A NONLINEAR SYSTEMS MODEL FOR THE CONTROL MECHANISM OF FREE FATTY ACID-GLUCOSE METABOLISM IN NORMAL HUMANS

Thesis by
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This work is dedicated to the author's parents.

Abstract

A mathematical model is proposed in this thesis for the control mechanism of free fatty acid-glucose metabolism in healthy individuals under resting conditions. The objective is to explain in a consistent manner some clinical laboratory observations such as glucose, insulin and free fatty acid responses to intravenous injection of glucose, insulin, etc. Responses up to only about two hours from the beginning of infusion are considered. The model is an extension of the one for glucose homeostasis proposed by Charette, Kadish and Sridhar (Modeling and Control Aspects of Glucose Homeostasis. Mathematical Biosciences, 1969). It is based upon a systems approach and agrees with the current theories of glucose and free fatty acid metabolism. The description is in terms of ordinary differential equations. Validation of the model is based on clinical laboratory data available at the present time. Finally procedures are suggested for systematically identifying the parameters associated with the free fatty acid portion of the model.

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LIST OF ABBREVIATIONS

ADP - Adenosine diphosphate

ATP - Adenosine triphosphate

CNS - Central nervous system

CoA - Coenzyme A

FFA - Free fatty acids

GH - Growth hormone

IV - Intravenous

RBC - Red blood cells

TG - Triglycerides

VLDL - Very low-density lipoprotein

I. INTRODUCTION

Mathematical modeling of biological and physiological processes is an area of active research at the present time. Mathematical representation has been attempted for several physiological processes such as respiration, systemic circulation, motor functions, glucose homeostasis etc., to mention a few. It is now well-known that the mechanism by which the body maintains the concentration of blood glucose at a specified level is a finely regulated control system – hence the well-accepted term glucose homeostasis. It is a feedback control system in which the desired value of the controlled quantity, namely the blood glucose level, is a constant. The primary task of the control mechanism is to maintain the actual blood glucose concentration at its desired value in the presence of disturbances. The control is effected by specific hormones released by the endocrine system in response to deviations from the equilibrium state.

Several authors have attempted modeling of the control mechanism of glucose homeostasis. An excellent review of the literature appears in a recent thesis by Charette.[1,2] With one exception, the models proposed for glucose homeostasis do not explicitly include the effects of FFA[1]. It is important to emphasize the dominant role of FFA in the supply of energy and in the regulation of blood sugar. It is estimated that approximately 50% of total respiration is derived from FFA oxidation under basal conditions. The important role of FFA in the endogenous supply of glucose by the liver is becoming increasingly

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1 Abbreviation for free fatty acids.

evident. Shames[3] presents a simple linear representation for the effects of FFA on blood glucose regulation based on the hypothesis of glucose-fatty acid cycle proposed by Randle et.al.[4]

In this thesis a nonlinear dynamic model is proposed for the control mechanism of FFA-glucose metabolism in normal healthy individuals under resting conditions. Models for FFA metabolism both under resting conditions and during exercise have been reported in the literature.[5,6,7] These are linear and are based on tracer studies. They mainly provide information regarding the various pathways and turnover rates of FFA under steady state conditions. For a review of compartment models for lipid metabolism the reader is referred to a recent article by Nome Baker.[8] The modeling efforts reported herein are quite different from those based on tracer studies. The main objective is to explain in a consistent manner with the aid of a mathematical model clinical laboratory observations such as glucose, insulin and FFA responses (up to 2 hours) to IV[1] infusions of glucose, insulin etc. Attention is focussed on the changes in plasma concentrations of glucose, FFA, insulin and other hormones due to disturbances introduced into the metabolic plant.[2] These are variables that can be directly measured. Only short-term responses such as the ones mentioned above are considered. Accordingly, the model proposed here does not include the effects of substrates such as amino acids and TG[3] and other hormones such as glucocorticoids and

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1 Abbreviation for intravenous.

2 The word metabolic plant refers to the aggregate of all metabolic processes taking place in the body.

3 Abbreviation for triglyecerides.

thyroxin. These substrates and hormones do not play any significant role in the 2-hour responses that are dealt with in this thesis. Inputs such as stress, exercise and exposure to cold are omitted for the sake of simplicity. Only IV inputs are considered; this eliminates the complexity introduced by the inclusion of gastrointestinal tract.

The approach taken here is a systems one. The model is comprised of interconnected subsystems, each subsystem representing one or more physiologic processes. The subsystems are modeled based on known stimulus-response characteristics. They are interconnected in a logical way based on current understanding of the metabolic processes. Each subsystem may include several biochemical reactions and these may be taking place simultaneously in several organs or locations in the body. It is emphasized that the model includes the major physiological quantities of interest and is intended to reproduce the gross effects of FFA-glucose metabolism. It is a systems representation obtained by properly interconnecting the relevant subsystems, even though some of them may be grossly approximated. Once we obtain a systems model, the mathematical representations of the subsystems can be refined as we understand more about the pertinent biochemical reactions. Validation of the model is based on clinical laboratory data available at the present time.

The modeling efforts reported here started with the aim of establishing a methodology for the investigation of human metabolic control systems. Bodily metabolic processes are enormously complex in nature. The substrates, enzymes and controls that participate are

so large in number that it is beyond the capability of any present-day computing machine to handle simultaneously all the pertinent equations, assuming that one can describe mathematically all the biochemical reactions and physiologic functions that are involved – an extremely difficult task, if not impossible! Even if it is possible, it is highly doubtful whether one can gain futher understanding of the metabolic processes by describing them in all their infinite details. On the other hand, overly simplified models (a second order differential equation, for example) are of questionable utility. The systems approach takes a central position between the above two extremes. A systems model aims at a simple representation that does not obscure the basic facts; yet it is made detailed enough to explain at once several clinical findings. The physiologic aspects are borne in mind throughout. The systems approach seems particularly suitable for analyzing complex systems such as bodily metabolic systems.

The author does not certainly claim to have constructed the ultimate model that will explain every aspect of FFA-glucose metabolism. The author's model is only one of the evolutionary series of models to be developed, tested and improved. Although the results presented are meagre, the limited success gives credence to the methodology. Methods and tools for analyzing higher dimensional nonlinear systems have become available only recently. These methods and tools combined with clinical tests such as tolerance tests and techniques such as tracer studies should undoubtedly lead to a better understanding of the metabolic processes and their use in alleviating disease states.

II. THE METABOLIC PROCESSES AND CONTROL

2.1. Introduction.

In this chapter some pertinent biochemical and physiological aspects of metabolism in general will be summarized. Special attention will be devoted to glucose homeostasis and FFA metabolism. Although the term metabolism in its broadest sense includes all physical and chemical processes involved in life activities it is commonly employed to denote the processes by which food substances – carbohydrates, proteins and fats – are converted into energy. We will use it in the latter sense throughout. The discussion presented here is extremely brief and is included so as to provide the necessary background material for the presentation of the proposed model in the next chapter. The metabolism of carbohydrate, protein and fat has been reviewed and discussed in great depth in several text books and articles.[9-14] The reader is referred to these publications for further details. A brief account appears also in Charette's thesis[2] and reference 9.

2.2. The Biochemical Aspects.

All living organisms constantly require energy for sustaining life and activity. All living cells are equipped with extremely complex mechanisms for transforming the chemical energy inherent in the molecular bonds of food substances into other forms of energy such as heat or mechanical work. The ultimate products of combustion are carbon dioxide and water and the principal mechanism is oxidation. Most of the energy derived from the substances being burned is not immediately released as heat during oxidation but is retained as chemical energy.

In other words the body stores energy in chemical form by transforming the food substances into other compounds. The stored energy is freed whenever there is demand. The precise means by which chemical energy is retained as such and not immediately released remains as one of the mysteries of life.

Central to the mechanism of storage and release of chemical energy of the body is a high energy compound called adenosine triphosphate, known universally by its initials ATP. This ubiquitous nucleotide is the principal intracellular carrier of chemical energy from the energy-yielding oxidation of food substances to those processes or reactions of the cell which do not occur spontaneously and can proceed only if chemical energy is supplied. Processes such as diffusion occur spontaneously and do not require external supply of energy; whereas mechanical work such as muscular contraction, electrical activity and synthesis of many chemical compounds are energy-dependent. Part of the energy of the food is conserved during oxidation by formation of ATP from adenosine diphosphate (ADP). The chemical energy of ATP is then utilized in the energy-dependent cellular processes, degrading ATP to ADP. The ATP-ADP system serves as a linking agent, so to speak, between the high-energy phosphate donors, formed during oxidation of food substances, and the low-energy phosphate acceptors. It is the primary energy carrier system of the cell.

We shall now briefly discuss some salient features of intermediary metabolism. The term intermediary metabolism refers to the intermediate chemical reactions in the intracellular transformation of foodstuffs within the body. Figure 1 depicts a highly simplified

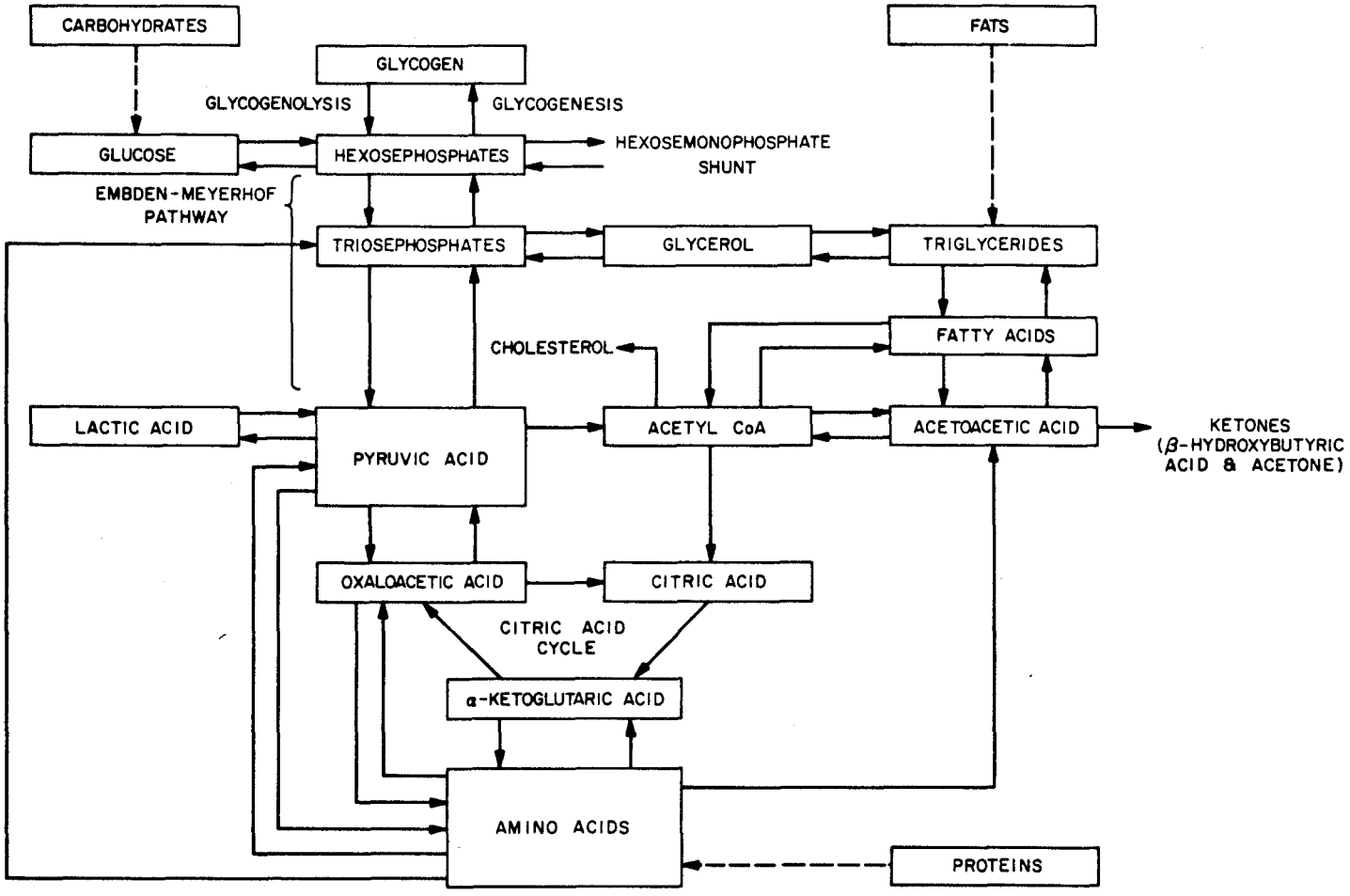

Figure 1. General Scheme of Intermediary Metabolism. Broken lines represent digestion and transport and solid lines represent intracellular biochemical processes.

scheme of intermediary metabolic pathways. Ingested food consists of carbohydrates, proteins, fats and a small fraction of minerals and vitamins. The principal end products of digestion are monosaccharides including glucose, amino acids, FFA and chylomicrons consisting mainly of TG. In the cells glucose is promptly phosphorylated to form glucose-6-phosphate, a hexosephosphate compound. It is then either catabolized or converted into glycogen, the stored form of glucose. The process of glycogen formation is called glycogenesis and that of glycogen breakdown is known as glycogenolysis. The catabolism of glucose can proceed via either the Embden-Meyerhof pathway or the hexosemonophosphate shunt. Glucose is converted into pyruvic and lactic acids through the Embden-Meyerhof pathway. The process is know as glycolysis. The reactions of this pathway are anaerobic, i.e., they do not require oxygen. On the other hand, the reactions of the hexosemonophosphate shunt are aerobic. For this reason it is also known as the direct oxidative pathway. Relatively a large number of ATP moleucles are produced through this pathway of glucose catabolism.

The citric acid cycle (also known as Krebs cycle or tricarboxylic acid cycle) is the common pathway for oxidation to CO_2 and H_2O of all the food substances. It requires oxygen and does not function under anaerobic conditions. The main entry into the cycle is through acetyl CoA[1], but pyruvic acid and a number of amino acids also enter it after conversion into some of its intermediates such as oxaloacetic acid, for example. 15 mols of ATP can be generated from

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[1] Abbreviation for acetyl coenzyme A.

1 mol of pyruvic acid in the citric acid cycle.

Triglycerides, the major end products of digestion of fats, are made up of fatty acids and glycerol (3 mols of fatty acids bound to 1 mol of glycerol). When hydrolyzed they liberate their contituent fatty acids and glycerol. The process is termed lipolysis. The reverse process, namely synthesis of triglycerides, is called lipogenesis. Glycerol is converted first into a triosephosphate and then into either glucose or CO_2 and H_2O. The fatty acids are broken down to acetyl CoA which then enters the citric acid cycle. The energy yield of this process is large. 38 mols of ATP can be generated by catabolism of 1 mol of a six-carbon fatty acid through the citric acid cycle. Acetyl CoA serves also as precursor for cholesterol production.

It should be noted that interconversions among amino acids, fatty acids and glucose are possible via acetyl CoA and intermediates of the citric acid cycle. Of the various interconversions that are possible the most important one is the production of glucose from non-carbohydrate sources, especially from amino acids. The process is known as gluconeogenesis.

The biochemical pathways indicated in the simplified scheme of Figure 1 are present in all the cells of the body to a greater or smaller extent. However, the rate at which a particular reaction or a group of reactions can take place in a particular cell in the body depends upon the function of the organ to which the cell belongs. For example, the storage of glucose in the form of glycogen takes place to a large extent only in liver, kidney and muscle. It is not a major pathway for glucose in adipose tissue.[15] The processes gluconeogene-

sis and glucose production from glycogen are exlcusive to liver and kidney. Another example is ketogenesis (production of ketones) which takes place only in liver. It is well-known that all biochemical reactions occuring in living organisms are enzyme-catalized reactions. Evidently for a given reaction to proceed the cell must have the necessary enzymatic machinery available to it. Muscle is not capable of producing glucose from glycogen because it lacks the needed enzyme, glucose-6-phosphatase. Ketogenesis is caused in liver due to an enzyme called deacylase which other cells do not possess. A common feature of all the cells of the body is the citric acid cycle. All cells are endowed with the enzymes required for the reactions of the citric acid cycle.

2.3. The Physiological Aspects

A diagrammatic summary of the interrelated processes associated with the metabolism of carbohydrate, protein and fat is depicted in Figure 2. The diagram is an attempt to systematize the known physiologic facts as a first step toward the eventual derivation of a detailed metabolic control model using the systems approach. It represents what may be the desired minimal complexity for obtaining meaningful results with a dynamic metabolic control model. The fat, carbohydrate and protein loops are shown together along with the couplings involved. The diagram includes all the major metabolic processes and physiologic variables. The lumped processes are indicated by arrows and the variables are shown inside rectangles. In addition to the couplings shown, the three major loops are coupled through the hormones that control the

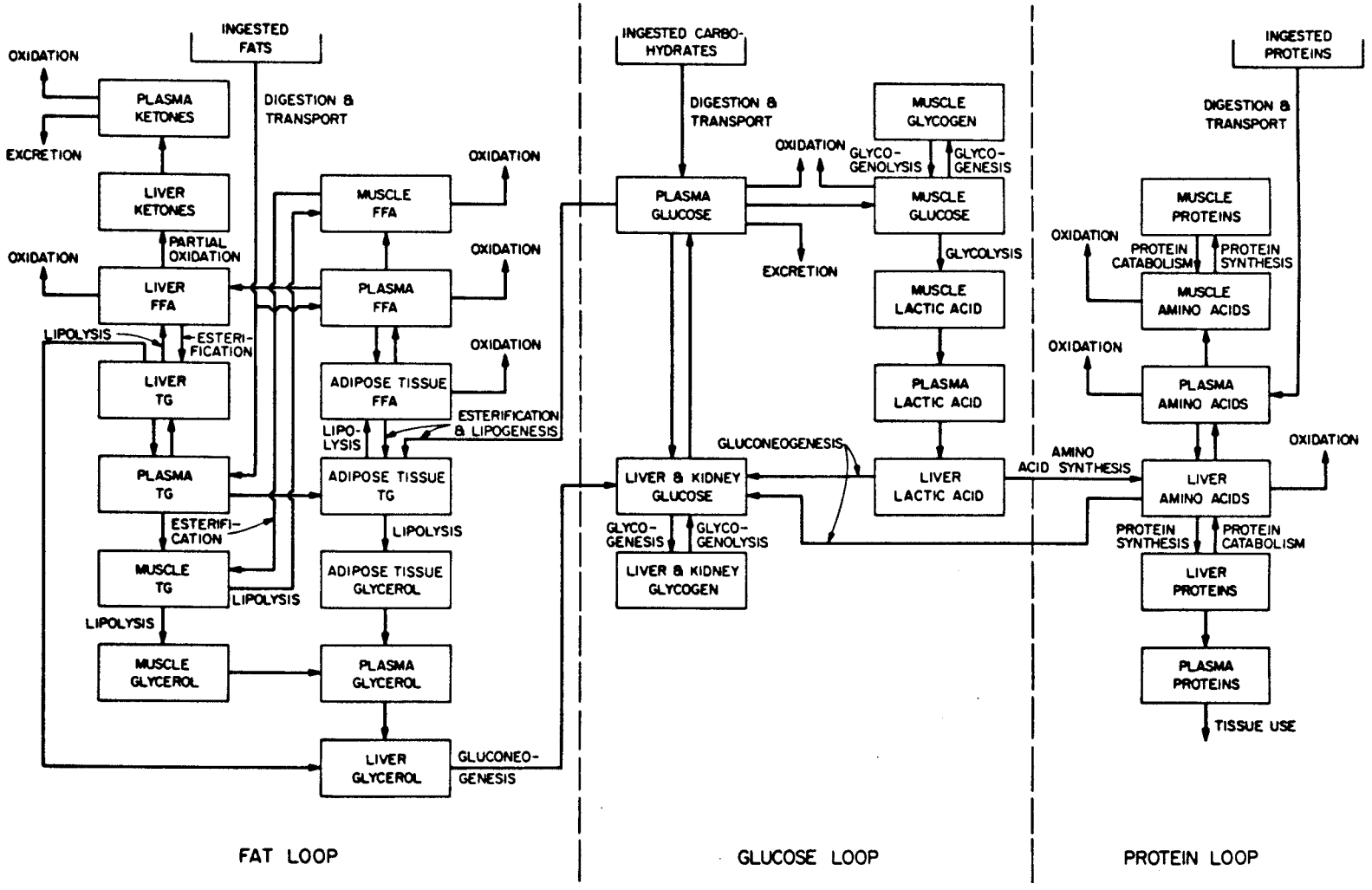

Figure 2. The Metabolic Plant (General Scheme). Lipogenesis in liver linking liver glucose and liver TG is not indicated.

various metabolic processes. Hormones are subtances secreted by particular organs into the general circulation which carries these substances to their sites of action where they regulate the rates of specific processes without contributing any significant amount of energy or matter to the tissues. Hormonal effects are not indicated in Figure 2. It should be noted that the diagram is the exact dual of an engineering representation in which the variables are indicated by arrows and the processes inside rectangles.

Glucose, the principal product of carbohydrate digestion and the dominant circulating blood sugar, is the major source of energy in the absorptive phase following ingestion of food. A small amount of fat is oxidized, but most of it is stored in adipose tissue as TG. Amino acids are either converted back into protein or catabolized by deamination and further oxidation. Liver and kidney are the major sites of metabolism of amino acids absorbed after digestion. Excess carbohydrate is stored as glycogen, but most of it is converted into TG by lipogenesis and stored. The pathway is via pyruvic acid and acetyl CoA (see Figure 1). The storage of glycogen is very small in adipose tissue.[16] Triglycerides are a more compact form of energy storage. They take up less volume per calorie of stored energy.

An important pathway for glucose in muscle is anaerobic glycolysis and the consequent production of lactic acid. This happens when the supply of oxygen is insufficient as, for example, following exercise. Under such conditions the muscle lactic acid concentration increases and it diffuses into the blood stream to be transported to the liver. In the liver it is either catabolized or converted into

glucose by gluconeogenesis. A smaller amount of pyruvic acid also undergoes the same process. The cycle, plasma glucose → muscle glucose → muscle lactic acid → plasma lactic acid → liver lactic acid → liver glucose → plasma glucose, is known as the Cori cycle.

As the postabsorptive phase progresses the oxidation of fatty acids becomes the predominant source of energy. Under fasting conditions, adipose tissue provides the fatty acids by breaking down its stores of TG. One molecule of TG, when broken down, gives rise to three molecules of FFA[1] and one molecule of glycerol. The glycerol fraction released cannot be reutilized in adipose tissue to any significant extent. It is carried by the blood stream to the liver where it is either converted into glucose or oxidized to CO_2 and H_2O. Apparently all tissues of the mammalian organism so far examined can oxidize fatty acids completely to CO_2 and H_2O. However the CNS[2] depends solely on glucose for its oxidative needs. It oxidizes glucose at a very nearly constant rate under most circumstances. Under fasting conditions, the glucose needs of the CNS are met chiefly by the liver which produces glucose by both glycogenolysis and gluconeogenesis.

Increased supply of fatty acids to the liver induces ketogenesis, resulting in the production of ketones – acetone, acetoacetic and β-hydroxybutyric acids. Since the liver cannot easily metabolize these substrates, they are released into the blood stream and are carried to

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1 Tri-, di- and monoglycerides are fatty acids in esterified form – esterified with glycerol. Unesterified fatty acids are called free fatty acids.

2 Abbreviation for central nervous system – the brain and the spinal cord.

extrahepatic sites (chiefly muscle) where they are readily utilized. Liver produces and releases also TG for utilization elsewhere in the body. There are thus five major substrates available to the tissues of the body for oxidative purposes. They are listed in Table 1 along with their turnover rates and oxygen requirements.[17]

Substrate	Major Sites of Oxidation	mM/min Oxidized	Oxygen Consumption (ml/min)
Glucose	Brain and CNS	0.33	45
FFA → Co_2	Liver and Extrahepatic tissues	0.22	114
FFA → Ketones	Liver	0.04	6
Ketones → Co_2	Extrahepatic tissues	0.16	15
Amino acids	Liver	-	70
Glycerides	All tissues	-	
All	Total Body		250

Table 1. Substrate utilization rates by man under basal conditions.

2.4. Hormonal Control of Metabolism

Substrates and their amounts that are transported and metabolized in the various organs of the body vary depending on the nutritional state, the level of exercise, the termperature of the surroundings, the psychic factors and so forth. Means must therefore be provided for the controlled storage and release of energy. The processes associated with the storage, release, transport and utiliza-

tion of metabolic fuels are under the precise control of the endocrine system (ductless glands which discharge their products into the general circulation). The endocrine glands, through the production and release of hormones regulate the various processes so as to maintain the homeostasis of the organism under varying environmental conditions.

The endocrine system is closely linked, both developmentally and functionally, to the nervous system. In fact, the two are often spoken of as a unit, the neuroendocrine system. In some respects the endocrine system acts more or less independently; in others it is so closely related to the nervous system that it may be considered functionally as an extension of it. This intimate connection between the two systems allows psychic influences to modify hormonal activities.

There are at least six hormones (four hormones and two hormone groups) that have dominant effects upon the metabolic processes in humans. They are listed in Table 2 along with their molecular weights, normal fasting plasma[1] concentrations, sources, stimuli and important effects on carbohydrate, protein and fat metabolism. Of these, glucocorticoids and thyroxin do not play any significant role in the short-term responses reported in this investigation.

2.5. Glucose Homeostasis and FFA Metabolism

The normal fasting level of glucose in plasma ranges from 80 mg/100ml to 100 mg/100ml (80 - 100 mg%) in healthy individuals. Under normal fasting conditions this level is regulated in the classical

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1 The fluid portion of blood excluding the cellular elements, principally the red blood cells.

TABLE 2. Major hormones that control the metabolism of carbohydrate, fat and protein.

↑ = Increase; ↓ = Decrease

NAME	APPROXIMATE MOLECULAR WEIGHT	TYPICAL FASTING PLASMA LEVEL OR SECRETION RATE IN NORMAL HUMANS	SOURCE	PRIMARY STIMULI	IMPORTANT EFFECTS ON METABOLISM OF CARBOHYDRATE, FAT, AND PROTEIN (18-22)
1. Insulin	6000	15 μU/mℓ	β-cells of pancreas	Hyper-glycemia	Uptake of glucose by liver, muscle and adipose tissue ↑ Muscle uptake of amino acids and protein synthesis ↑ Lipolysis ↓ Auguments lipogenesis
2. Glucagon	3450	0.4 ng/mℓ	α-cells of pancreas	Hypo-glycemia	Hepatic glycogenolysis ↑ Gluconeogenesis ↑ Proteolysis ↑* Insulin secretion ↑
3.Catecholamines					
(i)Epinephrine	183.2	0.1 ng/mℓ	Adrenal medulla	Hypo-glycemia; Physiologic stress	Glycogenolysis in both liver and muscle ↑ Lipolysis ↑ Insulin secretion ↓
(ii)Norepin-ephrine	170	0.4 ng/mℓ	Adrenal medulla; Sympathetic nerve endgs.	Physiologic stress; Emotional stress	Lipolysis ↑ Insulin secretion ↓

TABLE 2. (Continued)

4. Growth hormone	21500	2 ng/mℓ	Anterior pituitary	Hypo-glycemia	Lipolysis ↑ Protein Synthesis ↑
5.Glucocorticoids			Adrenal	Cortico-tropin from anterior pituitary	Gluconeogenesis ↑ Proteolysis ↑ Ketogenesis ↑
(i) Cortisol	329	20 mg/day	Cortex		
(ii) Cortico-sterone	346	3 mg/day			
6.Thyroxin	776.9	80 µg/day	Thyroid	Thyrotropin from anterior pituitary	Basal metabolic rate ↑ Plasma cholesterol level ↓ Hepatic glycogenolysis ↑ Gluconeogenesis ↑ Proteolysis ↑ Actions are interrelated to those of catecholamines

* Refers to catabolism of proteins.

control system sense, i.e., the level is maintained constant to within a small error of the order of $\pm$ 2 mg%. Liver plays a central role in this regulatory process. Tissue utilization depletes plasma glucose which is replenished by the liver through glycogenolysis and gluconeogenesis. In a normal 70 kg. man with a liver mass of approximately 1.8 kg. the maximum liver glycogen stores amount to about 125 gm. of glucose. Assuming a basal glucose turnover of 150 mg/min, time taken to deplete the liver glycogen stores completely = $\frac{(125)(1000)}{(150)\ (60)}$ = 14 hr. approximately. The fact that liver glycogen is never depleted completely indicates that the above figure is an overestimate and underscores the importance of gluconeogenesis under fasting conditions.

The major precursors of gluconeogenesis are: glycerol, amino acids, lactic and pyruvic acids. Glucose is produced from the latter two under anaerobic conditions through the Cori cycle (see page 13). Infusion of epinephrine also can cause this by its glycogenolytic action on muscle and the consequent increase of plasma lactic and pyruvic acids;[23] whereas glucagon enhances gluconeogenesis from amino acids.[24] Under fasting conditions the chief precursors of gluconeogenesis are amino acids. The amount of glucose contributed by glycerol is small. The basal glycerol turnover rate is around 0.3 mmoles/min;[25] if all of this is converted into glucose it can contribute a maximum of only about 30 mg/min of glucose – 20% assuming a basal glucose turnover of 150 mg/min.

There is an immediate rise in plasma glucose concentration following IV administration of glucose. After an oral load, maximum plasma level of glucose is attained in about 30 minutes in normal subjects. As the glucose level in plasma rises, the net output

of glucose from liver decreases and the liver becomes a net sink for plasma glucose at an absolute concentration of about 150 mg%.[26] Some amount of glucose is excreted in the urine when the absolute level exceeds 180 mg%. Until this level is reached the glucose filtered by the kidney from circulation is essentially reabsorbed. Increased levels of glucose stimulate the secretion of insulin from pancreas. Thus there is a concomitant rise in plasma insulin levels. The basic peripheral action of insulin is to promote the transport of glucose across the cell membrane. Adipose tissue is known to be highly sensitive in this respect. In addition to increasing the uptake of glucose, insulin inhibits lipolysis in adipose tissue and thus brings about a decrease in the supply of FFA and consequently in the level of FFA in plasma. A decreased supply of FFA results also from esterification of fatty acids. The essential pathways of glucose in adipose cell are indicated in Figure 3.

Under hypoglycemic conditions, the plasma glucose level is below nominal. Hypoglycemia can be induced by injection of insulin, for example. The accelerated rate of peripheral uptake of glucose results in a loss of plasma glucose. Simultaneously decreased rates of lipolysis lower the plasma FFA levels. Epinephrine, glucagon and GH[1] secreted in response to low levels of blood sugar tend to oppose the action of insulin. Epinephrine and glucagon enhance the endogenous supply of glucose by accelerating the rates of glycogenolysis and gluconeogenesis. Lipolysis is stimulated resulting in an increased outflow

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[1] Abbreviation for growth hormone.

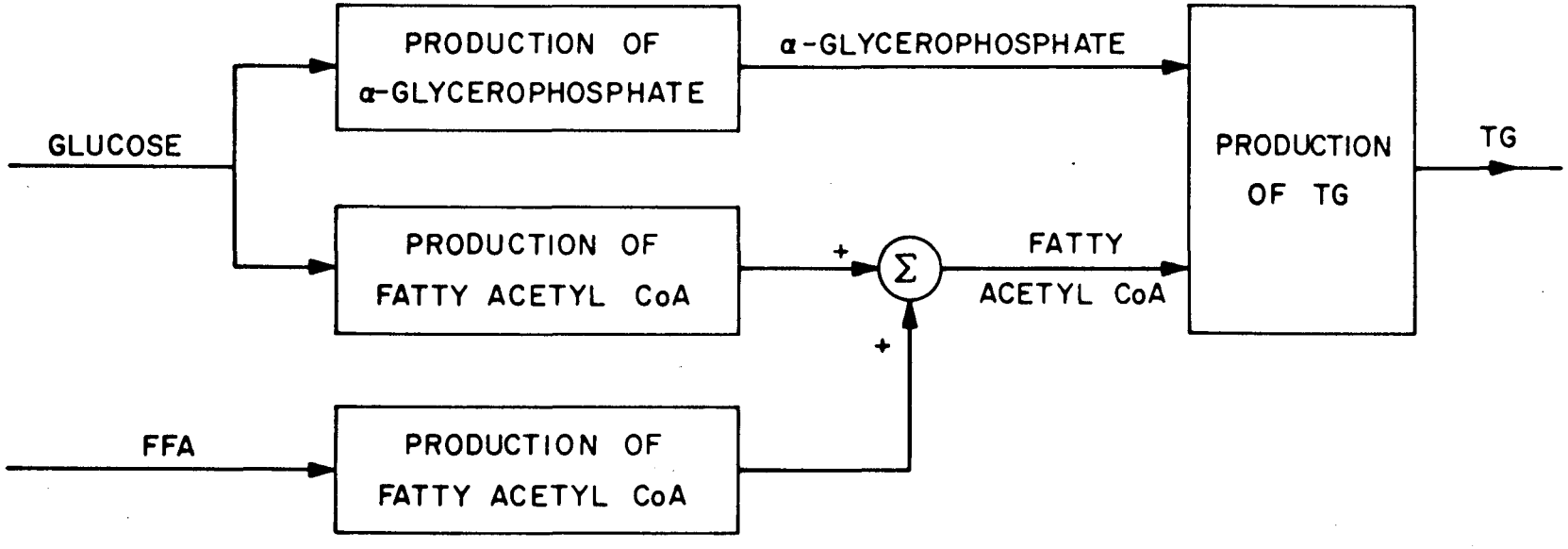

Figure 3. Synthesis of TG.

of FFA from adipose tissue. Equilibrium is thus restored by the action of the so-called hyperglycemic and lipolytic agents – chiefly epinephrine, glucagon and GH.

Adipose tissue is the organism's major reservoir of metabolic energy. By definition, it is composed of aggregates of fat cells located throughout the body at specific sites. Fat cells are now known to be metabolically highly active with a large blood flow in relation to active mass, important sympathetic innervation and both nervous and hormonal regulation. The primary functions of these cells are the storage of fat mainly in the form of TG and the release of FFA, a readily transportable source of energy, into the blood stream. The key reactions that govern the flow of FFA into and out of adipose tissue stores are TG breakdown and formation of TG from fatty acids and α-glycerophosphate. The latter is derived glucose (see Figure 3). It has now been confirmed that these two processes, lipolysis and esterification, go on continuously even at steady state.[27] Net mobilization of FFA occurs if either the rate of breakdown is increased or the rate of production is decreased. Net deposition of TG occurs if the steady state is disturbed in the opposite direction.

Breakdown of TG gives rise to FFA and glycerol. The process is inhibited by insulin and enhanced by lipolytic hormones such as catecholamines and GH. As mentioned earlier, most of the glycerol released is transported to the liver where it enters gluconeogenic pathways. The FFA are either re-esterified to TG in adipose tissue or enter the blood stream and are carried as FFA-albumin complexes. The amount of re-esterification depends upon the availability of glucose to

adipose tissue. Glucose is converted partly into α-glycerophosphate which is essential for esterification of fatty acids and partly into fatty acetyl CoA. α-glycerophosphate combines with fatty acetyl CoA, formed from both glucose and FFA, to yield TG (see Figure 3).

Adipose tissue is known to be the only endogenous source of plasma FFA. A large portion of FFA released into the blood stream is assimilated into the liver and the rest into other tissues (chiefly muscles). In both liver and muscle FFA are either oxidized to CO_2 and H_2O or stored as TG after esterification for latter use. A fraction of TG formed in the liver is released into plasma as lipoproteins — proteins combined with lipid (see Appendix for concentration and composition of plasma lipoproteins). Ketones — acetoacetic and β-hydroxybutyric acids — are produced in the liver as a result of partial oxidation of FFA. These ketones are either utilized by extrahepatic tissue for oxidation or excreted in the urine.

There does not seem to be any homeostatic regulation of plasma FFA level as in the case of plasma glucose concentration. The plasma sugar level returns to normal in about $1\frac{1}{2}$ hours after an IV administration of glucose and in about 3 hours after an oral glucose load. It takes much longer period of time for the establishment of steady state of plasma FFA level after a disturbance. Under fasting conditions the concentration of FFA in plasma increases slowly but steadily. Intake of food containing normal amounts of carbohydrate brings it down due to both increased re-esterification of fatty acids and decreased lipolysis in adipose tissue. The body begins to utilize more glucose and less FFA.

The role of amino acids is rather minor relative to glucose and FFA in the minute-to-minute supply of energy. Under basal conditions they supply only about 15% of the caloric needs. However they are the chief procursors for gluconeogenesis during fasting. Apparently FFA are necessary for the biochemical reactions involved in the conversion of amino acids into glucose to proceed.[1] Thus FFA seem to be responsible for the stimulation of gluconeogenesis in the liver under fasting conditions.[2] A prompt decrease in the level of FFA in plasma following ingestion of glucose would then be expected to result in diminished rates of gluconeogenesis. Liver ceases to produce glucose and even becomes a net sink for glucose depending on the amount ingested.

The switch-over from fat to carbohydrate following intake of food is accomplished with the aid of insulin. This ubiquitous hormone is essential for the utilization of glucose by many tissues in the body. Muscle and adipose tissue are known to be highly sensitive to the action of insulin. If sufficient amount of insulin is not secreted following administration of glucose, the entry of glucose into these tissues is severely impaired. Consequently the FFA accumulated in adipose tissue due to increased lipolysis during fasting are not re-esterified. Also, since the supply of insulin is lacking lipolysis is not diminished. Furthermore gluconeogenesis is not stopped. Thus both glucose and FFA levels remain high in the absence of insulin.

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1 FFA provide the needed hydrogen.

2 Some authors[28,29] view that gluconeogenesis is directly controlled by insulin rather than by FFA and that increased rates of glucose production under fasting conditions are triggered by low levels of insulin alone.

There are plenty of substrates in the blood but the tissues have no means of utilizing them. This is the situation in diabetes mellitus and it clearly indicates the important role of insulin in the minute-to-minute regulation of energy storage and release.

III. THE PROPOSED MODEL FOR FFA-GLUCOSE METABOLISM

3.1. Introduction.

Mathematical modeling is concerned with establishing reasonable mathematical representations relating the inputs or stimuli to the outputs or responses, both of which are often defined intuitively. The first matter for consideration in modeling is to decide as to the kind of description that is appropriate for the phenomenon of interest. The most common representation for metabolic control systems such as glucose homeostasis is in terms of ordinary differential equations. The choice implies subjective hypotheses and is greatly influenced by their use in classical control theory. The differential equation description of stimulus-response relations often introduces intermediate variables called states. From a mathematical point of view the choice of states is not unique. However, this does not lead to ambiguities in the stimulus-response relations. In biological applications the choice of states can be made unique by requiring that they represent biologically meaningful entities.

In control system terminology the metabolic plant is a multi-loop, multi-input-multi-output control system. For our purposes we shall define as outputs all those quantities that are directly available for measurement. Thus the plasma concentrations of substrates such as glucose, FFA, amino acids etc., and hormones that control the metabolic processes are outputs of the plant. If lymphatic cannulation is performed, interstitial fluid concentrations would also be outputs. In addition there are other outputs such as the amounts of glucose, nitrogen, etc., excreted in the urine, the volume of oxygen inhaled, the volume of CO_2 exhaled and so forth. Intravenous or oral admininstration of the various substrates and hormones and pharmacological agents such

as tolbutamide, nicotinic acid, etc., constitutes one class of inputs to the plant. Stress, exercise and exposure to cold or heat constitute another class of inputs.

Starting from the general scheme shown in Figure 2 and using as few basic analytical building blocks as possible, a mathematical model for the dynamics of FFA-glucose metabolism has been constructed. It incorporates nonlinearities such as saturation effects and threshold phenomena that are inherent in the metabolic processes. It is intended to explain quantitatively the short-term (up to 2 hours) responses of a normal subject to IV inputs of glucose, insulin and other hormones and some meaningful combinations of these. The description is in terms of ordinary differential equations (nonlinear). Some salient features of the model are:

(i) It includes the effects of four hormones, namely, insulin, epinephrine, glucagon and growth hormone.

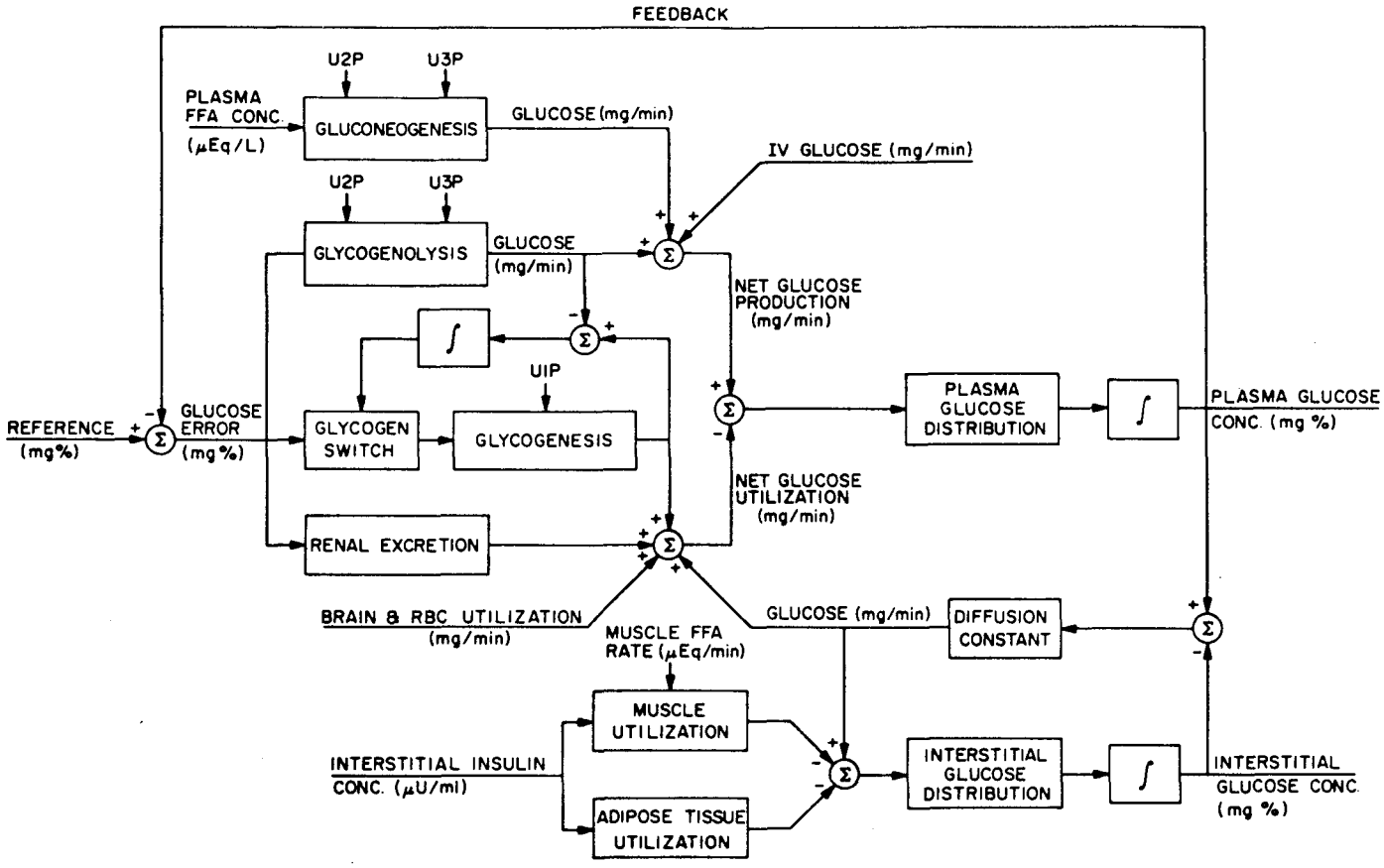
(ii) It includes gluconeogenesis as a function of plasma FFA concentration.

(iii) It includes the effects of FFA metabolism on glucose uptake by muscle.

3.2. The Proposed Model.

3.2.1. The Glucose Model.

Charette has suggested three different models for glucose homeostasis in normal humans based on the systems approach.[2] The glucose model included in this thesis is a modified version of his refined four hormone control model. It is depicted in Figure 4. In the dis-



GLUCOSE MODEL

U1P - PLASMA INSULIN CONC.
U2P - PLASMA GLUCAGON CONC.
U3P - PLASMA EPINEPHRINE CONC.

Figure 4.

cussion to follow we shall restrict our attention to the modifications that have been made. The reader is referred to Section 3.7 of Charette's thesis for further details.

(i) Perhaps the most significant modification is the inclusion of gluconeogenesis which is assumed to be stimulated by plasma FFA concentration. Gluconeogenesis is one of the major processes through which the glucose loop is coupled to the lipid and protein loops. The choice of plasma FFA level as the stimulus is supported by several pieces of evidence reported in the literature. Evidence suggesting the importance of FFA presentation in minute-to-minute glucose production by the liver has been discussed by Cahill et.al.[30] Based on experiments with rat liver, Walter et.al.[31] have postulated that fatty acids are not only the main energy supply for gluconeogenesis but that they also play a decisive role in stimulating this process.

The increased gluconeogenesis observed in fasting and in diabetes is associated with increased mobilization and oxidation of fatty acids. It has been suggested that stimulation of gluconeogenesis might result from accelerated hepatic catabolism of fatty acids.[32,33] It would therefore seem more reasonable to assume gluconeogenesis to be stimulated by liver uptake of FFA for oxidation. However, since the liver uptake of FFA increases with plasma FFA concentration the latter serves the purpose equally well in so far as the gross effects of FFA on glucose metabolism are concerned. Furthermore, identification of parameters associated with gluconeogenesis is facilitated if we assume that this process is stimulated by plasma level of FFA rather than by some other related quantity that is not readily available for measurement.

Such considerations dictate the choice whenever alternatives are available. The idea is to make the model as simple as possible, yet consistent with known physiologic facts.

The mechanisms of regulation of gluconeogenesis are not clear. Contrary to the assumption that FFA stimulate gluconeogenesis, Seyffert et.al.[28] noticed a significant increase in plasma insulin and a fall in hepatic glucose output of normal dogs when they increased plasma FFA to levels found during prolonged starvation. Exton and Park[34] in their in vitro perfusion studies on rat liver found no correlation between the rates of ketogenesis resulting from fatty acid oxidation and gluconeogenesis. Even the widely held theory of ketogenesis that it is caused by increased fatty acid mobilization has recently been challenged.[35]

The controversies regarding the regulation of gluconeogenesis indicate the serious difficulty that a modeler faces, in trying to arrive at a reasonable representation for a given process or subsystem. Even the bare minimum information concerning stimulus and response is not available in many instances. The picture one obtains from the increasing mass of physiological investigations is neither clear nor consistent. The conflicting results clearly indicate the fact that the metabolic plant is comprised of several intercoupled loops with several hormonal controls and emphasize the need for a consistent investigative framework for the overall process. Although a great amount of physiology has yet to be learned about the relevent subsystems involved before a definitive model can be established, it is the author's contention that the systems analyst can contribute to this effort by systematizing the known physiologic facts about the metabolic processes in a consistent mathematical framework, by proposing to the physiologist specific

experiments suggested by model building, simulation and analysis and by determining analytically the consequences of conflicting theories on the operation of specific portions of the overall plant.

It should be noted that the representation shown in Figure 4 takes into account gluconeogenesis from all the major precursors of this process, viz., amino acids, lactic and pyruvic acids and glycerol. Increased mobilization of glycerol concomitant with FFA under conditions of increased lipolysis can directly account for enhanced gluconeogenesis from glycerol when the plasma FFA level is elevated. Under basal conditions, the glucose utilization rate is approximately 150 mg/min.[17,36] The contribution by gluconeogenesis is assumed to be about 100 mg/min. The balance is supplied by glycogenolysis. If glycogenolysis produces glucose at a constant rate of 50 mg/min it would take more than 16 hours to deplete 50 gm. of stored glucose. Since liver glycogen is not diminished by more than 50 gm.[1] under basal conditions, the values chosen for the basal rates of glycogenolysis and gluconeogenesis seem reasonable.

(ii) In his refined four hormone model Charette lumps glucose uptake of muscle and adipose tissue together and represents them in one block which he calls the peripheral glucose utilization sink. He assumes that the uptake of glucose by peripheral tissues is stimulated by interstitial glucose concentration and enchanced by interstitial insulin concentration. The peripheral glucose uptake certainly depends upon both glucose and insulin concentrations in the interstitial space.

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[1] Refers to equivalent glucose mass. It is assumed that liver glycogen stores have a maximum value equivalent to about 125 gm. of glucose in a healthy individual and that they do not normally fall below 75 gm.

However, insulin undoubtedly plays a more decisive role in facilitating the transport of glucose from the interstitial space across the cell membrane of the peripheral tissues. There may be transport by simple diffusion in the absence of insulin at very high concentrations of glucose as seen in uncontrolled diabetes. It is assumed that in the range of glucose concentration that one normally encounters, the uptake of glucose by peripheral tissues is negligible in the absence of insulin. Thus in the model proposed here the peripheral glucose utilization is independent of interstitial glucose concentration. It is assumed to be stimulated by interstitial insulin concentration. Christensen and Orskov[37] have recently reported a highly significant correlation between muscular glucose uptake and simultaneous arterial serum insulin concentration. They found no correlation, on the other hand, between glucose uptake and simultaneous arterial glucose concentration. Their conclusions are based on measurements of glucose uptake in the forearm muscles of nondiabetics.

Charette assumes the peripheral glucose uptake to be inhibited by interstitial GH. This inhibitory effect is indirectly present in our model. Based on the findings of Rabinowitz et.al.[38], increased levels of interstitial GH are assumed to enhance FFA oxidation by muscle. This in turn inhibits muscle uptake of glucose as suggested by Randle and his associates.[39] Increased levels of GH have no effect on glucose uptake by adipose tissue in our model. This seems to be significant only at very high concentrations of GH as seen in acromegaly. For instance, Rabinowitz et.al. found a reduction in glucose uptake by forearm adipose tissue at a local GH concentration of about 400 ng/ml which is

well above the levels normally encountered. The exclusion of the GH effect on adipose tissue glucose utilization does not affect our results appreciably.

According to Randle et.al. the altered rates of glucose phosphorylation, glycolysis and pyruvate oxidation are the consequences of an increased rate of fatty acid oxidation. Hence muscle FFA oxidation has been assumed to be the variable that inhibits muscle glucose utilization. This and the assumption that muscle FFA oxidation is independent of plasma FFA concentration (see Page 39) indicate that an increased plasma FFA level per se does not cause a decrease in muscular glucose uptake. In support of this view, Schonfeld and Kipnis[40] observe that in man plasma FFA level should be increased by 300-400% before a detectable decrease in peripheral glucose utilization is noted.

(iii) The third modification that has been made in Charette's refined four hormone model is the introduction of an interstitial compartment for glucose distribution. Charette assumes for the distribution of glucose a single compartment comprising of plasma, interstitial fluid and liver and RBC[1] intracellular fluid. The volume of the compartment is taken to be 17.5L. in a normal 70 kg. man – 3.5L. of plasma and 10.5L. of interstitial fluid with the balance accounting for liver and RBC volumes. Suppose 35 gm. of glucose is given intravenously over a period of several minutes. Assuming that glucose is not degraded in the body during infusion and further that the distribution of glucose is instantaneous, the peak glucose concentration attained would be exactly

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1 Abbreviation for red blood cells.

200 mg% above the nominal fasting level. It is less in fact due to the utilization of glucose during the infusion period and the time constant associated with its distribution. On the other hand, the peak deviation in plasma glucose level has been observed to be greater than 250 mg% in glucose tolerance tests after an IV glucose load of 35 gm. given in a period of 3 to $3\frac{1}{2}$ minutes (see Figure 14, for example). The difference is certainly more than the experimental errors one would expect. The discrepancy in the peak value of glucose concentration that one obtains with a single compartment model for glucose distribution necessitated the introduction of a second fluid compartment. The two compartments, one for plasma, liver and RBC and another for interstitial fluid, are coupled by means of a constant that accounts for diffusion. Since the transfer of glucose across the liver and RBC is extremely rapid[41] their volumes are lumped with plasma volume.

Moreover the refined continuous measuring devices that are now available for the measurement of glucose concentration[42] justify to some degree the somewhat complex two compartment model for the dynamics of glucose distribution. Strictly speaking, one ought to have two compartment representation for the distribution dynamics of all substrates and hormones. But if nothing is to be gained by having two compartments, single compartment representation, being simpler, is the obvious choice. Thus the choice for FFA distribution is a single compartment model which includes plasma and interstitial fluid. As more refined techniques become available for the measurement of FFA concentration, one may have to use a two compartment model for FFA distribution also. For the time being a single compartment model suffices for our purposes.

Other subsystems in the glucose model are: glycogenolysis, glycogenesis[1] and renal excretion. All these are stimulated by glucose error, the latter two by negative glucose error (glucose concentration above nominal) and the former by positive glucose error (glucose concentration below nominal). Glycogenolysis in enhanced by glucagon and epinephrine and glycogenesis by insulin. Glycogenesis is cut off once liver glycogen stores reach their full capacity (equivalent to about 125 gm. of glucose). Renal excretion is essentially zero below an assigned threshold value of plasma glucose concentration. Utilization of glucose by the brain and RBC is a constant independent of both plasma and interstitial glucose concentrations.

3.2.2. Models for Hormone Controllers.

The models for the four hormone controllers are shown in Figures 5A and 5B. Except for the glucagon controller the others are the same as the ones proposed by Charette.(2) A single compartment model has been chosen for glucagon distribution and degradation considering its low molecular weight (relative to insulin and GH) and the fact that its degradation takes place mainly in the liver which has a rich supply of blood. Glucagon response to IV glucagon in a normal subject reported by Samols et.al.(43) indicates that a single compartment representation of distribution and degradation is quite adequate.

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1 Includes other hepatic pathways of glucose also. Thus it represents the liver uptake of glucose when the plasma glucose concentration is above nominal (see also Page 83).

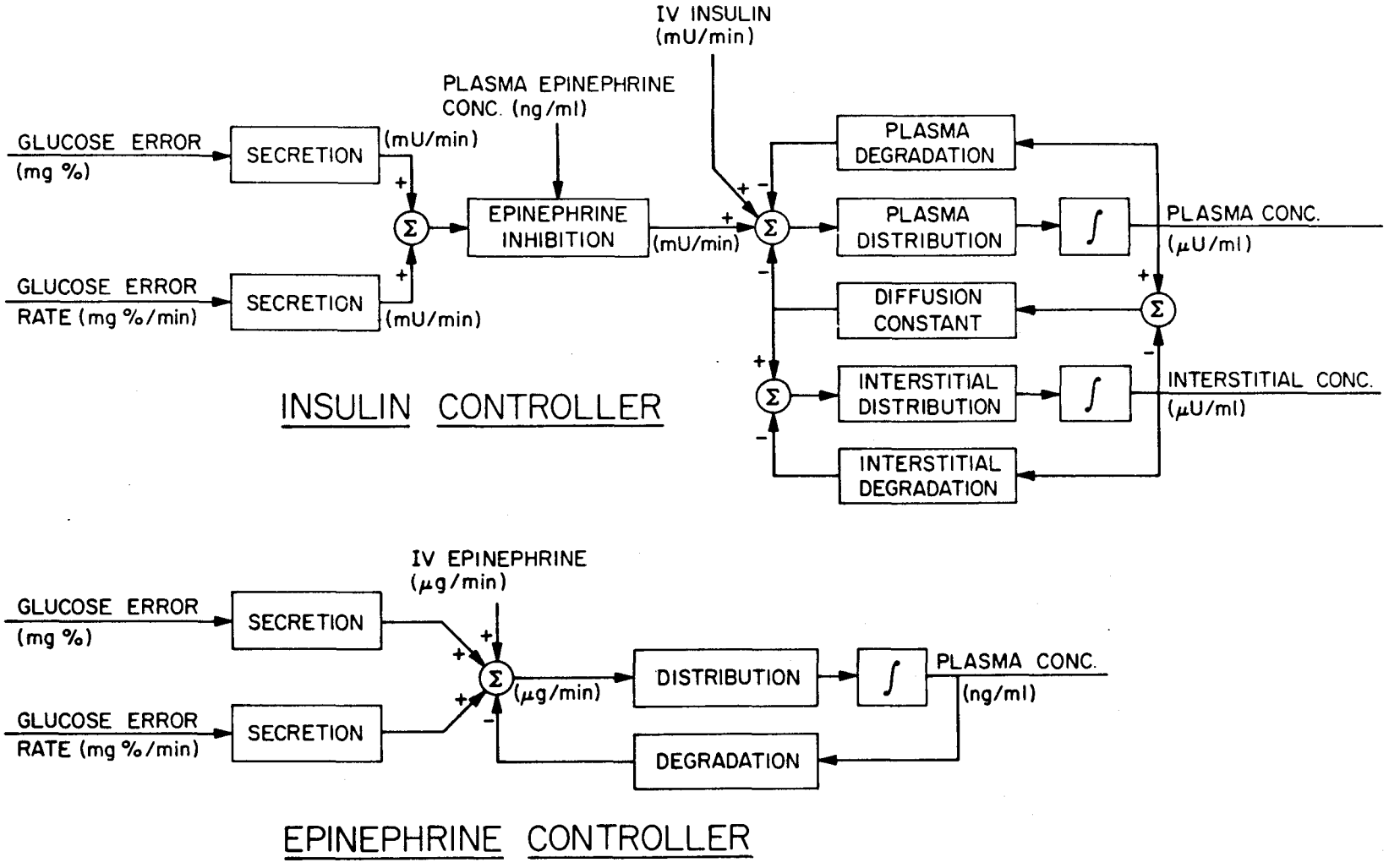
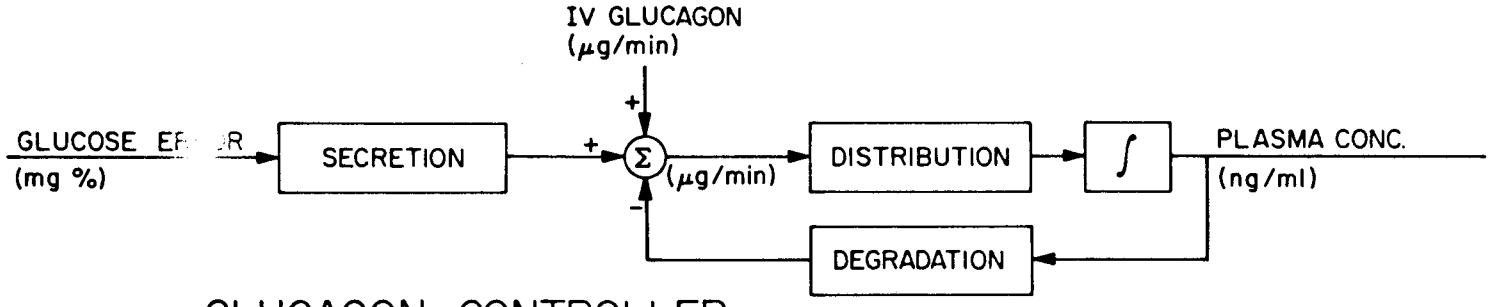
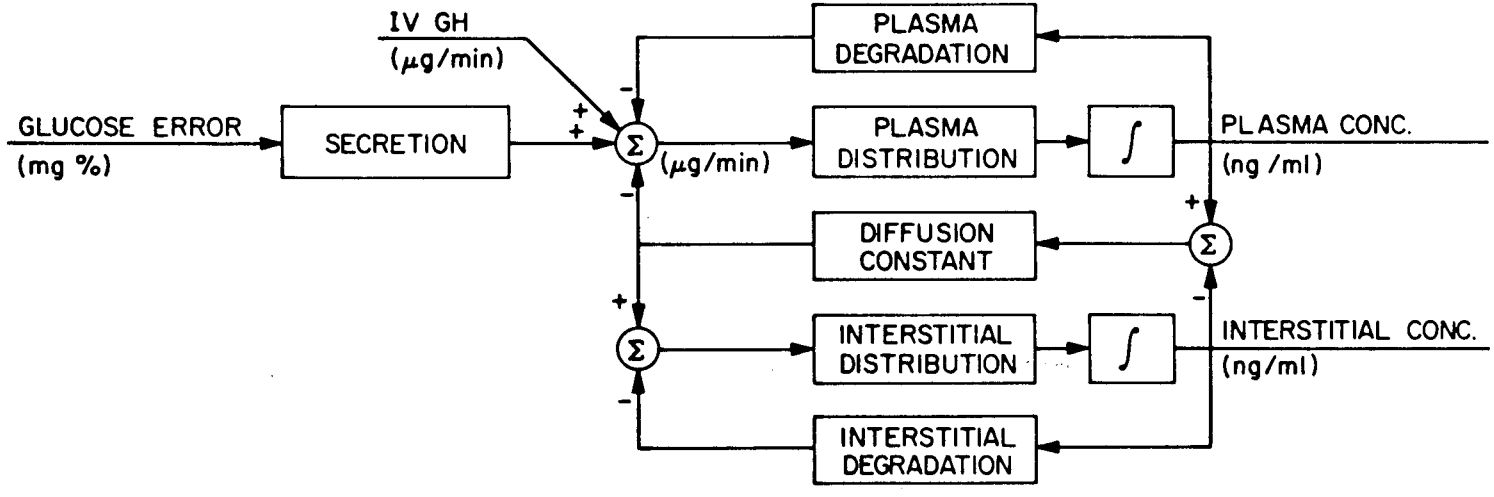


Figure 5A. Models for Hormone Controllers – Insulin and Epinephrine.



GLUCAGON CONTROLLER



GROWTH HORMONE CONTROLLER

Figure 5B. Models for Hormone Controllers – Glucagon and GH.

Simulation studies pointed out the need for some minor changes in Charette's insulin controller. Insulin secretion proportional to glucose error has a lower saturation value of zero in Charette's version. This was made positive in all the simulation studies reported here. Also a small amount of insulin secretion was assumed in the presence of epinephrine. In other words epinephrine does not turn off insulin secretion completely.

3.2.3. The FFA Model.

The major factors involved in fatty acid metabolism are shown in Figure 6. The intracellular FFA concentration is shown to be contained in a single intracellular pool, although this is actually not the case.[1] The flow of FFA into and out of this pool is controlled by various hormonal and other factors. In our model the representations of the processes that control the movement of FFA into and out of extracellular fluid are assumed to include the mechanism of transport across the cell membrane. Thus, for example, the endogenous release rate of FFA due to epinephrine is directly related to the plasma concentration of epinephrine. The effects of transport are thus lumped. The role of adipose tissue intracellular FFA in the control of storage and release of fatty acids is not clear at the present time.

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1 In fact it has been shown that there is not a single intracellular FFA pool for lipolysis and esterification.(44) It is well known that the vast majority (over 90%) of lipid in adipose tissue is stored in the form of TG which is seen morphologically as one or more very large spherical droplets. Much less is known concerning the precise distribution and state of FFA within the adipose cell.(45)

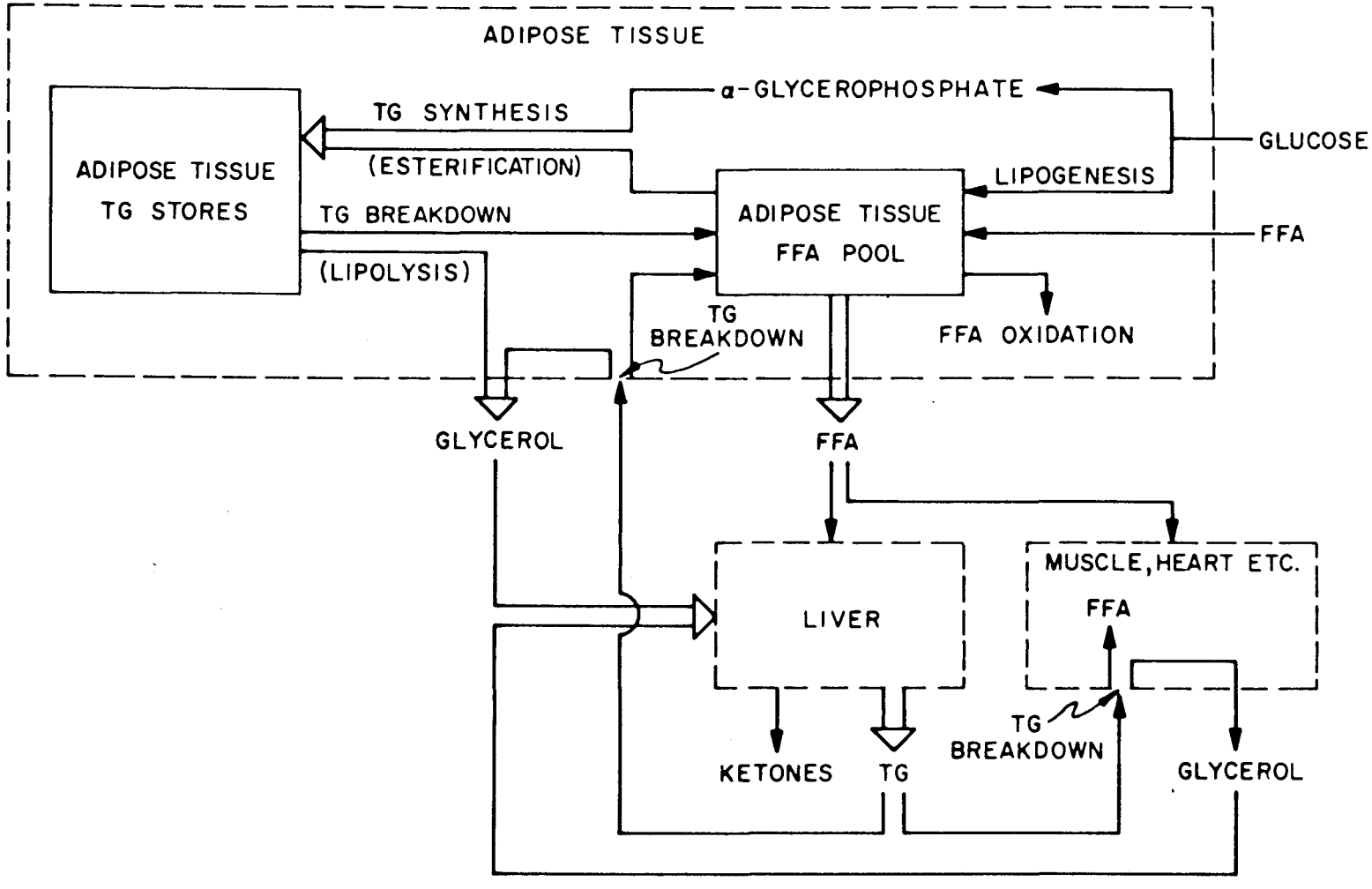


Figure 6. Factors Involved in Fatty Acid Metabolism

The proposed FFA model is shown in Figure 7. A single compartment representation has been chosen for FFA distribution in the extracellular space. The time constant was taken to be around 2 minutes in all simulations. The corresponding half-life is 1.4 minutes. The figure is reasonable considering the extremely short life of FFA in plasma.[46] The major assumptions made in the construction of the model are the following:

(i) The effects of glucose on adipose tissue are mediated entirely through insulin.

(ii) Epinephrine and GH are the most predominant lipolytic hormones which participate in the short-term responses reported here.

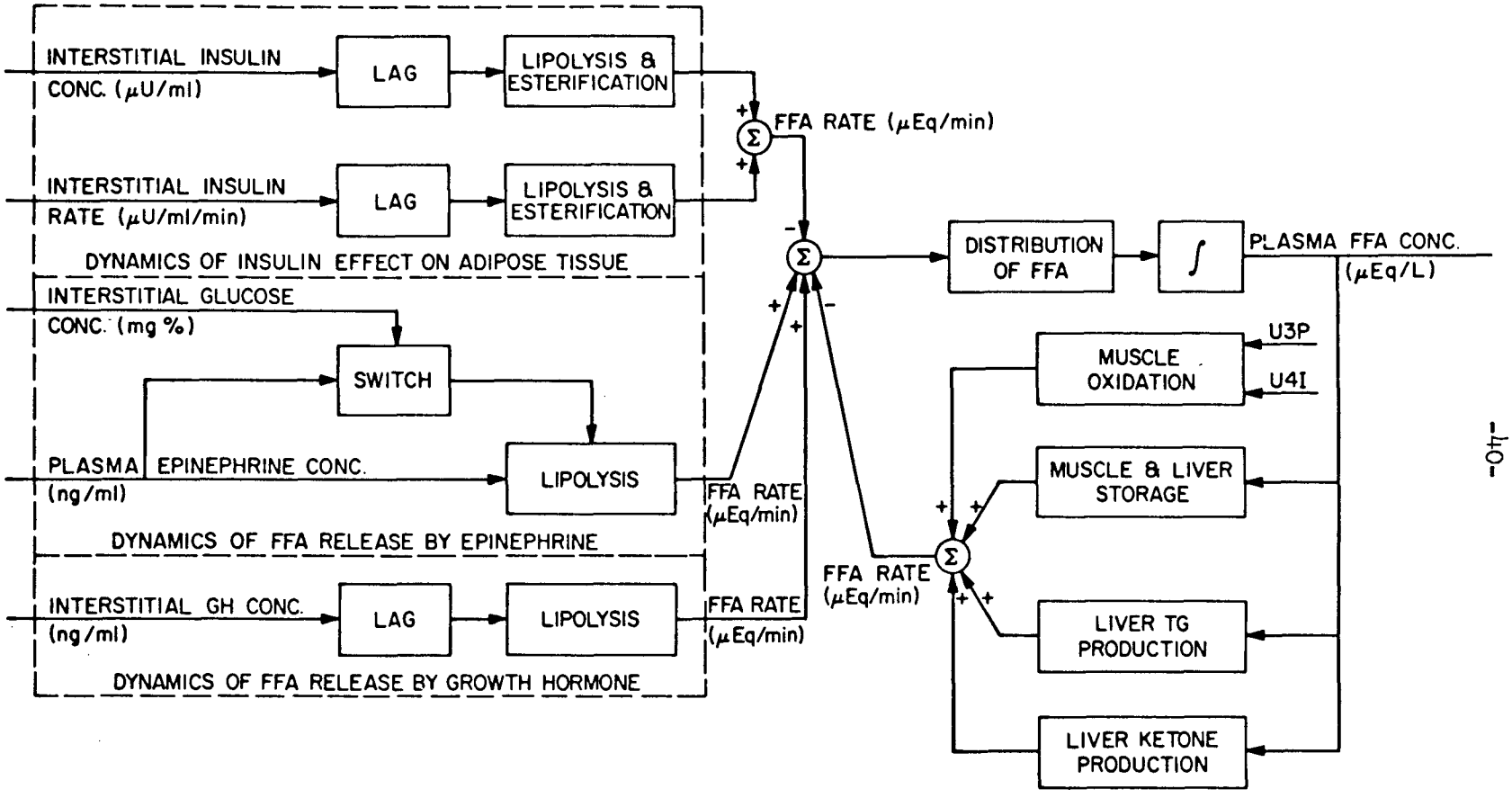
(iii) Muscle uptake of FFA for immediate oxidation is independent of plasma FFA concentration.

(iv) Plasma FFA concentration is the stimulus for FFA uptake by liver and muscle for storage and FFA uptake by liver for production and release of TG and ketones. Furthermore the rate of utilization of FFA along these pathways is saturation-limited at both ends.

FFA utilization: The major pathways of FFA utilization are:

(i) Muscle oxidation.
(ii) Muscle and liver storage.
(iii) Liver TG production.
(iv) Liver ketone production.

(i) Muscle oxidation: It is known that FFA entering the muscles are partly oxidized and partly stored. The fraction of FFA turnover that is immediately oxidized seems to be rather constant and independent of plasma FFA level. Evidence to this fact has been obtained by Issekutz et.al.[47] Their conclusions are based on experiments with



FFA MODEL

U3P – PLASMA EPINEPHRINE CONC.

U4I – INTERSTITIAL GH CONC.

Figure 7.

humans. In further evidence of our representation of muscle FFA oxidation Fredrickson et.al.[5] observe that in man it was not found possible to prevent appreciable oxidation of plasma FFA by supplying an excess of calories as carbohydrate. This would not be true if muscle oxidation of FFA depended upon plasma FFA level, for the latter is decreased by supply of carbohydrates. Muscle, in this context, refers to all the major utilizers of FFA such as skeletal muscle, heart muscle, bronchial musculature, etc. Adipose tissue and liver are excluded. FFA oxidation by the liver is included in the liver ketone production block. Adipose tissue needs of FFA are presumably met from its own stores of TG. Fredrickson et.al. point out that the movement of endogenous FFA from plasma back to adipose tissue is considerably less than the forward reaction. Bragdon and Gordon[48] found only 1-2% of injected labeled FFA in adipose tissue of both fasted and carbohydrate-fed rats. Hence it is assumed that there is no appreciable flow of FFA from plasma into adipose tissue. Muscle oxidation of FFA is enhanced by both GH and epinephrine in our model. Increase of muscle FFA uptake in the presence of GH has been reported by Rabinowitz et.al.[38] The increase due to epinephrine includes the changes due to its effects upon flow as well as its direct effect on cardiac and vascular FFA oxidation. It should be noted that the two effects of GH and epinephrine on FFA metabolism, namely FFA mobilization and increased muscle FFA oxidation are independent in our model.

(ii) Muscle and liver storage: This block represents the fraction of FFA turnover that is stored in muscle and liver in esterified form. In liver, newly synthesized TG are apparently contained in at least two

functional compartments, one slow and another that turns over rapidly.[6] Liver storage included here is associated with the slow turning portion of the newly formed TG.

(iii) Liver TG production: This subsystem is identified with the portion of the newly synthesized hepatic TG that turns over rapidly.

(iv) Liver ketone production: This subsystem includes liver oxidation of FFA and the resulting ketogenesis.[1] The mathematical function chosen for this process has a lower saturation level that represents the minimum FFA requirements of the liver. Liver is known to utilize mainly FFA for oxidation.

It should be noted that the processes (ii), (iii) and (iv) listed above depend on plasma FFA concentration. The mathematical functions chosen for representing these processes are identical except for the saturation levels. Although it is possible to lump (ii), (iii) and (iv) into a single process (which might be called the FFA utilization sink) without altering any of the simulation results which we shall discuss later, this was intentionally not done, thus leaving scope for building the model further. With the subsystems shown in Figure 7 for FFA utilization it is easier to couple the TG and ketone loops. There is, of course, no unique way of choosing the subsystems. The choice is dictated by simplicity, ease with which the relevant subsystems can be identified and the facility it provides for building the model further

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1 The theory that ketogenesis is directly related to mobilization of FFA from the periphery and their subsequent oxidation in liver has recently been challenged.[35]

without making drastic changes in its basic structure.

Lipolysis: The FFA model includes the effects of three hormones which are known to affect lipolysis profoundly — insulin, epinephrine and GH. The effects of other lipolytic hormones can easily be incorporated, if desired. They are not included since they do not play any significant role in the short-term responses that we are mainly concerned with.

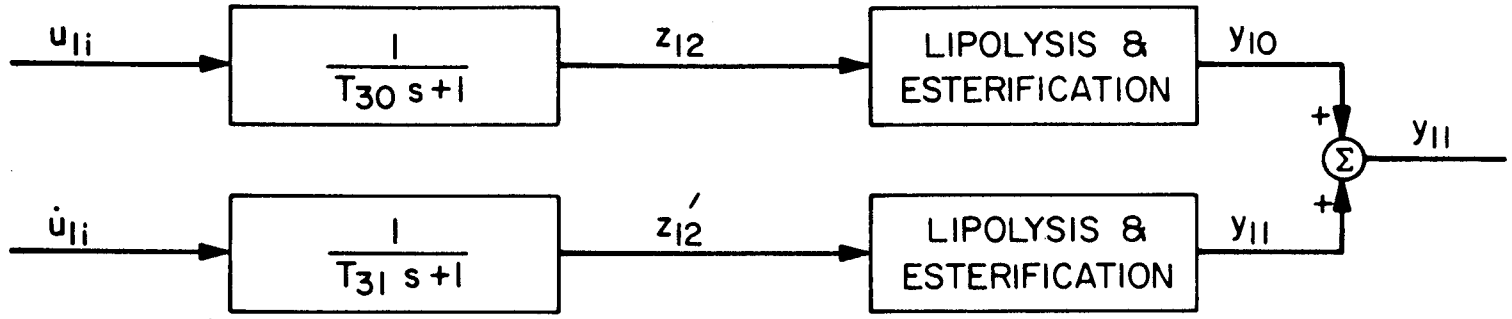
(i) Insulin: The inhibitory effect of insulin on lipolysis is well-known. The concentration of interstitial insulin and its rate are both assumed to stimulate this inhibition. The rate dependence was found necessary in order to explain the rapid fall of plasma FFA concentration following IV administration of glucose or insulin. The time constants of the two lag elements associated with insulin action were chosen to be the same in all simulation studies. It is therefore possible to simplify the configuration shown in Figure 7 with two time lags to one with only one lag element as indicated in Figure 8. Referring to Figure 8A

$$T_{30} \frac{dz_{12}}{dt} + z_{12} = u_{1i}$$

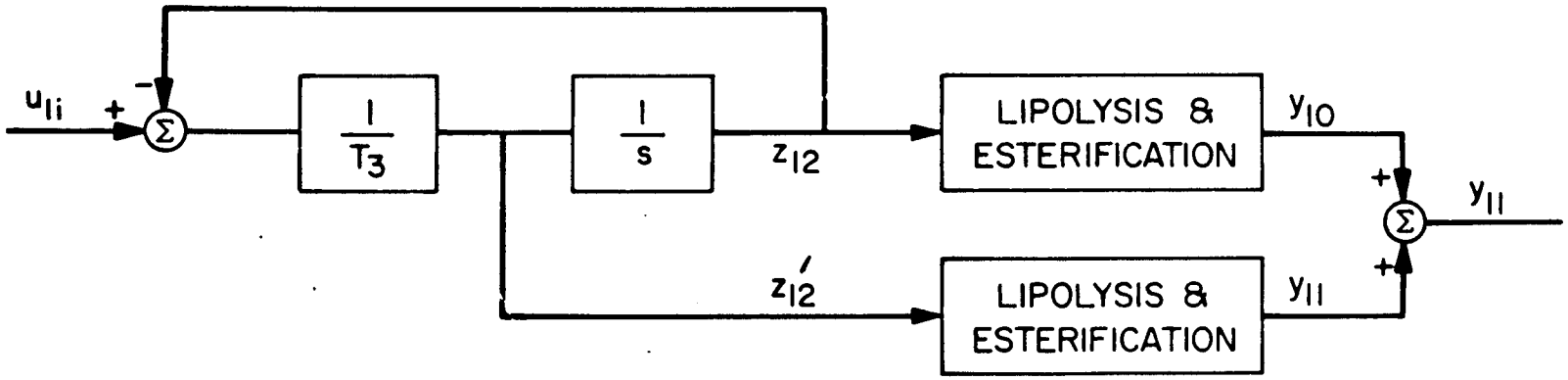
$$T_{31} \frac{dz_{12}'}{dt} + z_{12}' = \dot{u}_{1i} \qquad \text{where} \qquad \dot{u}_{1i} = \frac{du_{1i}}{dt}$$

If $T_{30} = T_{31}$, then $z_{12}' = \frac{dz_{12}}{dt}$. We can represent the dynamics of insulin effect on adipose tissue as indicated in Figure 8B.

It should be noted that the effect of glucose on adipose tissue is mediated entirely through insulin in our model. Current



A. Representation shown in Figure 7.



B. An alternative representation when $T_{30} = T_{31} = T_3$.

Figure 8. Model for the Dynamics of Insulin Effect on Adipose Tissue. s is the derivative operator $\frac{d}{dt}$.

theories support this viewpoint. Rabinowitz et.al[49,50] have produced evidence to conclude that the glucose uptake by adipose tissue (which provides α-glycerophosphate, the necessary precursor for the esterification of fatty acids) alone cannot account for the rapid fall of plasma FFA level caused by IV glucose or insulin.

(ii) Epinephrine: The in vivo effects of epinephrine on humans have been studied by Porte et.al.[51] The dynamics of FFA release shown in Figure 7 is intended to explain the observations of Porte et.al., viz., an initial rise in plasma FFA concentration followed by a decline to the normal level. An increase in glucose concentration results due to enhanced gluconeogenesis and glycogenolysis by epinephrine. The initial increase of FFA production is later inhibited once the interstitial glucose concentration reaches a certain value, possibly due to re-esterification. There are evidences in the literature in support of this idea. Firstly increase of interstitial glucose concentration increases the entry of glucose into adipose tissue and this has the effect of improving the supply of α-glycerophosphate necessary for esterification of fatty acids. As we mentioned earlier (see Page 31), such an increase in the uptake of glucose by adipose tissue may not be significant in the absence of insulin whose secretion is blocked by epinephrine[51]. However, it may be sufficient to improve the re-esterification of fatty acids and mask the lipolytic action of epinephrine. Secondly, the increased glucose entry could be a direct effect of epinephrine acting on the cell membrane. Based on in vitro results using labeled glucose, Bray and Goodman[52] have reported increased entry of glucose into adipose tissue and also augmented incorporation of radioactivity from

glucose into glyceride-glycerol by epinephrine. Increased re-esterification in adipose tissue could also result from a rise in the level of phosphorylase activity caused by epinephrine.[16]

The action of epinephrine on adipose tissue has not been clearly elucidated. Brooker and Calvert[53] have obtained dose-response curves that have a bell shape for catecholamine-induced lipolysis using isolated rat adipose tissue. This suggests the possibility of representing the lipolytic action of epinephrine in our model by means of a bell-shaped nonlinear curve relating plasma epinephrine concentration and FFA release rate. However, this would imply continued lipolysis for certain low levels of epinephrine in spite of increased muscle FFA oxidation and thus cannot be used to explain the in vivo observations on humans. Several suggestions have been made in the literature to explain the effects of epinephrine on adipose tissue. Bally et.al.[54] have suggested that as a working hypothesis the adipose tissue intracellular concentration of FFA may be assumed to inhibit the release of FFA from adipose tissue stores. Rodbell[55] also has advanced this viewpoint. Based on the above hypothesis the lipolytic action epinephrine was first modeled as shown in Figure 9. Although this representation successfully reproduced the FFA response to a dose of IV epinephrine, it gave rise in the case of IV insulin to an early impairment of FFA mobilization offsetting the rebound increase of plasma FFA concentration. It was found difficult to reproduce the FFA response caused by insulin hypoglycemia. Therefore the representation shown in Figure 7 was chosen. It serves as a working hypothesis to explain the FFA responses to both IV insulin and IV epinephrine without introducing

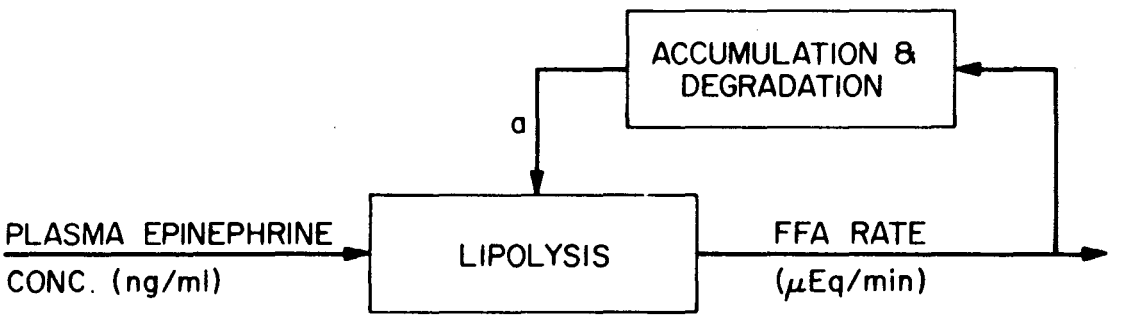


Figure 9. An Alternative Representation for Dynamics of FFA Release by Epinephrine. Accumulation and degradation is represented by a first-order lag and lipolysis by a saturation-type nonlinearity. The saturation level is a linear function of the variable a.

additional complications. In a small measure this demonstrates how models can be used to test alternate hypotheses.

(iii) Growth Hormone: GH has the following effects on FFA metabolism. First there is an initial decrease of plasma FFA level. This is accounted by the increased FFA oxidation by muscle as suggested by Rabinowitz et.al.[38] Secondly there is a delayed but significant lipolytic effect. A lag element accounts for the delay in the lipolytic action of GH in our model.

Under basal conditions, FFA turnover rate lies in the range 400 - 900 μEq/min.[7] It was taken to be around 700 μEq/min in all simulation results reported here. The contribution of circulating epinephrine and GH to fasting lipolysis was assumed to be only a very small fraction of the turnover. In other words, increased rates of lipolysis were assumed to be mostly due to low levels of insulin[1] under fasting conditions in accordance with the suggestion by Cahill et.al.[56] Numerical values for the basal rates of the various utilization pathways were obtained from the review article by Fritz.[17]

3.3. The Basic Building Blocks.

The basic building blocks used in the construction of the model are shown in Figure 10. In addition, the model uses multipliers, gain constants and summers. If the nonlinearity depends on more than one parameter, its saturation level is linearly dependent on each of

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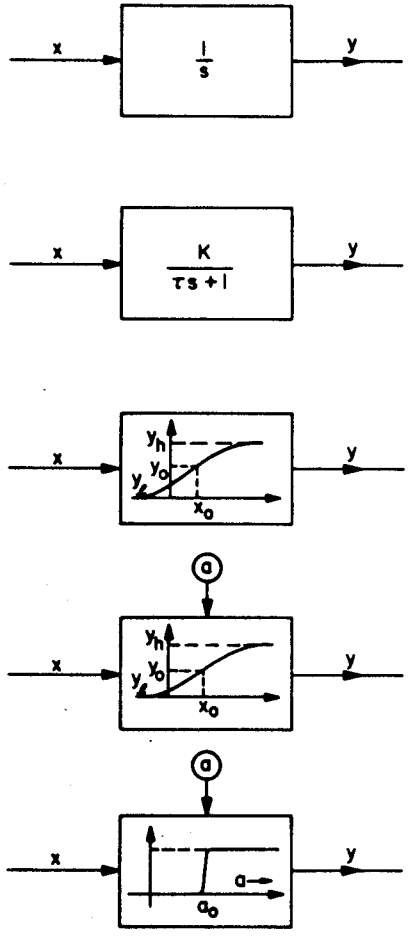
1 With glucose infusion studies on humans, Goodner et.al.[57] obtained results which "point to the operation of a glucose sensitive center which regulates lipolysis in the fasting individual independent from insulin secretion and probably mediated by the sympathetic nervous system."



BASIC BUILDING BLOCKS

Figure 10.

the parameters. It should be noted that the switch shown in Figure 10 does not have a sharp cut-off. A hyperbolic tangent function with a very high slope at the mid-point was used in all computer programs to represent the switch .

Many metabolic processes such as glycogenesis, glycogenolysis, lipolysis, etc. represent the overall effect of a series of enzyme-catalized reactions. The choice of saturation-type nonlinearity (with or without parameter dependence) for characterizing lumped processes arises from the fact a multi-enzyme sequence of reactions is rate-limited at some saturation value. For a further discussion on this the reader is referred to Section 3.4 of Charette's thesis.[2] Referring to Figures 4,5, and 7, a nonlinearity, either parameter dependent or parameter independent as the case may be, characterizes each of the following elements of the system: gluconeogenesis, glycogenolysis, glycogenesis, muscle utilization and adipose tissue utilization of the glucose model; the secretion elements of the controller models; lipolysis, muscle and liver storage, liver TG production and liver ketone production of the FFA model. Renal excretion of glucose is zero below a certain value of plasma glucose concentration and increases linearly above this value. Brain and RBC utilization of glucose is a constant. Muscle oxidation of FFA is represented by linear functions of both plasma epinephrine concentration and interstitial GH concentration. Epinephrine inhibition of insulin secretion is a switch. All the lag elements and distributions in the glucose and FFA models are first-order lags. Hormone distribution is a constant – reciprocal of the distribution volume.

The following examples illustrate the construction of the

model.

Example 1: Gluconeogenesis

Stimulus - Plasma FFA concentration, f_p (μEq/L).

Response - Gluconeogenesis rate, x_1 (mg/min).

Parameters - Plasma concentrations of glucagon and epinephrine, u_{2p} and u_{3p} respectively (ng/ml).

Let

U_{2p}, U_{3p} = Fasting values of u_{2p} and u_{3p} respectively

$x_{1\ell}$ = Lower saturation value of gluconeogenesis rate

X_{1h} = Higher saturation value of gluconeogenesis rate when $u_{2p} = U_{2p}$ and $u_{3p} = U_{3p}$

Then

$$x_{1h} = X_{1h} + a_{x1}(u_{2p} - U_{2p}) + b_{x1}(u_{3p} - U_{3p})$$

$$x_1 = \frac{x_{1h} + x_{1\ell}}{2} + \frac{x_{1h} - x_{1\ell}}{2} \tanh\{\beta_{x1}(f_p - \tilde{f}_p)\}$$

where

a_{x1}, b_{x1}, β_{x1} and $\tilde{f}_p$ are constants.

Example 2: Insulin distribution and degradation in plasma and interstitial fluid

Let

w_1 = Net endogenous insulin secretion (mU/min)

I_1 = IV insulin input (mU/min)

K_{10} = Plasma insulin degradation constant (L/min)

K_{11} = Diffusion constant (L/min)

K_{12} = Interstitial insulin degradation constant (L/min)

u_{1p} = Plasma insulin concentration ($\mu U/m\ell$)

u_{1i} = Interstitial insulin concentration ($\mu U/m\ell$)

V_p = Plasma volume (L)

V_i = Interstitial fluid volume (L)

Then

$$\frac{du_{1p}}{dt} = \{w_1 + I_1 - K_{10}u_{1p} - K_{11}(u_{1p} - u_{1i})\}/V_p$$

$$\frac{du_{1i}}{dt} = \{K_{11}(u_{1p} - u_{1i}) - K_{12}\, u_{1i}\}/V_i$$

Example 3: Dynamics of FFA release by epinephrine

Stimulus - Plasma epinephrine concentration, u_{3p}(ng/ml).

Response - FFA release rate, y_2 (μEq/min).

Parameters - Interstitial glucose concentration, g_i (mg%) and u_{3p}', modified value of u_{3p} (ng/ml).

u_{3p}' is equal to u_{3p} above a certain value of g_i denoted by $\tilde{g}_i$; it is zero for low values of g_i. That is,

$$u_{3p}' = u_{3p} \quad \text{if} \quad g_i \gg \tilde{g}_i$$

$$u_{3p}' = 0 \quad \text{if} \quad g_i \ll \tilde{g}_i$$

It is represented as follows:

$$u_{3p}' = u_{3p} \frac{1 + \tanh \{\beta_{u3p}(g_i - \tilde{g}_i)\}}{2}$$

β_{u3p} is chosen so as to obtain the desired switching characteristic. Under fasting conditions, $g_i \ll \tilde{g}_i$ and hence $u_{3p}' = 0$. Let

U_{3p} = Fasting value of u_{3p}

Y_{2h} = Higher saturation value of epinephrine-induced lipolysis rate when $u_{3p}' = 0$. The lower saturation value is zero.

Then

$$y_{2h} = Y_{2h} + a_{y2}u_{3p}'$$

$$y_2 = \frac{y_{2h}}{2} + \frac{y_{2h}}{2} \tanh \{\beta_{y2}(u_{3p} - \tilde{u}_{3p})\}$$

where

a_{y2}, β_{y2} and $\tilde{u}_{3p}$ are constants.

3.4. The Results.

The validity of the proposed model was tested with data obtained both from the Physio-Chemical Automation Research Laboratory at Cedars-Sinai Medical Center, Los Angeles, California and from the Research Laboratories of the Diabetes Foundation, Joslin Clinic, Boston, Massachusetts. The data were from a single test subject in each case. Since the parameters of the model characterize the peculiarities of the metabolism of a given individual, it does not make sense to use the average data from several test subjects. Numerical values for the

parameters were obtained initially in most instances from physiologic and medical literature. They were then refined to fit the experimental data on glucose, insulin and FFA taken after IV administration of either glucose or insulin. No sophisticated curve-fitting techniques were employed. The fit was based on judgement by the eye. In all cases the experiment was conducted after an overnight fast. In a few instances the parameter values could be obtained directly from the experimental data. For example, in one of the simulation studies insulin response to IV insulin was used to obtain the parameter values associated with insulin degradation. A time delay between 20 to 60 seconds in the input was assumed in all simulation studies to account for the delay in injection due to tubing, etc. It was necessary in order to obtain peak-times close to the observed values. All simulation studies were done on an IBM 7094 computer.

Figure 11 shows the simulated and experimental data from a male test subject after 30 gm. of IV glucose. Glucose concentration was measured continuously in this case using a continuous glucose monitoring device[42]. An on-line PDP-8/S computer along with an A/D convertor was used to print out the values of glucose concentration at some desired instants of time.[58] These values have been reproduced in Figure 11. Glucose was injected at a constant rate of 10 gm/min with the aid of a pump. The sampling times for the batch samples for the measurement of insulin and FFA concentrations were accurate to the second and special techniques were worked out to ensure this. Time was measured from the beginning of infusion. Significant changes in the metabolic variables occur in many instances immediately following

the disturbance introduced into the system — a very rapid rise in plasma glucose concentration after IV glucose infusion, for example. It is therefore absolutely important to make measurements from the beginning of infusion.

Figure 12 shows the results on the same subject after 1U of insulin injected intravenously at a constant rate over a period of 3 minutes. The last two experimental values of FFA concentration do not fit very well with the simulated curve. This could be due to other lipolytic hormones, not included in the model, operating under hypoglycemic conditions. Figure 13 shows a prediction result. Without altering the parameter values obtained in the two previous simulations, the ability of the model to reproduce the glucose response of the same subject to 15 gm. of IV glucose input was tested. The experiment was done twice separated by 8 weeks. The results were practically identical. The average of the two sets of experimental data is shown in Figure 13. The model has reproduced fairly well the peak and the time-to-peak, although the difference is somewhat large in the tail portion of the response. The results are good considering the preliminary stage of the modeling efforts reported here.

The errors in the measurements of glucose and FFA concentrations were less than 2% and 4% respectively. The expected error in the measurement of insulin concentration was about 50% at 10μU/ml and about 5% at 200μU/ml. The experimental set-up was same for all experiments. Hence the delay in injection was assumed to be the same in all simulations. The experiments were done after an overnight fast, thus making sure that the pretest regimen of the subject was same for all

of them. At this stage of modeling it is absolutely important that we disturb the system from the same initial state in all studies. As we understand more about the system we may be able to remove this restriction.

Figures 14 and 15 show the simulated and experimental data from normal subjects after 35 gm. of IV glucose. Experimental data were obtained from the research laboratories in Boston (J. S. Soeldner, Personal Communication). All quantities were measured at the sampled intervals shown. Glucose concentration was measured with a Technicon autoanalyzer. The standard deviations in the measurements of glucose, insulin and FFA concentrations were about 2%, 6% and 15%, respectively.

Figures 16 through 20 show the simulation results of IV injections of glucagon, epinephrine, GH and insulin on subject 174 (see also Figure 15). Although we do not have experimental data for comparison, these results indicate that the proposed model has enough flexibility to reproduce clinical observations after IV injections of the hormones listed above. The model failed to reproduce the reported responses[59] to continuous (for more than one hour) IV glucagon infusion. Prolonged infusion of glucagon lowers the plasma FFA concentration which stays low till the infusion is withdrawn. Since the effects of FFA are mediated through only insulin in our model, the simulation studies indicated an increase of plasma FFA level after insulin reached its normal level. Our model does not include the effect of glucagon on insulin secretion. If it did the plasma FFA level would stay low.

The model yields an almost linear increase in glucose con-

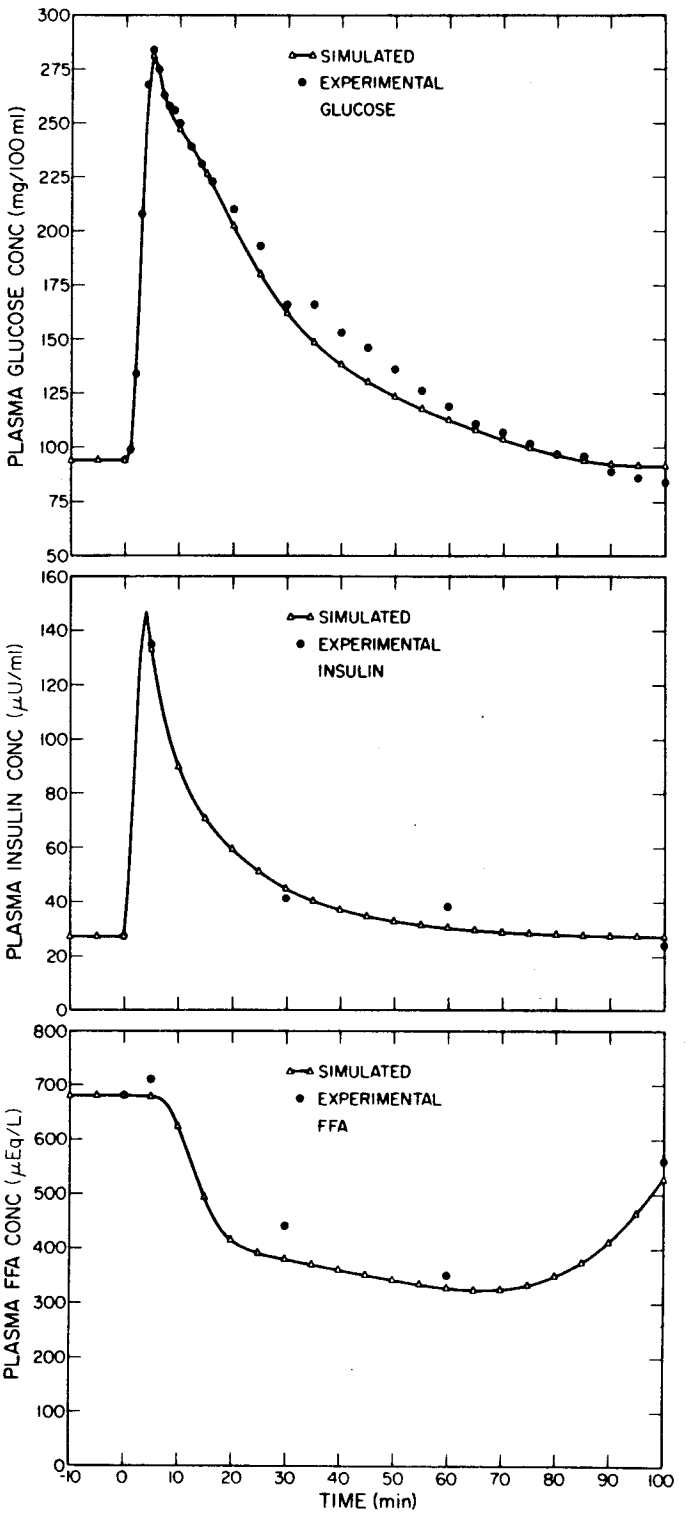


Figure 11. Responses to 30 gm. of IV glucose injected at a constant rate over a period of 3 min. Subject: B.

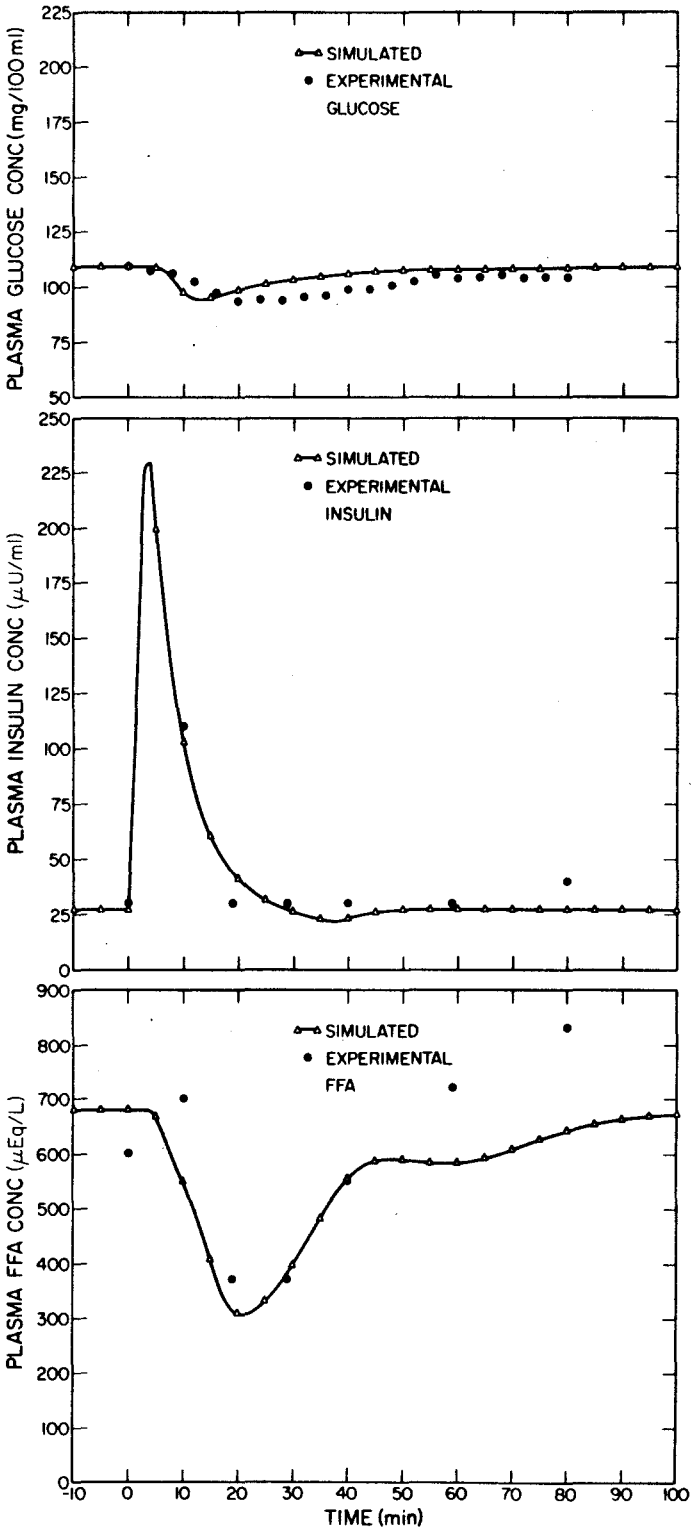


Figure 12. Responses to 1U of IV insulin injected at a constant rate over a period of 3 min. Subject: B.

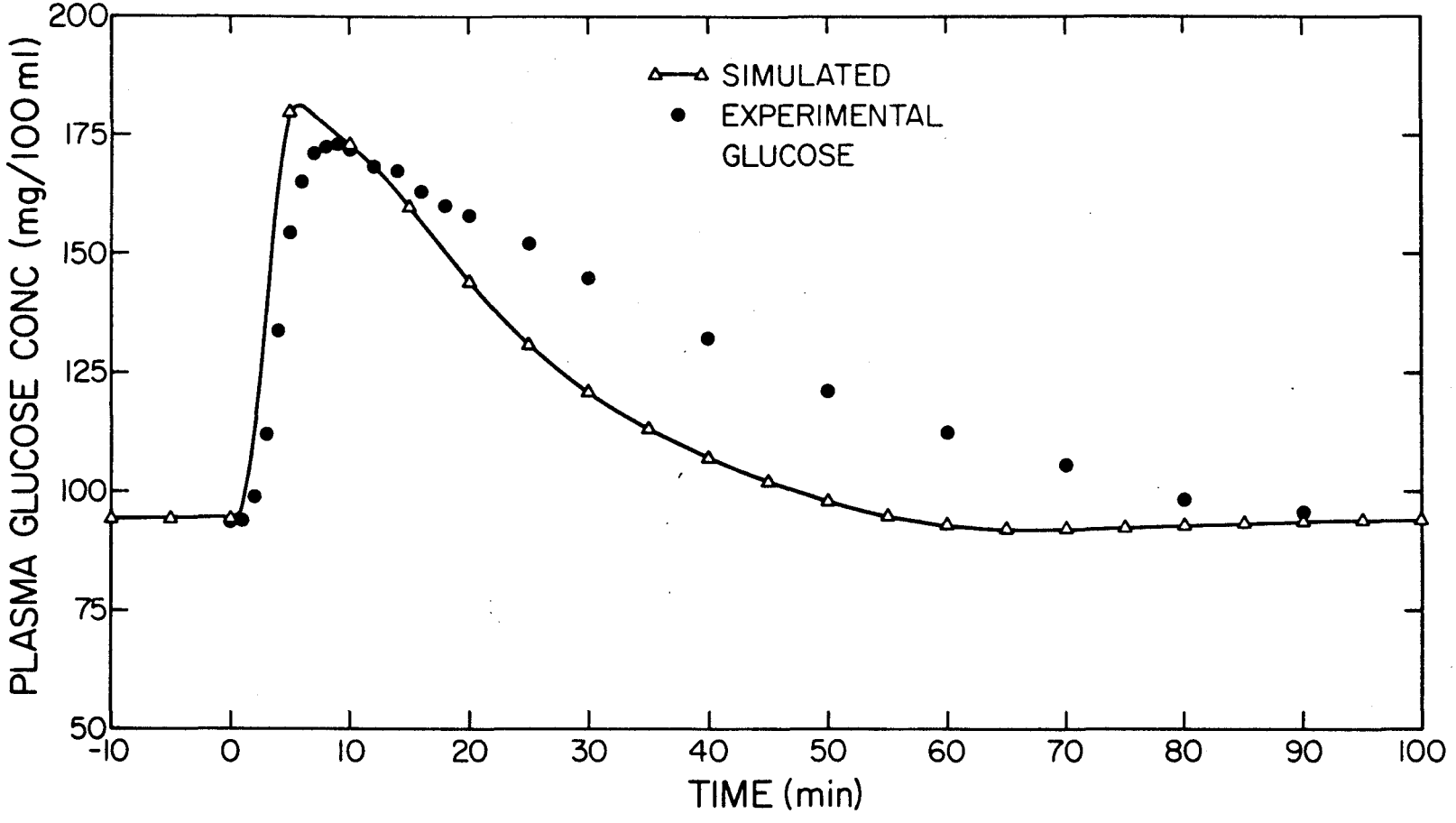


Figure 13. Glucose response to 15 gm. of IV glucose injected at a constant rate over a period of 3 min. Subject: B.

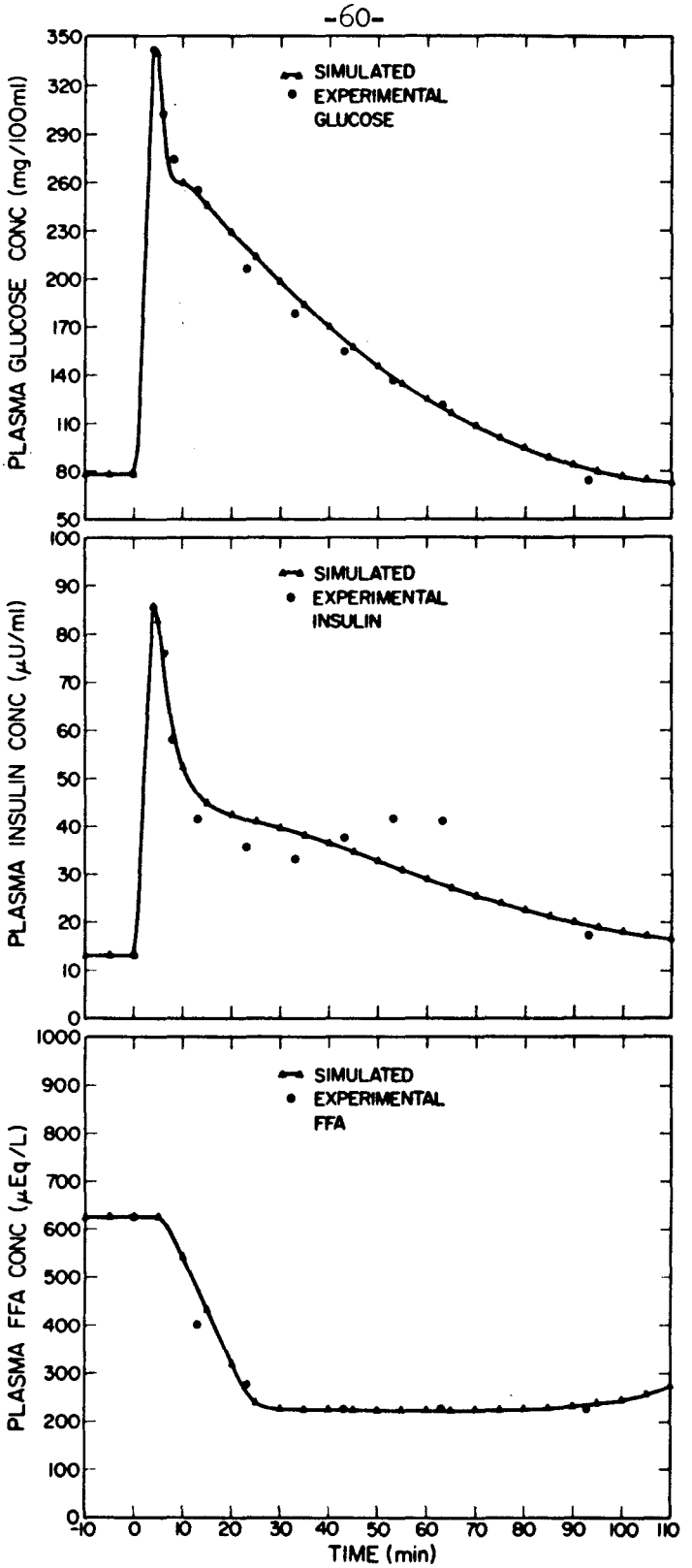


Figure 14. Responses to 35 gm. of IV glucose injected at a constant rate over a period of 3.5 min. Subject: 186.

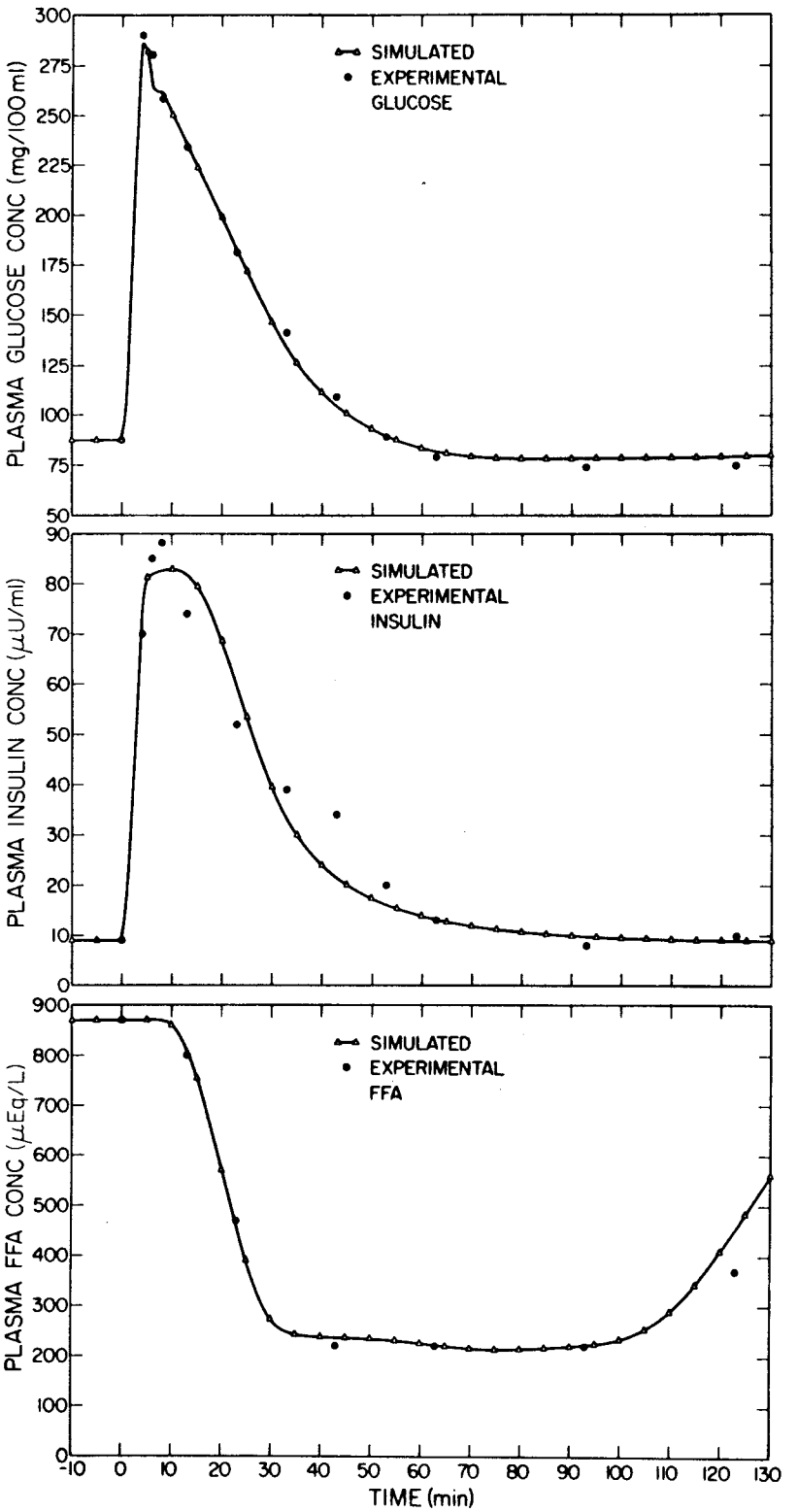


Figure 15. Responses to 35 gm. of IV glucose injected at a constant rate over a period of 3.5 min. Subject: 174.

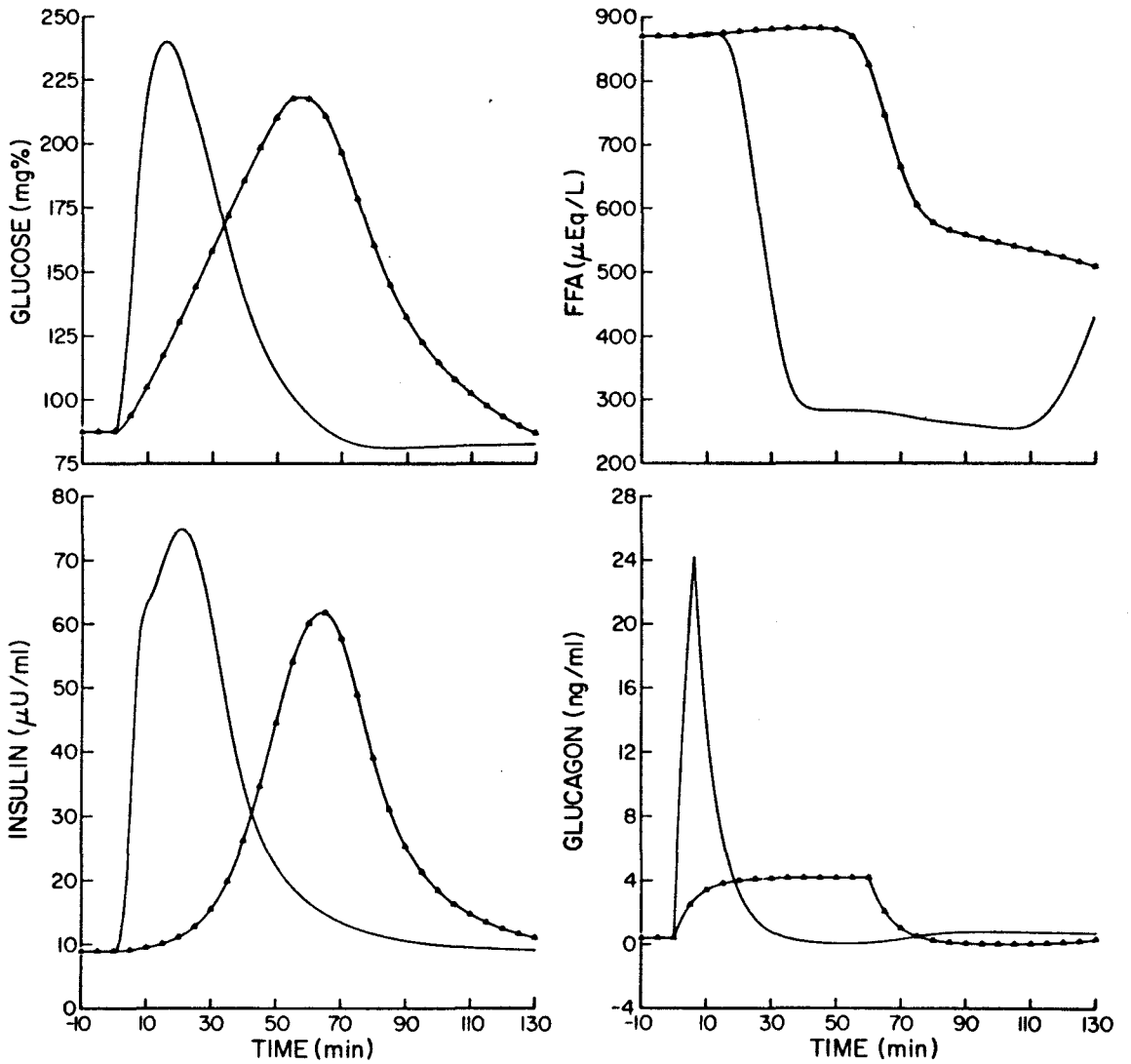


Figure 16. Simulation results of IV glucagon infusion. Subject: 174. —— 0.5 mg. at a constant rate over 6 min.; —▲—▲— 0.5 mg. at a constant rate over 60 min. All quantities refer to plasma levels. $t_{\frac{1}{2}}$ for glucagon = 4.85 min.

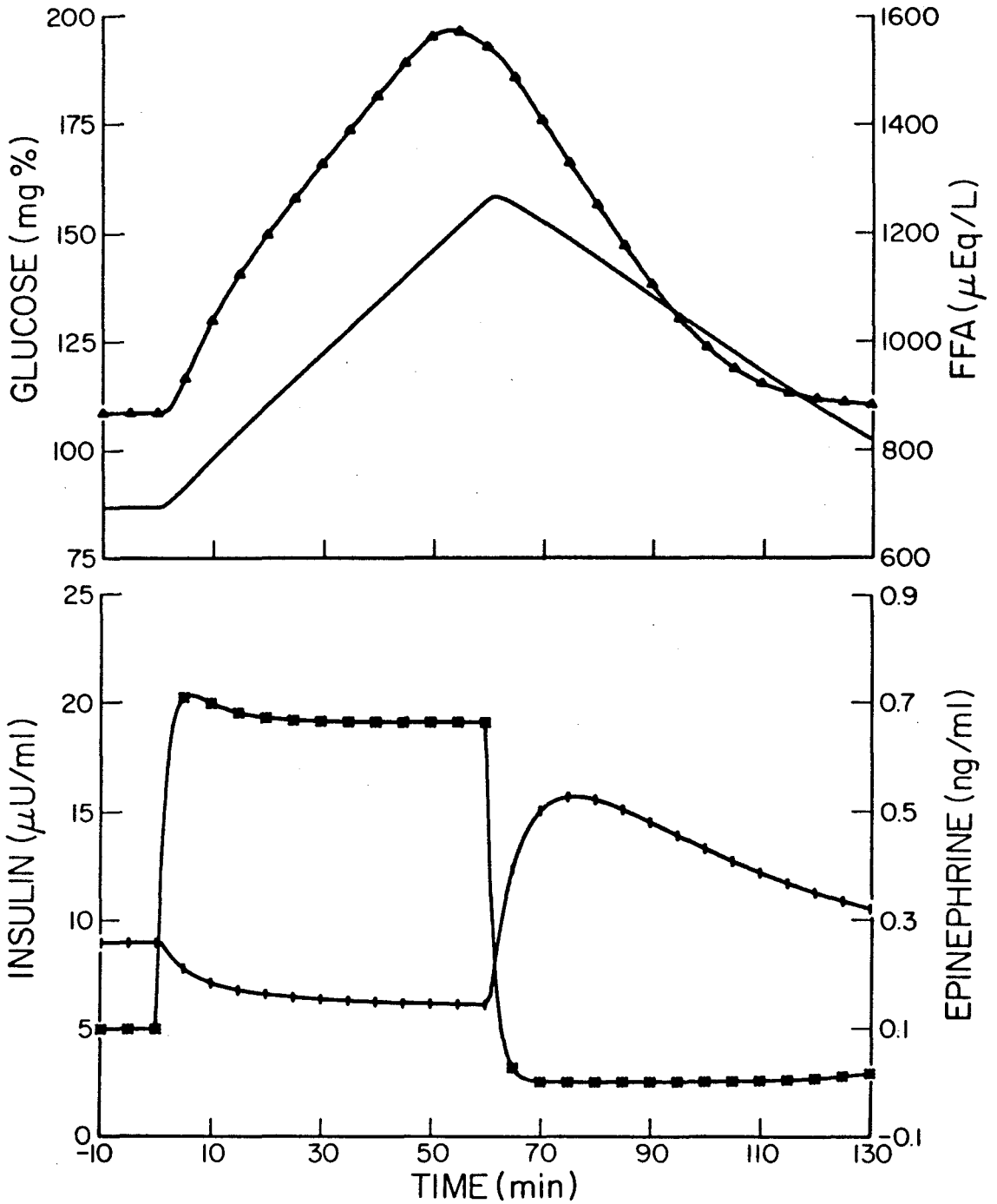


Figure 17. Simulation results of IV epinephrine infusion at 6 μg/min for 60 min. Subject: 174. ——— Plasma glucose conc.; —▲—▲— Plasma FFA conc.; —+—+— Plasma insulin conc.; —■—■— Plasma epinephrine conc. $t_{\frac{1}{2}}$ for epinephrine = 1.07 min.

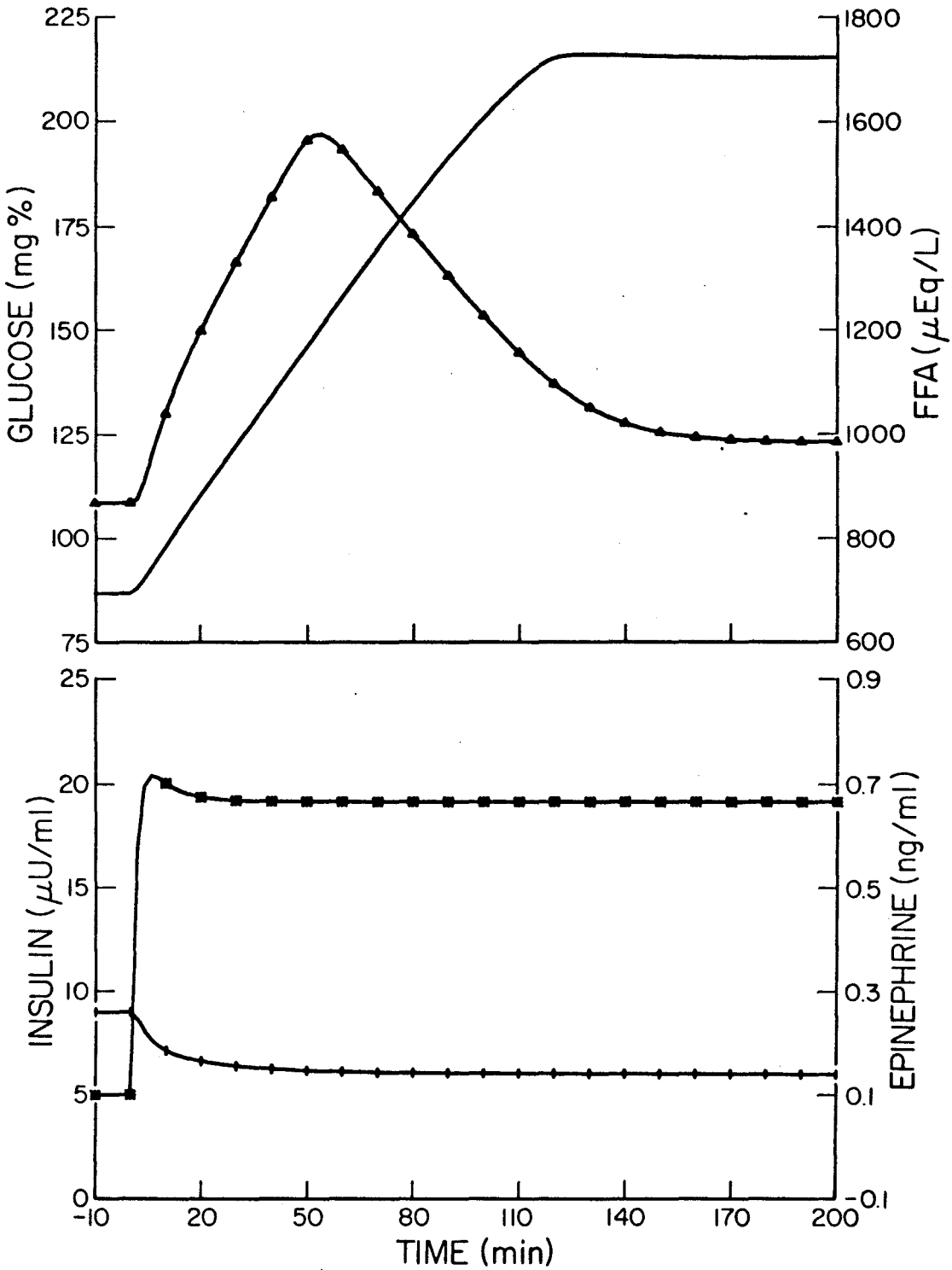


Figure 18. Simulation results of IV epinephrine infusion at 6 μg/min for 200 min. Subject: 174. See Figure 13 for explanation.

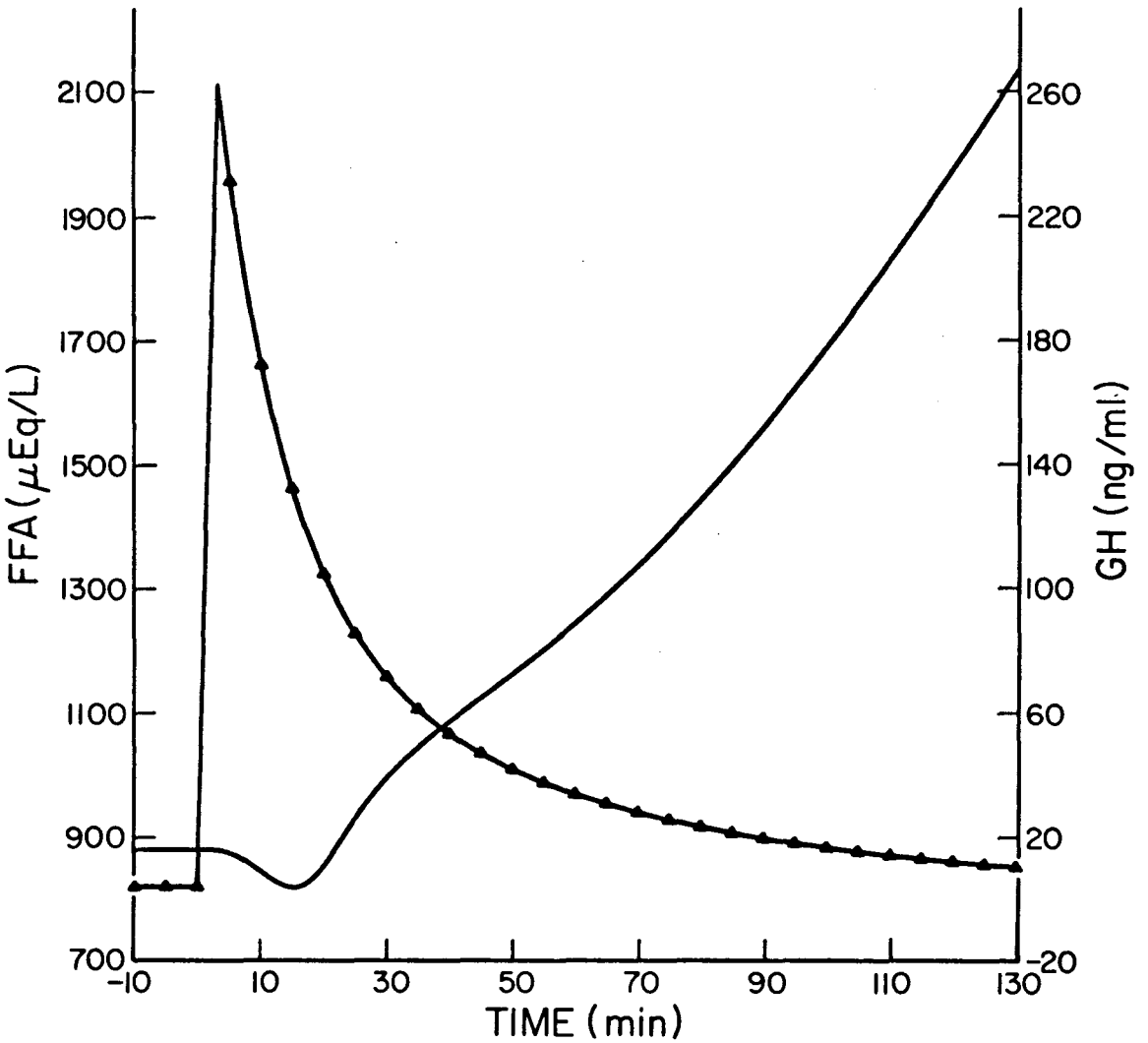


Figure 19. Simulation results of IV infusion of 0.5 mg. of GH at a constant rate over 3 min. Subject: 174. ——— Plasma FFA conc.; —▲—▲— Plasma GH conc. The changes in plasma glucose and insulin levels were very small. $t_{\frac{1}{2}}$ for GH = 7.69, 35.56 min.

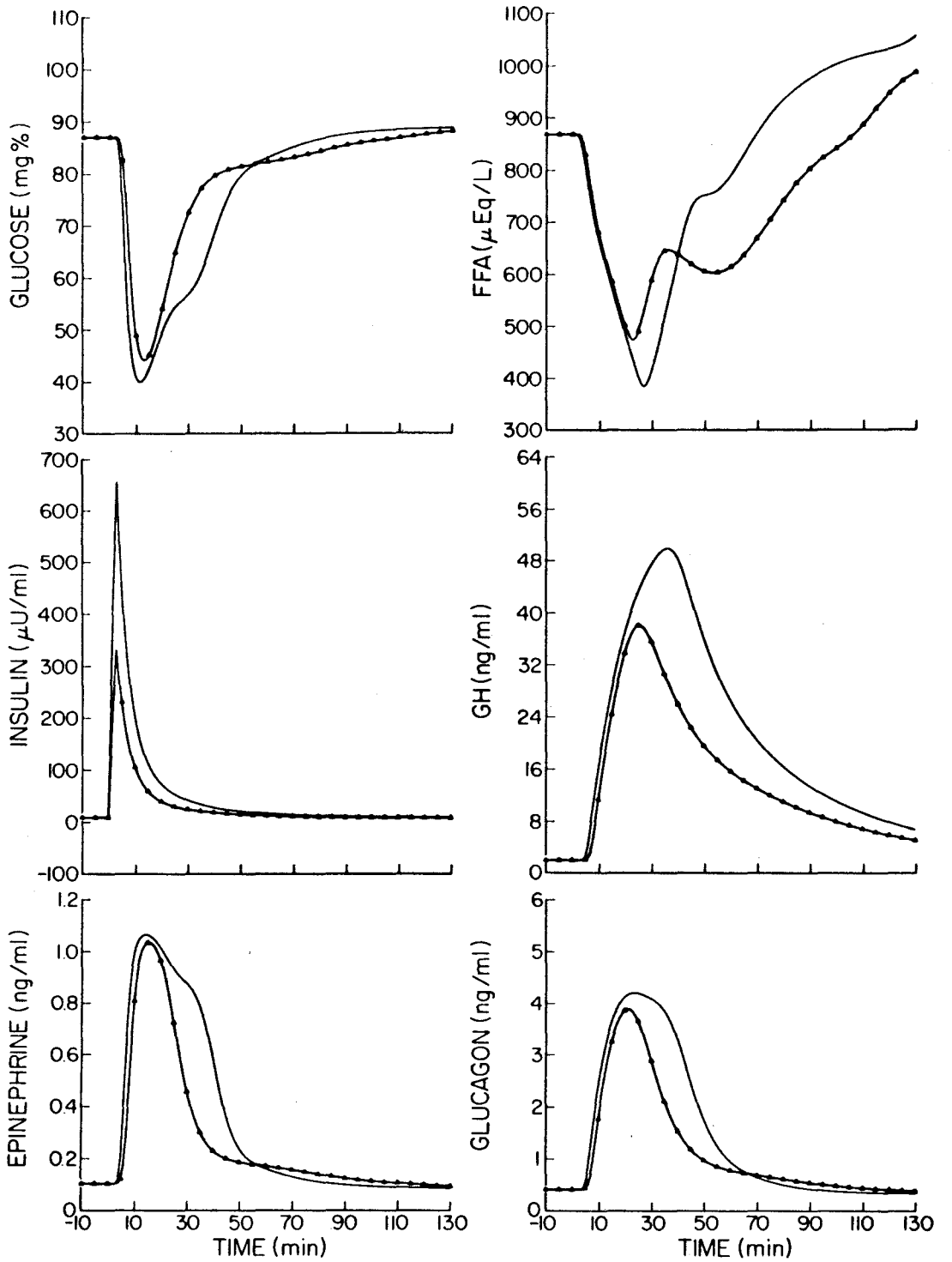


Figure 20. Simulation results of IV infusion of insulin. Subject: 174. ——— 3 U at a constant rate over 3 min.; —▲—▲— 1.5 U at a constant rate over 3 min. All quantities refer to plasma levels. $t_{\frac{1}{2}}$ for insulin = 3.03, 14.56 min.

centration to IV epinephrine infusion as shown in Figures 17 and 18, although the increase is not quite linear according to the results reported by Porte et.al.[51] Some refinements of the functions associated with the responses to IV epinephrine (dependence of gluconeogenesis and glycogenolysis on plasma epinephrine concentration, for example) may be necessary. It is premature to make such refinements at this stage of modeling. To the author's knowledge the results of Porte et.al. are the only ones reported in the literature concerning glucose, insulin and FFA responses to IV epinephrine. More clinical tests which would reveal the details and the salient features of these responses are needed before one attempts any refinements of the mathematical functions or changes in the model. The above comment applies equally well in the case of IV GH infusion also. The simulation results of IV injections of insulin (1.5U and 3U) depicted in Figure 20 compare favorably well with the observations of Greenwood et.al.[60]

In a complex model such as the one proposed here, the modeler has a wide choice of parameters to fit the experimental data. However, a serious restriction is that all the parameter values should lie within physiologic range and all the physiologic variables should vary within an expected range for the particular experiment in question. Care was taken to ensure this in all the simulations. The changes, as obtained from simulations, in plasma concentrations of epinephrine, glucagon and GH of subject 174 during IV glucose and insulin tolerance tests are shown in Table 3. Not only are all the quantities within physiologic range but also they agree with the observations reported in the literature. For example, the maximum value of plasma epinephrine

Time (min.)	35 gm. IV Glucose			3U IV Insulin		
	Epinephrine	Glucagon	GH	Epinephrine	Glucagon	GH
0	0.10	0.40	2.00	0.10	0.40	2.00
3	0.02	0.29	1.83	0.10	0.40	2.01
6	0.19	0.19	1.63	0.42	0.80	4.34
10	0.02	0.11	1.42	0.99	2.42	16.32
15	0.00	0.05	1.22	1.06	3.63	28.22
20	0.00	0.03	1.06	1.01	4.13	36.99
30	0.00	0.01	0.82	0.87	4.08	47.47
40	0.00	0.01	0.66	0.58	3.27	48.34
50	0.04	0.09	0.61	0.23	1.72	35.95
60	0.13	0.36	1.17	0.16	0.94	26.44
70	0.20	0.68	2.62	0.12	0.63	20.45
80	0.20	0.80	3.78	0.11	0.48	16.35
100	0.18	0.77	4.56	0.09	0.37	11.09
120	0.17	0.72	4.76	0.08	0.33	7.86

TABLE 3

Plasma concentrations of epinephrine, glucagon and GH during IV glucose and insulin tolerance tests (subject 174) as obtained from simulations. All concentrations are in ng/ml. Time is given from the beginning of infusion.

concentration is 1.06 ng/ml after 3U of IV insulin; Vendsalu[61] reports a maximum value of 0.8 ng/ml under hypoglycemic conditions. IV glucose reduces plasma GH level to very near zero as reported by Boden et.al.[62]

With the parameter values chosen, maximum pancreatic secretion of insulin would yield a plasma insulin concentration of about 250 μU/ml which is in the vicinity of the upper physiologic limit.[37] The maximum hormone-independent glycogenesis rate is 250 mg/min. Under the influence of insulin it increases to 850 mg/min when the plasma insulin level is about 250 μU/ml. Thus insulin increases the rate of hepatic uptake of glucose by a factor of about three which has been reported.[63] Maximum uptake of glucose by muscle and adipose tissue occurs at an interstitial insulin concentration of about 70 μU/ml corresponding to a plasma concentration of 140 μU/ml.under steady conditions. Christensen and Orskov[37] report maximum glucose uptake by the forearm muscles at a plasma insulin level around 200 μU/ml. Several such agreements support the physiological basis of the proposed model (see Section 3.5 for typical parameter values and Figures 16 through 20 for $t_{\frac{1}{2}}$ values associated with hormone distribution and degradation). Furthermore the simulation studies on subject 174 yielded a net glucose uptake of 15 gm. by muscle in 60 minutes after an IV glucose load of 35 gm. Butterfield et.al.[64] estimate a value of about 16 gm. after 25 gm. of IV glucose. Similar values were obtained in other simulation studies also. The renal glucose excretion of subject B was measured after IV glucose tolerance test (Figure 11) and found to be 0.5 gm.; the simulation gave a value 0.6 gm.

3.5 A Typical Example of the Proposed Model.

The equations used in the simulation studies of subject 174 are presented in this section as an example of the proposed model. The numerical values indicated are typical ones for the parameters. The parameter values for simulation of responses of subjects B and 186 were chosen in the same vicinity. The graphs shown in Figures 15 through 20 were generated using these equations and parameter values.

Glucose model:

t = Time (min)

g_p = Deviation of plasma glucose concentration from nominal (mg%)

g_i = Interstitial glucose concentration (mg%)

r = Nominal or reference level of plasma glucose (mg%); taken to be 0

e = Error in plasma glucose concentration (mg%)

V_p = Plasma volume (L)

V_i = Interstitial fluid volume (L)

V_e = Extracellular fluid volume (L)

V_t = Volume of plasma, liver and RBC (L)

T_1 = Time constant associated with plasma glucose distribution(min)

T_2 = Time constant associated with interstitial glucose distribution (min)

K_g = Diffusion constant (100 ml/min)

I_g = IV glucose input (mg/min)

x_1 = Gluconeogenesis (mg/min)

x_2 = Glycogenolysis (mg/min)

x_3 = Net glucose input into plasma (mg/min)

x_4 = Glucose error presented to the liver (mg%)

x_5 = Glycogenesis (mg/min)

x_6 = Renal excretion (mg/min)

x_7 = Brain and RBC utilization (mg/min)

x_8 = Muscle utilization (mg/min)

x_9 = Adipose tissue utilization (mg/min)

x_{10} = Net plasma glucose utilization (mg/min)

e_1 = Error in plasma glucose rate (mg/min)

e_2 = Error in interstitial glucose rate (mg/min)

z_1 = g_p ; $z_3 = g_i$

z_5 = Amount of glycogen in the liver (gm)

$$r = 0$$

$$e = r - g_p = - g_p$$

$$x_{1h} = 175 + 300\,(u_{2p} - 0.1) + 500\,(u_{3p} - 0.4)$$

$$x_1 = \frac{x_{1h} + 25}{2} + \frac{x_{1h} - 25}{2} \tanh\,\{0.003(f_p - 870)\}$$

$$x_{2h} = 200 + 250\,(u_{2p} - 0.1) + 400\,(u_{3p} - 0.4)$$

$$x_2 = \frac{x_{2h}}{2} - \frac{x_{2h}}{2} \tanh\,\{0.062(g_p + 10)\}$$

$$x_3 = x_1 + x_2 + I_g$$

$$x_4 = \frac{g_p}{2} - \frac{g_p}{2} \tanh\,\{0.6(z_5 - 125)\}$$

$$x_{5h} = 250 + 2.5(u_{1p} - 9)$$

$$x_5 = \frac{x_{5h}}{2} + \frac{x_{5h}}{2} \tanh\{0.025(x_4 - 160)\}$$

$$x_6 = 2.2\, g_p \frac{1 + \tanh\{0.4(g_p - 130)\}}{2}$$

$$x_7 = 98.57$$

$$x_{8h} = 1160 - 4(y_5 - 100)$$

$$x_8 = \frac{x_{8h}}{2} + \frac{x_{8h}}{2} \tanh\{0.0565(u_{1i} - 34.5)\}$$

$$x_9 = \frac{1160}{2} + \frac{1160}{2} \tanh\{0.082(u_{1i} - 34.5)\}$$

$$x_{10} = x_5 + x_6 + x_7 + K_g(g_p - g_i)$$

$$e_1 = x_3 - x_{10}$$

$$e_2 = K_g(g_p - g_i) - (x_8 + x_9)$$

$$\frac{dz_1}{dt} = z_2$$

$$\frac{dz_2}{dt} = (\frac{e_1}{10V_t} - z_2)/T_1$$

$$\frac{dz_3}{dt} = z_4$$

$$\frac{dz_4}{dt} = (\frac{e_2}{10V_i} - z_4)/T_2$$

$$\frac{dz_5}{dt} = (x_5 - x_2)/1000$$

$z_1(0) = 0.0$; $z_2(0) = 0.0$; $z_3(0) = 86.456$; $z_4(0) = 0.0$; $z_5(0) = 80.0$

$V_t = 7.14$; $V_i = 10.5$; $T_1 = 0.8$; $T_2 = 0.5$; $K_g = 85.0$

Fasting level of plasma glucose = 87.0 mg%

Glucose turnover under fasting conditions = $x_3(0) = x_{10}(0) = 144.887$ mg/min

Insulin Controller Model:

u_{1p} = Plasma insulin concentration (μU/ml)

u_{1i} = Interstitial insulin concentration (μU/ml)

w_{10} = Insulin secretion, concentration dependent (mU/min)

w_{11} = Insulin secretion, rate dependent (mU/min)

w_{1h} = Insulin secretion without epinephrine inhibition (mU/min)

w_1 = Net insulin secretion (mU/min)

I_1 = IV insulin input (mU/min)

K_{10} = Plasma insulin degradation constant (L/min)

K_{11} = Diffusion constant (L/min)

K_{12} = Interstitial insulin degradation constant (L/min)

$z_6 = u_{1p}$; $z_7 = u_{1i}$

$$w_{10} = \frac{58 + 3.9}{2} + \frac{58 - 3.9}{2} \tanh \{0.02(g_p - 120)\}$$

$$w_{11} = \frac{67}{2} + \frac{67}{2} \tanh \{0.2(z_2 - 15)\}$$

$$w_{1h} = w_{10} + w_{11}$$

$$w_1 = \frac{w_{1h} + 3}{2} - \frac{w_{1h} - 3}{2} \tanh\{20(u_{3p} - 0.4)\}$$

$$\frac{dz_6}{dt} = \{w_1 + I_1 - K_{10}z_6 - K_{11}(z_6 - z_7)\}/V_p$$

$$\frac{dz_7}{dt} = \{K_{11}(z_6 - z_7) - K_{12}z_7\}/V_i$$

$$z_6(0) = 9.0; \quad z_7(0) = 4.5; \quad V_p = 3.5; \quad V_i = 10.5$$

$$K_{10} = 0.3; \quad K_{11} = 0.4; \quad K_{12} = 0.4$$

Glucagon Controller Model:

u_{2p} = Plasma glucagon concentration (ng/ml)

w_2 = Glucagon secretion (μg/min)

I_2 = IV glucagon input (μg/min)

K_2 = Degradation constant (L/min)

$Z_8 = u_{2p}$

$$w_2 = \frac{9.98}{2} - \frac{9.98}{2} \tanh\{0.061(g_p + 20)\}$$

$$\frac{dz_8}{dt} = (w_2 + I_2 - K_2z_8)/V_e$$

$$z_8(0) = 0.4; \quad K_2 = 2.0; \quad V_e = V_p + V_i = 14.0$$

Epinephrine Controller Model:

u_{3p} = Plasma epinephrine concentration (ng/ml)

w_{30} = Epinephrine secretion, concentration dependent (μg/min)

w_{31} = Epinephrine secretion, rate dependent (μg/min)

w_3 = Net epinephrine secretion (μg/min)

I_3 = IV epinephrine input (μg/min)

K_3 = Degradation constant (L/min)

$z_9 = u_{3p}$

$$w_{30} = \frac{10.06}{2} - \frac{10.06}{2} \tanh \{0.058(g_p + 20)\}$$

$$w_{31} = \frac{4.0}{2} - \frac{4.0}{2} \tanh \{0.3(z_2 + 15)\}$$

$$w_3 = w_{30} + w_{31}$$

$$\frac{dz_9}{dt} = (w_3 + I_3 - K_3 z_9)/V_e$$

$z_9(0) = 0.1$; $K_3 = 9.0$

Growth Hormone Controller Model:

u_{4p} = Plasma GH concentration (ng/ml)

u_{4i} = Interstitial GH concentration (ng/ml)

w_4 = GH secretion (μg/min)

I_4 = IV GH input (μg/min)

K_{40} = Plasma GH degradation constant (L/min)

K_{41} = Diffusion constant (L/min)

K_{42} = Interstitial GH degradation constant (L/min)

z_{10} = u_{4p}; $z_{11} = u_{4i}$

$$w_4 = \frac{13.26}{2} - \frac{13.26}{2} \tanh \{0.095(g_p + 20)\}$$

$$\frac{dz_{10}}{dt} = \{w_4 + I_4 - K_{40}z_{10} - K_{41}(z_{10} - z_{11})\}/V_p$$

$$\frac{dz_{11}}{dt} = \{K_{41}(z_{10} - z_{11}) - K_{42}z_{11}\}/V_i$$

$z_{10}(0)$ = 2.0; $z_{11}(0) = 0.9$

K_{40} = 0.035; $K_{41} = 0.245$

Free Fatty Acid Model:

f_p = Plasma FFA concentration (μEq/L)

T_3 = Time constant associated with insulin effect on adipose tissue (min)

T_4 = Time constant associated with lipolysis by GH (min)

T_5 = Time constant associated with FFA distribution (min)

y_{10} = Insulin effect on adipose tissue, concentration dependent (μEq/min)

y_{11} = Insulin effect on adipose tissue, rate dependent (μEq/min)

y_1 = Net effect of insulin on adipose tissue (μEq/min)

u'_{3p} = Plasma epinephrine level as modified by interstitial glucose (ng/ml)

y_2 = Lipolysis by epinephrine (μEq/min)

y_3 = Lipolysis by GH (μEq/min)

y_4 = Net FFA release (μEq/min)

y_5 = Muscle oxidation of FFA (μEq/min)

y_6 = Muscle and liver storage of fatty acids (μEq/min)

y_7 = FFA utilization for liver TG production (μEq/min)

y_8 = FFA utilization for liver oxidation and ketone production (μEq/min)

y_4' = Net FFA utilization (μEq/min)

e_3 = Error in FFA rate (μEq/min)

$$z_{14} = f_p \; ; \quad \dot{z}_{12} = \frac{dz_{12}}{dt}$$

$$\frac{dz_{12}}{dt} = (u_{1i} - z_{12})/T_3$$

$$y_{10} = \frac{680 + 425}{2} - \frac{680 - 425}{2} \tanh\{0.745(z_{12} - 8.5)\}$$

$$y_{11} = \frac{530}{2} + \frac{530}{2} \tanh\{10(\dot{z}_{12} - 0.457)\}$$

$$y_1 = y_{10} - y_{11}$$

$$u_{3p}' = u_{3p} \frac{1 + \tanh\{0.2(g_i - 150)\}}{2}$$

$$y_{2h} = 590 - 450\, u_{3p}'$$

$$y_2 = \frac{y_{2h}}{2} + \frac{y_{2h}}{2} \tanh\{6(u_{3p} - 0.4)\}$$

$$\frac{dz_{13}}{dt} = (u_{4i} - z_{13})/T_4$$

$$y_3 = \frac{500}{2} + \frac{500}{2} \tanh \{0.445(z_{13} - 6)\}$$

$$y_4 = y_1 + y_2 + y_3$$

$$y_5 = 100 + 250(u_{2p} - 0.1) + 6(u_{4i} - 0.9)$$

$$y_6 = \frac{560 + 220}{2} + \frac{560 - 220}{2} \tanh \{0.005(f_p - 870)\}$$

$$y_7 = \frac{100 + 40}{2} + \frac{100 - 40}{2} \tanh \{0.005(f_p - 870)\}$$

$$y_8 = \frac{180 + 100}{2} + \frac{180 - 100}{2} \tanh \{0.005(f_p - 870)\}$$

$$y_9 = y_6 + y_7 + y_8 \quad ; \qquad y_4' = y_5 + y_9$$

$$e_3 = y_4 - y_4'$$

$$\frac{dz_{14}}{dt} = z_{15}$$

$$\frac{dz_{15}}{dt} = (\frac{e_3}{V_e} - z_{15})/T_5$$

$$z_{12}(0) = 4.5; \quad z_{13}(0) = 0.9; \quad z_{14}(0) = 870.0; \quad z_{15}(0) = 0.0$$

$$T_3 = 30.0; \quad T_4 = 60.0; \quad T_5 = 2.0$$

Fasting level of plasma FFA = 870 μEq/L

FFA turnover under fasting conditions = $y_4(0) = y_4'(0)$ = 700 μEq/min

3.6 The Choice of Parameter Values.

The numerical values of the parameters for the simulations reported in the previous sections were obtained from physiologic and medical literature to begin with. They were subsequently refined to fit actual experimental data. The physiological considerations which led to the choice of the typical parameter values indicated in the last section are discussed in this section. Owing to the paucity of experimental data it was not always possible to choose every parameter value based on physiological considerations. For example, the author does not know of any way of arriving at a number for the constant associated with glucose diffusion from the vascular compartment into the interstitial space. The choice was entirely arbitrary for this particular parameter.

Glucose Model:

(i) Distribution in extracellular space: The parameters are V_t, V_i, T_1, T_2 and K_g. V_t is the volume of plasma, liver, RBC and intestinal mucosa and is taken to be 7.0L. V_i is the interstitial fluid volume and is assumed to be 10.5L. T_1 is the time constant associated with gluocse distribution in the first compartment whose major component is plasma. It is less than one minute and is primarily accounted for by the time required for a few complete circuits of systemic circulation. T_2 is the time constant associated with glucose distribution in the interstitial space. It is also a fraction of a minute considering the rapid distribution of glucose in the extracellular space. The parameter K_g was fixed by trial and error in all simulations so as to obtain the proper peak and time-to-peak of

plasma glucose concentration.

(ii) Gluconeogenesis: The rate of gluconeogenesis, x_1, is given by[1]

$$x_1 = \frac{x_{1h} + x_{1\ell}}{2} + \frac{x_{1h} - x_{1\ell}}{2} \tanh \{\beta_{x1}(f_p - \tilde{f}_p)\}$$

where

$$x_{1h} = X_{1h} + a_{x1}(u_{2p} - U_{2p}) + b_{x1}(u_{3p} - U_{3p})$$

As noted on page 30, the basal gluconeogenesis rate is taken to be 100 mg/min. Owen et.al[65,66] have calculated a value of 33 gm/day for the theoretical maximum glucose turnover after 5 to 6 weeks of fasting. Since glucose production is entirely due to gluconeogenesis after such a prolonged fasting, this directly gives a value for the lower saturation level, $x_{1\ell}$. $x_{1\ell}$ = 33 gm/day = 23 mg/min. The value for subject 174 is 25 mg/min.

As the fasting proceeds the plasma FFA level steadily increases; gluconeogenesis is increased and glycogenolysis is depressed. Assuming that a double saturation curve (saturation-limited at both ends) is a valid representation of gluconeogenesis rate as a function of f_p, $\tilde{f}_p$ may lie anywhere within the permissible physiologic range

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[1] The definitions of symbols are same as in section 3.5. The suffixes h and ℓ refer to higher and lower saturation values respectively. The symbols β and $\sim$ are constants associated with the tangent hyperbolic function. a and b are constants associated with the saturation level function. Capital letters signify fasting steady state values, unless they are constants. For example, X_{1h} is the fasting value of x_{1h} when $u_{2p} = U_{2p}$ and $u_{3p} = U_{3p}$; whereas K_g, T_1, T_2 etc. are constants. Small letters denote either constants or functions of time.

of f_p depending on the number of hours of fast preceding the experiment. By insisting that the pretest regimen should be the same for all experiments we can make sure that the initial conditions are the same in all cases. However this does not help us determine the value of $\tilde{f}_p$. The difficulty arises from the fact that our FFA-glucose model is only a part of a bigger and more complex system with several "outer loops" that have been ignored. Since the present model is intended to explain only certain short-term effects typically due to disturbances introduced after a normal overnight fast, we will assume $\tilde{f}_p = F_p$, the fasting plasma FFA concentration, with the added requirement that all experiments be performed under identical conditions. It is worth mentioning that it is necessary to maintain the subject under controlled dietary conditions for at least two days preceding each test.

With $x_1 = 100$ at $f_p = \tilde{f}_p = F_p$ and $x_{1\ell} = 25$, $X_{1h} = 175$.

The plasma FFA level declines to about 200 μEq/L after an infusion of a large dose of glucose or insulin. Assuming this to be the lowest possible value of plasma FFA concentration and further that gluconeogenesis saturates at this level, we obtain $\beta_{x1} = 0.003$ for a smooth variation over the specified range of f_p – that is,

$|\beta_{x1} (200 - \tilde{f}_p)| \approx 2.0$.

Glucagon is known to increase gluconeogenesis from amino acids. Epinephrine increases gluconeogenesis by depleting muscle glycogen and increasing the availability of lactic and pyruvic acids to the liver. Since the present model does not include lactic, pyruvic and amino acids there is no logical way of separating the gluconeogenic effects of glucagon or epinephrine from its glycogenolytic effects. In other words, if glucagon, for example, increased the glucose turnover by

Δx mg/min, there is no way of finding out what fraction of this came from gluconeogenesis. The parameters, a_{x1}, b_{x1}, a_{x2} and b_{x2}, associated with the increments of gluconeogenesis and glycogenolysis by glucagon and epinephrine were fixed by trial and error so as to obtain the reported glucose responses to IV injections of these hormones (see Figures 16, 17 and 18)

(iii) Glycogenolysis: The glyocgenolysis rate, x_2, is given by

$$x_2 = \frac{x_{2h}}{2} - \frac{x_{2h}}{2} \tanh \{\beta_{x2} (g_p - \tilde{g}_{p2})\}$$

where

$$x_{2h} = X_{2h} + a_{x2}(u_{2p} - U_{2p}) + b_{x2}(u_{3p} - U_{3p})$$

The basal rate is about 50 mg/min as explained on page 30. In the simulation studies of subject 174 it was taken to be 45 mg/min. Under hypoglycemic conditions the plasma glucose concentration does not attain levels below 40 mg%. Therefore it is reasonable to assume that x_2 saturates at a plasma glucose concentration of about 50 mg% below nominal. That is,

$$x_2 \approx x_{2h} \quad \text{at} \quad g_p = -50$$

$\tilde{g}_{p2}$ is negative; its magnitude lies between 5 and 20. In the example of section 3.5, $\tilde{g}_{p2} = -10$ and $x_2 \approx x_{2h}$ at $g_p = -40$. β_{x2} is about 0.06 for a smooth variation – that is, $|\beta_{x2}(-40 - \tilde{g}_{p2})| \approx 2$. Given β_{x2}, $\tilde{g}_{p2}$ and $x_2(o)$, X_{2h} can be computed. $X_{2h} = 200$. As stated earlier, a_{x2} and b_{x2} were determined by trial and error to yield the responses shown in Figures 16, 17 and 18.

(iv) Glycogenesis: The glycogenesis rate, x_5, is given by[1]

$$x_5 = \frac{x_{5h}}{2} + \frac{x_{5h}}{2} \tanh \{\beta_{x5} (x_4 - \tilde{x}_4)\}$$

where $$x_{5h} = X_{5h} + a_{x5} (u_{1p} - U_{1p})$$

$$x_4 = \frac{g_p}{2} - \frac{g_p}{2} \tanh \{\beta_{x4}(z_5 - \tilde{z}_5)\}$$

and $$\frac{dz_5}{dt} = 0.001 (x_5 - x_2)$$

The maximum capacity of liver glycogen is assumed to be 125 gm. of equivalent glucose. Hepatic glycogenesis is stopped once the glycogen level reaches this value. The factor 0.001 in the last equation above converts mg. into grams. In fact, this factor should be less than 0.001 in order to account for other hepatic pathways of glucose. However, there is no error since our experiments are conducted after an overnight fast; the glycogen level is low to start with (assumed to be 80 gm.) and it certainly cannot reach the maximum value even with a large glucose load of 30 or 35 gm. This means that the "glycogen switch" in Figure 4 is never open and consequently $x_4 = g_p$ in all our experiments. β_{x4} is chosen so as to obtain the needed switch characteristic. $\beta_{x4} = 0.6$ gives $x_4 \approx o$ at $z_5 = 130$. Note that $\tilde{z}_5 = 125$ and $z_5(o) = 80$.

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[1] The variable x_5 truly represents the liver uptake of glucose to higher plasma glucose concentrations. Since glycogen formation is the most predominant pathway in liver for glucose when it is being taken up, the term glycogenesis has been used.

Following Shames[3] and Charette[2] we will assume a maximum hepatic glucose uptake of approximately 700 mg/min. Insulin has been reported to increase the hepatic glucose uptake by a factor of about three.[63] The upper physiologic limit of plasma insulin is around 200 μU/mℓ. From these considerations, typical values for X_{5h} and a_{x5} can be easily established. In our example,

$$x_{5h} = 250 + 2.5\ (u_{1p} - 9)$$

Liver becomes a net sink for glucose at an absolute glucose concentration of about 150 mg%[26] – that is, at $g_p \approx 50$. Assuming that x_5 saturates at $g_p \approx 300$, $\tilde{x}_4$ can be determined. β_{x5} is chosen to yield a smooth variation over the range of x_4. In our example,

$$\tilde{x}_4 = 160$$

$$\beta_{x5} = 0.025$$

The maximum rate of glycogenolysis when glucagon and epinephrine levels are at their peak (about 4 and 1.1 ng/ml respectively) is approximately 2000 mg/min. It is noteworthy that it is roughly three times the maximum glycogenesis rate as calculated by Charette.[2]

(v) Renal excretion: The renal excretion rate, x_6, is given by

$$x_6 = K_r\, g_p\, \frac{1 + \tanh\{\beta_{x6}\,(g_p - \tilde{g}_{p6})\}}{2}$$

where K_r = Slope of the renal excretion function when $g_p >> \tilde{g}_{p6}$.

$\beta_{x6} = 0.4$ gives $x_6 \approx 0$ at $g_p = \tilde{g}_{p6} - 10$. $\tilde{g}_{p6}$ is around 150 mg%.[2] K_r can be estimated by measuring the amount

of glucose excreted in the urine after an IV glucose tolerance test. In the example of section 3.5,

$$K_r = 2.2$$

$$\tilde{g}_{p6} = 130$$

(vi) Muscle utilization: The rate of glucose uptake by muscle, x_8, is given by

$$x_8 = \frac{x_{8h}}{2} + \frac{x_{8h}}{2} \tanh \{\beta_{x8} (u_{1i} - \tilde{u}_{1i})\}$$

where

$$x_{8h} = X_{8h} - a_{x8} (y_5 - Y_5)$$

y_5 = Muscle oxidation of FFA

The glucose turnover rate under basal conditions is in the vicinity of 150 mg/min. A reasonable figure for brain utilization is 80 mg/min.[67] Assuming an utilization rate of 100 mg/min by the CNS and RBC, 50 mg/min is utilized by the peripheral tissues under basal conditions. We will assume that about 40 mg/min is consumed by muscle and the balance by adipose tissue. Andres et.al.[67] have reported 22 mg/min by skeletal muscle and 14 mg/min by heart under basal conditions, giving a total of 36 mg/min. Since cardiac muscle is not separately included in our model, a value of 40 mg/min for basal muscle uptake of glucose seems very reasonable.

As mentioned earlier, the maximum physiologic concentration of plasma insulin is about 200 μU/mℓ. With the insulin degradation parameters indicated on page 88, this implies a maximum interstitial

insulin concentration of 100 μU/mℓ. It is reasonable to assume that the peripheral glucose utilization saturates at about this level of interstitial insulin. This implies $\tilde{u}_{1i} \approx 50$. A maximum glucose uptake of 2.5 mg/100mℓ forearm/min by forearm muscle has been reported by Christensen and Orskov.[37] This indicates a muscle uptake of (25)(35) = 875 mg/min for the whole body assuming a muscle mass of 35 kg. and that the measured forearm volume consisted entirely of muscle. The latter assumption is not quite true. Furthermore uptake by cardiac muscle has not been included. Hence a value in the vicinity of 1000 mg/min would seem more reasonable.

Given $\tilde{u}_{1i}$, U_{1i} and $x_8(o)$, β_{x8} can be computed.[1] In the example of section 3.5,

$$X_{8h} = 1160$$
$$\tilde{u}_{1i} = 34.5$$
$$x_8(o) = 37.8$$
$$\beta_{x8} = 0.0565$$

Since x_8 cannot become negative under any circumstances,

$$a_{x8}(y_5 - Y_5) < 1160$$

The maximum value for $(y_5 - Y_5)$ is about 250. This gives an estimate of a_{x8}. $a_{x8} = 4.0$ for subject 174.

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1 U_{1i} is the fasting value of u_{1i}. It can be calculated knowing U_{1p} and the degradation parameters of insulin.

(vii) Adipose tissue utilization:

$$x_9 = \frac{x_{9h}}{2} + \frac{x_{9h}}{2} \tanh \{\beta_{x9}(u_{1i} - \tilde{u}_{1i})\}$$

$$x_{9h} = X_{9h}$$

There are no data available in the literature from which a value for X_{9h} can be obtained. In the simulation studies it was assumed to be same as X_{8h}. Considering the fact that in a normal 70 kg. man adipose tissue mass is only about one-third of muscle mass, this implies that the maximum gluocse uptake per kg. of adipose tissue is 3 times higher than the maximum uptake per kg. of muscle. Furthermore $\tilde{u}_{1i}$ is assumed to be the same as for muscle. β_{x9} is computed as before. In our example,

$$X_{9h} = 1160$$

$$\tilde{u}_{1i} = 34.5$$

$$x_9(o) = 8.4$$

$$\beta_{x9} = 0.082$$

It is noteworthy at this point that assumptions such as $X_{8h} = X_{9h}$ are aimed at reducing the number of unknown parameters, if it is possible and physiologically consistent. This will greatly facilitate identification of parameters based on available limited data. The idea here is to obtain a simple representation, yet detailed enough for our purposes.

Models for hormone controllers:

(i) Insulin controller: The equations are:

$$w_{10} = \frac{w_{10h} + w_{10\ell}}{2} + \frac{w_{10h} - w_{10\ell}}{2} \tanh\{\beta_{w10}(g_p - \tilde{g}_{pu1})\}$$

$$w_{11} = \frac{w_{11h}}{2} + \frac{w_{11h}}{2} \tanh\{\beta_{w11}(z_2 - \tilde{z}_{2u1})\}$$

$$w_{1h} = w_{10} + w_{11}$$

$$w_1 = \frac{w_{1h} + w_{1\ell}}{2} - \frac{w_{1h} - w_{1\ell}}{2} \tanh\{\beta_{w1}(u_{3p} - \tilde{u}_{3p})\}$$

$$\frac{dz_6}{dt} = \{w_1 + I_1 - K_{10} z_6 - k_{11}(z_6 - z_7)\}/V_p$$

$$\frac{dz_7}{dt} = \{K_{11}(z_6 - z_7) - K_{12} z_7\}/V_i$$

The plasma and interstitial fluid volumes are assumed to be known. $V_p = 3.5L$ and $V_i = 10.5L$. K_{10}, K_{11} and K_{12} can be estimated from the insulin response data following an IV infusion of insulin. Since these data were not available in the case of subject 174, the parameter values were chosen to conform with the observations of Orskov and Christensen[68] with exogenous insulin and those of Samols and Marks[69] on endogenous insulin.

$$K_{10} = 0.3$$

$$K_{11} = 0.4$$

$$K_{12} = 0.4$$

The associated time constants[1] are 4.4 and 21.0 minutes. The values of K_{10}, K_{11} and K_{12} for subject 174 are roughly same as those for subject B. The latter were based on insulin response data (see Figure 12) taken on the subject following adminstration of 1U of insulin.

Knowing K_{10}, K_{11} and K_{12}, the parameters associated with insulin secretion functions, w_{10} and w_{11}, were adjusted to fit the insulin response obtained during an IV glucose tolerance test. Properly designed systems experiments can yield the necessary information to estimate these parameters reasonably accurately. The reader is referred to Charette's thesis[2] for a further discussion on this. As noted on page 37, $w_{10\ell}$ was taken to be nonzero. It was, however, made very small. Similarly $w_{1\ell} \neq 0$. This implies that epinephrine does not completely shut off the pancreatic secretion of insulin. $w_{1\ell}$ can be easily computed with the knowledge of K_{10}, K_{11} and K_{12} and the steady-state plasma insulin concentration during a prolonged epinephrine infusion experiment like the one performed by Porte et.al.[51]

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[1] If λ_1 and λ_2 are the reciprocals of the time constants, they are given by

$$\lambda_{1,2} = \frac{\alpha_1 + \alpha_2}{2} \pm \sqrt{(\alpha_1 - \alpha_2)^2 + \gamma}$$

where

$$\alpha_1 = \frac{K_{10} + K_{11}}{V_p}$$

$$\alpha_2 = \frac{K_{11} + K_{12}}{V_i}$$

$$\gamma = \frac{4K_{11}^2}{V_p V_i}$$

In our example of section 3.5,

$$w_{10h} = 58.0 \quad ; \quad w_{10\ell} = 3.9$$
$$\beta_{w10} = 0.02 \quad ; \quad \tilde{g}_{pu1} = 120$$
$$w_{11h} = 67.0 \quad ; \quad \beta_{w11} = 0.2$$
$$\tilde{z}_{2u1} = 15 \quad ; \quad w_{1\ell} = 3.0$$
$$\beta_{w1} = 20 \quad ; \quad \tilde{u}_{3p} = 0.4$$

The secretion of insulin is practically zero for plasma epinephrine levels higher than 0.5 ng/mℓ. The net secretion rate under fasting conditions $= w_{10}(o) + w_{11}(o) = w_1(o)$. It should correspond to the measured fasting concentration of insulin. It is noteworthy that the maximum secretion rate $= 58 + 67 = 125$ corresponds to a plasma insulin level of 250 μU/mℓ which is in the vicinity of the upper physiologic limit.

(ii) Glucagon controller: The equations are

$$w_2 = \frac{w_{2h}}{2} - \frac{w_{2h}}{2} \tanh \{\beta_{w2}(g_p - \tilde{g}_{pu2})\}$$

$$\frac{dz_8}{dt} = (w_2 + I_2 - K_2 z_8)/V_e$$

K_2 was chosen based on the observations of Samols et.al.[43] $K_2 = 2.0$. The time constant $= \frac{V_e}{K_2} = \frac{14.0}{2.0} = 7.0$ minutes.

Glucagon, epinephrine and GH are released under hypoglycemic conditions. Maximum secretion of these hormones would be expected before hypoglycemia reaches dangerous proportions, i.e., before plasma glucose declines by more than 50 mg%. We can choose $\tilde{g}_{pu2}$ based on

this argument. w_{2h} corresponds to the maximum physiologic concentration of glucagon - about 4 ng/mℓ.[70] The fasting concentration and the degradation constant determine the value of $w_2(o)$. Given $w_2(o)$, w_{2h} and $\tilde{g}_{pu2}$, β_{w2} can be calculated. For subject 174,

$$\tilde{g}_{up2} = - 20$$

$$w_{2h} = 9.98$$

$$\beta_{w2} = 0.061$$

(iii) Epinephrine controller: The equations are:

$$w_{30} = \frac{w_{30h}}{2} - \frac{w_{30h}}{2} \tanh \{\beta_{w30}(g_p - \tilde{g}_{pu3})\}$$

$$w_{31} = \frac{w_{31h}}{2} - \frac{w_{31h}}{2} \tanh \{\beta_{w31}(z_2 - \tilde{z}_{2u3})\}$$

$$w_3 = w_{30} + w_{31}$$

$$\frac{dz_9}{dt} = (w_3 + I_3 - K_3 z_9)/V_e$$

The choice of K_3 was based on the epinephrine response reported by Vendsalu.[61] $K_3 = 9.0$. The time constant $= \frac{V_e}{K_3} = \frac{14.0}{9.0}$ = 1.55 minutes. $\tilde{g}_{pu3}$, w_{30h} and β_{w30} are chosen in the same way as glucagon secretion parameters. It should be noted that in this case w_{30h} does not correspond exactly to the maximum physiologic concentration of epinephrine (about 1.0 ng/mℓ). For subject 174,

$$\tilde{g}_{pu3} = - 20$$

$$w_{30h} = 10.06$$

$$\beta_{w30} = 0.058$$

There are no physiological data which would help choose the parameters associated with w_{31}. One would expect $w_{31h} < w_{30h}$. We will assume $\tilde{z}_{2u3} = - \tilde{z}_{2u1}$ as a first guess in view of the fact that epinephrine and insulin act in opposite directions in several respects. β_{w31} is selected to yield a smooth nonlinear function. For subject 174,

$$\tilde{z}_{2u3} = - 15$$

$$w_{31h} = 4.0$$

$$\beta_{w31} = 0.3$$

(iv) GH controller: The equations are:

$$w_4 = \frac{w_{4h}}{2} - \frac{w_{4h}}{2} \tanh \{\beta_{w4}(g_p - \tilde{g}_{pu4})\}$$

$$\frac{dz_{10}}{dt} = \{w_4 + I_4 - K_{40} z_{10} - K_{41}(z_{10} - z_{11})\}/V_p$$

$$\frac{dz_{11}}{dt} = \{K_{41} (z_{10} - z_{11}) - K_{42} z_{11}\}/V_i$$

The choice of K_{40}, K_{41} and K_{42} was based on the reported response to IV growth hormone injection by Parker et.al.[71]

$$K_{40} = 0.035$$

$$K_{41} = 0.2$$

$$K_{42} = 0.245$$

The time constants are 7.7 and 35.5 minutes. The secretion parameters are chosen as explained for glucagon and epinephrine. Maximum physiologic concentration of GH is of the order of 50 ng/mℓ.[72] The parameters in our example are:

$$\tilde{g}_{pu4} = -20$$

$$w_{4h} = 13.26$$

$$\beta_{w4} = 0.095$$

FFA Model[1]:

(i) Distribution: A single compartment with a volume $V_e = V_p + V_i = 14.0$L is assumed. Since FFA are known for their very short half-life of 2 to 4 minutes in plasma[46], $T_5 < 5$ seems reasonable. $T_5 = 2$ for subject 174. It is indicated in the next chapter that T_5 is not a highly sensitive parameter.

(ii) FFA utilization: The rate of oxidation of FFA by muscle is denoted by the symbol y_5. It is linearly dependent on concentrations of epinephrine and growth hormone. If Y_5 is the basal rate, we have

$$y_5 = Y_5 + a_{y5}(u_{3p} - U_{3p}) + b_{y5}(u_{4i} - U_{4i})$$

U_{4i} can be readily calculated given the degradation and diffusion constants and plasma concentration of GH.

The turnover rates of FFA in fasting subjects at rest and

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1 Chapter 4 is devoted to procedures and algorithms for systematically identifying the parameters of the proposed FFA model.

during exercise have been measured by several authors.[7] In healthy individuals it lies in the range 400-900 μEq/min after an overnight fast of about 12 hours. The value assumed for subject 174 is 700 μEq/min. Approximately 33% of FFA turnover undergoes immediate oxidation in both lean and obese subjects.[47] Assuming a liver oxidation (both complete oxidation of CO_2 and H_2O and partial oxidation to ketones) of 140 μEq/min and a total of 240 μEq/min and neglecting the flux of FFA from plasma back to adipose tissue (see page 41), $Y_5 = 240 - 140 =$ 100 μEq/min. The values given for a_{y5} and b_{y5} are first guesses. b_{y5} was made large enough to obtain the desired initial dip in the FFA response following an IV dose of GH (see Figure 19).

β and $\tilde{\ }$ associated with utilization functions y_6, y_7 and y_8 were chosen to be same for the sake of simplicity. With the addition of TG and ketone loops, systems experiments can be designed to give information regarding the detailed behavior of these functions.

$$y_9 = y_6 + y_7 + y_8$$

$$= \frac{y_{9h} + y_{9\ell}}{2} + \frac{y_{9h} - y_{9\ell}}{2} \tanh \{\beta_{y9} (f_p - \tilde{f}_p)\}$$

Y_9 = Fasting value of y_9

$$= \frac{y_{9h} + y_{9\ell}}{2} \text{ if } \tilde{f}_p = F_p, \text{ fasting plasma FFA level}$$

$\tilde{f}_p$ was assumed to be same as F_p for reasons indicated on page 81. β_{y9} was chosen assuming a variation in plasma FFA concentration of ± 400 μEq/L about its fasting value. For subject 174,

$$\beta_{y9} = 0.005$$

$$Y_9 = 700 - 100 = 600$$

$$Y_8 = 140$$

$$Y_7 = 70$$

$$Y_6 = 600 - (140 + 70) = 390$$

Carlson and Ekelund[73] estimate a hepatic uptake of roughly 10 mEq/hr for oxidation and less than 5 mEq/hr for net transport to the periphery as TG. Based on their estimates, our figures for Y_8 and Y_7 seem reasonable. The saturation levels of y_6, y_7 and y_8 had to be guessed since there are no physiologic data to base their choice upon.

(iii) Effects of insulin: The equations are:

$$\dot{z}_{12} = \frac{dz_{12}}{dt} = (u_{1i} - z_{12})/ T_3$$

$$y_{10} = \frac{y_{10h} + y_{10\ell}}{2} - \frac{y_{10h} - y_{10\ell}}{2} \tanh \{\beta_{y10}(z_{12} - \tilde{z}_{12})\}$$

$$y_{11} = \frac{y_{11h}}{2} + \frac{y_{11h}}{2} \tanh \{\beta_{y11}(\dot{z}_{12} - \tilde{\dot{z}}_{12})\}$$

$$y_1 = y_{10} - y_{11}$$

The proposed FFA model assumes that the mobilization of FFA under fasting conditions is entirely due to diminished insulin levels (see page 48). Therefore

$y_{10h} \approx Y_1$, lipolysis rate due to insulin under basal conditions

$\approx$ Basal FFA turnover rate

A value of 680 was used in the example of section 3.5.

The plasma concentrations of epinephrine and GH decline and stay very low during the initial phase of an IV glucose tolerance test. The decrease in plasma FFA level is therefore entirely due to elevated levels of insulin in our model. The FFA response characteristically exhibits a sharp decrease followed by a plateau (see Figures 11, 14 and 15). Since essentially steady conditions prevail in the flat region of the response, $y_{10\ell}$ should be very nearly equal to the FFA utilization rate corresponding to the FFA concentration in the flat portion. Thus $y_{10\ell} = 425$ for subject 174. The fast decline in FFA level requires $|z_{12}(o) - \tilde{z}_{12}| < 10$. After choosing $\tilde{z}_{12}$, β_{y10} can be calculated to obtain a smooth variation. For subject 174,

$$z_{12}(o) = U_{1i} = 4.5$$

$$\tilde{z}_{12} = 8.5$$

$$\beta_{y10} = 0.745$$

$\tilde{\dot{z}}_{12}$ was chosen to be 0.46 in our example after observing the range of $\dot{z}_{12}$ in a few trial runs. y_{11h}, β_{y11} and T_3 were chosen to fit the initial fast decline of plasma FFA concentration. It should be noted that $y_{11} \approx 0$ for $\dot{z}_{12} < o$ and hence y_{11} contributes only in the initial phase.

(iv) FFA release by epinephrine: The equations are:

$$u_{3p}' = u_{3p} \frac{1 + \tanh \{\beta_{u3p}(g_i - \tilde{g}_i)\}}{2}$$

$$y_{2h} = Y_{2h} - a_{y2}\, u_{3p}'$$

$$y_2 = \frac{y_{2h}}{2} + \frac{y_{2h}}{2} \tanh \{\beta_{y2}(u_{3p} - \tilde{u}_{3p})\}$$

An estimate of $\tilde{g}_i$ can be obtained from the value of plasma glucose concentration at the instant at which the plasma level of FFA begins to drop during a prolonged epinephrine infusion experiment. β_{u3p} is chosen such that $u_{3p}' \approx u_{3p}$ for $g_i > \tilde{g}_i + 10$. Since the maximum physiologic concentration of epinephrine is about 1.5 ng/mℓ $\tilde{u}_{3p}$ lies in the range 0.0 - 0.8; that is, $|u_{3p}(o) - \tilde{u}_{3p}| < 0.8$. β_{y2} was selected to yield a smooth variation over the range of epinephrine concentration. Y_{2h} was chosen by trial and error to give the required peak FFA concentration obtained during IV epinephrine infusion tests (Figures 17 and 18). In our example,

$$\tilde{g}_i = 150 \quad ; \quad \beta_{u3p} = 0.2$$

$$\tilde{u}_{3p} = 0.4 \quad ; \quad \beta_{y2} = 6.0$$

$$Y_{2h} = 590$$

Since y_{2h} can never become negative,

$$a_{y2}\, u_{3p}' < Y_{2h}$$

Assuming $(u_{3p}')_{max} = (u_{3p})_{max} = 1.0$, $a_{y2} < Y_{2h}$. $a_{y2} = 490$ for subject 174.

(v) FFA release by GH: The equations are:

$$\frac{dz_{13}}{dt} = (u_{4i} - z_{13})/T_4$$

$$y_3 = \frac{y_{3h}}{2} + \frac{y_{3h}}{2} \tanh \{\beta_{y3}(z_{13} - \tilde{z}_{13})\}$$

The parameter values were mostly determined to obtain the required FFA responses following IV injections of GH and insulin (Figures 19 and 20). It was found that $\tilde{z}_{13}$ should be less than 15. As before, β_{y3} was chosen such that $|\beta_{y3} \{z_{13}(o) - \tilde{z}_{13}\}| \approx 2.0$ which ensures a smooth variation.

IV. ESTIMATION OF PARAMETERS OF THE PROPOSED FFA MODEL

4.1. Introduction.

A hypothesized model is not very useful unless methods and procedures are provided for estimating the parameters of the model. The problem of determining the numerical values of the parameters of a given model by suitably processing the data that can be obtained on the stimuli and the associated responses is the so-called "inverse problem". The inverse problem is far from trivial even from a strictly theoretical point of view and is often complicated by "observability" requirements. One has to make sure that the stimulus-response data contain enough information about the unknown parameters and that the response to a given stimulus is reasonably sensitive to changes in the values of the associated parameters.

The aim of this chapter is to demonstrate how certain techniques well-known to systems engineers can be readily employed to identify the parameters of the proposed FFA model. Charette[2] has already considered the identification of parameters associated with the glucose and hormone controller models. Attention is therefore focussed here on only the FFA portion of the proposed model. The results are intended to further illustrate the feasibility of the systems approach to modeling of biological systems. It is shown that despite the complexity of our model, it is possible to estimate the parameter values by suitably processing the stimulus-response data obtained from certain specific physiologic systems experiments.

4.2. The General Approach.

It is a formidable task to estimate simultaneously all the unknown parameters in a given model even if the required data on the stimuli and responses are available. However, by using specific portions of the available data, the parameters associated with specific portions of the model can be identified. Such possibilities are revealed by an analysis of the hypothesized model.

For example, infusion of a physiological dose of GH does not appreciably affect the levels of glucose and other hormones (insulin, glucagon and epinephrine) included in our model. There is a delayed but highly significant rise in plasma FFA concentration. The subsystems involved are the following: dynamics of FFA release by GH, FFA distribution in extracellular space and the various utilization pathways of FFA. The parameters associated with these subsystems can be identified using the data on FFA following an IV GH injection. The remaining part of the model does not enter the picture and can therefore be ignored. On the other hand, IV infusion of insulin causes almost all the variables in the model to vary appreciably. Hence the data obtained after insulin injection cannot be easily used.

In the sequel, physiologic systems experiments are proposed and algorithms are developed for estimation of parameters in the FFA model. Reliance is placed on tracer techniques,[74] well-known to life scientists, for obtaining certain steady state information. The entire model is identified by a sequence of identification problems, each involving estimation of not more than five parameters. Parameters already identified are, of course, assumed to be known in the subsequent identification problems. The algorithms are based on a modified version of

the quasilinearization method.[75,76,2] The fact that many of the physiologic parameters vary over only a limited range is fully exploited. The method does not require any statistical description of measurement errors. The criterion used is least-squares. The approach, it should be noted, is non-sequential, thus permitting computations to be done off-line.

The example of Section 3.5 is used to produce artificially the required experimental data. The true or ideal response for any given stimulus is first generated by integrating the model equations with the parameter values indicated. The data thus obtained is deliberately corrupted with noise to simulate the laboratory measurement errors. The resultant data along with guessed values for the unknown parameters are then used in the estimation algorithms. The following noise model is used to corrupt the data on FFA which is the only one of interest to us.

$$f_{pc}(t_i) = f_p(t_i) + \eta(t_i)$$
$$= f_p(t_i) + Mr \qquad (4.1)$$

where

$f_{pc}(t_i)$ = Observation at time t_i (μEq/L)

$f_p(t_i)$ = True value of plasma FFA concentration at time t_i (μEq/L)

$\eta(t_i)$ = Observational error at time t_i

M = Maximum possible error (μEq/L)

r = Uniformly distributed random variable in the range [-1, +1].

The largest value of M used is 30. This implies an error of $\pm 5\%$ at

a FFA concentration of 600 μEq/L; it is $\pm$ 1.5% when the FFA level is 2000 μEq/L. The figures are reasonable considering the fact that methods are now available to measure FFA concentration within errors less than 2%, especially at high concentrations.

The identification problems presented in Section 4.4 assume that the proposed FFA model is a valid representation of the human metabolic control system. It is certainly not the ultimate model and needs further improvements. The missing loops such as amino acids and TG and hormones such as glucocorticoids are to be included. It is therefore emphasized that the estimation algorithms presented here are not aimed at obtaining the final answers. The more important point is the approach; the results are intended to further illustrate the potentialities of the systems approach in modeling of biological control systems.

4.3. The FFA Model Equations.

In terms of symbols and definitions of Sections 3.5 and 3.6 the equations of the proposed FFA model are the following:

$$\frac{dz_{12}}{dt} = (u_{1i} - z_{12})/T_3$$

$$y_{10} = \frac{y_{10h} + y_{10\ell}}{2} - \frac{y_{10h} - y_{10\ell}}{2} \tanh \{\beta_{y10}(z_{12} - \tilde{z}_{12})\}$$

$$y_{11} = \frac{y_{11h}}{2} + \frac{y_{11h}}{2} \tanh \{\beta_{y11}(\dot{z}_{12} - \dot{\tilde{z}}_{12})\}$$

$$y_1 = y_{10} - y_{11}$$

$$u_{3p}' = u_{3p} \frac{1 + \tanh\{\beta_{u3p}(g_i - \tilde{g}_i)\}}{2}$$

$$y_{2h} = Y_{2h} - a_{y2}\, u_{3p}'$$

$$y_2 = \frac{y_{2h}}{2} + \frac{y_{2h}}{2} \tanh\{\beta_{y2}(u_{3p} - \tilde{u}_{3p})\}$$

$$\frac{dz_{13}}{dt} = (u_{4i} - z_{13})/T_4$$

$$y_3 = \frac{y_{3h}}{2} + \frac{y_{3h}}{2} \tanh\{\beta_{y3}(z_{13} - \tilde{z}_{13})\}$$

$$y_4 = y_1 + y_2 + y_3$$

$$y_5 = Y_5 + a_{y5}(u_{3p} - U_{3p}) + b_{y5}(u_{4i} - U_{4i})$$

$$y_9 = y_6 + y_7 + y_8$$

$$= \frac{y_{9h} + y_{9\ell}}{2} + \frac{y_{9h} - y_{9\ell}}{2} \tanh\{\beta_{y9}(f_p - \tilde{f}_p)\}$$

$$y_4' = y_5 + y_9$$

$$e_3 = y_4 - y_4'$$

$$\frac{dz_{14}}{dt} = z_{15}$$

$$\frac{dz_{15}}{dt} = (\frac{e_3}{V_e} - z_{15})/T_5 \qquad (4.2)$$

There are 27 unknown parameters in all. They are:

V_e , T_5

Y_5 , a_{y5} , b_{y5} ; y_{9h} , $y_{9\ell}$, β_{y9} , $\tilde{f}_p$

T_3 , y_{10h} , $y_{10\ell}$, β_{y10} , $\tilde{z}_{12}$; y_{11h} , β_{y11} , $\tilde{z}_{12}$

β_{u3p} , $\tilde{g}_i$; Y_{2h} , a_{y2} ; β_{y2} , $\tilde{u}_{3p}$

T_4 , y_{3h} , β_{y3} , $\tilde{z}_{13}$

The following are assumed to be known in the identification problems discussed in the next section: parameters associated with hormone controllers[1]; fasting levels of FFA and all hormones; the extracellular volume, V_e; the oxidation (immediate) of FFA under basal conditions $= Y_5 + Y_8$; the turnover rate of FFA under fasting conditions $= Y_4 = Y_4'$. The turnover rate and the amount utilized for direct oxidation can be estimated by tracer techniques.(77,47) Furthermore, as indicated on page 81, it is assumed that $\tilde{f}_p = F_p$, the fasting plasma FFA concentration.

4.4. The Identification Problems

The following three experiments were found to be adequate for the estimation of the unknown parameters of the FFA model. Only the observations needed for the identification of FFA model parameters are listed. The figures given for infusion rates, sampling instants etc. are only representative figures. They were used in generating the required experimental data by simulation on the computer. The units of time, concentrations, rates etc. are the same as given in Section 3.5.

Experiment #1: Prolonged IV epinephrine infusion.

Input: IV epinephrine at a constant rate of 6 μg/min for a

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1 See reference 2 for identification of parameters associated with hormone controller models.

period of 200 minutes until steady state conditions are established.

Observations[1]:

(i) Plasma FFA concentration at $t = 0,3,6,\ldots,18,21,25,30,\ldots,65,70,80,90\ldots190,200$.

(ii) Plasma glucose concentration (continuous measurement)

(iii) Basal oxygen consumption, O_b; oxygen consumption, O_{bn}, and FFA turnover rate, Y_{4n}, after establishment of steady state condtions with constant epinephrine infusion.

Experiment #2: IV growth hormone infusion.

Input: IV growth hormone at a constant rate of $\frac{1000}{3}$ μg/min for a period of 3 minutes.

Observations: Plasma FFA concentration at $t = 0,10,20,\ldots,120,130$.

Experiment #3: IV glucose tolerance test.

Input: IV glucose at a constant rate of 10 g/min for a period of 3.5 minutes.

Observations: Plasma FFA concentration, at $t = 0,5,10\ldots,35,40,50,\ldots,120,130$.

It is necessary to establish first the numerical values of the parameters associated with FFA utilization. It would be easier to estimate them if FFA can be directly injected into the blood. Unfort-

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[1] Blood requirement of 2 cc for each FFA measurement and 15 cc for one hour of glucose measurement is assumed.

unately this cannot be done[1]. The observations listed under experiment #1 above are intended to facilitate the identification of FFA utilization parameters, as will become evident from identification problem #1 discussed later. Now let[2]

$$y_1 = Y_1 + \Delta y_1$$

$$y_2 = Y_2 + \Delta y_2$$

$$y_3 = Y_3 + \Delta y_3$$

$$p_1 = z_{15} = f_p = \text{Plasma FFA concentration}$$

$$p_2 = \dot{p}_1 = \frac{dp_1}{dt}$$

$$\tilde{p}_1 = \tilde{f}_p$$

The equations describing the changes in p_1 and p_2 are:

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = (y_1 + y_2 + y_3) - \{Y_5 + a_{y5}(y_{3p} - U_{3p}) + b_{y5}(u_{4i} - U_{4i})\}$$

$$- \left[\frac{y_{9h} + y_{9\ell}}{2} + \frac{y_{9h} - y_{9\ell}}{2} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\}\right] \qquad (4.3)$$

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1 Direct infusion of large amounts of FFA has adverse reactions such as haemolysis, thrombosis etc. A special infusion technique which is free of adverse reactions has recently been reported by Greenough and Steinberg(78). They successfully performed it on dogs(79).

2 Recall that a small letter is used to denote a variable and the corresponding capital letter its fasting value.

Since we assume $\tilde{p}_1 = \tilde{f}_p = F_p$, fasting plasma level of FFA,

$$Y_9 = \frac{y_{9h} + y_{9\ell}}{2}$$

$$Y_4' = Y_5 + Y_9 = Y_4 = Y_1 + Y_2 + Y_3$$

Therefore, Eqs. (4.3) become

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = (\Delta y_1 + \Delta y_2 + \Delta y_3) - \{a_{y5}(u_{3p} - U_{3p}) + b_{y5}(u_{4i} - U_{4i})\}$$

$$- \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\} \qquad (4.4)$$

where

$$\alpha_{y9} = \frac{y_{9h} - y_{9\ell}}{2}$$

Consider the continuous IV epinephrine infusion experiment indicated earlier. Since insulin and growth hormone levels are not affected much we can ignore the terms Δy_1, Δy_3 and $b_{y5}(u_{4i} - U_{4i})$ from the right hand side of Eqs. (4.4). The term $a_{y5}\, U_{3p}$ can be neglected since the fasting concentration of epinephrine is usually very small compared to the concentrations attained during a continuous infusion of epinephrine at a rate of 6 μg/min. Furthermore, the contribution of FFA release by epinephrine is small under fasting conditions. Hence $\Delta y_2 \approx y_2$. With these approximations the following equations pertain to experiment #1.

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = y_2 - a_{y5}u_{3p} - \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\}$$

$$= \alpha_{y2} + \alpha_{y2} \tanh \{\beta_{y2}(u_{3p} - \tilde{U}_{3p})\}$$

$$- a_{y5}\, u_{3p} - \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\} \qquad (4.5)$$

where

$$\alpha_{y2} = \frac{y_{2h}}{2}$$

It should be noted that the terms neglected in the above equations, Δy_1, Δy_3, $b_{y5}(u_{4i} - U_{4i})$, $a_{y5}\, U_{3p}$ and $-Y_2$, have a cancelling effect. Epinephrine infusion causes insulin level to slightly decrease and GH level to slightly decrease. The latter is due to the increased glucose level caused by the glycogenolytic and gluconeogenic effects of epinephrine. Hence Δy_1 is positive and Δy_3 is negative and they tend to cancel each other.

Next consider the second experiment - GH infusion. There is little change in the levels of insulin and epinephrine, The same kind of approximations made in Eqs. (4.5) lead to the following set of equations pertaining to experiment #2.

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = y_3 - b_{y5}u_{4i} - \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\}$$

$$= \alpha_{y3} + \alpha_{y3} \tanh \{\beta_{y3}(p_3 - \tilde{p}_3)\}$$

$$- b_{y5}\, u_{4i} - \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\}$$

$$T_4\dot{p}_3 + p_3 = u_{4i} \qquad (4.6)$$

where

$$p_3 = z_{13},\ \tilde{p}_3 = \tilde{z}_{13} \quad \text{and} \quad \alpha_{y3} = \frac{y_{3h}}{2}$$

A similar set of equations (except for an additional term) hold in the case of experiment #3.

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = \alpha_{y10} + \alpha_{y10} \tanh\{\beta_{y10}(p_3 - \tilde{p}_3)\} - \alpha_{y11} - \alpha_{y11} \tanh\{\beta_{y11}(\dot{p}_3 - \tilde{\dot{p}}_3)\} - \alpha_{y9} \tanh\{\beta_{y9}(p_1 - \tilde{p}_1)\}$$

$$T_3\dot{p}_3 + p_3 = u_{1i} \tag{4.7}$$

where

$$p_3 = z_{12}$$

$$\alpha_{y10} = -\frac{y_{10h} - y_{10\ell}}{2}$$

$$\alpha_{y11} = \frac{y_{11h}}{2}$$

Eqs. (4.7) are valid only as long as the levels of epinephrine and GH are low. The plasma glucose level typically undershoots a little after about 60 minutes in an IV glucose tolerance test. Under these circumstances epinephrine and GH are released. However, the increase in their levels is small since the hypoglycemia is very mild. Consequently their effects on FFA metabolism can be neglected. Moreover these effects, namely, increase of lipolysis and muscle FFA oxidation, tend to cancel each other. We will therefore assume that Eqs. (4.7) are valid over the entire period of observation of approximately two hours for experiment #3.

We will make a further simplification at this point. We will

assume that the time constant, T_5, associated with FFA distribution is known. This is justified by the fact that the FFA response is relatively insensitive to changes in T_5. The maximum deviation obtained using Eqs. (4.4) and a constant input[1] was less than 1% when T_5 was varied over its normal range (1-5 minutes) with all other parameter values unchanged. It can therefore be chosen based on the results of a tracer experiment. The rest of the parameters of the FFA model are identified in a sequence of five identification problems discussed in the sequel. The input and the data required are indicated in Figures 21, 22 and 23.

Identification problem #1:

Parameters identified: $\tilde{g}_i$, β_{u3p}, α_{y9}, β_{y9}, a_{y5}

Observations required:

(i) Experiment #1; plasma FFA concentration at

$t = 40,45,\ldots,65,70,80,\ldots,190,200$.

(ii) Observations (ii) and (iii) in experiment #1 (see page 105).

The parameters identified first are $\tilde{g}_i$ and β_{u3p}. With the type of epinephrine infusion[2] indicated in Figure 21, u_{3p} attains a steady value in about 25 minutes, i.e., in about 10 minutes after the infusion rate is made steady. $y_2(u_{3p})$ is constant for approximately

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1 The term $\{a_{y5}(u_{3p} - U_{39}) + b_{y5}(u_{4i} - U_{4i})\}$ was discarded. $(\Delta y_1 + \Delta_{y2} + \Delta_{y3})$ was replaced by a constant. Values of α_{y9}, β_{y9} and $\tilde{p}_1$ for subject 174 were used.

2 Infusion is steadily increased in steps in order to increase the observability of the parameters identified in problem #2(see Page 118).

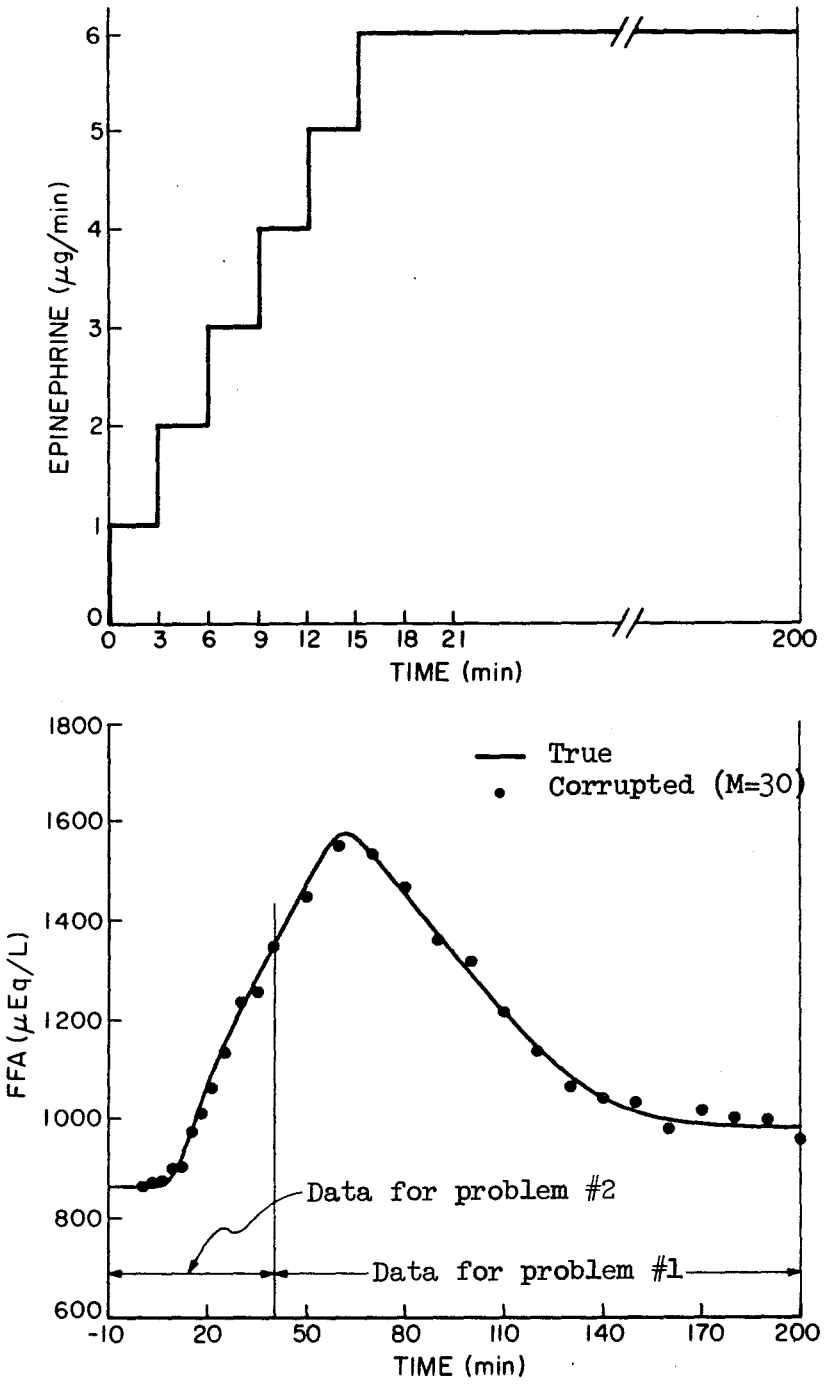

Figure 21. FFA Data for Identification Problems 1 and 2. Input is IV epinephrine.

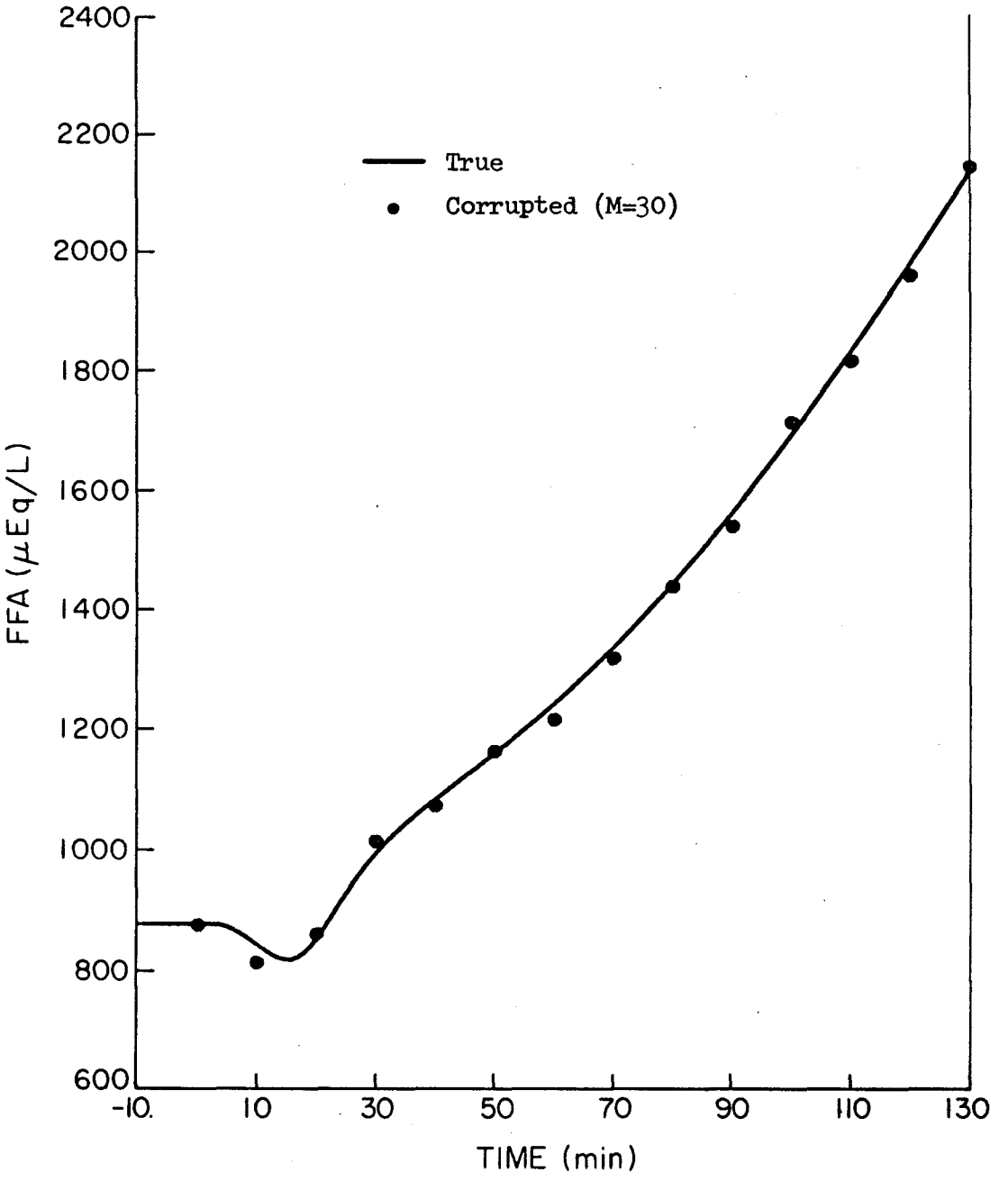

Figure 22. FFA Data for Identification Problem #3. Input is 1 mg of GH given intravenously at a constant rate over 3 minutes.

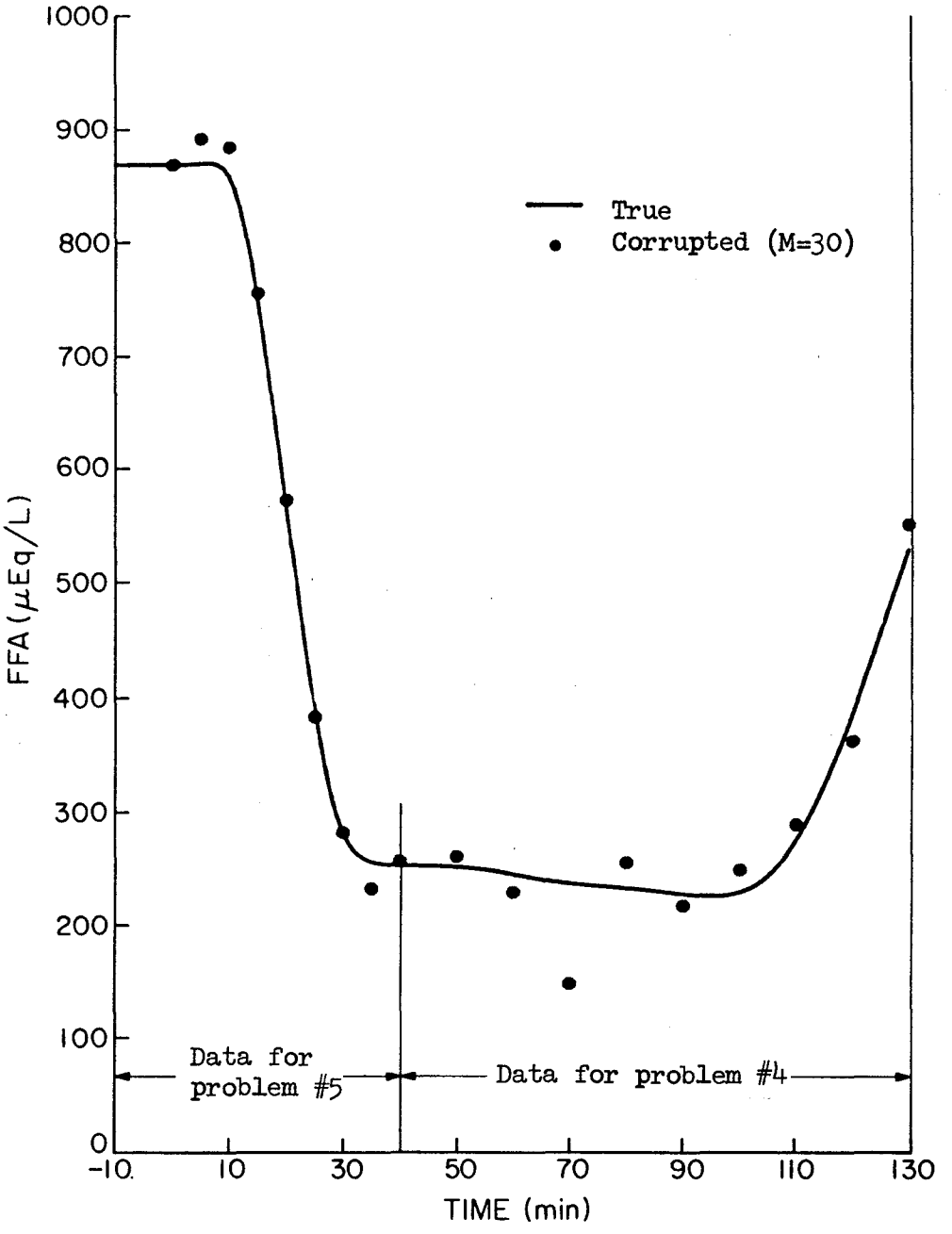

Figure 23. FFA Data for Identification Problems 4 and 5. Input is 35 gm. of glucose given intravenously at a constant rate over 3.5 minutes.

$25 < t < 45$. At about 45 minutes the interstitial glucose concentration begins to reduce the FFA release rate y_2. One can estimate $\tilde{g}_i$ from the value of plasma glucose concentration at the instant at which the plasma level of FFA begins to fall, i.e., $\dot{f}_p = 0$. Denote this instant by t_c. t_c can be figured by drawing a smooth curve through the observed values of FFA concentration from $t = 40$ to $t = 70$. Let g_p' be the plasma glucose concentration (deviation from nominal) at $t = t_c$. $\tilde{g}_i$ is slightly less than g_p for the following reasons. (i) There is a continuous movement of glucose from plasma into the interstitial space due to the glycogenolytic and gluconeogenic actions of epinephrine in the liver. (ii) The inhibition of FFA release must have been initiated a little while before g_p became equal to g_p'. Thus

$$\tilde{g}_i = g_p' - \delta \tag{4.8}$$

where δ is about 5 mg%.

From the simulated data the true value of g_p' is 63 mg%. Allowing $\pm$ 2 mg% for measurement errors, the observed value of g_p' lies between 61 and 65 mg%. Therefore the estimated value of $\tilde{g}_i$ = (58 $\pm$ 2) mg%, if δ = 5 mg%. The actual value is 58 mg%. The estimation error is very small indicating that no sophisticated estimation technique need be employed for identifying $\tilde{g}_i$.

β_{u3p} is not a critical parameter. Any value in the range 0.2 - 0.4 is a good estimate of β_{u3p}. If $\beta_{u3p} = 0.2$, $u_{3p}' \approx u_{3p}$ when $g_i > \tilde{g}_i + 10$; if $\beta_{u3p} = 0.4$, $u_{3p}' \approx u_{3p}$ when $g_i > \tilde{g}_i + 5$.

It remains to estimate the parameter values of α_{y9}, β_{y9} and a_{y5}. To this end, we will make use of the fact that the inhibition of

FFA release is complete and $y_2(u_{3p})$ is constant for $t > t_c + 10$, $g_i > \tilde{g}_i + 10$. If u_{3p}^{ss} is the steady state concentration of u_{3p} under the constant rate input,

$$y_2(u_{3p}^{ss}) = \frac{Y_{2h} - a_{y2}u_{3p}^{ss}}{2}[1 + \tanh\{\beta_{y2}(u_{3p}^{ss} - \tilde{u}_{3p})\}] \qquad (4.9)$$

Thus for $t > t_c + 10$, we have a constant but unknown input acting upon the distribution and nonlinear utilization mechanisms of the FFA model. Let C_1 denote this constant input. Then, referring to Eqs. (4.5),

$$C_1 = y_2(u_{3p}^{ss}) - a_{y5}\, u_{3p}^{ss} \qquad (4.10)$$

An approximate value for C_1 can be obtained from the measurements of rates of FFA turnover and oxygen consumption under basal conditions and after establishment of steady state conditions with a constant IV epinephrine injection.

$$y_2(u_{3p}^{ss}) = Y_{4n} - Y_4$$
$$a_{y5}u_{3p}^{ss} \approx (O_{bn} - O_b)/K_o \qquad (4.11)$$

where

Y_4, O_b = Basal rates of FFA turnover and oxygen consumption respectively.

Y_{4n}, O_{bn} = Rates of FFA turnover and oxygen consumption respectively after establishment of steady state under epinephrine input.

K_o = Oxygen required/μEq of FFA.

There are two assumptions involved in the second approximate equality above.

(i) Under a constant infusion of epinephrine the extra oxygen consumed is entirely due to increased FFA oxidation. There may however be contributions from other substrates.

(ii) The increased FFA oxidation takes place only in the muscle, the term $a_{y5}\, u_{3p}^{ss}$ accounting for all of it. A small contribution by the liver as indicated by the equation for y_8 on Page 78 is neglected. It can be positive or negative depending on the new steady state value of plasma FFA concnetration. There may also be a contribution from adipose tissue. However, our assumption is justified by the fact that catecholomines are the stimulators of large amounts of energy mainly in the form of FFA to the working muscles during exercise.(80,81)

The above assumptions imply that the error is on the higher side in the estimation of $a_{y5}\, u_{3p}^{ss}$; or equivalently it is on the lower side in the estimation of C_1. However, we will proceed under the assumption that C_1 is known approximately. The parameters α_{y9} and β_{y9} are to be identified, given C_1. We will make use of the observations on plasma FFA concentration in the interval [80,200] in experiment #1. The problem is then the following:

System: If the initial time corresponds to t = 80 in experiment #1, we have, for $0 \le t \le 120$[1]

$$\dot{p}_1 = p_2$$

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1 Initial conditions are unknown and are treated as unknown parameters.

$$V_e(T_5\dot{p}_2 + p_2) = C_1 - \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\} \qquad (4.12)$$

Observations: Number of observations, N = 13.

$$f_{pc}(t_i) = p_1(t_i) + \eta(t_i)$$

$$t_i = 0,10,20 \ldots 110,120.$$

Known Parameters: V_e, T_5, C_1, $\tilde{p}_1$

Unknown Parameters: α_{y9}, β_{y9}, $p_2(o)$, $p_1(o)$

Performance index: $J = \sum_{i=1}^{13} \{f_{pc}(t_i) - \hat{p}_1(t_i)\}^2$

Estimate the unknown parameters so that J is minimized. $\hat{p}_1(t)$ represents the estimated solution $p_1(t)$ using Eqs. (4.12).

The unknown parameter β_{y9} varies between 0.001 to 0.01. If $\beta_{y9} = 0.0001$, y_9 saturates for $f_p > F_p + 100$ and if $\beta_{y9} = 0.01$, it saturates for $f_p > F_p + 1000$. For a given value of β_{y9}, α_{y9} can be readily computed knowing C_1 and p_1^{ss}, the new steady state concentration of FFA in plasma[1].

$$\alpha_{y9} \tanh \{\beta_{y9}(p_1^{ss} - \tilde{p}_1)\} = C_1 \qquad (4.13)$$

It remains to identify $p_2(o)$ and $p_1(o)$. They are identified

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[1] When the successive measurements lie within experimental errors, one can assume that steady state has been attained. By taking the average of the last two or three measurements the error in the measurement of p_1^{ss} can be minimized.

α_{y9} cannot be calculated if $p_1^{ss} = \tilde{p}_1$, i.e., if the new steady state level of FFA is same as the fasting level. This implies that the increased mobilization and utilization of FFA exactly balance. The experiment will have to be repeated with a different dose of epinephrine.

via the method of quasilinearization. The algorithm starts with the largest possible value of β_{y9}, namely 0.01, computes the corresponding value α_{y9} using Eq. (4.13) and then finds out the values of $p_2(o)$ and $p_1(o)$ that minimize J. The procedure is repeated with β_{y9} = 0.009, 0.008, ... until J is minimized with respect to β_{y9}. The entire algorithm is repeated for several values of C_1 and the minimum with respect to C_1 is chosen. The computations need be done only for a few values of C_1 since its value is known approximately. The results are tabulated in Table 4. The initial guesses for $p_2(o)$ and $p_1(o)$ are obtained by drawing a smooth curve through the observations, $f_{pc}(t_i)$, and finding out its initial value and slope.

We can now estimate a_{y5} from Eq. (4.10).

$$a_{y5} = \{C_1 - y_2(u_{3p}^{ss})\}/\ u_{3p}^{ss} \qquad (4.14)$$

It is noteworthy that the above estimation procedure does not allow us to estimate y_{9h} and $y_{9\ell}$. We need to know $Y_9 = \frac{y_{9h} + y_{9\ell}}{2}$ in order to compute y_{9h} and $y_{9\ell}$. It does not matter, however, since this information is not needed in studies of dynamic characteristics.

Identification problem #2:

Parameters identified: Y_{2h}, β_{y2}, $\tilde{u}_{3p}$, a_{y2}

Observations required:

Experiment #1; plasma FFA concentration at $t = 0, 3, 6 \ldots 18, 21, 25, 30, 35, 40$.

The inhibition of epinephrine-induced lipolysis by interstitial glucose concentration is not present till approximately $t = t_c - 10$ where t_c is the instant at which the plasma FFA level begins to fall

Maximum Error M	$\frac{C_1}{V_e T_5}$	Estimated Values				Performance Index J/N	
		$p_1(0)$	$p_2(0)$	$\frac{\alpha_{y9}}{V_e T_5}$	β_{y9}		
15	3.3	1465.5	-12.95	7.673	0.004	100.17	
	4.3	1465.5	-16.10	8.285	0.005	85.97	← Minimum
	5.3	1465.6	-24.23	8.863	0.006	128.32	
30	3.3	1473.0	-16.49	7.673	0.004	318.81	
	4.3	1473.0	-19.77	8.285	0.005	314.41	← Minimum
	5.3	1473.1	-27.29	8.863	0.006	369.54	

Table 4. Estimation of C_1, α_{y9} and β_{y9}.

True values: $C_1/V_e T_5 = 4.0$; $\alpha_{y9}/V_e T_5 = 8.58$; $\beta_{y9} = 0.005$; $p_1(0) = 1458.0$

Initial guess: $p_2(0) = -9.0$; $p_1(0) = f_{pc}(0)$

(see Page 114). Hence in the observations interval [0,40], $u_{3p}' = 0$ and $y_{2h} = Y_{2h}$ (see Eqs. (4.2)). If U_{3p} is the plasma epinephrine concentration and Y_2 is the FFA release rate by epinephrine under fasting contidions,

$$Y_2 = \frac{y_{2h}}{2} [1 + \tanh \{\beta_{y2}(U_{3p} - \tilde{u}_{3p})\}]$$

$$= \frac{Y_{2h}}{2} [1 - \tanh \{\beta_{y2}(\tilde{u}_{3p} - U_{3p})\}] \qquad (4.15)$$

Recall that the contribution of Y_2 to the fasting FFA turnover rate, Y_4, was assumed to be small in the construction of the FFA model (see Page 48). Consequently Y_2 is only a small fraction of Y_{2h} which is of comparable magnitude to Y_4. This implies that $\tanh \{\beta_{y2}(\tilde{u}_{3p} - U_{3p})\}$ is close to 1. Let

$$\beta_{y2}(\tilde{u}_{3p} - U_{3p}) = C_2 \qquad (4.16)$$

The above relation is used in identifying the parameter values of Y_{2h}, β_{y2} and $\tilde{u}_{3p}$. It is assumed that $C_2 > 1.5$. If $C_2 = 1.5$, Y_2 is only 5% of Y_{2h}.

Furthermore the range of $\tilde{u}_{3p}$ is limited. When $u_{3p} = 0$, $y_2 \approx 0$ and when $u_{3p} = 3$, the upper physiologic concentration of epinephrine in plasma, $y_2 \approx y_{2h}$. This suggests that the range of $\tilde{u}_{3p}$ is 0 - 1.5. The identification problem is then the following:

System: The initial time corresponds to $t = 0$ in experiment #1. We have, for $0 \le t \le 40$

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = \frac{Y_{2h}}{2} [1 + \tanh \{\beta_{y2}(u_{3p} - \tilde{u}_{3p})\}]$$

$$- a_{y5}\, u_{3p} - \alpha_{y9} \tanh \{\beta_{y9}(p_1 - \tilde{p}_1)\} \qquad (4.17)$$

$u_{3p}(t)$ can be easily computed knowing the epinephrine input and degradation constant. If I_3 is the input and K_3 is the degradation constant,

$$V_e \dot{u}_{3p} + K_3\, u_{3p} = I_3(t) \qquad (4.18)$$

The fasting level of epinephrine is ignored in this calculation since the endogenous secretion of epinephrine declines as the plasma level of glucose is increased by its glycogenolytic and gluconeogenic effects.

Initial Conditions:

$p_1(o) = F_p$, fasting plasma FFA level.

$p_2(o) = 0.0$

$u_{3p}(o) = 0.0$

Observations: Number of observations, $N = 12$

$$f_{pc}(t_i) = p_1(t_i) + \eta(t_i)$$

$$t_i = 0, 3, 6, \ldots, 18, 21, 25, 30, 35, 40$$

Note that $f_{pc}(o) = p_1(o) = F_p$, assuming noiseless measurement..

Known parameters: V_e, T_5, α_{y9}, β_{y9}, $\tilde{p}_1$, a_{y5}

Unknown parameters: Y_{2h}, β_{y2}, $\tilde{u}_{3p}$

Performance index: $J = \sum_{i=1}^{12} \{f_{pc}(t_i) - \hat{p}_1(t_i)\}^2$

Estimate the unknown parameters so that J is minimized. $\hat{p}_1(t)$ represents the estimated solution $p_1(t)$ using Eqs. (4.17) and (4.18).

The algorithm starts with the largest value of $\tilde{u}_{3p}$. β_{y2} is computed using Eq. (4.16) for a given value of $C_2 > 1.5$. Y_{2h} is then estimated via the method of quasilinearization. J is minimized with respect to $\tilde{u}_{3p}$ by decreasing $\tilde{u}_{3p}$ in small steps. A coarse search followed by a finer one reduces the computation time. The entire algorithm is repeated for several values of C_2 and the minimum with respect to C_2 is chosen. Changes in C_2 were not made automatic in order to reduce the computation time. Since $C_2 > 1.5$ and furthermore any value of $C_2 > 3.0$ would result in a switch-type function for FFA release by epinephrine, the range of C_2 is limited. Thus the algorithm need be used only for a few values of C_2. The results are shown in Table 5.

Remark: It should be noted that the minimum values of J were obtained with $C_2 = 1.5$. In fact, lower values of J resulted in some runs with $C_2 < 1.5$. The difficulty here is due to the fact that both β_{y2} and $\tilde{u}_{3p}$ are not observable with the given observations. In other words more than one set of values for Y_{2h}, β_{y2} and $\tilde{u}_{3p}$ can be found to fit the given observations. Hence the restriction $C_2 > 1.5$ is imposed. This conforms with the way the model was constructed. The most sensitive parameter here is Y_{2h}. Our identification procedure makes a good estimate of it (less than 5% error) irrespective of the estimated values of β_{y2} and $\tilde{u}_{3p}$.

The remaining parameter a_{y2} can now be calculated using Eq. (4.9).

Identification Problem #3:

Parameters identified: T_4, y_{3h}, β_{y3}, $\tilde{z}_{13}$, b_{y5}

Observations required: Experiment #2; plasma FFA concentration

Maximum Error M	C_2	Estimated Values			Performance Index J/N	
		$\frac{Y_{2h}}{V_e T_5}$	β_{y2}	$\tilde{u}_{3p}$		
15	3.0	19.77	15.0	0.3	227.23	
	2.5	19.80	12.5	0.3	204.26	
	2.0	19.85	10.0	0.3	171.40	
	1.5	20.00	7.5	0.3	132.47	← Minimum
30	3.0	19.61	15.0	0.3	460.28	
	2.5	19.64	12.5	0.3	433.06	
	2.0	19.69	10.0	0.3	393.06	
	1.5	19.83	7.5	0.3	342.14	← Minimum

Table 5. Estimation of Y_{2h}, β_{y2} and $\tilde{u}_{3p}$.

True values: $Y_{2h}/V_e T_5 = 21.07$; $\beta_{y2} = 6.0$; $\tilde{u}_{3p} = 0.4$

Initial guess: $Y_{2h}/V_e T_5 = 10$ for $M = 15$ and 40 for $M = 30$

at $t = 0, 10, 20, \ldots, 120, 130$.

Following the procedure adopted in identification problem #2 and referring to Eqs. (4.6) which pertain to identification problem #3, we write

$$\beta_{y3}(\tilde{p}_3 - P_3) = C_3 \tag{4.19}$$

where

$C_3 > 1.5$

$\tilde{p}_3 = \tilde{z}_{13}$

$P_3 = Z_{13}$, fasting value of z_{13}

$= U_{4i}$, fasting value of u_{4i}

From simulation studies, the range of $\tilde{p}_3$ was found to be 0 - 20.

The parameter b_{y5} is associated with increased FFA oxidation due to GH and it is positive. The following substitution was found to avoid negative values of b_{y5} in the identification algorithm.

$$b_{y5} = \sigma^2 \tag{4.20}$$

The range of T_4 is limited. Based on simulation studies the range of T_4 was found to be the following:

$$20 < T_4 < 100 \tag{4.21}$$

The identification problem is the following:

<u>System</u>: The initial time corresponds to $t = 0$ in experiment #2. We have, for $0 \le t \le 130$

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = \frac{y_{3h}}{2}\left[1 + \tanh\{\beta_{y3}(p_3 - \tilde{p}_3)\}\right] - \sigma^2 u_{4i} - \alpha_{y9}\tanh\{\beta_{y9}(p_1 - \tilde{p}_1)\}$$

$$T_4 \dot{p}_3 + p_3 = u_{4i} \tag{4.22}$$

Knowledge of GH input and degradation constants enables us to compute $u_{4i}(t)$. If I_4 is the input and K_{40}, K_{41} and K_{42} are the degradation constants,

$$V_p \dot{u}_{4p} = I_4 - K_{40} u_{4p} - K_{41}(u_{4p} - u_{4i})$$

$$V_i \dot{u}_{4i} = K_{41}(u_{4p} - u_{4i}) - K_{42} u_{4i} \tag{4.23}$$

Initial Conditions:

$p_1(o) = F_p$, fasting plasma FFA level

$p_2(o) = 0.0$

$p_3(o) = U_{4i}$

$u_{4p}(o) = U_{4p}$

$u_{4i}(o) = U_{4i}$

Observations: Number of observations, $N = 14$

$$f_{pc}(t_i) = p_1(t_i) + \eta(t_i)$$

$$t_i = 0, 10, 20, \ldots, 120, 130$$

Note that $f_{pc}(o) = p_1(o) = F_p$, assuming noiseless measurement.

Known parameters: V_e, T_5, α_{y9}, β_{y9}, $\tilde{p}_1$

Unknown parameters: y_{3h}, β_{y3}, $\tilde{p}_3$, T_4, σ

Performance index: $J = \sum_{i=1}^{14} \{f_{pc}(t_i) - \hat{p}_1(t_i)\}^2$

Estimate the unknown parameters so as to minimize J. $\hat{p}_1(t)$

represents the estimated solution $p_1(t)$ using Eqs. (4.22) and (4.23).

As in identification problem #2, the algorithm starts with the largest possible value of $\tilde{p}_3$ and computes β_{y3} using Eq. (4.19) for a given value of $C_3 > 1.5$. The other parameters, y_{3h}, T_4 and σ are then identified by the method of quasilinearization. In the initial runs the algorithm failed to converge whenever the parameter T_4 assumed a value outside the range indicated in Eq. (4.21) in any iteration cycle.[1] The present procedure circumvents this difficulty by starting the computations with the lowest value of T_4. If T_4 attains a value outside a specified range, it is automatically reset as follows:

$$(T_4)_{new} = (T_4)_{old} + \Delta T_4 \qquad (4.24)$$

where ΔT_4 is the increment in T_4 (typically 5 or 10). In order to obtain convergence it was found necessary that the specified range of T_4 should be larger than the one indicated in Eq. (4.21). A range $20 < T_4 < 200$ was used in all runs. The rest of the procedure is same as in identification problem #2. The results are tabulated in Table 6. The parameter values that yield minimum value of J under the condition indicated in Eq. (4.21) are chosen as the estimates.

Remark: The FFA response is more sensitive to y_{3h} and b_{y5} than to other parameters, T_4, β_{y3} and $\tilde{p}_3$. Consequently the estimates of y_{3h} and b_{y5} are better. One encounters the same difficulty as in identification problem #2, namely, that the given data do not contain enough information to pinpoint more exactly the values of T_4, β_{y3} and $\tilde{p}_3$. One way of refining the estimated values of these parameters is to

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[1] Sometimes negative values were obtained for T_4! In such cases the procedure would quickly "blow-up".

C_3	Estimated Values					Performance Index J/N	
	T_4	$\frac{y_{3h}}{V_e T_5}$	β_{y3}	$\tilde{z}_{13}$	$\frac{b_{y5}}{V_e T_5}$		
3.0	48.32	17.94	0.50	6.9	0.208	88.63	
	35.89	17.98	0.375	8.9	0.208	85.12	← Minimum
	28.60	18.44	0.30	10.9	0.223	149.59	
2.5	90.24	19.94	0.833	3.9	0.208	88.63	
	70.74	19.94	0.625	4.9	0.207	77.95	← Minimum (estimated values)
	48.55	19.94	0.417	6.9	0.207	84.14	
	35.80	18.03	0.313	8.9	0.211	106.53	
2.0	123.83	19.94	1.00	2.9	0.207	90.12	
	70.21	19.92	0.50	4.9	0.206	96.65	← Minimum $T_4 < 100$
	48.63	19.92	0.333	6.9	0.206	103.80	

Table 6A. Estimation of T_4, y_{3h}, β_{y3}, $\tilde{z}_{13}$ and b_{y5} . M = 15

True values: $T_4 = 60$; $y_{3h}/V_e T_5 = 17.85$; $\beta_{y3} = 0.445$; $\tilde{z}_{13} = 6.0$;

$b_{y5}/V_e T_5 = 0.214$

Initial guess: $y_{3h}/V_e T_5 = 40.0$; $b_{y5}/V_e T_5 = \begin{cases} 1.0 & \text{for } C_3 = 3.0 \\ 0.7 & \text{for } C_3 = 2.5 \\ 0.3 & \text{for } C_3 = 2.0 \end{cases}$

C_3	Estimated Values					Performance Index J/N	
	T_4	$\frac{y_{3h}}{V_e T_5}$	β_{y3}	$\tilde{z}_{13}$	$\frac{b_{y5}}{V_e T_5}$		
3.0	39.69	18.53	0.50	6.9	0.236	232.65	
	29.45	18.61	0.375	8.9	0.238	225.59	← Minimum
	25.35	19.09	0.30	10.9	0.251	529.28	
2.5	101.95	18.54	1.25	2.9	0.236	224.22	
	74.31	18.53	0.833	3.9	0.236	225.49	← Minimum, $T_4 < 100$ (estimated values)
	58.10	18.53	0.625	4.9	0.236	227.92	
	47.32	18.53	0.500	5.9	0.236	229.89	
2.0	101.87	18.53	1.00	2.9	0.236	241.96	
	74.38	18.53	0.667	3.9	0.235	230.50	← Minimum
	58.06	18.52	0.50	4.9	0.235	238.80	

Table 6B. Estimation of T_4, y_{3h}, β_{y3}, $\tilde{z}_{13}$ and b_{y5}. M = 30.

See Table 6A for true values and initial guess.

make use of the FFA response obtained after IV injection of insulin. It will be recalled that insulin injection is not one among the experiments listed earlier (see Page 105) for the identification FFA model parameters. Following infusion in insulin, there is a decrease of FFA release from adipose tissue which is countered by epinephrine in the initial stages and by GH later. It is therefore possible to refine β and γ parameter values associated with FFA release by epinephrine and GH by making use of the FFA data taken after an IV dose of insulin, without significantly affecting any of the previous results - FFA responses to IV ephinephrine and GH.

Identification problem #4:

Parameters identified: T_3, y_{10h}, $y_{10\ell}$, β_{y10}, $\tilde{z}_{12}$

Observations required: Experiment #3; plasma FFA concentration at $t = 40, 50, \ldots, 120, 130$.

It will be recalled that lipolysis and esterification in adipose tissue are assumed to be affected by both interstitial insulin concentration and rate in our FFA model. However, the effect of interstitial insulin rate ceases in about 40 minutes by which time the FFA response has become almost flat, indicating that the rate of change of plasma FFA concentration is close to zero (see Figure 11, 14 and 15). Hence the parameters associated with the effect of interstitial insulin concentration on adipose tissue can be identified using the above observations.

Eqs. (4.7) pertain to this identification problem. The initial values of p_1, p_2 and p_3, are unknown. Designate them by p_{1I}, p_{2I} and p_{3I} respectively. Attempts to arrive at a workable algorithm that

treats p_{1I}, p_{2I} and p_{3I} as unknown parameters were not successful. In the sequel they are treated as known quantities. p_{1I} is taken to be equal to the measured value of the plasma FFA concentration at $t = 40$. Since the FFA response is almost flat by $t = 40$, we can take $p_{2I} = 0$. Furthermore, by about 40 minutes after the start of the infusion there is little difference in the values of $p_3 (= z_{12})$ and u_{1i}, interstitial insulin concentration. Hence we can assume $p_{3I} = u_{1i}(40)$.

With known initial values of p_1, p_2 and p_3, the identification problem is very similar to the preceding one. In fact, the number of parameters to be identified is one less in this case as will become evident from the formulation shown below.

System: The initial time corresponds to $t = 40$ in experiment #3. We have, for $40 \leq t \leq 130$

$$\dot{p}_1 = p_2$$

$$V_e(T_5\dot{p}_2 + p_2) = \alpha_{y10}\,[1 + \tanh\{\beta_{y10}\,(p_3 - \tilde{p}_3)\}] - \alpha_{y9}\tanh\{\beta_{y9}\,(p_1 - \tilde{p}_1)\}$$

$$T_3\dot{p}_3 + p_3 = u_{1i} \qquad (4.25)$$

where

$$\alpha_{y10} = -\frac{y_{10h} - y_{10\ell}}{2}$$

It is assumed that the insulin secretion functions are known (see reference 2 for the identification of hormone controller parameters). Then $u_{1i}(t)$ can be readily computed using the given glucose data.

Initial Conditions:

$p_1(o)$ = Observed value of plasma FFA concentration at

$t = 40$ in experiment #3.

$p_2(o) = 0.0$

$p_3(o)$ = Interstitial insulin concentration at $t = 40$ in experiment #3

Observations: Number of observations, $N = 10$

$$f_{pc}(t_i) = p_1(t_i) + \eta(t_i)$$

$$t_i = 0, 10, 20, \ldots, 90, 100$$

Known parameters: V_e, T_5, α_{y9}, β_{y9}, $\tilde{p}_1$

Unknown parameters: α_{y10}, β_{y10}, $\tilde{p}_3$, T_3

Performance index: $$J = \sum_{i=1}^{10} \{f_{pc}(t_i) - \hat{p}_1(t_i)\}^2$$

Estimate the unknown parameters so as to minimize J. $\hat{p}_1(t)$ represents the estimated solution $p_1(t)$ obtained by solving Eqs. (4.25).

The algorithm is the same as the one used for solving identification problem #3. The results are indicated in Table 7. Since the contributions by epinephrine and GH to fasting lipolysis are assumed to be negligible in our FFA model (see Page 48),

y_{10h} = Basal FFA turnover rate, Y_4

Knowing y_{10h} and using the relation

$$\alpha_{y10} = -\frac{y_{10h} - y_{10\ell}}{2}$$

$y_{10\ell}$ can be calculated.

The remaining parameters associated with the effect of insulin on adipose tissue are y_{11h}, β_{y11} and $\tilde{z}_{12}$. They can be readily identified (identification problem #5) using the FFA data of experiment #3 in

C_4	Estimated Values				Performance Index J/N	
	T_3	$\frac{\alpha_{y10}}{V_e T_5}$	β_{y10}	$\tilde{z}_{12}$		
3.0	30.06	4.38	0.75	8.5	51.34	
	45.02	4.43	0.50	10.5	49.97	← Minimum
	66.30	4.52	0.375	12.5	136.05	
2.5	17.12	4.36	1.25	6.5	69.15	
	30.04	4.40	0.625	8.5	43.23	← Minimum (estimated values)
	45.23	4.46	0.417	10.5	80.52	
2.0	8.66	4.37	2.00	5.5	64.94	
	17.01	4.38	1.00	6.5	48.72	← Minimum
	30.06	4.43	0.50	8.5	55.59	

Table 7A. Estimation of T_3, α_{y10}, β_{y10} and $\tilde{z}_{12}$. M = 15.

True values: $T_3 = 30$; $\alpha_{y10}/V_e T_5 = 4.55$; $\beta_{y10} = .745$; $\tilde{z}_{12} = 8.5$

Initial guess: $\alpha_{y10}/V_e T_5 = 14.0$

C_4	Estimated Values				Performance Index J/N	
	T_3	$\frac{\alpha_{y10}}{V_e T_5}$	β_{y10}	$\tilde{z}_{12}$		
3.0	17.05	4.35	1.50	6.5	244.96	
	29.70	4.38	0.75	8.5	230.60	← Minimum (estimated values)
	44.48	4.43	0.50	10.5	280.05	
2.5	8.67	4.35	2.50	5.5	250.01	
	16.92	4.36	1.25	6.5	237.62	← Minimum
	29.63	4.40	0.625	8.5	249.51	
2.0	8.48	4.36	2.00	5.5	244.86	
	16.79	4.38	1.00	6.5	244.16	← Minimum
	29.66	4.43	0.50	8.5	300.32	

Table 7B. Estimation of T_3, α_{y10}, β_{y10} and $\tilde{z}_{12}$. M = 30.

See Table 7A for true values and initial guess.

the time interval [0,40] and following the same procedure as in identification problems 3 and 4. The problem is even simpler since the parameter T_3 is already known.

4.5 A Feedback Control Experiment.[82,83,84,58]

One of the questions that is of particular interest to the clinicians is the closed-loop control of metabolic systems. How does one design a closed-loop control scheme that would maintain the equilibrium state of a metabolic system despite disturbances acting on it? For example, we would like to find out a feedback control law that would maintain the plasma glucose level constant when the glucose homeostatic system is under the influence of disturbances such as insulin. Problems of this nature are being currently investigated in the Physio-Chemical Automation Research Laboratory at Cedars-Sinai Medical Center, Los Angeles, California. They lead to better quantitative understanding of the operation of the glucose regulatory system and provide clues to better treatment of insulin-deficient diabetic patients.

A typical feedback control experiment is the following: The subject is given intravenously a dose of insulin sufficient to induce significant hypoglycemia. The plasma glucose level is measured continously using a continuous glucose monitor which gives a proportional voltage. An A/D convertor converts the analog data into digital data (sampled at regular intervals). The latter is processed by a PDP-8/S computer to obtain the feedback control policy. At present only glucose injection is being considered. A pump that operates on digital data (assembled by Digital Logic Corporation, Anaheim, California) is used to inject into the subject's blood stream the required amount of glucose.

The feedback control law is as follows:

$$I_g = D_1 g_p(t) + D_2 \dot{g}_p(t) + D_3 \int_0^t g_p(t')\, dt' \qquad (4.26)$$

where

I_g = Amount of glucose injected (mg/min)

$g_p(t)$ = Measured value of plasma glucose concentration (deviation from nominal in mg%) at time t including the effect of instrument time constant (approximately 1 minute)

$\dot{g}_p(t) = \frac{dg_p}{dt}$

D_1, D_2, D_3 = Coefficients

One of the serious difficulties in the implementation of the above scheme is the time delay involved in the measurement of glucose concentration. The delay is approximately 4 minutes. This necessitates the inclusion of some kind of prediction scheme in the feedback control loop. The prediction scheme that is being used at the present time is a very simple one, based on a straight line fitted in the least-square sense to the last three sampled values of glucose concentration. Let

t = Current time

τ = Delay

Δ = Sampling interval

$g_1 = g_p$ at time $(t - \tau)$

$g_o = g_p$ at time $(t - \tau - \Delta)$

$g_{-1} = g_p$ at time $(t - \tau - 2\Delta)$

$\hat{g}_p(t)$ = Predicted value of plasma glucose concentration (deviation from nominal in mg%) at time t including the effect of instrument time constant

$\hat{\dot{g}}_p(t)$ = Predicted value of the derivative of plasma glucose concentration at time t

Then

$$\hat{g}_p(t) = E_1 (\tau + \Delta) + E_2 \tag{4.27}$$

where

$$E_1 = \frac{g_1 - g_{-1}}{2}$$

$$E_2 = \frac{g_{-1} + g_o + g_1}{3}$$

Eq. (4.26) becomes

$$I_g = D_1\hat{g}_p(t) + D_2\hat{\dot{g}}_p(t) + D_3 \left[\int_o^{t-\tau} g_p(t')dt' + \int_{t-\tau}^{t} \hat{g}_p(t')dt' \right] \tag{4.28}$$

The amount of glucose to be pumped per minute is calculated using the above equation at the beginning of every sampling interval. However, it is limited by the capacity of the pump (7.5 cc/min for the pump used in the Research Laboratory at Cedars-Sinai Medical Center) and the concentration of the glucose solution. Concentrations upto 35000 mg% can be used without difficulty. If I_{gM} is the maximum permissible value of I_g, we have

$$0 \leq I_g \leq I_{gM} \tag{4.29}$$

One of the features of the program that is used to compute I_g is that the coefficients D_1, D_2 and D_3 can be changed, if desired, at any time during the course of the experiment without inter-

ruption. Furthermore, the feedback loop can be broken and the system can be operated open-loop whenever desired. This allows for any open-loop control policy that one might wish to execute. For example, it may be necessary to pump glucose at the maximum rate in the initial stages immediately following the infusion of insulin. A block diagram of the feedback control scheme is shown in Figure 24.

In order to obtain some idea as to the range of values of the coefficients D_1, D_2 and D_3 simulation studies of the feedback control experiment were conducted using the model of subject 174. Since noisy measurements of glucose concentration do not permit a fairly accurate prediction of the rate of change of glucose concentration it was decided to make $D_2 = 0$. D_1 and D_3 were adjusted by trial and error until satisfactory results were obtained. They were not altered during the closed-loop control period, although this is possible in the actual experiment. The result is indicated in Figure 25.

The prediction scheme described earlier makes use of the glucose data obtained in the interval $[o, t - \tau]$ where t is the current time and τ is the instrument delay. It does not make use of the information available in the interval $[t - \tau, t]$, namely, the feedback control policy that was adopted. One way of improving the prediction scheme is to correct the predicted value of glucose concentration as indicated below, based on the amount of glucose pumped during the interval $[t - \tau, t]$.

$$\hat{g}_{pc}(t) = \hat{g}_p(t) + D_4 A_g \qquad (4.30)$$

where

$\hat{g}_{pc}(t)$ = Predicted-corrected value of plasma glucose concentration (deviation from nominal in mg%) at time t

including the effect of instrument time constant.

A_g = Total amount of glucose injected in the interval $[t - \tau, t]$

D_4 = Coefficient.

From simulation studies, the predictor-corrector scheme was not found to improve the performance significantly. Hence a further improvement was made by linearly weighting the glucose infusion rate in the interval $[t - \tau, t]$. That is, A_g was computed as follows:

$$A_g = \Phi_1 I_g(t - \Delta) + \Phi_2 I_g(t - 2\Delta) + \ldots \qquad (4.31)$$

where

Δ = Sampling interval

$\Phi_1, \Phi_2 \ldots\ldots$ = Weighting coefficients

and

$$\Phi_1 > \Phi_2 > \Phi_3 \ldots\ldots$$

The result obtained using the predictor-corrector scheme with linear weighting is indicated in Figure 25. The values of D_1 and D_3 and the open-loop policy were the same as in the previous result with only prediction and no correction. Undoubtedly, better results can be obtained by allowing variations in D_1 and D_3. This means that D_1 and D_3 are not really constants but are functions of time.

The simulation results give some idea of the values of the "feedback coefficients" and demonstrate how models can be of use in answering some questions that arise in clinical studies.

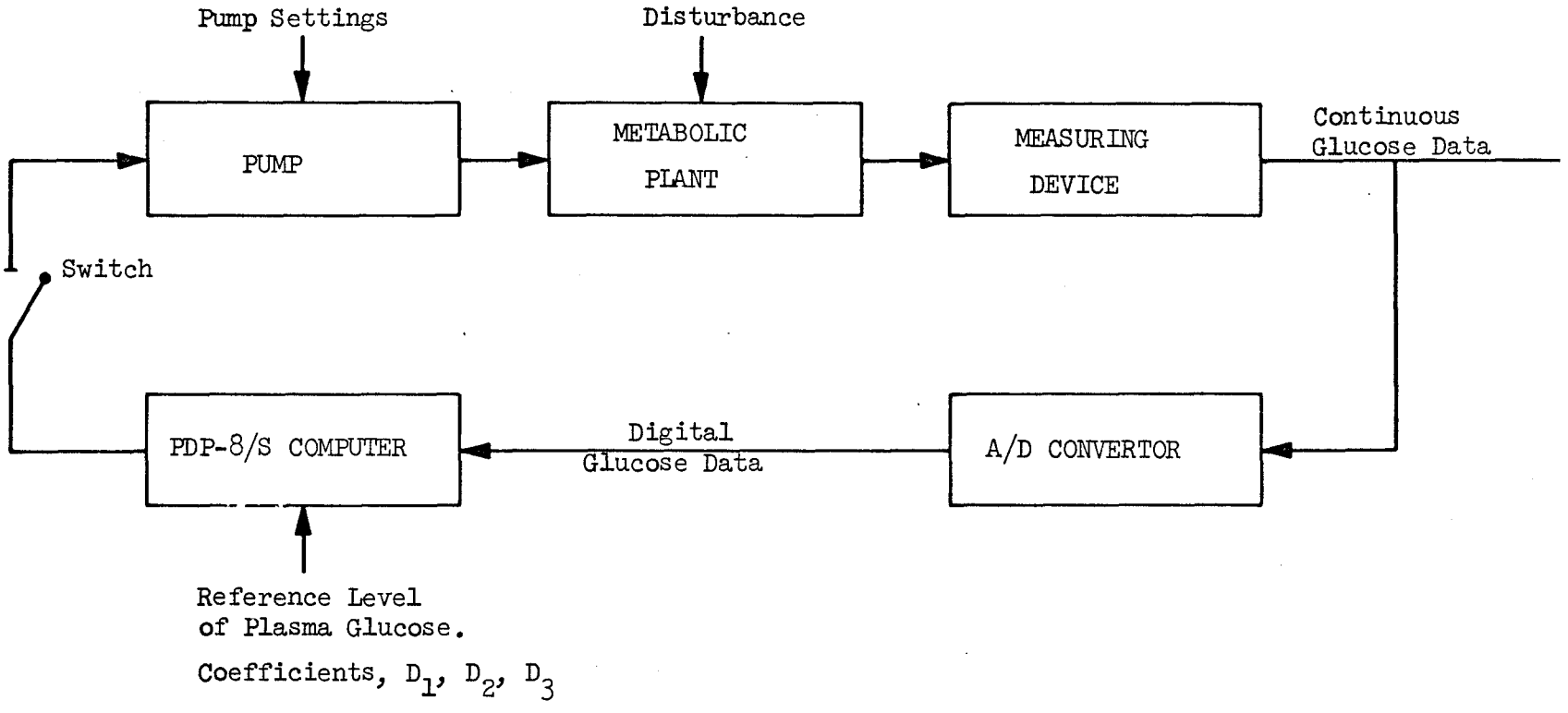

Figure 24. Block Diagram of the Feedback Control Scheme.

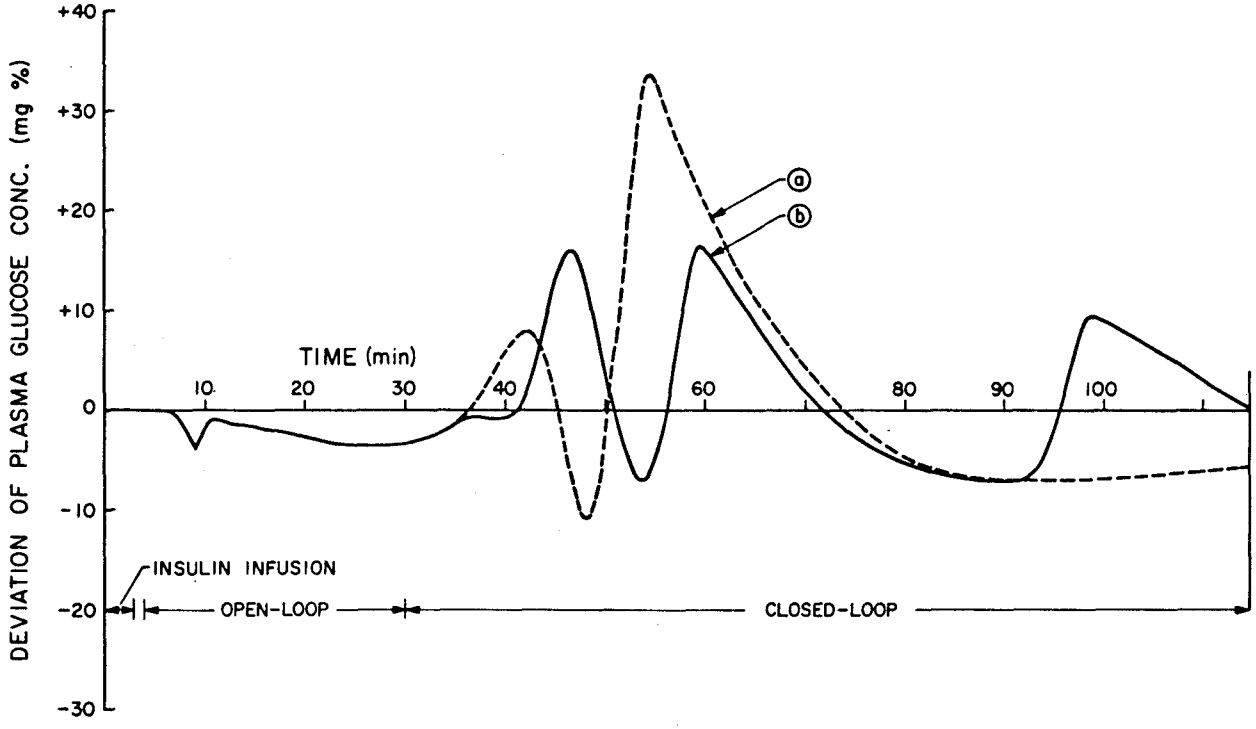

Figure 25. Simulation of Feedback Control Experiment. Deviation of plasma glucose concentration includes the effect of instrument time constant and delay. τ = 3.5 min; Δ = 0.5 min.

(a) Predictor only. Open-loop policy: $I_g = I_{gM}$ = 2250 mg/min.
Closed-loop policy: $D_1 = 40$; $D_2 = 0.0$; $D_3 = 30$.

(b) Predictor-corrector with linear weighting.
Open-loop policy: $I_g = I_{gM}$ = 2250 mg/min.
Closed-loop policy: $D_1 = 40$; $D_2 = 0$; $D_3 = 30$; $D_4 = 0.75$
$\Phi_i = 7 - i$, $i = 0, 1, 2 \ldots 6$.

V. CONCLUSIONS

5.1. Future Efforts.

There seems to be a lot of confusion about the term model since there is no clear-cut definition of the word. Restricting our attention to mathematical models, when does a given set of equations represent a model? A true model must satisfy the following two requirements. First its foundations must be on known laws and established facts, physical, chemical or physiological as the case may be. Secondly it must have predictive capabilities. This implies that if the parameters of the model were picked to fit the data from, let us say, two different experiments performed under identical conditions, then without altering the parameter values it should be possible to reproduce the data from a third experiment performed under the same conditions as the first two. It is assumed, of course, that we have a well-defined acceptable criterion for comparison of experimental and simulated data.

The validity of the proposed model was based on glucose, insulin and FFA responses following IV administration of either glucose or insulin in a single dose. The ability of the model to reproduce responses to IV infusions of glucagon, epinephrine, GH and combinations of glucose and insulin needs to be tested. It must be emphasized that all the necessary data must be obtained from experiments performed on the same individual starting from the same initial conditions. It is important to test how well the proposed model can reproduce responses to various stimuli before considering inclusion of oral and stress inputs and neglected portions such as TG and amino acid loops. This will undoubtedly suggest improvements - inclusion of other possible stimuli for

secretion of insulin, for example.

Provision for oral and stress inputs and inclusion of TG, ketones, glycerol, lactic and pyruvic acids, amino acids, glucocorticoids and thyroxin are obvious extensions of the proposed model. Models for the metabolism of the above substrates and hormones are briefly discussed here.

Model for TG metabolism: The term TG here refers to endogenous triglycerides[1] contained in very low-density or pre-β lipoproteins (see Appendix). It is commonly known as VLDL-TG[2]. The source of this endogenous TG is liver. Plasma FFA entering the liver are partly oxidized and partly converted into TG which are either stored or released into plasma. Tracer studies and compartment analyses have indicated that the hepatic TG pool is nonhomogeneous and that only a small portion of newly synthesized hepatic TG is delivered to the plasma, the rest being stored temporarily in an intrahepatic "sink".(85,7) Normal fasting plasma concentration of TG varies with age.(86) It is about 70 mg% in normal adults of age 20-40 years. The fasting turnover rate is about 15 mg/min in healthy individuals.(85)

The model for TG metabolism is shown in Figure 26. The variable y_7 is the amount of FFA taken up by the liver for synthesis and release of TG. The delay element[3] accounts for the delay in the appear-

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1 Chylomicrons which are rich in TG are exogenous since they are derived from dietary fat during absorption.

2 VLDL, pre-β and α_2 are synonymous.

3 Pure time delay is not one among the basic building blocks shown in Figure 10.

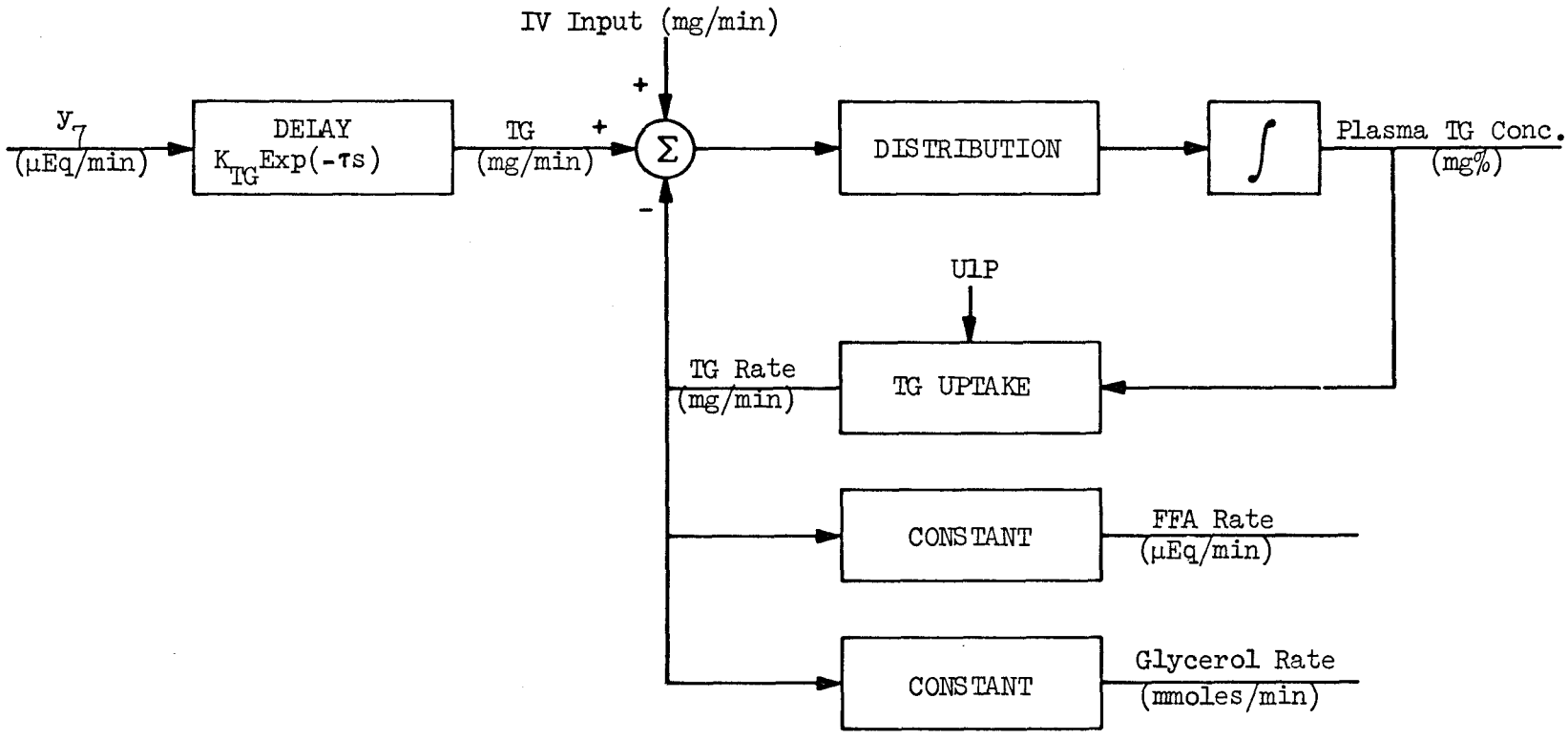

Figure 26. Model for TG Metabolism. K_{TG} - Conversion factor; τ - Delay; s - Derivative operator $\frac{d}{dt}$; UlP - Plasma insulin conc.

ance of newly synthesized TG in plasma following FFA uptake by the liver. τ is about 10 minutes.[6] K_{TG} is the conversion factor and s is the derivative operator $\frac{d}{dt}$. It should be noted that the saturation effects have already been included in the FFA model.

The endogenous TG released by the liver are taken up by muscle and adipose tissue. The transport of TG across the cell membrance has not been clearly understood. First of all, the TG undergo hydrolysis releasing FFA and glycerol (see Figure 6). It is not yet known just where between the vascular surface and intracellular TG this hydrolysis takes place.[87] The FFA are taken up by the target tissues and are re-esterified into TG. The glycerol fraction is carried to the liver. A fraction of the TG may be taken up intact without prior hydrolysis. Taking the evidence of both in vitro and in vivo experiments, Shapiro[88] concludes that uptake of TG by adipose tissue may be facilitated by both partial and complete hydrolysis and resynthesis.

The utilization or degradation of TG is represented in our TG model by a parameter-dependent saturation-type nonlinearity, based on the suggestion by Reaven et.al.[89] for concentration versus turnover rate. It is assumed to be enhanced by plasma insulin concentration.[90] Due to hydrolysis of TG both in the vascular space and at the cell membrane of the target organs, an increased utilization of TG would be expected to increase the plasma concentrations of both FFA and glycerol. In fact, several authors have elevated plasma FFA concentrations in man by infusion of TG.[91,92] This points to the coupling of TG model with FFA and glycerol models. It is indicated in Figure 26.

Model for ketone metabolism: The plasma level of ketones -

acetoacetic and β-hydroxybutyric acids - is about 1 mg% in healthy individuals under normal fasting conditions.[18] It increases significantly after 18-24 hours of fasting.[93,30] The suggested model for the metabolism of ketones is depicted in Figure 27. From our model for FFA metabolism, y_8 μEq/min of FFA are taken up by the liver for oxidation and production of ketone bodies. Since the nonlinear effects have already been taken into account in the FFA model, a constant relates y_8 to the release rate by the liver. Only a fraction of y_8 is converted into ketones, the rest being completely oxidized to CO_2 and H_2O. Ketone production results also from the so-called ketogenic amino acids. The process can be represented by a nonlinearity of saturation-type.

There are two utilization pathways for ketones, both of which depend on their plasma concentration. (i) Peripheral utilization, chiefly by muscle and (ii) Urinary excretion. Ketones are normally metabolized as rapidly as they are formed.[18] Increased production leads to ketosis, i.e., accumulation of ketone bodies in plasma. It indicates that the ability of the tissues to oxidize ketones has been exceeded. Thus a nonlinearity of saturation-type seems appropriate for representing peripheral utilization. The functional relationships between plasma concentration and urinary excretion of acetoacetic and β-hydroxybutyric acids in normal humans have been reported by Galvin et.al.[94]

Model for glycerol metabolism: The fasting concentration of plasma glycerol is about 35 mmoles/mℓ and the turnover rate is about 0.30 mmoles/min in normal subjects.[25] The suggested model for glycerol metabolism is shown in Figure 28. Glycerol release from adipose tissue is assumed to be proportional to FFA release $(y_1 + y_2 + y_3)$ in our

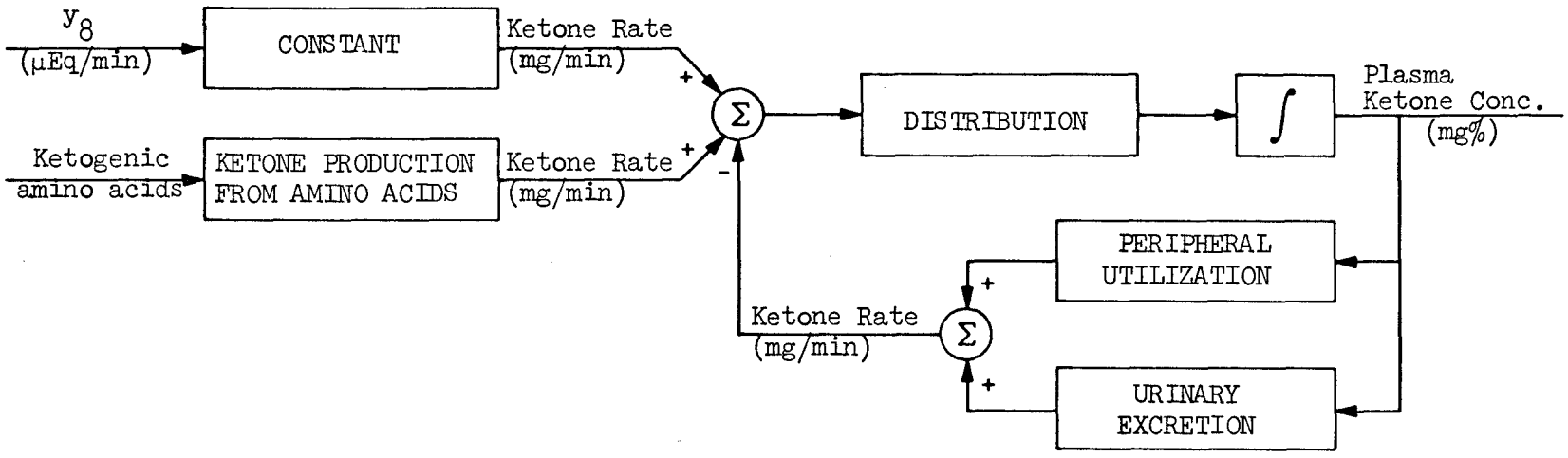

Figure 27. Model for Ketone Metabolism. y_8 - Liver uptake of FFA for oxidation and ketone production (from FFA model).

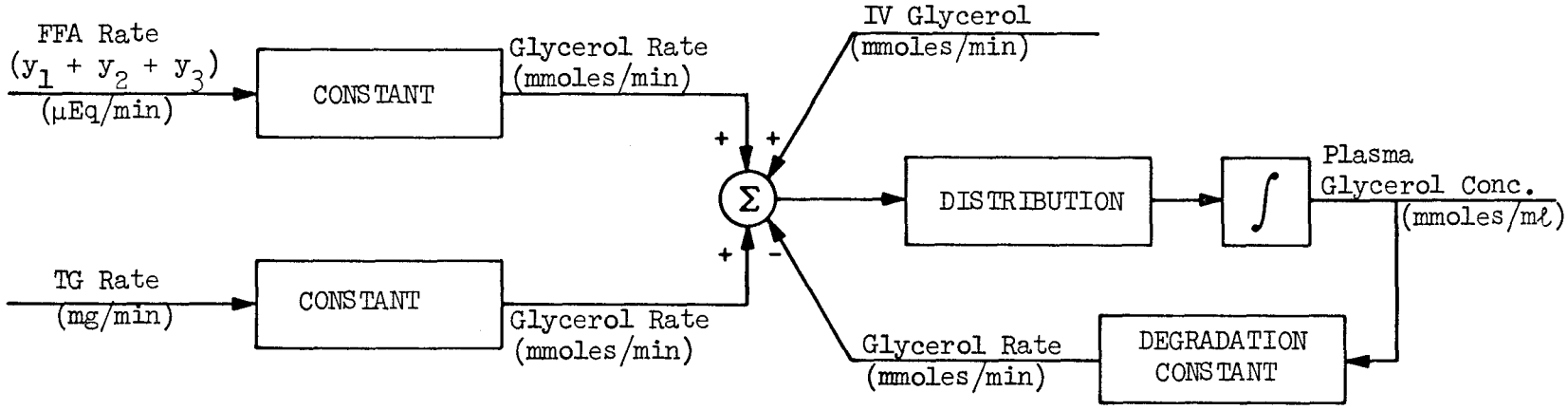

Figure 28. Model for Glycerol Metabolism

model. In addition there is contribution from hydrolysis of VLDL-TG (see Figure 26). Data of Senior and Loridan[95] suggest a simple linear representation for glycerol distribution and degradation. They found intravenously administered glycerol to disappear with a half-life of approximately 40 minutes.

Model for lactic and pyruvic acid metabolism: The lactic acid level in blood ranges from 10 to 15 mg% under resting conditions; whereas the amounts of pyruvic acid normally found do not exceed 1 mg%. The normal plasma concentration of pyruvic acid is thus only one tenth or one twentieth that of lactic acid.[13] Reichard et.al.[96] have estimated a lactate[1] turnover rate of about 22 to 24 mg/kg/hr in normal humans under resting conditions. Brain contributes about 50% of this, the balance being from the musculature. A constant rate of production of lactic acid by the brain would be expected since it utilizes glucose at a steady rate under most circumstances. Exercise, stress and infusion of catecholamines enhance the production of lactic and pyruvic acids by muscle by increasing glycogen breakdown and subsequent glycolysis.

A model for the metabolism of lactic and pyruvic acids that is based upon the above considerations is indicated in Figure 29. Production by muscle can be represented by a saturation-type nonlinearity. As in the case of glycerol model, distribution and degradation is represented by a simple linear model. Uptake by liver is the most important utilization pathway for lactic and pyruvic acids. A small fraction is excreted in the urine and sweat which has been neglected in the sug-

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[1] A salt of lactic acid.

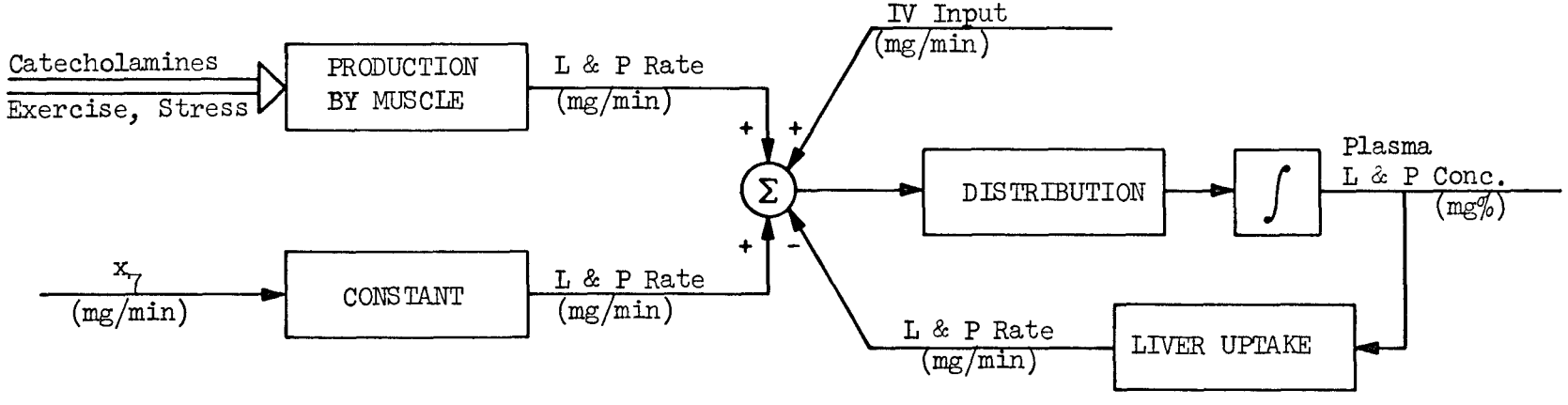

Figure 29. Model for Lactic and Pyruvic Acid Metabolism. L & P - Lactic and pyruvic acids; x_7 - Brain and RBC utilization of glucose (from glucose model).

gested model.

Model for amino acid metabolism: There are 10 essential amino acids in man and they do not all behave the same way. They can be broadly classified into two groups, viz., ketogenic and glucogenic. Leucine, isoleucine, phenylalanine and tyrosine are said to be ketogenic because they are converted to the ketone body, acetoacetic acid. Glucogenic or gluconeogenic amino acids such as threonine, valine and many others give rise to compounds that can readily be converted into glucose.

A highly simplified model for amino acid metabolism, constructed along the lines of the proposed FFA model in Figure 30. There are two pathways of utilization - liver uptake and extrahepatic tissue uptake, chiefly muscle. Glucocorticoids and throxin stimulate protein catabolism and thus increase the level of amino acids in plasma. GH and insulin produce the opposite effect. Glucagon decreases the level of plasma amino acids by primarily enhancing the hepatic utilization.[97,98]

The lumped representation of glucoenegenesis in the proposed model for FFA-glucose metabolism can now be refined as indicated in Figure 31 to include the effects of amino acids, lactic and pyruvic acids and glycerol.

Models for glucocorticoids and thyroxin can be based on the work reported in the literature.[99,100] A simple one-compartment model similar to that of glucagon is suggested for the metabolism of glucocorticoids. A linear model similar to that proposed for epinephrine is a good representation for the distribution and degradation mechanism of norepinephrine; however, the secretion of norepinephrine is somewhat more difficult to model since it is a neurohumor.

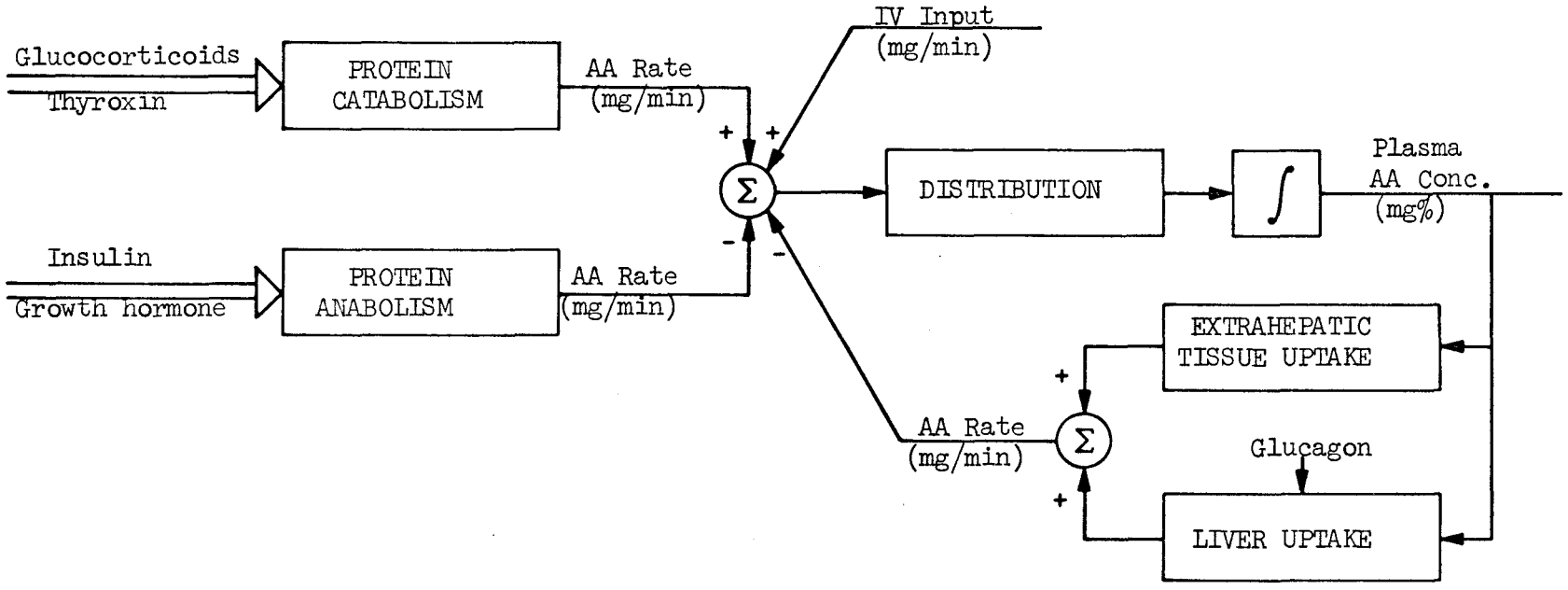

Figure 30. A Simplified Model for Metabolism of Amino Acids. AA - Amino acids.

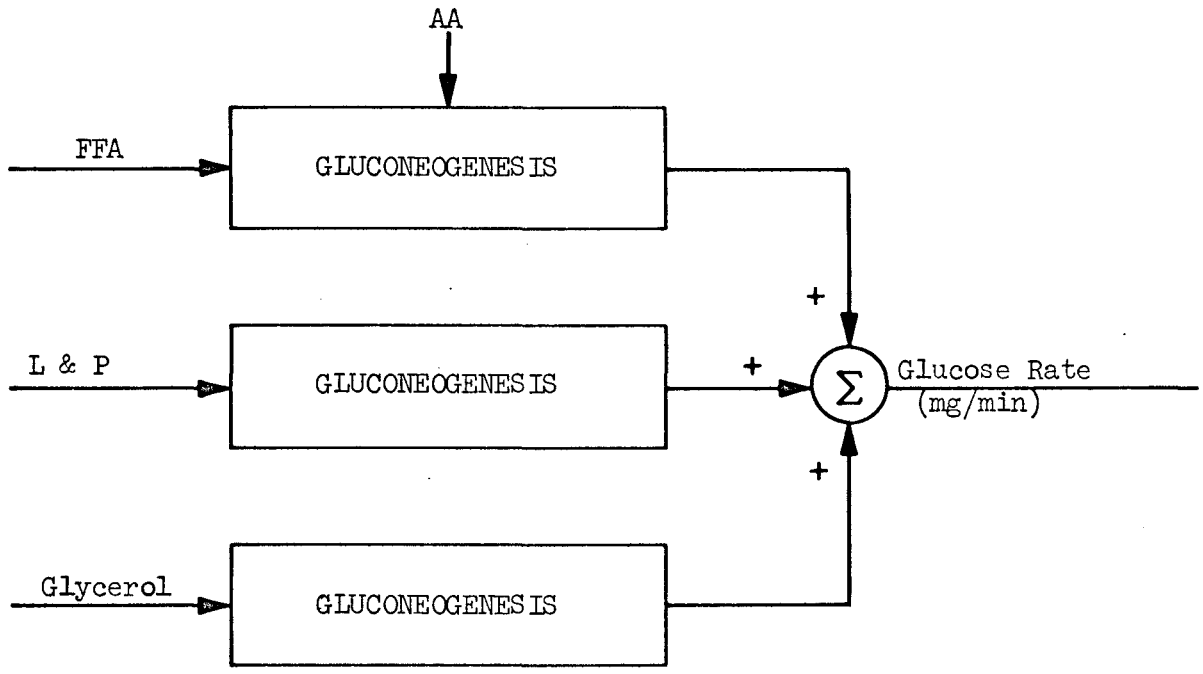

Figure 31. A Detailed Representation of Gluconeogenesis. AA - Amino acids; FFA - Free fatty acids; L & P - Lactic and pyruvic acids.

5.2. Concluding Remarks.

A mathematical model in terms of nonlinear ordinary differential equations for the control mechanism of FFA-glucose metabolism in normal humans was presented. Modeling was approached from a systems viewpoint. The model was comprised of integrators, first-order lage and saturation-type nonlinearities that are inherent in metabolic systems. It was constructed in such a way that additions such as amino acid and TG portions are possible without destroying its basic structure. It can be represented in the form:

$$\dot{z} = f(z, u, v)$$

$$\dot{u} = g(z, \dot{z}, u)$$

where

z = (15 x 1) metabolic state vector

u = (4 x 1) hormonal control vector

v = (5 x 1) input vector comprising of glucose and hormone inputs (intravenous)

Ample evidence was produced justifying the physiological basis of the model. Methods were suggested for systematically identifying the parameters of the FFA model. Although the model did not adequately reproduce the finer details of the actual responses in some instances, the limited success supports the approach. Inclusion of the remaining hormonal controls and refinements of mathematical relationships, as suggested by studies on specific portions of the model, would undoubtedly yield better results.

APPENDIX

SUMMARY OF LIPIDS IN PLASMA

Lipids are organic compounds which are insoluble in chloroform, ether or benzene. Ingested lipid contains chiefly triglycerides. After digestion they appear in the intestinal lymph as an emulsion of chylomicrons. The presence of chylomicrons causes, usually about 2-3 hours after meals, milkiness (lactescence) in the blood plasma; this is termed alimentary lipemia. It is cleared by the action of the clearing factor a substance now known to be the enzyme lipoprotein lipase. Chylomicrons are the largest lipid-bearing particles in plasma, containing more than 80% of triglycerides. They have the lowest density.

In addition to chylomicrons blood plasma contains lipids that are formed endogenously - phospholipids such as lecithin and chephalin, free chlesterol, chlesterol esters and free fatty acids. All lipids in plasma are associated with protein in some form of binding. The density of the various lipid-protein complexes in circulation varies with the amount of lipid and the amount of protein they contain, and on this basis they are divided into very low-density, low-density and high-density fractions, known respectively as pre-β, β and α lipoproteins. Since lipoproteins have a lower density than other serum proteins, they float to the surface in the ultracentrifuge and the rate of floatation can be measured. This rate is called the S_f value.

The S_f value, density, approximate plasma concentration and composition of chylomicrons and lipoproteins are given in the following table.[46]

	Chylomicrons	Pre-β Lipoproteins	β Lipoproteins	α Lipoproteins
S_f value	> 1000	10-1000	0-10	-
Density (gm/mℓ)	< 1.006	1.006 - 1.019	1.019 - 1.063	1.063 - 1.210
Plasma Conc. (mg%)	0 - 200	125	300	350
Components	Per Cent			
Triglyceride	81	52	9	8
Phospholipid	7	18	23	26
Free Chlesterol Chlesterol esters	9	22	47	19
Protein	2	7	21	46

Table 8. Density, concentration and composition of plasma lipids.

Free fatty acids are long chain fatty acids and in man they are chiefly oleic acid (45%), palmitic acid (25%), stearic acid (10%) with others in small amounts. They are complexed with albumin in blood plasma. The word "free" here means "unesterified" or "nonesterified". The FFA-albumin complexes contain 0.5% of FFA, 0.5% of phospholipids and 99% of albumin. They are formed immediately when fatty acids are released into the blood stream and they release their fatty acids at sites of utilization. The affinity of albumin for fatty acids is quite specific. When bound to albumin, the fatty acids are soluble in water.

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