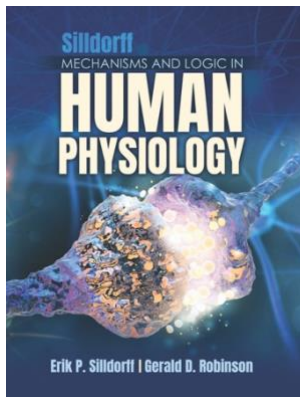


Chapter 4 Instructor Guide

The Energetic Basis of Physiology and General Metabolism

Mechanisms and Logic in Human Physiology | Silldorff & Robinson | Kendall Hunt

Logic-first companion to Chapter 4. Left column carries the instructor narrative in the author's voice; right column carries causal chains, common student errors, and prediction prompts. Emphasis throughout is the metabolic gist: inputs, outputs, and when each pathway is favored and why. Detail is supplied only where the logic needs it.



Companion to **Mechanisms and Logic in Human Physiology** by Erik P. Silldorff and Gerald D. Robinson (Kendall Hunt Publishing). The half-year and full-year web subscriptions and the print version are available at <https://he.kendallhunt.com/product/mechanisms-and-logic-human-physiology-2>. For those teaching A&P more classically in a 2-semester sequence, the book is also packaged with Visible Body to support the anatomical portions of those courses (365-day subscriptions): <https://he.kendallhunt.com/product/mechanisms-and-logic-human-anatomy-and-physiology-visible-body-1>.

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Section 1: Why Start With Energetics — The Logical Framework of the Whole Chapter

Instructor Narrative

The move: Establish two points before any pathway: physiology operates within the limits set by physical law, and metabolism is the transfer of chemical bond energy within those limits. The pathways that follow are specific cases of this energy transfer.

Energetics, not pathways, is the point

Open by telling students we are not here to memorize pathways. We are watching energy get transferred, and physical law sets the rules for what is allowed. Metabolism, all of intermediary metabolism, is the sum of the chemical reactions in our forty trillion cells, and it only goes in two directions.

Structured Outline / Causal Chain

Derivation Chain: Catabolism fuels anabolism

Physical law sets bounds → metabolism is bond energy transfer within those bounds → two directions only: catabolism (release) and anabolism (build/use) → some of the released energy is captured → funds the endergonic work of anabolism, transport, and contraction

Key Distinction: Catabolism vs. Anabolism

- Catabolism = degrade, releases bond energy.
- Anabolism = assemble, requires energy input.

Catabolism breaks nutrient molecules down and releases the bond energy. Anabolism builds biopolymers (proteins, carbohydrates, and nucleic acids) and non-polymeric biomolecules (lipids) and requires energy input. That is the entire map in one sentence.

Use the construction analogy to introduce energy coupling

The construction analogy makes the point efficiently. Putting up a building takes energy input and raises the stored energy of position. Knocking it down releases that energy, but normally you do not harness it. What cells do differently is to break down nutrient molecules and capture part of the released energy to do work, like lowering bricks in a basket and using the descent to lift workers up the other side. That capture, catabolism funding anabolism, is the central relationship of the chapter.

Set the energy expectation early

So set the expectation early. We will spend real time on energetics first, because once students understand spontaneity, coupling, and what ATP is for, the actual pathways stop looking like a list of names and start looking like the obvious solution to an energy problem.

Common Errors

- **Error:** Treating metabolism as a list of pathway names to memorize rather than a single energy-transfer story.
- **Error:** Assuming demolition always wastes the released energy. The cellular version captures part of it.

Prediction Prompt

***Predict:** If catabolism releases energy and anabolism requires it, what has to be true about the timing and location of the two for a cell to build anything?*

Section 2: The First and Second Laws — Conservation and the Entropy Tax

Instructor Narrative

***The move:** Cover only what physiology needs from thermodynamics: energy is conserved (so all of it must be accounted for), and every transfer releases some heat (so efficiency is generally low). The quantitative treatment is not required at this level.*

The first law: energy is only transferred

The first law applies here as follows: in an open system like a person, energy transfers cause equal and opposite changes in the environment. Nothing is lost; it is redistributed. When we oxidize a nutrient, all of the original bond energy is partitioned among the bonds of ATP, the bonds in the carbon dioxide and water produced, and the heat released. There is no net loss or gain, only redistribution. The aim is for students to be able to track the energy through every transfer and account for all of it.

Structured Outline / Causal Chain

First Law (Conservation)

Nutrient oxidized → bond energy redistributed into ATP bonds + CO₂/H₂O bonds + heat. Total energy unchanged

Derivation Chain: Second Law (Entropy Tax)

Every transfer is inefficient → heat released → environmental entropy rises. Meanwhile the cell builds order (its entropy falls), but the environment's entropy rises more → universe net entropy increases

Key Distinction: Local Order vs. Universal Entropy

- Local order is allowed; it is possible due to the larger disorder increase outside.

The second law is what actually constrains us

The second law is the one that sets the real constraint. Useful energy degrades toward heat, the less useful form, and natural processes have a preferred direction. Entropy is the measure of that inevitable heat gain by the surroundings. The point students miss is this: a cell building ordered structure is lowering its own entropy, but because every transfer is inefficient and releases heat, the entropy of the environment rises more than the cell's falls. Net entropy of the universe increases with every transfer. Order inside a cell is therefore always accompanied by a larger increase in disorder outside it.

Mention the other laws and move on

The zeroth and third laws are worth a brief mention and no more. The zeroth law states that two systems in thermal equilibrium are at the same temperature. The third law states that entropy reaches zero at absolute zero, where molecular motion stops. These provide useful context but are not central to the physiology in this chapter.

Common Errors

- **Error:** Claiming life violates the second law by creating order. It does not; the books balance once you include the environment.
- **Error:** Thinking heat release is a flaw in the machinery rather than an unavoidable tax on every energy transfer.

Prediction Prompt

Predict: A cell assembles a large, highly ordered protein. State the sign of the cell's entropy change and the sign of the universe's entropy change, and why they differ.

Section 3: Gibbs Free Energy — $\Delta G = \Delta H - T\Delta S$ and What Spontaneous Really Means

Instructor Narrative

The move: Define ΔG as the energy a reaction makes available to do work, determined by the net of the bond-energy (enthalpy) change and the entropy change. Spontaneous means energy is released, not that the reaction is fast.

Delta G compares reactants to products

The change in Gibbs free energy compares reactants to products and combines two separate terms. The first is the change in bond energy, the enthalpy, which can go in either direction: products may hold more or less bond energy than reactants. The second is the entropy change, multiplied by temperature, which reflects whether the system became more or less ordered. The free energy change is the net of those two terms, and it can be read as the energy a reaction makes available to do work.

Negative delta G describes spontaneous reactions

Structured Outline / Causal Chain

The Equation, in Words

$\Delta G = \Delta H - T\Delta S$, in words: available energy = bond-energy change (total energy change) minus the entropy term $T\Delta S$ (energy unavailable for work)

Reading the Sign

- **- ΔG :** ΔG negative (exergonic): energy released, reaction spontaneous, runs downhill.
- **+ ΔG :** ΔG positive (endergonic): energy stored in products, must be supplied.

Key Distinction: Spontaneous vs. Fast

- **Spontaneous:** Tells you direction and that energy is released.

Products are at lower free energy than reactants, energy is given off, and the reaction is called spontaneous. The word reliably confuses students, so emphasize it: spontaneous specifies the direction energy flows, downhill, and that the reaction will release energy. It says nothing about speed. Many spontaneous reactions proceed extremely slowly on their own, which is the reason enzymes are needed. Positive delta G is the reverse: products hold more energy than reactants, so energy must be supplied for the reaction to proceed at all.

Chemical potential is the same idea renamed

Chemical potential is the same concept applied to gradients. It is free energy based mostly on concentration differences, with pressure, electrical, and other components included. A gradient is stored free energy, and this connects to later material: the sodium gradient driving secondary active transport, the pressure gradient driving blood flow, the proton gradient driving ATP synthesis.

- **Fast:** A separate question, set by activation energy and catalysis.

Bridge Forward

Chemical potential = free energy stored as a gradient (concentration, pressure, charge) → reused for transport, blood flow, and ATP synthesis later

Common Errors

- **Error:** Equating spontaneous with rapid. A $-\Delta G$ reaction can be effectively frozen without an enzyme.
- **Error:** Forgetting the $T\Delta S$ term, so entropy-driven processes look impossible by enthalpy alone.

Prediction Prompt

Predict: Ice melts only when warm. Using $\Delta G = \Delta H - T\Delta S$, explain why temperature decides the sign of ΔG here.

Section 4: Coupling Exergonic to Endergonic — The Core Move in Metabolism

Instructor Narrative

***The move:** This is the central idea of the chapter and warrants the most time. An exergonic (downhill) reaction can drive an endergonic (uphill) one when the two are linked, and that linkage is the basis of metabolism.*

Coupling is how free energy is put to work

Once students have negative and positive delta G, introduce coupling. In biological systems, energy is rarely allowed to dissipate entirely as heat. Instead, an exergonic, downhill reaction is harnessed to drive an endergonic, uphill one. The standard example comes from glycolysis: several of the enzymatic steps release enough free energy to attach a phosphate to ADP and make ATP. This amounts to exchanging bond energies, spending the energy of one reaction to build the higher-energy bond of another.

Coupling organizes catabolism and anabolism

This relationship organizes the chapter. Catabolism is a sequence of mostly downhill steps, and at the large free-energy drops the release is coupled to

Structured Outline / Causal Chain

Causal Chain: Exergonic-endergonic linkage

An exergonic step ($-\Delta G$) is linked to an endergonic step ($+\Delta G$), so the uphill reaction proceeds on borrowed energy. Example: glycolytic step releases energy → ADP + Pi phosphorylated to ATP (substrate-level phosphorylation)

Why It Matters

- Catabolism is a chain of downhill steps, coupled at the big drops to make ATP.
- Anabolism is spending that ATP to run uphill reactions.

Common Errors

- **Error:** Believing the uphill reaction happens on its own. It only proceeds because it is coupled to a downhill source.
- **Error:** Thinking ATP is the energy. ATP is the carrier that moves energy from where it is released to where it is needed.

phosphorylating ADP. Anabolism then spends that ATP to drive uphill processes: building proteins, pumping ions, contracting muscle. The energy did not appear from nowhere and no law was broken. It was transferred, downhill funding uphill, with some heat lost at each transfer as the second law requires.

Get coupling and the rest follows

If a student leaves this section understanding coupling, the rest of the chapter is bookkeeping. If they do not, every pathway will look arbitrary.

Prediction Prompt

Predict: If a cell could not couple reactions and could only release catabolic energy as heat, what would happen to its ability to build structure or pump ions?

Section 5: Activation Energy, Enzymes, and Kinetics — Lowering the Hump, and What Makes an Enzyme Good

Instructor Narrative

The move: Two ideas, kept light. Enzymes lower the activation hump so spontaneous reactions actually run, and an enzyme's worth is affinity and turnover together, not either alone.

Enzymes lower the activation hump

Draw the reaction-energy profile: the hump between reactants and products is the activation energy. Even a spontaneous reaction, products well below reactants, has to get over that hump first, and if the hump is large you would need unreasonably high temperatures to push reactants together. Enzymes drop that hump. The reaction's delta G does not change, the enzyme does not make it more spontaneous, it just lowers the energy of activation so the reaction proceeds quickly at body temperature. The "boulder at the top of a hill" analogy works here: the catalyst adds a slippery surface under the boulder, lowering the energy of the push needed to get it moving, but the boulder still ends up at the same place at the bottom of the hill.

Keep kinetics to the Michaelis-Menten gist

For kinetics, keep it to the gist of the Michaelis-Menten picture. Raise substrate and reaction rate rises, because more substrate means more binding events, until the enzyme saturates at its maximum velocity. From that relationship we get affinity: the substrate concentration needed to reach half of maximum velocity is the K_m , and a low K_m means high affinity, the enzyme binds substrate at low concentrations. But affinity is not the whole story.

Structured Outline / Causal Chain

Causal Chain: Activation Energy

A spontaneous reaction still has an activation hump, and at body temperature few molecules clear it. An enzyme lowers $E_a \rightarrow$ a larger fraction of molecules can clear the energy hump $\rightarrow$ reaction runs fast at body temperature

- Enzyme lowers E_a only. ΔG and equilibrium are unchanged (the boulder lands in the same place).

What Makes an Enzyme Good

- **Affinity:** low K_m = binds substrate at low concentration.
- **Turnover:** K_{cat} = molecules processed per second at saturation.
- **Efficiency:** K_{cat}/K_m = the real measure; want every binding event to become a catalytic event.

Common Errors

- **Error:** Thinking enzymes make reactions more spontaneous or shift equilibrium. They change rate, not ΔG .
- **Error:** Calling a high-affinity enzyme good while ignoring turnover, or vice versa.
- **Error:** Reading high K_m as high affinity. It is the reverse.

Prediction Prompt

Turnover, the K_{cat} , is how fast the enzyme processes substrate once saturated, and that ranges from a few hundred to over a million per second. What actually matters is both, combined into catalytic efficiency, K_{cat} over K_m . The ideal is high affinity so the substrate sticks, and high turnover so every binding event becomes a catalytic event.

Stop there; that is enough enzyme detail

That is as far as the enzyme detail needs to go. The point is conceptual, an enzyme has to bind well and work fast, because the next section uses exactly those two knobs as the control points of metabolism.

Predict: Enzyme A has low K_m and high K_{cat} ; enzyme B has high K_m and low K_{cat} . At low physiological substrate levels, which clears substrate better, and why?

Section 6: Enzyme Regulation and Pacemaker Flux — Where Control Actually Lives

Instructor Narrative

The move: Tie regulation to flux. You control a pathway by controlling its rate-limiting enzyme, and you have three speeds of control: change the affinity, change the activity, or change the amount.

Metabolism is linked pathways that must be regulated

Frame metabolism as linked enzymatic pathways that have to be regulated, and give students three levers in order of speed. Fastest is allosteric modulation: a regulator binds away from the active site and bends the protein so the active site binds substrate better or worse, changing affinity. The key example is ATP feeding back on glycolysis, the product throttling its own production, classic negative feedback. Next is covalent modification, usually adding or removing a phosphate to flip an existing enzyme on or off, which is exactly how hormones act fast. Slowest is changing expression, transcribing and translating more or fewer enzyme molecules, which takes hours to days but can remodel a whole pathway, like building more Krebs-cycle enzymes in response to endurance training.

Regulation acts at the rate-limiting step

Then the idea that makes regulation tractable: not every enzyme matters equally. A pathway has a pacemaker, or bottleneck, enzyme, the one that is rate-limiting because of its low concentration or low efficiency. That is the tightest segment of the pipe, and it is the point worth regulating. Modulate the

Structured Outline / Causal Chain

Three Levers (Fast to Slow)

- **1.** allosteric modulation changes affinity (K_m). Fastest. ATP inhibiting glycolysis is the model case.
- **2.** covalent modification (phosphorylation on/off) flips existing enzymes. Fast; the hormone mechanism.
- **3.** expression change (transcription/translation) alters enzyme amount. Hours to days; training adaptation.

Derivation Chain: Pacemaker Enzyme is Where Control Lives

Rate-limiting (low amount or low K_{cat}/K_m); the tightest segment of the pipe → modulating it moves whole-pathway flux

Intrinsic vs. Extrinsic

- **Intrinsic:** pathway regulates itself; ATP/ADP ratio is the key sensor.
- **Extrinsic:** hormones/neurotransmitters retune for the whole body (sets up the hormone section).

Common Errors

- **Error:** Trying to regulate every enzyme. Flux is set at the pacemaker.

pacemaker and you move the flux of the entire pathway. Students who grasp this stop trying to track every enzyme and start asking which one is the bottleneck.

Separate intrinsic from extrinsic control

Separate intrinsic from extrinsic control here, because it sets up the hormone logic at the end. Intrinsic control is the pathway regulating itself, often through a product such as ATP feeding back. Extrinsic control is a signal from elsewhere in the body, a hormone or neurotransmitter, retuning the pathway for the needs of the whole organism. The ATP-to-ADP ratio is the principal intrinsic sensor; insulin, glucagon, cortisol, and epinephrine are the extrinsic ones.

- **Error:** Confusing fast covalent on/off control with slow expression-level control.

Prediction Prompt

***Predict:** A muscle's ATP demand spikes. Which intrinsic signal changes, in which direction, and how does that change act on a pacemaker enzyme to increase catabolic flux?*

Section 7: ATP — The Coupling Currency That Is Almost Always Empty

Instructor Narrative

***The move:** Present ATP as the hub of coupling, then establish the central constraint: cells hold only seconds' worth of it. That fact requires continuous catabolism and explains why production rate, not storage, sets the limit on work.*

ATP links energy release to energy use

ATP is the link between energy-releasing and energy-using processes, the currency we spend on synthesis, ion pumping, and contraction. We regenerate it by using nutrient bond energy to drive the uphill, positive delta G phosphorylation of ADP back to ATP, and that regeneration is always inefficient, so heat comes off every time. Each cell has to make its own because ATP is not shared between cells.

ATP stores last only seconds

The key quantitative point is that stores of ATP last only a few seconds. The body holds roughly half a pound of ATP at any instant yet turns over an amount equal to body mass every day. The cycle of breakdown and resynthesis must therefore run continuously, which is why catabolic rate must track demand closely. The short-term buffer is phosphocreatine, which carries a high-energy phosphate it can transfer to ADP, but that extends the

Structured Outline / Causal Chain

Causal Chain: ATP-ADP cycling

Nutrient bond energy → drives the +ΔG phosphorylation of ADP to ATP (with heat lost) → spent on work → back to ADP

The Defining Facts

- **Stores:** only seconds of ATP on hand; ~half a pound present, body-mass-worth turned over daily.
- **Buffer:** phosphocreatine donates a phosphate to ADP; extends supply to ~10 s.
- **No sharing:** ATP is made per cell and not transported between cells.

Consequence

Almost no reservoir → production rate (not storage) limits work → catabolism must run continuously and track demand

Common Errors

- **Error:** Picturing ATP as a large storage tank rather than a near-empty, fast-turnover stream.

supply only to roughly ten seconds. The sprinter makes this concrete: a hundred-meter world-record holder could complete the race breathing pure nitrogen, producing essentially no aerobic ATP, because stored ATP and phosphocreatine cover that short, intense effort. Extend the effort and that buffer is exhausted.

ATP is a flow, not a tank

So get students to stop picturing ATP as a tank you fill and start picturing it as a fast-moving stream. The relevant variable is the rate of production, because there is almost no reservoir. That reframes the whole catabolism discussion that follows.

- **Error:** Confusing phosphocreatine with a long-term store; it is a ~10-second bridge.

Prediction Prompts

Predict: A sprinter runs an all-out 10-second effort. Which energy sources actually power it, and why is aerobic ATP production nearly irrelevant on that timescale?

Predict: A cell holds only seconds of ATP yet turns over its own mass in ATP each day. What does that force to be true about how closely catabolic rate must track ATP demand at every instant?

Section 8: The Nutrient Pool and Stores — Size, Priority, and Accessibility

Instructor Narrative

The move: Set up fuel selection before any pathway by contrasting the three stores on three axes: size, the order in which each is drawn on, and how accessible each is. The carbohydrate paradox, the smallest store but the primary fuel, is the central point.

Cells draw from one shared nutrient pool

Cells draw from a nutrient pool of glucose, fatty acids, and amino acids that is continually replenished. At the whole-body level these are the nutrient stores, and their relative sizes are often unexpected. Carbohydrate, stored as glycogen in liver and skeletal muscle, is the smallest store, only about fifteen hundred calories, roughly a day's worth. Yet glucose is the primary fuel for many cells. Fat is by far the largest store, over a hundred thousand calories in adipose, because it holds more than twice the calories per gram and is stored without water, which makes it the efficient long-term reserve used during fasting. Protein totals around thirty thousand calories but has no true storage form, because every protein has a structural or functional role.

Priority of use falls out of the pool

Priority of use follows from that. Carbohydrate is the common short-term currency. Fat is generally second and dominates long-term use and resting metabolism in tissues such as resting skeletal muscle and liver. Protein is the

Structured Outline / Causal Chain

Three Stores, Three Axes

- **Carbohydrate:** smallest (~1500 kcal, ~1 day) yet primary fuel for many cells. Liver + skeletal muscle.
- **Fat:** largest (~100,000+ kcal), >2 kcal/gram, stored without water → efficient long-term reserve.
- **Protein:** ~30,000 kcal but no true storage form; every protein has a structural or functional role.

Priority of Use

Carbohydrate (short-term) → fat (long-term, and resting muscle/liver) → protein (last resort)

Accessibility (the Forgotten Axis)

- **Fast:** glucose/glycogen are immediately available to cytoplasmic enzymes.
- **Slow:** fat is locked in droplets with little surface area → slow to mobilize → cannot keep pace when demand is high.

Common Errors

- **Error:** Assuming the largest store (fat) is the primary fuel for intense effort. Accessibility, not size, limits it.

last resort, captured in an analogy: burning protein for energy is like burning the furniture to heat the house. It works, but it destroys functional machinery, and it generates the nitrogen problem as well.

Accessibility is the axis students forget

The axis students overlook is accessibility. Glucose and glycogen are immediately available to cytoplasmic enzymes. Fat is held in hydrophobic droplets with little relative surface area, so it can be released only from the droplet surface, which is slow. That single constraint underlies the fat-burning-zone concept and the bonk, and introducing it here makes the later exercise logic clear: when ATP demand is high, fat cannot be mobilized fast enough and carbohydrate takes over.

- **Error:** Thinking there is a protein store. Protein used for fuel is functional tissue being dismantled.

Prediction Prompts

Predict: An athlete burns ~1000 kcal/hr, mostly carbohydrate, during a bout of exercise. Why does the carbohydrate store run low long before the fat store, and what happens to pace when the body must switch to fat? (the bonk)

Predict: Two athletes have identical glycogen but very different fat stores. Once glycogen is depleted at high intensity, why does the larger fat store not let one of them hold the pace? Reason from accessibility, not size.

Section 9: Glycolysis — Anaerobic, Cytoplasmic, and Dual-Purpose (Pyruvate or ATP)

Instructor Narrative

The move: Teach the gist, not the steps. Three phases, a net of two ATP, two pyruvate. What glycolysis is for depends on the situation: usually the pyruvate, but the ATP when the cell stands alone. Then the output-versus-efficiency point: glycolysis yields far less ATP per glucose but delivers it faster than the aerobic pathways.

Teach glycolysis as a shape, not steps

Keep glycolysis to its shape. It is cytoplasmic and anaerobic, broken into three phases. A priming phase spends two ATP to phosphorylate (energize) the glucose, a splitting phase cleaves the six-carbon sugar into two three-carbon pieces, and a payoff phase generates four ATP and reduces NAD to NADH. Net, plus two ATP per glucose. There is no need to march students through the named intermediates; that buries the point.

What glycolysis is for depends on the situation

What glycolysis is for depends on the situation, and that is the framing to give students rather than a single fixed statement. In the usual aerobic case the essential product is the pyruvate: the two ATP are minor against the roughly thirty from fully oxidizing glucose in the mitochondria, and the significant output is the pyruvate that feeds the mitochondrion for that larger

Structured Outline / Causal Chain

The Gist (Skip the Intermediates)

- **1.** priming phase spends 2 ATP.
- **2.** splitting phase cleaves 6C glucose into two 3C pieces.
- **3.** payoff phase makes 4 ATP + 2 NADH and yields 2 pyruvate.

Net per glucose: +2 ATP, 2 NADH, 2 pyruvate

What It Is for Depends on the Situation

Usual (O₂ present, moderate demand): pyruvate is the significant product (feeds mitochondria for ~30 ATP); 2 ATP is a footnote here. Anaerobic / demand outruns mitochondria / no mitochondria: the 2 ATP are all the cell gets

- **Net read:** pyruvate dominates over time and across most cells; ATP is the point when glycolysis stands alone.

Two Different Axes: Efficiency vs. Output

- **Efficiency:** ATP per glucose. Aerobic wins (~30 vs. 2).
- **Output (power):** ATP per second. Glycolysis wins (short, low-resistance pathway).

yield. But when the cell is anaerobic, or demand outruns the mitochondria, or there are no mitochondria at all, those two ATP are the entire point, because they are all the cell obtains. Across most cells and over time the pyruvate role dominates, so it is accurate to say pyruvate is usually the key product, provided students understand that the ATP becomes the crucial product precisely in the situations where glycolysis operates alone.

Glycolysis is inefficient but high-power

This is the point students find counterintuitive and that is worth emphasizing. Glycolysis is highly inefficient, capturing only a few percent of glucose's energy, but it is high-power: it can produce ATP faster per unit time than the entire aerobic system, because it is a short, simple pathway. Cells that need ATP very quickly, such as hard-working skeletal muscle, rely on glycolysis despite its low efficiency. The common error is to conflate efficiency with output, so distinguish them explicitly. Efficiency is the amount of ATP extracted per glucose, and the aerobic pathways are far higher here, roughly thirty to two. Output, or power, is the amount of ATP produced per second, and glycolysis is higher here. High efficiency does not mean more energy per second. A pathway can be inefficient and still be the fastest source per unit time, which is what glycolysis is. The primary trigger is ATP demand rate, not oxygen. Glycolysis is a low-resistance, fast pathway, so when demand rises sharply and the slow mitochondrial pathways cannot keep up, glycolysis supplies the difference and those two ATP become significant, even with oxygen present. Genuine oxygen shortage is a separate, special case that also forces it. The next section develops this switch fully.

Independent measures: glycolysis is low efficiency but high output; aerobic is high efficiency but low output (slow)

Common Errors

- **Error:** Confusing efficiency with output. Efficient (more ATP per glucose) does not mean more ATP per second.
- **Error:** Treating glycolysis as always about one thing. Pyruvate usually, the 2 ATP when it stands alone.

Prediction Prompts

***Predict:** Sprinting muscle needs ATP faster than mitochondria can deliver. Why does it rely on glycolysis despite extracting only a few percent of glucose's energy?*

***Predict:** A red blood cell has no mitochondria. State its total ATP yield per glucose and explain why that number cannot rise no matter how much oxygen is available.*

Section 10: The Krebs Cycle — Follow the Carbons, Harvest the Hydrogens

Instructor Narrative

***The move:** Two instructions carry the whole cycle: follow the carbons (in as acetyl, out as CO₂) and harvest the hydrogens (the real product, on NADH and FADH₂). Names of intermediates are optional.*

Pyruvate becomes a two-carbon acetyl

Pyruvate enters the mitochondrion and is converted to a two-carbon acetyl group attached to coenzyme A, losing one carbon as carbon dioxide on the way in. Tell students to follow the carbons. The acetyl group, two carbons,

Structured Outline / Causal Chain

Causal Chain: Follow the Carbons

Pyruvate (3C) → lose 1 CO₂ → acetyl-CoA (2C) → + oxaloacetate (4C) → citrate (6C) → cycle drops 2 CO₂ → 4C regenerated

- **Carbon fate:** nutrient C and O leave as exhaled CO₂.

Harvest the Hydrogens (the Real Output)

joins a four-carbon oxaloacetate to make six-carbon citrate, the cycle turns, and the two carbons we added come back off as carbon dioxide, regenerating the four-carbon molecule so the next acetyl can enter. All our nutrients arriving here are carbon, hydrogen, and oxygen, and the carbon and oxygen leave as the carbon dioxide we exhale. The intermediate names are not required; tracking carbons in and carbon dioxide out is.

The real question is where the hydrogens go

Then the central question: where did the hydrogens go? The hydrogens are the metabolic gist of the Krebs cycle. They come off attached to the carriers, NAD becoming NADH and FAD becoming FADH₂. A hydrogen atom is an electron plus a proton, and these carriers ferry them out of the cycle to the electron transport chain, where most of the aerobic ATP is actually made. There is one step where the energy drop is big enough to phosphorylate GDP to GTP, equivalent to a little ATP, but like the glycolytic ATP it is a small share of the total.

The output that matters is reduced carriers

So the cycle's significant output is not ATP and not carbon dioxide; it is the loaded hydrogen carriers. If students conclude that the Krebs cycle is where ATP is made, they have missed its function. The cycle supplies the reduced carriers that deliver electrons to the next pathway.

H atoms (e⁻ + proton) loaded onto NAD → NADH, and onto FAD → FADH₂; both are delivered to the electron transport chain

- **Direct ATP:** one step makes GTP, energetically equivalent to ATP; small share of the total, like glycolysis.

Key Distinction: Carriers Delivered vs. ATP Made Directly

- **The point:** not ATP and not CO₂; it is the loaded H carriers feeding the ETC.

Common Errors

- **Error:** Believing the Krebs cycle is where most ATP is made. It supplies the carriers; the ETC makes the ATP.
- **Error:** Getting lost in intermediate names instead of tracking carbons in / CO₂ out.

Prediction Prompts

Predict: If NADH and FADH₂ could not be delivered to the electron transport chain, what happens to the Krebs cycle, and why?

Predict: Follow the six carbons of one glucose after glycolysis. Through pyruvate and two turns of the cycle, where does every carbon atom end up, and in what molecule does it leave the body?

Section 11: The Electron Transport Chain — A Proton Gradient Becomes ATP

Instructor Narrative

The move: Present it as energy conversion: electrons fall step by step, each large drop pumps protons into a gradient, the gradient is then converted into ATP, and oxygen at the end is the terminal electron acceptor that allows the chain to continue, which is why we breathe.

Carriers deliver electrons to the chain

The carriers deliver electrons and protons to the cytochromes of the inner membrane. NADH delivers its electrons at the start of the chain; FADH₂ delivers them further along, past the first pumping step. As electrons are

Structured Outline / Causal Chain

Energy Conversion, in Three Moves

- **1. Pump:** electrons fall through cytochromes; each big drop pumps a proton into the intermembrane space.
- **2. Store:** a proton gradient = stored (chemiosmotic) energy. The double membrane holds it.
- **3. Cash in:** ATP synthase lets protons fall back, converting flow into ATP. Bulk of aerobic ATP made here.

Why Oxygen

passed molecule to molecule there is a free energy drop at each handoff, and where the drop is large enough it powers a proton uphill, against its gradient, into the space between the two mitochondrial membranes. The double membrane matters here, because the enclosed space between the two membranes is what allows protons to accumulate. The net result is a proton gradient, a region of high concentration relative to the matrix.

Name what happened: hydrogens, stepped downhill

Then name what has happened: we took hydrogen atoms, ran a series of redox reactions passing electrons, and stored the released energy in a proton gradient. But a gradient cannot be spent around the cell. It has to be converted into a portable currency, and that conversion is ATP synthase, a channel-enzyme that lets protons run back down their gradient into the matrix and harnesses that movement to phosphorylate ADP. This is where the large majority of aerobic ATP is made, a little in glycolysis, a little in the Krebs cycle, the bulk right here.

Oxygen is the final electron acceptor

To keep electrons flowing we have to get rid of them at the end, and the final acceptor is oxygen. That is why we breathe and why this is aerobic, no oxygen to receive electrons and the whole chain backs up. Oxygen picks up electrons and combines with free protons to make metabolic water, so the byproducts of fully aerobic metabolism are the carbon dioxide from the Krebs cycle and water made right here from the hydrogens of our food and the oxygen of our breath.

O₂ is the final electron acceptor → removing electrons keeps the chain flowing; conversely, no O₂, chain backs up, everything upstream stalls

- **Water:** O₂ + electrons + 2 protons → metabolic water. CO₂ (Krebs) + H₂O (here) are the aerobic end products.

Common Errors

- **Error:** Thinking ATP synthase pumps protons. It does the opposite; protons fall through it and that powers ATP synthesis.
- **Error:** Treating oxygen as a reactant in ATP formation rather than the terminal electron acceptor that keeps the chain open.

Prediction Prompts

Predict: Oxygen delivery drops. Trace the backup: electron acceptor → chain → proton pumping → ATP synthase. Where and why does aerobic ATP production fail?

Predict: FADH₂ yields less ATP than NADH. Reason from where each carrier delivers its electrons into the chain to explain the difference.

Section 12: The Aerobic-Anaerobic Switch — Demand Rate, Pathway Resistance, and Lactate

Instructor Narrative

The move: Correct the most common misconception here. For most cells the switch to glycolysis is set by ATP demand rate, not oxygen availability. Glycolysis is a low-resistance, fast pathway recruited when demand rises sharply; the mitochondrial pathways are the slow, high-resistance step that cannot keep pace.

Correct the anaerobic story first

Structured Outline / Causal Chain

Causal Chain: The Switch (for Most Cells): Demand, Not Oxygen

Glycolysis = low-resistance, fast, high power/sec, low yield. Krebs/ETC = high-resistance, slow, high yield, dominant at low and moderate demand. Demand rises dramatically → ATP demand outruns the maximum mitochondrial rate → the shortfall is met by glycolysis, even with O₂ present

Begin with a correction, because the usual account misleads students. For most cells the shift to glycolysis is not a matter of running out of oxygen. It is a matter of the rate of ATP demand, and the clearest way to frame it is in terms of resistance. Glycolysis is a short, low-resistance pathway: few steps, so it produces ATP quickly, at high power per second, even though its yield per glucose is low. The mitochondrial pathways, Krebs and the electron transport chain, are long, high-resistance, slow pathways: far more efficient per glucose, but unable to deliver ATP quickly. The distinction students must retain is that efficiency and output are not the same thing. The aerobic pathways are efficient, with the most ATP per glucose, but low in output, slow per second. Glycolysis is the reverse, inefficient but high in output. High efficiency never means greater speed. At rest and at moderate effort, when demand is low, the slow aerobic pathways keep up and dominate. When ATP demand rises sharply, the mitochondria are too slow to match it, and the cell relies on glycolysis to supply the difference, regardless of how much oxygen is present.

NAD⁺ bookkeeping is what forces lactate

Next, the redox problem that requires lactate. When glycolysis runs fast it produces pyruvate and NADH faster than the mitochondria can take up the pyruvate and faster than the chain can reoxidize the NADH. To sustain that fast flux, glycolysis must regenerate NAD⁺, and the mechanism is lactate dehydrogenase, which converts the accumulating pyruvate to lactate and regenerates NAD⁺ from NADH. That is the entire purpose of the conversion. No additional ATP is produced by making lactate. It is a redox-balancing step that allows high-rate glycolysis to continue. Note that it occurs with oxygen present whenever demand outruns mitochondrial uptake, which is why lactate is produced even at rest and why during moderate exercise lactate use can exceed glucose use.

Low oxygen is the special case, not the rule

Oxygen availability is the separate, special case, not the general rule. True hypoxia does force glycolysis, because without an electron acceptor the chain backs up and the mitochondria stop, but for most working cells that is not what is happening, high demand is. The genuinely oxygen-defined cells are the obligate ones: red blood cells have no mitochondria at all, so they are anaerobic for life, and connective-tissue cells like the fibroblasts of tendons and ligaments sit too far from blood supply to stay aerobic, which is part of why those tissues heal so poorly.

Why Lactate (the Redox Fix)

Fast glycolysis makes pyruvate + NADH faster than mitochondria clear them → the excess pyruvate is reduced to lactate, which regenerates NAD⁺ → fast flux continues

- **Key:** no extra ATP; pure redox balance. Lactate forms even at rest / with O₂ present.

Special Cases (Here It Is Oxygen)

- **Hypoxia:** true hypoxia stops the chain → forces glycolysis.
- **RBCs:** no mitochondria → anaerobic for life.
- **Fibroblasts:** too far from blood → anaerobic, poor healing.

Cori Cycle (Clearance)

Lactate → liver → pyruvate → glucose → back to circulation. Carbon conserved.

- **Fuel limit:** anaerobic = carbohydrate only (fat/protein enter south of glycolysis).

Common Errors

- **Error:** Confusing efficiency (ATP/glucose, aerobic wins) with output (ATP/second, glycolysis wins). Efficient is not faster.
- **Error:** Teaching the switch as oxygen availability for all cells. For most, ATP demand rate sets it; the mitochondria are just too slow.
- **Error:** Calling lactate a waste or a poison. It is a recyclable fuel and a redox solution, made even at rest.

Prediction Prompts

Predict: A muscle goes from rest to all-out effort with O₂ still plentiful. Using pathway resistance, explain why glycolysis now dominates and lactate rises.

Predict: During moderate exercise, lactate use can exceed glucose use while oxygen is plentiful. Explain how the same tissue can be producing and consuming lactate at once, and why that reframes lactate as fuel rather than waste.

The Cori cycle clears the lactate

Clearance is the Cori cycle: lactate not used locally goes to the liver, which converts it back to pyruvate and then to glucose and ships it out again. So the carbon is conserved, not discarded, and lactate is better understood as a recyclable fuel than as a waste product. The acid and the burn of hard exercise come mostly from ATP hydrolysis, not from lactate itself.

Section 13: Beta-Oxidation — Why Fats Are Aerobic-Only

Instructor Narrative

***The move:** Present fat as a high-yield fuel that releases its energy only aerobically, and explain when it is mobilized. The carbons enter as acetyl groups, so beta-oxidation depends entirely on a functioning Krebs cycle and ETC.*

Fat use rises in two predictable situations

Fat use rises in two situations students should anticipate: prolonged fasting, when fat is mobilized as the major energy source, and prolonged exercise, when the small carbohydrate stores start to limit. In either case, triglycerides are enzymatically split to release free fatty acids from adipose, liver, and the lipid droplets inside skeletal muscle. The fatty acids are taken into the mitochondria and run through beta-oxidation.

Beta-oxidation cleaves the chain two carbons at a time

The mechanism in brief: beta-oxidation takes a long fatty-acid carbon chain and cleaves off two carbons at a time as acetyl-CoA, then the shortened chain repeats the process, yielding often eight or more acetyl groups per fatty acid. Each acetyl group enters the Krebs cycle, where its hydrogens are transferred onto NADH and FADH₂, and beta-oxidation itself also produces some of those carriers. This is why fat is such an effective energy store: a single fatty acid drives many turns of the Krebs cycle, and because it is stored without water it holds a high number of calories per unit weight.

Fat oxidation is strictly aerobic

The essential point is the dependence on oxygen. Acetyl groups from beta-oxidation enter directly at the Krebs cycle, which means fat use requires the

Structured Outline / Causal Chain

When Fat Is Mobilized

- **Prolonged fasting:** fat becomes the major fuel.
- **Prolonged exercise:** small carbohydrate store becomes limiting.

Causal Chain: Gist of the Mechanism

Triglyceride → free fatty acids → mitochondria → beta-oxidation cleaves 2C acetyl-CoA at a time (eight or more per fatty acid) → each acetyl-CoA enters the Krebs cycle → NADH/FADH₂ → ETC. Beta-oxidation also yields its own carriers

The Aerobic Requirement

- Acetyl groups enter at the Krebs cycle → fat requires a working Krebs cycle and ETC → without O₂ as terminal acceptor the chain stops, so fat yields no ATP anaerobically.

Payoffs of the Rule

- **Fat-burning zone:** highest intensity still aerobic; go anaerobic and fat burning stops.
- **Sprinting/lifting:** anaerobic → carbohydrate, not fat.
- **Ketone bodies:** fasting acetyl-CoA accumulation in the liver → ketone bodies → fuel for brain and heart.

Common Errors

Krebs cycle and the electron transport chain, both aerobic. Fat is therefore aerobic-only. This is the basis of the fat-burning zone in exercise: that zone is the highest intensity that can be sustained while remaining aerobic, because once metabolism becomes anaerobic the cell runs on glycolysis and oxidizes no fat. It is also why sprinting and heavy lifting are carbohydrate-dependent activities. During a prolonged fast, heavy beta-oxidation in the liver accumulates acetyl groups and produces ketone bodies, which the brain and heart can use when glucose is scarce.

- **Error:** Thinking you burn fat during all-out anaerobic effort. Fat needs oxygen; intense effort runs on glycogen.
- **Error:** Thinking fatty-acid carbons can become glucose. They enter as acetyl-CoA and are lost as CO₂ in the Krebs cycle; only the glycerol backbone of a triglyceride is gluconeogenic.

Prediction Prompts

Predict: Untreated diabetic with poor glucose uptake: predict their anaerobic sprint performance, given fat and ketones cannot fuel anaerobic ATP production.

Predict: One fatty acid yields far more ATP than one glucose. From the beta-oxidation mechanism, two carbons cleaved off at a time across a long chain, explain where that larger yield comes from.

Section 14: Amino Acid Catabolism — Deamination and the Nitrogen Problem

Instructor Narrative

The move: Lead with the obstacle that makes protein different: nitrogen has no place in these pathways. Strip the amino group first (making toxic ammonia), then the carbon skeleton enters as a keto acid wherever its structure allows.

Protein is the last-resort fuel

Protein is the last-resort fuel, and it carries a complication the other two do not. To use an amino acid for energy, the amino group must be removed first, because nitrogen has no role in the energy pathways. This removal is deamination, and it leaves a keto acid, which is the amino acid minus its nitrogen. Because there are twenty amino acid structures, there are twenty keto acid structures, and they enter the pathways at different points according to their structure, some as pyruvate, some as acetyl groups, some as other Krebs intermediates.

Stripping nitrogen makes toxic ammonia

The removed nitrogen becomes ammonia, which is toxic because it destabilizes proteins. A small amount can be excreted directly, and under

Structured Outline / Causal Chain

The Obstacle First

Nitrogen has no place in energy pathways → deaminate first → keto acid (amino acid minus N) enters by structure

- **Variety:** 20 amino acids → 20 keto acids → entry at pyruvate, acetyl-CoA, or various Krebs intermediates.

Causal Chain: The Nitrogen Problem

Amino group → ammonia (toxic) → liver combines it with bicarbonate → urea → excreted in urine

- **Cost:** urea synthesis costs ATP, which lowers the net yield from protein.
- **Overload:** extreme protein catabolism can outpace urea synthesis → ammonia on breath/skin.

Two Amino Acid Carbon Destinies

- **Ketogenic:** → acetyl-CoA → Krebs or ketone bodies.

extreme protein catabolism, such as very prolonged hard exercise after carbohydrate is depleted, it can be produced fast enough to be detected on the breath and skin. Normally it cannot be excreted fast enough, so the liver combines it with bicarbonate to make urea, which is far less toxic and is excreted by the kidney in urine. This detoxification step consumes ATP, which is part of why protein is an expensive, low-yield fuel.

Deaminated carbon skeletons are oxidized like other fuels

Once deaminated, the carbon skeletons behave like any other fuel: keto acids enter the Krebs cycle and supply the electron transport chain with electrons. It is worth naming the two fates here, because they become relevant in the anabolism section: ketogenic amino acids convert to acetyl-CoA and can form ketone bodies, while glucogenic amino acids pass through Krebs intermediates to oxaloacetate and can be diverted to make glucose. That second route is how, during prolonged fasting, muscle protein is broken down to maintain blood glucose.

- **Glucogenic:** → Krebs intermediate → oxaloacetate → glucose (gluconeogenesis).

Common Errors

- **Error:** Forgetting deamination must happen first; the carbon skeleton cannot enter with its nitrogen attached.
- **Error:** Ignoring the ATP cost of urea, which makes protein a low-net-yield fuel.

Prediction Prompts

***Predict:** Switching to a high-protein diet: predict the change in urine composition, tracing the path from deamination to excretion.*

***Predict:** During a prolonged fast, which class of amino acid keeps blood glucose up, and trace the route by which its carbon skeleton becomes new glucose.*

Section 15: The South of Glycolysis Rule — One Idea That Organizes the Whole Map

Instructor Narrative

***The move:** Collapse three nutrient pathways into one organizing rule. Only glucose enters at the top of glycolysis; fat and protein enter south of it, so only carbohydrate works anaerobically. This single picture is worth more than the three pathways separately.*

Draw the one summary picture

After working through carbohydrate, fat, and protein, draw the summary and give students one rule that connects them. Glycolysis sits at the top, and only carbohydrate, glucose, can enter there. Everything else, the acetyl groups from fat and the keto acids from amino acids, enters south of glycolysis, at the Krebs cycle. That geometry is the central point of the section.

The rules fall out of that one picture

From that one picture, the rules students keep needing fall out automatically. Glycolysis is anaerobic and processes only carbohydrate. The mitochondrial machinery, Krebs and the electron transport chain, processes all three

Structured Outline / Causal Chain

The Organizing Rule

Top of glycolysis: carbohydrate only enters here → anaerobic-capable. South of glycolysis (Krebs): fat (acetyl) and protein (keto acids) enter here → aerobic-only

What Falls Out Automatically

- **Glycolysis:** anaerobic, carbohydrate-only.
- **Mitochondria:** all three fuels, oxygen-required.
- **Go anaerobic:** fat and protein unavailable; only glucose, only 2 ATP (potential to be very fast, but very inefficient).

Aerobic-Specialist Tissues

- **Cardiac + slow-twitch:** more/larger mitochondria, dense capillaries, myoglobin → stay aerobic under load.
- **Plasticity:** training raises the lactate threshold → more work stays aerobic → fat stays available.

nutrient types but requires oxygen. So anything entering south of glycolysis, fat and protein, can only be used aerobically. When a cell goes anaerobic, fat and protein are unavailable and carbohydrate is the only fuel, falling back on those two glycolytic ATP. Draw the dividing line: above the line, carbohydrate and fast and oxygen-free; below the line, all fuels but oxygen-required.

Some tissues are adapted to stay aerobic

This is also the place to note that some tissues are adapted to remain aerobic under sustained high demand, cardiac muscle and slow-twitch fibers, with more and larger mitochondria, dense capillaries, and myoglobin to hold oxygen. Training raises the lactate threshold, the intensity above which lactate accumulates faster than it is cleared, by enhancing exactly these traits. The contrast reinforces the rule: staying below the lactate threshold means remaining aerobic, which keeps fat available as a fuel.

Common Errors

- **Error:** Thinking fat or protein can be burned anaerobically. They enter below glycolysis, so they need oxygen.

Prediction Prompts

Predict: A cell loses its oxygen supply. From the south-of-glycolysis rule alone, predict which fuels it can still use and its ATP yield per glucose.

Predict: Endurance training raises the lactate threshold. Using the south-of-glycolysis rule, explain why staying below that threshold keeps fat available as a fuel.

Section 16: Metabolic Rate, Body Size, and Thermogenesis — Where Energy Goes

Instructor Narrative

***The move:** Reframe metabolic rate around where energy is actually spent (ion pumping and protein synthesis, in organs more than muscle at rest), then explain warm-bloodedness as adaptive inefficiency rather than a failure.*

Most oxygen use is coupled to ATP

Most oxygen consumption is coupled to ATP synthesis, and most of that ATP is used at rest for two processes: ion pumping and protein synthesis. The point students find unexpected is that the brain and liver, small in mass, have far higher per-gram metabolic rates than muscle or fat, and together consume more energy than all resting skeletal muscle combined. Basal metabolic rate therefore tracks lean mass and organ mass, not body fat, which is why males generally have higher BMRs and why BMR falls as muscle is lost with age and inactivity. Weight training raises BMR beyond the added muscle mass; steady aerobic exercise mostly expends calories only during the activity itself.

Body size bends metabolic rate per kilogram

Structured Outline / Causal Chain

Where ATP Goes at Rest

- **Two big sinks:** ion pumping + protein synthesis dominate.

Brain + liver: high per-gram rate, outspend all resting skeletal muscle despite less mass.

- **BMR:** tracks lean/organ mass, not fat; weight training raises it beyond added mass.

Derivation Chain: Body Size (Allometric Scaling)

Larger body → less surface area per unit mass → slower heat and material exchange per kg, while heat must still be shed as fast as it is produced. Energy use per kg is low in large animals: at mouse-level metabolism a rhino would near-boil.

Thermogenesis = Useful Inefficiency

- **Mechanism:** proton leak across inner membrane bypasses ATP synthase → gradient dissipates → reduced

Body size affects metabolic rate in a way that is not intuitive: larger animals use less energy per kilogram than smaller ones. This negative allometric scaling tracks surface-area-to-volume ratio more than mass; smaller bodies have more surface per unit mass and exchange heat and materials faster. One illustration makes the point: a rhinoceros running a mouse's per-cell metabolism would have skin near the boiling point of water to shed the heat.

Thermogenesis illustrates that biochemical inefficiency can be adaptive

Thermogenesis demonstrates that physiological processes traditionally viewed as "inefficient" can confer a selective advantage. In birds and mammals, natural selection favored metabolic pathways where the inner mitochondrial membrane allows protons to leak and bypass ATP synthase. As a consequence of this continuous dissipation of the proton gradient, catabolic pathways proceed at an accelerated rate, yielding thermal energy as a byproduct.

Brown fat extends this with a channel that allows protons to leak in large volume, a futile cycle that performs no work and produces large amounts of heat. Shivering is the other mechanism: antagonistic muscle contractions consume ATP to release heat without producing movement. Warm-bloodedness therefore costs roughly five to ten times the calories of a same-size reptile, and the advantage it provides is the ability to function across a wide range of environmental temperatures.

back-pressure lets the chain pump faster and oxidize more substrate → extra heat.

- **Brown fat:** wholesale proton leak (futile cycle) for large heat output.
- **Shivering:** antagonistic contractions burn ATP for heat, no movement.

Common Errors

- **Error:** Assuming body fat drives BMR. Lean and organ mass do; fat is metabolically cheap per gram.
- **Error:** Treating mitochondrial inefficiency as a malfunction. In homeotherms it is an evolved heat source.

Prediction Prompt

***Predict:** Thyroid hormone boosts the Na^+/K^+ pump and protein synthesis. Given the resting energy sinks, predict its effect on heat production and why membrane leak must rise with it.*

Section 17: Measuring Metabolism — Calorimetry, RQ, and RER

Instructor Narrative

***The move:** Connect measurement back to the pathways. Oxygen consumption tracks heat production, and the CO_2 -to- O_2 ratio reveals which fuel is being oxidized.*

Metabolic rate equals heat production

Metabolic rate equals heat production when no external work is being done, because every transfer ends as heat, so it can be measured directly as heat. The historical reference point is Lavoisier's guinea pig in an ice chamber, with the rate of ice melt indicating heat output. Direct calorimetry is precise but cumbersome, so the indirect method, measuring oxygen consumption, is

Structured Outline / Causal Chain

Two Routes to Metabolic Rate

- **Direct calorimetry:** measure heat directly (Lavoisier's ice chamber).
- **Indirect:** measure O_2 consumption (tracks heat). Cheaper, standard.

RQ Reveals the Fuel

$\text{RQ} = \text{CO}_2 \text{ produced} / \text{O}_2 \text{ consumed}$

- **Carbohydrate:** $\text{RQ} = 1.0$.

more commonly used, because oxygen use correlates closely with heat production, exactly as Lavoisier proposed when he described respiration as a controlled combustion of food.

Gas exchange reveals which fuel is burning

A further useful feature is that gas exchange also indicates which fuel is being oxidized. For glucose, the balanced equation consumes six molecules of oxygen and produces six molecules of carbon dioxide, so the ratio of carbon dioxide produced to oxygen consumed, the respiratory quotient, is one. Fats contain fewer oxygens relative to carbon and hydrogen, so oxidizing them produces relatively less carbon dioxide per oxygen, and the RQ falls to about 0.7. Protein is intermediate, around 0.83. A single ratio therefore reports nutrient use: near 1.0 indicates carbohydrate, near 0.7 indicates fat, and intermediate values indicate mixtures.

Separate RQ from RER carefully

Distinguish RQ from RER carefully, because it connects to the earlier acid-base material. RQ assumes all the carbon dioxide comes from nutrient oxidation. At high intensity, however, acid accumulation shifts the carbonic acid equilibrium and releases additional carbon dioxide that is not from fuel oxidation. Measured at the lungs, that elevated ratio is the respiratory exchange ratio, and it can exceed one, which indicates that exercise has become significantly anaerobic and that bicarbonate buffering of the accumulating acid is releasing carbon dioxide beyond that from fuel oxidation. This is the same fuel-selection logic as before: as intensity rises, fat cannot be released fast enough, carbohydrate takes over and RQ rises toward one, and beyond that point the RER rises above 1.0.

- **Fat:** $RQ \approx 0.7$ (fewer O atoms $\rightarrow$ less CO_2 per O_2).
- **Protein:** $RQ \approx 0.83$.

Derivation Chain: RQ vs. RER

- **RQ:** assumes all CO_2 is from fuel oxidation.
- **RER:** measured at lungs; high-intensity acid adds non-metabolic $CO_2 \rightarrow$ can exceed 1.0 $\rightarrow$ signals anaerobic, uncompensated acid.

Common Errors

- **Error:** Reading RER above 1.0 as impossible. It flags acid-driven CO_2 beyond fuel oxidation.
- **Error:** Forgetting that rising intensity pushes RQ toward 1.0 because fat cannot mobilize fast enough.

Prediction Prompt

***Predict:** A person rests on a low-carbohydrate diet. Predict their RQ and justify it from the fuel mix being oxidized.*

Section 18: Anabolism and Insulin — Storage After the Meal

Instructor Narrative

***The move:** Present insulin as the postprandial storage signal and emphasize the action that is most often overlooked, anti-catabolism. Across all three fuels it both builds stores and inhibits their breakdown.*

Anabolism is the build direction, ATP-funded

Structured Outline / Causal Chain

Causal Chain: Insulin Trigger and Job

Blood nutrients rise (esp. glucose after a meal) $\rightarrow$ insulin $\rightarrow$ shift from release to uptake/storage

Anabolism is the build direction, funded by catabolic ATP, and it is largely directed by hormones, with insulin the most prominent. Insulin is released when blood nutrients rise, especially glucose after a meal, and it controls nutrient disposition, shifting the balance from release toward uptake and storage. For glucose it inserts the GLUT-4 transporter into the plasma membrane of muscle and adipose cells, the insulin-dependent tissues, and it also acts on the liver, stimulating glycogen synthesis while inhibiting glycogen breakdown, so hepatic glucose output drops and blood sugar falls.

Insulin acts on all three fuels at once

The pattern to extract is that insulin acts on all three fuels in the same two-part way: it builds the store and it inhibits the breakdown. Glucose is stored as glycogen, and its release is inhibited. For fat, insulin promotes uptake and lipogenesis and inhibits fat breakdown, which is why it is called fat sparing: it promotes carbohydrate use and preserves fat stores. For protein, it stimulates amino acid uptake and protein synthesis and inhibits protein breakdown, especially in muscle. The key point is that the anti-catabolic effect, the inhibition of breakdown, often matters more than the direct stimulation of synthesis.

Two applications reinforce the point

Two applications reinforce the point. The fat-sparing effect combined with carbohydrate-heavy diets is central to the development of obesity and type-two diabetes: high simple-sugar intake drives large insulin spikes, fat storage, and eventually insulin insensitivity. And insulin's anabolic action is pronounced enough that some athletes misuse it to promote muscle growth, which is dangerous, but it does reflect an understanding that insulin is strongly anabolic. This also sets up the contrast for the hormone section: insulin is the fed-state hormone, and the remaining hormones act when insulin levels fall.

- **Glucose:** inserts GLUT-4 in muscle/adipose; on liver, builds glycogen + blocks its breakdown → hepatic glucose output falls.

The Two-Handed Pattern (All Three Fuels)

- **Carbohydrate:** store glycogen / block glycogenolysis.
- **Fat:** promote lipogenesis / inhibit lipolysis → fat sparing.
- **Protein:** promote synthesis / inhibit breakdown (esp. muscle).
- **Key:** the anti-catabolic (block breakdown) effect often outweighs the direct stimulation of synthesis.

Clinical Application

- **Disease link:** high simple-carb diet → large insulin spikes → fat storage → eventual insulin insensitivity (type 2).

Common Errors

- **Error:** Reducing insulin to a blood-sugar-lowering hormone. It governs storage of all three fuels and blocks their release.
- **Error:** Overlooking anti-catabolism, which is often the dominant effect.

Prediction Prompts

Predict: After a high-carbohydrate meal, which metabolic hormone rises, and why does its action fit the elevated blood nutrients?

Predict: A person with chronically high simple-carbohydrate intake develops insulin insensitivity. Trace the path from repeated insulin spikes to fat storage to eventual insensitivity, and predict the effect on resting blood glucose.

Section 19: Gluconeogenesis and the Liver Hub — Making Glucose, Both Directions

Instructor Narrative

Structured Outline / Causal Chain

The move: Resolve a paradox: a one-day glycogen store, yet weeks of fasting do not run out of glucose. The answer is gluconeogenesis, and the liver is the organ that runs nutrient flux in both directions.

Glycogen alone would not last a day

Students reasonably expect that a one-day glycogen store would be depleted after a short fast, yet even weeks of fasting do not exhaust glucose. The resolution is gluconeogenesis, the production of new glucose from non-carbohydrate precursors. When blood sugar falls between meals, glucagon drives both liver glycogen breakdown and new glucose synthesis. Under stress, cortisol and epinephrine increase gluconeogenesis further. The precursors are glucogenic amino acids, glycerol released from fat breakdown, and lactate from the Cori cycle, all of which feed into a Krebs intermediate, oxaloacetate, that is diverted toward glucose.

Krebs is not purely catabolic

This is the point at which the Krebs cycle should stop appearing purely catabolic. It is amphibolic, operating in both directions: intermediates can be fully oxidized or withdrawn to build glucose. The cycle is thought to have originated as an anaerobic biosynthetic pathway and to have acquired its energy-harvesting role later, and it retains both functions.

The liver is the metabolic hub

All of this occurs in the liver, the metabolic hub. After a meal, nutrient-rich blood from the gut reaches the liver first, so it stores nutrients, building glycogen, fat, and protein. Between meals or during exercise it reverses, releasing stored nutrients, taking up glycerol, fatty acids, and lactate, and converting them to glucose for release into the circulation. It also produces ketone bodies for the brain and heart when glucose is scarce. The liver is therefore the clearest example of an organ that operates in both directions of the entire chapter, storing when fed and producing when fasted, all under hormonal control. That makes it a natural transition into the hormones themselves.

Causal Chain: The Paradox and Its Answer

Stores hold about a day of glycogen, yet weeks of fasting and blood glucose is maintained. The resolution is gluconeogenesis, which makes new glucose. The trigger sequence: low blood sugar → glucagon (glycogenolysis + gluconeogenesis); stress → cortisol + epinephrine push harder

- **Precursors:** glucogenic amino acids, glycerol, lactate → oxaloacetate → glucose.

Krebs Is Amphibolic

- **Both directions:** intermediates burned OR siphoned to build glucose; evolved anaerobic first, energy role later.

Liver = the Hub

- **Fed:** gut blood reaches the liver first → store glycogen, fat, protein.
- **Fasted:** release stores, take up glycerol/fatty acids/lactate → make glucose; make ketones for brain/heart.

Common Errors

- **Error:** Assuming a short fast empties glucose. Gluconeogenesis sustains it for weeks.
- **Error:** Treating the Krebs cycle as purely catabolic. It is amphibolic.
- **Error:** Listing fatty acids as gluconeogenic precursors. Their acetyl carbons cannot become net glucose; only glycerol, glucogenic amino acids, and lactate can.

Prediction Prompts

Predict: Given any anabolic reaction, predict the sign of the reaction's entropy change and of ΔG , and whether it is endergonic or exergonic.

Predict: A marathoner late in a race is running partly on gluconeogenesis. Name the three precursor types feeding it and explain why fatty acid carbons are not among them.

Instructor Narrative	Structured Outline / Causal Chain
<i>The move: This section integrates the chapter, and it is not a hormone catalog. The metabolic situation creates a demand, and each hormone produces the adaptive fuel shift that situation requires. Present the situation first, then name the hormone that addresses it.</i> Endocrine control is not one switch Tell students up front that endocrine control of metabolism is not a separate topic to memorize, it is the answer to a question every previous section has been building toward: when the metabolic situation changes, what retunes the pathways? The body faces a handful of recurring situations, fed, between meals, acute stress, prolonged stress, and each hormone is simply the signal that produces the right nutrient shift for one of them. So teach the situation, then the hormone that solves it, never the reverse. Start with the fed state Fed state: nutrients arrive in quantity, so the adaptive response is to store them and stop releasing stores. That is insulin, the postprandial hormone already covered. Between meals: blood sugar falls, and the requirement is to maintain it by drawing on stores. That is glucagon, from the pancreatic alpha cells, which drives liver glycogen breakdown and gluconeogenesis. Note the logic check here: a high-protein meal also stimulates glucagon, which seems contradictory until one notes that the protein meal stimulates insulin as well, and without some glucagon the insulin would lower blood sugar too far. The glucagon prevents blood glucose from falling too far during a protein meal. Then acute stress, with exercise as the model Acute stress, with exercise as the clearest example: the demand is rapid delivery of fuel into the blood. That is epinephrine from the adrenal medulla, which drives liver glycogen breakdown and fat breakdown and, importantly, inhibits insulin, because a storage signal would return the newly mobilized sugar to cells. Prolonged stress or fasting: carbohydrate is now genuinely scarce, and the demand shifts to sparing glucose for the brain while supplying the rest of the body with fat. That is cortisol, the glucose-sparing hormone: it promotes fat use, drives gluconeogenesis from muscle protein, and reduces insulin so the newly made glucose remains available to nerve tissue rather than being taken up by muscle and fat. Stated directly, what cortisol does over a long fast is convert muscle protein into glucose to supply	Causal Chain: The Framing Each situation poses a fuel problem, and the hormone is the body's signal that produces the fuel shift. Teach situation first, hormone second Situation → Hormone • Fed: flood of nutrients → insulin (postprandial) → store + stop nutrient release. • Between meals: blood glucose falling → glucagon → glycogenolysis and gluconeogenesis draw on energy stores. • Acute stress → epinephrine (glycogen + fat breakdown; inhibits insulin), putting rapid fuel into the blood now. • Chronic stress - Prolonged stress/fasting, with carbohydrate scarce → cortisol (glucose-sparing: fat use + protein-fed gluconeogenesis, insulin reduced), which holds glucose available for the brain. Growth hormone also acts here (anti-catabolic, glucose-sparing). Logic Check • Why? high-protein meal stimulates glucagon too → protects glucose against meal-driven insulin. Hormones Onto the Stress Timeline • Alarm (fast): epinephrine, norepinephrine, glucagon release glucose and fatty acids into the blood; HR and BP rise. • Resistance: cortisol dominates: fat use + protein gluconeogenesis, insulin suppressed; sustainable. • Exhaustion: fat gone, muscle wasted, homeostasis fails. Intake Side (Same Logic) • Leptin: reports fat-store size → suppresses hunger. • Ghrelin: stomach signal between meals → drives hunger. Common Errors

the brain, and simultaneous fat use is what limits how much muscle that conversion consumes. Growth hormone acts here as well, glucose-sparing and strongly anti-catabolic to muscle, which is how it preserves lean mass while fat is mobilized.

Lay the hormones onto the timeline

Then place the hormones onto the stress timeline so they form a single integrated sequence. The alarm phase is fast: epinephrine, norepinephrine, and glucagon release stored glucose and fat into the blood, with the familiar rise in heart rate and blood pressure. As the stress persists, the resistance phase takes over and cortisol dominates, shifting to fat use and protein-fueled gluconeogenesis with insulin suppressed, which can be sustained for a long period. Only when fat is exhausted and muscle is wasted does the exhaustion phase arrive and homeostasis fail. So the hormones are not a list; they are the control system of the metabolic response, sequenced in time by how long the stress lasts. Conclude by noting the long-term intake side: leptin from fat reporting store size to suppress hunger, and ghrelin from the stomach driving hunger between meals, so that students see the same principle, signal matched to situation, governing feeding as well as fuel use.

- **Error:** Memorizing hormones as an isolated catalog instead of as the control arm of the metabolic response.
- **Error:** Missing why epinephrine and cortisol suppress insulin: a storage signal would undo the mobilization.

Prediction Prompts

***Predict:** A person fasts for a week. Sequence the hormones over time and predict, at each stage, which fuel dominates and which tissue glucose is being spared for.*

***Predict:** A high-protein, low-carbohydrate meal stimulates both insulin and glucagon. Explain why secreting glucagon alongside insulin is adaptive here rather than contradictory.*