The Microbial Prologue

The Gut Ecosystem as the Upstream Origin of the Vagal–Coerulean Cascade in Neurodegeneration

How a Lifelong Drift in the Ecology of the Gut Sets the Inflammatory, Metabolic, and Proteinopathic Signal that the Vagus Nerve Delivers to the Locus Coeruleus — the Earliest and Most Vulnerable Casualty of Alzheimer's and Parkinson's Disease

ONS Methodology — Doctoral Thesis

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. Origin companion volume to the Collapse trilogy — Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and Bioenergetic Collapse — and to The Vagal Interface, The Coerulean Interface, The

Vago-Coerulean Relay, and The Tryptophan Partition.

“Before the cortex forgets and before the brainstem fails, an ecology drifts. The first event of a brain disease need not be a lesion, and need not be in the brain — it may be a change in which organisms ferment our food.”

— ONS Methodology Working Notes, 2026

For Heiko Braak, who followed the pathology down to the dorsal medulla and dared to point one synapse further — to the gut; and for the microbiologists who taught neurology to read an organ it had never seen.

THE COLLAPSE TRILOGY — COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition · The Vascular Phasing

V. The Vagal Interface · The Coerulean Interface · The Vago-Coerulean Relay

The Microbial Prologue □ this volume

The trilogy's three principal volumes address distinct axes of neurodegenerative collapse; its companion volumes added a shared metabolic substrate, a vascular gateway, and the vagal–coerulean conduit that couples the body to the brainstem. Those conduit volumes named the cable and the casualty, but treated the gut at the far end as a reservoir without an ecology. The present companion volume supplies the ecology. It is an origin volume: it characterises the resident microbial ecosystem of the gut as the upstream variable that writes the inflammatory, metabolic, and proteinopathic message the vagus delivers to the locus coeruleus — the prologue, written before the nerve, to the cascade the trilogy describes.

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Abstract

The companion volumes of this series established a conduit and a casualty. *The Vagal Interface* identified the tenth cranial nerve as the physical cable that couples the peripheral immunometabolic state to the brainstem; *The Coerulean Interface* identified the locus coeruleus as the nucleus that fails first in Alzheimer's disease and whose noradrenergic silence releases the microglial brake; *The Vago-Coerulean Relay* resolved the precise medullary wiring by which one speaks to the other; and *The Noxious Afferent* catalogued the harmful signals the cable carries. In all four, the gut appeared — as a source of endotoxin, of cytokines, of vanished butyrate — but only as a source, a generic upstream reservoir of "signal." This dissertation makes the gut itself the subject. It advances the thesis that the resident microbial ecosystem of the human gastrointestinal tract is the *upstream ecological variable* that sets the inflammatory, metabolic, and proteinopathic tone the vagus then reports to the locus coeruleus, and that a lifelong drift in the composition of that ecosystem is therefore a candidate first cause of a disease whose earliest brain lesion sits two synapses from the gut's own nerve.

The argument proceeds in seven analytical chapters. Chapter I treats the microbiome as an organ with a developmental and a degenerative trajectory, and consolidates the human cohort evidence that the Alzheimer and Parkinson gut carries a reproducible, pro-inflammatory dysbiotic signature. Chapter II reads the microbial metabolome as a chemistry of neurodegeneration: the loss of butyrate and the collapse of the cathelicidin (LL-37) anti-amyloid checkpoint that the gut-brain-axis node of the knowledge base records as the Barron axis; the double-edged action of short-chain fatty acids on microglia; the rise of lipopolysaccharide, trimethylamine N-oxide, and the secondary bile acids; and the microbial fork in tryptophan metabolism that links this volume directly to *The Tryptophan Partition*. Chapter III develops the cross-seeding hypothesis — that the functional bacterial amyloid curli (CsgA) can template the aggregation of α-synuclein and, by extension, of tau — and argues that the gut is a *seeding compartment*, not merely a signalling one. Chapter IV anatomises the two routes by which a

compromised gut barrier exports its contents: the humoral route through the circumventricular organs, and the neural route through the vagus, including the enteroendocrine neuropod-cell synapse that places a microbial sensor a single fast glutamatergic contact from a vagal afferent. Chapter V treats the enteric nervous system as the place where proteinopathy may literally begin, integrating the Braak caudo-rostral staging, the gut-to-brain α-synuclein propagation experiments, and the truncal-vagotomy and appendectomy epidemiology. Chapter VI brings the three exports — inflammatory tone, metabolic signal, and proteinopathic seed — onto the locus coeruleus, deferring the wiring to *The Vago-Coerulean Relay* and adding a *gut–coerulean spiral* to the coerulean–microglial spiral of the companion volume. Chapter VII develops the therapeutics that follow from an ecological cause — fibre and the restoration of butyrate, the barrier, targeted antimicrobials, probiotics, postbiotics, and faecal transplantation — and states the falsifiable predictions that distinguish a gut-origin model from the cephalocentric default.

The dissertation concludes that the trilogy's three axes of collapse, and the conduit that wires them to the body, all have a plausible point of origin not in the brain at all, but in a shift in the ecology of an organ we have only recently learned to read. The locus coeruleus fails first among brain structures; the microbiome may fail first among everything.

Keywords: gut microbiome, dysbiosis, microbiota-gut-brain axis, short-chain fatty acids, butyrate, cathelicidin, LL-37, lipopolysaccharide, metabolic endotoxemia, bacterial amyloid, curli, CsgA, cross-seeding, trimethylamine N-oxide, secondary bile acids, intestinal barrier, neuropod cells, enteric nervous system, Braak staging, body-first Parkinson's disease, truncal vagotomy, vagus nerve, locus coeruleus, Alzheimer's disease, Parkinson's disease.

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1. Introduction

1.1 The Research Problem

Neurodegenerative disease is described, taught, and treated as a disease of the brain. Its diagnostic lesions are cerebral; its symptoms are cognitive and motor; its imaging is cranial; its therapeutics aim, almost without exception, at targets inside the skull. Yet the chronology of the pathology has, for two decades, pointed somewhere else. In Alzheimer's disease the first hyperphosphorylated tau appears not in the cortex but in the locus coeruleus of the pons, in autopsy series before the third decade of life and decades before any symptom (Braak et al., 2011). In Parkinson's disease the first α-synuclein inclusions appear in the dorsal motor nucleus of the vagus and the olfactory structures, and a substantial fraction of cases show inclusions in the enteric nervous system of the gut wall years before a tremor (Braak et al., 2003; Hawkes et al., 2007). The earliest brain in both diseases is the brainstem, and the brainstem's caudal pole is wired, by a single nerve, to the abdomen.

The companion volumes of this series followed that wire. *The Vagal Interface* established the vagus nerve as the bidirectional conduit between the peripheral immunometabolic state and the brainstem; *The Coerulean Interface* established the locus coeruleus as the receiver whose failure is both the earliest event in the disease and the release of the brain's principal anti-inflammatory brake; *The Vago-Coerulean Relay* resolved the medullary circuitry into its specific synapses; and *The Noxious Afferent* asked which peripheral stimuli, carried by that wire,

actually injure the nucleus. Across all four, one terminus of the conduit was treated as given. The vagus *reads* the periphery — but the periphery it reads most continuously, and most informatively, is the gut, and the gut's chemical character is set not by the host alone but by the trillions of microorganisms that inhabit it. The companion volumes named the cable and the casualty; they did not characterise the *ecology that writes the message*.

This dissertation takes that ecology as its subject. The research problem it addresses is precise: **if the locus coeruleus fails first among brain structures, what fails before it — and is the gut microbiome a credible upstream origin of the signal that the vagus delivers to that nucleus?** This is not the claim that the gut is the sole cause of neurodegeneration; the trilogy's axes are genuinely multiplex and the brain has brain-intrinsic vulnerabilities the gut does not create. It is the more disciplined claim that there exists a continuous causal path — microbial ecology ☐ microbial chemistry and seed ☐ gut barrier ☐ vagal and humoral afferent ☐ brainstem relay ☐ locus coeruleus — and that the most upstream, most modifiable, and most neglected node on that path is the resident ecosystem of the gut.

1.2 Significance

Three things follow if the claim is even partly correct. First, the **timeline** of the disease acquires a prologue. The decades-long preclinical window that neuroimaging has revealed, and that the companion *Temporal Architecture* whitepaper formalised, would have, at its very start, an event that is neither neuronal nor proteinaceous but ecological — a shift in the relative abundances of bacterial taxa. Second, the **causal grammar** of neuroinflammation changes. The Homeostatic Microglial Collapse thesis and *The Coerulean Interface* argued that neuroinflammation is not merely a downstream consequence of plaques and tangles but an engine of the disease; an ecological origin supplies the engine with a fuel line that begins outside the body, in the diet and the organisms that ferment it. Third, and most consequentially, the **therapeutic surface** moves. A brain-intrinsic disease is approachable only through the blood-brain barrier; an ecologically originated disease is approachable through the lumen of the gut — through fibre, through the bacteria that ferment it, through the barrier that contains them, and through the antimicrobials that target the specific organisms implicated. The most upstream node on a causal chain is, by definition, the one whose correction prevents the most downstream harm.

1.3 Scope and Limitations

This volume is deliberately bounded. It does **not** re-derive the vagal anatomy, the cholinergic anti-inflammatory pathway, or the medullary relay; those are the work of the companion volumes and are here taken as established and cited. It does **not** treat the oral microbiome as a separate compartment except where the oral and gut ecosystems converge on the same host-defence checkpoint; the *Porphyromonas gingivalis* literature is acknowledged as a parallel pathogen-route argument and referenced through the knowledge base's gut-brain-axis node. It does **not** claim that the gut origin is the only origin: a brain-first subtype of Parkinson's disease is now well described, and the analogous question in Alzheimer's disease remains open.

The limitations of the evidence must be stated at the outset, because they recur in every chapter. Most mechanistic data come from rodent and invertebrate models, in which germ-free and gnotobiotic manipulation is possible and in which the gut-origin claim has been tested causally; the human data are overwhelmingly cross-sectional and associative, and cannot by themselves distinguish a dysbiosis that causes the disease from one that the disease, its medications, or its altered diet and motility produce. Sixteen-S ribosomal sequencing reports relative, not absolute, abundances, and is sensitive to batch, region, and method. The reader should therefore treat the human cohort evidence of Chapter I as establishing a reproducible *association* and a *direction*, and the animal and molecular evidence of Chapters II through V as establishing *mechanistic plausibility and sufficiency* — and should hold the integrated causal claim to the standard of a hypothesis with a defined set of falsifying experiments, which Chapter VII supplies.

2. Literature Review

2.1 The Microbiome as an Organ With a Trajectory

The human gut harbours a microbial community of a scale that warrants the language of an organ: on the order of tens of trillions of cells — comparable in number to the host's own — several hundred to a thousand or more bacterial species in a typical adult, and a collective gene catalogue that exceeds the human genome by roughly two orders of magnitude. This community is acquired at birth, matures through infancy into an adult configuration dominated in most populations by the Firmicutes and Bacteroidetes phyla, and remains, in health, individually stable across years. It performs metabolic functions the host genome does not encode: the fermentation of otherwise indigestible dietary fibre into short-chain fatty acids, the synthesis of vitamins, the deconjugation and transformation of bile acids, and the metabolism of dietary amino acids — among them tryptophan — into a large repertoire of bioactive compounds.

Crucially for a thesis on an age-related disease, the microbiome has a *degenerative* trajectory as well as a developmental one. The ELDERMET studies (Claesson et al., 2012) established that the gut microbiota of older adults is more variable between individuals and, in those who are frail or institutionalised, characterised by reduced diversity and a shift away from the fibre-fermenting, butyrate-producing taxa of the healthy adult gut. This age-associated drift — a loss of diversity, a loss of butyrate producers, and a relative expansion of pro-inflammatory Proteobacteria — is now discussed under the heading of microbial "inflammaging," and it provides the ecological backdrop against which the disease-specific signatures of the following section must be read.

2.2 The Dysbiotic Signature in Alzheimer's and Parkinson's Disease

A consistent body of human cohort work reports that the gut microbiome of patients with Alzheimer's disease differs reproducibly from that of cognitively healthy controls. Vogt and colleagues (2017) found reduced microbial diversity and a shifted composition — decreased Firmicutes and *Bifidobacterium*, increased Bacteroidetes — in AD patients. Cattaneo and colleagues (2017) made the more pointed observation that the abundance of a pro-inflammatory taxon (*Escherichia/Shigella*) correlated positively, and that of an anti-inflammatory butyrate producer (*Eubacterium rectale*) correlated negatively, with brain amyloid deposition and with peripheral inflammatory markers in cognitively impaired elderly subjects — linking, in a single human dataset, the composition of the gut to the inflammatory state of the blood and the amyloid burden of the brain.

The Parkinson's disease literature is, if anything, more developed, because the body-first hypothesis gave it a strong prior. Scheperjans and colleagues (2015) reported reduced Prevotellaceae and a correlation between *Enterobacteriaceae* abundance and postural instability; Keshavarzian and colleagues (2015) reported a pro-inflammatory, mucin-degrading shift. Across both diseases the qualitative pattern recurs — a loss of fibre-fermenting, barrier-supporting, butyrate-producing organisms and a relative gain of endotoxin-bearing, pro-inflammatory ones — and it is this pattern, rather than any single taxon, that this dissertation treats as the disease-relevant ecological variable.

2.3 The Microbial Metabolome

The mechanistic bridge from a shift in taxa to an effect on the brain runs through chemistry. The relevant microbial products are by now well catalogued: the short-chain fatty acids (acetate, propionate, and especially butyrate), produced by fibre fermentation and serving as the colonocyte's primary fuel, a barrier-strengthening signal, and a systemic immunomodulator (Erny et al., 2015); lipopolysaccharide (LPS), the endotoxin of the gram-negative outer membrane, a potent Toll-like-receptor-4 agonist that appears in elevated quantity in the AD brain and within amyloid plaques (Zhao & Lukiw, 2017); trimethylamine N-oxide (TMAO), a hepatic oxidation product of microbial trimethylamine, elevated in AD cerebrospinal fluid and correlated with biomarkers of neuronal injury (Vogt et al., 2018); the secondary bile acids, produced by microbial transformation of host primary bile acids and altered in profile in AD in proportion to disease severity (MahmoudianDehkordi et al., 2019); and the microbial metabolites of tryptophan, the subject of Chapter II's link to *The Tryptophan Partition*.

2.4 The Intestinal Barrier and Systemic Endotoxemia

For microbial chemistry to reach the brain it must first leave the gut, and the gut is built to contain it. A single layer of epithelial cells, sealed by tight junctions and overlaid by mucus and secretory immunoglobulin, separates the most densely populated microbial habitat on earth from the host's interior. The integrity of that barrier is itself partly microbially maintained — butyrate is a principal energy source for the colonocyte and a signal for tight-junction assembly — so that the dysbiotic loss of butyrate producers and the failure of the barrier are mechanistically coupled. When the barrier fails, microbial products translocate: the phenomenon of "metabolic endotoxemia," in which a low-grade elevation of circulating LPS drives systemic inflammation, was established by Cani and colleagues (2007) in the context of diet-induced metabolic disease and is now recognised as a general consequence of barrier failure. A leaky gut is, in the language of the companion *Noxious Afferent*, a chronic generator of precisely the inflammatory and endotoxic afferent load that injures the locus coeruleus.

2.5 The Enteric Nervous System and the Braak Origin Hypothesis

The most radical version of the gut-origin claim is anatomical rather than chemical: that the proteinopathy itself begins in the gut. Braak's caudo-rostral staging of Parkinson's disease (Braak et al., 2003), and the dual-hit hypothesis that followed (Hawkes et al., 2007), proposed that α-synuclein pathology enters the nervous system at two portals exposed to the environment — the olfactory mucosa and the enteric nervous system of the gut wall — and ascends, in the gut's case, along the vagus to the dorsal motor nucleus and thence rostrally. The hypothesis generated a series of causal tests, reviewed in Chapter V, that constitute the strongest evidence in the entire field for a literal gut-to-brain route of a neurodegenerative protein.

2.6 The Established Conduit

This dissertation does not re-derive the conduit. The afferent and efferent anatomy of the vagus, the location of its central terminus at the nucleus tractus solitarius, the cholinergic anti-inflammatory pathway of Tracey (2002), the dominantly indirect medullary relay from the solitary nucleus to the locus coeruleus through the nucleus paragigantocellularis and the nucleus prepositus hypoglossi, and the humoral parallel through the area postrema, are the subject of *The Vagal Interface* and *The Vago-Coerulean Relay* and are cited here as established. The present volume's contribution begins where the gut's contents meet that conduit, and it treats the conduit as a given pipe whose *input* it characterises.

2.7 Gaps in the Literature

Two literatures run in parallel and rarely meet. The microbiome literature documents dysbiosis and its metabolites in exhaustive taxonomic detail but typically terminates its causal chain at a generic "neuroinflammation" or "amyloid," with the brainstem unmentioned and the locus coeruleus absent. The locus-coeruleus and brainstem literature documents the earliest pathology in fine anatomical detail but rarely names the gut as the source of the afferent load it acknowledges the nucleus receives. No integrated account places the specific ecology of the dysbiotic gut at the upstream end of the specific vagal-coerulean conduit the companion volumes mapped. Supplying that account — connecting a named ecological variable to a named first-failing nucleus through a named conduit — is the gap this dissertation exists to fill.

3. Methodology

This dissertation is a work of mechanistic synthesis conducted under the Organic Network Synthesis (ONS) methodology of AdultCognitiveDisease.com. The method is not experimental; it is integrative. It takes as its units the established findings of disparate literatures — here, microbial ecology, gut immunology, brainstem neuroanatomy, and neurodegenerative neuropathology — and constructs the mechanistic adjacencies that connect them into a single causal chain, distinguishing at each link what is demonstrated from what is inferred.

The method imposes three disciplines that structure the chapters that follow. First, **directionality must be argued, not assumed**: because the human data are associative, each chapter that draws on them states explicitly what would be required to upgrade the association to a cause, and defers the causal weight to the animal and molecular evidence where it exists. Second, **the chain must be continuous**: a synthesis that skips a link — that asserts "the gut affects the brain" without naming the route — is treated as incomplete, which is why Chapter IV anatomises the barrier and the routes out of the gut in detail, and why Chapter VI explicitly hands the brainstem relay to the companion volume rather than waving at it. Third, **the synthesis must be falsifiable**: an integrative claim that no experiment could refute is, by the methodology's standard, not a scientific claim, and Chapter VII therefore closes the volume with a set of predictions whose failure would refute the gut-origin thesis.

The volume's relationship to its companions is itself methodological. It is an *origin volume*: where the companions characterised the conduit and the casualty, this one characterises the source, and its principal synthetic act is to connect a body of microbiological knowledge that has developed in near-total isolation from the brainstem to the brainstem-centred framework the trilogy has built. Its evidentiary standard is correspondingly explicit — the strongest claims it makes are those for which gnotobiotic or vagotomy experiments supply causal closure, and the weakest, flagged as such, are those that rest on cross-sectional human association alone.

4. Chapter I — The Resident Ecology and Its Drift

4.1 The Microbiome as a Late-Recognised Organ

The intellectual difficulty of the gut-origin thesis is, in part, historical. For the whole of the period in which the neuropathology of Alzheimer's and Parkinson's disease was established, the gut microbiome was unreadable. It could not be cultured comprehensively, it could not be sequenced affordably, and it was therefore, in practice, invisible to the disciplines that built the cephalocentric model of neurodegeneration. The model was not wrong to look in the brain; it was, for technical reasons, unable to look anywhere else. The arrival of culture-independent sequencing made the gut ecosystem legible for the first time, and it revealed an organ — by mass comparable to the brain, by gene content vastly larger, by metabolic output a continuous chemical influence on every other organ including the brain — that the disease model had been built without.

The consequence for this dissertation is that the gut microbiome should be understood not as an exotic add-on to neurodegeneration but as a major physiological system whose absence from the classical model is an artefact of measurement rather than of biology. An organ this large, this metabolically active, and this directly wired to the first-failing nucleus of the brainstem has a strong prior claim to relevance; the burden the cephalocentric default has implicitly carried — that an organ of this consequence is somehow irrelevant to a disease of the structure it is wired to — has simply never been discharged.

4.2 The Healthy Ecosystem and Its Services

In health the adult gut microbiome performs a set of services that are, almost item for item, protective against the mechanisms the trilogy identifies as drivers of collapse. It ferments dietary fibre into short-chain fatty acids that fuel the gut barrier, restrain inflammation, and — through the cathelicidin checkpoint of Chapter II — support an anti-amyloid host defence. It maintains the barrier that prevents the translocation of its own endotoxin. It transforms bile acids and metabolises tryptophan along pathways the host benefits from. It competitively excludes pathogens. And it tonically conditions the immune system, including, as Chapter IV develops, the microglia of the brain. A healthy microbiome is, in the framework of this series, a continuous *suppressor* of the afferent inflammatory load that *The Noxious Afferent* identified as the injurious input to the locus coeruleus.

4.3 The Drift: Aging, Diet, and Dysbiosis

The ecological drift that this dissertation places at the origin of the cascade is the systematic reversal of those services. The ELDERMET work (Claesson et al., 2012) established the age-associated pattern — loss of diversity, loss of butyrate producers, expansion of pro-inflammatory taxa — and tied it to diet and to the loss of dietary variety that accompanies frailty and institutionalisation. Onto this age-related drift the disease-specific signatures of the cohort studies (Vogt et al., 2017; Cattaneo et al., 2017; Scheperjans et al., 2015; Keshavarzian et al., 2015) are superimposed. The drift is not a single deficiency but a *coordinated reversal*: the same dysbiotic shift that lowers butyrate also weakens the barrier (because butyrate fuels the barrier), which raises circulating endotoxin, which drives inflammation, which the now-permeable barrier no longer contains. The ecology does not fail one service at a time; it fails as a system, and the failures compound. This systemic, self-amplifying character of the drift is the first of several spirals this volume identifies, and it is the most upstream.

4.4 The Causal Status of the Signature

Honesty requires the chapter to close on the limitation that governs the human evidence. Every cohort study cited establishes association, and association in this domain is doubly suspect: the disease alters diet, motility, and medication, all of which alter the microbiome, so that a dysbiotic signature in a patient could be wholly an effect of the disease rather than a cause. The signature's claim to causal relevance does not rest on the human cross-sectional data; it rests on the animal experiments of the following chapters, in which the microbiome is *manipulated* — eliminated in germ-free animals, perturbed by antibiotics, transplanted between hosts — and the brain pathology moves with it. The cohort signature establishes that the human disease is *accompanied* by the predicted ecology; the gnotobiotic experiments establish that the ecology is *sufficient* to move the pathology. The dissertation's causal claim lives in the conjunction.

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5. Chapter II — The Microbial Chemistry of Neurodegeneration

5.1 The Logic of a Chemical Bridge

A shift in the relative abundance of bacterial species is, in itself, inert with respect to the brain. It becomes consequential only through chemistry — through the changed profile of metabolites that a changed ecology produces and exports. This chapter reads the microbial metabolome as a chemistry of neurodegeneration, taking in turn the protective metabolite whose loss matters most, the metabolites whose gain matters most, and the metabolite whose *partition* connects this volume to its companion on tryptophan.

5.2 Butyrate and the Cathelicidin Checkpoint

The single most important protective output of the healthy microbiome, for the purposes of this series, is butyrate. As the colonocyte's primary fuel and a signal for tight-junction assembly it maintains the barrier; as a histone deacetylase inhibitor it exerts broad anti-inflammatory and epigenetic effects; and, in the mechanism that the knowledge base's gut-brain-axis node records as the Barron axis, butyrate upregulates the *CAMP* gene that encodes the antimicrobial peptide cathelicidin (LL-37). LL-37, in turn, acts as a molecular chaperone that prevents the fibrillation of amyloid-β at near-equimolar ratios. The chain is therefore continuous and consequential: fibre-fermenting bacteria ☐ butyrate ☐ *CAMP*/LL-37 ☐ suppression of amyloid aggregation. Dysbiotic loss of butyrate producers removes the upstream input to an anti-amyloid host-defence checkpoint, and the same checkpoint is attacked from the oral compartment, where the periodontal pathogen *P. gingivalis* both disseminates to the brain (Dominy et al., 2019) and degrades LL-37 directly. The cathelicidin checkpoint is thus a node at which the gut ecology, the oral ecology, and vitamin-D status (through the vitamin-D response element of *CAMP*) converge on a single anti-amyloid defence — and the loss of butyrate is the gut's contribution to its failure.

5.3 The Short-Chain Fatty Acid Paradox

The same short-chain fatty acids that maintain the barrier and the cathelicidin checkpoint also condition the brain's microglia, and here the literature requires an honest complication rather than a tidy story. Erny and colleagues (2015) demonstrated that the host microbiota continuously control the maturation and function of microglia, that germ-free mice have malformed and functionally defective microglia, and that supplementation with short-chain fatty acids restores them — a finding that places the microbiome upstream of the very cell type whose homeostatic collapse the companion microglial volume describes, and that, on its face, casts short-chain fatty acids as protective. Yet Sampson and colleagues (2016), in an α-synuclein-overexpressing mouse model of Parkinson's disease, found the opposite valence: gut microbiota were *required* for motor deficits and α-synuclein pathology, germ-free animals were protected, and short-chain fatty acids were *sufficient* to restore the pathology in germ-free hosts.

The contradiction is real and instructive, and this dissertation does not resolve it by choosing a side. Short-chain fatty acids are best understood as a *context-dependent immunomodulatory signal* whose effect depends on the state of the system receiving it: in a healthy host they support barrier and microglial maturation, while in a host already carrying a proteinopathic load they can act as a microglial-activating, pathology-permitting signal. The lesson for the gut-origin thesis is not that short-chain fatty acids are good or bad but that the microbiome's outputs are genuinely *causal* — sufficient, in a clean gnotobiotic system, to switch brain pathology on and off — which is precisely the property the cross-sectional human data cannot supply and the gut-origin claim requires.

5.4 The Endotoxin, the Amine, and the Bile Acids

Three metabolites enter the cascade by their *gain* rather than their loss. Lipopolysaccharide, the endotoxin of gram-negative bacteria, is the prototypical pro-inflammatory microbial product; it is the agonist behind metabolic endotoxemia (Cani et al., 2007), it has been detected in elevated quantity in AD brain tissue and within amyloid plaques (Zhao & Lukiw, 2017), and it is the canonical injurious afferent of *The Noxious Afferent*. Trimethylamine N-oxide, the hepatic oxidation product of microbial trimethylamine derived from dietary choline and carnitine, is elevated in AD cerebrospinal fluid and correlates with cerebrospinal-fluid markers of neuronal injury and tau pathology (Vogt et al., 2018), supplying a second, blood-borne microbial signal with a measurable central correlate. The secondary bile acids — host primary bile acids transformed by microbial enzymes — show an altered profile in AD that tracks disease severity (MahmoudianDehkordi et al., 2019), implicating microbial bile-acid metabolism in the disease's progression. Marizzoni and colleagues (2020) brought two of these strands together, proposing short-chain fatty acids and lipopolysaccharide as paired mediators between gut dysbiosis and amyloid pathology in human AD. None of these metabolites acts alone; together they constitute the chemical content of the afferent load.

5.5 The Tryptophan Fork — Link to The Tryptophan Partition

The metabolite that most directly connects this volume to its companions is tryptophan, and the connection is mechanistically exact rather than thematic. Dietary tryptophan is partitioned among three fates — serotonin synthesis, the kynurenine pathway, and direct microbial conversion to indole and its derivatives — and the gut microbiome is a major controller of that partition. The companion *Tryptophan Partition Node* thesis treats the kynurenine fork as a shared metabolic variable upstream of multiple collapse axes; the present volume supplies the ecological controller of that fork. Microbial indole derivatives are ligands of the aryl hydrocarbon receptor, through which they shape mucosal immunity and barrier function; microbial influence on the kynurenine pathway bears on the production of the neuroactive and neurotoxic kynurenines, including quinolinic acid. The gut microbiome is therefore not merely *a* source of tryptophan metabolites but the *upstream regulator of the partition* that the companion volume placed at the centre of the metabolic axis. The two theses describe the same fork from two ends: the partition volume from the metabolic consequence, this volume from the microbial cause.

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6. Chapter III — Bacterial Amyloid and the Cross-Seeding Hypothesis

6.1 The Surprising Existence of Functional Bacterial Amyloid

The cross-seeding hypothesis rests on a fact that is counter-intuitive to anyone schooled in the view of amyloid as a uniquely pathological accident: amyloid is a common, ancient, and *functional* protein fold, and bacteria build it on purpose. The best-characterised example is curli, the extracellular amyloid fibre that *Escherichia coli*, *Salmonella*, and other Enterobacteriaceae secrete to scaffold their biofilms and to adhere to surfaces and host tissues. Curli's major structural subunit is the protein CsgA, which is exported as a soluble monomer and polymerises into a cross-β amyloid fibre indistinguishable, by the defining biophysical criteria, from the amyloids of human disease. The dysbiotic gut, with its relative expansion of Enterobacteriaceae, is therefore a habitat *enriched in amyloid* — a fact with no place in the cephalocentric model and a central place in this one.

6.2 The Cross-Seeding Mechanism

The hypothesis, developed principally by Friedland and Chapman (2017), is that exposure of the host to bacterial amyloid can template, or "cross-seed," the aggregation of the host's own aggregation-prone proteins — that a curli fibre in the gut can serve as a heterologous nucleus that lowers the kinetic barrier to α-synuclein (and, by extension, tau) aggregation, in the same prion-like templating logic by which a pathological seed of one conformer recruits soluble monomer to its fold. The mechanism has experimental support of escalating directness. Chen and colleagues (2016) showed that exposure of aged rats and of *Caenorhabditis elegans* to curli-producing *E. coli* enhanced α-synuclein aggregation in both gut and brain. Sampson and colleagues (2020) closed the loop in the mouse: a gut bacterial amyloid (curli/CsgA) promoted α-synuclein aggregation and motor impairment, and bacterial amyloid was *required* for the gut microbiota to enhance the pathology — a gnotobiotic demonstration that the bacterial amyloid is not an incidental correlate but a causal contributor.

6.3 The Gut as a Seeding Compartment

The consequence for this series is a categorical upgrade in the gut's role. In Chapters I and II the gut is a *signalling* compartment — it sends inflammatory and metabolic messages along the conduit. In the cross-seeding frame it is a *seeding* compartment: a place where the aggregation of a neurodegenerative protein may be *initiated*, in the enteric nervous system embedded in the gut wall, by templating contact with the amyloid of the gut's own bacteria. This reframes the Braak origin hypothesis of Chapter V at the molecular level. The body-first model asks how α-synuclein pathology, once present in the enteric nervous system, ascends to the brain; the cross-seeding model offers a candidate answer to the prior question of how it arose in the enteric nervous system in the first place — by contact, across a compromised barrier, between enteric neurites and the bacterial amyloid of a dysbiotic, Enterobacteriaceae-enriched gut. Whether the same logic extends to tau, and thus to the locus-coeruleus pathology of Alzheimer's disease, is at present an inference from the shared cross-β mechanism rather than a demonstrated fact, and Chapter VII states it as a prediction rather than a finding.

7. Chapter IV — The Barrier and the Two Routes Out of the Gut

7.1 The Barrier as the Gating Variable

Everything the preceding chapters describe — the metabolites, the endotoxin, the bacterial amyloid — is, in the healthy host, *contained*. The single-cell intestinal epithelium, sealed by tight junctions, overlaid by mucus, and patrolled by mucosal immunity, holds the densest microbial habitat on earth at arm's length from the body's interior. The barrier is therefore the gating variable of the entire gut-origin thesis: a perfectly dysbiotic gut behind a perfectly intact barrier would export little, and the disease-relevant question is not dysbiosis alone but *dysbiosis behind a failing barrier*. The coupling developed in Chapter I — that butyrate fuels the barrier, so that the dysbiotic loss of butyrate producers weakens the very barrier that would otherwise contain the consequences of dysbiosis — makes barrier failure a near-automatic sequel of the ecological drift, and turns the gut from a contained compartment into an exporting one.

7.2 The Humoral Route

The first route out is the bloodstream. When the barrier fails, microbial products translocate into the portal and systemic circulation: the metabolic endotoxemia of Cani and colleagues (2007), in which circulating lipopolysaccharide drives a low-grade systemic inflammation, is the prototype. Blood-borne microbial products and the cytokines they elicit reach the brain by several means, but the route most relevant to this series is the one the companion *Vago-Coerulean Relay* identified: the circumventricular organs, and in particular the area postrema, which lie outside the blood-brain barrier, sample the circulating milieu directly, and project into the same nucleus-tractus-solitarius relay that the vagus feeds. The humoral and neural channels are therefore not independent; they *converge* on the brainstem relay before reaching the locus coeruleus, a redundancy the relay volume emphasised and this volume inherits.

7.3 The Neural Route and the Neuropod Synapse

The second route out is the vagus itself, and recent work has made the gut-vagus connection far more intimate than the diffuse paracrine picture once assumed. The afferent vagus does not merely bathe in gut contents; it receives a *wired, synaptic* input. Enteroendocrine cells of a specialised type — the neuropod cells characterised by the Bohórquez laboratory — form genuine synaptic contacts with vagal afferent neurons and transduce luminal information across that synapse on a millisecond timescale through glutamatergic transmission (Kaelberer et al., 2018). The significance for the gut-origin thesis is structural: a sensor of the luminal environment — of nutrients, and plausibly of microbial signals — sits a *single fast excitatory synapse* from a vagal afferent, which is itself, through the relay of the companion volume, a small number of synapses from the locus coeruleus. The gut's chemical state is not merely sensed by the brainstem; it is, in part, *hard-wired* to it.

That the vagus is the operative neural route, and not merely an available one, is established by the behavioural microbiome literature: specific bacterial strains alter host behaviour and central neurochemistry through the vagus, effects abolished by vagotomy (Bravo et al., 2011; Sgritta et al., 2019). These experiments demonstrate, in the cleanest available form, that a defined change in the gut microbiome produces a defined central effect *via the vagus nerve* — the exact causal architecture the gut-origin thesis requires, here proven for behaviour and proposed, in this volume, for the inflammatory and proteinopathic load on the locus coeruleus.

7.4 The Two Routes as One Input

The chapter closes by collapsing the two routes into the single input the next chapter delivers to the locus coeruleus. The humoral route carries the slow, tonic, blood-borne signal of metabolic endotoxemia and the microbial metabolites to the circumventricular organs and the systemic immune system; the neural route carries the fast, wired, synaptically transduced signal of the luminal and inflammatory state along the vagus. Both terminate in the nucleus tractus solitarius and its medullary relay; both are amplified by barrier failure; both are set, upstream, by the gut's ecology. From the locus coeruleus's point of view there is one input with two arrivals, and its content is written by the microbiome.

8. Chapter V — The Enteric Origin of Proteinopathy

8.1 The Strongest Form of the Claim

The chapters to this point have argued that the gut *sends signals* — inflammatory, metabolic, and, in Chapter III, potentially seeding — that load the conduit. This chapter takes up the strongest and most specific form of the gut-origin thesis: that in Parkinson's disease the proteinopathy itself begins in the gut wall and travels, as a physical object, to the brain. This is the body-first hypothesis, and it is supported by the most nearly decisive evidence in the entire gut-brain literature.

8.2 The Staging and the Dual-Hit Hypothesis

Braak and colleagues (2003) proposed, from the topographic distribution of α-synuclein inclusions across disease stages, that Parkinson pathology follows a caudo-rostral course beginning in the dorsal motor nucleus of the vagus and the olfactory structures and ascending through the brainstem to the substantia nigra and beyond. The dual-hit hypothesis (Hawkes et al., 2007) interpreted the two earliest sites as the two environmentally exposed portals of the nervous system — the olfactory mucosa and the enteric nervous system of the gut — and proposed that a pathogen or pathological seed enters at both and ascends, in the gut's case, along the vagus. Enteric α-synuclein inclusions have been reported in patient gut biopsies years before motor onset, consistent with the gut as an early, possibly originating, site.

8.3 The Propagation Experiments

The hypothesis's distinction is that it has been tested causally, in a way little else in neurodegeneration has. Holmqvist and colleagues (2014) injected α-synuclein into the rat gut and traced its transport along the vagus to the dorsal motor nucleus. Pan-Montojo and colleagues showed that an enteric insult could induce α-synuclein pathology that ascended the vagus, and that vagotomy interrupted it. The most complete demonstration is that of Kim and colleagues (2019): pathological α-synuclein preformed fibrils injected into the mouse gut propagated transneuronally to the brain, reproduced the caudo-rostral spread, and produced motor and non-motor deficits — and truncal vagotomy, or the genetic absence of α-synuclein, *blocked* the propagation. This is a causal chain of the kind the gut-origin thesis requires: a defined seed in the gut, a defined route through the vagus, a defined brain pathology at the end, and a defined surgical interruption that abolishes it.

8.4 The Human Epidemiology

The human counterpart to the vagotomy experiments is the vagotomy epidemiology, which supplies the strongest available human evidence for a vagal route. Svensson and colleagues (2015) found that full truncal vagotomy — which severs the route — was associated with a reduced subsequent risk of Parkinson's disease; Liu and colleagues (2017), in a Swedish register-based matched-cohort study, reached a concordant conclusion. Killinger and colleagues (2018) extended the logic to the appendix, a reservoir of enteric α-synuclein, reporting that appendectomy was associated with altered Parkinson's-disease risk. These studies are observational and not without inconsistency across cohorts and vagotomy types, but their convergence — severing the cable, or removing a reservoir at its origin, lowers the risk — is precisely the pattern the gut-origin, vagus-route thesis predicts, and it is difficult to explain under a purely brain-first model.

8.5 The Boundary and the Extension to Alzheimer's Disease

Two boundaries must be drawn. First, the body-first route is not universal even in Parkinson's disease: Borghammer and Van Den Berge (2019) describe a brain-first subtype in which the pathology appears to begin centrally, and the gut-origin claim is properly a claim about a *subtype and a route*, not about every case. Second, the propagation evidence is, at present, an α-synuclein story; the extension to the tau pathology of the Alzheimer locus coeruleus is an inference from the shared prion-like templating mechanism and the shared brainstem-first chronology, not a demonstrated gut-to-brain tau route. This dissertation draws the parallel deliberately and flags it honestly: the Parkinson body-first model is the *proof of principle* that a neurodegenerative proteinopathy can begin in the gut and ascend the vagus, and the Alzheimer locus-coeruleus question is whether the same architecture — possibly through the cross-seeding of tau by bacterial amyloid of Chapter III, possibly through the inflammatory loading of Chapter VI rather than literal seed transport — applies to the nucleus that fails first in the more common disease. The extension is the central open question this volume bequeaths to the field.

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9. Chapter VI — Convergence on the Locus Coeruleus

9.1 Three Exports, One Receiver

The preceding chapters identified three things the dysbiotic, barrier-compromised gut exports: an *inflammatory and endotoxic tone* (Chapters II and IV), a set of *metabolic signals* including the loss of the cathelicidin checkpoint and the shift in tryptophan partition (Chapter II), and, in the strongest form, a *proteinopathic seed* (Chapters III and V). This chapter brings all three onto a single receiver. It does not re-derive the path; the path is the subject of *The Vago-Coerulean Relay*, and is taken here as established: vagal afferent ☐ nucleus tractus solitarius ☐ the dominantly indirect medullary relay through the paragigantocellularis and the prepositus hypoglossi, with the area-postrema humoral channel converging at the solitary nucleus. The question of this chapter is why the locus coeruleus, of all the structures that relay reaches, is the one on which the gut's exports come to matter most.

9.2 Why the Locus Coeruleus Is the Receiver That Matters

The companion *Coerulean Interface* established the three properties that make the locus coeruleus uniquely catastrophic, and each makes it the critical receiver of the gut's exports. First, it is the *first to fail*: the earliest hyperphosphorylated tau in Alzheimer's disease appears there, decades before symptoms (Braak et al., 2011), so that whatever loads it loads the disease's earliest lesion. Second, it is the *anti-inflammatory brake*: locus-coeruleus noradrenaline is an endogenous suppressor of microglial activation, and experimental coerulean lesioning worsens amyloid pathology and disinhibits neuroinflammation (Heneka et al., 2010), so that a gut-driven inflammatory load that injures the nucleus also *releases the brake on the very inflammation the gut is driving*. Third, it is *bioenergetically marginal*: the Bioenergetic Collapse thesis identified the locus coeruleus as a structure operating at the edge of its metabolic ceiling, so that the chronic, sustained excitatory drive a chronic afferent load imposes is precisely what an already marginal nucleus cannot sustain (*The Noxious Afferent*). The gut's exports do not fall on a random target; they fall on the brain's first, most pivotal, and most fragile point of failure.

9.3 The Gut–Coerulean Spiral

The companion volume named a coerulean–microglial spiral: locus-coeruleus failure releases the noradrenergic brake, neuroinflammation is disinhibited, and the disinhibited inflammation feeds back onto the surviving coerulean neurons. This dissertation adds an upstream, body-spanning loop that drives that spiral from the gut, and names it the **gut–coerulean spiral**. Its links are now all in place. Dysbiosis lowers butyrate and weakens the barrier (Chapter I); the weakened barrier exports endotoxin and metabolites and raises the inflammatory afferent load (Chapters II, IV); the chronic load drives and bioenergetically stresses the locus coeruleus (Chapter VI, §9.2); coerulean noradrenaline falls; the falling noradrenaline disinhibits both central microglia *and*, through reduced anti-inflammatory autonomic tone, the periphery — including the gut barrier and the gut's own immune environment — which worsens the dysbiosis and the barrier failure that began the loop. The spiral closes outside the brain. This is the dissertation's central synthetic claim: that the earliest, most upstream, and most modifiable segment of the loop that destroys the locus coeruleus runs through the ecology of the gut, and that the loop is therefore, in principle, *interruptible at its origin* — the subject of the final chapter.

10. Chapter VII — Therapeutic Implications and Falsifiable Predictions

10.1 The Therapeutic Logic of an Origin

The therapeutic significance of an origin volume is categorical: the most upstream node on a causal chain is the one whose correction prevents the most downstream harm, and it is reachable, in this case, through the lumen of the gut rather than across the blood-brain barrier. The interventions that follow are ordered, as the gut–coerulean spiral is ordered, from the most upstream.

• **Restore the fermentation.** The most upstream lever is the substrate of the protective ecology: dietary fibre, and the butyrate-producing taxa that ferment it. Fibre, prebiotic substrates, and butyrate-producing probiotics aim to restore the butyrate supply that fuels the barrier and the cathelicidin checkpoint, attacking the spiral at its first link. Direct or pro-drug butyrate supplementation is the corresponding postbiotic strategy.

• **Repair the barrier.** Because barrier failure is the gating variable (Chapter IV), interventions that restore tight-junction integrity — including, indirectly, the restoration of butyrate — convert an exporting gut back into a contained one and lower the afferent load regardless of the residual dysbiosis behind it.

• **Subtract the noxious organisms and seeds.** Where specific pathobionts are implicated — the Enterobacteriaceae that bear endotoxin and build curli (Chapter III), the oral *P. gingivalis* that disseminates and degrades LL-37 — targeted antimicrobial and anti-virulence strategies (including the gingipain inhibitors of the Dominy programme, referenced through the knowledge base) aim to remove the specific injurious input rather than the ecosystem wholesale.

• **Replace the ecology.** Probiotics, defined consortia, and, at the extreme, faecal microbiota transplantation aim to restore the protective community directly. The gnotobiotic transfer experiments (Sampson et al., 2016) are the proof of principle that transferring an ecology transfers its brain phenotype; the therapeutic inversion is to transfer a *protective* ecology.

• **Defend the receiver.** Finally, the interventions of the companion volumes — noradrenergic support, vagal stimulation read through the relay volume's caution, and the heart-rate-variability and neuromelanin-MRI biomarkers — act downstream, on the conduit and the receiver, and are complementary to, not substitutes for, correcting the origin.

10.2 Falsifiable Predictions

The gut-origin thesis is falsifiable, and the methodology requires it to state how. The following predictions, if they failed, would refute or sharply constrain it.

• **Temporal primacy.** In longitudinal cohorts with serial sampling, a measurable dysbiotic drift — loss of butyrate producers, rise of endotoxin-bearing taxa — will *precede* the earliest detectable locus-coeruleus signal (neuromelanin-MRI decline, or a coerulean tau-PET signal) in individuals who later progress. If the coerulean signal reliably precedes the ecological one, the origin claim fails.

• **Conduit dependence.** The association between the dysbiotic signature and locus-coeruleus injury will be *attenuated in vagotomised individuals*, in whom the neural route is severed. If severing the conduit does not weaken the gut–coeruleus association, the neural-route component of the thesis fails.

• **Cross-seeding extension.** Bacterial amyloid (curli/CsgA) exposure will accelerate not only α-synuclein but *tau* aggregation in appropriate models, and germ-free or curli-deficient conditions will retard it. If bacterial amyloid proves specific to synuclein and inert toward tau, the Alzheimer extension of Chapter III fails while the Parkinson core survives.

• **Butyrate–cathelicidin causality.** Restoring butyrate will raise LL-37 and lower amyloid aggregation in vivo, and the effect will be lost where the *CAMP*/cathelicidin pathway is genetically disabled. If butyrate's anti-amyloid effect is independent of the cathelicidin checkpoint, the specific Barron-axis mechanism is wrong even if the broader butyrate claim survives.

• **Therapeutic upstream-dominance.** An intervention at the gut origin (fibre/butyrate, barrier repair, or ecology replacement), begun in the preclinical window, will alter the locus-coeruleus trajectory more than an equally timed intervention aimed only at the receiver. If origin-directed and receiver-directed interventions are equivalent, the thesis's central therapeutic claim — that the origin is the high-leverage node — fails.

10.3 What Would and Would Not Survive

The dissertation states plainly which of its claims are load-bearing and which are expendable. The body-first Parkinson route (Chapter V) is the best-supported and would survive nearly any negative result elsewhere, because it rests on causal animal experiments and convergent human epidemiology. The metabolite chemistry (Chapter II) is robust as association and sufficiency but context-dependent in valence, as the short-chain-fatty-acid paradox shows. The cross-seeding extension to tau (Chapter III, §6.3) and the Alzheimer locus-coeruleus origin (Chapter V, §8.5) are the most speculative and the most important, and are offered explicitly as the field's next experiments rather than as settled conclusions. The gut–coerulean spiral (Chapter VI) is the synthesis that the volume contributes; its value is that it makes the whole chain *interruptible at its origin*, and its fate rests on prediction 5.

Synthesis and Conclusion — The Ecology Before the Nerve

The companion volumes of this series built outward from the brain and arrived at the body. *The Bioenergetic Collapse*, *Homeostatic Microglial Collapse*, and *Convergent Synaptic Collapse* identified three substrates of failure inside the brain; *The Tryptophan Partition* and *The Vascular Phasing* identified a shared metabolic variable and a shared gateway; *The Vagal Interface*, *The Coerulean Interface*, and *The Vago-Coerulean Relay* identified the nerve that couples the body to the brainstem and the nucleus on which the coupling lands. At the end of that progression stood an open terminus: the vagus reads the periphery, and the periphery it reads is the gut — but the gut, in those volumes, was a reservoir without an ecology.

This dissertation supplied the ecology. It argued that the resident microbial community of the gut is a late-recognised organ whose age- and diet-driven drift coordinately reverses a set of services that are, almost item for item, protective against the trilogy's mechanisms; that the drift exports a definite chemistry — the loss of butyrate and the cathelicidin checkpoint, the gain of endotoxin, trimethylamine N-oxide, and altered bile acids, and the dysregulation of the tryptophan partition that the companion volume placed at the metabolic centre; that in its strongest form the gut is not only a signalling but a *seeding* compartment, where bacterial amyloid may template the proteinopathy and where, in Parkinson's

disease, the proteinopathy demonstrably begins and ascends the vagus; that the gut's exports leave through a failing barrier by a humoral and a neural route that converge on the brainstem relay; and that all of it lands on the locus coeruleus — the first nucleus to fail, the brake whose loss releases the inflammation the gut is driving, and a nucleus too bioenergetically marginal to sustain the chronic load. The volume closed the loop into a gut–coerulean spiral whose most upstream segment runs through an ecology we can change.

The conclusion is a reframing of where the disease begins. The locus coeruleus fails first among brain structures; this dissertation's claim is that it is not the first thing to fail at all. Before the nerve there is the ecology, and before the tangle there is the drift. If that ordering is correct, then the prologue to neurodegeneration is written not in the cortex, nor even in the brainstem, but in an organ of microbial cells we have only just learned to read — and the most hopeful sentence in the whole of this series is that a prologue, unlike a final chapter, can still be rewritten.

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