POSTANESTHETIC GLYCOSURIA AS INFLUENCED BY DIET, BODY TEMPERATURE AND PURITY OF THE ETHER*

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In 1904 one of us¹ reported the occurrence of glycosuria when meat-fed or fasting dogs were subjected to ether anesthesia for varying periods of time. In the case of the meat-fed animals the percentage of dextrose in the urine fraction first voided after anesthesia ranged from 1.32 per cent. to 6.94 per cent. In the case of the fasting dogs the percentage ranged from a negative test to 0.52 per cent.² In 1905 Seelig³ confirmed these findings. At this time (1904-6) all ethers used for purposes of anesthesia contained aldehyd and other impurities. Recently Prof. Charles Baskerville has succeeded in purifying ethers,⁴ and it was he who suggested that we investigate the relationship of this purified or so-called "dehydrated" ether to postanesthetic glycosuria.⁵

Two other phases of the glycosuria question were incorporated with the study of the glycosuria-producing properties of the "dehydrated" ether, that is, the influence of diet and of the lowering of body temperature on the production of post-anesthetic glycosuria. We shall first discuss the body temperature factor.

I.—RELATIONSHIP OF BODY TEMPERATURE TO GLYCOSURIA

Araki⁶ was one of the first investigators to demonstrate that a pronounced lowering of the body temperature of an animal by *external* means caused the appearance of sugar in the urine of that animal. He experimented with rabbits and dogs, using baths of ice-water and of snow to secure low body temperatures. Of five experiments on rabbits three were positive, the urine containing from 0.75 per cent. to 2.5 per

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1. Hawk, P. B.: Proceedings of American Physiological Society, Am. Jour. Physiol., 1904, x, 37.

2. Hawk, P. B.: Postanesthetic Glycosuria, THE ARCHIVES INT. MED., 1911, viii, 39.

3. Seelig: Arch. f. exper. Path. u. Pharm., 1905, lii, 481, also 1906, liv, 206.

4. Baskerville and Hamor: Jour. Indust. and Engin. Chem., 1911, iii, 1. See also Gwathmey and Baskerville's Anesthesia, 1914, Appleton.

5. We wish to thank Professor Baskerville and Squibb & Sons for their kindness in furnishing the ether used in these experiments.

6. Araki: Ztschr. f. physiol. Chem., 1891-2, xvi, 453.

cent. of sugar. Two tests on dogs showed urinary sugar percentages of 1 per cent. and 1.5 per cent., respectively. The rabbits were given snow baths ranging in length from one hour forty minutes to two hours twenty minutes. The body temperature was lowered to 27 C. or lower. One of the dogs which was subjected to a snow bath for three hours twenty minutes showed a drop in body temperature to 23 C., whereas the other dog, which was placed in an ice-water bath for fifty minutes showed a minimum temperature of 26 C. The former animal had 1.5 per cent. sugar in its urine; the latter animal voided a urine containing 1 per cent. of sugar. The appearance of the sugar was interpreted as due to incomplete oxidation.

Several years later Lühje⁷ and Embden, Lühje and Liefman⁸ demonstrated that the quantity of sugar present in the urine of dogs subjected to pancreatic diabetes was dependent to a degree on the temperature of the dog's environment. For example, one dog kept in a cold room excreted 47 gm. of sugar, whereas the excretion of this same animal was only 4 gm. when the dog was maintained in a warm environment. Lühje interpreted his results as indicating that under the influence of a cold environment more sugar was produced in an attempt to maintain body temperature by its oxidation.

Brasch⁹ and Minkowski¹⁰ in turn strongly criticized Lühje's findings and conclusions. Brasch experimented with dogs subjected to phlorhizin diabetes and found that the lowering of body temperature had no influence on the sugar excretion. Minkowski and Allard, working with dogs after pancreas extirpation, also demonstrated that a lowered body temperature had no effect on the sugar output. The findings of Lühje are interpreted by Brasch and Minkowski as being due to the fact that the pancreas was only partly extirpated. This being the case, under the influence of the lowered temperature some glycogen was changed into sugar and passed into the circulation. Mohr¹¹ confirmed the findings of Brasch and Minkowski in that he was unable to influence the sugar excretion in pancreatic diabetes by lowering the temperature of the animal's environment.

Glaessner¹² calls attention to observations which indicate that a pronounced cooling of the human body by external means, such as cold water, may produce a transient glycosuria. In nine cases of reduced temperature sugar was present in only four instances in the first fractions of urine subsequently passed.

7. Lühje: *Verhandl. d. Cong. f. inn. Med.*, 1905, p. 268.

8. Embden, Lühje and Liefman: *Beitr. z. chem. Physiol. u. Path. (Hofmeister's)*, 1907, x, 265.

9. Brasch: *München. med. Wehnschr.*, 1906, vii, 805.

10. Minkowski: *Verhandl. d. Cong. f. inn. Med.*, 1907, p. 272.

11. Mohr: *Ztschr. f. exper. Path.*, 1907, iv, 910.

12. Glaessner: *Wien. klin. Wehnschr.*, 1906, xix, 920.

An interesting experiment on the influence of cold on the sugar excretion in phlorhizin glycosuria has been made by Lusk.¹³ In one experiment an 18 kg. dog after fasting for three days and then being permitted to shiver "in the cold of a north wind" for six hours showed an increase of 8.47 gm. in the dextrose output. Exposure to a cold environment for seven and one-half hours on the following day caused an increase of only 6 gm. in the sugar excretion. In the case of another dog (9 kg.) which had fasted one and one-half days, exposure to cold for six hours produced an increase of 4.44 gm. in the dextrose output, whereas a second exposure of six and three-quarter hours on the following day caused no increase in the sugar excretion.

Lusk concludes that the reduction of body temperature by external means "has no effect on sugar production in the fasting organism, except in so far as body glycogen may be converted into dextrose.

Grube¹⁴ has more recently reported data from a series of observations which indicate that no glycosuria follows the anesthetization of meat-fed dogs by means of ether, provided care is taken to maintain the body temperature approximately normal during the anesthesia period. He reports five experiments on dogs ranging in weight from 3.5 kg. to 8.7 kg. in which sugar excretions ranging from a trace to 7.16 per cent. were obtained. The lowering of body temperature ranged from 2.6 to 4.6 C. Grube then noted that no glycosuria resulted in one experiment in which for some unexplained reason the body temperature of the dog under examination was not lowered under the influence of the ether. Following this he made two or three tests in which the body of the animal was maintained at or above the normal temperature during the period of anesthesia. The temperature was regulated by wrapping the dog in cloths and placing the animal on a specially prepared water-bath. In no case was there any sign of glycosuria in an animal whose body temperature had been maintained near the normal by artificial means.

OUR EXPERIMENTS

Dogs were used as subjects. The animals were fed a diet of meat, lard, graham crackers, bone-ash and water during Experiments 1 to 14 (see Table 1) whereas in Experiments 15 to 24 the animals were fed a "carbohydrate-free" diet (see Table 2). Urine collections were made in fractions as voided for thirty-six hours after each anesthetization. The urines were examined by polariscope before and after fermentation.

Three methods of anesthetization were employed, the period of anesthesia being two hours in each instance. The "cone method" consisted in inserting the dog's nose into a perforated tin cone which contained in its bottom a wad of cotton saturated with ether. The so-called "improved method," devised by

13. Lusk: *Am. Jour. Physiol.*, 1908, xxii, 163.

14. Grube: *Arch. f. d. ges. Physiol.*, 1911, cxxxviii, 601.

us, was accomplished by the use of a special apparatus. This apparatus furnishes the animal with warm ether vapor which is saturated with water vapor and mixed with air. This procedure reduces the loss of heat from the body by warming the vapors which are breathed, and by insuring the saturation of the vapors with water causes a reduction in the heat lost by evaporation from the respiratory organs. The current of compressed air insures an abundance of oxygen. For purposes of experiment cold ether vapor was secured by replacing the warm water of the bath by a freezing mixture of salt and ice.

In order to permit the maintenance of normal body temperature during the progress of anesthesia a so-called "thermos-box" was devised. This box was fitted with sixteen sockets for electric light bulbs, each light being capable of individual manipulation. By this means the body temperature of the animal was easily maintained practically constant even during long periods of anesthesia. Losses by radiation and conduction from the surface of the animal were compensated for by the heat furnished by the "thermos-box."

TABLE 1.—ANESTHETIZATION OF DOGS WHICH WERE FED ON A MIXED DIET *

Experm't No.	Dog No.	Date	Ether Used	Method of Anesthesia	Range of Body Temperature
1	13	11/19	Dehydrated	I. M. cold †	39.0-33.0
2	12	11/21	Dehydrated	I. M. cold	39.0-35.5
3	13	11/23	Dehydrated	I. M. warm ‡	Constant
4	14	11/24	Dehydrated	I. M. warm	Constant
5	12	11/25	Dehydrated	I. M. warm	Constant
6	14	11/28	Dehydrated	I. M. cold	Constant
7	13	11/27	Common	I. M. warm	Constant
8	12	11/29	Common	I. M. warm	Constant
9	13	11/30	Common	I. M. cold	39.2-34.8
10	12	12/ 2	Common	I. M. cold	39.6-36.2
11	13	12/ 3	Common	Cone	39.3-31.6
12	12	12/ 4	Common	Cone	38.8-29.0
13	13	12/ 5	Common	Cone	39.3-32.1
14	12	12/ 6	Common	Cone	39.8-28.7

*Fehling and fermentation tests on urine negative throughout.

†I. M. cold signifies improved method using cold ether vapor.

‡I. M. warm signifies improved method using warm ether vapor.

If the data from Experiments 1, 2 and 9 to 14, listed in Column 6 of Table 1, be examined, it will be observed that temperature depressions ranging from 3.4 C. to 11.1 C., were obtained in the course of eight experiments. Even with such pronounced lowerings of body temperature, however, the urine never contained a trace of sugar. It is evident, therefore, that so far as our experimental animals are concerned, the lowering of their body temperature by means of ether inhalation did not produce glycosuria.

The body temperature underwent the most pronounced reduction when the anesthetic was given by the "cone method." This was due principally to the extreme dryness of the inhaled ether vapor.

II.—THE FACTOR OF DIET IN POSTANESTHETIC GLYCOSURIA

If the data contained in the final columns of Tables 1 and 2 be examined it will be observed that every anesthetization listed in Table 2 was accompanied by glycosuria, whereas sugar was never present in the urine after the periods of anesthesia listed in Table 1. The only variable factor in the two sets of anesthetizations was the diet. The same animals were used in each series, the same kinds of ether were employed, the anesthetic was given by the same methods and for the same length of time. Previous to the administration of the ether in Experiments 1 to 14, however, the dogs were fed the usual mixed diet, whereas previous to Experiments 15 to 24 they were fed a carbohydrate-free diet.

TABLE 2.—ANESTHETIZATION OF DOGS WHICH WERE FED ON A CARBOHYDRATE-FREE DIET

Experi'm't No.	Dog No.	Date	Ether Used	Method of Anesthesia	Range of Body Temperature	Dextrose in Urine gm.
15	13	12/14	Dehydrated	I. M. cold	39.0-36.7	0.53
16	12	12/15	Dehydrated	I. M. warm	Constant	0.39
17	13	12/16	Dehydrated	I. M. warm	Constant	0.19
19	13	12/20	Dehydrated	I. M. warm	Constant	0.45
20	15	12/21	Dehydrated	I. M. warm	Constant	0.53
21	14	12/22	Dehydrated	I. M. warm	Constant	0.65
23	12	12/13	Common	Cone	39.7-35.0	1.44
24	14	12/17	Common	I. M. cold	39.0-32.9	0.38

At the beginning of our tests we were exceedingly surprised at our inability to detect any trace of sugar in the urine of our dogs even after the animals had been under ether for a period of two hours. After conducting fourteen experiments on four different animals, using two different ethers and administering the ether by three different methods and failing in any case to produce any sign of glycosuria we decided to note the influence of the removal of carbohydrate from the diet. The data from the series of tests on the carbohydrate-free diet are given in Table 2. An examination of the final column of that table will show that in every instance the anesthetization of an animal which had been fed a carbohydrate-free diet, resulted in the production of glycosuria. Further work is contemplated in order to determine the minimum carbohydrate ingestion which will prevent the occurrence of postanesthetic glycosuria. The data may have a clinical application.

In order to determine whether lack of oxygen during the ether inhalation could of itself cause glycosuria several experiments were made by various methods of anesthesia. A mixed diet was used in

every instance. By the so-called "improved method" the maximum amount of air was mixed with the ether vapor before inhalation, whereas in the "cone method" the minimum amount of air was allowed to be breathed with the ether vapor. There was no glycosuria in any case, indicating that the lack of oxygen in these cases was not sufficient to cause glycosuria.

III.—"DEHYDRATED" VERSUS COMMON ETHER

The dehydrated ether employed was specially prepared for us by Professor Baskerville, whereas the common ether was the regulation Squibb ether. The opinion having been expressed that the postanesthesia glycosuria and other undesirable features accompanying or following ether inhalation were due not to the ether per se, but to some impurity in the ether, we were very glad of the opportunity of making a series of tests in an attempt to elucidate this problem. The particular thing in view in this instance was to determine the relationship of these two types of ether to the ether glycosuria.

In Table 1 are listed six experiments with "dehydrated" ether and eight experiments with common ether. *In no case was glycosuria observed.* The animals were fed a mixed diet. In Table 2 are listed six experiments with "dehydrated" ether and two with common ether. *Glycosuria was observed in each instance.* The dogs were fed a carbohydrate-free diet.

The experiments force us to the conclusion that the glycosuria following ether inhalation is not due to impurities present in the ether, since the purest ether obtainable yields just as pronounced glycosuria as does the regulation Squibb ether used for anesthesia purposes. Our experiments indicate that the occurrence or non-occurrence of glycosuria hinges on the character of the diet, the ingestion of a carbohydrate-free diet yielding glycosuria, whereas the ingestion of a mixed diet is unaccompanied by glycosuria.

CONCLUSIONS

1. The reduction of body temperature during ether anesthesia does not of itself cause glycosuria.
2. The reduction to a minimum of the oxygen content of the ether vapor inhaled does not cause glycosuria.
3. The response of the animal body to "dehydrated" ether (that is, ether from which aldehyd and other impurities have been removed) in so far as glycosuria is concerned, is no different from the response to the ether ordinarily used (Squibb) as an anesthetic.
4. The inhalation of ether administered by the cone method causes a more pronounced reduction in body temperature than does the inha-

lation of the same kind of ether for a similar period when administered by the so-called improved method. The dryness of the ether vapor in the cone method is the contributing factor.

5. The inhalation of either "dehydrated" or common ether for a period of two hours by dogs fed a carbohydrate-free diet was in every instance accompanied by glycosuria. When the same animals were fed a mixed diet glycosuria was not in evidence.

6. There was no evidence of "emotional" glycosuria, the factor regulating the occurrence or non-occurrence of glycosuria in every instance being a dietary one.

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