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SOME STUDIES ON SUGAR IN INFANT FEEDING *

LANGLEY PORTER, M.D.

SAN FRANCISCO

AND

CHARLES HUNTER DUNN, M.D.

BOSTON

Some years ago Finkelstein¹ caught the attention of the world by formulating a new conception of the underlying causes of what were then considered diseases of gastro-intestinal origin. He described them as purely nutritional disturbances, divorced them from any relationship with the bacterial invaders of the intestine, and laid the blame of their genesis on an element of diet that had heretofore been considered innocuous, namely, the sugar. Especially did he attribute that serious, acute form of infantile disease accompanied by stupor, mellituria, and fever to the sugars. The last two symptoms were, he taught, directly and proportionately due to its presence in the food. Later, he implicated the mineral salts of cows' milk, still later prepared his celebrated "Eiweissmilch" and offered it as a remedial food for sugar intoxications, apparently overlooking the fact that as this mixture contained 1.5 per cent. of the deadly lactose its use in practice contradicted his theory. Lactose was especially the sugar he feared, so much so that he stated that even minute doses of milk containing its natural carbohydrate were damaging. Babies were injured with lactose, dextrose, lactose salt mixtures, and dextrose alkali or lactose alkali mixtures, given in isotonic, hypertonic, or hypotonic proportions. The injury was considered always to express itself in mellituria and fever, and F. M. Schapps, Leopold and Von Reuss were one in thinking with Finkelstein that lactose was "exquisitely pyrogenic." This point was emphasized by the findings of Finkelstein and Meyer that 3 gm. of sodium chlorid in 100 c.c. of water given by mouth could produce fever in many healthy infants, while if nutritional disorders were present 1 gm. sufficed to produce pyrexia.

In the next few years the men of this school decided that sugar damage was not alone a simple sugar injury, but made itself felt as the result of the previous or coincident action of salts in improper

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proportions in the food, the presence of the chlorin ion combination with sodium being especially blamed. About four years ago the idea that fermentation of sugar in the intestine played some rôle in these disorders began to be emphasized in Finkelstein's writings, and Finkelstein and Meyer laid greater stress on the fermentation of lactose in the intestine and less on the toxicity of sugar acting parenterally. They even admitted that human milk, which of course is high in lactose, may be the optimum food for certain of the cases that occurred under their classification of intoxication, apparently thus abandoning the view that milk sugar is a fatal poison in such disorders. This inference from the writings of Finkelstein is confirmed by his pupil Schultz, whose experiments did not bear out the pyrogenic or intoxicating action of the sugars. The latest position of Finkelstein's school seems to be that fermenting lactose injures the permeability of the intestinal wall, permits the absorption of salts in abnormal kind or quantity, and that these salts, either alone or in combination with the sugar, produce the poisoning which is evidenced by the glycosuria.

As to fever, there was some reason to believe that when it occurs it is the result of tissue damage such as is often seen following injections of sterile water or salt solution when they break up the erythrocytes, analogous to the fever not at all infrequently seen in childhood that follows extensive bruising or the production of hematomata.

The most convincing work among the group of men that oppose the Finkelstein-Langstein view was done by Allen working in Rose-nau's laboratory. In a long series of experiments with animals in the nursing stage the effects of sugars were tested when given both by mouth and subcutaneously. Experimental animals were used and the experiments ingeniously devised to meet all objections. The animals were given large doses and small doses, some were given repeated injections and some single large doses. Those animals which received their sugars by mouth, especially lactose, showed as effects vomiting and diarrhea, which undoubtedly were due to the fermentation of the sugars in the intestine. In no one of the animals was there any sign or symptom of an intoxicating action of sugar, nor was Allen able to produce any symptoms at all approaching the clinical picture of the sugar intoxications as outlined by the Germans. On the contrary, in spite of glycosuria, which occurred in all experimental animals, he was able to see that subcutaneous injections of glucose were very definitely beneficial to his kittens and puppies, especially to one group that was weaned early and doing very badly. This seems a more rational finding than the view that implicates sugar as a poison to metabolism, as every one has seen the apparent benefit of glucose injections in the case of very sick babies.

The study of the literature would make it seem that the origin of the idea of sugar damage went back to Grosz, and was later elaborated by Langstein and Steinitz in a paper, "Lactase und Zucker Ausscheidung," published in 1906, which seems to have turned Finkelstein's interest toward the sugars as agents of possible damage in infantile nutritional disturbances. These authors in fourteen cases of severe gastro-intestinal disorders proved to their own satisfaction that a part at least of the sugar excreted into the urine was lactose. In five cases they found a second sugar which they believed to be galactose. They conclude that there can be no doubt that infants with severe gastro-intestinal disease excrete milk sugar, and its split-off product, galactose, in the urine, and that this excretion is independent of the excretion of lactase in the stool. They further say that in severe cases of gastro-intestinal disease only part of the milk sugar is split by lactase into dextrose and galactose. These are then burned in the organism or the galactose is excreted if the oxidizing power of the tissues has suffered. The second portion is absorbed unsplit and excreted as lactose in the urine. They admit that the largest proportion may be split by fermentation in the intestine and may be lost to the organism.

The views of Kendall are that lactose, far from being an injurious food, is of essential importance in so maintaining the flora of the intestine that the fermentative processes will always be slightly dominant, and will prevent the putrefactive action on protein which produces soluble toxin of undoubted damage to the general metabolism. The work of Allen and the paper of Kendall are both worthy of very close study by any one who is interested in the subject. Raphael showed that many patients assimilate large doses of sugar better than small ones. Schlessinger says that the appearance of the traces of sugar in the urine are no indication that the sugar tolerance of the body has been passed. Naunyn says that small traces of sugar may be ignored in animals who may show a slight glycosuria, with small doses and none with large. Platenze says sugar is often to be found in urine of babies who show no sign of intoxication and who seem perfectly well.

The dosage usually given for pure dextrose as one that will exceed the sugar tolerance is between 100 and 250 gm. for the adult, but many individuals can assimilate more. After the subcutaneous injection of 100 gm. of glucose, glycosuria may last as long as eight hours. The single dose maximum seems to be from 2 to 4 gm. per kilo, by mouth, 10 gm. per kilo per day, and subcutaneously 1 to 1.5 gm. per kilo per dose.

The presence of traces or of even considerable amounts of reducing bodies in the urine does not mean that sugar is present. Schultz says that a reduction test which will exclusively demonstrate the presence

of sugar is not known, and further, reducing substances such as uric acid, creatinin, albumen, coloring matter, acetone, glycuronic acid, all or any may be present. Fluckiger reports the presence in normal adult urines of non-fermentable reducing bodies which produce osazones of a value equal to 1/1500 to 1/2500 gm. of grape sugar in the twenty-four hours. Salkowski put it at 0.4 gm., Monk at 0.3 gm., and other observers at variable points. Creatinin has especially been dealt with by Sedgwick, Steinitz, Fluckiger, Amberg and Morris, so that it is clear that in infants' urines there may be considerable reducing power due to bodies other than carbohydrates, a fact well substantiated for the normal urine of adults.

This fact, together with the report by the Finkelstein school of the frequent presence of sugars in the urines of infants suffering with a less severe nutritional disturbance, made it seem desirable to test the urine of a group of infants in the Boston Infants' Hospital, who were suffering from what would be known in Europe as "balance disturbance," but which in the nomenclature of the Boston school is called "chronic indigestion." There were eighteen of these babies investigated; none of them were of the premature type such as Aschenheim found to have intestines more permeable to sugar than those of older nurslings. The first tests were all made while the children were receiving what was considered a normal amount of sugar advisable for their individual peculiarities. Later, attempts were made on a number of the cases to find the limit of physiologic tolerance for the sugars. The reagent used in the determinations was one recommended by Folin as the most sensitive to reducing bodies. It was made in two solutions, of which 3.5 c.c. of each were mixed at the time of using and from 1 to 3 c.c. of the urine added after boiling the mixture. The mixture was then centrifuged. Solution 1 contained copper sulphate 10 gm., glycerin 150 c.c., and water to make 500 c.c. Solution 2 contained 500 c.c. of a 50 per cent. solution of potassium carbonate. This reagent has shown definite amounts of reducing bodies in every adult urine tested with it. This is not true of infants' urines. Twelve per cent. showed no reduction whatever, and of the remainder, 50 per cent. gave no reduction on repetition of the test after saturation with picric acid and shaking through ten minutes to remove the creatinin which is present in appreciable quantities in nearly all infants' urines, and which reduces nearly all the copper reagents especially the more delicate. In none of the urines was it possible to measure the reduction quantitatively by Benedict's solution.

The fact having been determined that there was no measurable sugar in any of the urines tested, attempts were made to pass the sugar tolerance limit of 2 to 4 gm. per kilogram of body weight without the production of a measurable glycosuria. Such attempts

have been made before and have always failed to cause a glycosuria except in those cases of deep intoxication such as were studied by Finkelstein and his pupils.

A summary of the work done in this investigation is as follows: Patients observed, 18; samples of urines tested, 105; number of tests made, 235; signs double + and triple + are used as follows: + indicates on the addition of the urine to the heated reagent a few grains of copper oxid; ++ indicates that on centrifuging definite layer of copper oxid forms in the bottom of the tube; +++ that there is a visible reduction in the tube before centrifuging. Sixteen of the eighteen patients showed reducing bodies in some tests before the treatment with picric acid. Eight showed a loss of reducing power after shaking with picric acid. Three of the patients (+++) showed appreciable amounts of reduction constantly in all samples of urine after the picric acid treatment. One of these had an eczema corresponding in type to the exudative diathesis of the Czerny school, but in spite of the fact that this patient received as much as 120 gm. of lactose, 15 per cent. of his intake per day while he was receiving 4 per cent. of fat at the same time, there was never enough sugar in the urine to be assured by any of the usual quantitative methods and coincidently the skin condition improved steadily under local treatment. The other two patients of this group were suffering from rather extreme malnutrition. Of the 105 samples of urine, 58 showed reducing powers to our solution before shaking with picric acid. Of these 58, 27 lost their reducing power after such treatment. Of the eighteen patients, excepting the three referred to above, none showed reducing bodies every day, and in no instance did there seem to be any relation between the amounts of sugar ingested and the presence of these bodies as they were found in the urine with minimum intake, and were frequently absent following the highest ingestion.

The clinical results in these cases in which an effort was made to surpass the supposed limits of sugar tolerance were very interesting. Not knowing how severe the symptoms of intolerance might prove to be, we did not wish to give large doses of sugar suddenly, but adopted the method of a gradual increase in the amount of sugar given. The percentage of sugar in the food was increased at the rate of 0.5 per cent. a day until symptoms of intolerance developed. Lactose only was used in nine cases, dextrimaltose only in 1 case, and the tolerance for both lactose and dextrimaltose was tested in six cases.

None of the cases tested were of the severest type of malnutrition. One or two of the patients were babies having no gastro-intestinal disturbance. One presented a case of congenital obliteration of the bile ducts. The majority were babies who had presented difficult

feeding cases in the Out-Patient Clinic, and had been sent in to the hospital to be straightened out. None showed any marked intolerance for any of the food elements. The majority were comparatively mild cases of fat intolerance, showing indigestion and excessive fat in the stools when the fat was increased. No case known to have a marked intolerance of carbohydrate was tried.

Symptoms of intolerance developed eventually in twelve of the sixteen cases. Three patients were taken home, and one patient died, before the experiment was completed.

TABLE 1.—MAXIMUM SUGAR TAKEN WITHOUT SYMPTOMS

Case	Percent. in Food	Gm. in 24 Hours	Gm. in 24 Hrs. per Kg. of Body Weight	Gm. in a Single Feeding per kg. of Body Weight
1	Lactose, 9.5	91	9	2.25
2	Lactose, 7	83	20	3.00
3	Lactose, 14.5	169	31	4.75
4	Lactose, 14	119	40	4.00
5	Lactose, 11.5	134	28	4.00
6	Lactose, 15.5	144	32	4.40
7	Lactose, 8.5	79	18	3.00
7	Maltose, 9.5	91	20	3.00
8	Lactose, 15.5	168	27	4.50
9	Lactose, 5	53	10	2.00
9	Maltose, 12.5	158	27	4.50
10	Lactose, 7.5	67	24	2.00
11	Lactose, 8.5	100	20	3.00
11	Maltose, 8.5	100	20	3.00
12	Lactose, 12	160	17	3.00
13	Maltose, 11.5	119	33	3.10
14	Lactose, 10.5	140	30	3.00
14	Maltose, 18.5	170	54	5.40
15	Lactose, 11.5	150	18	3.00
15	Maltose, 17.5	225	27	4.50
16	Lactose, 13	146	22	3.10
16	Maltose, 18	182	30	4.00

The symptoms of intolerance were very constant. The first symptom, showing the coming on of intolerance, was marked irritation of the skin of the buttocks, in spite of the most careful nursing. The symptoms which soon followed were loose green movements, usually about five or six daily, distention of the abdomen with gas, eructations of gas, and vomiting. Loss of weight was slight; on the development of distinct signs of intolerance, the sugar was at once cut down. In no case were seen any toxic symptoms, or any signs of sugar intoxication, or any fever, except that one case developed fever at about the

time of the other signs of sugar intolerance, but at the same time this baby had an acute otitis media. The symptoms of sugar intolerance, therefore, judging from this series of cases, are in no way suggestive of intoxication, but are suggestive only of a fermental process localized within the intestinal canal.

The amount of carbohydrate taken without intolerance was surprising. The quantities of sugar given to the several cases are shown in the tables. Table 1 shows the maximum quantities of sugar taken

TABLE 2.—AMOUNT OF SUGAR ON WHICH SYMPTOMS OF INTOLERANCE DEVELOPED

Case	Percent. in Food	Gm. in 24 Hours	Gm. in 24 Hrs. per Kg. of Body Weight	Gm. in a Single Feeding per kg. of Body Weight
1 *		...	...	...
2 †		...	...	...
3	Lactose, 15	141	26	4.0
4	Lactose, 14.5	113	40	4.0
5	Lactose, 12	144	30	4.25
6	Lactose, 16	146	32	4.40
7	Lactose, 9	76	17	3.00
7	Maltose, 10	105	32	3.20
8 †		...	...	...
9	Lactose, 6	53	10	2.00
9	Maltose, 13	150	26	4.60
10	Lactose, 8	72	26	2.00
11	Lactose, 9	105	20	3.00
11	Maltose, 9	105	20	3.00
12	Lactose, 12.5	172	18	3.00
13 †		...	...	...
14	Lactose, 11	145	30	3.00
14	Maltose, 19	170	55	5.40
15	Lactose, 12	152	18	3.00
15	Maltose, 18	227	19	4.50
16	Lactose, 13.5	148	22	3.10
16	Maltose, 18.5	186	31	4.00

* Patient died before intolerance developed.

† Patient discharged before intolerance developed.

without intolerance. These quantities were in general far above the supposed limit of 10 gm. daily per kilogram of body weight. The percentage of sugar taken without intolerance varied from 5 to 18.5 per cent., the grams in twenty-four hours varied from 53 to 225, the grams daily per kilogram of body weight varied from 9 to 54, and the grams of sugar at a feeding per kilogram of body weight varied from 2 to 5.40. The quantities on which intolerance eventually developed were slightly higher, and are shown in Table 2. Only one baby in

TABLE 3.—PERIODS OF INCREASED SUGAR, QUANTITY OF SUGAR TAKEN, AND GAIN OR LOSS IN BODY WEIGHT

Case	Food	Period of Increased Sugar (Days)	Percent. of Sugar in Food at Beginning of Period	Percent. of Sugar in Food at End of Period	Sugar in 24 Hours per kg. of Body Weight at Beginning of Period gm.	Sugar in 24 Hours per kg. of Body Weight at End of Period gm.	Gain or Loss in Body Weight During Period gm.	Average Daily Gain or Loss in Body Weight During Period gm.
1	Lactose	8	9.5	9.5	9	9	—	—63
2	Lactose	13	7.0	7.0	20	20	+	+22
3	Lactose	20	7.0	15.0	16	31	+	+36
4	Lactose	18	7.0	14.5	22	40	+	+7
5	Lactose	18	6.5	12.0	18	28	+	+13
6	Lactose	20	6.5	16.0	14	32	+	+33
7	Lactose	8	5.5	9.0	13	18	+	+27
7	Maltose	10	6.0	10.0	14	20	+	+26
8	Lactose	19	6.5	15.5	12	27	+	+52
9	Maltose	16	6.0	13.0	14	27	+	+31
10	Lactose	4	6.5	8.0	21	26	+	+120
11	Lactose	7	7.0	9.0	16	20	+	+30
11	Maltose	7	7.0	9.0	16	20	+	+4
12	Lactose	13	6.5	12.5	9	18	+	+13
13	Lactose	20	6.5	16.5	11	33	+	+16
14	Lactose	7	7.0	10.5	20	30	+	+50
14	Maltose	22	7.0	18.5	20	55	+	+27
15	Lactose	10	6.5	11.5	9	18	+	+30
15	Maltose	22	6.5	17.5	9	28	+	+22
16	Lactose	13	6.5	13.0	14	28	+	+36
16	Maltose	22	6.5	18.0	14	36	+	+19
							+	+26

the series showed inability to take more than 7 per cent. of sugar, or more than 10 gm. per kilogram of body weight in twenty-four hours.

In the six cases in which the comparative tolerance for maltose and lactose was tried, it was found to be about the same in two cases, but distinctly higher for maltose than for lactose in the other four cases. In no case was there the slightest evidence of any relation between the amount of sugar given and the presence of a positive sugar test in the urine. The sugar was just as likely to be absent as present in cases taking a maximum of sugar, or in cases showing symptoms of intolerance. The three cases showing the constant presence of sugar, showed the same reaction irrespective of the amount of sugar given. The other cases show positive and negative urinary tests at all stages. The last three cases, numbered 14, 15 and 16, showed sugar more often present with maltose than with lactose. Whether this is the rule requires further observation.

The effect of the increased quantity of sugar on the weight curves of the babies was most surprising, and is shown in Table 3. The majority of the cases not only gained weight, but gained weight very rapidly during the period of sugar increase. Also the gain, while less rapid after sugar intolerance developed and the sugar was cut down, was in all cases maintained. In some instances the gain was really enormous. Patients 8 and 13, both on lactose, gained 1,000 gm. in twenty days. Only one case, which afterward proved to be tuberculous, failed to gain. Excluding this case, the average daily gain for the whole series during the sugar period was 26 gm.

It seems to us that the idea of sugar injuries and sugar intoxication has possibly kept us from the use of large amounts of soluble carbohydrate in certain cases, particularly those unable to take a quantity of fat sufficient to meet their nutritive requirements. That many such babies have intolerance of sugar is indoubtedly true. But the danger of pushing the sugar to the limit of tolerance we believe to have been exaggerated. The signs of sugar indigestion are distinct and easily recognized, and do not appear to be in any way serious. In many cases great benefit appears to be obtainable by greatly increasing the carbohydrate content of the food, and therefore this proceeding may prove a valuable addition to our stock of resources in dealing with difficult feeding cases.

240 Stockton Street, San Francisco—178 Marlboro Street, Boston.

REFERENCES

- Finkelstein, H.: *Zur Aetiologie der Ernährungsstörungen der Säuglinge*, *Gesellsch. f. Kinderh.*, 1906, xxiii, 117.
Schapps, F. M.: *Salz und Zuckerinjektion beim Säugling*, *Gesellsch. f. Kinderh.*, 1907, xxiii, 153.

Leopold, J. S. and v. Reuss, A.: Experimentelle Untersuchungen über Milchzuckerausscheidung nach wiederholten subkutanen Injektionen, *Monatschr. f. Kinderh.*, viii, 1 and 453.

Finkelstein, H. and Meyer, L. F.: (1A) Ueber Eiweissmilch, *Jahrb. f. Kinderh.*, 1910, lxxi, 525.

Finkelstein, H. and Meyer, L. F.: Ueber Ernährung magendarmkranker Kinder mit Eiweissmilch, *Berl. klin. Wchnschr.*, 1910, p. 1165.

Schlutz: *AM. JOUR. DIS. CHILD.*, February, 1912.

Allen, F. M.: Quoted in *Glycosuria and Diabetes*.

Grosz, J.: Beobachtungen über Glykosurie im Säuglingsalter nebst Versuchen über alimentäre Glykosurie, *Jahrb. f. Kinderh.*, 1892, xxxiv, 83.

Langstein-Steinitz: Laktase und Zuckerausscheidung bei magendarmkranken Säuglingen, *Beitr. z. chem. Phys. u. Path.*, 1906, vii, 575.

Kendall, A. L.: Certain Fundamental Principles Relating to Activity of Bacteria in the Intestinal Tract; Their Relation to Therapeutics. *Jour. Med. Research*, 1911, xxv, 117.

Kendall, A. L. and Farmer, C. J.: Studies in Bacterial Metabolism, I, II, III, *Jour. Biol. Chem.*, 1912, xii, 1, 19, 215.

Kendall, A. L. and Farmer, C. J.: Studies in Bacterial Metabolism, V, VI, VII, *Jour. Biol. Chem.*, 1912, xii, 465; *Ibid.*, 1912, xiii, 63.

Kendall, A. L., and Farmer, C. J., Bagg, E. P., and Day, A. A.: Studies in Bacterial Metabolism, IV, *Jour. Biol. Chem.*, 1912, xii, 219-21.

Rapheal, F.: Untersuchungen über alimentäre Glykosurie, *Ztschr. f. klin. Med.*, 1899, xxxvii, 19.

Schlesinger, W.: Zur Klinik und Pathogese des Lävulosediabestes, *Arch. f. exper. Path. u. Pharm.*, 1903, I, 273.

Naunyn, B.: *Diabetes Mellitus*, Wien, 1906.

Platenza, B. P. B.: Finkelstein's Doctrine Concerning Disturbances of Nutrition in Children, *Nederl. Tijdschr. v. Geneesk.*, 1910, xi, 1304; ref. in *Maly's Jahresbericht*, 1910, p. 625.

Schultz: *Nebaur's des Harnes*, p. 288.

Fluckiger: *Ztschr. f. physiol. Chemie*, 1885, ix, 322.

Sedgwick: *Jour. Am. Med. Assn.*, 1910, lv, 1178.

Steinitz: *Zentralbl. f. inn. Med.*, 1904, No. 3.

Fluckiger: *Ztschr. f. physiol. Chemie*, 1891, xxiv, 521.

Amberg and Morris: *Jour. Biol. Chem.*, iii, 311.