The Biomolecular Neuropsychiatry Series

ACE Factor Deficiency Theory Series

Biomolecular Autism Spectrum Disorder

Addressing Cellular Incompleteness and Restoring Synaptic Architecture



By

Dr. Alaa Abdelkarim

Prof. Dr. Yasser Saif | Prof. Mike Chan

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Dedication

To the two most precious souls in my life,
the ones who shaped my heart, my mind, and my path.

My father, your words still live within me, echoing in every decision and every difficult moment, even after more than thirty-four years of your absence.

My mother, your endless encouragement, your insistence on excellence, and your belief in what I could become still guide me and push me forward to this day.

One of you built the man within me, and the other shaped the doctor I became.

What gratitude could ever be enough for such love, such sacrifice, and such lasting influence?

I miss you both every day, every hour, every second.
Until we meet again, no love in my life has ever been greater than the love I carry for you both.

Alaa

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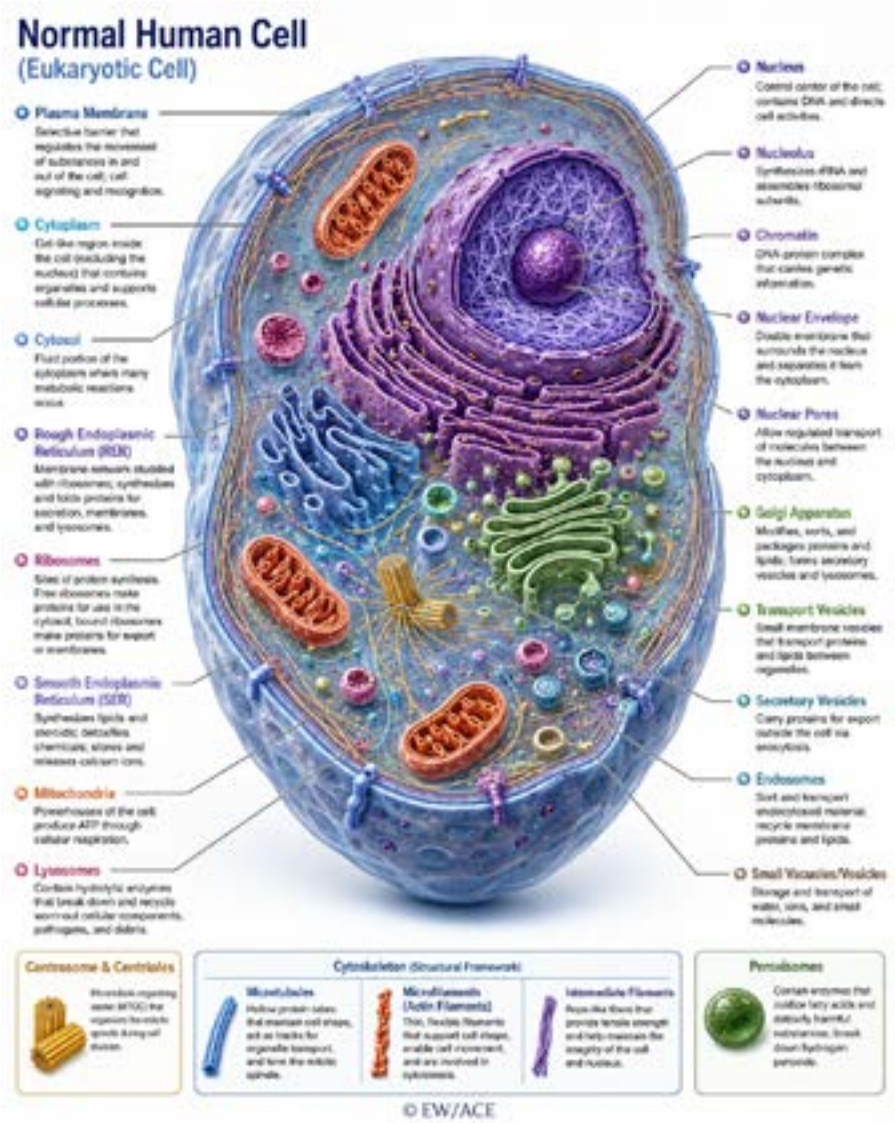
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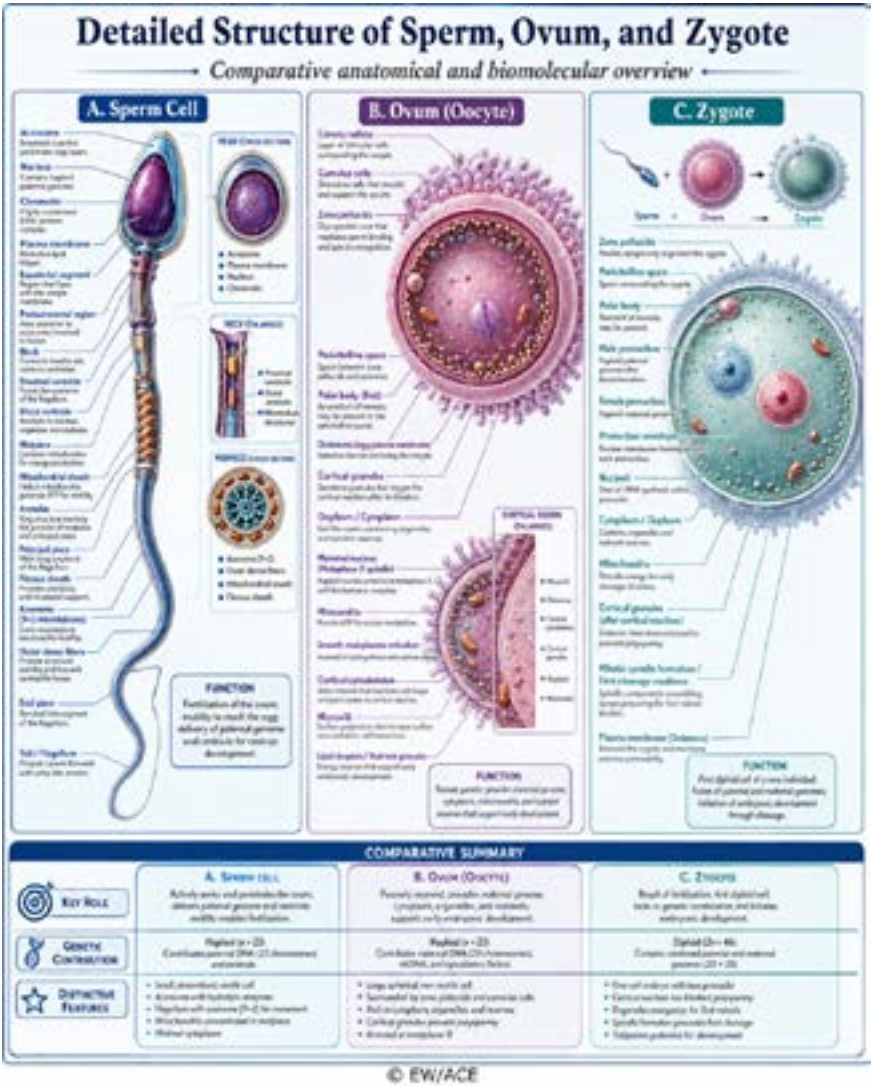
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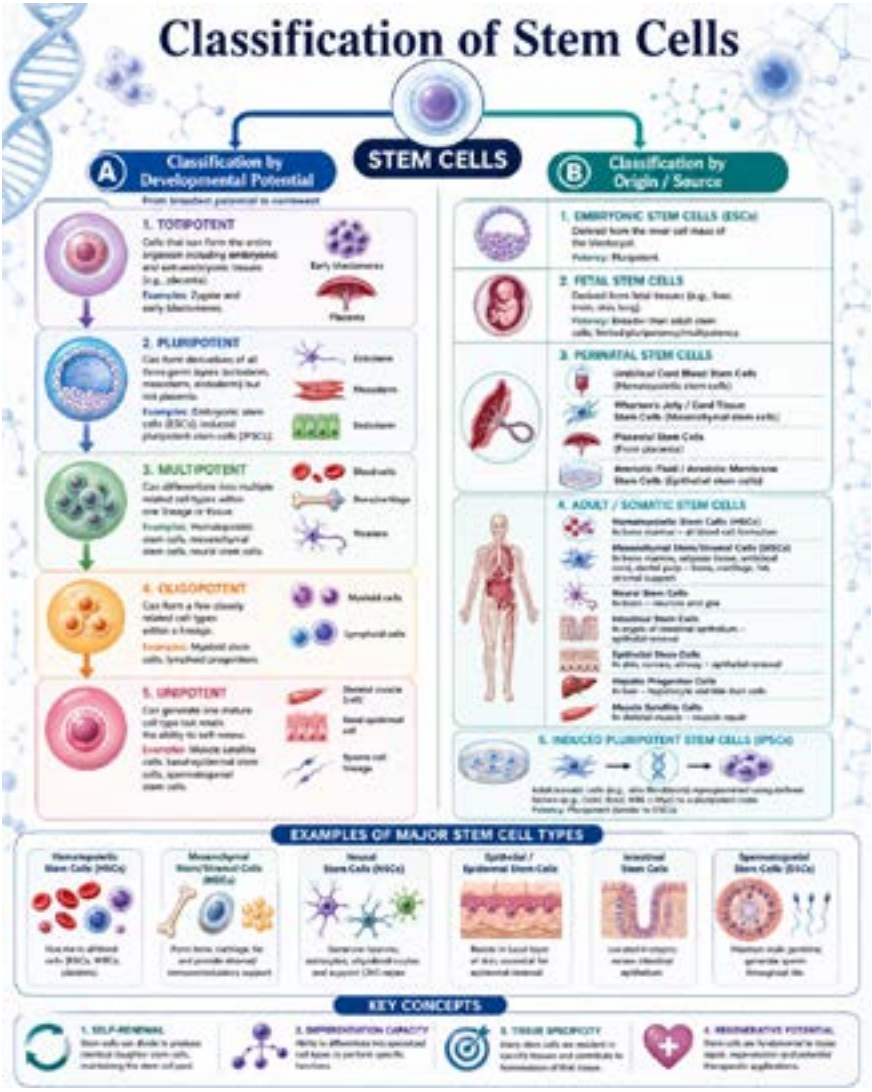
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The human cell is the fundamental unit of life, where structure and function meet in perfect harmony. Inside this microscopic world, the nucleus directs genetic activity, mitochondria produce energy, ribosomes build proteins, and the endoplasmic reticulum and Golgi apparatus process and deliver vital molecules. The cytoskeleton maintains shape, movement, and intracellular organization, while the plasma membrane controls communication with the outside environment. Understanding the normal cell is the first step toward understanding disease, regeneration, repair, and the future of biomolecular medicine.



Sperm, ovum, and zygote represent the essential cellular sequence of fertilization. The sperm delivers the paternal haploid genome and contributes motility structures, while the ovum provides the maternal haploid genome, cytoplasm, mitochondria, and developmental reserves. Their fusion forms the zygote, the first diploid embryonic cell, initiating genomic activation and early embryonic development.



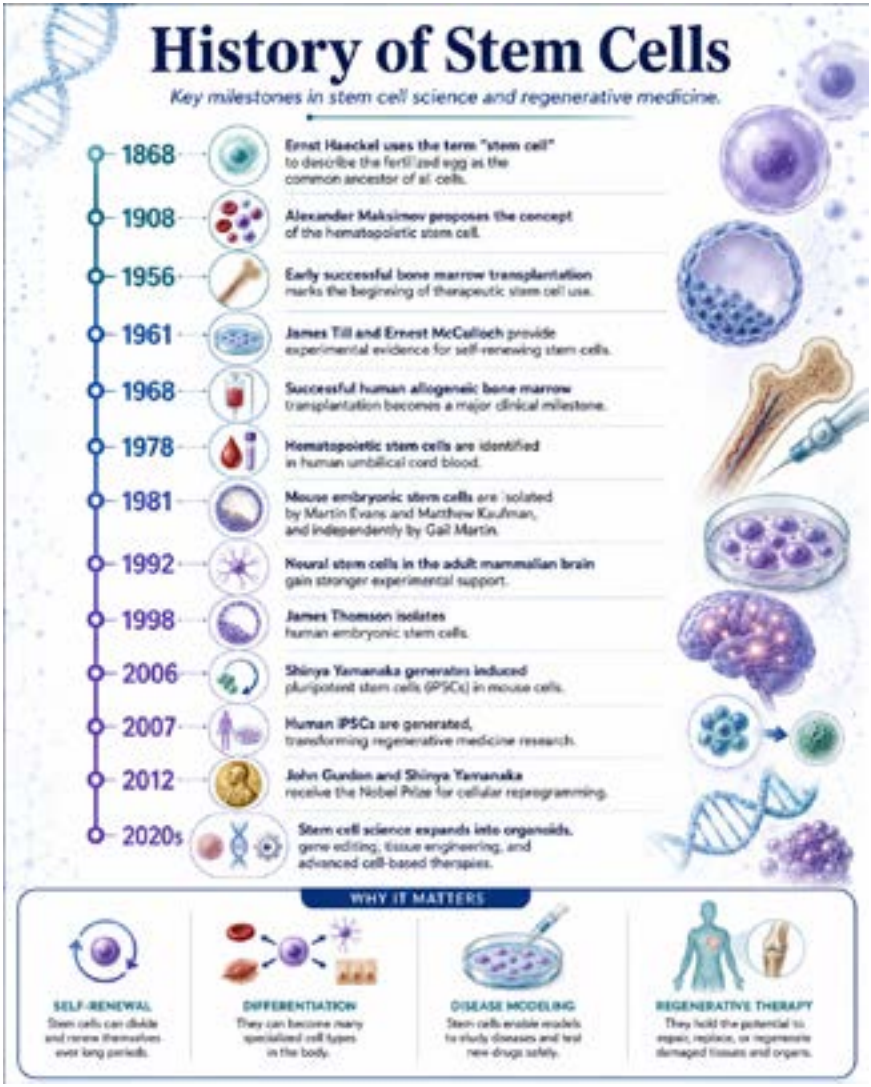
Stem cells are classified according to their developmental potential and biological origin. By potency, they range from totipotent cells, capable of forming the whole organism, to pluripotent, multipotent, oligopotent, and unipotent cells with progressively restricted differentiation capacity. By source, stem cells may be embryonic, fetal, perinatal, adult/somatic, or induced pluripotent stem cells.

This classification helps define their biological behavior, regenerative potential, and possible applications in developmental biology, tissue repair, and regenerative medicine.


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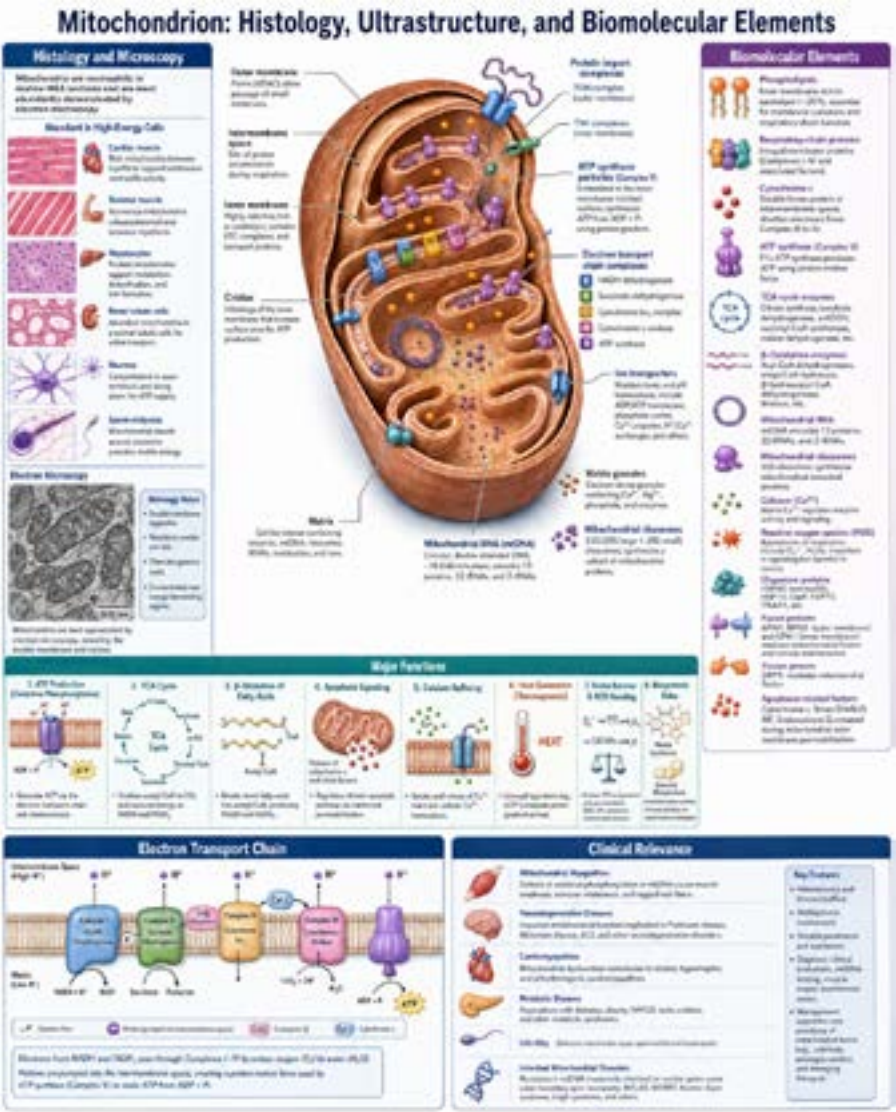
Regenerative medicine did not begin with stem cells. Its roots began thousands of years ago, when ancient physicians tried to help damaged tissues close, resist infection, restore function, and recover vitality. Ancient Egypt gave the world some of the earliest structured wound-repair practices, while Ancient China developed a systemic biological philosophy of restoration, balance, and tissue healing. Modern regenerative medicine is the scientific continuation of this ancient human ambition: not only to treat disease, but to rebuild what disease or injury has damaged.



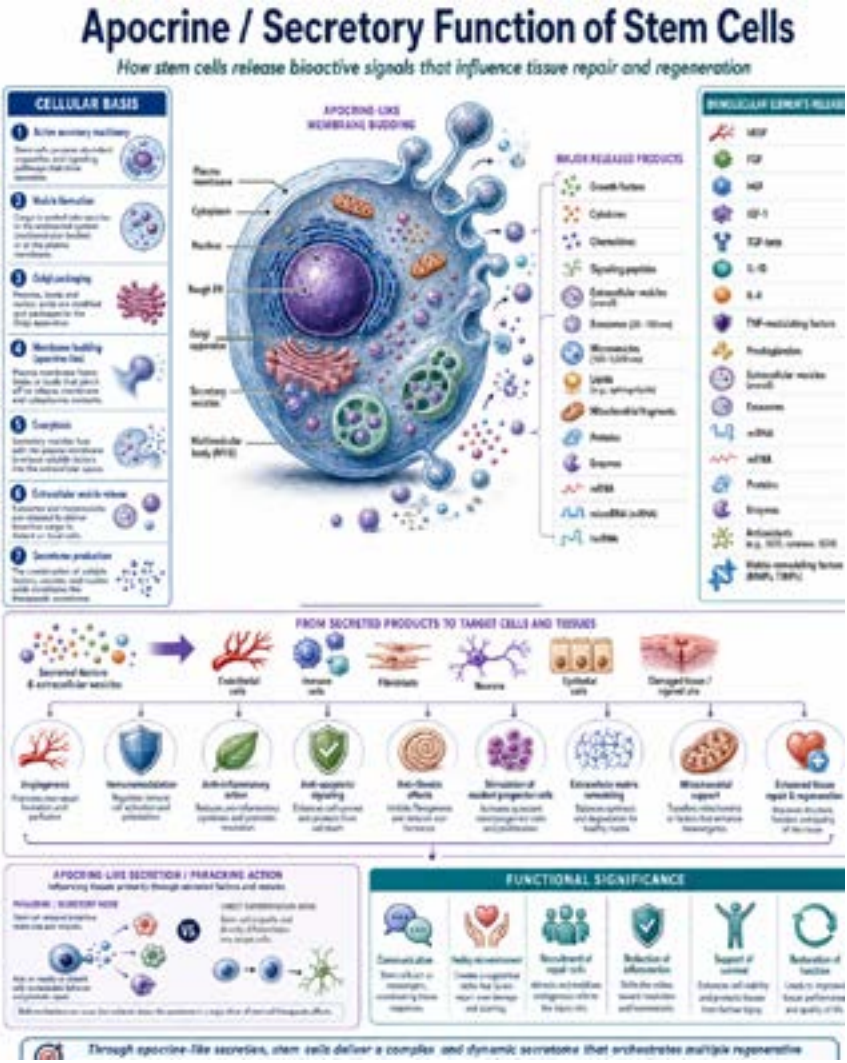
The history of stem cells began with early concepts of cellular origin and tissue renewal. In 1868, Ernst Haeckel used the term "stem cell" to describe the fertilized egg as the origin of all cells. In 1908, Alexander Maksimov proposed the idea of hematopoietic stem cells. Bone marrow transplantation in the mid-20th century marked the first major therapeutic use of stem cells. Later, embryonic stem cells, neural stem cells, and induced pluripotent stem cells transformed the field. Today, stem cell science forms a foundation for regenerative medicine, disease modeling, tissue engineering, and future cell-based therapies.


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full version


ANCIENT WISDOM
OF REGENERATIVE MEDICINE
(c. 1500 BCE)
OLD CHINESE PRACTICES
(c. 1000 BCE)
TRADITIONAL CHINESE MEDICINE (TCM):
BALANCING QI & ESSENCE
QI & JING
VITAL FORCE QI & ESSENCE
HERBAL MEDICINE
TONIFYING & REPAIRING HERBS
ACUPUNCTURE & MERIDIANS
MERIDIAN STIMULATION FOR REPAIR
DIETARY & EXERCISE
DIET & ELIXIR THERAPY
EGYPTIAN MEDICINE:
MAGICO-RELIGIOUS & SURGICAL HEALING
HUMORS & ENERGIES
Blood
Phlegm
Yellow bile
Black Bile
BALANCING THE METU CHANNELS
WOUND HEALING & OINTMENTS
Honey
Frankincense
NATURAL OINTMENTS & WRAPPINGS
SURGICAL INTERVENTION
RECONSTRUCTIVE SURGERY
(Limited)
SPIRITUAL RITUALS
INCUBATION & GODDESS SEKHMET'S GRACE
OLD INDIAN PRACTICES
(AYURVEDA, c. 1000 BCE)
AYURVEDIC MEDICINE:
HARMONY & REJUVENATION (RASAYANA)
DOSHA BALANCE
Vata
Pitta
Kapha
Kapha
MAINTAINING HEALTHY HUMORS
HERBAL FORMULATIONS
Ashwagandha
Triphala
Turmeric
Ghee
REGENERATIVE HERBS & RASAYANAS
RASAYANA THERAPY
REVITALIZING TREATMENTS
(Panchakarma)
SURGERY & MARMA POINTS
MARMA POINT STIMULATION
& SHALYA CHIKITSA (Surgery)



Mitochondria are the cell's main energy and metabolic control centers.
Through their double membrane, cristae, mitochondrial DNA, enzymes, and electron transport chain, they generate ATP, regulate calcium, control oxidative stress, and participate in apoptosis. Their structure explains their vital role in cell survival, tissue function, aging, degeneration, and regenerative medicine.



Apocrine-like secretion is one of the key therapeutic functions of stem cells. Through membrane budding and release of bioactive vesicles and soluble factors, stem cells deliver growth factors, cytokines, proteins, lipids, and nucleic acids that modulate inflammation, support angiogenesis, enhance cell survival, and promote tissue repair and regeneration.

PREFACE

This book began not with a theory, but with an observation. Over the course of my clinical career in regenerative and biological medicine, I encountered patients with Autism Spectrum Disorder who were enrolled in or had undergone treatment with stem cell-based therapies. Some of these patients showed improvements that exceeded what could be explained by the interventions alone. Separately, a small number of children who received a biological preparation developed under our clinical programme — the ACE Pico Protocol — showed functional improvements in social communication, language, and behaviour that sustained over time.

These observations raised a question I could not leave unanswered: why? What is happening at the cellular and molecular level that could explain such changes? What is the biological mechanism that connects the administration of embryonic biological material to the functional improvement of a child with ASD?

This book is my attempt to answer that question — not with certainty, but with the best scientific reasoning I can bring to bear on the available evidence.

Understanding Before Claiming

I am a clinician and a scientist, but I am also honest enough to acknowledge that the intersection of regenerative biology and neurodevelopmental medicine is territory where our collective knowledge is still incomplete. The biomolecular complexity of Autism Spectrum Disorder is formidable. Its genetic heterogeneity, synaptic pathology, neuroinflammatory dimensions, mitochondrial vulnerabilities, and epigenetic layers do not yield easily to simple explanations.

What I have attempted in this book is to work through that complexity systematically — to map what is known about the cellular and molecular deficits of ASD, to compare those deficits with the biological content of embryonic brain tissue, and to ask whether the match between what is missing and what the embryonic formula contains provides a coherent biological explanation for the clinical observations we made. That

comparison, which forms the core of Chapter V, is not a claim of proof. It is a scientific hypothesis — a structured attempt to understand what we may have been witnessing.

The Central Question This Book Asks:

If the biomolecular deficits of ASD-affected cells precisely match the biological elements present in embryonic foetal brain tissue — and if supplying those elements via a sustained, non-invasive delivery route is clinically feasible — then is cellular regeneration and functional restoration a scientifically defensible therapeutic goal? This book argues that it is. It does not argue that the question has been fully answered.

Thinking Outside the Established Framework

I am aware that the approach proposed in this book does not follow the conventional pathway of pharmaceutical development for neurodevelopmental conditions. The dominant research paradigm in ASD — single-target molecular interventions, subtype-specific genetic approaches, symptom-focused pharmacology — has yielded important insights but has not yet produced a treatment capable of addressing the full biological complexity of the condition.

The hypothesis presented here takes a different direction. Rather than targeting one pathway, it asks whether a broad biological matrix derived from the tissue type that builds the very structures ASD failed to complete might address the cellular incompleteness at a more fundamental level. This is not a rejection of precision medicine. It is a recognition that, in complex biology, completeness sometimes requires complexity.

Thinking outside established frameworks is, by its nature, uncomfortable. It invites scepticism — and rightly so. Scientific progress is built on the tension between new ideas and the rigorous scrutiny that tests them. I do not ask the reader to accept the hypothesis on my authority. I ask only that they engage with the evidence presented and evaluate the logic on its merits.

A Note on the Scope of the Evidence:

The clinical observations described in this book — including the preliminary findings in six children with ASD who received the ACE Pico Protocol — are presented as exploratory observations, not as proof of efficacy. They represent the clinical signal that motivated the scientific inquiry this book documents. They are offered in the spirit of transparency, not as a basis for clinical recommendations. Formal controlled investigation is required before any such claims could be made, and the research programme required to achieve that is outlined in the final chapter.

An Open Invitation for Scientific Dialogue

I publish this work knowing that it will be met with a range of responses — from genuine interest to rigorous challenge. I welcome both. The scientific community's scrutiny of this hypothesis is not an obstacle to its development. It is the process by which any hypothesis either strengthens into evidence or is corrected and refined into something more accurate.

If the evidence presented here is incomplete — and it is — I invite those with the tools, the data, and the expertise to complete it. If the argument contains errors of reasoning or gaps in the science — and it may — I invite those who identify them to say so explicitly and to propose what would correct them. The goal is not to defend a personal theory. The goal is to advance our understanding of a condition that affects millions of children and families worldwide, and to find the best possible path toward their benefit.

Every established treatment in medicine began as an observation that could not yet be fully explained. Insulin was isolated before its mechanism was understood. Aspirin was used for decades before prostaglandins were described. The history of medicine is a history of clinical observation leading to biological understanding — not always the other way around. This book follows that tradition: it begins with what was observed and works toward an explanation that can be tested, challenged, and improved.

To the Scientific Reader:

This book does not claim to have solved ASD. It claims to have identified a biologically coherent mechanism that may explain clinical observations made in a small number of patients, and to have proposed a hypothesis that is specific enough to be tested. That is the appropriate first step. The work that follows — the controlled trials, the pharmacokinetic studies, the brain delivery confirmation, the long-term safety evaluation — is work I hope this book will motivate others to join.

A Word to Families

To the parents, caregivers, and families of children with ASD who may read these pages: this book was written with you in mind. The clinical observations that motivated this inquiry were made possible by families who trusted us with the care of their children, and who shared with us the changes they witnessed. Their experience is the reason this work exists.

I want to be direct with you: this book is not a treatment guide. It does not recommend a course of action for any individual child. It is a scientific document presenting a hypothesis that requires formal investigation before it can be offered as clinical guidance. The distance between a promising observation and a validated treatment is real, and it must be crossed responsibly.

What I can offer is this: the science presented in this book suggests that the biology of ASD may be more responsive to the right biological inputs than conventional medicine has assumed. That is a reason for measured, evidence-based hope — not for premature conclusions, but for continued and rigorous scientific enquiry pursued with urgency and with the patient always at its centre.

The Guiding Principle of This Work:

Every decision made in the development of this hypothesis — every research design, every clinical observation, every formulation decision — has been guided by a single question: what serves the patient best? Not what is most convenient, not what is most commercial-

ly promising, not what confirms a pre-existing belief — but what, if true and validated, would most benefit the children and families living with this condition. That question remains the standard against which this work should be judged.

Dr. Alaa Abdelkarim

Physician, Regenerative Medicine Specialist

May 2026

Chapter [I] Biomolecular Mechanisms of Inflammation-Induced Mitochondrial Dysfunction, Trace Element Redistribution, and the Pathogenesis of Cellular Fibrosis

Introduction: The Missing Pillar of Modern Medicine

The most critical objective of this book is to define the pivotal role of **regenerative medicine** within the context of the modern clinical landscape.

For decades, the global pharmacopeia has been structured around a binary model: eradicating the primary aetiology and managing the subsequent symptoms. When we analyse a standard clinical prescription, the active agents are almost exclusively designed to neutralize a pathogen or chemically modulate a patient's discomfort. While this "dual-action" approach is essential for acute stabilization and disease control, it leaves a significant therapeutic void. It fails to address the residual **biological debt**: the tissue damage sustained during the inflammatory response.

Regardless of the trigger—be it microbial (viral, bacterial, protozoal), physical, autoimmune, or neoplastic—the universal denominator of disease is **inflammation**. At the biomolecular level, this process disrupts mitochondrial homeostasis and depletes "essential" elements. In a clinical context, "essential" refers to components that the cell cannot synthesize endogenously; they must be supplied externally to maintain viability.

When these elements are absent, the cell's biochemical pathways become dysregulated, leading to functional failure. If a cell fails to regain its **histological integrity** and full physiological capacity during the recovery phase, the natural endpoint is not health, but **fibrosis**. Thus, the next frontier of medicine must move beyond "clearing the infection" and toward "restoring the architecture."

This last statement will be the subject of discussion on the following pages; this statement build the new vision of regenerative medicine and its importance in medical file, therefore the reader will see the word statement (referring to the previous paragraph) to be discussed and analysed.

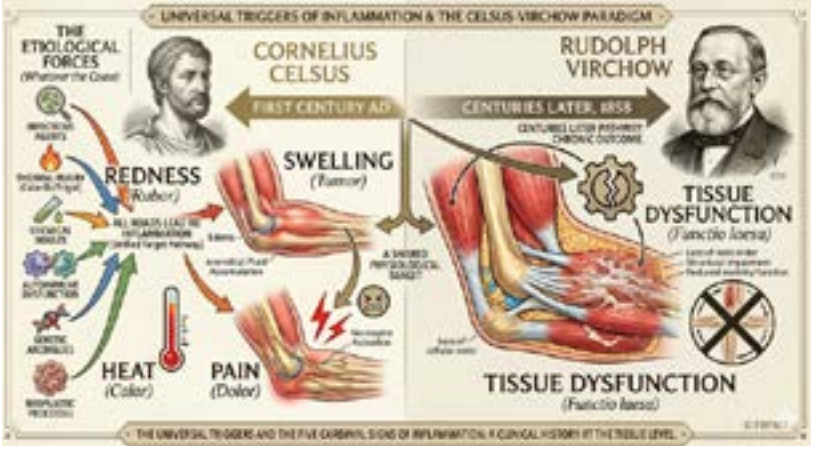
To be able to step into understanding autism on biomolecular base

we need to discuss In this introduction 4 main topics:

- Biomolecular mechanism of inflammation induced-Mitochondrial dysfunction, trace elements distribution and the pathogenesis of cellular fibrosis.
- 'Essential: difference in meaning between English language and medical language.
- What may happen if the essential elements were not available to the damaged cells to regenerate after inflammation?
- ACE Factor Deficiency theory.
- What can support this from the available credited literature.

Biomolecular Mechanisms of Inflammation

Figure 1 At the tissue level, inflammation is characterized by five cardinal signs: redness,



swelling, heat, pain, and tissue dysfunction (rubor, tumor, calor, dolor et functio laesa). The first four signs were clinically defined in the first century AD by a Roman Physician, Cornelius Celsus. The fifth was added centuries later by Rudolph Virchow in 1858 [1]

The intricate relationship between inflammatory signalling and cellular bioenergetics represents a cornerstone of modern molecular pathology. Inflammation is classically defined as a complex biological response to deleterious stimuli, such as pathogens, damaged cells, or

irritants, aimed at neutralizing the threat and initiating tissue repair.[1] However, at the biomolecular level, this process triggers a profound shift in cellular homeostasis, primarily mediated through the alteration of mitochondrial function and the redistribution of essential elements required for metabolic stability.[1] When these inflammatory processes become chronic or the resolution phase is incomplete, the resulting cellular failure serves as a primary driver for fibrotic remodelling, a process characterized by the replacement of functional parenchyma with a pathological extracellular matrix.[4]

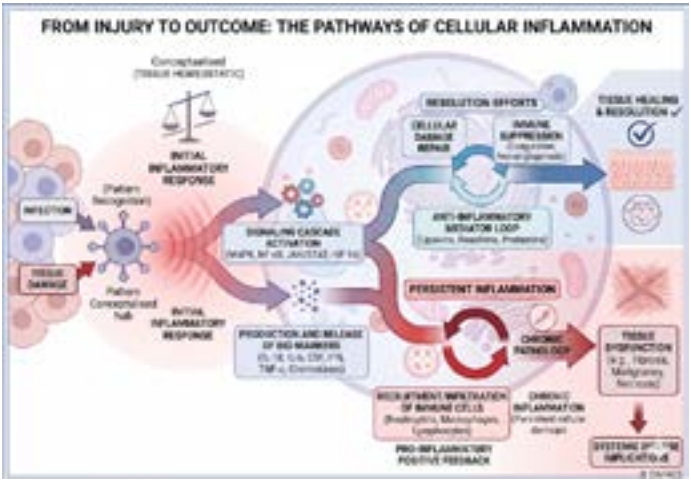


Figure 2 biomolecular pathway of cellular inflamation

The Inflammatory Cascade and Mitochondrial Homeostasis

The initiation of an inflammatory response relies on the detection of specific molecular patterns by pattern recognition receptors (PRRs) expressed on the surface and within the cytosol of both immune and non-immune cells.[6]

These receptors recognize two distinct classes of ligands: pathogen-associated molecular patterns (PAMPs), derived from exogenous microbes, and damage-associated molecular patterns (DAMPs), which are endogenous molecules released during cell stress or death.[1]

Mitochondria are central to this recognition process. Beyond their traditional role as the "powerhouse of the cell," they serve as critical signalling hubs and sources of DAMPs.[3] Under normal physiological conditions, mitochondria maintain a highly regulated environment, characterized by a stable transmembrane potential ($\Delta\Psi m$) and the efficient production of adenosine triphosphate (ATP) through oxidative phosphorylation.[8] However, the onset of inflammation induces immediate changes in mitochondrial dynamics and biochemistry.

The production of reactive oxygen species (ROS) is a physiological byproduct of the mitochondrial electron transport chain (ETC), but during inflammation, ROS generation becomes excessive and uncontrolled.[1] This surplus of ROS leads to oxidative stress, which causes significant damage to mitochondrial membranes, proteins, and genetic material.[1] Mitochondrial DNA (mtDNA) is particularly vulnerable to this oxidative insult because it lacks protective histones and is located in close proximity to the sites of ROS production in the inner mitochondrial membrane.[10]

Table 1 Biomolecular changes in Mitochondria due to inflammation

Inflammatory Stimulus	Biomolecular Impact on Mitochondria	Cellular Consequence	Source
PAMPs / DAMPs	Activation of PRRs (TLRs, NLRs)	Initiation of pro-inflammatory cytokine cascade	[1]
Oxidative Stress	mtDNA mutations and strand breaks	Impaired synthesis of ETC subunits	[10]
ROS Overproduction	Lipid peroxidation of mitochondrial membranes	Loss of $\Delta\Psi m$ and mPTP opening	[1]
Cytokine Signaling	Metabolic reprogramming (Glycolytic shift)	Energetic insufficiency and ATP depletion	[12]
Calcium Overload	Mitochondrial swelling and cytochrome c release	Activation of apoptotic and necrotic pathways	[7]

When mitochondrial integrity is compromised, the release of mitochondrial constituents into the cytosol acts as a powerful inflammatory stimulus. The release of mtDNA, for instance, can activate the cGAS-STING and NLRP3 pathways, further amplifying the production of pro-inflammatory mediators like IL-1ß and TNF- **α**.[6] This creates a "mito-inflammatory" cycle where the inflammation damages the

mitochondria, and the damaged mitochondria, in turn, sustain and exacerbate the inflammation.[1]

The Medical Taxonomy of Essential Elements

A critical component of the user's query involves the distinction between the common English meaning of "essential" and its specific application in medical and nutritional sciences. In general parlance, "essential" may simply mean "important" or "necessary." However, in medicine, an essential nutrient or element is strictly defined as a substance required for survival and physiological function that the body cannot synthesize at all or cannot produce in sufficient quantities to sustain life.[15] Consequently, these substances must be obtained from an external source, primarily through dietary intake.[18]

The human body requires approximately 40 essential nutrients, which are broadly categorized into macronutrients and micronutrients.[19] Macronutrients include proteins (composed of essential amino acids), fats (including essential fatty acids like omega-3 and omega-6), and carbohydrates, which provide the bulk of the body's energy requirements.[15] Micronutrients consist of vitamins and minerals.[15]

Vitamins are organic compounds classified as either water-soluble (the B-complex vitamins and Vitamin C) or fat-soluble (Vitamins A, D, E, and K).[15] Minerals are inorganic elements, including macro-minerals like calcium and magnesium, and trace elements like iron, zinc, selenium, and copper.[15] These essential elements are indispensable because they function as structural components, signalling molecules, and cofactors for enzymes that catalyse the biochemical reactions fundamental to life.[8]

Table 2 example of essential elements and the biomolecular role it plays

Category	Essential Element/Nutrient	Primary Biological Role	Consequence of Deficiency	Src.
Macronutrients	Essential Amino Acids	Protein synthesis, enzyme production	Growth failure, muscle wasting	[16]
Macronutrients	Essential Fatty Acids	Cell membrane integrity, signalling	Skin lesions, impaired healing	[15]
Vitamins	B-complex Vitamins	Enzymatic cofactors for ATP production	Metabolic failure, neurological symptoms	[21]
Vitamins	Vitamin C	Collagen synthesis, antioxidant	Scurvy, impaired immunity	[16]
Minerals	Magnesium (Mg^{2+})	Cofactor for 600+ enzymes, ATP use	Inflammation, cardiac arrhythmia	[8]
Minerals	Zinc (Zn^{2+})	Structural integrity of proteins	Immune dysfunction, poor repair	[24]
Minerals	Iron (Fe^{2+}/Fe^{3+})	Heme synthesis, ETC function	Anaemia, mitochondrial failure	[26]
Minerals	Selenium (Se)	Antioxidant (selenoproteins)	Oxidative stress, fibrosis	[28]

Inflammation-Driven Imbalance and Loss of Essential Elements

The inflammatory process directly influences the homeostasis of essential elements within the cell and the systemic circulation. This phenomenon, often referred to as “nutritional immunity,” is a coordinated effort by the host to redistribute minerals to limit their availability to pathogens and to prioritize their use for the immune response.[26] However, in chronic inflammatory states, this redistribution leads to localized or functional deficiencies that impair the “operation” and “cycles” of the cell.

One of the most prominent examples of inflammation-induced element redistribution is the regulation of iron. During the acute phase response, pro-inflammatory cytokines, specifically IL-6 and IL-1ß, stimulate the liver to produce hepcidin, a peptide hormone that serves as the master regulator of iron homeostasis.[26] Hepcidin binds to ferroportin, the only known cellular iron exporter, on the surface of macrophages, hepatocytes, and enterocytes, leading to its inter-

nalization and degradation.[26]

This action traps iron within the intracellular environment, resulting in a rapid decline in plasma iron concentrations—a state known as hypoferremia of inflammation.[27] While this response denies iron to invading microbes, it creates a "functional iron deficiency" for the host's own cells, particularly erythroid progenitors and cells with high mitochondrial demand.[26] Without adequate iron, the synthesis of heme and iron-sulphur clusters—essential components of the mitochondrial respiratory chain—is severely impaired.[26]

Zinc homeostasis is similarly altered during inflammation. Cytokines like TNF- **α** upregulate the expression of zinc-binding proteins such as metallothionein and alter the activity of ZIP-family transporters, leading to the sequestration of zinc in the liver and other tissues.[24] Chronic zinc deficiency, exacerbated by inflammatory states, impairs the function of over 3,000 proteins, including the antioxidant enzyme superoxide dismutase (SOD) and DNA repair enzymes, thereby heightening cellular vulnerability to oxidative damage.[21]

Magnesium levels are also frequently compromised in inflammatory disorders. Magnesium (Mg^{2+}) is an essential mineral that acts as a natural calcium antagonist and a critical cofactor for every enzymatic reaction that utilizes or synthesizes ATP.[8] Inflammation can lead to increased renal excretion (magnesium wasting) or impaired intestinal absorption of magnesium.[34] The loss of magnesium removes a critical check on calcium signalling; excessive intracellular calcium then drives further inflammatory signalling through the NF-K B and MAPK pathways, creating another self-sustaining cycle of damage.[21]

Alteration of Biochemical Cycles and Cellular Operation

The statement that the absence of essential elements leads to an "altered cycle or operation or biochemical reaction" is grounded in the fundamental biochemistry of cellular respiration and metabolic signalling. The mitochondria are the primary sites where these operations occur, specifically the Citric Acid Cycle (Krebs Cycle) and the Electron Transport Chain (ETC).[8]

The transition from fuel (glucose, fatty acids) to energy (ATP) is a multi-step "operation" that is entirely dependent on the continuous availability of essential cofactors. For example, the entry of pyruvate into the Krebs cycle is catalysed by the pyruvate dehydrogenase complex. This complex requires five distinct cofactors, including the essential B-vitamins Thiamine (B1), Riboflavin (B2), Niacin (B3), and Pantothenic acid (B5), along with Magnesium.[8] A deficiency in any of these elements stalls the reaction, preventing the efficient generation of NADH and $FADH^+$ needed for the ETC.[21]

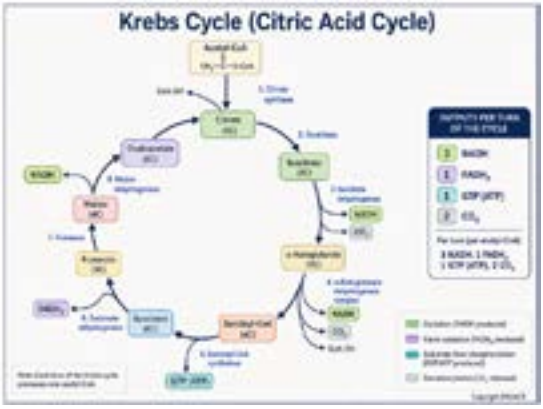


Figure 3 Krebs cycle

Within the Krebs cycle itself, several enzymes depend on essential minerals. Aconitase, which catalyses the isomerization of citrate to isocitrate, contains an essential iron-sulphur (Fe-S) cluster.[26] When inflammation-driven hepcidin causes iron sequestration, the availability of iron for Fe-S cluster assembly is reduced, potentially inhibiting aconitase activity and stalling the cycle.[13] This stall leads to the accumulation of metabolic intermediates like succinate, which can escape the mitochondria and function as a pro-inflammatory signalling molecule.[13]

The Electron Transport Chain represents the ultimate "biochemical reaction" for energy production, and it is a massive consumer of essential elements:

- **Complex I and II:** Require multiple Fe-S clusters for electron transfer.[7]

- **Complex III:** Contains heme groups (requiring iron) and is sensitive to the antioxidant status of the cell (requiring Selenium).[28]
- **Complex IV:** Requires copper (Cu) and heme centres for the final reduction of oxygen to water.[20]
- **Complex V (ATP Synthase):** Dependent on Mg^2 to stabilize the ATP molecule and facilitate the transfer of phosphate.[8]

When these reactions are "altered" or fail due to the absence of essential elements, the cell experiences bioenergetic collapse. ATP levels drop, leading to the failure of ion pumps like the Na^+/K^+-ATPase.[14] This results in cellular swelling, loss of membrane potential, and a shift toward anaerobic glycolysis—a process that is far less efficient and produces lactic acid, further disrupting the local environment.[12] This "alteration of function" is the metabolic precursor to cellular failure and eventual death or fibrotic transformation.[1]

ACE FACTOR DEFICIENCY THEORY

From Known Deficiencies to the Frontier of Undiscovered Biological Factors

Part A — The Full Scope of the ACE Factor Deficiency Theory

A.1 What the Theory Actually Proposes

Before presenting the clinical evidence that validates the ACE Factor Deficiency Theory, it is essential to state the theory's full scope clearly — because it is broader, and more ambitious, than the classical single-factor deficiency models that medicine already accepts.

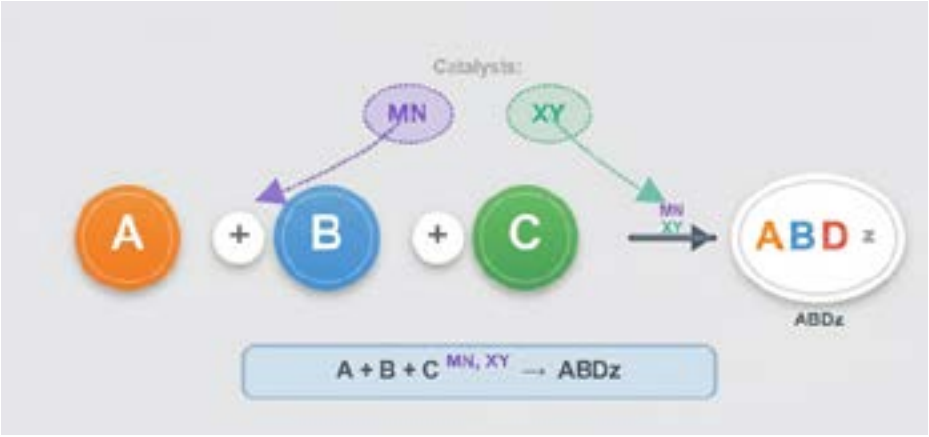


Figure 4 ACE Factor Deficiency theory: Where: A= normal element present in most dietary components, B = essential element from an animal source, C = essential element from a plant source, MN = essential enzyme, XY = cofactor.

The ACE Factor Deficiency Theory does not merely propose that "missing a known vitamin causes disease." That principle is already established. The theory proposes something more fundamental: that biological dysfunction — across a wide range of conditions, from well-understood enzyme defects to currently inexplicable chronic diseases — can be understood as the consequence of one or more essential biological factors being absent, insufficient, mistimed, or inaccessible to the cells that require them. And critically: some of those factors are already known to science, while others have not yet been discovered, named, or measured.

Core Statement of the ACE Factor Deficiency Theory:

For any biological cycle to operate, all of its essential components must be present simultaneously. The absence of any single component — whether it is a known enzyme, a known cofactor, a known signalling peptide, or a factor not yet identified by current science — will disrupt or halt that cycle. Functional disease may therefore exist not because cells are irreversibly destroyed, but because they are missing one or more essential biological inputs that current medicine has not yet fully catalogued.

A.2 The Spectrum of Missing Factors: Known, Partially Known, and Undiscovered

The ACE Factor Deficiency Theory recognises that biological knowledge is not static. The Krebs cycle, for example, was not fully characterised until the mid-twentieth century. The role of tetrahydrobiopterin (BH4) as a cofactor in neurotransmitter synthesis was not understood until decades after phenylketonuria was first described. The discovery that intrinsic factor — not Vitamin B12 itself — was the missing element in pernicious anaemia required a Nobel Prize-winning investigation that spanned multiple decades. In each case, a disease that was once labelled "idiopathic" or "inexplicable" became perfectly logical once the missing factor was identified.

The ACE theory therefore organises missing factors into a spectrum, not a single category:

Table 3

Category	Examples	Clinical Strategy
Tier 1 — Known factor, known replacement	Vitamin C in scurvy; B12 in pernicious anaemia; insulin in Type 1 diabetes; Factor VIII in haemophilia A	Identify and supply the exact missing factor. High precision, high efficacy.
Tier 2 — Known factor, complex replacement pathway	CYP17A1 deficiency (supply downstream hormone products); PKU (restrict substrate + supply cofactor)	Supply the downstream product or the essential cofactor. May require bypassing the defect rather than correcting it.
Tier 3 — Partially known factors, multiple deficiencies	Mitochondrial disease (multiple respiratory chain cofactors); ASD subgroups with known synaptic and neurotrophic deficits	Broad supplementation of known factors combined with support for the surrounding biological environment.
Tier 4 — Unknown or undiscovered factors	Many idiopathic diseases; complex neurodevelopmental conditions where known factors do not fully explain the phenotype	Broad-spectrum biological matrix from the relevant tissue type — supplying both known and potentially uncharacterised factors together.

This spectrum has a direct and important implication: the absence of a known, named factor is not a prerequisite for the ACE principle to apply. A

disease may be driven by the absence of a factor that no laboratory currently measures, no textbook currently lists, and no clinician currently considers — precisely because it has not yet been discovered. Such a factor is real. It is operating — or failing to operate — in the cell right now. Its absence is causing measurable dysfunction. It simply does not yet have a name.

A.3 Why Medicine Cannot Claim to Know All Essential Factors

A foundational assumption of the ACE Factor Deficiency Theory is one of scientific humility: we do not yet know all the essential biological factors required for every cellular cycle in the human body. This is not a speculative claim — it is a demonstrable fact supported by the history of biochemistry itself.

Consider the following established realities:

1. The human proteome contains an estimated 20,000–25,000 protein-coding genes, but the functional role of a substantial proportion of their protein products remains incompletely characterised or entirely unknown [1].
2. The human metabolome — the full set of small molecules operating within human cells — is estimated to contain over 100,000 metabolites, of which only a fraction have been functionally annotated [2].
3. New enzymatic cofactors, post-translational modifications, and cell-signalling molecules continue to be discovered regularly. Pyrroloquinoline quinone (PQQ), for example, was proposed as a novel B-vitamin cofactor relatively recently and continues to be investigated [3].
4. The secretome of mesenchymal stem cells — the range of paracrine molecules these cells release to influence neighbouring tissue — is still being characterised, with new bioactive peptides and extracellular vesicle cargoes described in recent literature [4].
5. The gut microbiome produces hundreds of bioactive metabolites — short-chain fatty acids, neurotransmitter precursors, immune-modulatory molecules — many of which influence brain function through mechanisms that are still being mapped [5].

The logical conclusion is straightforward: if we do not yet know all the essential factors, then we cannot exclude the possibility that some currently unexplained diseases — including some ASD subtypes — involve the absence or insufficiency of factors we have not yet named. Labelling such conditions as “idiopathic” does not mean they have no cause. It means we have

not yet found the cause. And the ACE Factor Deficiency Theory proposes that the cause, in many such cases, may be the absence of one or more essential biological factors that current medicine has not yet characterised.

Key Distinction — Idiopathic vs. Uncharacterised ACE Deficiency:

An "idiopathic" disease is not a disease without a cause. It is a disease whose cause has not yet been identified by current methods. The ACE Factor Deficiency Theory reframes idiopathic conditions as potential Tier 3 or Tier 4 deficiencies: diseases in which one or more essential biological factors — known or unknown — are missing from the affected cell's operating environment.

A.4 The Multi-Factor Dimension: Why Multiple Factors Are Usually Missing Together

A further extension of the theory addresses the reality that biological deficiencies rarely occur in isolation. In the simple classical models — scurvy, B12 deficiency, haemophilia — a single missing factor produces a recognisable syndrome. But in complex chronic conditions, the picture is different. Chronic inflammation, for example — as described extensively in Chapter I — simultaneously depletes iron, zinc, magnesium, selenium, and multiple B-vitamins through different mechanisms. The cell is not missing one factor. It is missing several.

When multiple factors are absent simultaneously, the consequences are compounded. Restoring one factor while the others remain depleted may produce only partial improvement. This explains why some clinical responses to single-nutrient supplementation in complex diseases are disappointingly modest: the correct ingredient was identified, but it was only one of several that the cell required. The cycle remained incomplete.

In ASD — a condition characterised by disturbances across synaptic scaffolding, glial regulation, neurotrophic signalling, myelination, immune balance, and mitochondrial metabolism — it would be biologically naive to expect a single-factor intervention to address the full deficit. The ACE theory therefore predicts that interventions offering a broad spectrum of potentially relevant biological factors will be more relevant than single-molecule approaches, particularly when those factors are drawn from the same tissue type and developmental context in which the deficiencies occur.

Therapeutic Implication of the Multi-Factor Dimension:

If multiple factors — some known, some not yet identified — are simultaneously missing from a cell's operating environment, then a therapeutic strategy that supplies a comprehensive biological matrix from the relevant tissue type may be more physiologically complete than any single-molecule approach. This is not a rejection of precision medicine — it is a recognition that precision, in complex biology, may require complexity.

Part B — Clinical Validation: Four Established Examples

The following four examples demonstrate the ACE Factor Deficiency principle operating with known, identified, and well-characterised missing factors. They serve a dual purpose: first, they validate the core logic of the theory through established medicine; second, they establish the precedent that once a missing factor is identified — regardless of whether it was previously known — restoring it is sufficient to restore function. This precedent is essential when the theory is subsequently applied to conditions where the missing factors are not yet fully characterised.

B.1 CYP17A1 (17α-Hydroxylase) Deficiency and Infertility

The Missing Factor

17α-Hydroxylase, encoded by the CYP17A1 gene, is a bifunctional cytochrome P450 enzyme expressed in the adrenal cortex and gonads. It catalyses two essential reactions in the steroidogenesis pathway: the hydroxylation of pregnenolone to 17α-hydroxypregnenolone, and the conversion of progesterone to 17α-hydroxyprogesterone. These steps are indispensable for the downstream synthesis of cortisol, androgens (androstenedione, testosterone), and oestrogens (oestradiol) [6, 7].

In CYP17A1 deficiency, loss-of-function mutations prevent the cell from producing this enzyme. All the substrate is present. The cofactor NADPH is available. The mitochondrial and endoplasmic reticulum machinery is intact. Yet the biosynthetic cycle is completely blocked, because one essential enzymatic factor is absent [6].

ACE Model Applied:

Pregnenolone (Substrate A) + NADPH cofactor (Element B) + CYP17A1 enzyme {ABDz} → 17α-hydroxy pregnenolone → … → Oestradiol / Testosterone Absence of {ABDz} = complete cycle blockade regardless

of substrate or cofactor availability.

Biological Consequence

Affected individuals present with primary amenorrhoea, absent secondary sexual characteristics, sexual infantilism, and complete infertility, combined with mineralocorticoid excess causing hypertension and hypokalaemia [7, 8]. The cell has not been infected or poisoned. It is missing one essential factor, and an entire biosynthetic system has failed as a consequence.

The Restoration Principle

Because the cell cannot make the missing enzyme, the clinical solution is to supply the downstream hormonal products the blocked pathway would have generated. Oestrogen replacement therapy restores secondary sexual development. Assisted reproductive technology using exogenous gonadotrophins and hormonal supplementation bypasses the enzymatic block entirely. Successful pregnancies have been documented in women with CYP17A1 deficiency following such protocols [9, 10].

The lesson is direct and applicable beyond this single disease: the biological cycle does not need to be "cured" at the genetic level. It needs to be completed by supplying what the cell cannot produce itself — through whatever route makes that supply available.

B.2 Phenylketonuria (PKU) — Enzyme and Cofactor Deficiency Together

The Missing Factor

Phenylketonuria is an autosomal recessive metabolic disorder caused by deficiency of phenylalanine hydroxylase (PAH), the hepatic enzyme converting phenylalanine to tyrosine. This reaction also requires the cofactor tetrahydrobiopterin (BH4). In classical PKU, PAH itself is absent or severely reduced; in BH4-responsive PKU, the cofactor is insufficient [11, 12].

PKU is notable in the context of the ACE theory because it demonstrates that multiple components can be deficient within a single pathway: the enzyme itself, and the cofactor it requires to function. Restoring only one of them produces only partial correction.

Biological Consequence and Restoration

Untreated PKU leads to progressive intellectual disability, seizures, and behavioural disturbance. Treatment requires both dietary phenylalanine restriction to prevent toxic accumulation and, in BH4-responsive cases, direct BH4 (sapropterin) supplementation to restore enzymatic activity [12, 13]. Newborn screening programmes for PKU represent perhaps the world's most successful application of the ACE principle in preventive medicine: identify the missing factor early, intervene before irreversible failure [14].

B.3 Scurvy — Single Cofactor, Complete Structural Failure

The Missing Factor

Scurvy results from deficiency of Vitamin C (ascorbic acid), the obligatory cofactor for prolyl 4-hydroxylase and lysyl hydroxylase in collagen biosynthesis. The human body cannot synthesise Vitamin C endogenously. Without it, the hydroxylation of proline and lysine residues in procollagen chains cannot occur, preventing triple-helix formation and collagen cross-linking [15, 16].

Biological Consequence and Restoration

Without collagen matrix integrity, connective tissues progressively fail: perifollicular haemorrhage, gingival destruction, impaired wound healing, and in advanced cases death. Administration of Vitamin C — oral or parenteral — immediately restores cofactor availability. Within days to weeks, collagen synthesis resumes and tissue repair proceeds [16]. The restoration is complete without any genetic correction — the cell's own machinery, once given the missing factor, resumes normal function.

Scurvy also demonstrates the ACE theory's "ratchet effect": *each day without Vitamin C, more collagen is degraded than replaced. Recovery requires timely restoration of the missing factor before irreversible structural loss occurs.*

B.4 Pernicious Anaemia — Bypassing the Missing Absorptive Factor

The Missing Factor

Pernicious anaemia results from absence of intrinsic factor (IF), a glycoprotein secreted by gastric parietal cells that binds dietary Vitamin B12 and escorts it to cubilin receptors in the terminal ileum for absorption. Without

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acterised. These vesicles are now understood to be essential for tissue repair, immune regulation, and neural plasticity [21]. Their potential role in disease through absence or dysfunction is an active area of research.

In each case, the biological factor was real and essential before it was discovered. Patients were suffering from its absence before science had the vocabulary to describe it. The ACE Factor Deficiency Theory asks medicine to hold this historical pattern in mind when approaching currently unexplained diseases.

C.3 Implications for ASD: When Known Factors Are Not the Whole Story

Applied to Autism Spectrum Disorder, this dimension of the ACE theory is particularly significant. Current ASD biology has identified a range of molecular disturbances: synaptic scaffolding protein deficits (SHANK3, NRXN, NLGN), excitation-inhibition imbalance, neurotrophic factor signalling differences, glial and immune dysregulation, mitochondrial vulnerability, and altered myelination. These are the known factors.

But the clinical heterogeneity of ASD — the enormous variability in phenotype, severity, comorbidities, and treatment response across individuals who share the same diagnostic label — suggests that the known factors do not tell the complete story. Some of this heterogeneity is explained by genetic variation. Some is explained by environmental modifiers. But some may reflect the presence of additional, as-yet- uncharacterised biological deficiencies that differ between individuals and subtypes.

The ACE theory does not claim to know what these undiscovered factors are. It claims something more intellectually honest: that we cannot yet know, and that this uncertainty should shape therapeutic strategy.

Therapeutic Implication for ASD:

If some ASD subtypes involve the absence of biological factors that are not yet named or measured, then a therapeutic approach that supplies a comprehensive, organ-specific biological matrix — one derived from the tissue type in which those factors would normally operate during development — may deliver both the known and the potentially unknown factors simultaneously. This is not a substitute for identifying specific factors. It is a scientifically rational interim strategy while the full map of essential neurodevelopmental factors continues to be drawn.

C.4 Why a Broad Biological Matrix Is Logically Justified

The preceding argument leads to a logical and clinically important conclusion about therapeutic design for complex conditions involving multiple and potentially undiscovered missing factors:

1. A single-molecule intervention can only address factors that have been identified. It is, by design, blind to factors not yet discovered.
2. A broad biological matrix derived from the relevant tissue type contains, by its nature, both the known and the as-yet-uncharacterised components of that tissue's biological environment. It does not require advance knowledge of every factor it contains.
3. This approach has historical precedent: raw liver extract reversed pernicious anaemia before its active ingredient was known. Pancreatic extract reversed diabetic ketoacidosis before insulin was isolated. Tissue-derived preparations have repeatedly demonstrated biological activity through mechanisms that were only understood retrospectively.
4. The limitation of this approach is also real: without knowing exactly which factors are responsible for any observed effect, it is difficult to standardise, optimise, or selectively improve the preparation. This is why analytical characterisation — proteomics, lipidomics, metabolomics, growth factor profiling — is a scientific priority, not an optional step.

The ACE theory therefore proposes a two-track research strategy for conditions like ASD:

1. Supply a broad, tissue-appropriate biological matrix that provides both known and potentially unknown essential factors, as a clinically accessible and biologically comprehensive starting point.
2. Systematically characterise the matrix through advanced analytical methods to progressively identify which specific factors are present, in what quantities, and which correlate with any observed biological or clinical effects — thereby converting the undiscovered Tier 4 factors into the known Tier 1 and Tier 2 factors of future medicine.

This is not an argument against scientific rigour. It is an argument for a form of scientific rigour that is proportionate to the current limits of biological knowledge — one that does not wait for the complete map before beginning the journey, but that maps as it travels.

Part D — Synthesis and Summary

D.1 Summary Table: From Known Deficiencies to Undiscovered Factors

Five Categories of ACE Factor Deficiency — Known to Undiscovered

Table 4

Clinical Example	Missing Essential Factor	Biological Consequence	Restoration Strategy	ACE Principle Illustrated
CYP17A1 (17α-Hydroxylase) Deficiency	17α-hydroxylase enzyme — absent due to loss-of-function mutation	Complete steroidogenesis blockade → infertility, absent sexual development	Hormone replacement; assisted reproduction bypassing the enzymatic block	One known missing factor → whole cycle fails. Supply the product → function restored.
Phenylketonuria (PKU)	Phenylalanine hydroxylase (PAH) + cofactor BH4	Phenylalanine accumulation → neurotoxicity, intellectual disability	Phenylalanine-restricted diet + BH4 (sapropterin) supplementation	Restoring cofactor + reducing toxic substrate = restored pathway. Multiple factors (enzyme + cofactor) both required.
Scurvy (Vitamin C Deficiency)	Vitamin C — cofactor for prolyl/lysyl hydroxylase in collagen synthesis	Collagen cross-linking failure → tissue breakdown, haemorrhage	Oral or parenteral Vitamin C replacement	Single missing cofactor blocks entire structural biosynthesis. Restoration is complete and rapid.
Pernicious Anaemia (Intrinsic Factor Deficiency)	Intrinsic factor — glycoprotein required for ileal B12 absorption	B12 deficiency → megaloblastic anaemia, spinal cord degeneration	Intramuscular B12 injection, bypassing the missing absorptive factor	Missing transport factor prevents delivery. Bypass route restores function without fixing the defect.


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plication — for ASD and for medicine more broadly — is that the goal of regenerative medicine should be to restore biological completeness, not only to suppress symptoms, correct individual abnormalities, or eliminate pathogens.

The Kerb's cycle is complete. We know all its steps. But we cannot claim the same about every biological cycle in the human brain, the human immune system, or the human developmental programme. The ACE Factor Deficiency Theory holds that space — the space of what we do not yet know — open as a scientific frontier rather than closing it with premature certainty.

The Progression toward Fibrosis: A Consequence of Cellular Failure

Fibrosis is characterized by the excessive deposition of extracellular matrix (ECM) proteins, primarily collagen, by activated myofibroblasts.[4] While transient inflammation and ECM deposition are necessary for normal wound healing, chronic inflammation and the "failure" of damaged cells to regain their "histological integrity and full physiological function" lead to pathological fibrosis.[5]

The link between cellular failure (driven by mitochondrial collapse and nutrient depletion) and fibrosis is mediated by several complex signalling pathways. When epithelial or parenchymal cells are chronically stressed and unable to restore their bioenergetic cycles, they often undergo a phenotypic shift known as epithelial-to-mesenchymal transition (EMT).[37] In this state, the functional cell "fails" its specialized role and begins to produce pro-fibrotic factors.[36]

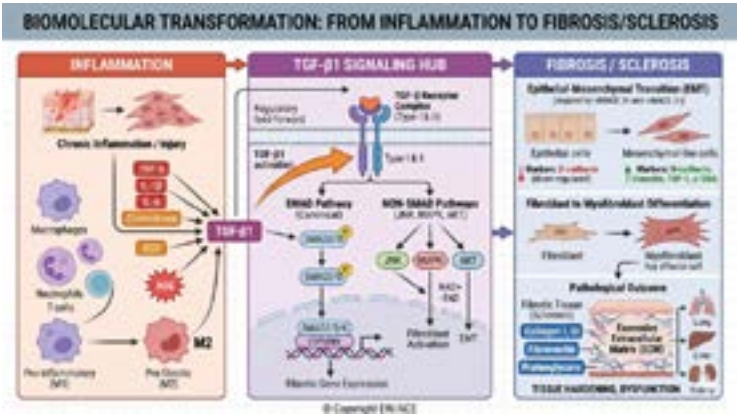


Figure 5 Biomolecular transformation from inflammation to fibrosis/sclerosis

The central mediator of this process is Transforming Growth Factor-beta (TGF-ß).[4] Mitochondrial dysfunction is a direct driver of TGF-ß signaling. Excessive mitochondrial ROS can activate latent TGF- ß and stimulate the phosphorylation of Smad2 and Smad3, which translocate to the nucleus to upregulate the expression of genes associated with collagen synthesis and myofibroblast differentiation.[4]

Myofibroblasts, the primary effectors of fibrosis, are not just passive producers of collagen; they are highly metabolic cells that require significant energy to maintain their contractile and secretory functions.[4] Paradoxically, while the original functional cells fail due to mitochondrial collapse, the fibrotic environment they leave behind is sustained by myofibroblasts that have undergone their own metabolic reprogramming toward glycolysis to support their rapid proliferation.[13]

Table 5 Biomolecular elements that participate in the process of fibrosis

Pathway / Factor	Role in Fibrosis	Link to Cellular Failure	Source
TGF- ß / Smad	Master regulator of collagen synthesis	Stimulated by mitochondrial ROS and oxidative stress	[4]
NF-^{K}B	Pro-inflammatory gene transcription	Activated by DAMPs and low Mg^{2} levels	[1]
JNK Pathway	Promotes dedifferentiation and inflammation	Triggered by mitochondrial stress and ROS	[10]


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Synthesis and Conclusion

The biomolecular evidence overwhelmingly supports the provided statement. The inflammatory process is not an isolated event but a deep disruptor of cellular bioenergetics and nutrient homeostasis. By causing "changes in the mitochondria" and an "imbalance or loss of... essential elements," inflammation breaks the vital "biochemical cycles" that allow a cell to function.[1]

The medical definition of "essential" is central to this pathology; because these elements cannot be "manufactured by the cell itself," any inflammation-induced loss or redistribution creates a critical bottleneck that the cell cannot overcome without external replenishment.[15] When this failure persists, the body's default repair mechanism—fibrosis—takes over, replacing the functional but failing cell with non-functional scar tissue.[4] Thus, the "failure to recover completely" is the literal bridge between acute inflammation and chronic, irreversible organ fibrosis.

Accredited Literature Proofs for the Bracketed Statement

In accordance with the request to separate specific proofs from the accredited literature, the following evidence directly validates the components of the user's statement:

1. **Mitochondrial and Homeostatic Changes:** Studies confirm that inflammation induces oxidative stress, dissipation of mitochondrial membrane potential, and the release of DAMPs (mtDNA, ATP), which disrupt cellular homeostasis and amplify the inflammatory response.[1]

2. **Medical Definition of Essential Elements:** Accredited nutritional and medical sources define "essential nutrients" as substances vital for health that cannot be synthesized by the organism and must be obtained from an external diet.[15]

3. **Inflammation-Induced Loss/Imbalance of Elements:** Peer-reviewed evidence demonstrates that the inflammatory cytokines (IL-6, TNF- **α**) drive the sequestration of iron via the

hepcidin-ferroportin axis and the redistribution of zinc and magnesium, creating functional deficiencies at the cellular level.[23]

4. **Altered Biochemical Cycles and Operations:** Research highlights that mitochondrial bioenergetic cycles (Krebs Cycle, ETC) are strictly dependent on essential minerals (Fe, Mg, Zn, Se, Cu) and B-vitamins as cofactors. Their absence results in a "biochemical blockade," leading to ATP depletion and failure of cellular operations.[7]

5. **Failure and Subsequent Fibrosis:** Clinical and experimental studies, such as the Selenium-deficiency mouse model, provide direct proof that the failure of cells to recover from inflammatory/oxidative stress leads to the activation of TGF-ß pathways, myofibroblast transformation, and pathological fibrosis.[4]

6. **Incomplete Recovery and Histological Integrity:** Literature on the AKI-to-CKD transition and chronic organ injury confirms that incomplete resolution of inflammation and the failure to restore mitochondrial quality control prevent the return to "histological integrity," driving the tissue toward chronic fibrotic remodeling.[3]

Chapter [II] Comprehensive Epidemiology of Autism Spectrum Disorder Worldwide

Global, regional, and country-level prevalence statistics with separated resources

Key message: Autism spectrum disorder affects approximately 0.8-1.0% of the global population by current global models, but diagnosed childhood prevalence is often higher in countries with active surveillance, reaching 1-3% and in some school-age groups above 4%. Lower recorded prevalence in many countries often reflects limited detection rather than true absence of autism.

1. Important clarification

Autism spectrum disorder is not measured equally across the world. In high-income countries, autism prevalence often appears higher because of better awareness, screening, school records, diagnostic services, and disability registration. In many low- and middle-income countries, autism is probably underdiagnosed, especially in girls, adults, rural communities, and children with milder or masked presentations. WHO states that the prevalence of autism in many low- and middle-income countries remains unknown.

Table 6

Type of figure	Meaning
Estimated true prevalence	Modelled estimate of how many people may actually be autistic.
Diagnosed prevalence	Number formally diagnosed or registered in health, school, or disability systems.
Screening prevalence	Number who screen positive for autistic traits; usually higher than confirmed diagnosis.
Clinical-centre prevalence	Proportion among children attending clinics; not representative of the general population.
National surveillance prevalence	Usually the strongest form, but available in only a few countries.

2. Global epidemiology

The most important current global estimate comes from the Global Burden of Disease Study 2021, published in The Lancet Psychiatry. It estimated that 61.8 million people worldwide were on the autism spectrum in 2021, equal to approximately 1 in 127 people, or 0.788% of the global population. The global age-standardised preva-

lence was 788.3 per 100,000 people.

WHO's 2025 fact sheet also states that in 2021 approximately 1 in 127 persons globally had autism, while emphasizing that some well-controlled studies report substantially higher figures and that prevalence remains unknown in many low- and middle-income countries.

Table 7

Indicator	Best current estimate
Global autistic population, 2021	~61.8 million people
Global prevalence	~0.788%
Equivalent ratio	~1 in 127 people
Age-standardized prevalence	788.3 per 100,000
Male prevalence, GBD 2021	1064.7 per 100,000 males
Female prevalence, GBD 2021	508.1 per 100,000 females
Male:female ratio	roughly 2-4:1, depending on diagnostic method

3. Why autism prevalence appears to be increasing

The increase is real in the sense that more people are being identified, but this does not necessarily mean that biological incidence has increased by the same amount. The main drivers are:

- Broader diagnostic criteria after DSM-IV and DSM-5.
- Better screening in schools and pediatric services.
- Increased public and professional awareness.
- More access to services and disability benefits after diagnosis.
- Improved recognition in children without intellectual disability.
- Better identification in racial, ethnic, and socioeconomic groups previously missed.
- Possible contribution from environmental, prenatal, perinatal, and demographic factors, although these do not fully explain the rise.

CDC notes that differences in autism prevalence across sites and over time can reflect differences in evaluation practices, identification, service access, and diagnostic eligibility rules.

4. Epidemiology by continent / major world region

The Global Burden of Disease 2021 model provides one of the most

comparable worldwide estimates because it applies a consistent modelling framework across regions. The global prevalence was 0.788%, with the highest modelled prevalence in high-income Asia Pacific, Australasia, high-income North America, and Western Europe.

Table 8

Region / super-region	Age-standardized prevalence estimate
Global	788.3 per 100,000
High-income Asia Pacific	~1559.5 per 100,000
Australia	~1191.0 per 100,000
High-income North America	~1097.2 per 100,000
Western Europe	~896.6 per 100,000
Sub-Saharan Africa	~890.2 per 100,000
Central/Eastern Europe & Central Asia	~927.5 per 100,000
North Africa & Middle East	~771.8 per 100,000
South Asia	~686.2 per 100,000
Latin America & Caribbean	~689.5 per 100,000
Southeast Asia, East Asia & Oceania	~669.2 per 100,000
Tropical Latin America	~614.5 per 100,000, among the lowest modelled regions

5. North America

United States

The United States has one of the strongest autism surveillance systems through the CDC Autism and Developmental Disabilities Monitoring Network. The latest CDC estimate for children aged 8 years in 2022 was 1 in 31, or 3.2%, across ADDM Network sites. CDC also reports that autism is more than 3 times more common among boys than girls.

Table 9

United States statistic	Estimate
Children aged 8 years, CDC ADDM 2022	1 in 31
Percentage	3.2%

Previous CDC estimate, 2020	1 in 36
Previous CDC estimate, 2018	1 in 44
Male predominance	>3 times higher in boys
Site variation	High; some sites much higher than others

The CDC report is not a full national census; it is surveillance from selected sites. Still, it is one of the most rigorous repeated autism monitoring systems globally.

Canada

Canada's chronic disease surveillance data show a major increase in identified autism among children and youth. Canadian estimates increased from 1 in 714, or 0.14%, in 2000-2001 to 1 in 44, or 2.25%, in 2023-2024.

Table 10

Canada statistic	**Estimate**
Children/youth, 2000-2001	1 in 714, 0.14%
Children/youth, 2023-2024	1 in 44, 2.25%
Newly identified cases, 2023-2024	365 per 100,000 children/youth
Canadian survey estimate, children/youth 1-17	1 in 50, 2.0%

6. Europe

European data vary by country and by whether the estimate comes from school records, health registers, or active population screening. Autism-Europe summarizes recent research as approximately 1 in 100 people in Europe.

A European review reported that prevalence among primary school children varied widely, from 0.8% in Pisa, Italy to much higher estimates in some Romanian screening contexts, with a median around 1.2% in primary-school studies.

United Kingdom / England

A large English cohort study of 7,047,238 pupils found national au-

tism prevalence of 1.76%, approximately 1 in 57 schoolchildren.

Table 11

UK / England statistic	Estimate
English school pupils	1.76%
Equivalent	~1 in 57
Highest prevalence group in that study	Black pupils, 2.11%
Lowest group in that study	Roma/Irish Traveller pupils, 0.85%

NHS England autism statistics mainly measure referrals and waiting times, not true prevalence. In December 2024, NHS data showed 212,964 patients with an open referral for suspected autism, and 90.0% had been waiting at least 13 weeks.

Table 12

Country / area	Best available statistic
Europe overall	around 1%, but varies by method
England schoolchildren	1.76%
Pisa, Italy primary-school estimate	~0.8%
European review range	roughly 0.38-1.55% in many studies
ASDEU project estimate	about 12.2 per 1000, or 1.22%, among children aged 7-9 in participating datasets

7. Asia

Asia has very heterogeneous data. Some countries have advanced surveillance or population studies, while others have limited data.

Japan / high-income Asia Pacific

GBD 2021 modelled the highest age-standardised autism prevalence in high-income Asia Pacific, especially Japan. Japan was reported in the GBD-related summary as having one of the highest modelled country-level rates, around 1586.9 per 100,000, or about 1.59%.

South Korea

South Korea produced one of the landmark active population-screen-

ing studies. A total-population study of school-age children aged 7-12 estimated autism prevalence at 2.64%, equivalent to 1 in 38 children. This study was important because it actively screened children, including those not previously diagnosed.

Table 13

South Korea statistic	Estimate
School-age children 7-12	2.64%
Equivalent	1 in 38

China

A 2024 systematic review and meta-analysis estimated the prevalence of ASD in mainland China from 2017 to 2023 at 7 per 1000 children, or 0.7%, with a male-to-female ratio of about 5:1. A Beijing study reported prevalence among 6-year-old children in 2021 of 10.5 per 1000, or 1.05%, with a male-to-female ratio of 4.3:1.

Table 14

China statistic	Estimate
Mainland China pooled 2017-2023	7/1000, 0.7%
Beijing 6-year-olds, 2021	10.5/1000, 1.05%
Male:female ratio	~4.3-5:1

India

India's data vary widely. Older systematic reviews found lower rates, likely reflecting underdiagnosis and methodological limits. More recent Indian pediatric literature cites an estimate of 1.12 per 100 children aged 2-9 years, approximately 1 in 68.

Table 15

India statistic	Estimate
Children aged 2-9 years, cited estimate	1.12%
Equivalent	~1 in 68
Estimated children with ASD in reviews	often cited around 1.8-2 million children, but likely variable

Table 16

Country / area	Estimate
Japan, GBD model	~1.59%
South Korea, active school study	2.64%
China pooled recent studies	0.7%
Beijing, 6-year-old children	1.05%
India, children 2-9 cited estimate	1.12%
South Asia, GBD region	~686.2 per 100,000

8. Middle East and North Africa

The MENA region has very heterogeneous and often limited data. A 2025 systematic review of MENA studies found 19 eligible studies from Iran, Oman, Libya, Egypt, Saudi Arabia, Lebanon, UAE, Bahrain, Qatar, and Iraq. Country-specific estimates ranged from 0.01% in Oman in an older 2009 study to 6.50% in one Iraqi study in 2024, with a pooled MENA prevalence of 0.14%, but with extremely high heterogeneity. This pooled number is probably affected by underdiagnosis and inconsistent methods, so it should not be interpreted as the true biological prevalence.

Egypt

A recent population-based Egyptian study confirmed ASD by DSM-5 and CARS and estimated prevalence at 1.1%, or 455 out of 41,640 children, with highest prevalence in children aged 3-6 years at 1.5%. Boys were affected about four times more than girls, with male prevalence 1.7% and female prevalence 0.4%.

Table 17

Egypt statistic	Estimate
Confirmed ASD prevalence	1.1%
Highest age group, 3-6 years	1.5%
Boys	1.7%
Girls	0.4%
Male:female ratio	~4:1


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Chapter [III]

Aetiology and Pathogenesis of Autism Spectrum Disorder

1. Introduction: autism as a neurodevelopmental spectrum

Autism spectrum disorder, or ASD, is a heterogeneous neurodevelopmental condition characterized mainly by persistent differences in social communication and social interaction, together with restricted, repetitive, or highly focused behaviours, interests, and sensory patterns. It is called a spectrum because the clinical presentation varies widely: some autistic people have average or high intellectual ability and fluent language, while others have intellectual disability, epilepsy, language impairment, sleep disorders, gastrointestinal symptoms, or high support needs. Current clinical diagnosis is still based on developmental history and behavioural assessment, not on a single blood test, brain scan, or biomarker.

The Lancet Commission emphasizes that autism is lifelong, heterogeneous, and requires individualized assessment rather than one universal explanatory model or one universal treatment. It also identifies well-established clinical risk indicators, including preterm birth, family history of autism, and genetic syndromes such as tuberous sclerosis complex and fragile X syndrome.

2. Central concept of aetiology: no single cause

The current scientific consensus is that autism is multifactorial. In simple terms, autism usually arises from the interaction of multiple genetic susceptibilities with early developmental, prenatal, perinatal, immune, metabolic, and environmental influences. In some children, autism is strongly linked to a clear genetic syndrome or a high-impact mutation. In many others, the condition results from many common genetic variants, each contributing a small amount of risk, plus environmental or biological modifiers.

Therefore, autism should not be described as one disease with one cause. It is better understood as a final common neurodevelopmental phenotype reached through different biological routes. These routes may converge on similar brain systems: cortical development,

synapse formation, neuronal communication, excitation-inhibition balance, immune signalling, and network connectivity.

3. Genetic contribution

3.1 Heritability and family risk

Genetics is one of the strongest contributors to autism liability. Large family and population studies show that autism is highly heritable, although heritability does not mean that autism is purely genetic or inevitable. One large multinational population study estimated ASD heritability at approximately 80%, meaning that much of the variation in autism liability across populations is attributable to inherited genetic differences.

Family history is clinically important. Children with an autistic sibling have a higher probability of ASD than the general population. Public-health sources list having a sibling with ASD and having certain genetic or chromosomal conditions, such as fragile X syndrome or tuberous sclerosis, among recognized risk factors.

3.2 Common polygenic risk

In many autistic individuals, there is no single identifiable mutation. Instead, autism risk is polygenic: many common variants, each with small effect, act together to influence early brain development. These common variants can affect neural proliferation, synaptic development, neuronal migration, neurotransmission, immune regulation, and behavioural traits across the general population. This explains why autistic traits can exist dimensionally in families and why autism often overlaps genetically with other neurodevelopmental or psychiatric conditions.

3.3 Rare and de novo variants

A smaller but clinically important proportion of autism is associated with rare inherited or de novo variants. De novo variants are genetic changes that appear for the first time in the child and are not present in either parent's blood DNA. These can have large effects, particularly when they affect genes essential for early neurodevelopment.

A major exome-sequencing study involving tens of thousands of


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tion.

- Altered excitatory synapses: glutamatergic synapses may be excessive, deficient, immature, or poorly regulated depending on the subtype.
- Altered inhibitory synapses: GABAergic interneuron development may be impaired, reducing inhibitory control.
- Abnormal synaptic plasticity: learning requires synapses to strengthen and weaken appropriately. In ASD, long-term potentiation and long-term depression may be altered in some circuits.

This synaptic framework explains why autism often includes sensory hypersensitivity, epilepsy, repetitive behaviours, learning differences, and variable language development.

8. Excitation-inhibition imbalance

A major mechanistic hypothesis is that autism involves imbalance between excitatory and inhibitory signalling in the brain. Excitatory signalling is mainly mediated by glutamate, while inhibitory signalling is mainly mediated by GABA. Normal cortical function requires a precise balance between the two.

If excitation is excessive or inhibition is insufficient, neural circuits may become noisy, unstable, hypersensitive, or seizure-prone. If inhibition is excessive or excitation is poorly coordinated, circuits may become under-responsive or inefficient. Either direction can disrupt social communication, sensory processing, attention, sleep, and behavioural regulation.

Large-scale genetic studies support this idea by showing enrichment of ASD risk-gene expression in excitatory and inhibitory neuronal lineages. This theory is also compatible with the high prevalence of epilepsy in ASD and with the frequent sensory symptoms seen in autistic children.

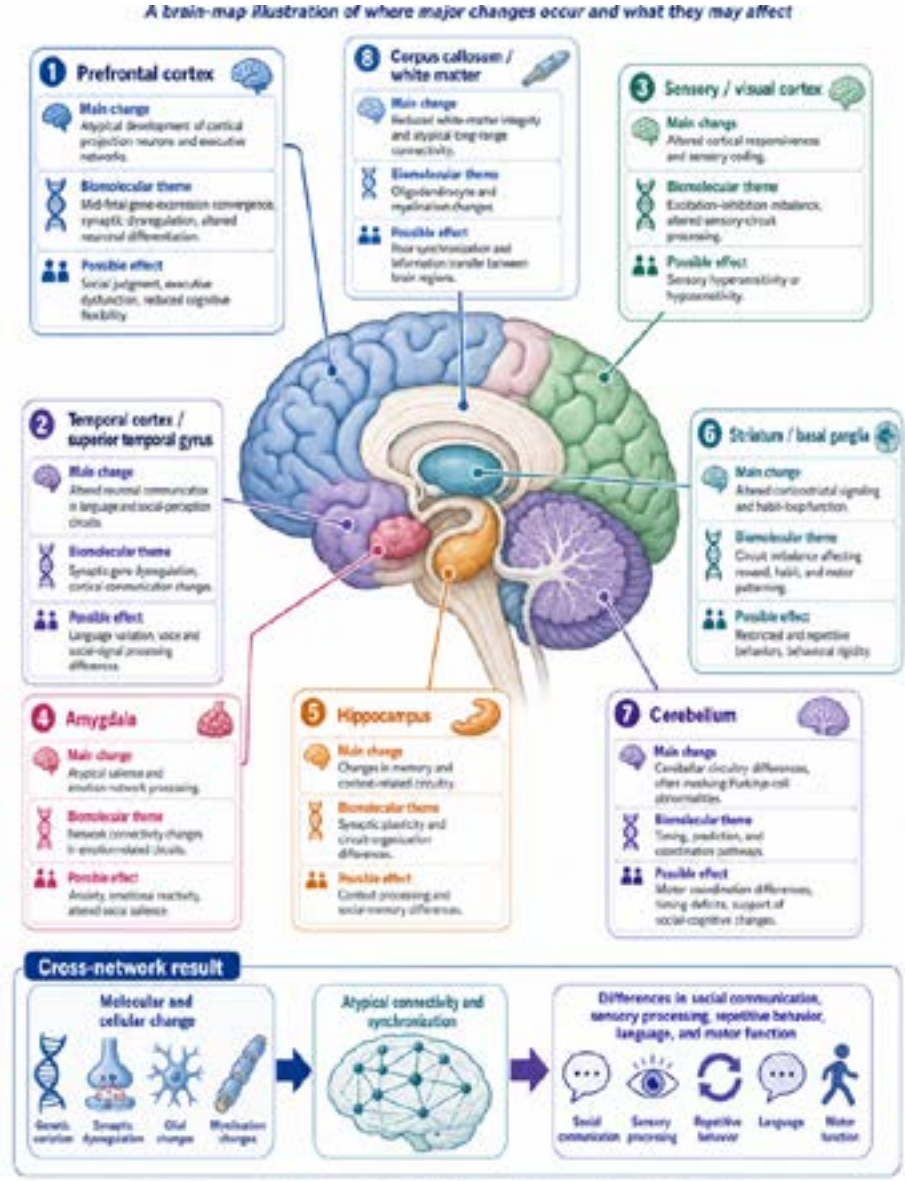


Figure 6 Brain regions, synaptic changes and clinical impact in ASD

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18. What autism is not

Autism is not caused by poor parenting. It is not caused by emotional neglect. It is not caused by vaccines. It is not a simple toxic accumulation disorder. It is not one uniform neurodegenerative disease. It is primarily a neurodevelopmental condition in which early brain development, synaptic function, neuronal communication, and network organization follow atypical trajectories.

The Lancet Commission also warns that many non-mainstream biomedical treatments, including stem-cell treatments advertised for autism, are not supported by adequate evidence and may be costly, distracting, or potentially harmful. This is important because understanding pathogenesis does not automatically prove that any regenerative or biological intervention is effective.

19. Integrated model of autism pathogenesis

Autism spectrum disorder arises when genetic susceptibility, rare or common neurodevelopmental variants, and prenatal or perinatal biological modifiers alter early brain development. These factors affect neural progenitor proliferation, neuronal migration, cortical organization, synapse formation, synaptic pruning, neurotransmitter balance, immune signalling, and long-range network connectivity. The most consistent molecular convergence points are synaptic function, chromatin regulation, gene-expression control, mTOR/PI3K signalling, excitation-inhibition balance, and neuroimmune modulation.

The clinical phenotype depends on the timing, location, and severity of these disruptions, as well as the child's sex, genetic background, comorbidities, environment, education, and early support. This model explains why autism is highly heterogeneous, why some children have intellectual disability or epilepsy while others do not, why symptoms emerge early in development, and why no single biomarker or single treatment applies to all autistic individuals.

Chapter [IV]

Biomolecular explanation of autism

Autism spectrum disorder is best understood as a **heterogeneous neurodevelopmental network disorder**, not a single disease caused by one molecule. The strongest current model is that genetic susceptibility and environmental/developmental modifiers disturb the timing of **brain cell development, synapse formation, synaptic pruning, excitation–inhibition balance, glial maturation, immune signalling and white-matter connectivity**. This produces atypical development of social communication, sensory processing, language, attention, repetitive behaviour and adaptive function. (NCBI)

1. Main molecular level: altered gene regulation during foetal brain development

Many ASD-risk genes are not simple "autism genes"; they are genes controlling **when brain cells divide, migrate, mature and connect**. High-confidence ASD genes are enriched in pathways involving **chromatin remodelling, transcription regulation, RNA splicing, synaptic proteins, ion channels and intracellular signalling**. Nature Reviews Neuroscience summarizes that more than 100 genes can confer large ASD risk, but they converge biologically on developing cortical excitatory neurons, neurogenesis, chromatin modification and synaptic function. (Nature)

A major developmental window appears to be **mid-foetal cortical development**, especially **layer 5/6 projection neurons** in the **prefrontal and primary motor-somatosensory cortex**. These neurons later become long-range cortical output neurons, so early disturbance can affect distributed circuits rather than only one local brain area. (ScienceDirect)

2. Core cellular target: the synapse

At the cellular level, ASD is strongly linked to **synaptopathy** — abnormal synapse formation, synapse maturation, synaptic pruning or synaptic plasticity. Synapses are the contact points where neurons communicate, and small changes in synaptic protein balance during

development can produce large changes in neural circuits.

Important synaptic molecules include **SHANK1/2/3, NRXN, NLGN, SYNGAP1, CNTNAP2, SCN2A, FMR1, TSC1/2, PTEN, CHD8 and MECP2**. SHANK proteins, for example, are postsynaptic scaffolding proteins at glutamatergic synapses; mutations in SHANK genes can alter excitatory synapse composition, spine morphology and neuro-transmission. (Nature)

The practical implication is that autism is not simply “too many” or “too few” neurons. It is often about **how neurons are wired, how stable their synapses are, how they prune connections, and how they regulate signal strength**.

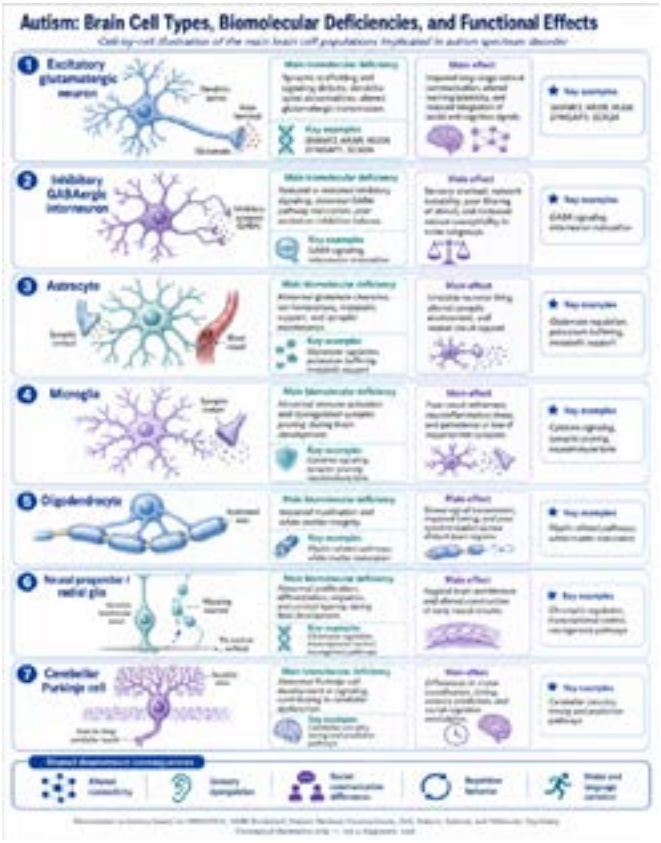


Figure 7 Brain cell types, biomolecular deficiencies and functional effect

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Chapter [V]

THE REGENERATIVE CELLULAR INCOMPLETENESS HYPOTHESIS

Why the Embryonic Biological Programme Contains the Answer to What ASD Has Left Unfinished

Section 1 — The Philosophical Foundation: Incompleteness, Not Destruction

1.1 The Question That Changes Everything

The preceding chapters of this book have described the biomolecular landscape of Autism Spectrum Disorder in considerable detail: the synaptic scaffolding deficits, the neurotrophic signalling disruptions, the excitation-inhibition imbalance, the mitochondrial dysfunction, the neuroinflammatory dysregulation, and the epigenetic and genetic variants that underlie them. This body of evidence is well-established, well-referenced, and not in dispute.

But there is a question that this evidence base has not yet answered — and it is the most important question in the clinical management of ASD:

The Central Question:

Are the cellular and synaptic abnormalities of ASD the result of irreversible destruction — or are they the result of incomplete development that, given the right biological inputs, could be completed? If the answer is destruction, the therapeutic goal is management and compensation. If the answer is incompleteness, the therapeutic goal is restoration and completion. This chapter argues that the evidence supports incompleteness — and that this distinction has profound and practical therapeutic consequences.

1.2 The Evidence for Incompleteness Rather Than Destruction

The distinction between destruction and incompleteness is not philosophical speculation. It is supported by several converging lines of biological evidence:

6. **Structural neuroimaging evidence:** The ASD brain is not a damaged brain in the conventional sense. It is a differently organised brain. Studies consistently show altered connectivity patterns, differences in cortical thickness and gyrification, and atypical


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Chapter [VI] composition model for suggested biomolecular formula for autism:

The preceding chapters described ASD as a spectrum of neurodevelopmental states rather than a single disease with one molecular defect. The current understanding of ASD points toward interacting biological layers: genetic susceptibility, foetal and early-life modifiers, altered cortical neurogenesis, abnormal excitatory and inhibitory neuronal maturation, synaptic scaffolding and pruning disturbance, glial and immune dysregulation, atypical myelination, and network-level changes affecting social communication, sensory processing, cognition, and behaviour [1-5].

If ASD is approached from this broad biological perspective, then a narrow "single-molecule replacement" model is unlikely to explain all subtypes. The question becomes different: could a broad, organ-specific, developmentally rich mixture of brain-derived biomolecular factors contribute to the support of cellular repair, synaptic remodelling, and neuroplastic regulation in selected ASD subgroups?

This chapter therefore introduces a research hypothesis: a purified, sterile-filtered, sublingual food-supplement concept derived from sheep foetal brain cells, supported by mesenchymal-stem-cell-associated paracrine elements, and processed through ACE Pico Protocol, may provide a comprehensive spectrum of peptides, proteins, membrane-derived lipids, extracellular-matrix fragments, growth factors, neurotrophic factors, and signalling molecules relevant to neurodevelopmental repair. The hypothesis is not that ASD is caused by deficiency of one peptide. Rather, the hypothesis is that certain ASD subtypes may involve cells and networks that lack, mistime, or mis-handle multiple regenerative and synaptic-supporting factors; therefore, a broad biological matrix may be more relevant than a single isolated molecule.

Formulation Concept to Be Discussed

For the purpose of this book, the proposed studied formulation may be described without brand naming as follows:


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Chapter VII

Final Synthesis and Recommendations

Core conclusion: Autism spectrum disorder should not be reduced to a single cause, a single peptide deficiency, or a single therapeutic target. It is better understood as a heterogeneous neurodevelopmental spectrum in which genetic susceptibility, developmental timing, environmental modifiers, neuronal maturation, synaptic organization, glial regulation, immune signaling, mitochondrial function, myelination, and network connectivity may converge to produce different clinical phenotypes. A regenerative-medicine hypothesis must therefore be broad, testable, cautious, and integrated with established diagnostic, educational, behavioural, medical, and family-support systems.

1. Closing Overview

The purpose of this book has been to move the discussion of autism spectrum disorder (ASD) from a purely descriptive clinical label toward a deeper biological and biomolecular interpretation. ASD is diagnosed clinically through patterns of social-communication difficulty and restricted or repetitive behaviours, but the clinical definition does not by itself explain why one child presents with severe language delay, another with sensory over-reactivity, another with epilepsy or sleep disturbance, and another with relatively preserved cognition but major social or emotional difficulty. This heterogeneity is the central reason why ASD cannot be approached as one uniform disease.

The chapters of this book have therefore followed a logical path. First, the book introduced the wider gap in modern pharmacopoeia: medicine often focuses strongly on eliminating causes, suppressing symptoms, correcting biochemical abnormalities, or replacing missing hormones, but gives less formal attention to the damaged cell itself and to the complete set of factors that may be required for cell repair, maturation, reconnection, and functional recovery. Second, the book reviewed ASD epidemiology and showed that ASD is not a rare condition; it represents a major and growing public-health, educational, family, and economic challenge. Third, the book analysed the established aetiological and pathogenic framework of ASD, including genetic susceptibility, developmental modifiers, altered foetal cortical development, synaptic and glial dysregulation, and network-level changes. Fourth, the book moved from the clinical phenotype to the

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and fibrosis.

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[Ch I-B:26] Iron Deficiency in Immune-Mediated Inflammatory Skin Diseases: A Missing Link Between Systemic Inflammation, Immunometabolism, and Disease Burden - MDPI, accessed on May 4, 2026, https://www.mdpi.com/2073-4409/15/5/478 *Used in text: Chapter I, biomolecular mechanisms of inflammation, mitochondrial homeostasis, essential elements, biochemical cycles, and fibrosis.*

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matory Injury in the Lungs of Mice - PubMed, accessed on May 4, 2026, https://pubmed.ncbi.nlm.nih.gov/35397105/ *Used in text: Chapter I, biomolecular mechanisms of inflammation, mitochondrial homeostasis, essential elements, biochemical cycles, and fibrosis.*

[Ch I-B:29] Selenium Deficiency Caused Fibrosis as an Oxidative Stress-induced Inflammatory Injury in the Lungs of Mice - ResearchGate, accessed on May 4, 2026, https://www.researchgate.net/publication/359853899_Selenium_Deficiency_Caused_Fibrosis_as_an_Oxidative_Stress-induced_Inflammatory_Injury_in_the_Lungs_of_Mice *Used in text: Chapter I, biomolecular mechanisms of inflammation, mitochondrial homeostasis, essential elements, biochemical cycles, and fibrosis.*

[Ch I-B:30] Iron homeostasis in host defence and inflammation - PMC - NIH, accessed on May 4, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC4801113/ *Used in text: Chapter I, biomolecular mechanisms of inflammation, mitochondrial homeostasis, essential elements, biochemical cycles, and fibrosis.*

[Ch I-B:31] Inflammation, dysregulated iron metabolism, and cardiovascular disease - Frontiers, accessed on May 4, 2026, https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2023.1124178/full *Used in text: Chapter I, biomolecular mechanisms of inflammation, mitochondrial homeostasis, essential elements, biochemical cycles, and fibrosis.*

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[Ch I-B:33] Mechanisms of magnesium in modulating inflammatory signaling - Consensus, accessed on May 4, 2026, https://consensus.app/search/mechanisms-of-magnesium-in-modulating-inflammatory/Me44OvaDRuOwDXuNJyPnfA/ *Used in text: Chapter I, biomolecular mechanisms of inflammation, mitochondrial homeostasis, essential elements, biochemical cycles, and fibrosis.*

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Chapter II - Comprehensive Epidemiology of Autism Spectrum Disorder Worldwide

Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.

[Ch II:1] World Health Organization. Autism fact sheet, 2025. Global estimate: about 1 in 127 persons in 2021; prevalence unknown in many low- and middle-income countries. https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:2] Global Burden of Disease Study 2021 / Lancet Psychiatry 2025. Estimated 61.8 million autistic people globally; age-standardised prevalence 788.3 per 100,000. https://pubmed.ncbi.nlm.nih.gov/39709974/ *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:3] CDC ADDM Network, United States, 2025 report using 2022 data. Autism prevalence among 8-year-olds: 1 in 31, or 3.2%. https://www.cdc.gov/autism/data-research/index.html *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:4] Public Health Agency of Canada / Canadian Chronic Disease Surveillance System. Children and youth prevalence increased to 1 in 44, or 2.25%, in 2023-2024. https://health-infobase.canada.ca/autism/ *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:5] Roman-Urrestarazu et al., JAMA Pediatrics, England. Autism prevalence in more than 7 million pupils: 1.76%. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2777821 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:6] Autism-Europe prevalence summary. European estimate around 1 in 100 people. https://www.autismeurope.org/about-autism/prevalence-rate-of-autism/ *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:7] European prevalence review / ASDEU-related data. European prevalence among children varies widely; examples include 0.8% in Pisa and median primary-school prevalence around 1.2%. https://www.intechopen.com/chapters/84388 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age*

distribution, intellectual disability, and comorbidity sections.

[Ch II:8] Australian Bureau of Statistics, Autism in Australia 2022. 290,900 autistic Australians; 1.1% population prevalence; 4.3% among ages 5-14. https://www.abs.gov.au/articles/autism-australia-2022 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:9] South Korea total-population study. School-age prevalence 2.64%, or 1 in 38 children. https://news.yale.edu/2011/05/09/prevalence-autism-south-korea-estimated-1-38-children *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:10] China systematic review/meta-analysis, 2024. Mainland China prevalence 7 per 1000 children from 2017-2023; male:female ratio about 5:1. https://link.springer.com/article/10.1186/s12888-024-05729-9 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:11] Beijing preschool/child prevalence study. Six-year-old prevalence 10.5 per 1000 in 2021; male:female ratio 4.3. https://journals.sagepub.com/doi/abs/10.1177/13623613241290388 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:12] Indian pediatric autism prevalence literature. Estimate cited as 1.12 per 100 children aged 2-9 years, about 1 in 68. https://www.indianpediatrics.net/apr2024/321.pdf *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:13] Egypt population-based autism mapping study, 2025. Confirmed prevalence 1.1%; highest in age 3-6 years at 1.5%; boys four times more affected than girls. https://link.springer.com/article/10.1186/s13229-025-00665-1 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:14] Qatar population-based child study. Prevalence 1.14% among children aged 6-11. https://acamh.onlinelibrary.wiley.com/doi/10.1111/jcpp.13066 *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:15] MENA systematic review/meta-analysis, 2025. Pooled MENA estimate 0.14%, country estimates from 0.01% in Oman to 6.50% in one Iraqi study, with high heterogeneity. https://link.springer.com/article/10.1186/s12889-025-23651-x *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:16] Africa systematic review/meta-analysis. Seven studies from Egypt, Kenya, Uganda, and Nigeria; clinically confirmed pooled prevalence around 1%, high-risk screening around 4%. https://www.researchgate.net/publication/400461237_Prevalence_of_autism_in_African_countries_a_systematic_review_and_meta-analysis *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

[Ch II:17] Brazil national census estimate. 1.2% self-reported diagnosis nationally; about 2.42 million people; boys aged 5-9 reached 2.6%. https://www.researchgate.net/publication/401795476_Brazil%27s_first_national_census_estimate_of_au-

tism_prevalence_Implications_for_surveillance_and_policy_in_the_Global_South *Used in text: Chapter II, global, regional, and country-level epidemiology of ASD, sex differences, age distribution, intellectual disability, and comorbidity sections.*

Chapter III - Aetiology and Pathogenesis of Autism Spectrum Disorder

Used in text: Chapter III, autism aetiology, genetic contribution, environmental/prenatal risk factors, core pathogenesis, and integrated pathogenesis model.

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[Ch III:2] World Health Organization. Autism. Fact sheet and related public-health statements. https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders *Used in text: Chapter III, autism aetiology, genetic contribution, environmental/prenatal risk factors, core pathogenesis, and integrated pathogenesis model.*

[Ch III:3] Centers for Disease Control and Prevention. About Autism Spectrum Disorder. https://www.cdc.gov/autism/about/index.html *Used in text: Chapter III, autism aetiology, genetic contribution, environmental/prenatal risk factors, core pathogenesis, and integrated pathogenesis model.*

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[Ch III:6] Satterstrom FK, Kosmicki JA, Wang J, et al. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell. 2020. https://www.cell.com/cell/fulltext/S0092-8674(19)31442-0 *Used in text: Chapter III, autism aetiology, genetic contribution, environmental/prenatal risk factors, core pathogenesis, and integrated pathogenesis model.*

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[Ch III:8] WHO. Statement on autism-related issues, including acetaminophen/paracetamol discussion. https://www.who.int/news/item/24-09-2025-who-statement-on-autism-related-issues *Used in text: Chapter III, autism aetiology, genetic contribution, environmental/prenatal risk factors, core pathogenesis, and integrated pathogenesis model.*

Chapter IV - Biomolecular Explanation of Autism

Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.

[Ch IV:1] important in ASD pathophysiology, not only neurons. (Nature) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:2] Nature Reviews Neuroscience, immune review — immune dysregulation, cytokines, maternal immune activation and neuroglial activation are documented biological themes in ASD research. (Nature) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:3] NIMH / NIH — official definition: autism is a neurological and developmental disorder affecting communication, learning, behavior and social interaction, usually evident early in life. (National Institute of Mental Health) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:4] NCBI Bookshelf / NIH — summarizes ASD as heterogeneous, with no diagnostic biomarker yet; diagnosis is clinical/behavioral, while proposed biology includes altered brain development, brain function and synaptic defects. (NCBI) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:5] Nature Reviews Neuroscience, 2022 — high-level genomics review: more than 100 genes can increase ASD risk; convergence is seen in developing excitatory neurons of the mid-gestational prefrontal cortex, with neurogenesis, chromatin regulation and synaptic function as major pathways. (Nature) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:6] Cell, 2013 — co-expression study showing ASD-risk genes converge especially in mid-fetal layer 5/6 cortical projection neurons. (ScienceDirect) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:7] Nature, 2022 — post-mortem RNA-seq across 11 cortical areas found upregulated microglial, astrocytic and neural-immune genes, downregulated synaptic genes, and cell-type-specific changes affecting excitatory neurons and glia. (Nature) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:8] Science, 2024 / PsychENCODE — deep single-nucleus RNA-seq, snATAC-seq and spatial transcriptomics identified cell-type-specific regulatory-network dysregulation in ASD brain. (PubMed) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:9] Science, 2019 — single-cell genomics found preferential effects on upper-layer excitatory neuron synaptic signaling and microglial molecular state. (Science) *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

[Ch IV:10] Molecular Psychiatry, 2026 — review emphasizing oligodendrocytes, myelin and white-matter abnormalities as *Used in text: Chapter IV, foetal brain development, synaptic targets, excitation-inhibition imbalance, glia/neuroimmune mechanisms, myelin, and mitochondrial/energy sections.*

Chapter V - The Regenerative Cellular Incompleteness Hypothesis

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[Ch V:2] Zielinski BA, Prigge MB, Nielsen JA, et al. Longitudinal changes in cortical thickness in autism and typical development. Brain. 2014;137(6):1799–1812. doi:10.1093/brain/awu083. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

[Ch V:3] Monteiro P, Bhatt DL. SHANK proteins: roles at the synapse and in autism spectrum disorder. Nature Reviews Neuroscience. 2015;16(2):78–90. doi:10.1038/nrn3861. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

[Ch V:4] Bhatt DL, Bhatt P, Bhatt K. Neurexins and neuroligins: a synaptic code for neural circuits in health and disease. Nature Reviews Neuroscience. 2011;12(7):381–393. doi:10.1038/nrn3052. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

[Ch V:5] Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. Handbook of Experimental Pharmacology. 2014;220:223–250. doi:10.1007/978-3-642-45106-5_9. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

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[Ch V:7] Frye RE, Rossignol DA. Mitochondrial dysfunction can connect the diverse medical symptoms associated with autism spectrum disorders. Pediatric Research. 2011;69(5 Pt 2):41R–47R. doi:10.1203/PDR.0b013e318212f16b. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

[Ch V:8] Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Molecular Psychiatry. 2012;17(3):290–314. doi:10.1038/mp.2010.136. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation*

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[Ch V:10] Maenner MJ, Shaw KA, Bakian AV, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network. MMWR Surveillance Summaries. 2021;70(11):1–16. doi:10.15585/mmwr.ss7011a1. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

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[Ch V:17] Kolevzon A, Bush L, Wang AT, et al. A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome. Molecular Autism. 2014;5(1):54. doi:10.1186/2040-2392-5-54. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

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[Ch V:19] Bhatt DL, Bhatt P. Bhatt K. Mitochondria and apoptosis. Science. 1998;281(5381):1309–1312. *Used in text: Chapter V, regenerative cellular incompleteness hypothesis, ASD heterogeneity, mitochondrial prerequisite, and preliminary clinical observation sections.*

Chapter VI - Formulation Model and Non-Invasive Delivery: primary references

Used in text: Chapter VI, formulation concept, sheep foetal brain cells, MSC-associated component, neurotrophic peptides, sublingual/oral delivery, absorption study, and dosing architecture.

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[Ch VI-A:3] Bhang SH, Lee S, Shin JY, Lee TJ, Kim BS. Transplantation of cord blood mesenchymal stem cells as spheroids enhances vascularization. Tissue Engineering Part A. 2012. doi:10.1089/ten.tea.2011.0385. *Used in text: Chapter VI, formulation concept, sheep foetal brain cells, MSC-associated component, neurotrophic peptides, sublingual/oral delivery, absorption study, and dosing architecture.*

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[Ch VI-A:8] Massa SM, Yang T, Xie Y, et al. Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. Journal of Clinical Inves-

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Your clinical observations and personal experience are invaluable to the ongoing development of the ACE Factor Deficiency Theory. Complete this form and return it by post to contribute to our research registry. As a gesture of our appreciation, you will receive a complimentary full skincare kit from our product range, plus a 20% discount on all products for one full year.

SECTION A — READER DETAILS

Full name _____ Country _____

Email address _____ Professional title / role _____

I am reading this book as a:

☐ Clinician / physician ☐ Researcher / academic ☐ Parent / family member ☐ Allied health professional ☐ Other

SECTION B — ACCEPTED DOMAIN

1. Which aspect of the ACE Factor Deficiency Theory do you find most scientifically compelling?

2. Do you have clinical or personal observations that may relate to the Regenerative Cellular Incompleteness Hypothesis? Please describe briefly.

3. Overall, how would you rate the scientific rigour of this book?

☐ Exceptional ☐ Strong ☐ Adequate ☐ Needs development

4. What question would you most like future editions or research papers to address?

SECTION C — READER REFLECTIONS

5. How did you hear about this book?

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Summary

Biomolecular Autism Spectrum Disorder presents a new vision of autism through the lens of regenerative medicine and the ACE Factor Deficiency Theory.

Rather than viewing ASD only as a behavioural or developmental condition, this book explores the biomolecular changes that may lie beneath the surface, including altered synaptic signalling, mitochondrial dysfunction, immune-glial activation, oxidative stress, impaired neural communication, and reduced regenerative support.

Dr. Alaa Abdelkarim argues that the future of autism research should not stop at diagnosis and behavioural management. It should also ask whether affected neural cells can be biologically supported, repaired, or rebalanced.

About the Author

Dr. Alaa Abdelkarim is a medical doctor, researcher, and founder of ACE Cells Lab and the British Center for Regenerative Medicine. With more than three decades of medical experience and over twenty years focused on stem cells, biomolecular medicine, and regenerative science, he developed the ACE Factor Deficiency Theory as a framework for understanding degeneration, repair, and cellular dysfunction.

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