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Research Article

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MANNOSE UTILIZATION IN MAN *

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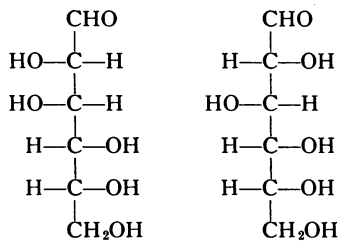
The metabolic similarities of D-mannose and D-glucose in isolated tissues from normal and diabetic rats have been previously reported (1).



Others have described the ability of mannose and glucose to provide substrate for the central nervous system after the hypoglycemia of hepatectomy or insulin administration (2–6). Administered parenterally, both hexoses protect animals against alloxan (7) and equally stimulate hepatic glycogenesis (8–10). The effects of insulin on their distribution in various tissues is similar (11–13). Both sugars support the motility of spermatozoa (14), and are similarly metabolized in the chick embryo (15).

On the other hand, there are differences between the metabolism of mannose and glucose. First, orally ingested mannose is difficult to detect in blood (16) and results in little deposition of glycogen in liver (8). The rate of mannose transport across the intestine is approximately one-tenth that of glucose both *in vivo* (17) and *in vitro* (18), suggesting diffusion of mannose in contrast to active transport of glucose. Second, mannose, in contrast to glucose, fails to stimulate measurable pancreatic release of insulin in both dogs (19) and man (20). Last, mannose appears in significant amounts in the urine after oral administration (16), suggesting a low or absent renal threshold. Others (21) have noted, in agreement, that 45% of rapidly infused mannose was excreted in the urine. The studies to be reported characterize further the utilization of mannose in man after both rapid and prolonged intravenous infusions. A preliminary report of this work has appeared (22).

METHODS

Mannose [1] for iv administration was obtained as a 50% solution (wt/vol) in water. Glucose and mannose concentrations in blood and urine were determined by the Somogyi-Nelson method (23, 24) before and after incubation with glucose oxidase (25). Mannose was not significantly metabolized by the enzyme, and appropriate corrections with known standards were made for mannose reduction (75% of that of glucose). Plasma FFA were determined by the method of Gordon (26).

Glucose or mannose (0.5 g per kg body weight) was administered into an antecubital vein through a no. 18 needle as a 25% solution in water in 3 to 5 minutes. Venous blood samples (about 3 ml) were collected every 10 minutes for 1 hour starting 10 minutes after the end of infusion, were gently mixed in tubes containing 20 mg potassium oxalate and 25 mg sodium fluoride, and frozen until hexose assay. Appropriate additional blood samples were similarly collected for the determination of FFA concentration in the supernatant plasma after centrifugation.

In one experiment on a normal subject, portions of the supernatant fluid, after precipitation of protein from blood samples, were deionized by passage through a mixed-bed resin (Amberlite MB-3), lyophilized, and chromatographed on Whatman 1 paper with *n*-butanol; acetic acid: water (4:1:5) as solvent. Similar chromatograms were run with glucose and mannose standards, either developed with ammoniacal silver nitrate or eluted, and their glucose and mannose determined by reduction before

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[1] Courtesy of Dr. Edwin B. McLean, Cutter Laboratories, Berkeley, Calif.

and after incubation with glucose oxidase. This procedure verified mannose as the primary reducing substance in blood not removed by glucose oxidase at all intervals after infusion of mannose.

Subjects for rapid-infusion studies included seven normal men, two normal women, four mild maturity-onset diabetic subjects on no treatment, and one severe, ketosis-prone diabetic subject whose last insulin dose was 24 hours before.

Other tests included iv administration of either crystalline zinc insulin [2] (0.1 U per kg) or sodium tolbutamide [3] (1 g in 20 ml distilled water) immediately before the glucose or mannose infusions. In these studies, blood was collected every 5 minutes. Also, the effect of insulin on mannose disappearance rate was studied in a normal person both with the normal concomitant fall in blood glucose, and also with this fall prevented by glucose infusion. All studies were performed with the subject supine after an overnight fast. Although there was no specific dietary pretreatment, the subjects had not been restricting calories or losing weight. Successive studies in a single subject were always separated by at least 1 week.

Disappearance rates were calculated on semilogarithmic paper by the method of Conard and associates (27, 28). The best straight line was drawn by eye, and the slope K determined as the logarithmic mantissa of the blood hexose concentration 23 minutes before the intersection of the line with that representing 100 mg per 100 ml (28). Although this technique introduces the possibility of subjective error, it is far simpler than detailed mathematical analysis, and paired calculations (28) have shown the subjective error to be minimal. With mannose, loss in the urine was also assumed to be exponential, and K was corrected accordingly (see Appendix). No correction was made for basal nonglucose reducing substance in the urine, which usually approximated 50 mg or less glucose equivalents per hour, since the amount of this material was minor relative to the 5 to 10 g of mannose in urine during the hour after infusion. An exception was diabetic patient EH, whose glucosuria resulted in a correction to a negative slope, signifying a net appearance of glucose in the plasma after exclusion of the glucose lost in the urine.

In a second series of experiments, mannose was administered for several hours at a rate of 0.5 g per kg body weight per hour, and plasma concentration and urinary excretion were determined. These studies included two normal subjects, one mild diabetic subject, and one severe, ketosis-prone diabetic subject, both of whom received no insulin for 24 hours before the test. In one of the normal subjects, insulin was also infused, and plasma and urine levels were determined (29) in order to characterize the mechanism of renal excretion of mannose.

Finally, to corroborate the animal studies demonstrating poor gastrointestinal absorption of mannose, a single normal subject received 0.5 g per kg body weight of mannose by mouth as a 20% solution. Appropriate blood and urine samples were collected for 2 hours, when he experienced marked abdominal cramps followed by sudden diarrhea. Further studies on oral absorption were not performed.

[2] Iletin, Eli Lilly & Co., Indianapolis, Ind.

[3] Orinase, The Upjohn Co., Kalamazoo, Mich.

RESULTS

Rapid infusion. Table I summarizes data from the rapid-infusion studies in nine normal and in five diabetic subjects. The percentage of administered mannose excreted in the urine is relatively constant except in one diabetic patient (WH) who was unable to empty his bladder completely. The correlation between mannose and glucose disappearance rates is evident.

Several weeks after regular mannose and glucose tolerance tests, two normal subjects received repeated glucose and mannose infusions immediately after an iv injection of 0.1 U per kg body weight crystalline zinc insulin.[2] Two others similarly received 1 g iv sodium tolbutamide [3] before administration of either hexose. Results of these studies are summarized in Table II and show acceleration of both glucose and mannose disappearance rates by both hypoglycemic agents. FFA concentrations in plasma were also determined in four normal and in four mild, maturity-onset diabetic subjects. Figure 1 illustrates that the characteristic decrease with glucose administration also occurs after mannose.

Since the effect of insulin in accelerating mannose disappearance could be secondary to lowering of glucose concentration and thereby to removal of a competitive inhibitor to mannose uptake, successive studies were designed in a single subject to support or exclude this possibility. Figure 2 shows that insulin accelerated mannose disappearance to a similar degree whether the blood glucose was allowed to fall, or whether it was sustained by glucose infusion. Thus insulin stimulated mannose disappearance primarily, and not secondarily by removal of a competitor.

In all the rapid mannose and glucose infusions, no subjective or objective symptoms or signs were noted by either subjects or observers, except for an occasional temporary flushing of the face after the start of the hypertonic infusion.

Prolonged infusion. In two normal subjects, mannose or glucose was given at the rate of 0.5 g per kg body weight per hour by a calibrated constant-infusion pump for 10 hours. In Figure 3 are

TABLE I.

*Concentration of glucose (G) and mannose (M) in blood after rapid infusion of 0.5 g mannose per kg body weight**

						Time in minutes after end of infusion															
				Preinfusion		10		20		30		40		50		60		Urine mannose	% of dose in urine	K_M	K_G
Subject	Sex	Age	Wt	G	M	G	M	G	M	G	M	G	M	G	M	G	M				
		years	*kg*															*g/l hr*			
Normal																					
FW	M	31	85	98	0	112	224	103	179	95	153	88	131	80	112	76	101	9.5	22	1.10	1.40
GC	M	32	85	78	0	92	220	90	183	87	153	86	133	90	115	76	96	8.0	19	1.15	1.55
AR	M	36	80	86	0	109	241	103	172	98	131	88	115	80	80	82	67	8.7	22	1.77	3.56
WM	M	30	64	72	0	80	202	98	171	84	138	80	116	72	101	66	93	8.5	27	1.90	1.43
YD	M	29	64	94	0	98	228	90	176	90	141	82	123	74	105	82	80	7.1	22	1.40	1.40
HF	M	43	118	86	0	89	230	72	179	70	157	56	133	56	115	52	93	9.9	17	1.37	2.10
LO	M	27	90	75	0	84	179	76	149	60	133	60	115	54	99	58	93	8.8	20	1.25	1.34
DC	F	24	50	62	0	58	136	36	93	42	64	28	51	28	43	32	32	4.3	17	2.16	3.62
MC	F	23	57	78	0	67	220	59	160	53	123	60	107	54	99	52	83	4.8	17	1.41	2.69
Mean ± SE				87±6		88±6	209±11	81±7	167±10	78±7	133±7	69±7	112±8	65±6	97±8	64±6	82±7		20±1	1.34 ±0.08	2.34 ±.29
Diabetic																					
HS	M	73	60	118	0	117	160	122	145	114	134	112	117	100	111	96	101	5.3	18	0.58	0.49
JK	M	72	51	89	0	87	128	90	117	92	96	88	88	82	83	76	76	4.1	16	0.64	0.49
RH	M	74	65	114	0	114	183	112	145	114	136	118	117	114	107	110	101	4.9	15	0.73	0.68
WH	M	76	85	79	0	76	183	65	160	79	147	70	131	66	120	60	112	2.0	5	0.81	0.83
EH	M	26	49	324	0	326	160	338	142	316	136	326	128	328	117	324	107	4.5	18	0.36	−1.33
																				0.62 ±0.08	

* Concentration in milligrams per 100 ml. K_M = disappearance rate constant of mannose into tissues, corrected for loss in urine (see Appendix). K_G = disappearance rate constant of glucose, calculated from glucose tolerance test done at another time.

TABLE II

*Effect of insulin and tolbutamide on glucose and mannose disappearance rate constants**

Subject	Experiment	K_G	K_M†
GC	Control	1.55	1.15
	Insulin	7.32	6.65
MC	Control	2.69	1.41
	Insulin	6.12	5.02
FW	Control	1.40	1.10
	Tolbutamide	2.24	2.03
DC	Control	3.62	2.10
	Tolbutamide	5.11	4.36

* Hexose (0.5 g per kg body weight) administered intravenously in 3 to 5 minutes. Insulin (0.1 U per kg) or sodium tolbutamide (1 g) given intravenously immediately before hexose infusion.

† Corrected for mannose loss in the urine (see Appendix).

plotted plasma and urinary hexose values. In both subjects, plasma mannose concentration rose to between 150 and 250 mg per 100 ml, and plasma glucose fell to 27 and 10 mg per 100 ml, respectively, by 5 hours and gradually returned to 40 mg per 100 ml until the end of the infusion. In both cases, urinary loss of mannose was proportionate to the plasma concentration, without evidence of a threshold. The second subject (RH) also received inulin according to clearance techniques (29), and the tubular reabsorption of mannose at all plasma concentrations studied for nine hourly periods was calculated to be 12.6 ± 4.0 (SD)% of the quantity filtered, with inulin clearance assumed to be equivalent to glomerular filtration. This observation also supports the assumption that the loss of mannose in urine is exponential, thereby permitting the correction for urine loss in the rapid-infusion studies (see Appendix).

At the end of the infusion, the first subject (PB) felt fatigued and anorectic. These symp-

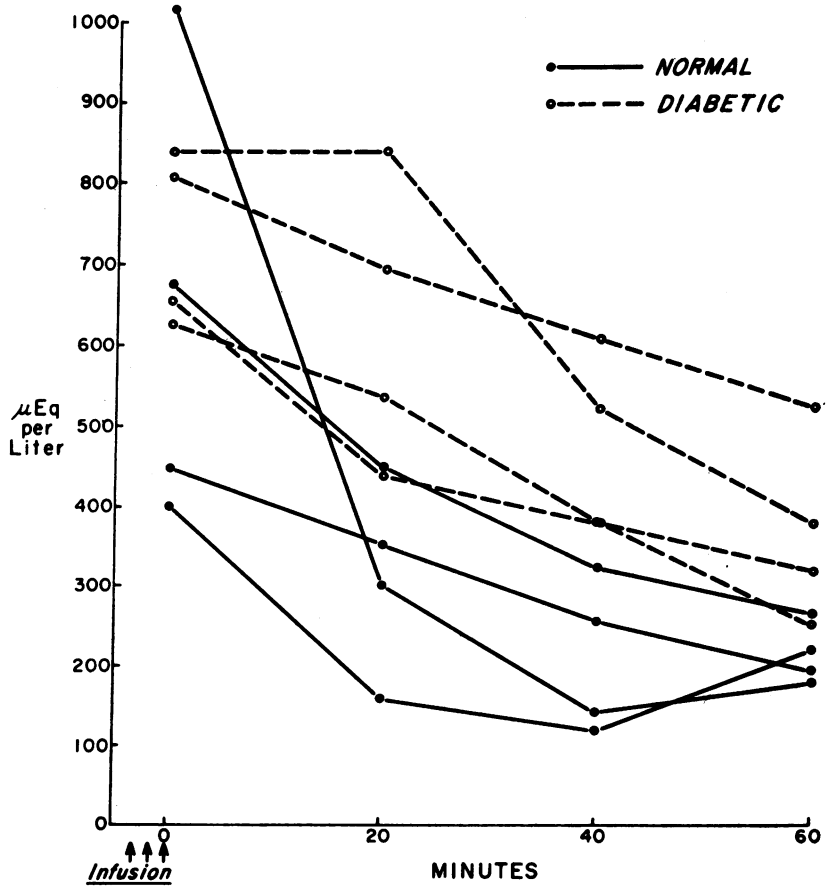


FIG. 1. DECREASE IN THE CONCENTRATION OF PLASMA FFA AFTER RAPID INFUSION OF MANNOSE (0.5 G PER KG) TO FOUR NORMAL AND FOUR DIABETIC SUBJECTS.

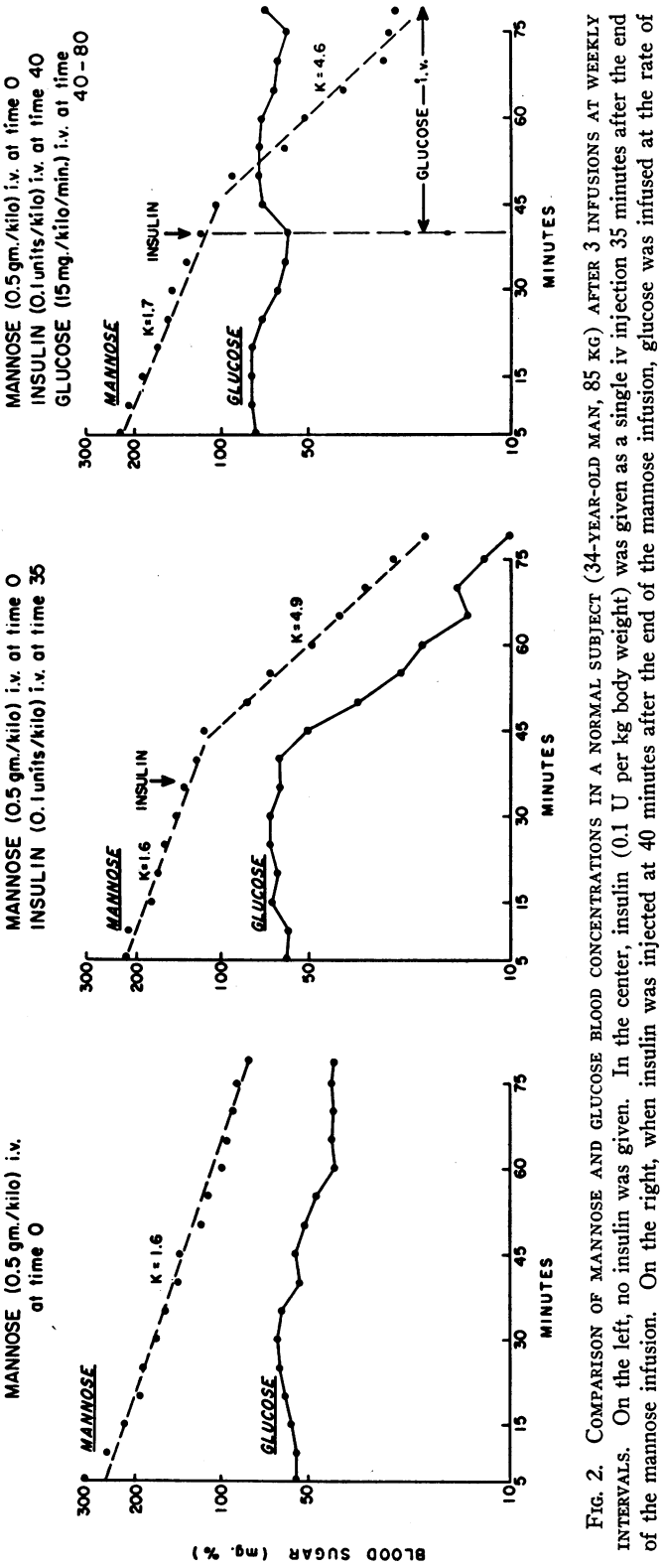


FIG. 2. COMPARISON OF MANNOSE AND GLUCOSE BLOOD CONCENTRATIONS IN A NORMAL SUBJECT (34-YEAR-OLD MAN, 85 KG) AFTER 3 INFUSIONS AT WEEKLY INTERVALS. On the left, no insulin was given. In the center, insulin (0.1 U per kg body weight) was given as a single iv injection 35 minutes after the end of the mannose infusion. On the right, when insulin was injected at 40 minutes after the end of the mannose infusion, glucose was infused at the rate of 15 mg per kg body weight per minute in order to keep blood glucose concentration approximately constant.

toms were thought to be related solely to immobility and mild phlebitis at the infusion site. The second subject (RH), however, felt more uncomfortable and 36 hours after the infusion noted malaise, anorexia, scleral icterus, and urine deeply orange in color. Hepatic function tests [4] revealed only a rise in indirect-reacting bilirubin. Alkaline phosphatase, 24- and 48-hour cephalin flocculation, thymol turbidity, and thymol flocculation tests all remained within normal limits. Bromsulfalein retention performed 2 weeks later was also normal. The urinary pigmentation was related to massive uric acid crystalluria (as identified by crystal structure after dissolution and recrystallization) (30), although that was not quantitated. Serum uric acid, however, remained unchanged at 4.6 mg per 100 ml. By the third postinfusion day, appetite and strength returned. Sequential levels of serum bilirubin in this subject are plotted in Figure 4. Retrospective determinations on plasma from the first subject revealed an initial bilirubin value of 0.23 mg per 100 ml rising to 2.90 mg per 100 ml by the end of the infusion, again owing entirely to elevation of the indirect-reacting moiety. Plans for further studies using prolonged infusions on human subjects were therefore permanently abandoned.

Two diabetic subjects were given infusions of mannose (before the infusions in normal subjects) at the same rate, but for only 5 hours. One diabetic subject (BB) received 40 U NPH insulin daily until 3 days before the test. Previous discontinuation of insulin in this patient resulted in only moderate glycosuria (5 to 15 g per day) and no ketosis. Although the second subject's (CA) diabetes was first discovered at age 50, he had had several episodes of acidosis. He received his usual 34 U NPH insulin 2 days before the test, 15 U crystalline zinc insulin before each meal on the preceding day, and no insulin on the day of the infusion. In both subjects (Figure 5), plasma mannose rose to twice the level in the normal subjects at the same rate of infusion. Only in the mild diabetic subject was there any fall in plasma glucose concentration (220 to 76 mg per 100 ml). In the ketosis-prone diabetic subject, there was no marked change in plasma glucose, nor was there any significant decrease or increase in the degree of glucosuria. Neither subject experienced any subjective change, either during or after the infusion. In both, blood mannose concentration rose to twice the level noted in the normal subjects.

[4] Performed in the laboratory of Dr. Rudi Schmid.

TABLE III

*Oral mannose tolerance test**

Time	Plasma glucose	Plasma mannose	Plasma FFA	Urine excretion	
				Glucose	ORS†
min	*mg/100 ml*	*mg/100 ml*	*μEq/L*	*mg/hr*	
0	102	0	380	20	14
30	86	0	380		
60	76	6	280	33	24
90	66	13	220		
120‡	82	10	220	8	163

* Mannose (0.5 g per kg) taken as a 20% solution in water in an 85-kg normal man at time 0.
† ORS = other reducing substances, including mannose.
‡ Test terminated at 120 minutes owing to gastrointestinal disturbance.

Table III presents the results of the oral mannose test in a normal subject clearly demonstrating the poor gastrointestinal absorption.

DISCUSSION

For hexose tolerance determinations, rapid infusions with the exponential determination of K as described (27, 28) were used rather than other intravenous or oral techniques. The synthesis of six or more points into a single value characterizing tolerance is more logical for comparative studies than one or more single values at specific times. Whether K should be calculated from total hexose values, or from the increments above the fasting value has also led to much discussion and elaboration (31–33) without any clear evidence of practical or theoretical superiority of either method. There is some suggestion (33) that the disappearance rate of the absolute glucose level is better related to glucose utilization than the disappearance of increment blood glucose. Total values were therefore selected for simplicity and for easy comparison between the two hexoses. This method does permit a minimal subjective error, but comparison of this method with mathematical calculation of the exponential curve has shown the difference to be insignificant (28).

These studies suggest that glucose and mannose are removed from the blood at a similar rate by peripheral tissues in man. This would be consistent with the similar metabolic pathways illustrated by animal studies (1). Further sup-

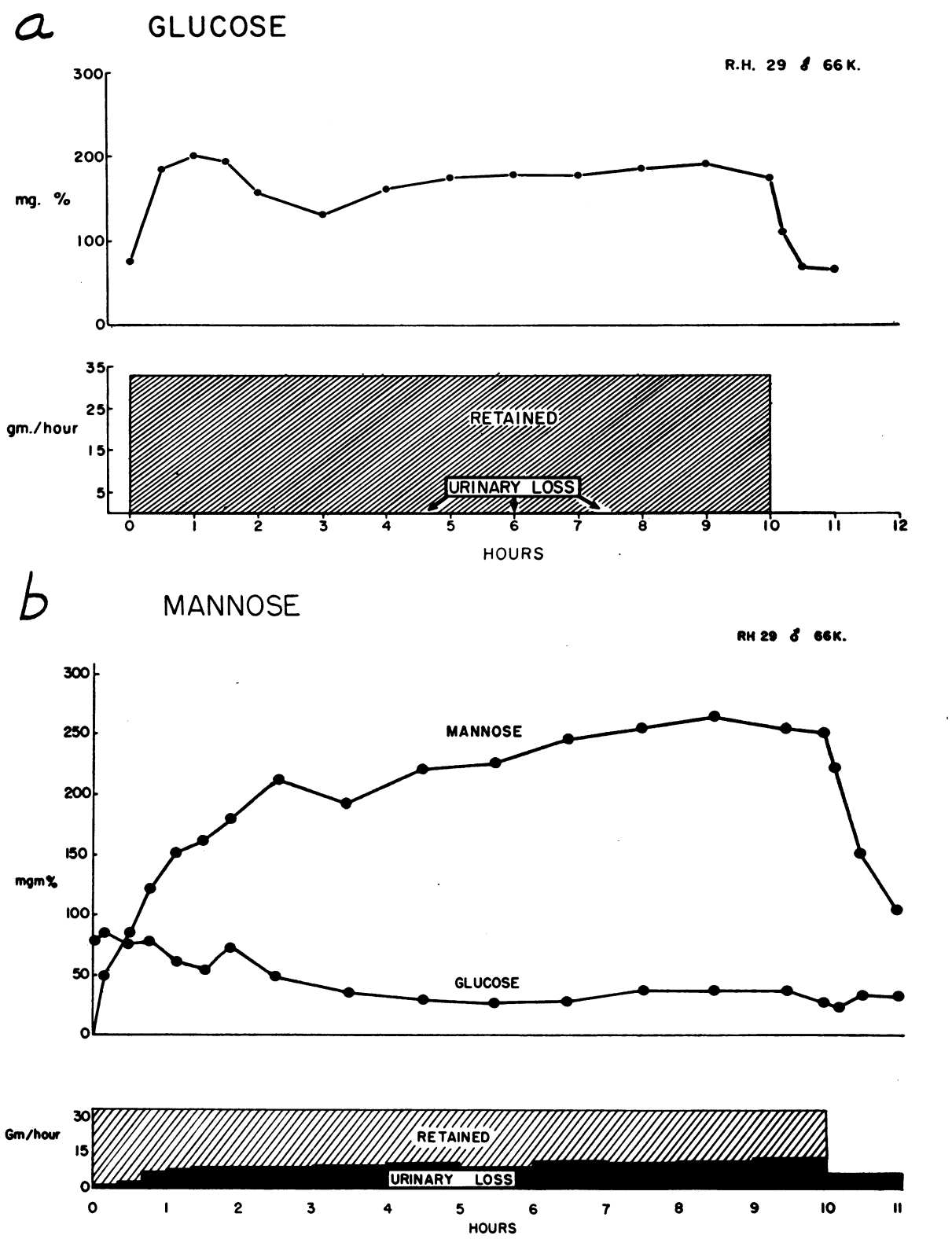
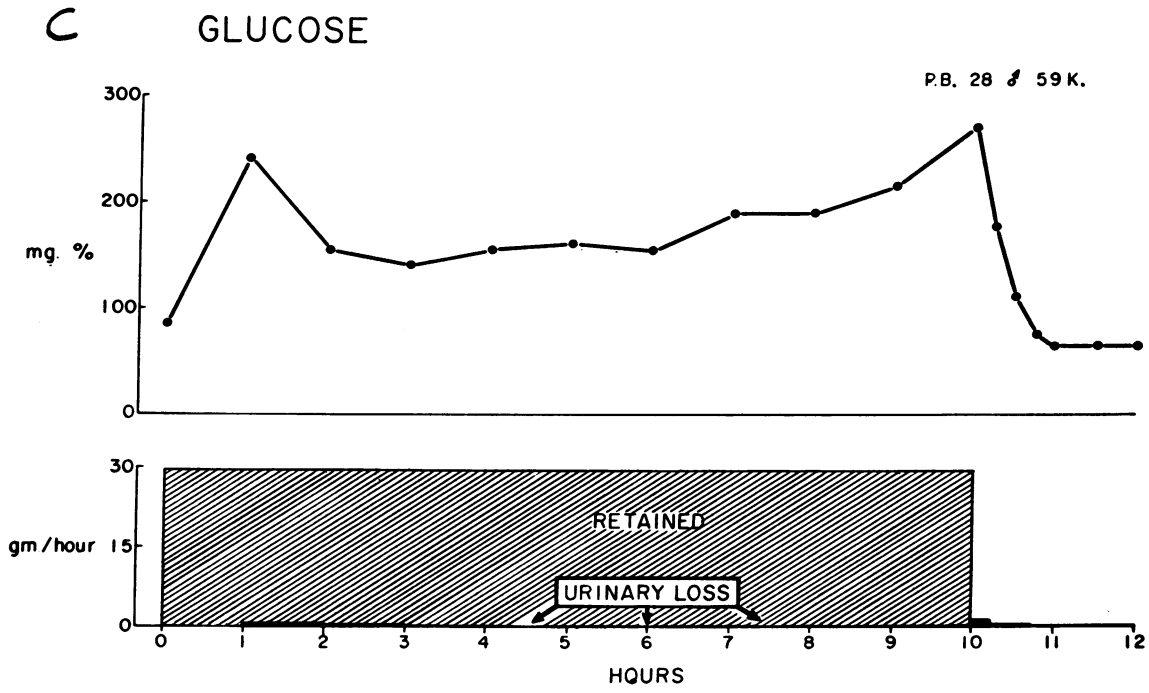


FIG. 3. Comparison of infusions of glucose or mannose (0.5 g per kg body weight per hour) in two normal subjects for 10 hours.



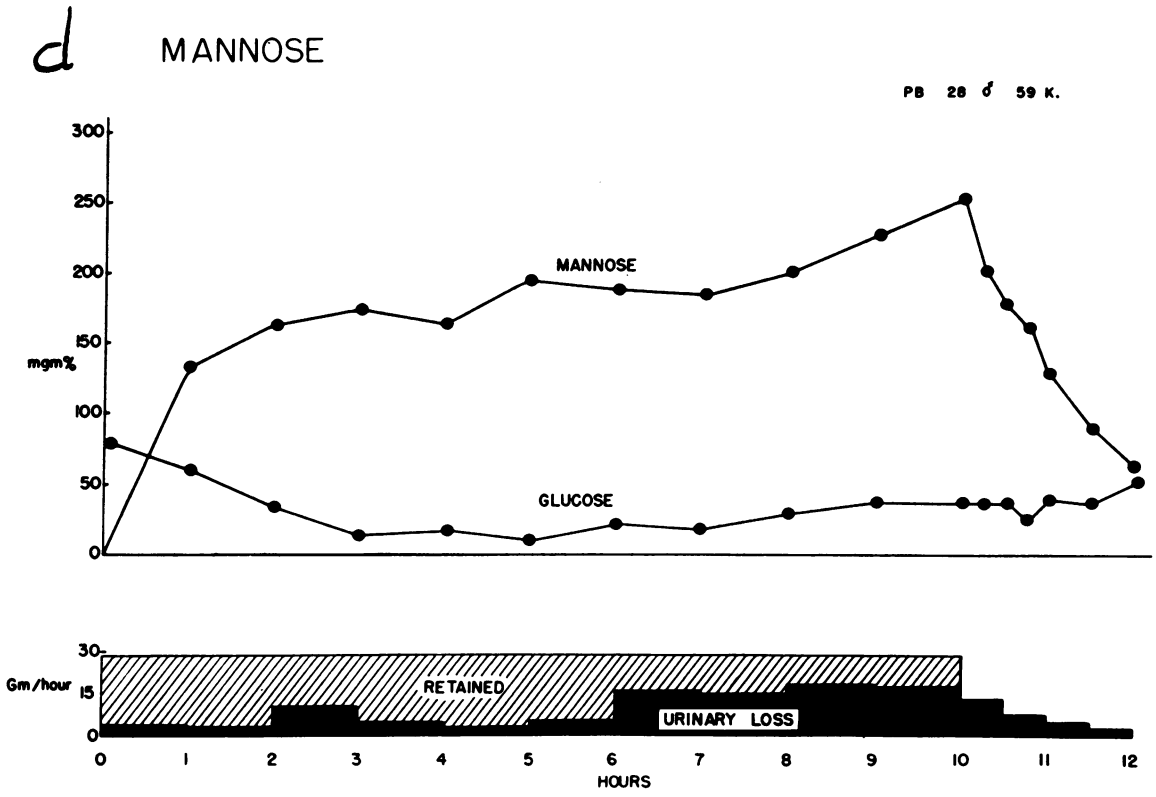


FIG. 3.—(*Continued*).

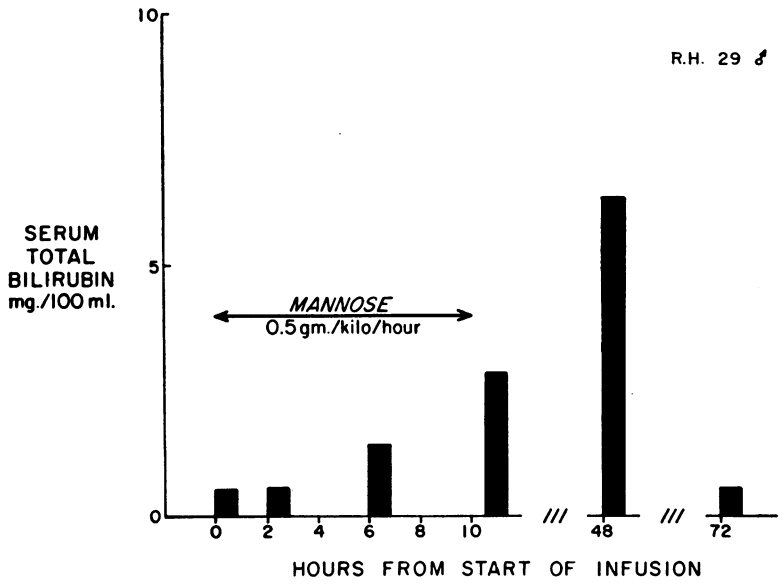


FIG. 4. SERUM BILIRUBIN CONCENTRATION BEFORE, DURING, AND AFTER A 10-HOUR INFUSION OF MANNOSE IN A NORMAL SUBJECT (SUBJECT OF FIGURE 3a, b).

port for metabolic similarity is provided by the effect of mannose on decreasing FFA concentration and by the response of glucose and mannose to insulin or tolbutamide. Likewise, the complete absence of hypoglycemic symptoms with a plasma glucose concentration of 10 mg per 100 ml supports the evidence in animals that the central nervous system is capable of metabolizing mannose.

In the prolonged-infusion studies, mannose induced a decrease in plasma glucose concentration in the two normal subjects and in the mild diabetic subject. The ketosis-prone diabetic subject maintained a blood glucose concentration of 400 mg per 100 ml during the 5-hour infusion of mannose. In this same patient, however, similarly administered infusions of fructose, galactose, or sorbitol induced marked hyperglycemia, with an increase in blood glucose concentration from 300 up to 600 to 700 mg per 100 ml (34). Suppression of this glucose increment seems to represent a depressing effect on plasma glucose concentration in the severe diabetic subject corresponding to the decrease in glucose levels in the other subjects.

Since mannose does not accelerate peripheral glucose uptake by stimulating measurable release of insulin (19, 20) and since small changes in peripheral glucose uptake would normally be compensated by increased hepatic glucose production, these observations suggest that mannose may induce hypoglycemia by decreasing hepatic glucose production. Isotopic studies *in vitro* (1) have shown almost equal metabolism of glucose and mannose by rat liver slices with mutual competitive inhibition. Since the major portion of liver water is freely permeated by monosaccharides (35), this competition probably occurs at phosphorylation of mannose by glucokinase (Figure 6). Mannose, once phosphorylated to mannose 6-phosphate, is readily metabolized by glucose 6-phosphatase (36) to free mannose, and thereby, after accumulating as mannose 6-phosphate, may compete with glucose 6-phosphate [5] for the enzyme.

Changes after the prolonged infusions in the two normal subjects were disconcerting. Review of the 40 acute mannose infusions in a group of patients with various endocrine anomalies revealed no untoward effects, except in one patient with a past history of chronic infectious hepatitis who experienced a transient elevation of serum bilirubin to 1.35 mg per 100 ml 12 hours later and

[5] Experiments with isolated rat liver microsomes (37) have corroborated the experiments of Crane (36) showing rapid hydrolysis of mannose 6-phosphate.

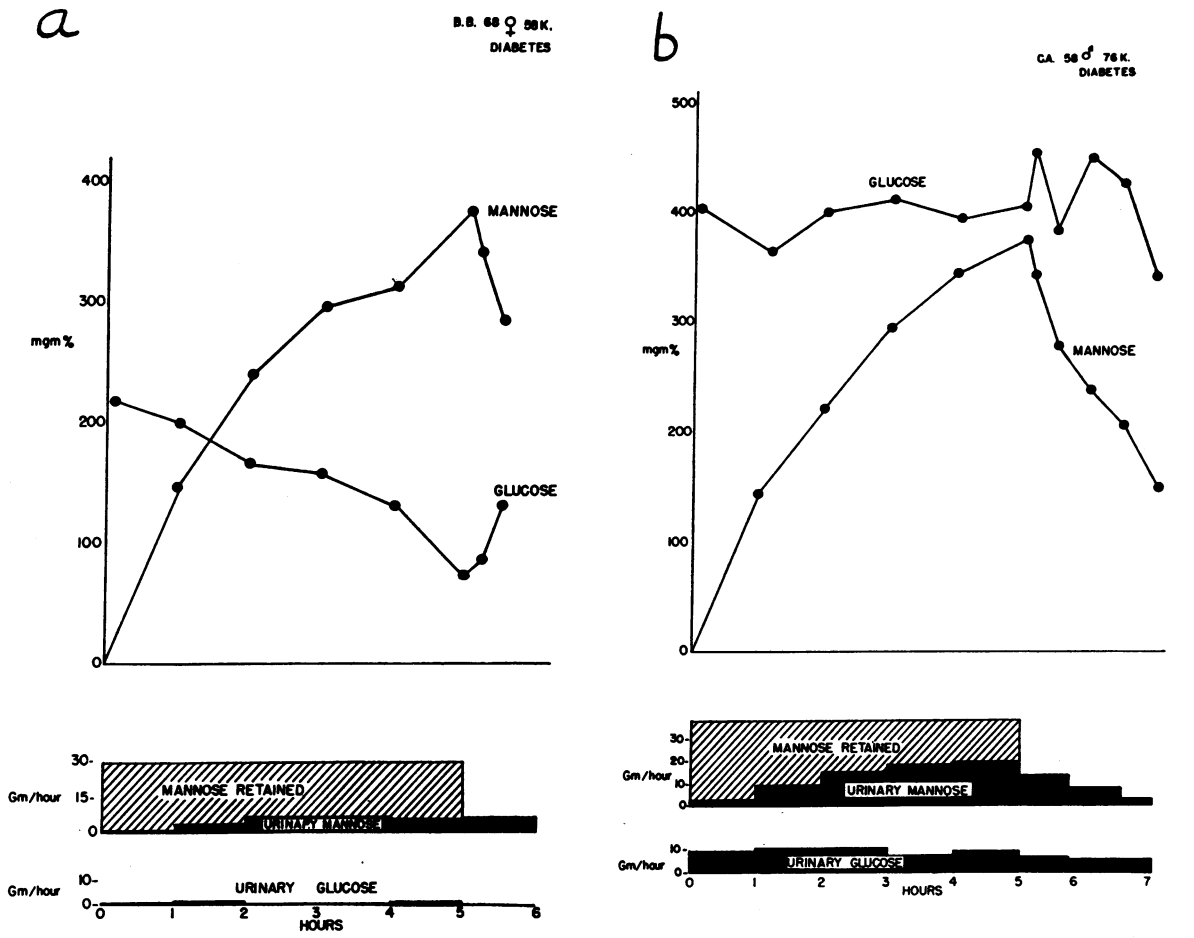


FIG. 5. RESULTS OF 5-HOUR INFUSIONS OF MANNOSE (0.5 G PER KG BODY WEIGHT PER HOUR) IN a) MILD DIABETIC SUBJECT (BB) AND b) KETOSIS-PRONE DIABETIC SUBJECT (CA). In CA, blood glucose concentration did not change, and in spite of increasing blood mannose and excretion of mannose in the urine, urinary glucose did not increase, suggesting lack of mannose competition for glucose transport by the kidney.

a return to his preinfusion level of 0.71 mg per 100 ml in 24 hours. The mechanism whereby mannose inhibits the conjugation of bilirubin remains obscure. The effect progresses hours after the mannose has disappeared from the blood, and probably is most marked 18 to 36 hours later. It is questionable whether a metabolite of mannose, such as mannose 6-phosphate, directly inhibiting the uridine system of glucuronide synthesis or conjugation, could account for this progression over such a prolonged period. Attempts to reproduce even transient hyperbilirubinemia in rats, guinea pigs, and cats by prolonged infusions of mannose have not yet been successful (38).

It is interesting, however, to compare the hypoglycemia, malaise, and disturbed hepatic function after infusion of large quantities of mannose with the metabolic derangements noted in hereditary galactose intolerance (39) and the fructose intolerance recently described by Froesch and associates (40, 41) and characterized by Nikkila, Somersalo, Pitkanen, and Perheentupa (42). In these two diseases, excessive intracellular accumulations of galactose 1-phosphate and fructose 1-phosphate, respectively, are thought to account for aspects of the clinical picture. Loeb (43) has recently demonstrated, using the specific activity of blood glucose after administration of C^{14}-glucose as an index, that the hypoglycemia of patients with galactosemia and fructosemia is due to decreased hepatic glucose production after ad-

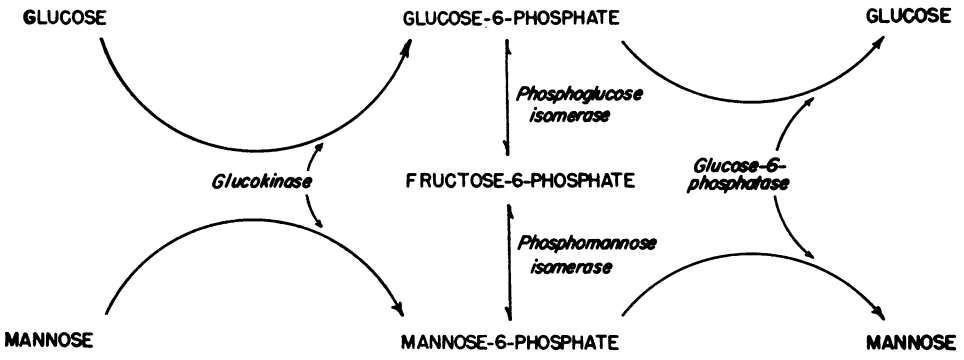


FIG. 6. PRELIMINARY STEPS IN THE HEPATIC METABOLISM OF MANNOSE AND GLUCOSE.

ministration of these respective sugars. Similarly, recent studies on the metabolism of *l*-sorbose in man (44) have shown a decrease in blood glucose followed by a marked derangement in hepatic metabolism after its administration, and again, accumulation of a phosphorylated intermediate might be considered. An interesting corollary to these studies of mannose toxicity in man is the metabolic situation in the honey bee, in which mannose ingestion (apparently a substance foreign to this organism) results in a fatal accumulation of mannose 6-phosphate (45) secondary to a lack of phosphomannose-isomerase activity relative to the rate of phosphorylation of mannose by hexokinase.

Mannose appears as a normal component in many foods, probably entirely in bound form. In any case, available mannose would never approach the quantities infused in these experiments (25 to 400 g). Also, such amounts would not gain entrance to the body owing to lack of active transport by the gastrointestinal tract (18), as confirmed by the oral mannose tolerance test (Table III), and because many of the mannosidic linkages would not be susceptible to intestinal enzyme action.

The marked uricosuria noted with mannose toxicity is also reminiscent of the disturbed renal tubular function associated with other congenital enzymatic deficiencies in carbohydrate metabolism. Amino acid and phosphate excretions were not studied in these experiments. Further classification of the renal effects after mannose administration should be interesting.

Finally, mannose metabolism, as previously discussed, apparently is similar to that of glucose in the aspects studied, excepting gastrointestinal absorption, renal tubular transport, and stimulation of the beta cell. For glucose, the first two processes are thermodynamically active and thereby differ from passive transport (or facilitated diffusion) of monosaccharides in other tissues. The mechanism of stimulation of the beta cell by glucose and the failure of mannose to effect this process suggest a special metabolic or transport process. Likewise, *in vitro* experiments with kidney cortical slices (46) have shown approximately equal metabolism of glucose and mannose to CO_2, glycogen, and tissue fatty acids, in contrast to the marked difference in the transport of these two hexoses, suggesting again a separation between transport and metabolism. Previous *in vivo* experiments by Chinard, Taylor, Nolan, and Enns (47) clearly segregated renal tubular transport of glucose from renal glucose metabolism, and recent *in vitro* experiments with pancreatic islet tissue, including human tumor and isolated islets from the toadfish (*Opsanus tau*), have shown equal metabolism of glucose and mannose into CO_2 and protein (48), suggesting (analogously to kidney) segregation of islet substrate utilization from the capacity of the substrate to stimulate insulin release. Although these are scattered metabolic observations from different species, together they suggest that the spatial configuration of carbon-2 is not specific for glucose metabolism or responsiveness to insulin, but is specific for transport by kidney and gut, and also for insulin stimulation.

SUMMARY

Mannose administered intravenously to normal or diabetic subjects is metabolized in each at rates proportionate to those of glucose.

In man as in animals, mannose does not stimulate pancreatic release of insulin, nor is it actively absorbed from the gastrointestinal tract, nor does there appear to be significant active reabsorption of mannose by the kidney.

ACKNOWLEDGMENTS

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APPENDIX

Method of calculating correction for mannose loss in urine. If first-order kinetics of mannose disappearance into both urine and tissues are assumed, the total disappearance rate K_T for both routes can be obtained from blood levels M_0 and M' by $M^1 = M_0 e^{-K_T \Delta t}$. If K_U = disappearance rate into urine, it can be assumed that $du/dt = K_U M'$, or, substituting for M', $du/dt = K_U M_0 e^{-K_T \Delta t}$. If q_U is the fractional amount of that administered appearing in time t, then, solving for K_U, $K_U = (K_T \cdot q_U)/(1 - e)^{-K_T \Delta t}$. Finally, with K_T and K_U known, disappearance rate into tissues K_M can be calculated: $K_M = K_T - K_U$.

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