**University of Cambridge**

**Biochemistry Part IA**

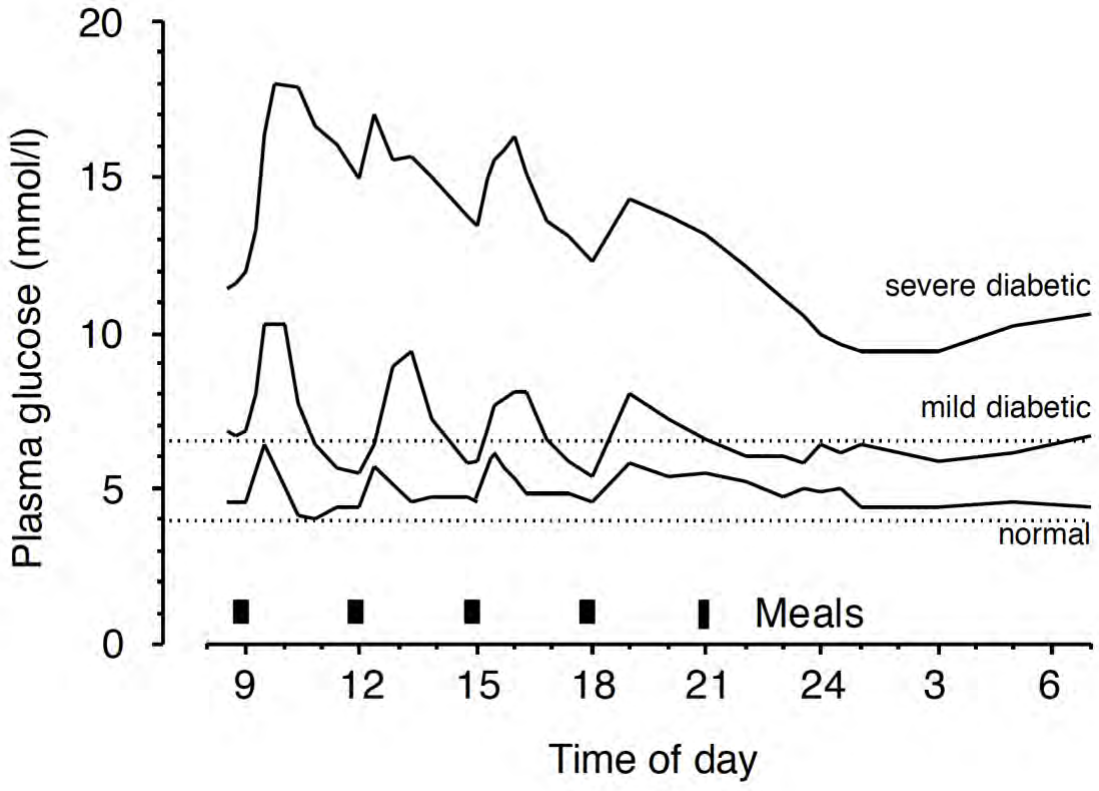
**Dr Yeo Summaries**

**Diabetes**

## Lecture 1: Clinical diabetes

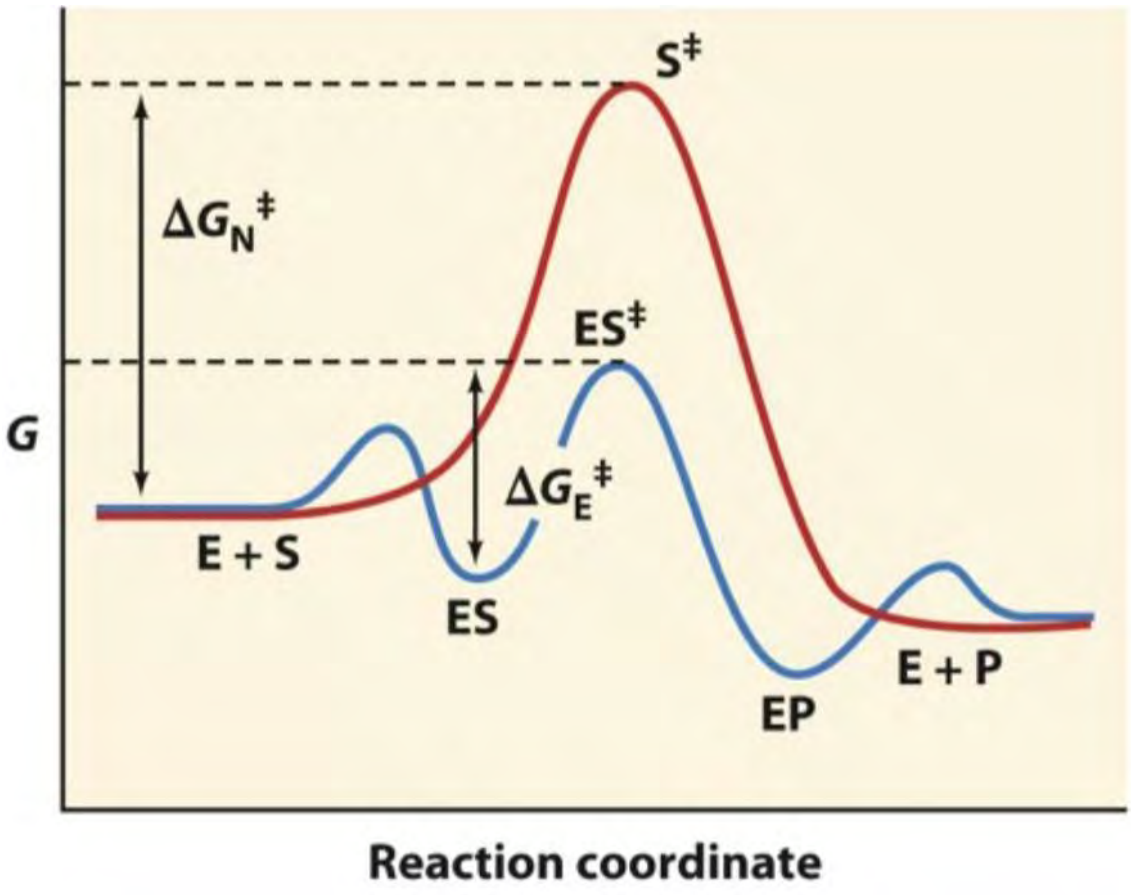
- Glucose is filtered into urine when there is an abnormally high concentration of glucose in the blood, exceeding the capacity of the kidneys to retain it and requiring large volumes of fluid for its excretion

- Diabetes = Disease where blood glucose concentration is abnormally high
  - When eating meals, a glucose spike follows as shown below
  - For a healthy person, the spike is well controlled in an optimum range
  - For diabetics, the spike is much bigger and retained for much longer. This leads to abnormally high blood (plasma) glucose concentrations throughout the day



**Lecture 4: Enzyme Reaction Rates**

- Enhance by more than billion-fold
- Operate at body temp (37°), 1atm, neutral pH (depending on their function) unlike industrial catalysts.
- Provide: alternate route for reaction to take place with a lower activation energy
- A catalyst does not alter ΔG for the reaction or change the equilibrium position.
- Instead it reduces the energy of the transition state (TS), reducing the activation energy and overcoming the kinetic barrier.
- More reactions can overcome the barrier per unit time > higher rate
- ΔG ‡ = energy required to form the transition state from the substrate




1) Covalent catalysis = with unstable intermediates or transition states to stabilise them
2) Acid-base catalysis = AA side chains, donate or accept protons

- Glycogen phosphorylase = dimer, on Ser14
- AMP allosteric activator vs ATP, G6P

- Influenza:
  - Haemagglutinin: binds to sialic acid on PM
  - Neuraminidase: release new viral particles that are stuck to sialic acid,
  - TS analogues, poor selectivity
  - Structure-based design: fill active site pockets e.g. +charged group added to make H-bonds with Glu side chains

- Viagra: blocks phosphodiesterase 5 for cGMP (SM relaxation, more blood flow)

- Enzyme assays enable drug screening

**Lecture 7: Principles of molecular recognition**

- High Affinity – strength of interaction e.g. Glucokinase (lower glucose sensor) vs hexokinase

- Specificity – select target only e.g. DNA binding recognise specific promoter sequence

- Control – growth factor signalling pathway only active present

- Needed: signalling (development, differentiation, defence); enzyme; maintain structure

- Permanent interaction = large hydrophobic regions = high affinity = but not specific = AA can change orientation

- Complementary polar/charged groups = specificity = H-bonds, salt bridges

- Association constant = Ka = ratio rate constants = depends on affinity and concentration

- Kd is reciprocal = moldm$^{-3}$ = concentration at which 50% ligand bound

- Fraction ligand bound = $\frac{[L]}{[L]+Kd}$ where L = concentration free ligand at eq; when ligand in excess

**Measuring interaction affinities:**

1. Isothermal titration calorimetry > ΔH when titrating ligand into protein solution.
   - ΔG° = RT ln(Kd) where $Kd = \frac{1}{Keq}$

2. Surface plasmon resonance > ligand binding changes the refractive index of light

## Lecture 8: Organ specialization and Integration of metabolic pathways

- Blood glucose usually over 3.5mM. 50% of brain requirement met by ketone bodies
- Muscle can store glycogen, can't export glucose or do gluconeogenesis
- Heart: only aerobic respiration and works continuously
  - resting fuel FA
  - under stress uses limited glycogen stores.
  - Insulin stimulates glucose uptake GluT4 transporters

- Liver: crossroads for central metabolism
  - acts buffer blood glucose
  - synthesise or breakdown TAG
  - malonyl-CoA prevents FFA entering mt so not broken down
  - makes ketone bodies but can't use
  - proteins degraded to AA, skeletal muscle useful energy resource

- Adipose: stores and release fatty synthesis according demand
  - releases hormones regulate metabolism via AMPK
  - doesn't have glycerol kinase, if glucose low then glycerol-3-p low so FFA not re-esterified and exported
  - Glut4 so glucose uptake directly controlled by insulin which also influences intracellular enzymes
- Pancreas: blood glucose sensed by Glucokinase
  - All G6P goes straight to oxidative phosphorylation
  - Linked to insulin synthesis and release

- Kidney: disposes of urea
  - Maintains blood pH
  - Gluconeogenesis in starvation

Fed state:

- Long term adaptive change: insulin stimulates enzymes for fat synthesis PFK and ACC
  - Indirectly increasing NADPH production and acetyl-CoA transport into cytosol
- VLDL and liver: TAG not stored in liver except in obesity and excessive alcohol.
  - Packed with Apo B-100 and packaged with Very Low Density Lipoprotein (VLDL) exported to blood, most stored in adipose
- Digestion dietary triacylglycerol: emulsified by bile from gall bladder in small intestine.
  - Makes fat micelles with large total SA
  - Lipase from pancreas acts on surface, FA and MAG absorbed at brush border
  - Converted to TAG packaged into chylomicrons (lipoprotein) with Apo B-48 and phospholipids to stabilize structure
  - Chylomicrons secreted into lymph and enter blood at thoracic duct.
- Removing TAG from blood: lipoprotein lipase at PM of aerobic muscle and adipose,
  - recognize Apoproteins on VLDL and chylomicrons surface
  - hydrolyse TAG at surface, FA released into cells