MODELING THE GLUCOSE REGULATORY SYSTEM IN MAN

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Introduction

The application of system dynamics to medicine offers the possibility of greatly accelerating medical research and treatment. Figure 1 lists the ways in which a System Dynamics model can be used in the biological sciences. In addition to the traditional model uses of organizing information, improving understanding of behavior, and identifying sensitive points in a system, the model can be a significant guide to medical research and practice.

For example, it is possible to address causes or theories of disease states as a separate topic. Of course, any system dynamics model of probable causes of disease states is purely speculative, but it is necessary that the model of a biologic system be capable of exhibiting all known behaviors of the system with known or plausible causes of these behaviors.

Separate from the causes of disease states in biologic systems, it is possible to explore and improve treatment of the disease. Often the end result of a disease is the total malfunction of one organ system. Simulation of various treatments can therefore be accomplished regardless of whether the model accurately depicts how the malfunctioning system altered its behavior from normal.

It is also possible with a system dynamics model to test the model itself. After all, a model is only a mathematical, explicit statement of how a system functions. An analysis of this explicit statement can lead to new research and new theories (indeed it can also lead to new models). Thus, the model becomes a powerful educational tool, as well as a means to reconcile apparently conflicting theories.

This paper deals with one biologic control phenomenon--the control of blood sugar (glucose) in man. It will focus on the development of a system dynamics model and the use of that model in evaluating alternative theories

of diabetes and in suggesting treatment alternatives for poor blood sugar control.[1] Moreover, analysis of the model itself suggested a critical experiment which led to a better understanding of blood sugar control, a new model, and the resolution of two conflicting theories of insulin release.[2]

Nature, Importance, and Treatment of Diabetes

[For the reader who lacks knowledge of the glucose regulatory system, a brief description follows. Substantial liberties have been taken by the authors in simplifying the medical description of blood sugar regulation to both save space and emphasize the use of system dynamics in this field.[3]]

Glucose is one of two main fuels for the body. The other is free fatty acids. Both are transported by the blood stream through the body where they are stored for later use or burned to generate energy. Most tissues can use either fuel for energy with the exception of the brain, which normally uses glucose exclusively. Since brain tissue has almost no fuel storage capability, it must continually receive glucose from the circulation in order to function.

Insulin is the primary substance controlling the levels of both glucose and fatty acids in the circulation. Insulin facilitates peripheral glucose utilization and depresses release of fatty acids by adipose (fat) tissue. The primary controller of insulin secretion from the beta cell in the pancreas (where insulin is synthesized and stored) is the glucose concentration.

The level of glucose in the body is continually altered by eating and exercise. In the normal person, the regulatory system is able to maintain the level of glucose within an acceptable range. In the diabetic, however, the level of glucose is too high.

(Several other factors play a lesser role in the normal control of blood sugar. It is not unusual in biologic systems to find a high degree of inter-

connectness between various control systems and therefore wide ranges of normalcy in each individual system. It should always be kept in mind that the exact performance of any control system is secondary to the overall functioning of the person. This phenomenon is in particular true of the body's "emergency" control systems, which have a universal and dramatic impact on all normal control mechanisms in the body.)

In order to maintain a proper perspective on blood sugar, the body must be viewed as a whole. The body is like a corporation having specialized departments and a high degree of internal communication. It takes in raw materials and puts out finished products of many kinds, and there is some scrap and waste in this process. As with any well-run business, efficiency is very important. Waste should be minimized; all usable materials should be metabolized; excess materials should be disposed of efficiently; metabolism should be adjusted to best utilize whatever materials are available. The most frequent physiologic derangement of efficient body functioning is diabetes.

Diabetes is improper blood sugar control. Carbohydrates, sugars, and starches that are eaten enter the blood stream as sugar through the intestines. From the blood stream, the rest of the body receives its nourishment. Insulin is the chemical agent which facilitates the transfer of sugar from the blood stream into fat, muscle, and liver tissues where the sugar is stored or burned. In the diabetic, an absence of insulin makes the transfer of sugar into tissues of the body grossly inadequate. Thus, we see "starvation in the midst of plenty". Sugar (energy) abounds outside of the cells and little sugar exists inside the cells where it can be used as a source of energy. Increased hunger is commonly seen in uncontrolled diabetics.

The "excess" sugar in the blood stream is removed by the kidneys and excreted in the urine. The removal of the large amounts of sugar requires large

amounts of water; diabetics often drink large quantities of fluids. A diabetic may become dehydrated, however, while drinking quarts of water a day. Absence or deficiency of insulin also affects the body's use of fats for energy. Free fatty acids are mobilized in increasing quantities; their partial breakdown products, called ketone bodies, cause a marked acid shift in the pH of body fluids. The importance of pH can be clearly understood from its primary role in almost every chemical reaction in the body!

There are approximately 5 million diabetics in the U.S.. A predisposition toward diabetes is known to be inhereted; current theories also link diabetes to viral and dietary factors. There is a definite relationship between the onset of diabetes and age; furthermore, it is normal to become more "diabetic" with age. Diabetes may be fatal if not properly treated; prior to the discovery of insulin in 1921 by Drs. Banting and Best, diabetes was frequently fatal.

The complications and symptoms associated with diabetes are numerous. In addition to those previously mentioned are:

- overweight babies
- repeated stillbirths or miscarriages
- severe congenital defects in the child
- infections, especially of the bladder or kidneys
- loss of weight
- itching
- marked fatigue
- slow healing of cuts and scratches
- diabetic coma
- insulin reactions (these are caused by the <u>treatment</u>)
- arteriosclerosis (hardening of the arteries)
- gangrene
- neuropathy
- hemorrhages of the retina of the eye and blindness
- kidney failure

There is also a relationship between diabetes and all kinds of circulatory disorders, including heart disease. The nature and reasons for this relationship are still not understood.

Diet is the keystone in the treatment of diabetes. Often, dietary restrictions are coupled with exercise programs and either oral anti-diabetic medicines or injections of insulin. Treatment is always individualized.

Despite the fact that great strides have been taken in the treatment of diabetes in the last 50 years, the average diabetic lifetime is still only two thirds that of the non-diabetic. Furthermore, the diabetic wages a constant battle against overeating, overweight, infections, blindness, heart and peripheral vascular disease.

Initial Model of the Glucose Regulatory System

The glucose regulatory system is a complex system. It is a non-linear, multi-loop, self-regulating feedback system which exhibits behavior which has been difficult to understand and which is insensitive to many external interferences.[4]

Figure 2 shows the six levels which are commonly assumed to play a significant role in controlling the behavior of the glucose regulatory system: glucose in glucose space GG, liver glycogen GLYLIV, muscle glycogen PGS, serum insulin I, plasma free fatty acids FFA, and plasma glucagon G. Twenty-two rates control these six levels. The primary feedback loops in this system are shown in Figure 3.

The level of glucose is increased by external stimulus and by glucose release from glucose stored in the liver as glycogen. Glucose is reduced by glucose uptake to liver glycogen and by glucose usage by muscle and adipose (fat) tissue (the periphery), nerve tissue, and red blood cells. Only release and uptake to liver glycogen and peripheral usage are an active part of the regulation system. Usage by nerve tissue or red blood cells depends on glucose concentration but only to the extent that low levels of glucose constrain usage. Glucose concentration similarly constrains usage by the periphery.

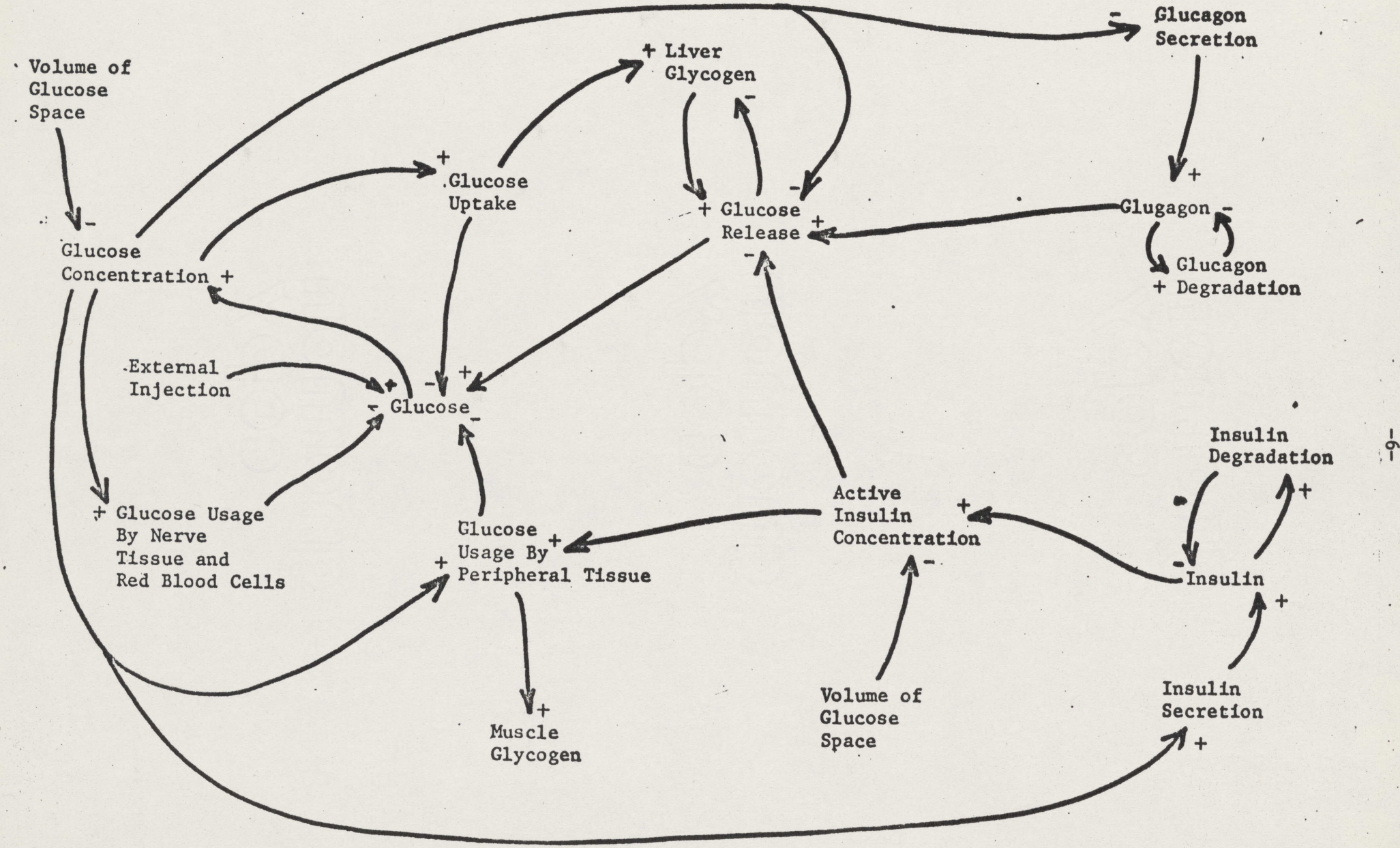
Volume of Glucose Space
Glucose Concentration
Glucose Uptake
Liver Glycogen
Glucose Release
Glucagon Secretion
Glugagon
Glucagon Degradation
External Injection
Glucose
Glucose Usage By Nerve Tissue and Red Blood Cells
Glucose Usage By Peripheral Tissue
Muscle Glycogen
Active Insulin Concentration
Volume of Glucose Space
Insulin Degradation
Insulin
Insulin Secretion

Figure 3

Four major negative feedback loops regulate the level of glucose. In two loops, an increase in glucose increases insulin concentration. Increased glucose concentration stimulates insulin secretion, thereby increasing the level of insulin and active insulin concentration. An increase in active insulin concentration has two effects. First, the increase stimulates glucose usage by muscles, thereby reducing the level of glucose (and completing the first negative feedback loop). And second, the increase constrains glucose release from liver glycogen, thereby reducing the conversion by the liver of glycogen to glucose. (The second negative feedback loop is completed.) The two feedback loops through insulin are the primary control loops for high levels of glucose.[5]

The third and fourth feedback loops are the dominant control loops for low levels of glucose. A decrease in glucose reduces glucose concentration. Such a reduction has two effects. First, it stimulates glucose release from liver glycogen (subject to the level of liver glycogen), thereby increasing glucose (and completing the third negative feedback loop). And second, the reduction in glucose concentration stimulates glucagon secretion, thereby increasing the level of glucagon. As glucagon increases, glucose release by the liver is further enhanced. The fourth negative feedback loop is complete.

There are, of course, many other feedback loops in the model (and in real life), but these four are the ones which are most significant for our discussion of diabetes; and of these, the most important are the two which depend on the secretion of insulin. [It is not surprising that almost all of the feedback loops are negative. Bodily systems are almost always well-compensated. Furthermore, there is good teleologic (evolutionary) support for the important levels in the body being well-regulated; those organisms demonstrating poor control of important levels became extinct. In some cases,

multiple control loops have evolved all seeking to control the same variable and to constrain its variance. For example, there are no less than three primary controllers of arterial muscle tone (blood pressure). If any one or even two control mechanisms fail there will still be good blood pressure control; all three control mechanisms must break down before blood pressure is poorly regulated.]

Figure 4 shows the detailed flow diagram for muscle and adipose tissue glucose usage. The most significant factor controlling these rates is insulin. It should be noted that insulin acts on both muscle and adipose tissue. It should also be noted that the action of insulin on these tissues is not as primary controller at all times; glucose (blood sugar) must be available so that insulin can facilitate glucose uptake by peripheral tissues.

Figure 5 shows the detailed flow diagram for glucose release by the liver. It will be seen again that insulin plays a primary role in the control of this rate. Insulin also plays a role in glycogen synthesis. It should be clear that insulin has a significant and primary impact on almost every tissue in the body with regard to its ability to make sugar available as a fuel.

Given that the two most important rates having a direct impact on the glucose level are peripheral utilization of glucose and glucose release by the liver and given that insulin is the most significant controller of both these rates, it is not surprising to find that the one most significant influence point in this system is insulin secretion. Figure 6 shows the flow diagram for the insulin release rate. Three factors have an impact on insulin release.[6] The first of these is the level of free fatty acids (FFA), although this is a comparatively minor influence. (Figure 7) [Indeed, substantial testing with the model has demonstrated the relative unimportance of FFA in the overall control of glucose.] Of more interest to us in this discussion is the fact that

the level of glucose has a much more significant impact on insulin release through its normal operating range (as much as a four-fold increase in insulin release at its extreme) (Figure 8). Also, there is greatest sensitivity in the region of normal glucose equilibrium (80 mg percent). A secondary impact of glucose on insulin release seems to be through the rate of change of blood glucose (Figure 9). Apparently, the beta cell of the pancreas (the organ secreting insulin) is able to sense that the glucose level is rising or falling and to compensate for this rate of change in glucose level by releasing more or less insulin accordingly. It is significant to note, however, that only when the body is subjected to an exogenous disruption of glucose level does this mechanism have a perceptible impact on insulin release. The level of blood glucose does not change rapidly unless directly stimulated by an exogenouse pulse of glucose. Therefore, the longer-term dynamics and the overall system behavior will not be appreciably affected by the presence or absence of a "rate-of-change-sensor" in the beta cell.

Two questions are immediately apparent from the previous discussion: (1) Why bother to model a phenomenon which is known to have an insignificant impact on overall system behavior? and (2) Is there any plausible physiologic explanation for a "rate-of-change-sensor"? Is it not true that real physical systems sense levels and not rates?

Although the answers to these questions were not apparent at the time that this model was first conceived, it was a qualitative analysis of those factors impacting insulin secretion which led to a critical clinical experiment. Eventually, two apparently contradictory schools of thought were brought together. It must be emphasized that this analysis (presented later in this paper) is based only on the structure of the system and the shapes of the curves already

presented; a change in any parametric value will have no impact on the validity of this analysis.

We may model a behaviorally insignificant phenomenon for a number of reasons. (1) It may be that we do not know at the time of model creation whether the phenomenon is important or not; in other words, we may wish to test for importance. (2) It may also be politically necessary that a behaviorally unimportant feedback loop be present. The omission of common knowledge because of its insignificance may alienate any potential model users before they have an opportunity to judge the model validity for themselves. (3) Some well-known short-term behavior of the real system may depend on the existence of this feedback loop of long-term unimportance, in this case the observed "dumping" of insulin from the pancreas in conjunction with a sudden distortion of the glucose level via intravenous injection of glucose. (4) The inclusion of an "incorrect" model structure may be necessary to demonstrate its incorrectness. After all, a model is only a tool, a means to an end. A model is a convenient way of assembling a body of data into a consistent theory which can be tested. All four of the aforementioned reasons played a role in the decision to include a "rate-of-change sensor" in the blood glucose model.

How is it possible then for a physical, biologic system to sense rates of change? An a priori test of model validity should be that one can postulate a mechanism (hopefully a simple one) which can demonstrate the behavior he has modeled. This mechanism need not be the actual one, but there must exist a plausible explanation. In this case the explanation was that the beta cell of the pancreas functions much like a nerve cell does. It is constantly pumping ions across a potential barrier, the cell membrane. Furthermore, this pumping action will always seek to establish or re-establish the

same potential difference across the cell membrane. The insulin release then becomes a by-product of an ion pumping action. The harder the ion "pump" works, the more the insulin is secreted. This theory is made complete if the permeability of the cell membrane to free exchange of ions is governed by the level of glucose or an immediate by-product thereof. Since glucose is a mildly polar molecule, it could have the above property. A rapid increase in permeability of the membrane to a particular ion would then result in a rapid pumping action and an associated high rate of release of insulin until the ion balance is re-established; however, since the permeability of the membrane has been increased, there will be a steady-state with higher ion exchange rates both into and out of the cell. In other words, both the glucose rate-of-change sensor (ECBSIS) and the glucose level sensor (EBSIR) become part of one physical phenomenon by this explanation. Furthermore, since it is a well-understood phenomenon that nerve cells deliver information as a result of "ion pumping", perhaps a beta cell secretes insulin by a similar mechanism. This explanation only gains credibility if one understands that both the beta cells and the nervous system (along with several other body tissues) develop from the same embryonic cell group; the derivation from similar cells is often an indicator of similar cell characteristics.

Thus, the evidence seems conclusive that a "rate-of-change sensor" must be included in a model of blood sugar control. Assuming the aforementioned explanation to be correct, how would one model the impact of a progressive breakdown in the "ion pump"of the beta cell if both phenomena were not modeled? (The breakdown in the proper functioning of this "pump" could be a plausible explanation of the cause of diabetes.) It is of interest to note that one physical activity may lead to two observable table functions.

We want to clarify at this time that the previous explanation of beta cell function is incorrect. In fact, we shall evolve a means of demonstrating the incompleteness of this theory by designing an experiment with the model which will dramatize its inadequacy. However, there are some very important points for proper model-building which should be derived from the above discussion:

(1) It ought to be possible to postulate a physical mechanism which will demonstrate the behavior postulated in each non-linear table function.

(2) The postulated mechanism should have historical precedence in the field where systems dynamics is being applied. This necessitates a broad knowledge of the field for the systems dynamicist.

(3) Frequently there are no experiments or data available to support or discredit the postulated mechanism. [In this case, the beta cell has not been specifically studied as a "pump". In fact, the whole field of membrane physiology is in its infancy. The new model which will evolve from this one will dramatize our currently poor knowledge of beta cell physiology and the importance ot its membrane characteristics to the proper overall function of beta cell. It seems that modeling studies and membrane studies might best proceed together. Modeling could provide a means of interpreting data and setting directions for research, and membrane studies could provide the empirical data and physiologic understanding necessary to make good models.]

The model here presented was subjected to a variety of tests which are presented elsewhere.[7] Suffice it to admit that the testing incorporated:

(1) A comparison of system behavior based on existant published data, which required an extensive and broad knowledge of publications in the field of blood sugar control.

(2) A comparison of system behavior with previously unpublished data and informal observations.

(3) A comparison of system behavior with experiments designed and performed specifically to test the model.

(4) Validation of as many detailed relationships in the model as possible by comparison with published documents.

The model demonstrated acceptable behavior for all of the above, including the ability to simulate certain disease states and certain modified normal states, such as "starvation".

It is significant that the model was exposed to a host of comparisons with observed behavior and that it compared favorably on all counts. Among the tests of overall system behavior were:

- Normal Glucose Tolerance Test
- Response of model and humans to varying doses of glucose in the normal glucose tolerance test
- Normal Insulin Tolerance Test
- Comparison of human and model dynamics after 7 days fasting (starvation).
- Comparison of model dynamics and human dynamics for the pre-diabetic, chemical diabetic, and severe diabetic states.

Only the normal glucose tolerance test will be presented in this paper at this time.

Figure 10 shows the observed behavior of free fatty acids, blood glucose, and serum insulin over time during a standard intravenous glucose tolerance test (IVGTT). On the vertical axis is the blood glucose concentration and the horizontal axis is time in minutes. The standard glucose tolerance test consists of giving an individual an intravenous bolus of glucose of 0.5 grams per kilogram of body weight over approximately a three-minute time period.

Subsequent to giving the glucose, the glucose levels are then measured over time and the rate of glucose utilization is computed from these measurements. The standard terminology in the field of diabetes measures the glucose utilization by the "K-rate". In this Figure, the levels of glucose, fatty acids, and insulin have been averaged for the 60 subjects at each point in time where glucose was sampled. A "best-fit" first-order decay curve is then established for glucose and the time constant of decay is recorded. In this example, the time constant is 45.2 minutes. It is customary to express this time constant in an inverse form called the "K-rate". In this example the K-rate is 2.21 (= 100/45.2 minutes). For a large K-rate, the rate of glucose utilization will be great; for a small K-rate, the rate of glucose utilization will be small. The higher the K-rate, the better the glucose utilization rate is. Diabetics have poor glucose utilization rates and low K-rates. A K-rate below 1.1 is generally considered diabetic; above 1.1 is "normal".

It is not insignificant that both free fatty acids and serum insulin were also measured over the same time period in the same subjects during the same glucose tolerance tests. Since these levels were specifically modeled, we needed comparison data from normal subjects to test the model. Although every diabetes research laboratory in the world maintains its own data on normal glucose tolerance tests, we were unable to locate any publication presenting the same information as shown in Figure 10. Therefore, these tests were performed specifically to test the model and were published with it.

Figures 11, 12, and 13 compare the model behavior with that shown in Figure 10. Much of the discrepancy in these results is due to the measurement interval for the clinical tests and the graphing technique on these figures. There is also the distortion in the clinical data due to averaging which is not present in the computer data; in addition to the distortion in the model of a non-distributive glucose space (see section on use of the model to guide research for more explanation).

Using the Model to Suggest Alternate Treatments for Diabetes[8]

There are two goals for any treatment program:

(1) Keep the patient alive.

(2) Avoid unnecessary complications (see earlier section on why blood sugar control is important for a detailed explanation).

We always like to add a third goal:

(3) Restore the patient to as near normal as possible.

Prior to 1970, little, if any, attention was given to the third treatment goal. Now there are a variety of new treatments being explored which all have "normalcy" as a goal.

(1) Innoculation. If diabetes proves to be not only hereditary, but also viral, then this treatment stands out as the first choice. It focuses on prevention. It will be many years, however, before we will have an answer to whether diabetes is a virus and a vaccine is commercially available.

(2) Transplantation. It may be possible to transplant a pancreas or some beta cells from one person (or a petri dish) to another person. There still remain significant problems of tissue rejection with this approach.

(3) Implantation. It appears to be very possible to design and build an artificial implantable beta cell which will sense glucose levels and release insulin accordingly. Simulation will play a role in the design of the response characteristics of such a device and in its physical placement in the body.

(4) Refinement. Refine the existing treatment techniques so that control of blood sugar levels is improved. It is worth noting

at this point the ineffectiveness of existing treatments at curtailing undesireable diabetic complications.

However, it is widely believed that the inability of the diabetic patient to properly manage a glucose or carbohydrate load over the short-term may have a significant negative impact on the blood vessels, particularly capillaries. The fact that glucose control mechanisms are almost never in a steady state, due to eating and exercise, it can be assumed that any short-term glucose mismanagement is also a continual glucose mismanagement situation.[9]

In the area of clinical diabetic treatment, modeling will be useful in only two areas:

(1) The design of an artificial beta cell, where it should be placed, and what response characteristics it should have,[10] etc; and

(2) How current treatment methods can be improved outside of the context of diet.

The model has been used to explore both of these. How current treatment may be improved is discussed in this section, while the artificial beta cell is addressed in the section on model evolution.

Figure 14 shows the clinical results of giving a standard intravenous glucose tolerance test to the same diabetic individual on different days. In this individual an extremely long-acting preparation of insulin had been injected prior to each test, so that during each test the level of insulin remained constant. The only difference between the six tests was the level of circulating insulin. The "K-rate" is indicated on the right of each curve in Figure 14. In Figure 14, we see that it is possible to obtain both normal and diabetic rates of glucose utilization by simply varying the level of circulating insulin. As the level of circulating insulin is increased, the glucose utilization rate increases. This increase in utilization rate is made possible by lowering the fasting ("steady-state") glucose level.

The observations above were first brought to light by the blood sugar model. Computer runs on the model were performed at varying fixed insulin concentrations. The effect of increasing insulin dose readjusts the system (Figures 3,4, and 5) steady state such that glucose turnover rates are increased substantially. The increase in blood glucose therefore permits a higher utilization rate. The fasting (steady-state) levels in the system are determined by the level of glucose (glucose availability) rather than a glucose-insulin "balance". The model further showed that when the K-rate was restroed to normal, the distribution of the glucose load in the liver, muscle, etc. was more normal. The diabetic glucose distribution moves a disproportionate amount of a glucose load to peripheral tissues, instead of the liver. As a consequence of these model observations, the then unpublished data in Figure 14 were presented and subsequently published. (Cahill, 1972).

Practically, what do these results mean to the treatment of diabetes today? The standard diabetic treatment will prevent the loss of sugar in the urine in fasting by the administration of insulin. Our results show that this treatment does little to aid glucose utilization. Years of observation have also shown that this treatment does little to prevent the occurance of diabetic complications. Are these two observations related? No one knows. The key point is that merely preventing the loss of sugar in the urine may not be enough. It is possible to give more insulin and to allow a slightly lower than normal glucose utilization and distribution.

Using the Model To Guide Research and Propose Alternative Theories

Given that there really is a "rate-of-change" sensor in the pancreas, what test will maximally excite this mechanism as opposed to the level sensor? The answer lies in the hypothesized shape of the curve given in Figure 9. In the standard 3-minute intravenous glucose tolerance test (3-min IVGTT), the

rate of change of blood sugar concentration is approximately 80 mg %/min (= (320 - 80)/3). From Figure 9, there is approximately an 8-fold increase in insulin release as a consequence of this rate of change. An 8-fold increase for 3 minutes constitutes approximately 21 times as much insulin secretion as would have occurred without the rate of change sensor (= (8-1) X 3). For a slower rate of glucose infusion, however, an even greater amount of insulin should be released. If, for example, the same amount of glucose were given over a 12-minute period instead of a 3-minute period, the rate of change of glucose would be 20 mg %/1 min., causing a 4.5 fold increase in insulin release for 12 minutes or 42 times as much insulin secretion as would have occurred with no rate of change sensor (= (4.5 - 1) X 12). Therefore, the insulin level in the 12-min IVGTT should be approximately twice the insulin level in the 3-min IVGTT at the end of the infusion period.

Figure 15 shows the results of performing this experiment on 12 normal subjects and on the model. The model behaved in the way anticipated; the normal subjects did not. The bottom curve in Figure 15 compares the insulin levels in the computer model with those observed in normal subjects. Insulin levels were measured (for the first time) during the period of the glucose infusion. Of particular interest is the period from -6 min. to -4 min. in the normal subjects. During this period, the insulin levels fell in the normal subjects while the glucose levels were rising. All normal subjects showed this behavior. Clearly, it is not possible for any strictly monotonically increasing relationship between glucose level or the rate of change in glucose level and insulin release to demonstrate the observed behavior in normal subjects. There must be some kind of "saturation" or "exhaustion" phenomenon taking place in the normal pancreas during this time period which requires an alteration to our model of insulin release.

The above conclusions along with others have indeed led to a new model of glucose regulation.[11] Figure 16 shows the new distributed "glucose space" and the flows of glucose to the various glucose storage compartments. Glucose is distributed by the circulation through the heart and lungs to the liver, the kidney, the head, and to peripheral tissues. Vascular (blood) and extracellular fluid compartments for glucose are represented for the brain, peripheral tissues, and the central viscera (heart, lungs, and gut). Exchange between blood and extracellular fluid is so rapid in liver and kidney that only one compartment is represented for each of these organs. Once glucose enters cells in any organ except liver, it cannot return to the circulation. Therefore, only in the liver is a "compartment" for intracellular glucose shown (glucose is stored intracellularly in the liver as glycogen.)

Figure 17 shows the same distributive storage of insulin. Only insulin and glucose remain in this new model as significant controllers of system behavior. Insulin release is directed first into the liver where a significant fraction of the insulin is degraded. Already it is clear that in the normal subject, the liver is exposed to significantly higher insulin levels than the rest of the body. Any treatment program which administers glucose peripherally (for example, in an arm or leg) cannot achieve the same distribution of insulin concentration and therefore the same distribution of a glucose load. The clinical implications of this observation are not clear.

Figure 18 shows the new modified insulin release mechanism that is postulated. The formulation has been suggested by the work of Grodsky[12] along with observations from the old blood sugar regulation model. Basically, a large pool of insulin is hypothesized to be stored in the beta cell of the pancreas. This large pool of insulin is constantly turning over with a smaller pool of insulin which is presumably stored at the surface of the beta

cell in an area called "holding sites" and "releasing sites". A particular "site" can be transformed from a "holding" to a "releasing site" and vice versa, presumably by the action of some migrating surface protein which is sensitive to glucose concentration. Only a "releasing site" can release insulin into the circulation. Of course, this is all pure speculation; however, there is electron microscopic evidence to support the theory and this model is consistent with the proposed mechanism of action by the beta cell suggested by these photographs. It is clear, however, that the model formulation itself suggests a vast void of knowledge in the area of membrane physiology.

The proposed model leads to a whole new discussion of glucose and insulin dynamics. It also raises a series of new questions. As could be expected, however, more of the answers to the questions raised by the new model must come from medical research than an analysis of the dynamics of the model itself. This paper will not present the new model, nor its dynamics, nor the questions it raises. All of these can be found elsewhere.[12] The answers to the new questions will lead to even better understanding of glucose control and diabetes and to yet another model.

Conclusions

At this point, it would seem that a full cycle has been traced of having presented a theory of glucose control and having shown much of that theory to be invalid or unimportant. If this observation is true (which it is), then why publish a model with obvious faults? There are several good answers to this question:

1) This model represents the generally accepted understanding of glucose regulation and insulin release.

2) The model has been a useful learning tool.

3) The model has suggested important experiments testing its validity which would not have been performed if the model did not exist.

4) Our understanding of glucose regulation has been improved.

5) It may be possible to improve our existing treatment of diabetes.

In short, the model has served a useful purpose which has upgraded our understanding of glucose regulation. In other words, it is time to upgrade our model. It is important to understand that no model is static. Models serve a purpose and evolve into other models with other purposes. The process of model evolution is constant. The evolution of a new model should not be viewed as a failure of the old model, but rather as a sign that progress is being made and that the model has fulfilled its purpose.

To summarize the significant findings from the old model of glucose regulation (this model is presented in the appendix):

- The rate of change sensor theory is rejected.
- The role of free fatty acids and glucagon are not sifnificant in the control of blood sugar levels.
- The role of the liver in the dynamics of blood sugar regulation needs more attention.
- The circulation dynamics may be important to explain the phenomenon observed in Figure 11 and to explore the physical placement of an artificial beta cell.
- The concept of a "glucose space" is rejected in favor of a distributive model of where glucose is.

NOTES

1. The initial model of blood sugar control is described in Foster, R.O., "The Dynamics of Blood Sugar Regulation", MSc Thesis, Massachusetts Institute of Technology, 1970.

2. Guyton, J.R., "A Mathematical Model of Immediate Glucose Homeostasis", MD Thesis, Harvard Medical School, 1973.
A summary of the work is available in Foster, R.O., Soeldner, J.S., Tan., M.H., Guyton, J.R., "Short Term Glucose Homeostasis in Man: A System Dynamics Model", Journal of Dynamic Systems, Measurement, & Control, Sept., 1973, p. 308.

3. Further descriptions of diabetes are contained in Bowdy, P.K., Ed., Duncan's Diseases of Metabolism, 6th Edition, W.B. Sanders, Philadelphia, Pa., 1969.
Cahill, G.F., Jr., "Physiology of Insulin in Man", Diabetes, Vol. 20, 1971, p. 785, and
Codley, D.G., Ed., Family Medical Guide, 5th Edition, Meredith Corporation, New York, N.Y., 1976.

4. A recent explanation of the glucose regulatory system and promising treatments for diabetes can be found in:
Cahill, G.F., Jr., Soeldner, J.S., Harris, G.W., and Foster, R.O., "Practical Developments in Diabetes Research", Diabetes, Vol. 21 (Supplement 2) 1972, p. 703.

5. Another feedback loop stimulates glucose uptake to liver glycogen as glucose increases.

6. The determination of what factors influence insulin secretion (although based on medical literature) is not easy. All publications in this area deal largely with measurement of input/output characteristics of the pancreas, rather than the biochemistry or cell membrane physiology associated with insulin release. This body of knowledge, however, represents the currently accepted understanding of insulin release. The exact parameters of these curves have not been directly obtainable in human beings. The values used in the model were therefore determined by a "trial and error" process. The medical references of importance on insulin secretion are: Grodsky, G.M., Bennett, L.L., Smith, D.F., and Schmidt, F.G., "Effect of Pulse Administration of Glucose or Glucagon on Insulin Secretion in Vivo", Metabolism, Vol. 16, 1967, p. 222; Grodsky, G.M., "A Threshold Distribution Hypothesis or Packet Storage of Insulin and Its Mathematical Modeling", J. Clin. Invest., Vol. 51, 1972, p. 2047; and Bowdy, P.K., (1969).

7. See Foster (1970).

8. See Cahill (1971) for a further discussion of the various treatments for diabetes.

9. See Cahill, G.F., Jr., Herrera, M.G., Morgan, A.P., Soeldner, J.S., Steinke, J., Levy, G.A., Reichard, G.A.,Jr., and Kipnis, D.M., "Hormone-Fuel Interrelationships During Fasting", J. Clin. Invest., Vol. 45, 1966, p. 1751.

10. More information about the artificial beta cell can be found in: Soeldner, J.S., Chang, K.W., Aisenberg, S., and Hiebert, J.M., "Progress Toward An Implantable Glucose Sensor and An Artificial Beta Cell", Proceedings of the Second Alza Research Conference, J. Urgqhart, Ed., Plenum Press, New York, 1973.

11. Guyton (1973).

12. See Grodsky, G.M., Bennett, L.L., Smith, D.F., and Schmidt, F.G., "Effect of Pulse Administration of Glucose or Glucagon on Insulin Secretion in Vivo", Metabolism, Vol. 16, 1967, p. 222. Grodsky, G.M., "A Threshold Distribution Hypothesis or Packet Storage of Insulin and Its Mathematical Modeling", J. Clin. Invest., Vol. 51, 1972, p. 2047.

13. Guyton (1973).