is unjustifiable, as a patient may have constantly a blood-sugar content of 0.18 per cent. or even higher without the appearance of sugar in the urine.

For example, in Case 9, in Table 2, at the first examination of the blood after the patient had been rendered aglycosuric by a carbohydrate-free diet, a sugar-content of 0.127 per cent. was found. Following this the tolerance was tested, and it was found that the patient could take about 200 gm. of carbohydrate daily without a glycosuria. After six weeks on such a diet a second examination of the blood was made, and a sugar-content of 0.182 per cent. was found. It would manifestly be wrong to allow such a patient to continue on such a liberal allowance of carbohydrate, for though the urine was sugar-free, the presence of 0.182 per cent. of sugar in the blood may lead to various complications, and is almost certain to lead to a diminished tolerance to sugar. The diet regulation in such cases should aim at keeping the concentration in the blood at approximately normal, and not merely at keeping the urine sugar-free. In other cases, too, of very mild diabetes, unnecessary starving of the patient may often be avoided. The effect of the dietetic measures of the blood-sugar also affords a valuable key to the prognosis. In cases in which a normal concentration is easily reached and maintained, the prognosis should be good, though the other factors of acidosis, age of patient, etc., must always be taken into account. The actual amount of sugar found in the blood, as also the amount found in the urine, gives no guide to the severity of the case unless these observations are made after careful regulation of the diet.

In other forms of glycosuria the chief value of the blood-sugar determination lies in the ability of the clinician to rule out diabetes mellitus, and thus to find a better prognosis and often to allay the fears of the patient, who has in many cases been told that he has an incurable and rapidly fatal disease. For example, it has recently been shown[16] that in most cases of glycosuria occurring in pregnancy the blood-sugar remains normal or even slightly diminished, showing that the glycosuria is entirely of renal origin, and that it is by no means to be regarded as diabetes mellitus. In these cases, of course, the prognosis is good, and it is unnecessary to burden the patient with the dietetic regimen of a diabetic. Cases of cerebral glycosuria, so-called, are usually transitory, and occur after injury, or from pressure of a tumor, etc. As shown above, they are due to a disturbance of the center in the floor of the fourth ventricle. In these cases, as in Case 10, the blood-sugar rapidly falls to normal following the excretion of the sugar set free in the circulation from the liver. In such cases it may be of value to determine whether the glycosuria is a result of a cerebral condition or whether the cerebral symptoms are a result of diabetes, and this may readily be done by blood-sugar estimations under proper control. In cases of alimentary glycosuria[17] the hyperglycemia due to overfeeding with carbohydrates rapidly diminishes after the ingestion of carbohydrates is stopped, and such a test should be made when a transitory glycosuria is accidentally discovered. This transitory hyperglycemia and glycosuria are not to be regarded as diabetic symptoms, and one may often reassure the patient after a careful study of the case. This feature may come to be of value in life-insurance examinations, for though some of these patients later develop true diabetes, it is quite probable that an injustice is done in some cases by refusing insurance to them.

In conclusion I wish to thank those physicians who have so kindly cooperated in furnishing assistance and material for this work.

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The Homeostasis of Blood Sugar—1914-1964

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The title of this paper is taken from a chapter heading in Walter B. Cannon's *The Wisdom of the Body.*[1] The term homeostasis had been introduced by Cannon in 1926, but the concept of self-regulation goes back to Claude Bernard, who wrote in 1878[2] that "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment."

When the paper which this is written to accompany was published in 1914, it drew chiefly on the teachings of MacLeod and of von Noorden for the idea that the glucose content of the blood is a physiologic constant, and the scheme illustrating the regulatory mechanism, reproduced in that paper, was adapted from von Noorden. The role of the central nervous system, acting through the sympathetic system, and mediated by the adrenal medulla, to control the mobilization of glucose from the liver, while subject to modification in detail, is still described substantially as it was by Claude Bernard. The other half of the mechanism, however, concerned with control of the internal secretion of the islands of Langerhans of the pancreas, and with the mode of action of insulin, has had a long history of investigation and speculation, with the end not yet in sight. It is the purpose of this note to call attention to the evolution that has taken place during the past half

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century, and to attempt to outline, in general terms, the present state of the problem of the homeostasis of blood glucose and relate the latter to some newer concepts of self-regulation.

Since 1914 there have been three important landmarks in the story of self-regulation of the blood glucose concentration. In 1922 Banting and Best discovered insulin, and extracted it from the pancreas; it was later (1926) obtained in crystalline form by Abel. Also in 1926, as above noted, Cannon introduced the term *homeostasis,* now in common use. Wiener, in 1948, published his book *Cybernetics*[3] which deals with control and communication theory, both in the machine and in the animal. In the period since 1948 there has been increasing interest in the applications of cybernetic theory to homeostasis, and it is in terms of cybernetics that knowledge of self-regulating systems can best be integrated.

The term *cybernetics* includes the entire field of the theory of information and control in both mechanical and biologic systems; the word itself is derived from a Greek word meaning steersman. Information theory, in the biologic sense, refers to a type of information that is transmitted by humoral or nervous pathways and is capable of eliciting a physiologic response. In such a system the difference between the desired, or the normal, and the actual output—i.e., the deviation from the normal—is called the *error.* The term *negative feedback* refers to a signal that is fed back from the output to the source, leading to correction of the error, and may operate, in the case of blood glucose, for example, to correct a concentration that is either too high or too low. A closed cycle system, such as that under consideration, is called a *servosystem,* of which there are many in living organisms. A servosystem characteristically includes three parts: (1) an *error-sensing device,* which detects the deviation from the normal and initiates the feedback signal; (2) a *feedback transducer,* which transforms the error signal from one form to another, e.g., a nerve impulse to a changed output of a hormone; and (3) a *control signal transducer,* which brings about a further change in the nature of the signal, ordinarily controlling the output of the end product of the system.

Goldman, in 1960, in a comprehensive review of the cybernetic aspects of homeostasis,[4] used the control of blood glucose concentration as an example of the application of cybernetic theory. Figure 1 is reproduced from his review. This illustrates the types of information fed into the system by deviations in the blood glucose concentration, and the pathways through which the signals are carried, together with their targets and their effects on carbohydrate metabolism. Goldman's review should be read by anyone desiring to pursue this method of analysis.

However, from our point of view, Goldman's diagram does not adequately integrate the complex system required to maintain the blood glucose at a constant level. Specifically, it does not provide for a central control mechanism to serve as an error-sensing device. Nor does it clarify the role of the feedback transducers, which respond to the error in the concentration of glucose in the blood, and transmit an altered signal in the form of nerve impulses in the sympathetic and parasympathetic systems. Moreover, it does not indicate the points at which these nerve impulses are transformed, by control signal transducers, into hormonal signals, with insulin and epinephrine carried to the points of their peripheral actions through humoral pathways.

Supplementing Goldman's scheme, but omitting much of its detail, Figure 2 illustrates, in terms of cybernetic theory, the major features of the control mechanisms involved in homeostasis of the concentration of glucose in the blood. The stimulus to these mechanisms is the error, i.e., the deviation from the normal blood glucose concentration. The stimulus may be: (1) *proportional control,* $\Delta C(\pm)$, proportional to the error; (2) *derivative control,* $dC/dt\ (\pm)$, responding to the rate of change of the error; or (3) *integral control,* $\int \Delta C dt (\pm)$, responding to the accumulated error over a period of time. While this diagram represents the hypothalamus as an error-sensing device from which signals pass over both sympathetic and parasympathetic pathways, controlling secretion of epinephrine and insulin, respectively, it provides also for a stimulus reaching the islands of Langerhans direct from the blood, in accord with commonly accepted evidence for such an alternate error-sensing device. In fact, the origin of signals from the hypothalamus, reaching the pancreas over the vagus, while accepted by some authors, including Houssay[5] and Soskin and Levine[6] is questionable, and will receive further attention below.

Several hormonal influences on carbohydrate metabolism, with possible direct or indirect effects on the concentration of blood sugar, have been omitted from this discussion and from the diagram in figure 2, since they have not been shown to play any important part in homeostasis. They do, however, deserve mention. They include four adenohypophyseal hormones: growth hormone, luteotropic hormone, corticotropin, and thyrotropic hormone. All of these elevate the blood glucose concen-

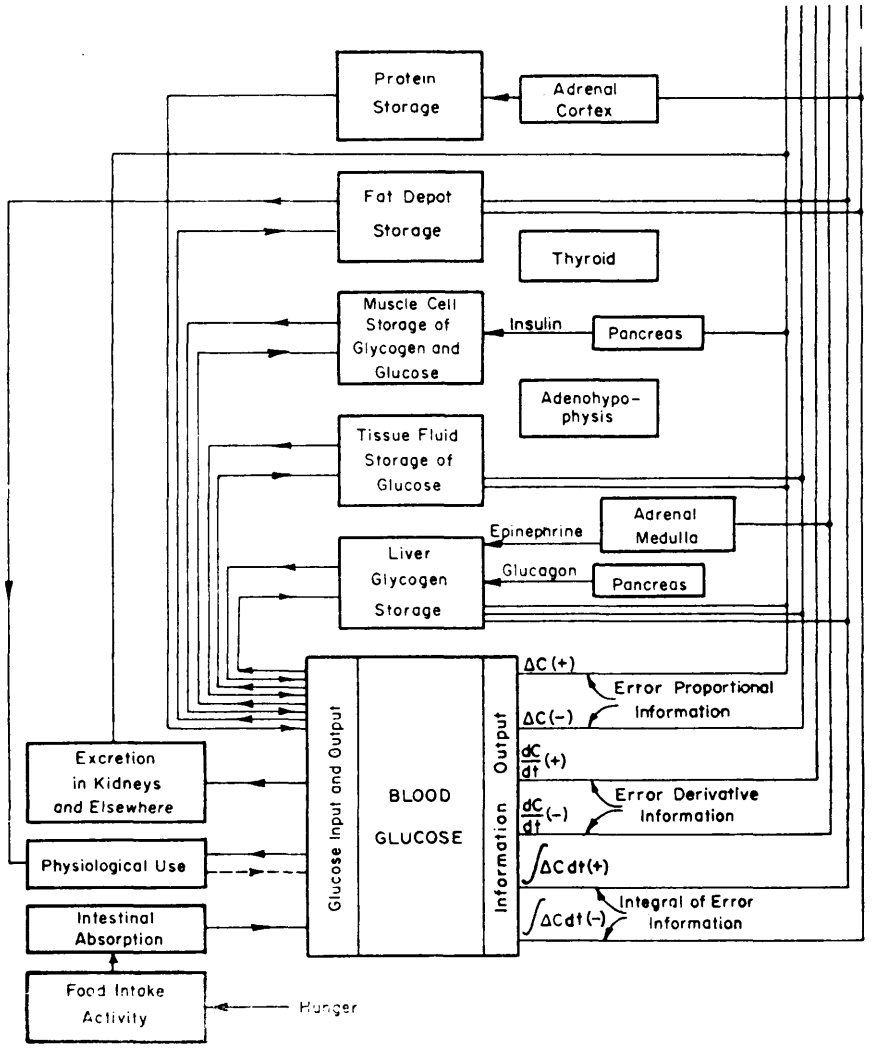

FIG. 1. Certain aspects of the blood glucose control system. The pathways indicated by the arrows may be via the blood circulation or via the nervous system. From "Mineral Metabolism," Vol. I, Part A, p. 88 (reference 4). Reproduced by permission of Academic Press, Inc.

tration and thereby stimulate secretion of insulin. Because of their ability to overstimulate the beta cells of the islands of Langerhans, when administered to animals over a long period of time, resulting in diabetes mellitus, the diabetogenic effects of the adenohypophyseal hormones are recognized.

The growth hormone of the adenohypophysis occupies a special place in this group, in that it stimulates the islands of Langerhans directly, in addition to the indirect stimulation resulting from the elevation of the blood glucose. Moreover, administration of growth hormone results in rapid release of fatty acids from adipose tissue, and hypoglycemia, exercise, fasting, and interference with glucose utilization by means of deoxyglucose are all followed by secretion of growth hormone, providing for increased availability of a noncarbohydrate source of oxidizable substrate, namely fatty acids.[7]

Roth et al.[8] have found that hypoglycemia is a potent stimulus to secretion of growth hormone; its plasma concentration has been increased by at least 500 per cent in fasting normal subjects, following administration of insulin. They report also that measurement of the growth hormone level in the plasma after hypoglycemia appears to be a specific, sensitive and direct test of pituitary somatotropic function, independent of insulin, glucagon, or epinephrine. There is some indication that the increase in secretion of growth hormone, by the adenohypophysis, is mediated by the hypothalamus, and it may turn out that this affords another pathway through which the error-sensing device, herein postulated for the hypothalamus, influences the level of glucose in the blood.

A fifth substance, glucagon, secreted by the alpha cells of the islands of Langerhans, also acts to increase the blood glucose concentration by causing glycogenolysis in the liver, believed to result from the activation of phosphorylase in the liver cells. Whether it plays an ac-

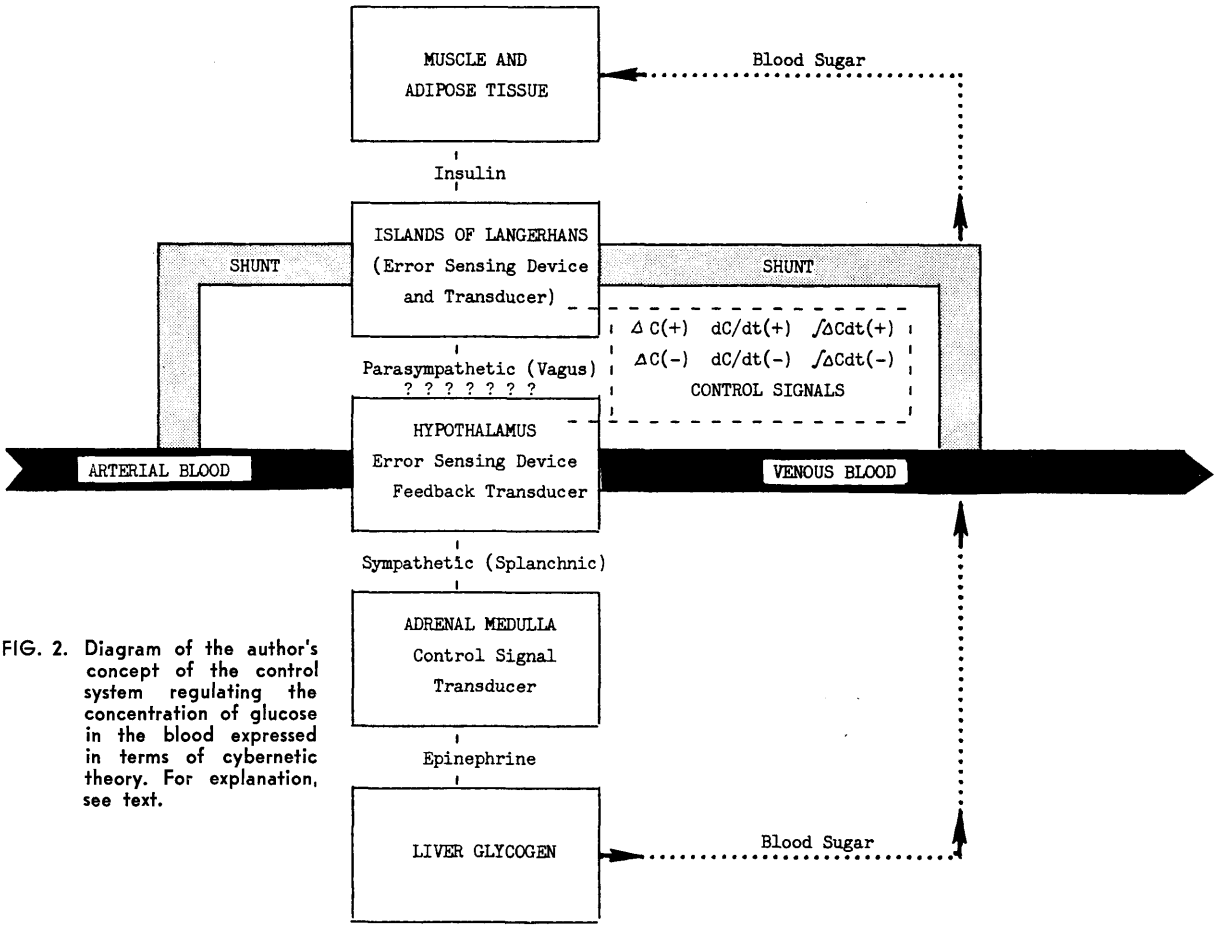

FIG. 2. Diagram of the author's concept of the control system regulating the concentration of glucose in the blood expressed in terms of cybernetic theory. For explanation, see text.

tive part in regulation of the blood glucose concentration is still uncertain.

Another omission from figure 2 is the possible influence of an intrinsic factor in the liver itself, as postulated by Soskin and Levine[6] and their co-workers. They found that when glucose is administered to patients, as in a glucose-tolerance test, or to experimental animals in comparable amounts, mobilization of glucose from the liver promptly ceases, and that this is independent of the concentration of insulin in the blood. Such inhibition of the output of glucose is attributed to the liver itself, and it has been demonstrated in vitro in suspensions of liver brei. While it has been assumed that small quantities of glucose, entering the circulation via the portal vein, may be compensated for by hepatic inhibition alone, the relation of this mechanism to over-all homeostasis remains uncertain.

Subject to the above qualifications, figure 2 includes the advances in understanding the control system for homeostasis of the blood glucose level since the scheme of von Noorden was advanced more than fifty years ago. Putting the hypothalamus in the commanding position is in accord with Houssay,[5] but it is not generally accepted at the present time. As to the vagus, Soskin and Levine, as late as 1952, accepted the evidence for stimulation of insulin secretion through the right vagus nerve, and give supporting references, without, however, specifying the source of the vagal impulses.[6] It seems desirable to show the hypothalamus as exerting control of the adrenal medulla, through the sympathetic nervous system, while questioning the pathway from the hypothalamus through the vagus nerve. It may be that these mechanisms and pathways are present and available, but called upon only under conditions of stress.

On the other hand, an information or master control center is implicit in cybernetic theory and is not easily dismissed. The principle implied is that an error-sensing device monitors the concentration of glucose in the blood and by means of negative feedback signals causes glucose to be added or taken away, to correct for deviations from the normal. Such a system, operating in the presence of the myriads of demands on the blood for glu-

cose to sustain carbohydrate metabolism in every tissue in the body, is responsible for the maintenance of a physiologically constant blood glucose concentration and is indispensable to health and to life itself.

An analogy may be found in the respiratory center, now believed to receive afferent stimuli from a variety of peripheral receptors, and to integrate the information thus received into efferent nerve impulses which control the respiratory movements.[9] The scheme for homeostasis of blood glucose has been deliberately oversimplified, in order to give emphasis to the major factors in control of the blood glucose level. It offers a method of testing current knowledge, in an effort to construct a unifying concept, and may thus be useful in further exploration of the system it attempts to illustrate.

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Trivalent Chromium and Glucose Tolerance

W. Mertz and K. Schwarz (Arch. Biochem. Biophys. *58*:504, 1955) noted that rats which developed liver necrosis as a result of consuming a Torula yeast diet showed a slow rate of removal of excess glucose from the blood and that this could be corrected by dietary means. Later they demonstrated that the glucose tolerance factor was distinct from factor 3 (a selenium compound) which prevented the liver necrosis. . . .

Later Schwarz and Mertz (Arch. Biochem. Biophys. *85*:292, 1959) reported the identification of trivalent chromium as the active ingredient of the glucose tolerance factor. During fractionation of sources of glucose tolerance factor such as defatted pork kidney, it became apparent that the factor showed cationic properties and was not destroyed by wet ashing. A number of mineral elements were then screened for activity (a total of forty-seven elements have been tested). Only mixtures containing trivalent chromium were active. Compounds such as sodium dichromate which contained chromium in other valency states were not active unless components were included to convert some of the chromium to the trivalent state. However, not all trivalent chromium compounds were active; those complexes which are very stable had little activity. Subsequently, chromium was identified in concentrates of the glucose tolerance factor.

The method used by Schwarz and Mertz to assay for glucose tolerance factor was to feed young rats a diet lacking this factor for four to five weeks. Glucose tolerance was measured after a sixteen- to eighteen-hour fast by measuring blood glucose at intervals for about an hour following the intravenous administration of 125 mg. glucose per 100 gm. of body weight. Because the rate of decrease of the *excess* blood glucose was logarithmic, the glucose tolerance was expressed as the percentage decrease of *excess* blood glucose per minute. Diets which were deficient in the glucose tolerance factor, such as the Torula yeast diet, usually produced excess glucose removal rates of about 2 per cent per minute, whereas diets containing or supplemented with the factor produced rates above 1 per cent per minute.

Of great interest is the finding that diets need not necessarily be of the "semi-synthetic" type to be deficient in glucose tolerance factor (Mertz and Schwarz: Amer. J. Physiol. *196*:614, 1959). A natural diet composed of wheat, crude casein, whole milk powder, Wesson oil, calcium carbonate, sodium chloride, and fat soluble vitamins and supplemented with kale (designated McCollum's wheat casein diet) and a diet composed of homogenized table scraps contained the glucose tolerance factor. However, three widely used commercial brands of laboratory animal ration or dog food were deficient in the factor. These feeds were routinely used to produce rats which exhibited low rates of excess glucose removal.

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