RECENT ADVANCES IN OUR KNOWLEDGE CONCERNING THE CAUSES OF GLYCOSURIA*

THOMAS B. FUTCHER, M.B.

Associate Professor of Medicine, The Johns Hopkins University
BALTIMORE

Our views concerning carbohydrate metabolism in health and disease are constantly changing. New facts are gradually being added to our knowledge of the subject. In attempting to explain the causes of diabetes we have been forced to abandon various theories in succeeding decades. The accumulated results of innumerable investigators may make obsolete to-day a theory which seemed to hold good yesterday. Profiting by this experience, we must ever bear in mind that we should not be carried away by any new theory that is advanced to explain diabetes, even though it may be based on accurate experimental research.

In all cases of diabetes, with the exception of the experimental phlorizin diabetes, it is generally conceded that the appearance of the sugar in the urine is dependent on the existence of a hyperglycemia. It has generally been held that the glucose content of the blood normally ranges between 0.1 and 0.2 per cent., although Jacobson, working under Cushing's direction in the Hunterian Laboratory at the Johns Hopkins University, believes that these figures are too high and that the normal content is approximately 0.08 per cent. Undoubtedly some regulatory mechanism controls the glucose content of the circulating blood, for in the healthy individual it is found that, even after a meal rich in carbohydrates, the percentage of glucose in the circulating blood remains within very narrow limits. The carbohydrates in the food are stored up after a meal in the liver and muscles in the form of glycogen. Glycogen is believed to be gradually reconverted again into glucose and given up to the tissues as they need it for the production of heat and energy. Whenever the glucose content of the circulating blood rises above the physiologic limit a hyperglycemia results and the excess then passes over into the urine and produces either a transitory glycosuria or a permanent glycosuria, as in true diabetes mellitus.

The explanation of a transitory or a permanent glycosuria therefore rests on the determination of the cause or causes of the hyperglycemia. An excess of glucose in the circulating blood may be conceived as occurring in one of two ways. 1. It may be due to an overproduction of glucose from the glycogen of the liver. 2. It may be due to an inability of the tissues, particularly the muscles, to destroy the glucose, or, in other words, to defective oxidation. Each of these theories has been supported by able investigators in the past, but the trend of opinion at the present time is in favor of the overproduction theory.

THE RELATIONSHIPS OF THE DUCTLESS GLANDS TO CARBOHYDRATE METABOLISM

Investigations in recent years have shown that the internal secretions of the ductless glands have a marked influence on carbohydrate metabolism in health and disease. The internal secretions which have been shown up to the present to possess this relationship are those of

the pancreas, adrenals, thyroid, parathyroids and pituitary. Strictly speaking, the pancreas is not a ductless gland, but it incorporates within its substance the islands of Langerhans, which are really ductless glands. According to our present knowledge, it is in these islands that the internal secretion of the pancreas which so strongly influences carbohydrate metabolism is produced. It may be shown later that other ductless glands, such as the thymus, ovary, etc., must be added to the list. The function of influencing carbohydrate metabolism is only one of the numerous activities each of these glands is known to possess.

As Cammidge¹ recently said in a most interesting article bearing on this subject, "It is now believed that chemical correlation and chemical control exists between practically every gland and tissue of the body." It has been possible, in some instances, to isolate the specific chemical activator or "hormone" through which one tissue activates another. It has been shown by Bayliss and Starling² that the hydrochloric acid secreted by the stomach acts on the mucous membrane of the upper part of the intestine and gives rise to a substance to which they have given the name "secretin." The latter, when absorbed into the blood, travels to the pancreas and stimulates it into functional activity and causes a flow of its secretion. Other similar examples might be cited.

THE INTERRELATIONSHIP OF THE ACTION OF THE DUCTLESS GLANDS

It will be of interest to discuss at this point the noteworthy results of Falta, Eppinger and Rudinger³ who have devoted special attention to the study of the interrelationship of the action of the internal secretions of the ductless glands. They believe that the removal of a gland with an internal secretion works in two ways. There is, first, the direct result of the absence of its secretion, and secondly, the indirect effect due to the disturbance of metabolism consequent on its relations to other glands. They hold that the ductless glands may be divided into two groups according to the disturbances of the metabolic functions of the body to which alterations in their secretory activities may give rise. They divide them into (1) an accelerator group and (2) an inhibitory group. To the accelerator group belong the thyroid, the adrenals and the hypophysis, since it has been shown that a study of the reactions of the body to injections of preparations from these organs and observations on the result of experimental interference with their functions suggest that all three increase protein exchange; the adrenals cause mobilization of carbohydrates, and the thyroid causes increased fat destruction. To the inhibitory group belong the pancreas and parathyroids, because it has been shown that both retard protein destruction, the pancreas being the more active; further, both restrain the mobilization of carbohydrates, the pancreas again being the more active of the two. The pancreas also causes a decrease in fat consumption. These investigators have correlated their results and have come to the following conclusions:

1. The internal secretions of the thyroid and pancreas mutually retard each other's activities.
2. The internal secretions of the pancreas and chromaffin system mutually retard each other's action.
3. The internal secretions of the thyroid and chromaffin system mutually increase or accelerate each other's action.

* Read in the Symposium on Genital Pathology and Surgery in the Section on Genito-Urinary Diseases of the American Medical Association, at the Sixty-Third Annual Session held at Atlantic City, June, 1912.

* Because of lack of space this article is abbreviated in THE JOURNAL. The complete article appears in the Transactions of the Section and in the author's reprints.

1. Cammidge, P. J.: Relation of the Ductless Glands to Glycosuria, Practitioner, London, 1912, lxxxviii, 237.

2. Bayliss and Starling: Proc. Roy. Soc., 1902, lxi, 352.

3. Falta, W., Eppinger, H., and Rudinger, C.: Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion, Ztschr. f. klin. Med., 1908, lxi, 1.

In explanation it may be said that the chromaffin system has reference to those groups of cells which have a particular affinity for the salts of chromic acid. These cells are found chiefly in four situations: (1) they occur in the adrenals, where the largest collection of such cells occurs; (2) they accompany the nerves of the sympathetic system; (3) they occur in abundance in the retroperitoneum; (4) they are grouped together in the pelvis to form the so-called Zuckerkindl organ. For all practical purposes, the word "adrenals" may be substituted for "chromaffin system" in the above classification of the accelerator and inhibitory activities of the internal secretions of the ductless glands.

THE RELATIONSHIP OF THE PANCREAS AND ADRENALS TO CARBOHYDRATE METABOLISM

Owing to the intimate relationships that are now believed to exist between the internal secretions of the pancreas and adrenals and carbohydrate metabolism the functions of these two glands will be considered together.

Although a relationship between the pancreas and carbohydrate metabolism had been suspected for nearly a century, it remained for von Mering and Minkowski⁴ to demonstrate in 1889 that complete removal of the gland in dogs was invariably followed by a fatal diabetes, with practically all the features as observed in severe cases in man. They subsequently showed that the diabetes was not dependent on the loss of the external secretion of the glands but rather on the absence of some internal secretion which is poured directly into the blood- or lymph-stream.

Lépine believed that this internal secretion was of the nature of a "glycolytic ferment," whose presence in the circulating blood was necessary for the proper combustion of the glucose of the blood.

In 1900 Opie found that a certain percentage of cases of chronic interstitial pancreatitis were accompanied by diabetes. Histologic examination of the pancreas in all cases in which the gland was sclerosed showed that glycosuria occurred only in those cases in which there was extensive destruction of the islands of Langerhans. Later Opie showed that many cases of diabetes with apparently normal-looking glands macroscopically showed on microscopic examination extensive hyaline degeneration of the islands of Langerhans. This important observation led to two natural inferences: first, that the internal secretion of the pancreas which influenced carbohydrate metabolism was probably produced by the islands of Langerhans; and second, that it might subsequently be shown that many if not all cases of diabetes would probably be found to be due to degenerative changes in the islands of Langerhans. Subsequent investigations have shown that there are many cases of diabetes which cannot be explained in this way, for it has been found that in certain cases of diabetes the islands are intact.

The publication of Cohnheim's⁵ experiments in 1903 seemed to afford a satisfactory explanation as to how the carbohydrates are utilized in the body under normal conditions and by inference gave us an explanation of the cause of diabetes. According to his view, in order that carbohydrate metabolism should be properly carried on, it was necessary that some substance in the muscle juice be activated by a hormone contained in the internal secretion of the pancreas. If for any reason this pancreatic hormone be lacking, the glucose would not be utilized in the muscles and would accumulate in the circulating

blood, producing a hyperglycemia and a consequent transitory or permanent glycosuria. Although Cohnheim's views were hailed with enthusiasm they have not been universally accepted. It is quite possible that there is some interaction between the internal secretion of the pancreas and muscle juice, which results in the production of a substance which favors the combustion of carbohydrates. More light, however, needs to be shed on this phase of the subject.

Although the influence of the internal secretion of the pancreas on carbohydrate metabolism cannot be questioned, its method of action, as we have already seen, is uncertain. There is a growing belief that the internal secretions of the pancreas and adrenals are complementary to one another and that each exerts its influence on carbohydrate metabolism by regulating the formation of glucose from the glycogen of the liver.

Zuelzer¹¹ is responsible for the theory, now possessing many adherents, that the internal secretion of the adrenals influences carbohydrate metabolism by "mobilizing" the carbohydrates of the body, particularly of the liver. In other words, unless its action is counteracted, the function of the internal secretion of the adrenals is to set free the carbohydrates of the liver and other tissues, causing a hyperglycemia with consequent glycosuria. Zuelzer further showed that an antagonistic action exists between the adrenal secretion and the internal secretion of the pancreas.

Zuelzer thinks that the internal secretions of the adrenals and pancreas normally react on each other within the liver in such a way as to maintain the normal sugar production from the glycogen and consequently glycosuria is prevented. As Falta, Eppinger and Rudinger³ have shown, the internal secretions of the pancreas and adrenals mutually retard the action of each other. Thus, when Zuelzer used the liver of a depancreatized dog, the output of sugar in the urine was increased because there was no pancreatic secretion to retard the "mobilizing" action of the adrenal secretion on the glycogen of the liver. In the second experiment, in which the liver from a dog with adrenal diabetes was used, the further increase in the sugar output was due to the "mobilizing" action of the epinephrin that had been used in inducing the adrenal diabetes. He further found that when the function of both the adrenals and pancreas was destroyed glycosuria failed to occur. In the depancreatized dog he found that glycosuria did not occur if the adrenal veins were ligated. In a large number of pancreatectomies performed by Zuelzer, glycosuria always followed except when the adrenal veins were also tied off. He believes that one of the most important functions of epinephrin is its influence on sugar metabolism in the liver.

Accepting for the time being this view of carbohydrate metabolism, the hyperglycemia in pancreatic diabetes is believed to be due to the absence of the restraining hormone normally produced by the pancreas. The "mobilizing" action of the epinephrin consequently causes an overproduction of sugar in the liver with resultant excess of glucose in the circulating blood followed by the inevitable glycosuria.

Undoubtedly the nervous system has a marked influence on carbohydrate metabolism. Owing to the intimate relationship that is known to exist between the sympathetic and autonomic nervous systems and the chromaffin system, it is easy to conceive how psychic

4. Von Mering and Minkowski: *Centralbl. f. klin. Med.*, 1889, p. 394.

5. Cohnheim: *Ztschr. f. physiol. Chem.*, 1903, xxxix, 336.

11. Zuelzer, G., Dohrn, M., and Marxer, A.: *Neuere Untersuchungen über den experimentellen Diabetes*, *Deutsch. med. Wchnschr.* 1908, xxxiv, 1380.

disturbances and disturbances particularly of the autonomic system can stimulate the chromaffin system and cause an overproduction of the internal secretion of the adrenal glands, leading to a "mobilization" and overproduction of glucose in the liver and other storehouses for carbohydrates. This would lead to hyperglycemia and glycosuria. It was formerly thought that the glycosuria that resulted from Claude Bernard's puncture of the floor of the fourth ventricle was due to direct stimulation of the liver through its nervous connections. It has been found, however, that if the left adrenal is cut off from the left sympathetic nerve, no sugar appears in the urine after the medulla has been punctured, and it is now believed that the stimulus is transmitted by the left sympathetic nerve to the left adrenal, whence it is passed to the right adrenal by the connecting nerves. As a consequence of the medullary puncture the adrenals secrete more actively and the increased flow of the adrenal secretion in its turn brings about an excessive output of sugar by the liver. A number of toxic influences possibly act in the same way, the glycosuria to which they give rise being partly the result of the action they exert on the diabetic center in the medulla, and partly an effect of their stimulating action on the sympathetic nerves, or on the adrenals directly, thus, in any case, causing hyperfunction of the chromaffin system, with consequent overproduction of sugar by the liver.

THE RELATIONSHIP OF THE THYROID AND PARATHYROIDS TO CARBOHYDRATE METABOLISM

Every observer who has had a wide experience with diseases of the thyroid gland has been impressed with the fact that in hyperthyroidism and hypothyroidism there is a marked disturbance in carbohydrate metabolism. Kraus, Ludwig, Chvostek and many others have observed that spontaneous glycosuria is not uncommon in exophthalmic goiter. Further, it has been shown that the administration of small amounts of carbohydrates in this condition often causes a temporary glycosuria. In other words, in overactivity of the gland the tolerance for carbohydrates is reduced.

On the other hand, in hypothyroidism, myxedema, the occurrence of spontaneous glycosuria is so rare as to practically never occur.

THE RELATIONSHIP OF THE PITUITARY TO CARBOHYDRATE METABOLISM

We are chiefly indebted to Cushing¹⁸ and his associates for the demonstration in the last few years of the fact that the pituitary gland contains in its internal secretion a hormone that has a powerful influence on carbohydrate metabolism. It is thought that one of the functions of the pituitary glands is to preside over the regulation of carbohydrate tolerance. It will be impossible here to give a description of the gross and histologic anatomy of the pituitary gland, but it may be of interest to enumerate the important functions that have been demonstrated to be possessed by its two lobes.

I. FUNCTIONS OF THE ANTERIOR LOBE

1. It influences body growth. If a hypersecretion (hyperpituitarism) occurs during the years of the individual's growth, gigantism results. If the hyperactivity occurs after the individual's full growth has been attained then acromegaly results. If a diminished secretion (hypopituitarism) occurs, a form of infantilism results, to which attention was first drawn by Fröhlich. This condition is known as Fröhlich's syndrome, or

"dystrophia adiposa genitalis." It is characterized by small stature, amenorrhea in women, infantile genitalia in both sexes, hypotrichosis, excessive deposition of fat and increased carbohydrate tolerance.

2. Injections of extract of the anterior lobe cause an increase in temperature.

3. Extract of the anterior lobe increases thyroid function.

II. FUNCTIONS OF THE POSTERIOR LOBE

1. Its extract causes an increase in blood-pressure.

2. It is a powerful diuretic.

3. It has a remarkable influence over carbohydrate metabolism.

4. Schaefer and Vincent think it also contains a substance which may lower blood-pressure.

5. Rinon and Delille think that the extract stimulates the function of the adrenals and lessens that of the thyroid.

It is most interesting that the hypophysis, which previous to two decades ago was considered without function, has now been shown to possess so many important properties. Cushing has shown in dogs that the gland is essential to life, for complete removal of the gland invariably results in death. It is believed that it is the anterior lobe that is necessary to life, for its removal alone will produce death. Cushing holds that the secretion of the pituitary passes by way of the infundibulum into the cerebrospinal fluid in the third ventricle, for he has shown that death also occurs if the hypophyseal stalk is excised while the gland is left behind.

It is the influence which the pituitary secretion of the posterior lobe has on carbohydrate metabolism that concerns us most here. It was Cushing and his co-workers who first demonstrated by partial hypophysectomies on dogs that it is the posterior lobe of the pituitary which influences carbohydrate tolerance. It has now been definitely shown that hyperpituitarism, clinically represented by gigantism and acromegaly, is nearly always accompanied by a lowering of the individual's tolerance for carbohydrates resulting frequently in either a transitory or permanent glycosuria. On the other hand, hypopituitarism, clinically represented by the various types of pituitary infantilism, is practically always accompanied by an enormous increase in the tolerance for carbohydrates, so that the patient can ingest from two to five times the amount of glucose and other sugars that a normal individual can without alimentary glycosuria occurring.

It was in 1889 that Marie first pointed out the association of acromegaly with pituitary enlargement, although he had described the disease in 1886. Since 1889 there have been numerous reports of cases in which glycosuria has been found in association with acromegaly. Out of 176 cases of the disease reported in the literature up to 1908, Borchardt found that glycosuria occurred in 35.5 per cent. of the cases. Cushing comments on the discordant results which different observers have found in the study of carbohydrate tolerance in acromegaly. Some observers have found an actual glycosuria, others only a diminished tolerance, and still others a decidedly increased tolerance. Cushing is of the opinion that these discrepancies are entirely dependent on the stage of the disease in which the case comes under observation. He holds that the adenomas or other tumors of the anterior lobe of the pituitary, which cause the characteristic features of acromegaly, also produce hyperplasia and overactivity of the posterior lobe in the early stages (hyperpituitarism), with the result that an excess of the secretion reaches the circulation and a lowered tolerance to carbohydrates ensues. In the later stages a hypoplasia with consequent destruction and lack of secretion of the

18. Cushing, Crowe and Howmans: Bull. Johns Hopkins Hosp. 1910, xxii, 127. Cushing, H., Goetsch, E., and Jacobson, C.: Bull. Johns Hopkins Hosp., 1910, xxii, 165.

posterior lobe occurs (hypopituitarism), with the result that there is an increased tolerance to carbohydrates.

CONCLUSIONS

1. It is unwise, from past experience, to accept as settled any new theory advanced to explain the cause of diabetes mellitus.

2. It must now be accepted as positively proved that not only the pancreas but also the adrenals (chromaffin system), thyroid, parathyroids and pituitary have a very important influence on carbohydrate metabolism.

3. Although lesions of the pancreas have been found in a considerable percentage of cases of diabetes, it is now clear that morbid changes in that organ will not explain all cases, even when alterations in the islands of Langerhans are also taken into account. The essential and primary disturbance may be in one or another of the ductless glands.

4. There is undoubtedly a marked correlation of the internal secretions of the ductless glands. Thus the internal secretions of the adrenals (chromaffin system) and pancreas mutually retard the action of each other. The most recent theory concerning carbohydrate metabolism is that first advanced by Zuelzer and now supported by many physiologists. According to this view, one of the important functions of the adrenals is to "mobilize" or set free the carbohydrates in the liver and possibly in other storehouses also. Under normal conditions, however, this influence is counteracted or exactly balanced by the hormone contained in the internal secretion of the pancreas, and we have a constant normal flow of sugar from the liver. When, however, the chromaffin system is for any reason overstimulated, as it may be through the sympathetic nervous system, there is an overproduction of the "accelerator" hormone of the adrenals; the "retarding" hormone of the internal secretion of the pancreas is more than counterbalanced, the glycogen in the liver is rapidly "mobilized" or set free and a hyperglycemia and glycosuria result. A similar result occurs in the cases of so-called pancreatic diabetes. Here the adrenal hormone may be normal in amount, but owing to the pancreatic disturbance the pancreatic hormone is absent or diminished and again the adrenal hormone is enabled to mobilize the glycogen of the liver.

5. A somewhat analogous explanation may subsequently be found to explain the glycosurias in pituitary and thyroid diseases.

6. The theory that hyperglycemia results from deficient consumption or oxidation of glucose in the tissues has fewer adherents than formerly. It may still be shown, however, that Cohnheim's theory is in part correct. At present the trend of opinion is in favor of the view that the hyperglycemia and glycosuria are dependent on overproduction of sugar in the liver as expressed under Conclusion 4.

23 West Franklin Street.

ABSTRACT OF DISCUSSION

DR. ROBERT T. MORRIS, New York: In some cases of "gall-stones without symptoms" glycosuria is the chief symptom. After removal of a gall-stone or drainage of a septic gall-bladder the glycosuria ceases. One of our best-known New York surgeons suffered from lumbago for years and was incapacitated for work a large part of the time by a glycosuria; when gall-stones were removed the lumbago and glycosuria ceased. This relationship between glycosuria and gall-stones we have assumed to be due to influence on the islands of Langerhans by the gall-stones, the reflex irritation causing

a congestion of the pancreas to the point of lessened efficiency. Is that the correct view, or is a toxic impression made on the pancreas by an infected gall-bladder neighbor?

DR. EMIL GOETSCH, Baltimore: In a paper published together with Drs. Cushing and Jacobson in the *Bulletin of Johns Hopkins Hospital*, June, 1911, some facts were pointed out concerning carbohydrate metabolism in hypophysectomized animals, and its relationship to the posterior lobe secretion. The manner of hitting on these facts was interesting. I was studying the growth of dogs after hypophysectomy, and noticed that in cases of total or "near total" removal of the pituitary body there was produced frequently a transient glycosuria, which appeared almost immediately after the operation and disappeared in two or three days. This was inexplicable until we began to test the carbohydrate tolerance of these animals before and after operation. It was found that after removal of the hypophysis either "near total" or even of the posterior lobe there was found invariably an almost immediate great reduction in the carbohydrate tolerance to a point often of spontaneous glycosuria, to be followed in the course of about ten days by recovery of the normal tolerance and then a gradual increase during a period of a week or two more until the tolerance reached often to double the normal. Cane-sugar and glucose were used both by mouth and intravenously in these tests. It was found also that we could reduce this overtolerance by injecting intravenously or hypodermically extract of hypophysis. A comparable action was found to exist in the thyroid gland indicating a similar influence of these two glands at least on some features of carbohydrate metabolism. It is still an open question as to how the pituitary secretion (posterior lobe) exerts this influence. We felt that it was possibly due to some influence on the pancreas or liver. For example, we found that after hypophysectomy the liver cell was filled with fat; there was an apparent transformation of glycogen into fat with storage of the latter. Oxidative processes in the body were also low. There was frequently subnormal temperature which could be made to rise until a definite febrile response of 3 or 4 degrees could be obtained. Then, also, in a number of clinical cases with hypophyseal disease a hyperglycemia was observed. These are a few of the facts concerning hypophyseal activity which bear very closely on the problems of glycosuria as brought out by Dr. Fletcher.

DR. T. B. FUTCHER, Baltimore: I am not prepared to give an explanation of the manner in which glycosuria is brought about by an attack of gall-stone colic. Two possible explanations are conceivable. One is that there may be some direct effect on the liver itself, causing it to give up the glycogen in the form of glucose, or it may exert its effect through the sympathetic nervous system, which we know is so intimately associated with the chromophilic system and the adrenals; and there may be at the time a hypersecretion of the adrenals which leads to a mobilization of the carbohydrates in the liver with resultant hyperglycemia. Whether that is the explanation or not, I cannot say.

It was demonstrated in 1859 that puncture of the fourth ventricle led to a temporary glycosuria. Claude Bernard believed that the glycosuria was due to certain impulses sent to the liver. More recent work has shown that that explanation is probably not true. If one severs the nerves going to the left adrenal, a hyperglycemia does not follow the medullary puncture. The latest explanation for the glycosuria that follows certain traumatism and fractures of the base of the brain is that impulses are sent out by way of the sympathetic system to the left adrenal, and thence to the right adrenal, causing a hypersecretion which mobilizes or sets free the glycogen of the liver producing a hyperglycemia and transitory glycosuria.

Factory Hygiene.—Men think as they are trained to think. Therefore, an educational campaign should precede hygienic changes in factory conditions and processes. Let us make it our business as physicians to teach the cost of the human mechanism, the mechanics of humanity and the extravagance of human waste.—W. Talbot in *Am. Jour. Public Health*.