DIABETES MELLITUS AND ITS DIFFERENTIATION FROM ALIMENTARY GLYCOSURIA.

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TEN years ago anyone whose urine reduced Fehling's copper solution on boiling was considered to be suffering from diabetes mellitus, and the patient was directed by the attending physician to regulate his earthly affairs and prepare for death at any moment. So many of these individuals were seen to outlive all expectations, and finally to show no sugar whatever in their urines, that it led to a more thorough study and understanding of the condition. To the work of von Noorden,¹ with his oatmeal diet, more than to anyone else is due the credit of first establishing a scientific therapy for such; while Opie,² Mohr,³ von Mering and Minkowski,⁴ Lusk,⁵ and others have given us a deeper insight into the pathology of the disease. Opie⁶ has shown that in the majority of cases there is a degeneration of the cells in the islands of Langerhans in the pancreas, with atrophy of same. While there is no doubt that pathological changes in the pancreas will cause glycosuria, the writer has seen fatal cases of diabetes in which no pathological changes could be demonstrated in this organ, but in which they seemed to be limited to the liver, while other cases are reported in which no lesions whatever could be demonstrated. We must, therefore, content ourselves with a meager knowledge of the pathology of this disease and turn to physiology to explain many of the phenomena observed.

The various changes through which the carbohydrates pass before final utilization by the tissues as fuel is shown in the accompanying table.

Von Noorden⁷ believes that the pancreas through its hormone inhibits the liver in its normal tendency to part with its glycogen, and that failure of this action results in a hyperglycemia from overproduction of glucose. He does not think there is any lack of ability in the tissues to utilize the glucose in the blood. However, the recent experiments of Knowlton and Starling⁸ would tend to disprove this latter idea, and show that the pancreas while it does

¹ Metabolism and Practical Medicine, Chicago Med. Book Co., 1907.

² Jour. Exper. Med., 1901, v, 527; Johns Hopkins Hosp. Bull., 1901, xii, 263; Disease of the Pancreas, Philadelphia, 1910.

³ Sammlung klin. Abhandlungen über Path. u. Ther. der Stoffwechsel u. Ernährungsstörungen—II, 4, Aug. Hirschwald, Berlin, 1904.

⁴ Arch. f. exper. Path. u. Pharm., 1890, xxvi, 371.

⁵ Science of Nutrition, Philadelphia, 1909.

⁷ New Aspects of Diabetes Mellitus, New York, 1912.

⁸ Jour. Phys., No. 3, xlv, 162.

⁶ Loc. cit.

have an influence on the glycogenic function of the liver most certainly has a decided influence on the utilization of glucose by the tissues. The main point to bear in mind from a clinical standpoint is that whenever the normal glucose content of the blood (that is, 0.09 per cent.) is exceeded, the kidneys will excrete the excess and glucose will appear in the urine. It has been thoroughly accepted that the pancreas secretes a hormone which is absorbed by the blood and in some way presides over the glycogenic function of the liver.

Food substance.	In alimentary canal split up into:	Absorbed by porta. system and transformed by liver into:	Stored up in muscles as:	Burned up by tissues into:	Remarks.
Saccharose, $C_{12}H_{22}O_{11}$.	Dextrose, $C_6H_{12}O_6$, and Levulose, $C_6H_{12}O_6$.	Glycogen, $C_6H_{12}O_6$. Glycogen.	Glycogen. Glycogen.	CO_2 and H_2O glycuronic acid. CO_2 and H_2O glycuronic acid.	Dextrose and levulose are excreted by the kidneys if not utilized by the tissues.
Starch, $C_6H_{10}O_5$.	Dextrose.	Glycogen.	Glycogen.	CO_2 and H_2O glycuronic acid.	
Maltose, $C_{12}H_{22}O_{11}$.	Dextrose, $C_6H_{12}O_6$.	Glycogen.	Glycogen.	CO_2 and H_2O glycuronic acid.	Excess maltose excreted by kidneys.
Lactose, $C_{12}H_{22}O_{11}$.	Dextrose and galactose.	Glycogen.	Glycogen.	CO_2 and H_2O .	When liver is deranged, galactose appears in urine.
Cellulose, $C_6H_{10}O_5$.	Very little if any effect in human.				
Proteids.	Peptones, amino-acids, xanthine bases, Ammonia. Toxic amines from intestinal putrefaction.	Serum, albumin, and globulin. Urea. Non-toxic compounds.	Syntonin, creatin, etc. Creatin. Creatin.	Urea, uric acid, glycol, and dextrose.	If liver function is deranged, have lowered alkalinity of blood.
Fats.	Absorbed through lacteals and into general circulation through the liver. Do not pass through the liver. Incomplete combustion results in diacetic acid.				

Anything affecting the cycle between the liver and the pancreas will result in glycosuria, or anything causing a rapid rise of the dextrose in the general circulation will cause a glycosuria, maltosuria, or galactosuria, depending in great part upon the particular carbohydrate eaten. Patients partaking of large amounts of milk often show a reduction of Fehling's solution; not because they have a true diabetes, but because their normal liver function has been overtaxed, with consequent chronic passive congestion of this organ, so that it is unable to transform into glycogen the galactose formed from the lactose in the milk. A liter (one quart) of milk yields about 48 grams of lactose, which is split up into 24 grams of

dextrose and 24 grams of galactose. The latter is differentiated from the former by its failure to ferment with a pure culture of *Saccharomyces Ludwigii* and its action on polarized light, while both reduce Fehling's solution. In hepatic insufficiency the liver is able to transform the dextrose into glycogen, but has lost this power for galactose. So constantly is this the case that the ingestion of 40 grams of lactose on an empty stomach, with a subsequent determination of the amount of galactose in the urine for four to six hours is universally adopted in the German and Austrian clinics as a test for liver function. This is an example of what one would regard as an "alimentary glycosuria," although glucose is not the sugar present.

Another type of alimentary glycosuria is exemplified by a case recently referred to me as a case of diabetes mellitus:

CASE I.—R. P., wholesale grocer, had suffered some prostatic trouble, and in the routine examination of his urine, by Drs. Hunke and Logan, a heavy reduction of Fehling's solution was obtained, and he was referred to me. There was no thirst, no loss of weight, nor nervous manifestations of diabetes, and his urine was inactive to polarized light, yielding 7 per cent. calculated dextrose by reduction. Urine fermented by yeast. There was no diacetic acid or acetone. Specific gravity, 1.028, with a heavy reaction for indican. He gave a history of eating large amounts of sugar during the day, as he made a practice of grabbing a handful every time he passed the open sugar barrel in his warehouse. His liver dulness was increased to 14 cm., but otherwise all his organs were normal. On account of the failure in action to polarized light, it was evident that there was not a simple glycosuria, and inasmuch as the reduction ceased on the second day after his arrival in New Orleans, I concluded that it was a glycoleveuloseuria, due to the rapid absorption of the dextrose and levulose formed from the cane-sugar, with insufficient action of the liver and prompt excretion of both saccharides by the kidneys, together with some glycuronic acid.

He was put upon a low proteid diet to rest up the liver. No sugar was allowed, but glutinous substances and vegetables were given, while his liver function was stimulated by an initial calomel purge and a two weeks' stay at one of the spring resorts, whose water is rich in phosphate and sulphate of soda. On his return his liver dulness had diminished to 8 cm., there was no reduction with Fehling's solution, and after taking 100 grams of lactose on an empty stomach no galactose could be detected in the urine.

He went home happy in the thought that he had been cured of diabetes, but, fortunately, he never had a true diabetes, but had a simple alimentary glycosuria from insufficient liver action and an overindulgence in cane-sugar. Such cases as this von Noorden classes as prediabetic, and yet "they may go for a lifetime and never develop a true diabetes."

In diabetes mellitus there is a failure of the entire body to utilize not only the dextrose of the circulating blood, but there is a predilection for fat and proteid as fuel in preference to carbohydrate, with subsequent formation of beta-oxybutyric acid, acetone, diacetic acid, etc., from incomplete combustion of these foodstuffs. That incomplete combustion of proteids, or their excessive putrefaction in the intestines, can cause an acid condition in the blood identical with that seen in diabetic coma, I am firmly convinced, although I am not in accord with modern text-books on this point. Diacetic acid, acetone, and beta-oxybutyric acid are not particularly toxic, and I have seen fatal cases of diabetic coma whose urines just previous to death showed very little of these substances, but which were loaded with the products of intestinal putrefaction. Most practitioners make the mistake of considering the carbohydrate metabolism and not paying any attention to the proteid metabolism.

The following case shows the importance of a consideration of the latter:

CASE II.—L. N., white male, aged fifty years, manager of a saw mill, was referred to me by Dr. Picard on May 20, 1912, complaining of drowsiness, occasional headaches, with excessive thirst and ravenous appetite. Other than an attack of lobar pneumonia, twelve years before, he had never had a day's illness until 1905, when he consulted Dr. Picard for retention of urine, which was very abundant. Dr. Picard informs me that at this time he had vague abdominal pains and crampy pains in the limbs, and that his urine showed 2- per cent. of glucose. He had been getting along very well until ten days previous to his visit to me, when he had a sudden attack of nausea and vomiting, succeeded by a constant drowsiness and inability to remain awake sufficiently to attend to his business. He had been losing weight steadily for the past four years, but during the past ten days he had lost nearly twenty pounds.

Examination revealed a robust, ruddy individual, with all organs apparently normal, with the exception of a hypertrophied heart and a general emphysema. There was only moderate peripheral arteriosclerosis, and examination of the fundi showed both disks normal, with no pathological changes in the retina. Examination of his urine showed: specific gravity, 1.040; acid; 1.5 per cent. glucose by polariscope; large amount of albumin; great excess of indican and diacetic acid; negative urobilinogen; a few hyaline casts.

He was sent to Touro Infirmary, and was put upon Vichy and large amounts of bicarbonate of soda. A purgative of calomel, phenolphthalein, and rhubarb was administered, and a reduction in proteid food, with increase of carbohydrate food, instituted at once.

The following table shows his diet and the results of same:

Date.	C.c. urine passed in 24 hours.	Grams glucose in 24 hours.	Total calories.	Carbo-hydrate calories.	Calories lost in urine.	Per cent. calories lost in urine.	Weight, lbs.	Indi-can.	Remarks.
May 22	1280	28.1	1215	600	115.4	9.5	151	++++	Full proteid diet.
May 23	Lost	...	3175	1025	...	...	...	++	Full carbo-hydrate diet
May 24	2050	41.5	3825	1550	221.4	5.7	...	+	Oatmeal and corn-bread.
May 25	1570	35.8	3125	1440	146.7	4.5	...	0	Oatmeal and corn-bread.
May 26	1650	33.0	2150	775	135.3	5.5	155	0	Oatmeal and corn-bread.
May 27	1600	39.3	2500	1250	143.4	5.5	...	0	Macaroni.
May 28	2040	34.1	2325	1125	148.0	5.8	156	0	Oatmeal.
May 29	1650	25.1	2475	1150	103.2	4.1	...	+	Macaroni.
May 30	1760	35.2	2675	1075	141.3	5.4	...	0	Rice and potatoes.
May 31	1760	41.8	2675	975	172.0	6.4	...	0	Rice and potatoes.
June 1	1760	37.4	3175	1325	153.6	4.4	...	0	Oatmeal.
June 2	1170	37.1	4200	2850	152.3	3.6	159	0	Oatmeal and corn-bread.

He left the infirmary in two weeks, a changed man; his mind perfectly clear, no headaches, and an increase in weight of five pounds. I have heard from him at intervals of from three to four weeks, and he has continued to improve on a liberal carbohydrate diet. His urine contains 3 per cent. of sugar still, but there is no albumin and no diacetic acid, and he is to all intents and purposes a well man. He is able to assimilate oatmeal, corn-bread, and macaroni, as well as large amounts of fruit, but he cannot metabolize saccharose, rice, and potatoes.

It must be borne in mind that approximately 50 per cent. of the proteid molecule is transformed into glucose in the body metabolism, and that for every 1 gram of nitrogen in the urine, 5 grams of glucose are either burned up by the tissues or excreted by the kidneys, so that in endeavoring to rid the urine of sugar one must take this fact into account. It has been my experience, (and upon this fact also depends the good results of the von Noorden "Hafer Kur") that the excretion of sugar may increase for a short while after giving carbohydrates, but even during this greater excretion of glucose a greater percentage is utilized by the tissues. This is well exemplified in the diet table accompanying Case II.

It is not the purpose of this paper to consider all of the many points in physiological chemistry involved in a consideration of diabetes, but merely to call attention again to the fact generally accepted that complete withdrawal of carbohydrate food from a diabetic for a long period of time, invariably results in an acidemia, commonly spoken of as diabetic coma, in which beta-oxybutyric acid, diacetic acid, and acetone are usually found in the urine. It is also well to again mention that in the metabolism of proteids,

approximately 50 per cent. of the proteid molecule is split off as a carbohydrate radical, and that this accounts for the continued presence of dextrose in the urine even after complete withdrawal of all carbohydrate food. Dextrose itself is relatively non-poisonous in comparison to the other cleavage products of proteids, and before outlining a diet a consideration of the cleavage products of proteids should be considered, even more than those of carbohydrates.

The amount of glucose excreted by the kidneys is of far less importance than a consideration of the amount of diacetic acid, beta-oxybutyric acid, acetone, and indican. In referring to the tabulated chart of Case II, it will be noticed that on days of carbohydrate feeding, while he excreted a larger amount of glucose, the percentage of wasted calories compared to that ingested was progressively less, while he gained steadily in weight and all symptoms disappeared.

In the treatment of diabetes, drugs or proprietary medicine are of no benefit, if we are to judge by published reports, and the treatment resolves itself into a regulation of the patient's diet and personal hygiene, so as to avoid acidemia, which, however, when present, can be relieved by drug therapy. In overcoming the tendency to intestinal toxemia the writer has experienced good results from the administration of massive doses of cultures of the *Bacillus bulgaricus*, but the number of cases are as yet too few to draw any conclusions. Since Knowlton and Starling's⁹ article, we have administered 10 to 20 grains of an active extract of pancreas, every four hours on an empty stomach, with decided and rapid reduction, and even complete absence of glucose in the urine in two cases of diabetes, while in two others there was apparently no effect.¹⁰

Therapy along this line should, theoretically, yield good results, but the difficulty of obtaining absorption of the pancreatic hormone before it can be destroyed by the gastric juice will always remain a difficult problem. It is to be hoped that in the near future this hormone can be isolated and preserved in such a manner that it can be administered hypodermically, when the ideal drug for the disease will have been found. Until then, strict regulation of the diet will have to be relied upon, and for successful results one must consider the proteid metabolism, as well as the carbohydrate metabolism, and be ever mindful of the physiology underlying the condition.

⁹ *Loc. cit.*

¹⁰ Eustis. Acidosis, *New Orleans Med. and Surg. Jour.*, September, 1913, vol. lxvi.