The Metabolism of Mannitol and Sorbitol

Their use as sugar substitutes in diabetic therapy

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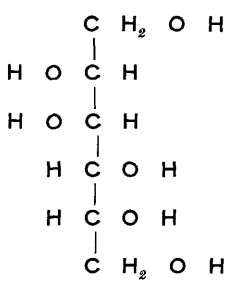
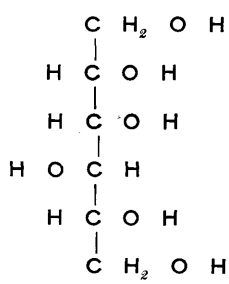
The universal taste for sweet foods is the impetus for the search for sweeteners that may be used by diabetics. Glucose, fructose and sucrose are so rapidly absorbed that their use places a strain on the diabetic organism and they are avoided in the usual diabetic diet. Substitute sweeteners are of two classes, the chemical agents of which saccharine is the oldest representative and the hexahydric alcohols of which mannitol and sorbitol are best examples. This review is concerned with the metabolism of the latter in relation to their use by diabetics.



D Mannitol



D Sorbitol

Sorbitol is a white crystalline powder which is very soluble in water. It is a hydroscopic agent, a moisture conditioner widely used commercially to control the water content of a large number of manufactured products. In foods it is used to preserve the moisture content and texture and to impart a sweet taste. It is 60 per cent as sweet as sucrose. It was first recommended for use by diabetics in 1929 by Thannhauser in Germany. His suggestion stimulated discussion as to the suitability of sorbitol for use in diabetic diets; a discussion which is still active.

Mannitol is a white crystalline powder only 15 per cent soluble in cold water. It is the main constituent of manna, the solidified sap of a variety of ash found in southern Europe. It has been used for centuries as a mild cathartic. Since about 1940, when both mannitol and sorbitol were first made by an electrolytic reduction process from cornstarch or glucose, these alcohols have been available commercially at low cost. Mannitol is used in foods and pharmaceutical products as an inert powder filler. It is also useful in physiological studies. In 1940, Smith and others[19] showed that after injection intravenously, it is filtered by the renal glomeruli and not reabsorbed or excreted by the tubular epithelium. It also has been recommended for the determination of extracellular fluid volume. Both mannitol and sorbitol have been used by bacteriologists since the turn of the century in procedures for the identification of bacteria.

In the following discussion of the literature, no attempt has been made to record a complete bibliography. The important papers bearing on the physiology of these substances will be reported in some detail.

ABSORPTION

It long has been recognized that both mannitol and sorbitol are absorbed slowly from the gastro-intestinal tract of both animals and man. Carr and co-workers in 1933[3] and 1938[4] used a mixture of mannitol (one-third) and cacao-butter (two-thirds) to prevent diarrhea in experimental animals. When mannitol was given by stomach tube in a small amount (0.6 gm.) one-sixth was recovered from the intestine. In studying the nutritive value of mannitol and sorbitol in rats,

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Ellis and Krantz[12] fed a mixture of sugars consisting of 35 per cent glucose and only 5 per cent of one or the other of these alcohols, presumably because larger amounts would cause diarrhea. In man, these observers found the laxative dose of mannitol to be from 10 to 20 gm.

Blatherwick and others[2] gave 500 mg. of sorbitol to rats by tube, but the results of their experiments could be questioned because the animals had diarrhea. Ellis and Krantz[12] fed monkeys 2 gm. daily for 3 months and 10 gm. daily to 3 human subjects for 1 month without any evidence of toxicity (or, presumably, diarrhea).

Very recently experiments making use of glucose and sorbitol labeled with radioactive carbon (C^{14}) have appeared. Wick, Almen and Joseph[22] administered 300 mg. of glucose or sorbitol by stomach tube to female rats weighing 210 to 252 gm. Animals were sacrificed 1, 2 and 3 hours after ingestion of the test substance. The stomach and intestinal tract were removed and washed free of their contents. Absorption was calculated by the amount of radioactive material recovered from the intestinal contents. Glucose was absorbed rapidly, 97 per cent the first hour and 99 per cent by the third hour. In the case of sorbitol, on the other hand, 75 per cent was absorbed the first hour and 84 per cent by the end of three hours. The rate of absorption was further clearly demonstrated by tests of whole blood by Geiger counts made during absorption; glucose was absorbed 10 times more rapidly than sorbitol.

From the study of the literature one must distinguish between two different procedures used by experimenters. In one, the animal is starved for 48 hours and then fed by stomach tube an amount of the material to be studied; the animals being sacrificed at various times, from 1 hour to 12 hours. In such acute experiments it is difficult to demonstrate absorption. The other procedure is to incorporate the material in the diet in small amounts for several days. By this method, good evidence of its absorption can be obtained.

Eitel[10] long ago summarized the use of mannitol and sorbitol (along with many other carbohydrates) by fermentation procedures to identify bacteria, and more recently Dozois, Hochtel, Carr and Krantz[9] studied 127 strains of the colon-aerogenes groups of bacteria. All species produce acid and gas from cultures containing 1 per cent. Since mannitol and sorbitol in larger amounts escape absorption, they would be attacked by the bacterial populations of the lower gastro-intestinal tract with the production of the volatile fatty acids as shown by Grove, Olmsted and Koenig.[14] These acids stimulate the motility of the intestinal tract.[24] Mannitol and sorbitol also favor retention of fluid within the intestinal lumen.

METABOLISM

The metabolism of mannitol and sorbitol have been studied since 1933. Data is available bearing on the following effects: formation of glycogen both in the liver and muscles; appearance of hyperglycemia after feeding; elimination through the kidney, their usefulness in the study of kidney function, and for determination of extracellular fluid volume; effect on the respiratory quotient; antiketogenic agents; and, lastly, as agents to relieve insulin shock.

Mannitol: In 1933 Carr and others[3] fed mannitol mixed with cacao-butter to rats. The glycogen content of the livers was slightly, although significantly, increased over those of the controls. The respiratory quotient, however, was not significantly increased. When rabbits were given the alcohol by stomach tube, the blood sugar (glucose) rose slightly. In the same year Silberman and Lewis[17] gave mannitol by stomach tube to rats but found no significant rise in liver glycogen. Carr and Krantz[4] (1938) again fed a mannitol-cacao-butter mixture to rats and again found a liver glycogen content of 0.98 per cent compared to 0.18 per cent in controls. Glucose fed in the same amounts resulted in liver glycogen value of 3.14 per cent. In acute experiments when mannitol was given by stomach tube the effects were negative as in the experiments of Silberman and Lewis.

Todd, Myers and West[21] injected 22.5 gm. intravenously into dogs but found no increase in the true blood sugar. Mannitol was given by stomach tube or intraperitoneally but no rise in liver glycogen was detected. They repeated the feeding experiments in rats of Carr (one-third mannitol, two-thirds cacao-butter), and confirmed the latter's finding of increased liver glycogen (0.98 per cent); control (0.27 per cent). Ellis and Krantz[12] in Carr's laboratory (1941) reviewed the work on the sugar alcohols up to that time. They gave 9 gm. of mannitol per kg. by stomach tube to Macaca monkeys. Three hours later the liver glycogen had risen, much less so in case of mannitol than sorbitol. Mannitol was given to normal men and the respiratory quotient, as well as the true blood sugar, were determined at the end of ½, 1 and 2 hours. No significant influence either on true blood sugar or respiratory quotient was found. Johnston and Deuel[15]

(1943) using rats, studied the effects of mannitol, sorbitol and dextrose on muscle and liver glycogen and their antiketogenic effects in both exogenous and endogenous ketosis. The sugars were given intraperitoneally in two doses. They found mannitol to be antiketogenic, and therefore glucose forming, but only one-fourth as effective as glucose. As a glycogen former they found it only weakly active. In 1945 Carr and Krantz[6] again reviewed the literature on the metabolism of the sugar alcohols. They said: "To summarize, the fate of mannitol in the animal body appears to proceed along the following pattern: absorption from the alimentary tract; partial conversion to glycogen in the liver, and the elimination of much of the sugar alcohol unchanged in the urine."

In 1940 Smith and others[19] introduced mannitol as one of the substances that when given intravenously, is filtered through the glomeruli without being reabsorbed by the kidney tubules. In two human experiments 10 gm. of mannitol was given intravenously and, in 10½ hours, 81 and 89 per cent had been recovered in the urine. They reported that as much as 80 gm. of mannitol or sorbitol had been injected into human individuals. When sorbitol was injected intravenously in man, only 32 per cent was recovered in the urine. Dominguez, Corcoran and Page[8] studied mannitol as a measure of glomerular filtration and volume of extracellular fluid. They confirmed Smith's findings that 80 per cent of intravenously injected mannitol can be recovered in 10 hours. They concluded that it is metabolized at a very slow rate and that this rate could be expressed in mg. per minute per unit of plasma, a figure equalling 21 for human beings. Elkinton[11] studied mannitol as a measure of the volume of extracellular fluid. He injected 12 to 25 gm. of mannitol intravenously into three human subjects, two of them edematous. In an 8-hour collection of urine, he recovered from 89 to 99 per cent of injected mannitol. Clark and Barker[7] review their experience with mannitol injected to determine kidney function. In 90 unselected clearance periods in 29 tests on 22 patients, 100.4 mg. of mannitol were recovered for each 100 mg. injected. Therefore, they believe there is no extrarenal disposal of mannitol.

Sorbitol: After the introduction of sorbitol into the treatment of diabetes in 1929 much excellent work was done to reveal its metabolism. In Europe in the next few years, clinicians made claims both for and against its use in diabetic diets. Blatherwick and others[2] and Todd, Myers and West,[21] and later Ellis and Krantz,[13] who reviewed this controversy agreed that the reports were confusing. The particular interest in sorbitol is dependent on its better absorption, sweet taste and solubility.

Payne, Lawrence and McCance[16] (1933) fed 25 gm. of glucose, and at another time a like amount of sorbitol, to two juvenile diabetics. The blood sugar was determined at intervals up to 3 hours. After administration of sorbitol by mouth, the blood sugar values rose from 200 mg. per 100 cc. to 280 in one patient and from 83 to 120 in another. Sorbitol was added to the diet of diabetics and a reduction in acetone excretion was noted. Twenty gm. of sorbitol failed to relieve mild insulin hypoglycemia. Experimental animals (rats) on receiving sorbitol failed to show an increase in liver glycogen. From this observation the authors concluded that sorbitol could be safely used as a sweetening agent by diabetics. Silver and Reiner[18] fed 50 gm. of sorbitol to an individual with essential fructosuria and followed the glucose and fructose levels of the blood. Controls were a normal individual and a diabetic. In the case of the normal control there was no rise either in the blood or blood fructose. In the diabetic, the blood glucose rose from 180 to 260 mg. per 100 cc. in 3 hours. In the fructosuric patient, blood glucose did not rise but fructose values increased from 0 to 0.35 mg. per 100 cc. It was concluded that sorbitol may give rise to fructose. This observation is of particular interest in the light of the fact, later proved, that fructose is an intermediate product in the metabolism of sorbitol in the liver. Carr and Forman[5] (1939) fed to rats sorbitol and cacao-butter, in the manner previously referred to, and found the liver glycogen to be 1.25 gm. in contrast to 0.25 gm. in the controls.

They showed that sorbitol is not harmless, for if 2.6 gm. per 100 gm. of rat is fed, the rats died. Todd, Meyers and West[21] gave a 50 ml. of a 50 per cent solution of sorbitol intravenously to dogs; 39 per cent was recovered in the urine. Blood sorbitol and blood glucose levels were raised. The former returned to normal in 2 hours; the latter had returned to normal in one hour. They also found the liver glycogen increased after giving sorbitol by stomach tube to rats. Blatherwick and others,[2] however, after giving 500 mg. of sorbitol to rats found no increase in liver glycogen. Such an amount may be toxic (cathartic). Ellis and Krantz[12] (1941) obtained an increase in the liver glycogen of monkeys after giving 8 gm. per kg. by stomach tube. They further obtained an increase in the respiratory quotient of man, but no increase in blood sugar,

after giving sorbitol syrup by mouth. The same observers in 1943[13] gave 50 gm. of sorbitol by mouth to 13 diabetics and compared its effect on the blood sugar and respiratory quotient with 50 gm. of glucose. The averaged results revealed no rise either of the blood sugar level or of the respiratory quotient. In the case of glucose there was a great rise in blood sugar, as expected, but in addition a significant rise of the respiratory quotient.

Carr and Krantz[6] reviewing the metabolism of sorbitol say: "In the authors opinion, it (sorbitol) owes its value, in diabetes, to the fact that it is capable of being stored as glycogen and that its subsequent depolymerization and utilization fail to supply to the blood a plethora of glucose which would produce hyperglycemia." And further: - "Although the ingestion fails to produce a hyperglycemia, there can be no question about the presence of a sorbitolemia. The question, therefore, which remains unanswered is the relative effect on the impaired islet tissue of a hyperglycemia or a high blood-sorbitol level." Johnston and Deuel,[15] in experiments designed to test the glycogen production in both muscle and liver and the antiketogenic power of sorbitol in rats, came to these conclusions: Sorbitol is slightly *more effective* than glucose in causing deposition of liver glycogen when injected intraperitoneally. But, glucose acts more promptly in this respect. The ketolytic effect of sorbitol was only 50 per cent of that of glucose, in the case of exogenous ketonuria, and only 25 per cent of that of glucose when the ketonuria was of endogenous origin. The exogenous ketosis was produced by feeding sodium butyrate and the endogenous by feeding a high fat diet (Crisco). The liver, they concluded, converts sorbitol to glycogen, but in the case of extremely fatty livers, it fails to do so.

Stetten and Stetten[20] injected intraperitoneally into rats glucose and sorbitol made radioactive by the incorporation of C^{14} into the sugars. The animals were sacrificed at 6, 12, and 24 hours and the glycogen of both the liver and carcass was determined. The same procedure was applied to rats, made severely diabetic by alloxan. In addition the carbon dioxide of the expired air was collected and the urine was examined. With C^{14} labeled glucose and normal rats 50 to 60 per cent of the injected C^{14} found in the expired air and 11 to 13 per cent in the urine. When sorbitol was injected into normal rats, 64 per cent appeared in the expired air and 19 per cent in the urine; 0.7 percent of the liver glycogen contained C^{14} when glucose was injected; 0.12 per cent when sorbitol was given. These values for glycogen, which are low compared to other observations, were explained on the basis that the rats were not starved preceding injection. These observers concluded that sorbitol is metabolized as rapidly as glucose when injected intraperitoneally but is a poorer source of glycogen. They believed that fructose is an intermediate in the transformation of sorbitol to glucose. With diabetic rats, the sugars were largely excreted in the urine; in the case of glucose, 89 per cent and after sorbitol 78 per cent. Only small amounts appeared as labeled carbon dioxide, which was interpreted to mean that neither glucose or sorbitol had been metabolized.

Wick, Almen and Joseph[22] also used tagged glucose and sorbitol for administration by stomach tube or for intraperitoneal injection. Normal rats were used. The rate of oxidation was followed by the collection of the expired carbon dioxide every 3 hours up to 24 hours. Glucose by stomach tube or by injection gave almost identical rates of oxidation. In contrast the rate of oxidation for sorbitol was very much slower when the alcohol was administered by stomach tube. For instance, at the end of 3 hours, 11 per cent of sorbitol given orally had been oxidized, while 40 per cent was oxidized when sorbitol had been injected. When glucose was given, 55 per cent had been oxidized at the end of 3 hours. For the determination of glycogen, starved rats were used. In the case of both glucose and sorbitol, the livers contained 4.5 and 4.0 per cent respectively of glycogen. Of this amount, the authors calculated 40 per cent originated from the test substances. Equal amounts of tagged glycogen, but in small quantities, were recovered from the carcasses.

Blakely[1] studied the metabolism of sorbitol with liver slices and homogenates in the Warburg apparatus. As early as 1914, Embden and Guisbach had perfused the livers of phloridzinized dogs and concluded that sorbitol was oxidized to fructose and later transformed to glucose. Anschiel in 1930 had come to a like conclusion. Breusch (1942) had demonstrated sorbitol dehydrogenase in the brei of the liver of starved cats. Edson, using liver slices from starved cats, had found sorbitol more antiketogenic than glucose or fructose in rat livers. Blakely isolated in pure form the enzyme sorbitol dehydrogenase from the livers and kidneys of cats, mice, guinea pigs, and rabbits. Sorbitol dehydrogenase is specific and its action reversible:

Sorbitol$\rightleftarrows$fructose. Fructose$\rightarrow$fructose 6 phosphate. Fructose 6 phosphate$\rightleftarrows$glucose 6 phosphate. Glucose 6 phosphate$\rightarrow$glucose. Thus glycogen of liver is slowly

formed through fructose. This necessary series of enzyme phosphorylations takes some time and accounts for the delay observed by Johnston and Deuel for the formation of glycogen from sorbitol. Wick and Drury[23] have confirmed Blakely's findings by failing to find radioactive carbon in the expired air of eviscerated, nephrectomized rabbits.

SUMMARY

Mannitol is absorbed so slowly and to such a slight degree that it does not affect the blood sugar or respiratory quotient of man. What is absorbed would be eliminated in the urine to the extent of 80 per cent or more. The only positive evidence that mannitol enters the carbohydrate metabolism, is the small amount of glycogen found in the livers of starved rats fed mannitol for several days. Since only 10 to 20 gm. of mannitol can be fed to man without laxation, it does not appear to be of much importance as an adjunct to diabetic diets, and if used could probably be safely disregarded.

Sorbitol requires several hours for its absorption. In addition, a series of enzymatic phosphorylation reactions in the liver must take place to form glycogen from it. It does not raise the true blood glucose to any great degree. Given the time necessary for conversion, sorbitol is an excellent source of glycogen. In the diabetic rat, Stetten and Stetten found approximately as much sugar in the urine after sorbitol was injected intraperitoneally as after glucose. One would expect, therefore, that insulin would be required after sorbitol ingestion. However, since glucose formation from sorbitol is a delayed process, it may very well be that sorbitol might require less insulin than the rapidly absorbed glucose. Exact data on this point is not available. The literature would justify the classification of sorbitol as available carbohydrate and it should be calculated as such in diabetic diets.

How much sorbitol can be absorbed by man without the production of laxation? Ellis and Krantz fed 10 gm. of sorbitol to three human subjects for a month without ill effects. They found that 20 to 30 gm. of the commercial syrup was laxative but subjects could ingest 50 gm. of the crystalline product before laxation occurred. It is apparent, therefore, that the amount of sorbitol that can be absorbed is limited and that it cannot be considered a significant source of calories. One wonders whether sorbitol is not a physiological laxative agent in the sense that it is a substrate for the colonic bacterial population. Further, one wonders what effects it may have on bacterial metabolism and whether the result is favorable or unfavorable in human nutrition.

If sorbitol has a useful purpose in diabetic diets, it must be as an adjunct. As such it has two properties, that of a sweetener and as a moisture conditioner. In the former role it is but 60 per cent as sweet as glucose and is hardly a competitor of the chemical sweeteners. As a moisture conditioner it may be of considerable value. At this time one cannot predict what place sorbitol will occupy in diabetic diets and we must rely on the practical experiments of dietitians to solve that problem.

Finally, it seems highly important that foods containing sorbitol should be labeled in such a way as to show the amount of this substance present in the product.

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Experimentation in Human Beings

The Physician's Point of View

Present types of experimentation on the sick clearly challenge tremendously the basic concepts of the original patient-physician relationship. All the encroachments imposed by society upon this relationship, such as reporting certain diseases, requesting certain types of inoculations, evaluating fitness for work or right to compensation, shrink before the challenge the profession itself raises. . . .

Perhaps a glance at the way the legal profession meets the moral and technical demands of society and the individual when a conflict arises between the two will offer a cue to a solution of our problem. As we all know, that profession provides each of the two with a representative of equal stature: there, the prosecuting attorney, and here, the defense attorney. Similar arrangements may have to be developed in the field of human experimentation, performed not for the good of the individual patient but made to confirm or disprove or suggested biological generalization. Research and care would not be pursued by the same doctor for the same person, but would be kept distinct. The physician-friend and the physician-experimenter would be two different persons as far as a single patient is concerned—for instance, my patients would become research objects for someone else, and I would be permitted to experiment only with the patients of another physician. The responsibility for the patient as patient would rest, during the experimental period, with the physician-friend, unless the patient decided differently. Retaining his original physcian as personal adviser, the patient would at least be under less conflict than he is at present when the question of experimentation arises.

With reference to increasing technicalities, the forms that patients must sign when about to volunteer for experimentation, or even to undergo an operation might be so phrased as to state not only the patient's consent, but also the physician's affirmation of his utmost effort to protect the patient from harm and of his most careful judgement in deciding on an operation. Under those circumstances the obligations of the profession toward the individual and society would not be blurred.

The problem we face thus presents a true dilemma, being tragic in the classical sense; both its aspects are of equal value in thought, and a course of action must be decided anew for each actual situation, because the varieties of actual situations are as infinite as history itself. . . .

It is not the conquest of nature but the re-evaluation of man that appears to be the basic problems of our times. It is the re-evaluation of man as—to express it in old yet valid terms—"created in the image of God and tempted by the devil", not as a replica of innocent beasts, which, however cruel, cannot commit any crime. We must be alert with ourselves lest, in our zeal for the truth, we create healthy bodies at the cost of morally dulled minds.

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