(a) To define basal metabolic rate and to describe its measurement.

(b) To describe the factors that influence metabolic rate.

Metabolic rate (MR):
- Defined rate of energy output or production in a subject
- BUT since all energy produced ultimately appears as heat (as this form as energy has the highest entropy) → MR can also be defined as energy output of heat production in a subject

Basal metabolic rate (BMR):
- Defined as energy output of heat production in a subject (or metabolic rate) measured under a defined set of standard conditions:
  o (i) Subject in a state of mental and physical rest
  o (ii) Comfortable environment (Eg. room temperature)
  o (iii) 12 hours after a meal
- Expressed as “watts” (1 W = 1 J/sec) → can be indexed to BSA (W/m²)
- BMR for 70 kg adult ♂ = 100 W or 58 Wm² → 70-100 kcal/min (or 2000 kcal/day)

Note: Standard measurement conditions of BMR are of importance → allows:
- (1) Reproducibility of measurement for an individual
- (2) For comparison of MRs between individuals or for an individual at different times (ie. before/after treatment)

Note: BMR is NOT the lowest possible MR → MR during sleep is lower!

Measuring MR and BMR:
- (1) Direct calorimetry
  o Person stays in a special insulated chamber for several days → total heat energy output by the body (as amt heat energy produced per hour) is directly measured
  o Issue → difficult to measure and impractical
- (2) Indirect calorimetry
  o O₂ consumption by the body is measured to indirectly estimate the total heat energy output by the body → this is based on the fact that metabolic rate of the body is proportional to its O₂ utilisation (such that 1 L O₂ used = 4.8 kcal of energy produced)

Note – This is because:
- Vast majority of body’s energy is derived from aerobic metabolism → where ATP is produced via [O] phosphorylation in mitochondria → this process requires O₂ consumption in the final reaction in the ETC:

\[ 2 \text{H} + \frac{1}{2} \text{O}_2 \rightarrow \text{H}_2\text{O} \text{ (irreversible reaction catalysed by cytochrome oxidase)} \]

- Three methods exist:
  - (i) Benedict-Roth spirometer – Closed-circuit breathing system filled with 6L O₂ and held in drum → subject breathes in from drum via inspiratory valve, then exhales back into drum via expiratory value (but CO₂ removed via CO₂ absorber) → drum volume decreases with each breath → this is proportional to the rate of O₂ consumption
  - (ii) Douglas bag technique – Expired air is collected using a mouthpiece with inspiratory/expiratory valves → air is analysed for O₂ (and CO₂) content → O₂ consumption (and CO₂ production) then determined
(iii) Max-Plank respirometer (used when very ↑ rate of O₂ consumption or prolonged measurements required) – Dry gas meter is used to measure the volume of expired gas → a device in the machine then diverts an adjustable volume of expired gas into a breathing bag → gas analysed like Douglas bag technique

Factors that influence MR and BMR:
- (1) Body size (BSA → height and weight)
  - ↓ BSA → ↑ MR
- (2) Fat/LBM body content
  - LBM produces a ↑ MR cf. fat → this explains why MR of ♂ > MR of ♀ (as ♀ have more fat content than LBM)
  - Note – There is no gender difference in MR based on LBM alone
- (3) Age
  - MR is highest in newborn (MR 2x ↑ cf. adult) and childhood/puberty → due to growth needs
  - MR ↓ with age (due to declining growth rate) → in adults, MR ↓ 2% per decade
- (4) Food intake
  - MR ↑ (by 10-15%) 4-6 hrs postprandial due to processing of food → due to “Specific dynamic action” (SDA) of food (esp of hepatic oxidative deamination of proteins from food)
  - MR ↓ due to starvation/malnutrition → due to ↓ tissue metabolism and cell mass
- (5) Temperature
  - (i) Ambient temperature:
    - ↑ ambient temperature (> core body temp.) → ↓ MR due to ↓ heat loss efficiency
    - ↓ ambient temperature (< core body temp.) → ↑ MR due to heat conserving mechanism activated (esp shivering)
  - (ii) Core body temperature → 1°C ↑ = 10% ↑ in MR (likewise for ↓ temp.)
    - Fever → cellular metabolism → ↑ MR
    - Slight ↓ core body temp. → shivering → ↑ MR
    - Severe hypothermia → ↓ cellular metabolism → ↓ MR
- (6) Skeletal muscle activity → MAJOR factor in influencing MR → this is b/c it is the largest organ in the body and its heat energy production is variable (can ↑↑↑ with activity)
  - ↑ skeletal muscle activity (Eg. exercise, shivering) → ↑ MR
  - ↓ skeletal muscle activity (Eg. sleep, sitting, paralysis with GA) → ↓ MR
- (7) Hormones
  - Thyroxine and SNS outflow (Adr/NAd) → ↑ cellular oxidative metabolism and heat production → ↑ MR
  - GH → ↑ MR (10-15%)
  - Testosterone → ↑ MR
- (8) Pregnancy
  - MR ↑ progressively to 20% above normal levels (esp 2nd and 3rd trimesters) → due to foetal metabolism, placenta, ↑ cardiorespiratory demands, metabolism of additional tissue (esp uterine and breast tissue)
- (9) Lactation → ↑ MR due to milk production and secretion
- (10) Emotional state
  - Anxiety/tension → ↑ SNS activity and muscle tensing → ↑ MR
To describe relevant, cellular biochemical pathways and the control of fat, carbohydrate and protein metabolism, including the role of vitamins and trace elements.

**Cellular Energy Metabolism: Overview**

**Metabolism:**
- Defined as sum of chemical processes in the cell → involves (i) anabolism (synthesis of macromolecules) and (ii) catabolism (breakdown of macromolecules)

**Generation of cellular energy:**
- Cellular energy is generated from aerobic oxidation of metabolic fuels (carbohydrates, fats, proteins) derived from digestion of meal or from breakdown of internal stores:
  o These metabolic fuels are broken down into basic substrates (glucose, a.a., FFA, glycerol) → electrons removed (i.e. oxidation) at high potential from these substrates and transferred to a lower potential → release energy in doing so
  o Reduced coenzymes (NAD⁺ and FADH) are intermediate energy storage compounds that aid electron (and energy) transfer from metabolic reactions (glycolysis and TCA cycle) to the electron transport chain (ETC)
  o In the ETC, electrons are transferred through a series of carriers of lower potential → energy released by this is used to form ATP → electrons finally combine with the end electron acceptor (O₂) to form H₂O

With aerobic metabolism → O₂ consumed at the end of ETC; CO₂ produced (via TCA cycle)

- Cellular energy can also be generated anaerobically → via anaerobic glycolysis of glucose only (see below)

**Cellular energy compounds:**
- (1) ATP
  o “Energy currency” of the cell – energy stored in high-energy PO₄³⁻ bond → loss of PO₄³⁻ group via hydrolysis forms ADP → this releases energy required for most cellular reactions
  o Body uses 100 mol ATP daily but at any time the body stores only 25 mmol ATP (sufficient for 1.5 mins of resting metabolic functions only) → thus, ATP needs to be continuously recycled from ADP (i.e. very rapid turnover)
  o ATP is generated by harnessing energy from metabolic fuels via:
    ▪ (i) Substrate phosphorylation (glycolysis, TCA cycle) → 5% only
    ▪ (ii) Oxidative phosphorylation (ETC) → 95%

  Aerobic metabolism (glycolysis, TCA cycle, ETC) → 1 mol glucose produces 38 mol ATP
  Anaerobic metabolism (anaerobic glycolysis) → 1 mol glucose produces only 2 mol ATP

Note – Production of 1 mol ATP by addition of PO₄ to ADP requires ~ 7 kcal

- (2) Creatine phosphate
  o Acts as a back-up energy store in brain and muscle cells → it is formed by transfer of high-energy PO₄³⁻ bond from ATP to creatine

  \[
  \text{ATP + creatine} \leftrightarrow \text{ADP + creatine phosphate}
  \]

  o With ↑ cellular activity → ATP regenerated for cellular use by transfer of PO₄³⁻ from creatine phosphate back to ADP

- (3) Reduced coenzymes (NAD⁺, FADH, NADP)
Intermediate energy storage compounds that transfer electrons to ETC to generate ATP via oxidative phosphorylation
- NADH (and NADPH) donate electrons early in ETC $\rightarrow$ 3 ATP made per NADH (or NADPH) oxidised
- FADH$_2$ donate electrons late in ETC $\rightarrow$ 2 ATP made per FADH$_2$ oxidised

Note: During catabolic reactions $\rightarrow$ large energy fall forms NADH, intermediate energy fall forms FADH$_2$, small energy fall produces ATP

Cellular Energy Metabolism: Catabolic pathways

Overview of catabolic pathways:
- Metabolic fuel substrates (glucose, a.a., FFA, glycerol) undergo 3 catabolic phases:
  - Phase 1 reactions – Partial oxidation of metabolic fuel substrates (via glycolysis, $\beta$-oxidation, oxidative deamination) $\rightarrow$ 33% of total energy of substrates released
  - Phase 2 reactions – Complete oxidation of phase 1 reaction products via TCA cycle $\rightarrow$ remaining 66% of substrates’ total energy released
  - Phase 3 reaction – Oxidative phosphorylation via ETC

Phase 1 reactions:
- (1) $\beta$-oxidation of FFA
  - FFA derived from diet and lipolysis of fat stores (via lipoprotein transport) is partially oxidised in mitochondrial matrix by removal of 2-C moieties (as acetyl CoA) at a time
  - Lipolysis of fat stores is ↑ by GH, GC and Adr (stimulates TAG lipase)

- (2) Glycolysis of glucose
  - Glucose (6-C) derived from diet, GCN (liver) or glycogenolysis (liver, muscle) is partially oxidised via a series of 10 reactions in cytoplasm to 2x pyruvate (3-C):
    - Glucose converted to fructose diphosphate (using 1 ATP) $\rightarrow$ later cleaved into 2x triose phosphate units $\rightarrow$ each triose phosphate unit is converted to produce pyruvate (while forming NADH and 2x ATP)
    - Produces net 2x ATP (4x ATP made via substrate phosphorylation, but 2x consumed by hexokinase) and 2x NADH
  - Pyruvate then enters mitochondria and irreversibly reacts with Coenzyme A to produce $\rightarrow$ (i) Acetyl-CoA (2-C), (ii) CO$_2$, and (iii) NADH + H$^+$
  - Glycolysis is ↑ by insulin (stimulates hexokinase, phosphofructokinase, pyruvate dehydrogenase)
(3) Oxidative deamination of a.a.
  o A.a. derived from breakdown of protein in liver (↑ by glucagon/GC) and muscle (↑ by GC) undergoes oxidative deamination as follows:
    ▪ (i) Transamination – Amino group transferred from C-residue of an a.a. to an α-keto acid to form a new a.a. → this recurs repeatedly until glutamate and aspartate are formed → glutamate dehydrogenase then converts glutamate to NH₃
    ▪ (ii) Urea cycle – NH₃ is converted by liver to urea (see “urea cycle” in liver physiology)
    ▪ (iii) C-residue of a.a. (α-keto acid) is partially oxidised to form intermediates that can (a) enter TCA to produce energy, or (b) be converted to glucose and FFAs

Nb. Muscle transports transaminated a.a. to liver via “glucose-alanine cycle” → b/c muscle cannot produce urea!

Phase 2 reactions (TCA cycle):
  - TCA cycle occurs in mitochondrial matrix under aerobic conditions only → consumes breakdown products of glucose (as acetyl CoA), FFA (as acetyl CoA) and a.a (as TCA intermediates – α-ketoglutarate, oxaloacetate, fumarate, succinyl CoA) to produce → (i) 2x CO₂, (ii) 1x ATP, (iii) 3x NADH + H⁺ / 1x FADH₂ – per acetyl-CoA metabolised
- TCA cycle stimulated by ↓ NADH/NAD⁺ ratio (as NADH inhibits dehydrogenase enzymes of the cycle)

**Phase 3 reactions (ETC):**
- Electrons donated to ETC by NADH/FADH₂ → passed along series of cytochromes (along inside surface of inner mitochondrial membrane) down its energy gradient until they are accepted by O₂ at the end (via cytochrome a)
- At each cytochrome, NADH/FADH₂ are re-oxidised → releases energy to extrude H⁺ across IMM from matrix into inner membrane space → produces a [ ] gradient of H⁺ → also regenerates NAD⁺/FADH for reuse in phase 1 and 2 reactions (see above)
- At 3 separate points in IMM, channels allow H⁺ to flow down its [ ] gradient back into matrix → this releases energy to produce ATP from ADP (via oxidative phosphorylation)
- At end of ETC → O₂ is reduced by H⁺ released by re-oxidation of NADH/FADH₂ along IMM → forms H₂O

- ETC stimulated by ↓ NADH/NAD⁺ ratio (as NADH ↓ oxidation rate of ETC enzymes)

**Gluconeogenesis:**
- Occurs 1°ly in liver but also in kidney → glucose is synthesised from non-CHO precursors derived from anaerobic glycolysis, fat and protein catabolism – (i) Lactate (muscle and RBC), (ii) Glycerol (fat), (iii) Glucogenic a.a. (muscle) → released into blood
- Cytoplasmic process → except conversion of pyruvate to oxaloacetate (mitochondria)
- Gluconeogenesis \( \uparrow \) with glucagon, Adr, and GH (stimulates fructose diphosphatase and pyruvate carboxylase); \( \downarrow \) with insulin

**Ketone body metabolism:**
- Ketone bodies (acetoacetate, \( \beta \)-OH-butyrate) are formed in liver only when there is extra acetyl CoA formed by \( \beta \)-oxidation of excess FFA (2° to \( \uparrow \) lipolysis by GH, GC, Adr)
  
  - Ketone bodies are released from liver \( \rightarrow \) utilised peripherally by skeletal muscle, heart, kidney (and brain/nervous tissue during starvation)

**Cellular Energy Metabolism: Anabolic pathways**

**Glycogen synthesis:**
- Glycogen stores \( \rightarrow \) branched polymer of glucose (\( \alpha \)1,4 and \( \alpha \)1,6 links) \( \rightarrow \) (i) Liver (100 g; \( \frac{1}{2} \) day supply), (ii) Muscle (400 g), (iii) Brain (minimal; 4 mins supply)
  - Glycogen synthesis (glycogenesis) \( \rightarrow \) when excess glucose available:
    - \( \uparrow \) BGL \( \rightarrow \) \( \uparrow \) insulin level \( \rightarrow \) (i) promotes glucose entry in muscle (Nb. glucose entry in liver is insulin-independent \( \rightarrow \) dependent on [ ] gradient), and (ii) stimulates glycogen synthetase \( \rightarrow \) builds glycogen store from glucose
  - Glycogen breakdown (glycogenolysis) \( \rightarrow \) during glucose deficiency:
    - \( \downarrow \) BGL \( \rightarrow \) \( \uparrow \) glucagon/Adr \( \rightarrow \) stimulate glycogen phosphorylase \( \rightarrow \) break down glycogen to G6P \( \rightarrow \) liver has enzyme to convert this into glucose and release it into blood (but muscle/brain lack this enzyme and must use G6P locally only)

**Fat synthesis:**
- FFA synthesis occurs mainly in liver (and adipose tissue) in the presence of excess glucose \( \rightarrow \) stimulates \( \uparrow \) insulin which causes:
  - (i) \( \uparrow \) glycolysis \( \rightarrow \) \( \uparrow \) formation of acetyl CoA \( \rightarrow \) acetyl CoA diffuses out of mitochondria \( \rightarrow \) \( \uparrow \) conversion to malonyl CoA (via acetyl-CoA carboxylase) in cytoplasm \( \rightarrow \) finally to FA
  - (ii) \( \uparrow \) TCA cycle \( \rightarrow \) \( \uparrow \) formation of citrate \( \rightarrow \) diffuses out of mitochondria \( \rightarrow \) splits into acetyl CoA and oxaloacetate in cytoplasm \( \rightarrow \) acetyl CoA converted to malonyl CoA then FA (as above)

\[\text{Nb. Liver cannot utilise ketone bodies as they lack oxo-acid CoA transferase} \rightarrow \text{cannot transfers CoA from succinyl CoA to AcAc} \rightarrow \text{cannot cleave AcAc into 2x acetyl CoA}\]
- Nb. NADPH from pentose phosphate shunt is required for FFA synthesis

- FFA can be used to:
  - (i) Store excess chemical energy of foods as TAGs → in liver and adipocyte
    - Lipogenesis (TAG synthesis) → within cytoplasm and ER → 3x Acyl CoA + glycerol phosphate → TAG
    - Lipolysis (TAG breakdown) → forms FFA + glycerol → both released systemically (except in liver where glycerol is converted to glycerol phosphate and utilised locally)
  - (ii) Form phospholipid

Protein synthesis
- Protein (such as muscle protein, plasma proteins, CT, enzymes) is synthesised from a.a.
  → note that synthesis is limited by availability of essential a.a.’s (which body cannot synthesise and must extract from diet)
- Protein can be catabolised to a.a. → a.a. used for (i) gluconeogenesis, (ii) tissue energy production via TCA cycle (during fasting), or (iii) conversion to FFA

Factors Influencing Cellular Energy Metabolism:
- (1) Cellular energy demands
  - ↓ IC [ATP] → opposite happens
- (2) Hormonal regulation (Eg. insulin, glucagon, GC, GH, Adr)
  - Acute control → rapid modification of enzyme activity
  - Chronic control → control expression (and quantity) of enzymes present
Aside: Nutrition and metabolic energy of food.

Nutrition: Types of nutrients

**Carbohydrates:**
- Provide 50% of total caloric intake (1200-2000 kcal/day) → avg intake of 300-500 g/day (with caloric value 4 kcal/g)
- Derived from → starch (esp plant foods – polymer of glucose), sucrose (table sugar – glucose-fructose), lactose (milk – glucose-galactose), and glycogen (meat)

**Fats:**
- Provide 40% of total caloric intake (1200 kcal/day) → avg intake of 140 g/day (with caloric value of 9 kcal/g → very ↑ energy-concentrated nutrient)
- Derived from 1°ly TAGs but also cholesterol/phospholipids (plants and animals)

**Proteins:**
- Provide 10% of total caloric intake (300-400 kcal/day) → avg intake of at least 1 g/kg/day (with caloric value of 4 kcal/g)
- Derived from plant/animal proteins → MUST include essential a.a.’s (isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophane) → as body CANNOT synthesise these via transamination

Note – Body catabolises 200-400 g/day of protein, but a.a. formed is reused → thus, a minimum intake of 20-40 g/day is required for protein balance (although > 1 g/kg/day recommended)

**Vitamins:**
- Organic compounds that cannot be synthesised by the body and must be derived from diet → they are vital to enzyme systems and metabolic pathways in body
- Two types:
  - (i) Fat-soluble → stored in large amounts in liver
    - Vit A – Derived from β-carotene (fruits/veg) → retinal pigment (rhodopsin) and epithelial tissue repair
    - Vit D – Ca²⁺ homeostasis, bone formation/deposition
    - Vit E – Mixture of tocophers → anti-oxidant
    - Vit K – Coagulation (CF II, VII, IX, X, C/S)
  - (ii) Water-soluble → freely circulate in body (not stored in any large amount) and excreted in urine
    - Vit C (ascorbic acid) – Prevents scurvy (haemorrhage of skin/internal organs)
    - Vit B1 (thiamine) – Required in pyruvate dehydrogenase → deficiency causes peripheral neuropathy and CCF
    - Vit B2 (Riboflavin) – Required for FADH₂ synthesis for oxidative phosphorylation
    - Vit B3 (Nicotinic acid) – Required for NADH/NADPH synthesis for oxidative phosphorylation → deficiency causes dermatitis and diarrhea
    - Vit B12 (cyanocobalamin) – Contains Co in porphyrin ring → required for nucleic acid synthesis, RBC maturation, and myelin integrity → deficiency causes peripheral neuropathy/spinal degeneration and anaemia
    - Folic acid – Me group transfer and RBC maturation → deficiency causes anaemia and neural tube defects

**Minerals:**
- Inorganic trace elements (Eg. Zn, Fe, Cu, Mn, Co, Se, I, Cr, Mb) that cannot be synthesised by the body and must be derived from diet → they are vital to enzyme systems and metabolic pathways in body
Metabolic energy of food:

Overview:
- Chemical energy of food is transformed to heat, even in the absence of external work → BUT when external work is done, up to 20% of energy is converted to it (and > 80% of energy is still transformed to heat)

Measuring chemical energy of food:
- Calorie (cal) → amount of energy needed to raise temperature of 1 g of H₂O by 1°C (from 15 to 16°C) → used as the standard unit of heat energy
- Kilocalorie (kcal or Cal) → amount of energy needed to raise temperature of 1 kg of H₂O by 1°C (from 15 to 16°C) → unit of energy used for metabolic studies

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>CVF</th>
<th>CEEO</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>4 kcal/g</td>
<td>5 kcal/L O₂</td>
<td>1.0</td>
</tr>
<tr>
<td>Protein</td>
<td>4 kcal/g</td>
<td>4.6 kcal/L O₂</td>
<td>0.8</td>
</tr>
<tr>
<td>Fat</td>
<td>9 kcal/g</td>
<td>4.7 kcal/L O₂</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Important to note → 1 kcal or Cal = 1000 cal = 4.18 kJ

Note – RQ varies with non-metabolic factors also → Eg. RQ ↑↑ with exercise and metabolic acidosis (due to ↑ CO₂ expired with hyperventilation); opposite occurs with metabolic alkalosis and sedentary activity
(d) To explain the physiological principles of parental nutrition.

Overview of parental nutrition:
- Parental nutrition is the delivery of nutrients into venous circulation (peripherally or centrally) instead of the enteral route → it can be used to supplement nutrient delivery via enteral route, or supplement nutrient delivery in its entirety (total parental nutrition)
- It is prepared by sterile technique → typically a 3L bag of hyperosmolar solution (containing glucose, amino acids, lipids, H₂O, electrolytes, vitamins and trace elements)
- It can only be administered by CVC due to its ↑ tonicity (Nb. issues with irritation and thrombosis if given via PIVC) → infused over 24 hrs
- It also requires multidisciplinary team involvement

Indications for parental nutrition:
- Indicated for those unable to ingest or digest nutrients or to absorb them from GI tract for a prolonged period of time (> 3-4 days) → includes those who have:
  o (1) A failed trial of enteral feeding
  o (2) Contraindications to enteral nutrition:
    ▪ GI obstruction
    ▪ Upper GI strictures and fistulae (Eg. enterocutaneous fistulae)
    ▪ Severe pancreatitis
    ▪ Prolonged ileus (Eg. major abdominal surgery where feeding not anticipated for days, paralytic ileus)
    ▪ Inflammatory conditions (Eg. IBD or mucositis due to chemotherapy)
    ▪ Short gut syndromes (Eg. major SB resection)

Daily nutritional requirements for parental nutrition:

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>30-40 mL/kg/day</td>
</tr>
<tr>
<td>Energy</td>
<td>25-30 kcal/kg/day (can ↑ up to 1.5-1.75x with disease/stress)</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>0.5 g/kg/day (can ↑ to 1-1.5 g/kg/day with disease/stress)</td>
</tr>
<tr>
<td>Glucose</td>
<td>3 g/kg/day</td>
</tr>
<tr>
<td>Lipid</td>
<td>2 g/kg/day</td>
</tr>
<tr>
<td>Na⁺</td>
<td>1-2 mmol/kg/day</td>
</tr>
<tr>
<td>K⁺</td>
<td>0.7-1 mmol/kg/day</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>0.1 mmol/kg/day</td>
</tr>
</tbody>
</table>

BUT these vary according to:
- (1) Physiological factors:
  o Age, gender, body size
  o Pregnancy
  o Activity level
  o Hydration status
- (2) Pathological factors
  o Burns and sepsis → ↑ protein and caloric intake
  o Renal failure → ↓ volume, protein and electrolyte (esp K⁺) content
  o CCF → fluid reduction
  o Hepatic failure → ↓ a.a/protein content to prevent encephalopathy
  o Respiratory failure → ↓ glucose to minimise CO₂ production

Components of parental nutrition:
- (1) Energy source → glucose:l lipid mixture (60:40 or 50:50)
  o (a) Glucose (as 50% dextrose)
    ▪ Used as an energy substrate → provides 50% of daily caloric needs
- Glucose has ↓ energy density → 3.4 kcal/g only (cf. 4 kcal/g for carbohydrates) → 50% dextrose needs to be given (1 L = 940 kcal) → BUT this is hypertonic (1900 mosm/L) and requires delivery via CVC
- Insulin can be given to aid glucose utilisation (esp in stressed patients)
- Need to avoid excess glucose delivery → risk of ↑ BGL, lipogenesis (liver disease), ↑ MR and ↑ CO₂ production (delayed ventilatory wean)
  o (b) Lipid (as 10% or 20% intralipid)
    - Used as (i) an energy substrate (provides 30-40% daily caloric needs), and (ii) provision of essential FAs (vital for cell membranes and PG synthesis)
    - ↑ energy density cf. glucose → 1.1 kcal/mL (10%) and 2 kcal/mL (20%) → thus 1000 kcal can be achieved by 500 mL of 20% or 1L of 10%
    - Can be infused separately (i.e. not mixed with glucose/a.a. solution) → can be given 1x/week BUT usually given daily to aid caloric delivery in the smallest volume of solution
- (2) Nitrogen-source (as synthammin 17)
  o Used for (i) tissue protein synthesis (Eg. enzymes) and (ii) caloric needs
  o Includes > 50% essential a.a.’s (isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophane) and > 25% branched chain a.a
  o Nb. A.a. are all L-isomers (as the body cannot use D-isomers)
- (3) H₂O → to maintain body H₂O balance and replace losses (Eg. dehydration, bleeding)
- (4) Electrolytes (Na⁺/K⁺/Cl⁻/PO₄³⁻/Mg²⁺/Ca²⁺) → to maintain and replace losses
- (5) Vitamin/trace elements → vital to enzyme systems and metabolic pathways in body
  o Vitamin solutions – both H₂O and fat-soluble vitamins (esp folic, thiamine, vitamin K)
  o Trace elements (Zn, Fe, Cu, Mn, Co, Se, I, Cr, Mb)

Monitoring of parental nutrition:
- Needed to assess for (i) progress of nutritional state and (ii) complications of therapy
  - Involves:
    o (i) Clinical r/v (Eg. fluid balance, weight, nutritional assessment, infections)
    o (ii) Frequent ward glucose testing (until BGL stabilises)
    o (iii) Investigations → daily EUC, CMP, BGL; weekly FBC, LFT (incl albumin), Coags, Lipid studies, and plasma/urine osmolality

Complications of parental nutrition:
- (1) Catheter-related (MOST common) → PTX, chylothorax, embolism (air/thrombus), infection, Etc.
- (2) Fluid/electrolyte disturbances
  o Fluid overload or hyperosmolar dehydration
  o Electrolyte disturbances
  o Normal AG metabolic acidosis (due to ↑ Cl⁻ content)
- (3) Metabolic disturbances
  o Hyperglycaemia (initially) → delay in ↑ endogenous insulin (thus supplemental insulin required)
  o Rebound hypoglycaemia (with abrupt cessation of TPN) → due to ↑ levels of endogenous insulin
  o Metabolic bone disease
- (4) Others:
  o Immune suppression (due to fat component)
  o Liver disease → initially deranged LFTs → later fatty liver/steatohepatitis
  o ↑ PaCO₂ (due to excessive glucose metabolism)
To describe the consequences of anaerobic metabolism.

Anaerobic metabolism:
- Anaerobic metabolism occurs when there is a cellular environment that is either:
  - (i) Lacking mitochondria (Eg. RBC) → this is b/c mitochondria is required for aerobic metabolism of metabolic substrates (Ie. via TCA cycle, ETC, β-oxidation)
  - (ii) Hypoxic (↓ PO2) → this is b/c aerobic metabolism requires O₂

Note – In the absence of O₂:
- ETC cannot function as it requires O₂ as a terminal acceptor of electrons → causes accumulation of NADH/FADH₂ and loss of oxidative phosphorylation
- TCA cycle cannot function because → pyruvate is no longer converted to acetyl CoA (↑ NADH inhibits pyruvate dehydrogenase), and there is lack of NAD⁺/FADH (due to ↑ NADH/FADH₂ levels 2° to defunct ETC)
- β-oxidation and KB metabolism cannot function because → lack of NAD⁺/FADH and their products cannot be fed into TCA cycle/ETC

- During anaerobic conditions, glycolysis is the ONLY catabolic pathway that can occur:
  - (i) Glucose (6-C) is partially oxidised via a series of 10 cytoplasmic reactions to 2x pyruvate (3-C) → this also produces net 2x ATP (4x ATP made via substrate phosphorylation, but 2x consumed by hexokinase) and 2x NADH + H⁺

  ![Glycolysis Diagram]

  o (ii) Under anaerobic conditions, pyruvate is instead reduced to lactate within the cytoplasm → this requires LDH (lactate dehydrogenase) and NAD (as a reducing agent)

  \[
  \text{Pyruvate} + \text{NAD} + \text{H}^+ \rightleftharpoons \text{Lactate} + \text{NAD}^+
  \]

catalysed by Lactate Dehydrogenase (LDH)

  o (iii) This is vital for anaerobic glycolysis to continue b/c this allows NADH to be reoxidised to regenerate NAD⁺ for reuse in glycolysis

Note: Under aerobic conditions, pyruvate is instead oxidised to acetyl CoA → fed into TCA cycle (producing CO₂ and NADH/ATP) → then into ETC (consuming O₂ to produces H₂O and ATP)

Consequences of anaerobic metabolism:
- (1) ↓ ATP production → total 2 ATP produced per glucose via substrate phosphorylation alone (cf. aerobic metabolism where total 38 ATP produced per glucose via both substrate and oxidative phosphorylation)
- (2) Unable to metabolise other metabolic substrates (Ie. FFA, KB, a.a) → glycolysis is the only catabolic pathway available
- (3) Production of lactate (see below)

Anaerobic metabolism: Lactate
- Lactate is the conjugate base of lactic acid (an organic 3-C acid)
- It is produced by anaerobic metabolism of pyruvate (see above reaction) either:
  o (i) Physiologically → in RBC (no mitochondria), renal medulla (↓ PO₂), cornea/lens (↓ PO₂) → hence, normal plasma [lactate] is 0.5-2 mM (and NOT zero!)
  o (ii) Pathologically → reduced tissue perfusion and/or O₂ delivery (Eg. shock, hypoxaemia) → thus, plasma [lactate] ↑↑↑ (> 2 mM)

Note: Plasma [lactate] is an indicator of anaerobic metabolism → so ↑ [ ] = ↑ anaerobic metabolism

- Plasma [lactate] is 0.5 – 2 mM (and NOT zero) due to physiological production → it can be measured clinically as an indicator of anaerobic metabolism (Ie. ↑ anaerobic metabolism due to pathological situations lead to ↑ [lactate])
- Fate of lactate:
  o (1) Persistent anaerobic metabolism (Ie. ongoing hypoxia) causes an accumulation of cellular lactate → this diffuses out of the cell into plasma along its [ ] gradient → lactate can then be: (a) Used as a fuel source by the heart and brain
    - (b) Transported to the liver where it is:
      • (i) Converted back to glucose via gluconeogenesis (requires 6x ATP), which is then transported back peripherally for use → “Cori cycle”
      • (ii) Converted to pyruvate intermediate → utilised locally in TCA cycle for ATP production via oxidative phosphorylation

- (2) Resolution of hypoxia (Ie. tissue O₂ tension restored) → intracellular lactate can be oxidised back to pyruvate for use in local tissue aerobic metabolism (Ie. fed into TCA cycle)
To describe the physiological consequences of starvation.

**Body energy substrate reserves and utilisation:**

- **Body energy substrate reserves:**
  - Glycogen stores: (i) Liver (100 g; ½ day supply), (ii) Muscle (400 g), (iii) Brain (minimal; 4 mins supply) → source of glucose
  - Fat stores (as TAG) → liver and adipose tissue → source of FFA and glycerol
  - Protein stores → muscle protein, plasma proteins, CT, enzymes → source of a.a.

- **Body energy substrate utilisation:**
  - Brain/nervous tissue – 1°ly uses glucose for energy, but uses KBs with fasting
  - Cardiac muscle – Use FFA, lactate and KB for energy
  - RBC – 1°ly uses glucose for energy
  - Skeletal muscle
    - Uses FFA and ketone bodies for energy
    - Glucose can be used for energy (esp with hyperglycaemia or anaerobic conditions (Eg. exercise)) or glycogen storage
  - Adipose tissue – Uptake of glucose, glycerol and FFA → forms TAG for storage (lipogenesis); also breaks TAG into FFA/glycerol (lipolysis)
  - Liver → integral role in starvation
    - Control BSL by controlling glycogen stores and gluconeogenesis
    - Takes up all metabolic fuel substrates → can interconvert them (Eg. gluconeogenesis, ketogenesis)
    - Vital source of circulating metabolic fuel substrates

**Body fluid reserves and utilisation:**

- **Body fluid reserves:**
  - TBW 60% of weight (~ 42 L in 70 kg adult) → 1°ly intracellular (Eg. adipose, muscle, liver, lungs, GIT, interstitium, etc.)
  - Metabolic H₂O (350 mL/day)

- **Body fluid utilisation:**
  - IWL from skin/lungs (900 mL), faecal loss (100 mL) and sweat loss (50 mL)
  - Renal loss can be varied

**Physiological effects of early fasting (< 24 hrs):**

<table>
<thead>
<tr>
<th>Nature of fasting</th>
<th>Fasting 6-12 hrs is a daily occurrence (Ie. sleeping) → generally well-tolerated due to adequate fuel/fluid body reserves → a/w mild hunger/thirst and minimal lethargy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloric losses</td>
<td>Up to 25-30 kcal/kg in 24 hrs (~ 1 kcal/kg/hr)</td>
</tr>
<tr>
<td>Effect on energy substrate source</td>
<td>Initially → glucose main energy substrate → derived from: - Food intake prior to fast → continued absorption of glucose from food remaining in the GI tract - Glycogenolysis → glycogen stores rapidly exhausted within 12-24 hrs:  - Liver stores → glucose released systemically (important)  - Peripheral stores (muscle, brain) → glucose used locally only (cannot release it systemically due to lack of glucose-6-phosphatase) - Gluconeogenesis in liver (and kidneys) → very minor role Later → other fuel sources become main energy substrates: - FFA → released from adipose tissue by lipolysis → next major energy source - Ketone bodies (acetoacetate, β-OH butyrate) → small amounts produced by liver from FFA derived from lipolysis → minor energy source</td>
</tr>
<tr>
<td>Effect on energy substrate utilisation</td>
<td>- Brain/nervous tissue maintains glucose utilisation for energy - ↑ utilisation of FFAs and KBs by other tissues for energy (Eg. heart, kidney, skeletal muscle, adipose, etc.) → preserves glucose use for brain/nerve tissue - ↓ glucose uptake and utilisation by insulin-dependent tissues (muscle, adipose)</td>
</tr>
<tr>
<td>Fluid losses</td>
<td>Up to 25-35 mL/kg in 24 hrs (~ 1-1.5 mL/kg/hr)</td>
</tr>
<tr>
<td>Effect on water balance</td>
<td>- Mobilisation of body fluid reserves - Ongoing losses as part of IWL, and in faeces/sweat</td>
</tr>
</tbody>
</table>
Physiological effects of sustained fasting (> 24 hrs):

<table>
<thead>
<tr>
<th>Nature of fasting</th>
<th>Rare occurrence → poorly tolerated due to significant mobilisation of fuel/fluid reserves needed to compensate for lack of fluid/caloric intake → a/w significant hunger, thirst and lethargy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloric losses</td>
<td>25-30 kcal/kg per day</td>
</tr>
<tr>
<td>Effect on energy</td>
<td>Gluconeogenesis is main source of glucose as glycogen stores depleted → synthesises glucose using glucogenic a.a. (esp alanine; from skeletal muscle protein), glycerol (from TAGs in adipose and liver stores), and pyruvate/lactate (from RBC, skeletal muscle)</td>
</tr>
<tr>
<td>substrate source</td>
<td></td>
</tr>
<tr>
<td>Effect on energy</td>
<td>Brain/nervous tissue → ketone bodies replace glucose as main fuel source</td>
</tr>
<tr>
<td>substrate utilisation</td>
<td>Other tissues → heavily reliant on FFA/KB as fuel sources</td>
</tr>
<tr>
<td>Fluid losses</td>
<td>25-35 mL/kg per day</td>
</tr>
<tr>
<td>Effect on water</td>
<td>Fluid reservoirs depleted</td>
</tr>
<tr>
<td>balance</td>
<td>Ongoing IWL, losses in faeces and sweat</td>
</tr>
<tr>
<td></td>
<td>Obligatory urine loss (430 mL/day)</td>
</tr>
<tr>
<td>Hormones</td>
<td>↓↓↓ insulin levels</td>
</tr>
<tr>
<td></td>
<td>↑↑↑ ADH and Aldosterone levels</td>
</tr>
<tr>
<td></td>
<td>↑ glucagon levels → causes:</td>
</tr>
<tr>
<td></td>
<td>- Liver: ↑ glycoegenolysis and GCN (with glucose release), ↑ ketogenesis</td>
</tr>
<tr>
<td></td>
<td>- Muscle and adipose: Minimal effects</td>
</tr>
<tr>
<td></td>
<td>- Nb. Levels peak at day 4 then ↓ to prefasting levels at day 10 → a/w ↓ gluconeogenesis (esp using a.a.’s) → protein-sparing mechanism</td>
</tr>
<tr>
<td></td>
<td>↑ cortisol levels → causes:</td>
</tr>
<tr>
<td></td>
<td>- Liver: ↑ glycoegenolysis and GCN with glucose release</td>
</tr>
<tr>
<td></td>
<td>- Muscle: ↑ protein catabolism (and a.a. release), ↓ glucose uptake</td>
</tr>
<tr>
<td></td>
<td>- Adipose: ↑ lipolysis (and FFA/glycerol release)</td>
</tr>
<tr>
<td></td>
<td>↑ Adr levels → causes:</td>
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<tr>
<td></td>
<td>- Liver: ↑ glycoegenolysis and GCN (with glucose release), ↑ ketogenesis</td>
</tr>
<tr>
<td></td>
<td>- Muscle: ↑ FFA utilisation, ↑ glycoegenolysis, ↓ glucose uptake</td>
</tr>
<tr>
<td></td>
<td>- Adipose: ↑ lipolysis (and FFA/glycerol release), ↓ glucose uptake</td>
</tr>
<tr>
<td></td>
<td>↑ GH levels over first 24-48 hrs → then ↓</td>
</tr>
</tbody>
</table>
To describe the metabolic consequences of sepsis, burns and trauma.

Metabolic consequences of sepsis, burns and trauma involve “stress” response which is characterised by:

- (1) General hypercatabolic state involves breakdown of:
  - Carbohydrates → ↑ BGL due to ↑ hepatic glycogenolysis and gluconeogenesis
  - Fat → ↑ lipolysis of TAG stores, ↑ FFA utilisation peripherally, ↑ ketogenesis
  - Protein → ↑ skeletal muscle breakdown (lose LBM), net –ve N-balance, conversion of a.a. to glucose in liver

- (2) Hypermetabolic state (↑ BMR and MR) due to ↑ catabolism

- (3) Pyrexia → due to pyrogen- or cytokine-induced rise in core body temperature (via central hypothalamic effect)

- (4) ↑ resting energy expenditure (and ↑ energy intake demands) due to:
  - (i) hypermetabolic state
  - (ii) ↑ thermogenesis (a/w pyrexia and loss of body heat (le. 2° to wounds))

- (5) “Stress” hormonal response promotes hypercatabolic response
  - ↑ plasma levels of glucagon, catecholamine, cortisol → hypercatabolic response
  - ↑ plasma levels of insulin BUT a/w tissue insulin resistance
  - ↓ plasma GH levels

- (6) Tissue hypoxia → due to arterial hypoxaemia, tissue hypoperfusion, autoregulatory dysfunction and DIC
  - Anaerobic metabolism occurs due to insufficient tissue O₂ delivery → ↑ diversion of pyruvate substrate from glycolysis to form lactic acid → inefficient production of energy (2 ATP with substrate phosphorylation vs 38 ATP with oxidative phosphorylation)
  - Hepatic hypoperfusion means lactic acid cannot be processed in liver via Cori cycle back into glucose

- (7) Metabolic acidosis
  - ↓ pH due to depletion of HCO₃⁻ and ↑ H⁺ production from tissue metabolic acid production (Eg. Lactic acid)
  - Compensated by buffering (acute), respiratory compensation (hrs-days), renal correction (days-weeks)