Independent Research & Further Reading

Guest: Dr. Thomas N. Seyfried

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Glucose Ketone Index

> *“Well, it's it's it's a long process to determine, to have a tool that we've developed, which is the ratio of blood glucose to ketones. And we've, we've, we've published that glucose ketone index some years ago from glioblastoma to help brain cancer patients get into zones of therapeutic…”*

The glucose-ketone index (GKI) in glioblastoma is used mainly to track whether a ketogenic metabolic intervention is actually lowering glucose relative to ketones, not as a proven stand-alone treatment marker for better survival. Human studies show feasibility and biologic activity, but evidence that GKI-guided therapy improves outcomes is still limited, mostly early-phase, observational, or case-based. **Personal use of ketogenic diets, fasting, or GKI targets should be discussed with a licensed oncology team**, since the current evidence is promising but still preliminary.

References 1-5.

Warburg and the Mitochondrial Origin of Cancer

> *“my work is based on what Otto Warburg, the famous German scientist, said from the 1920s, 30s and 40s. He clearly showed that cancer was a mitochondrial metabolic disease. (...) It means that the origin of the disease resides in the organelle called the mitochondrion.”*

In the early 1920s, Warburg reported that tumours convert glucose to lactate even when oxygen is abundant. He tied the high lactate output to a defect in oxidative phosphorylation, with glycolysis serving as a compensatory source of ATP. Later summaries of his position state that he viewed decreased oxygen consumption and increased lactate production as the quantitative signs of this respiratory insufficiency.

By 1956, Warburg’s claim had become that irreversible respiratory injury was a universal cause of oncogenesis. Reviews also summarise him as proposing a two-step process: chronic insufficiency of oxidative phosphorylation first, then compensatory lactic acid fermentation that allows the damaged cell to survive and become cancerous.

Some later authors argue that Warburg's original measurements were later misread and that his observation of aerobic glycolysis did not necessarily prove complete mitochondrial failure. That is why modern papers distinguish sharply between the Warburg effect as an observation and the Warburg hypothesis as a universal causal theory of cancer. Warburg also extended the claim into prevention and treatment thinking, arguing that cancer was tied to nutritional and environmental conditions that impair respiration, and even in 1970 he still attributed spontaneous tumour metabolism to lack of oxygen or vitamin B1 deficiency.

Later work largely rejects Warburg's claim as a universal explanation because many tumours show active oxygen consumption and functional mitochondrial metabolism. Several reviews conclude that in most cancers the Warburg effect reflects regulated metabolic reprogramming, while primary mitochondrial defects matter in only a minority of tumours.

Current reviews state that Warburg's original thesis is not accepted as a universal explanation of cancer, because aerobic glycolysis often occurs with functioning mitochondria. Several reviews now frame the Warburg effect as a regulated adaptation driven by oncogenes, tumour suppressor loss, HIF-1, and the microenvironment rather than by primary mitochondrial failure in most tumours. At the same time, modern literature still treats Warburg's work as foundational for cancer metabolism research. The concept has also expanded beyond cancer into immunity, inflammation, metastasis, drug resistance, and some non-tumour diseases.

References 6-23.

Mitochondria and Lifespan

> *"So all of the mitochondria, they*
> *determine our destiny. They will determine how long you will live on the planet. If if you don't have an unfortunate accident or something like this, they have an expiration date. Different species die at different times. You don't find people living 400 years."*

Mitochondria are a major regulator of lifespan across species, but reviews argue they are one part of a broader ageing network rather than the sole determinant. Mitochondria affect lifespan mainly by controlling cellular energy, stress signalling, quality control, and tissue maintenance, and age-related mitochondrial decline is repeatedly linked to faster ageing and more age-related disease.

The evidence also shows that lifespan is not set by mitochondria alone, because ageing reflects interactions among mitochondrial biology, nuclear genes, environment, lifestyle, and broader longevity pathways.

References 24-28.

Cold-Blooded Animals, Metabolic Rate, and Longevity

> *"I learned yesterday that cold blooded animals live longer on average, because the mitochondria having to, I guess, work well.*
>
> *They're dependent on the thermal regulation. The cold blooded, I mean, they can become. They're not. It takes a lot of energy. And warm blooded animals from this has to be on all the time which generate reactive oxygen species. "*

Across species, lower body temperature is repeatedly linked to longer lifespan, and this pattern is reported in both ectotherms and endotherms. But the thermoregulation-ageing link is still mechanistically incomplete, especially in ectotherms. Both groups also appear to have a species-specific optimal temperature zone, defended physiologically and behaviourally, that shapes senescence risk.

Recent work argues that cold-related longevity is not explained only by slower chemistry, lower metabolic rate, or reduced mitochondrial ROS production. Instead, cold appears to affect nutrient sensing, proteostasis, RNA structure, temperature-sensitive channels, epigenetic state, inflammation, cold-shock proteins, and splicing programmes that can reshape cellular ageing. That broader framing fits the general view that mitochondria are central signalling hubs in ageing, but not the sole determinant.

Mitochondria clearly matter because temperature strongly changes respiration, ATP synthesis, ROS production, and maintenance costs in ectotherms. Within a species' optimal thermal range, these processes can remain coordinated so ATP synthesis stays efficient and maintenance costs stay relatively low, but above that range, mitochondrial economy becomes dysregulated. Elevated temperatures tend to decrease ATP synthesis efficiency, increase ROS generation, and raise antioxidant costs, which can reduce whole-organism performance and fitness.

Cold adaptation does not mean cold-climate animals simply have intrinsically superior mitochondria. In fishes, species from colder latitudes show higher mitochondrial respiration and aerobic enzyme activity when compared at a common temperature, but they still have lower absolute metabolism in their actual cold habitats, meaning adaptation only partly offsets thermodynamic constraints. In insects, cold acclimation can preserve oxidative phosphorylation efficiency during cold stress, while freeze-tolerant species sometimes suppress respiration to limit ROS and membrane damage, showing that longevity-relevant mitochondrial strategies include both maintenance and strategic metabolic suppression.

More broadly, ageing is increasingly framed as an energy supply-demand imbalance involving mitochondria, and interventions such as exercise, calorie restriction, mitophagy support, and mitochondria-targeted compounds appear promising, although translation remains limited and model complexity matters.

References 29-39.

Wrinkles

> *"So you can see I have*
> *wrinkles and this kind of thing. This is from living on the planet, and this is from wear and tear on this organelle, which allows, us to make energy efficiently."*

Mitochondria appear to contribute to wrinkles mainly by increasing reactive oxygen species (ROS), damaging mtDNA, and weakening extracellular matrix maintenance. UV exposure worsens mitochondrial dysfunction by driving mtDNA mutations, ROS overproduction, and loss of mitochondrial membrane potential, which feeds back into photoaging. Additionally, in dermal fibroblasts, mitochondrial injury is associated with reduced collagen production and increased collagen-degrading metalloproteinases, a combination directly relevant to wrinkle formation. Ageing fibroblasts also accumulate damaged mitochondria and mtDNA deletions, which alter the extracellular matrix and promote inflammation that accelerates wrinkles.

Most evidence supports involvement, not exclusivity: wrinkles also depend on UV exposure, inflammation, extracellular matrix breakdown, and broader skin ageing processes. The strongest causal evidence comes from animal and cell studies, while human evidence is more often

correlational or early interventional. Mitochondria, therefore, are involved in wrinkles, particularly in photoaging-related wrinkles, but they are one mechanistic hub within a larger skin-ageing network.

Other Causes of Wrinkles

UV is the dominant non-mitochondrial driver of wrinkle formation, with photoaging characterised by loss of elasticity, fine lines, wrinkles, and reduced epidermal and dermal components.

- Extrinsic ageing also reflects the broader exposome: pollution, smoking, inadequate nutrition, lack of sleep, infrared, and blue light act together to worsen oxidative, inflammatory, and structural skin damage.
- Intrinsic ageing includes genetics, cellular senescence, telomere shortening, hormonal change, metabolic processes, and immune decline. Genetic variation contributes to wrinkle susceptibility, and newer work adds epigenetic aging: blood-based GrimAge and FitAge acceleration correlated with wrinkle area, photoaging, telangiectasias, and perceived facial age.

Wrinkles emerge when extracellular matrix support fails: collagen declines, becomes fragmented, and is degraded by increased MMP activity, while impaired TGF-β signalling further reduces new collagen production. Elastic fibres, glycosaminoglycans, and proteoglycans also change with age, reducing skin elasticity and function.

References 40-54.

Mitochondrial Control of Neighbouring Cells

> *"But let me say something else. It not only controls the internal environment of the cell, it also controls the neighbouring cells."*

Mitochondria and mitochondrial components can cross cell boundaries and alter neighbouring-cell metabolism, stress responses, immunity, proliferation, and survival. The strongest caveat is that the magnitude, direction, and physiological importance vary by tissue and disease

context, and several reviews note that mechanisms and normal-state relevance remain incompletely defined.

Inside cells, mitochondria already act as signalling hubs that regulate metabolism, calcium handling, apoptosis, stress responses, and cell fate, which gives transferred mitochondria the capacity to change recipient cell behaviour. Across cells, horizontal mitochondrial transfer has been linked to tissue homeostasis, rescue of injured cells, and mitochondrial quality control.

References 55-67.

Mitochondria as Regulators of the Cell Nucleus

> *"It's a systemic they communicate with each other across cells, across tissues. So it's a really interesting organelle. It's always been a second place a position to the nucleus. Everybody thought everything was done by the nucleus. We got to look at all the genes, the chromosomes controlling everything. I'll tell you, this organelle controls a lot of what that nucleus does, it tells the cell when to divide.*
> *It tells the cell when to slow down."*

Mitochondria do more than make energy: they continuously signal their condition to the nucleus, and this can change nuclear gene expression, stress responses, metabolism, and whether a cell keeps dividing or slows down. They influence cell-cycle timing through several signals, including energy availability, membrane potential, and mitochondrial fission and fusion, and problems in these systems can delay the G1-to-S transition, trigger checkpoints, or slow growth. Mitochondrial dynamics are tightly linked to mitosis because mitochondria must be properly divided and inherited by daughter cells, and blocking mitotic fission can cause arrest or apoptosis. They also affect what the nucleus does through metabolites, calcium, ROS, mtDNA-derived signals, and even mitochondrial RNAs that move to the nucleus and regulate nuclear genes involved in processes such as chromatin control, metabolism, stress adaptation, and nuclear division. At the same time, most mitochondrial proteins and much of mitochondrial biogenesis are directed by nuclear genes, so the overall picture is a two-way partnership rather than mitochondria being the sole dictator of the cell.

References 68-79.

Cross-Organ Communication via Mitochondrial Bioenergetics

> *“Now we're beginning to realize they actually can commute. Liver communicates with the brain with all the other organs. That's all done by the bioenergetics of this organelle.”*

Liver mitochondria can influence brain function by controlling fuel availability, redox state, and metabolic signalling, but the strongest direct evidence comes from animal and mechanistic studies rather than definitive human experiments. The clearest disease context is hepatic encephalopathy, where both liver and brain mitochondrial dysfunction are linked to cerebral energy failure.

The liver–brain axis is described as a bidirectional metabolic network that uses hepatokines, metabolites, and neural inputs to transmit information between organs. The liver is framed not only as a metabolic hub but also as an endocrine organ whose secreted factors can influence the central nervous system (CNS).

The most specific bioenergetic mechanism is fuel delivery to the brain. Hepatic mitochondrial respiration supports gluconeogenesis and ketogenesis, and when this fails, glucose and ketone supply to the brain falls before coma in experimental hepatic encephalopathy. Fasting and exercise studies support the same logic, showing that the shift from liver-derived glucose toward ketone-based metabolism acts as a brain-relevant adaptive signal, with 3-hydroxybutyrate highlighted as a liver-derived mediator.

Liver and brain mitochondria are not bioenergetically interchangeable. They differ in substrate use, ROS behaviour, calcium handling, and vulnerability to respiratory-chain defects, which means liver-to-brain signalling likely works through circulating fuels and signals rather than shared intrinsic mitochondrial programmes. More broadly, the research supports a modern view of mitochondria as signalling organelles, not just ATP generators, which makes inter-organ communication biologically plausible. Thus, liver–brain bioenergetic communication occurs mainly through liver-derived metabolites and endocrine signals, especially ketone bodies, with neural pathways also contributing; direct evidence that liver mitochondria themselves communicate with the brain as a distinct causal system in humans remains limited.

References 80-96.

How Carcinogens Cause Damage

> *“For example, when you talk about carcinogens, it's a chemical that causes cancer. How does that chemical cause cancer? It damages the proteins and the lipids."*

Carcinogens damage proteins and lipids, especially via reactive oxygen species (ROS), and this can disrupt cellular functions. But the clearest first step in carcinogenesis across the literature is DNA damage that is copied into mutations before repair can remove it. Protein and lipid injury often matter because they feed into DNA damage or growth dysregulation rather than replacing them as the core step. Oxidative stress also alters signalling pathways, gene expression, intercellular communication, and membrane function, which can promote initiated cells during cancer promotion and progression.

Carcinogens usually cause cancer by creating DNA damage that is copied into mutations, while some also promote cancer without directly changing DNA. The main pathways in the literature are direct DNA binding, metabolic activation into reactive intermediates, oxidative stress, epigenetic disruption, chronic inflammation, immune evasion, and altered growth signalling. Many carcinogens act by directly interacting with DNA, forming adducts, cross-links, distorted bases, or strand breaks. Ionising radiation can also generate double-strand breaks directly or through free radicals produced from water radiolysis, and misrepaired breaks can cause translocations, loss of heterozygosity, and genomic instability. Other carcinogens are activation-dependent: they become dangerous only after metabolism converts them into reactive electrophiles that bind DNA. A common sequence is metabolic activation, DNA adduct formation, replication across the damaged site, and then a fixed mutation that gives a growth advantage if it hits an oncogene or tumour suppressor gene.

If repair fails, lesions become heritable mutations in daughter cells, especially in genes controlling growth, DNA repair, apoptosis, and the cell cycle. Mutations in proto-oncogenes such as RAS or tumour suppressors such as p53 can remove normal brakes on proliferation and apoptosis.

Carcinogenesis is typically a multistep process of initiation, promotion, and progression rather than a single event. Nongenotoxic carcinogens can promote this process by stimulating

proliferation, endocrine signalling, receptor-mediated effects, immunosuppression, or tissue-specific toxicity even without direct DNA reactivity.

Some carcinogens drive cancer through oxidative stress and chronic inflammation, which increase DNA lesions, impair repair, and create a tissue environment that favours tumour growth. Heavy metals and tobacco smoke are examples where reactive oxygen species are implicated alongside direct mutagenic effects. Some carcinogens also alter epigenetic regulation such as DNA methylation and histone modification, changing gene expression without changing sequence. Infections and tumour viruses add further routes, including persistent inflammation, viral oncogenes, insertional mutagenesis, and immunosuppression.

Carcinogens cause cancer mainly by producing DNA lesions and other cellular changes that escape repair, accumulate, and eventually give mutant cells a survival or growth advantage. The exact route differs by carcinogen, but across the literature the core theme is sustained genetic or epigenetic disruption plus selection for uncontrolled cell growth.

References 97-116.

Ancient Fermentation Pathways

> *"There's a little pathway there that makes*
> *energy without oxygen from the evolutionary past. So we have it in the cytoplasm of the*
> *cell because they can use they can ferment in the cytoplasm."*

Cytoplasmic glycolysis and fermentation are evolutionarily ancient ATP-producing pathways that arose in a low-oxygen world and still operate in modern cells when oxygen is absent or fluctuating or when glycolytic metabolism supports proliferation and stress adaptation.

References 117-123.

Compensatory Fermentation in Cancer

> *"And in cancer what happens in a particular tissue, whether it's bone, lung, bladder, brain, they gradually compensate with these ancient fermentation pathways. So this thing, this organelle signals to the nucleus. I'm not getting enough energy. So the nucleus turns on. The transporters on the surface of the cell to bring in fuels that will elevate energy through what we call 'oxygen-independent mechanisms'."*

Cancers in many tissues often upregulate ancient fermentative glycolysis/lactate pathways as part of a broader, plastic metabolic programme that helps them survive hypoxia, acidosis, treatment, and rapid growth.

Aerobic glycolysis is now viewed less as a fixed mitochondrial defect and more as an active cancer programme driven by HIF-1, oncogenes, tumour-suppressor loss, and growth signalling pathways such as AKT and PI3K-Akt-mTOR. The metabolic shift often appears early in oncogenesis, can precede overt hypoxia, and is widely described across tumour types, including colorectal cancer.

Its main advantage is not ATP yield per glucose molecule, but fast flux through pathways that generate ATP rapidly while supplying intermediates for nucleotides, lipids, amino acids, and other biomass needed for rapid division. Reviews also emphasise that the modern Warburg framework extends beyond glycolysis alone to coordinated rewiring of transporters, the pentose phosphate pathway, amino acid metabolism, one-carbon metabolism, and antioxidant programmes.

Lactate is no longer treated as a mere waste product because it acts as a fuel, signal, and shuttle metabolite within and beyond tumours. Lactate export through MCT transporters helps maintain intracellular pH while acidifying the extracellular space, producing the inverted pH gradient typical of many tumours. That acidic, lactate-rich microenvironment tends to suppress anti-tumour immunity by impairing effector T cells, promoting regulatory or pro-tumour immune states, and reshaping macrophages and endothelial cells. The same environment also supports angiogenesis, invasion, metastasis, and broader stromal remodelling, including reverse Warburg interactions in which some oxidative cells consume lactate produced by more glycolytic neighbours.

Tumours often contain mixed cell populations with glycolytic, oxidative, and hybrid glycolysis/OXPHOS states in the same lesion, shaped by spatial oxygen and nutrient gradients. In

colorectal cancer and other tumours, this heterogeneity includes perivascular regions with greater OXPHOS activity and more distant hypoxic regions with stronger glycolytic behaviour. This plasticity helps explain why glycolysis supports resistance to chemotherapy, radiotherapy, anti-angiogenic therapy, and immunotherapy but also why blocking one pathway alone often produces compensation through another. Experimental evidence shows that fully suppressing lactate production can reduce growth without abolishing it because tumours can reactivate OXPHOS, whereas disrupting lactate transport can impose intracellular acidosis and stronger growth suppression.

References 124-128.

Carcinogenesis and Mitochondrial Damage

> *"But with chronic disruption, smoking, lack of exercise, you can go right down the list of all of the different things that can elicit to cancer any kind of carcinogens, microplastics, forever, chemicals, glyphosate, and any of these kinds of things that would chronically damage the ability of this organelle to produce energy. What else do we have? Viruses, oncogenes. You have chronic inflammation.* ***Any of those things damaged the sophisticated ability of this organelle to produce sufficient energy****. That's why the paradox which we solved."*
>
> *(...)*
>
> *"Now, you don't need to ferment when you have oxygen in the environment. And the mitochondria can utilize the oxygen the environment, cancer cells too. Warburg said. It's the weirdest thing. These cancer cells, continue to ferment even in 100% of oxygen. Why are they doing that? And he speculated that this organelle was damaged. Irreversible damage to the organelle happened in these cancer cells."*

Some carcinogens and cancer-related changes directly damage the parts of mitochondria that make energy, while others mainly shift cells toward using more sugar without fully shutting mitochondria down. Across the literature, the strongest pattern is partial damage and adaptation, not complete mitochondrial failure. In some tumours, both oxidative phosphorylation and glycolysis are active at the same time, and cells can shift between them depending on conditions. Thus, some

carcinogens clearly weaken mitochondrial energy production, but many cancer cells survive by adapting and keeping enough mitochondrial function to grow.

Carcinogenesis usually involves metabolic rewiring, not uniform mitochondrial failure. Reviews across cancer biology state that oncogenic events often promote aerobic glycolysis while preserving mitochondrial function and that tumours frequently upregulate mitochondrial biogenesis, quality control, or respiration because intact mitochondria support growth. Some papers go further and state that many tumours rely heavily on mitochondrial ATP production. Across cancer types, oxidative phosphorylation can remain active, sometimes exceed glycolytic ATP production, and become especially important in slow-dividing cells, therapy-resistant cells, and cancer stem cells.

Mitochondrial damage still matters in carcinogenesis, but it is not universal and often partial rather than catastrophic. mtDNA mutations, electron transport defects, oxidative stress, TCA-cycle enzyme defects, and oncogene or tumour-suppressor signalling can all produce respiratory dysfunction, altered redox balance, and lower OXPHOS in subsets of cancers. The direction and degree of dysfunction vary. Mild electron transport chain (ETC) defects can promote ROS and transformation, whereas severe mitochondrial compromise can reduce tumour formation or progression, which argues against the idea that all carcinogens simply damage mitochondria until they cannot make enough energy.

Not all carcinogens damage mitochondria so severely that cells cannot produce sufficient energy. The broader literature shows a spectrum from mitochondrial impairment to preserved or enhanced mitochondrial ATP production, with cancer cells often surviving by switching between glycolysis and OXPHOS rather than losing energy generation altogether.

References 129-131.

Szent-Györgyi's Paradox of Carcinogenesis

> *"That was the paradox that was first put out by Albert Szent-Györgyi, Hungarian scientists who received the Nobel Prize, I think, for vitamin C, he said. He said he was very interested in cancer and living systems. He said there's a paradox. He said, we know multiple things in the environment can elicit cancer. We've identified these oncogenes, viruses, chronic inflammation, carcinogens, intermittent hypoxia, rare, rare germline mutations, he said. We don't understand the common pathophysiological mechanism by which any of those provocative agents would elicit dysregulated cell growth, which is cancer."*

Szent-Györgyi's 1937 Nobel recognised two linked advances: identifying ascorbic acid as vitamin C and clarifying parts of the biological oxidation machinery of cells, especially the catalytic role of fumaric-acid-related compounds in respiration. He showed that the substance he had called hexuronic acid prevented scurvy and was therefore the anti-scorbutic factor, vitamin C. He then renamed the crystalline compound ascorbic acid.

Szent-Györgyi's theory of cancer held that cancer is a failure of cells to return from a proliferative, fermentative state to a regulated oxidative state and that this failure reflects disrupted electron transfer or "electronic" organisation rather than energy shortage alone. That idea is historically influential and mechanistically provocative, but the evidence base remains largely conceptual, biochemical, and preclinical rather than clinically established.

The theory starts from an evolutionary contrast: fermentation supports unstructured proliferation, whereas oxygen-enabled oxidation supports structure, differentiation, and regulation. Cancer, in this framing, is not just fast growth but a regulatory reversion in which cells divide yet fail to re-establish the more ordered oxidative state after division. He explicitly rejected a purely energetic explanation of the Warburg-type shift. Energy from oxygen made complex life possible, but he argued that energy offers no mechanism; the mechanism had to involve electron flow and charge transfer.

The broad intuition that cancer links to altered metabolism and oxygen handling remains alive in research, including Szent-Györgyi's emphasis on redox chains and oxidation. The specific electronic theory is still preliminary here because its strongest support comes from theory pieces,

interpretive essays, and limited animal or cell observations rather than convergent modern validation.

Some proposed regulators showed preclinical activity: retine inhibited tumour growth in mice and cell cultures, while promine promoted growth, but these findings were not translated here into usable therapy. He also reported a redox-pair combination effect, where ascorbic acid plus 2,6-dimethoxybenzoquinone inhibited cancer more than either alone, but this too appears as an early mechanistic lead, not settled treatment evidence.

Szent-Györgyi's cancer theory was therefore a theory of dysregulated oxidative-electronic control of growth, not just a claim that tumours need energy. In research, its historical importance is clear, but where research stands now is that the framework remains suggestive rather than established, with enduring influence on redox and metabolism thinking but little direct validation of its full mechanistic programme.

References 139-145.

Aerobic Fermentation in Cancer

> *"Even in the presence of oxygen, 100% oxygen, they're still fermenting. That shouldn't happen."*

While many cancer cells still ferment in the presence of oxygen, for 100% oxygen specifically, the evidence found supports the broader claim of fermentation under sufficient oxygen, not a universal proof that 100% abolishes or preserves fermentation in every cancer type. This does not mean cancer cells stop using oxygen. Many cancers retain an active TCA cycle, electron transport, and OXPHOS, and some evidence argues that oxidative metabolism is required for efficient proliferation. A current model is that lactate secretion reflects mitochondrial bottlenecks or overload, so excess carbon is diverted to lactate while mitochondria remain active.

Aerobic fermentation is broader than cancer. It appears in yeast, bacteria, brain cells, endothelial cells, pollen, immune cells, and other proliferating mammalian cells, which argues that it is a **general adaptive metabolic state rather than a uniquely malignant defect.** Its function depends on context. In brain tissue, aerobic glycolysis in astrocytes helps supply lactate and oxygen-demand

support to neurons. Its function depends on context. In brain tissue, aerobic glycolysis in astrocytes helps supply lactate and oxygen-demand support to neurons.

References 146-159.

Fermentation Byproducts During Cardiac Arrest

> *"When people have heart attacks, they stop breathing. The heart seizes. The bloodstream immediately fills with these fermentation waste products, which are lactic acid. And the other one, which we now know is succinic acid. These two waste products. Now, if you don't start breathing in a short period of time, you're going to be dead. You die because the neurons in your brain cannot sustain this kind of fermentation energy for very long."*

A heart attack kills mainly by stopping blood flow to heart muscle, which rapidly deprives cells of oxygen and ATP, causes the heart to fail electrically or mechanically, and then cuts blood flow to the brain and other organs. The brain is especially vulnerable because reduced cardiac output or cardiac arrest lowers cerebral blood flow, reducing brain oxygen and glucose delivery and triggering mitochondrial dysfunction, blood-brain barrier injury, and cell death in regions such as the hippocampus.

When a coronary artery suddenly occludes, aerobic metabolism in the heart becomes impaired within the ischemic territory. **The ischemic myocardium then switches to anaerobic glycolysis, the "fermentation"-like process, because oxygen-dependent oxidative phosphorylation can no longer meet demand. That shift produces lactate and H+, lowers intracellular pH, and accumulates other metabolic catabolites and osmotic waste products in tissue.** ATP then falls, ion pumps fail, calcium rises, membranes are damaged, and cardiomyocytes die by necrosis, apoptosis, and other regulated death programmes, including ferroptosis, pyroptosis, and necroptosis.

Restoring blood flow is essential, but reperfusion also causes a second wave of injury through ROS burst, mitochondrial permeability transition pore opening, inflammation, and additional cell death. Reoxygenation can remove some metabolites and correct pH, yet it can paradoxically damage marginally viable myocardium and worsen later heart function.

In short, a heart attack causes death by ischemic pump failure, arrhythmia, and cardiac arrest, while “fermentation” refers to anaerobic glycolysis that temporarily sustains ATP but generates lactate, acidosis, and other harmful metabolites. The brain is injured mainly because the failing or arrested heart can no longer deliver enough blood, oxygen, and glucose, and because heart injury can trigger additional brain mitochondrial, barrier, and apoptotic damage.

Lactate and Succinate

The mechanistic interpretation of lactate is more limited than its prognostic value. Elevated lactate reflects anaerobic glycolysis, systemic inflammation, persistent tissue hypoperfusion, myocardial dysfunction, mitochondrial injury, reduced clearance, or combinations of these, so it is best viewed as a marker of metabolic stress rather than a proven direct cause of death.

Succinate has a stronger causal hypothesis in ischemia-reperfusion injury. Human metabolomics in resuscitated out-of-hospital arrest found that TCA-cycle metabolites, especially succinate-related signatures, were higher in non-survivors and best explained survival-related variation.

Adjacent trauma and circulatory-death models support the same biology: succinate rises rapidly during hypoxia, can outperform lactate as a mortality biomarker in severe trauma, and broader metabolomics suggest lactate alone captures only part of post-ischemic metabolic injury.

The evidence supports lactate primarily as a marker of hypoperfusion and shock burden, with clearance adding important prognostic value, whereas succinate appears more directly tied to reperfusion injury mechanisms but has less direct outcome validation in cardiac arrest patients.

References 160-174.

Oxygen Consumption Without Efficient ATP Production in Cancer Cells

> *"Some cancer cells continue to take in oxygen and make ATP. Therefore, Warburg must be wrong. We show them that we showed the cancer cell takes an oxygen, but it's not making energy through ATP in any great amount. It's using it for ROS. These radicals that further damage and cause the DNA mutations that everybody is chasing. It's all downstream effects of damage."*

Cancer cells do use oxygen to generate reactive oxygen species (ROS), but they also use oxygen to produce ATP through oxidative phosphorylation (OXPHOS). The relative contribution of each process varies by tumour type, oxygen availability, and metabolic state. In most cancer cells, the majority of oxygen consumed by mitochondria supports OXPHOS, while a smaller proportion contributes to ROS production through electron leak from the electron transport chain or ROS-producing enzymes such as NOX.

ROS are an unavoidable byproduct of mitochondrial respiration and play important biological roles. At low to moderate levels, ROS promote cancer cell proliferation, migration, invasion, angiogenesis, and survival signalling. At high levels, however, ROS damage proteins, lipids, and DNA and can ultimately kill cancer cells. Rather than simply using oxygen to maximise ATP production or ROS generation, many cancer cells appear to adjust their metabolism to maintain ROS within a narrow range that supports signalling while avoiding excessive oxidative damage.

This reflects the metabolic plasticity of cancer. Some tumours rely heavily on glycolysis, others depend more on mitochondrial respiration, and many use both simultaneously. Even cancers exhibiting the Warburg phenotype generally retain some mitochondrial respiration, meaning oxygen consumption does not disappear. In some situations, cancer cells shift towards glycolysis or reduce pyruvate oxidation to limit mitochondrial ROS when oxidative stress becomes excessive, particularly during metastasis or other forms of cellular stress.

Seyfried interprets oxygen consumption differently. He argues that high oxygen consumption does not necessarily indicate that ATP is being generated efficiently through OXPHOS. Instead, he proposes that cancer is fundamentally a disease of impaired mitochondrial energy metabolism, in which chronic OXPHOS insufficiency is compensated by fermentation of glucose and glutamine,

together with mitochondrial substrate-level phosphorylation. This differs from the broader literature, which generally concludes that many cancers retain substantial, and sometimes dominant, ATP production through OXPHOS despite increased glycolysis. Nevertheless, there is broad agreement that oxygen consumption alone is an imperfect measure of ATP production in cancer cells because respiration also supports ROS generation, biosynthesis, and redox regulation.

Finally, the statement that ROS-driven DNA mutations are "all downstream effects of damage" reflects the mitochondrial metabolic theory of cancer rather than the prevailing scientific consensus. While mitochondrial dysfunction, oxidative stress, and ROS can contribute to DNA damage and genomic instability, most researchers view cancer development as arising from complex interactions between genetic mutations, epigenetic alterations, metabolic changes, inflammation, and the tumour microenvironment, with the relative importance of these factors differing among cancer types.

References 175-185.

Fermentation Waste Products in Cancer Cells

> *"We have clearly shown that*
> *the mitochondria are fermenting and they're blowing out succinic acid. The cytoplasm is blowing out lactic acid from as a waste product. The mitochondria is blown out succinic acid as a waste product."*

Lactate accumulates when glycolysis produces pyruvate faster than mitochondria can oxidise it. Converting pyruvate to lactate regenerates NAD^+, allowing glycolysis and ATP production to continue. In cancer, lactate is therefore often an overflow product of aerobic glycolysis, but it is not simply a waste product. Many tumours retain functional mitochondria, and oxidative cancer cells can import lactate through MCT1 transporters, convert it back to pyruvate, and use it to fuel the TCA cycle and oxidative phosphorylation. As a result, lactate functions not only as a metabolic fuel but also as a key mediator of the tumour microenvironment. High extracellular lactate promotes immune suppression, macrophage polarisation, angiogenesis, metastasis, and receptor-mediated growth signalling. In acute myeloid leukaemia (AML), inhibition of mitochondrial complex II creates a lactate-dependent vulnerability, as cancer cells compensate by importing extracellular lactate to sustain mitochondrial respiration.

Succinate is another molecule that can build up in cancer cells. Rather than being a waste product, it can actively promote cancer growth. High levels of succinate switch on pathways that help tumours survive in low-oxygen conditions, alter how genes are regulated, and stimulate the formation of new blood vessels. Like lactate, succinate can also be released by cancer cells and act as a chemical signal that influences nearby cells, helping create an environment that supports tumour growth.

References 186-199.

Damaged Mitochondria in Cancer

> *"I published that big paper where I spent over a year of my time going through the early electron microscopy literature. Warburg didn't have that opportunity because that technology was not there for him. So he speculated that based on the biochemistry. But I went back and I looked at these electron micrographs of mitochondria in various cancers, and they're all damaged."*

Mitochondrial alterations are common across cancers, but they are heterogeneous across tumour types, and not every cancer shows the same mitochondrial defect or the same direction of change. The specific mitochondrial phenotype differs by cancer type: copy number, dynamics, respiration, and mutation patterns vary widely within and across cancers.

Multiple reviews converge that cancers commonly reprogram mitochondrial function even when mitochondria are not "broken". Some papers reject the older idea that cancer generally stems from globally defective respiration. They state that oncogenic programmes often rewire metabolism without typically impairing mitochondrial function and that many cancers maintain active mitochondrial biogenesis, quality control, and oxidative phosphorylation. Cancer cells often retain functional mitochondria, and many tumours depend on mitochondrial respiration, ATP production, biosynthesis, redox control, or mitochondrial quality control for growth and survival.

References 200-215.

Glucose and Glutamine: Major Fuels for Cancer Cells

“Why the cell is growing out of control. Well, first of all, it's fermenting. That means it's getting energy from sources other than oxidative phosphorylation. You can take a cancer cell and treat it with cyanide or azide or in absence of [oxygen]. And it's still living, it's still growing because it's not using the oxygen. They're not using the falling back on oxygen-independent mechanisms which are called 'fermentation'.

(...)

You must have tremendous supply of of the fuels that will give us energy. Which are glucose, the sugar. Yeah. And the amino acid glutamine. Our bodies are loaded with glutamine. That's the most abundant amino acid in our bloodstream. And evolution provided that for us because if we stop breathing, we use that fuel to keep thcells alive. Our gut is controlled by glutamine. Our immune system uses glutamine.”

Cancer cells often remain viable under low oxygen because hypoxia induces HIF-dependent metabolic adaptation, especially greater reliance on glycolysis and other pathways that maintain redox balance and biomass production. That adaptation helps explain why hypoxia is repeatedly linked to tumour progression and poor prognosis rather than simple cell death.

Many cancer cells exhibit aerobic glycolysis (the Warburg effect), taking up large amounts of glucose and converting much of it to lactate even when oxygen is available. However, in many tumours, mitochondrial oxidative phosphorylation (OXPHOS) continues to generate a substantial proportion of cellular ATP. Cancer cells do not rely on glucose alone, and many tumours can shift toward greater OXPHOS when glycolysis is limited. This metabolic flexibility is one reason a single "energy source" explanation is incomplete, as tumour metabolism varies across cancer types, genetic backgrounds, and microenvironments. Glutamine is a major second fuel in many cancers and is frequently described as a metabolic dependency or "glutamine addiction". Cancer cells use glutamine to replenish tricarboxylic acid (TCA) cycle intermediates through α-ketoglutarate, support nucleotide and amino acid synthesis, maintain redox balance, and sustain survival when nutrient availability changes.

Glucose is the dominant fuel for many cancers, but not the only one. Depending on tumour type, genetic alterations, oxygen availability, nutrient supply, and cell state, cancer cells may also derive energy and biosynthetic precursors from glutamine, mitochondrial OXPHOS, lactate, and, in some contexts, fatty acids. No single fuel or metabolic pathway defines all cancers.

References 216-223.

Prenatal Carcinogen Exposure and Pediatric Cancer

> *"It's because children can get these cancers right, or a 90-year-old can get the cancer. And it doesn't appear to me that a three-year-old has necessarily made life choices. Yet. That could, as I said, when you consider 'forever chemicals' that are in the environment, things that we have that we use in our technologically advanced societies can get through the placental wall and get these into these children's organs. You know, you have to put it together. We usually it's a constellation of things because don't forget It. I said carcinogens, some of these carcinogens are fat-soluble. Some of these carcinogens can get in and damage those that during early stages of development. people always say, how are you? Explain brain cancer in a six-month-old baby. Okay. When did he wasn't smoking and drinking and partying all the time. But but his the mitochondria in a population of cells in his brain became damaged."*

Prenatal carcinogen exposure appears to be linked to higher pediatric cancer risk for some exposures, especially pesticides, air pollution, ionising radiation, and DES, but the evidence is much stronger for some agents than for others. Human evidence is strongest for ionising radiation and DES, while pesticide and air-pollution associations are supported by growing epidemiology but remain more heterogeneous and exposure-specific.

- In utero ionising radiation is the most established prenatal carcinogenic exposure in humans, although more recent low-dose diagnostic imaging studies often show weaker or null associations than older studies.
- DES exposure in utero is causally linked to later cancer, especially clear-cell vaginal or cervical cancers in exposed daughters, with newer reviews also noting possible links to testicular cancer and intergenerational effects.

- Prenatal pesticides and air pollution are associated with higher risks of several pediatric cancers, especially leukemia and some CNS tumours, but findings vary by pollutant, tumour type, and study design.

Radiation is the clearest prenatal carcinogen in the literature, with large reviews supporting excess cancer risk below 0.1 Gy after in utero exposure and generally higher relative risks for exposures in utero or childhood than in adulthood. A separate review of 89 studies also found overall support for excess childhood cancer risk after medical diagnostic radiation in utero, even though risk estimates declined over calendar time as doses fell.

However, a separate review of 89 studies also found overall support for excess childhood cancer risk after medical diagnostic radiation in utero, even though risk estimates declined over calendar time as doses fell. A newer review similarly concluded that most recent studies of prenatal diagnostic imaging show no association overall, possibly because modern doses are lower or because studies are underpowered to detect small risks. DES is the other exposure with long-standing human causal evidence. Reviews identify in utero DES as causally associated with adolescent clear-cell vaginal and cervical cancers, and newer evidence suggests possible links to testicular cancer in sons and ovarian cancer in granddaughters.

Biomarker and mechanistic studies strengthen plausibility by showing that environmental carcinogens cross the placenta and can induce fetal genotoxic damage, cytogenetic injury, and epigenetic changes associated with carcinogenesis. Proposed mechanisms include DNA adduct formation, oxidative DNA damage, incomplete repair during rapid fetal cell proliferation, altered drug-metabolising capacity, and heritable epigenetic disruption.

Benzene is a good example of this gap between mechanistic plausibility and epidemiologic certainty. Mechanistic reviews argue that maternal benzene exposure could damage fetal hematopoietic stem and progenitor cells and increase later leukemia susceptibility, but they also state that direct proof in childhood leukemia remains scarce. Similar fetal genotoxic signals have been reported for particulate air pollution, with prenatal PM exposure associated with cytogenetic effects in infants.

Prenatal carcinogen exposure and pediatric cancer are therefore linked most convincingly for ionising radiation and DES, while pesticides and air pollution show a broader but more mixed pattern of association that still needs sharper exposure measurement and mechanistic confirmation.

Evidence for some other prenatal exposures, including chemotherapy during maternal cancer and modern diagnostic ultrasound, does not currently show excess pediatric harm in the available studies.

References 224-236.

Chronic Inflammation as a Cancer Risk Factor

> *"So we have shown that inflammation produces the cytokines. When you have an inflammatory heat inflammation, they they damaged the ability of this organelle to make energy efficiently. Chronic inflammation is known to be a risk factor for cancer, chronic inflammation, intermittent hypoxia, carcinogens."*

Inflammatory mediators impair mitochondrial energy production, and chronic inflammation promotes cancer-related processes. Immune and tissue cells produce cytokines during inflammation, while intermittent hypoxia appears to intensify inflammatory and tumour-promoting signalling rather than act as a universal standalone carcinogen.

Inflammatory cells produce cytokines, and those cytokines can directly damage mitochondrial energy metabolism. Multiple papers describe a vicious cycle in which inflammation impairs mitochondria, lowering ATP and increasing oxidative stress, while dysfunctional mitochondria then amplify inflammation through ROS, mtDNA, and innate immune signalling.

Chronic inflammation is widely described as a cancer risk factor or hallmark of cancer, with examples including inflammatory bowel disease and COPD-associated lung cancer. Chronic hypoxia and especially cycling or intermittent hypoxia activate NF-κB, HIF-1, and inflammatory genes linked to tumour growth. Intermittent hypoxia increased inflammatory cytokines in patients, rats, and cell models. In mouse and cell models, intermittent hypoxia promoted colon carcinogenesis or cancer-related signalling, but this evidence is mechanistic and not enough to call intermittent hypoxia a general carcinogen by itself.

As a summary, inflammation is associated with cytokine production, inflammatory cytokines can impair mitochondrial energy production, and chronic inflammation is linked to higher cancer risk.

Cells in inflamed tissues produce cytokines, and intermittent hypoxia is best described as a tumour-promoting inflammatory stressor, not a proven universal carcinogen on its own.

References 237-247.

Neuronal Cancer

> *"Cancer is very rare in neurons of the brain. Neurons that glial cells of the brain form these brain tumors, mostly, but neurons can't compensate with fermentation, so they die. So you either get compensatory ancient fermentation leading to dysregulated cell growth, which we call cancer, or we get cell death, leading to chronic diseases."*

Neuronal cancer is very rare because mature neurons are post-mitotic and strongly resist sustained cell-cycle re-entry. Mature brain neurons rarely become cancerous because cancer requires uncontrolled proliferation, while mature neurons are post-mitotic cells that generally do not divide. The main explanation is not just "few mutations", but a combination of durable cell-cycle arrest, differentiation programmes, and tumour-suppressive mechanisms that push damaged neurons toward dysfunction or death rather than neoplastic growth.

The rarity of neuronal tumours in the clinical literature matches the biology. Rare neuronal, glial, and glioneuronal tumours together account for less than 2% of primary CNS tumours, and some purely neuronal lesions such as MVNT show an absence of mitoses or very low Ki-67, consistent with inert behaviour. Neurocytomas are also rare, comprising only about 0.25–0.5% of CNS tumours, and extraventricular forms are described as extremely rare.

References 248-256.

Cancer Rates in High-Income Countries

> *"High income countries like Australia and New Zealand and the United States have the highest rates of cancer."*

Across global datasets, high-income countries do have the highest incidence of cancer overall, and Australia/New Zealand sit at or near the top of world rankings, while the United States

and North America are also among the highest-incidence regions. That pattern does not mean they have the highest death rates, because mortality is often lower than in some lower-income regions despite high incidence.

References 257-260.

Albert Schweitzer's Observations of Cancer in African Tribes

> *“And this is what Albert Schweitzer found the famous humanitarian physician. He was specifically looking for cancer in African tribes. And he said, remarkably, it's extremely low. What are these guys doing where Western society has has a lot of cancer and these Africans have living, living according to the traditional ways.”*

There is evidence that Schweitzer publicly expressed this view, but it's important to distinguish an anecdotal observation from a scientific finding. The quote most often attributed to him comes from a preface he wrote for Alexander Berglas's 1957 book Cancer: Cause and Cure. Schweitzer wrote:

"On my arrival in Gabon in 1913, I was astonished to encounter no cases of cancer. I saw none among the natives two hundred miles from the coast. I cannot, of course, say positively that there was no cancer at all, but, like other frontier doctors, I can only say that, if any cases existed, they must have been quite rare. This absence of cancer seemed to be due to the difference in nutrition of the natives compared to the Europeans."

There are several major confounding factors, including:

- many cancers were difficult to diagnose in remote settings without pathology services;
- life expectancy was lower, so fewer people survived to the ages when many cancers become common;
- infectious diseases caused many deaths before cancer could develop or be detected;
- there were no comprehensive cancer registries.

There is a publication out of his hospital. The paper reports a hospital-based pathology series from Lambaréné, Gabon, showing 196 histologically confirmed cancers among 64,297 people seen between 1950 and 1965. Across the 16-year period, the hospital records identified 196 malignancies in 64,297 patients, and all were histologically proven. The cancer profile was dominated by carcinomas, especially cancers of the genitourinary and alimentary tracts. The series also included substantial numbers of lymphomas and sarcomas, indicating that the cancer burden was not limited to epithelial tumours alone. Primary liver cancers were present, but the authors found no evidence for several tumour types reported as common in other African settings.

The main limitation is that this is a single-hospital, histology-confirmed case series, so it reflects cancers detected and biopsied at that institution rather than population incidence for all of Gabon. In sum, the paper found a modest, stable number of confirmed cancers in Lambaréné from 1950–1965, dominated by carcinomas of the genitourinary and alimentary tracts, with several cancer types notably absent.

Several publications report cancer incidence, mortality, or relative risk in African ethnic or tribal groups, although truly tribe-specific data are uncommon and usually come from registries or hospital-based series rather than national censuses. The strongest direct example is a Nairobi registry study that explicitly recorded “tribe” and compared cancer risks across Kikuyu, Kamba, Kisii, Luhya, Luo, Kalenjin, Somalis, and other groups. That study found marked differences in cancer risk by tribe within the African population.

In Nairobi, the Kamba had higher risks of melanoma, Kaposi sarcoma, liver, and cervix cancer, and lower risks of oesophagus, stomach, corpus uteri, and nervous system cancers relative to Kikuyu. Luo and Luhya had much higher odds of Kaposi sarcoma and Burkitt lymphoma.

Beyond tribe-specific papers, several publications quantify the overall African cancer burden. A 2008 Lancet Oncology review estimated about 650,000 cancers diagnosed annually in Africa and identified cervical, breast, and HIV-associated Kaposi sarcoma as the highest-incidence cancers. A 2022 continent-wide GLOBOCAN analysis estimated 1.1 million new cases and 711,429 deaths in Africa in 2020, rising to a projected 2.1 million new cases and 1.4 million deaths by 2040. A sub-Saharan Africa review estimated 801,392 new cases and 520,158 deaths in 2020, with breast and cervical cancer together making up about three in ten diagnosed cancers, and prostate cancer leading male incidence in 40 countries. A 2020 review using GLOBOCAN 2018 estimated 811,200 new

cases and 534,000 deaths in WHO AFRO countries, with breast and cervical cancer leading in women and prostate and liver cancer leading in men.

Large gaps remain because many African and Caribbean nations still lack national cancer registries, and even current estimates often rely on population-based registries in only some countries or on neighbouring-country data when local data are missing.

References 261-267.

Cancer Cells Fuel Sources: from Glucose to Ketones

> *"I was measuring because we knew that the tumor cells needed sugar to grow out of. Warburg showed that and many other people show that. And they can't burn ketones because because the fatty you need a very efficient mitochondria to burn ketones for energy. Our normal cells can burn ketones for energy. And that gives us tremendous we can actually breathe lower oxygen, more energy. If you have efficient if you can burn ketones efficiently in this organelle. But if the organelle is damaged, they can't use the ketones, they can't burn fatty acids or ketones, which stores lipid drops"*

Many cancers increase glucose uptake and channel glucose through aerobic glycolysis to generate ATP and biosynthetic intermediates that support proliferation and division. Blocking glucose transport or uptake often suppresses tumour-cell growth, including selective effects in cancer cell lines and brain tumour–initiating cells. Tumour dependence on glucose is context-dependent because cancers can compensate with glutamine, amino acids, glycogen, or mixed glycolysis-plus-OXPHOS programmes.

Cancer cells commonly reprogram metabolism toward aerobic glycolysis, and this shift supports rapid proliferation by supplying both energy and carbon for proteins, lipids, and nucleic acids. Several reviews state that this creates a selective growth advantage and explains why tumours often require higher glucose flux than normal tissues. However, not all tumour cells are limited mainly by glucose, because many cancers also rely heavily on glutamine metabolism. Some tumours use alternative carbon sources or stored glycogen under stress, which helps sustain survival and aggressiveness when glucose access changes. Glycolysis often works alongside oxidative

phosphorylation, rather than fully replacing it, and the balance varies by tumour type and environment.

Tumour cells generally do need substantial glucose use to grow, because glucose supports ATP production, anabolic metabolism, and aggressive behaviours across many cancers. But they do not always need glucose alone or in the same way, since many tumours can reroute metabolism toward glutamine, amino acids, glycogen, or mixed energy programmes when conditions change.

Cancer Cells and Ketone Body Metabolism

Some cancer cells can use ketone bodies for ATP production, lipid synthesis, growth, and metastasis, but this capacity is strongly tumour- and context-dependent, with support seen in pancreatic cancer, hepatocellular carcinoma, chondrosarcoma, lung tumour-initiating cells, glioma in vivo, and engineered breast cancer models, while other glioma, breast, pancreatic, and colon models show neutral or inhibitory effects. A recurring mechanistic conclusion is that response depends on ketolytic competence and microenvironmental conditions—especially BDH1/OXCT1/SCOT/ACAT1 expression, oxygenation, nutrient stress, and whether ketones are used oxidatively or diverted into biosynthesis or signalling.

The main limitations are that the evidence is mostly preclinical, often contradictory across tumour models, and highly sensitive to experimental conditions such as glucose concentration, hypoxia, diet composition, and whether studies measure true in vivo ketone flux rather than enzyme expression alone. Clinical translation therefore remains uncertain: ketogenic states can inhibit some tumours yet fuel others, and current reviews emphasise the need for biomarker-stratified, standardised human studies before broad therapeutic conclusions are justified.

References 268-283.

Cancer as the Leading Cause of Death in Domestic Dogs

> *"The domestic dog cancer is the number one killer of the domestic dog."*

Across multi-thousand-dog datasets from North America, Taiwan, Italy, and elderly necropsy cohorts, neoplasia/cancer is the leading overall cause of death, often accounting for about one-third

to nearly one-half of deaths. The strongest age pattern is that older dogs die more often from neoplastic and neurologic disease, while younger dogs die more often from infectious and gastrointestinal causes.

References 284-287.

Inherited Genetic Risk Factors and Cancer

> *"Now people say, well, cancer has to be genetic because we have inherited genes that put us at higher risk, like the one for breast cancer and the leave from many for a variety of other cancers. Our paper in this pile done by Bob Kaplan, he went through and looked at all the genetic risk factors."*

The Bob Kaplan paper mentioned (co-authored by the guest) seems to be the 2025 review on hereditary cancer syndromes and oxidative phosphorylation insufficiency, and it argues that inherited variants are risk factors rather than fully penetrant causes of cancer. Kaplan's central claim is that germline mutations in hereditary cancer syndromes commonly impair mitochondrial OXPHOS, and that this metabolic impairment is the condition through which inherited variants elevate cancer risk. The paper explicitly states that no inherited mutations are fully penetrant for cancer, so these variants should be treated as secondary risk factors rather than primary causes.

It further argues that if an inherited variant does not compromise OXPHOS, it does not elevate cancer risk enough to define a hereditary cancer syndrome. The proposed mechanism is a shift away from mitochondrial ATP production toward substrate-level phosphorylation, with oxidative stress and respiratory insufficiency as common features across syndromes.

Reference 288.

Penetrance of Cancer-Associated Gene Mutations

> *"But none of these mutations are 100% penetrant, meaning that their secondary risk factors, a primary risk factor would be every time that mutation is there 100% of the People. (...) There's no gene that we know of in cancer. The leaf Romney is the highest one with a p53 inherited mutation. There's no gene mutation. That's 100%. You have that gene, you're going 100% get cancer. Most of them are are are what they call incompletely penetrant."*

Cancer susceptibility mutations span a penetrance spectrum, not a single category, with genes and even specific variants ranging from high to low risk. High-penetrance mutations exist, but much of inherited cancer risk appears to come from moderate- and low-penetrance variants, and penetrance can be modified by genetic background, environment, and family history. The practical implication is that cancer mutations are penetrant in some cases, but not uniformly or fully penetrant, and risk assessment has to be gene-, variant-, family-, and population-specific.

References 289-293.

The Glucose Ketone Index as the First Metabolic Health Biomarker

> *"Well, that's why we develop the glucose ketone index calculator, the first biomarker tool that can allow people to know the level of health of the amount of of their mitochondria. "*

The Glucose Ketone Index (GKI) is a proposed quantitative biomarker that reflects the body's metabolic state by combining blood glucose and blood ketone concentrations into a single value. It is intended to indicate the balance between glucose availability and ketone production. According to the authors, the GKI is not a biomarker of disease itself, but rather a biomarker of metabolic status.

The authors discuss potential applications in cancer, epilepsy, diabetes, obesity, and neurodegenerative diseases, but they stress that the GKI is currently a proposed biomarker. **More clinical research is needed to establish disease-specific target ranges and determine whether achieving particular GKI values improves patient outcomes.**

References 294-296.

Psychological Stress, Cortisol, and Blood Sugar

> *"Stress elevates corticosteroids. When you're under stress, you get into a fight, into an argument, or you're stressed out by business deal going bad or whatever. Corticosteroids elevate, elevate blood sugar, contributing to systemic inflammation."*

Stress activates the HPA axis and sympathetic system, increases cortisol or corticosterone, and raises blood glucose through hepatic glucose production, reduced peripheral uptake, and insulin resistance.

Stress hyperglycemia does appear to contribute to systemic inflammation, but the relationship is two-way rather than one-directional. Acute stress and critical illness raise glucose through cortisol, catecholamines, cytokines, insulin resistance, and increased liver glucose output, and once glucose is high, it can further worsen oxidative stress, cytokine release, and immune dysfunction. Across clinical settings, people with higher stress-hyperglycemia ratio usually show more inflammation and worse outcomes than those with lower relative glucose elevations.

Mechanistically, stress hormones and inflammatory mediators act together. Catecholamines, glucocorticoids, glucagon, and cytokines increase gluconeogenesis, reduce insulin effectiveness, impair GLUT4-mediated glucose uptake, and raise free fatty acids, all of which push blood glucose upward during severe stress. Once glucose rises, it can feed inflammation back in several ways. Reviews consistently describe oxidative stress as a central link: hyperglycemia increases reactive oxygen species and activates pathways such as PKC, NF-κB, AGE-RAGE, and related stress signalling, and these changes promote inflammatory cytokines, endothelial dysfunction, and insulin resistance.

The evidence does not suggest that all hyperglycemia is equally harmful. Several reviews describe early acute endogenous hyperglycemia as partly adaptive because it supplies energy during severe stress, while prolonged, excessive, or externally driven hyperglycemia appears more likely to amplify inflammation and organ injury.

References 297-307.

Oxidative Damage

> *“it's damaging because you produce reactive species that damage the efficiency of this organelle to produce energy effectively. And that either will kill the cell gradually if it can't use compensatory fermentation or predispose you to cancer. So either way it's unhealthy. So we have chronic disease. ”*

Inflammation can impair mitochondrial respiration and oxidative phosphorylation, lowering ATP synthesis capacity. Several papers describe this as a shift from balanced redox signalling to oxidative stress, with downstream damage to mitochondrial membranes, ETC components, and cardiolipin that decreases ATP production efficiency.

The mechanism appears bidirectional rather than one-way: inflammation raises ROS, ROS damages mitochondria, and damaged mitochondria then generate more ROS and inflammatory signals. Evidence is strongest in chronic inflammatory and autoimmune diseases, sepsis, cardiometabolic disease, and critical illness, where mitochondrial dysfunction, ROS excess, and impaired energy metabolism recur together. Reviews tie oxidative mitochondrial damage and chronic inflammation to cardiovascular disease, diabetes, obesity, neurodegeneration, chronic kidney disease, respiratory disease, and ageing-related degeneration.

For cancer, persistent inflammation drives repeated tissue damage and repair, raises replication error risk, and creates a permissive tumour microenvironment. ROS appear to be a central mechanistic bridge. They promote oxidative DNA lesions such as 8-OHdG, genomic instability, and pro-oncogenic signalling, while inflammatory cells continuously add more ROS in chronic lesions.

Classic examples include H. pylori–gastric cancer, HBV/HCV–liver cancer, HPV–cervical cancer, inflammatory bowel disease–colorectal cancer, smoking-related bronchitis–lung cancer, and chronic oral inflammation–oral cancer.

Mitochondria are not just bystanders; mitochondrial ROS and dysfunction can be necessary for some oncogenic programmes and inflammation-associated cancers.

Important Caveats

Not every episode of inflammation leads to cancer or chronic disease. The risk signal comes from persistence, dysregulation, and feedback amplification, especially when ROS overwhelm antioxidant control and mitochondrial quality control fails. Cancer-specific ROS biology is also bidirectional: ROS can support tumour initiation and progression, but excessive ROS can also trigger senescence, apoptosis, necrosis, or ferroptosis, which is why antioxidant-based prevention or treatment remains contested. So, persistent systemic inflammation that drives ROS excess and mitochondrial dysfunction is strongly linked to chronic disease, and it also promotes cancer risk and progression, particularly through oxidative DNA damage, chronic tissue injury-repair cycles, and tumour-supporting inflammatory signalling.

References 308-317.

Fasting in Cancer Therapy

> *"When you enter a fasted or ketogenic state, your healthy cells essentially go into bunker mode. They slow their division, conserve energy and build up their defenses. Cancer cells, however, do not have this evolutionary off switch. They continue trying to rapidly divide. When the toxic chemotherapy hits, your shielded, healthy cells survive it much better, while the exposed, rapidly dividing cancer cells take the full hit."*
>
> *(...)*
>
> *"Doctor Valter Longo… his extensive research, clinical trials prove that fasting[-]mimicking diets drastically lower IGF-1, which triggers cellular autophagy and actually makes standard cancer therapies up to three times more effective by removing the metabolic shield of cancer cells."*

Preclinical evidence shows short-term fasting or fasting-mimicking diets protect normal cells from chemotherapy stress while failing to protect, and often sensitising, many cancer cells. The important caveat is that this pattern is strongest in cell and mouse studies, whereas human data are still early, small, and focused more on feasibility and side effects than definitive tumour outcomes.

Normal-cell protection during fasting is reported across mice, normal mammalian cells, and reviews of the field, with reduced chemotherapy toxicity linked in part to lower glucose and IGF-1 signalling. Cancer cells usually do not enter the same protected state because oncogenic signalling blocks the fasting-induced stress-resistance switch, leaving many tumours more vulnerable to therapy.

Human evidence is preliminary: small case series and early trials suggest fasting is feasible and may reduce side effects without obvious loss of anticancer activity, but controlled trials are still needed.

In a 101-patient trial, a 5-day fast-mimicking diet (FMD) lowered median IGF-1 by 30.3%, alongside lower glucose and insulin, and these effects repeated across cycles. The autophagy part is more nuanced than the quote suggests. Several reviews and mechanistic papers describe fasting-like states as activating autophagy through lower IGF-1, mTOR suppression, and AMPK signalling. But not all tumour settings move in the same direction: in acute lymphoblastic leukemia models, FMD actually inhibited autophagy, and this inhibition helped vincristine work better, while chloroquine could substitute for FMD.

In breast cancer, one randomised trial found radiologic response odds about 3.17-fold higher with FMD during neoadjuvant chemotherapy. The same trial found pathologic response odds about 4.11-fold higher in per-protocol analysis, not a universal 3× effect across cancers or endpoints. A newer 44-patient breast cancer trial also reported more frequent near-complete tumour-cell loss and better imaging responses with FMD. In contrast, the larger 101-patient trial primarily established safety, feasibility, metabolic changes, and immune remodelling and explicitly called for phase II/III trials to test anti-tumour efficacy. In contrast, the 101-patient trial mentioned primarily established safety, feasibility, metabolic changes, and immune remodelling and explicitly called for phase II/III trials to test anti-tumour efficacy.

References 318-333.

Mitochondrial Dysfunction Across Chronic Diseases

> *"Type two diabetes, cardiovascular disease, dementia all of these are part of damage to this organelle in one way or another. And like I say said for Parkinson's disease, when that organelle gets damaged, the cells of the substantia nigra die, they are incapable of compensating with fermentation."*

Type 2 diabetes

Type 2 diabetes usually begins as a combination of insulin resistance, early β-cell stress, and nutrient overload, with mitochondrial dysfunction acting as an early driver and amplifier. Mitochondria sit at the centre of glucose oxidation, ATP generation, ROS signalling, and apoptosis, so even modest mitochondrial defects can impair insulin secretion in β-cells and insulin action in muscle and liver. The best-supported model is a vicious cycle: excess glucose and fatty acids raise mitochondrial ROS, oxidative stress, and dysmetabolism, which then worsens insulin resistance and β-cell dysfunction.

Dementia/Alzheimer's Disease

Mitochondrial dysfunction is an early and widespread feature of Alzheimer's disease that contributes to neuronal dysfunction and cognitive decline. Bioenergetic failure and oxidative stress are core mechanisms: impaired electron transport, lower ATP production, and excess ROS damage neurons and synapses. Defective mitophagy and abnormal mitochondrial dynamics allow damaged mitochondria to accumulate, reinforcing amyloid/tau pathology and neurodegeneration.

Mitochondrial dysfunction appears early in AD and may even precede amyloid and tau accumulation in some longitudinal models, which is why some authors frame it as a possible upstream driver rather than only a downstream consequence. But causality is still contested, and several reviews explicitly describe mitochondria as either a primary or secondary event in pathogenesis rather than a settled first cause.

Functionally, failing mitochondria reduce ATP, weaken calcium buffering, and impair axonal transport and synaptic support, which fits the high energy demands of neurons and helps explain memory and cognitive symptoms. Oxidative stress is a recurring mechanism, with elevated ROS both damaging mitochondria and feeding forward into tau phosphorylation, inflammation, and neuronal death.

Parkinson's Disease

Mitochondrial dysfunction is a major contributor to dopaminergic neuron loss in the substantia nigra in Parkinson's disease, although it is not the only mechanism. Respiratory-chain defects, especially complex I impairment in substantia nigra neurons, are repeatedly reported in PD and can drive oxidative stress and energy failure. Mitochondrial dysfunction alone can produce parkinsonism-like progression, but some models show early metabolic compensation rather than immediate neuron death.

The literature reports mitochondrial respiratory failure or electron transport chain impairment, especially complex I deficiency, with reduced ATP synthesis and increased reactive oxygen species. Substantia nigra dopaminergic neurons appear especially vulnerable because they have high energy demand, sustained oxidative phosphorylation, calcium loading, dopamine-linked oxidative burden, high iron, and relatively low mitochondrial reserve. Mitochondrial dysfunction also interacts with α-synuclein aggregation, impaired autophagy/mitophagy, inflammation, and several cell-death pathways rather than acting as a single isolated cause. Some evidence shows neurons can initially compensate metabolically; complex I disruption induced a Warburg-like shift that preserved survival for a time while dopaminergic function progressively failed.

References 334-353.

Sleep and Mitochondria

> *“If we have good sleep. Yeah. If you you know, everybody feels good when you have a good night's sleep, your body feels rejuvenated because you're not you're not stressing out. You're reducing the ability of this organelle to manage the metabolic environment. If you're up all night and your and you're, like, stressed out and you're never given this organelle in a particular cell, in a particular part of the organ of the body, you know, you get neuropsychiatric problems, you can get digestive problems*
> *You have a whole. And we put it in the paper. There are all the different stress, all the different things that can chronically or acutely damage oxidative phosphorylation.”*

Sleep and Mitochondria

The most direct evidence is that short-term sleep deprivation reduces mitochondrial respiration linked to oxidative phosphorylation and the electron transport system. In mice, 72 hours of paradoxical sleep deprivation decreased brain mitochondrial electron transport activity, with significant reductions in complex I-III activity and additional complex II-related deficits after rebound sleep. Human overnight total sleep deprivation also reduced plasma ATP, which was interpreted as consistent with altered mitochondrial function, but this is a more indirect marker than direct respirometry or enzyme assays.

A consistent mechanistic theme is that prolonged wakefulness raises metabolic demand and mitochondrial oxygen-dependent ATP synthesis, increasing ROS generation that can damage lipids, proteins, and DNA. Sleep loss also elevates mitochondrial ROS in sleep-control neurons, linking electron transport byproducts directly to sleep pressure and oxidative signalling. Reviews of animal and human work conclude that sleep deprivation commonly alters mitochondrial gene expression, protein levels, enzyme activity, and morphology, supporting a mitochondria-centred stress response even when OXPHOS is not always measured head-on.

Sleep, Stress, and Neuropsychiatric Problems

Sleep deprivation and chronic stress are consistently associated with anxiety, depression, cognitive impairment, and other neuropsychiatric symptoms. Mitochondrial dysfunction appears to contribute to these brain effects through oxidative stress, neuroinflammation, altered

neurotransmission, and impaired synaptic plasticity. The claim that mitochondria are the main causal driver remains unresolved; several reviews explicitly frame them as one important contributor rather than the sole cause.

Chronic stress and poor sleep reinforce each other through HPA-axis activation, glial dysfunction, neuroinflammation, and impaired protein clearance, creating a self-perpetuating loop that increases risk for depression, anxiety, PTSD, cognitive decline, and neurodegeneration. More specifically, sleep deprivation can damage mitochondrial morphology and respiration, promote mtDNA oxidation and release in microglia, and activate inflammatory pathways such as NF-κB and cGAS-STING, which plausibly link mitochondrial injury to behavioural and cognitive changes.

Digestive and Gut Effects

Sleep deprivation also disrupts the gut system, causing dysbiosis, reduced short-chain fatty acids, intestinal inflammation, circadian dysregulation, and barrier dysfunction. Acute sleep deprivation increased anxiety-like behaviour alongside gut dysbiosis and colon inflammation in mice. Sleep loss reduced butyrate-related signals and tight-junction integrity, consistent with leakier gut barriers and systemic inflammation. Stress also appears to act via the gut, with dysbiosis and permeability changes affecting glia and immune cells partly through mitochondrial regulation.

For the gut, the evidence is indirect. Sleep deprivation clearly harms gut physiology, and gut dysbiosis can impair mitochondrial function through LPS, butyrate loss, ceramide signalling, and circadian disruption, but the supplied papers do not show as directly that mitochondrial damage alone causes digestive symptoms as they do for brain outcomes.

References 354-365.

Paleolithic Hunting Behaviour and Species Extinction

> *"this is another thing that was really interesting came out of Israel. I think it was last year. They looked at the cavemen, what they were eating. They were eating the strongest members of the herd, leading to the indirect extinction of these animals. They found out that if you can eat the strongest member of the herd, you'll get the vitality of that one. or buffalo or elephant or whatever the hell they were eating, because they knew the marrow and the physiology of that, of that organism at that point in its life could provide you with the strength that that had.Now, when you eat the strongest members of the herd because you want to be tough, you're putting the old and the young vulnerable to predators, leading to the extinction. And this is what a big paper came out of, out of Israel. They looked at these cavemen, what they were eating like 500,000 years ago, whatever were doing. So humans indirectly caused the extinction of other species in part, and not in part because they were eating the toughest guys in the herd."*

According to Stiner et al. (2021), humans consistently preferred the largest animals available. At each stage of prehistory, hunters appeared to target the biggest prey because these provided the greatest amount of food for the least hunting effort. The average size of hunted animals declined steadily over time. Around 1–1.5 million years ago, giant elephants (up to ~13 tonnes) dominated the diet. By about 400,000 years ago, hunting focused more on deer, horses and wild cattle. By 50,000–10,000 years ago, gazelles formed the majority of hunted animals. Human hunting may have contributed to megafaunal extinctions. The authors argue that humans repeatedly overhunted the largest species until they became rare or disappeared locally, after which people shifted to the next largest prey. Climate alone did not explain the pattern. In their statistical analyses, climatic variables showed little relationship with the observed decline in prey size, leading the authors to argue that hunting pressure was an important driver. This remains a debated interpretation within archaeology. Changes in prey may have driven human evolution. The authors hypothesised that as large prey disappeared, humans had to develop new hunting technologies, greater cooperation and eventually agriculture once large game became scarce. This is presented as a hypothesis rather than an established fact.

The underlying idea that prehistoric humans preferentially hunted large, prime-aged animals and that this contributed to the decline of many large mammals is a legitimate scientific hypothesis

supported by archaeological evidence. The rest of the statement, that humans deliberately sought the "strongest" animals to absorb their vitality and that this was the principal mechanism behind extinctions, is speculative and is not supported by the archaeological literature. It reflects an interpretation added on top of the research rather than the conclusions of the research itself.

References 366, 367.

Glyphosate and Non-Hodgkin Lymphoma Risk

> *"Synthetic pesticides… increases the chance of [non-Hodgkin] lymphoma by a staggering 41%." – Steven. "Yeah, because they damage all those things. What is that? Glyphosate. The thing in the in the roundup, they all damage the oxidative phosphorylation, putting the cell at risk for compensatory fermentation, dysregulated cell growth."*

The 41% increase refers to high cumulative glyphosate-based herbicide exposure in one meta-analysis, not to all pesticides. Several large recent datasets found that most pesticide associations were null, arguing against a blanket statement that synthetic pesticides increase Non-Hodgkin Lymphoma (NHL) risk by one common amount.

High glyphosate-based herbicide exposure appears to raise NHL risk through genotoxic, immune, and formulation-related mechanisms. The evidence does not identify one proven mechanism, but it repeatedly points to DNA damage, oxidative stress, immune dysregulation, and possibly endocrine effects, with stronger concern for heavily exposed applicators using formulated products rather than the general population. Genotoxicity is the most consistently proposed mechanism: reviews report that glyphosate and glyphosate-based formulations damage human lymphocytes, the normal cell of origin for NHL.

References 368-370.

PFAS “Forever Chemicals” Carcinogen Classification

> *“In late 2023, the International Agency of Research on Cancer officially upgraded these forever chemicals, which are used in nonstick pans and food packaging, to a grade one carcinogen in humans. Cancer-causing in humans based on strong mechanistic evidence that it induces epigenetic, which is gene alterations and suppresses the immune system.”*

In 2023, IARC classified PFOA, a type of PFAS ('forever chemical'), as a Group 1 carcinogen. The decision was based on limited evidence of cancer in humans, sufficient evidence in experimental animals, and strong mechanistic evidence, including immune suppression and other biological effects associated with carcinogenesis. PFOS was classified separately as possibly carcinogenic (Group 2B).

References 371, 372.

Arsenic and Cadmium in Public Water Supplies

> *“Heavy metals are found in local water supplies to run off and ultimately are carcinogenic in some cases. The [IARC] classifies arsenic and [cadmium] as Group one carcinogenic, and they're frequently found in unfiltered public water infrastructure.”*

Runoff is a well-supported source of heavy metals in local supplies, not a complete explanation. Heavy metals in runoff have been measured from mining areas, residential areas, trafficked roads, roofs, surface runoff, storm collectors, and snowmelt, with downstream receiving waters sometimes showing higher concentrations. Urban runoff often becomes more contaminated as water moves across built surfaces. Storm collector samples had the highest metal concentrations in one urban catchment, and street runoff can contain 2-15 times more heavy metals than roof runoff. Traffic intensity, atmospheric deposition, and longer dry periods before rain all increase runoff metal loads.

Arsenic in drinking water comes from both natural geologic sources and human activities. Reviews identify weathering, rock abrasion, and volcanism as natural inputs, while mining, industrial effluents, municipal wastewater, and agricultural chemicals are major anthropogenic sources. A major arsenic pathway is groundwater mobilisation from local geology. In the Bengal basin, installing boreholes changed local geochemistry and mobilised arsenic into groundwater used for drinking.

Other papers link arsenic to mining and industrial activities, dust deposition, domestic sewage, and industrial discharges, especially in contaminated river corridors.

Cadmium in drinking water is more consistently tied to anthropogenic sources. Across reviews and field studies, the main reported sources are phosphate fertilizers, pesticide use, mining, industrial activities, textile and tannery effluents, traffic-related runoff, and infiltration of industrial effluents and agricultural runoff.

In regulated public systems, the evidence points to occasional arsenic exceedance and rare cadmium exceedance, not frequent contamination. The strongest quantitative US data show arsenic exceeded the MCL in 2.6% of community water systems, while other metals in that analysis were below 0.1%; cadmium was not among the commonly detected metals there. The main settings where arsenic and cadmium are often found are groundwater wells and private or unregulated supplies, especially geogenic arsenic hotspots, not typical regulated network water.

In the United States, arsenic is the relevant regulated-public-supply metal of concern, but it is still uncommon at the system level. Across 37,915 community water systems, 2.6% exceeded the arsenic MCL, and less than 0.1% exceeded the MCL for the other metals analysed. A second national US analysis found arsenic MCL exceedance fell from 1.5% of CWSs in 2006–2008 to under 1% in 2009–2011, with persistent problems concentrated in small, groundwater-fed Southwestern systems.

In the UK, public supplies are described as highly regulated with outstanding compliance for arsenic at the 10 µg/L standard, although many supplies still contain low, sub-regulatory arsenic concentrations. Detailed estimates suggest about 130,000 consumers received water at or above 5 µg/L, 1.08 million at or above 2 µg/L, and 9.75 million at or above 1 µg/L.

For the EU, the supplied evidence supports a 10 µg/L arsenic standard and identifies regional hotspots such as Hungary, Serbia, and Romania, including one Hungarian dataset where 20% of samples exceeded 10 µg/L, but it does not support a claim that regulated EU public supplies in general are frequently contaminated.

The International Agency for Research on Cancer (IARC) classifies arsenic and inorganic arsenic compounds, and cadmium and cadmium compounds, as Group 1 carcinogens (carcinogenic to humans).

References 373-387.

ACS 2026 Cancer Incidence and Mortality Projections

> *"The American Cancer Society recently released its latest projections for '25 and '26… the ACS projects over 2.11 million new cancer diagnoses in 2026. This translates roughly to 5800 new cases every single day. Approximately 626,000 Americans are expected to die from cancer in 2026, right about 1700 deaths per day."*

Reference 388.

Lung Cancer as the Leading Cause of Cancer Death

> *"Lung cancer remains the leading cause of cancer death, projected to cause more fatalities than colorectal and pancreatic cancer combined."*

Lung cancer remains the leading cause of cancer death in the United States across recent annual statistics and future projections to 2030-2040. In the United States in 2026, lung cancer is projected to kill more people than colorectal and pancreatic cancers combined. Globally, lung cancer is the leading cause of cancer death across GLOBOCAN-based estimates from 2018, 2020, and 2022.

References 389-395.

Nuclear Transfer Experiments

> *"Then you take the nucleus of the normal cell and put it into the cytoplasm of a tumor cell. And you get dysregulated cell growth." – Thomas Seyfried, in response to Steven: "So it must be something other than the nucleus." – "Yes. The mitochondria."*

Israel and Schaeffer's 1988 study was a cell-fusion (cybrid) experiment investigating the relative contributions of the nucleus and cytoplasm to malignant behaviour. The authors tested whether cytoplasm from transformed cells could induce or maintain malignancy by creating cybrid

clones and reconstructed cells with different combinations of normal and transformed nuclei and cytoplasm.

Cybrids produced by fusing transformed-cell cytoplasts (enucleated cells) with normal whole cells formed tumours in 17% of injected animals, indicating that tumour cytoplasm alone was not sufficient to produce a robust or highly penetrant malignant phenotype. In contrast, reconstructed cells created by combining transformed-cell cytoplasts with normal-cell karyoplasts (nucleus plus a thin rim of surrounding cytoplasm) formed tumours in 97% of animals, demonstrating a much stronger malignant phenotype in that specific cellular configuration.

The findings are best interpreted alongside the authors' earlier 1987 study. There, transferring normal cytoplasm into transformed cells reduced tumour formation from 92% in the parental transformed line to 51% in the resulting cybrids, and animals that did develop tumours survived longer. The authors also reported that when virtually all of the cytoplasm was derived from the normal cell, the tumorigenic phenotype was abolished. Together, these studies indicate that the cytoplasm can both promote and suppress malignant behaviour, depending on the direction and extent of cytoplasmic transfer, rather than demonstrating that tumour cytoplasm, or mitochondria specifically, is by itself sufficient to convert a normal nucleus into a cancer cell.

In Koura et al. (1982), adding non-tumourigenic rat cytoplasm to highly tumourigenic melanoma-derived nuclear material initially suppressed tumourigenicity rather than promoting it. Koura et al. (1982) supports a more nuanced view: cytoplasm can strongly modulate malignant behaviour, but the effect can be temporary and context-dependent.

References 396-398.

Ketogenic Diet Plus Hyperbaric Oxygen in Mouse Models

“There was a study in 2013 that demonstrated that one of the ketogenic diet alone significantly slowed tumour growth in systemic metastatic cancer mouse models; combining the diet with hyperbaric oxygen therapy elicited a profound synergistic decrease in tumor growth and drastically increased survival times.” “We published that paper with Dominic… hyperbaric oxygen will create oxidative stress in cells that do not have efficient oxidative phosphorylation.”

This was a preclinical mouse study using the luciferase-tagged VM-M3 model of systemic metastatic cancer in immunocompetent VM/Dk mice. Forty adult male mice were randomised at tumour inoculation into four groups: standard diet, standard diet plus hyperbaric oxygen, ketogenic diet, or ketogenic diet plus hyperbaric oxygen. Hyperbaric oxygen was delivered as 100% oxygen at 2.5 ATA for 90 minutes, three times weekly, and tumour progression was tracked by in vivo bioluminescent imaging.

Main Findings

- The ketogenic diet alone increased mean survival from 31.2 to about 48.9 days, a 56.7% rise.
- A combined ketogenic diet plus hyperbaric oxygen increased mean survival by about 24 days, a 77.9% rise versus controls.
- The combination group showed significantly lower tumour bioluminescence by week 3, consistent with slower tumour growth.

Limitations

The evidence is limited to one mouse model, so it does not establish efficacy in humans. Mice on the ketogenic diet lost about 10% body weight by day 7, which makes it hard to separate effects of ketosis from possible inadvertent calorie restriction or reduced diet palatability. Hyperbaric oxygen alone did not improve the outcome in this model, so the “synergy” claim is specific to the combination and this experimental setting.

Reference 399.

Mebendazole as a Metabolic Anti-Cancer Therapy

> *"I've looked at one and that's mebendazole. How did I come to that realisation? People knew that mebendazole had some therapeutic benefit against cancer, but they don't believe it until you show the mechanism. That paper shows the mechanism. It targets glucose and glutamine. ... This one targets glucose and glutamine, the two fuels driving the dysregulated growth of the tumour. ... You have to block glycolysis and glutaminolysis. You have to restrict the availability of glucose and glutamine together at the same time. ... The cancer field doesn't understand that the cancer can't grow without glucose and glutamine, and can't switch to fatty acids or ketone bodies."*

Mebendazole appears to affect cancer through direct cytotoxicity, anti-angiogenesis, anti-metastatic activity, immune modulation, and several signalling and metabolic pathways, with the strongest evidence still coming from cell and animal models rather than controlled clinical trials.

Mebendazole inhibits tumour growth across multiple preclinical cancer models and can improve survival in some xenograft systems, including medulloblastoma, adrenocortical cancer, ovarian cancer, hepatocellular carcinoma, breast cancer, and AML. Mebendazole disrupts microtubules, causing G2/M arrest and apoptosis, a mechanism reported across lung, breast, colon, ovarian, gastric, TNBC, and AML models.

Human evidence is early: phase I glioma studies and small clinical observations suggest safety and possible activity, but the literature repeatedly calls for controlled trials before routine oncology use.

Mechanisms

Mebendazole's best-supported mechanism is tubulin interference, which destabilises microtubules, drives mitotic arrest, and triggers classical apoptosis with caspase activation, mitochondrial dysfunction, and DNA fragmentation. Beyond that core effect, the mechanistic literature is broad and increasingly tumour-specific.

Mebendazole appears to target glucose metabolism more directly and more consistently. In gastric cancer cells, it altered mRNA expression of glycolytic genes, including SLC2A1, HK1, GAPDH, and LDHA. The same study also reported altered glucose uptake, LDH activity, and ATP production, which ties the transcriptional changes to functional metabolic effects.

Evidence for glutamine targeting is more limited but more explicit in one model. In VM-M3 glioma cells and juvenile mouse tumours, mebendazole was reported to inhibit glutaminolysis as well as glycolysis. That study also reported higher intracellular glutamine, lower glutamate, lower succinate-pathway metabolites after treatment, and reduced glutaminase C expression in vivo, all consistent with restricted glutamine use.

References 400-413.

Stem Cell Tumors and Metastatic Potential

> *“Stem cell tumors cannot metastasize. How do I know? Because I have stem cell tumors diagnosed as stem cell tumors with stem cell markers. I've grown them. They grow very angry. They get a lot of blood vessels, but they can't spread.”*

Cancer stem cells (CSC) are linked to metastasis across many reviews, which describe them as cells responsible for tumour progression, dissemination, metastatic outgrowth, and recurrence. Stemness and plasticity help metastatic success by supporting self-renewal, dormancy, adaptation, and colonisation in distant tissues. Direct proof of exactly which CSCs seed metastases remains incomplete in some settings, and marker-based associations do not by themselves prove metastatic function.

Notes:

- “Stem cell tumours" is imprecise; the papers mainly discuss cancer stem cells within tumours, not a universal class of tumours that arise from stem cells.
- Evidence is strongest that stem-like tumour subpopulations contribute to metastasis, not that every stem-like cell metastasises.
- Some stem-cell-related contexts are mixed, such as mesenchymal stem cells, which can promote or suppress tumour progression depending on context.

References 414-420.

Nutritional Ketosis and Enhanced Chemotherapy Drug Delivery

> *"If you put the patient in nutritional ketosis, the ketogenic state of nutritional ketosis facilitates the delivery of drugs to the tumour cell. It actually means you can use lower doses of drugs, and… you get a bigger effect. The therapeutic benefit increases with lower dosing.”*

No strong clinical proof of dose de-escalation appears in the human literature; reviews consistently say clinical evidence is lacking, inconclusive, or based on low-quality, heterogeneous studies rather than trials designed to show reduced chemo- or radiotherapy dosing is safe.

Ketogenic diets might enhance standard therapy in some settings, but this is supported much more strongly by preclinical work and early outcome signals than by definitive patient trials. Human trials mostly evaluate feasibility and tolerability, and some report poor adherence or toxicities during concurrent chemoradiation, which cuts against claims of established safe de-escalation.

Some patient studies do show promising signals. A randomised breast cancer trial during chemotherapy reported reduced tumour size and downstaging in locally advanced disease but not better response in metastatic disease, and it did not study dose reduction. A recent glioblastoma phase 1 trial found the diet safe and feasible during standard chemoradiation, with stable or improved quality-of-life measures, but it was single-arm and aimed at safety rather than de-escalation.

Other trials make the limitation clearer. In head and neck cancer, only 4 of 12 patients completed 5 weeks of ketogenic diet during chemoradiation, and 3 were removed for dose-limiting toxicities, including grade 4 hyperuricemia and grade 3 pancreatitis. Earlier lung and pancreatic phase 1 trials also found poor compliance and poor tolerance during concurrent chemoradiation, with no observed PFS or OS difference by diet completion status.

References 421-430.

Trudy DuPont and Pablo Kelly

> *"There was a woman, an American woman, a lawyer, Trudy DuPont, who… developed a kind of a brain stem tumor… Trudy wanted to use this metabolic therapy. She stayed alive much longer[,] over ten years… She eventually passed away."*
>
> *"People like Pablo Kelly from Devon, England. He had the glioblastoma. He didn't take any radiation or chemo. He just did metabolic therapy. He lived for ten years. He was diagnosed with an inoperable glioblastoma… He lived with it for ten years, had a couple of kids. He died from a cerebral hemorrhage on the last day of a debulking surgery. He never died from the tumor."*

Case reports provide valuable clinical observations, but they cannot establish that a treatment worked because there is no comparison group and many other factors could explain the outcome.

Meal Replacement Shakes in Standard Cancer Nutrition Care

> *"Patients are frequently told to eat whatever they can and eat whatever they can keep down. It is incredibly common for cancer patients to be handed meal replacement shakes, which are often packed with corn syrups and refined sugars, ice cream, and high-carbohydrate comfort foods just to keep their calorific intake up."*

Clinical nutrition guidelines recommend that all cancer patients be screened for malnutrition and offered nutrition interventions as needed across the disease course. That broad recommendation exists because malnutrition and muscle loss are frequent in cancer and worsen outcomes.

The products themselves are also described as routine parts of practice and the commercial nutrition market for oncology, often as milkshake-like oral supplements or modified-texture products. In a 2025 cross-sectional study of 201 chemotherapy patients, 78.1% had previously used medical foods, and 87.5% understood them as supplements to main meals rather than full replacements.

This does not mean every cancer patient is simply handed shakes by default; the evidence repeatedly frames them as targeted support for patients with inadequate intake, weight loss, cachexia risk, surgery recovery, or chemotherapy-related eating problems. Evidence for benefit is generally positive but not uniform, with some reviews finding mixed effects on body weight, BMI, PG-SGA, survival, or adherence depending on population and study quality.

Some studies also suggest a practical limit: supplements are often well tolerated and feasible, but nutrition alone may not reverse cachexia, especially in advanced disease. So the best-supported answer is that meal replacement shakes are indeed very common in oncology nutrition care, especially for patients at nutritional risk, but they are usually one part of a broader, staged supportive-care strategy rather than a one-size-fits-all standard for every patient..

References 431-440.

Oncologist Attitudes Toward the Ketogenic Diet and Cachexia

> *"The vast majority of mainstream oncologists do not recommend the ketogenic diet to… newly diagnosed patients. In fact, if a patient brings it up, many doctors will actively advise against it… the fear of [cachexia]… is a massive problem and a leading cause of mortality in cancer patients because the ketogenic diet suppresses appetite and often leads to weight loss, and oncologists are terrified that a strict keto diet will accelerate [cachexia] and weaken the patient."*

Reviews consistently conclude that mainstream oncology guidelines do not recommend ketogenic diets because clinical efficacy remains unproven, adherence is often poor, and weight loss can be concerning in patients already at risk for malnutrition or cachexia.

Weight loss is common during ketogenic diets in cancer studies, which raises legitimate concern for patients with malnutrition, sarcopenia, or cachexia risk. Acceleration of cachexia is not established; several studies found weight loss came mainly from fat mass with relative lean-mass preservation, especially in selected or overweight patients under monitoring.

The most evidence-backed reason oncologists hesitate is lack of proven efficacy, not a demonstrated consensus that ketogenic diets directly worsen cachexia. Multiple reviews found no conclusive evidence for improved survival, anti-tumour effects, or broad quality-of-life benefit, and they call for larger controlled trials before recommending ketogenic diets to most cancer patients.

Concern about cachexia is still evidence-based because weight loss repeatedly occurs on ketogenic diets in cancer cohorts, and low palatability, nausea, constipation, fatigue, and appetite loss can reduce intake and adherence. Reviews explicitly warn that in patients with increased risk of cancer cachexia, ketogenic diets can be detrimental and should raise serious safety concerns.

Important Nuance

- Weight loss does not always equal cachexia; several reports found greater fat loss than fat-free-mass loss, making interpretation dependent on body composition, cancer type, and stage.
- In overweight patients, moderate weight loss during ketogenic diets was sometimes judged non-detrimental because lean tissue was preserved and loss was not greater than control diets.

- In advanced pancreatic or lung cancer, the same weight loss is more concerning because lean-mass loss and cachexia are harder to exclude clinically.
- Some supervised trials found ketogenic diets feasible and safe with no severe diet-related events or excessive weight loss, including advanced cancer and newly diagnosed glioblastoma cohorts.

References 441-451.

Maternal Inheritance of Mitochondria

> *"All of the mitochondria for the developing embryo are in the cytoplasm from the mother… The egg. We have a cell and you have a nucleus and you have the cytoplasm… I'm saying the mitochondria are not in the nucleus. They're in the cytosol."*

The embryo's mtDNA is maternal in origin in most animals, including humans, and is transmitted through the oocyte cytoplasm. The oocyte supplies the main mitochondrial pool used in early development, with very high mtDNA copy number and no increase in mitochondrial number during early cleavage.

References 452-454.

Carnitine Deficiency and Ketone Body Production

> *"Some people have carnitine deficiencies. Carnitine prevents fatty acids from being made into ketone bodies. So… Carnitine supplementation can help them. But you need a physician to know this."*

Carnitine supplementation does help some people with carnitine deficiencies, especially those with primary carnitine deficiency and some well-defined secondary deficiencies such as dialysis-related deficiency, but it is not uniformly effective across all disorders with low carnitine, and the mechanism is that carnitine enables mitochondrial fatty-acid oxidation rather than preventing ketone formation.

Carnitine's main role here is to enable mitochondrial entry of long-chain fatty acids, so when carnitine is low, fewer long-chain fatty acids reach hepatic β-oxidation and less acetyl-CoA is available for ketogenesis. Ketone bodies are then made downstream from β-oxidation-derived acetyl-CoA in liver mitochondria, so blocking fatty-acid entry upstream reduces ketone production rather than increasing it.

References 455-459.

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