

The vesicle situated at *A* has two layers of compressed epidermal cells for its floor. The vesicle situated at *B* has the lateral half of its floor situated at the dermoepidermal junction.

Figures 3 and 4 demonstrate a necrotic lamina of epidermis overlying a bulla that contains red blood cells and amorphous, pink-staining debris. There is a complete epidermal layer beneath or on the floor of the bulla. There is slight edema at the dermoepidermal junction. Many of the epidermal cells show a vacuolated cytoplasm. The blood vessels and the sweat glands appear normal.

### DISCUSSION

In the sections studied, the marked edema that accumulated rapidly after the injury caused the epidermis to be elevated at the dermoepidermal junction. There were no intercellular or intracellular changes within the epidermis, nor was there any acantholysis, as may be noted with some bullous dermatoses. Rather, the histologic findings observed in the earliest clinical lesions were reminiscent of those noted experimentally by various technics employed in the production of dermoepidermal separation.<sup>1-8</sup> In the fracture blister, however, a single layer of compressed epidermal cells was usually noted in a segment of the floor of the bullae. These cells served as the nidus in the regeneration of the epidermis, along with those on either margin of the bulla at its adjacent skin level. The finding is confirmed clinically in that scarring subsequent to healing of fracture blisters is extremely rare.

The rate of healing of the epidermis underlying a fracture blister depends on the size of the bulla, retention of epidermal cells on its floor to serve as a

nidus and its dermal blood supply. From sections of the lesions studied histologically, it may be shown that when its size has been constant for approximately five days, treatment may consist of unroofing and application of a dry sterile dressing.

Clinically, although fracture blisters seem to occur more frequently on the lower extremities, they may occur in any location, in any age group, and in either sex when the fracture is produced by direct trauma, and the intervening soft tissues are severely contused.

### SUMMARY

Ten cases of fractures with concomitant fracture blisters are discussed.

Histologic studies on the formation of early clinical lesions and on the healing of older lesions are described. Treatment determined by histologic study of clinical lesions is outlined.

The fracture blister is presented as a dermatologic entity.

We are indebted to Drs. O. Sherwin Staples and Stuart Russell, of the Orthopedic Department, Hitchcock Clinic, for making available the records of the cases included in this study.

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## GLUCOSTATIC MECHANISM OF REGULATION OF FOOD INTAKE\*

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**T**HE regulation of energy intake is fundamental to all homeostatic mechanisms. Yet this basic process has received less attention than many of the physiologic regulations that it makes possible.

Before this century, three theories were advanced to account for the phenomenon of hunger. The theories of peripheral origin (Haller, Erasmus Darwin, Johannes Müller and Weber) held that the taking of food resulted from the stimulation either of all afferent nerves by some change in the tissues or of a strictly local group of sensory nerves,

mainly in the stomach. The theory of central origin (Magendie, Tidewald and Milne-Edwards) postulated that a hunger center was sensitive to a starvation state of the blood. The theories of general sensation (Roux and Michael Foster) considered that the hunger center of the blood was stimulated not only by the hunger state of the blood but also indirectly by afferent impulses from all organs of the body.

After Cannon and Washburn, as well as Carlson, had shown that epigastric sensations of "hunger pain" coincided with waves of contractions of the empty stomach, Carlson<sup>1</sup> suggested that hypoglycemia, mediated by its effect on the stomach, might be responsible for inducing these hunger sensations. Although hunger pangs are found in most persons, the idea that the sensations elicited

\*From the Department of Nutrition, Harvard School of Public Health. Supported in part by grants-in-aid from the National Institute of Arthritis and Metabolism and the National Heart Institute, National Institutes of Health, Public Health Service, Nutrition Foundation, Incorporated, New York City, Chemistry Scholarship Fund, New York City, National Biscuit Company, New York City, McCallum Foundation, Incorporated, New Brunswick, New Jersey, and Swift and Company, Chicago.

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by stomach contractions due to hypoglycemia<sup>2</sup> were at the basis of the regulation of food intake was abandoned for the following reasons: it was repeatedly shown, in particular by Sherrington, that total denervation and surgical removal of the stomach did not fundamentally alter the characteristics of food intake regulation. Adolph<sup>3</sup> demonstrated, by diluting the ration of laboratory animals with inert material, that differences in the bulk of the diet had only a transient influence. Scott and his collaborators<sup>4</sup> were unable to correlate spontaneous fluctuations of blood sugar levels with a desire for food. The existence of diabetic hyperphagia and of the phenomenon of hunger diabetes also presented seemingly insurmountable difficulties. Even the increase in spontaneous intake due to insulin-induced hypoglycemia was held by some authors to be of no general significance because of the abnormal "unphysiologic" circumstances in which the organism was placed.<sup>5</sup>

The demonstration by Hetherington and Ranson<sup>6</sup> that destruction of parts of the medioventral nuclei of the hypothalamus leads to obesity and the work of Anand and Brobeck<sup>7</sup> showing that more lateral lesions cause anorexia reopened the problem of the nature of the physiologic mechanism of the regulation of food intake.

Experimental work on rats, mice, dogs and human subjects culminated in the proposal of a "glucostatic mechanism" of regulation of food intake.<sup>8-10</sup> The initial reasoning was as follows: the regulation of food intake proceeds by relatively frequent partaking of food (meals). It appears improbable that hypothalamic centers are sensitive to decrease of the body content in fat or protein — during the short interval between meals, this decrease is proportionally very small. On the other hand, the body stores of carbohydrate are limited. The postprandial liver glycogen content in man is approximately 75 gm. — only 300 calories' worth. In the postabsorptive period, in spite of gluconeogenesis (the synthesizing of glycogen from body proteins), glycogen stores become rapidly depleted. This synthesis of glycogen from proteins and the shifting of metabolic oxidation in non-nervous tissues from glucose to fat (as measured by the lowering of the respiratory quotient) tend to minimize the drop in blood glucose resulting from depletion of liver glycogen stores. Thus, minimum levels necessary for the survival of the central nervous system are maintained. Only partaking of food, however, can restore full homeostasis of the central nervous system. It appeared, as a working hypothesis, that the central nervous system, dependent exclusively on a continued supply of glucose in blood, should maintain "glucoreceptors" sensitive to fluctuations of available blood glucose. (That glucoreceptors do in fact exist in the central nervous system has been implicitly recognized by surgeons; a common method for testing the completeness of vagotomies

consists in administering insulin and ascertaining that the resultant hypoglycemia fails to elicit or delays gastric secretion of hydrochloric acid.)\* In this "glucostatic" view, hunger would be integrated among the mechanisms through which the central nervous system ensures its homeostasis.

A first (and rather crude) test of this hypothesis was provided by a systematic survey of the effect of administration of various metabolites<sup>9</sup> on the food intakes of groups of normal animals. Increases in levels of reducing sugar in blood were obtained by injections of glucose or fructose or small doses of epinephrine. Decreases were obtained by injections of small, graded doses of insulin. Levels below normal fasting values were avoided, so as to stay within physiologic limits. The effects of the injection of substances without influence on blood glucose levels, like sucrose and fat emulsions, were also studied. It was found that temporary increases in blood glucose levels corresponded to decreases in food intake and vice versa, even when the caloric equivalent of injected metabolites was taken into account. Substances without effect on blood glucose did not influence food intake over and beyond caloric value, if they were metabolizable. Although significant, variations in food intake induced by these variations in blood sugar were small because of the efficiency of homeostatic mechanisms concerned with blood glucose levels. To demonstrate more clearly the inhibitory effect of high blood glucose levels on food intake, animals of the "Houssay" type, in this case alloxan-treated hypophysectomized rats, were injected with glucose.<sup>9</sup> (Although these animals do not normally present hyperglycemia, they have been deprived of the mechanisms that ensure the rapid removal of injected glucose; hyperglycemia can thus be conveniently maintained for a much longer period.) Two daily glucose injections were found to reduce food intake by half; three such injections, maintaining hyperglycemia around the clock, caused death of these animals from inanition in spite of the presence of food in their cage.

The apparent paradoxes afforded by the hyperphagia of diabetes mellitus, by the phenomenon of hunger diabetes, in which a previously fasted person will continue to eat in spite of a blood glucose reaching abnormally high levels, by the hyperphagia accompanying tendency to higher glucose levels in the obese, still had to be resolved before it could be concluded that blood glucose levels regulate food intake. It appears that all these conditions may have one factor in common — namely, that whereas absolute levels of blood glucose are increased, utilization is decreased. For variations of blood sugar levels to influence hypothalamic glucoreceptors, glucose has to cross the mem-

\*This phenomenon was recently analyzed experimentally by Porter et al.<sup>11</sup> It was shown specifically that in monkeys the anterior hypothalamus was responsible for the secretion of hydrochloric acid after insulin administration.

branes of these cells. This presumably implies phosphorylation through the hexokinase reaction. If phosphorylation is impaired, "effective sugar levels" will be in fact lower than absolute values as measured.

This concept was tested and put on a quantitative basis in a series of experiments performed on human subjects.<sup>10, 12</sup> Because of the inaccessibility of the hypothalamic centers, peripheral arteriovenous differences were determined as an index of rates of glucose utilization. These differences (designated as " $\Delta$ -glucose") were measured in the antecubital region (between finger blood and antecubital-vein blood). With one exception, discussed in some detail below,  $\Delta$ -glucose values were found to correlate closely with the caloric intake of the subject and with hunger feelings (Fig. 1).

Diets calorically adequate were associated with  $\Delta$ -glucose values that remained large<sup>8</sup> throughout the day, decreasing only at mealtime. By contrast, submaintenance diets were followed by rapid shrinkage of  $\Delta$ -glucose after meals; at the same time, hunger returned. When hunger diabetes was present, blood glucose values rose until a difference appeared between arterial and venous levels—only then was hunger assuaged. Generally speaking, there appeared to be a quantitative relation between food intake and the area represented by the  $\Delta$ -glucose as a function of time. There was also a quantitative relation between  $\Delta$ -glucose values and the incidence of hunger feelings; antecubital arteriovenous differences of more than 15 mg. per 100 cc. were never associated with hunger; values staying near 0 for any length of time were always associated with hunger.

In uncontrolled diabetes mellitus, a similar picture was obtained; blood sugar values had to be forced up through ingestion of food to levels where arteriovenous differences were introduced for ravenous hunger feelings to be satisfied. Cortisone administration accompanied by increased appetite caused an elevation of absolute glucose levels but a decrease in  $\Delta$ -glucose.

The effect of epinephrine deserves special mention since it represents an apparent exception to the general rule. Administration of epinephrine caused an immediate increase in blood glucose; it drastically reduced or eliminated any effect of hunger. However, at the same time, it decreased peripheral  $\Delta$ -glucose to levels near 0. Although it may be an oversimplification to ascribe this seeming contradiction to one of the many physiologic effects of epinephrine, it is worth noting that epinephrine introduces a differential between peripheral and central blood flow.<sup>13</sup> By the same token, experiments conducted on animals demonstrate that, whereas it decreases peripheral  $\Delta$ -glucose values, it increases carotid-jugular glucose differences; thus it not only produces hyperglycemia but also in-

creases the proportion of glucose made available to the nervous centers.\*

Insulin treatment first causes a fall in blood sugar owing to increased peripheral utilization of glucose. In a second phase, a compensatory rise takes place that is secondary to decreased utilization of glucose in the periphery.<sup>15</sup> Delta glucose values rapidly decline when the blood sugar falls to or below post-absorptive levels. The occurrence of increased hunger after insulin administration is therefore easily

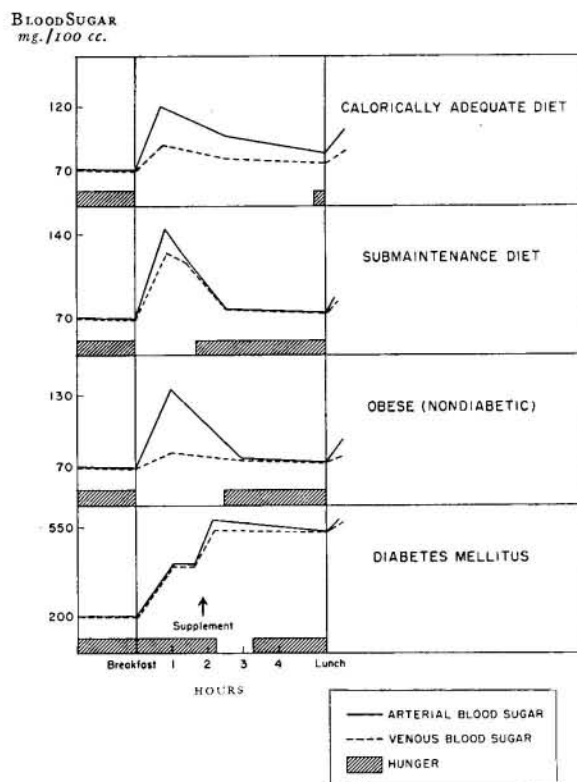


FIGURE 1. Typical Morning Correlations of  $\Delta$ -Glucose and Hunger Feeling.

The size of the  $\Delta$ -glucose (peripheral glucose arteriovenous difference) correlates with hunger feelings. No hunger feeling appears if the  $\Delta$ -glucose is greater than 10 mg. per 100 cc.

interpreted if hunger is seen as a direct response to carbohydrate deprivation.

In hyperthyroidism, alimentary hyperglycemia typically occurs and is followed regularly by a postalimentary hypoglycemia. It has been suggested<sup>16</sup> that accelerated metabolism of glucose takes place in the hyperthyroid patient and that the alimentary hyperglycemia may be only a manifestation of starvation diabetes that follows rapid depletion of carbohydrate stores. It appears that the metabolic hypoglycemia of hyperthyroidism

\*Keller and Roberts<sup>14</sup> recently demonstrated that glucose consumption of hypothalamic tissue is increased in vitro within a few minutes of the administration of epinephrine.

may thus be related to the increased food intake characteristic of this condition.\*

The possibility that the "feeding centers" in the lateral hypothalamus represent the sensitive area with facilitatory properties in terms of eating mechanisms has been discussed by Brobeck.<sup>18†</sup> In the glucostatic view proposed here these centers would represent the glucoreceptors. There is an obvious need for a mechanism that would translate available blood glucose into variations in the physiologic state of the tissues. Such a mechanism is suggested by the observation that a drop in serum inorganic phosphate and in potassium consistently accompanies large  $\Delta$ -glucose values.<sup>12, 20, 21</sup> It is possible that the passage of potassium ions into the glucoreceptor cells along with the glucose phosphate represents the point at which effective glucose level is translated into an electric or neural mechanism.

It is recognized that hypothalamic impulses still have to be interpreted, integrated and acted upon by the cerebral cortex; that other afferent impulses (gastric hunger pangs, in particular) also play a role in determining conscious states of hunger; and that other psychologic and physiologic factors may intervene to modify appetite at least temporarily. Conditioned reflexes, particularly in the dog, and habits in man also play an important role. Still, although feelings involving desire for food or satiety are not in any sense quantifiable, they represent a conscious expression of one of the most precise regulatory devices in biology. The glucostatic mechanism suggested here seems to provide a basis for such a precise regulation. It may be added that, because of the established decrease by available glucose of the rate of fat<sup>22</sup> and amino acid<sup>23</sup> utilization in non-nervous tissue, and probably of the rate of gluconeogenesis as well,<sup>24</sup> the regulation of food intake is easily integrated into the general regulation of metabolism.

Finally, it may be noted that the glucostatic theory seems to permit interpretation of certain types of alteration of the regulation of energy intake, in particular hypothalamic obesity,<sup>25</sup> the hereditary obese hyperglycemic syndrome of mice<sup>26</sup> and at least one form of human obesity.<sup>27</sup> The demonstration<sup>28</sup> that, in the hereditary obese-hyperglycemic syndrome of mice, the alpha cells of the islands of Langerhans oversecrete a hormone with hyperglycemic, glycogenolytic and antiinsulin properties opens the possibility that this hormone plays a major role in the regulation of food intake and in the etiology of obesity.

The broadening of the initial theory and its application to special cases were evolved in collaboration with Dr. T. B. Van

Itallie, for two years a member of the Department of Nutrition, Harvard School of Public Health, and now at St. Luke's Hospital, New York City. The work summarized here was done with the collaboration of Dr. Rachel Beaudoin, a former graduate student in the Department, now at the University of Montreal, and of Miss Margaret Bates, also a graduate student. I am also indebted to Dr. Fredrick J. Stare, head of the Department, for his constant support, interest and encouragement.

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\*It has recently been shown<sup>17</sup> that, in the cold, carbohydrate metabolism is also accelerated and glycogen reserves are decreased. A similar situation is known to prevail in growth.

†It was later demonstrated that electric stimulation of this lateral area causes an increase in food intake.<sup>19</sup>