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THE GLYCOSURIAS.

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Gentlemen of the Southern Medical Association: I wish to express my sincere appreciation of the honor conferred upon me in being asked to address such a learned and representative body of men as are included in this Association. I have chosen for my theme not a disease, but a symptom—glycosuria—the subject of more investigation and more controversy perhaps than any other single disease condition. At the same time it must be kept clearly in mind that glycosuria is a symptom and not a disease, since failure in the past to distinguish properly between glycosuria and diabetes has been the occasion of much confusion and useless investigation.

In discussing in a limited space a subject about which so much is known, and yet so little is certain, brevity demands that one speak with a degree of positiveness, which I trust you will pardon.

Any discussion of the glycosurias or at

tempts to classify them should include a consideration of what is known as the paradoxical law. This law concerns itself with the assimilation limits of sugars; to quote the words of Allen, "If with a given dose any utilization of carbohydrate occurs at all, an increase of the dose causes the utilization of a larger quantity."

In all glycosurias, except one, the limit to the ability of the tissues to utilize sugar is relative, not absolute. Should dextrose be given an individual already glycosuric, not all of this added sugar serves to augment the glycosuria, for at least a part is utilized by the tissues, and if he is given still further sugar, even more is consumed by the tissues, and yet more if more is added. At no time does the increment of glycosuria account fully for the additional sugar administered, whether this be by mouth or subcutaneously. Diabetic glycosuria offers the only exception to this law.

Thus, fully developed diabetes mellitus is distinguished by an absolute limit of sugar tolerance. If the patient with diabetes is already glycosuric, he responds to the administration of additional dextrose by an equal and frequently surpassing glucose increment in the urine.

And in still another way the diabetic organism shows its peculiar inability to handle sugars. To the diabetic, sugar is a diuretic, while to others it is anti-diuretic. This

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may be explained upon the hypothesis that sugar ordinarily circulates in chemical combination with some other substance which makes of it a colloid, and, according to the law of colloids, an anti-diuretic. In the diabetic, however, sugar is permitted no such combination and must circulate in its crystalline state, exerting the diuretic influence of crystalloids.

To distinguish clearly between diabetes mellitus and other conditions accompanied by glycosuria, I should define diabetes as a progressive disease of carbohydrate metabolism, characterized by hyperglycemia, by a form of glycosuria which fails to obey the paradoxical law and by the profuse diuresis which follows the administration of dextrose.

With this understanding, I have divided the glycosurias into diabetic and non-diabetic, according to the following plan:

NON-DIABETIC	Alimentary Tract	Simple Hunger-vagabond Dyspeptic Cachectic
	Liver	Mineral poisons Bacterial poisons Drugs Foreign Albumins and Serums Pregnancy Asphyxia
	Kidney	Diuretics Clinical glycosuria Phloridzin (Glycogen-Dextrin)
	Nervous System	Sympathetic-Piqure Asphyxia Infections Heat and Cold Fever Adrenal Thyroid Parathyroid Hypophysis
DIABETIC	Pancreas	
	Nervous System	

Sugar appears in the urine under the greatest variety of conditions. Why is it

that the small amount of sugar which normally circulates in the blood to the extent of 0.063 per cent does not make itself evident in the urine? To assume that the kidney acts as a sort of dam, over which the sugar flows when its height in the blood exceeds a given point, say 0.2 per cent, does not satisfactorily explain, for as we have seen, the limit of the ability of the tissues to utilize sugar is relative and not absolute.

The explanation may be that the kidney excretes only such sugar as appears in the blood in the crystalloid state, normal blood sugar being protected by some sort of chemical union. A union of blood sugar with lecithin has been demonstrated, the so-called Jecorin, and we speak of "Jecorin-like substances." When sugar in excess of the combining powers of the tissues is thrown into circulation, that portion which reaches the kidney in the crystalloid state is excreted. This view which permits the kidney no quantitative sense or regulatory power seems to me the rational one.

The belief that glycosuria presupposes hyperglycemia is usually, though not invariably, true, for it is occasionally seen both in human diabetes and in animal experiment that glycosuria persists in the presence of normal blood sugar.

Man's tolerance for carbohydrates varies within rather wide limits. Among other conditions, it depends upon whether the sugar is taken fasting, or with other foods. The rate of absorption is important. It is arbitrarily assumed that the individual who can take only 100 grams of sugar without the appearance of dextrose in the urine possesses a lowered carbohydrate tolerance, and various clinical tests depend upon this assumption. Von Noorden administers the sugar fasting. Naunyn gives about 100 grams of bread and 250 c.c. of milk, and then two hours later 100 grams of sugar. Most individuals can utilize sugar considerably in excess of this minimum.

The least important perhaps of all gly-

cosurias is that arising in the alimentary tract. It means simply that carbohydrates beyond the assimilative powers of the tissues have been eaten and absorbed.

Alimentary glycosuria, the so-called vagabond glycosuria, dyspeptic glycosuria, and that appearing in various cachectic states, practically all belong together. In the chronic starvation of certain dyspeptic and cachectic states, the tissues seem to become unused even to normal metabolic demands, and when there is given what under other circumstances would be regarded as normal carbohydrate diet they are taken by surprise, so to speak, and are unequal to the emergency. Thus, a certain amount of sugar remains uncombined and is excreted by the kidneys. This may be regarded as physiological or pathological, just as you please to view it.

Whether an alimentary glycosuria long continued can produce real diabetes is still a field for experiment. Today's evidence, based on both clinical observation and animal experiment, would indicate that the excessive use of sugar in the normal individual can never produce diabetes.

Because of its prominent and at times spectacular role in carbohydrate metabolism, the liver has been held responsible for various glycosurias, including even that of diabetes mellitus. But knowledge gained through animal experiment tends more and more to exonerate the liver and to place much of the blame elsewhere, frequently upon the nervous system. True, the liver does play an important contributory part in most of these states, but the blame for originating the glycosuric impulse must be sought elsewhere.

Numerous poisons, phosphorus, arsenic, and foreign albumins and serums can all, through their influence upon the liver produce glycosuria. The glycosuria of pregnancy and that of acute yellow atrophy perhaps belong here. Some of these agents, such as phosphorus, for instance, probably act through destruction of the liver cells,

causing them to suddenly release their stored glycogen. Many other poisons exert their influence first upon the central nervous system and secondarily upon the liver through its nerve supply. The occasional glycosuria seen in the bacterial infections probably arises in this manner. The glycosuria of asphyxia, no doubt, is of nervous origin. It has been suggested that the appearance of sugar in the urine during pregnancy may be due to hyperthyroidism or perhaps to an unusually large adrenalin output with its consequent glycolytic influence upon the liver.

As a result of animal experiment we must ascribe to the liver a purely passive role in the production of various glycosurias. This organ is intimately concerned in the metabolism of carbohydrates, proteids, and fats, and is influenced by many factors, a disturbance of any one of which may so upset the normal course of metabolism as to lead, among other symptoms, to glycosuria.

A long continued, true hepatic glycosuria does not exist. Any injury or stimulus which will cause the liver to suddenly release its stored glycogen will temporarily produce glycosuria, but a permanent diabetes never results, and even those chronic diseases of the liver which are accompanied by most extensive parenchyma loss do not produce glycosuria. All of these so-called hepatic glycosurias are transient and are limited to the duration of the exciting cause, and no one has been able to connect them in any convincing manner with diabetes mellitus.

There is evidence, however, for assuming a genuine renal glycosuria. That produced by the diuretics, caffeine, for instance, is frequently the result of an untoward influence of the drug upon certain of the cerebral centers. In addition to this, a diuretic can, through the resulting polyuria, aid in the excretion of sugar where there exists a mild hyperglycemia which otherwise is not of sufficient intensity to lead to glycosuria. It must be borne in mind, however, that

polyuria alone can never be the cause of glycosuria, diabetes insipidus being the best evidence of this.

Phloridzin glycosuria unquestionably represents a true renal type, but the earlier belief that this drug increased the permeability of the kidney epithelium to sugar is giving way to another view. There is ground for belief that sugar thus excreted comes from some larger and more complex molecule, with which phloridzin is perhaps united in chemical combination. Numerous instances are known in normal metabolism where the pairing of some substance with another leads to its excretion, and it is conceivable that phloridzin may unite itself to some colloidal sugar compound and thus render it liable to a splitting within the kidney with consequent excretion of the sugar radi-
cle.

Numerous clinical instances of renal glycosuria have been reported, it being not unusual to observe nephritis and glycosuria in the same patient. The glycosuria in such cases, however, is usually slight and temporary and is frequently dependent upon errors in diet with consequent hyperglycemia. It is, of course, not impossible to have nephritis and diabetes existing in the same patient, though there is an old belief among clinicians that the onset of nephritis in a diabetic leads to lessened glycosuria and other evidences of improvement. Before judgment, however, is passed upon such cases, estimations of blood sugar as well as that in the urine should be made, and their relation to the paradoxical law should be tested.

The nervous system in the last analysis originates the impulse which leads to most glycosurias. That Claude Bernard's puncture exerts its influence by causing the liver to suddenly release its glycogen is shown by the fact that this symptom ceases when the store of glycogen has been exhausted, and that no sugar appears in the urine if previous to puncture the animal has, through exercise or fasting, consumed all of his gly-

cogen. Attempts to produce a permanent glycosuria analogous to diabetes by inflicting a permanent injury in this location have always failed of their purpose, even though the trauma persisted. Repeated and frequent piqûre gradually loses its effect, for the glycosuria resulting from each new operation is of ever less intensity. That this impulse is carried through the splanchnics is evidenced by the fact that if both nerves are cut no glycosuria results.

That the emotions have a very definite and real influence in the production of glycosuria is seen not only in clinical observation, but in animal experiment. Cats offer the best example of this among the lower animals, and the frequency with which sugar appears in the urine after the fright of being bound has given rise to the term "Fesselungs Glycosuria." In man, glycosuria and even diabetes, as a sequel of profound mental shock, is too frequently and reliably reported to admit of doubt, and I am constantly impressed with the powerful influence which the emotions exert upon the sugar output of diabetic patients.

The adrenals, thyroid, parathyroids, and hypophysis all have an influence, probably indirect and remote, in the production of glycosuria. By many writers, particularly those of the so-called polyglandular school, they have been endowed with diabetogenic powers. These glands, together with the pancreas, according to this view, bear to one another certain synergistic and antagonistic relations, the thyroid, adrenals and hypophysis forming one physiological group and the pancreas and parathyroids the other. It is said that the glands of the former group hasten metabolism and stimulate the sympathetic fibres, while those of the latter conserve metabolism and stimulate the autonomic nerves, the secretion of each being kept in check by the glands of the opposed group.

Hyperfunction of the adrenals is usually accompanied by transient, mild glycosuria, and hypofunction, such as is seen in Addi-

son's disease, is said to lead to increased sugar tolerance. Figure glycosuria does not appear if the rabbit has been deprived of both adrenals, and painting the surface of the pancreas with adrenalin will produce glycosuria.

Deductions which endow the adrenals with specific diabetogenic powers do not take cognizance of its complex functions. The adrenal medulla is in most intimate relationship with the sympathetic nervous system, being perhaps an integral part of it, and thus influences every organ supplied by these nerves. No one has demonstrated an increase of adrenalin in the blood of diabetics, and we sometimes see cases of adrenalinemia with normal sugar tolerance. In short, no antagonistic relation between the pancreas and adrenal has been proven, and the latter certainly plays no etiologic role in diabetes.

Hyperthyroidism is occasionally accompanied by glycosuria, and patients with the myxedema of hypothyroidism are said to have increased sugar tolerance, though exceptions to both of these rules are frequent. The glycosuria of increased thyroid activity is probably a toxic one, the result of excessive thyroid influence upon the liver. Here again no direct antagonism toward the pancreas has been shown. The parathyroids and the hypophysis in their relation to the pancreas have been comparatively little studied, but their influence in the production of glycosuria is probably indirect and remote.

None of these organs of internal secretion, excepting the pancreas, have at autopsy shown an anatomic relationship to diabetes, and there seems to be no good ground for looking upon them as in any sense truly diabetogenic.

Diabetes mellitus presents a form of glycosuria separate and distinct from all others, representing as it does a disease *sui generis*. Vast amounts of brilliant experimental work and painstaking clinical observation have brought us very close to an understanding of the etiology of diabetes, but a great deal

yet remains to be worked out. It would be fruitless to discuss the various theories which have been held from time to time and are now largely discarded. The polyglandular view of Falta and others which I have just discussed seem to me to belong to this category.

All evidence, both clinical and experimental, would indicate that the pancreas is the organ most intimately concerned in the production of diabetes. Conflicting views as to whether the islands of Langerhans represent separate physiologic structures or are immature, perhaps reserve. Acini do not concern us, for whatever their ultimate nature, they are the structures in which the pathological changes characteristic of experimental diabetes are most often found.

Allen, by removing varying amounts of the pancreas of dogs, produces at will diabetes of any degree. The mildest he calls diabetes levis, and the severest absolute form in which the tissues utilize no sugar is termed diabetes gravis. If a dog with diabetes levis is by appropriate diet kept sugar free his remnant of pancreas when he is finally killed appears perfectly healthy and the islets intact. If, however, food in excess of his carbohydrate tolerance is permitted, as evidenced by continued glycosuria, he enters finally upon a severe form of the disease, and rigid diet is no longer effectual in rendering the urine sugar free. If this dog is now killed the islands will be seen to have undergone certain characteristic degenerative changes.

The dog with a pancreas remnant representing one-eighth or perhaps one-ninth of the original gland, and consequent diabetes levis, whose carbohydrate tolerance has been exceeded only slightly or for a short time, shows changes in the islands which Homan believes to be evidence simply of stimulation. In other appropriately treated animals, changes which he regards as characteristic of regeneration may be found, and in those with grave and continued diabetes, the islets show a characteristic form of complete degeneration, which are best described in his

words: "The acinous tissue is normal and presents its usual content of zymogen. Remarkable alterations, however, are noticeable in the islands, of Langerhans. For the most part these structures, usually dense masses of closely-packed cells, have the appearance of irregular, coarse-meshed sieves. The cell outlines, the shrunken nucleus, a few mitochondrial filaments attached to fine shreds of protoplasm, alone are left. The secretory granules have disappeared." "Such changes are universally apparent in the pancreas of animals subjected to a rapidly fatal experimental diabetes. In instances of a less rapid manifestation of the disease, it is easy to see how islands may disappear or become altogether unrecognizable."

This demonstration of stimulation, of rest with regeneration, and of excessive activity with exhaustion and consequent degeneration, all depending upon whether or not the islet cells are able to meet the metabolic demands made upon them, is the most valuable contribution to the subject of diabetes which has been made in years. Its direct therapeutic application enhances wonderfully its value.

Why is it that such changes in the islets are not more frequently reported in the necropsy material from man? Many authors do report changes of this nature, while others deny their existence or at least their frequency in diabetes. Hanseman could not find that diabetes exhibited any unusual preponderance of island changes, though he found frequent disease of the acini and considered this characteristic of diabetes. Recently Labbé, Laiguel, Lavastine and Vitry have published their studies of the pancreas from nineteen diabetics and thirty-seven non-diabetics, in which they could trace no relation between diabetes and organic disease of the islands. Opie's observations to the contrary are well known. It is significant that those pathologists who have at their disposal the largest amount of autopsy material are most frequently adherents to the insular

theory. Weichselbaum, in 50 per cent of 185 cases of diabetes, found evidence of degeneration of the islet cells and describes, among other changes, hydropic degeneration identical with that described by Allen and by Homans. In addition, regenerative changes, similar to those of experimental diabetes, have been found in the same pancreas alongside evidences of degeneration. We cannot escape the fact that true diabetes identical with that in man can be produced experimentally in animals only by removal or destruction of a large part of the pancreas.

Nevertheless, as some one has remarked, a pathologist who is asked to examine pancreas specimens from a large amount of autopsy material, would have a hard time picking out those from diabetic patients. The most plausible explanation is that in man we are studying a relatively mild form of diabetes in which functional pancreatic derangement predominates as opposed in animals to the diabetes gravis of extensive organic disease.

Evidently the islands of Langerhans contribute an internal secretion essential to carbohydrate utilization, and the lack of this substance produces diabetes. Something thus given to the blood by the pancreas acts upon the sugar, probably combining with it in order to give the tissues a handle, so to speak, by which they can grasp it and convert it to their uses.

This is no doubt a sort of stereochemical union, and the existence of a specific amboceptor in the secretion from the islets is assumed. There is abundant experimental evidence in support of the view that the body cells can fasten upon the sugar only by means of this amboceptor, and that its absence results in non-utilization of sugar. All attempts at modifying diabetes by feeding fresh pancreas or its extract have, however, been fruitless, as would be expected, since the bodies under discussion are of such delicate nature and are so easily destroyed.

But how can the amboceptor theory explain diabetes of nervous origin? For, from

authentic clinical evidence, we must recognize that nervous states not only influence the course of an existing diabetes, but that emotional and other shocks actually produce the disease.

The pancreas is abundantly supplied with nerves from the sympathetic ganglia, from which filaments go to the islands of Langerhans and come into intimate contact with its cells. Whether these nerves carry a direct secretory impulse or indirectly influence secretion through vasomotor control is in dispute, but their influence is unquestionable. It is possible that, under certain circumstances, the nice balance of the sympathetic system becomes so disturbed that the pancreas receives constantly an abnormal innervation. Changed bodily conditions, particularly of the abdominal organs, can produce such a state, and it is conceivable that even a single profound shock can so upser the nerve centers as to lead to permanent derangement.

In addition to clinical observations upon the ability of the nervous system to produce diabetes, numerous anatomical studies have been offered in support of this view. Rosenberger reports Windle as having found disease of the central nervous system and sympathetics in 153 out of 259 diabetics—more than 50 per cent—while Schmitz, at the other extreme reported only eighteen instances of important central nervous disease in 600 diabetics. It must be borne in mind, however, that these figures include all patients with nervous disease, such as paresis, tabes, brain tumor, etc., who incidentally have diabetes, many of them having developed the disease previous to the acquisition of the brain lesions. Diabetes of nervous origin cannot be likened to piqure glycosuria, for the former is usually slow in onset and frequently reaches its greatest intensity months after the initial injury or shock.

Thus it appears that there are only two diabetogenic organs, the pancreas and the brain.

We get a view of diabetes mellitus not only

as an organic disease of the pancreas, as in animal experiment, but as a functional derangement of the islands of Langerhans. If this view is correct, we should endeavor in some way to discover the causes which alter this sympathetic mechanism, and by removing them to restore normal nerve balance—and, when this is done, to cure diabetes.

But is there not possible another sort of functional disturbance? Perhaps, after all, the islets depend for their normal stimulation upon some substance brought to them by the blood, just as the acini are activated by secretion from the duodenal mucous membrane. Attempts at finding this hypothetical substance or even its source have invariably failed. Pfleger did a great deal of experimental work toward this end, cauterizing and otherwise injuring the duodenal mucous membrane, but could demonstrate no influence on carbohydrate metabolism.

Yet many facts point to some sort of relation between the duodenal mucous membrane and the internal secretion of the islets, or, better perhaps, between the latter and the secretion from the acini. Witness the occasional improvement and even cure in experimental diabetes which follows permanent ligature of the pancreatic duct, or from a clinical standpoint consider the influence of Von Noorden's accidentally discovered oat cure. Certainly the absorbed end products of digested oatmeal are identical with that from all other starches, and no one has been able to show that the oatmeal offers to man any substance of peculiar value; yet in diabetes a diet of oatmeal gruel produces at times distinct improvement, due, no doubt, to the sedative effect of gruel upon the duodenal mucous membrane.

In connection with this relation of the duodenum to diabetes, I cannot forego a word regarding the possible etiologic influence of years of faulty diet—not of excessive sugar, for I think it has been shown that this probably can never produce diabetes in the normal animal, but of meats and other piquant foods. For we see diabetes melli-

tus most often in those races and individuals who are most accustomed to what is termed "high living."

Before closing a discussion of the glycosurias and diabetes, some mention should be made of the practical results of the animal experiments above mentioned. The older writers knew that starvation benefited diabetes, and that to permit the continuance of glycosuria would result in lowered carbohydrate tolerance, but it remained for Allen, through his brilliant experiments, to explain this and to devise an entirely new and rational therapy, the essential feature of which is occasional and properly adjusted starvation.

His method of treatment is the direct result of these painstaking experiments. The endeavor is to keep the urine sugar free, and thus, through rest and consequent regeneration of the island cells, to restore some degree of carbohydrate tolerance. He does this by means of starvation, the patient being given no food except alcohol for 2, 3, 5, or even 7 days at a time. When the urine is once sugar free, it can usually be kept so by appropriate diet and occasional single starvation days. During starvation the patient receives liberal quantities of whiskey or brandy and sodium bicarbonate.

Feeding is resumed, not with fats and meats, but with small quantities of carbohydrates, preferably in the form of twice-boiled green vegetables. When there has been established a fair degree of tolerance for carbohydrates, say 80 grams, albumins and fats are cautiously added. The tolerance for each of the three classes of foods must be determined separately and the diet kept well within these limits, being increased only as tolerance is raised.

Recourse must be had to starvation, one day at a time, when sugar reappears, and,

even without sugar, starvation days must be interspersed at regular intervals.

The diet must be planned with nicety and accuracy. As an aid in this, Locke's little book of food values has proven indispensable. I have put this book in the hands of patients who, after a little instruction, were able to arrange very satisfactorily their own diet. Joslin teaches them to examine the urine as well as to arrange the diet, and lets them return home to remain under "long distance treatment."

It seems essential to keep the patient's weight down. Most of them finally reach an optimum at which they do best, and attempts at increasing this weight frequently lead to trouble.

To enter upon a detailed discussion of Allen's treatment would transcend the limits of this paper, but two observations which have been impressed upon me seem pertinent. One is that mental and physical rest are valuable and at times essential adjuncts; the other, that when the regime is once started, careless feeding may bring rapid disaster.

During the past year I have used this treatment with several of diabetic patients. It is, of course, too early to judge. It may be after all that diabetes is an ever-progressive disease, and that treatment at best can only arrest its course for a time. But if anything will cure or modify the course of diabetes, the greatest promise seems to me to be in this mode of treatment devised by Allen.

To sum it all up, glycosurias are of two kinds, separate and distinct—diabetic and non-diabetic—the former an important part of a clearly defined disease complex, the latter a symptom of metabolic disorder arising in any one of a number of organs, the alimentary tract, the liver, the kidneys, or the nervous system.