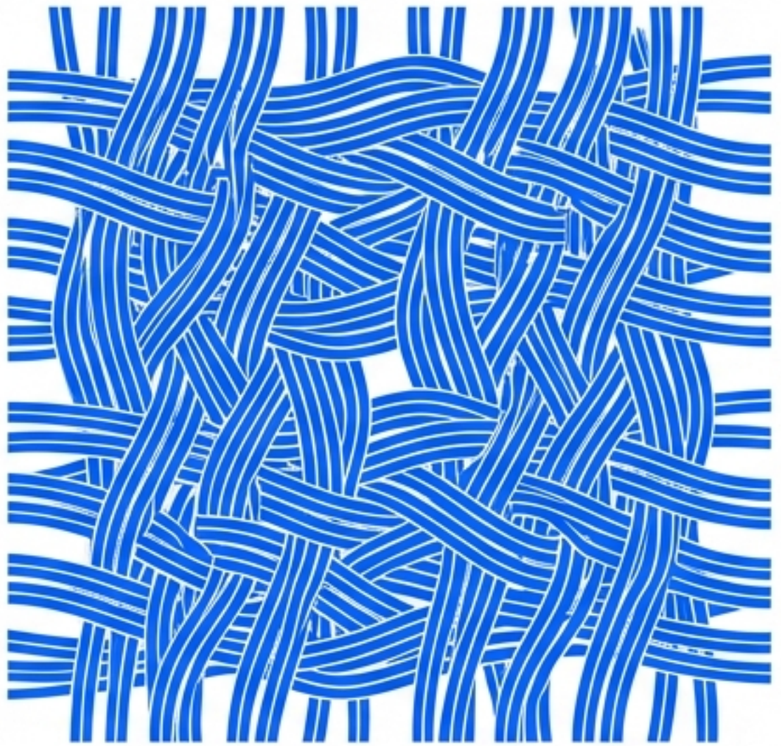
Mechanisms of Cellular Injury

From the chaos of unpaired electrons to the architecture of misfolded proteins.

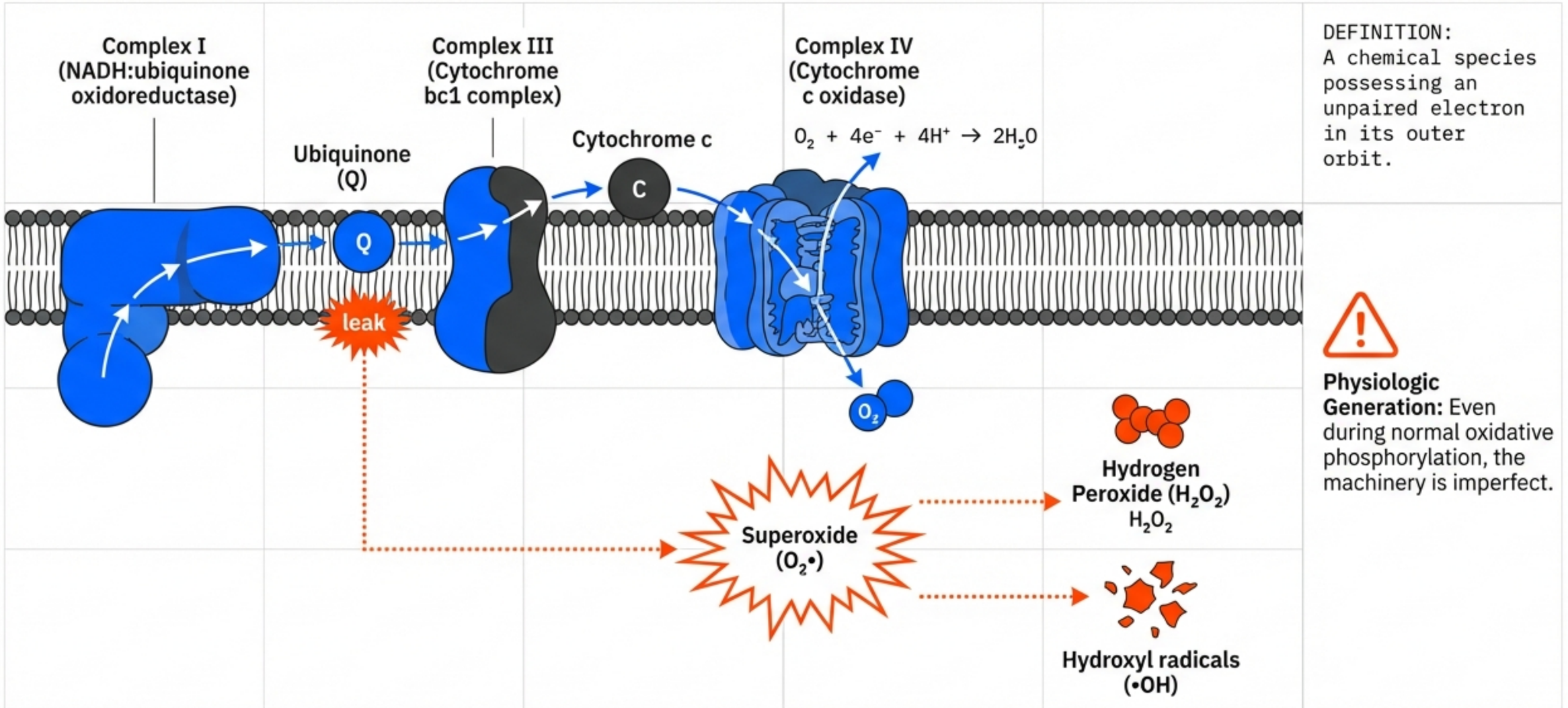


Acute Chemical Instability: Free Radicals oxidize and degrade cellular machinery.

Chronic Structural Failure: Amyloidosis aggregates physically obstruct tissue function.

NotebookLM

The Anatomy of a Free Radical

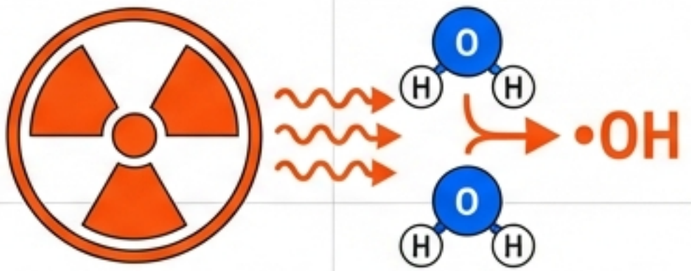


DEFINITION:
A chemical species possessing an unpaired electron in its outer orbit.

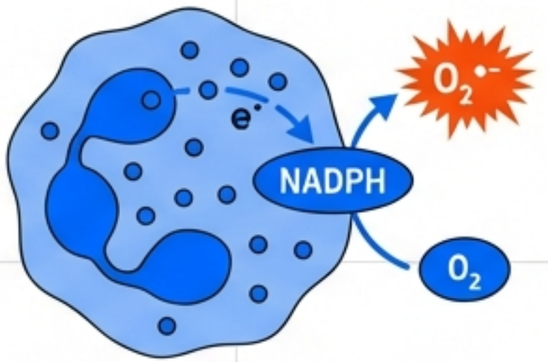
Physiologic Generation: Even during normal oxidative phosphorylation, the machinery is imperfect.

NotebookLM

Sources of the Spark: Pathologic Generation

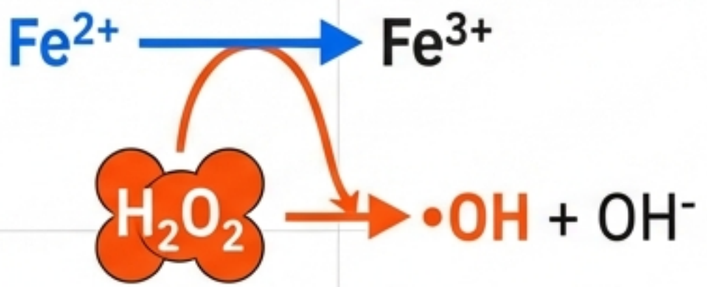


Ionizing Radiation.
Water hydrolysis yields Hydroxyl radical (•OH).

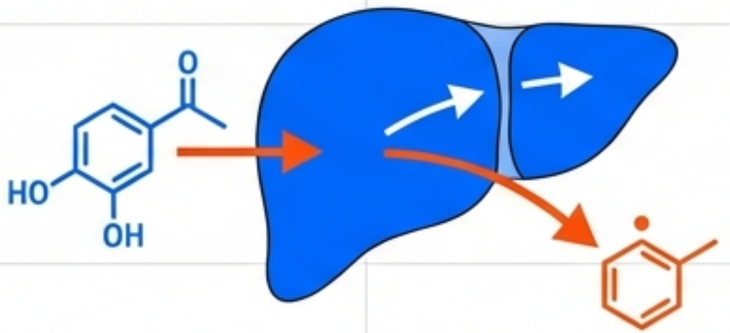


Neutrophil

Inflammation.
NADPH oxidase generates superoxide during oxygen-dependent killing.



Metals.
The Fenton Reaction.
Iron and Copper generate Hydroxyl radicals.



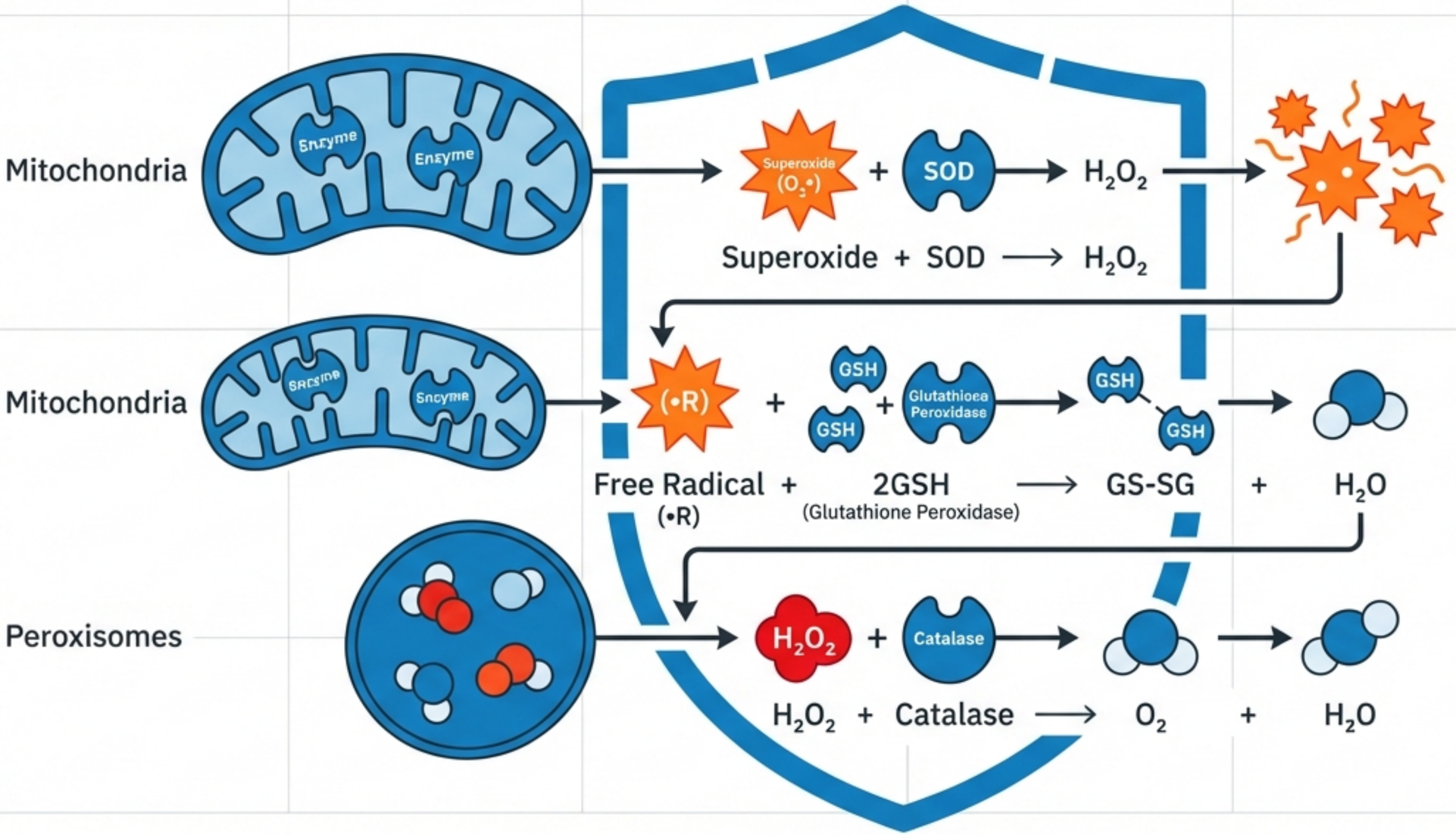
Drugs & Chemicals.
P450 system metabolizes drugs (e.g., Acetaminophen), releasing radical byproducts.

Consequence: Peroxidation of lipids, oxidation of DNA, and oncogenesis.

NotebookLM

A Modern Medical Atlas

Cellular Defenses and Neutralization



The Carriers

Transferrin & **Ceruloplasmin** sequester iron/copper to prevent Fenton reactions.

The Scavengers

Vitamins A, C, and E directly neutralize radicals.

NotebookLM

Case Study: Carbon Tetrachloride (CCl_4) Toxicity

Input

CCl_4
(Dry Cleaning Solvent)

Conversion

P450 System creates
CCl_3 radical

Injury

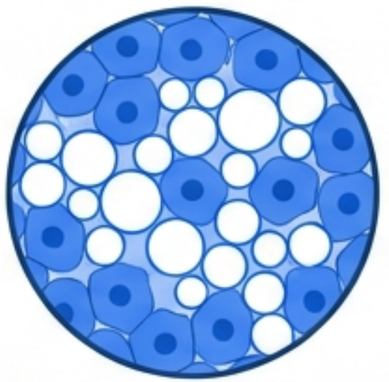
RER Swelling

Mechanism

Ribosome detachment halts protein synthesis

Result

Fatty Change (Steatosis)

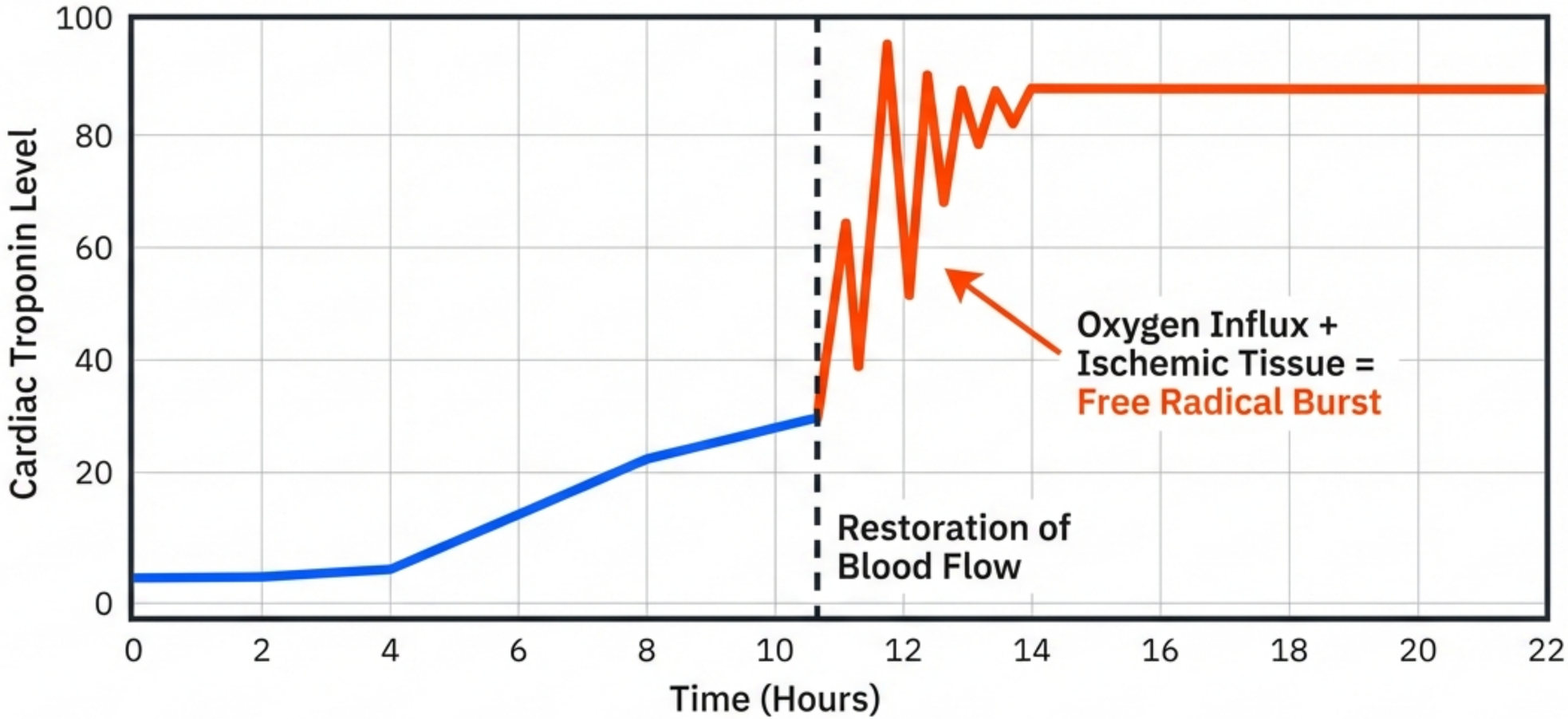


Histology: Fatty Change

IBM Plex Mono

NotebookLM

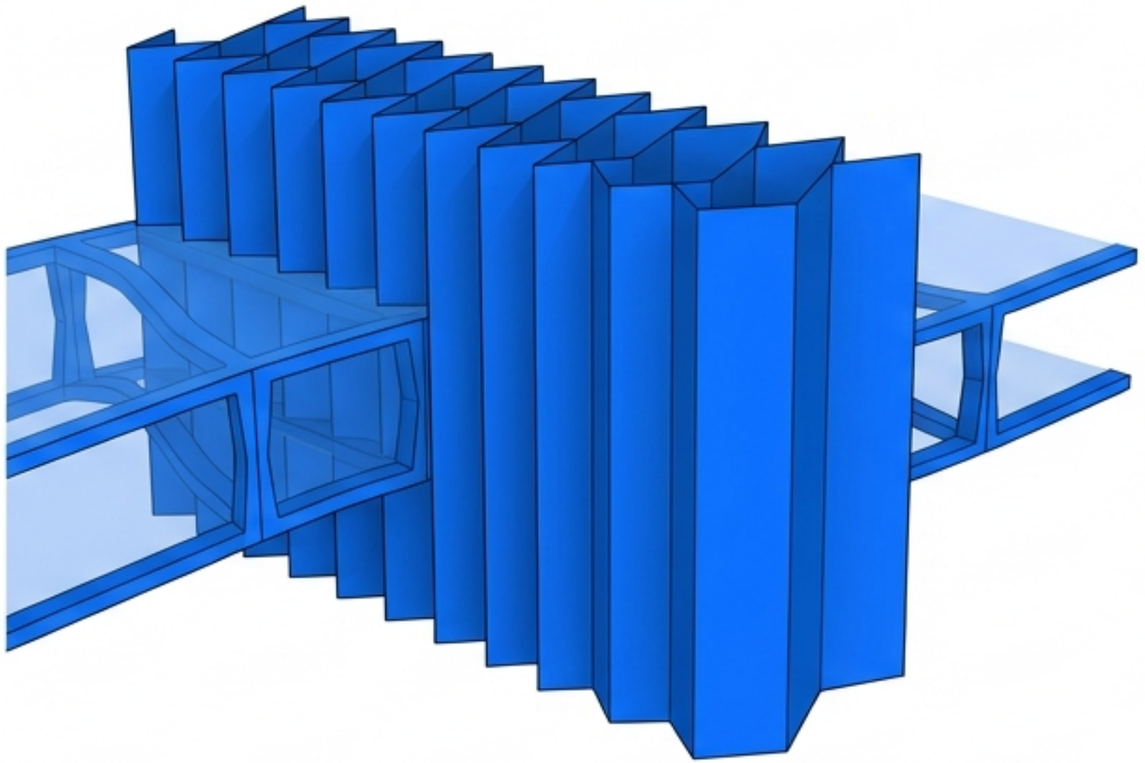
The Reperfusion Paradox



Paradox: Restoring blood flow introduces O2 to damaged tissue, fueling a second wave of injury via free radicals. This causes continued myocardial damage despite successful reperfusion.

NotebookLM

The Architecture of Failure: Amyloidosis



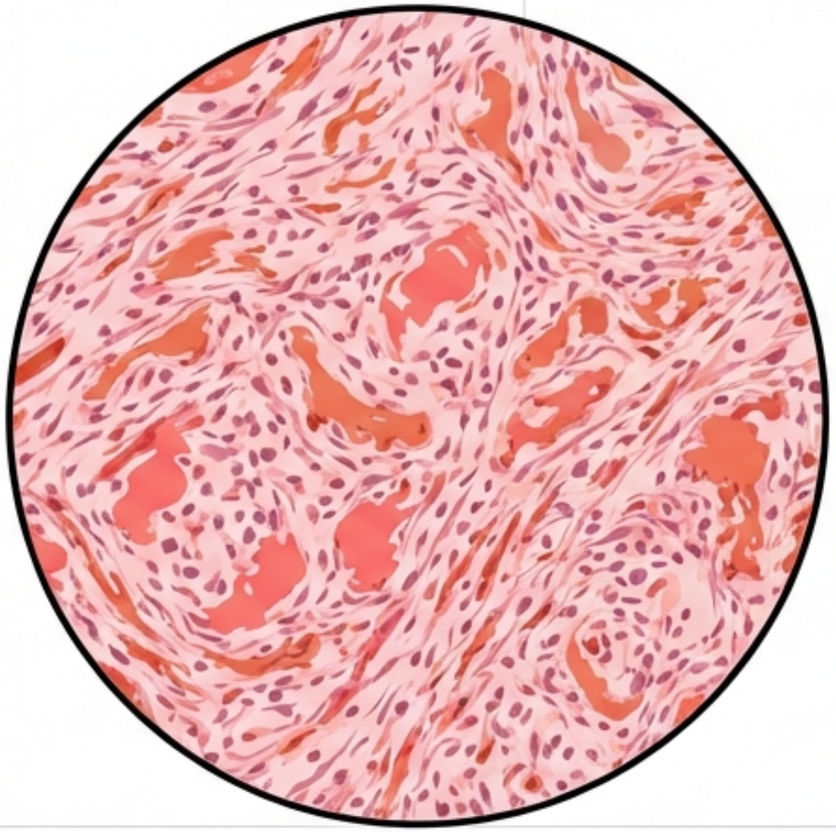
3D Structural Schematic: Beta-pleated Sheet obstructing cellular channel.

- **Definition:** Amyloid is not a single disease. It is a shared structural configuration of misfolded proteins that deposit in extracellular space.
- **The Unifying Feature:** Regardless of the precursor protein, all amyloid forms Beta-pleated sheets.
- **Mechanism:** These sheets aggregate to form insoluble fibrils that physically damage and obstruct tissue.

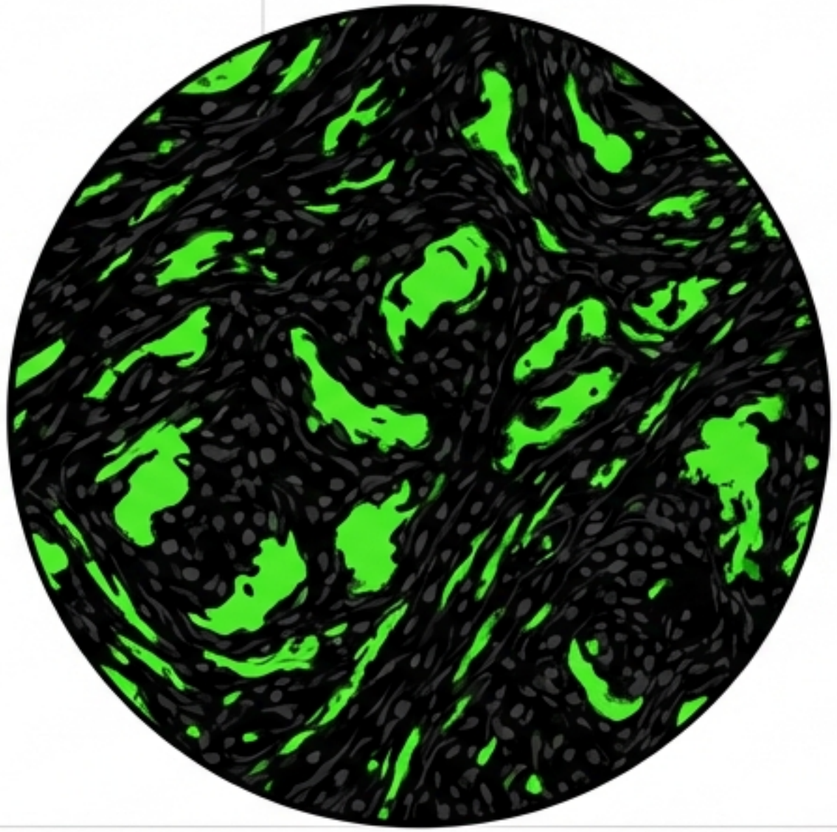
NotebookLM

The Diagnostic Standard

Congo Red Stain



Polarized Light

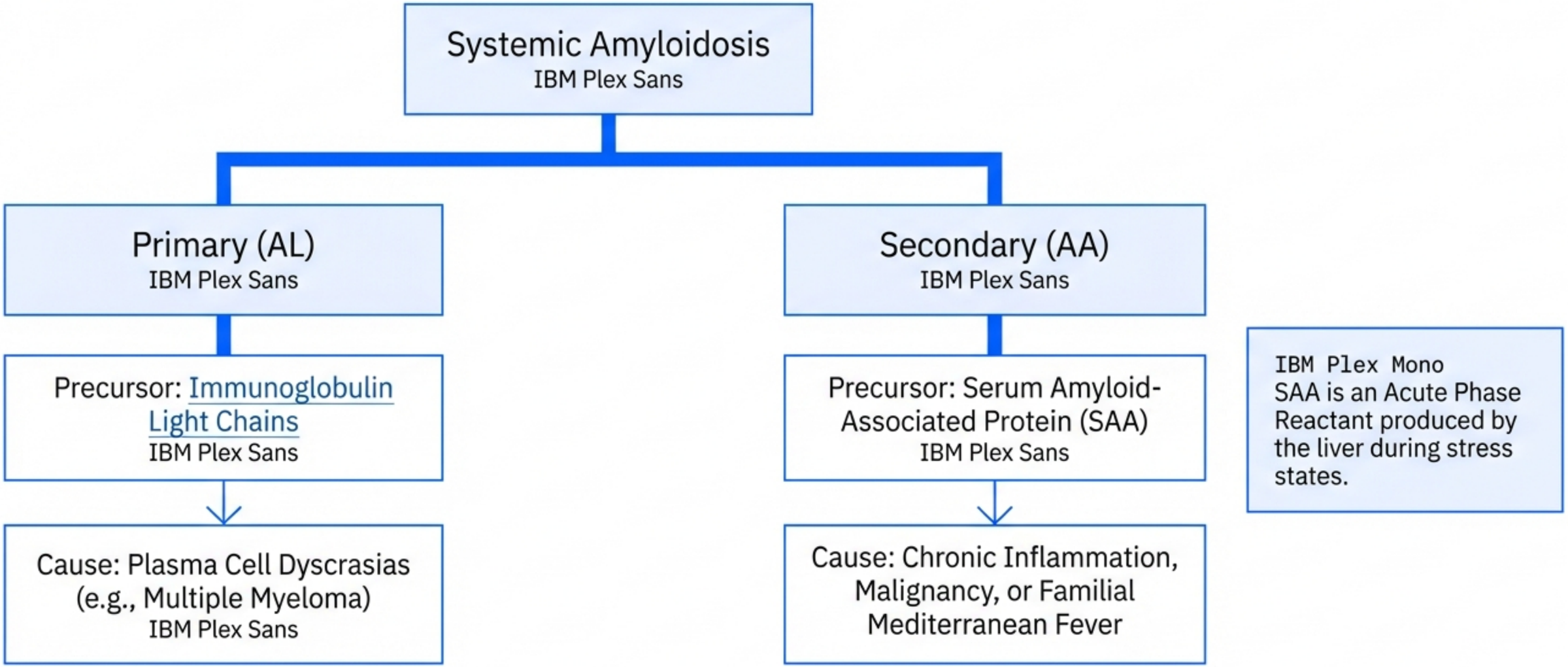


Apple-Green Birefringence in IBM Plex Mono

This optical property is the universal identifier for amyloid. Any protein depositing in a Beta-pleated sheet configuration will show this specific green glow under polarized light.

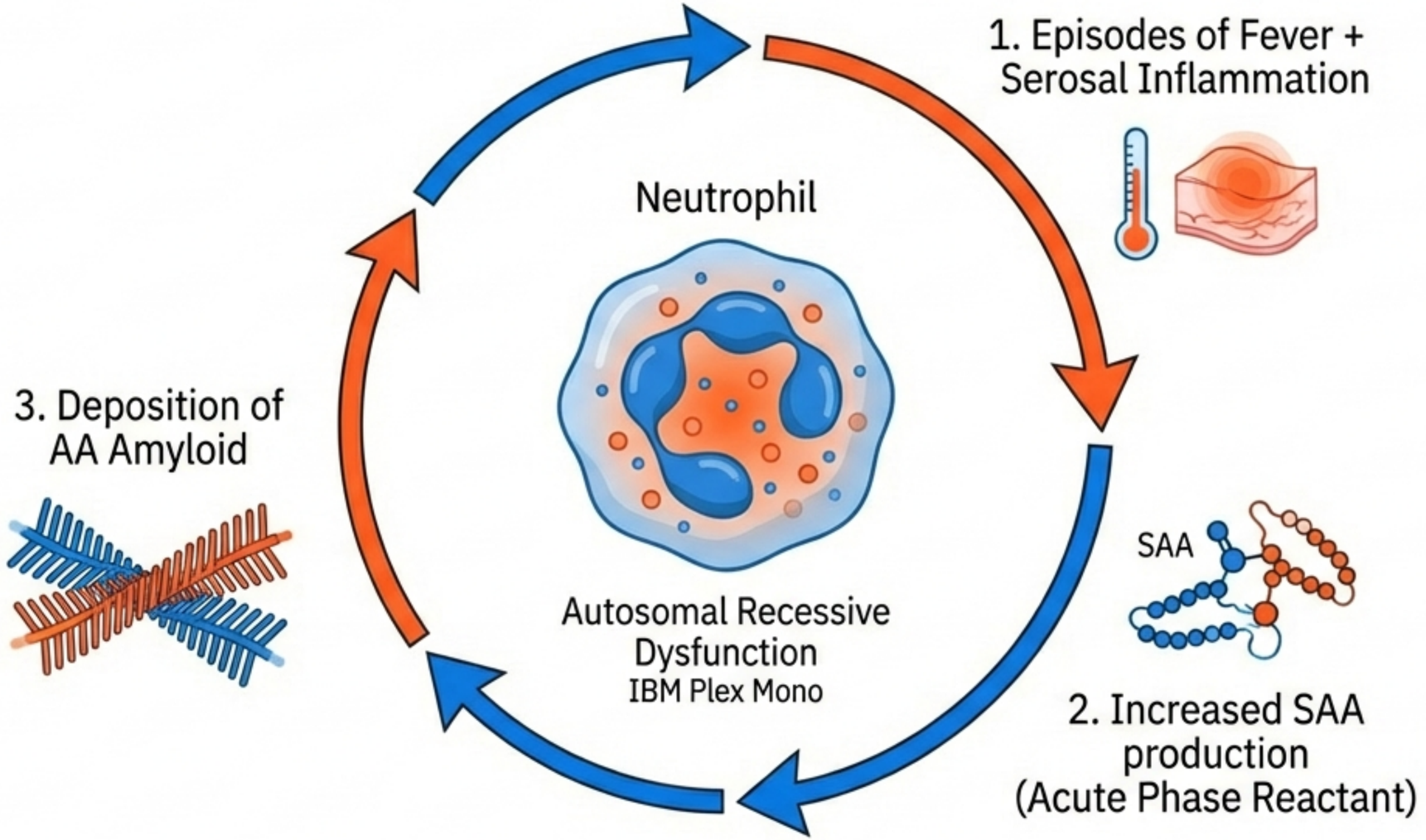
NotebookLM

Helvetica Now Display: Systemic Amyloidosis Classifications



NotebookLM

Helvetica Now Display:
Secondary Amyloidosis & Familial Mediterranean Fever



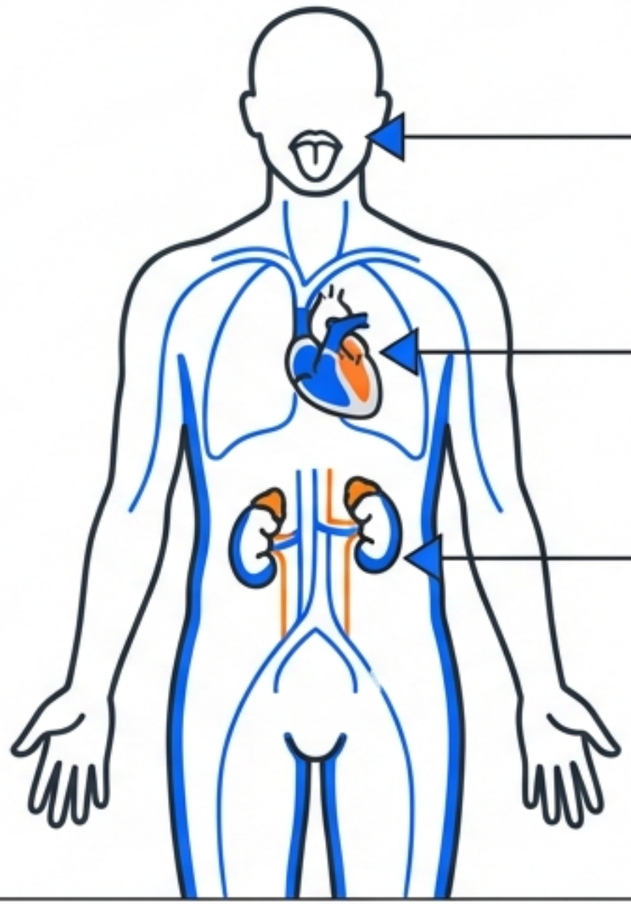
Clinical Presentation: Mimics appendicitis, arthritis, or myocardial infarction.

Demographic note: Primarily affects populations of Mediterranean origin.

NotebookLM

Modern Medical Atlas

Clinical Manifestations: The Great Imitator



Macroglossia

Enlargement of the tongue; malabsorption.

Restrictive Cardiomyopathy

Stiffening of heart muscle, arrhythmia.

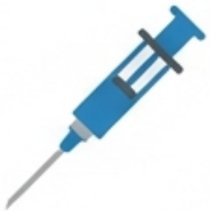
Nephrotic Syndrome

Most common organ involved. Filtration failure.

Clinical findings are diverse because almost any tissue can be infiltrated.

NotebookLM

Modern Medical Atlas: Diagnosis and Prognosis



Biopsy Target

Abdominal Fat Pad or Rectum are preferred accessible targets.

Confirmation

Must show **Apple-Green Birefringence** under **polarized light**.

Treatment

Amyloid cannot be removed.

Outcome

Damaged organs require transplantation.

NotebookLM

Localized Variations: Cardiac & Pancreatic

Senile Cardiac Amyloidosis

Protein:
Non-mutated Serum Transthyretin

Demographics:
25% of individuals >80 years old

Status:
Usually Asymptomatic

Familial Amyloid Cardiomyopathy

Protein:
Mutated Serum Transthyretin

Demographics:
5% of African Americans carry the gene

Status:
Restrictive Cardiomyopathy

Type II Diabetes

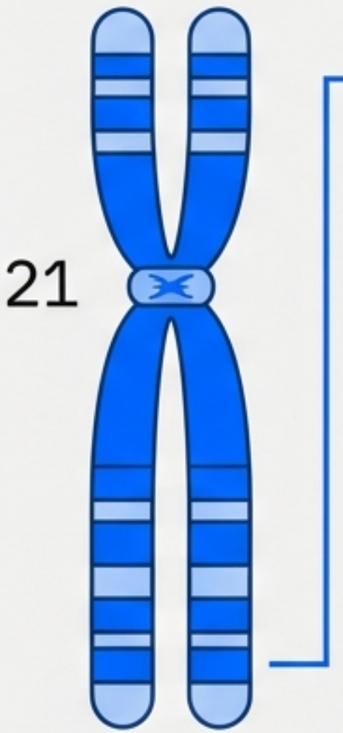
Protein:
Amylin (Insulin derivative)

Location:
Islets of the Pancreas

NotebookLM

Localized Variations: Neurological & Endocrine

Alzheimer Disease

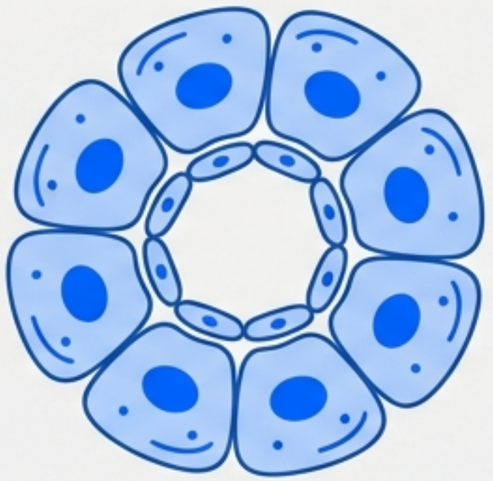


Protein: **A-Beta Amyloid** (from Beta-APP).

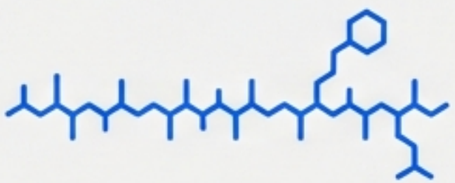
Gene for **Beta-APP** is on **Chromosome 21**. **Down Syndrome** (**Trisomy 21**) leads to **early-onset Alzheimer's** by age 40.

IBM Plex Mono

Medullary Thyroid Carcinoma



Protein: **Calcitonin**.



Tumor cells produce **Calcitonin** which deposits within the **tumor stroma**.

NotebookLM

Summary: Precursors and Pathology

Condition	Precursor Protein	Pathology/Notes
Systemic Primary	Immunoglobulin Light Chain	**AL Amyloid** (Multiple Myeloma)
Systemic Secondary	SAA (Acute Phase Reactant)	**AA Amyloid** (Inflammation/FMF)
Senile Cardiac	Non-mutated Transthyretin	Asymptomatic in elderly
Familial Cardiac	Mutated Transthyretin	**Restrictive Cardiomyopathy**
Type II Diabetes	Amylin	Pancreatic Islet deposition
Alzheimer Disease	A-Beta Amyloid	**Gene on Ch21** (Down Syndrome link)
Dialysis-Associated	Beta2-microglobulin	Deposits in joints
Medullary Thyroid Ca	Calcitonin	Tumor stroma deposition

NotebookLM