. R. Galle, and D. Porte, Jr. 1975. A simulation model of extra-cellular glucose distribution in the human body. Ann. Biomed. Eng. 3:34-46.

Turner, R. C., J. A. Graybourn, and J. D. N. Nabarro. 1971. Measurement of insulin delivery rates in man. J. Clin. Endocrinol. 33:279-282.

Turner, R., and J. Bagnara. 1976. General endocrinology. W. B. Saunders Co.,Philadelphia, Pa.

Vranic, M., and M. Berger. 1979. Exercise and diabetes mellitus. Diabetes 28:147-163.

Vranic, M.,and R. Kawamori. 1979. Essential roles of insulin and glucagon in regulating glucose fluxes during exercise in dogs. Diabetes 28(Suppl. 1):45-52.

Vranic, M., and G. A. Wrenshall. 1969. Exercise, insulin, and glucose turnover in dogs. Endocrinology 85:165-171.

Vranic, M., J. Radziuk, and A. Cherrington. 1973. The role of glucagon and insulin in the glucoregulatory system as assessed by tracer methods. Pages 487-490 in A. S. Ibersall and A. C. Guyton, eds. Regulation and control in physiological systems. International Federation of Autonomic Control, Pittsburgh, Pa.

Vranic, M., G. Ross, K. Doi, and L. Lickely. 1976a. The role of glucagon-insulin interactions in control of glucose turnover and its significance in diabetes. Metabolism 25 (Suppl. 1):1375-1380.

Vranic, M., R. Kawamori, S. Pek, N. Kovacevie, and G. A. Wrenshall. 1976b. The essentiallity of insulin and the role of glucagon in regulating glucose utilization and production during strenuous exercise in dogs. J. Clin. Invest. 57:245-255.

Wahren, J. 1979. Glucose turnover during exercise in health and diabetes mellitus. Diabetes 28 (Suppl. 1):82-88.

Wahren, J., L. Hagenfeldt, and P. Felig. 1975. Splanchnic and leg exchange of glucose, amino acids, and free fatty acids during exercise in diabetes mellitus. J. Clin. Invest. 55:1303-1314.

Wahren, J., P. Felig, G. Ahlborg, and L. Jorfeldt. 1971. Glucose metabolism during leg exercise in man. J. Clin. Invest. 50:2715-2725.

Wahren, J., P. Felig, L. Hagenfeldt, R. Hendler, and G. Ahlborg. 1973. Splanchnic and leg metabolism of glucose, free fatty acidsa and amino acids duringprolonged exercise in man. Pages 144-153 in H. Howald and J. R. Poortmans, eds. Metabolic adaptation to prolonged physical exercise. Birkhauser Verlag, Basel, Switzerland.

Walter, P. 1973. Quantification and regulation of hepatic gluconeogenesis. Pages 287-293 in The liver. Quantitative aspects of structure and function. Karger, Basel, Switzerland.

ACKNOWLEDGEMENTS

The author wises to express her thanks to Dr. R. C. Seagrave for his valuable guidance and encouragement throughout this work. I wish to express my sincere graditude to Herb Harmison, Engineering Placement Office of his assistance and provision of terminal time for the completion of this paper. Thanks are also extended to the Vax Consultants for their help in debugging the Fortran programs and to the biomedical engineering program at Iowa State University for its financial assistance during the last year.

APPENDIX A. MODEL PARAMETER VALUES

Vb	= 3.2 liters	(Cramp and Carson, 1979)
Vl	= 1.6 liters	(Cramp and Carson, 1979)
Rcns	= 0.000445 moles/min	(Cramp and Carson, 1979)
R5o	= 3.99 mU/min	(Cramp and Carson, 1979)
R4o	= 0.2 mg/min	(Cramp and Carson, 1979)
R6o	= 0.9 ug/min	(Cramp and Carson, 1979)
Rgneo	= 0.005 moles/min	(Cramp and Carson, 1979)
Rgly	= 0.005 moles/min	(Cramp and Carson, 1979)
K1/Vb	= 0.04 1/min	(London, 1966)
K4/Vb	= 0.625 1/min	(London, 1966)
K5/Vb	= 0.134 1/min	(London, 1966)
k1/Vb	= 0.15 1/min	(London, 1966)
x	= 2	(Cramp and Carson, 1979)

APPENDIX B. MODEL EQUATIONS

Plasma Glucose

$$Vb[dC1b/dt] = -Rcns - K1(C1b-C11) - k1C1b + R21 - R1bm$$

where:

$$R21 = \begin{cases} 6.82*C2/(2+1000*C2) & (\text{if } C'5b \leq 300) \\ 6.82*C2/(2+1000*C2*(C'5b-293)/7 & (\text{if } C'5b > 300) \end{cases}$$

and

$$R1bm = \begin{cases} 0.25*C1b/(22.7+1150*C1b) & (\text{if } 65 < C'5b \leq 700 \text{ and } C'4b \leq 0.42) \\ 0.215*C1b/(22.7+1150*C1b) & (\text{if } 65 < C'5b \leq 700 \text{ and } C'4b > 0.42) \\ 0.25*C1b(C'5b-699)/(22.7+1150*C1b(C'5b-699) & (\text{if } C'5b > 700) \\ 0 & (\text{if } C'5b \leq 65) \end{cases}$$

Portal Glucose

$$V1[dC11/dt] = k1C1b + K1(C1b-C11) - R12$$

Glucose-6-Phosphate

$$V1[dC2/dt] = Rgneo - Rgly + R12 - R21 - R23 + R32$$

where:

$$R12 = 4.27*C1b/(22.7+1150*C1b)$$

$$R23 = \begin{cases} 1.25*C2/(0.10722+1848.3*C2) & \text{(if } C'51 \geq 32 \text{ and } C3 \leq 0.5 \text{ and } C'41 \leq 0.35\text{)} \\ 0 & \text{(if } C'51 < 32 \text{ and } C3 > 0.5 \text{ and } C'41 > 0.35\text{)} \end{cases}$$

and

$$R32 = \begin{cases} (0.03-31.2*C2)/(32-1000*C2)+11.1/(4000*C2+1) & \text{(if } C'41 \geq 0.35 \text{ and } C'6 \geq 0.32\text{)} \\ 0 & \text{(if } C'41 < 0.35 \text{ and } C'6 < 0.32\text{)} \end{cases}$$

Glycogen

$$V12[dC3/dt] = R23 - R32$$

Plasma Insulin

$$[dC'5b/dt] = -K5/Vb(C'5b-xC'51) - R5D$$

Portal Insulin

$$[dC'51/dt] = R5o + K5/Vb(C'5b-xC'51) + R5$$

where:

R5D = nonlinear insulin loss rate given in Table 4.

and

$$R5 = \begin{cases} 18000(C11-0.005) & (\text{if } C11 > 0.005) \\ & + \\ 0 & (\text{if } C11 \leq 0.005) \end{cases} \quad \begin{cases} 36000(dC11/dt) & (\text{if } dC11/dt > 0) \\ 0 & (\text{if } dC11/dt \leq 0) \end{cases}$$

Plasma Glucagon

$$[dC'4b/dt] = K4/Vb(xC'41-C'4b) - R4D$$

Portal Glucagon

$$[dC'41/dt] = R4o - K4/Vb(xC'41-C'4b) + R4$$

where:

R4D = 0.625*C'4b

and

$$R4 = \begin{cases} 90*(0.005-C11) & (\text{if } C11 < 0.005) \\ & + \\ 0 & (\text{if } C11 \geq 0.005) \end{cases} \quad \begin{cases} 90*(-dC11/dt) & (\text{if } dC11/dt < 0) \\ 0 & (\text{if } dC11/dt \geq 0) \end{cases}$$

Epinephrine

$$[dC'6/dt] = R6o - R6D + R6$$

where:

R6D = 5.62*C'6

and

$$R6 = \begin{cases} 180(0.005-C11) & (\text{if } C11 < 0.005) \\ 0 & (\text{if } C11 \geq 0.005) \end{cases} + \begin{cases} 90*(-dC11/dt) & (\text{if } dC11/dt < 0) \\ 0 & (\text{if } dC11/dt \geq 0) \end{cases}$$