12.3.2 Inborn errors of fructose metabolism 1993 T

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12.3.2 Inborn errors of fructose metabolism 1993 may then confirm the diagnosis of a GSD. Electron microscopy can also be helpful if structurally abnormal glycogen is present. A diag- nostic fast, with measurement of glucose, lactate, and ketones can also provide useful information. Hepatomegaly with glycogen storage is not, however, always due to a GSD: hepatic glycogenosis is a well-recognized complication of poorly controlled diabetes mellitus. Muscle GSDs either present as exercise-induced muscle pain or rhabdomyolysis, or progressive skeletal myopathy or cardiomyop- athy. For patients who have exercise intolerance, and in whom de- fects of energy metabolism are suspected, the ischaemic forearm exercise test has traditionally been the diagnostic test of choice, demonstrating a rise in ammonia but not lactate in GSD V. This test is always unpleasant for the patient, and can precipitate rhabdo- myolysis, and is now seldom performed. A 12-min walking test, monitoring speed and heart rate, can be used to demonstrate the second wind effect in patients with GSD V. A number of the en- zymes involved can be assayed in leucocytes, but for others muscle is needed (Table 12.3.1.2). Testing for individual enzymes is laborious and expensive and, increasingly, molecular genetics is becoming the diagnostic test of choice. Next-generation sequencing allows large arrays of genes to be sequenced at the same time, and genetic panels to screen for all causes of rhabdomyolysis, or all known GSDs, are now available. FURTHER READING Boers SJB, et al. (2014). Liver transplantation in glycogen storage dis- ease type I. Orphanet J Rare Dis, 9, 47. Brambilla A, et al. (2014). Improvement of cardiomyopathy after high- fat diet in two siblings with glycogen storage disease type III. JIMD Rep, 17, 91–5. Dagli A, Sentner CP, Weinstein DA (2010). Glycogen storage disease type III. In: Pagon RA, et al. (eds) GeneReviews®. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/ books/NBK26372/ Derks TGJ, Smit GPA (2015). Dietary management in glycogen storage disease type III: what is the evidence? J Inherit Metab Dis, 38, 545–50. Hedberg-Oldfors C, Oldfors A (2015). Polyglucosan storage myop- athies. Mol Aspects Med, 46, 85–100. Julián MT, et al. (2015). Hepatic glycogenosis:

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 has not been found. Symptoms improve when the offending sugars are avoided. Three inborn errors of fructose metabolism are recognized and these disorders are vivid examples of gene–environment interactions:

1. Essential or benign fructosuria due to fructokinase deficiency—a very rare disorder with apparently no ill effects.
2. Hereditary fructose intolerance (fructosaemia)—an autosomal recessive disease caused by deficiency of aldolase B. Typically presents at weaning when most fatalities occur. May come to light at any age with postprandial abdominal pain and vomiting, symptomatic

hypoglycaemia (which may induce seizures), hypophosphataemia, acidosis, and other metabolic disturbances after consumption of offending foods and drinks. Unrecognized disease causes failure to thrive/growth retardation, a Fanconi-like renal syndrome with nephrocalcinosis, and jaundice with lethal liver injury. Parenteral infusion of fructose or its congeners may cause death from acute hepatorenal injury. Diagnosis formerly depended on a controlled intravenous fructose challenge test or demonstration of deficient aldolase B isozyme activity in liver or small intestinal biopsy material; currently molecular analysis of the aldolase B gene is preferred and usually decisive. Treatment requires institution of a strict sugar-exclusion diet supplemented by folic acid and vitamin C. Early diagnosis and dietary modifica- tion are critical for well-being and normal development.

3. Fructose-1,6-diphosphatase deficiency—a very rare disease of infancy and childhood associated with failure of hepatic gluconeogenesis causing bouts of severe hypoglycaemia, ke- tosis, and lactic acidosis provoked by infection and starvation. Metabolic decompensation is provoked by dietary fructose, related sugars, and/or ketogenic fat. Diagnosis depends on en- zymatic assay of fructose 1,6-diphosphatase in fresh liver biopsy samples or molecular analysis of the cognate gene. Treatment requires a fructose-exclusion diet containing abundant carbohy- drate energy, restricted fat, and protein. Acute episodes of acidosis or hypoglycaemia are controlled by intravenous glucose infu- sions, with bicarbonate if required. Introduction Fructose is an important and burgeoning component of the modern diet; it occurs as a free monosaccharide in fruit, nuts, honey, and some vegetables but is now abundant and practically ubiquitous in popular, mass-produced drinks. Free fructose is released from the disaccharide sucrose in the gut lumen by the sucrase–isomaltase complex at the brush-border membrane of the mucosal epithelium; in modern times, sucrose is the principal source of fructose for most persons. Finally, the sugar alcohol, sorbitol (a constituent of medi- cines and tablets, as well as diabetics), is converted quantitatively to fructose in the liver and intestine. Inborn errors of fructose metabolism provide unique ex- amples of gene–environment interactions in recent economic his- tory. Emergence of these conditions reflects revolutionary dietary changes resulting from the mass industrialization of sugar farming and manufacture. Were it not for the sugar industry, it is unlikely that these disorders would have come to light, even though several mutations in ALDOB (encoding the specific aldolase B isozyme) which cause hereditary fructose intolerance are widespread and shared in different populations, indicating ancient origins. Given the primacy of fructose and sucrose in the phenotypic ex- pression of these disorders, an understanding of the driving forces responsible for the disease is of central importance for holistic clin- ical management. Certainly, the relatively rare conditions that are due to disturbance of fructose metabolism share features with en- vironmentally driven syndromes of obesity, nonalcoholic hepatic steatosis, and hyperlipidaemia. In the background, a succession of regrettable historical events led to the introduction of sugar pri- marily into the modern European diet. Insatiable demands for sugar obtained in plantations by foreign slave labour in New World col- onies has left many painful consequences, for example, the wide geo- graphic dissemination of sickle cell disease and other effects such as economic deprivation and social injustice. Consumption of fructose and sucrose The sugar trade expanded during the 16th to 19th centuries ce as the mass capture and trading of slaves took hold. Partially modelled on earlier Arabic trading in Africa, the use of slave labour in the sugar plantations in New World and other colonies has a haunting legacy. Nowadays,

however, this history has an ironic payback in the consequential effects of sugar on global health. The mass industri- alization of sugar production declares the nature of the human ap- petite for sweet flavours, and exogenous sugar is added to food and drinks in modern societies across the world. Disorders of fructose metabolism and its assimilation mirror the ubiquity of sucrose and fructose in the diet. Consumption of free sugars varies greatly by age and country. Most people in developed countries ingest 50 to 100 g fructose equivalents daily in the diet. The top cane and beet sugar (sucrose)- consuming countries are shown in Table 12.3.2.1. Global production of sugar (sucrose from cane and beet) continues to rise, but over the last three decades, novel manufacture of fructose as a high-fructose corn syrup, enzymatically derived from starch in maize (corn), has also burgeoned. This intensely sweet sugar, first enzymatically pro- duced commercially from excess maize in the early 1970s, mainly from United States mid-Western agriculture, has been popular in the United States of America, Mexico, and China, but is now manu- factured and used in the European Union and Australia. Sugar manufacture—a challenge for global health World manufacture of sugar and sweeteners is growing; the global 2017 market was about $97 billion, representing an estimated 184 million metric tons of sugar as sucrose. Until recently, all large- scale sugar production came from sugar beet and sugar cane, which in modern times yield products that are indistinguishable in taste and composition. Cane sugar, principally from tropical countries, represents about 80% of the global market and is generally cheaper to manufacture than beet sugar, which has enjoyed political and eco- nomic support from local farming systems, generally in nontropical countries. Direct market competition of beet with cane sugar had occurred in postcolonial times because beet sugar-producing coun- tries mitigated losses on exports by high revenue in domestic mar- kets, thus allowing expansion of domestic beet cultivation.

12.3.2 Inborn errors of fructose metabolism 1995 High-fructose corn syrup is now used extensively as a sweetener in drinks and processed foods. In 2017, the global market for this preparation alone was $4.5 billion dollars (c.5% of cane and beet sugar) and this continues to rise by more than 2% annually. In 1970, the average per capita daily consumption in the United States of America of 105 g calorific sweetener contained only 0.5 g from high- fructose corn syrup, but by 2004 this had risen to 52.4 g of the 124.8 g of the sweetener ingested on average each day. As the World Health Organization emphasizes—and as patients who are genuinely intolerant realize—many of the sugars consumed today are ‘hidden’ in processed foods and drinks; they are neither overtly present nor declared as sweeteners. An average portion of ketchup sauce contains about 4 g of free sugar; a single can of soda contains up to 40 g sucrose and/or fructose. Depending on the re- gional manufacturing and local distribution, the most popular international carbonated drinks obtained from one long-established company based in the United States of America contain 100 to 140 g/litre sugar, mostly as fructose. Food and drink labels are often deceptive: a popular mint-flavoured confection in the United Kingdom is described as con- taining several grams of carbohydrate but ‘sugar-free’. In fact, all the carbohydrate is present as sorbitol—a direct source of fructose. These mints, peppery rather than sweet to the taste, caused seizures and nephrocalcinosis in a strictly controlled and food-conscious mathematician with hereditary fructose intolerance (whose affected brother had died in infancy). While a popular carbonated mixer drink flavoured with quinine contains 80 g/litre sugar, its ‘naturally light’ alternative contains nearly 30 g/litre. In Europe, sugar intake in adults ranges from about 8% of total energy intake in Hungary

and Norway, to more than twice this pro- portion in Spain and the United Kingdom. Intake is relatively greater among children, ranging from about 12% in Denmark, Slovenia, and Sweden, to nearly 25% in Portugal. Generally, consumption of additional sugar is greater in urban compared with rural commu- nities, but this may not hold in countries where production of cane sugar is still a dominant industry, such as Brazil. Changes in the sugar economy and mitigating factors Production of sugar from cane, beet, and increasingly from cereal starch is a massive global industry, but more than 70% of world sugar production is never traded on the open market. Brazil, one of the first since its early Portuguese colonization, and still the largest pro- ducer, controls half the global market but pays subsidies measured in billions annually to its sugar industry. Until very recently, a complex tariff rate system providing direct support of domestic sugar pro- duction was used in the United States of America, which maintained the price there up to 90% higher than the world market price at an annual charge of 3.7 billion dollars to American consumers. As of August 2018, a 'zero-for-zero' policy is poised for legislation to end domestic sugar subsidies after other major international producers such as Brazil and India agree reciprocally to cease sugar industry subsidies. Strong subsidies also operated in the European Union, but with a ruling from the World Health Organization some quotas were abolished in 2015. Perhaps reflecting former colonial respon- sibilities, in 2009 the European Union granted Least Developed Countries zero-tariff access status to the European market as part of its 'Everything but Arms' initiative. Control of sugar consumption The World Health Organization and American Heart Association recommend that women consume less than six teaspoons of sugar per day, which amounts to 25 g; men are recommended to ingest no more than nine teaspoons of sugar per day (38 g). The American Academy of Pediatrics recommends that children between 2 and 18 years take in no more than six teaspoons (25 g) per day. It is note- worthy that none of these recommendations apply to sugar that oc- curs naturally in foods, such as the fructose present in fruits, nuts, and honey. Given the increasing awareness of the growth of sugar consump- tion, the food and beverage industry is replacing sugar or corn syrup with non-nutritive sweeteners in a range of products that tradition- ally contained sugar. Aspartame has been a popular artificial sweet- ener in the US food industry, and its price dropped after expiry of the relevant patent in 1992. However, since 2008, sucralose has become the most popular nonsugar sweetener, replacing aspartame to artifi- cially sweeten foods and beverages. Hidden practices also operate in the United States of America, where it has until recently been possible to mislabel foods and greatly minimize their apparent sugar content. From 2018, in a con- tested mandate, the Food and Drug Administration required all food manufacturers to identify and explicitly list all 'added sugars' in their Nutrition Facts labels. This new food labelling regime clearly regards sugar as a major public enemy. As in many other countries, previ- ously these sugars were concealed under the 'Total Carbohydrates' section of the label, and only naturally occurring sugars were em- phasized. Given the strong influence of food labels on the public, the new regulation is likely to have a salutary effect, and particularly for patients with disorders of fructose metabolism. Some consider that sugar sales and promotion will soon be on the wane, but while this seems to be a premature judgement, sugar is starting to rival tobacco in perception as a major public ill in some quarters. Biochemistry of fructose metabolism The pathways of fructose metabolism are summarized in Fig. 12.3.2.1. Phosphorylated forms of fructose are critical intermediates in the glycolytic and gluconeogenic metabolic pathways in all cells. Table 12.3.2.1 Daily sugar consumption (grams per capita) 1 United States 126.4 2 Germany 102.9 3 Netherlands 102.5 4 Ireland 96.7 5 Australia 95.6 6 Belgium 95.0 7 United Kingdom 93.2 8 Mexico 92.5 9 Finland 91.5 10 Canada 89.1 Data from the World Agricultural Outlook Board—United States Department of Agriculture USDA

https://public.govdelivery.com/accounts/USDAFAS/subscriber/new and Statista: https://www.statista.com/statistics/496002/sugar-consumption-worldwide/ (accessed 26 August 2018).

SECTION 12 Metabolic disorders 1996 Fructose is absorbed by a carrier mechanism that facilitates trans- port across the intestinal epithelium; this process is mediated by the glucose transporter isoforms GLUT5 and GLUT2, the latter prob- ably contributing to efflux across the basolateral membrane of the enterocyte. Uptake of fructose is rapid and notable for its lack of dependence on insulin. Fructose is then conveyed via the portal bloodstream to the liver, where it is assimilated. The jejunal mucosa and proximal tu- bule of the kidney are subsidiary sites of fructose metabolism. Assimilation of fructose depends on the concerted activities of the enzymes ketohexokinase (fructokinase), aldolase B, and triokinase, which are expressed specifically in these tissues. Uptake of fructose occurs independently of insulin and its incorporation into inter- mediary metabolism bypasses the regulation of glycolysis at the level of phosphofructokinase-1. For these reasons, solutions of fruc- tose or sorbitol were advocated and, in the past, extensively used for parenteral nutrition, particularly in German-speaking countries. However, the occurrence of lactic acidosis, hyperuricaemia, and other serious consequences has led to their withdrawal from hyper- alimentation regimens in most, if not all, regions. Fructokinase rapidly phosphorylates fructose at the 1-carbon position. This enzyme has a high affinity for its substrates and the intestinal mucosa and liver rapidly convert fructose to fructose 1-phosphate; in other tissues, the capacity of hexokinase to phos- phorylate fructose at the 6-carbon position is limited. Similarly, the fate of fructose 1-phosphate in the fructose-metabolizing tissues is dependent on a specific isozyme of aldolase, aldolase B. This has greater activity towards fructose 1-phosphate than does its ubi- quitous counterpart aldolase A, the natural substrate of which is fructose 1,6-diphosphate. Cleavage of fructose 1-phosphate gen- erates glyceraldehyde and dihydroxyacetone phosphate. These tri- oses enter the intermediary pools of carbohydrate metabolism, and, as a result of triokinase activity, glyceraldehyde is phosphorylated so that the two triose phosphates may be condensed by aldolase A to form the glycolytic and gluconeogenic intermediate fructose 1,6-diphosphate. Fructose malabsorption The occurrence of abdominal symptoms and diarrhoea, reminiscent of intestinal disaccharidase deficiency, in response to ingested fruc- tose is well recognized by gastroenterologists and often attributed to incomplete absorption of fructose: it is therefore called ‘fructose malabsorption’. The symptoms occur in adults and children after in- gestion of fructose-rich or sorbitol-rich foods and drinks such as apple juice, and usually recede when the sugars are excluded from the diet. Many such individuals, as well as a high proportion of healthy control subjects, have findings suggestive of fructose malab- sorption based on hydrogen breath tests, but definitive evidence of true malabsorption is usually lacking. The molecular basis of this syndrome and of the wide variation of tolerance to dietary fructose and its congeners is not known. Moreover, in several patients complaining of fructose-related intestinal symptoms, molecular analysis of the human GLUT5 gene, which encodes a major intestinal fructose transporter, has so far failed to identify causal mutations. Recently, mice lacking the action of a critical glucose-activated transcription factor— carbohydrate-responsive element-binding protein (ChREBP)— that regulates glucose and lipid metabolism develop diarrhoea and weight loss after administration of diets high in sucrose or fructose, but not high-glucose diets. These effects are associated with poor induction of the fructose carrier, GLUT5, in the small intestine. Given these findings, it is conceivable that genetic vari- ation in the activity of this nutritional regulatory pathway in the intestine accounts for dietary idiosyncrasy to fructose and sucrose in humans. While

no information about ChREBP in patients com- plaining of fructose malabsorption is yet available, the field is one of great interest for large-scale investigations that extend to obesity and the metabolic syndrome. Other studies have suggested that the distal small intestine and colon of patients who experience abdominal flatulence and diar- rhoea after ingesting fructose-containing foods contain a bacterial population with enhanced uptake and anaerobic metabolism of fructose. No conclusive evidence has yet been provided to support these observations and more investigative studies are needed in those patients who experience symptoms attributed to malabsorp- tion of this sugar, including measurement of intestinal fructose ab- sorption, metabolism, and transport. Essential (benign) fructosuria (OMIM 229800) This is a rare disorder (estimated birth frequency 1 in 130 000) of little clinical consequence. The abnormality is transmitted as an autosomal recessive condition and is demonstrated by the pres- ence of a reducing sugar in the blood and urine, especially after meals rich in fructose. The abnormality is caused by the defi- ciency of fructokinase activity in the liver and intestine, signifi- cantly reducing the capacity to assimilate this sugar. Mutations in Sucrose Fructokinase Fructose 1-phosphate ALDOLASE B Glyceraldehyde FRUCTOSE triokinase triose phosphate isomerase dihydroxyacetone phosphate Krebs’ cycle pyruvate glyceraldehyde 3-phosphate ALDOLASE A Fructose 1,6-diphosphate Fructose diphosphatase Fructose 6-phosphate Glucose 6-phosphate Glucose 1-phosphate GLYCOGEN GLUCOSE Sorbitol Fig. 12.3.2.1 Fructose metabolism. Gluconeogenesis from triose phosphates, lactate, glycerol, amino acids, and Krebs cycle intermediates such as oxaloacetate, requires reversal of the committed reactions of glycolysis. It is the enzyme fructose 1,6-diphosphatase that releases the glucose precursor fructose 6-phosphate from fructose 1,6-diphosphate. Thus, when the remaining reactions of glycolysis are reversed, exogenous fructose provides a source of glucose or glycogen. Fructose 1,6- diphosphatase is active in the liver, kidney, and intestine, and is a key enzyme of gluconeogenesis.

12.3.2 Inborn errors of fructose metabolism 1997 the human ketohexokinase gene on chromosome 2p23.3–p23.2 have been identified in patients with essential fructosuria, thus confirming the suspected molecular defect in this condition. Fructose metabolism occurs slowly in essential fructosuria as a re- sult of conversion to fructose 6-phosphate by hexokinase in adi- pose tissue and muscle, but, while plasma concentrations remain high postprandially, large amounts of fructose appear in the urine. Essential fructosuria may be confused with diabetes mellitus if the nature of the mellituria is not defined; with the use of glucose oxi- dase strips in preference to the older chemical methods for urin- alysis, such confusion is now unlikely in the routine clinical testing of urine worldwide. No treatment beyond recognition and explan- ation appears to be necessary. Hereditary fructose intolerance (fructosaemia) (OMIM 229600) This disorder, first recognized in 1956, is the most common in- herited defect of fructose metabolism with an estimated frequency of about 1 in 20 000 births in Europe. Determination of aldolase B mutation frequency in DNA obtained from neonatal blood spots in- dicated a frequency of 1 in 18 000 live births in the United Kingdom. The disease has been reported in populations throughout the world, including China and Israel. Hereditary fructose intolerance is transmitted as an autosomal re- cessive trait and, although it manifests itself first in early infancy, the effects of clinical disease may not be recognized until late childhood or even adult life. Provided the diagnosis is made before visceral damage occurs, hereditary fructose intolerance responds completely to a strict exclusion diet and patients can survive to old age. The first patient ever reported (as a young adult) was healthy and an active grandparent at well over 80 years of age. Clinical features The cardinal features of this illness are vomiting, diarrhoea, upper abdominal pain, and hypoglycaemia that are induced by the

con- sumption of foods, drinks, or medicines containing fructose, or the related sugars, sucrose or sorbitol. The infant is first exposed to the offending sugars at weaning or on first transfer from breast milk to artificial feeds, and—with continued exposure to the harmful foods—a generalized metabolic disturbance with lactic acidosis, hyperuricaemia, and hypophosphataemia develops. Hypoglycaemia causes trembling, irritability, and cognitive im- pairment. Attacks are associated with pallor, sweating, and, when severe, result in loss of consciousness, sometimes accompanied by generalized seizures. These episodes typically occur within 30 min of meals that contain large quantities of fructose or sucrose. Continued ingestion of noxious sugars is associated with renal tubular disease, liver injury with jaundice, and impaired blood co- agulation. In children and infants, there is marked failure to thrive; growth retardation becomes apparent and the child becomes listless and miserable. Persistent exposure to fructose and the related in- jurious sugars in feeds and drinks given to infants leads to structural liver injury with cirrhosis, aminoaciduria, coagulopathy, and coma leading to death. Survival is dependent on recognition of the effects of fruit and sugar by the mother or, especially in older infants, by vomiting or forcible rejection of food by the patient. Infants who survive the stormy period of weaning develop a strong aversion to sweet-tasting foods, vegetables, and fruits. This usually affords protection against the worst effects of fructose and sucrose, but abdominal symptoms with bouts of tremulousness, irritability, and altered consciousness due to hypoglycaemia usually continue. It has become clear that many cases escape diagnosis in infancy and childhood, but the risk of illness related to dietary indiscretion remains throughout life. Characteristically, children and adults with hereditary fructose intolerance show a striking reduction in, or ab- sence of, dental caries. They usually have notable preferences for foods and drinks, with striking dietary peculiarities. As explained in relation to the growth of the sugar industry, nutritional behaviours are changing worldwide, and increasingly it is found that hidden or undeclared sugars are the culprit in patients with fructose intoler- ance who remain unwell despite attempts to modify food and drink intake. A syndrome of chronic sugar intoxication has been identi- fied in older children and adolescents with hereditary fructose in- tolerance and may persist in the adult. General lack of vigour and developmental retardation are prominent features. Hypoglycaemia, though obvious after heavy fructose loading, may be insignificant after chronic low-level exposure in older children. Similarly, tests of hepatic and renal function may be only mildly abnormal. The intermittent presence of reducing sugar in the urine may indicate fructosuria; amino aciduria may also be present. Persistent ingestion of fructose and sucrose is toxic to the kidney and liver, so that renal tubular acidosis (occasionally with calculi) as well as hepatosplenomegaly occur in younger patients. Severe growth retardation may be accompanied by rachitic bone disease that complicates the Fanconi-like syndrome of proximal renal tubular disturbance with bicarbonate wasting. Growth retardation responds to dietary treatment and is usually accompanied by regres- sion of the other disease manifestations. Metabolic defect Hereditary fructose intolerance is caused by a deficiency of aldolase B in the liver, small intestine, and proximal renal tubule. These tis- sues experience injury as a result of persistent exposure to fructose in patients affected by the disorder. In the absence of the fructose- 1-phosphate-splitting activity of aldolase B, the intracellular pool of inorganic phosphate is depleted. Studies in vivo by 31P magnetic res- onance spectroscopy show that 80% of hepatic free phosphate is se- questrated as sugar phosphates after the infusion of small quantities of fructose (250 mg/kg body weight). The secondary metabolic dis- turbances are initiated by the accumulation of fructose 1-phosphate in a milieu where free inorganic phosphate is reduced: there is competitive inhibition of aldolase A and inhibition of phosphor- ylase activity so that glycogenolysis and gluconeogenesis are im- paired. Thus, challenge with fructose leads to hypophosphataemia and hypoglycaemia that is refractory to

glucagon or the infusion of gluconeogenic metabolites such as glycerol or dihydroxyacetone. During challenge with fructose, high concentrations of fructose 1-phosphate cause feedback inhibition of fructokinase, thereby limiting the incorporation of fructose in the liver. As a result, fructosaemia occurs and, when the blood concentration exceeds about 2 mmol/litre, fructosuria is apparent. Although the assimila- tion of fructose by the specialized pathway is blocked, only a small fraction of the fructose load is recovered in the urine. Studies show that 80 to 90% of the fructose is taken up under these circumstances

SECTION 12 Metabolic disorders 1998 by adipose tissue and muscle, where it can serve as an alternative substrate for hexokinase with conversion to fructose 6-phosphate. Electrolytic disturbances occur during challenge with fructose. Hypokalaemia results from acute renal impairment with defective urinary acidification. There is a defect of proximal tubule function with bicarbonate wasting and acidosis. Occasionally, acute flaccid weakness due to hypokalaemia accompanies the other effects of fructose exposure. In patients with hereditary fructose intolerance, the administration of fructose reproducibly increases serum magne- sium concentrations. This is probably explained by the breakdown of magnesium–ATP complexes, releasing intracellular magnesium ions as a result of nucleotide degradation by adenosine deaminase. Significant ingestion of fructose is thus also accompanied by marked hyperuricaemia in patients with hereditary fructose intolerance. In the absence of acute exposure to fructose, only minor ab- normalities of blood analytes are detectable and the blood glucose concentration is normal, even after prolonged fasting. Often trivial elevation of serum transaminase activities occur; red cell folate and white cell ascorbate concentrations may be reduced as a result of re- strictive dietary habits. Pathology and molecular genetics Persistent ingestion of fructose and related sugars in hereditary fruc- tose intolerance causes hepatic injury; there is diffuse fatty change and increased glycogen deposition. Hepatocyte necrosis with intralobular and periportal fibrosis occurs and fully developed cir- rhosis results from continued exposure to fructose. After acute ex- perimental challenge, electron microscopy has shown irregular electron-dense material surrounded by membranous structures, sug- gesting a florid lysosomal reaction to intracellular deposits of fruc- tose 1-phosphate. Parenteral administration of fructose or sorbitol may induce the abrupt onset of hepatorenal failure associated with bleeding. Histological examination shows hepatic necrosis in these cases (Fig. 12.3.2.2). Loss of cellular functions (e.g. in the proximal renal tubule) is probably caused by depletion of ATP resulting from the arrested metabolism of fructose by the specialized pathway. The source of the severe abdominal pain that follows ingestion of fructose is unknown, but stimulation of visceral afferent nerves by the local release of purine nucleotides or lactate may be responsible. The genetic basis of aldolase B deficiency has been studied inten- sively and numerous mutations responsible for hereditary fructose intolerance have been identified. The human aldolase B gene maps to chromosome 9q22.3. Several point mutations affecting the func- tion of the enzyme are sufficiently widespread in patients of European origin to merit focused diagnostic investigation. One particular mu- tation, originally termed Ala149→Pro, which disrupts residues in a substrate-binding domain of aldolase B, is prevalent in populations of European descent. This mutation accounts for most alleles responsible for fructose intolerance, but others, including those originally named Ala174→Asp, Asn334→Lys, and a four-base deletion in exon 4, are suf- ficiently frequent and widespread to merit initial examination in a specialized molecular diagnostic laboratory (see following ‘Molecular diagnosis’ subsection). The intragenic deletion has also been reported from China. Biochemical and structural studies of the expressed mu- tant enzymes reveal two main classes of aldolase B in hereditary fruc- tose intolerance, active

tetrameric variants which are unstable and readily lose their quaternary structure and mutant aldolases that re- tain their normal tetrameric structure but are catalytically impaired. Differential diagnosis In infancy and childhood, presentation of persistent vomiting, with failure to thrive, acidosis, hypoglycaemia, and/or jaundice suggest a wide differential diagnosis, but fructose intolerance may be indi- cated by the nutritional history and feeding difficulties. Possibilities include surgical diseases such as pyloric stenosis and even biliary atresia, but particularly inborn errors of metabolism, including galactosaemia, Reye's syndrome, hepatitis, renal tubular disease, Wilson's disease, mitochondrial DNA depletion syndrome, con- genital defects of glycosylation, hereditary tyrosinaemia type 1, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, classic methylmalonic aciduria, and citrullinaemia type 1. A carbohydrate-deficient glycoprotein syndrome may be sus- pected on the basis of biochemical screening tests carried out in paediatric investigations, since untreated patients with hereditary fructose intolerance almost invariably show a type I pattern of carbohydrate-deficient serum transferrin on isoelectric focusing; this is corrected within a few weeks of fructose exclusion and is due to transient inhibition of phosphomannose isomerase implicated in glycoprotein processing and biosynthesis. In older infants and chil- dren, poisoning might have occurred, and this will mainly reflect inadvertent exposure to toxins, of which paracetamol in paediatric elixir preparations and suspensions is a prominent accidental risk. If fructose intolerance is considered, then sucrose, sorbitol, and fructose should be excluded completely and immediately before de- finitive diagnosis. Striking improvement, suggestive of hereditary fructose intolerance, may be seen on institution of the appropriate exclusion diet (including fluids) within a few days, and this can be life-saving in infants and children. Diagnosis Formerly, diagnosis of fructose intolerance required the demon- stration of fructose-1-phosphate aldolase deficiency in tissue (liver or small intestinal mucosa), but increasingly demonstration of the presence of two causal mutant alleles of ALDOB is employed. Molecular analysis of the ALDOB gene in genomic DNA from an oral swab or blood sample can be carried out as soon as the diagnosis is suspected. Fig. 12.3.2.2 Post-mortem needle liver aspirate (Mallory's trichrome stain). Reproduced from Ali M, Rosien U, Cox TM (1993). DNA diagnosis of fatal fructose intolerance from archival tissue. Q J Med 86, 25–30 with permission from Oxford University Press.

12.3.2 Inborn errors of fructose metabolism 1999 Molecular diagnosis Direct genetic diagnosis of hereditary fructose intolerance is now possible and is the preferred method, particularly (but not exclu- sively) for patients of European ancestry, from whom most of the widespread causal mutant alleles of ALDOB hitherto have been re- ported. The nomenclature currently adds one to the mutated residue that occurs in the aldolase B protein (A149P is currently pAla150Pro or more conveniently A150P). Widespread founder mutations have been reported from regions elsewhere, including North India. While molecular analysis of aldolase B genes for the presence of common mutations responsible for the disease can be carried out by specialized laboratories equipped for genetic testing, the rapid spread of DNA diagnostic methods worldwide is greatly improving recognition of the disease and its severity. Some specialized diag- nostic facilities, usually based in hospital laboratories offering paediatric services, have reported useful practical protocols for hier- archical ALDOB mutation screening. Failure to identify two of the more frequent mutant alleles in patients with suspected hereditary fructose intolerance should encourage a systematic approach to mo- lecular diagnosis, if necessary to include definitive sequencing of the entire human aldolase B gene (ALDOB). It is obvious that this stratagem obviates invasive or hazardous investigations using tissue biopsy procedures, or cumbersome parenteral challenge with sugar solutions, and ultimately

is likely to reduce overall healthcare costs. The diagnosis has important consequences for relatives of the propositus and will provide information critical for the introduction of a rigorous and life-long exclusion diet. Enzymatic analysis Aldolase B deficiency may be demonstrated definitively by enzym- atic analysis of biopsy samples obtained from the liver or small intes- tinal mucosa. Biochemical assay of fructaldolases characteristically demonstrates markedly reduced or absent fructose 1-phosphate cleavage activity with a partial deficiency of fructose 1,6-diphosphate aldolase. Since fructaldolase deficiency may accompany other par- enchymal disease of the liver, and because liver biopsy for biochem- ical analysis is invasive, these assays are of limited value in the acutely ill or jaundiced patient. Intravenous fructose tolerance test (see Fig.12.3.2.3) The intravenous fructose tolerance test was previously useful for diagnosis, particularly in adults; however, preparations of fructose suitable for intravenous use are now difficult to obtain and direct diagnosis by molecular analysis of ALDOB is preferred. In any event, failure to obtain fructose solutions suitable for parenteral use should not encourage the administration of fructose or sucrose orally, since administration by this route may induce catastrophic effects with severe pain, acidosis, and even shock. A child or adult is unlikely to return for further care after such a casual toxic exposure to a highly offensive sugar load given orally, usually against their will. Even in recent times, critical illness polyneuropathy has occurred in at least one affected child after misconceived diagnostic oral challenge with fructose (hereditary fructose intolerance was formally diagnosed by retrospective molecular analysis of the aldolase B gene). If no other method for investigating the patient is available, then the intravenous tolerance test should be carried out under controlled conditions with medical personnel at hand. It requires the infusion of 0.25 g/kg (0.2 g/kg in infants) of d(+)-fructose as a 20% solution over a few minutes; blood samples for potassium ions, magnesium ions, phosphate ions, and glucose are taken before the administration and at regular intervals over a 2-h period. In fructose intolerance, epigastric and loin pain usually accompany the infusion, and hypo- glycaemic coma may occur; hypophosphataemia is characteristic. Characteristically, since gluconeogenesis is blocked during exposure to fructose or its congeners, the acute hypoglycaemia fails to respond to glucagon and therefore glucose for parenteral injection must be available. Responses differ between individuals, and hypoglycaemia is usually milder in adults; typical responses in hereditary fructose in- tolerance and a control subject are shown in Fig. 12.3.2.3. The toler- ance test should not be carried out in patients with overt signs of liver disease where it may occasionally yield misleading results, and in a patient with hereditary fructose intolerance the challenge will dan- gerously aggravate the disease—particularly in infants and children. The ability to identify disease alleles by analysing genomic DNA obtained from very small samples of blood or tissue may not only be beneficial for the investigation of infants with this disorder but also for neonatal testing before dietary exposure occurs. There is a strong case for trials in which the utility of mass population screening for fructose intolerance, a preventable nutritional disease, is investigated but despite much effort this apparently justifiable course has yet to be adopted. (a) 5.0 4.0 3.0 2.0 1.0 2.0 1.6 1.2 0.8 0.4 –10 Time (min) (b) Blood glucose (mmol/l) Serum phosphate (mmol/l) 4.0 3.0 2.0 1.0 1.6 1.2 0.8 0.4 90 80 70 60 50 40 30 20 10 0 Fig. 12.3.2.3 (a) Intravenous fructose tolerance tests in a 39-year-old woman with hereditary fructose intolerance proved by fructaldolase assay and DNA analysis. (b) An age-matched and sex-matched control subject with alcohol-related episodic hypoglycaemia.

 Treatment Provided that organ failure and serious tissue injury do not super- vene, patients with hereditary fructose intolerance recover rapidly when the toxic sugars are withdrawn. Children who survive by ac- quiring a protective pattern of eating

behaviour avoid foods which provoke abdominal symptoms. The aversion extends to most sweet-tasting items of food and drink as well as fruits and vegetables; it re- mains lifelong and consumption of fructose (and sucrose) is usually reduced to less than 5 g daily. It has been shown that normal growth and development can be assured in growing children and adoles- cents if less than 40 mg/kg fructose equivalents are ingested daily. Dietary treatment of fructose intolerance mitigates the disorder but requires the almost complete exclusion of sucrose, fructose, and sorb- itol. A changing and notable feature of the disease is the increasing con- tribution of added sweeteners and additives to the diet and present in drinks. The daily consumption of sugar should be reduced to less than 40 mg fructose equivalents per kilogram of body weight (i.e. 2–3 g for an adult) in order to reverse the disease manifestations and establish normal development in affected infants and children. The ubiquity of fructose and its congeners in the Western diet presents serious diffi- culties. Not only are fructose and its congeners present in unexpected foods, such as certain types of potato, but the sugars are added to foods unexpectedly and deceptively. Adult patients have usually restricted their consumption of fructose to less than 20 g daily and the source of the residual sugar may be difficult to establish. For this reason, the ad- vice of an experienced dietitian should be sought (Box 12.3.2.1). Particular care needs to be taken with sugar-coated pills and espe- cially with liquid medications for paediatric use, as large amounts of fructose, sucrose, and sorbitol are frequently present. Children and adults with hereditary fructose intolerance may tol- erate the taste of confectionery that contains large quantities of nox- ious sugars but in which the sweetness is masked by other flavours, such as peppermint, which they enjoy. This behaviour may lead to unexplained hypoglycaemic symptoms and other signs of sugar toxicity. Occasionally, patients are unable to tolerate certain foods that are permitted on their diet sheets; in doubtful cases it is advis- able to avoid the offending item or to have it analysed. Patients with hereditary fructose intolerance may lack folic acid and vitamin C. Supplements of these vitamins in particular are re- commended, especially during pregnancy, but, as with other medi- cines, care has to be taken to avoid harmful sugars contained in the preparation. Although the use of fructose-containing or sorbitol- containing preparations for intravenous nutritional supplementation has now been stopped, in the era before fructose and sorbitol infu- sions were banned in Europe, at least 16 patients developed toxicity and died (Fig. 12.3.2.2). Some medicines that are given parenterally are still reconstituted in solutions containing harmful quantities of sorbitol or fructose. Hepatorenal failure has recently been reported after the administration of amiodarone in a polysorbate solution to a patient with hereditary fructose intolerance, with dire consequences. Prognosis Untreated hereditary fructose intolerance is a potentially fatal disease in infants and young children in whom it ultimately causes irreversible liver disease, renal tubular impairment, and episodic, life-threatening hypoglycaemia. The proportion of infants that die of unrecognized fruc- tose toxicity is unknown but given the discrepancy between the preva- lence of mutant aldolase B alleles and the apparent rarity of the disease, the author estimates this to be at least one half of all those born with the condition. Occasionally, adolescents and adult patients may succumb to the inadvertent use of parenteral fructose or sorbitol, but this practice, which until recently was popular in German-speaking countries, is now obsolete. With the introduction of a strict exclusion diet, the disorder is compatible with a normal quality and duration of life. Fructose diphosphatase deficiency

(OMIM 229700) Clinical features This very rare, recessively inherited disorder presents with hypo- glycaemia, ketosis, and lactic acidosis in early infancy. Fewer than 100 cases have been reported since its original description in 1970. Severe, sometimes fatal, acidosis is associated with infection and starvation, and most cases present within the first few days of life or in the neonatal period.

Onset during the first year of life is the rule. In newborn infants, the severe metabolic disturbance shows it- self by acidotic hyperventilation, which may be accompanied by ir- ritability, disturbed consciousness, seizures, or coma. The unusual combination of ketonaemia, lactic acidaemia, and hypoglycaemia is induced by fasting, the administration of fructose, sorbitol, and glycerol, and by ingestion of a diet rich in fat. Episodes in the neo- natal period respond well to infusions of glucose and bicarbonate but, after an interval, further attacks occur, often provoked by inter- current infection. Lethargy accompanied by hyperventilation is fol- lowed abruptly by prostration, coma, and seizures. Investigations reveal hypoglycaemia, ketosis, and profound lactic acidosis; there is also hyperuricaemia, aminoaciduria, and ketonuria. If the infant survives, hepatomegaly due to fatty infiltration may be detected but overt clinical disturbances of hepatic or renal tubular function are not seen. The untreated disease is associated with growth retardation. Box 12.3.2.1 Food items not allowed for patients with hereditary fructose intolerance and fructose diphosphatase deficiencya • Table sugar • Fruit sugar, all fruit and fruit products, including tomatoes • Sorbitol—often used in confectionery (especially), as an excipient or stabilizer in medication or diabetic foods • Honey, syrup, treacle, and molasses • Diabetic foods • Chocolate and sherbet • Preserves, jams, and marmalade • Frankfurters, honey-roast ham, and sweet-cured ham • Processed cheese spreads • Cream and cottage cheese with chives, pineapple, etc. • Flavoured milks and yoghurts • Wheatgerm, brown rice, and bran • Breakfast cereals • Coffee essence and powdered milk • Carbonated sweet drinks • Allspice, nuts, coconut, carob, and peanut butter • Mayonnaise, pickles, salad dressings, and sauces • Some potatoes (especially stored, new potatoes) • Most legumes a More information is provided in ‘Further reading’.

12.3.2 Inborn errors of fructose metabolism 2001 The first infant to be affected by fructose diphosphatase deficiency in a given family may succumb before the diagnosis is established and in any case fares worse than siblings for whom the appropriate diet and prompt control of the condition are instituted. The response to treatment is favourable, however, and fructose diphosphatase deficiency is ultimately compatible with a benign course and with normal growth and development. Metabolic defect Deficiency of fructose 1,6-diphosphatase causes failure of gluconeogenesis in the liver, although the abnormality may be de- tected in intestinal mucosa, kidney, and in cultured mononuclear cells from peripheral blood. The muscle isozyme of fructose 1,6- diphosphatase is not affected. Between meals, blood glucose is maintained by glycogenolysis and hence the onset of disturbed metabolism in fructose diphosphatase deficiency depends on the availability of hepatic glycogen. Since fe- brile illnesses accelerate the consumption of liver glycogen, the accom- panying anorexia with or without vomiting may deplete glycogen stores critically. Acidosis results from the accumulation of gluconeogenic precursors including lactate, pyruvate, and alanine as well as ketone bodies, which cannot be utilized. Hypoglycaemia that is unresponsive to glucagon and associated with exhaustion of glycogen stores occurs; it does not respond to normal gluconeogenic substrates (e.g. glycerol, amino acid solutions, dihydroxyacetone, sorbitol, or fructose); indeed, administration of these aggravates the metabolic disturbance. The pathogenesis of hypoglycaemia and accompanying disturbances in fructose diphosphatase deficiency is complex and not completely explained by exhaustion of hepatic glycogen stores. Well-fed patients have a normal response to glucagon but are intolerant of high-fat diets, as well as fructose, sorbitol, alanine, glycerol, and dihydroxyacetone administration. Challenge with these nutrients induces hypogly- caemia, hyperuricaemia, and hypophosphataemia, accompanied by an exaggerated rise in blood lactate levels. The hypoglycaemia is then unresponsive to glucagon, indicating a secondary inhibition of phosphorylase activity in the liver, which results from the build-

up of phosphorylated sugar intermediates that cannot be further metab- olized in the context of reduced intracellular free inorganic phosphate. Adenosine deaminase is activated primarily because of reduced phos- phate concentrations, so that purine nucleotides are broken down to uric acid. Failure to utilize glucogenic amino acids and metabolites such as dihydroxyacetone and glycerol appears to stimulate trigly- ceride formation in the liver, which induces steatosis. Unlike heredi- tary fructose intolerance (discussed previously), high concentrations of hepatic fructose 1-phosphate do not occur, and profound disturb- ances of blood coagulation or hepatic or renal tubule function with progressive structural damage are absent in fructose diphosphatase deficiency. Similarly, aversion to foods that aggravate the disorder does not develop in affected infants and children; this may be explained by the absence of pain and abdominal symptoms in the condition. Diagnosis The importance of establishing the diagnosis of fructose diphosphatase deficiency cannot be overemphasized. Proper dietary control and protocols for the institution of appropriate therapy depend on recog- nizing the complex disturbance that underlies this disease. Fructose diphosphatase deficiency should be considered in other- wise normal infants who develop unexplained severe acidosis or hypoglycaemia associated with episodes of infection. The combination of ketosis and lactic acidosis with hypoglycaemia is highly suggestive of a disorder affecting the gluconeogenic pathway, including deficiency of glucose 6-phosphatase, pyruvate carboxylase, pyruvate dehydrogenase, and phosphoenolpyruvate carboxykinase. The absence of abdominal distress, haemolysis, jaundice, coagulopathy, and disturbances of the proximal renal tubule differentiates the condition from hereditary fruc- tose intolerance, tyrosinosis, and Wilson’s disease. Confusion may arise with disorders associated with secondary defects in gluconeogenesis, es- pecially the Reye’s-like syndrome caused by deficiencies of long-chain, medium-chain, and short-chain acyl coenzyme A dehydrogenase activ- ities, as well as defects of carnitine metabolism. Organic acidaemias are also readily distinguished by biochemical screening methods. Provocative tests using food deprivation and the administration of infusions of fructose, sorbitol, or glycerol should be avoided in the acutely ill infant or child with suspected deficiency of fructose 1,6-diphosphatase (or fructose intolerance). The definitive diagnosis depends on the demonstration of selectively decreased fructose diphosphatase activity in tissue samples. Most frequently, the enzym- atic defect will be identified by biochemical assay of a freshly obtained liver biopsy specimen, which allows other metabolic disorders and gluconeogenic defects to be confidently excluded. The defect may also be demonstrated in biopsy samples of jejunal mucosa and in cultured monocyte-derived macrophages obtained from peripheral blood. However, the presence of fructose 1,6-diphosphatase in these tissues is metabolically inconsequential and, although useful for confirm- ation of the diagnosis where it is strongly suspected, in practice, de- cisive identification of this disorder normally depends on a systematic biochemical analysis of liver tissue in an experienced laboratory. The human fructose-1,6-diphosphatase (FBP1) gene maps to chromo-some 9q22.2–q22.3, and inactivating mutations have been identified in the disease. Unlike fructose intolerance, however, these mutations tend to be private and thus individually of less diagnostic significance for routine laboratory use in this disorder since mutational heterogen- eity appears to be the rule. However, a minor exception to this occurs in the Japanese population, where one mutation (960–961insG) ap- pears to account for almost one-half of mutant FBPI alleles. Treatment Dietary control and avoidance of starvation with rapid relief of fe- brile illnesses are the mainstays of management. Minor infections and injuries require prompt attention, and intravenous glucose therapy should be instituted early in acute episodes to avoid hypo- glycaemia and acidosis. Fasting should be avoided as far as possible, while night-time feeding may be needed in infants during recovery from injuries or infections, and after strenuous exercise in older chil- dren. The habit of

taking meals at regular 4-h intervals is best incul- cated when the patient is young. The diet should exclude excess fat; sorbitol, sucrose, and fructose must be strictly avoided. Breast milk is rich in lactose, which is readily assimilated, but difficulties arise on transfer to artificial feeds during weaning. In addition, medications and syrups containing fructose, sucrose, or sorbitol present a special danger to patients with fructose diphosphatase deficiency. A diet excluding these sugars but containing 56% calories as carbohydrate, with 32% calories as fat and 12% as protein, has produced normal growth and development. Acute episodes of acidosis or hypogly- caemia are controlled rapidly by intravenous administration of glu- cose with or without bicarbonate as required.

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