A STUDY OF THE URINE SUGAR IN INFANTS *

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It has long been considered probable that the urine of normal individuals contains a reducing sugar. Benedict, Osterberg and Neuwirth¹ recently demonstrated the constant presence of sugar in normal urine and devised a method for its quantitative determination. They found that the amount of sugar in the urine was directly influenced by the quantity of sugar ingested. They also demonstrated that the urine sugar can be separated into two fractions by fermentation with yeast, a fermentable and a non-fermentable portion.²

During the course of work in this laboratory on the sugar tolerance of infants, a number of determinations of urine sugar have been made. These determinations have led to observations which seem of sufficient interest to report.

Technic.—The infants on whom observations were conducted were all practically normal in the sense of being free from infections or gastro-enteric disturbances. Many were of normal weight, a few were underweight for their age. All of the patients were under 7 months of age. If at any time an infant became ill, observations were discontinued until after complete recovery. Most of the infants were on four hour feeding intervals and received six feedings daily. The urine was usually collected over a period of eight hours. Each separate voiding was immediately transferred to a bottle kept on ice and as a further precaution toluene was added as a preservative. The analyses of the urines were made as soon after collection as possible. These precautions are necessary, as much of the sugar present in the urine is very easily lost by fermentation when kept in a warm room. The determinations were made according to the method of Benedict and Osterberg with a few slight modifications. In order to insure complete precipitation of all reducing substances other than sugar, urines with a specific gravity of more than 1.010 were diluted with sufficient water to reduce the specific gravity to that point. The mercuric

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1. Benedict and Osterberg: J. Biol. Chem. **24**:195, 1918. Benedict, Osterberg and Neuwirth: J. Biol. Chem. **24**:217, 1918.

2. Throughout this report, the reducing substance in urine which is not fermented by yeast will be referred to as non-fermentable sugar. The exact nature of this substance is unknown at present.

nitrate reagent was diluted with water in the proportion of seven parts of the reagent to three parts of water. In producing the color reaction, the tubes were immersed in boiling water for twenty minutes³ instead of ten minutes.

In all specimens the total sugar was determined and also the non-fermentable portion was determined by fermenting the urine with yeast for from 18 to 24 hours. The fermentable portion was derived by subtraction.

The twenty-four hour sugar excretion was calculated on the basis of the period of observation. Each specimen of urine was tested with Benedict's qualitative reagent.

At the beginning of the observations, the baby was usually placed on a formula consisting of 1½ ounces of milk per pound of body weight in order to fulfil the fat and protein requirements. Sugar was added in moderate amount and then gradually increased at from three to four day intervals, leaving the rest of the formula constant. In this way the relation of the amount of sugar secreted in the urine to the amount of sugar ingested was studied. In some cases the sugar was first increased and then reduced in order to ascertain further the relation of the sugar in the food to the urine sugar. Frequent analyses of the urine sugar were made on other infants whose formula was unchanged. This was to determine the sugar excretion, both fermentable and non-fermentable on the basis of a constant sugar intake.

AMOUNT OF SUGAR IN INFANT'S URINE

One hundred and seventy urine sugar determinations were made on 37 infants. Considering all cases, the calculated twenty-four hour total sugar excretion varied from 100 to 815 mg. The non-fermentable portion varied from 45 to 253 mg. Similar to the work of Benedict, Osterberg and Neuwirth on adults, our results show that the amount of urine sugar in infants is dependent to a considerable degree on the amount of sugar ingested. For this reason, the larger values obtained by us do not indicate the normal sugar excretion, as in many cases the infants received much larger amounts of sugar than are usually fed. Considering only the amount of urine sugar in infants receiving from 6 to 7.5 per cent. sugar, the values for total sugar range from 100 to 400 mg., and for the non-fermentable portion from 45 to 150 mg. Benedict, Osterberg and Neuwirth found that adults excrete from 600 to 1,200 mg. of total sugar on an ordinary diet. The non-

3. These modifications were made at the suggestion of Dr. Benedict (personal communication to Dr. Schloss).

fermentable portion varied from 340 to 660 mg. As would be expected, infants excrete a smaller absolute amount of sugar, but the amount in proportion to body weight is much greater.

It was found that the quantity of sugar excreted is quite independent of the volume of urine. For example, one infant, A. H., excreted 65 c.c. of urine containing 63 mg. of sugar during one period. At another time he excreted only 28 c.c. of urine during a period of equal length, but this specimen contained 76 mg. of sugar. The first urine contained 97 mg. of sugar per hundred c.c., while the second contained 228 mg. per hundred c.c.

TABLE 1.—SHOWING EFFECT ON URINE SUGAR OF FEEDING INCREASING AMOUNTS OF SUGAR. A. G., AGED 4 MONTHS. COLLECTION PERIOD
8 HOURS: 8 A. M. TO 4 P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fer- ment- able, Sugar, Mg.	Weight, Pounds and Ounces Lb. Oz.	Formula	Bene- dict's Quali- tative Test
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar				
2/ 5	95	0.056	52.9	0.031	29.5	57	23.4	11 5	Milk, 20 oz. Lactose, 1 oz. Barley water to 30 oz. 6 × 5 oz.	0
2/16	125	0.047	58.6	0.017	21.8	38	26.8	11 11	Milk, 22 oz. Lactose, 1½ oz. Barley water to 30 oz. 6 × 5 oz.	0
2/28	70	0.167	116.6	0.040	27.2	24	93.2	12 4	Milk, 22 oz. Lactose, 2½ oz. Barley water to 30 oz. 6 × 5 oz.	+
3/ 5	80	0.158	130.1	0.035	28.4	22	101.7	12 8	Milk, 22 oz. Lactose, 3¼ oz. Barley water to 30 oz. 6 × 5 oz.	+
3/10	75	0.186	139.8	0.039	29.4	20	110.4	13 4	Milk, 22 oz. Lactose, 4 oz. Barley water to 30 oz. 6 × 5 oz.	+

Relation of Sugar Intake to Sugar in Urine.—It has been mentioned that the excretion of sugar in the urine is directly dependent on the amount of sugar ingested. This was found to be true of all the cases studied. An example of a typical case is given in Table 1. It will be seen that as the sugar in the formula was increased, the total urine sugar was also increased. The increased excretion of sugar was confined chiefly to the fermentable portion. It is also to be noted that as the total urine sugar increased the percentage of nonfermentable sugar became less. On the first formula the nonfermentable sugar was 57 per cent. of the total and on the last formula, which contained

the greatest amount of sugar, the nonfermentable portion dropped to 20 per cent. of the total. The total urine sugar excreted on the last formula was nearly three times as great as on the first formula.

TABLE 2.—SHOWING SUGAR EXCRETION IN URINE WHEN SUGAR WAS FIRST INCREASED AND THEN DECREASED. R. H., AGED 5 WEEKS.
COLLECTION PERIOD 8 HOURS: 8 A. M. TO 4. P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable, Sugar, Mg.	Weight, Pounds and Ounces Lb. Oz.	Formula	Benedict's Qualitative Test
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar				
4/9	68	0.099	59.6	0.031	21.6	36	38.0	9 4	Milk, 13 oz. Dextrin-maltose, 1 oz. Barley water to 24 oz. 6 × 4 oz.	+
4/16	57	0.136	75.7	0.047	26.8	35	48.9	9	Milk, 14 oz. Dextrin-maltose, 1½ oz. Barley water to 24 oz. 6 × 4 oz.	+
4/21	55	0.213	116.9	0.064	35.0	30	81.9	9 8	Milk, 14 oz. Dextrin-maltose, 2 oz. Barley water to 24 oz. 6 × 4 oz.	+
4/29	53	0.251	132.6	0.059	31.5	23	101.1	9 10	Milk, 14 oz. Dextrin-maltose, 2½ oz. Barley water to 24 oz. 6 × 4 oz.	+
5/11	27	0.179	48.3	0.085	22.9	47	25.4	8 15	Milk, 12 oz. Dextrin-maltose, 1 oz. Barley water to 24 oz. 6 × 4 oz.	+
5/17	81	0.106	86.1	0.042	33.9	40	52.2	8 14	Milk, 12 oz. Dextrin-maltose, 1½ oz. Barley water to 24 oz. 6 × 4 oz.	+

In Table 2 are given the results of increasing the ingested sugar and then decreasing it. The rise and fall of the sugar excretion in the urine is clearly shown. The loss of weight between April 29 and May 11 was due to an intercurrent infection (rhinopharyngitis) during which time the patient was on a low formula and no determinations were made. The determination on May 11 was made one week after recovery as the sugar was being gradually increased again. It will also be noted that on two occasions during the observations (April 16 and May 17) the formula was practically the same. The sugar excretion, total, fermentable and nonfermentable, was practically constant. The collection periods were both of eight hours' duration but the amount of urine excreted was nearly 50 per cent. greater on May 17 than on April 16. This shows again that the amount of sugar in the urine is quite independent of the volume of urine.

In Table 3 the sugar excretion on a given formula is shown. It will be seen that the amount of sugar excreted remained practically constant. In adults this was also found to be true by Benedict, Osterberg and Neuwirth.

In this series of 170 determinations, a positive reaction with Benedict's qualitative sugar reagent was obtained in seventy-one. As a rule, the test was positive when the urine contained approximately 0.1 per cent. or more of sugar.

TABLE 3.—SHOWING URINE SUGAR EXCRETION WITH CONSTANT SUGAR INTAKE.
C. N., AGED 2 MONTHS. FORMULA: MILK, 12 OUNCES; DEXTRI-MALTOSE,
1¾ OUNCES; BARLEY WATER TO 24½ OUNCES; 7 × 3½ OUNCES.
COLLECTION PERIOD 6 HOURS: 8 A. M. TO 2 P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermen- table Sugar, Mg.	Weight	
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar		Lb.	Oz.
11/29	55	0.092	50.8	0.037	19.3	38	31.5	8	5
12/ 2	80	0.068	54.6	0.032	25.8	47	28.8	8	6
12/ 5	80	0.055	44.0	0.023	18.0	41	26.0	8	8
12/ 8	180	0.045	58.2	0.022	29.0	49	29.0	8	8

Our results lead to conclusions quite opposed to those of Porter and Dunn.⁴ They examined the urines of infants who received large amounts of sugar in their food and concluded that there was no direct relationship between the amount of sugar ingested and the presence of sugar in the urine. The difference between their results and ours is probably due in part to the fact that they used a purely qualitative test for sugar and did not estimate the total sugar output. A qualitative test is positive only when the urine contains sugar in a definite concentration and is in no way indicative of the actual sugar output.

For example, 100 c.c. of urine containing 0.1 gm. of sugar would probably give a positive reaction with a copper reduction test, while 0.15 gm. of sugar in 200 c.c. of urine, which represents a larger output of sugar, would probably not reduce a copper test solution owing to the lower sugar concentration. F. H., receiving a moderate amount of sugar, excreted 40 c.c. of urine in eight hours containing 53 mg. sugar. The urine contained 0.33 gm. of sugar per 100 c.c., and Benedict's qualitative reagent was reduced. J. T., receiving a large amount of sugar, excreted 255 c.c. of urine in eight hours containing 147 mg. sugar. The sugar concentration of this urine was only 0.058 gm. per hundred c.c., and Benedict's test was negative.

4. Porter and Dunn: *Am. J. Dis. Child.* **10**:77 (July) 1915. Dunn: *Pediatrics*, Ed. 1 **2**:475.

Porter and Dunn make no mention of what length of time elapsed between the collection and examination of the urine specimens. It has been our experience that the amount of sugar will diminish very rapidly unless the specimen is very carefully preserved.

As mentioned previously, based on a quantitative determination of the urine sugar, our results show definitely that with increased ingestion of sugar there is an increased elimination of sugar in the urine. Based on a qualitative test alone, the greater number of positive reactions occurred when large amounts of sugar were given but positive reactions also occurred when moderate or small amounts of sugar were fed. In such instances, the urine was concentrated.

On the basis of these results, it seems that the quantitative determination of the urine sugar may prove of distinct value in estimating sugar tolerance. Its use in this connection will be the subject of a separate report.

CONCLUSIONS

1. The urine of all normal infants contains a determinable amount of reducing sugar.
2. The amount of sugar excreted is not dependent on the volume of urine but is directly proportional to the amount of sugar ingested. As the amount of sugar in the diet is increased, the total urine sugar increases. This increase is chiefly in the fermentable portion and as a result the percentage of nonfermentable sugar becomes less.
3. Sugar excretion in infants, both fermentable and nonfermentable, is fairly constant when the intake of sugar is constant.

I desire to express my appreciation to Dr. Oscar M. Schloss, at whose suggestion the problem was undertaken, for his kind criticism and advice during this study. I also desire to acknowledge my indebtedness to Miss Elizabeth S. Morris, nurse in charge of the children's wards, for invaluable aid in supervising the patients on whom observations were conducted.