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THE METABOLISM OF FRUCTOSE IN MAN§¶

The metabolism of fructose has been studied with varying intensity and enthusiasm since Kulz[18] in 1874 first reported that diabetic patients were able to utilize fructose given orally better than other sugars. Although Naunyn[20] confirmed these results, he maintained that tolerance for fructose was eventually lost, and Joslin,[11] as late as 1946, stated that in his experiments "at first the fructose was well-utilized, but later hyperglycemia and glycosuria usually followed." Interestingly enough, however, the same authors found that a diet containing Jerusalem artichokes, which on digestion yield fructose, could be taken for a period of at least three years without the subject losing his ability to utilize it more efficiently as compared with an equal amount of starch. The advent of insulin eliminated much of the clinical interest in fructose as an adjunct in the treatment of diabetes mellitus in man.

Despite the inconsistent and often contradictory results reported in patients, it seemed clear in experimental diabetes in animals that fructose was handled differently from glucose and did not require the intervention of insulin. Minkowski[19] in 1893 observed that fructose, in contrast to glucose, led to the formation of glycogen in the liver when given to depancreatized dogs. In 1929 Cori[3] studied the utilization in muscle of known amounts of intravenously injected fructose and glucose in eviscerated, depancreatized rats. By subsequently analyzing the entire carcasses for free sugar, he found that 39 per cent of the fructose and only 10 per cent of the glucose had disappeared in one hour. The injection of insulin resulted in a marked increase in the rate of disappearance of glucose but had no effect on the metabolism of fructose. A possible explanation for these findings lies in the

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demonstration in 1950 by Slein and Cori[28] that separate enzymes existed in muscle for the phosphorylation of fructose and glucose. Insulin apparently acts only on the glucokinase. In liver, also, a separate enzyme has been identified for the phosphorylation of fructose. In 1951 Chernick and Chaikoff,[8] using C^{14}-labelled fructose, found no significant difference in the capacities of normal and diabetic rat livers to oxidize fructose to CO_2.

AVERAGE CURVES OF BLOOD HEXOSE AFTER INTRAVENOUS GLUCOSE

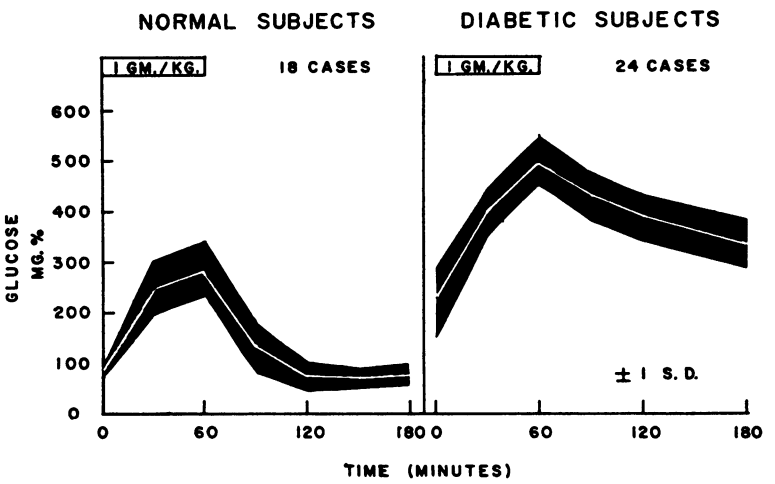

FIG. 1.

With these definitive results in the experimental animal it seemed logical to re-investigate the metabolism of fructose in man. The increase in knowledge of intermediary metabolism in the last two decades, the introduction of isotopes for clinical use, the development of accurate chemical methods for determining glucose and fructose separately in body fluids, and the availability of purified fructose for oral and intravenous use* suggested to us that the time was opportune. Beginning in 1951[4,17] an intensive and systematic study has been pursued in our laboratories. Since the oral administration of fructose could not be expected to demonstrate quantitatively the full effects of fructose, because of the conversion of at least a portion to glucose by both intestinal mucosa and liver,[1,30] attention was directed mainly

* The fructose in the studies to be reported was generously supplied by Dr. Warren Cox, Jr., and Dr. Robert Little of Mead Johnson and Company.

toward the metabolism of intravenously administered fructose. In most of the experiments fructose in amounts of 1.0 gm. per Kg. was given intravenously in a 10 per cent solution at a constant rate over a period of 60 minutes. Where possible, the results obtained were compared in the same individual with glucose administered in a similar way. In the diabetic subjects all tests were performed in the absence of any detectable insulin effects,

AVERAGE CURVES OF BLOOD HEXOSE AFTER INTRAVENOUS FRUCTOSE

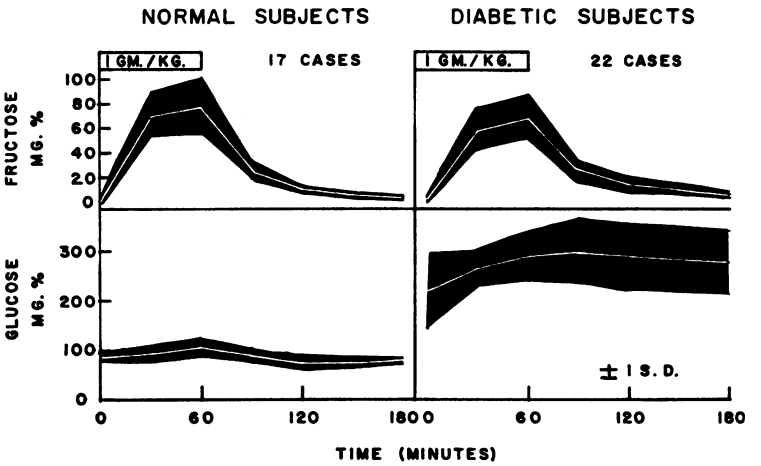

FIG. 2.

since the patients had previously been controlled on regular or crystalline insulin, the last dose having been given at least 14 hours before the test. In addition, in certain instances the results in the diabetic subject were compared with those obtained in the normal person. Fructose and glucose levels were determined separately in both blood and urine. Changes in blood pyruvic acid and serum inorganic phosphorus levels were determined in certain cases as additional indices of carbohydrate metabolism (see reference 17 for details of methods).

COMPARISON OF THE METABOLISM OF INTRAVENOUS GLUCOSE AND FRUCTOSE IN NORMAL SUBJECTS[17]

In 18 normal individuals after the infusion of 1.0 gm./kg./hr. of glucose the average maximum rise in blood glucose above the initial level was 215 mg./100 ml. (Fig. 1). With fructose, however, the average rise in

blood fructose above the control value in 17 of these same cases was 77 mg./100 ml., less than one-half that obtained with glucose given in comparable amounts and at the same rate. A slight rise in blood glucose following fructose administration was noted in some instances, the average maximum rise being 18 mg./100 ml., occurring at one hour (Fig. 2). The excretion of hexose in the urine during the period of the infusions and the

AVERAGE CURVES OF BLOOD PYRUVIC ACID AND PLASMA INORGANIC PHOSPHORUS AFTER INTRAVENOUS GLUCOSE

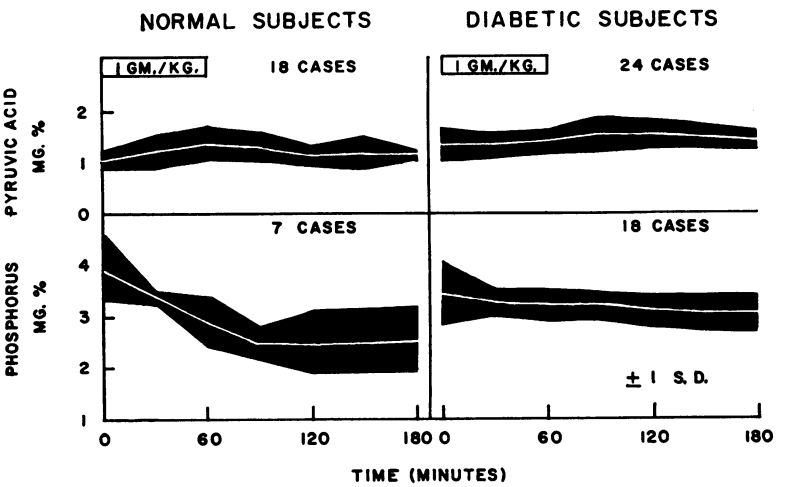

FIG. 3.

subsequent two hours was less than 10 per cent of the amount administered, 9.3 per cent after glucose and 5.3 per cent after fructose. That any fructose is excreted is explained by the fact that fructose continues to be excreted even at blood levels as low as 4 mg./100 ml., but the smaller rise in blood level minimizes the amount lost in the urine.

Pyruvic acid levels in the blood rose after glucose infusion on the average of 28 per cent, or 0.30 gm./100 ml. above the control level, the peak occurring at 60 minutes (Fig. 3). This rise, although small in absolute terms, is significant, the associated probability being of the order of less than one-half of 1 per cent that so great a difference should arise by chance in random sampling. In contrast, the pyruvate rise after fructose was strikingly higher, averaging 110 per cent, or 1.22 mg./100 ml. above the level at the start (Fig. 4). Serum inorganic phosphorus fell after either glucose or fructose,

but the magnitude and rate of change differed slightly. With glucose the phosphorus fell progressively 1.39 mg./100 ml., or 31 per cent below the initial level over a period of 90 minutes and then leveled off. After fructose the phosphorus fall was more rapid, reaching its lowest point at 30 minutes and then leveling off at a slightly higher value after 90 minutes (compare Figs. 3 and 4, normal subjects).

AVERAGE CURVES OF BLOOD PYRUVIC ACID AND PLASMA INORGANIC PHOSPHORUS AFTER INTRAVENOUS FRUCTOSE

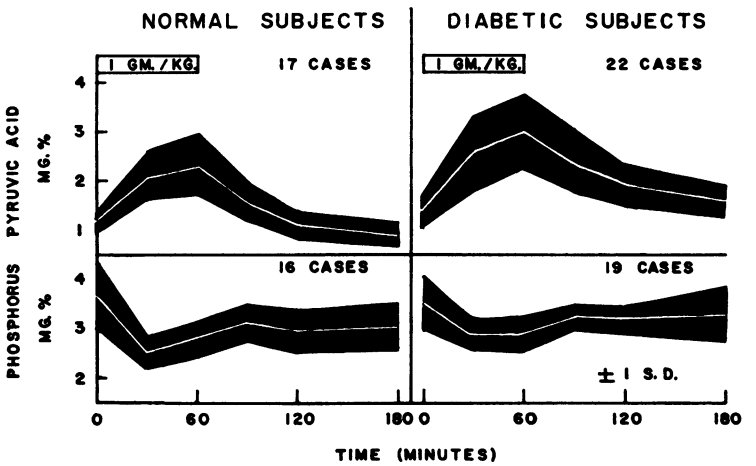

FIG. 4.

These results in the normal subject permit the following conclusions: (i) Fructose is removed from the blood stream more than twice as rapidly as glucose during the period of infusion; (ii) the rise in blood glucose following fructose administration indicates that a fraction of the fructose must have been converted to glucose; (iii) the rise in pyruvate can be interpreted as an indication that both glucose and fructose are metabolized by the way of the Embden-Meyerhof series of reactions. The much greater rise after fructose is probably a reflection of its entrance into the metabolic scheme closer to pyruvic acid. Hers[10] has shown in rats that fructose is transformed into liver and muscle glycogen by splitting to the triose state and entering the glycolytic scheme just below fructose-1, 6-diphosphate. The *in vivo* studies in man are consistent with this hypothesis. If the fall in serum inorganic phosphorus reflects the process of phosphorylation in

the metabolism of carbohydrate, the more rapid decrease in phosphate after fructose administration is an indication of the more rapid metabolism or utilization of this hexose.

The above changes in the concentrations of hexose, pyruvate, and phosphate after intravenously administered glucose and fructose are compared in Table 1. Statistical measures of the variability are included.

TABLE 1. CHANGES IN GLUCOSE, FRUCTOSE, PYRUVATE, AND PHOSPHATE IN NORMAL SUBJECTS AFTER THE INTRAVENOUS INFUSION OF 1.0 GM./KG. IN ONE HOUR OF (A) GLUCOSE (B) FRUCTOSE

Substance measured in blood	*Time minutes from start*	*(A) After glucose*		*(B) After fructose*	
		Δ mg./100 ml.	*Per cent change*	*Δ mg./100 ml.*	*Per cent change*
Fructose	60			+77.2 ±23.2*	
Glucose	60	+214.7 ±52.2*		+18.5 ±18.4	
Pyruvate	60	+0.30± 0.34	+28	+1.22± 0.62	+110
Phosphate	30	—0.56± 0.11	—14.7	—0.93± 0.34	—25.6
"	90	—1.39± 0.31	—36.5	—0.51± 0.37	—14.1

* ± 1 Standard deviation.

COMPARISON OF THE METABOLISM OF INTRAVENOUS FRUCTOSE AND GLUCOSE IN DIABETIC SUBJECTS (Figs. 1, 2, 3, 4)

Intravenous glucose and fructose tolerance tests were performed one or more times in each of 15 patients with diabetes mellitus. Two other subjects were given glucose and one fructose, making a total of 24 glucose and 22 fructose tolerance experiments. The diabetes in general was of moderate to severe intensity, with an average fasting blood sugar of 220 mg./100 ml. In only two patients was the fasting blood sugar below 140 mg./100 ml., and these were the only two that did not require insulin for control. When both tests were performed in the same individual, they were done at one- to three-day intervals, and the fasting blood sugars were in the same range on each occasion.

Following intravenous glucose (Fig. 1) the changes in blood glucose were characteristic of diabetes mellitus, with marked hyperglycemia and a delayed fall. In marked contrast, the blood disappearance curve for fructose was in every case essentially identical with that found in the normal group (Fig. 2). Corresponding to these similar blood levels, the amount of fructose excreted in the urine of the diabetic patients during the period of

the infusion and the subsequent two hours was essentially the same (average 3.2 gms., range 0.9-5.7 gms.) as in the normal (average 3.6 gms., range 1.2-5.9 gms.).

The diabetic subject differed from the normal in that there was a more marked rise in blood glucose following fructose, a rise roughly proportional to the severity of the diabetes (Fig. 5). In every instance where direct comparisons were made, this blood glucose elevation was always less than after glucose injection. This is shown in Figures 1 and 2, where the changes in blood glucose in diabetic subjects are averaged. Direct quantitative comparison is shown in Table 2, where the increment in glucose and total hexose above the control level is shown at various intervals following this infusion. Since the blood sugar curves are not as high after fructose infusion, the excretion of hexose (glucose + fructose) is correspondingly less. In each of 12 subjects whose initial blood glucose levels were similar at the time of the glucose and fructose experiments, significantly less hexose was found in the urine after fructose. As pointed out above, the excretion of fructose was the same as that found in normal subjects, but the amount of glucose lost varied with the severity of the diabetes. Approximately 20 per cent more of the total amount infused was retained or "utilized" when fructose was administered (Table 3). It is interesting that this advantage is independent of the severity of the diabetes. In Table 3 the subjects are arranged according to increasing amounts of glucose lost in the urine in the three-hour period. In the first six subjects who excreted an average of 30 per cent (range 20.7 to 36.9 per cent) of the infused glucose, 19.9 per cent more hexose was "utilized" after fructose. In the other six patients whose diabetes was of such severity that 58.6 per cent (range 39.1 to 89.6 per cent) of the infused glucose was excreted, the "advantage" of fructose was still 20.7 per cent. Furthermore, in one case of experimentally produced diabetic acidosis, the subject "utilized" 178 grams of fructose or 21 per cent of the 850 grams administered intravenously during the phase when insulin

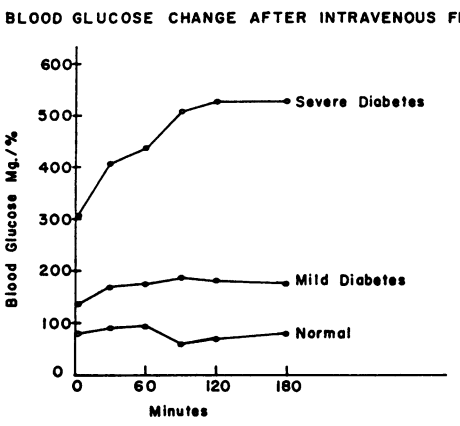

FIG. 5.

was withheld. Less than 4 per cent of the 850 grams of fructose was excreted as such in the urine. In three other similar experiments in the same volunteer, when fructose was not administered, there was a quantitative excretion of all available glucose during the withdrawal phase. Thus, even the "complete" diabetic individual obtains the same "advantage" from intravenous fructose as the less severe case.

Another striking difference in the metabolism of glucose and fructose in the diabetic subject was shown by the changes in blood pyruvic acid (Figs.

TABLE 2. INCREASE IN BLOOD GLUCOSE AND TOTAL HEXOSE FOLLOWING FRUCTOSE INFUSION COMPARED TO INCREASE IN BLOOD GLUCOSE FOLLOWING GLUCOSE INFUSION IN DIABETIC SUBJECTS
AMOUNT INFUSED: 1.0 GM./KG. IN ONE HOUR

No. of experiments	*Rise after fructose* 22			*Rise after glucose* 24
Time minutes	*Blood fructose mg./100 ml.*	*Blood glucose mg./100 ml.*	*Total blood hexose mg./100 ml.*	*Blood glucose mg./100 ml.*
30	58.3±16.9*	43.1±35.4*	101.4	176.7±48.5*
60	67.9±17.6	69.0±49.6	136.9	280.1±47.5
90	23.0± 8.5	82.1±66.0	105.1	207.0±49.2
120	12.3± 5.7	68.6±64.6	80.9	166.8±46.0
180	3.7± 2.8	56.8±64.0	60.5	116.1±47.4

* ± 1 Standard deviation.
Initial blood glucose values 221.1±76.6 and 220.1±69.1 mg./100 ml., respectively.

3 and 4). After glucose a significant rise in pyruvate did not occur until 90 minutes and this rise was sustained even at 180 minutes. In 18 normal subjects the maximum rise occurred at 60 minutes or earlier in 10 instances, compared with a similar early rise in only 1 out of 24 experiments in diabetic subjects. Furthermore, in 7 of these 24 diabetic patients no rise at all was found. In contrast, the rise in pyruvate after fructose administration in the diabetic state occurred just as promptly as in the normal subject. The magnitude of this increase was at least as great as in the nondiabetic, and was significantly higher at from 90 to 180 minutes.

In diabetic subjects the response of serum inorganic phosphorus to the administration of intravenous glucose and fructose is also markedly different (Figs. 3 and 4). After glucose, only a slight fall, statistically not significant, occurs in the first 90 minutes. After fructose, however, there is the

TABLE 3. COMPARISON OF UTILIZATION OF FRUCTOSE AND GLUCOSE IN DIABETIC SUBJECTS

Subject no.	*Hexose* infused*	*% of amount infused excreted as hexose*		*Additional amount of hexose "utilized" after fructose % of amount infused*
		After glucose†	*After fructose‡*	
1	Glucose	20.7		
	Fructose		6.0	14.7
2	Glucose	23.4		
	Fructose		5.6	17.8
3	Glucose	28.7		
	Fructose		5.9	22.8
4	Glucose	32.6		
	Fructose		15.2	17.4
5	Glucose	35.0		
	Fructose		15.7	19.3
6	Glucose	36.9		
	Fructose		9.3	27.6
			Average of Subjects No. 1-6:	19.9%
7	Glucose	39.1		
	Fructose		6.4	32.7
8	Glucose	43.1		
	Fructose		17.6	25.5
9	Glucose	54.0		
	Fructose		37.4	16.6
10	Glucose	55.6		
	Fructose		36.0	19.6
11	Glucose	70.0		
	Fructose		59.3	10.7
12	Glucose	89.6		
	Fructose		70.6	19.0
			Average of Subjects No. 7-12:	20.7%

* 1.0 gm./kg. infused intravenously in one hour.
† Glucose in urine in first three hours.
‡ Glucose and fructose in urine in first three hours.

same rapid fall, somewhat less in magnitude compared to the normal, in the first 30 minutes, with a rise after 90 minutes.

The results in the diabetic subject in the absence of insulin effect indicate that there is very little impairment in the metabolism of fructose as shown by: (i) The essentially similar rate of removal from the blood stream as in the normal person; (ii) no reduction in the height of pyruvate rise, and

TABLE 4. CHANGES IN GLUCOSE, FRUCTOSE, PYRUVATE, AND PHOSPHATE IN DIABETIC SUBJECTS AFTER THE INTRAVENOUS INFUSION OF 1.0 GM./KG. IN ONE HOUR OF (A) GLUCOSE (B) FRUCTOSE

Substance measured in blood	*Time minutes from start*	*(A) After glucose*		*(B) After fructose*	
		mg./100 ml.	*Per cent change*	*mg./100 ml.*	*Per cent change*
Fructose	60			+67.9 ±17.6*	
	180			+3.7 ± 2.8	
Glucose	60	+280.1 ±47.5*		+69.0 ±49.6	
	180	+116.1 ±47.4		+56.8 ±64.0	
Pyruvate	30	+0.001± 0.25	0.0	+1.17± 0.77	+85.4
	60	+0.06 ± 0.25	+4.8	+1.62± 0.76	+118.2
	90	+0.23 ± 0.33	+18.3	+1.04± 0.65	+75.9
	120	+0.25 ± 0.30	+19.9	+0.55± 0.43	+40.1
Phosphate	30	—0.17 ± 0.27	—4.9	—0.63± 0.31	—18.0
	60	—0.23 ± 0.31	—6.7	—0.61± 0.35	—17.4
	90	—0.26 ± 0.27	—7.5	—0.27± 0.27	—7.1

* ± 1 Standard deviation.

(iii) rapid fall in serum inorganic phosphate. In contrast, in parallel circumstances, glucose disappearance from the blood is markedly delayed, the rise in pyruvate is either abolished or delayed in appearance, and phosphate fall is not significant.

These changes in the diabetic subject after the intravenous administration of glucose and fructose are summarized in Table 4. The values should be compared with those found in normal subjects shown in Table 1.

ORAL FRUCTOSE VERSUS INTRAVENOUS FRUCTOSE IN THE DIABETIC SUBJECT

The effects of fructose given by mouth were compared in three individuals with the same amount given intravenously. The fructose was dissolved in water and ingested as a 10 per cent solution within a few minutes at the

beginning of an experiment, while the same amount was given intravenously as a 10 per cent solution in 60 minutes on another occasion. In each instance after oral administration the blood fructose level was much lower than that found after intravenous injection, while the elevation of blood glucose was more than twice as great and remained higher for a longer period of time. Part of the fructose, therefore, must have been converted to glucose in its passage through the intestinal mucosa and the liver. A typical experiment is shown in Table 5. The augmented excretion of glucose after oral fructose emphasizes the advantages of the intravenous route.

In order to determine more directly the amount of conversion of fructose to glucose by the intestinal mucosa a patient with cirrhosis of the liver and

TABLE 5. COMPARISON OF EXCRETION OF HEXOSE IN A DIABETIC SUBJECT AFTER (A) ORAL AND (B) INTRAVENOUS FRUCTOSE

				Amount excreted in 3 hours		
Subject	*Amount given gm.*	*Route of administration*	*Fasting blood glucose*	*Glucose gm.*	*Fructose gm.*	*Total hexose gm.*
S.	100	Oral	279	28.6	0.9	29.5
	100	Intravenous	283	15.7	5.2	20.9

portal obstruction with large superficial abdominal anastomotic veins was given 50 grams of fructose by mouth. Femoral artery blood and portal anastomotic vein blood samples were collected simultaneously in 30 and 60 minutes and analyzed for fructose and glucose. The results in this experiment are shown in Table 6. If the assumption is made that the *utilization* of hexose by the intestinal wall is negligible, then the ratio of the increase in portal anastomotic vein (PAV) blood glucose to total hexose (fructose + glucose) will be an approximate measure of the conversion of fructose to glucose during the passage through the wall. Thus, in the first sample obtained at 30 minutes, the concentration of glucose in PAV blood was 5 mg./100 ml. higher than in the arterial blood reaching the intestine. Since this could only have been derived by conversion from fructose (no other food being given), and the total hexose absorbed from the intestine was 28 mg./100 ml. (23 + 5) the fraction of fructose converted to glucose during the transfer through the wall was 5/28 or approximately 18 per cent. The results obtained in the second sample were in agreement with the first. Thus, about one-sixth of the fructose in this experiment was converted to glucose during absorption. Consequently, there is less "advantage" in giving fructose by mouth than by the intravenous route.

RÔLE OF THE LIVER IN FRUCTOSE METABOLISM

The liver plays an important rôle in carbohydrate metabolism and this is particularly true for fructose. To obtain more direct information in man hepatic vein catheterizations were performed in diabetic and nondiabetic subjects,[4] splanchnic blood flow being determined by the bromsulfalein technique. Samples of femoral artery and hepatic vein blood were drawn at frequent intervals, and estimates of splanchnic balances of glucose, fructose, and pyruvic acid were calculated by multiplying the appropriate arterial-

TABLE 6. ARTERIAL AND PORTAL ANASTOMOTIC VEIN CONCENTRATIONS OF FRUCTOSE AND GLUCOSE FOLLOWING ORAL ADMINISTRATION 50 GRAMS OF FRUCTOSE

	Portal anastomotic vein mg./100 ml.	*Femoral artery mg./100 ml.*	*Difference in concentration mg./100 ml.*	*"Conversion" per cent*
30 minutes after ingestion				
Fructose	43	20	23	
Glucose	121	116	5	18
60 minutes after ingestion				
Fructose	47	20	27	
Glucose	130	125	5	16

hepatic venous blood concentration difference by the corresponding estimated splanchnic blood flow. After control samples were collected, 10 per cent glucose or fructose was infused into a peripheral vein at such a rate that one gram of hexose per kilogram of body weight was given in one hour. As shown in Table 7, fructose was taken up by the splanchnic system twice as rapidly as was glucose in the nondiabetic subject, and this ratio was maintained in the diabetic state in the absence of exogenous insulin effect. Even in severe diabetic ketosis the ability of the liver (splanchnic system) to take up fructose remains unimpaired. This more rapid uptake of fructose by the liver is an important factor in the more rapid disappearance of fructose from the blood stream described in the previous sections.

Studies of pyruvic acid splanchnic balance in these cases showed that the normally slow uptake of pyruvic acid was reversed when either glucose or fructose was infused. However, the output was equivalent to only 0.5 per

cent of the hexose uptake when glucose was given and to 3.6 per cent when fructose was administered. Consequently, at least part of the greater peripheral concentration of pyruvic acid that occurs when fructose is given is the result of this output by the liver.

UPTAKE OF FRUCTOSE BY MUSCLE

The utilization of fructose by muscle tissue has been studied almost entirely in species other than man. Van Itallie[81] in 1953 measured fructose uptake in the forearm (composed 80 per cent of muscle) of 10 nondiabetic

TABLE 7. PERCENTAGE OF ADMINISTERED HEXOSE (1.0 GM./KG.) ASSIMILATED BY SPLANCHNIC SYSTEM DURING HOUR OF INFUSION

		Per cent uptake of hexose infused	
Subject	*No. of cases*	*Glucose*	*Fructose*
Nondiabetic	6	19	..
	4	..	37
Diabetic	5	19	..
(minimal or no ketosis)	4	..	42
Diabetic	1	0	..
(severe ketosis)	2	..	48

subjects. After injection of a priming dose of between 25 and 30 gms. of fructose administered intravenously as a 10 per cent solution in approximately a 30-minute period, the infusion was continued at a constant rate of 0.58 gm./min. Capillary and venous bloods were taken at 15-minute intervals for one hour beginning 30 to 100 minutes from the start of the experiment and the arterio-venous difference of fructose was determined. At an average arterial level between 66.1 and 68.9 mg./100 ml. the A-V difference ranged between 10.6 and 13.4 mg./100 ml., even up to two and a half hours from the beginning of the infusion. Using the same approach, modified so that 30 gms. of fructose was given in the first 30 minutes and then continued at 0.58 gm./min. for two and a half hours, we found a similar uptake of fructose in three experiments on stable diabetic subjects. Figure 6 shows the results in one of these tests. It can be seen that at the end of 150 minutes the A-V difference was more than 7 mg./100 ml. In an experiment on another diabetic patient, the arterial level for fructose under these conditions at the end of 75 minutes was 30 mg./100 ml. higher than that in the vein. Another priming dose was then given, and the rate of infusion was

doubled to 1.2 gm./min. At the higher arterial levels obtained (225-250 mg./100 ml.) the A-V difference immediately increased and at the end of two and a half hours was 70 mg./100 ml. The magnitude of the amount taken up after such a long period of infusion suggests the conclusion that direct assimilation ("utilization"?) by muscle cells must have been taking place.

OXIDATION OF FRUCTOSE IN VIVO AS MEASURED WITH ISOTOPES

The whole problem of fructose metabolism in man is complicated by the fact that knowledge of its utilization by various tissues is still not sufficiently detailed. Ultimately these data will become available and the sum total of its metabolism can then be determined. Lacking this information, we have turned to the study of the oxidation *in vivo* of C^{14} fructose. Ninety μc of evenly labeled C^{14} fructose without carrier were injected intravenously into normal and diabetic subjects, and the specific activity of CO_2 in the expired air was measured at frequent intervals for a period of at least eight hours. In Figures 7 and 8 these results are compared with the specific activity of CO_2 in the expired air following the intravenous injection of the same amount (90 μc) of uniformly labeled glucose-C^{14} in the *same* normal or diabetic subject on another occasion. After fructose in the diabetic subject (Fig. 8) a peak activity was attained very rapidly in not more than 10 or 15 minutes, and in this instance this was even faster than that achieved in the normal subject (Fig. 7). In contrast, the peak activity of CO_2 after glucose in the diabetic patient was significantly delayed as compared with the nondiabetic subject. It appears, therefore, that there is a rapid metabolic transport of fructose to the CO_2 pool and that there is no significant reduction in this rate in diabetes even in the absence of insulin. The oxidation of fructose to carbon dioxide does not seem to be under the control of insulin.

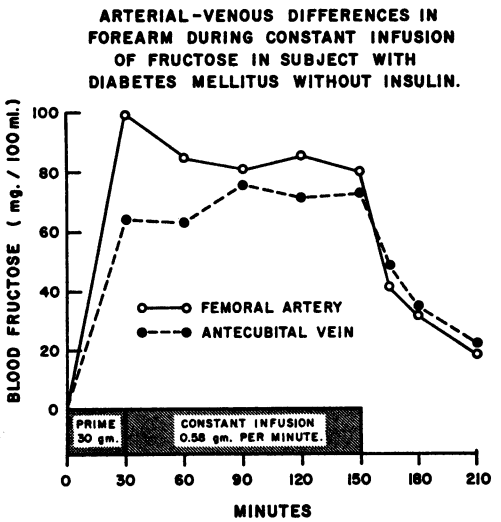

FIG. 6.

COMPARISON OF FRUCTOSE AND GLUCOSE IN VARIOUS CLINICAL STATES ASSOCIATED WITH DISTURBANCES IN CARBOHYDRATE METABOLISM

Trauma and infection

Because of the well-documented effects of stress situations on glucose metabolism, a series of experiments was performed in nondiabetic human subjects in order to compare the manner in which fructose was handled in the same circumstances.[6] Five patients scheduled for elective herniorrhaphies under spinal anesthesia and six patients scheduled for "major" surgery (gastrectomy, etc.) under general anesthesia were given intra-

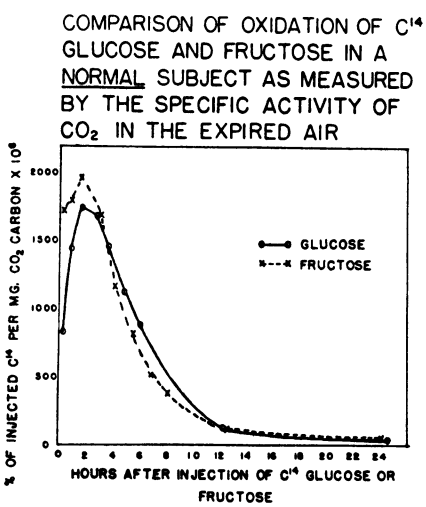

FIG. 7.

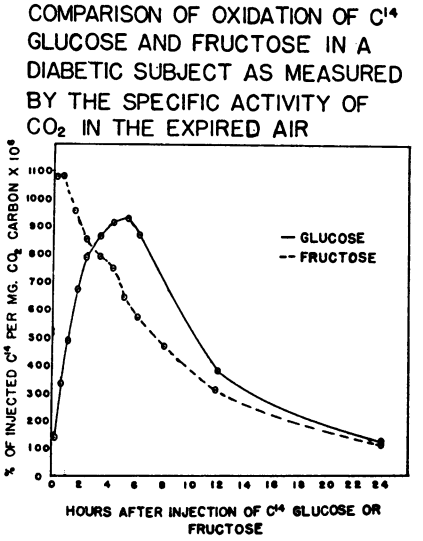

FIG. 8.

venous glucose and fructose (1.0 gm. per kg. in one hour as a 10 per cent solution) on successive days pre-operatively, and these were repeated on the first and second post-operative days. All four tolerance tests were done in each patient. The order in which the glucose and fructose was given was alternated from case to case. The results of these tolerance tests are shown in Table 8. Even the relatively simple trauma of the herniorrhaphy operation was sufficient to elevate the peak value of glucose at the end of the infusion and result in a delayed fall. In the major surgical cases the lag in the fall of glucose was even more evident (58 mg./100 ml. above control values at 180 minutes compared to 34 mg./100 ml. in the herniorrhaphy operations). The fructose tolerance tests in contrast were essentially unaltered by the procedure.

Similarly, a patient with typhoid fever studied during the height of the febrile phase showed an alteration in glucose tolerance as compared with the test after recovery, while again the fructose tolerance curves were both normal and identical (Fig. 9).

The mechanisms by which stress situations alter the metabolism of glucose are still being vigorously debated. It is tempting to speculate that,

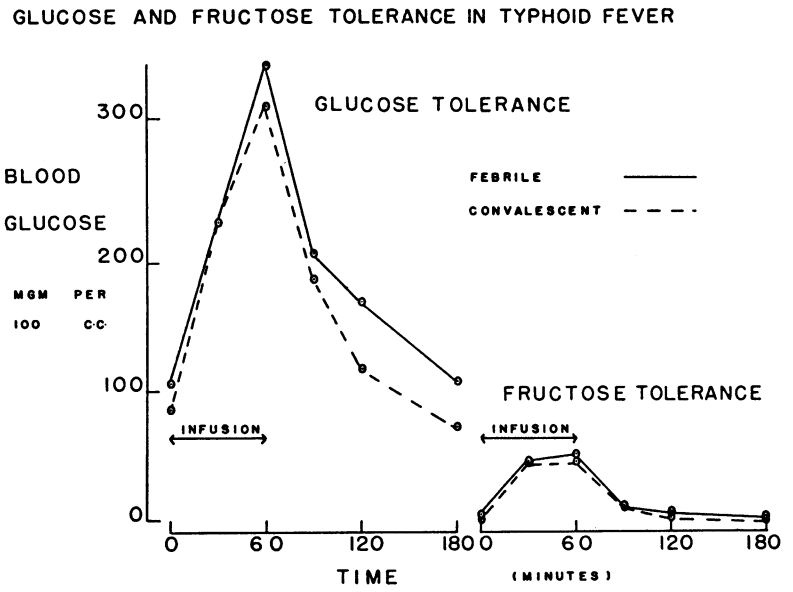

FIG. 9.

if stress results in a stimulation of the pituitary-adrenal axis (Selye) and the hormones released inhibit the action of glucokinase[25] resulting in a delay in the entrance of glucose into the metabolic pool, the normal disappearance curves of fructose could then be explained by the fact that fructose has its own separate fructokinase not influenced by these hormones. On the other hand, if insulin acts upon a cellular membrane system to accelerate transport of glucose[18, 21, 22] but has no effect on the entrance of fructose into the cell, it must be assumed that the stress must have some inhibitory effect on the factor or factors responsible for glucose transport but does not affect the permeability of the cell wall to fructose.

Anesthesia

General anesthetics, particularly ether, have been reported to elevate the blood sugar and diminish the utilization of carbohydrate.[24] Twelve volunteer

TABLE 8. THE EFFECTS OF SURGERY ON INTRAVENOUS GLUCOSE AND FRUCTOSE TOLERANCE (1.0 GM./KG./1 HR.) BEFORE AND AFTER OPERATION

	Herniorrhaphies Average of 5 subjects				*Major surgery Average of 6 subjects*			
	Glucose tolerance		*Fructose tolerance*		*Glucose tolerance*		*Fructose tolerance*	
Time minutes	*Pre-op. blood glucose mg./100 ml.*	*Post-op. blood glucose mg./100 ml.*	*Pre-op. blood fructose mg./100 ml.*	*Post-op. blood fructose mg./100 ml.*	*Pre-op. blood glucose mg./100 ml.*	*Post-op. blood glucose mg./100 ml.*	*Pre-op. blood fructose mg./100.ml.*	*Post-op. blood fructose mg./100.ml.*
0	91	93	1	2	93	132	2	3
60	311	360	61	54	322	375	83	81
120	107	157	10	9	142	190	14	12
180	69	103	4	5	78	136	4	6

subjects hospitalized for rehabilitation at Highland View Hospital were given ether anesthesia without surgery for a period of 90 minutes.[7] Anesthesia was induced by the intravenous administration of 150-300 mg. of thiopental sodium in order to minimize the excitement and physical activity frequently encountered during the induction of ether narcosis. Thirty minutes after surgical anesthesia was achieved, a specimen of blood was drawn and 1 gm./kg. of a 10 per cent solution of glucose (six subjects) or

TABLE 9. EFFECTS OF ETHER ANESTHESIA ON FASTING BLOOD GLUCOSE AND FRUCTOSE LEVELS AND ON INTRAVENOUS GLUCOSE AND FRUCTOSE TOLERANCES

No. of subjects	*Glucose tolerance*			*Fructose tolerance*		
	6	6	3	6	6	4
Time minutes	*Control blood glucose mg./100 ml.*	*During anesthesia blood glucose mg./100 ml.*	*24 hours after anesthesia blood glucose mg./100 ml.*	*Control blood fructose mg./100 ml.*	*During anesthesia blood fructose mg./100 ml.*	*24 hours after anesthesia blood fructose mg./100 ml.*
—30		91*			1.5*	
0	93	133	92	1.3	1.5	1.6
60	309	396	315	90.5	99.9	96.7
120	144	199	158	12.2	19.0	13.3
180	82	137	74	5.2	12.7	7.3

* Pre-anesthesia values obtained in four of six subjects tested.

fructose (six subjects) was infused intravenously at a constant rate for one hour, at the end of which time both the infusion and the ether were discontinued. Similar tolerance tests were done as controls in each subject one or more days preceding the anesthesia and 24 hours afterwards (three and four subjects in each group, respectively). The effect on blood glucose and fructose levels of the first 30 minutes of anesthesia alone was studied in four subjects in each group. The results of these tests are shown in Table 9. Ether anesthesia (30 minutes) increased the fasting blood glucose significantly from 91 to 133 mg./100 ml. but did not alter the fasting blood fructose level. The glucose tolerance test also showed definite impairment during anesthesia, but this effect was gone by the next day. There was a slight delay in the return of the blood fructose as compared with the control curve, but this was only a fraction of that seen with glucose (7.5 mg./100 ml. compared with 55 mg./100 ml. above control values at 180 minutes, respectively).

Starvation diabetes

The phenomenon of starvation diabetes, or the induction of impaired carbohydrate tolerance by the restriction of dietary carbohydrate, was first described in 1874 when Lehmann[14] found that the injection of sugar into the mesenteric veins produced greater glycosuria in fasted than in fed dogs. The same alteration in glucose tolerance after deprivation or reduction in carbohydrate intake has been repeatedly shown in man. Peters,[28] in his comprehensive review of this problem in 1945, concluded that the available evi-

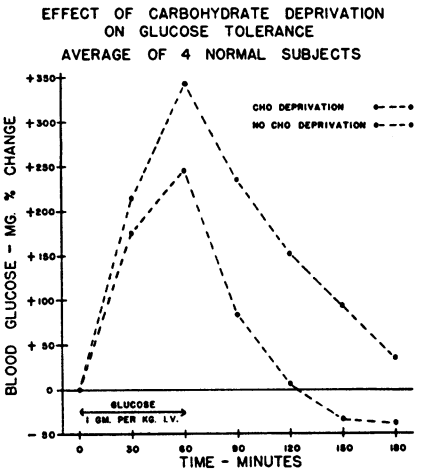

FIG. 10.

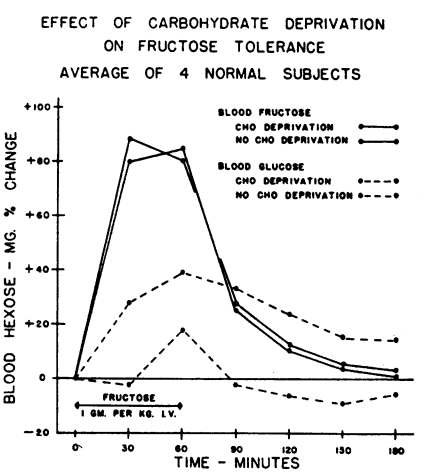

FIG. 11.

dence at the time pointed to "defective combustion" as the cause of this impairment. The study of fructose metabolism in states of carbohydrate deprivation was undertaken in man to determine where the possible sites of the block in "combustion" might exist. Intravenous glucose tolerance tests were performed on four normal human subjects who had previously been on adequate diets. After two days of fasting (two cases) or two days during which the diet consisted of meat and butter only (two cases), the tolerance tests were repeated (Fig. 10). Under similar circumstances at another time, fructose tolerance tests were performed on the same four subjects (Fig. 11). The rate of removal of administered fructose was not found to be significantly altered. However, the blood glucose rise associated with fructose administration was greater after carbohydrate restriction than in the well-fed state, and the return of the blood glucose to the initial level was delayed after dietary restriction. These results afford further evidence that the metabolism of fructose differs from the metabolism of glucose in man

and indicate that the block in glucose utilization following carbohydrate deprivation involves one (or more) of the reactions between glucose and the entry of fructose into the glycolytic scheme. The findings are consistent with the hypothesis of Wyshak and Chaikoff[32] that the glucokinase reaction is impaired by fasting, while the phosphorylation of fructose, which is under the influence of a separate enzyme (fructokinase), is not altered during starvation.

The importance of these observations in the management of clinical diabetes seems clear. The alterations in carbohydrate tolerance in diabetes produced by trauma, infection, or starvation are much more marked than

TABLE 10. BLOOD ANALYSES AT BEGINNING OF TREATMENT

		Fructose	*Glucose*	*No CHO*
Blood sugar	mg./100 ml.	700	488	794
N.P.N.	mg./100 ml.	56	51	40
Serum acetone	mg./100 ml.	64	62	42
Serum chloride	mEq./l.	82	91	85
Serum sodium	mEq./l.	121	128	120
Serum potassium	mEq./l.	7.0	5.9	6.0
CO_2	vol.%	33	39	42
Hours since last insulin		42	41.5	47.5

in normal subjects. Since, under these circumstances, parenteral fluids are often necessary, the evidence accumulated so far indicates the value of fructose as the carbohydrate of choice in management.

THE METABOLISM OF FRUCTOSE IN DIABETIC ACIDOSIS AND ITS USE IN EARLY TREATMENT

The physiological changes usually accompanying diabetic acidosis provide theoretical reasons for using fructose in therapy. There is considerable evidence to indicate that the patient in acidosis is under "stress" either "spontaneously"[16] or as a result of trauma or infection that may have precipitated the acidosis. Undoubtedly, there exists a state of insulin "resistance" and insulin, accordingly, is less effective early in treatment. Field and Stetten[9] have demonstrated recently the presence of an insulin antagonist in diabetic acidosis, disappearing within hours after treatment is instituted. This antagonist was nondialyzable and migrated electrophoretically with the alpha-globulin fraction of the serum proteins. Peters[28] has emphasized that diabetic acidosis is almost invariably associated with carbohydrate starvation and has summarized the evidence for using glucose even in the initial

stage. Later, however, Seldin and Tarail[27] reported on 17 cases of diabetic acidosis receiving moderate or massive injections of glucose early in treatment. They found that hyperglycemia resulted in an increase of the effective osmotic pressure of the extracellular fluid, producing cellular dehydration. The administration of glucose, even though it might replenish glycogen stores and facilitate the combustion of carbohydrate, enhanced the cellular dehydration and perpetuated the polyuria because of the increased excretion of glucose in the urine. Other authors[9, 26] have strongly opposed the use of carbohydrate. Since fructose does not require insulin for its metabolism, is more rapidly removed from the blood stream, is a better glycogen former than glucose,[15] and its metabolism is not affected by stress states or starva-

TABLE 11. TREATMENT IN FIRST SIX HOURS

Experiment	*Insulin units*	*Fluids ml.*	*NaCl mEq.*	*CHO gm.*
I	350	3300	482	175 Fructose
II	350	3250	475	175 Glucose
III	350	3250	475	No CHO

tion, it was logical to assess its value in the early treatment of diabetic acidosis under controlled conditions.[18]

Experimental acidosis was produced by the withdrawal of insulin in a human volunteer on three separate occasions. Within 40 to 50 hours after the last dose of regular insulin, clinical acidosis regularly ensued, with serum ketone levels of over 40 mg./100 ml. and blood sugars over 450 mg./100 ml. Complete balance studies were done during the withdrawal, treatment, and recovery periods. During insulin withdrawal periods all exogenous carbohydrate derived from protein and fat catabolism were excreted almost quantitatively. The results of the blood analyses at the beginning of treatment in each of the three experiments is shown in Table 10.

The period of study described here covered the first six hours of treatment. The amounts of insulin, water, and NaCl were similar in each experiment, with hexose as the variable to be investigated (Table 11).

One hundred units of insulin were given initially and 50 units each hour thereafter for a total of 350 units in the six-hour period. Approximately 475 mEq. of NaCl was given as normal saline in each of the three experiments. In Experiment I, 75 grams of fructose were given intravenously as a 10 per cent solution in the first hour, and thereafter 20 gm. each hour for a six-hour total of 175 gm. In the second experiment glucose was given in

similar amounts and at the same rate. In the third experiment saline alone was used as the constituent of the fluids. Solutions were combined in such a way that the total water administered was given at the same rate and amount in each test. Figure 12 shows the changes in blood glucose concentrations during therapy. For purposes of comparison the levels are referred to the initial blood glucose concentrations as zero. When no exogenous carbohydrate was given, the blood glucose fell at an approximately constant rate. After 75 gm. of glucose there was an initial rise at one hour of approximately 125 mg./100 ml. and then a steady fall when the amount of

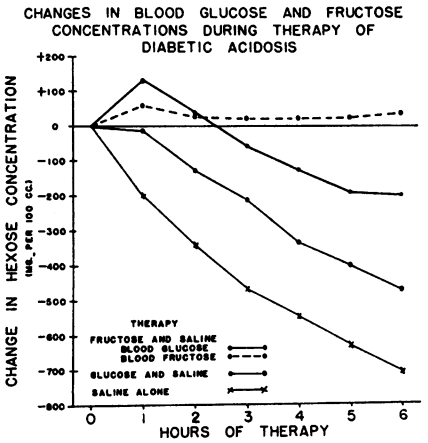

FIG. 12.

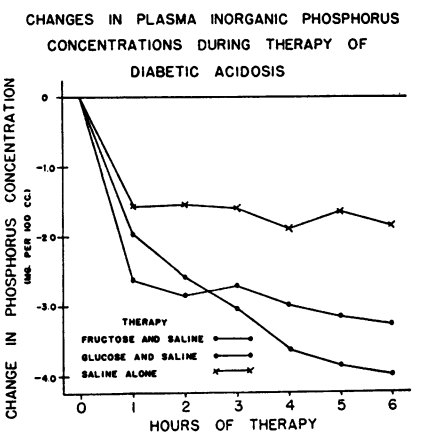

FIG. 13.

glucose infused was reduced to 20 gm. per hour. After 75 gm. of fructose there was a slight fall in blood glucose at the end of the first hour and then a rapid fall at approximately the same rate as after saline alone. Blood fructose levels were found to be in the same range as to be expected in normal subjects, the highest level being less than 75 mg./100 ml.

Carbohydrate balances for the first six hours were as follows: in Experiment I the administration of 175 gm. of fructose resulted in a net balance of 163 gm.; with glucose administration the net balance was 124 gm.; while with saline alone the total carbohydrate either stored or utilized measured only 18 gm. The excretion of fructose as such in the urine in Experiment I amounted to less than 7 gm.

Plasma inorganic phosphorus fell least after saline and most after fructose (Fig. 13). The administration of carbohydrate did not result in any increased excretion of either sodium or potassium in the urine during treat-

ment (Table 12). Since potassium was not included in the treatment schedule in the first six hours, serum potassium levels fell (Fig. 14), the fall being approximately the same in each instance. After fructose administration there was evidence of some transference of potassium into the cells which was lacking in the other two experiments.

TABLE 12. EFFECT OF HEXOSE THERAPY IN DIABETIC ACIDOSIS ON SODIUM AND POTASSIUM EXCRETION IN THE URINE

(First six hours)

	Therapy		
	Fructose	*Glucose*	*No CHO*
Sodium mEq.			
Intake I.V.	482	475	475
Output in urine	40	36	43
Potassium mEq.			
Intake I.V.	0	0	0
Output in urine	21	18	20

TABLE 13. CHANGES IN CO_2 COMBINING POWER DURING FIRST SIX HOURS OF THERAPY WITH AND WITHOUT ADDED HEXOSE

Experiment no.	*Hexose used*	*Co_2 value (Vol./100 ml.)*		
		initial	*final*	*increase*
I	Fructose	33	52	19
II	Glucose	39	56	17
III	No CHO	42	59	17
IV	Fructose	29	51	22

Urinary volume was definitely greater with glucose therapy, but fructose, because of the much smaller excretion of hexose in the urine, caused only a slightly greater water output as compared with the control regime. Serum ketone levels fell on the average about 25 per cent faster when carbohydrate was administered. No significant difference was found between fructose and glucose.

Some writers have suggested that recovery from the acidosis would be delayed with fructose therapy because of the markedly increased rate of formation of pyruvic and lactic acid in the blood. Data pertinent to the discussion were obtained in these three experiments and on a fourth occasion

when fructose again was used in treatment under similar controlled conditions (Table 13). The results show that the use of fructose actually increases the rate of recovery from acidosis, a conclusion that might have been anticipated from the known facts of fructose metabolism.

This same plan of experiment has also been applied to cases of clinical diabetic acidosis admitted to the University Hospitals during a period of 13 years. Patients entering in acidosis without known complicating factors were treated according to the schedule in Table 11. Seven cases were treated without carbohydrate, 5 with fructose, and 16 with glucose. The effects in mg./100 ml. per hour, on excretion of carbohydrate, on carbohydrate utilized or stored, on blood ketone fall, and on water balance are summarized in Table 14.

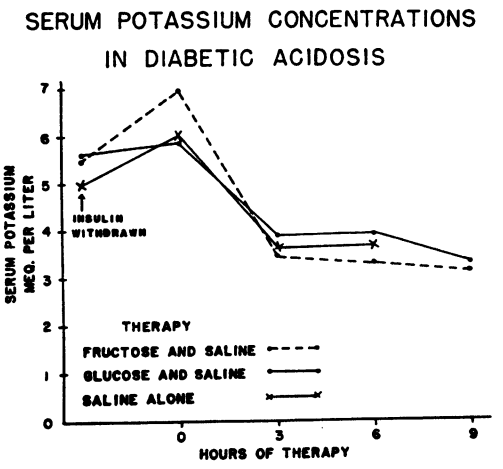

FIG. 14.

It is apparent that the results in the treatment of clinical diabetic acidosis are similar to those found in the experimentally induced type. With fructose therapy, *other factors being equal,* there are significant advantages, as measured by carbohydrate and water balances, and a more rapid fall in blood ketones. There is no delay in the recovery from acidosis, despite the increased production of pyruvic and lactic acids.

SUMMARY

The metabolism of fructose in normal and diabetic human subjects has been reviewed. The blood fructose tolerance test has been shown to be unaltered in diabetic subjects even in the absence of exogenous insulin. Fructose produces a much greater rise in blood pyruvic acid as compared with glucose, and this rise is the same or greater in diabetes. In hepatic vein catheterization studies, the livers of both normal and diabetic subjects remove intravenously administered fructose twice as rapidly as they do glucose in comparable situations. A considerable portion of administered fructose is converted in the body, but the "net advantage" of fructose over glucose in diabetic subjects is between 20 per cent and 25 per cent. Oral

administration is less advantageous, probably because of further conversion of fructose to glucose by the intestinal mucosa during absorption. It has been shown that stress situations (trauma, infection), ether anesthesia, and starvation states do not depress fructose metabolism as they do glucose. Studies in diabetic acidosis indicate the value of fructose in the initial hours of therapy.

TABLE 14. EFFECT OF HEXOSE IN TREATMENT OF DIABETIC ACIDOSIS
(First six hours)

	No CHO	*Glucose*	*Fructose*
Number of cases	7	16	5
Blood sugar fall mg./100 ml./hr.	84	11	66
Excretion CHO gm./6 hrs.	30	116	60
CHO "utilized" gm.	18	63	147
Blood ketone fall mg./100 ml./hr.	5.3	6.6	6.9
Water balance ml./6 hrs.	1970	650	1900

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