Pediat. Res. 9: 774–778 (1975)

Fructose-induced hyperuricemia
galactosemia
hereditary fructose intolerance
hyperuricemia

Fructose-induced Hyperuricemia: Observations in Normal Children and in Patients with Hereditary Fructose Intolerance and Galactosemia

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Extract

After the infusion of fructose, 0.25 g/kg body wt, the mean peak plasma uric acid level was 5.4 ± 0.7 (SEM) mg/100 ml in six normal children and was not significantly increased compared with that of the mean basal value of 4.1 ± 0.5 mg/100 ml. The mean blood inorganic phosphate (P_i) levels were significantly less than the mean fasting value after fructose. Blood glucose, lactic acid, and fructose levels were significantly increased after fructose, but serum magnesium levels did not change.

In two patients with hereditary fructose intolerance (HFI) the peak blood uric acid levels were 12.1 and 7.6 mg/100 ml, respectively, after fructose. In both patients the blood glucose concentrations decreased 69 and 26 mg/100 ml below the fasting levels after fructose. The serum P_i level decreased 2.3 and 1.2 mg/100 ml below fasting values, decrements greater than the mean decrement in serum P_i of 0.8 ± 0.2 mg/100 ml which occurred in six normal children.

The mean uric acid excretion, expressed as milligrams per mg urinary creatinine, was 0.6 ± 0.1 (SEM) before fructose in the normal children and increased significantly to 1.0 ± 0.1 mg/mg creatinine after fructose. In two patients with HFI the uric acid excretion increased four- to fivefold after fructose administration; the increased uric acid excretion in HFI exceeded that of normal children.

In three patients with galactosemia, increases in blood uric acid levels after galactose ingestion were similar to those in normal children after fructose, but less than those in patients with HFI after fructose. The serum P_i levels decreased less in galactosemic patients after galactose administration than in patients with HFI after fructose infusion.

These studies support the hypothesis that fructose-induced hyperuricemia results from degradation of adenosine monophosphate. This effect appears to be specific for fructose. The lack of hyperuricemia in galactosemia patients after galactose ingestion may be explained by the observation that galactose is phosphorylated more slowly than fructose.

Speculation

Fructose administration in individuals predisposed to hyperuricemia and gout may induce urate overproduction by decreasing intrahepatic P_i and ATP content and ultimately lead to enhanced nucleotide catabolism. The pathogenesis of increased urate production in glycogen storage disease, type I, may be similar to that proposed for fructose-induced hyperuricemia.

Abnormalities of uric acid metabolism characterized by hyperuricemia resulting from increased urate production or decreased excretion have been described in children with a variety of diseases (2, 28, 30, 31). Although hyperuricemia may result from excessive urate production due to absence (49) or partial deficiency (28) of an enzyme involved in the normal regulation of purine biosynthesis, the precise mechanism responsible for increased production of uric acid in many children remains unknown. Recent observations suggest, however, that normal metabolic intermediates may play an important role in increasing urate production in man.

Fructose administration has induced hyperuricemia in rats (33), normal subjects (17, 39, 51), children with HFI (17, 39), and in patients with gout (18, 51). Hyperuricemia after fructose administration in man, however, has not been a consistent finding (13, 44). Because of this conflicting information and that the effect of fructose administration on urate metabolism in normal human subjects appears to be dose related (24), the administration of a small dose of fructose may allow a greater discrimination of those individuals who are metabolically predisposed to hyperuricemia.

Although patients with HFI and galactosemia have some similar clinical and biochemical characteristics, hyperuricemia has not been reported in untreated patients with galactosemia. Accordingly, investigation of uric acid metabolism in patients with galactosemia might provide insight into the mechanism of fructose-induced hyperuricemia.

The purposes of this study were to determine the effects of the infusion of a smaller dose of fructose than that previously reported on blood levels of uric acid, P_i, lactic acid, and glucose in normal children and in patients with HFI, and to determine the effects of galactose administration on similar blood constituents in patients with galactosemia.

MATERIALS AND METHODS

The study group consisted of six healthy children aged 2–15 11/12 years; two children, aged 3 and 12 11/12 years, with proven HFI (absent hepatic fructose-1-P aldolase activities, characteristic histories, and diagnostic responses to fructose infusion); three patients, aged 20–23 years, with galactosemia (with absent erythrocyte galactose-1-P uridyl transferase activities and who satisfied the clinical criteria).

All patients were admitted to the Clinical Research Center of the Children's Hospital of Los Angeles. These studies were approved by the Committee on Human Experimentation of the Children's Hospital of Los Angeles, and informed patient and/or parental consent was obtained before the subjects entered the study. The normal children were given a 50% carbohydrate diet for age, the patients with HFI received a fructose-restricted diet, and those with galactosemia were continued on a galactose-restricted diet; the diets were isocaloric. Healthy children and patients with HFI received a fructose tolerance test as follows. After an overnight fast, fructose, 0.25 g/kg body wt, was administered intravenously in a 10% solution over 3–5 min. Blood levels of glucose, fructose, P_i, lactic acid, magnesium, and uric acid were measured in the fasting state and at 10, 20, 30, 40, 50, 60, 80, 100,

and 120 min. In four normal children and in two patients with HFI, urine was collected for 4 hr before and for 4 hr after fructose administration, and urinary excretion of uric acid and creatinine were measured.

The patients with galactosemia received 50 g galactose orally after an overnight fast and blood uric acid, glucose, galactose, P_i, lactic acid, and erythrocyte galactose-1-phosphate (gal-1-P) were measured in the fasting state and at 15, 30, 60, 120, 180, and 360 min. The dose of galactose was a standard dose used in galactosemic patients (14).

Blood glucose was measured by a glucose oxidase method (25), serum lactic acid was measured by the method of Barker and Summerson (5), blood fructose by the method of Schreiner (46), blood galactose and erythrocyte gal-1-P were measured by a modification of the method as described by Gitzelmann (21). Plasma and urinary uric acid were determined by an enzymatic spectrophotometric method (41). Magnesium was measured by fluorometric analysis (45) and P_i by a modification of the Fiske and SubbaRow method (16). Data were analyzed for statistical significance by using a two-tailed, paired Student's test (50).

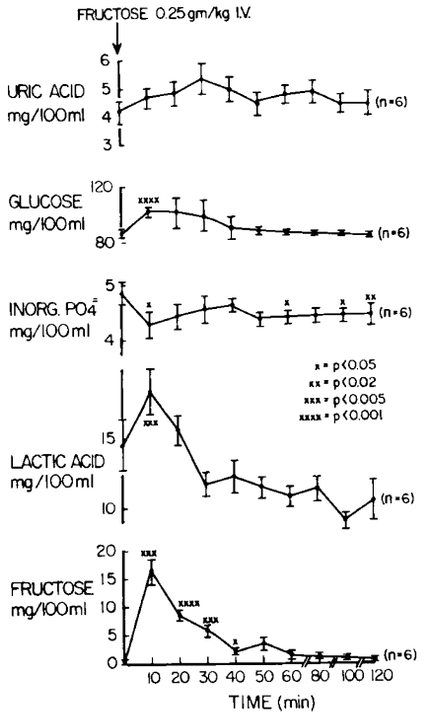

Fig. 1. Mean ± SEM responses of blood uric acid, glucose, inorganic (*INORG.*) phosphate, lactic acid, and fructose in normal children after the intravenous administration of fructose. The number (*n*) of subjects is indicated in parentheses. The *P* values indicate the significance of the differences between the mean resting (0) values and the mean values at each time after fructose administration.

RESULTS

NORMAL CHILDREN

Blood. The levels of blood uric acid, glucose, P_i, lactic acid, and fructose after the administration of fructose in six normal children are indicated in Figure 1.

After the infusion of fructose the mean peak plasma uric acid level was 5.4 ± 0.7 (SEM) mg/100 ml and was not significantly increased compared with the mean basal value of 4.1 ± 0.5 mg/100 ml ($P > 0.05$). Ten minutes after fructose was administered the mean blood glucose concentration was 101.8 ± 2.4 mg/100 ml and significantly greater than the mean fasting glucose value of 88.3 ± 2.6 mg/100 ml ($P > 0.001$). The mean delta (Δ) glucose was 20.8 ± 7.7 mg/100 ml. The mean blood P_i levels were significantly less than the mean fasting value 10, 60, 100, and 120 min after fructose. The mean blood lactic acid level 10 min after fructose was 18.3 ± 1.9 mg/100 ml and significantly greater than the mean fasting value of 14.3 ± 2.1 mg/100 ml ($P > 0.005$).

Urine. The mean uric acid excretion in four healthy children, expressed as milligrams per mg urinary creatinine, was 0.6 ± 0.1 before fructose and increased significantly to 1.0 ± 0.1 after the administration of fructose ($P > 0.02$) (Table 1).

HEREDITARY FRUCTOSE INTOLERANCE

Blood. The levels of blood uric acid, glucose, P_i, lactic acid, magnesium, and fructose after an infusion of fructose in two patients with HFI are indicated in Figure 2.

In one patient (*RV*) the fasting blood uric acid level was 8.7 mg/100 ml and higher than the mean fasting value noted in our normal children. In *RV* and in the other patient (*JV*) the blood uric acid levels increased to 12.1 and 7.6 mg/100 ml, respectively. The Δ uric acid concentrations were 3.4 and 3.3 mg/100 ml in these two patients and were higher than the mean Δ uric acid concentration of 1.1 ± 0.4 mg/100 ml of normal children. In the HFI patients the peak uric acid responses occurred within 20 min after fructose and were earlier than the peak response in normal children. In both HFI patients the blood glucose concentrations decreased 69 mg/100 ml and 26 mg/100 ml below the fasting values, respec-

Table 1. *Excretion of uric acid 4 hr before and after intravenous fructose, 0.25 g/kg, in normal children and in children with hereditary fructose intolerance (HFI)*

	Before fructose			After fructose		
	Creatinine, mg/4 hr	Uric acid, mg/4 hr	Uric acid, mg/mg creatinine	Creatinine, mg/4 hr	Uric acid, mg/4 hr	Uric acid, mg/mg creatinine
Normal children						
ML	167.0	79.2	0.47	222.0	226.9	1.02
EL	82.0	40.0	0.49	145.0	139.3	0.96
GC	48.5	27.8	0.57	68.5	56.6	0.83
RK	27.3	29.9	1.02	28.2	35.2	1.24
Mean	81.20	44.22	0.64	115.92	114.50	1.01
±SEM	30.74	11.96	0.13	42.86	43.67	0.08
			$P < 0.02$[1]			
HFI						
RV	46.0	68.0	1.48	57.8	330.0	5.53
JV	101.2	44.0	0.43	105.6	241.0	2.28

[1] *P* value refers to the difference between the mean values for urinary uric acid-creatinine before and after fructose in the normal children.

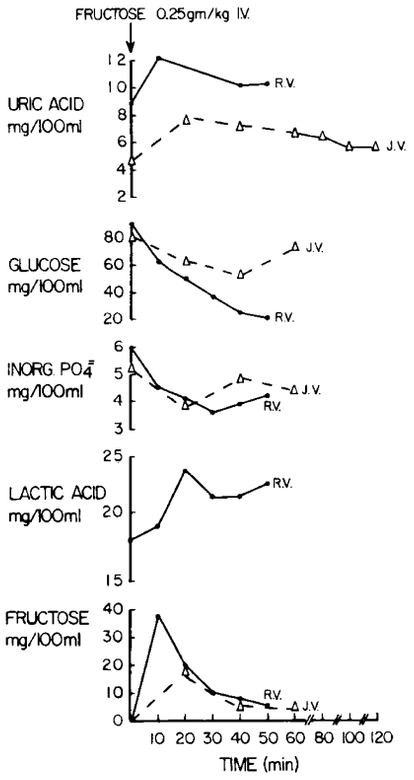

Fig. 2. Responses of blood uric acid, glucose, inorganic (*INORG.*) phosphate, lactic acid, and fructose in two patients (*RV* and *JV*) with hereditary fructose intolerance after the intravenous administration of fructose.

tively (Fig. 2). The decreases in P_i levels in the two patients with HFI exceeded the mean decrement in serum P_i of 0.8 ± 0.2 mg/100 ml of normal children. In one patient (*RV*) the elevation of the blood lactic acid level after fructose was similar to that of normal children; however, elevated blood lactic acid levels persisted for 60 min in this patient. In one patient (*RV*) the serum magnesium level increased from 2.1 to 2.9 mg/100 ml, an increment of almost 40%; the mean serum magnesium levels did not increase after fructose in normal children. The peak blood level of fructose was 37 mg/100 ml in *patient RV* and was higher than the mean peak level of 16.7 ± 2.5 mg/100 ml in normal children after fructose administration. The rate of fructose disappearance in both HFI patients was similar to that of normal children.

Urine. The excretion of uric acid increased four- fivefold in two patients with HFI after the administration of fructose, and was several times greater than that of normal children (Table1).

GALACTOSEMIA

Blood. The levels of uric acid, glucose, P_i, galactose in blood, and gal-1-P in erythrocytes after galactose ingestion in three patients with galactosemia are indicated in Figure 3.

The peak uric acid levels occurred 60 to 360 min after the ingestion of galactose. The uric acid elevations were similar to those of healthy children after fructose, but much less than the increases in the HFI patients. The blood glucose levels decreased 4–16 mg/100 ml below the fasting glucose levels between 60 and 120 min after galactose, and the blood galactose concentrations increased slowly to peak levels 120 min after ingestion of galactose. The concentrations of gal-1-P in erythrocytes increased gradually, reaching peak values 120–360 min after the ingestion of galactose. The changes in galactose concentration and that of gal-1-P were accompanied by a slight decrease in the serum P_i levels 120–180 min after ingestion. In the patients with galactosemia the P_i levels devreased 50% less after galactose ingestion than in the patients with HFI after fructose; the nadir was reached 120–180 min after galactose as compared with 30 min after fructose in HFI.

DISCUSSION

Recent reports concerning the effect of fructose administration on serum uric acid levels in man have been conflicting. Perheentupa and Raivio (39) described hyperuricemia in normal children and in patients with HFI after the intravenous administration of 0.5 g/kg body wt of fructose. Hyperuricemia resulted in adults with gout (18) after 0.5 g/kg body wt of fructose intravenously over a 10 -min period but not in normal man when similar doses were given at a slower rate (13, 44). Oral administration of 1.0 g/kg body wt of fructose resulted in elevations in serum uric acid levels in gouty patients and in their children (51) in contrast to the changes noted in normal subjects. Although a significant increase in serum uric acid levels has been observed in normal men after the intravenous administration of 1.5 g/kg body wt/hr of fructose (24), fructose in amounts less than 1.0 g/kg/hr failed to induce significant hyperuricemia (24).

In the present study, using a smaller dose of fructose than that previously reported (18, 24, 39, 51) and after a rapid infusion, an observable but not statistically significant increase in serum uric acid levels occurred which was, however, accompanied by a marked uricosuria in normal children. A similar response has been noted in normal adults (44). In contrast, hyperuricemia and hyperuricosuria after fructose were much greater in the two patients with HFI than in normal children; these observations are in accord with those of others (39). Our findings emphasize the

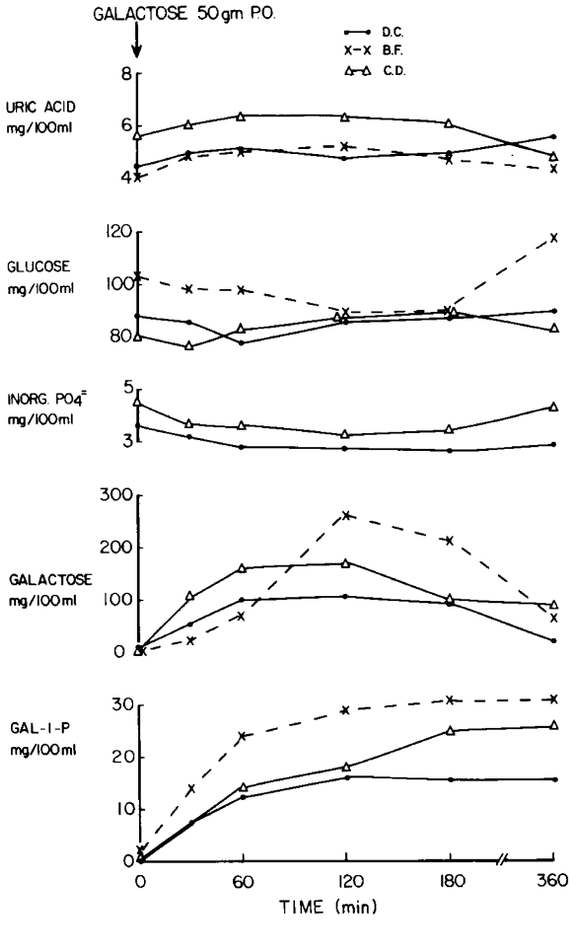

Fig. 3. Responses of blood uric acid, glucose, inorganic (*INORG.*) phosphate, galactose, and erythrocyte galactose-1-P (*GAL-1-P*) after the ingestion of 50 g galactose in three patients with galactosemia.

previous observations (24, 44) that a higher total dose given over a brief period of time is required for the hyperuricemic effect of fructose in normal subjects.

Since lactic acid decreases the renal clearance of uric acid (54), the increased blood lactate levels induced by fructose in one of our patients and others (12, 39) with HFI may have contributed to the hyperuricemia. Becuase there was an increase in urinary uric acid excretion in our normal children and in patients with HFI after fructose administration, as was also observed by others (36, 42), it is unlikely that increased blood lactic acid levels have an important role in increasing serum urate levels.

The mechanism of fructose-induced hyperuricemia has been attributed to the breakdown of preformed hepatic adenine nucleotides induced by fructose (8, 9, 10, 18, 33, 53). It has been shown that the rapid phosphorylation of fructose by fructokinase (1, 22, 53) results in the accumulation of fructose-1-P in animal (11, 27, 53) and in normal human (9) liver when fructose is given. This has been associated with a marked decrease in hepatic ATP and P_i levels (10, 33, 53). Both ATP and P_i are essential for the stabilization of AMP (37, 43); depletion of ATP and P_i results in degradation of AMP to IMP (9, 52). The increased concentration of IMP which inhibits fructose-1-P aldolase (53) may accentuate the sequestration of P_i as fructose-1-P in normal human and animal liver. Both IMP and adenosine accumulate in liver and are then degraded to inosine, hypoxanthine, xanthine, and uric acid or allantoin (9, 33, 53). In rats, the observation that the administration of P_i in combination with fructose increased AMP content and prevented the loss of total adenosine phosphate content in liver provides support for the proposed mechanism (9).

The fructose-induced hyperuricemia observed in HFI patients is in accord with this hypothesis. Patients with HFI lack hepatic fructose-1-P aldolase (23, 38). Because fructokinase activity is normal in liver cells in patients with HFI (19, 32), fructose-1-P accumulates (34). Although fructose-1-P is increased four- to fivefold in normal man after 0.6–0.8 g fructose/kg body wt (9), the intracellular concentrations of fructose-1-P, P_i, and ATP after a fructose load in patients with HFI are not known. Indirect evidence suggests, however, that the levels of hepatic fructose-1-P and sequestration of P_i attained after a given dose of fructose in HFI are probably higher than in normal man (19, 23).

The fall in serum P_i levels after fructose within 10–20 min in our patients and those of others (12, 20, 32, 36), suggests increased hepatic P_i uptake (35). Because early alterations in serum P_i levels in our normal children could not be detected, it is unlikely that significant changes in hepatic P_i and ATP concentrations occurred, which could explain the failure of fructose infusions to cause elevations in blood uric acid levels in normal children.

Perheentupa and Raivio (39) noted that the magnitude of uric acid elevations in normal and HFI children in response to a higher dose of fructose than that used in this study was similar. The observation that the effect of fructose on the ATP content in rat liver is dose dependent (8, 42) would explain the observation that the higher doses of fructose produce hyperuricemia in normal man.

The rapidity of the effect of fructose in our patients and others (36, 40) with HFI and in normal animal (53) and human (8) liver suggests that an accelerated catabolism of purine nucleotides is probably the major mechanism of fructose-induced hyperuricemia. However, in a recent study (15), an increased rate of purine synthesis *de novo* has been demonstrated after oral administration of fructose for a period of 12 days in three adults without gout. It is possible that the mechanism of fructose-induced hyperuricemia may differ depending on the duration and route of fructose administration. Regardless of the precise mechanism, these observations emphasize the importance of the effect of fructose upon urate production.

Hereditary fructose intolerance and galactosemia share clinical and biochemical abnormalities and therefore investigation of the effect of galactose on uric acid metabolism might provide further insight into the mechanism of fructose-induced hyperuricemia. Accordingly, the results in patients with galactosemia are of interest. The concentrations of gal-1-P are increased in erythrocytes of patients with galactosemia (26, 48), in liver (34, 47), and kidney (47) because of gal-1-P uridyltransferase deficiency (3, 26). Elevated gal-1-P levels have been associated with a markedly lower level of P_i in red blood cells (48) and in plasma (29, 32), which suggests that a decrease in intracellular hepatic ATP might also occur after galactose ingestion; hepatic ATP content in galactosemic patients is not known.

Gal-1-P accumulated within erythrocytes and P_i levels decreased in blood after galactose administration in our galactosemic patients. The rates of changes in these compounds were slow and were not accompanied by significant alterations in blood uric acid concentrations. In contrast, the P_i levels in blood decreased rapidly and to a greater degree after fructose in our patients with HFI.

Although the results of galactose administration were similar to those observed in our normal children given intravenous fructose, it may be questioned whether the dose and oral route of administration of galactose provided conditions strictly comparable with those of the fructose infusion experiments. Allowing for this variation in experimental conditions, the difference in the uric response to fructose in HFI and to galactose in our patients with galactosemia may be explained by the rapid initial phosphorylation of fructose. In human liver, fructokinase activity is fourfold that of glucokinase and hexokinase, and fructose can be phosphorylated faster than glucose (22) and galactose (1, 4, 22). Because galactose is phosphorylated more slowly than fructose, rapid utilization of ATP and sequestration of P_i are less likely to occur to the same extent as with fructose (42). In accord with this explanation is the observation that hepatic ATP and total adenine nucleotides were not depressed in rats injected with galactose (29), whereas an identical dose of fructose resulted in a depression of P_i, ATP, and adenine nucleotides (33). These results suggest that fructose-induced hyperuricemia is specifically induced by fructose.

SUMMARY

The results of the present study emphasize previous observations that the occurrence of hyperuricemia resulting from fructose administration in normal subjects is dependent upon the amount of fructose given and the rate of infusion. Elevations of blood urate levels in response to fructose in patients with HFI occur at a lower dose of fructose than that required for a response in normal subjects. Because hyperuricemia does not occur in galactosemia patients after galactose administration, fructose-induced hyperuricemia appears to be specific for that monosaccharide.

REFERENCES AND NOTES

1. Adelman, R. C., Ballard, F. J., and Weinhouse, S.: Purification and properties of rat liver fructokinase. J. Biol. Chem., *242:* 3360 (1967).
2. Alepa, F. P., Howell, R. R., Klinenberg, J. R., and Seegmiller, J. E.: Relationships between glycogen storage disease and tophaceous gout. Amer. J. Med., *42:* 58 (1967).
3. Anderson, E. P., Kalckar, H. M., and Isselbacher, K. J.: Defect in uptake of galactose-1-phosphate into liver nucleotides in congenital galactosemia. Science, *125:* 113 (1957).
4. Ballard, F. J.: Kinetic studies with liver galactokinase. Biochem. J., *101:* 70 (1966).
5. Barker, S. B., and Summerson, W. H.: The colorimetric determination of lactic acid in biological material. J. Biol. Chem., *138:* 535 (1941).
6. Bartlett, G. R.: Human red cell glycolytic intermediates. J. Biol. Chem., *234:* 449 (1959).
7. Bergström, J., Hultman, E., and Roch-Norlund, A. E.: Lactic acid accumulation in connection with fructose infusion. Acta Med. Scand., *184:* 359 (1968).
8. Bode, C., Shumacher, H., Goebell, H., Zelder, O., and Pelzel, H.: Fructose induced depletion of liver adenine nucleotides in man. Horm. Metab. Res., *3:* 289 (1971).
9 Bode, J. C., Zelder, O., Rumpelt, H. J., and Wittkamp, U.: Depletion of liver adenosine phosphates and metabolic effects of intravenous infusion of fructose or sorbitol in man and in the rat. Eur. J. Clin. Invest., *3:* 436 (1973).
10. Burch, H. B., Lowry, O. H., Meinhardt, L., Max, P., Jr., and Chyu, K.-J.: Effect of fructose, dihydroxyacetone, glycerol, and glucose on metabolites and related compounds in liver and kidney. J. Biol. Chem., *245:* 2092 (1970).
11. Burch, H. B., Max, P., Jr., Chyu, K., and Lowry, O. H.: Metabolic intermediates in liver of rats given large amounts of fructose or dihydroxyacetone. Biochem. Biophys. Res. Commun., *34:* 619 (1969).

12. Cornblath, M., Rosenthal, I. M., Reisner, S. H., Wybregt, S. H., and Crane, R. K.: Hereditary fructose intolerance. New Eng. J. Med., *269:* 1271 (1963).
13. Curreri, P. W., and Pruitt, B. A., Jr.: Absence of fructose-induced hyperuricemia in men. Lancet, *i:* 839 (1970).
14. Donnell, G. N., Bergren, W. R., and Roldan, M.: Genetic studies in galactosemia. I. The oral galactose tolerance test and the heterozygous state. Pediatrics, *24:* 418 (1959).
15. Emmerson, B. T.: Effect of oral fructose on urate production. Ann. Rheum. Dis., *33:* 276 (1974).
16. Fiske, C. H., and SubbaRow, Y.: The colorimetric determination of phosphorus. J. Biol. Chem., *66:* 375 (1925).
17. Förster, H.: Kurze Wissenschafliche Mitteilungen. Klin. Wschr., *45:* 436 (1967).
18. Fox, I. H., and Kelley, W. N.: Studies on the mechanism of fructose-induced hyperuricemia in man. Metabolism, *21:* 713 (1972).
19. Froesch, E. R., Prader, A., Wolf, H. P., and Labhart, A.: Die hereditare fructoseintoleranz. Helv. Paed. Acta, *14:* 99 (1959).
20. Froesch, E. R., Wolf, H. P., Baitsch, H., Prader, A., and Labhart, A.: Hereditary fructose intolerance: An inborn defect of hepatic fructose-1-phosphate splitting aldolase. Amer. J. Med., *34:* 151 (1963).
21. Gitzelman, R.: Estimation of galactose-1-phosphate in erythrocytes: A rapid and simple enzymatic method. Clin. Chim. Acta, *26:* 313 (1969).
22. Heinz, F., Lamprecht, W., and Kirsch, J.: Enzymes of fructose metabolism in human liver. J. Clin. Invest., *47:* 1826 (1968).
23. Hers, H. G., and Joassin, G.: Anomalie de l'aldolase hepatique dans l'intolerance au fructose. Enzymol. Biol. Clin., *1:* 4 (1961).
24. Heuckenkamp, P.-U., and Zöllner, N.: Fructose-induced hyperuricemia. Lancet, *i:* 808 (1971).
25. Hugget, A. S. G., and Nixon, D. A.: Use of glucose oxidase, peroxidase and o-dianisidine in determination of blood and urinary glucose. Lancet, *ii:* 368 (1957).
26. Kalckar, H. M., Anderson, E. P., and Isselbacher, K. J.: Galactosemia, a congenital defect in a nucleotide transferase: A preliminary report. Proc. Nat. Acad. Sci. U. S. A., *42:* 49 (1956).
27. Kjerulf-Jensen, K.: The phosphate esters formed in the liver tissue of rats and rabbits during accumulation of hexses and glycerol. Acta Physiol. Scand., *4:* 294 (1942).
28. Kogut, M. D., Donnell, G. N., Nyhan, W. L., and Sweetman, L.: Disorders of purine metabolism due to partial deficiency of hypoxanthine-guanine phosphoribosyltransferase. Amer. J. Med., *48:* 148 (1970).
29. Komrower, G. M., Schwarz, V., Holzel, A., and Goldberg, L.: A clinical and biochemical study of galactosemia. Arch. Dis. Childhood, *31:*254 (1956).
30. Krakoff, I. H., and Murphy, M. L.: Hyperuricemia in neoplastic disease in children: Prevention with allopurinol, a xanthine oxidase inhibitor. Pediatrics, *41:* 52 (1968).
31. Lesch, M., and Nyhan, W. L.: A familial disorder of uric acid metabolism and central nervous system function. Amer. J. Med., *36:* 561 (1964).
32. Levin, B., Oberholzer, V. G., Snodgrass, G. J. A. I., Stimmler, L., and Wilmers, M. J.: Fructosaemia: An inborn error of fructose metabolism. Arch. Dis. Childhood, *38:* 220 (1963).
33. Maenpää, P. H., Raivio, K. O., and Kekomäki, M. P.: Liver adenine nucleotides: Fructose-induced depletion and its effect on protein synthesis. Science, *161:* 1253 (1968).
34. Milhaud, G.: Technique nouvelle de mise em evidence d'erreurs congenitales du metabolisme chez l'homme. Arq. Bras. Endocrin. Metab., *13:* 49 (1964).
35. Miller, M., Drucker, W. R., Owens, J. E., Craig, J. W., and Woodward, H., Jr.: Metabolism of intravenous fructose and glucose in normal and diabetic subjects. J. Clin. Invest., *31:* 115 (1952).
36. Morris, R. C., Jr.: An experimental renal acidification defect in patients with hereditary fructose intolerance. II. Its distinction from classic renal tubular acidification defect associated with the Fanconi syndrome of children with cystinosis. J. Clin. Invest., *47:* 1648 (1968).
37. Nikiforuk, G., and Colowick, S. P.: The purification and properties of 5-adenylic acid deaminase from muscle. J. Biol. Cem., *219:* 119 (1956).
38. Nikkilä, E. A., Somersalo, O., Pitkanen, E., and Perheentupa, J.: Hereditary fructose intolerance, an inborn deficiency of liver aldolase complex. Metabolism, *11:* 727 (1962).
39. Perheentupa, J., and Raivio, K.: Fructose-induced hyperuricemia. Lancet, *2:* 528 (1967)
40. Perheentupa, J., Raivio, K. O., and Nikkilä, E. A.: Hereditary fructose intolerance. Acta Med. Scand. Suppl. *542:* 65 (1972).
41. Praetorius, E.: An enzymatic method for the determination of uric acid by ultraviolet spectrophotometry. Scand. J. Clin. Invest., *1:* 222 (1949).
42. Raivio, K. O., Kekomäki, M. P., and Maenpää, P. H.: Depletion of liver adenine nucleotides induced by D-fructose. Dose-dependence and specifically of of the fructose effect. Biochem. Pharmacol., *18:* 2615 (1969).
43. Ronca-Testoni, S., Raggi, A', and Ronca, G.: Muscle AMP aminohydrolase. III. A comparative study on the regulatory properties of skeletal muscle enzyme from various species. Biochim. Biophys. Acta, *198:* 101 (1970).
44. Sahebjami, H., and Scalettar, R.: Effects of fructose infusion on lactate and uric acid metabolism. Lancet, *i:* 366 (1971).
45. Schacter, D.: Fluorometric estimation of magnesium with 8-hydroxy-5-quinolinesulfonate. J. Lab. Clin. Med., *58:* 495 (1961).
46. Schreiner, G. E.: Determination of insulin by means of resorcinol. Proc. Soc. Exp. Biol. Med., *74:* 117 (1950).
47. Schwarz, V.: The value of galactose phosphate determinations in the treatment of galactosemia. Arch. Dis. Childhood, *35:* 428 (1960).
Dis. Childhood, *35:* 428 (1960).
48. Schwarz, V., Goldberg, L., Komrower, G. H. and Holzel, A.: Some disturbances of erythrocyte metabolism in galactosemia. Biochem. J., *62:* 34 (1956).
49. Seegmiller, J. E., Rosenbloom, F. M., and Kelley, W. N.: Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis. Science, *155:* 1682 (1967).
50. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, Ed. 6 (Iowa State University Press, Ames, Iowa, 1967).
51. Stirpe, F., Dellacorte, E., Bonetti, E., Abbondanza, A., Abbati, A., and De Stefano, F.: Fructose-induced hyperuricemia. Lancet, *ii:* 1310 (1970).
52. Woods, H. F., and Alberti, K. G. M. M.: Dangers of intravenous fructose. Lancet, *ii:* 1354 (1972).
53. Woods, H. F., Eggleston, L. V., and Krebs, H. A.: The cause of hepatic accumulation of fructose-1-phosphate on fructose loading. Biochem. J., *119:* 501 (1970).
54. Yu, T. F., Sirota, J. H., Berger, L., Halpern, M., and Gutman, A. B.: Effect of sodium lactate on urate clearance in man. Proc. Soc. Exp. Biol. Med., *96:* 809 (1957).
55. The authors are grateful to the nurses of the Clinical Research Center for their invaluable assistance, to Ms. Betty Knoch and Mrs. Joanne Lin for their expert technical assistance, to Ms. Carol Smith for her secretarial help, and to Ellin Lieberman, M.D., for her help in preparation of the manuscript.
56. This research was supported in part by grants from the General Clinical Research Centers Program (RR-86) of the Division of Research Resources, National Institutes of Health; Health, Education and Welfare (No. 422); and the Michael J. Connell Foundation.
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58. Accepted for publication June 12, 1975.

Printed in U.S.A.