Mitochondrial Resilience

The cellular biology of adaptation, explained so you can teach it tomorrow.

Anthony Castore · SSRP Fellow

CASTORE Method · castoremethod.com

Edition 1 · 2026

How to read this primer

A short note before we start — read this, even if you usually skip prefaces.

Richard Feynman had a rule for himself: *if you can't explain it simply, you don't understand it yet.* That is the rule for this primer too. Every chapter is built so that, by the end of it, you can put the book down and explain the idea to a friend over coffee — without notes, without jargon hiding the gaps. If you can't, the chapter hasn't done its job yet. Go back.

The structure follows the 80/20 principle the whole way through. Every section opens with a short summary box that captures the twenty percent of the material that gives you eighty percent of the value. Then the chapter expands. If you are tired, read only the boxes. If you want to teach, read the boxes *and* the expansions, and pay attention to the analogies — they are the handles your memory will reach for later.

A practical note on style. I write the way I coach: in analogies, with some repetition, and with a bias toward what you can actually *do* on Monday. The body is not a textbook. It is a system that responds to signals. The job of this primer is to teach you which signals matter, which knobs you can turn, and which ones you should leave alone for now.

Three more things. First, the diagrams are not decoration; each one encodes a piece of the mental model you need. Spend the extra ten seconds. Second, the citations at the bottom of pages are real — follow the ones that catch you, and you will go deeper than this primer can. Third, the glossary at the back is the cheat sheet. If a word ever loses its grip, flip back.

> **THE RULE OF THIS PRIMER**
>
> If you can't teach it back tomorrow, you don't own it yet. Re-read the box, redraw the diagram on a napkin, and try again. Understanding is something you build, not something you receive.

The 80/20 of the whole primer

If you read only one page, read this one. Everything else is detail and proof.

THE WHOLE PRIMER IN EIGHT BULLETS

- **A mitochondrion is a negotiator, not a furnace.** It matches food (substrate) to demand (work) and writes the receipt in ATP. Most fatigue stories are really negotiation stories.
- **Glycolysis pays in cash (~2 ATP); oxidative phosphorylation pays in salary (~32 ATP).** Both are correct in different situations. Health is having access to both.
- **Mitochondria fail in four ways — S.L.A.M.: S**ubstrate mismatch, electron **L**eak, **A**rchitecture damage (cardiolipin/membrane), and failed mitophagy (**M**) — bad mitochondria not being cleared.
- **Stress is the teacher.** The hormetic curve is an inverted U: small dose, no effect; right dose, adaptation; too much, damage. Heat, cold, exercise, and fasting all live on this curve.
- **There are three classes of intervention:** substrate & cofactor (CoQ10, NAD precursors, creatine), signaling modulators (urolithin A, PQQ, etc.), and lifestyle inputs (Zone 2, sprints, sleep, cold/heat). *Match the layer to the failure mode.*
- **Measure a few things, well.** Resting + post-exercise lactate, HRV, fasting glucose, waking heart rate, and recovery sleep beat any single fancy lab.
- **Adaptation is slow and honest.** The body responds to consistent signal over weeks, not to perfect days. Minimum effective dose, then iterate.
- **You don’t own it until you can teach it.** Read the box. Redraw the diagram. Say the idea out loud to someone. Repeat.

Everything in the chapters that follow is either a piece of evidence for one of these eight bullets, or a practical hand-off — what to actually do with the idea on Monday morning.

Chapter 1

What a mitochondrion actually does

A power plant is the easy answer. A negotiator is the better one.

> **THE 20% (READ THIS, EVEN IF YOU SKIP THE REST)**
> Mitochondria turn food and oxygen into ATP — the energy currency every cell uses. They do it by passing electrons along a chain of proteins (Complexes I–IV) embedded in their inner membrane, using that flow to pump protons across the membrane, and then letting the protons rush back through an enzyme called ATP synthase, which spins like a turbine and makes ATP. Glycolysis (no oxygen) yields about 2 ATP per glucose. Oxidative phosphorylation (with oxygen) yields about 32. Same glucose, very different return.

Most explanations of mitochondria start with “the powerhouse of the cell.” It’s not wrong, but it’s incomplete in a way that costs you. A power plant only does one thing: produce. A mitochondrion does something more interesting — it *negotiates*. On one side of the table sits whatever fuel just arrived: glucose, fatty acids, lactate, ketones, amino acids. On the other side sits the cell’s demand: am I sprinting, am I sitting, am I cold, am I fighting an infection? The mitochondrion has to read both sides and decide, second by second, what to burn and how fast. Most fatigue, most “midlife slow,” most failure to recover, is really a negotiation that broke down.

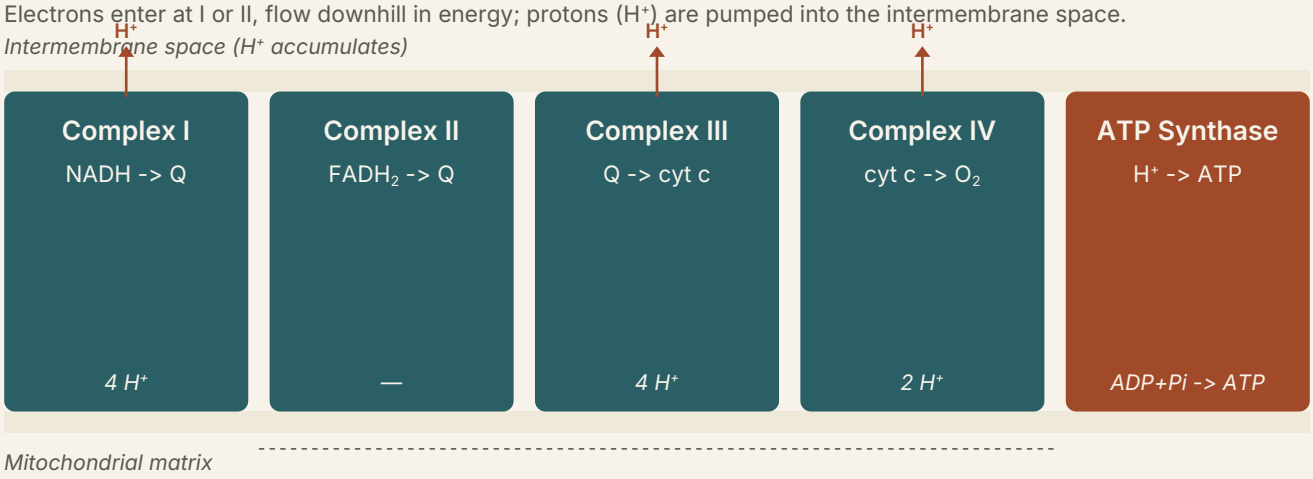
How it actually makes ATP

Imagine a stair-step inside the inner membrane of the mitochondrion. Each step is a protein complex. Electrons hop down the stairs, losing a little energy at each one. That lost energy is not wasted — it is used to push hydrogen ions (protons) from inside the matrix into the intermembrane space. After a few seconds of this, the intermembrane space is packed with protons and the matrix is depleted. There is a gradient. A pressure difference, like behind a dam.

The dam has exactly one door, and the door is a turbine called **ATP synthase**. Protons rush back through it. The turbine spins. Each spin grabs an ADP and a phosphate and fuses them into ATP. That is the whole trick. *The chain doesn’t make ATP directly — it makes a gradient, and the gradient makes ATP.* Once you see that, you see why anything that ruins the membrane (Chapter 2) also ruins everything downstream.

Inner mitochondrial membrane — electron transport chain

Electrons enter at I or II, flow downhill in energy; protons (H^+) are pumped into the intermembrane space.



Dashed arrow: electron flow (left to right, downhill in free energy).

Note: $FADH_2$ enters at Complex II — skipping Complex I and its proton-pumping step.

Lower ATP yield per $FADH_2$ than per NADH.

Figure 1.1 — The electron transport chain. Electrons from NADH enter at Complex I; electrons from $FADH_2$ enter at Complex II, skipping Complex I and its proton pump.[1]

Sources cited on this page

[1] Wallace, D.C. (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer. *Annual Review of Genetics*, 39, 359–407. https://doi.org/10.1146/annurev.genet.39.110304.095751

Glycolysis vs. oxidative phosphorylation

Now the part that explains why nutrition and training arguments get heated. There are two fundamentally different ways to extract energy from glucose. The first one, **glycolysis**, happens in the cytoplasm, doesn't need oxygen, and is fast — it can produce ATP in milliseconds. But it's also crude. Per glucose, you get a net of about **2 ATP**. That's it. Glycolysis is cash: small bills, instantly available, useful in emergencies.

The second, **oxidative phosphorylation**, happens inside the mitochondrion. It needs oxygen, takes longer to spool up, and is much more efficient: roughly **32 to 36 ATP per glucose**.[2] Oxidative phosphorylation is salary — slower to arrive, larger in total, and what you live on for ninety-nine percent of the day. A healthy person can switch between the two cleanly. An unhealthy person gets stuck — usually in glycolysis at rest, which feels like wired, restless fatigue.

ATP yield per glucose molecule
Net ATP produced by each pathway, single glucose substrate.

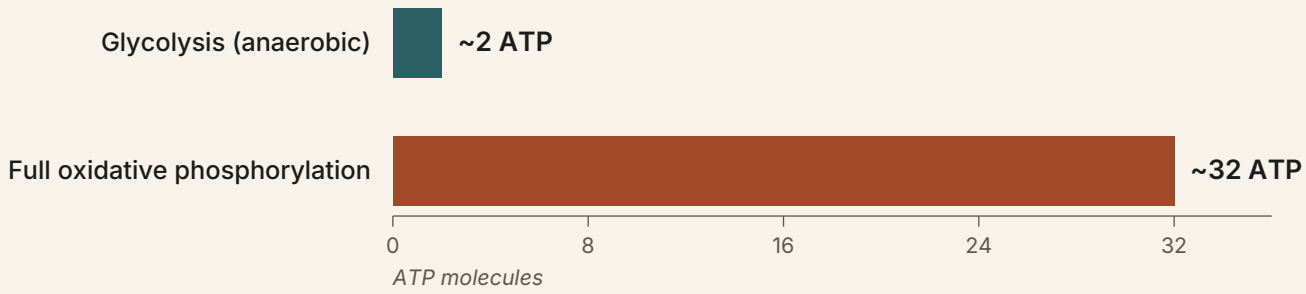


Figure 1.2 — Same glucose, very different yield. Glycolysis is cash; oxidative phosphorylation is salary.

$FADH_2$ hands off at Complex II — "Skip-The-Front-Door."

Memory hook: NADH enters at the front door (Complex I) and pumps the most protons. $FADH_2$ enters at the side door (Complex II) and pumps fewer. That's why each NADH yields more ATP than each $FADH_2$.

Sources cited on this page

[2] Rich, P.R. (2003). The molecular machinery of Keilin's respiratory chain. *Biochemical Society Transactions*, 31, 1095–1105. https://doi.org/10.1042/bst0311095

Why the negotiator metaphor matters

Here is the part that changed how I coach. A power plant fails by running out of fuel. A negotiator fails by misreading the room. Most of the people I work with in their fifties and sixties have *plenty* of fuel — they're carrying it on their hips. They aren't low on substrate. They're low on the *flexibility* to pick the right one. They wake up burning sugar when they should be burning fat. They burn fat when they should be burning lactate. The mitochondria are still there, but the negotiation has gotten stiff.

This is what we mean by **metabolic flexibility**. A flexible system fluently switches between fuels as conditions change: glucose when you sprint, fatty acids when you walk, ketones when you fast, lactate as a shuttle between muscle and brain. An inflexible system locks into one mode and gets stuck there. Goodpaster and Sparks have a good review on this; their work shows that flexibility can be re-trained at almost any age.[3]

What "more mitochondria" actually means

When people say a training program "makes more mitochondria," they're talking about a process called **mitochondrial biogenesis** — your cells literally building new mitochondria and improving the quality of the ones they already have. The signal that kicks this off is mostly a transcription co-activator called PGC-1 alpha, and the things that wake it up are the same things your grandmother would have called "honest work": endurance, cold, heat, fasting, lifting heavy. We will pick this thread back up in Chapter 3.

So when you hear that something "boosts your mitochondria," the right next question is always: *which part of the negotiation does this fix?* Substrate? Membrane? Cleanup? Without that question, every supplement looks the same. With it, you can throw most of them out.

> **TEACH-IT-BACK CHECK**
>
> Can you draw the electron transport chain on a napkin right now? Can you explain why the gradient is the actual product, and ATP is downstream of the gradient? If yes, move on. If no, flip back to Figure 1.1 before you turn the page.

Sources cited on this page

[3] Goodpaster, B.H., & Sparks, L.M. (2017). Metabolic flexibility in health and disease. *Cell Metabolism*, 25(5), 1027–1036. https://doi.org/10.1016/j.cmet.2017.04.015

Chapter 2

Why mitochondria fail

If a mitochondrion is a kitchen, these are the four ways the kitchen goes down.

THE 20%

Mitochondria don't fail randomly. They fail in four specific ways, and almost every clinical pattern you'll see maps to one of them. Memorize the acronym S.L.A.M.: **S**ubstrate mismatch (wrong fuel for the demand), electron **L**eak (oxidative stress), **A**rchitecture damage (the inner membrane and its signature lipid, cardiolipin), and **M**itophagy failure (the cell can't clear bad mitochondria). Each failure mode responds to a different intervention. Mismatching them is why so much of "mitochondrial support" quietly does nothing.

Run with the kitchen analogy. The first failure is **wrong groceries**: **substrate mismatch**. The cell wants to burn fat at rest, but has been trained for decades to expect a sugar drip every two hours, so it sits idle on fat and waits for the next snack. The fix is not a supplement — it's changing what the kitchen expects.

The second is **a kitchen fire**. Electrons are supposed to stay on the chain. When they leak — always a little, sometimes a lot — they react with oxygen to form **reactive oxygen species (ROS)**. A small amount is a signal; a lot is a fire. This is what people mean, loosely, by "oxidative stress."[4]

The third is **a broken stove**. The inner membrane of the mitochondrion is a delicate piece of architecture, and one specific lipid — **cardiolipin** — holds the electron transport chain in the right shape. When cardiolipin gets oxidized, the chain literally falls apart. Electrons fall off where they shouldn't. The whole machine becomes leaky, inefficient, and pro-inflammatory. You can do everything right at the substrate layer and still be stuck because the stove itself is bent.[5]

The fourth is **the dishes never get done**. Cells are supposed to identify damaged mitochondria and recycle them — a process called **mitophagy**. When mitophagy slows, broken mitochondria pile up, leak more, and trigger chronic low-grade inflammation that looks, to the outside world, exactly like "getting older."

Sources cited on this page

[4] Murphy, M.P. (2009). How mitochondria produce reactive oxygen species. *Biochemical Journal*, 417(1), 1–13. https://doi.org/10.1042/BJ20081386

[5] Paradies, G., et al. (2019). Role of cardiolipin in mitochondrial function and dynamics in health and disease. *Cells*, 8(7), 728. https://doi.org/10.3390/cells8070728

Mapping the four failure modes

S.L.A.M. is easy to remember, but it's more useful when you can see how the four modes differ in *timing* and *nature*. Some failures are acute — they happen in a single bad week of training or a single illness. Others are chronic — they're the slow drift of a decade. Some are *structural* — physical damage to the hardware. Others are *signaling* — the hardware is fine, but the messages going in or coming out are wrong.

Failure modes by timing and by nature

Where each letter of S.L.A.M. tends to sit on two axes a clinician can feel.

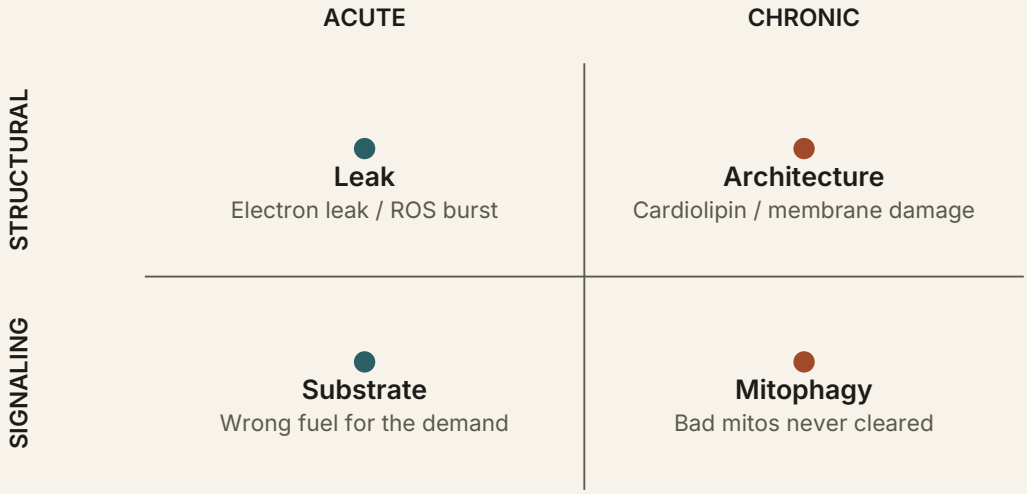


Figure 2.1 — The four failure modes plotted by timing and nature. Substrate mismatch and electron leak tend to be the more acute, more swing-able problems; architecture damage and failed mitophagy are the long-game problems that compound over years.

S.L.A.M. — Substrate · Leak · Architecture · Mitophagy

Four modes. Four answers. Don't mix them up.

Why this matters in practice

Two clinical sketches, both real, both common.

The over-fueled, under-walked executive

Forty-eight, sedentary, sleeps badly. Eats reasonably. Wakes up tired even after eight hours in bed. Resting lactate is creeping up. Fasting glucose is 105. He is convinced he needs "more energy," so he buys a stack with CoQ10 and a B-complex. Six weeks later he feels exactly the same. The reason is that his failure mode is *substrate mismatch*, not substrate shortage. His mitochondria don't need more fuel. They need to learn how to choose. Zone 2 work, two short sprint sessions a week, and a longer overnight fast would have moved him in three weeks. Pills can't teach flexibility.

The over-trained, under-recovered athlete

Thirty-six, runs twelve hours a week, eats clean, sleeps six. Performance has been flat for ten months. He is in the *leak* quadrant: chronic high-volume training without enough recovery is keeping his ROS load elevated. The fix is not more training. The fix is more sleep, periodized intensity, and giving mitophagy time to catch up. He's not under-trained. He's under-cleaned.

> **DIAGNOSTIC HEURISTIC**
>
> Before reaching for any intervention, ask: *which letter of S.L.A.M. is this?* If you cannot name the letter, you cannot name the answer. Most over-prescribing in this space — supplements, peptides, fancy lab panels — happens because the letter was never named in the first place.

Hold this idea, because in Chapter 4 we'll line the interventions up against the failure modes one by one. The whole game is matching the layer to the letter.

Chapter 3

Hormesis, or why stress is the teacher

The thing that breaks you in the wrong dose is exactly the thing that builds you in the right one.

THE 20%

Hormesis is the dose–response curve every biological adaptation rides on: **small dose, no effect; right dose, you get stronger; too much, damage.** An inverted U. The same stressor — heat, cold, exercise, fasting — can be teacher or bully depending on dose, frequency, and recovery. Mitochondria are particularly sensitive to this curve because the signals that build new mitochondria are the same signals that, in excess, break them.

The hormetic curve

Low dose: no effect. Right dose: adaptation. Too much: damage.

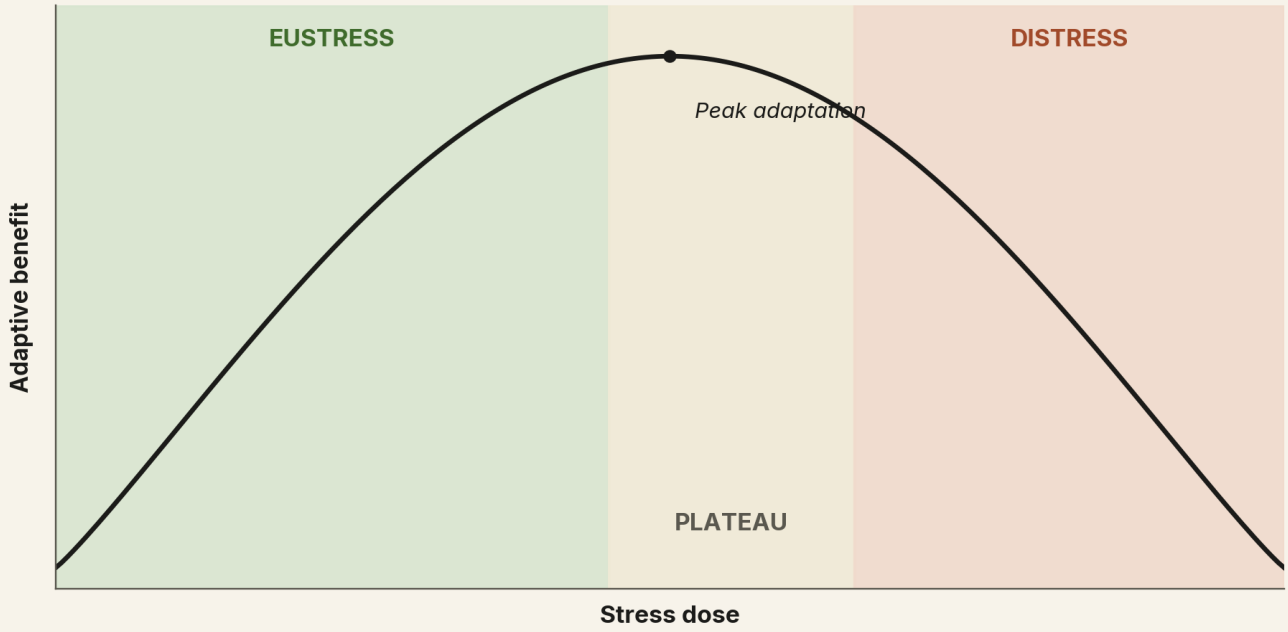


Figure 3.1 — The hormetic curve. The green zone (Eustress) is where adaptation lives. The plateau is where most people quietly stall. The rust zone (Distress) is where well-meaning athletes break themselves and call it discipline.

Edward Calabrese has spent thirty years collecting evidence that this curve shows up absolutely everywhere in biology — across organisms, across stressors, across outcomes.[6] It's less a theory and more a rule of how living systems handle insult. Every adaptation you care about — strength, endurance, glucose control, even resilience to cold — has a hormetic dose-response curve underneath it.

Sources cited on this page

[6] Calabrese, E.J., & Mattson, M.P. (2017). How does hormesis impact biology, toxicology, and medicine? *npj Aging and Mechanisms of Disease*, 3, 13. https://doi.org/10.1038/s41514-017-0013-z

The four practical levers

1. Heat

Sauna at 175–195°F for fifteen to twenty minutes activates heat shock proteins — molecular chaperones that help refold damaged proteins and protect mitochondrial membranes. The well-known Finnish cohort data showed dose-dependent reductions in cardiovascular mortality with frequency.[7] Two to three sessions a week is the sweet spot for most people. More is not better; it just moves you toward the right end of the curve.

2. Cold

Cold exposure — a two-to-five-minute cold shower or a brief plunge at 50–55°F — activates brown adipose tissue, norepinephrine, and mitochondrial biogenesis through a different signaling pathway than heat. You don't need to suffer; you need to be honestly cold for a few minutes, a few times a week. Treat it as a signal, not a contest.

3. Exercise

This is the most studied hormetic stressor in biology. Zone 2 (the highest pace at which you can still nose-breathe and hold a conversation) is the strongest known driver of mitochondrial *quantity*. High-intensity intervals push mitochondrial *quality* — better-functioning Complex I and IV per unit mitochondrion. You want both. Ninety minutes of Zone 2 weekly, plus two short sprint sessions, is more than enough to start.

4. Fasting

Going without food for twelve to sixteen hours periodically does two useful things at once: it forces the cell to switch fuels (training flexibility) and it activates autophagy — the broader version of mitophagy. You don't need to be exotic about this. An overnight fast from dinner to a slightly later breakfast, three or four days a week, does most of the work. Bigger fasts are tools for specific cases, not daily practice.

Sources cited on this page

[7] Laukkanen, T., et al. (2015). Association between sauna bathing and fatal cardiovascular and all-cause mortality events. *JAMA Internal Medicine*, 175(4), 542–548. https://doi.org/10.1001/jamainternmed.2014.8187

How to dose stress without breaking yourself

Two practical rules that separate the eustress zone from the distress zone.

Rule one: signal beats severity. A short, sharp, well-recovered stressor builds you. A long, smeared, under-recovered one wears you down — even if the total "dose" looks similar on paper. Three thirty-second hill sprints with full recovery is a signal. Twenty minutes of sustained high heart rate on tired legs is, for most people, noise.

Rule two: recovery is the adaptation. The stress is not the adaptation — the stress is the message. The adaptation happens during the recovery, when the cell reads the message, builds new mitochondria, lays down new capillaries, and synthesizes new proteins. If recovery is poor (bad sleep, chronic underfueling, emotional load), the message lands but no one answers it. The whole effort is wasted.

"Stress is a signal, not a sentence."

The dose is the difference between teacher and bully. Always ask: am I in the green or the rust?

If you take one thing from this chapter, take this: every supplement, every peptide, every fancy mitochondrial intervention in Chapter 4 is downstream of this curve. You can't out-supplement chronic distress. You can't out-supplement chronic plateau either. The fastest, cheapest, and most powerful mitochondrial interventions are the four levers above. Get them right first.

Chapter 4

The three classes of intervention

Once you can name the failure mode, the right intervention picks itself.

THE 20%

Every credible mitochondrial intervention belongs to one of three classes. **Class 1 — Substrate & cofactor** (e.g., CoQ10, NAD precursors, B-vitamins, creatine) restocks the raw materials the chain needs. **Class 2 — Signaling modulators** (e.g., urolithin A, PQQ, SLU-PP-332, BAM15) nudge the cellular conversation about how many mitochondria to build, when to clear them, and how tightly to couple the machine. **Class 3 — Lifestyle inputs** (Zone 2, sprints, cold/heat, sleep, fasting) are the hormetic signals from Chapter 3. *Match the class to the failure mode.*

Class 1 — Substrate and cofactor

These are the raw materials the chain literally needs. **CoQ10** is the mobile shuttle between Complex I/II and Complex III; deficiency is genuinely common in people on statins and in some forms of fatigue.[8] **NAD precursors** (nicotinamide riboside, nicotinamide mononucleotide) feed the cell's pool of NAD+, the electron-carrier that delivers electrons to Complex I — Sinclair's lab has been the loudest voice on this, and the human data is steadily catching up to the mouse data.[9] **B-vitamins** (especially B2, B3, B6) are coenzymes throughout the chain. **Creatine** isn't a mitochondrial cofactor per se, but it directly buffers ATP turnover and there's no longer any reasonable case against five grams a day for most adults.

When this class helps: when the substrate or cofactor really is missing. **When it doesn't:** when the failure mode is leak, architecture, or mitophagy. Filling a leaky tank with better gasoline doesn't fix the leak.

Sources cited on this page

[8] Hernández-Camacho, J.D., et al. (2018). Coenzyme Q10 supplementation in aging and disease. *Frontiers in Physiology*, 9, 44. https://doi.org/10.3389/fphys.2018.00044

[9] Yoshino, J., Baur, J.A., & Imai, S.-I. (2018). NAD+ intermediates: the biology and therapeutic potential. *Cell Metabolism*, 27(3), 513–528. https://doi.org/10.1016/j.cmet.2017.11.002

Class 2 — Signaling modulators

This is the class that's getting the most attention and the most marketing, and it's where you have to be careful. These compounds don't deliver substrate. They change the conversation the cell is having with itself.

Urolithin A is the most rigorously studied. It's a metabolite that some gut bacteria produce from ellagitannins (pomegranate, walnuts). In humans, supplementation has increased markers of mitophagy and improved muscle function in older adults.[10] Mechanistically, it nudges the cell toward clearing damaged mitochondria — directly addressing the "M" in S.L.A.M. **PQQ** (pyrroloquinoline quinone) has decent biogenesis data in vitro and weaker but real human data.

SLU-PP-332 and **BAM15** are at the frontier — far more experimental, and named here so you know what they are when you hear them. SLU-PP-332 is an ERR-alpha agonist that mimics many endurance-training adaptations in mice; BAM15 is a mild mitochondrial uncoupler that increases substrate burn at modest doses. Neither has the clinical track record to recommend broadly yet. Watch the literature; don't be a first adopter.

When this class helps: chronic, signaling-layer problems — failed mitophagy, biogenesis plateau, sluggish substrate switching. **When it doesn't:** when the lifestyle inputs in Class 3 are not yet in place. Signaling modulators on top of a sedentary, under-slept baseline are a tax write-off, not a strategy.

RULE OF THE LAYER

Intervene at the layer that matches the failure mode. If the kitchen is on fire, don't reorder groceries. Substrate problems need substrate. Signaling problems need signaling. Lifestyle inputs underwrite both.

Sources cited on this page

[10] Andreux, P.A., et al. (2019). The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nature Metabolism*, 1(6), 595–603. https://doi.org/10.1038/s42255-019-0073-4

Class 3 — Lifestyle inputs

I am going to say this plainly: this is the class that does the most work, and it's the class people most want to skip. **Zone 2 endurance work** is the single most powerful intervention for mitochondrial quantity and substrate flexibility we know of. Ninety minutes a week is a good starting dose. **Sprint intervals** (six to ten rounds of thirty-second hard efforts, full recovery) drive mitochondrial quality. **Cold and heat**, as covered in Chapter 3, recruit pathways the other two miss. **Sleep** is the recovery substrate — no recovery, no adaptation. **Fasting** trains the fuel switch.

None of this is exotic. None of this is expensive. All of it is harder than swallowing a pill. And all of it is what your supplement is trying to imitate, badly, after the fact.

A comparison table

Class	Mechanism	Time to effect	Risk profile	Example
1 — Substrate & cofactor	Restocks raw materials of the chain	Days to weeks	Low (when dosed sensibly)	CoQ10, NAD precursors, creatine
2 — Signaling modulator	Changes the cellular conversation	Weeks to months	Low–moderate; limited long-term data for newer compounds	Urolithin A, PQQ, SLU-PP-332*
3 — Lifestyle input	Hormetic signal: trains the whole system	Weeks to years (compounds)	Very low when properly dosed; high if overdone	Zone 2, sprints, sauna, sleep, fasting

*Table 4.1 — Three classes of intervention. *SLU-PP-332 is experimental; included for completeness, not as a recommendation.*

Matching layer to letter

Put it together. If a client's primary failure mode is **substrate mismatch (S)**, the highest-leverage interventions are lifestyle — Zone 2 plus an honest overnight fast — and, if needed, a small assist from Class 1 (creatine, B-vitamins). Throwing urolithin A at this person is fine but inefficient. They don't need better mitophagy. They need better fuel choice.

If the failure mode is **leak (L)**, the answer is recovery first: more sleep, more polyphenols in the diet, and only then a careful Class 1 stack (CoQ10, B-vitamins). If the failure mode is **architecture damage (A)**, you are playing a longer game: consistent Zone 2 to drive remodeling, careful management of polyunsaturated-fat oxidative load, and time. There is no "cardiolipin pill." If the failure mode is **mitophagy failure (M)**, this is where Class 2 — particularly urolithin A — has its clearest case, paired with fasting to drive autophagy from the lifestyle side.

> **THE ORDER MATTERS**
>
> Layer 3 (lifestyle) is the floor. Layer 1 (substrate) fills gaps. Layer 2 (signaling) fine-tunes. Inverting the order — leading with Class 2 because it's the new, exciting thing — is the single most common mistake I see in this space. It rarely fails spectacularly; it just fails to compound.

One last thing. Every intervention in this chapter has dose-response of its own. None of them escape the hormetic curve from Chapter 3. Even creatine. Even Zone 2. The right question is never "will this work?" — the right question is always "at what dose, for whom, paired with what?" That's the question a coach is paid to answer.

Chapter 5

How to measure what you're doing

A few honest signals beat a dashboard of expensive ones.

THE 20%

You don't need a $4,000 mitochondrial assay to know if you're adapting. Six boring, cheap measurements — **resting and post-exercise lactate, heart-rate variability (HRV), fasting glucose, waking heart rate, sleep quality, and how you actually feel** — will tell you almost everything you need to know if you track them weekly for twelve weeks. The job is not to chase any single number. The job is to triangulate.

The six signals

Resting lactate (and post-exercise lactate). Resting lactate above ~1.5 mmol/L in a rested, fed, sedentary state is a soft sign of metabolic inflexibility — mitochondria spinning glycolysis in the background. A post-exercise lactate that doesn't clear within twenty minutes after a moderate effort is another. These are slow to change (six to twelve weeks) and very honest.

Heart-rate variability (HRV). Measured with a chest strap or a halfway-decent ring, first thing in the morning, before coffee. HRV is autonomic balance — high vagal tone equals high HRV equals a recovered system. Day-to-day swings are noisy; the seven-day rolling average is the signal. A trending-up rolling average over weeks is a real adaptation.

Fasting glucose. A simple morning finger-stick. Sustained fasting glucose above 100 mg/dL in someone who is not actively diabetic is, more often than not, a metabolic flexibility problem before it's anything else. Improvements in fasting glucose with Zone 2 plus fasting are usually the first thing to move.

Resting metabolic rate (if you have access). An indirect calorimetry test reveals your respiratory quotient (RQ). An RQ near 0.7 at rest means you're burning mostly fat; near 1.0 means mostly carbs. A healthy, fasted, rested person should be closer to 0.7. Most aren't.

Waking heart rate. Cheapest tool in the kit. Track it daily. A downward drift of five to ten beats over twelve weeks of training is what real adaptation looks like.

Recovery sleep. Total time-in-bed is necessary but not sufficient. Sleep efficiency and time in deep/REM stages matter more. Any decent ring or under-mattress sensor gets you in the ballpark.

How to read a dashboard

Below is a sketch of what a typical mentee's dashboard looks like at baseline and after twelve weeks of layered interventions — Zone 2 endurance, two sprint sessions weekly, sauna two to three times weekly, a sane sleep window, and a modest overnight fast. No supplements beyond creatine. No peptides. The point of the sketch is not to promise these specific numbers — your numbers will differ — but to show what a coordinated set of changes looks like when many small signals move together. *That* coherence is the real proof of adaptation. A single number moving in isolation is noise.

Adaptive Capacity Dashboard

Indicative ranges for a typical mentee at baseline (gray) and after twelve weeks (teal).

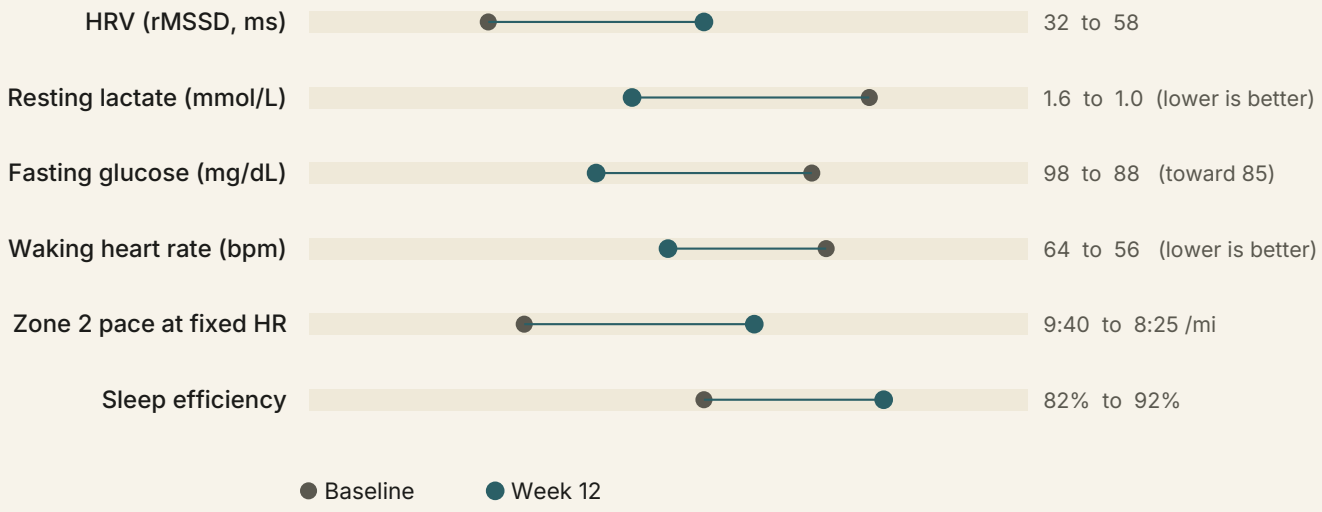


Figure 5.1 — Indicative dashboard. The pattern of coordinated improvement is the point, not the absolute numbers.

On "feeling better"

Subjective feel is a real signal — but it's a slow one, and it can lie. Two patterns to know. First, real adaptation often *feels* dull at first because the cell is using energy to rebuild rather than to spend. Second, stimulants and quick fixes feel great tomorrow and tell you nothing about month three. Triangulate feel with the six numbers above. If feel and the numbers are both moving up over six to twelve weeks, you have a real adaptation. If feel is up and the numbers are flat, you have a story you're telling yourself.

Chapter 6

A 30-day starter protocol

Minimum effective dose, then iterate. You can start tomorrow.

THE 20%

Three layers, run for thirty days, then reassessed against the six signals in Chapter 5. **Inputs:** protein-forward meals in a 10-hour eating window, morning daylight, two minutes of nasal breathing before training. **Training:** Zone 2 for ninety minutes a week (three thirty-minute sessions), plus two short sprint sessions. **Recovery:** a fixed sleep window, sauna two to three times weekly. That's it. No supplements in the first thirty days except creatine (5 g/day). The point is to find the floor before adding the ceiling.

Layer 1 — Inputs (food, light, breath)

Eat in a ten-hour window, dinner before 8pm where possible. Front-load protein: thirty to forty grams at the first and last meal. Get ten minutes of direct daylight within thirty minutes of waking. Before every training session, do two minutes of slow nasal breathing — in for four, out for six, eyes closed. Small lever; consistent lever.

Layer 2 — Training (Zone 2 + sprints)

Three Zone 2 sessions, thirty minutes each. Choose a pace where you can hold a conversation or nose-breathe — that's the boundary, not heart rate. Two sprint sessions: six rounds of thirty seconds hard, two minutes easy. Total weekly training time: roughly two hours. If that sounds like "not enough," good — the point is consistency, not heroism.

Layer 3 — Recovery (sleep, sauna)

Pick a fixed bedtime and stick to it for thirty days; consistency beats duration. Two to three sauna sessions of fifteen to twenty minutes each at 175–195°F. Cold exposure is optional in month one; if you do it, two-to-three minutes is enough.

THE 30-DAY CONTRACT

Don't add anything in the first thirty days. No new supplements, no peptides, no fancy lab panels. Run the floor cleanly. At day thirty, reassess against the six signals from Chapter 5. *Then* decide what, if anything, to layer on. This rule alone catches more downstream confusion than any single intervention I can name.

The teach-it-back checklist

Eight questions. If you can answer each one out loud, in plain language, without notes — you own this material.

1. Why is a mitochondrion better described as a *negotiator* than as a power plant? What is being negotiated, between which parties?
2. Walk through the electron transport chain. What is the actual product of the chain, and why is ATP technically downstream of that product?
3. Why does glycolysis yield only ~2 ATP while oxidative phosphorylation yields ~32? When is glycolysis still the right call — and why is the answer not "never"?
4. What are the four S.L.A.M. failure modes? For each one, give the kitchen-analogy version and a real clinical pattern someone might recognize in themselves.
5. Why does *failed mitophagy* end up looking like chronic low-grade inflammation? Trace the path: broken mitochondria, ROS leak, signaling cascade, immune response.
6. Draw the hormetic curve from memory. Label the three zones. Place sauna, cold, Zone 2, sprints, and fasting where they typically sit when used well — and where they sit when they're overdone.
7. Match each of the three intervention classes to the S.L.A.M. failure modes it best addresses. Why is leading with Class 2 (signaling modulators) before Class 3 (lifestyle) almost always inefficient?
8. If a friend told you "I started a supplement and I feel better," what three questions would you ask before agreeing the supplement is working?

HOW TO USE THIS CHECKLIST

Pick a friend who doesn't know any of this. Walk them through the eight answers in one sitting, with a napkin and a pen. The places you stumble are the chapters you need to re-read. Teaching is the most reliable diagnostic of your own understanding that anyone has ever invented.

Glossary

Short, working definitions. Not exhaustive — exhaustive would be the textbook.

ATP. Adenosine triphosphate — the energy currency every cell spends to do work.

ADP / Pi. ATP after it has been spent; the mitochondrion's job is to recombine them.

ETC (Electron transport chain). The four protein complexes (I–IV) in the inner mitochondrial membrane that pass electrons downhill and use the energy to pump protons.

ATP synthase. The molecular turbine that lets protons rush back into the matrix and uses the spin to fuse ADP and Pi into ATP.

Glycolysis. The cytoplasmic pathway that splits glucose into pyruvate; fast, oxygen-independent, low-yield (~2 ATP per glucose).

Oxidative phosphorylation. The mitochondrial process of making ATP using the proton gradient generated by the electron transport chain; high-yield (~32 ATP per glucose).

NAD^+ / NADH. Electron-carrier pair that delivers electrons from food to Complex I. Falling NAD+ pools are a hallmark of mitochondrial aging.

$FADH_2$. Alternate electron carrier that enters at Complex II — "skip-the-front-door" — yielding fewer ATP per molecule than NADH.

CoQ10 (ubiquinone). Mobile lipid shuttle that ferries electrons from Complexes I and II to Complex III.

Cardiolipin. Signature phospholipid of the inner mitochondrial membrane; holds the ETC in functional shape. Sensitive to oxidative damage.

ROS (reactive oxygen species). Highly reactive oxygen-containing molecules formed when electrons leak from the chain. Small amounts: useful signals. Large amounts: damage.

Hormesis. Inverted-U dose-response: a stressor that is harmful at high doses is beneficial at lower, recoverable doses.

Mitophagy. The selective recycling of damaged mitochondria — the kitchen cleanup crew.

Mitochondrial biogenesis. The cellular process of building new mitochondria. Driven largely by PGC-1 alpha and triggered by endurance, cold, heat, and fasting.

Metabolic flexibility. The ability to switch fluently between fuels (fat, glucose, ketones, lactate) as conditions demand. The most under-rated marker of metabolic health.

Zone 2. Training intensity at which you can still hold a conversation or nose-breathe; the strongest known driver of mitochondrial quantity in trained and untrained adults alike.

A closing note

From Anthony

The body is honest. Give it the right signal, give it time, and it will adapt.

Thirty years of coaching has taught me one thing more than anything else: the people who transform are not the people with the most exotic protocols. They're the people who did fewer things, more consistently, while paying attention. They got their sleep window. They walked at Zone 2 four mornings a week instead of three. They ate protein before they ate sugar. They sat in the sauna. They added the next layer only after the last one had actually landed.

That's the whole game. Mitochondria are not magic and they are not mysterious. They are the body's honest accountant: every signal you send them gets written down, summed, and paid back in months. Send them confusing signals — overtraining one week, sedentary the next, stimulants stacked on top of bad sleep — and the books come out illegible. Send them clear, repeated signals — "we move at this pace, we eat in this window, we sleep at this time, we get cold sometimes, we get hot sometimes" — and the books balance. Adaptation is not complicated. It's just slow.

The other thing I've learned: *you don't really own a piece of knowledge until you can teach it*. Read this primer once, sure. But the goal is for you to sit across from someone you care about — a partner, a friend, a client, a kid — and explain why their fatigue is a negotiation problem, not a fuel problem. Draw the chain on a napkin. Tell them about the kitchen on fire. Watch them get it. That's the moment the material becomes yours.

Keep teaching what you learn. That's how it actually sticks.

Anthony Castore · SSRP Fellow · CASTORE Method

castoremethod.com · Built to Adapt