

Zero Age

Why every life begins at
nothing, and why the brain
can never go back

The cells that never age
and the cells that always do

Entropy Lab



Zero Age

The cells that never age and the cells that always do

Zero Age

The cells that never age and the cells that always do

First edition, October 2026

Compiled by Entropy Lab, Jeju, Republic of Korea.

This book grew out of a long research conversation at Entropy Lab. Every study cited here was checked against its record in PubMed, and the references at the back carry DOIs.

This is a work of popular science. It offers no diagnosis, no treatment and no advice about medication. Decisions about your health belong with a qualified clinician.

Contents

PROLOGUE	The Mayfly’s Question	1
CHAPTER ONE	Ageing Is Subtraction	4
INTERLUDE ONE	The Power Plant Inside the Cell	9
CHAPTER TWO	The Egg Puts Out the Fire	14
CHAPTER THREE	Parts Built to Last	20
CHAPTER FOUR	You Have to Break It to See It	25
CHAPTER FIVE	Discarding Almost Everything	30
INTERLUDE TWO	From Flies to People	35
CHAPTER SIX	The Clean-Up Between Generations	39
CHAPTER SEVEN	What the Neuron Lost	44
CHAPTER EIGHT	How to Measure a Rate	50
CHAPTER NINE	Which Curve Do You Move?	56
CHAPTER TEN	The Erasers We Have Not Found	62
EPILOGUE	Finite Things, Joined End to End	68
GLOSSARY	Words Used in This Book	72
CHRONOLOGY	The Order in Which It Was Found	76
REFERENCES	The Studies Cited Here	80

PROLOGUE

The Mayfly’s Question

Is everything a finite creature does ultimately pointless? This book takes that old question and asks it again — not in the language of philosophy, but in the language of cells.

IN THIS CHAPTER

The thing that does not end	2
The cell on the downslope	2
What this book asks	3

A mayfly spends a year or two underwater as a nymph. When it finally takes to the air, its mouthparts have withered away. It cannot eat. It finds a mate, lays its eggs, and dies. What we call a mayfly is really those last few days, sometimes those last few hours. People have used that brevity as a symbol of futility for as long as they have written things down. If the ending is fixed, what is the striving for?

Philosophy has worked on this question for a very long time. Biology asks something that sounds similar but is not quite the same. What exactly does it mean for an ending to be fixed? What ends, and what does not?

The thing that does not end

A single mayfly dies in a matter of days. But trace that mayfly back to the egg it came from, and the germ cells that made the egg, and the germ cells that made those — and the line never breaks. For something like four billion years, since life first appeared, the ancestral lineage of every organism alive today has run without skipping a single generation. One break anywhere and we would not be here.

The same is true of us. Our bodies are built from tens of trillions of cells, and nearly all of them will fail within a few decades. But one very small population, the germ line that makes eggs and sperm, lives a different kind of life. Those cells came from your mother, who had them from her mother, and the line runs backwards without end. It is a strange thing. Inside the same body, built from the same DNA and the same proteins and the same mitochondria, one kind of cell collapses in decades and another is effectively immortal.

Cells made of identical chemistry: one kind fails in decades, the other has carried on for four billion years.

The cell on the downslope

The second character in this book is the neuron. Most of the neurons in your brain took their places around the time you were born and have never been replaced since. The neurons carrying the thoughts of an eighty-year-old are mostly eighty years old themselves. Skin cells turn over in weeks and the lining of the gut in days, but a neuron has to make the original equipment last a lifetime.

And it never rests. The brain accounts for about two per cent of body mass but consumes something like a fifth of the body's energy at rest — a figure quoted often enough to have become proverbial. Nearly all of that energy comes from small power plants inside the cell called mitochondria. Power plants wear out as they run, and worn plants smoke. The neuron spends decades replacing its failing plants and scrubbing the smoke, until at some point the repairs stop keeping pace with the damage. At the bottom of that slope lie Alzheimer's disease and Parkinson's disease.

What this book asks

Set the two cells side by side and the question sharpens. What does the germ line do that keeps it unbroken? What can the neuron not do, that puts it on a downslope? And is there anything in the germ line's repertoire that a neuron could borrow?

That is the path this book follows. Chapter 1 turns ageing into a single inequality. Chapters 2 through 6 look at what the germ line does with that inequality. Chapter 7 asks why the neuron is so badly placed, chapter 8 asks how anyone actually measures a repair rate, and chapter 9 covers what is being tried on the neuron's behalf right now. Chapter 10 asks whether there is a mechanism nobody has found yet.

A warning in advance: there is no recipe for living forever in these pages. The closer you look at how the germ line manages it, the clearer it becomes what immortality costs. The germ line keeps its line going by discarding almost everything and handing on one survivor. The individual ends; the lineage does not. Somewhere in that fact there may be an answer to what a finite creature's striving is for.

GOING DEEPER · HOW TO READ THIS BOOK

Every study cited here was checked against its record in PubMed, and the references at the back carry a DOI for each one. Pay particular attention to which organism each result came from. A fact established in a fruit fly or a roundworm is not thereby a fact about people. The text tries never to hide that difference.

CHAPTER ONE

Ageing Is Subtraction

Why does a living system eventually lose the ability to repair itself? Every thread in this book runs back to that question.

IN THIS CHAPTER

One inequality	5
Repair has a price	6
But one line never breaks	7
The second character	8
What to take from this chapter	8

Comparing a cell to a factory invites a misunderstanding. A factory ships finished goods out of the door; a cell is endlessly rebuilding itself. Proteins are made, put to work, broken down and replaced — some within minutes, some only after years. Damaged mitochondria are torn apart whole. Enzymes find breaks in DNA and patch them. While you read this sentence, repair crews in your body are working without pause.

If that work were perfect, nothing would ever grow old. The problem is not that it is imperfect, nor that it makes occasional mistakes. The problem is **rate**.

One inequality

Put as simply as possible, ageing looks like this.

$$\begin{aligned} &\text{rate at which damage accumulates} = \text{rate at which damage appears} \\ &\quad - \text{rate at which it is repaired} \end{aligned}$$

While the second term is larger, nothing accumulates. From outside it looks as though nothing is happening at all, when in fact relentless destruction is being matched by relentless repair. A boat holding its position in a river looks still, but somebody is rowing.

Then at some point the rowing stops matching the current, and the boat begins to slip back. That point is ageing, and in the brain it is neurodegenerative disease.

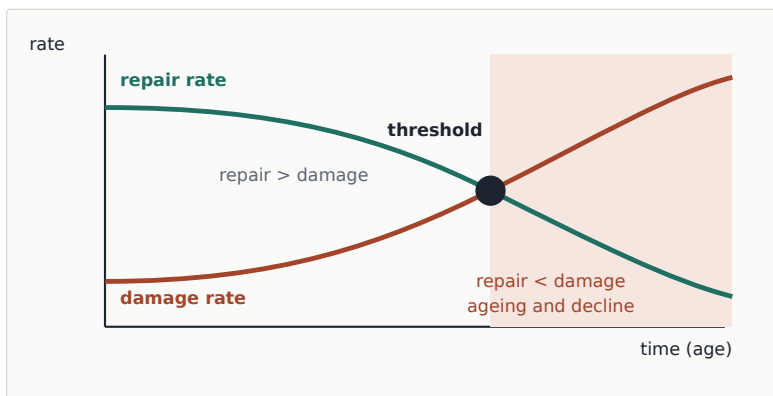


Figure 1 Repair rate and damage rate. Where the curves cross is the threshold of ageing. The shapes are schematic; real curves differ by tissue and by individual.

Figure 1 makes two things visible. First, damage may begin to accumulate not because damage suddenly increased but because repair fell behind. Second, the moment it begins is not an event but a relationship between two curves.

Repair has a price

Why does the cell not simply row harder? Because rowing is expensive.

Building a protein costs amino acids and energy. Dismantling a damaged mitochondrion and building a replacement costs more. Keeping a full complement of DNA repair enzymes on hand costs again. An organism's resources are finite, and the same resources are wanted for growth and for reproduction.

In the 1970s the biologist Thomas Kirkwood drew a conclusion from this. Natural selection does not favour maintaining a body indefinitely; it favours maintaining a body for as long as reproduction requires. Kirkwood used the Greek word for body, **soma**, and called the idea the disposable soma theory. The body is a vehicle for carrying genes into the next generation, and a vehicle only has to reach its destination.

In Kirkwood's own framing, ageing is the accumulation of unrepaired somatic defects, and the main genetic control on longevity works by raising or lowering the investment in basic cellular maintenance to match the level of hazard in the environment.

The body is a vehicle for carrying genes to the next generation, and a vehicle only has to reach its destination.

The theory explains why a mouse lives three years and an elephant sixty. An animal very likely to be eaten gains nothing from investing in maintenance, because it will die before the investment pays. Growing fast and breeding early is the better strategy. An animal at low risk can afford to build for the long run.

But one line never breaks

The disposable soma theory carries an obvious corollary. If the body is a vehicle to be discarded, something must be the cargo. That something is the germ line.

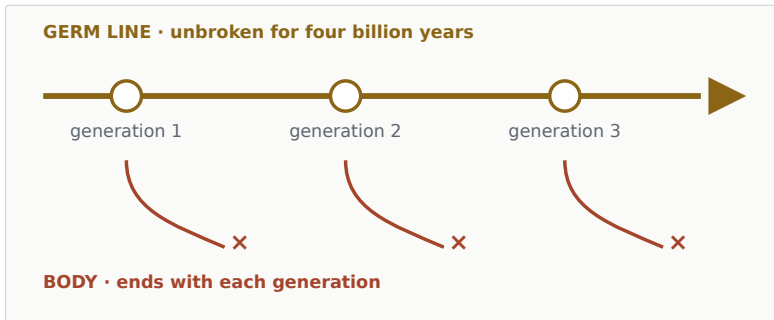


Figure 2 The unbroken germ line (above) and the body that ends in every generation (below). The body is closer to a disposable vehicle that carries the line to the next round.

Here is the central tension of this book. The germ line is made of the same molecules and obeys the same physics. Thermodynamics applies to a germ cell exactly as it applies to a muscle cell. And yet that line has never broken. Which raises the possibility that finitude is not a law of life but a condition the body has settled for.

If that is right, the question inverts. Not **why does the body age**, but what does the germ line do that keeps it from ageing?

GOING DEEPER · A CORRECTION, BEFORE WE GO FURTHER

Strictly speaking, germ cells do age. Anything that runs a metabolism accumulates damage. As we will see, the germ line's real trick is not avoiding age but minimising it and then erasing it at the moment one generation becomes the next. Chapter 6 takes that apart in detail.

The second character

Among the cells of the body, one is in a worse position than any other. The neuron.

Most cells divide, and division is itself a repair strategy: when a damaged component is split between two daughters, each carries half the burden. Dividing tissues can also discard a failing cell and replace it.

A neuron can do neither. It does not divide, so it cannot share out its damage; it is not replaced, so it cannot be discarded. And all the while it burns energy at a high rate for a lifetime. In the inequality above, the neuron holds the worst possible combination: a large term on the damage side and very few options on the repair side.

That is why this book keeps the two cells side by side. The germ line uses nearly every tool available on the repair side. The neuron has lost most of them. Comparing the two shows which tools actually matter.

What to take from this chapter

- Ageing is the rate at which damage appears minus the rate at which it is repaired.
- Repair costs resources, and selection does not pay for unlimited maintenance.
- The germ line has never broken. Finitude may be a condition the body settled for, not a law.
- The neuron has lost more repair tools than any other cell.

INTERLUDE ONE

The Power Plant Inside the Cell

Before the argument proper, a short account of what a mitochondrion is and how it works. Readers who already know this can skip ahead.

IN THIS CHAPTER

A bacterium that moved in	10
Earning a living by passing electrons	10
The electrons that leak	11
How the cell manages all this	12
Words used often in this book	13
What to take from this interlude	13

The word that appears most often in this book is **mitochondrion** — the organelle you were taught to call the powerhouse of the cell. But the powerhouse metaphor will not carry the argument on its own. A few more things need saying.

A bacterium that moved in

The strangest thing about a mitochondrion is that it has DNA of its own. Your genome sits in the nucleus; the mitochondrion carries a separate small circle of DNA alongside it.

The leading explanation is endosymbiosis. A very long time ago, a bacterium good at making energy ended up inside another cell, the two carried on together, and over time the lodger became an organelle. Mitochondrial DNA is circular, like a bacterium's, and mitochondria carry ribosomes of their own. Both facts fit.

Over that long cohabitation the mitochondrion handed most of its genes to the nucleus. Human mitochondrial DNA now codes for just thirteen proteins. The other thousand-odd proteins that make up a mitochondrion are built by the nucleus and shipped in.

That single fact creates the axon problem of chapter 7: nearly every part has to be manufactured at a distant head office.

Earning a living by passing electrons

A mitochondrion makes energy rather the way a cascade makes electricity.

Food is broken down, and the breakdown loads electrons onto carrier molecules — NADH and FADH

2

are the main ones. Those carriers hand their electrons to the inner mitochondrial membrane, which has two entrances. NADH delivers to complex I and succinate to complex II; the two sit side by side, not one after the other. From either entrance the electrons pass to complex III, then to complex IV, where they are handed to oxygen. Complex V carries no electrons at all. It is the channel through which protons flow back.

Complex I – the entry point for electrons from NADH
 Complex II – a second entry point, for electrons from succinate
 Complexes III and IV – pass the electrons along and pump protons out
 Complex V – lets the protons back in and makes ATP from the flow

Every time electrons move through complexes I, III and IV, protons are pumped across the membrane. A difference in proton concentration and a difference in electrical charge build up on either side. Together they make the proton-motive force, and the electrical part of it is called the membrane potential. It is a dam filling with water. Complex V is the turbine in the dam: protons flowing back through it turn the machinery that makes ATP, the cell's energy currency.

At the end of the line, oxygen takes the electrons. Oxygen plus electrons plus protons makes water. That is what breathing is for.

The electrons that leak

The flow is not perfect. Some electrons slip out partway and meet oxygen directly, and instead of water you get reactive oxygen species, often called free radicals.

A radical is an unstable molecule with an unpaired electron. To stabilise itself it takes an electron from whatever is nearby, and DNA, proteins and lipids are all damaged in the process. Much of what this book calls “damage” starts here.

The leaks happen mostly at complexes I and III. And at complex I there are two different ways to leak.

Leaking forwards

Electrons travelling in the normal direction, some of which go astray into oxygen.

Leaking backwards

Under the right conditions electrons run the other way. Electrons that entered at complex II travel back up through complex I. This happens when the membrane potential is high and the electron carrier pool is in a reduced state, and it can release a substantial quantity of radicals. This is reverse electron transport, and it is the subject of chapter 9.

How the cell manages all this

Mitochondria are not fixed granules. They fuse and divide continually, changing shape as they go, and that restlessness is the basis of quality control.

Fusion

When mitochondria merge, their contents mix, and a shortfall in one can be covered by another. This is called complementation. As chapter 4 shows, it cuts both ways: it keeps the cell going, and it hides defects.

Fission

Split them apart and each fragment is judged on its own. Defects have nowhere to hide.

Mitophagy

A mitochondrion past saving is removed whole: wrapped in a membrane to form an autophagosome and delivered to a lysosome for digestion. The word joins **mitochondrion** and **autophagy**.

The best-known signalling system for it is PINK1 and Parkin. In a healthy mitochondrion, PINK1 is imported and rapidly destroyed. When the membrane potential falls, import fails and PINK1 piles up on the surface instead. The accumulated PINK1 recruits Parkin, which tags surface proteins with a label that means **dispose of this**. Both genes were discovered as causes of early-onset Parkinson's disease.

Replacing parts

As chapter 3 will show, disposing of the whole organelle is not the only option. Individual proteins inside a mitochondrion also turn over on their own schedules.

Words used often in this book

mtDNA	the circular DNA a mitochondrion carries; in humans it codes for thirteen proteins
heteroplasmy	a mixture of different mtDNA sequences within one cell or one body
membrane potential	the electrical difference across the inner membrane, one component of the proton-motive force; also used as a measure of quality
reactive oxygen species	the reactive molecules formed when leaked electrons meet oxygen
mitophagy	disposal of an entire damaged mitochondrion
lysosome	the acidic, enzyme-filled organelle where material is digested; the cell's incinerator
proteasome	a barrel-shaped machine that destroys tagged proteins; a separate route from the lysosome

What to take from this interlude

- A mitochondrion has its own DNA but imports almost all its parts from the nucleus.
- Electrons flow from complexes I and II through III to IV; the protons pumped out drive complex V to make ATP.
- Leaked electrons become radicals; complex I leaks both forwards and backwards.
- The cell manages mitochondria by fusion, fission, mitophagy and part replacement.

CHAPTER TWO

The Egg Puts Out the Fire

A human egg is made while its mother is still a foetus, and then waits — for decades. The way it survives that wait turns out to be startling. It simply never builds one part of the engine.

IN THIS CHAPTER

A fire without smoke	15
The first of five is missing	15
Not switched off — never built	17
The fire does not go out	17
Making less, or clearing better?	17
Light the fire and the smoke appears	18
The limits, stated plainly	18
What to take from this chapter	19

A girl is born with all her eggs already made. More exactly, the cells that will become eggs are formed inside her mother's womb, while she is still a foetus. The egg a thirty-five-year-old woman ovulates was built thirty-five years earlier and has been waiting in the ovary ever since.

In the world of cells this is extraordinary. Most cells do not live anything like that long. Stranger still, the egg comes through the wait intact. A cell that has waited for decades can, on fertilisation, produce an entire person.

A fire without smoke

A cell makes energy rather as one makes a fire. Inside the mitochondrion, electrons are handed along in stages and energy is drawn off at each step; along the way some electrons escape, meet oxygen and become reactive radicals. Radicals attack DNA, proteins and lipids without discrimination. Light a fire and you get smoke.

For a cell that waits decades, this is a serious problem. One day's smoke is nothing; ten thousand days' smoke is another matter. So what does the egg do — filter the smoke better, or make less of it in the first place?

In 2022 Elvan Böke's laboratory in Barcelona answered the question. The answer was the second one, and the method was bolder than anyone expected.

The first of five is missing

The electron transport chain comes in five complexes, numbered I to V. Electrons enter at I or at II, travel through III and IV, and the force that builds up is used by V to make ATP.

When the researchers examined early oocytes from humans and from frogs, complex I was not there. Not merely scarce — never assembled.

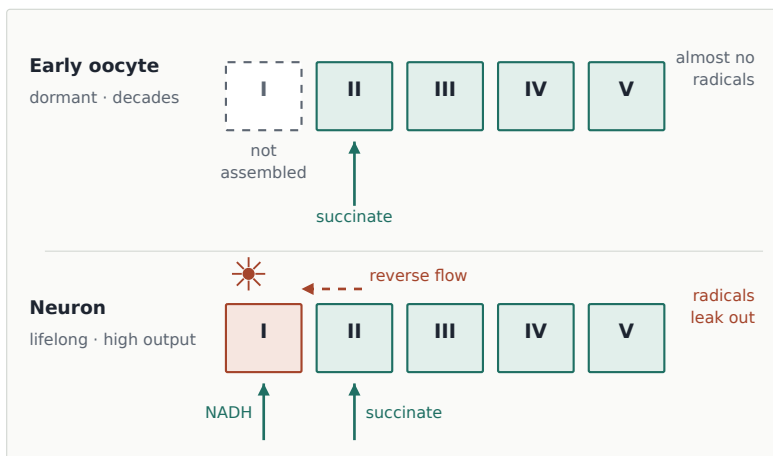


Figure 3 The complexes of the electron transport chain. In the early oocyte (above) complex I is never assembled, so electrons enter only through complex II. The neuron (below) runs complex I without pause, and under the right conditions electrons run backwards through it — reverse electron transport — and oxygen radicals leak out.

Five independent lines of evidence support this. First, when the team applied rotenone, a drug that blocks complex I, seventy-eight per cent of early oocytes survived untouched; mature oocytes died. Second, on gels that separate proteins by size, complex I was not present in assembled form and showed no activity. Third, a direct assay of the reaction complex I performs — oxidising NADH — detected nothing, while complex IV activity was normal. Fourth, levels of FMN, a cofactor that is an integral part of complex I, were around two hundred times lower than in mature oocytes. Fifth, a survey of the whole protein complement found complex I subunits depleted more sharply than anything else.

One control matters especially. When drugs blocking complexes II, III, IV and V were applied, the early oocytes died as readily as any other cell. The mitochondria are running perfectly well. The only missing piece is complex I.

In the authors' phrase, this is the first physiological cell type found in animals that gets by without a functional complex I while its mitochondria are still working.

The egg is not filtering the smoke better. It never builds the chimney that smokes.

Not switched off — never built

The language matters here. Saying that the egg “switches off” complex I misleads. Nobody threw a switch; the parts were never assembled.

The point of control has been located too. Some complex I subunits are coded by the nucleus and some by mitochondrial DNA. In early oocytes the nuclear transcripts were reduced, while the mitochondrially encoded ones were not significantly changed. The order comes from the nucleus.

The fire does not go out

Without complex I there is only one entrance for electrons: through complex II, by way of succinate. The whole chain therefore runs at reduced throughput, and indeed basal respiration in early oocytes was low.

But the mitochondria have not stopped. The membrane potential, that electrical gradient, was lower than in neighbouring cells yet clearly present — and it needs to be, because the cell uses it to make haem, essential amino acids and nucleotides. The egg has not put out the fire. It is keeping it very low and doing only the work that must be done.

There is a side effect worth noting. Without complex I, the larger assemblies called supercomplexes do not form either, and that contributes to the general reduction in activity across the whole chain.

Making less, or clearing better?

Return to the question posed earlier. How would you tell whether an egg is low in radicals because it makes few or because it clears them well?

The team devised a neat test. They deliberately raised radical levels with a compound called menadione. If the egg were a cell with excellent clearance, it should shrug off a modest load. The opposite happened: 78.3 per cent of early oocytes died. Mature oocytes survived. Adding an antioxidant rescued them.

The conclusion is unambiguous. Early oocytes are exquisitely vulnerable to reactive oxygen. They are clean not because their defences are strong but because production has been shut off at source.

Light the fire and the smoke appears

One more observation completes the story. The researchers traced when complex I is assembled during oogenesis and when radical levels rise.

Complex I activity peaked as the oocyte matured. A protein called Prdx3, whose state reports on peroxide levels, showed almost no response in early oocytes and progressively more as maturation proceeded. The ratio of reduced to oxidised glutathione — a measure of how chemically reduced the interior is — was twenty times higher in early than in late oocytes.

The two timings coincide. Radicals begin to accumulate from the moment complex I is assembled.

GOING DEEPER · A CLINICAL PUZZLE, SOLVED IN PASSING

The finding also resolves an unexpected question. Why do patients with inherited complex I disorders, such as Leber's hereditary optic neuropathy, not suffer from infertility? The authors' explanation runs like this. Selection among mitochondrial genomes happens early in oogenesis, and at that stage complex I is not working. A defect in a part that is not running cannot be penalised by a selection process. So the mutation passes through unfiltered to the next generation.

The limits, stated plainly

It is only fair to record what this study could not do. Complex I activity was never measured directly in a human oocyte. By the authors' own calculation such an experiment would require thirty thousand donated ovaries. The human evidence rests on protein surveys, imaging and a downstream signal described in the next chapter; the direct biochemistry came from frogs.

Even so, the finding sits at the centre of this book. The surest way to avoid radicals is to remove the place they are made, and the egg has done exactly that. As chapter 7 will show, it is not an option open to a neuron.

What to take from this chapter

- Early oocytes never assemble complex I of the electron transport chain.
- It is not switched off but never built, and the instruction comes from the nucleus.
- They are low in radicals because they make few, not because they clear them well.
- Radicals begin to accumulate the moment complex I is assembled.

CHAPTER THREE

Parts Built to Last

*Some strategies assume replacement. Others assume endurance.
The ovary chose endurance — and so, it turns out, did the brain.*

IN THIS CHAPTER

Proteins have lifetimes	21
Ten days on average, with a long tail	21
The ovary holds on even longer	22
A tension worth naming	22
Human eggs tell a slightly different story	23
A resemblance, and a difference	24
What to take from this chapter	24

The previous chapter showed the egg choosing to make less damage. The next question follows naturally. What about the damage that is made anyway? And how do the parts built at the start survive all those years?

Proteins have lifetimes

Proteins are not permanent. They are made, put to work, broken down and replaced, and the period of that cycle is a protein's lifetime.

Measuring it is simpler than it sounds. You feed an animal amino acids that are chemically ordinary but slightly heavier — labelled with a stable isotope. From that moment, only newly made proteins carry the heavy version. Take tissue later, run it through a mass spectrometer, and you can read off the ratio of new to old for each protein.

One complication makes this hard inside a living animal. Cells recycle amino acids from the proteins they break down, so heavy amino acids from the diet get mixed with light recycled ones. In 2018 Silvio Rizzoli's laboratory in Göttingen solved the problem by modelling the amino acid pool mathematically, and measured the lifetimes of about 3,500 proteins in the mouse brain with unusual precision.

Ten days on average, with a long tail

Their result: the median lifetime of a protein in the mouse cortex is about 8.1 days and the mean about 10.7 days, with most falling between three and thirteen.

But the distribution has a long tail. Some proteins last hundreds of days. The short-lived end held proteins that bind DNA transiently and proteins involved in signalling and RNA processing. The long-lived end held histones, components of myelin and constituents of the extracellular matrix.

Mitochondrial proteins were long-lived as a group but far from uniform. Subunits of complexes III and V lasted unusually long, while proteins involved in fatty acid metabolism and peroxisomal function were short-lived. Even within one organelle, different parts are replaced on very different schedules.

GOING DEEPER · MITOCHONDRIA ARE NOT REPLACED WHOLE

This calls for an important correction. If mitophagy — tearing out a damaged mitochondrion entire — were the only route, then every mito-

chondrial protein should have a similar lifetime, since they would all be discarded together.

In 2021 Jeffrey Savas's laboratory in Chicago took the problem head on. They found mitochondrial proteins in mouse brain and heart that persist for months, and showed that these were enriched in the inner membrane, specifically in the folded compartment called the cristae. The team concluded that the mitochondrial proteome is not turned over in bulk, and that these long-lived proteins are co-preserved within complexes with little exchange of subunits.

So the cell manages mitochondria in two ways: discarding them whole, and swapping out individual parts. As chapter 8 will show, that distinction changes a great deal when you try to measure a repair rate.

The ovary holds on even longer

In 2024 Melina Schuh's laboratory turned to the mammalian ovary, and the result was striking. The mouse ovary contained more extremely long-lived proteins than any other tissue examined, the brain included.

The functions were varied: mitochondria, cytoskeleton, chromatin and the machinery of protein quality control itself. The researchers proposed that mammals extend protein longevity and strengthen proteostasis using chaperones and cellular antioxidants in order to maintain the female germ line over long periods.

Consistent with that, protein aggregation inside oocytes did not increase with age, and the activity of the proteasome did not decay.

A tension worth naming

Here a temptation arises, and it should be resisted. Set chapter 2's complex I story beside this chapter's long-lived proteins and a tidy chain assembles itself: no complex I, therefore no radicals, therefore no oxidised proteins, therefore no need to replace them.

Tidy, but premature — because an observation in the same study cuts against it. The long-lived proteins were not confined to oocytes. They were also present in long-lived somatic cells of the ovary, and those cells run complex I perfectly normally. If cells that have complex I also hold long-lived proteins, then the absence of complex I cannot be the whole explanation.

What is more, the same study describes chaperones and antioxidants actively protecting those proteins. That is not “no damage, so no replacement needed”; it is “actively defended”.

The tidy causal chain is attractive, and another observation in the very same paper unsettles it.

In fact the chapter 2 team proposed a different route. Without complex I, the balance of the chain’s components is disturbed, and the cell registers a problem with protein folding inside the mitochondrion. This is the mitochondrial unfolded protein response, or mitochondrial UPR. Among the most abundant proteins in the mitochondria of early oocytes were proteases and chaperones — evidence that the response is switched on.

Activating that response is itself known to extend lifespan in worms and in mice. The authors therefore raised the possibility that suppressing complex I further extends oocyte longevity by way of the UPR. They were explicit that this is speculation; the causal link has not been tested.

So there are two possible routes between complex I and protein longevity. Either the proteins last because less damage is made, or they last because the absence of complex I triggers a response that actively defends them. Which of the two is right remains open.

Human eggs tell a slightly different story

In 2025 Elvan Böke’s laboratory in Barcelona, which we met in Chapter 2, examined more than a hundred human oocytes, and found an interesting difference.

Proteolytic activity in human oocytes was roughly half that of the surrounding somatic cells, and it fell further as the oocyte matured. Mitochondrial membrane potential also declined with maturation. The researchers read this as a strategy of lowering organelle activity in order to preserve components needed for early embryonic development.

That mouse ovaries maintain proteasome activity with age, while human oocytes show low and falling proteolytic activity, looks at first like a contradiction. The measurements are of different things in different species, so a direct comparison is unsafe — but it is a fair signal that this field has not settled.

A resemblance, and a difference

The conclusion of this chapter places the two protagonists oddly close together. The ovary and the brain are both tissues rich in long-lived proteins. Both lean towards maintenance over replacement.

The difference is the setting. The egg endures with the fire out. The neuron endures with the fire burning. The same strategy under opposite conditions, with predictably different results.

What to take from this chapter

- The median mouse brain protein lasts about eight days; some last hundreds.
- Mitochondria are not replaced whole — individual parts have their own lifetimes.
- The ovary holds more extremely long-lived proteins than any other tissue measured.
- Whether the absence of complex I causes that longevity is still unresolved.

CHAPTER FOUR

You Have to Break It to See It

A defect mixed in with the healthy is invisible. The germ line separates first, and only then selects.

IN THIS CHAPTER

A ratchet that turns one way	26
The bottleneck filters nothing	26
The bottleneck, confirmed in human families	27
Break it apart and there is nowhere to hide	28
The one sentence that travels furthest	28
What to take from this chapter	29

Mitochondria carry DNA of their own. Unlike the DNA in the nucleus, this mtDNA passes only down the maternal line — the paternal copies are destroyed at fertilisation — and it almost never recombines.

That combination carries a built-in danger.

A ratchet that turns one way

One of the central advantages of sex is recombination. When two parents' DNA is shuffled, harmful and helpful mutations get separated, and the harmful ones can be weeded out.

Without recombination that opportunity disappears. A harmful mutation, once it arises, stays in that lineage forever; another lands on top of it, and then another. Mutational load only climbs, like a ratchet turning in one direction. Geneticists call it Muller's ratchet, after Hermann Muller.

mtDNA is effectively asexual, so the ratchet should turn. And in the somatic cells of our bodies it does: mtDNA mutations and deletions accumulate with age.

Yet the maternal line has not collapsed in billions of years. Something somewhere is filtering defects out.

The bottleneck filters nothing

The first stage of that filtering is the bottleneck — and the name invites a misreading, because the bottleneck itself filters nothing at all.

In the primordial germ cells that will become eggs, the number of mtDNA copies falls sharply. In 2018 Patrick Chinnery's laboratory analysed primordial germ cells isolated from human female embryos at single-cell resolution and reported a profound reduction in mtDNA content, with discrete mitochondria holding on the order of five mtDNA molecules each.

What happens when a population collapses to a handful and is then amplified back up? The statistics are inevitable. The proportion of defective copies varies widely between eggs from the same mother. Some eggs come out nearly clean; in others the defects are concentrated.

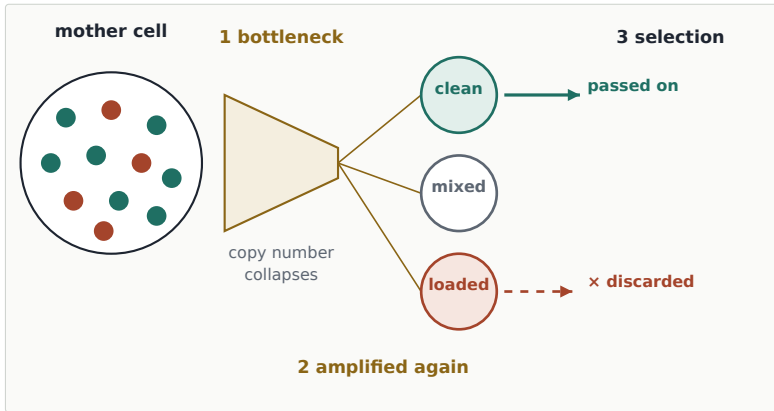


Figure 4 The mitochondrial bottleneck. The bottleneck itself filters nothing. It separates healthy (teal) from defective (red) genomes into different proportions in different eggs, and so creates the variation that selection can act on.

The bottleneck is not a sieve. It is a device for creating difference. It takes defects that were invisible because they were mixed together and distributes them into different proportions in different eggs, generating the variation that selection can then act on.

The bottleneck does not filter. It creates the differences that filtering needs.

The same study also found traces of selection. In later primordial germ cells, rare variants were reaching higher proportions, and there were signals of selection against variants that change proteins and against variants in transfer RNA genes. During this period the cells shift from a glycolytic to an oxidative metabolism, and the researchers argued that this shift is what exposes deleterious mutations to selection. Only when the mitochondria are made to work properly does it become apparent which of them work.

The bottleneck, confirmed in human families

In 2019 a group at Penn State approached the same problem from another direction, analysing 249 mother-to-child transmissions across 96 families and 345 individuals.

Two independent population-genetic methods agreed. The germ line bottleneck was severe — on the order of seven to ten segregating

units of mtDNA — and it occurred independently in different oocyte lineages from the same mother. Somatic bottlenecks were less severe.

The researchers also showed that the divergence between a mother and her child increases with the mother's age at childbirth, which they attributed to continued drift in heteroplasmy frequencies while oocytes sit in meiotic arrest. And they found evidence that selection acts during germ line development to keep the frequency of apparently deleterious variants from rising.

Break it apart and there is nowhere to hide

If the bottleneck creates difference, what recognises that difference and acts on it? In 2019 researchers at NYU and Toronto caught the process happening in a fruit fly.

The sequence runs like this. Early in oogenesis, levels of mitofusin — the protein that fuses mitochondria together — fall. Mitochondria then fragment, and each fragment ends up holding only a few genomes.

Why does that matter? When mitochondria fuse and share their contents, proteins made by a healthy genome make up the shortfall of a defective one. This complementation means a defect never shows on the surface. A faulty part surrounded by working ones goes unnoticed.

Break them apart and there is nowhere to hide. A fragment holding only defective genomes has to make its own ATP, and it cannot. That failure becomes the mark, and the mitophagy proteins Atg1 and BNIP3 select the fragment for removal.

The one sentence that travels furthest

The study's most far-reaching finding is something else. The researchers showed that fragmentation is not only necessary for selection in germ tissue but sufficient to induce selection in somatic tissue, where selection is normally absent.

Which means the germ line's advantage need not be some mystical property of germ cells. It may be a general mechanism that can be transplanted into ordinary body cells. That possibility is what licenses the question this book puts to the neuron.

GOING DEEPER • BNIP3, NOT PINK1

It is worth noticing that the mitophagy route used in the fly germ line was Atg1 and BNIP3, not PINK1 and Parkin. PINK1/Parkin dominates

Parkinson's research and is often treated as synonymous with mitophagy, but it is not the only route a cell has. The distinction matters again in chapter 9.

What to take from this chapter

- mtDNA does not recombine, so mutations risk accumulating in one direction only.
- The bottleneck filters nothing; it creates variation between eggs.
- Fragmenting mitochondria strips defects of the cover that complementation gives them.
- In flies, fragmentation alone was enough to induce selection in somatic tissue.

CHAPTER FIVE

Discarding Almost Everything

A human ovary starts with millions of oocytes and ovulates a few hundred. Is that enormous waste a selection, or merely a probability?

IN THIS CHAPTER

Make many, lose most, and it looks like choosing	31
Neutrality has no universal signature	31
There is still a way through	32
How to hold both chapters at once	33
Is the germ line special at all?	33
What to take from this chapter	34

A girl acquires millions of oocytes while still a foetus. By puberty the number has fallen sharply, and over a lifetime only a few hundred are ovulated. All the rest disappear.

The natural reading of this is selection: from a vast pool of candidates, only the best are released. Many researchers have taken that view, and the evidence for bottleneck and selection in the previous chapter seems to support it.

Then in 2025 a review arrived that put the reading squarely in question.

Make many, lose most, and it looks like choosing

Diana Laird's laboratory at the University of California, San Francisco, together with mathematical biologists at the Flatiron Institute, set out to examine whether selective quality control really operates in mammalian oogenesis.

They begin from two observations: that the follicle reserve is established through a massive overproduction of oocyte precursors, and that the number ovulated across a fertile lifetime is a very small proportion of that initial reserve. Many have treated this as evidence of quality control.

The question the authors pose is whether the existing evidence actually distinguishes the active selection of specific germ cell subsets from neutral dynamics.

The difficulty is this. Make a great many and lose most of them at random, and the outcome looks like selection anyway. The survivors are a small minority by construction, and their appearing better than average may be nothing more than statistical fluctuation.

Make many, lose most at random, and the survivors will look as though they were chosen.

Neutrality has no universal signature

The methodological lesson of this review applies to every other chapter in the book.

The authors state plainly that there is no universal signature of neutral dynamics or of selection, and consequently no blanket statistical test for neutrality. A hypothesis must first be translated into a

mathematical model — or several competing hypotheses into competing models — and only then can statistics be applied.

They point to a concrete case. In studies of mtDNA heteroplasmy it has been standard to compare measured distributions against a theoretical one, the Kimura distribution, in order to detect selection beyond neutral expectation. But the method-of-moments estimator commonly used for this is biased, and combined with bootstrap-style tests it can wrongly conclude that data are inconsistent with a Kimura distribution.

The alternatives they recommend are maximum likelihood estimation and approximate Bayesian computation. One instance is particularly striking: when a group compared several modelling hypotheses using approximate Bayesian computation on data drawn from the literature, the best-supported model assumed stochastic turnover of mitochondria and random partitioning at cell division. That is, the neutral side.

GOING DEEPER • THE LESSON OF LURIA AND DELBRÜCK

The authors note that this argument closely mirrors a classic experiment from the 1940s. Salvador Luria and Max Delbrück set out two hypotheses for how bacteria acquire resistance to a virus. Does resistance arise in response to exposure, or do pre-existing random mutations get selected by it?

The two hypotheses predict different shapes for the distribution of surviving bacteria: a Poisson distribution under the first, a much more variable distribution under the second. The data supported the second, and the result became a foundation of modern genetics.

The point is not the conclusion but the method. Each competing hypothesis was written as a mathematical model, and statistics decided which fit the data better. The authors argue that analyses of neutrality should follow the same path.

There is still a way through

The review does not end in pessimism. It contains one particularly useful proposal.

The authors acknowledge the difficulty of telling genuine randomness from our ignorance of some underlying quality metric. But then they add this: even where neutral and non-neutral models fit counts of oocytes or follicles equally well, they may still give different

predictions for clonal labelling or perturbation experiments, and can therefore be distinguished empirically.

That is strategically important advice. Analysing the same data more cleverly is not the way out. Finding a new observable on which the two models diverge is the way out.

How to hold both chapters at once

Placing this chapter beside chapter 4 can be disorienting. One showed evidence of selection; the other warns that the evidence may be explained by neutral models.

The accurate response is to accept both, while distinguishing carefully.

	reasonably solid	still open
molecular	in flies, fragmentation exposing defective genomes and mitophagy removing them was directly observed	whether the same mechanism carries the same weight in mammals
population	human pedigree analysis shows deleterious variants held back from rising in frequency	whether the observed distributions are statistically distinguishable from neutral models
cellular	the mass loss of oocytes is not in doubt	whether that loss is selection on quality or random attrition

The fragmentation and selection of chapter 4 belong to the column where a mechanism was watched directly. What this chapter chiefly calls into question is the interpretation of whole-cell mass loss as quality control.

Is the germ line special at all?

A further review, published in 2026, pushes the question one step harder. Written by Patrick Chinnery's group in Cambridge among others, it argues that the dynamics of mtDNA heteroplasmy follow common principles in germ line and soma alike.

The picture it assembles runs as follows. Stochastic processes — relaxed replication, vegetative segregation at division — generate variation between cells, and genetic bottlenecks amplify it. On top of that,

selection mechanisms such as intercellular competition, mitophagy and preferential replication produce directional shifts. And as single-cell techniques have improved, phenomena long seen only in germ line studies are turning out to operate in somatic tissues throughout life.

On this view the difference between germ line and soma is not a difference of kind but of parameters. The same principles in a different configuration.

For this book's purposes that is encouraging news. If the germ line had magic of its own, nothing could be borrowed. If it is the same principles under different settings, then settings can be changed.

What to take from this chapter

- Overproduction followed by mass loss looks like selection even without any.
- Neutrality has no universal signature; hypotheses must be written as competing models.
- The way forward is not reanalysis but finding observables where predictions diverge.
- Germ line and soma may be the same principles under different settings.

INTERLUDE TWO

From Flies to People

*The evidence in this book comes from five kinds of organism.
Here is what carries across between them, and what does not.*

IN THIS CHAPTER

Why it cannot be done in people	36
What each organism is for	36
What carries across	37
Species differ, and so do the results	37
A reading habit worth keeping	38
What to take from this interlude	38

You will have noticed by now that almost none of the research in this book was done in humans. Flies, worms, frogs and mice are the protagonists, and the organism changes from one discovery to the next.

That is a weakness of the field and also the way it works. Understanding why will let you read the remaining chapters more accurately.

Why it cannot be done in people

The reason is simple: it cannot be done.

Recall the complex I study from chapter 2. The team wanted to measure complex I activity directly in human oocytes and could not, because the calculation came out at thirty thousand donated ovaries for a single experiment. Human oocytes can only be obtained through invasive surgery, and only a few at a time.

The brain is worse. There is no way to extract mitochondria from a living human brain for analysis. Most human brain research examines post-mortem tissue, which gives you a state at one moment and never a rate. The measurement limits of chapter 8 follow directly from this.

So researchers go elsewhere.

What each organism is for

organism	advantage	role in this book
roundworm	transparent, with a fixed number of cells and a generation time of days	the germ line’s clean-up and the lysosomal switch
fruit fly	easy to manipulate genetically, and can be grown in large populations	mitochondrial fragmentation and selection; reverse electron transport and lifespan
frog	eggs are large and plentiful, making biochemistry possible	direct measurement of complex I assembly and activity
mouse	a mammal, open to genetic manipulation and long-term study	protein lifetime maps, mitophagy reporters, ovary studies
human	the thing we actually want to know about	pedigree analysis, post-mortem tissue, a handful of oocytes

There is something to read in that table. As you move down it you get closer to the organism you care about, and at the same time the experiments you can do contract. The firmest mechanistic evidence comes from the most distant organisms, and about the subject of real interest you get only the most indirect evidence.

*The firm evidence comes from distant organisms;
about ourselves we get only indirect signs.*

What carries across

None of this makes model organism research pointless. There are reasonable rules about what transfers.

Transfers well: conserved molecular machinery

The basic machines of life have barely changed in hundreds of millions of years. The complexes of the electron transport chain, the autophagy machinery, the proteasome. Many of the autophagy genes that work in yeast are present in humans and do much the same job.

PINK1 and Parkin belong here too. Functions discovered in flies were confirmed in mammalian cells, and in humans mutations in the two genes cause early-onset Parkinson's disease.

Transfers badly: timescale and tissue architecture

A fly lives weeks and a person lives decades. A process that takes a week in a fly does not scale proportionally to a human.

Architecture differs just as much. A fly's nervous system is far simpler than ours and its axons are nowhere near as long. The metre-long axon problem of chapter 7 only arises in large mammals.

The awkward middle: how strongly selection acts

The dispute in chapter 5 lives here. That a mechanism exists and that it accounts for a large share of what happens in a given organism's life are different claims. Fragmentation-driven selection was established in the fly germ line; whether the same mechanism carries the same weight in mammals is a separate question.

Species differ, and so do the results

A few of the mismatches encountered in the text, gathered in one place.

First, chapter 3 reported that proteasome activity in the mouse ovary does not decline with age. Yet a 2025 study of human oocytes found proteolytic activity at about half that of neighbouring somatic

cells, falling further with maturation. Different measurements in different species, so a direct comparison is unsafe — but it is clear that “the germ line does this” cannot be said in a single sentence.

Second, chapter 9 reports that radicals produced by reverse electron transport extended lifespan in flies. Whether the same manipulation would do the same in a mammal is unknown.

Third, in the same chapter, kinetin reduced mtDNA deletions in the liver of ageing mice. Whether the same happens in the brain has not been shown; the preservation of dopaminergic neurons was a result in flies.

A reading habit worth keeping

For that reason the text states, for each study, which organism it came from. The same habit is worth recommending to the reader. When you meet a claim, ask three questions.

1. Which organism produced this result?
2. Was a mechanism observed directly, or is this a correlation?
3. Was a state measured, or a rate?

The third is the subject of chapter 8. Those three questions alone will change how you read science journalism and research papers alike.

What to take from this interlude

- Very little of this work can be done directly in humans.
- Conserved molecular machinery transfers; timescale and architecture do not.
- That a mechanism exists and that it matters are separate questions.
- Always ask: which organism, direct or correlational, state or rate.

CHAPTER SIX

The Clean-Up Between Generations

Germ cells do age. What happens is that the age is erased at the moment one generation becomes the next. This is the most dramatic scene in the book.

IN THIS CHAPTER

The stretch where the clock runs backwards	40
The moment oxidised protein disappears	40
The signal the sperm sends	41
Five stages, in order	42
And still the germ line fails	42
Back to the mayfly	43
What to take from this chapter	43

So far this book has used the phrase “the germ line does not age” rather loosely. It is time to correct it.

Germ cells run a metabolism, and anything with a metabolism accumulates damage. Ever since August Weismann proposed in the nineteenth century that the germ plasm does not age, the idea has had a long life — but time passes for germ cells too.

How, then, is the line maintained? Not by avoiding age. By erasing it.

The stretch where the clock runs backwards

In 2021 Vadim Gladyshev’s laboratory at Harvard Medical School captured that erasure in numbers.

The researchers built an epigenetic clock that could be applied across multiple tissues and used it to follow prenatal development in mice and in humans. The method relies on the fact that chemical marks attached to DNA change in a regular way with age.

The result was this. During early development, biological age decreased significantly, and then increased again at later stages. The team called the minimum “ground zero” — the point at which the ageing of the organism begins.

A new life does not inherit its parents’ age. Early in the embryo, the clock is wound back.

The finding changes the frame. That a fertilised egg starts at zero is not self-evident. The mother’s egg is a cell that has lived for decades, and the father’s sperm is not brand new either. Yet the embryo they make is wound back to zero at some point. That does not happen by itself; something makes it happen.

The same study reported that pluripotent stem cells do not age even after extensive passaging, and that the pattern of epigenetic age dynamics is conserved across species.

The moment oxidised protein disappears

If the epigenetic reset is erasure at the level of information, there is erasure at the level of matter as well.

When a protein is attacked by reactive oxygen, it undergoes a chemical modification called carbonylation. The damage is irreversible

and it accumulates with age. So somewhere, between generations, it must be erased.

In 2010 Hugo Aguilaniu's laboratory in Lyon caught the moment in the roundworm *C. elegans*, by developing a technique that made carbonylated proteins visible under a microscope inside the cell.

The scene was dramatic. Carbonylated proteins disappeared abruptly within the germ line at the time of oocyte maturation. The removal required the activity of the proteasome, the cell's protein-shredding machine.

The most unexpected finding was something else. The germ line was more oxidised than the surrounding somatic tissue. It is not clean because little damage occurs. It is clean because the damage can be erased.

The signal the sperm sends

When does that erasure begin, and on what signal? In 2017 Cynthia Kenyon's laboratory in San Francisco found the switch.

They first observed something odd. In oocytes whose maturation had stalled for want of sperm, the hallmarks of collapsing proteostasis appeared: proteins clumped into aggregates. Direct evidence that germ cells deteriorate with time.

When fertilisation becomes imminent, the situation reverses. Hormones secreted by sperm reach the oocyte and activate the V-ATPase, a proton pump that acidifies lysosomes. The chain runs as follows: the sperm signal triggers degradation of GLD-1, a translational repressor that had been blocking V-ATPase synthesis; the pump is then built, and lysosomes acidify. The activated lysosomes drive a metabolic shift that mobilises the aggregated protein for degradation, then envelop and clear the aggregates.

Noting that lysosomal acidification also occurs during the maturation of frog oocytes, the researchers suggested the switch may be conserved in other species.

GOING DEEPER • A BRIDGE TO THE BODY

A follow-up study in 2021 ran a genome-wide screen for the genes involved. The picture that emerged was that lysosomes acidify as a consequence of changes in endoplasmic reticulum activity that permit the

V-ATPase to assemble, and that those lysosomes then clear the aggregates by microautophagy.

For the purposes of this book the conclusion matters most. Many of the genes from the screen also regulated lysosomal acidification and age-dependent protein aggregation in somatic tissue. The researchers wrote that there may be a fundamental mechanistic link between proteostasis renewal in the germ line and somatic longevity.

Five stages, in order

Arranged across a lifetime, what chapters 2 through 6 have shown looks like figure 5.



Figure 5 Five stages in how the germ line handles ageing. Note that the evidence for each stage comes from a different organism.

Two things in that figure deserve attention.

First, the evidence for each stage comes from a different organism. Complex I removal from humans and frogs, long-lived proteins from mice, fragmentation and selection from flies, the lysosomal switch from worms, the epigenetic reset from mice and humans. No study has yet shown all five operating within one species, or how they interlock.

Second, the character of the strategy changes across the life. The first two are prevention, the middle two are filtering, and the last is erasure.

And still the germ line fails

It would be a lie to call these strategies complete.

The authors of the ovarian longevity study in chapter 3 recorded the limit themselves: increasing protein longevity cannot fully block the senescence of the female germ line. In the ageing ovary many long-

lived proteins of the proteostasis network decline and the proteome is extensively remodelled, and that eventually drives the fall in fertility.

The same holds in humans. A 2025 study reported that oocytes from women of advanced maternal age had lower mitochondrial activity and a lower rate of completing meiosis successfully.

So the germ line's real trick is not that any individual egg avoids ageing. It is that most of the eggs are discarded and the one that is handed on is reset at the moment of handing over. A single egg is finite; only the lineage continues.

Back to the mayfly

Return for a moment to the prologue. What is a finite creature's striving for?

This chapter's answer is cool-headed. The individual is built to end, and that ending is not a defect but the price of the lineage continuing. The body only has to last while it carries the germ line to the next generation; spending resources on maintenance beyond that is evolutionarily wasteful.

But the same fact can be read another way. Every organism now alive stands at the end of a line that has never once broken. The cells that carried that line across four billion years were each of them finite. Finite things, joined end to end, made something that does not end.

What to take from this chapter

- Germ cells age. What is special is that the age is erased between generations.
- There is a stretch in the early embryo where biological age decreases.
- The worm germ line is more oxidised than the soma, and clears it at maturation.
- The switch is lysosomal acidification, thrown by a signal from sperm.

CHAPTER SEVEN

What the Neuron Lost

The germ line uses four tools. The neuron has one and a half of them left. Working out what is missing shows why the brain fails first.

IN THIS CHAPTER

It cannot divide	45
It cannot choose	46
It can discard, but the distance is wrong	46
It cannot burn less	47
Why the substantia nigra	48
Not entirely alone	48
Summing up	48
What to take from this chapter	49

Now for the second protagonist. Taking the germ line's strategies as a checklist, let us work through what a neuron can and cannot use.

Reduce the germ line's repertoire to four: dividing damage, choosing between cells, discarding faulty parts, and burning less to begin with.

It cannot divide

Division is itself a way of handling damage. When a cell splits in two, the damage inside splits as well. And division allows something more active still.

An observation in yeast makes the point. A 2003 study showed that when budding yeast divides, carbonylated proteins carrying oxidative damage stay with the mother cell rather than passing to the daughter. In a strain lacking **sir2**, a gene that determines lifespan, the asymmetry broke down. Pushing the damage to one side and sending the other out clean is a genetically regulated process.

A neuron can do none of this. Neurons in the brain stop dividing when development ends. Each carries the mitochondrial population it was given for life, and accumulated damage is never halved — it simply stays.

There is a more uncomfortable fact. Inside a cell that does not divide, defective genomes can actually increase.

In 2006 a group at Newcastle analysed single neurons from the human substantia nigra, the region that fails first in Parkinson's disease. The numbers were startling. In aged controls, deleted mtDNA averaged above 43 per cent of the total; in people with Parkinson's disease, above 52 per cent. These mutations were not inherited but acquired during the person's life, with different deletions clonally expanded in individual cells. Cells with high levels showed respiratory chain deficiency.

In the aged substantia nigra, deleted mtDNA can make up close to half of all copies.

Why defective genomes expand is still debated. One explanation is that a shortened genome replicates faster; another is random drift. Either way the conclusion is the same: in a cell that cannot dilute by dividing, defects do not merely persist. They can spread.

It cannot choose

The ovarian strategy in chapter 5 was mass disposal: millions reduced to hundreds. Whether that constitutes selection or attrition is disputed, but at least the ability to discard is beyond question.

In the brain that strategy is unavailable. Most neurons are as old as the person and are not replaced. Discarding a neuron means losing part of the circuit it belonged to, and accumulated circuit loss is precisely what neurodegenerative disease is.

There is a strange inversion here. What serves as a tool of quality control in the germ line becomes the outcome of failed quality control in the brain.

It can discard, but the distance is wrong

The one tool the neuron keeps is organelle-level cleaning: mitophagy, finding a damaged mitochondrion and digesting it.

Neuronal geometry makes even that difficult.

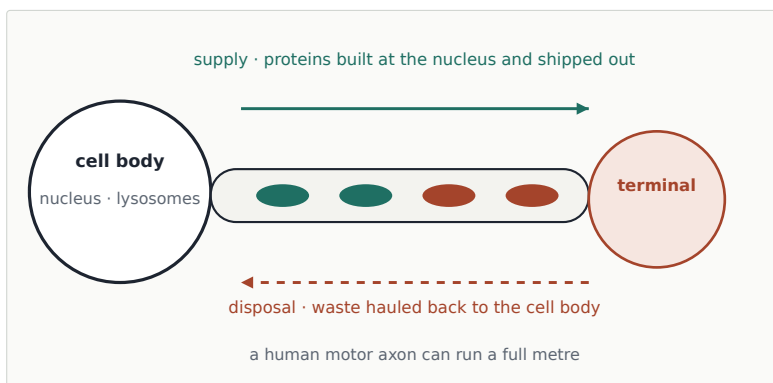


Figure 6 The distance problem. Almost every mitochondrial protein is built in the cell body and shipped out (above), while waste generated at the terminal has to travel all the way back for proper disposal (below).

A human motor axon can run a full metre. Because most mitochondrial proteins are built by the nucleus and shipped out, mitochondria at the far end of an axon age at the end of the supply line. And autophagosomes formed at the terminal have to travel back along the axon to the cell body to be properly degraded in a lysosome. The rubbish must be hauled a metre to the incinerator.

The cell appears to know this. In 2022 Angelika Harbauer and Thomas Schwarz reported an elegant workaround. PINK1, the central sensor of mitophagy, is a very short-lived protein — built in the cell body it would decay before arriving. So the cell ships the blueprint instead. PINK1 messenger RNA is carried out along the axon on mitochondria themselves and translated locally, and the researchers showed this local translation is crucial for mitophagy in distal parts of the cell.

Rather than send a short-lived part a long way, send the machine that makes it.

GOING DEEPER · PINK1 MAY MATTER LESS THAN YOU WOULD THINK

PINK1 and Parkin are treated as synonymous with mitophagy, but in a living animal their share may be smaller than expected.

In 2018 a group at Dundee used mito-QC reporter mice, which make mitophagy visible in vivo, to survey multiple tissues. Mitophagy was proceeding vigorously in neural tissue, including the midbrain dopaminergic neurons relevant to Parkinson's disease, and in microglia. Yet deleting **Pink1** changed basal mitophagy in no tissue except the pancreatic islets — even though depolarisation-induced Parkin activation was clearly disrupted.

The authors concluded that basal mammalian mitophagy occurs independently of PINK1, and that multiple yet-to-be-discovered pathways must be managing mitochondrial integrity in a context-dependent way.

That pushes PINK1 and Parkin towards being an emergency alarm rather than the daily cleaning service. It fits with chapter 4, where the fly germ line's selection ran through BNIP3 rather than PINK1.

It cannot burn less

The egg skips building complex I and waits for decades. A neuron cannot.

The brain is about two per cent of body mass and uses roughly twenty per cent of resting energy. Worse, the neuron deliberately ties itself to its mitochondria by holding glycolysis down.

The mechanism is known in detail. PFKFB3, the enzyme that promotes glycolysis, is continuously degraded in neurons. Glucose is therefore routed into the pentose phosphate pathway instead, where the NADPH produced keeps glutathione reduced and antioxidant

capacity high. The neuron has traded flexibility in energy production for antioxidant defence — and the price is near-total dependence on mitochondria.

Comparison with astrocytes shows what that costs. Block mitochondrial respiration and neurons die quickly, while astrocytes make ATP glycolytically and carry on.

Why the substantia nigra

All these disadvantages converge on one cell: the dopaminergic neuron of the substantia nigra.

Its axon is unmyelinated and branches extraordinarily widely, and it fires spontaneously and without rest through calcium channels. Energy demand is extreme and so is oxidative stress. That this is the cell in which deleted mtDNA accumulates to nearly half the total, and the cell that fails first in Parkinson's disease, is unlikely to be a coincidence.

Not entirely alone

The neuron does not do all of this by itself. One more tool remains: handing the job to a neighbour.

In 2014 a group at Johns Hopkins reported a remarkable phenomenon at the optic nerve head in mice. Axons of retinal ganglion cells, while otherwise healthy, extrude mitochondria through large protrusions, and adjacent astrocytes internalise and degrade them. The researchers called it transmitophagy.

The proportions are the striking part. A greater share of retinal ganglion cell mitochondria were being degraded at the optic nerve head than in the cell body. Noting that structurally similar accumulations appear along neurites in the superficial cerebral cortex, the authors argued that the assumption that cells necessarily degrade their own mitochondria should be reconsidered.

This tool has its own weakness. As disease progresses, glia themselves turn reactive and drive inflammation. The contractor fails alongside the client.

Summing up

Against the germ line's four tools, the neuron's position looks like this.

tool	neuron	why
divide	lost	no division to dilute damage; defective genomes may even expand
choose	lost	discarding a cell is itself the loss of a circuit — the disease
discard	kept but hampered	mitophagy exists, but axon length obstructs both supply and disposal
burn less	lost	the brain is energy-hungry, and neurons suppress glycolysis to depend on mitochondria
outsource	partly available	glia will digest mitochondria, but they fail too as disease advances

Laid out this way, the neuron's finitude looks less like a defect than like the price of spending energy on thought. Thinking is expensive, and the bill is paid by giving up the capacity to repair.

What to take from this chapter

- Neurons cannot divide to share damage, and cannot be discarded and replaced.
- In the aged substantia nigra, deleted mtDNA can approach half of all copies.
- Mitophagy remains, but axon length obstructs both supply and disposal.
- Much of basal mitophagy proceeds independently of PINK1.
- Glia can take on the work, but they fail as the disease advances.

CHAPTER EIGHT

How to Measure a Rate

*Filling in the inequality from chapter 1 means measuring rates.
Almost every tool we have measures states instead.*

IN THIS CHAPTER

A level is not a flow	51
Plugging the drain	52
Measuring with heavy amino acids	52
Do not read half-life as mitophagy rate	53
The damage side is harder	54
Where that leaves us	54
What to take from this chapter	55

This book began with an inequality. The rate at which damage accumulates is the rate at which it appears minus the rate at which it is repaired. Everything since has been about one side or the other.

So what are the actual numbers? In a human brain neuron, what is the repair rate, and what is the damage rate?

The honest answer is that nobody knows. Understanding why is the purpose of this chapter.

A level is not a flow

Most measurements look at a state, not a rate: how many damaged mitochondria are present at a given moment, how much oxidised protein has built up.

The trouble is that a state is what remains after damage and repair have cancelled. If few damaged mitochondria are visible, there are two readings. Either little damage was made, or clearance was fast enough to take it away.

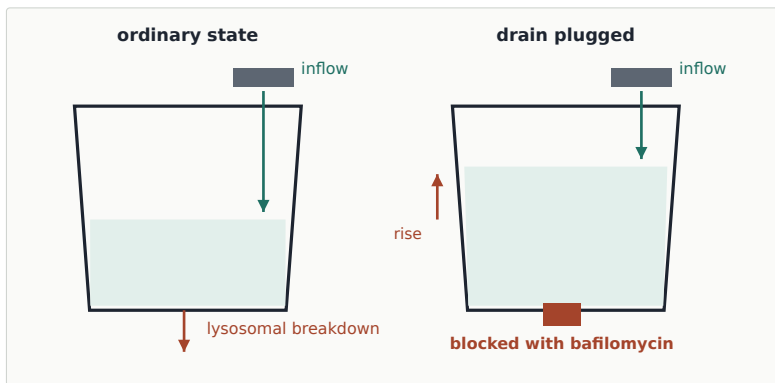


Figure 7 Flux, seen as a bathtub. Two tubs can hold the same water (a state) while very different amounts flow through them (a rate). Plug the drain briefly and the rise in level gives you the flow.

A bathtub makes it concrete. Water flows in from the tap and out through the drain. A steady level does not mean there is no flow; it means inflow equals outflow. And from the level alone you cannot tell whether one litre a minute is passing through or a hundred.

To get a rate you need a time axis. The simplest method is to plug the drain for a while: the speed at which the level then rises is the size of the flow that had been leaving.

Plugging the drain

In a cell, the drain is degradation in the lysosome. Lysosomes keep their interior acidic so that their enzymes work, and a drug such as bafilomycin blocks that acidification.

Split a matched population of cells in two, treat one for a few hours, and compare. Whatever would have been degraded during those hours is still sitting in the treated sample.

clearance rate $\approx$ (amount in treated – amount in control) $\div$
treatment time

Conversely, if blocking the drain produces little accumulation, the flow was slow to begin with.

GOING DEEPER · REPORTERS AND DRAIN-PLUGGING DO NOT MIX

The standard tools for watching mitophagy are fluorescent reporters called mt-Keima and mito-QC. Both work by changing colour when a fluorescent protein attached to a mitochondrion enters the acidic interior of a lysosome.

Bafilomycin removes exactly that acidity. Plug the drain and you break the gauge. The two approaches are therefore normally used separately. Drain-plugging comparisons are paired with readouts that do not depend on acidity — the quantity of a mitochondrial protein, or the amount of mtDNA — while the fluorescent reporters are read as a change over time.

The method has clear limits. Blocking lysosomes for long damages the cell, so treatment usually stays within a few hours. It assumes the inflow is constant over that window. And it works in cultured cells or tissue slices, not in the brain of a living animal.

Measuring with heavy amino acids

The more quantitative approach was introduced in chapter 3: feed isotope-labelled amino acids, take tissue at intervals, and read the ratio of new to old for each protein.

Its strength is scale — thousands of proteins measured at once. A considerable body of data now exists.

dataset	content	scale
2010, mouse, whole animal	turnover rates compared across brain, liver and blood; brain proteins live markedly longer	~2,500
2018, mouse brain	amino acid pool modelled for precision; neurons and glia calculated separately	~3,500
2022, young and old brain	changes in protein lifetime with age	—
2025, many tissues and brain regions	a map of lifetimes by tissue and brain region, with phosphorylation sites	~11,000

The 2010 study reported an average brain protein lifetime of about nine days against three days in liver and three and a half in blood. Within certain organelles, mitochondria among them, proteins fell into a narrow range of lifetimes, which the authors read as a synchronised turnover mechanism.

The 2022 study went straight at ageing. In physiologically aged mice, protein lifetimes in the brain were extended by about twenty per cent — turnover had slowed across the board. Interestingly, a set of neuroprotective proteins became longer-lived while certain mitochondrial proteins linked to neurodegeneration became shorter-lived. The researchers found metabolism adjusting towards parsimonious turnover of proteins with high biosynthetic costs, and suggested this adaptation preludes neurodegeneration.

The large 2025 atlas mapped the abundance and lifetime of around 11,000 proteins and 40,000 phosphosites across eight tissues and several brain regions. One result stands out: phosphorylation regulates the stability of neurodegeneration-related proteins such as tau and α -synuclein.

Do not read half-life as mitophagy rate

Here the lesson of chapter 3 becomes decisive. Mitochondria are not replaced whole.

If mitophagy were the only route, measuring the lifetime of a mitochondrial protein would give you the mitophagy rate. But if different parts have different lifetimes, a half-life is a blend of two processes: the share discarded wholesale and the share replaced piecemeal.

That is bad news and good news. The bad news is that you cannot convert a half-life into a mitophagy rate. The good news is that the spread of lifetimes between proteins may be a way to estimate the ratio of the two processes.

A 2013 fly study was already pointing this way. In **parkin** mutants the turnover of mitochondrial proteins slowed overall, but less severely than in mutants where autophagy itself was broken. Yet looking only at respiratory chain subunits, the **parkin** mutants were the more impaired. The researchers concluded that the PINK1–Parkin pathway promotes not only mitophagy but also the selective turnover of respiratory chain subunits.

*The cell manages mitochondria two ways:
discarding them whole, and swapping out parts.*

The damage side is harder

The other side of the inequality — the rate at which damage appears — is more awkward still.

Reactive oxygen is watched with genetically encoded sensors placed inside the mitochondrial matrix, which report hydrogen peroxide in real time. The older dye-based methods accumulate in proportion to membrane potential, which makes quantification treacherous.

mtDNA damage is measured by sequencing. Reading both strands and cross-checking removes errors and lets you count extremely rare mutations. Analysed at single-cell resolution, as in the substantia nigra study of chapter 7, clonal expansion becomes visible.

But whichever marker you choose, the same problem returns. Oxidative marks and mutations are accumulated quantities, not rates. Again you need a time axis.

Where that leaves us

The state of measurement today comes down to three limitations.

First, there is no standard method for measuring clearance rate and damage rate in the same cell at the same time. Most work stitches numbers from separate experiments together in a model.

Second, in the human brain it is close to impossible. Almost all of these techniques are for mice or cultured cells. For humans, there is

post-mortem tissue, and imaging methods for watching mitophagy in a living brain have yet to arrive.

Third, damage has more than one definition. Reactive oxygen, mtDNA mutation, protein oxidation, loss of membrane potential – the numbers depend on which you pick.

Even so, the path from the schematic of chapter 1 to a real curve is not entirely blocked. A substantial body of protein lifetime data is public, and catalogues of the proteins involved in mitochondrial quality control have been assembled. Putting the two together – mapping which quality control module turns over most slowly in the brain – is work that needs no new experiment at all.

What to take from this chapter

- Most measurements capture a state, not a rate.
- To see a rate you must add a time axis, or briefly block one flow.
- Isotope labelling gives the lifetimes of thousands of proteins at once.
- But a mitochondrial protein's half-life is not the mitophagy rate.
- No method yet measures both rates in the same cell at the same time.

CHAPTER NINE

Which Curve Do You Move?

There are three broad routes to helping a neuron. One lowers damage, two raise repair, and all three have a weakness.

IN THIS CHAPTER

Route one: plug the leak only	57
But is reverse flow only harmful?	58
Route two: get the tag on in time	59
How to read that result	59
Route three: let a neighbour do it	60
The three routes side by side	60
What to take from this chapter	61

Back to the inequality. To slow the accumulation of damage there are only two options: reduce the rate at which damage appears, or raise the rate at which it is repaired.

Everything currently being attempted on the neuron's behalf falls into one of the two.

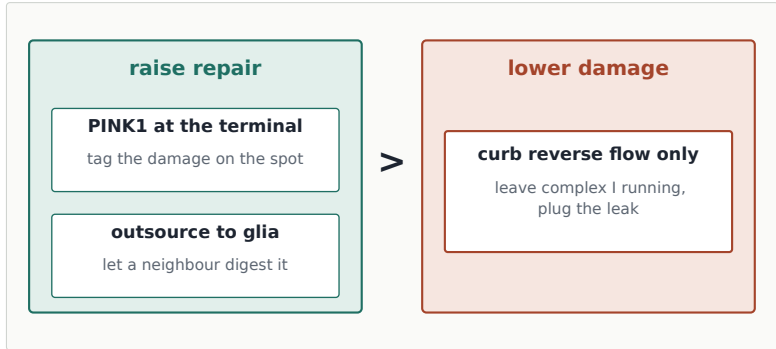


Figure 8 Which side of the inequality each route moves. Two of them raise the repair rate; one lowers the damage rate.

Route one: plug the leak only

The egg avoided radicals by never building complex I. A neuron cannot follow. Without complex I there is only one entrance for electrons and throughput falls, and the brain has no such margin.

Could you then leave complex I in place and stop only the leak?

The possibility opens when you look at how the radicals are produced. Complex I leaks in two ways: electrons going astray on the way forward, and electrons running backwards. The second is reverse electron transport.

Reverse flow happens under specific conditions — a high membrane potential and a reduced electron carrier pool — and when it does, the quantity of radicals is substantial.

Compounds exist that block that specific site. They suppress radical production at one site in complex I without appreciably blocking electron flow. A compound reported in 2023 halved radical production at a concentration five hundred times lower than the one needed to inhibit electron flow through complex I, and even at fifty times that concentration it did not suppress production from other sites. Fed to

mice on a high-fat diet, it reduced fat accumulation and protected glucose tolerance.

There is a parallel result in the heart. A 2023 study found the same class of compound limited infarct size in mouse hearts subjected to ischaemia–reperfusion injury.

But is reverse flow only harmful?

There is a large thorn in this route.

In 2016 Alberto Sanz’s laboratory at Newcastle produced a disconcerting result. Increasing radical production specifically through reverse electron transport at complex I extended lifespan in fruit flies.

Their interpretation was that whether radicals are harmful or useful depends not only on quantity but on where they are produced. Radicals from reverse flow act as signalling molecules and switch on responses that leave the cell healthier. The manipulation even rescued pathology induced by severe oxidative stress. Conversely, knocking down PINK1 to prevent reduction of the electron carrier pool shortened lifespan and accelerated ageing — and increasing reverse flow rescued that phenotype.

Observations in other cells point the same way. A 2026 study reported that part of the hydrogen peroxide signal required for insulin secretion in pancreatic β -cells comes from reverse electron transport at complex I.

So a strategy of suppressing reverse flow may be lowering damage and erasing a signal at the same time. Which tissue, by how much and when turn out to be everything.

The same radical is poison or signal depending on where it was made.

GOING DEEPER · THE PARADOX OF INHIBITING GENTLY

A still more confusing approach exists. A study released in 2026 proposed a compound that weakly inhibits complex I as a candidate treatment for Alzheimer’s disease. The idea is to induce mild energetic stress and thereby wake the cell’s adaptive responses.

As reported, the compound crosses the blood–brain barrier and activates the energy sensor AMPK, initiating a coordinated response of enhanced antioxidant defence, suppressed inflammatory signalling, induced au-

tophagy, and increased mitochondrial biogenesis and turnover. Deleting AMPK abolished the effects.

Is inhibition good, or is preservation? That there is no simple answer to that question is an honest summary of where the field stands. Note also that this work is a preprint and has not yet been through peer review.

Route two: get the tag on in time

The second route works the repair side: making sure a damaged mitochondrion gets its **dispose of this** label promptly.

As chapter 7 showed, distance makes that hard in a neuron. PINK1 is short-lived and would decay before arriving, so the cell sends the blueprint and builds it on site.

Drug development targets the same point. Compounds that activate PINK1, or that inhibit the enzyme which strips the tag off so that the tag persists, are in development for Parkinson's disease.

Kinetin, met in chapters 6 and 8, is the leading example. In 2022 a group at UCSF showed in a fly model that purifying selection against heteroplasmic mtDNA operates during development and growth but loses its effect during adult ageing. Feeding kinetin restored some of that selection in aged flies, maintained climbing activity, and reduced the loss of dopaminergic neurons. The effect disappeared in **Pink1** mutants.

It was tried in mice as well. Mice of 16.5 months fed kinetin for six weeks showed the age-associated mtDNA deletion in the liver reduced about tenfold — below the level characteristic of the age at which feeding began.

How to read that result

Encouraging as it is, the result must be read with the caveats its authors attached.

First, the reversal in a mammal was shown in the liver. The preservation of dopaminergic neurons was a fly result. Proof in a mammalian brain is still missing.

Second, and more fundamentally, the authors stated that they measured the impact of purifying selection rather than the process itself. They noted it is possible that selection in the opposite direction became stronger rather than purifying selection becoming weaker. In

an adult, they suggested, evolution might favour maximising energy output even by increasing the DNA content of weak mitochondria.

If so, the summary “quality control switches off with age” is premature. Whether it switches off or something else switches on remains open.

Third, as chapter 7 showed, basal mitophagy in vivo proceeds largely without PINK1. And if the bottleneck lies downstream of tagging — in transport or in degradation — then no amount of tagging will clear the rubbish.

Route three: let a neighbour do it

The third route has the outside world perform the choosing and discarding the neuron cannot. Transmitophagy, from chapter 7, is the starting point.

Its appeal is obvious. It goes around the neuron’s intrinsic constraints rather than through them. A cell that cannot divide, cannot rest and cannot ship things far has a neighbour do what it cannot.

Its weakness is equally obvious: the evidence is thinnest. Whether transmitophagy is general beyond specialised sites such as the optic nerve head is unclear, and as disease advances the glia themselves turn inflammatory.

The three routes side by side

	curb reverse flow	PINK1 supply	outsource to glia
moves	damage ↓	repair ↑	repair ↑
main tool	site-selective suppressors	PINK1 activators	none yet
weight of evidence	moderate	moderate; unproven in brain	thin
key risk	may erase a signal too	bottleneck may lie downstream	the contractor also fails

Nobody yet knows which route is right. But the shape of the question is clear. For reverse flow, everything turns on whether those radicals

are damage or signal. For PINK1, on whether the bottleneck is tagging or what follows it. For glia, on how general the phenomenon is.

What to take from this chapter

- Compounds exist that plug the leak without switching complex I off.
- Yet raising reverse-flow radicals extended lifespan in flies.
- A PINK1 activator reduced mtDNA deletions in aged mouse liver; the brain is untested.
- Whether purifying selection weakens or an opposing force strengthens is unresolved.
- Outsourcing to glia is the most appealing route and the least supported.

CHAPTER TEN

The Erasers We Have Not Found

Do the mechanisms described so far fully account for the germ line’s persistence? Several lines of evidence say they do not.

IN THIS CHAPTER

Three reasons to expect more	63
Candidate one: what a sister cell hands over	63
Candidate two: can a condensate be a sieve?	64
Candidate three: is the polar body a bin?	64
Candidate four: simple dilution	65
Perhaps it is not one mechanism	65
Balancing the books	66
What to take from this chapter	67

The five strategies of chapters 2 through 6 were all uncovered within the last decade or so. Complex I's absence in 2022, the ovary's long-lived proteins in 2024, selection by fragmentation in 2019, the lysosomal switch in 2017, the epigenetic reset in 2021.

That fact is itself a signal. In a field whose framework is essentially complete, discoveries of this size do not arrive every few years. It means there is a good deal of blank space on the map.

Three reasons to expect more

First, the pieces come from different organisms. As the table at the end of chapter 6 showed, the evidence for each stage comes from a different species. No study has demonstrated all these strategies operating within one organism, or shown how they interlock. The group that found the lysosomal switch said only that it **may** be conserved in other species.

Second, every discovery was a surprise. An oocyte without complex I was the first such physiological cell type reported in animals. In a tidy, well-mapped field that does not happen.

Third, the known mechanisms cover a narrow range of damage. What has been explained so far is mtDNA mutation, carbonylated protein, protein aggregates and epigenetic marks. Yet the ovary is said to hold proteins that last for decades. The cytoplasm of the egg becomes the embryo directly — so where is the damage in those ancient proteins erased? What about lipid oxidation and other kinds of damage? No mechanism answering that has been reported.

Candidate one: what a sister cell hands over

In 2016 Lei Lei and Allan Spradling at the Carnegie Institution reported an intriguing process in mice.

Mouse primordial germ cells form interconnected clusters called germline cysts. Within them, the researchers showed, some cells receive organelles and cytoplasm from neighbouring cyst cells and become oocytes, while the cells that gave up their organelles die. Organelle movement and the resulting determination of oocyte fate were blocked by drugs that interfere with microtubule-dependent transport. The researchers noted the resemblance to nurse cells dumping cytoplasm in **Drosophila**.

An open question follows. Is the transfer selective? If only healthy mitochondria are chosen for handover, that is a powerful filter in itself.

A 2026 review states that selective transfer of mtDNA into primordial oocytes, together with large-scale germ cell loss, maintains germline mtDNA quality. Whether that selectivity has actually been measured quantitatively in a mammal is something I could not confirm.

Candidate two: can a condensate be a sieve?

The oocyte that receives those organelles gathers them into a structure called the Balbiani body. First described in the mid-nineteenth century, it appears in the oocytes of most animal species.

A 2026 review summarises what is known. The Balbiani body is a membraneless compartment made of RNA–protein complexes and enriched organelles — a molecular condensate. Assembly is initiated by phase separation of seed proteins and reinforced by microtubule-dependent transport and scaffolding; the condensate then matures into a stable solid-like structure and later undergoes regulated disassembly. Depending on the species it handles RNA storage and localisation, mitochondrial selection and quality control, and translational regulation.

A 2026 study in a fish reported something more direct: various stages of autophagic degradation of mitochondria were visible within the Balbiani body. The authors took this as supporting the hypothesis that the structure's primary evolutionary role is to select healthy mitochondria and transfer them to the next generation.

If that holds, the implication is interesting. Quality control research has largely been about enzymes and signalling pathways. If a condensate formed by phase separation can act as a physical sieve, a different kind of mechanism opens up.

If a physical structure rather than an enzyme can do the sorting, the picture of quality control changes.

Candidate three: is the polar body a bin?

Recall the asymmetric division in yeast from chapter 7, where oxidatively damaged protein stayed with the mother.

Meiosis in an egg is among the most asymmetric divisions in biology. Virtually all the cytoplasm stays with the egg, while a small cell called the polar body leaves carrying only a set of chromosomes.

But does the polar body carry out only chromosomes? Whether it also serves as a bin for damage has not, as far as I could establish, been settled.

This candidate is interesting because of its practicality. Polar bodies are already recovered as clinical waste during in vitro fertilisation. Research access is better than for any other candidate on this list.

Candidate four: simple dilution

The plainest possibility should not be left out. As an embryo begins transcribing its own genes and manufacturing protein in quantity, the old material is diluted. Division dilutes it further.

The principle is self-evident. The question is magnitude. How much of the reset in chapter 6 is active removal and how much is simple dilution has never been quantified. Separating the two would itself be a real advance.

Perhaps it is not one mechanism

From here on this is my own reading. Lay the pieces side by side and the same pattern repeats at several scales.

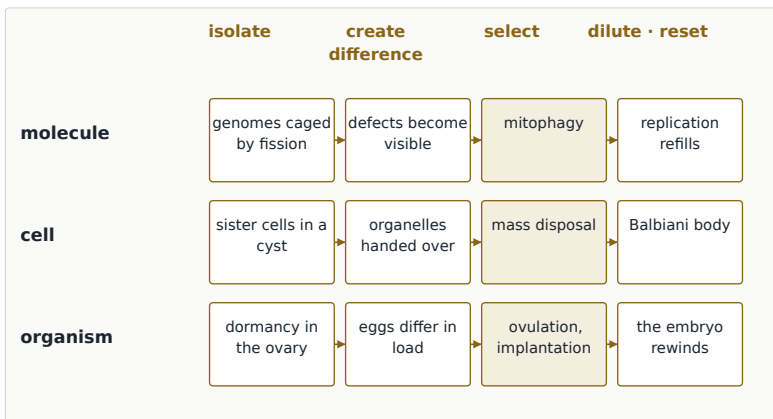


Figure 9 Isolate, create difference, select, dilute or erase. The same sequence repeats from molecules up to whole organisms. This diagram is the author's reading, not a published scheme.

At the molecular scale, fragmentation isolates genomes so that defects become visible, and mitophagy selects. At the cellular scale, organelles are concentrated into one cell within a cyst and most cells are discarded. At the organismal scale, a few hundred of millions of oocytes are ovulated, and the embryo resets its epigenetic clock.

The order is the same every time. Isolate, create difference, select, then dilute or erase.

A 2026 review in evolutionary biology offers a larger frame. It argues that selection for mitochondrial quality drove the evolution of sexes themselves, and that the architecture of the female germ line is a product of that selection. On that account, the high mtDNA ploidy of an oocyte allows early embryonic divisions to proceed without replication, reducing mutational variance across tissues, while mitotic over-proliferation of germ cells, selective mtDNA transfer into primordial oocytes and massive apoptotic germ cell loss together maintain germline mtDNA quality.

If so, the decisive principle may not be any particular enzyme but the layered architecture itself. What we are missing may be less the principle than the components of each layer.

Balancing the books

There is a way to test whether unknown mechanisms remain. Put the rate measurements of chapter 8 to work as an audit.

Measure the total damage entering an oocyte across its life, and add up what the known mechanisms remove. If the books do not balance and something is left over, that remainder is the share belonging to a mechanism nobody has found.

It is the same logic that led physicists to predict the neutrino when the energy budget of beta decay failed to balance: inferring the invisible from a discrepancy among the visible.

The warning from chapter 5 applies in full, though. Without a way to tell which entries in the ledger are selection and which are neutral drift, an unbalanced book cannot distinguish a new mechanism from measurement error.

What to take from this chapter

- Every known strategy was discovered in the last decade. The map has blank regions.
- Candidates: selective organelle handover, physical filtering by a condensate, disposal via the polar body.
- How much of the reset is simple dilution has never been quantified.
- The decisive principle may be the layered architecture rather than any single enzyme.

EPILOGUE

Finite Things, Joined End to End

This book has no recipe for living forever. What it offers instead is one answer to what finitude is for.

IN THIS CHAPTER

What permanence costs	69
What thought costs	69
Two things this book avoided	70
The questions that remain	70
One last word	70

The book began with the mayfly's question. Is everything a finite creature does ultimately pointless?

Ten chapters on, it is time to attempt an answer — though the answer takes the shape of a fact rather than a consolation.

What permanence costs

The closer you look at how the germ line has lasted four billion years, the clearer one thing becomes. That permanence was not free.

The egg pays for the absence of complex I with extreme vulnerability: raise its radical load slightly with menadione and seventy-eight per cent of early oocytes die. The germ line makes millions of oocytes and discards nearly all of them. In the fly, mitochondria are deliberately fragmented so that defects are exposed, and the fragments carrying them are removed without mercy. The worm germ line sits more oxidised than the body around it, and then, at the moment the generation turns, it is wiped clean.

The trick was never that individual cells avoid ageing. It was discarding almost all of them and handing on one — and rewinding the clock at the moment of handover.

What is permanent, then, is not a cell but a lineage. The cells that made up the line were each of them finite.

*Finite things, joined end to end, made something
that does not end.*

What thought costs

The neuron's half of the story has the same shape.

That the neuron lost its repair tools is not a defect. It stopped dividing in order to keep its circuits: a memory persists only if the cell holding it persists. It is not replaced for the same reason. It suppressed its own glycolysis in order to gain antioxidant capacity.

The sum of those choices placed the neuron at the worst position in chapter 1's inequality. Thinking is expensive, and the bill is paid by giving up the ability to repair.

The reason we carry decades of memory, and the reason the cells carrying it eventually fail, are two faces of a single design.

Two things this book avoided

Two temptations were deliberately refused.

The first was telling a tidy story. Join chapters 2 and 3 and you get a clean chain: no complex I, therefore no damage, therefore no need for replacement. Attractive — and an observation in the very same paper unsettles it. Chapter 4 presents evidence of selection, and chapter 5 warns that the same phenomenon may be explained by neutral models. Chapter 9 introduces a strategy for blocking reverse electron transport and then, immediately afterwards, a study in which increasing those same radicals extended lifespan.

Erase those tensions and the reading gets easier while the account gets further from the truth. Science in progress is rarely tidy, and when it looks tidy that usually means nobody has looked hard enough yet.

The second was making this sound actionable. Nearly every experiment in these pages was done in mice, flies, worms, frogs or cultured cells. Kinetin reduced mtDNA deletions in the liver of aged mice; it preserved dopaminergic neurons in flies. Whether any of this works in a human brain, nobody knows.

The questions that remain

Closing the book, these are what is left.

- Do the egg's proteins last because damage is lower, or because something actively defends them?
- Which of the phenomena called selection cannot be explained by a neutral model?
- In ageing, does the part that reads damage weaken, the part that executes, or does an opposing force strengthen?
- Are radicals from reverse electron transport damage, or signal?
- Is there an eraser in the germ line that nobody has found?

Not one of these has been answered here. What this book tried to do was make the shape of the questions a little sharper.

One last word

Back to the mayfly.

The adult that leaves the water cannot eat, because its mouthparts have withered. It does not need them. There is one task left in the time

remaining, and when it is done the role is finished. That is precisely the structure the disposable soma theory describes.

And yet the eggs that mayfly lays become nymphs, and the nymphs become adults. That line has not broken once, up to this moment. The fact that we are able to watch a mayfly at all is the proof.

If you want biology's answer to what a finite creature's striving is for, it probably looks like this. The individual is built to end, and that ending is not a flaw but the condition on which the lineage continues. What carried on was never the individual but the line the individuals made.

The thought I kept returning to while writing this book was that one. I set out looking for something permanent, and what I found was the unbrokenness that finite things make when they are joined end to end.

Entropy Lab

GLOSSARY

Words Used in This Book

The technical terms of the text, in alphabetical order. The definitions are shaped to this book's argument and are not complete scholarly ones.

autophagy the process by which a cell wraps its own components in a membrane and delivers them to a lysosome for digestion. Mitophagy is the case where the target is a mitochondrion.

Balbani body a membraneless structure found in the oocytes of most animals, in which mitochondria and RNA gather. There is a hypothesis that it selects healthy mitochondria for the next generation. Chapter 10.

basal mitophagy mitophagy occurring under ordinary conditions, without imposed stress. Mouse studies found much of it proceeds independently of PINK1. Chapter 7.

bottleneck the sharp fall and subsequent recovery in mtDNA copy number as germ cells form. It widens the spread of mutation load between eggs. Chapter 4.

carbonylation a chemical modification produced when reactive oxygen attacks a protein. It is irreversible and accumulates with age. Chapter 6.

complementation the sharing of contents when mitochondria fuse, so that proteins from a healthy genome cover the shortfall of a defective one. It keeps the cell going and hides defects at the same time. Chapter 4.

complex I the first complex of the electron transport chain: the entry point for electrons from NADH and a principal site where radicals leak. It is not assembled in early oocytes. Chapter 2.

disposable soma theory the proposal that natural selection maintains a body only as far as reproduction requires, rather than indefinitely. Chapter 1.

epigenetic clock a method for estimating biological age from the pattern of chemical marks on DNA. A stretch in which that age decreases was found in the early embryo. Chapter 6.

glia the collective name for the non-neuronal cells of the brain, including astrocytes and microglia. Once regarded as mere support, they are now seen as active participants.

heteroplasmy the state in which different mtDNA sequences coexist within one cell or one body. How those proportions change is the central subject of mitochondrial disease and ageing research. Chapters 4 and 5.

isotope labelling feeding molecules that are chemically identical but slightly heavier, so that material made after that moment can be distinguished. The standard technique for measuring protein lifetimes. Chapters 3 and 8.

Kimura distribution the theoretical distribution of variant frequencies expected under genetic drift alone. It has served as the benchmark for neutrality in mtDNA heteroplasmy studies. Chapter 5.

membrane potential the electrical difference across the inner mitochondrial membrane, generated as electrons flow and protons are pumped. Together with the proton concentration difference (ΔpH) it makes up the proton-motive force, which drives ATP synthesis and is also used as an index of mitochondrial health.

mitochondrial UPR the response triggered when protein folding inside a mitochondrion goes wrong; it raises levels of chaperones and proteases. Activating it has been reported to extend lifespan in worms and mice. Chapter 3.

mitophagy the process of wrapping a damaged mitochondrion in a membrane and sending it to a lysosome for digestion.

Muller's ratchet the one-way accumulation of harmful mutations in a population without recombination. Because mtDNA does not recombine, it is exposed to this risk. Chapter 4.

neutral model a model assuming the observed outcome could arise from stochastic processes alone, with no selection. To claim selection you must show a neutral model fails. Chapter 5.

phase separation the phenomenon in which particular molecules condense into droplets within a liquid, rather as oil separates from water. It is drawing attention as the principle behind membraneless structures inside cells. Chapter 10.

PINK1 / Parkin the best-known signalling system for mitophagy. When a mitochondrion is damaged, PINK1 accumulates on its surface and recruits Parkin, which attaches a **dispose of this** tag. Both genes were discovered as causes of early-onset Parkinson's disease.

proteasome a barrel-shaped machine that degrades tagged proteins; a route distinct from the lysosome.

purifying selection the process by which individuals or cells carrying harmful mutations are disadvantaged, so that those mutations decline in the population. It operates in the germ line, and its effect has been reported to fade during adult ageing. Chapter 9.

reactive oxygen species the highly reactive molecules formed when leaked electrons meet oxygen. They damage DNA, proteins and lipids, and also act as signalling molecules.

reverse electron transport the phenomenon in which electrons travel backwards up complex I, producing radicals, when the membrane potential is high and the electron carrier pool is reduced. It is read as damage by some and as signal by others. Chapter 9.

C. elegans a roundworm about a millimetre long, widely used in research. It is transparent and has a fixed number of cells, which makes observation straightforward. Interlude Two.

substantia nigra a group of dopaminergic neurons in the midbrain. It is the region that fails first in Parkinson's disease, and the one where deleted mtDNA accumulates most with age. Chapter 7.

transmitophagy the phenomenon in which a neuron extrudes its own mitochondria and a neighbouring glial cell takes them up and digests them. First reported at the optic nerve head in mice. Chapter 7.

CHRONOLOGY

The Order in Which It Was Found

The research in this book arranged by year of publication. That most of it falls within the last decade is itself a message.

Theory came first

- 1992** The disposable soma theory accounts for differences in lifespan between species
Kirkwood

Protein lifetimes begin to be measured

- 2003** Dividing yeast keep oxidatively damaged proteins in the mother cell
Aguilaniu and colleagues
- 2006** Deleted mtDNA reaches nearly half of all copies in aged substantia nigra neurons
Bender and colleagues
- 2010** The worm germ line clears oxidised protein at the moment of oocyte maturation
Goudeau and Aguilaniu
- 2010** Protein turnover rates compared across mouse brain, liver and blood
Price and colleagues

The machinery of quality control is uncovered

- 2013** PINK1–Parkin promotes both mitophagy and selective respiratory chain turnover
Vincow and colleagues
- 2014** Neighbouring astrocytes take up and digest a neuron's mitochondria
Davis and colleagues
- 2016** Mouse oocytes differentiate by receiving organelles from sister cells
Lei and Spradling
- 2016** Raising radicals through reverse electron transport extends lifespan in flies
Scialò and colleagues
- 2017** The lysosomal switch thrown by a signal from sperm is identified
Bohnert and Kenyon

The last decade, where the discoveries cluster

- 2018** An mtDNA bottleneck and traces of selection seen in human embryonic germ cells
Floros and colleagues
- 2018** The lifetimes of about 3,500 mouse brain proteins measured precisely
Fornasiero and colleagues

- 2018** Basal mitophagy in vivo proceeds without PINK1
McWilliams and colleagues
- 2018** Disease-associated tau blocks Parkin's translocation to mitochondria
Cummins and colleagues
- 2019** Mitochondrial fragmentation drives selective removal of defective mtDNA
Lieber and colleagues
- 2019** The size of the germ line bottleneck estimated from 249 human transmissions
Zaidi and colleagues
- 2021** A stretch of decreasing biological age found in the early embryo
Kerepesi and colleagues
- 2021** Mitochondrial proteins lasting months found in brain and heart
Bomba-Warczak and colleagues
- 2022** Complex I is never assembled in early oocytes
Rodríguez-Nuevo and colleagues
- 2022** Kinetin reverses mtDNA deletion accumulation in aged mice
Tsai and colleagues
- 2022** PINK1 messenger RNA rides mitochondria out along the axon
Harbauer and Schwarz
- 2022** Protein lifetimes lengthen by about twenty per cent in the aged brain
Kluever and colleagues
- 2024** The ovary holds more extremely long-lived proteins than any other tissue
Harasimov and colleagues

Still in progress

- 2025** A map of protein lifetimes across eight tissues and several brain regions
Li and colleagues
- 2025** Proteostasis surveyed in more than a hundred human oocytes
Zaffagnini and colleagues
- 2025** The statistical standard for separating selection from neutrality in oogenesis questioned
Zussman and colleagues

2026 Selection for mitochondrial quality argued to have driven the evolution of sexes

Lane and Pomiankowski

2026 Common principles proposed for heteroplasmy dynamics in germ line and soma

Ryall and colleagues

2026 The state of Balbiani body research summarised

Kar and Elkouby

The colours mark **the germ line**, **the neuron**, **quality control machinery** and **measurement and theory**. More than half the entries fall after 2018. The map of this field is still being drawn.

REFERENCES

The Studies Cited Here

Full bibliographic details for every study in the text. Each was checked against its record in PubMed and carries a DOI. Entries are grouped by chapter; a study spanning several chapters appears under the first.

Chapter One · Ageing Is Subtraction

Kirkwood TB (1992). Comparative life spans of species: why do species have the life spans they do?. *Am J Clin Nutr* 55(6 Suppl):1191S–1195S. doi:10.1093/ajcn/55.6.1191Sa
 Shanley DP, Kirkwood TB (2000). Calorie restriction and aging: a life-history analysis. *Evolution* 54(3):740–750. doi:10.1111/j.0014-3820.2000.tb00076.x

Chapter Two · The Egg Puts Out the Fire

Rodríguez-Nuevo A, Torres-Sanchez A, Duran JM, De Guirior C, Martínez-Zamora MA, Böke E (2022). Oocytes maintain ROS-free mitochondrial metabolism by suppressing complex I. *Nature* 607(7920):756–761. doi:10.1038/s41586-022-04979-5

Bahety D, Böke E, Rodríguez-Nuevo A (2024). Mitochondrial morphology, distribution and activity during oocyte development. *Trends Endocrinol Metab* 35(10):902–917. doi:10.1016/j.tem.2024.03.002

Chapter Three · Parts Built to Last

Price JC, Guan S, Burlingame A, Prusiner SB, Ghaemmghami S (2010). Analysis of proteome dynamics in the mouse brain. *Proc Natl Acad Sci USA* 107(32):14508–14513. doi:10.1073/pnas.1006551107

Fornasiero EF, Mandad S, Wildhagen H, Alevra M, Rammner B et al. (2018). Precisely measured protein lifetimes in the mouse brain reveal differences across tissues and subcellular fractions. *Nat Commun* 9(1):4230. doi:10.1038/s41467-018-06519-0

Bomba-Warczak E, Edassery SL, Hark TJ, Savas JN (2021). Long-lived mitochondrial cristae proteins in mouse heart and brain. *J Cell Biol* 220(9):e202005193. doi:10.1083/jcb.202005193

Bomba-Warczak E, Savas JN (2022). Long-lived mitochondrial proteins and why they exist. *Trends Cell Biol* 32(8):646–654. doi:10.1016/j.tcb.2022.02.001

Fornasiero EF, Savas JN (2023). Determining and interpreting protein lifetimes in mammalian tissues. *Trends Biochem Sci* 48(2):106–118. doi:10.1016/j.tibs.2022.08.011

Harasimov K, Gorry RL, Welp LM, Penir SM, Horokhovskiy Y et al. (2024). The maintenance of oocytes in the mammalian ovary involves extreme protein longevity. *Nat Cell Biol* 26(7):1124–1138. doi:10.1038/s41556-024-01442-7

Zaffagnini G, Solé M, Duran JM, Polyzos NP, Böke E (2025). The proteostatic landscape of healthy human oocytes. *EMBO J* 44(16):4611–4630. doi:10.1038/s44318-025-00493-2

Chapter Four · You Have to Break It to See It

Floros VI, Pyle A, Dietmann S, Wei W, Tang WCW et al. (2018). Segregation of mitochondrial DNA heteroplasmy through a developmental genetic bottleneck in human embryos. *Nat Cell Biol* 20(2):144–151. doi:10.1038/s41556-017-0017-8

Lieber T, Jeedigunta SP, Palozzi JM, Lehmann R, Hurd TR (2019). Mitochondrial fragmentation drives selective removal of deleterious mtDNA in the germline. *Nature* 570(7761):380–384. doi:10.1038/s41586-019-1213-4

Zaidi AA, Wilton PR, Su MSW, Paul IM, Arbeithuber B et al. (2019). Bottleneck and selection in the germline and maternal age influence transmission of mitochondrial DNA in human pedigrees. *Proc Natl Acad Sci USA* 116(50):25172–25178. doi:10.1073/pnas.1906331116

Chapter Five · Discarding Almost Everything

Zussman JW, Skinner DJ, Wagner DE, Shvartsman SY, Laird DJ (2025). Evaluating selective quality control in mammalian oogenesis: evidence and opportunities. *Annu Rev Genet* 59(1):237–270. doi:10.1146/annurev-genet-021925-093551

Ryall C, Chinnery PF, van den Ameel J (2026). Common principles underlie mitochondrial DNA heteroplasmy dynamics in the germline and soma. *Annu Rev Genomics Hum Genet* 27(1):247–275. doi:10.1146/annurev-genom-120324-032239

Chapter Six · The Clean-Up Between Generations

Goudeau J, Aguilaniu H (2010). Carbonylated proteins are eliminated during reproduction in *C. elegans*. *Aging Cell* 9(6):991–1003. doi:10.1111/j.1474-9726.2010.00625.x

Bohnert KA, Kenyon C (2017). A lysosomal switch triggers proteostasis renewal in the immortal *C. elegans* germ lineage. *Nature* 551(7682):629–633. doi:10.1038/nature24620

Samaddar M, Goudeau J, Sanchez M, Hall DH, Bohnert KA, Ingaramo M, Kenyon C (2021). A genetic screen identifies new steps in oocyte maturation that enhance proteostasis in the immortal germ lineage. *eLife* 10:e62653. doi:10.7554/eLife.62653

Kerepesi C, Zhang B, Lee SG, Trapp A, Gladyshev VN (2021). Epigenetic clocks reveal a rejuvenation event during embryogenesis followed by aging. *Sci Adv* 7(26):eabg6082. doi:10.1126/sciadv.abg6082

Pietroforte S, Martins M, Barragan M, Ibañez E, Vassena R et al. (2025). Mitochondrial metabolism influences meiotic maturation in human oocytes of young and advanced maternal age women. *Hum Reprod* 40(12):2260–2271. doi:10.1093/humrep/deaf207

Chapter Seven · What the Neuron Lost

Aguilaniu H, Gustafsson L, Rigoulet M, Nyström T (2003). Asymmetric inheritance of oxidatively damaged proteins during cytokinesis. *Science* 299(5613):1751–1753. doi:10.1126/science.1080418

Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK et al. (2006). High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat Genet* 38(5):515–517. doi:10.1038/ng1769

Bolaños JP, Almeida A, Moncada S (2010). Glycolysis: a bioenergetic or a survival pathway?. *Trends Biochem Sci* 35(3):145–149. doi:10.1016/j.tibs.2009.10.006

Davis CO, Kim KY, Bushong EA, Mills EA, Boassa D et al. (2014). Transcellular degradation of axonal mitochondria. *Proc Natl Acad Sci USA* 111(26):9633–9638. doi:10.1073/pnas.1404651111

McWilliams TG, Prescott AR, Montava-Garriga L, Ball G, Singh F et al. (2018). Basal mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand. *Cell Metab* 27(2):439–449.e5. doi:10.1016/j.cmet.2017.12.008

Cummins N, Tweedie A, Zuryn S, Bertran-Gonzalez J, Götz J (2018). Disease-associated tau impairs mitophagy by inhibiting Parkin translocation to mitochondria. *EMBO J* 38(3):e99360. doi:10.15252/embj.201899360

Harbauer AB, Schwarz TL (2022). Mitochondrial hitch-hiking of PINK1 mRNA supports axonal mitophagy. *Autophagy* 18(12):3048–3049. doi:10.1080/15548627.2022.2070332

Chapter Eight · How to Measure a Rate

Vincow ES, Merrihew G, Thomas RE, Shulman NJ, Beyer RP et al. (2013). The PINK1-Parkin pathway promotes both mitophagy and selective respiratory chain turnover in vivo. *Proc Natl Acad Sci USA* 110(16):6400–6405. doi:10.1073/pnas.1221132110

Kluever V, Russo B, Mandad S, Kumar NH, Alevra M et al. (2022). Protein lifetimes in aged brains reveal a proteostatic adaptation linking physiological aging to neurodegeneration. *Sci Adv* 8(20):eabn4437. doi:10.1126/sciadv.abn4437

Li W, Dasgupta A, Yang K, Wang S, Hemandhar-Kumar N et al. (2025). Turnover atlas of proteome and phosphoproteome across mouse tissues and brain regions. *Cell* 188(8):2267–2287.e21. doi:10.1016/j.cell.2025.02.021

Chapter Nine · Which Curve Do You Move?

Scialò F, Sriram A, Fernández-Ayala D, Gubina N, Löhmus M et al. (2016). Mitochondrial ROS produced via reverse electron transport extend animal lifespan. *Cell Metab* 23(4):725–734. doi:10.1016/j.cmet.2016.03.009

Tsai PI, Korotkevich E, O'Farrell PH (2022). Mitigation of age-dependent accumulation of defective mitochondrial genomes. *Proc Natl Acad Sci USA* 119(31):e2119009119. doi:10.1073/pnas.2119009119

Watson MA, Brar H, Gibbs ET, Wong HS, Dighe PA et al. (2023). Suppression of superoxide/hydrogen peroxide production at mitochondrial site IQ decreases fat accumulation, improves glucose tolerance and normalizes fasting insulin concentration in mice fed a high-fat diet. *Free Radic Biol Med* 204:276–286. doi:10.1016/j.freeradbiomed.2023.05.022

Sánchez-Pérez P, Mata A, Torp MK, López-Bernardo E, Heiestad CM et al. (2023). Energy substrate metabolism, mitochondrial structure and oxidative stress after cardiac ischemia-reperfusion in mice lacking UCP3. *Free Radic Biol Med* 205:244–261. doi:10.1016/j.freeradbiomed.2023.05.014

Klöppel E, Engstová H, Duspiva P, Tauber J, Mozheitova O, Jabůrek M, Ježek P (2026). Mitochondria-to-plasma-membrane H₂O₂ signaling induced by branched-chain keto acid oxidation essentially stimulates insulin secretion in pancreatic beta-cells. *Redox Biol* 96:104309. doi:10.1016/j.redox.2026.104309

Chapter Ten · The Erasers We Have Not Found

Lei L, Spradling AC (2016). Mouse oocytes differentiate through organelle enrichment from sister cyst germ cells. *Science* 352(6281):95–99. doi:10.1126/science.aad2156

Lane N, Pomiankowski A (2026). Why selection for mitochondrial quality drives the evolution of sexes. *Philos Trans R Soc Lond B Biol Sci* 381(1947):20250076. doi:10.1098/rstb.2025.0076

Kar S, Elkouby YM (2026). The Balbiani body at a glance. *J Cell Sci* 139(9):jcs264644. doi:10.1242/jcs.264644

Żelazowska M, Kujawa R (2026). The Balbiani body, developing egg envelopes, and follicular cells in the previtellogenic ovarian follicles of the Eurasian ruffe. *J Morphol* 287(6):e70143. doi:10.1002/jmor.70143

One source is a preprint that has not been through peer review; the text says so where it is used.

Discovery and preclinical validation of a clinically optimized mitochondrial complex I modulator for Alzheimer's disease (2026). preprint. *bioRxiv*. doi:10.64898/2026.04.10.717554