1997b(4): Briefly describe the influence of a general anaesthetic on intraoperative temperature regulation

General: GA is the absence of awareness
  - Includes loss of consciousness / hypnosis
  - May include use of a muscle relaxant

Body can be separated into thermoregulatory zones
  - Core Zone: Core of body
  - Shell: Skin and other surfaces exposed to external environment

Effect of GA on thermoregulation

1. Widening of interthreshold range i.e. the range of core body temp where no autonomic thermoregulatory responses occur
   - Normally: 36.8°C → 37.2°C
   - Under GA: 34.5°C → 38.5°C
   - ↑Risk of hyperthermia / hypothermia → in this range Pt essentially becomes poikylothermic and changes to body temperature occur relative to ambient temp
     - Outside of this range, normal reflexes will occur (if not paralysed etc)

2. Heat redistribution
   - Phase I: Vasodilatation of non-core zones (skin etc) on induction of anaesthetic (VA/IV induction)
     - Shift leads to ↓core T°C due to equilibration of heat energy in all zones (core → skin)
     - Occurs during 0-1hr of anaesthetic
   - Phase II: characterised by ongoing heat loss / ↓heat production
     - 2° unimpaired skin blood flow
     - ↓BMR 2° ↓O₂ consumption, paralysis / ventilation
     - Occurs during 1-4hr
   - Phase III: Occurs at lower T°C 2° widened interthreshold range
     - Vasoconstriction occurs with resolution of thermoregulatory zones
     - Ongoing ↓BMR may mean heat loss > production →→ maintenance of temp at lower level

3. Inability to effect response
   - Only response available to anaesthetised, paralysed, hypothermic Pt → non-shivering thermogenesis
   - Non-shivering thermogenesis: production of metabolic heat without mechanical work.
     - Heat production via uncoupled oxidative phosphorylation in brown fat / skeletal muscle → most important in neonates

By Amanda Diaz
Outline the actions of insulin that affect fat metabolism

General: Insulin is a 51-amino acid hormone synthesised and stored in β cells of the Islets of Langerhans in the pancreas.
- It is an anabolic hormone
- Binds to insulin receptors on the cell membranes of tissues
  - Internalised
  - Activates GPCR → ↑tyrosine kinase activity → activate protein cascade which ↑transcription of genes

Effect on Fat Metabolism
1. ↑Fat Synthesis in adipose tissue
   - ↑Glucose uptake by adipose tissue
     - ↑Glucose transporters (GLUT 4) insertion in cell membranes of adipose tissue → ↑facilitated diffusion of glucose
     - Glucose is converted to fatty acids
       - Glucose → pyruvate → Acetyl CoA → fatty acid
     - Converted to glycerol for synthesis of triglycerides in cell
       - ↑α-glycerophosphate formation
   - ↑Lipid uptake by adipose tissue
     - ↑LDL receptor activity of adipose tissue
     - Activation of endothelial lipoprotein lipase → splits triglyceride carried within LDL into FFA and glycerol → ↑absorption → reconstituted within cell for storage
2. ↓Lipolysis
   - Inhibition of hormone-sensitive lipase
     - ↓triglyceride hydrolysis in adipose tissue → promotes storage
   - ↓Ketone body formation in liver
3. ↑Triglyceride synthesis in liver
   - Excess glucose in liver (after glycogenesis is completed (100g)) glucose is converted to fatty acids and stored in liver
     - More important than adipose tissue formation
     - ↑glucose uptake via ↑activity of glucokinase in hepatocytes (nil glucose transporters required) → traps glucose within the cell
4. ↑Glucose-6-phosphatase activity in liver
   - Allows for increased glucose uptake by hepatocyte (this doesn’t require the insertion of glucose transporters into the cell membrane)
   - Increased G-6-P activity maintains the glucose concentration gradient
2001a(5)/1996b(2): Explain briefly the role of the skin in maintaining a normal body temperature

General: The skin is the largest organ of the body
- Receives 10% (500ml) of CO in the resting 70kg male
- Is the largest interface with environment in the body (respiratory tract has much less exposure)

Normal body temperature: Maintained within narrow limits (37°C is average)
TNZ: range of ambient temperatures at which O₂ consumption is minimal
  o 22-28°C (adult); 32-34°C (neonate)
- Within this range, heat loss can be accommodated by changes in A-V anastomoses tone alone (doesn’t require energy)

Role of Skin
Sensor system: Detect ambient temperature
- Warm receptors (bulbs of Raffini) via unmyelinated C fibres
  o ↑receptor firing at >30°C, maximal discharge rate 44°C, cease 46°C
- Cold receptors (bulbs of Krause) via Aδ fibres
  o ↑receptor firing <25°C

Effector System: Efferents from hypothalamus (central integrator)
- Smooth muscle tone of cutaneous arteriovenous anastomoses
  o Anterior hypothalamus stimulation → ↓SNS → vasodilatation → ↑blood flow to skin (up to 30-fold)
    ▪ ↑radiation, convection, conduction heat loss → outside of TNZ tend to favour absorption rather than loss
  o Posterior hypothalamus stimulation → ↑SNS → α adrenergic stimulation blood vessels → constriction of A-V anastomoses → ↓blood flow to skin → ↓heat loss
- Sweating (Evaporation)
  o ↑ambient temp (>TNZ) → ↑sweat production (via ACh mediated SNS activity)
    ▪ Bradykinin in sweat → further vasodilatation at anastomoses
    ▪ Can ↑sweat production up to 2L/hr
    ▪ Outside of TNZ is 1° method of heat loss (other forms favour heat absorption)
  o ↓efficacy with ↑ambient humidity
- Piloerection (insignificant in humans)

Barrier System:
- Prevents loss of uncontrolled H₂O evaporation by latent heat of vapourisation (2.4Mj/kg)
- Prevents loss of core body temperature to environment
  o Subdermal fat is insulating
  o Counter-current exchange b/n cutaneous arteries and deep veins to maintain core temp especially with ↓ambient temp
2001b(3): Describe the fuel sources used during early and sustained fasting in man

General: Fuel sources are used to provide energy substrates for utilisation by tissues
- Some tissues (e.g., brain, RBC) are obligate glucose utilisers
- Most other tissues are able to switch substrate utilisation in order to preserve glucose for brain
- Liver is the 1st source of circulating substrate

Early Fasting (<24hrs)

Hormonal changes:
- ↓Insulin secretion by pancreas
  - ↓BSL detected by β cells of IoL / inhibited by ↑adrenaline
  - Effect:
    - Adipose tissue: ↓TG uptake, ↓glucose uptake, ↑FFA release
    - Muscle: ↓Protein synthesis, ↓glucose uptake, ↓glycogen synthesis
    - Liver: ↓Glycogen synthesis, ↑glucose release, ↑KB
- ↑Adrenaline
  - ↓BSL stimulates adrenal release of adrenaline
  - Effect:
    - Pancreas: Inhibit insulin
    - Adipose tissue: ↑FFA release, ↓glucose uptake
    - Muscle: ↑FFA utilisation, ↑glycogenolysis, ↓glucose uptake
    - Liver: ↑glycogenolysis, ↑gluconeogenesis, ↑KB

Effect:
- Dependent on previous food intake, intragastric food contents can continue to be absorbed into the fasting period
- ↓Glucose uptake by dependent tissues: Skeletal muscle, adipose tissue → ↓GLUT 4 transporters (insulin dependent) → ↓uptake glucose
- ↓Glycolysis: Majority of peripheral tissues switch to fatty acid metabolism (β oxidation) and smaller amounts of ketone body oxidation in order to produce acetyl-CoA for TCA cycle
- ↑Glycogenolysis: Liver produces most of the glucose via glycogen stores
- ↑Gluconeogenesis: Small amount of glucose produced in the liver and kidneys is via glycerol (triglyceride breakdown adipose tissue) and lactate (anaerobic glycolysis in RBC)
- ↑Lipolysis: Small amount of ketone bodies (acetooacetate, β hydroxybutyrate) formed in liver by fatty acid oxidation

Sustained Fasting (>24hrs)

Hormonal changes:
- ↓insulin: see above for effect
- ↑adrenaline: see above
- ↑cortisol: in response to ↓BSL, stress
Endocrine & Metabolism

Effect:
- Adipose tissue: ↑FFA release
- Muscle: ↓protein synthesis, ↓glucose uptake, ↑amino acid release
- Liver: ↑gluconeogenesis (from amino acid), ↑glycogenolysis, ↑glucose release

- ↑Glucagon: from α cells of IoL
  o Special note: Glucagon peaks at 4 days fasting. Causes peak of gluconeogenesis at this time
  o Effect:
    ▪ Adipose tissue: Nil effect
    ▪ Muscle: Nil effect
    ▪ Liver: ↑glycogenolysis, ↑gluconeogenesis, ↑amino acid catabolism, ↑KB synthesis

Effect:
- ↑Hepatic gluconeogenesis: Nil glycogen stores
  o Via: amino acids (muscle), glycerol (adipose tissue), lactate (RBC)
- ↑FFA release: to maintain total energy release (↓glucose)
  o Mostly converted in liver to ketone bodies
    ▪ Used 1° by muscle
    ▪ Brain, CNS able to supplement some of previous glucose requirement with ketone bodies
2003a(11)/1996a(6): Define the term thermoneutral zone. Briefly explain how
the body regulates temperature when the ambient temperature exceeds the
thermoneutral zone
Definition: Thermoneutral zone (TNZ) is the range of environmental
temperatures at which the metabolic rate (and oxygen consumption) is
minimal and steady
- Normal Range:
  - 22-28°C Adult,
  - 32-34°C Neonate
Regulation of body temperature during ambient temp > TNZ (>28°C)
Sensor Systems
- Cutaneous warm receptors (bulbs of Raffini) detect ↑ambient T°C
- Travels via unmyelinated C fibres in lateral spinothalamic tract to
  synapse in medulla → anterior hypothalamus
Integrating System
- ↑ activity in anterior hypothalamus (NA, 5-HT, dopamine, PGs)
Efferent Response
- ↓SNS activity
  - Opening of cutaneous A-V anastomoses → cutaneous vasodilatation
    ▪ ↑Skin blood flow up to 30 x normal
  - ↑Sweat production
    ▪ Bradykinin released in sweat to further dilate A-V anastomoses
  - Behavioural change
    ▪ ↓clothing, moving out of direct heat, ↓activity, ↑thirst
- Aim of Response:
  - ↓Body T°C via convection / conduction (in TNZ: 15%),
    evaporation (in TNZ: 30%), radiation (in TNZ: 40-50%)

>>>37°C
Sensor System
- Cutaneous warm receptors continue to send afferents via C fibres
- Anterior hypothalamus detects ↑core body T°C
Integrating System
- Anterior hypothalamus
Efferent Response
- Continued cutaneous vasodilatation
- ↑↑Sweat production → ↑importance → Max production: 2L/hr (up to 6L/hr
  if conditioned)
  - Latent heat of vapourisation of water becomes 1° method of
    heat loss
    ▪ Impaired if ↑ambient humidity
2003a(15): Describe the physiological actions of thyroid hormones

General: Thyroid hormones include tri-iodothyronine (T₃) and thyroxine (T₄).

- Synthesised in thyroid gland within follicular cells
  o Iodination of tyrosine residues in thyroglobulin backbone
  o Synthesised hormones stored within thyroglobulin in colloid of follicular cells
- Synthesis and release stimulated by TSH released from anterior pituitary
- TSH release stimulated by TRH released from median eminence of hypothalamus via hypothalamic-hypophyseal portal system

Release of T₃ and T₄
- TSH binds to receptors on cell membrane of follicular cells
  o GPCR → ↑cAMP → ↑adenylyl cyclase
- Effect of TSH:
  o ↑I⁻ uptake (active transport) into follicular cells → ↑Iodine trapping
  o ↑synthesis of T₃ and T₄ via ↑iodination and ↑rate of coupling reactions
  o ↑proteolysis of thyroglobulin within follicular cells → liberate T₃ (7%) and T₄ (93%) for diffusion into circulation

Physiological action of T₃ and T₄

Activity
- T₃ and T₄: highly protein bound (>99%)
  o Bound predominantly to thyroxine binding globulin (TBG), albumin, thyroxine binding pre-albumin (TBPA)
- t½
  o T₃: 24hr
  o T₄: 7 days
- T₃ is 3-5 x more active than T₄

Effects:
- Cellular Effect:
  o T₄ is de-iodinated to T₃ → binds intracellular receptors
    ▪ ↑gene transcription → ↑protein synthesis, ↑mt activity
    (↑size, ↑numbers) → → ↑cellular activity
- BMR:
  o ↑Metabolic rate of cells
    ▪ Excess T₃/T₄ → ↑BMR by 60-100%
    ▪ ?2° ↑stimulation Na⁺/K⁺ ATPase → ↑Na⁺ and K⁺ transport through cells
  o ↑appetite / food intake
- ↑CHO Metabolism (T₄ and T₃):
  o ↑absorption from GIT
  o ↑glycolysis, ↑cellular uptake, ↑gluconeogenesis
- ↑fat metabolism (1° T₄)
  o ↑FFA release from adipose tissue
  o ↓plasma cholesterol, ↓plasma triglycerides, ↓phospholipids
- Protein metabolism (T₃ and T₄) / muscles
  o Physiological amounts: Anabolic (↑protein synthesis)

By Amanda Diaz
Excess amounts: Catabolic (↑muscle breakdown)
- Excess: fine tremour 2° ↑excitability of spinal cord
- CNS:
  - Intra-uterine and neonatal brain development dependent on thyroid hormones
    - Deficiency: Mental retardation
  - Sexual function 2° direct gonadal effect and indirect negative feedback on anterior pituitary control of sexual hormones
    - Deficiency: ♂ → ↓libido
    - Excess: ♂ → erectile dysfunction
- Bones:
  - T4 important in regulating bone growth
- CVS:
  - Direct: Positively chronotropic and ionotropic
  - Indirect (2° ↑BMR): ↑systemic blood flow → ↑CO
  - Nil effect on MAP (balanced by vasodilation (↓diastolic))
    - Excess: tachycardia, AF
- Resp:
  - Indirect (2° ↑BMR): ↑metabolic demand → ↑depth / rate respiration
- Thyroid Function:
  - Negative feedback (free thyroid hormones) on hypothalamus (inhibit TRH release) and anterior pituitary (inhibit TSH release)
2006a(13): Describe the factors that influence metabolic rate

Definition: Basal metabolic rate is the rate of energy output or heat production in a subject comfortable and at rest 12 hours after a meal

- In 70kg ♂ → 8000kJ/day (2000kcal/day)

Factors influencing metabolic rate

1. Body size as a measure of body surface area
2. Body fat content
   a. ♀ have ↓ metabolic rate cf ♂ → 2° higher body fat content
      i. Nil gender difference on calorimetry based on lean body mass
3. Age: ↓ metabolic rate with age
   a. Neonates 2 x BMR than adult
      i. 2° high rate of growth
   b. ↓BMR by 2% per decade of adult life
4. Feeding status:
   a. ↑metabolic rate 4-6hr following meal
      i. Known as specific dynamic action (SDA) of food → 1° due to deamination of food in liver
   b. Starvation → ↓metabolic rate 2° ↓cell mass / ↓tissue metabolism (seen in prolonged fasting > 2 weeks)
5. Climate:
   a. Warmer climate → ↓metabolic rate 2° ↓heat loss efficiency
      i. 10% less BMR in tropics cf temperate climate
6. Core body temperature: ↑metabolic rate effected by ↑skeletal muscle activity (shivering)
   a. Slight ↓T°C → ↑metabolic rate
   b. Severe ↓T°C → ↓metabolic rate 2° inhibition metabolic pathways
   c. Anaesthesia / NMBD → ↓metabolic rate 2° inhibition skeletal muscle activity
7. Pregnancy: Progressive ↑metabolic rate during pregnancy
   a. Maximal during 2nd / 3rd trimesters (20% above resting BMR)
8. Lactation: ↑metabolic rate
9. Hormones:
   a. Thyroid hormones / adrenaline → cellular activity → ↑metabolic rate
2006b(14)/1996a(5): Compare & contrast the physiological effects of a 6hr fast of fluids & food with a 24hr fast in a healthy adult

Central mediator for BSL regulation is the liver

**Hormonal Changes with fasting from food and fluids:**

**BSL-related hormones**

- **↓Insulin:** ↓BSL detected by β cells of IoL
  - **Adipose Tissue:** ↓glucose uptake (↓GLUT 4 transporter insertion), ↓fat uptake (↓lipoprotein lipase activity), ↑FFA release
  - **Muscle:** ↓glucose uptake (↓GLUT 4 transporter), ↓glycogenesis, ↑glycogenolysis, ↓protein synthesis
  - **Liver:** ↓glycogenesis, ↑glycogenolysis, ↑gluconeogenesis, ↑KB (small amount), ↑glucose release

- **↑adrenaline:** stimulated by ↓BSL, stress
  - **Pancreas:** Inhibition of insulin
  - **Adipose tissue:** ↑FFA release, ↓glucose uptake
  - **Muscle:** ↓glucose uptake, ↑FFA metabolism
  - **Liver:** ↓glycogenesis, ↑glucose release, ↑KB

- **↑Cortisol, ↑GH:** stimulated by ↓BSL, stress
  - **Adipose tissue:** ↑FFA release
  - **Muscle:** ↓protein synthesis, ↑amino acid release, ↑FFA metabolism
  - **Liver:** ↑gluconeogenesis (amino acid), ↑glucose release, ↑KB

- **↑Glucagon:** ↓BSL detected by α cells of IoL
  - Peak release occurs after **4 day fast** → corresponds with peak liver gluconeogenesis
  - **Adipose tissue:** minimal effect
  - **Muscle:** Minimal effect
  - **Liver:** ↑gluconeogenesis, ↑amino acid catabolism, ↑KB

**Body Water-related hormones:**

- **↑ADH:** osmoreceptors detect 1-2% change osmolality → ↑ADH release from posterior pituitary
  - **Renal:** Aquaporin insertion CD: ↑H₂O reabsorption → production of concentrated urine, ↑ADH-urea transporter CD: ↑urea reabsorption → ↑concentrating capacity of kidney (↑medullary osmolality)
    - ↑TPR
  - **RAA system:** renin release stimulated by SNS activation / adrenaline release, ↓circulating vol >10% (high pressure baroreceptors aortic arch, carotid sinus)
    - **Central:** thirst, ↑ADH release
    - **Renal:** ↑Na⁺ and H₂O reabsorption in collecting duct (direct effect ATII / Aldosterone)
    - **Vascular:** ↑TPR

**6 hour Fast:** Overnight fast, well tolerated

Hormone change:

- ↓Insulin, ↑adrenaline
- ↑ADH, activation RAA system

Effect:

By Amanda Diaz
Maintain circulating glucose
- GIT: ongoing absorption from GIT of residual food / fluid
- Liver:
  - Hepatic glucose derived 1° from glycogenolysis
  - Small amount gluconeogenesis from lactate (RBC) and glycerol (adipose tissue)
  - Small amount ketone body formation (acetoacetate, β hydroxybutyrate)
- Peripheral tissues (skeletal, cardiac muscle) convert to FFA metabolism, KB metabolism
- Brain, CNS use glucose

Conserving body water, maintain circulating vol:
- Mobilisation of fluid reservoirs: liver, lungs, interstitium, GIT, metabolic water
- Renal: Formation of concentrated urine → UO
- Insensible loss: 900ml (skin, lungs), Sweat: 50ml, Faeces: 100ml

24 hour fast
Hormone change:
- ↓insulin, ↑glucagon, ↑adrenaline, ↑cortisol, ↑GH
- ↑ADH release, ↑RAA system (inhibition of ANP, BNP)

Effect: Hunger
Maintain Energy release, ↓energy usage (lethargy)
- Liver:
  - Glycogen stores exhausted
  - Glucose from gluconeogenesis from amino acids (muscle), glycerol (adipose tissue), lactate (RBC)
  - ↑FFA release to maintain constant energy release
  - ↑KB
- Peripheral tissues:
  - ↑protein catabolism / amino acid release
  - ↑KB metabolism
  - ↑FFA metabolism
- CNS, Brain:
  - ↑KB metabolism to partially supplement previous glucose requirement

Maintain body water: thirst
- Central: ↑↑Thirst, continued ADH release, lethargy → ↓insensible loss
- Renal: Maximal concentrated urine → UO decreased to obligatory urine output (430ml/day)
2006b(16): Describe the physiological consequences of acute hypoglycaemia

General: BSL is usually maintained within a narrow range (4-7mmol/L in adult)
- Maintained by negative feedback system:
  - Detector = Islets of Langerhans’ cells, Stimulus: BSL, Effector: Insulin:glucagon release/ratio
- Aim: ↑BSL to provide substrate for brain, RBC (obligate glucose metabolisers)

Hypoglycaemia occurs when BSL < 3.0mmol/L

**Acute hypoglycaemia**
- Nil compensatory mechanisms activated (hormonal changes have not occurred → min change glucagon, cortisol, GH)
- Early sign: Hunger
- Neurological impairment: confusion, agitation
  - Progresses with ↓BSL → coma, seizure, death

**Physiological consequences of acute hypoglycaemia**

**SNS activation:** ↑catecholamine release
- Effect:
  - Central: Nausea, agitation, hunger
  - Liver: ↑glycogenolysis, ↑glucose release
  - Pancreas: Inhibit insulin release
  - CVS: ↑HR, ↑SVR, peripheral shutdown, sweatiness

**↓Insulin release:** ↓BSL release detected by β cells of IoL
- Effect:
  - Adipose tissue: ↓glucose uptake (↓GLUT 4 transporters in membrane), ↓fat uptake (inhibition of lipoprotein lipase in endothelium), ↑FFA release (HSL)
  - Muscle: ↓glucose uptake (↓GLUT 4), ↓protein synthesis, ↓glycogenesis, ↑FFA metabolism
  - Liver: ↑glucose release (glycogenolysis), ↑FFA release, some KB formation, gluconeogenesis via glycerol (fats), and lactate (RBC metabolism)

**Late Effect:** ↓BSL will stimulate other hormonal changes which aim to ↑BSL over a sustained period
- ↑Glucagon → hepatic gluconeogenesis from amino acids, lactate and glycerol
- Cortisol, GH → ↑FFA release from adipose tissue
MAKUP: Adrenocorticoid Synthesis

General: Androcorticoids are produced in the **adrenal cortex**

- Principle hormones:
  - **Aldosterone** (mineralocorticoid) → produced in **zona glomerulosa**
  - **Cortisol** (glucocorticoid) → produced in **zona glomerulosa** and **zona reticularis**
  - Sex hormones are also produced

**Cortisol**

- 90% protein bound
  - 75% cortisol-binding globulin
  - 15% albumin
- 10% active unbound drug
- Diurnal variation
  - ↑morning, ↓night
- Release under control of **ACTH** release from **anterior pituitary**
  - ACTH under control of **CRH** release from hypothalamus (hypophyseal portal system)
    - ↑with ‘stress’: ↓BSL, ↑T°C, trauma
- ACTH → ↑cortisol production / secretion via GPCR → ↑AMP
- Negative feedback loop of cortisol on pituitary and hypothalamus
- Effects:
  - Liver: ↑BSL → ↑gluconeogenesis via amino acid catabolism, ↑glycogenolysis, ↑KB
  - Metabolic: ‘anti-insulin’ effect, permissive effect on glucagon → ↑diabetes
  - Muscle: ↑amino acid release (↑protein catabolism), ↓glucose uptake, ↑FFA metabolism → myopathy
  - Adipose tissue: ↑FFA release, ↓fat storage, redistribution fat to classical ‘Cushing’ areas
  - Bone: ↓bone formation, ↓collagen synthesis, ↑osteoclast activity → ↑osteoporosis
  - Haematological: ↑RBC/Plts, ↓WCC/eosinophils
  - Immunological: Immunosuppressive, membrane stabilising (↓mast cell degranulation), ↓capillary permeability (↓leukocyte diapedesis)
  - GIT: ↓PG synthesis → ↑stress ulceration

**Aldosterone**

- Release controlled by:
  - RAA system (SNS activation)
  - ACTH
  - Plasma K⁺ (1% change → ↑production)
  - Plasma Na⁺ (10% change → ↑production) → overridden if ↑ECF vol (2° ANP release)
- Effects:
  - ↑Na⁺/K⁺ ATPase activity → ↑Na⁺ (H₂O) reabsorption, ↑K⁺ excretion
  - ↑H⁺ / NH₄⁺ excretion, ↑Cl⁻ reabsorption → tendency to hyperchloreaemic alkalosis

By Amanda Diaz
Makeup: Briefly discuss the functions of the liver
M.I.S.S.R.E.A.D

Metabolic
Immunological (complement, RES)
Synthetic
Storage (amino acid, iron, glycogen, lipid)
Reservoir (blood)
Endocrine
Acid-Base
Drug biotransformation

General: Liver has multiple functions
**Anabolic / Catabolic Metabolism**
- Role is hormonally influenced
  - Catabolic hormones: glucagon, cortisol, adrenaline
  - Anabolic hormones: Insulin, GH
- Anabolic Functions:
  - CHO: glycogenesis
    - ↑glucose trapping (hepatocytes) 2° ↑glucokinase activity
  - Fat:
    - Fatty acid formation
      - Once maximal glycogen stores → glucose metabolised to pyruvate → AcetylCoA → fatty acid
    - Cholesterol / phospholipid formation
  - Protein synthesis
    - Lipoproteins
- Catabolic Functions:
  - CHO: Glycogenolysis, gluconeogenesis (via acetyl CoA formation from fatty acid breakdown) → maintain BSL
  - Fats: ↑lipolysis
    - Ketone body formation
    - Bile Acid formation (for fat absorption)
  - Proteins
    - Ammonium formation (via glutathione synthesis for transport to PCT renal)
    - Urea: by product aa metabolism → ↑concentrating ability of kidney
- Immune System
  - Complement proteins
  - Kupffer cells (reticuloendothelial system within sinusoids)
    - Filtration
    - Storage of Iron as ferritin
- Haematological
  - Coagulation factor formation (II, VII, IX, X)
  - Haematopoiesis (<10% adult liver, more important in fetal liver)

By Amanda Diaz
Drug Biotransformation
  o Phase I: Oxidation (enzyme systems eg cytP450) → unmask conjugation sites
  o Phase 2: Conjugation to ↑solubility for excretion
- Blood reservoir: 450ml in liver at resting state
  o Can ↑ to 1500ml in fluid overload
  o ↓intravascular vol → able to mobilise 350ml
MAKEUP: Calcium absorption & metabolism

General: Calcium is a vital ion

Required for:
- **Membrane excitation**: Most membrane depolarisation requires rapid influx of Ca\(^{2+}\)
- **Homeostasis**: Clotting factors require Ca\(^{2+}\) for activation
  - Coagulopathy doesn’t occur with hypocalcaemia → to get that low would be incompatible with life
- **Muscle contraction**: excitation-contraction coupling
- **Excitation-Secreation**: Secretion for endocrine & exocrine organs require Ca\(^{2+}\) influx. Neurotransmitter release as well.
- **Structural** support: Ca\(^{2+}\) bound to outer surface cell membranes for structural stability and intercellular adhesion

Distribution:
- Normal range **total calcium** 2.45-2.55mmol/L
- Readily exchangeable pool: 1%
- Non-readily exchangeable pool: 99%
- Plasma Calcium
  - Free / ionised calcium (diffusible): 45%
  - Complexed with HCO\(_3^-\) / citrate (diffusible): 10%
  - Bound to globulins / albumin (non-diffusible): 45%

Regulation:
Calcium is under **tight hormonal control** → Release of hormones is based on plasma [Ca\(^{2+}\)]

**Parathyroid Hormone (PTH)**
- Produced in **chief cells** of parathyroid glands
  - Pre-prohormone → cleaved to prohormone → hormone (ER & Golgi apparatus)
- \(\downarrow[Ca^{2+}]\) → \(\uparrow\)synthesis / release PTH
- Actions: Overall effect → \(\uparrow[Ca^{2+}]\) plasma
  - Kidney:
    - \(\uparrow\)DCT / CD Ca\(^{2+}\) reabsorption,
    - \(\downarrow\)phosphate reabsorption in PCT
    - \(\uparrow\)1,25-dihydroxycholecalciferol (calcitriol) production
  - Bone: \(\uparrow\)bone resorption / \(\downarrow\)bone formation → \(\uparrow\)Ca\(^{2+}\) / phosphate release
    - Initial rapid phase → osteolysis (osteoblast, osteocyte activity)
    - Slow phase → \(\uparrow\)osteoclast activity

**Vitamin D**
- Cholecalciferol (Vit D\(_3\)) produced in **skin** exposed to UV light
- Hydroxylated in liver → 25-hydroxycholecalciferol
- Hydroxylated in proximal nephron → 1,25-dihydroxycholecalciferol (calcitriol)
  - Hydroxylase activity dependent on PTH

By Amanda Diaz
- Actions:
  o GIT: Calcitriol → ↑Ca^{2+} absorption in SI by ↑Calcium binding protein in mucosa
  o Bone: ↑bone reabsorption
  o Kidney: ↑Ca^{2+} and phosphate reabsorption from PCT

Calcitonin
- Secreted by parafollicular cells of thyroid
  o Stimulated by ↑[Ca^{2+}] > 2.4mmol/L, stimulated by gastrin
- Actions:
  o Bone: Direct inhibition of osteoblast activity (↓bone reabsorption)
  o Kidney:
    ▪ ↑Ca^{2+} / phosphate excretion
    ▪ ↓hydroxylase activity → ↓calcitriol synthesis
  o GIT: ↓jejunal absorption of dietary calcium
MAKEUP: Thyroid Hormone Synthesis
General: Thyroid hormones (T₄ & T₃) have effects on all cells
- ↑cellular transcription →↑cellular activity →↑BMR

Synthesis
Iodine: Dietary iodine 500μg /day (min requirement 120-150μg/day)
  - Converted to iodide for absorption
I´ actively transported into follicular cells in thyroid gland
  - Called iodine trapping
  - Concentrates I´ to 30 x blood conc.
  **iodide pump activity ↑with TSH, ↓with perchlorate/SCN⁻ ions**
I´ oxidised to iodine in cell
  - Catalysed by thyroid peroxidase
  **↑activity with TSH**
Iodine rapidly binds 3 position of tyrosine in thyroglobulin molecule
  - Catalysed by iodinase
  **↑activity with TSH**
  - Forms mono-iodotyrosine then di-iodotyrosine
Mono-iodotyrosine + Di-iodotyrosine = Tri-iodothyronine (T₃)
  - Calaysed by peroxidase
  **↑activity with TSH**
  - 7% of thyroid hormone produced
  - 4-5 x more active than T₄
  - >99% protein bound
  - Binds 1° albumin and thyroxine binding pre-albumin (TBPA)
  - t½: 24 hrs
Di-iodotyrosine + Di-iodotyrosine = Thyroxine (T₄)
  - Catalysed by peroxidase
  **↑activity with TSH**
  - 93% of thyroid hormone produced
  - Less active than T₃ → thyroxine is de-iodinated to T₃ for activity
  - >99% protein bound
  - Binds thyroxine binding globulin (TBG) and TBPA
  - t½: 7 days
Thyroid hormones formed within thyroglobulin (70 tyrosine residues)
  - Synthesised in Golgi apparatus
Thyroglobulin stored in follicular colloid
  - Vesicular lysosomal activity breaks down thyroglobulin to release T₃ and T₄, which diffuse out of follicular cell and into circulation via surrounding capillaries
  **↑activity with TSH**

Metabolism of Thyroid Hormones
T₄ de-iodinated to T₃ / rT₃ (inactive compound) 1:1
Both de-iodinated in liver, kidney, skeletal muscle, other tissues to inactive compounds

By Amanda Diaz
Negative Feedback Role

Hypothalamus
  TRH
  +
  Ant. Pituitary
  TSH
  +
  Thyroid
  T₃/T₄
  +
  Target Cells