Purines and Pyrimidines have an essential role in the production of high energy compounds (e.g. ATP), building blocks for DNA, RNA, as signalling molecules (e.g. cAMP) and as intermediates of glycosylation reactions (e.g. UDPglucose). There are biosynthetic, catabolic and salvage pathways involved in their metabolism. Depletion of these crucial metabolites and/or the accumulation of toxic/inhibitory intermediates contribute to the pathogenesis of disorders of these pathways.

This presentation discusses some of the more common purine and pyrimidine disorders where these pathways are affected and the significance of abnormal uric acid and orotic acid concentrations.
Biosynthesis – Phosphoribosyl Pyrophosphate Synthetase superactivity

Defective regulation of PRPP can lead to overabundance of phosphoribosyl pyrophosphate with a consequential increase in purine biosynthesis and increased concentrations of the end products of these pathways eg uric acid and hypoxanthine. Combined regulatory and catalytic overactivity defects or an increased affinity for the ribose-5-phosphate are described as mechanisms for PRPP synthetase superactivity.

It is an X-linked disorder expressed as two clinical phenotypes:

1) **Severe**
   - Affected male hemizygotes: Neurodevelopmental delay and sensorineural deafness in early childhood
   - Female heterozygous carriers: Adolescent gout

2) **Late Juvenile/Early Adult onset**
   - Males only: Gout/uric acid urolithiasis
     - No neurological symptoms

**Diagnosis:**
- Raised plasma urate (600-900µM) and urine urate (14mmol/24hr)
- Raised hypoxanthine.

**Treatment:**
- Allopurinol inhibition of xanthine oxidase, low purine diet and high fluid intake with alkalinisation of the urine to prevent precipitation of uric acid.
Purine nucleotides are catabolised by adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP), 5’ nucleosidases and xanthine oxidase. Adenosine is irreversibly catabolised by adenosine deaminase to inosine. PNP catalyses the catabolism of:

- Adenosine → adenine
- Inosine → hypoxanthine
- Guanosine → guanine

The primary effect of deficiencies in ADA and PNP is a form of severe combined immunodeficiency (SCID) due to accumulation of nucleosides that inhibit DNA synthesis, particularly in T-cells. Both are autosomal recessive disorders that present with severe infections. In ADA deficiency both cellular and humoral functions are affected whilst in PNP deficiency cellular functions are affected and humoral functions are variably affected. Neurological symptoms may also often occur. In particular in PNP deficiency patients have reduced plasma and urine urate due to the block in hypoxanthine and guanine catabolism. Diagnosis is by assay of ADA and PNP in red cells.

Bone marrow transplantation can be an effective treatment.
Salvage – HPRT & APRT Deficiency

90% of the purines generated by intracellular metabolism are recycled. There are two key enzymes that are involved in the recycling/salvage of purines:

1) Hypoxanthine-guanine phosphoribosyl transferase (HPRT)
   This recycles free hypoxanthine and guanine into IMP and GMP

2) Adenine phosphoribosyl transferase (APRT)
   This recycles free adenine into AMP

Defects in either of the salvage enzymes results in clinical disorders associated with stone production and in the case of HPRT deficiency neurological symptoms.
HPRT Deficiency: Lesch Nyhan Syndrome

This is a X-linked disease virtually exclusively presenting in males with an estimated incidence of 1:380,000.

The typical presentation is at 3-4 months of age with progressive neurological deterioration including developmental delay, movement disorders, spasticity, seizures and a characteristic self-destructive behaviour including biting of the lips and fingers. Sometimes uric acid stones are formed noted as “orange sand in the nappies”. Occasionally megaloblastic anaemia is reported. Usually patients have a gross deficiency in HPRT when measured in red cells.

Partial HPRT Deficiency

A level of 1.5-8% residual enzyme activity presents with hyperuricaemia and neurological abnormalities but the self-destructive behaviour is absent.

Patients with >8% residual enzyme activity present with hyperuricaemia, gout and stone formation but do not have neurological or behavioural abnormalities.

All forms are diagnosed initially on the basis of raised plasma uric acid and urine uric acid/creatinine ratio. In the severe forms this is gross but partial defects are more difficult to diagnose and may need enzymological or DNA analysis.

Treatment involves reduction of uric acid levels with allopurinol although severe neurological symptoms are treated symptomatically.
Interpreting Uric Acid Results

If there is a clinical suspicion of a purine disorder it is important to measure plasma urate and the urine urate/creatinine ratio. However it is important to use age-related ranges and to remember that they will not detect all forms of these disorders – particularly the milder ones.

In particular infants have a higher rate of urate clearance which can normalise plasma urate levels, renal failure can mask a genuine increase in uric acid concentrations, urate and creatinine concentrations can show diurnal variations and bacterial degradation may elevate urinary uric acid levels.

**Causes of high urate levels:**
- Lesch-Nyhan syndrome, PRPP-synthetase superactivity
- Glycogen Storage Disease Type I
- Fructose 1,6-bisphosphatase deficiency
- Fatty acid oxidation disorders
- Lactic Acidaemia

**Low urate concentrations** may also be very significant and these should be followed up.

**Causes of low urate levels:**
- Xanthine oxidase & Molybdenum Cofactor Deficiency
- PNP deficiency
- Fanconi syndrome
Pyrimidine Metabolism

HCO₃⁻ + glutamine → Carbamyl-P → Orotic acid → PRPP

Pyrimidine synthesis

Pyrimidine catabolism

CMP → cytidine → uridine → uracil → dihydouracil → β-ureidopropionate → β-alanine

UMP → uridine → uracil → dihydouracil → β-ureidopropionate → β-alanine

TMP → thymidine → thymine → dihydrothymine → β-ureidoisobutyrate → β-aminoisobutyrate

Pyrimidine salvage
Hereditary Orotic Aciduria

This is a rare disorder of pyrimidine synthesis which presents with megaloblastic anaemia with anisocytosis and poikilocytosis. Orotic acid crystals appear in the urine. It is due to a defect in the enzyme Uridine Monophosphate Synthase that catalyses the first two steps of orotic acid catabolism. Diagnosis is by haematological analysis and quantitation of urinary orotic acid. Treatment is by uridine supplementation which inhibits pyrimidine biosynthesis and hence orotic acid formation.

Orotic acid also accumulates in defects of the urea cycle secondary to the accumulation of carbamoyl phosphate eg ornithine transcarbamylase deficiency (see Urea Cycle Defects Module). However the levels of orotic acid are much higher in this disorder and there is no hyperammonaemia.
Self Assessment Questions

1. Which disorders are a cause of severe combined immunodeficiency:
   - a) Hypoxanthine: Guanine Phosphoribosyl transferase Deficiency
   - b) Purine nucleoside phosphorylase deficiency
   - c) Adenine phosphoribosyl transferase deficiency
   - d) Adenosine deaminase deficiency

2. Uric acid is elevated in which of these conditions:
   - a) Purine nucleoside phosphorylase deficiency
   - b) Glycogen Storage Disease Type 1
   - c) Hypoxanthine: Guanine Phosphoribosyl transferase Deficiency

3. Orotic Acid is elevated in which of these conditions:
   - a) Carbamoyl Synthase Deficiency
   - b) UMP Synthase Deficiency
   - c) Ornithine Transcarbamylase Deficiency
   - d) Glycogen Storage Disease Type 1
Self Assessment Answers

1 Which disorders are a cause of severe combined immunodeficiency:-
   - b) Purine nucleoside phosphorylase deficiency
   - d) Adenosine deaminase deficiency

2 Uric acid is elevated in which of these conditions:-
   - b) Glycogen Storage Disease Type 1
   - c) Hypoxanthine: Guanine Phosphoribosyl transferase Deficiency

3 Orotic Acid is elevated in which of these conditions:-
   - b) UMP Synthase Deficiency
   - c) Ornithine Transcarbamylase deficiency