THE METABOLISM AND TOXICITY OF MANNITOL AND SORBITOL IN MAN AND ANIMALS

By

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Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for
the degree of Doctor of Philosophy

1941

ACKNOWLEDGMENTS

The author wishes to express his appreciation to Dr. John C. Krantz, Jr. for his suggestions and guidance in this study; to Dr. C. Jelleff Carr and Dr. W.E. Evans, Jr. for their collaboration in certain parts of the experimental work; to Dr. Henry Wollenweber for the pathological examinations and interpretations reported herein; to Mr. W.G. Harne and Mr. Lloyd Yeager for their assistance in the animal work and to other colleagues and friends who have acted as subjects in the human experiments.

Grateful acknowledgment is also made to the Atlas Powder Company for permission to include in this thesis certain experimental work performed during tenure of a fellowship provided by the firm.

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INTRODUCTION

The sugar alcohols constitute a group of substances which are closely related chemically to the monosaccharides and are referred to generally as the "rare" sugars. They represent reduction products of the aldoses and ketoses and contain an OH group attached to each carbon atom in the molecule. The name "saccharol" has been suggested for this group of compounds.

Mannitol and its isomer, sorbitol, are perhaps the most common, but yet important members of this group. Mannitol is the chief constituent of manna, the dried saccharine exudate obtained from Fraxinus ornus. Sorbitol occurs naturally in mountain ash berries and in other plants of the Rose family. These sugar alcohols are produced commercially by the reduction of dextrose.

The physiological behavior of mannitol and sorbitol has been investigated by a number of workers for many years. However, the available literature relative to the glycogenic ability and metabolic fate of these compounds in the animal body is quite confusing and of a highly controversial nature. Sorbitol has been used especially in Europe as a substitute carbohydrate in the treatment of diabetes. The variations in the results obtained concerning its value for this purpose have contributed to the controversy. A thorough review of this literature reveals a considerable amount of variation in species responses and in techniques employed. This may explain in part the discrepancies reported.

In 1937 Lafon studied the nutritional value of mannitol and sorbitol in mice. When mannitol comprised 30 per cent of the diet the animals suffered from severe intestinal disturbance and many of the mice died. If the mannitol content of the diet was reduced to 5 per cent the animals showed greater tolerance but in each concentration mannitol was identified in the urine. Sorbitol was not toxic up to 30 per cent of the diet and apparently was completely utilized. On the other hand, Lecoq (1934) observed that mannitol and sorbitol were utilized by pigeons when these compounds were the only carbohydrate source and comprised 35 per cent of the diet. However, 66 per cent of either substance in the diet resulted in death of the animals. Mannitol has also been shown to be inferior to dextrose in the diet of rats (Ariyama and Takahashi 1929).

Voegtlin, Dunn and Thompson (1924) found that mannitol had only a slight antagonistic action on the hypoglycemic effect of insulin in rats. Roche and Raybaud (1933) claimed that sorbitol did not prevent insulin hypoglycemia in rabbits.

When fed to fasted rats over a period of days mannitol (Carr, et al. 1933, Carr and Krantz 1938, Todd, et al. 1939) and sorbitol (Todd, et al. 1939, Carr and Forman 1939) produces hepatic glycogen. Deposition of glycogen also occurs when sorbitol is administered intraperitoneally to fasted rats (Waters 1938, Todd, et al. 1939) but there is some controversy concerning glycogen formation following the administration by stomach tube of this substance (Payne, et al. 1933, Waters 1938, Todd et al. 1939, Blatherwick, et al. 1940). Blatherwick and his associates (1940) reported a significant increase in the lactic acid content of the livers of their animals after the administration of sorbitol in the same manner. In the livers of mice Salter et al. (1935) found sorbitol to serve as a precursor of glycogen following stomach tube administration. Mannitol is not converted into glycogen in the livers of fasted rats following either stomach tube (Silberman and Lewis 1933, Carr and Krantz, 1938, Todd et al. 1939) or intraperitoneal administration (Todd et al. 1939). However, Carr and Krantz (1938) reported that the oral administration of mannitol slightly but significantly increased the respiratory quotient of the rat.

In rabbits mannitol produced a mild hyperglycemia after oral administration (Carr and Krantz 1938) and the intraperitoneal administration of sorbitol increased the blood sugar and blood lactic acid of these animals (Koike 1934). On the other hand, Roche and Raybaud (1933) stated that sorbitol is not transformed into liver glycogen by the fasting rabbit. According to Drury and Salter (1934) sorbitol failed to prolong the survival time of hepatectomized rabbits.

It has been demonstrated that large quantities of mannitol were excreted unchanged in the urine (Jaffe 1883) while no significant increase in liver glycogen occurred (Rosenfeld 1900) after this compound was fed to dogs. Thannhauser and Meyer (1929) have shown that when sorbitol is fed with lean meat to fasted dogs liver glycogen is deposited as readily as after similarly administered glucose.

Todd, et al. (1939) observed an elevation of blood sugar in dogs after intravenous injection of sorbitol but mannitol did not produce this effect. These authors stated further that after sorbitol was administered intravenously to dogs the blood was almost completely cleared of this compound within 2 hours, while only 40 to 50 per cent was recovered in the urine in 24 hours. The remainder of the sorbitol was apparently utilized. According to Waters (1938) the intravenous administration of sorbitol to fasting dogs produced only a mild hyperglycemia and markedly depressed the glucose tolerance curve of the normal and depancreatized animal.

When sorbitol was perfused through isolated livers from fasted dogs, considerable amounts of levulose and glucose were formed (Embden and Griesbach 1914, Reinwein 1929) while these compounds were not formed after perfusion with mannitol (Embdem and Griesbach 1914).

In the phloridzinized rabbit (Roche and Raybaud 1933) and dog (Embden and Griesbach 1914, Roche and Raybaud 1933, Koike 1934) extra glucose was found in the urine after the administration of sorbitol.

The literature contains only a few reports relative to the use of mannitol as a substitute carbohydrate in man. Sollmann (1936) listed mannitol among the sweetening agents useful to diabetics. Rosenfeld (1900) observed no demonstrable effect on the blood-sugar level or urine sugar when small quantities (about 20 gm.) of mannitol were administered to diabetics. Larger doses, however, frequently produced extra urinary dextrose but the patients experienced diarrhea and anorexia. Following the administration of 100 gm. of mannitol to normal subjects, Field (1919) reported an average increase in the blood sugar of 10 mgm. per cent as compared to 40 mgm. per cent rise after the ingestion of glucose. Falus (1938) observed no elevation of the blood sugar or increase in urinary sugar in diabetics receiving 50 gm. of "glukonon" (reported to be pure d-mannitol) per day for 3 days.

Sorbitol was introduced into therapeutics in Europe under the name of "sionon" by Thannhauser and Meyer (1929). Other workers became interested in this compound and used it clinically. Following the administration of sorbitol to diabetics Reinwein (1929) observed an increase in the R.Q. but no rise in blood sugar while only traces of sorbitol were excreted unchanged. Kaufman (1929) reported that sorbitol exhibited a protein-sparing action and was useful to the diabetic. Gottschalk (1929) ascribed an "insulin-enticing" action to sorbitol and recommended its use in diabetes. von Noorden (1929) also recommended the use of sorbitol in the diet of the mild and moderately severe diabetic. Bertrand, Radais and Labbe' (1934) observed good utilization of sorbitol by diabetic patients with and without insulin.

In normal subjects Porrati and Rowinski (1938) found that sorbitol increased the R.Q. as effectively as an equal amount of dextrose, while the blood-sugar level was not changed after sorbitol.

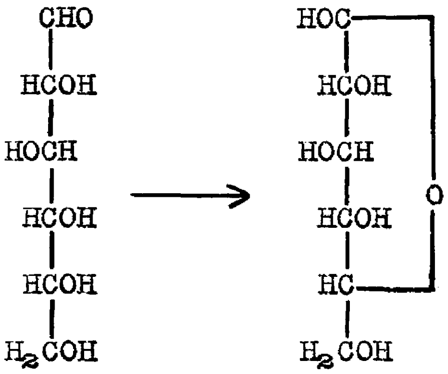
Other workers either have questioned the value of sorbitol in the diabetic diet or have said it is not metabolized at all. Donhoffer and Donhoffer (1930) reported that sorbitol produced a rise in blood sugar in normal metabolism and in diabetes and that the sensitivity to sorbitol increased in diabetes to a greater extent than to dextrose. According to Payne, Lawrence and McCance (1933) sorbitol did not enter directly into carbohydrate metabolism and, therefore, was an inert compound which could be used as a sweetening agent. These authors stated further that sorbitol was ineffective in relieving insulin hypoglycemia. Roche and Raybaud (1933) observed no increase in R.Q. after giving 50 gm. of sorbitol to normal and diabetic patients. Later(1934) these workers reported that sorbitol was not a satisfactory substitute carbohydrate and questioned its value in diabetes.

Purpose of the Present Investigation. Although opinions differ extensively regarding the metabolism of these compounds, some of the literature contains evidence of utilization of a good part of the sorbitol administered. In view of this fact the work reported herein was undertaken in an attempt to broaden our knowledge of the fate of mannitol and sorbitol in the animal body and to evaluate further their use as substitute carbohydrates. In some of this work the corresponding metabolism of dextrose was studied.

Materials Employed. The compounds used in this study were crystalline mannitol and sorbitol and a commercial sorbitol syrup. This syrup is a noncrystallizing aqueous solution having a polyhydroxylic alcohol content of about 83 per cent which consists chiefly of sorbitol with varying amounts of sugar alcohol anhydrides. It was thought the syrup might offer certain advantages over crystalline sorbitol.

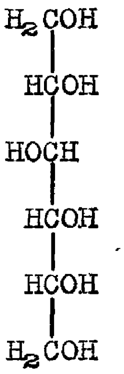
Table I

The Structural Relationship of Dextrose, Mannitol and Sorbitol



Dextrose

Mannitol



Sorbitol

METABOLISM OF MANNITOL AND SORBITOL

Nutritive Value in Mice and Rats. Nutritional studies are limited in mice and rats owing to the laxative action produced by the sugar alcohols. An attempt was made to ascertain the value of mannitol and sorbitol in several generations of mice by replacing a portion of the carbohydrate content of the diet with these compounds. When as much as 10 per cent of mannitol, sorbitol or sorbitol syrup was present in the diet the animals developed diarrhea after 3 or 4 weeks. The animals receiving mannitol appeared very weak and many died. The use of mice in this experiment was finally abandoned.

Feeding experiments using young rats were then undertaken but no further attempt was made to feed these compounds to successive generations of animals. Male white rats, 20 to 28 days old and weighing about 40 gm., were divided into four experimental groups each of which consisted of 20 animals. One group of animals served as a control and to the diet of each of the other 3 groups one of the sugar alcohols was added. The duration of this experiment was 3 months. The following diet was modified from Greisheimer and Johnson (1929) and was employed in this work.

Sugar alcohol	5 parts
Dextrose	35 parts
Casein	30 parts
Crisco	20 parts
Salt Mixture (McCollum No. 185)	5 parts
Yeast	5 parts
	100 parts

Cod liver oil was added daily. The control animals received a diet whose carbohydrate content (40 per cent) consisted entirely of dextrose.

All of the animals were weighed at intervals during the experiment and their average weights plotted to determine growth curves. These curves are shown in Fig. 1.

These results do not indicate any significant difference between the

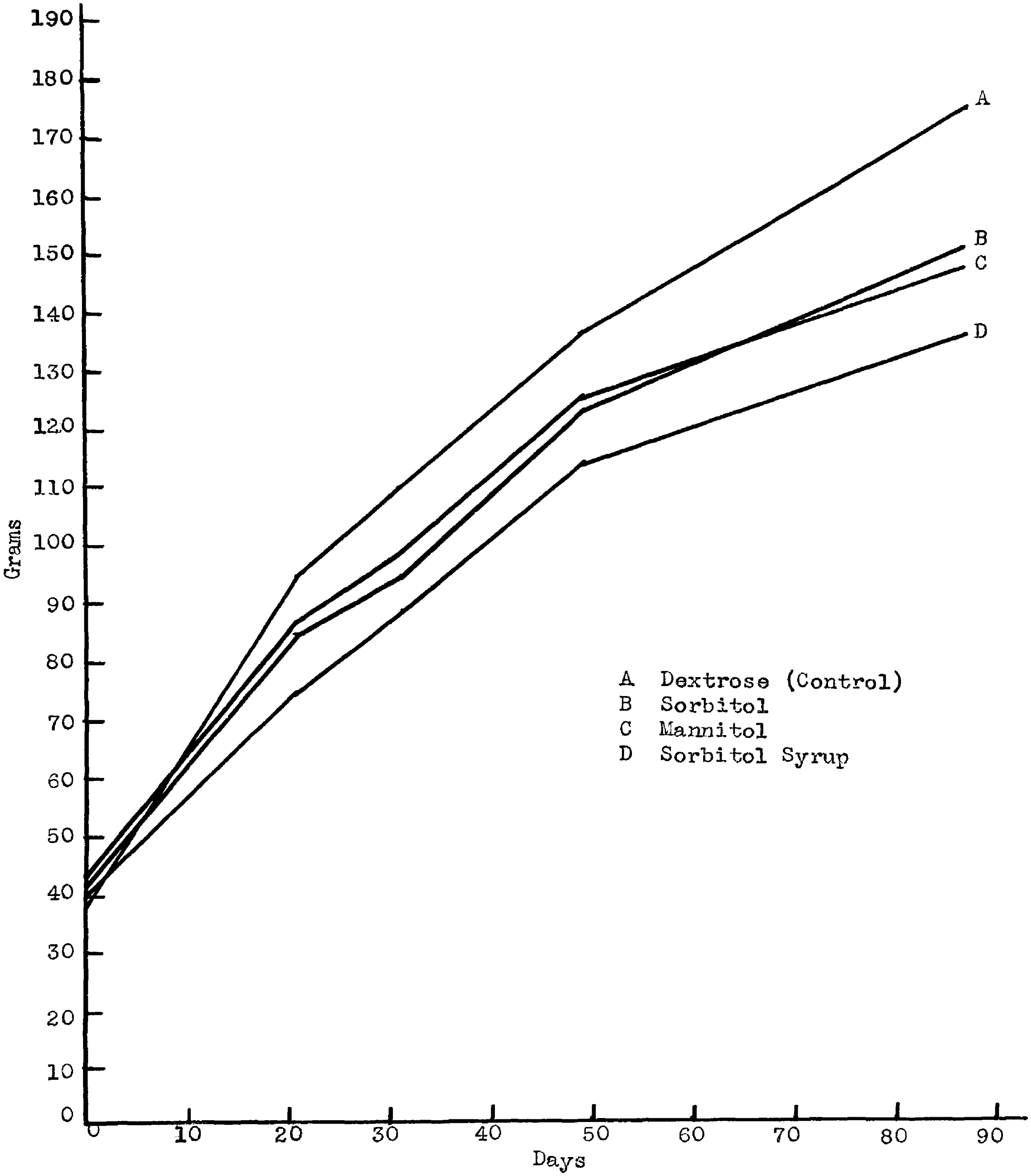


Fig. I Growth curves of rats receiving 5 per cent of mannitol and sorbitol in the diet.

relative nutritional values of mannitol and sorbitol under the foregoing experimental conditions. However, dextrose appears to be superior and the sorbitol syrup inferior to mannitol and sorbitol under similar conditions. No signs of diarrhea were observed in these animals after the first week of feeding.

<u>Glycogen Storage in the Livers of Monkeys</u>. The author is unaware of any previous work in which the monkey was used to determine the glycogenic ability of these sugar alcohols. Male and female Rhesus monkeys weighing from 3 to 4 kg. were employed in these studies which were carried out in two series, A and B. In each series three experimental animals were used for each of the 3 compounds studied and two animals served as controls.

These monkeys were fasted for 24 hours before receiving by stomach tube 8 gm. per kg. of body weight of the respective sugar alcohols. Three hours were allowed for absorption and then the animals were anesthetized with 50 mgm. per kg. of sodium pentobarbital. Two or three portions of liver were taken from different lobes of each animal for individual glycogen determinations. Small samples of liver were removed under aseptic conditions from two monkeys which recovered from the operation. All of the other animals were sacrificed.

The glycogen was estimated by the procedure of Good, Kramer and Somogyi (1933). According to this method the weighed liver tissue was submerged in 30 per cent KOH and heated in a boiling water bath until solution was effected. The glycogen was precipitated with 95 per cent alcohol, the mixture heated to boiling again, cooled and centrifuged and the supernatant liquid decanted. The glycogen was washed with alcohol twice in the same manner and was hydrolyzed with 0.6 N HCl for 2 to 2-1/2 hours. The dextrose formed by hydrolysis was determined by the method of Shaffer and Hartmann (1920-21).

The results of individual determinations are shown in Tables II and III

Table II

Glycogen Storage in the Livers of Rhesus Monkeys After Administration of Sugar Alcohols by Stomach Tube

Series A

24 Hours Fasting Period

Monkey No.	Weight Kgm.	Liver Sample No.	Weight Gm.	Glycogen Gm.	Glycogen per cent
		Control			
20	3.79	11	4.1760	0.0180	0.43
		14	4.6424	0.0030	0.06
		8	5.3559	0.0057	0.10
		Average			0.19
22	3.97	B	2.9625	0.0038	0.12
		1	6.2534	0.0015	0.02
		9	8.4476	0.0025	0.03
		Average			0.06
		Mannitol - 8 Gm./Kgm.			
17	3.55	17	4.2116	0.0175	0.41
		24	1.0678	0.0090	0.84
		Average			0.62
100	3.52	B	2.8131	0.0190	0.67
		1	3.4880	0.0105	0.30
		2	5.0391	0.2500	0.49
		Average			0.49
101	3.72	8	1.7036	0.0050	0.29
		10	4.1571	0.0100	0.24
		Average			0.27

Table II (continued)

Glycogen Storage in the Livers of Rhesus Monkeys After Administration of Sugar Alcohols by Stomach Tube

Series A

24 Hours Fasting Period

Monkey No.	Weight Kgm.	Liver Sample No.	Weight Gm.	Glycogen	
				Gm.	per cent
		Sorbitol - 8 Gm./Kgm.			
12	3.93	9	5.7065	0.0250	0.43
		11	2.6213	0.0200	0.76
		14	3.3150	0.0225	0.67
		Average			0.62
13	3.48	15	3.7124	0.0200	0.54
		17	4.2770	0.0180	0.42
		24	3.5193	0.0170	0.48
		Average			0.48
16	3.87	B	2.5280	0.0080	0.32
		1	4.0158	0.0135	0.33
		8	5.1297	0.0167	0.32
		Average			0.32
		Sorbitol Syrup - 8 Gm./Kgm.			
11	3.51	B	3.9708	0.0193	0.48
		9	5.8066	0.0171	0.30
		14	4.5573	0.0150	0.33
		Average			0.37
14	3.12	B	4.0854	0.0087	0.21
		1	5.4148	0.0095	0.17
		9	4.5922	0.0128	0.28
		Average			0.22
15	3.78	11	4.3885	0.0084	0.19
		14	5.5111	0.0081	0.15
		Average			0.17

Table III

Glycogen Storage in the Livers of Rhesus Monkeys After Administration of Sugar Alcohols by Stomach Tube

Series B

24 Hours Fasting Period

Monkey No.	Weight Kgm.	Liver Sample No.	Weight Gm.	Glycogen	
				Gm.	per cent
		Control			
96	4.31	B	5.1289	0.0240	0.46
		20	3.7578	0.0170	0.45
		Average			0.45
97	3.73	8	3.9422	0.0180	0.45
		14	4.4846	0.0190	0.42
		Average			0.43
		Mannitol - 8 Gm./Kgm.			
89	3.56	1	4.1203	0.0280	0.68
		9	3.4709	0.0130	0.27
		Average			0.47
90	3.98	B	6.0004	0.0290	0.48
		11	5.1775	0.0250	0.48
		Average			0.48
102	3.38	9	2.1407	0.0150	0.70
		14	1.7201	0.0180	1.04
		Average			0.87

Table III (continued)

Glycgoen Storage in the Livers of Rhesus Monkeys After Administration of Sugar Alcohols by Stomach Tube

Series B

24 Hours Fasting Period

Monkey No.	Weight Kgm.	Liver Sample No.	Weight Gm.	Glycogen	
				Gm.	per cent
		Sorbitol - 8 Gm./Kgm.			
95	3.86	B	3.9946	0.0260	0.62
		1	1.6942	0.0196	1.15
		Average			0.88
98	4.18	11	3.4924	0.0170	0.49
		14	1.7326	0.0142	0.82
		Average			0.66
99	3.50	8	1.5336	0.0180	1.17
		9	2.0676	0.0320	1.54
		Average			1.35
		Sorbitol Syrup - 8 Gm./Kgm.			
91	3.88	12	3.3966	0.0160	0.47
		15	2.5750	0.0145	0.56
		Average			0.51
92	4.10	2	6.0476	0.0290	0.48
		10	6.5853	0.0270	0.41
		Average			0.45
94	3.25	18	2.9965	0.0240	0.80
		24	4.8225	0.0060	0.12
		Average			0.46

Table IV

Glycogen Storage in the Livers of Rhesus Monkeys After Administration of Sugar Alcohols by Stomach Tube

Summary

24 Hours Fasting Period

Monkey No.	Weight Kgm.	Liver Glycogen av. per cent	Monkey No.	Weight Kgm.	Liver Glycogen av. per cent
Control - 30 cc. Water			Sorbitol - 8 Gm. per Kgm.		
20	3.79	0.19	12	3.93	0.62
22	3.97	0.06	13	3.48	0.48
96	4.31	0.45	16	3.87	0.32
97	3.73	0.43	95	3.86	0.88
			98	4.18	0.66
			99	3.50	1.35
Mean		0.28	Mean		0.72
Mannitol - 8 Gm./Kgm.			Sorbitol Syrup - 8 Gm./Kgm.		
17	3.55	0.62	11	3.51	0.25
89	3.56	0.47	14	3.12	0.22
90	3.98	0.48	15	3.78	0.17
100	3.52	0.49	91	3.88	0.51
101	3.72	0.27	92	4.10	0.45
102	3.38	0.87	94	3.25	0.46
Mean		0.53	Mean		0.34

and the data from both series are summarized in Table IV. These results indicate that sorbitol significantly serves as a precursor of hepatic glycogen; mannitol questionably leads to glycogen deposition; and sorbitol syrup does not give rise to increased glycogen in the livers of Rhesus monkeys under these conditions.

Respiratory Metabolism in Monkeys. In 3 Rhesus monkeys the influence of mannitol and sorbitol on the respiratory quotient was compared with that of an equal quantity of dextrose. An animal metabolism box provided with a removable top, an inlet and an outlet, was employed in these experiments. A constant flow of air at a rate which permitted adequate respiratory exchange was passed through the box. Expired air of two-minute periods was collected in a small spirometer and samples were taken for respiratory quotient determinations using the Haldane-Henderson technique.

All of the animals were fasted for 15 hours prior to the beginning of each experiment and 2 different control experiments were run on each monkey. In one case the fasted animal was placed directly into the metabolism box while in the other 30 cc. of water were given by stomach tube before putting the animal in the box. On 4 subsequent days each monkey was given by stomach tube 4 gm. per kg. of dextrose, mannitol, sorbitol and sorbitol syrup. In each experiment the respiratory quotient was determined at hour intervals for 6 hours.

The results of these experiments are shown in Tables V to VII. The first hour values are subject to some variation since it is doubtful if the circulating air had reached equilibrium with the expired air in the box within that time.

Laxative Action in Man. Manna is well known to the laity and has been used for years as a laxative. This exudate contains about 90 per cent of

Table V

Respiratory Metabolism in Monkeys

Monkey No. 30

Time Hours	Per cent Oxygen			Per cent Carbon Dioxide Eliminated	Respiratory Quotient
	Inspired Air	Expired Air	Consumed		
		Control			
1	21.10	17.59	3.51	2.77	0.79
2	21.10	17.30	3.80	3.09	0.81
3	21.09	17.45	3.64	2.97	0.81
4	21.10	17.56	3.54	2.80	0.79
5	21.13	17.49	3.64	2.80	0.77
6	21.13	17.63	3.50	2.66	0.76
		30 cc. Water			
1	21.16	17.70	3.46	2.42	0.70
2	21.12	17.58	3.54	2.71	0.77
3	21.13	17.55	3.58	2.67	0.75
4	21.14	17.42	3.72	2.77	0.75
5	21.14	17.37	3.77	2.83	0.75
6	21.15	17.46	3.69	2.70	0.73
		Dextrose			
1	21.09	18.12	2.97	2.28	0.73
2	21.04	17.97	3.07	2.65	0.86
3	21.05	17.95	3.10	2.62	0.85
4	21.01	17.98	3.13	2.71	0.87
5	21.05	18.04	3.01	2.54	0.85
6	21.06	18.17	2.89	2.38	0.82

Table V (continued)

Respiratory Metabolism in Monkeys

Monkey No. 30

Time Hours	Per cent Oxygen Inspired Air	Per cent Oxygen Expired Air	Per cent Oxygen Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient
			Mannitol		
1	21.06	18.76	2.30	1.78	0.77
2	21.03	18.52	2.51	2.14	0.85
3	21.01	18.57	2.44	2.13	0.87
4	21.00	18.64	2.36	2.13	0.90
5	21.02	18.51	2.51	2.17	0.86
6	21.03	18.40	2.63	2.22	0.84

Animal was very restless after this substance

Time Hours	Per cent Oxygen Inspired Air	Per cent Oxygen Expired Air	Per cent Oxygen Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient
			Sorbitol		
1	21.08	18.55	2.53	1.88	0.74
2	21.08	18.42	2.66	2.06	0.77
3	21.08	18.48	2.60	1.98	0.76
4	21.07	18.45	2.62	2.06	0.79
5	21.08	18.38	2.70	2.09	0.77
6	21.07	18.45	2.62	2.06	0.79
			Sorbitol Syrup		
1	21.10	18.27	2.83	2.11	0.75
2	21.10	18.11	2.99	2.26	0.76
3	21.08	18.01	3.07	2.43	0.79
4	21.09	17.93	3.16	2.47	0.78
5	21.09	17.88	3.21	2.52	0.79
6	21.13	17.47	3.66	2.78	0.76

Table VI

Respiratory Metabolism in Monkeys

Monkey No. 31

Time Hours	Per cent Oxygen Inspired Air	Per cent Oxygen Expired Air	Per cent Oxygen Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient
		Control			
1	21.22	16.42	4.80	3.46	0.72
2	21.20	16.43	4.77	3.58	0.75
3	21.19	16.59	4.60	3.44	0.75
4	21.18	16.56	4.62	3.51	0.76
5	21.18	16.64	4.54	3.41	0.75
6	21.18	16.59	4.59	3.48	0.75
		30 cc. Water			
1	21.21	17.29	3.92	2.65	0.68
2	21.21	16.57	4.64	3.36	0.72
3	21.21	16.82	4.39	3.13	0.71
4	21.22	16.12	5.10	3.77	0.74
5	21.21	16.51	4.70	3.46	0.74
6	21.22	16.31	4.91	3.57	0.73
		Dextrose			
1	21.20	16.47	4.73	3.52	0.74
2	21.12	16.56	4.56	3.75	0.82
3	21.09	16.44	4.65	3.97	0.85
4	21.07	16.49	4.58	4.04	0.88
5	21.08	16.58	4.50	3.88	0.86
6	21.13	16.47	4.66	3.80	0.81

Table VI (continued)

Respiratory Metabolism in Monkeys

Monkey No. 31

Time Hours	Per cent Oxygen Inspired Air	Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient
		Mannitol			
1	21.21	17.22	3.99	2.71	0.68
2	21.20	17.12	4.08	2.89	0.71
3	21.17	17.12	4.05	2.97	0.73
4	21.17	17.12	4.16	3.08	0.74
5	21.20	16.84	4.36	3.14	0.72
6	21.20	16.86	4.34	3.13	0.72
		Sorbitol			
1	21.19	17.02	4.17	3.01	0.72
2	21.16	16.63	4.53	3.51	0.77
3	21.18	16.70	4.48	3.36	0.75
4	21.19	16.80	4.39	3.22	0.73
5	21.20	16.62	4.58	3.38	0.74
6	21.18	16.54	4.64	3.52	0.76
		Sorbitol Syrup			
1	21.18	17.17	4.01	2.88	0.72
2	21.13	16.93	4.20	3.32	0.79
3	21.10	17.10	4.00	3.24	0.81
4	21.14	16.71	4.43	3.50	0.79
5	21.13	17.00	4.13	3.23	0.78
6	21.17	16.78	4.39	3.32	0.76

Table VII

Respiratory Metabolism in Monkeys

Monkey No. 32

Time Hours	Per cent Oxygen Inspired Air	Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient
		Control			
1	21.20	17.45	3.75	2.51	0.70
2	21.20	17.15	4.05	2.87	0.71
3	21.20	17.18	4.02	2.83	0.70
4	21.14	17.31	3.83	2.88	0.75
5	21.14	17.34	3.80	2.86	0.75
6	21.11	17.29	3.82	2.85	0.75
		30 cc. Water			
1	21.13	17.71	3.42	2.51	0.73
2	21.17	17.50	3.67	2.59	0.71
3	21.14	17.78	3.36	2.42	0.72
4	21.16	17.60	3.56	2.53	0.71
5	21.15	17.75	3.40	2.42	0.71
6	21.17	17.55	3.62	2.55	0.70
		Dextrose			
1	21.13	17.76	3.37	2.50	0.74
2	21.05	17.95	3.10	2.58	0.83
3	21.04	17.57	3.47	3.04	0.88
4	21.01	17.85	3.16	2.85	0.90
5	21.02	17.94	3.08	2.74	0.89
6	21.08	17.87	3.21	2.59	0.81

Table VII (continued)

Respiratory Metabolism in Monkeys

Monkey No. 32

Time Hours	Per cent Oxygen Inspired Air	Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient
Mannitol					
1	21.08	18.04	3.04	2.40	0.79
2	21.08	17.76	3.32	2.70	0.81
3	21.08	17.65	3.43	2.80	0.82
4	21.07	17.83	3.24	2.68	0.83
5	21.12	17.64	3.48	2.66	0.76
6	21.10	17.58	3.52	2.77	0.79
Animal restless after this substance					
Sorbitol					
1	21.20	17.35	3.85	2.61	0.68
2	21.20	17.36	3.84	2.67	0.70
3	21.15	17.63	3.52	2.54	0.72
4	21.13	17.55	3.58	2.70	0.75
5	21.15	17.52	3.63	2.65	0.73
6	21.13	17.63	3.50	2.61	0.75
Sorbitol Syrup					
1	21.14	17.86	3.28	2.34	0.71
2	21.12	17.93	3.19	2.37	0.74
3	21.14	17.57	3.56	2.64	0.74
4	21.14	17.66	3.48	2.55	0.73
5	21.14	17.62	3.52	2.60	0.74
6	21.14	17.47	3.67	2.75	0.75

mannitol (Sollmann 1936) which is responsible for its laxative action. Sorbitol also possesses this laxative property when ingested in sufficient quantity. This action, therefore, limits the amount of these compounds that can be tolerated at one time. In order to make the metabolic study in man useful, it seemed desirable to determine the amount of each substance which would produce a laxative action.

Several adult individuals ingested these compounds in progressively increasing amounts until a laxative action was produced. The time of ingestion was usually an hour or so before a meal and at least 2 days elapsed between the administration of successive doses to the same person. By this procedure the approximate laxative threshold of each compound was established in several normal subjects, the "threshold dose" being the minimum amount of each substance which produced very soft or watery stools in 50 per cent or more of the subjects.

The findings,presented in Table VIII, show that the defined laxative action was produced after the oral administration of 10 gm. of mannitol, 25 gm. of sorbitol syrup and 50 gm. of sorbitol

Influence on Respiratory Quotient and Blood-Sugar Level in Man. Observations which comprise this part of the study were made in several normal individuals. The effects of these sugar alcohols on the respiratory quotient and blood-sugar level were taken as criteria of utilization and compared to the effects produced by dextrose. Standard procedures employed in basal metabolism and carbohydrate tolerance curve determinations were observed in this work.

Expired air of ten-minute periods was collected in a Tissot tank and samples were taken for respiratory quotient determinations using the Haldane-Henderson technique. Capillary blood for sugar determinations was obtained

Table VIII

Laxative Threshold in Man

Amount Ingested Gm.	Number of Subjects	Number Reporting Laxative Action
	Mannitol	
5	12	0
*10	12	9
15	6	4
20	3	2
25	5	5
	Sorbitol	
10	6	0
25	10	0
*50	4	2
	Sorbitol Syrup	
10	8	0
20	5	1
*25	8	5
30	1	1

*Threshold dose.

from the finger tip after each respiration period and was analyzed by the method of Folin (1928).

All of these experiments were started early in the morning and were conducted between 8:30 A.M. and 12 noon on subjects who had fasted since the previous evening meal. Upon arrival at the laboratory the fasted subject reclined on a cot and was undisturbed for at least 30 minutes. The basal respiratory quotient and fasting blood sugar were then determined and the subject ingested a weighed quantity of the compound under investigation. While the subject remained on the cot respiratory quotient and blood-sugar concentration were estimated at intervals of 1/2 hour , 1 hour and 2 hours thereafter. In this routine manner it was possible to study the metabolic activity of dextrose, mannitol, sorbitol and sorbitol syrup in each individual.

Only 2 subjects were used in experiments in which 50 gm. of sorbitol were ingested. This amount is about the maximum quantity of this substance which can be tolerated without producing a laxative action. Mannitol and sorbitol syrup were not ingested in this quantity for the same reason. The standard amount of 25 gm. of each compound was adopted and, for comparison, only 25 gm. of dextrose were used in this series of tests.

The results of each experiment are shown in Tables IX to XVII. A summary of this data is compiled in Table XVIII.

Table IX

Respiratory Quotient and Blood-Sugar Level in Man

Subject, N.C.

Time Hours	Per cent Oxygen Inspired Air	Per cent Oxygen Expired Air	Per cent Oxygen Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
Dextrose - 50 Gm.						
Basal	21.08	17.25	3.83	3.15	0.83	80
1/2	21.20	16.57	4.63	3.38	0.75	104
1	21.07	17.61	3.46	2.85	0.82	111
2	21.02	17.77	3.25	2.86	0.88	111
Sorbitol - 50 Gm.						
Basal	21.16	16.42	4.74	3.67	0.77	85
1/2	21.20	16.42	4.78	3.56	0.75	97
1	21.08	16.93	4.15	3.45	0.83	101
2	20.92	17.62	3.30	3.39	1.02	93

Table X

Respiratory Quotient and Blood-Sugar Level in Man

Subject, S.F.

Time Hours	Per cent Oxygen Inspired Air	Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
			Dextrose - 50 Gm.			
Basal	21.13	16.74	4.39	3.46	0.79	85
1/2	21.08	16.89	4.19	3.48	0.83	143
1	20.99	17.35	3.64	3.40	0.93	120
2	20.96	17.19	3.77	3.68	0.97	108
			Sorbitol - 50 Gm.			
Basal	21.14	16.31	4.83	3.84	0.79	101
1/2	21.02	16.95	4.07	3.67	0.90	111
1	20.93	17.66	3.27	3.33	1.02	93
2	20.97	17.62	3.35	3.18	0.95	93

Table XI

Respiratory Quotient and Blood-Sugar Level in Man

Subject, R.S.

Time Hours	Per cent Oxygen Inspired Air	Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
			Dextrose - 25 Gm.			
Basal	21.18	15.66	5.52	4.35	0.78	115
1/2	21.14	15.53	5.61	4.62	0.82	182
1	21.09	15.84	5.25	4.52	0.86	119
2	12.08	16.05	5.03	4.36	0.87	110
			Sorbitol - 25 Gm.			
Basal	21.30	14.74	6.56	4.83	0.74	102
1/2	21.17	15.47	5.70	4.58	0.81	114
1	21.12	15.84	5.28	4.40	0.83	110
2	21.13	15.77	5.36	4.45	0.83	102

Table XII

Respiratory Quotient and Blood-Sugar Level in Man

Subject, S.S.

Time Hours	Per cent Oxygen Inspired Air	Per cent Oxygen Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
			Dextrose - 25 Gm.			
Basal	21.17	15.96	5.21	4.12	0.79	123
1/2	21.21	15.43	5.78	4.50	0.78	143
1	21.17	15.41	5.76	4.65	0.81	123
2	21.17	16.00	5.17	4.08	0.79	119
			Sorbitol - 25 Gm.			
Basal	21.23	15.11	6.12	4.71	0.77	118
1/2	21.21	15.26	5.95	4.66	0.78	127
1	21.25	15.48	5.77	4.28	0.74	118
2	21.18	15.53	5.65	4.49	0.79	118

Table XIII

Respiratory Quotient and Blood-Sugar Level in Man

Subject, C.J.C.

Time Hours	Per cent Oxygen			Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
	Inspired Air	Expired Air	Consumed			
Dextrose - 25 Gm.						
Basal	21.26	15.30	5.96	4.41	0.74	97
1/2	21.33	14.83	6.50	4.64	0.71	125
1	21.21	15.35	5.86	4.56	0.78	125
2	21.10	15.75	5.35	4.58	0.86	125
Mannitol - 25 Gm.						
Basal	21.14	17.27	3.87	2.90	0.75	100
1/2	21.18	16.97	4.21	3.06	0.73	100
1	21.14	17.12	4.02	3.07	0.76	99
2	21.15	17.32	3.83	2.79	0.73	99
Sorbitol - 25 Gm.						
Basal	21.20	16.17	5.03	3.80	0.75	120
1/2	21.13	17.09	4.04	3.11	0.77	130
1	21.11	17.25	3.86	3.04	0.79	119
2	21.09	17.32	3.77	3.02	0.80	118
Sorbitol Syrup - 25 Gm.						
Basal	21.24	15.10	6.14	4.68	0.76	98
1/2	21.16	15.41	5.75	4.69	0.82	95
1	21.19	15.09	6.10	4.90	0.81	98
2	21.17	15.15	6.02	4.90	0.81	95

Table XIV

Respiratory Quotient and Blood-Sugar Level in Man

Subject, N.M.C.

Time Hours	Per cent Oxygen Inspired Air	Per cent Oxygen Expired Air	Consumed	Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
			Dextrose - 25 Gm.			
Basal	21.14	16.86	4.28	3.31	0.77	96
1/2	21.16	16.95	4.21	3.15	0.75	161
1	21.08	17.18	3.90	3.24	0.83	148
2	21.00	17.65	3.35	3.04	0.91	99
			Mannitol - 25 Gm.			
Basal	21.13	17.18	3.95	3.02	0.76	85
1/2	21.18	17.05	4.13	2.96	0.72	87
1	21.13	17.16	3.97	3.06	0.77	85
2	21.11	17.23	3.88	3.07	0.79	85
			Sorbitol - 25 Gm.			
Basal	21.16	16.98	4.18	3.11	0.74	87
1/2	21.20	16.70	4.50	3.25	0.72	89
1	21.13	17.00	4.13	3.19	0.77	89
2	21.16	16.94	4.22	3.17	0.75	86
			Sorbitol Syrup - 25 Gm.			
Basal	21.13	16.80	4.33	3.39	0.78	100
1/2	21.20	16.58	4.62	3.36	0.73	101
1	21.17	16.64	4.53	3.43	0.76	101
2	21.13	16.83	4.30	3.37	0.78	99

Table XV

Respiratory Quotient and Blood-Sugar Level in Man

Subject, W.E.E.

Time Hours	Per cent Oxygen			Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
	Inspired Air	Expired Air	Consumed			
Dextrose - 25 Gm.						
Basal	21.18	17.00	4.18	3.03	0.72	110
1/2	21.13	16.76	4.37	3.46	0.80	154
1	21.08	17.03	4.05	3.40	0.84	147
2	21.12	17.03	4.09	3.23	0.79	93
Mannitol- 25 Gm.						
Basal	21.18	16.09	5.09	3.94	0.77	102
1/2	21.18	15.85	5.33	4.16	0.78	100
1	21.18	15.65	5.55	4.36	0.79	99
2	21.17	15.79	5.38	4.26	0.79	99
Sorbitol - 25 Gm.						
Basal	21.05	18.29	2.76	2.21	0.79	98
1/2	21.04	17.52	3.52	3.05	0.86	107
1	21.02	17.24	3.78	3.41	0.90	100
2	20.96	17.32	3.64	3.54	0.98	97
Sorbitol Syrup - 25 Gm.						
Basal	21.24	16.14	5.10	3.66	0.72	103
1/2	21.21	16.13	5.08	3.77	0.74	103
1	21.17	16.26	4.91	3.79	0.77	100
2	21.20	16.34	4.86	3.63	0.75	93

Table XVI

Respiratory Quotient and Blood-Sugar Level in Man

Subject, W.C.G.

Time Hours	Per cent Oxygen			Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
	Inspired Air	Expired Air	Consumed			
			Dextrose - 25 Gm.			
Basal	21.14	16.77	4.37	3.39	0.77	102
1/2	21.15	16.55	4.60	3.58	0.78	145
1	21.11	16.70	4.40	3.60	0.82	118
2	21.09	16.86	4.23	3.50	0.83	101
			Mannitol - 25 Gm.			
Basal	21.11	16.73	4.38	3.57	0.81	99
1/2	21.12	16.79	4.33	3.45	0.80	100
1	21.12	16.61	4.51	3.65	0.81	98
2	21.09	16.70	4.39	3.65	0.83	98
			Sorbitol - 25 Gm.			
Basal	21.16	15.53	5.63	4.57	0.81	98
1/2	21.16	15.66	5.50	4.43	0.81	99
1	21.17	15.67	5.50	4.40	0.80	100
2	21.18	15.23	5.95	4.80	0.81	99
			Sorbitol Syrup - 25 Gm.			
Basal	21.15	16.73	4.42	3.40	0.77	98
1/2	21.15	16.84	4.31	3.29	0.77	105
1	21.11	16.74	4.37	3.55	0.81	98
2	21.14	16.50	4.64	3.65	0.78	99

Table XVII

Respiratory Quotient and Blood-Sugar Level in Man

Subject, M.M.R.

Time Hours	Per cent Oxygen			Per cent Carbon Dioxide Eliminated	Respiratory Quotient	Blood Sugar Mgm. per cent
	Inspired Air	Expired Air	Consumed			
Dextrose - 25 Gm.						
Basal	21.12	16.67	4.45	3.59	0.80	107
1/2	21.17	16.82	4.35	3.26	0.75	120
1	21.08	16.65	4.43	3.76	0.85	105
2	21.10	17.08	4.02	3.24	0.81	90
Mannitol - 25 Gm.						
Basal	21.19	15.52	5.67	4.48	0.79	94
1/2	21.14	15.95	5.19	4.20	0.81	90
1	21.13	16.40	4.73	3.82	0.81	90
2	21.09	16.30	4.79	4.01	0.84	90
Sorbitol - 25 Gm.						
Basal	21.14	16.60	4.54	3.54	0.77	102
1/2	21.03	17.29	3.74	3.31	0.89	102
1	21.13	16.78	4.35	3.41	0.78	100
2	21.06	17.42	3.64	3.07	0.84	101
Sorbitol Syrup - 25 Gm.						
Basal	21.08	16.92	4.16	3.50	0.84	93
1/2	21.13	16.54	4.59	3.69	0.80	95
1	21.14	16.54	4.60	3.64	0.79	93
2	21.08	16.66	4.42	3.74	0.84	95

Table XVIII

Respiratory Quotient and Blood-Sugar Level in Man After Dextrose, Sorbitol and Mannitol

Summary

			Average Values							
		No.	Basal		1/2 hr.		1 hr.		2 hrs.	
Substance	Amt. Gm.	of Exp.	R.Q.	Blood Sugar	R.Q.	Blood Sugar	R.Q.	Blood Sugar	R.Q.	Blood Sugar
Dextrose	50	2	0.81	82	0.79	123	0.87	115	0.92	109
Sorbitol	50	2	0.78	93	0.83	104	0.93	97	0.98	93
Dextrose	25	7	0.77	107	0.77	147	0.82	126	0.83	105
Sorbitol	25	7	0.77	104	0.81	110	0.80	105	0.83	103
Sorbitol Syrup	25	5	0.77	98	0.77	100	0.79	98	0.79	96
Mannitol	25	5	0.78	96	0.77	95	0.79	94	0.79	94

TOXICITY OF MANNITOL AND SORBITOL

Chronic Toxicity in Monkeys. An attempt was made to use Capuchin monkeys in these studies but they proved to be unsatisfactory laboratory animals. Some of the experiments which are described below were conducted on these monkeys but when control animals showed pathological indications, it was decided to abandon the use of this species in this work.

The chronic toxicity of these compounds was then studied in male and female Rhesus monkeys, weighing from 3 to 4 kg., by means of 2 series of feeding experiments, A and B, each of which lasted for 3 months. In each series, 9 experimental animals, divided into 3 equal groups, and 2 control animals were employed.

For one week prior to the beginning of these experiments, all of the animals were fed a regular diet consisting of apples, carrots and sunflower seeds and were maintained on this diet for the duration of the feeding period. At the end of this week, the animals were weighed and the blood sugar and urea nitrogen were determined. The blood sugar was estimated by the method of Folin (1928) and Karr's direct Nesslerization method (1924) was used to determine the urea nitrogen.

At this point the feeding experiments were started and about 3 gm. of one of the sugar alcohols were added daily to the diet of each group of the experimental animals. This was accomplished by putting the material into a small hole bored in the apple and covering it with scrapings. The sweet taste which these substances possessed appealed to the monkeys in such a way that they always ate this part of the apple first.

The weight, blood sugar and urea nitrogen of each monkey were determined at intervals of 2 or 3 weeks throughout the course of these feeding periods. These values showed no significant variations from the normal values and only the initial and terminal determinations of each series are shown in Tables XIX and XX. During the course of these experiments 2 animals were lost from the first series and one animal was lost from the second series. Bacteriological and pathological examinations revealed the cause of all deaths was due to tuberculosis.

At the conclusion of each experiment the animals were sacrificed and routine autopsies were performed. Sections of the livers and kidneys were prepared and examined histopathologically. The results of these examinations are reported below.

Series A

Control Monkeys:
- No. 20 Kidney - granular casts in scattered collecting tubules
  - Liver - no significant lesions
- No. 22 Kidney - nearly all glomeruli show fine to coarse dusting with brown pigment, probably hemosiderin.
  - Liver - Sinusoids dilated and scattered. Kupfer cells contain brown pigment. Centers of lobules are relatively pale staining.

Mannitol Monkeys:
- No. 17 Kidney - no lesions
  - Liver - generalized pallor
- No. 19 Died during course of experiment
- No. 21 Died during course of experiment

Sorbitol Monkeys:
- No. 12 Kidney - a few glomeruli contain spindle shaped pigment related to urinary sediment.
  - Liver - halo of rarefied cells around each efferent vein. In scattered areas cells are swollen, obliterating the sinusoids. The greater portion of the parenchyma appears normal.
- No. 13 Kidney - negative findings
  - Liver - pale staining
- No. 16 Kidney - glomerular tufts dusted with brown pigment
  - Liver - Kupfer cells dusted with brown pigment. Two periportal collections of neutrophiles noted.

Sorbitol Syrup Monkeys:
No. 11 Kidney - no significant lesions.
Liver - fatty vacuolization of cells around and between each portal triad.
No. 14 Kidney - no significant lesions.
Liver - no significant lesions.
No. 15 Kidney - no significant lesions.
Liver - no significant lesions.

Series B

Control Monkeys:
No. 96 Kidney - no significant lesions.
Liver - generalized pallor, most marked in centrolobular areas.
No. 97 Kidney - occasional glomeruli contain subcapsular serum.
Liver - generalized pallor, most marked in centrolobular areas.

Mannitol Monkeys:
No. 89 Kidney - no significant lesions.
Liver - no significant lesions.
No. 90 Kidney - no significant lesions.
Liver - no significant lesions.
No. 93 Died during course of experiment

Sorbitol Monkeys:
No. 95 Kidney - focal collections of lymphocytes, plasma cells and monocytes are scattered through cortex.
Liver - slight to marked rarefaction of cytoplasm in centrolobular areas. One-half of lobule involved and process is most marked beneath the capsule.
No. 98 Kidney - no significant lesions.
Liver - slight rarefaction in centrolobular areas.
No. 99 Kidney - no significant lesions.
Liver - slight rarefaction in centrolobular areas.

Sorbitol Syrup Monkeys:
No. 91 Kidney - no significant lesions.
Liver - no significant lesions.
No. 92 Kidney - No significant lesions.
Liver - rarefaction of parenchyma, conspicuous near capsule.
No. 94 Kidney - no significant lesions.
Liver - slight centrolobular rarefaction.

Conclusions - no significant degenerative changes which could be related to toxicity were noted in any of the animals except No. 95. In this animal the cytoplasm of the parenchymal liver cells showed areas of marked rarefaction. This condition may have been due to inflammatory changes in the kidney.

Table XIX

Effect of Sugar Alcohols on Weight, Blood Sugar and Urea Nitrogen of Rhesus Monkeys

Series A

3 Gm. Daily for 3 Months

Monkey No.	Weight Kgm.	Blood Sugar mgm. per cent	Urea Nitrogen mgm. per cent	Weight Kgm.	Blood Sugar mgm. per cent	Urea Nitrogen mgm. per cent
		Before			After	
			Control			
20	3.65	121	16.1	3.79	133	13.6
22	4.02	129	32.1	3.97	166	19.7
			Mannitol			
17	3.90	166	15.7	3.55	133	16.7
19	4.49	114	13.6	Lost - Tuberculosis		
21	4.22	133	22.1	Lost - Tuberculosis		
			Sorbitol			
12	4.46	129	17.8	3.93	153	13.9
13	3.73	102	15.5	3.48	148	16.4
16	4.21	153	17.4	3.87	200	23.0
			Sorbitol Syrup			
11	4.48	114	17.4		75	14.4
14	3.62	111	18.7	3.12	141	13.6
15	3.92	100	20.5	3.78	166	

Table XX

Effect of Sugar Alcohols on Weight, Blood Sugar and Urea Nitrogen of Rhesus Monkeys

Series B

3 Gm. Daily for 3 Months

Monkey No.	Weight Kgm.	Blood Sugar mgm. per cent	Urea Nitrogen mgm. per cent	Weight Kgm.	Blood Sugar mgm. per cent	Urea Nitrogen mgm. per cent
	Before			After		
			Control			
96	3.25	123	20.4	4.31	126	7.3
97	3.25	120	16.8	3.73	90	10.4
			Mannitol			
89	3.20	105	20.0	3.56	90	11.8
90	3.47	143	17.3	3.98	125	5.4
93	3.10	119	17.4	Lost - Tuberculosis		
			Sorbitol			
95	3.40	137	13.4	3.86	117	5.4
98	3.60	105	17.5	4.18	105	14.1
99	2.62	136	20.1	3.50	104	11.7
			Sorbitol Syrup			
91	3.76	133	15.7	3.88	126	11.8
92	4.10	140	15.0	4.10	128	10.0
94	3.02	109	15.4	3.25	91	7.9

The liver changes observed in one monkey, a sorbitol animal, have been interpreted as the result of the kidney involvement rather than as the result of sorbitol feeding since only one animal out of six receiving this compound was affected. The results of these experiments indicate generally that these compounds are non-toxic when fed over a long period of time to monkeys.

Chronic Toxicity in Man. The literature contains no report on the toxic effect of mannitol and sorbitol after prolonged administration to man. It has been shown, however, that the intravenous administration to normal men of as much as 80 gm. of either mannitol or sorbitol produced no acute toxic symptoms (Smith, et al. 1940). In as much as the feeding experiments in monkeys indicated no pathology it seemed desirable to investigate the chronic effects in man.

In this investigation the chronic toxicity was studied in 3 adult individuals. In 3 separate experiments each person ingested 10 gm. of sorbitol syrup, sorbitol and mannitol, respectively, each day for a period of one month. At the beginning and end of each period the red blood cell count (R.B.C.), non-protein nitrogen (N.P.N.) and carbon dioxide combining power (CO_2) of the blood were determined in the clinical laboratory of the University Hospital. Kidney function was estimated by the phenolsulfonephthalein test (P.S.P.).

During each experiment several 24-hour urine samples were analyzed for sugar alcohol content by the method of Todd, et al. (1939). This method is not specific for sugar alcohols and a correction factor must be determined for reducing substances normally present in the urine. According to this method there was no significant excretion of mannitol or sorbitol in the urine during these experiments. The urine was tested frequently for the presence of proteins and negative results were always obtained.

The results of the blood analyses and kidney function tests are summarized in Table XXI. These data show no appreciable variations from the normal values and no impairment of kidney function is indicated.

Table XXI

Results of Prolonged Administration of Mannitol and Sorbitol to Man

10 Gm. Daily for One Month

Subject	R.B.C. x 10^3	CO_2 Volumes per cent	N.P.N. mgm. per cent	P.S.P. per cent Elimination	R.B.C. x 10^3	CO_2 Volumes per cent	N.P.N. mgm. per cent	P.S.P. per cent Elimination
	Before				After			
				Mannitol				
A.K.	4450	54	28	65	4550	53	25	70
F.E.	4750	61	26	65	4240	52	22	75
G.L.	4710	63	37	70	4650	55	33	75
				Sorbitol				
A.K.	4830	45	28	55	4450	54	28	65
F.E.	4320	51	26	70	4750	61	26	65
G.L.	4900	48	38	65	4710	63	37	70
				Sorbitol Syrup				
A.K.	4060	39	28	55	4830	45	28	55
F.E.	5490	47	35	65	4320	51	26	70
G.L.	4960	47	35	65	4900	48	38	65

DISCUSSION

In studying the metabolism of true carbohydrates one logically assumes that the primary concern is with the changes dextrose undergoes after absorption. Mannitol and sorbitol are not true sugars and one can not presuppose theoretically that their fate in the body follows the same course as dextrose. However, the close resemblance between the chemical structures of dextrose and these sugar alcohols is of sufficient significance and interest to warrant their metabolic study. In this investigation the capacity of mannitol and sorbitol to furnish energy and store reserve carbohydrate in the body has been studied by some of the same methods employed in tracing the fate of dextrose.

The results obtained in the nutritional evaluation of mannitol and sorbitol agree in general with the findings of previous workers. Mice and rats seem to tolerate sorbitol better than mannitol which is probably due to the fact that the laxative property of sorbitol is not as great as that of mannitol. Therefore, these compounds can serve only to a limited extent as carbohydrates in the diet of mice and rats.

This work appears to be the first investigation relating to the capacity of mannitol and sorbitol to form glycogen in monkeys. In this species of animal the oral administration of these compounds leads to a deposition of liver glycogen. As a precursor of glycogen in the monkey sorbitol seems to be better than mannitol while sorbitol syrup apparently does not significantly store glycogen. The difference in utilization of sorbitol syrup may be explained on the basis of the composition of the syrup as will be pointed out later in the discussion.

The studies of respiratory metabolism in monkeys were somewhat disappointing. A considerable amount of time was consumed trying to accustom the animals to the procedure but because of their extremely excitable nature they very rarely remained quiet during an experiment. It was observed that the animals were particularly restless after receiving mannitol. Perhaps this was due to the severe intestinal irritation produced by this substance. In view of this fact very little significance has been attached to the high respiratory quotient values obtained after mannitol. The general interpretation of this part of the work is that these compounds do not significantly influence the respiratory quotient of the monkey according to the previously described procedure. It might be added, however, that perhaps this method is unsuited for a reliable metabolic study.

In the human experiments the results demonstrate the capacity of sorbitol to increase the respiratory quotient without appreciably elevating the blood sugar. This is in agreement with the late work of Porrati and Rowinski (1938) who administered 50 Gm. of sorbitol to normal subjects and observed an increase in the respiratory quotient above the basal level which was similar within 4 hours to that of an equal quantity of glucose. The blood-sugar level after sorbitol remained practically normal. In the present investigation it was found that after 25 gm. or 50 gm. of sorbitol the respiratory quotient was raised within 2 hours as high or higher than after an equivalent amount of dextrose and the blood sugar was not significantly elevated. There were, of course, exceptions and variations within the individual experiments but the average values obtained support this general conclusion. Mannitol and sorbitol syrup did not produce a notable effect on either the respiratory quotient or the blood-sugar level.

Throughout these experiments it has been observed that sorbitol syrup apparently was not utilized at all. On the other hand, sorbitol was metabolized, at least in part, in all of the experiments. At the beginning of this study it was naturally assumed that the syrup would be utilized to some extent on the basis of its high sorbitol content and it was interesting to learn that experimentation did not support this assumption. Therefore, any explanation of this metabolic inactivity of sorbitol syrup that might be offered by the author would be purely theoretical. However, in reviewing the composition of sorbitol syrup as described earlier in this report, one observes that the syrup contains sugar alcohol anhydrides. It has been shown that certain of these anhydrides possess the unusual capacity to deplete the residual glycogen content of the livers of fasted rats after oral administration (Carr 1937). It is conceivable that the failure of sorbitol syrup to be metabolized may be attributed to the presence of such anhydrides in the syrup. Another point to be considered in explaining this phenomenon is that the laxative property of sorbitol syrup is about twice that of sorbitol and undoubtedly significant quantities of the syrup are eliminated through the intestinal tract by this mechanism.

The relative metabolic inactivity of mannitol as compared with the metabolism of sorbitol when ingested by human subjects is still more difficult to explain. The chemical structure of mannitol suggested that it might be oxidized to levulose in the body but this supposition had to be discarded when mannitol failed to influence either the blood sugar or respiratory quotient of normal subjects. Inasmuch as a small amount of mannitol produces intestinal irritation and is thereby probably eliminated from the body, it should be pointed out again here that this action may oppose absorption and indirectly be responsible, to a great extent,for its metabolic inactivity. However, Smith et al. (1940) reported that when 10 gm. of mannitol were administered intravenously to 2 normal men an average of 85 per cent of this compound was eliminated in the urine within 10 hours. These workers were primarily interested in the renal clearance of mannitol and, therefore, did not discuss its metabolism. The author is unable to offer further explanation on this point.

The mechanism by which sorbitol is utilized has received some attention but an explanation of this phenomenon is not entirely unchallenged. There is a great deal of evidence available to show that sorbitol is oxidized to levulose and probably, to some extent, directly to dextrose in the body. In some of the earlier European work sorbitol increased the urinary dextrose of phloridzinized animals and sorbitol perfusion of isolated livers from fasted dogs gave rise to levulose and dextrose in the perfusion fluid. This is a strong indication that sorbitol is oxidized to levulose in the liver, polymerized to glycogen and finally released into the blood stream as dextrose. Some of the work on human subjects also suggests that this change occurs in the body. Anschel (1930) reported a case of spontaneous levulosuria in which the subject was given 30 gm. of sorbitol. The blood dextrose was only slightly elevated but the blood contained 36 mgm. per cent of levulose. The author stated that the use of sorbitol was probably dependent upon its conversion to levulose and subsequent metabolism.

Silver and Reiner (1934) observed the effects of 50 gm. of sorbitol when given to a diabetic and to a fructosuric patient. In the diabetic hyperglycemia was produced and a small amount of dextrose was found in the urine. In the fructosuric patient the blood levulose was increased to 35 mgm. per cent and levulose was also excreted in the urine. In this patient about one-half as much levulose was excreted after sorbitol as after the same amount of levulose. These findings further indicate that the possible intermediate metabolism of sorbitol is through levulose.

If such a conversion of sorbitol takes place in the body it seems logical that the blood sugar would be elevated accordingly. As a matter of fact, the blood sugar is not significantly elevated after sorbitol and, therefore, it is conceivable that this compound undergoes oxidation to fructose so gradually that the liver liberates into the blood stream only a small but constant amount of dextrose which is available for ultimate utilization by the tissues. This would tend to keep the blood-sugar level relatively normal and at the same time provide enough fuel to maintain tissue metabolism.

The "insulinlockenden" (insulin-enticing) property described to sorbitol by Gottschalk (1929) may also help to explain the metabolism of this substance. This author listed sorbitol with dioxyacetone, fructose and inulin as substances which exert a strong stimulation of the secretion of insulin. According to this explanation sorbitol apparently requires as much insulin as dextrose but it is more capable of "attracting" the insulin needed for its oxidation than dextrose.

The renal threshold for sorbitol seems to be low as a small portion of this compound is excreted in the urine after the oral administration of 50 gm. or more. The small amount eliminated by the kidneys apparently does not affect significantly the quantity metabolized. After giving 100 gm. of sorbitol to normal subjects only 2 per cent was excreted in the urine (Gottschalk 1929). Porrati and Rowinski (1938) found small quantities of sorbitol in the urine of their patients after they had received 50 gm. of this compound, nevertheless, the respiratory quotient reached unity within 4 hours. After the intravenous administration of 9 gm. of sorbitol to one subject, 32 per cent of this sugar alcohol was excreted in the urine (Smith, et al. 1940). This may be explained by the fact thatafter such administration a considerable amount of the sorbitol must pass to the liver and, presumably, undergo transformation as discussed previously before it is available to the tissues. The information now at hand suggests the following course of intermediate metabolism for this sugar alcohol: sorbitol → levulose → glycogen → dextrose → lactic acid.

Although dextrose is formed as an intermediate metabolite of sorbitol the foregoing explanation suggests that this sugar-like substance may prove to be a very valuable substitute carbohydrate.

CONCLUSIONS

1. In mice and rats the laxative action of mannitol and sorbitol limited nutritional studies when these compounds comprised a portion of the diet.
2. Sorbitol served as a better precursor of glycogen in the liver of the fasted monkey than mannitol. Sorbitol syrup did not significantly store glycogen under similar conditions.
3. The laxative property of mannitol and sorbitol syrup rendered them unsuitable for metabolic study in human subjects. The moderately laxative property of sorbitol after oral administration interfered slightly with quantitative studies.
4. In normal subjects sorbitol increased the respiratory quotient without significantly elevating the blood-sugar level. The effect was similar within 2 hours to that of an equal quantity of dextrose. Mannitol and sorbitol syrup did not significantly influence either the blood-sugar level or the respiratory quotient.
5. The feeding of 3 gm. per day of mannitol and sorbitol to Rhesus monkeys over a period of 3 months produced no significant histopathological findings or toxicological indications which were attributed to these compounds.
6. In man the daily ingestion of 10 gm. of mannitol and sorbitol, respectively, for one month produced no significant changes in the N.P.N., the R.B.C., or the CO_2 combining power of the blood. The phenolsulfonephthalein test indicated no kidney damage.

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