Topic A – Regulation of Metabolism	
Give an overview of the central role of the liver	• Acts as a processor and distributor of nutrients to other tissues • The liver takes up carbohydrates, lipids and amino acids after a meal which are metabolised, stored or transported to other tissue • Smooths out broad fluctuations in the availability of nutrients for peripheral tissues

Describe the transport of glucose into different tissues	• GLUT1 - everywhere
	  ○ Recognition and binding of glucose causes conformational change
	  ○ Returns to original conformation when glucose is released
	• GLUT2 – liver and pancreas
	  ○ High Km for glucose – maximal glucose uptake when blood glucose is high
	  ○ When blood glucose is low, liver GLUT2 doesn't take up glucose and leaves it for other tissues
	  ○ In pancreatic beta cells, glucose uptake signals that blood glucose is high, initiating secretion of insulin
	• GLUT3 - brain
	• GLUT4 – muscles, fat, heart
	  ○ Insulin stimulates GLUT4 expression in myocytes (synthesising glycogen) and adipocytes (synthesising triacylglycerols)
	  ○ Insulin causes more GLUT4 to come to the membrane, resulting in increase in glucose uptake
	• GLUT5 – intestine, kidneys

Discuss the regulation of enzyme concentration in cells and its role in the regulation of cellular metabolism	• Ubiquitination signalling protein breakdown • Regulation by metabolites, hormones and growth factors ○ Glukokinase and phosphofructokinase are induced by insulin • Repression of synthesis – usually by an end product of a metabolic pathway • Localised expression
Discuss kinetic regulation of enzyme activity	• Substrate concentration • Product concentration • Coenzyme concentration

Discuss allosteric enzyme regulation and regulation by reversible	• Allosteric
	  ○ Reversible, non-covalent binding of a modulator at a site other than the active site
	  ○ Binding of modulator causes conformational change in enzyme structure
	  ○ Binding of substrate occurs more readily to one conformation

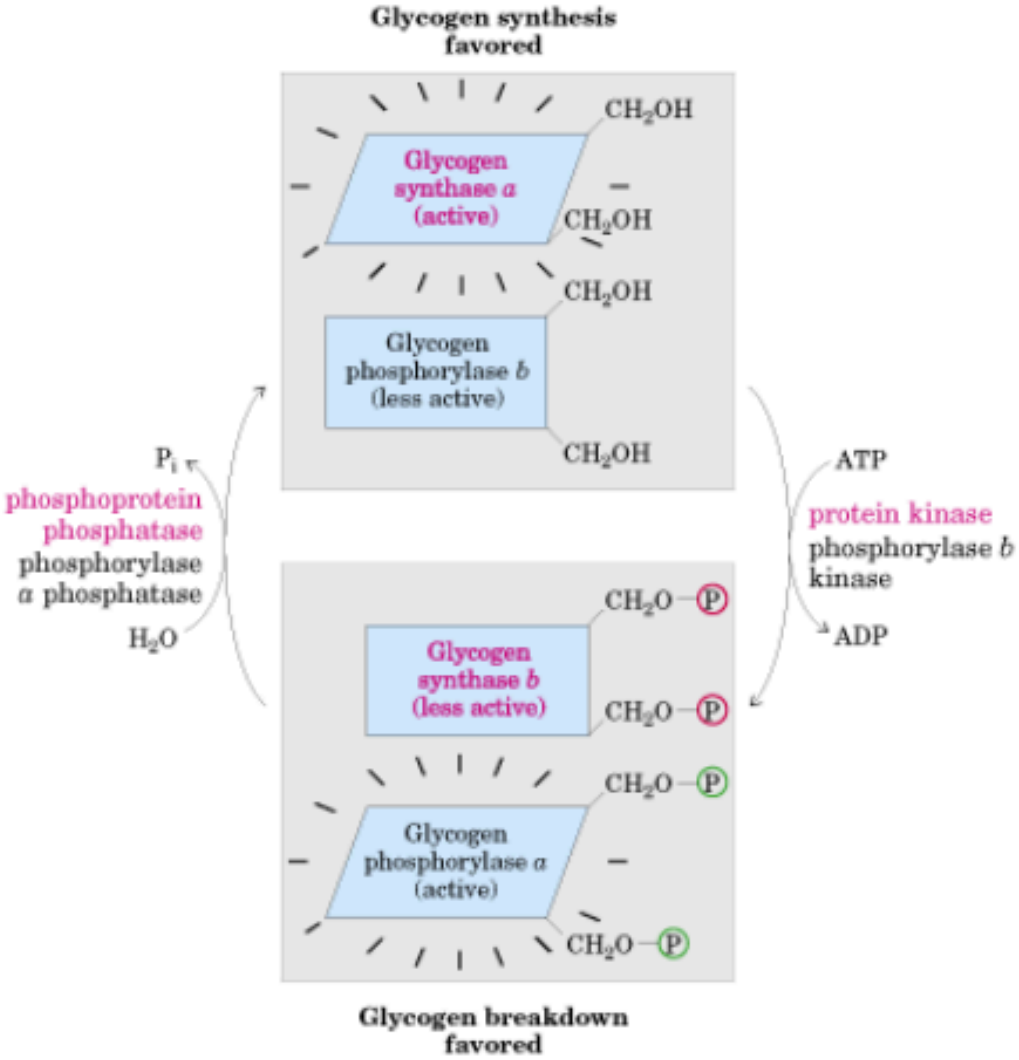
covalent modification	• Covalent modification
	  ○ Reversible
	  ○ Linkage of a chemical group to activate/inactivate enzyme (e.g. Phosphorylation, adenylation, methylation)

Discuss the use of enzymes to detect various diseases	• Isoenzymes, found in different tissues, can be identified based on different physical and chemical properties an thus can identify which area of the body is suffering damage
	  ○ Lactate dehydrogenase
	  ○ Creatine kinase
	  ○ Aspartate amino transferase

Explain the importance on regulating the pathways of glycolysis and gluconeogenesis	• Maintain homeostasis – rate of synthesis of a metabolite equals the rate of breakdown of this metabolite • Allows storage of metabolites in case of starvation • Ensures all tissues obtain required energy

Discuss the three key reactions where regulation occurs and outline how they are regulated	• Hexokinase
	  ○ Glucose <-> G6P
	  ○ Isoenzymes regulated by sequestration and transcription
	• Phosphofructokinase
	  ○ F6P <-> F-1,6-bisP
	  ○ Complex allosteric enzyme – multiple substrate and regulatory binding sites
	  ○ ATP inhibits (an end product of glycolysis)
	  ○ AMP activates (and end product of gluconeogenesis)
	  ○ Fructose-2,6-bisphosphate is produced to regulate glycolysis/gluconeogenesis by increasing the affinity of PFK-1 for F-6-P and reducing affinity of FBPase-1 for F-1,6-bisP
	• Pyruvate kinase
	  ○ Allosterically activated by fructose-1,6-bisphosphate
	  ○ Allosterically inhibited by signs of abundant energy supply (ATP, acetyl-CoA, long chain fatty acids and alanine)
	  ○ Inactivated by phosphorylation by glucagon

Discuss the regulation of glycogen phosphorylase	• Glycogen phosphorylase removes glucose residues from glycogen • Activated by glucagon (when blood glucose drops) or adrenaline (when sudden energy is required) is released, starting a phosphorylation cascade via cAMP • Allosteric regulation • When glucose levels return to normal, glucose enters the liver cells and binds to an allosteric site on phosphorylase A to inhibit the enzyme
Explain reversible	• Proteins can be modified in order to activate or inactivate them • Covalent binding to an allosteric site can modify the active site,

covalent protein modification	decreasing or increasing tis ability to bin substrate
Outline reciprocal regulation of glycogen synthesis and breakdown	

Describe the cAMP-dependent protein kinase cascade	• G-protein-coupled receptor-triggered signalling cascade used in cell communication
	• The activated G subunit binds to and activates adenylyl cyclase, which then catalyses the conversion of ATP into cyclic adenosine monophosphate (cAMP)
	• Increase in cAMP can lead to activation of
	  ○ Cyclic nucleotide-gated ion channels
	  ○ Exchange proteins activated by cAMP
	  ○ Protein kinase A (PKA)
	• PKA then phosphorylates a number of other proteins, including glycogen phosphorylase

Describe the mechanism of deamination of amino acids	• Glutamate dehydrogenase is the major enzyme • Releases the amino group from glutamate and produces alpha-ketoglutarate and ammonium • Closely linked with the citric acid cycle • Occurs in the mitochondria • Produces NADH
Discuss the fate of the amino	• Turned to glucose and sent back into the bloodstream • Carbon skeletons form alpha-keto acids and enter the citric acid