Condition	Incidence
Familial hypercholesterolemia	1:500
Cystic fibrosis	1:2500
Phenylketonuria	1:12,000

Inherited metabolic diseases (most in infancy & childhood)

Introduction:

- Inherited diseases due to:
    1- Modification or absence of specific protein (e.g. sickle cell anemia)
    2- Defective receptor synthesis (e.g. familial hypercholesterolemia: only in adults).
    3- Defects involving carrier proteins (e.g. cystinuria).
- Many inherited metabolic diseases can arise because of one of a number of genetic defects.
- Common clinical feature of inherited metabolic disorders are:
    * **hypoglycemia.**
    * **vomiting and other GI abnormalities.**
    * **failure to thrive.**
    * acidosis
    * central nervous system dysfunction.
    * unusual odor.
- Most metabolic diseases show AR inheritance & heterozygotes are usually phenotypically normal.

Effects of enzyme defects:

- Decreased formation of the product. Clinical features will arise due to a lack of the product if it is essential with no alternative pathway for its synthesis.
- Accumulation of the substrate.
- Increased formation of other metabolites of minor pathways.

Inherited metabolic disorders:

- Glucose 6-phosphatase deficiency (lack of formation of the product):
    * Clinical manifestation: hypoglycemia – hepatomegaly (accumulation of glycogen) – lactic acidosis – hyperlipidemia – hyperuricemia – bleeding tendency.
    * Treatment of hypoglycemia: intravenous glucose infusion – uncooked corn starch.
    * Diagnosis: demonstrating lack of enzyme activity in a sample of liver obtained by biopsy.
- Galactosemia:
    * Absence of the enzyme galactose 1-phosphate uridyl transferase, which is required for the conversion of galactose to glucose, is most common.
    * Clinical features: hypoglycemia – hepatomegaly – failure to thrive – vomiting – jaundice – cataract.
    * Treatment: withdrawal of galactose and lactose from the diet.
- Phenylketonuria:L
    * The defective enzyme is phenylalanine hydroxylase, which hydroxylates phenylalanine to form tyrosine.
    * The name of the condition derives from the urinary excretion of phenylpyruvic acid, a phenylketone. This is normally a minor metabolite of phenylalanine but is produced in excess when the normal, major metabolic pathway is blocked.
    * Clinical features: fair hair - blue eyes – learning difficulties.
    * Diagnosis: demonstration of an abnormally high concentration of phenylalanine in blood.
    * Management: restricting dietary intake of phenylalanine. Phenylalanine is an essential amino acid and a certain amount must be provided in diet.

- Steroid 21-hyroxylase deficiency:

* Causing congenital adrenal hyperplasia.
* Increased activity of a minor metabolic pathway ---> adrenal androgens.
* 17-OH progesterone is converted to adrenal androgens (minor) instead of cortisol (major).

- Cystic fibrosis:

* Impaired chloride transport leading to increased viscosity of exocrine secretions (especially in lungs, pancreas and intestines). Sweat Na concentration is increased (for diagnosis). Increased immunoreactive trypsin.

Neonatal screening:

- **Screening:** is designed to detect individuals affected with a condition before it is apparent clinically.
- Indications for neonatal screening tests:
  * Condition is fatal or leads to severe disability if untreated.
  * Condition is treatable.
  * condition is relatively common.
  * reliable cheap screening test are available.
- Phenylketonuria screening:
  * Measurement of the concentration of phenylalanine in a sample of blood taken from heel-prick (6-9 days after birth).
  * In the past: Guthrie test, a microbiological test using a strain of bacillus subtilis in conditions such that growth is only seen if excess phenylalanine is present, was used.
- Screening of congenital hypothyroidism is also widely practiced.

Prenatal diagnosis:

- Indications for prenatal diagnosis:
  * Disease sufficiently serious to justify termination of pregnancy.
  * No treatment for the disease.
  * Reliable, safe diagnostic test.
  * parents are willing pregnancy should be terminated if fetus is affected.
- Most of metabolic disease have recessive mode of inheritance, and thus prenatal diagnosis should usually be considered only if there is:
  * An affected child from previous pregnancy.
  * One of the parents is affected.
  * Family history of the disease.

Maternal and fetal screening:

- Techniques available for prenatal diagnosis:
  * Chorionic Villus Sampling (CVS)---> 10 – 12 wks of pregnancy.
  * Amniocentesis ---> 16 – 22 wks of pregnancy.
  * Cordocentesis ---> 16 – 17 wks of pregnancy.
  * Fetoscopy (المنظار الجنيني).
  * Maternal serum screening (e.g. measurement of α-fetoprotein to detect neural tube defect).
  * Ultrasonography (e.g. nuchal translucency is down syndrome).
- Triple test of down syndrome (16 wks of pregnancy).
  * α-fetoprotein: low

* Unconjugated estriol: low
* hCG: high

Treatment:

- Restriction of substrate intake: removing galactose (and lactose) from diet in galactosemia.
- Supply of missing product: giving cortisol in congenital adrenal hyperplasia.
- Addition of vitamin cofactors.
- Increased excretion of toxic substances: removing copper in Wilson's disease.
- Replacement of missing protein.
- Replacement of the defective gene.