Graphical analyses have been used for a number of years in the study of physiology as a means to better understand the workings of dynamic processes and to visualize the mechanisms of their interactions (5, 7). These analyses represent an intermediate between the complex methodology of computer simulations and the limited explanations provided by simplistic text and functional graphs (13). Because graphical analyses symbolize generalized relationships, they can be used to examine broad physiological concepts and systemic interactions. The graphic analysis of glucose homeostasis presented here is also general in its approach and does not pretend to encompass all of the details of this complex subject. However, when taken in context of the learning environment of the beginning student, it can provide a starting point for the conceptual visualization of these dynamic interactions.

THE ANALYSIS

A graphic analysis of glucose homeostasis can be achieved by considering the main factors that influence glucose dynamics (13). In the basal fasting state, the blood glucose concentration is maintained constant by a dynamic relationship that balances the uptake and utilization of glucose by the peripheral tissues with release of glucose by the liver. Glucose production by the liver is determined by glycogenolysis and gluconeogenesis and by the hormones and factors that control these processes (i.e., glucagon, cortisol, growth hormone, epinephrine, etc.). The curve depicting the change in rate of glucose produc-
Peripheral Glucose Uptake & Liver Glucose Output

FIG. 1. General graphic analysis of glucose homeostasis. Top curve represents change in rate of glucose uptake with varying insulin concentration. Hepatic glucose production is represented by straight line in which glucose output falls with increasing insulin concentration. Point where these 2 curves intersect is steady-state equilibrium.

Point where these 2 curves intersect is steady-state equilibrium. When a meal is ingested and the insulin levels rise in response to rising glucose, there then arises a discrepancy between hepatic glucose release and peripheral uptake as determined by the graphic relationship. This disparity of uptake and release continues until the glucose levels fall and consequently insulin levels return to the steady state. The point where the hepatic glucose release reaches zero is the liver “switching point” (Fig. 2). At this point, the liver changes from an organ of production to a reservoir for glucose storage in the form of glycogen. With this switch, the body’s metabolism changes from a net catabolic deficit to the anabolic activity of substrate storage (15). The dotted line of Fig. 2 begins at the liver switching point and separates the catabolic and anabolic states of the metabolic system. Note that the fasting steady-state equilibrium point is within the catabolic range as would be expected. Glucose uptake never reaches a zero point on its curve. This is because there is a certain insulin-independent obligatory uptake of glucose by the brain, red blood cells, renal tubules, and other select tissues.

It may be noted that the absolute value of blood glucose is not considered for the most part in the analysis. Figure 2 depicts the relationship between absolute blood glucose concentrations and insulin concentrations as would be seen in the steady state. Although the analysis is mostly concerned with the dynamic relations of glucose exchange, the blood glucose concentration is only useful as it determines the concentrations of insulin and other hormonal factors and cannot be equated to the glucose exchange directly. This is similar to the noted absence of blood pressure from the Guyton (5, 7) graphic analysis of cardiac output in which arterial pressure is independent of flow. In this case, glucose exchange or flow is not necessarily dependent on the blood glucose concentration.

In the steady state, the equilibrium point defines the rate of glucose exchange between the storage depot...
and the point of glucose utilization by the peripheral tissues. Hence, this point reflects the basal metabolism of glucose at a given fasting insulin concentration, as shown in Fig. 3. Increases in this level of transfer of glucose result in greater utilization of glucose, whereas a lower exchange would limit the substrate available to the tissues for energy formation. If the metabolic needs of the tissues exceed this flow of glucose, then gluconeogenic factors such as amino acids and free fatty acids are released to increase hepatic production. In this way, balance is maintained to meet the metabolic energy expenditure. This finely tuned balance is determined by the factors that control the positioning of the curves. Glucose uptake is determined by the insulin receptors, the insulin concentration, and the elements that facilitate glucose transport such as exercise or growth hormone (1). Under physiological circumstances, hepatic glucose release is regulated mainly by the contradictory influences of insulin inhibiting glucose release and the stimulatory actions of hormones such as glucagon, growth hormone, cortisol, and epinephrine (9, 14). The glucose production curve can be shifted from its insulin-dependent position by these counterregulatory hormones.

With an understanding of the factors that determine the shape and function of this graphic representation of glucose homeostasis, one can begin to explore the characteristics of many physiological and pathophysiological metabolic states. It is recognized that these curves do not encompass all physiological and pathophysiological conditions. Also, there are some aspects of any general analysis of this nature that many specialists in the field would find controversial and have points of disagreement. However, despite these inherent inadequacies, the method does allow for a general approach that provides insights into the overall functioning of glucose homeostasis and metabolism and can readily be adapted to meet the specific needs of the teacher or student.

EXPLORING METABOLIC STATES

Stress. One of the most primeval and elementary physiological reactions is the body’s adjustments to conditions of stress. During stress, the body increases its blood flow, sympathetic output, and sensory awareness. In the metabolic system, the goal is to increase the flow of metabolic substrate and to increase the rate of metabolism in certain tissues (i.e., skeletal muscle). Increases in stress hormones such as epinephrine, cortisol, growth hormone, and glucagon stimulate gluconeogenesis and glycogenolysis and shift the glucose production curve to the right, as depicted in Fig. 4. This shift results in a new equilibrium point at a higher rate of metabolism with greater exchange of glucose to help the organism through the stressful situation. Because the production curve is shifted to the right and is closer to the plateau of the uptake curve, any input of new glucose into the system would take longer to be assimilated and would require higher insulin levels before there is the eventual return to the steady state. This condition is known as glucose intolerance and is a known complication of stress states (3).

Exercise. It is a well documented phenomenon that exercise facilitates the uptake of glucose in muscle
Influence of exercise on glucose homeostasis.

This often results in a reduction in the daily insulin requirements of many diabetics. Such a facilitation of transport can be represented graphically by an elevation in the glucose uptake curve, as shown in Fig. 5. This results in a new equilibrium point at a lower basal insulin obligation and at a higher glucose exchange, implying a higher rate of metabolism as would be expected. A similar curve may result from the use of oral hypoglycemics that enhance peripheral uptake.

Obesity and type II diabetes mellitus. The pathophysiology of obesity and the subsequent metabolic derangement of type II diabetes mellitus have received a great deal of attention in recent years (8). It is interesting to apply a graphic analysis to help clarify this problem. Obesity and type II diabetes mellitus are characterized by mildly elevated glucose, fasting hyperinsulinemia, and glucose intolerance. There is significant experimental evidence to suggest that these patients have difficulty with glucose uptake, possibly through a problem with the insulin receptors or postreceptor signaling pathways (11, 16). The functional consequences of a reduction in peripheral receptors can be illustrated graphically by lowering the uptake curve, as depicted in Fig. 6. This results in a new equilibrium point at a slightly higher basal insulin level. If the insulin receptors in the liver and alpha cells are also defective, as has been suggested, then this would result in the hyperglucagonemia often seen in these patients and would shift the liver output curve to the right (12). These changes in turn would result in a much greater fasting hyperinsulinemia than would occur with only defective peripheral receptors. From Fig. 7, it is easy to see how these patients often have fasting insulin levels that are three times those seen in normal individuals.

Type I diabetes mellitus. In type I diabetes mellitus, the problem arises from a lack of insulin in the system. Although the position and form of our curves in the graphic analysis are not directly affected, the relationship between the two curves is out of balance (Fig. 8). An inability of the beta cells of the pancreas to secrete insulin in response to a glucose load results in a basal level of insulin that is below that required by the functioning equilibrium point determined by the two curves. Thus the system is continually in a state of disequilibrium, resulting in a reduced glucose uptake coupled with an increased glucose output by the liver. If the glucose rises high enough to stimulate the beta cells to secrete enough insulin to reach the equilib-
Influence of type I diabetes mellitus on glucose dynamics.

If the secretory function of the beta cells is so weak as to be unable to reach this equilibrium point, then the blood glucose continues to rise, and the counterregulatory hormones begin to become active. If the system is still unable to come into balance, then there is a positive feedback in which the counterregulatory hormones shift the glucose output curve further and further to the right, and the equilibrium point becomes even more unobtainable. This is what happens to the patient in hyperglycemic crisis or in ketoacidosis. At this point, only the introduction of insulin from outside the system can bring about a balance.

**Hypopituitarism.** In patients with hypopituitarism, there is a lack of growth hormone and cortisol. This condition tends to shift the glucose output curve only slightly to the left due to the relative lack of a basal effect of these hormones in glucose counterregulation (Fig. 9). However, even this small shift has importance due to its relative position counter to the steepest portion of the glucose uptake curve. The new equilibrium is formed at a lower state of glucose exchange and at a reduced rate of metabolism as would be expected in this condition. The lower position on the uptake curve also results in an exaggerated tissue uptake in response to glucose-stimulated insulin secretion and results in the insulin-glucose sensitivity seen in these patients. Similar dynamics might be seen in patients with hepatic failure where the liver is unable to respond to a need for increased glucose production. Patients with alcoholic liver disease often experience hypoglycemic episodes in the fasting state, especially if there is an associated hypoglucagonemia from pancreatitis and a resultant alpha cell dysfunction. If the lack of growth hormone lowers the glucose uptake curve, then these effects can be further amplified.

**Hyperpituitarism or hyperthyroidism.** Figure 10 demonstrates the expected consequences of an increase in the hormones that are responsible for growth and stimulation of metabolism. Growth hormone is known to facilitate glucose uptake and, along with cortisol, will increase hepatic glucose production in their roles as counterregulatory hormones. Likewise, thyroid hormone causes a generalized enhancement of all the processes of metabolism. The shift created by the
effects of these hormones results in an equilibrium point much higher than that seen under normal conditions, causing a greater turnover of glucose substrate and a higher rate of metabolism of glucose. Depending on the relative degrees of shifts of these hormones, there may or may not be a significant glucose intolerance. These features are all consistent with observations in patients with these disease states.

**Starvation.** The human body normally has glucose stores within the liver to last for ~24 h. This is the time period that we typically term the fasting state. Beyond this time of fasting is the condition known as starvation. In this condition, the body begins to utilize its fat and protein stores to produce glucose and other substrates by the process of gluconeogenesis. The body senses this wasting of body stores and downregulates the receptors for glucose utilization as a means of self-preservation. This subsequent drop in the exchange of glucose manifests itself in the lowering of the rate of metabolism in starvation. Glucagon and other stress hormones are responsible for stimulating the gluconeogenic process, and when starvation becomes severe can shift the glucose production curve to the right to maintain the flow of glucose in the system. It is interesting that the curves predict the counterintuitive feature of glucose intolerance often seen in individuals initially recovering from starvation (Fig. 11). Because the position of the equilibrium point is on the plateau of the uptake curve, any introduction of glucose into the system will result in a prolonged disposal time for this substrate.

**DISCUSSION**

An important goal of education in physiology is to introduce the student to the dynamic interactions of the body systems. Due to the sequential nature of language, it is often difficult to verbally describe processes that are inherently parallel in nature. Although functional graphs depicting singular time-dependent relationships can represent the consequences of an insulin or glucose bolus, they do not adequately describe the dynamic processes necessary to bring the system into balance. After all, that is what physiological homeostasis is all about.

Graphic analyses allow the student to view these interactions in a concise way and within a limited scope. With these graphs, the student does not need to know how to manipulate a computer simulation or decipher an immense amount of data from the literature. The disadvantage is that these analyses can sometimes be viewed to oversimplify what are often complex issues in the fields that they represent. They do not allow for the controversy or debate on the detailed specific mechanisms controlling insulin levels in type II diabetes mellitus, nor do they completely represent the many factors that interact with the processes of metabolism. They also lack descriptive content concerning the functioning on the cellular level and broadly lump many parameters. However, for the student who is grasping to integrate detailed mechanisms into an overall conceptual view of a physiological system, they provide a foothold from which to begin a field of study. The methodologies of graphic analyses have been used successfully in the past in physiology and in other areas of science. It appears that they may also be useful in the study of metabolic states. Perhaps in this way a picture is worth a thousand words.

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**References**


