STORAGE DISEASES

Metabolic derangement in cells causes abnormal accumulation of various substances

For didactic use only

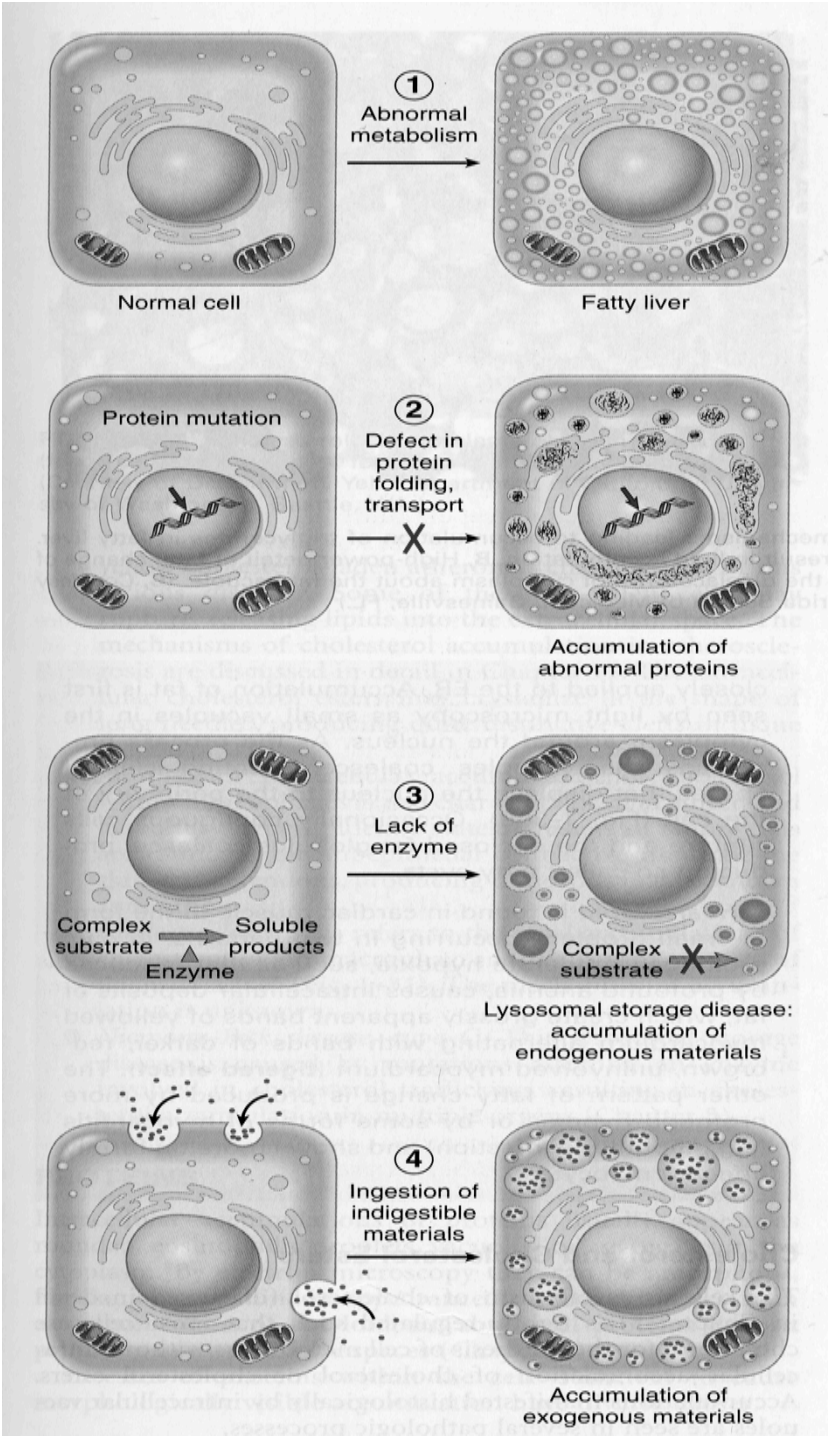
Four different mechanism of intracellular accumulation

1. Inadequate rate of metabolism

2. Inability to degrade misfolded or untransportable protein

3. Inherited gene defect of a specific enzyme

4. Non-metabolizable chemical



STORAGE DISEASES

Regressive processes of the cell

STEATOSIS

GLICOGENOSIS

LISOSOMIAL DEFICIENCY

Regressive processes of the extracellular matrix

AMYLOIDOISIS

FIBROSIS

COLLAGENOPATHY

Steatosis

- Abnormal accumulation of triglicerides in parenchymal cells.
- Principal target organ: LIVER.
- Extraepatic steatosis: less frequent and due to reduced Oxygen level in kideny and myocardium.
- Reversible damage.
- Steatosis does not include increased fat quantity in adipocytes or enrollment of new cells in the pool.
- Genetically determined Steatosis are: Wolman Disease and abetalipoproteinemia.

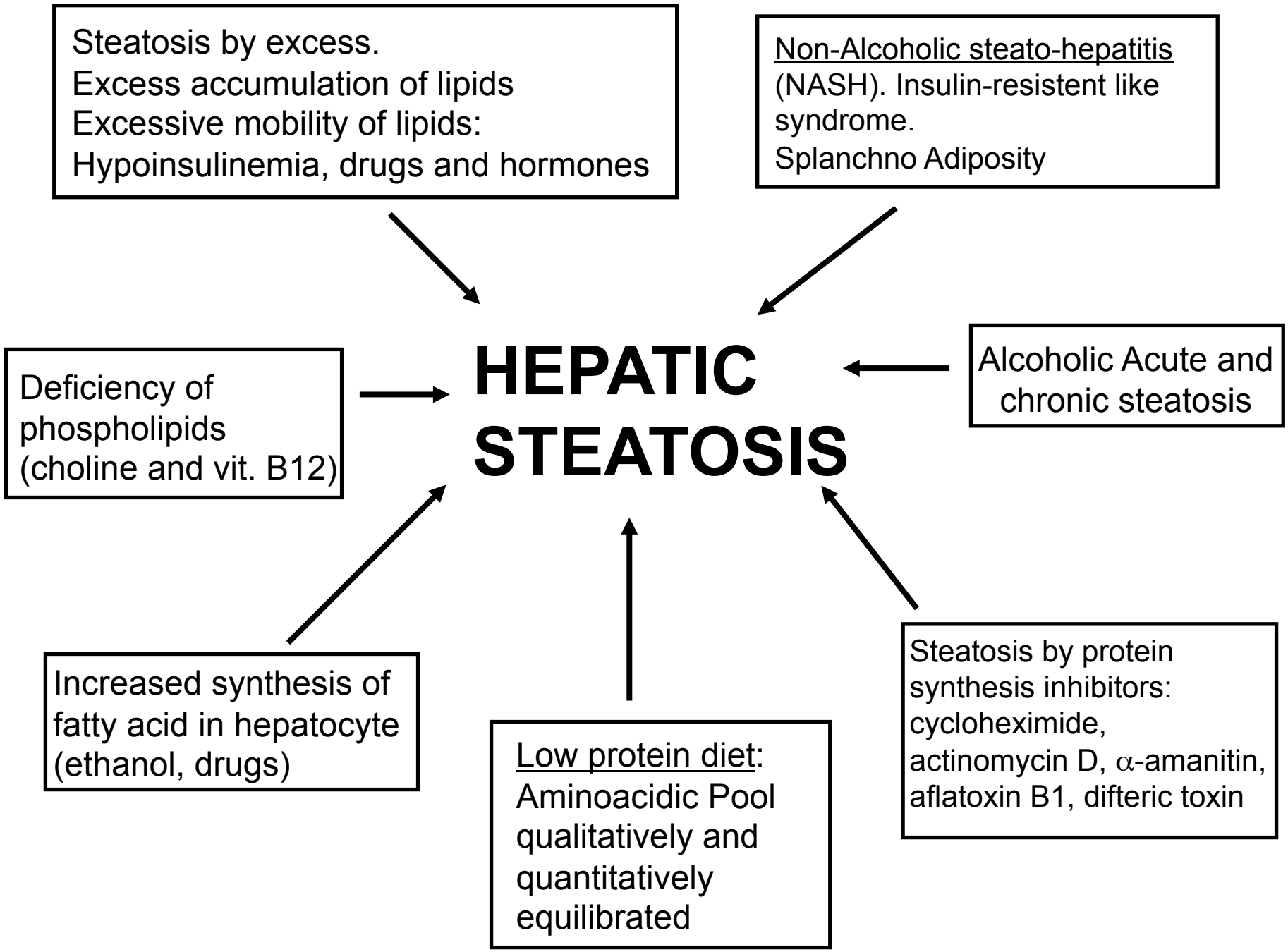
Genetically Inherited Steatosis

WOLMAN DISEASE

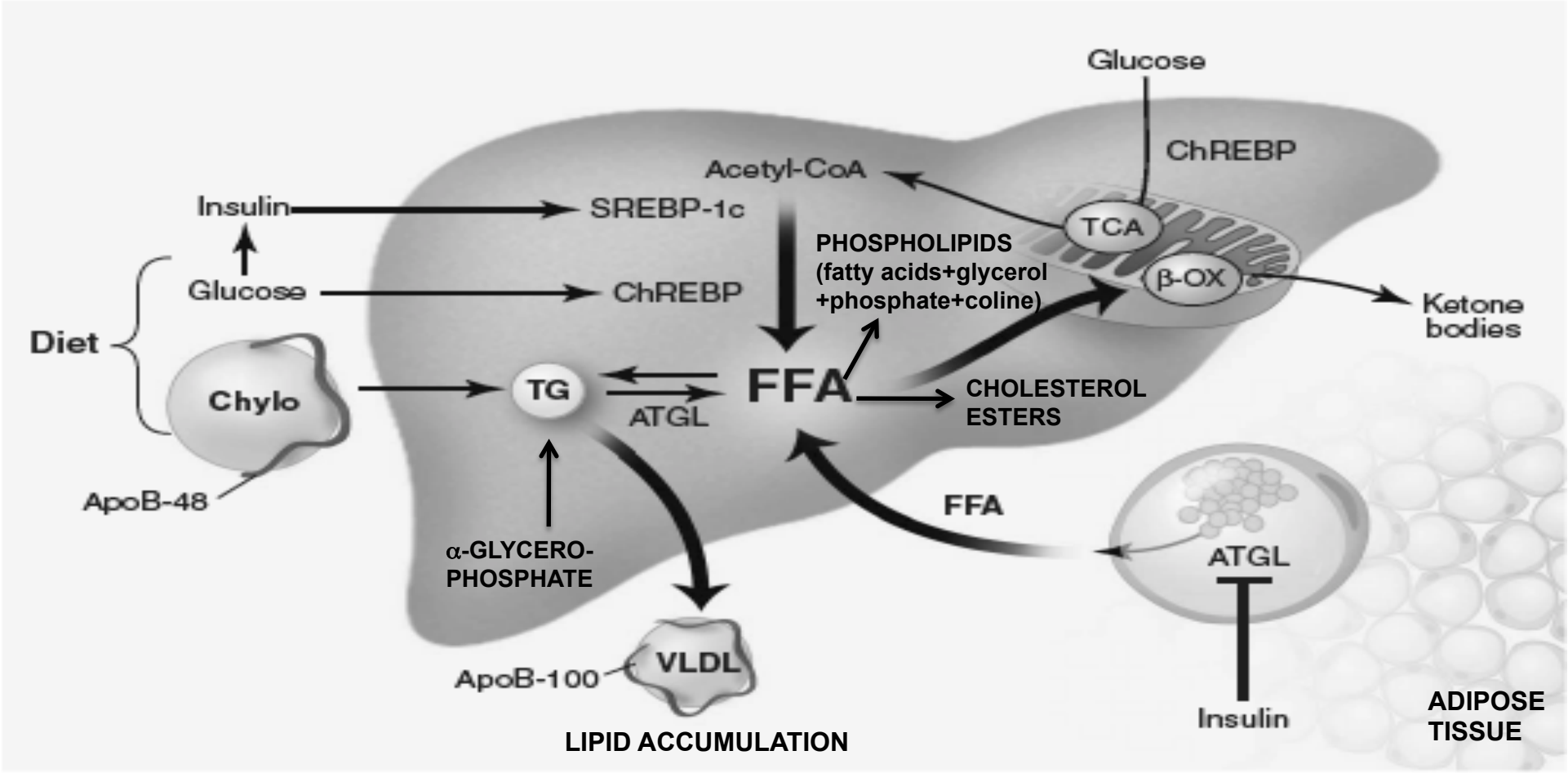
- harmful amounts of lipids accumulate in the parenchymal cells and histiocytes of liver.
- Rare inherited lysosomial disease due to mutations in the LIPA gene lead to a shortage of lysosomal acid lipase.

ABETALIPOPROTEINEMIA

- affects the cells of intestinal mucosa causing malabsorption of dietary fats, cholesterol, and fat-soluble vitamins. Rare genetic disorder approximately 100 cases described worldwide.
- Mutations in MTTP gene coding for microsomal triglyceride transfer protein.


Steatosis by excess.
Excess accumulation of lipids
Excessive mobility of lipids:
Hypoinsulinemia, drugs and hormones
Non-Alcoholic steato-hepatitis
(NASH). Insulin-resistent like
syndrome.
Splanchno Adiposity
Deficiency of
phospholipids
(choline and vit. B12)
HEPATIC
STEATOSIS
Alcoholic Acute and
chronic steatosis
Increased synthesis of
fatty acid in hepatocyte
(ethanol, drugs)
Low protein diet:
Aminoacidic Pool
qualitatively and
quantitatively
equilibrated
Steatosis by protein
synthesis inhibitors:
cycloheximide,
actinomycin D, α-amanitin,
aflatoxin B1, difteric toxin

METABOLISM OF TG IN THE LIVER



Three main sources of fatty acids:

- ❖Dietary fat, as triclycerides drops (chylomicrons)
- ❖Fat deposited in adipocytes. Triglycerides are cleaved and released as free fatty acids (FFA) and carried by albumin.
- ❖De novo synthesis from acetate, minor pathway

CAUSES OF FATTY LIVER

1.Oxygen deprivation→reduced FFA oxydation

2.Nutritional alteration:

-high nutrients level

-low nutrients level:

reduced protein synthesis→reduced lipoproteins

-fast →increased mobilization from adipose tissue

3.Toxic effects modify lipid, proteic and energetic metabolism

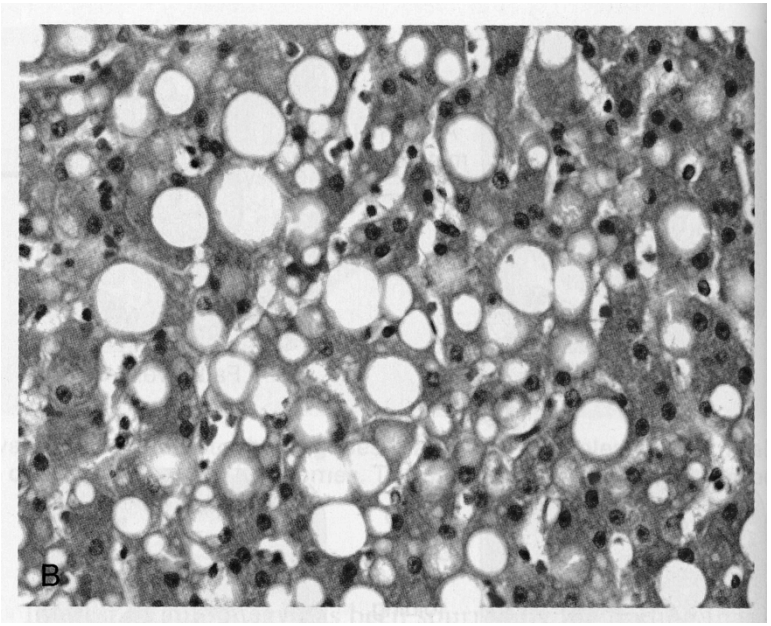
Toxin:alfa-amanitin

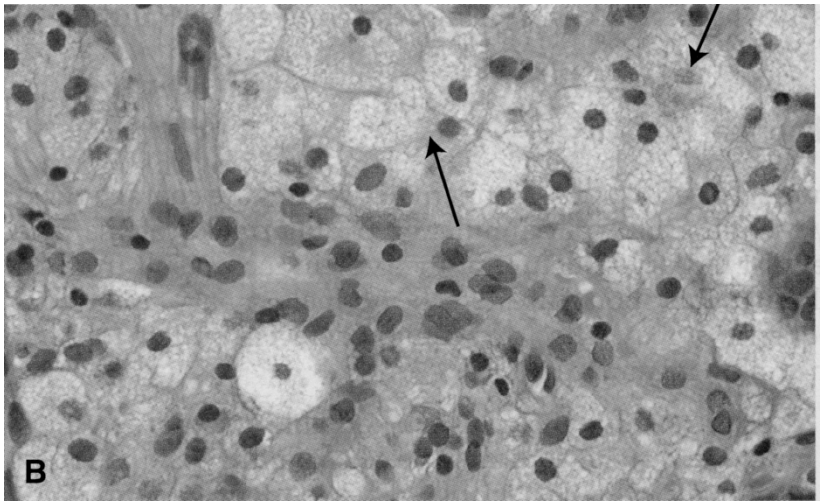
Ethanol: -increased synthesis of fatty acids and glycerol

-reduced FFA oxydation

-reduced lipoprotein release

-Increased lipolysis of adipose tissue





Fatty liver

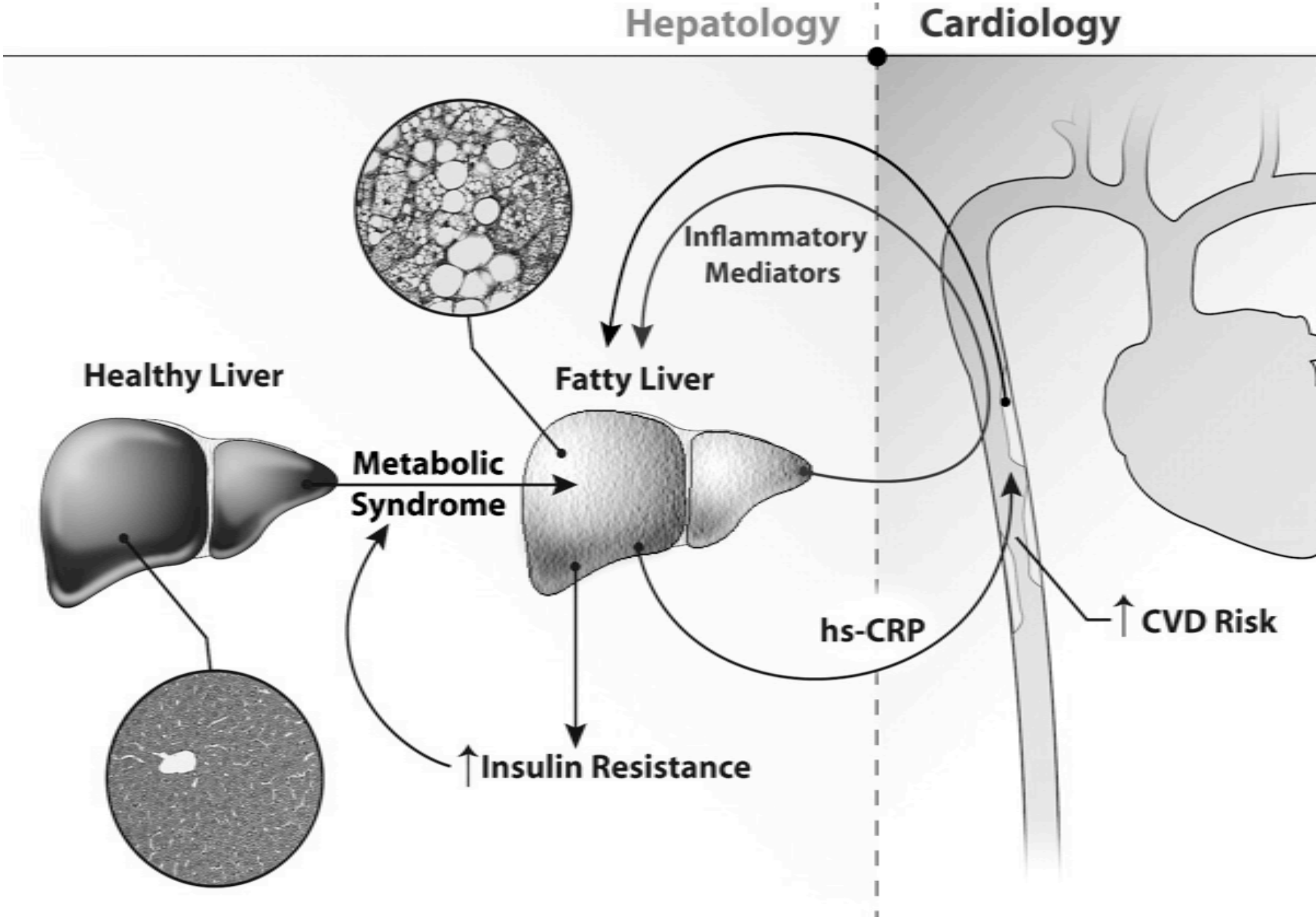
- Accumulation of triglycerides within hepatocytes generally occurs in a predictable fashion.

- Two morphologic patterns are recognized:

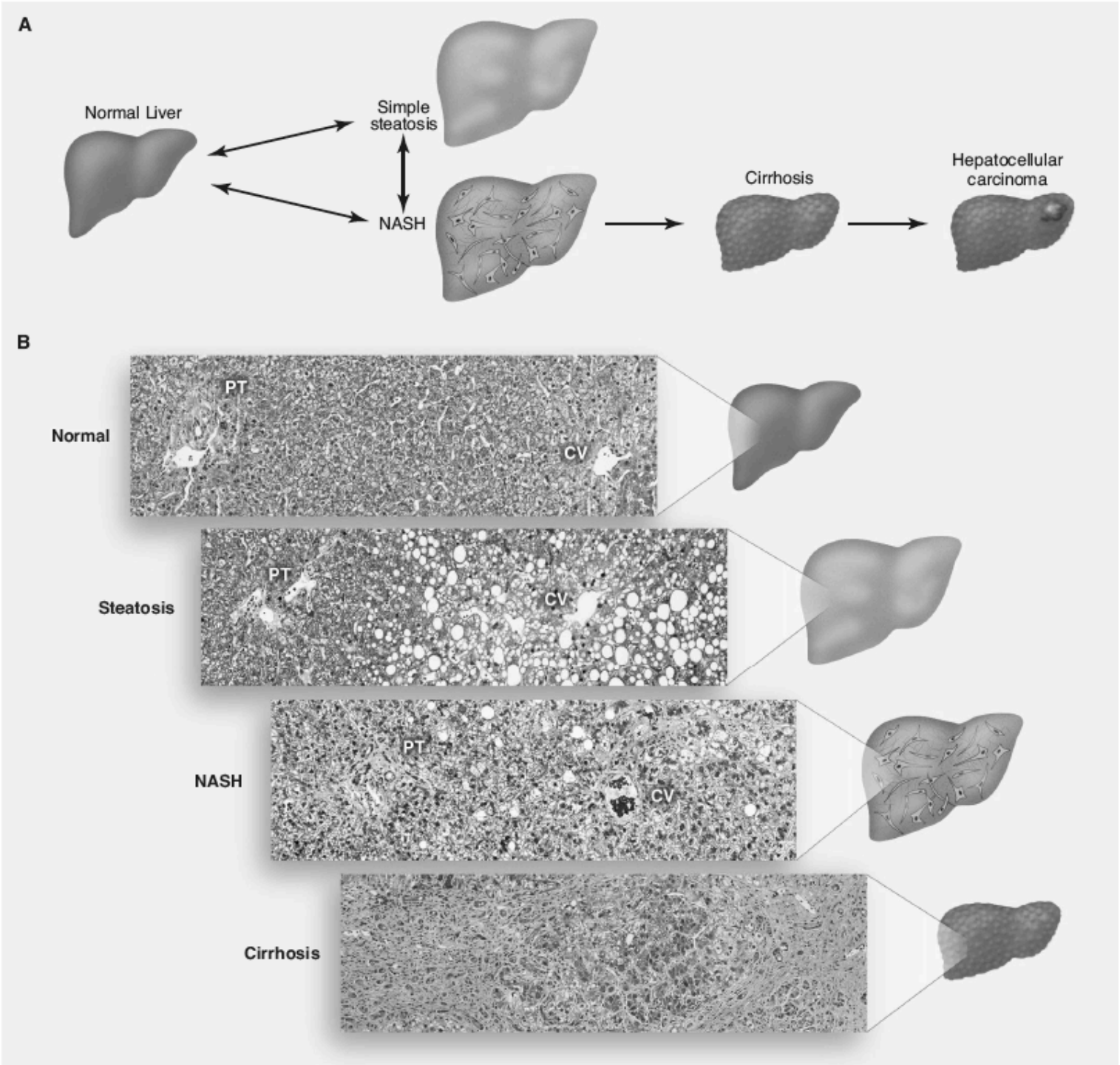
  Macrovescicular Steatosis

  And

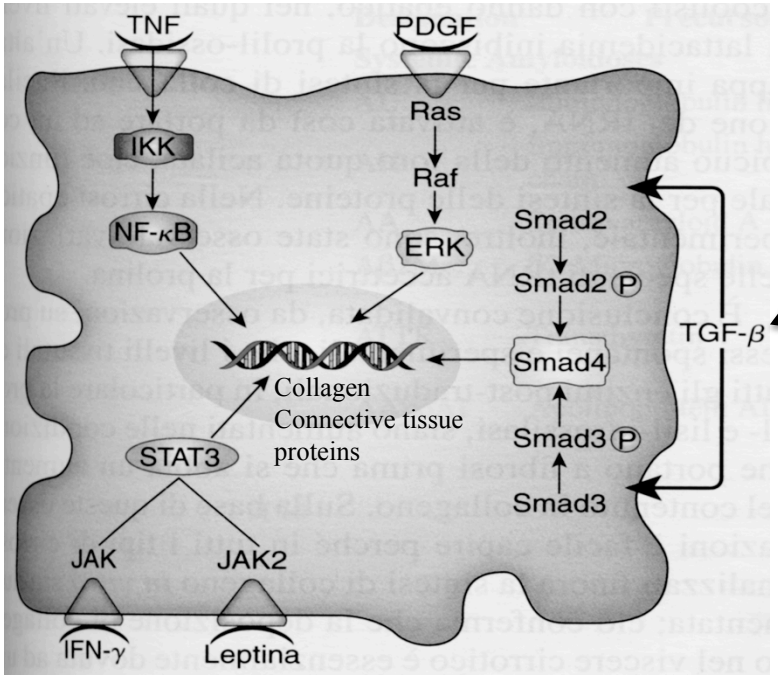
  Microvescicular Steatosis


Hepatology
Cardiology
Inflammatory Mediators
Healthy Liver
Fatty Liver
Metabolic Syndrome
hs-CRP
↑ CVD Risk
↑ Insulin Resistance

Non alcoholic liver disease



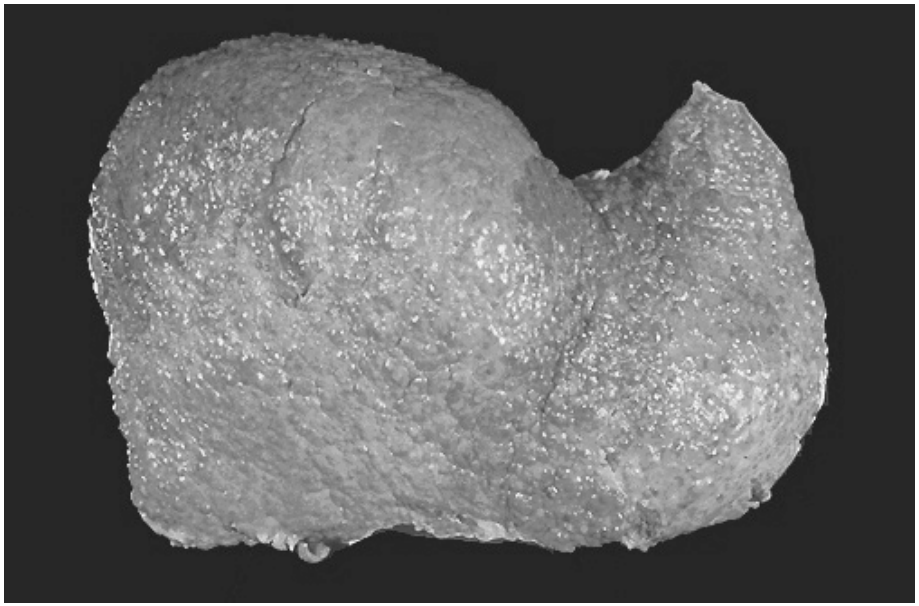
- The liver injury with chronic alcoholism leads to fibrosis and regeneration of the hepatocytes in nodules. This firm, nodular appearance of the liver as seen here is called cirrhosis



Inflammation

Activated Kupffer cells

Stellate cells



Dense bands of fibrosis surround regenerative hepatocellular nodules

Accumulation of carbohydrates

- Excess deposits of Glycogen are associated to altered metabolism of Glucose and glycogen. Are pale vacuoles within the cytoplasm.

- In Diabetes mellitus: glicogen accumulate in epithelial cells of renal distal tubules, in hepatocytes, in β cells of Langherans islet and in muscle celll of heart.

- Glycogenosis : massive accumulation due to specific enzyme deficiency involved in synthesis and degradation of glycogen, causing damage and cell death.

Abnormal Protein Accumulation

- Proteins accumulate in vacuoles, rounded, eosinophil droplets or cytoplasmic aggregates.

Excess is found in cells with insufficient metabolic ability.

- Reabsorption droplets in renal proximal tubules associated with proteinuria.
- Excessive amounts of normal secreted proteins
- Abnormal or misfolded proteins:
  - Alterations of the intracellular transport and release of critial proteins.
  - Toxicity of aggregated protein, abnormally folded.

INTERSTITIAL STORAGE DISEASES

Deposition and changes of different macromolecules in the interstitial spaces

↓

Extracellular matrix disorganization

↓

Loss of extracellular matrix functionality
Molecular trafficking slow-down
Microenvironmental change
Modified parenchyma/blood exchanges

↓

Compression and malnutrition of parenchymal cells
Structural and functional damages
Atrophy

↓

Necrosis

The Amyloidoses

Clinical disorders caused directly by localized or systemic amyloid deposition.

A specific group of life-threatening disorders.

Amyloid

Amyloid-forming proteins can exist in two completely different stable structures:

- **A native form**
- **β-sheets**, massive refolding of the native form into β-sheets that can aggregate in a highly ordered manner to produce characteristic fibrils.

Minor constituents:

- ***glycosaminoglycans*** (GAGs)
- the normal plasma protein ***serum amyloid P component*** (SAP)
- Various trace proteins such as apolipoprotein E
- Laminin
- Collagen IV

Cross-β-pleated sheet

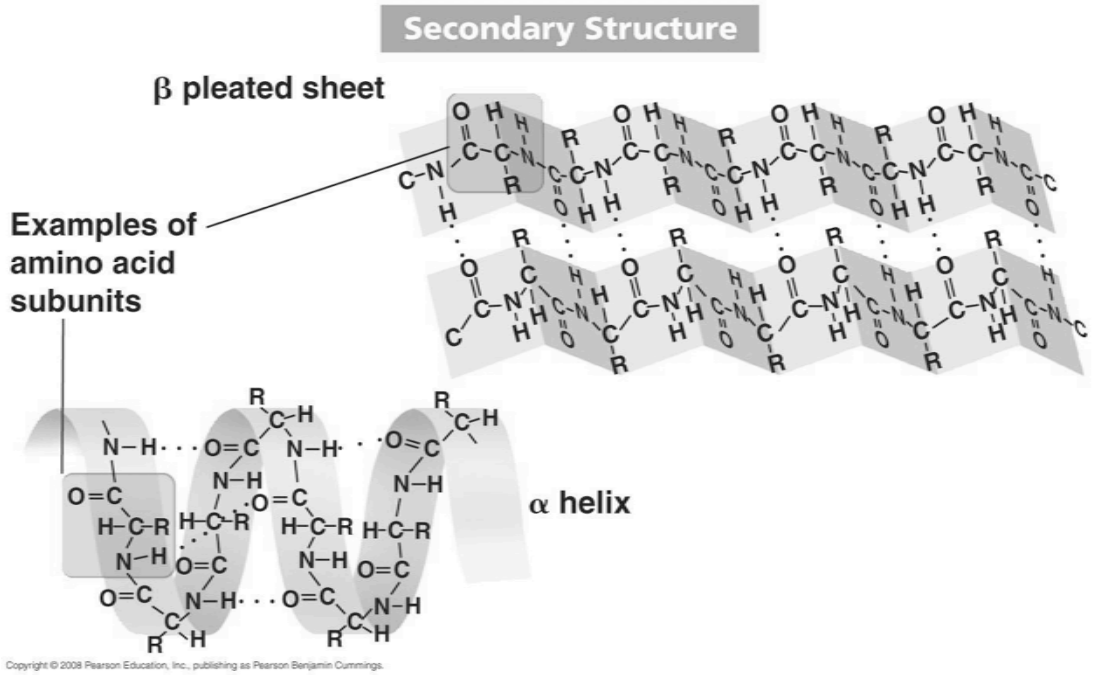
The fibrils are rigid, unbranched, variable in size with a section of 100A°.

Fibril assembly is the result of a longitudinal aggregation of protofilaments, stabilized by the Hydrogen bond (NH and CO) between the polypeptidic chains, folded in β−sheets.

β−conformation depends on AA composition

No tissue enzymes are able to degrade that fibrils

Kidney, spleen and liver mainly affected



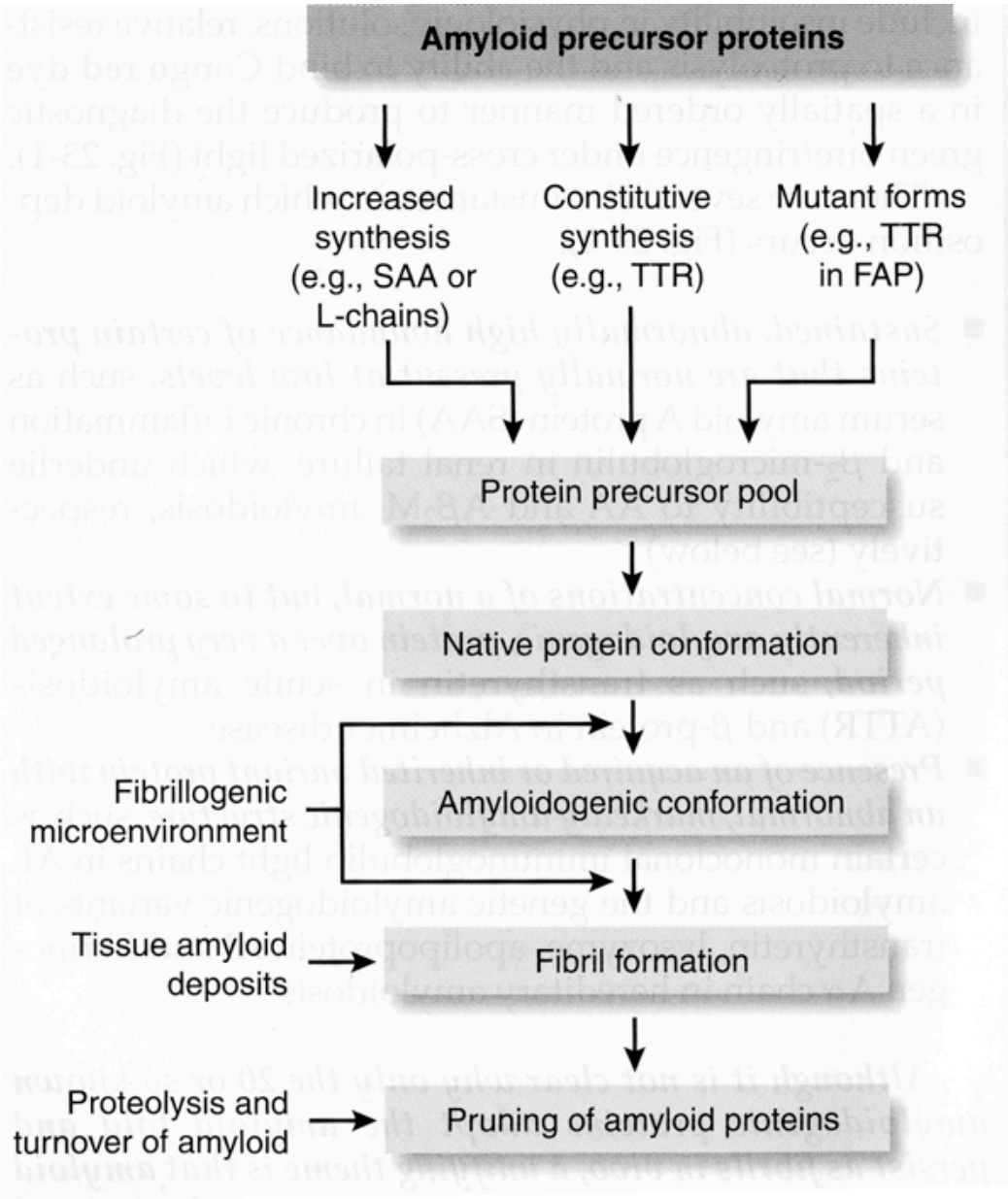
Amyloid deposition occurs:

-Sustained, abnormally high abundance of certain proteins that are normally present at low levels.
(SAA in chronic inflammation)

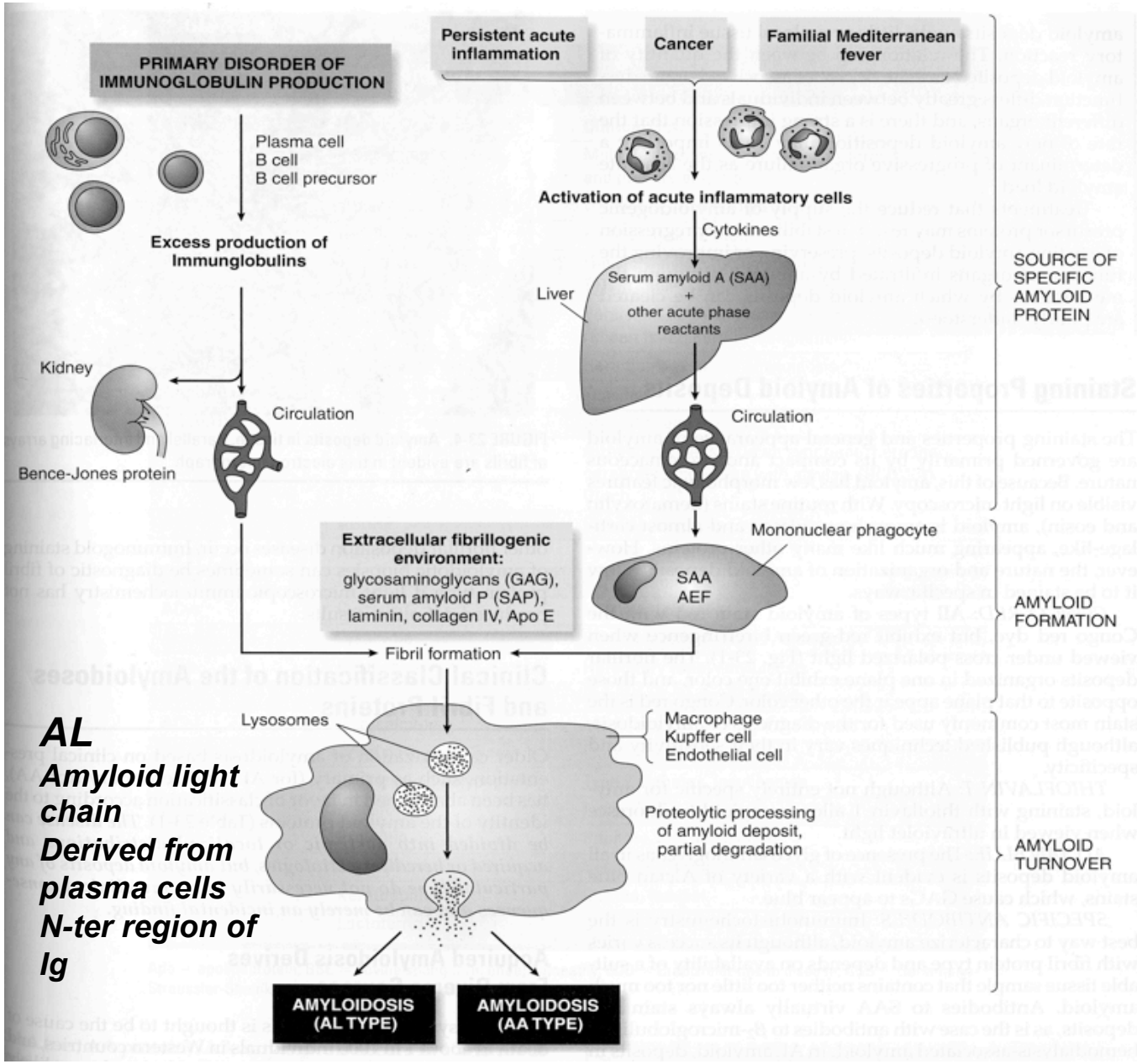
-Normal concentrations of a normal, but to some extent inherently amyloidogenic, protein over a very prolonged period.
(tranthyretin in senile amyloidosis, Alzheimer D)

-Presence of an acquired or inherited variant protein with an abnormal, markedly amyloidogenic structure.
(monoclonal Ig light chains in AL amyloidosis)

Amyloidogenesis



The mechanisms of amyloid deposition



AL
Amyloid light chain
Derived from plasma cells
N-ter region of Ig

AA
-Amyloid Associated 8500d non immunoglobulin
-Synthesized by hepatocytes
-N-ter cleavage fragment of SAA

Amyloidoses classification

A. PRIMARY SISTEMIC

- Heredo-familiar
- By Hemodialysis

A. SECONDARY SYSTEMIC

- Reactive
- Immunocytic

A. LOCALIZED

B. Endocrine
C. Senile
D. Cerebral

A. PRIMARY SISTEMIC

Hereditary sistemic

- mutations in the genes for transthyretin (TTR), Cystatin C, gelsolin, lysozyme, fibrinogen A α-chain, apolipoprotein AI.
- All inherited dominantly
- The commonest is hereditary transthyretin amyloidosis
- Best characterized form is familial Mediterranean fever

  mutations in *pyrin* gene

  The amyloid is of AA type.
- Imperative correct identification to distinguish from acquired amyloidosis

A. PRIMARY SISTEMIC

Dialysis related amyloidosis

- Microglobulin amyloid deposition
- Synthesized at a rate of 150/200mg/day
- Long-term Dialysis-dependent for chronic renal failure
- Articular and periarticular structures affected

A. SECONDARY SYSTEMIC

Reactive secondary amyloidosis

- Is due to AA-type amyloid.
- Is associated with chronic inflammatory states and non-immunocyte tumors.
- Liver modifies protein synthesis pattern
- Increased serum level of the precursor form SAA
- Long-term overproduction of SAA a prerequisite for AA deposition.
- AA amyloidosis is dominated by progressive proteinuria.

• Immunocytic secondary amyloidosis

-AL fibrils are derived from monoclonal Ig light chain.

-Only a small percentage are amyloidogenic, and amyloidogenecity is inherent in certain monoclonal light chains.

-Occurs in about 25% of people with monoclonal B-cell dyscrasias.

A. LOCALIZED

- ✓ Endocrine

  -Occurs in tumors associated with hormone synthesis.

  -5 polypeptidic hormones are prone to autoaggregation and to form amyloid.

- ✓ Senile

  -Clinically silent deposits of wt “senile” TTR amyloid are common in the elderly.

  Transthyretin (TTR) a normal serum protein binding thyroxine and retinol.

  -heart and blood vessel walls, smooth and striated muscle, fat tissue, renal papillae and alveolar walls are involved.

- ✓ Cerebral

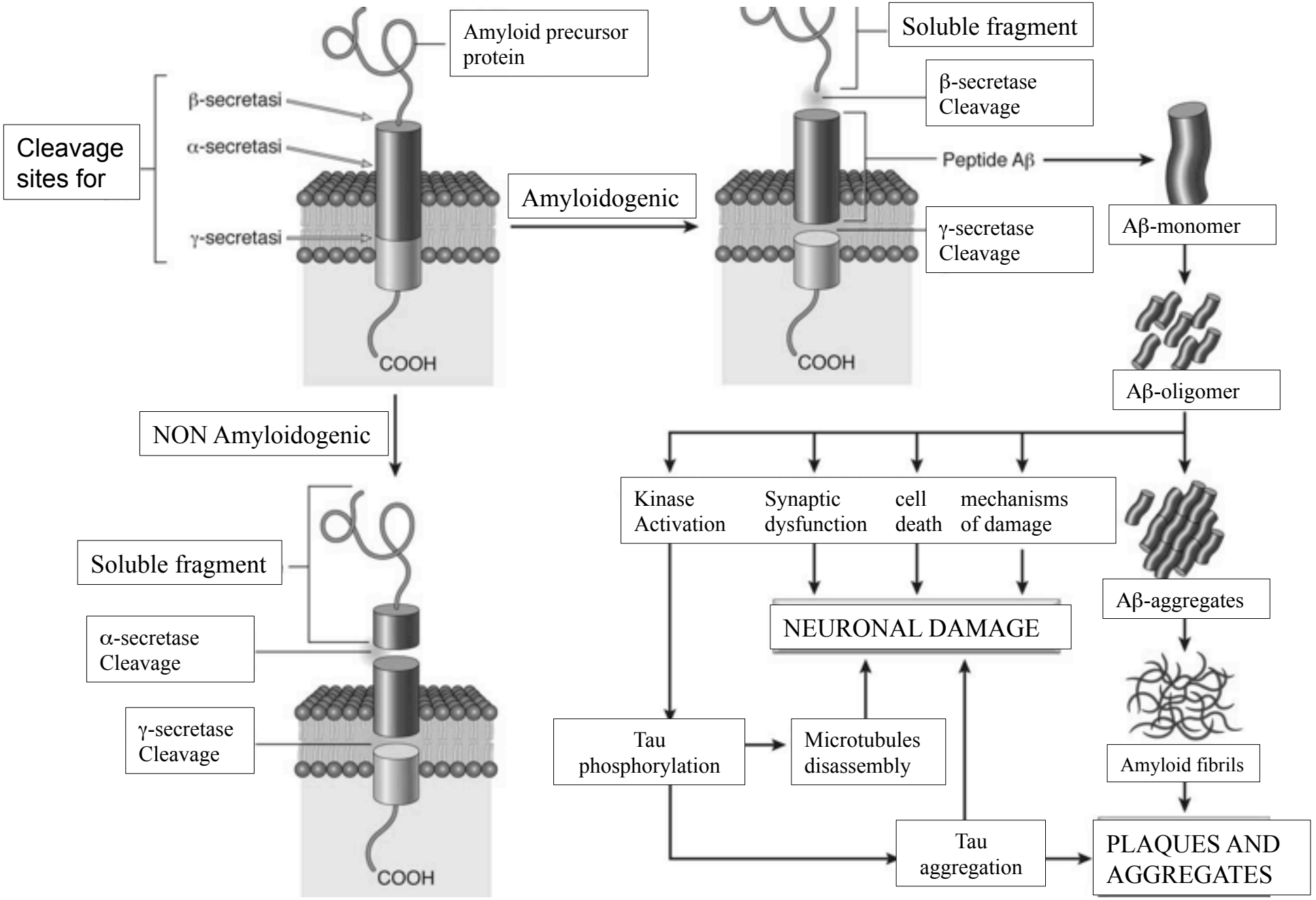
  -the brain is a common and important site of amyloid deposition.

  -major forms of brain amyloid are associated with Alzheimer disease.

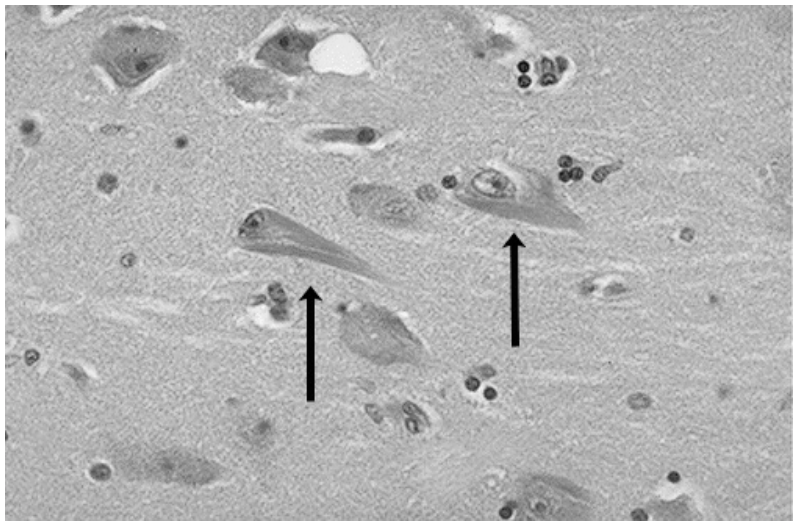
Alzheimer Disease (AD)

- Is the most common dementing illness of the elderly.
- Progressive neurologic disorders that usually begins after fifthy years of age.
- Is characterized by abnormal accumulation of two different polymerized proteins: β-amyloid and *tau*.
- AD brains show cortical atrophy with hydrocephalus *ex vacuo*.
- Neuritic plaque and neurofibrillary tangles are characteristic.
- The amyloid predominantly contains Aβ deriving from APP processing.

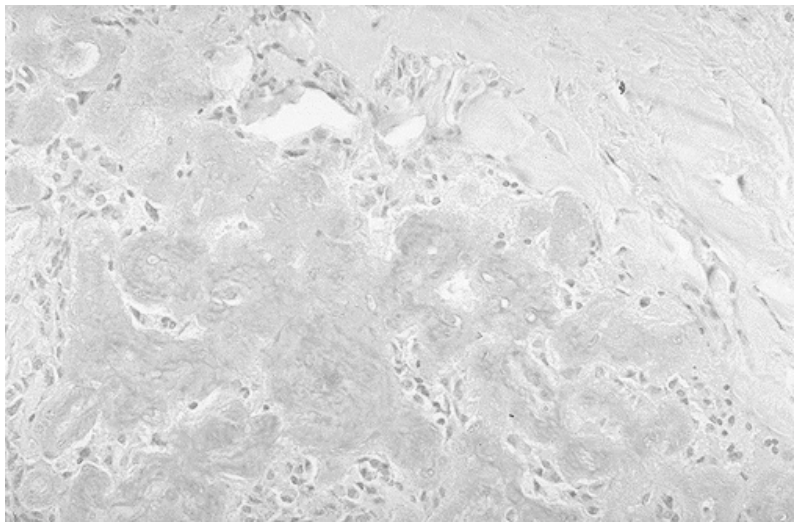
Aβ amyloid generation



Alzheimer's Disease (AD)

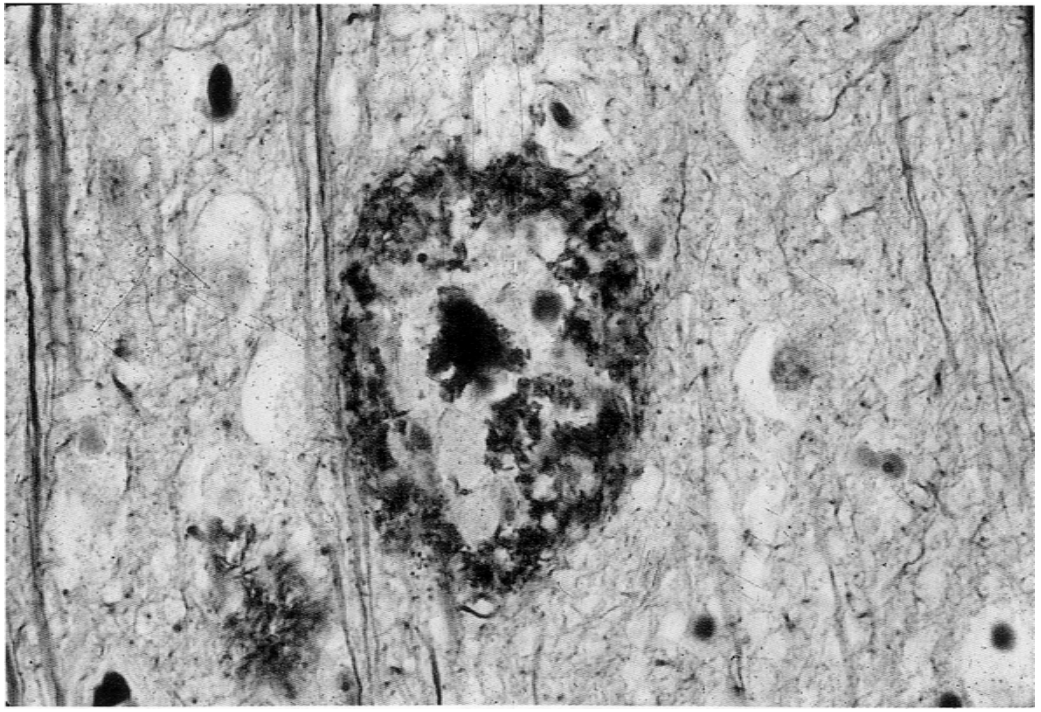


Neurofibrillary tangles in neurons. The cytoskeletal filaments are grouped together in the elongated pink tangles. They are intracytoplasmatic intraneuronal accumulations of polymerized phosphorylated *tau* proteins.



Congo red stain reveals orange-red deposits of amyloid, which is an abnormal accumulation of breakdown products of proteinaceous material that can collect within cells and tissues

Neuritic plaques are extracellular spherical deposits of polymerized β-amyloid centrally.
In end-stage disease occupy large volumes of affected cerebral grey matter.



They are surrounded by reactive astrocytes and microglia and display swollen distorted neuronal processes.

Several genetic risk factors for AD

Mutations in the APP gene have been associated with early onset familial variants of AD

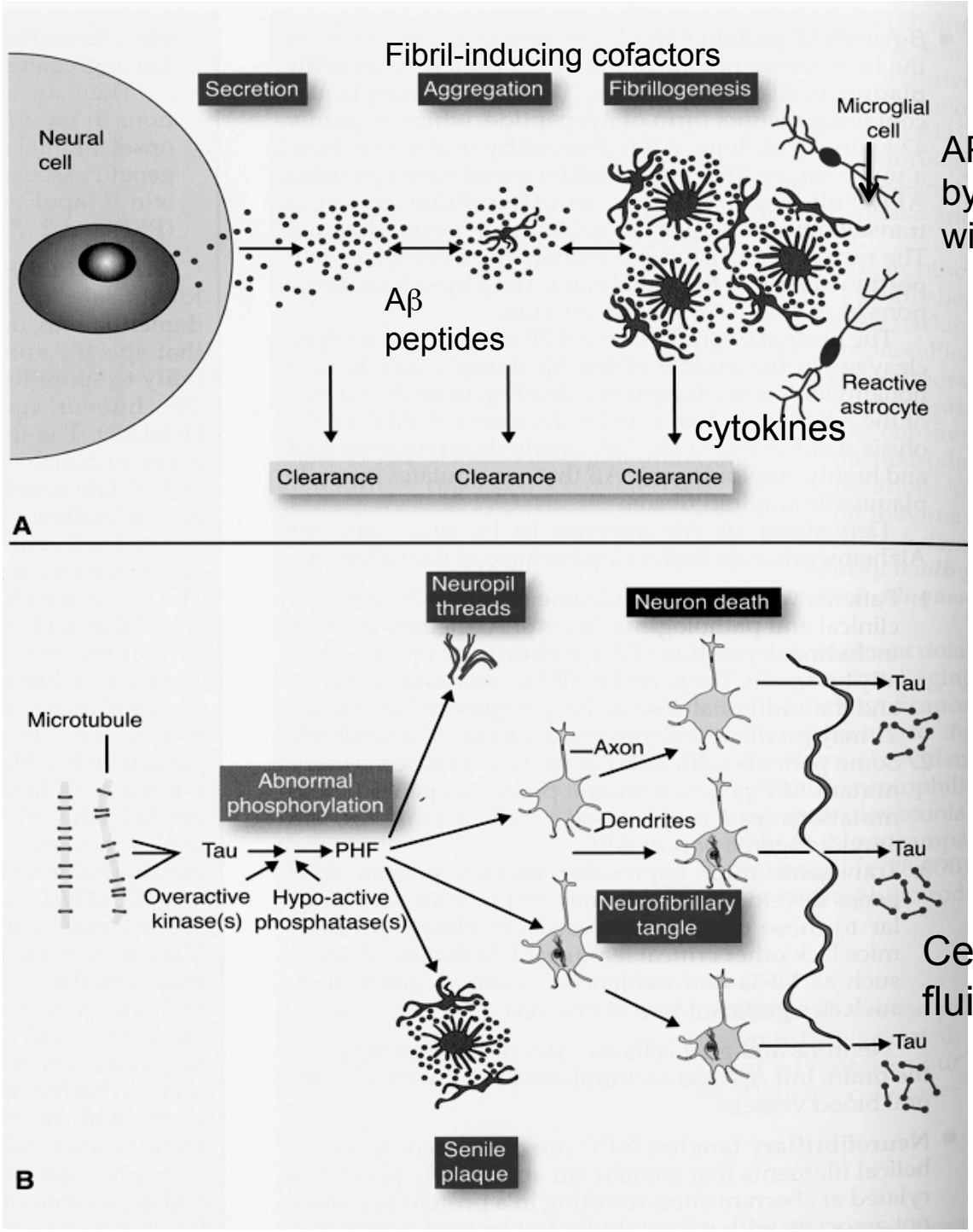
Genetic associations involve the apolipoprotein E (ApoE) genotype and the genes for presenilin1 (PS1) and 2 (PS2).

Table 28-4

Genetic Factors in Alzheimer Disease

Gene	Chromosome	Disease Association
Amyloid precursor protein (*APP*)	21	Mutations of the *APP* gene are associated with early-onset familial Alzheimer disease
Presenilin 1 (*PS1*)	14	Mutations of the *PS1* gene are associated with early-onset familial Alzheimer disease
Presenilin 2 (*PS2*)	1	Mutations of the *PS2* gene are associated with Volga German familial Alzheimer disease
Apolipoprotein E (*apoE*)	19	Presence of the $\varepsilon 4$ allele is associated with increased risk and younger age of onset of both inherited and sporadic forms of late-onset Alzheimer disease

Proposed mechanisms leading to development of Alzheimer disease



APP cleavage by γ secretase will produce Aβ

Tau in paired helical fibrils (PHFs) loses the ability to bind microtubules thus their depolimerization, disruption of axonal transport and degeneraton of neurons

Cerebrospinal fluid

Cilinical features:

- Gradual loss of memory and changes in behaviour
- Cognitive impairment increase at a rate of 15% per year
- Full dementia
- Bronchopneumonia and urinary tract infections and pressure decubiti are common medical complications.

Diagnosis, prognosis and therapy

Splenomegaly and Hepatomegaly and proteinuria

AA amyloidosis plasma estimation SAA levels

Serial SAP scintigraphy

Potent anti-inflammatory, cytokine-inhibiting and immunosuppressive drugs.

AL amyloidosis chemotherapeutic treatment

Liver transplantation is effective in familial polyneuropathy associated with

TTR gene mutations.