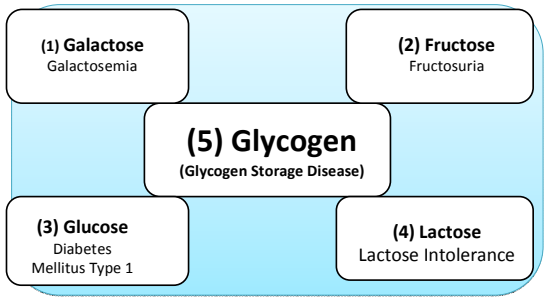
Inborn errors of carbohydrate metabolism



Galactose

- The most common signs **are failure to thrive, hepatic insufficiency, cataracts** and **developmental delay.**
- **Galactosemia** is caused by mutations in the gene that makes the enzyme **galactose-1-phosphate uridylyltransferase.**
- Approximately 70% of galactosemia-causing alleles have a single **missense mutation** in **exon 6.**
- A milder form of galactosemia, called **Galactokinase deficiency,** is caused a lack of the enzyme **uridine diphosphate galactose-4-epimerase** which breaks down a byproduct of galactose.
- Screening is performed by measuring **GAL-1-P urydil transferase** activity.

Fructose

- The most common is caused by mutations in the gene encoding **hepatic fructokinase**, an enzyme that catalyzes the first step in the metabolism of dietary fructose.
- Inactivation of the hepatic fructokinase results in **asymptomatic fructosuria.**
- **Hereditary fructose intolerance** (HFI) results in poor feeding, failure to thrive, hepatic and renal insufficiency, and death.
- HFI is caused by a deficiency of **fructose 1,6-biphosphate aldolase** in the liver, **kidney cortex and small intestine**.
- **Deficiency** of **hepatic fructose 1,6-biphosphate** causes impaired **gluconeogenesis, hypoglycemia** and **severe metabolic acidemia**.

Glucose

- **Diabetes mellitus type 1** is a genetic disorder caused by reduced or absent levels of **insulin,** a hormone that metabolizes **glucose**

Lactose

- intestinal enzyme called **lactase**.
- production of lactase diminishes after infants are **weaned** from maternal milk.
- However, 5% to 90% of the human population possess an advantageous **autosomal mutation** in which lactase production persists after infancy.
- **Lactase non-persistence** is common in tropical and subtropical countries.
- Individuals with lactase non persistency may experience **nausea, bloating** and **diarrhea** after ingesting dairy.

Glycogen

- Carbohydrates are most commonly stored as **glycogen** in humans.
- Consequently, enzyme deficiencies that leads to impaired synthesis or degradation of glycogen are also considered disorders of carbohydrates metabolism.
- Glycogen storage disorders that affect the liver typically cause **hepatomegaly** and **hypoglicemia.**
- Those that affect skeletal muscle cause **exercise intolerance, progressive weakness** and **cramping**.

(1) Galactosemia

- **Galactosemia** is a **genetic metabolic disorder** that affects an individual's ability to metabolize the sugar **galactose** properly.
- Galactosemia follows an **autosomal recessive** mode of inheritance that confers a deficiency in an enzyme responsible for adequate **galactose degradation.**
- **Goppert** (1917), with its cause as a defect in galactose metabolism being identified by a group led by **Herman Kalckar** in 1956.
- Its incidence is about 1 per 60,000 births

Cause

- **Lactose** in food (such as **dairy** products) is broken down by the enzyme lactase into **glucose** and **galactose**.
- In individuals with **galactosemia**, the enzymes needed for further metabolism of galactose are severely diminished or missing entirely, leading to toxic levels of galactose in the blood, resulting in **hepatomegaly** (an enlarged liver), **cirrhosis, renal failure, cataracts,brain damage,** and **ovarian failure.**
- Without treatment, mortality in infants with **galactosemia** is about 75%.

Types

Type	Enzyme	Name
Type 1	galactose-1-phosphate uridyl transferase	classic galactosemia
Type 2	galactokinase	galactokinase deficiency
Type 3	UDP galactose epimerase	galactose epimerase deficiency, UDP-Galactose-4-epimerase deficiency

Diagnosis

- Infants affected by galactosemia typically present with symptoms **of lethargy, vomiting, diarrhea, failure to thrive,** and **jaundice.**
- A **galactosemia test** is a blood test (from the heel of the infant) or **urine test** that checks for three enzymes that are needed to change galactose sugar that is found in milk and milk products-into glucose, a sugar that your body uses for energy.
- Detection of the disorder through newborn screening (NBS) does not depend on protein or lactose ingestion, and, therefore, it should be identified on the first specimen unless the infant has been transfused.
- Three screening tests are used to screen infants affected with galactosemia - the **Beutler's test,** the **Hill test** and the **Florida test**.

Treatment

- is eliminating lactose and galactose from the diet.
- Even with an early diagnosis and a restricted diet, however, some individuals with galactosemia experience long-term complications such as **speech difficulties, learning disabilities, neurological impairment (e.g. tremors, etc), symptoms** have not been associated with **Duarte galactosemia,**
- Infants with **classic galactosemia** cannot be breast-fed due to lactose in human breast milk and are usually fed a soy-based formula.
- Long term complication of galactosemia includes:
  - **Speech deficits**
  - **Ataxia**
  - **Dysmetria**
  - **Diminished bone density**
  - **Premature ovarian failure**
  - **Cataract**

2(a): Essential Fructosuria

- **Essential fructosuria**, also known as **hepatic fructokinase deficiency** or **ketohexokinase deficiency**, is a **hereditary metabolic disorder** caused by a **deficiency in hepatic fructokinase**, leading to **fructose** being excreted in the **urine** .
- It is essentially a **benign condition**, as fructose cannot be broken down, so it is simply excreted in the urine.
- Inheritance is **autosomal recessive.**
- prevents proper release of glucose from glycogen, uses up free phosphate, and causes a rise in uric acid, leading to growth abnormalities and, in severe

2b-Hereditary Fructose Intolerance

- **Hereditary fructose intolerance** (HFI) or **fructose poisoning** is a **hereditary condition** caused by a deficiency of **liver enzymes** that **metabolise fructose**.
- It is also known as **hereditary fructosemia.**

Cause

- The deficient enzyme is **aldolase-B,** which converts **fructose-1-phosphate** to **glyceraldehyde**.
- fructose cannot be further metabolised beyond fructose-1-phosphate.
- This traps **phosphates;** which are needed to **phosphorylate glycogen phosphorylase** which carries on to release units of **glucose-1-phosphate** from glycogen.
- Glucose-1-phosphate gets converted to **glucose-6-phosphate** and then **dephosphorylated** to form **glucose**.
- In addition, **Aldolase A** plays an important role in **gluconeogenesis,** producing **fructose-1,6-bisphosphate** from **glyceraldehyde-3-phosphate .**
- But, glucose may still be released through the breakdown of **glycogen**. Although, it cannot be synthesized from **gluconeogenesis,** resulting in severe **hypoglycemia.**

Common Characteristics

- Refusal to eat or dislike of many fruits, vegetables, and baked foods.
- Love of dextrose based foods.
- Primary beverages are: milk, water, unsweetened tea, unsweetened coffee.
- Feeling nauseated, sick, queasy, shaky, and/or foggy shortly after consuming fructose or sucrose.
- **Kidney pain, hypoglycemia, shaky, weak, tired** and **inwardly focused** (no real awareness of environment) a few hours to a couple days after consuming fructose or sucrose.
- Tendency to eat only safe foods after consuming fructose.
- Safe foods can include dairy, potato chips, pasta and/or rice.

Treatment

- Treatment is with a **fructose free diet**, which if adhered to, is concordant with a **good prognosis**.
- **Fructose** and **sucrose** eliminated from diet.

3-Diabetes Mellitus Type 1

- **Diabetes mellitus type 1** (juvenile diabetes) results from **autoimmune destruction** of **insulin-producing beta cells** of the **pancreas.**
- symptoms of **polyuria** (frequent urination), **polydipsia** (increased thirst), **polyphagia** (increased hunger), and weight loss result.
- Type 1 diabetes is fatal unless **treated with insulin**.
- Injection is the most common method of administering insulin; **insulin pumps** and **inhaled insulin** .
- influencing **gut flora, intestinal permeability**, and immune function in the gut.
- Type 1 can be distinguished from **type 2 diabetes** via a **C-peptide assay**, which measures endogenous insulin production.
- Low blood sugar may lead to **seizures** or **episodes of unconsciousness**.

Signs and Symptoms

- The classical symptoms of type 1 diabetes include:
  - **polyuria** (frequent urination),
  - **polydipsia** (increased thirst),
  - **polyphagia** (increased hunger),
  - **tiredness**, and
  - **weight loss**.

Cause

- **Environment**
  - environmental factors, in addition to genetic factors, can influence disease prevalence.
- **Genetics**
  - Type 1 diabetes is a **polygenic disease,** meaning many different genes contribute to its expression.
  - Depending on locus or combination of loci, it can be dominant, recessive.
  - The strongest gene, is located in the region on chromosome 6,.
  - This is responsible for the **histocompatibility disorder** characteristic of type 1:
  - Insulin-producing pancreas cells (beta cells) display improper antigens to T cells.

Pathophysiology

- type 1 diabetes is a **virally** triggered **autoimmune response.**
- The **Coxsackie virus** family or German measles is implicated
- In type 1, **pancreatic beta cells** in the **Islets of Langerhans** are destroyed decreasing endogenous **insulin production**.
- autoimmune response is influenced by **antibodies** against **cow's milk** proteins. No connection between **autoantibodies,**
- **A subtype of type 1** (identifiable by the presence of antibodies against beta cells) typically develops slowly and so is often confused with type 2.
- use antibody testing (**glutamic acid decarboxylase** antibodies, **islet cell antibodies ,** and **insulinoma-associated autoantibodies**)
- **Pyrinuron** (**Vacor, N-3-pyridylmethyl-N'-p-nitrophenyl urea),** a **rodenticide**
- **Zanosar** is the trade name for **streptozotocin,** an **antibiotic** and **antineoplastic** agent used in chemotherapy for **pancreatic cancer**;
- Other pancreatic problems, including trauma, **pancreatitis** or **tumors** (either malignant or benign

Diagnosis

- Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).
- **Plasma glucose** at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in **a glucose tolerance test.**
- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1 mmol/L (200 mg/dL).
- **Glycated hemoglobin** (hemoglobin A1C)
- fatigue.
- such as a **heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia**.
- Patients with fasting glucose levels from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) are considered to have **impaired fasting glucose.**
- Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to

WHO Diabetes criteria		
Condition	**2 hour glucose**	**Fasting glucose**
	mmol/l(mg/dl)	mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

Prevention

- an uncontrolled **autoimmune** response that attacks the insulin producing **beta cells.**
- Some research has suggested that **breastfeeding** decreased the risk in later life.
- Giving children **Vitamin D** during their first year of life is associated with reduced risk of type 1 diabetes, though the causal relationship is obscure.
- Children with antibodies to beta cell proteins (i.e. at early stages of an immune reaction to them) but no overt diabetes, and treated with vitamin B_3 (**niacin**.

Management

- Type 1 is treated with insulin replacement therapy—usually by insulin injection or **insulin pump**, along with attention to dietary management, typically including **carbohydrate** tracking, and careful monitoring of **blood glucose** levels using **glucose meters.**
- Untreated type 1 diabetes commonly leads to coma, often from **diabetic ketoacidosis,** which is fatal if untreated.
- In more extreme cases, a pancreas transplant can restore proper glucose regulation.
- However, the surgery and accompanying **immunosuppression**

Pancreas Transplantation

- Pancreas transplants are generally performed together with or some time after a **kidney** transplant.
- One reason for this is that introducing a new kidney requires taking **immunosuppressive drugs** such as **cyclosporin**.
- Nevertheless this allows the introduction of a new, functioning pancreas to a patient with diabetes without any additional immunosuppressive therapy.
- However, pancreas transplants alone can be wise in patients with extremely **labile** type 1 diabetes mellitus.

Islet cell Transplantation

- In one variant of this procedure, islet cells are injected into the patient's **liver,** where they take up residence and begin to produce insulin.
- The liver is expected to be the most reasonable choice because it is more accessible than the pancreas, and islet cells seem to produce insulin well in that environment.
- The **immune system** will attack the cells as it would a bacterial infection or a skin graft.
- Thus, patients now also need to undergo treatment involving **immunosuppressants,** which reduce immune system activity.

Prognosis

- Complications of poorly-managed type 1 diabetes mellitus may include **cardiovascular disease, diabetic neuropathy, diabetic retinopathy** etc.
- Overweight or obese are especially likely to have these problems if substandard diet is involved or the **cholesterol** or **blood pressure** is not well-controlled.
- There is some evidence that cardiovascular disease as well as neuropathy may, in fact, have an autoimmune basis as well.

Prevention

- **"Immunization"**
- via a change in the type of **cytokine** signaling molecules in acquired **immune tolerance** through a subcutaneous injection
- **Intra-nasal insulin**
- **BCG research**
- **Tumor necrosis factor-alpha**, or TNF-α, is part of the immune system.
- **Denise Faustman** theorizes that giving **Bacillus Calmette-Guérin** , used to immunize against ***Mycobacterium tuberculosis*,**

3-Lactose Intolerance

- **Lactose intolerance** is the inability to **metabolize lactose,** because of a lack of the required enzyme **lactase** in the digestive system.
- About 75% of adults worldwide show some decrease in lactase activity during adulthood.

Background Information

- **Disaccharides** cannot be absorbed through the wall of the small intestine into the bloodstream, so in the absence of **lactase, lactose** present in ingested dairy products remains **uncleaved** and passes intact into the **colon**.
- The **operons** of **enteric bacteria** quickly switch over to lactose **metabolism**, and the resulting in-vivo **fermentation** produces **copious** amounts of gas (a mixture of **hydrogen, carbon dioxide**, and **methane**).
- This, in turn, may cause a range of abdominal symptoms, including stomach **cramps, bloating**, and **flatulence.**
- In addition, as with other unabsorbed sugars (such as **sorbitol, mannitol**, and **xylitol**), the presence of lactose and its fermentation products raises the **osmotic pressure** of the **colon** contents.

Diagnosis

- the intestinal function is challenged by ingesting more dairy than can be readily digested.
- Clinical symptoms typically appear within 30 minutes but may take up to 2 hours, depending on other foods and activities.
- clinical response (**symptoms of nausea, cramping, bloating, diarrhea, and flatulence)**.
- it is important to distinguish lactose intolerance from **milk allergy,** which is an abnormal **immune response** (usually) to milk

Managing lactose intolerance

- Lactose intolerance is not usually an all-or-nothing condition: the reduction in lactase production—and hence, the amount of lactose that can be tolerated—varies from person to person.
- Since lactose intolerance poses no further threat to a person's health, managing the condition consists of minimizing the occurrence and severity of symptoms.
- **Berdanier** and **Hargrove** recognise four general principles:
  - avoidance of dietary lactose,
  - substitution to maintain nutrient intake,
  - regulation of calcium intake, and
  - use of enzyme substitute.

4-Glycogen storage disease

- **Glycogen storage disease** (**GSD**, also **glycogenosis** and **dextrinosis**) is the result of defects in the processing of **glycogen** synthesis or breakdown within **muscles, liver**, and other cell types.
- GSD has two classes of cause: **genetic** and **acquired.**
  - **Genetic GSD** is caused by any **inborn error of metabolism** (genetically defective **enzymes**) involved in these processes.
  - **acquired GSD** is caused by **intoxication** with the **alkaloid castanospermine.**
- approximately 2.3 children per 100 000 births (1 in 43,000) have some form of glycogen storage disease