Les atteintes cellulaires chez l'enfant: le cas du cerveau et du foie

Cycle de conférence facultaire

Décembre 2015

Université Catholique de Bukavu (RDC)

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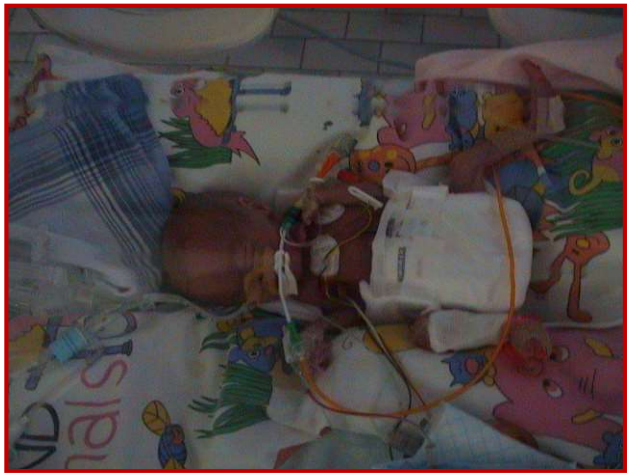
Soins qui Respectent le développement



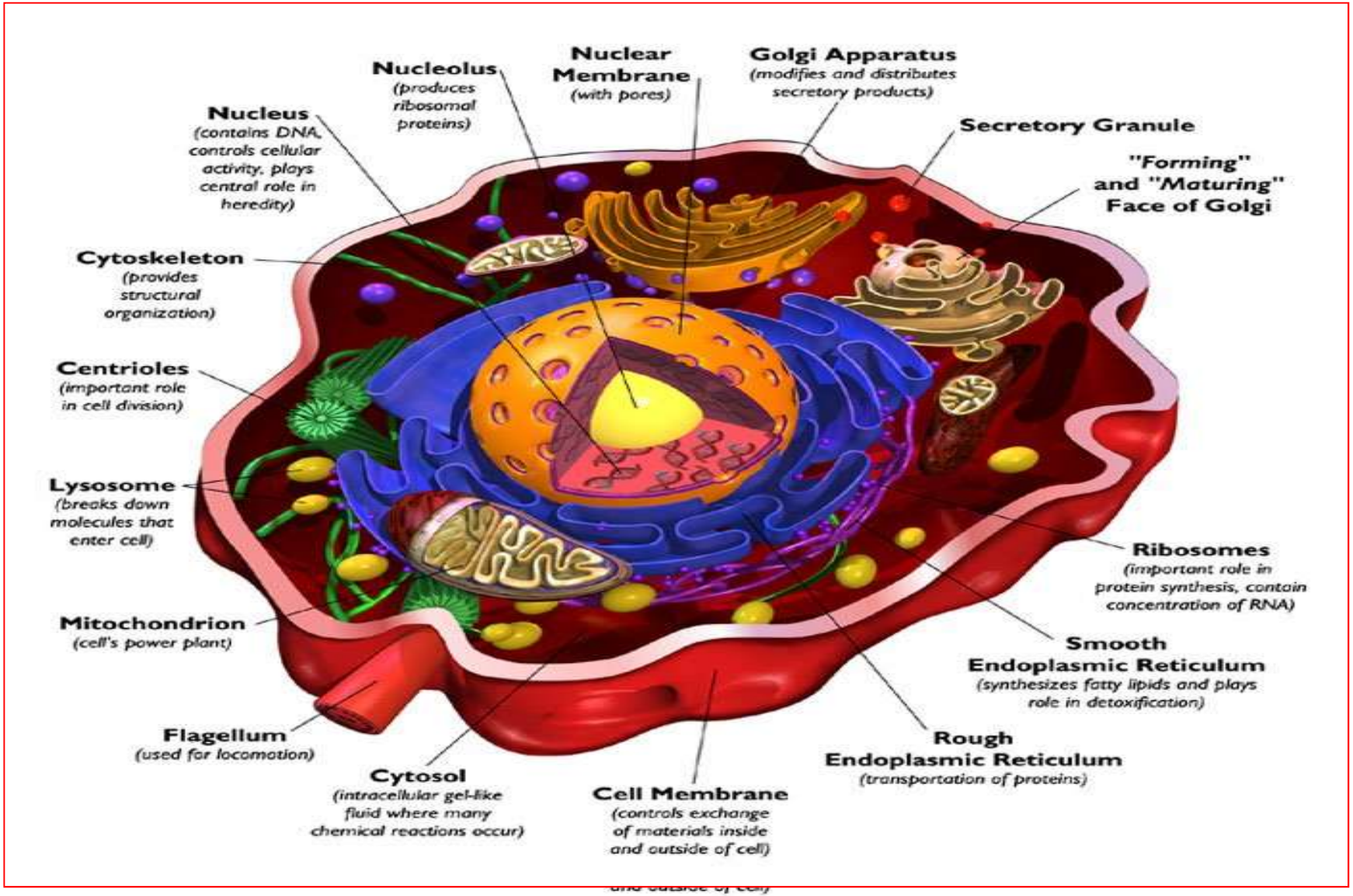
« les soins de Développement: NIDCAP, WEECARE

Hommage

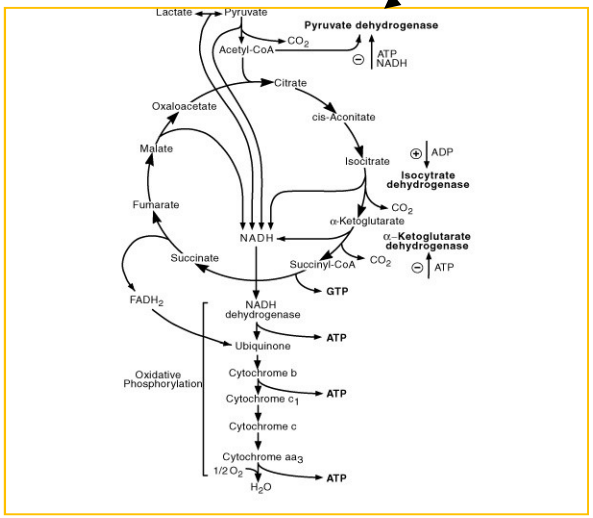
V Apgar	J Volpe	H Sarnat	P Evrard

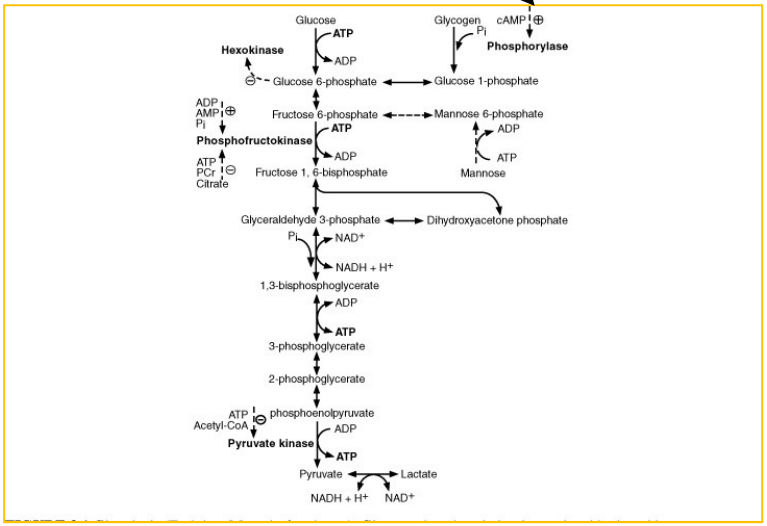
Données générales sur Les Atteintes cellulaires

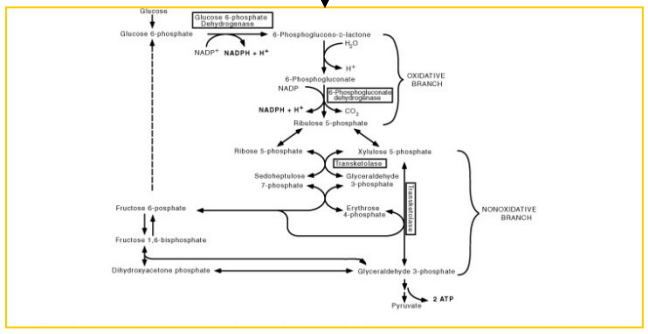
La cellule fait partie d'un tout



Voies métaboliques oxydatives:
le cycle de Krebs, le cycle des PP et la glycolyse

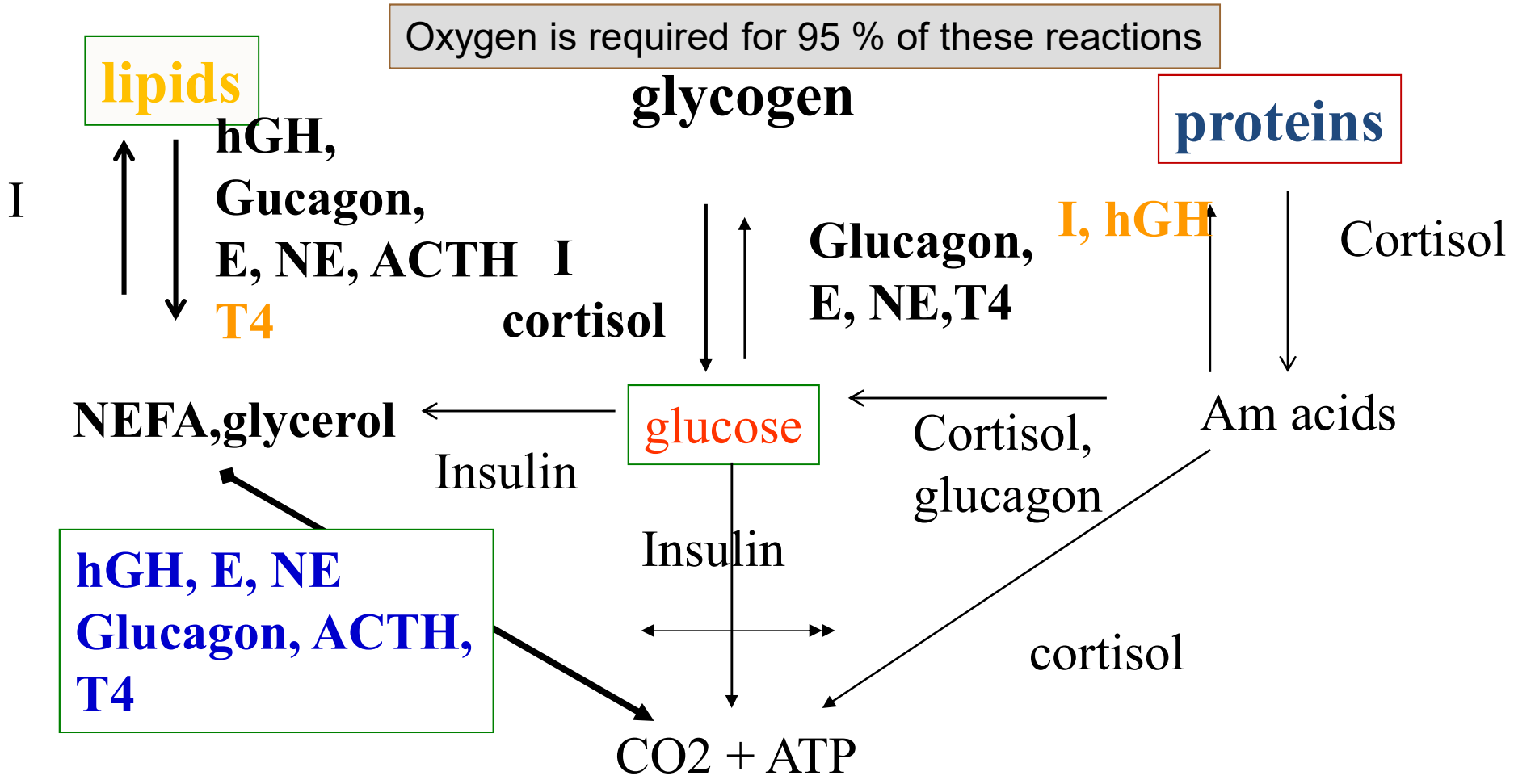






∑ = 95 % de la QO2, le restant = glycolyse anaérobique et gestion des radicaux libres

Le milieu de vie dépend d'hormones et de métabolites



Le métabolisme de base MB
il représente environ 50 % de la maintenance
la réserve cellulaire pour l'intégrité est environ 1/5 du MB
calcul clinique du MB kcal/kg/j = 0.372 FC moyenne

- Définition = ensemble des activités métaboliques pour le maintien des activités cellulaires de base
- Corrélation avec la consommation en O2 et la production de CO2 et notion de quotient respiratoire
- Corrélation de la FC avec le MB et la QO2
- « Découpage » du MB:

- 17 % pour le turnover protéique
- 9 % pour l'absorption
- 26 % pour la protéosynthèse
- 23 % pour la lipidosynthèse
- 6 % pour la glucosynthèse (glycogène, néoglucogenèse)
- 19 % pour l'homéostasie cellulaire

	H	F	E
foie	21	21	14
cerveau	20	21	44
coeur	9	8	4
reins	8	9	6
muscles	22	16	6
adipocytes	4	6	2
autres	16	19	24

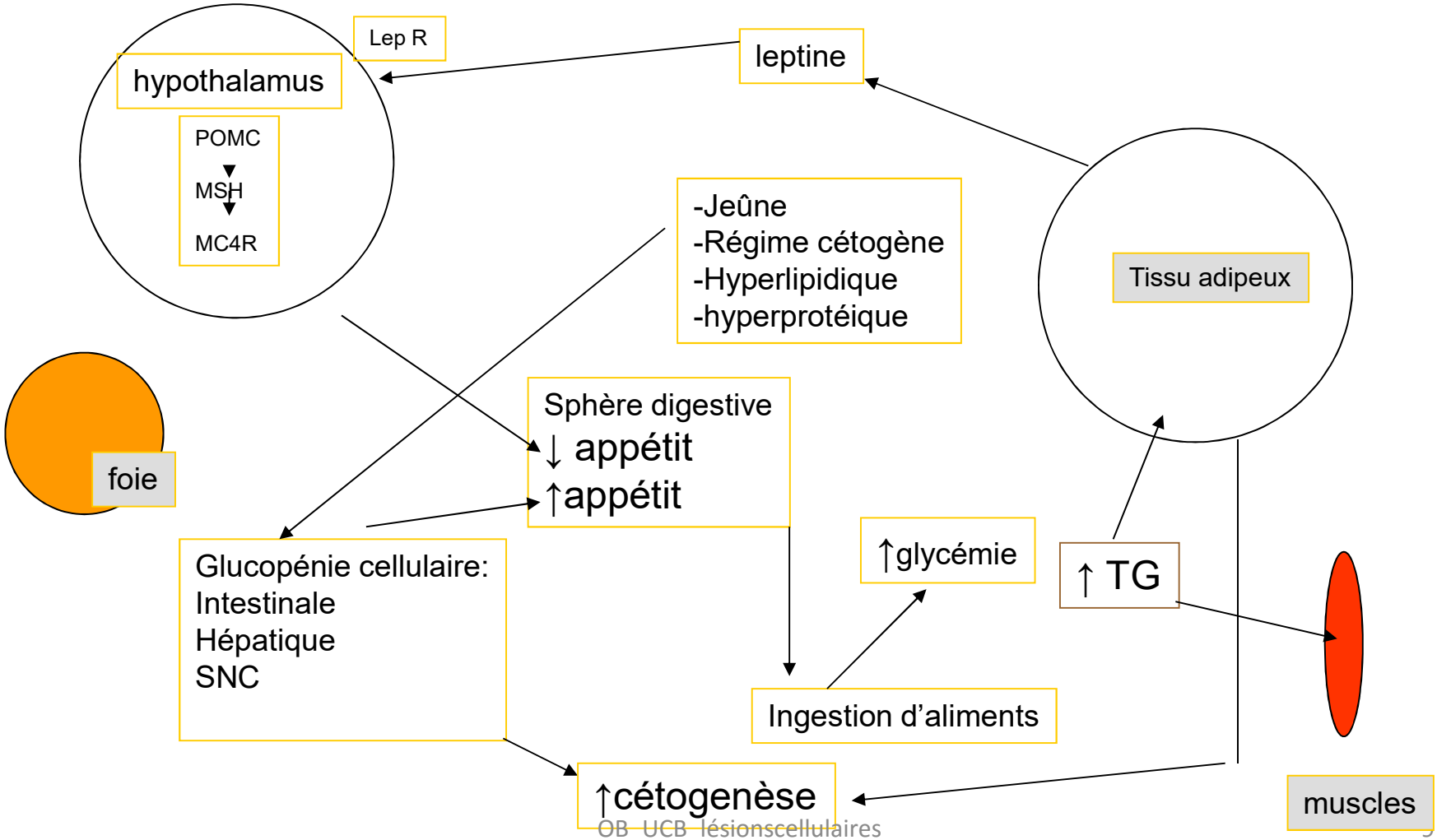
L'ensemble des activités (A) et le minimum (M)
des activités cellulaires
(glucose in mg/100ml and O2 in ml/100ml)

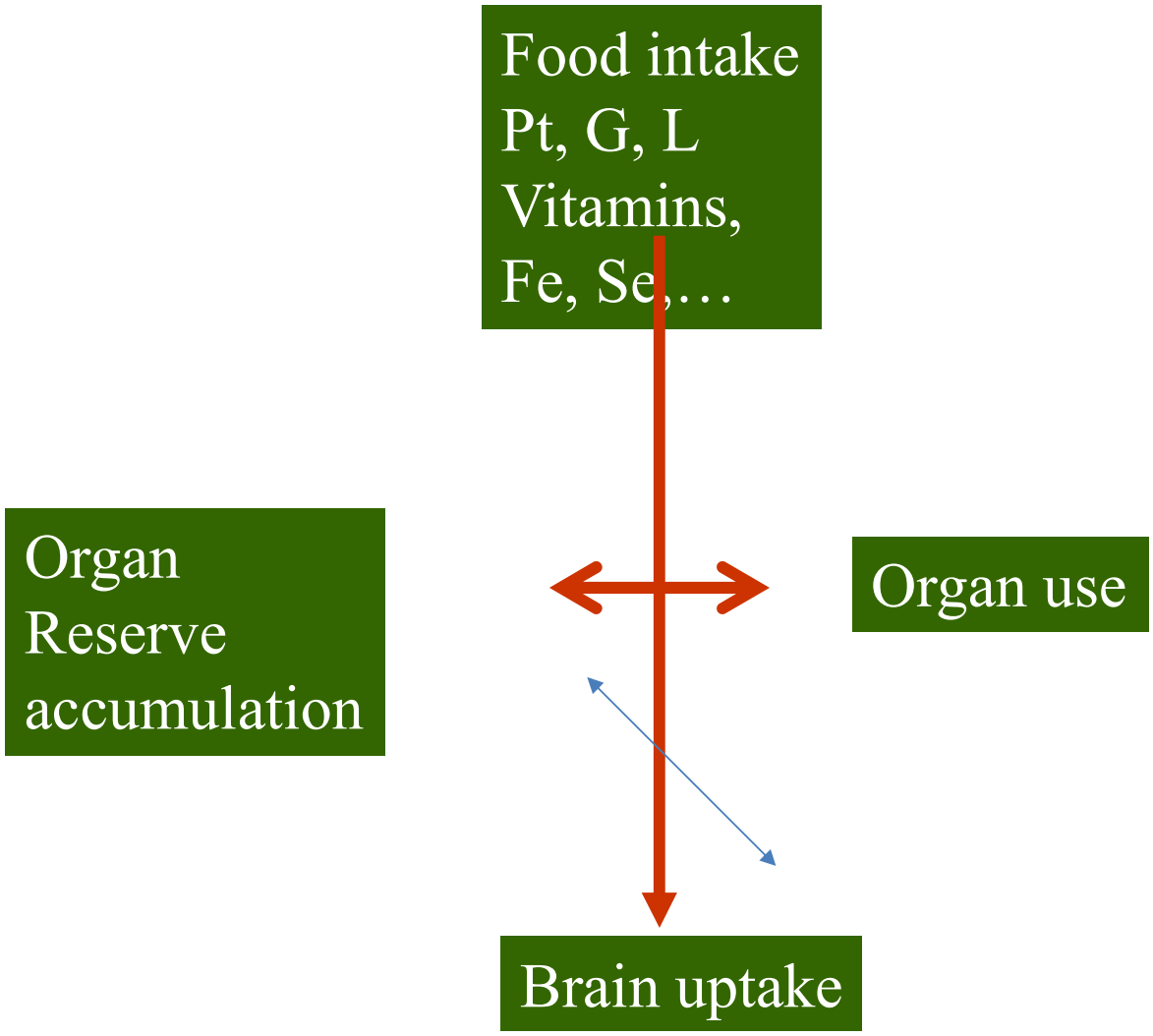
Exemple du cerveau

CBF ml/100g/m	[aGlucose] ->M	[aGlucose] -> A	[aO2] ->M	[aO2] -> A
60	**25**	**65**	**10**	**22**
40	**40**	**100**	**12**	**17**
20	**70**	**175**	**10**	**22**
10	**85**	**220**	**13**	**29**

Extraction capacity of substrate by tissue is around 0.65

Les apports en nutriments et SNC



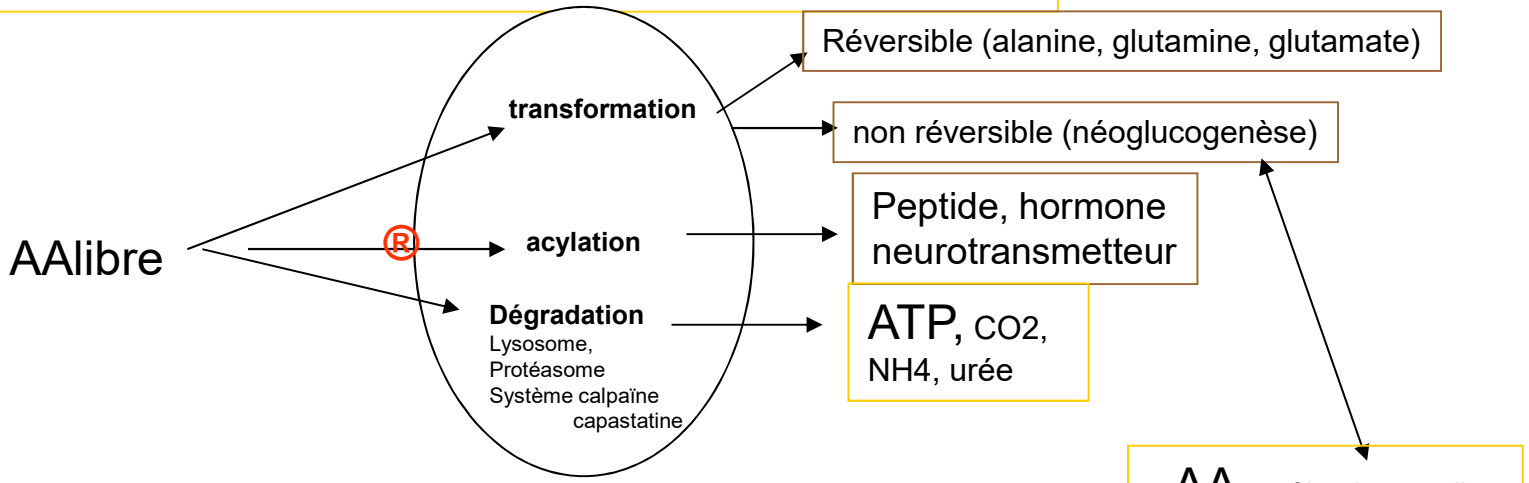

Food intake
Pt, G, L
Vitamins,
Fe, Se,…
Organ
Reserve
accumulation
Organ use
Brain uptake

Le turnover protéique

tissu	Dans le tissu Taux de renouvellement protéique Petits	adultes
foie	50 %	57 %
cerveau	44 %	18 %
Muscles reins	3-4 % ?	15 % 50 %

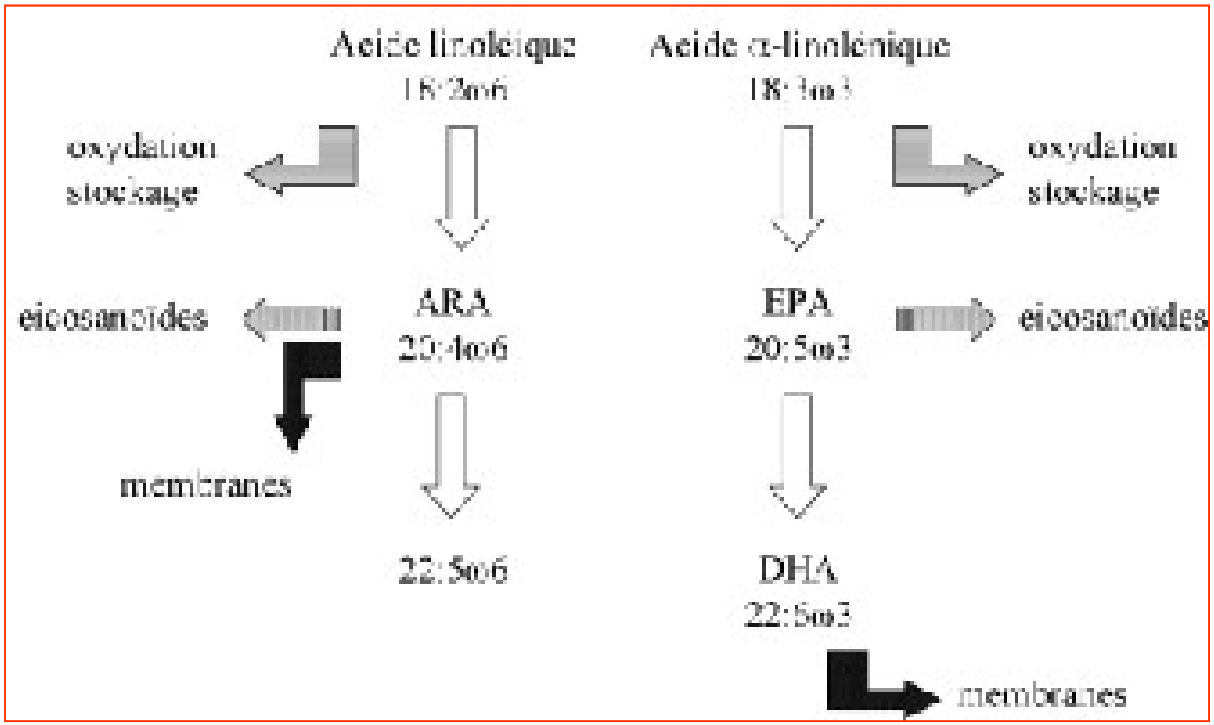
Voies métaboliques des protéines

→Synthèse pour la croissance
→ synthèse pour l'équilibre de la masse protéique
peptides dégradés, bloqués et ou erronés en cours de synthèse →∑ → **Turnover protéiques**
→Certains acides aminés ont des fonctions spécifiques
exemples: ADN, ARN, neurotransmetteurs
néoglucogenèse

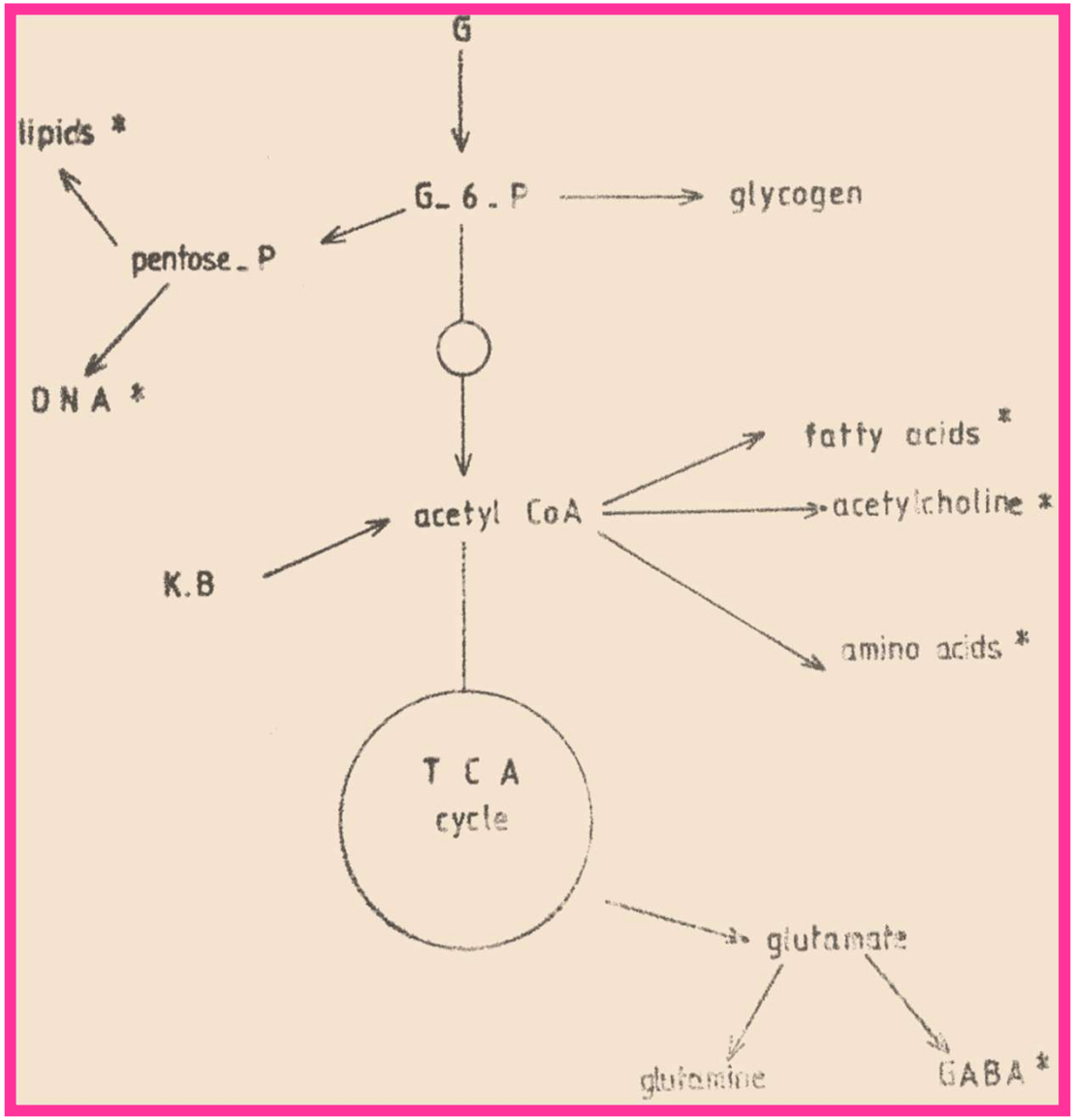


Le flux sera différent selon
L'AA et le tissu concerné

Les voies métaboliques des AGPI = acides gras poly-insaturés)



Les rôles du glucose



-Énergétique:
aigu et stockage
- synthétique

L'O2 dans les tissus: flux sanguin et concentration sanguine

	Abord spontané	avidité pour l'O2	en relation avec les Pt
Tissu	**QO2 ml/min/100g**	**QO2 ml/min/100 ml DS**	**QO2 ml/min/100 g PT**
Myocarde ↑	9	11	69
Cerveau ↑	3	6	30
Reins ↓	5.5	1.5	32
Foie ↓	4.5	5	20
Tube digestif ↓	2.2	4	19

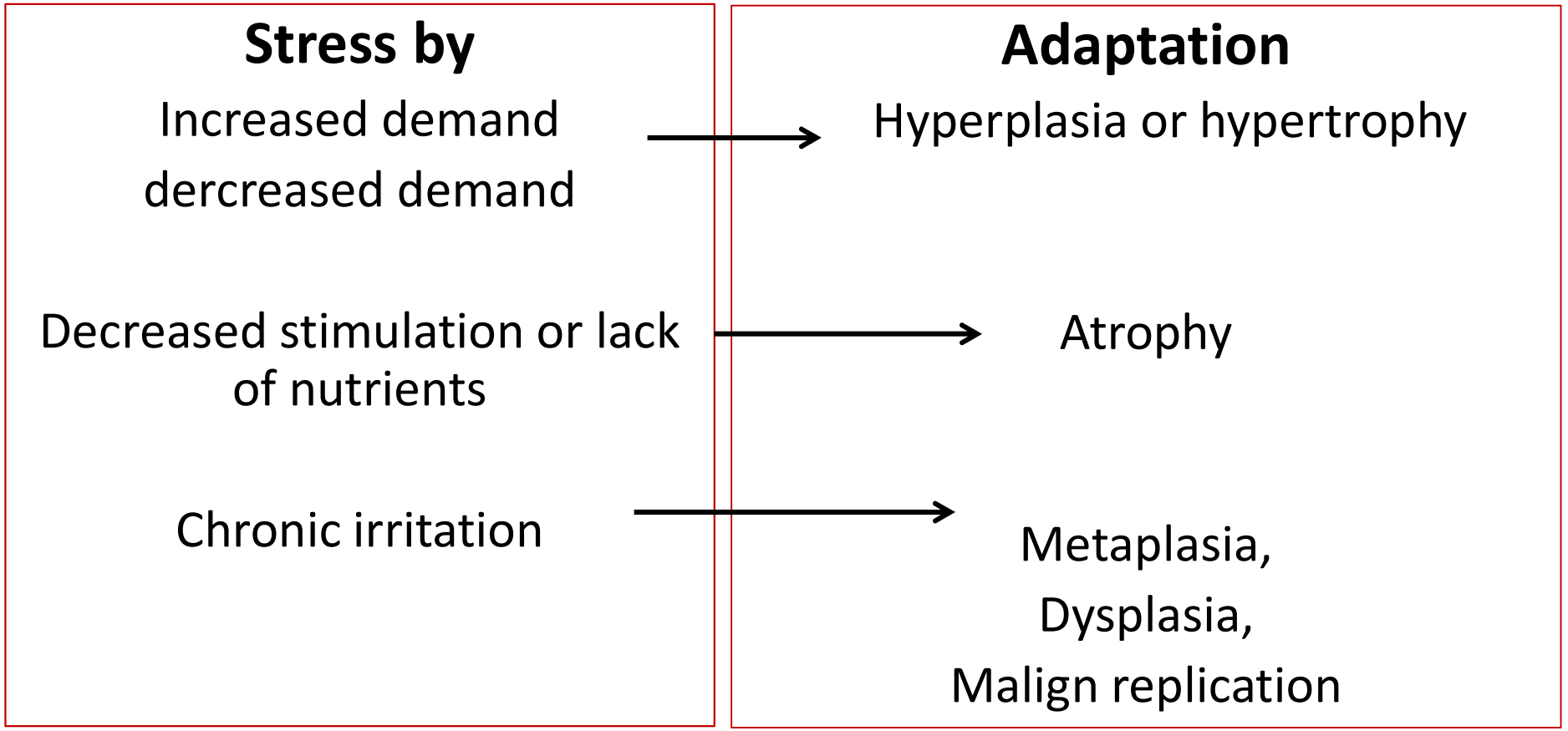
→En cas de difficulté les flux sanguins sont redistribués,
→au détriment des muscles, du tube digestif et des reins

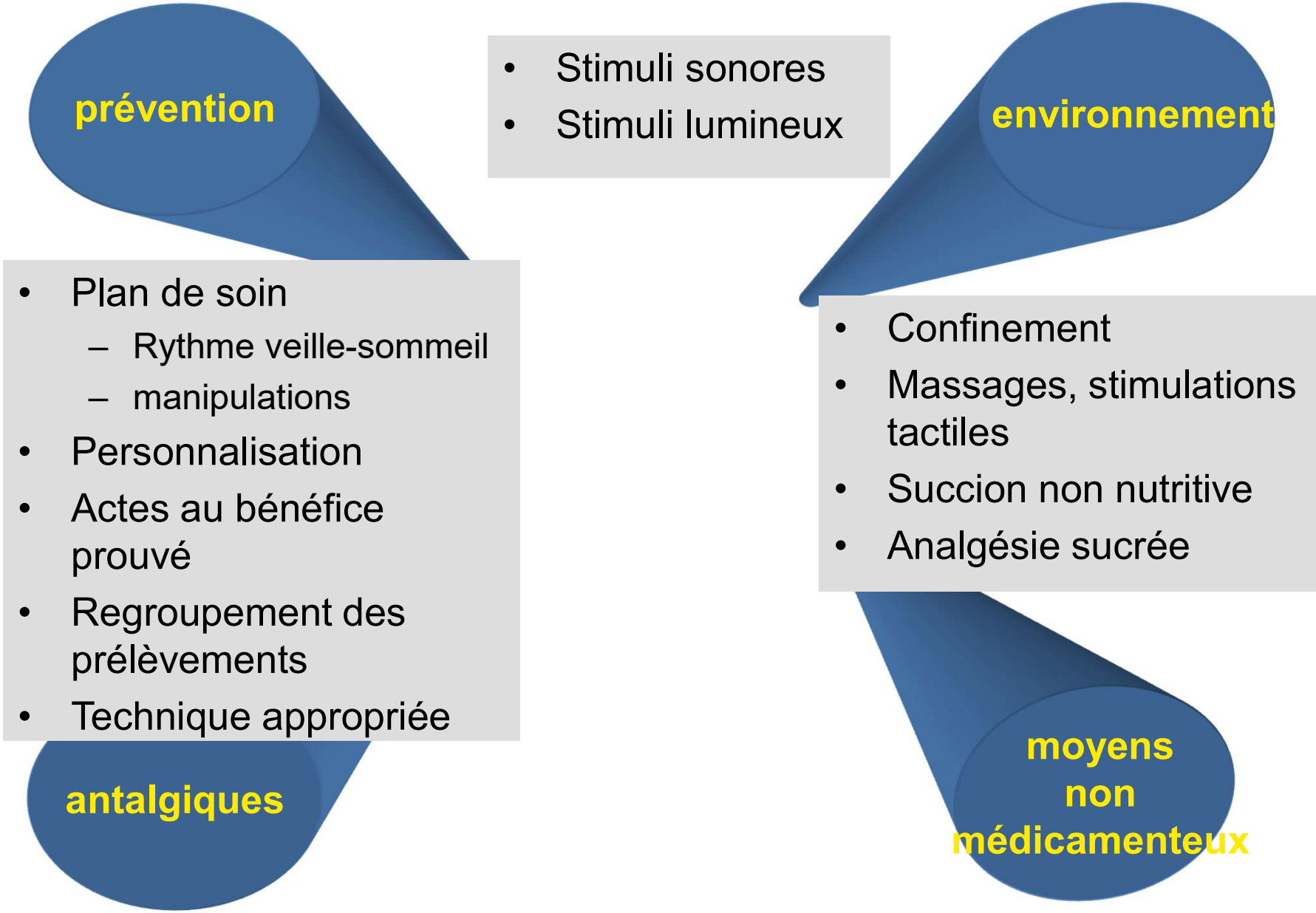
→En dessous d'un apport en AA ou PTde 0.8g/kg/j
L'enfant sera obligé d'utiliser les sources internes

l'origine ou le focus de la perturbation cellulaire

- **intrinsèque:**
  - Le cytoplasme
  - Les organelles (exemples: mitochondries, lysosomes)
  - La membrane
  - Le noyau
- **extrinsèque**
  - Chez des Cellules normales
  - chez et venant de cellules anormales

Cellular Adaptation to Injury or Stress



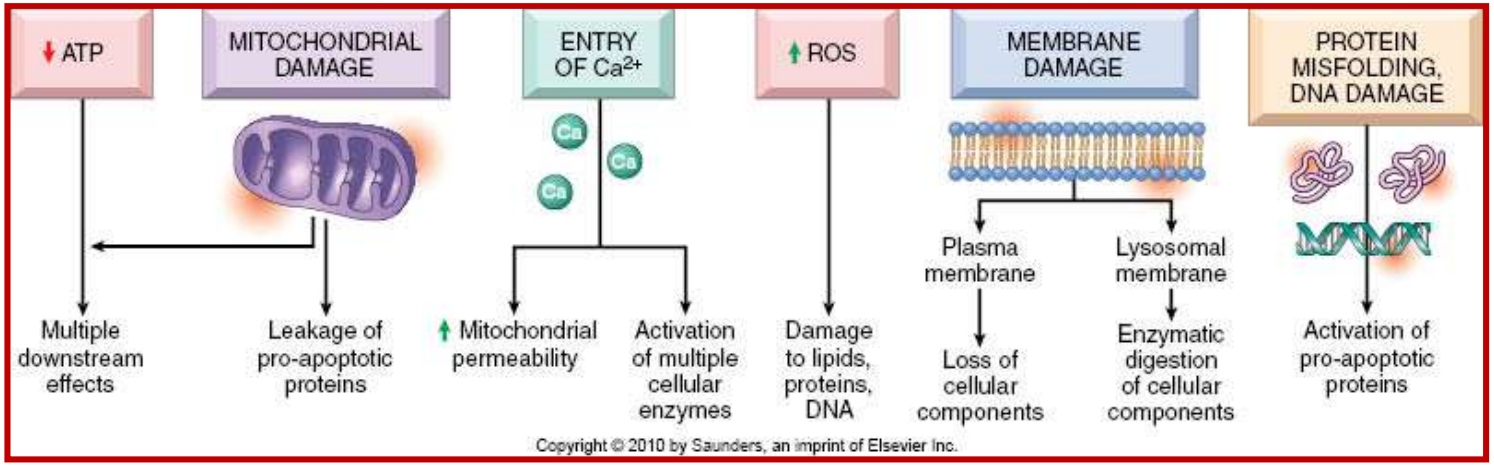

prévention
• Plan de soin
– Rythme veille-sommeil
– manipulations
• Personnalisation
• Actes au bénéfice prouvé
• Regroupement des prélèvements
• Technique appropriée
antalgiques
• Stimuli sonores
• Stimuli lumineux
environnement
• Confinement
• Massages, stimulations tactiles
• Succion non nutritive
• Analgésie sucrée
moyens non médicamenteux

Les Atteintes cellulaires

- Les fonctions cellulaires peuvent être perturbées de manière aiguë ou chronique
- Par déficit de la source énergétique
- par accumulation d'une substance mal métabolisée
- Par entrée ou sortie intempestive d'un composant par ailleurs normal ou toxique

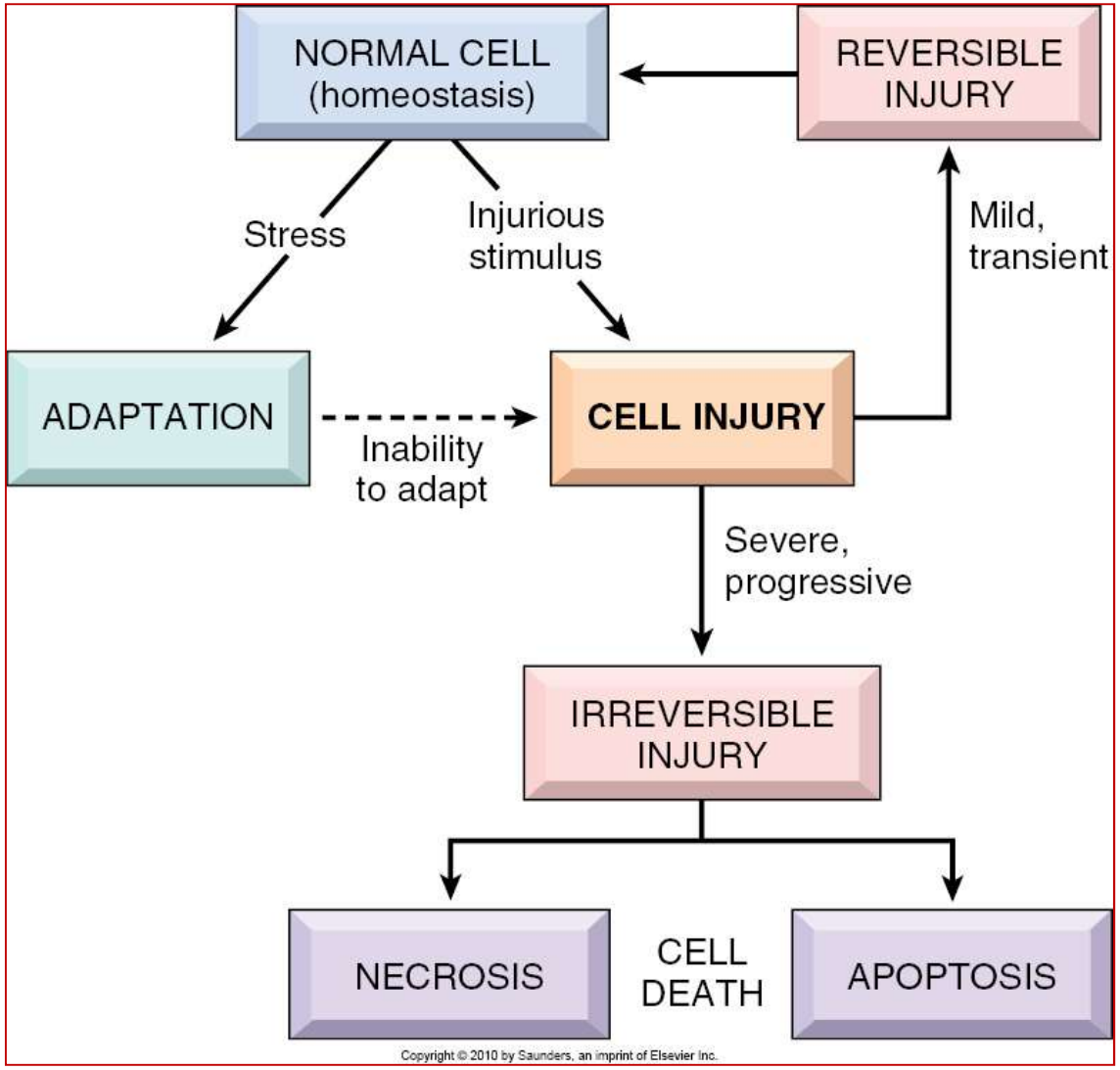
Mechanisms of cell injury

- Depletion of ATP
- Damage to Mitochondria
- Influx of Calcium
- Accumulation of Oxygen-Derived Free Radicals (Oxidative Stress)
- Defects in Membrane Permeability
- Damage to DNA and Proteins

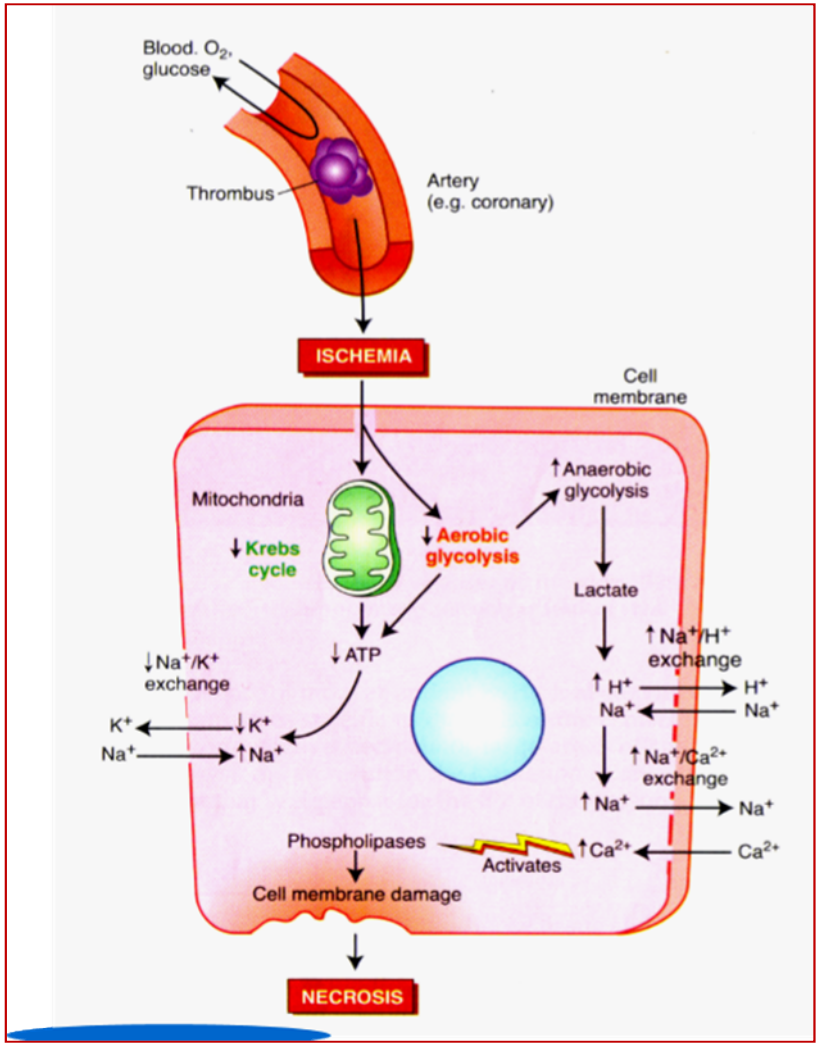


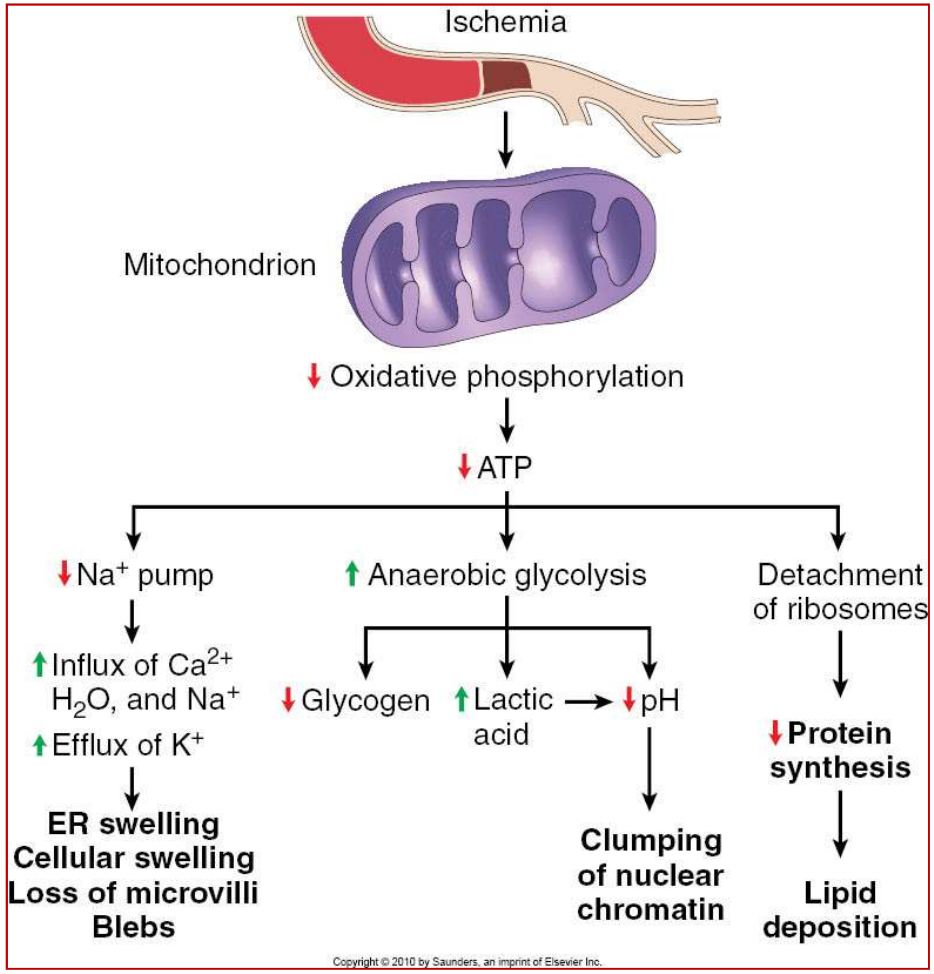
Maintien de la vie cellulaire
croissance
pH, énergie, O2, flux sanguin, potentiel intrinsèque

Hypertrophy
hyperplasia
Hypotrophy
Atrophy
metaplasia



Ischemic hypoxic injury





Early stage Hypoxic cell injury

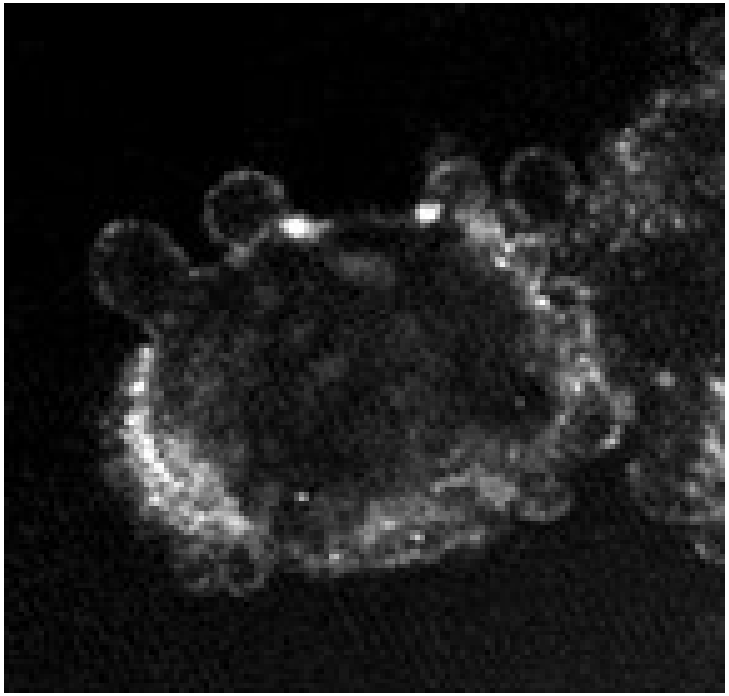
- Decrease in production of ATP
- Changes in cell membrane
- Cellular swelling
  - endoplasmic reticulum
  - mitochondria
- Ribosomes disaggregate
- Failure of protein synthesis
- Clumping of chromatin

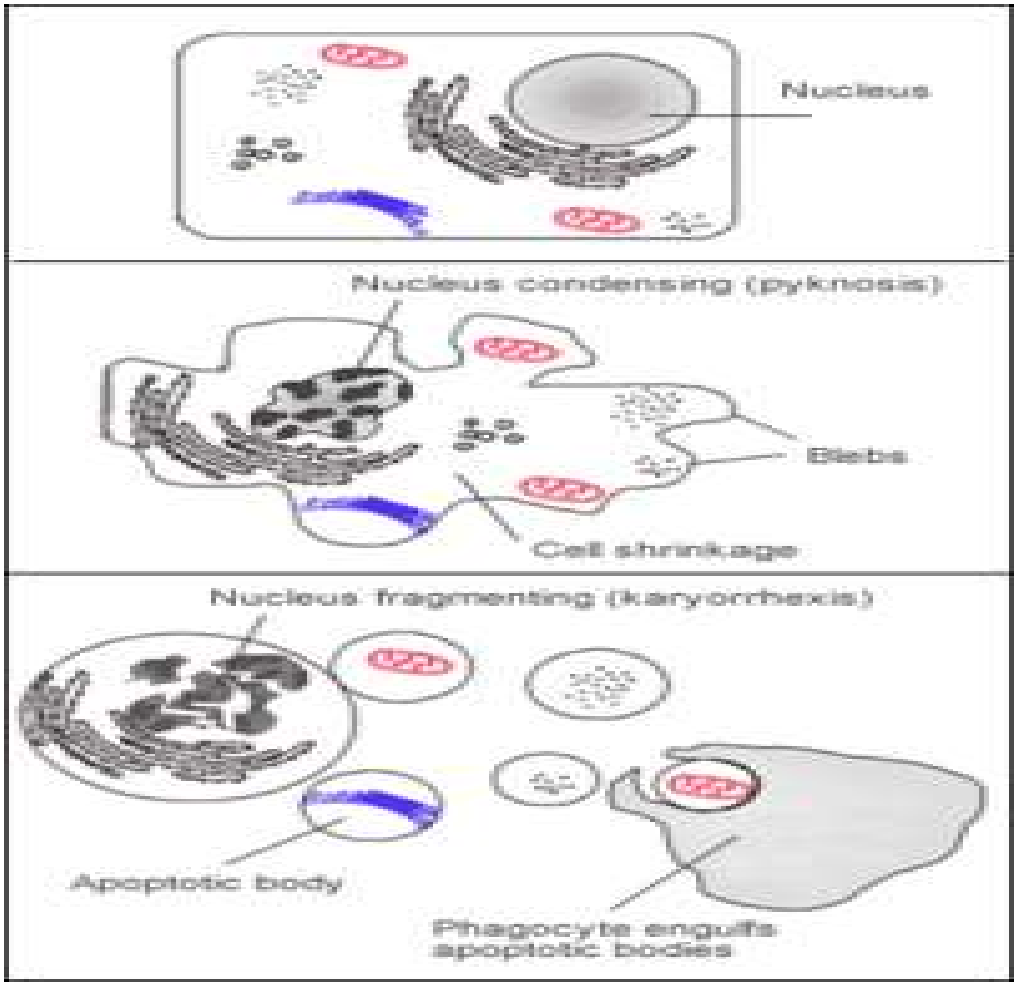
Late stage

- Cell membrane damage

  myelin blebs

  cell blebs





Glucose and energy in cells: cytoplasm and mitochondria also dependent of body temperature

In normal cell: G + O2 —(> 95 %)→ ATP + CO2 + H2O

Free radicals —→ coupled radicals (< 5%)

cell with mitochondrial impairement:

G + O2 hypoxia → ATP + CO2 + lactic acid

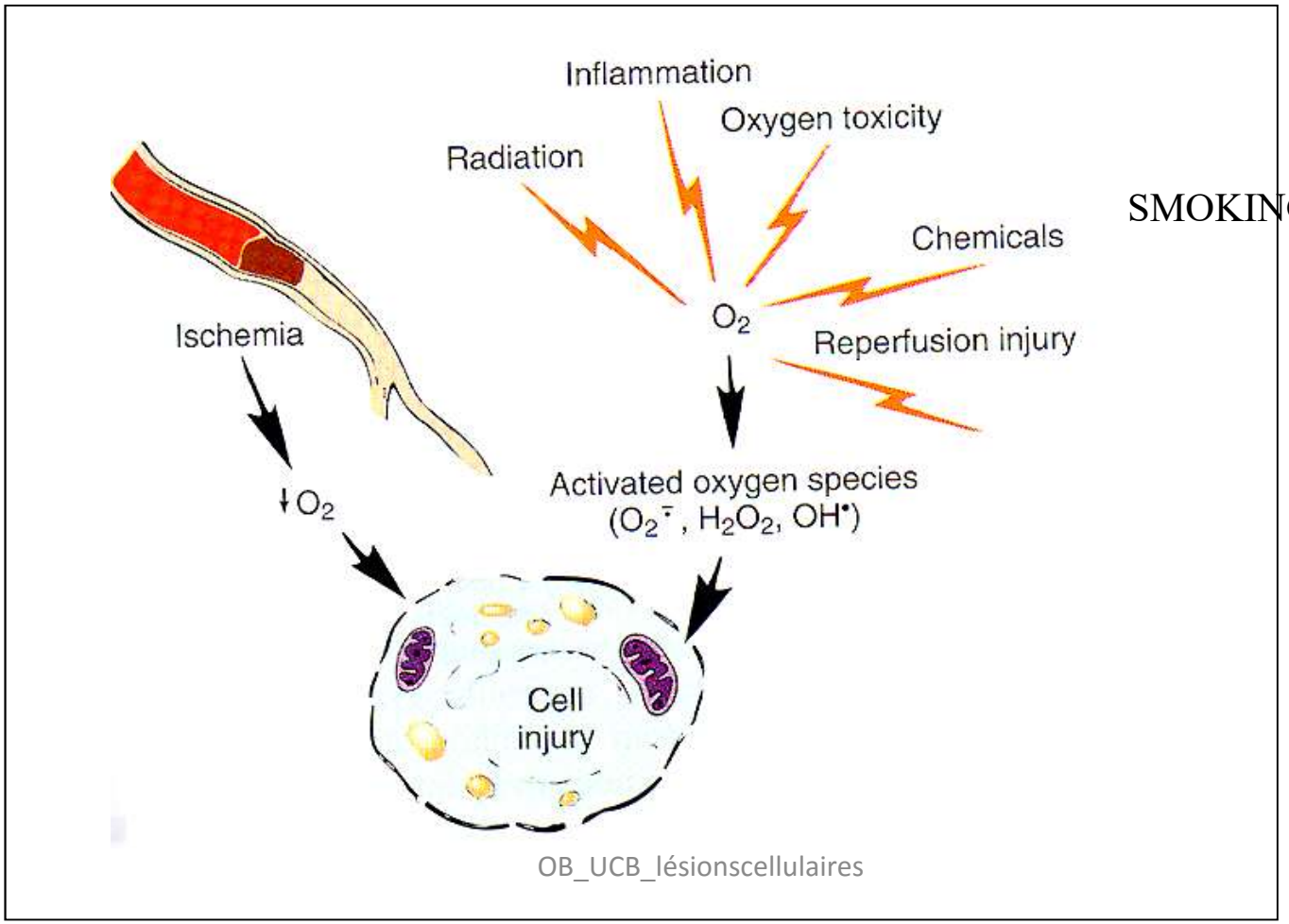
reoxygenation → Loss of energy and Electrolytes disturbances

→ Free radicals

25

Free Radical-Induced Cell Injury

Generation of reactive oxygen free radicals



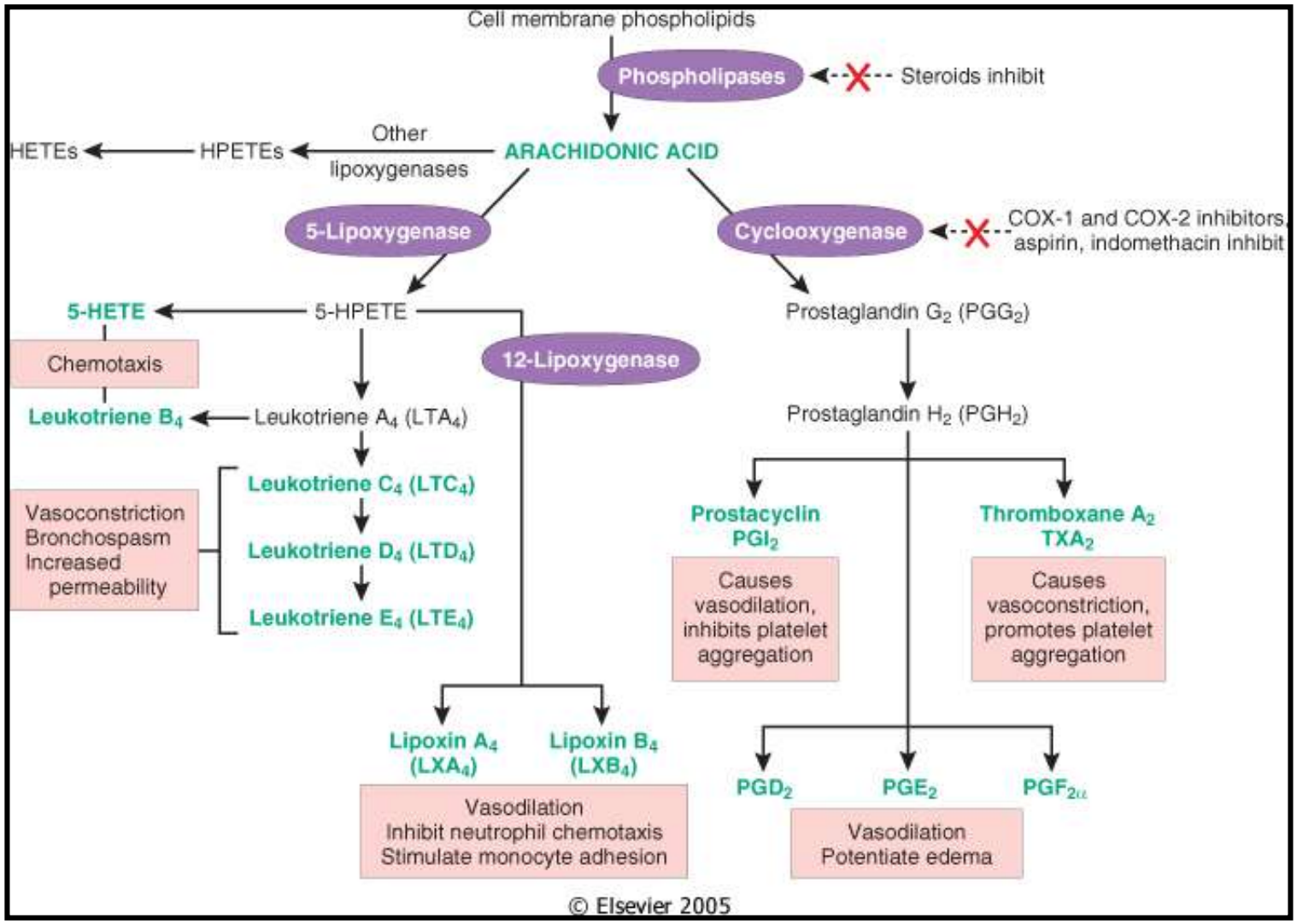
SMOKING

Free Radicals

- Antioxidant defenses =
- Glutathione
- Catalase
- Superoxide dismutase
- Vitamin A, C, E
- Cysteine, selenium, ceruloplasmin
- Spontaneous decay

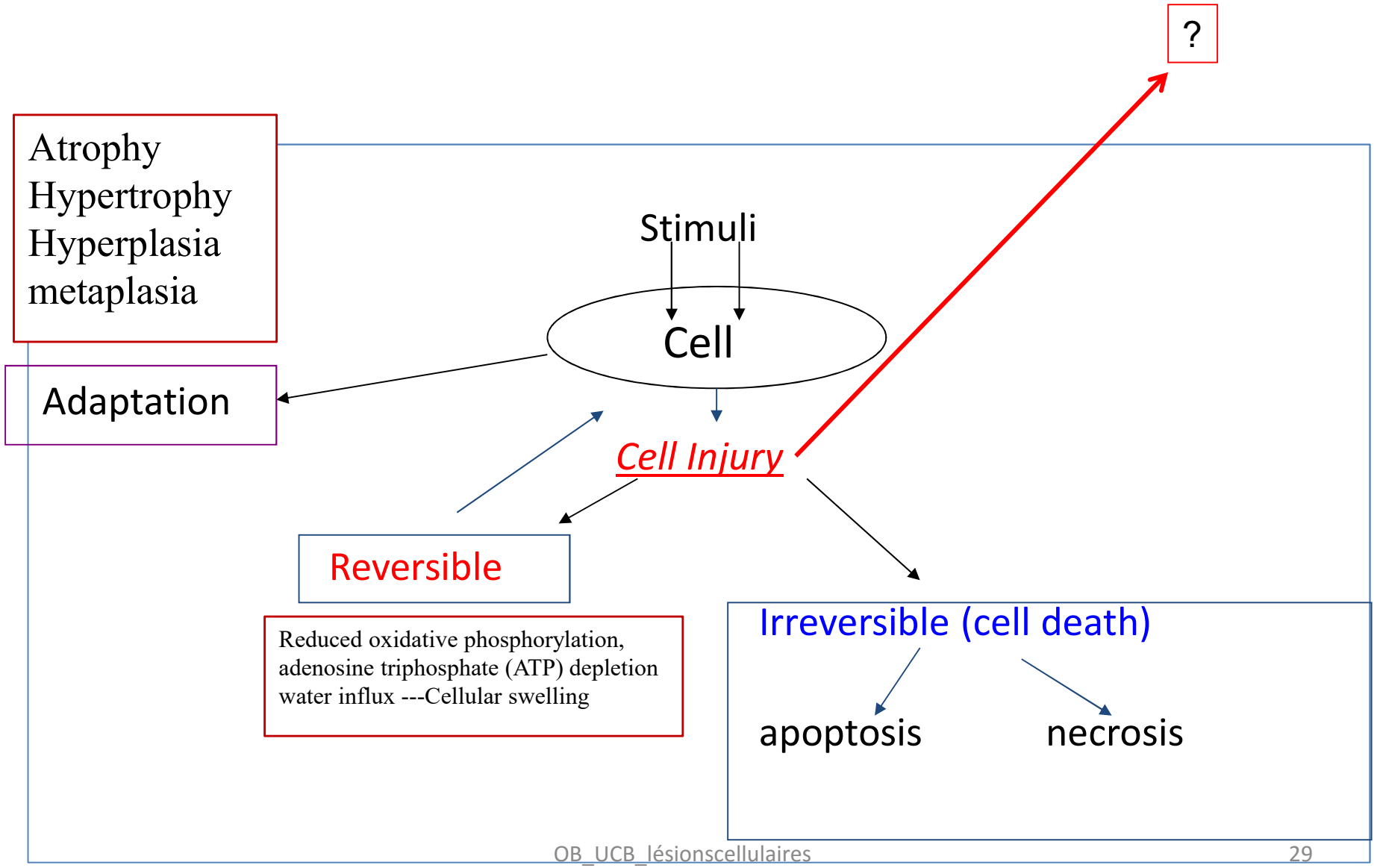
1.

Dans le cerveau humain, les oligodendrocytes sont le lieu principal D'évacuation. Ce rôle n'est pas suffisant avant 34-35 semaines. Ce rôle précède le rôle de la synthèse de la myéline



« la ou les cascades inflammatoires

Elle est dans un environnement qui peut être “hostile”



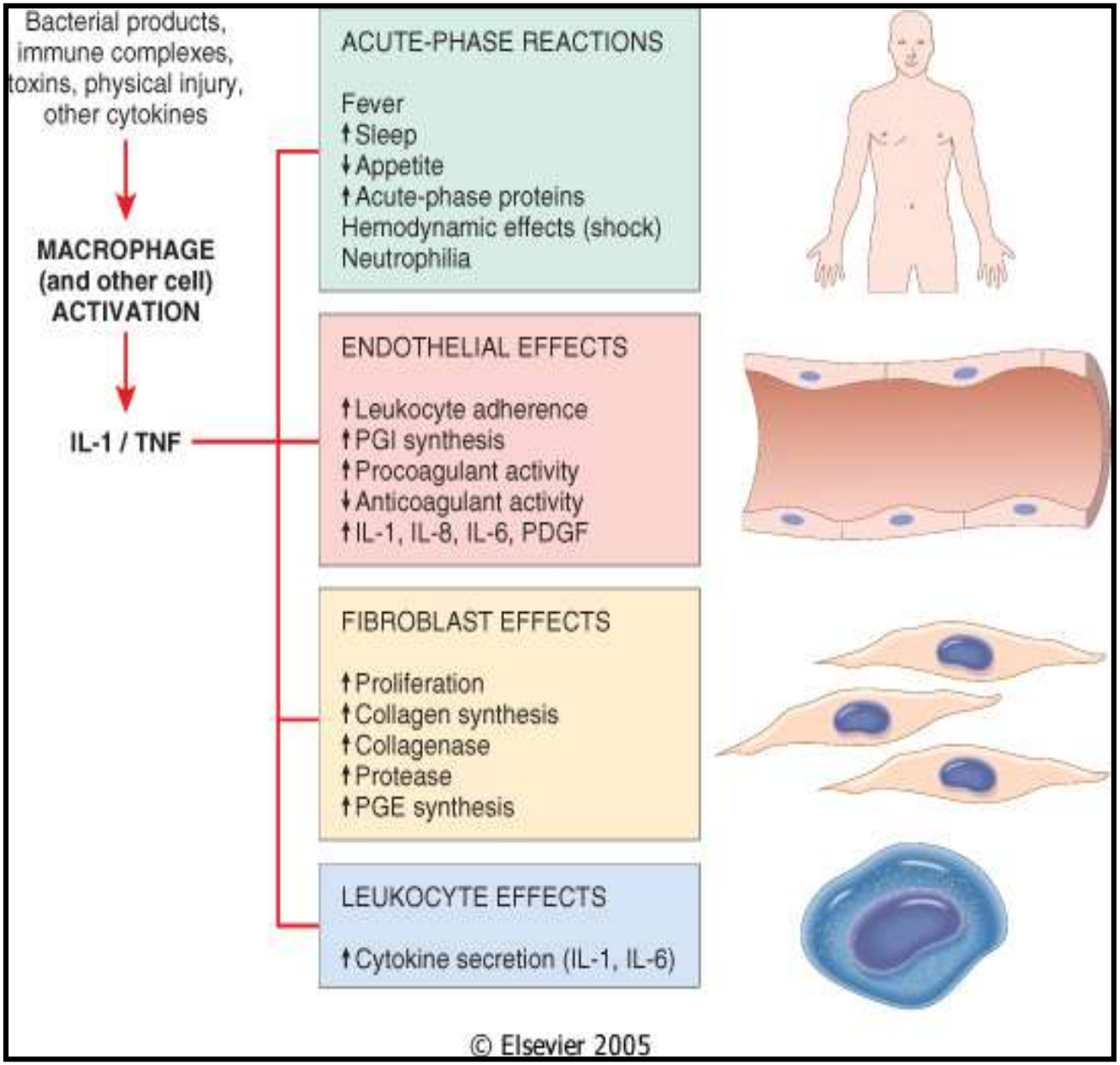


Figure 2-18 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Le Syndrome d'activation macrophagique dans le cerveau

From protecting to damaging « biochemical parameters »

Depending on the environmental conditions, actual and preceding, factors can protect or damage

iCe and iNu Ca++
FR
CREB, CAMD, caspase 3 and 6

Appoptotic cascade :

- if > 1h ofLow pCO2 (< 27 mmHg;)
- if > 6 h of high pCO2 (> 65 mmHg)
-if hypoxia (> 65 mmHg? pO2)
-for > 1 h ? Time ?

TABLE 1
The Relationship of Some Presumably Protective Substances to Oligodendrocytes and Neurons

Category	Molecule	Oligotrophic Functions: Promotion of Oligodendrocyte Differentiation	Oligotrophic Functions: Promotion of Oligodendrocyte or -Precursor Survival	Oligotrophic Functions: Protection of Oligodendrocyte or Promotion of Remyelination	Neurotrophic Functions: Promotion of Neuronal Survival or Protection
Hormones	Corticosteroids	42, 121	121	122	123-125
	Thyroid Hormones	42, 43, 126	127	128, 129	44-46
Neurotrophins	BDNF		37		115, 130-134
	NGF		35 *killer: 135*		136-140
	NT-3		35, 37, 59		132, 133, 141
IL-6 family	IL-6		37, 105		
	LIF	58 *astrogenic: 105*	37, 58		142
	CNTF	58 *astrogenic: 105*	37, 58	58, 102, 103	143-145
Angiogenic cytokines	VEGF			*Expressed by glial cells during hypoxia: 146-148*	*Expressed by neurons during hypoxia: 146*
	bFGF	*Inhibitor: 64, 67*	149-151	152, 153	136, 154-157
Other cytokines and growth factors	EGF	*Inhibitor: 158*		159	155-157, 160-162
	IGFs	25, 55, 163, 164	37, 66, 165	25, 166, 167	168-172
	PDGF		66, 150	173	132, 174, 175
	TGFβ	176		177	178-182
	GGF/Neuregulin		183		
	IL-2	184-187			

The numbers identify relevant references (*controversial issues in italics*). Abbreviations: NGF, nerve growth factor; LIF, leukocyte inhibitory factor; EGF, epidermal growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF-β, T-cell growth factor-β.

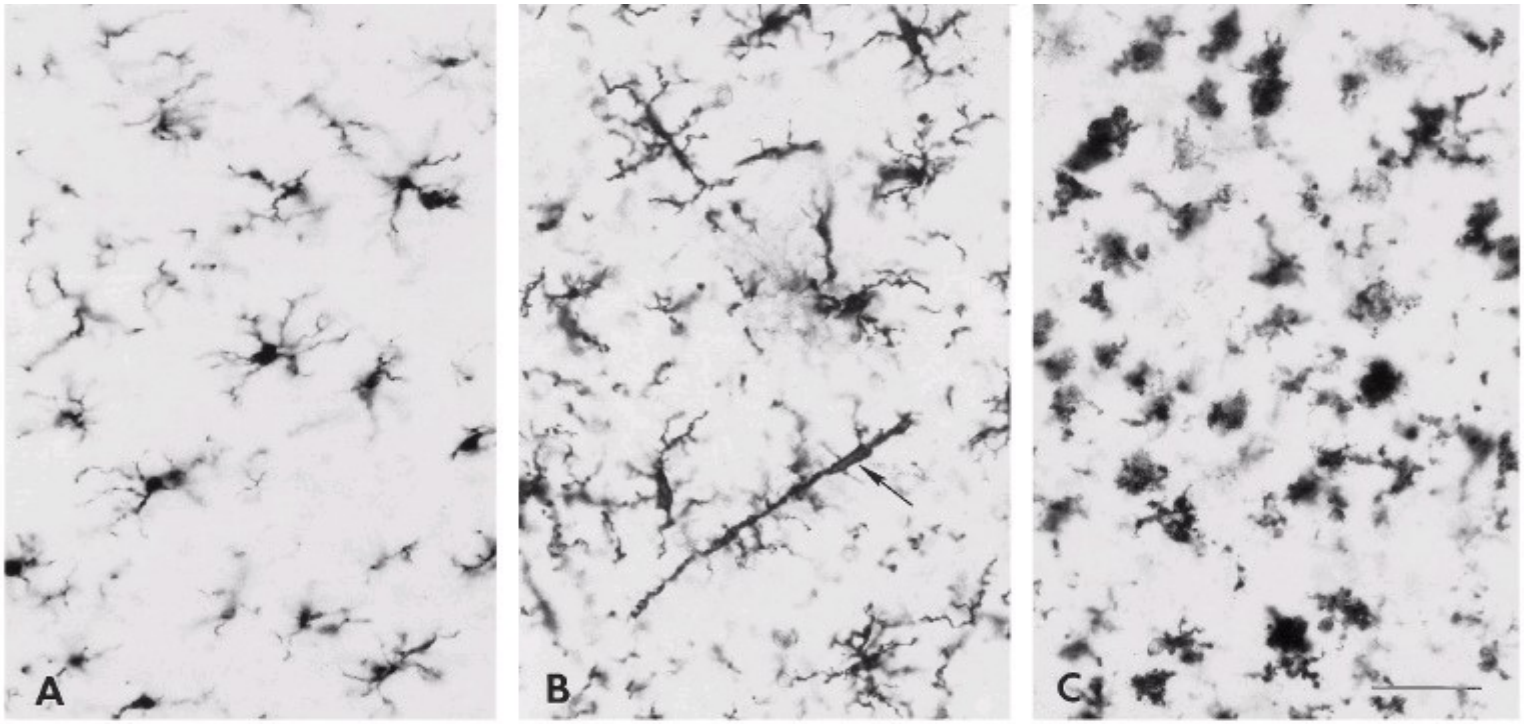


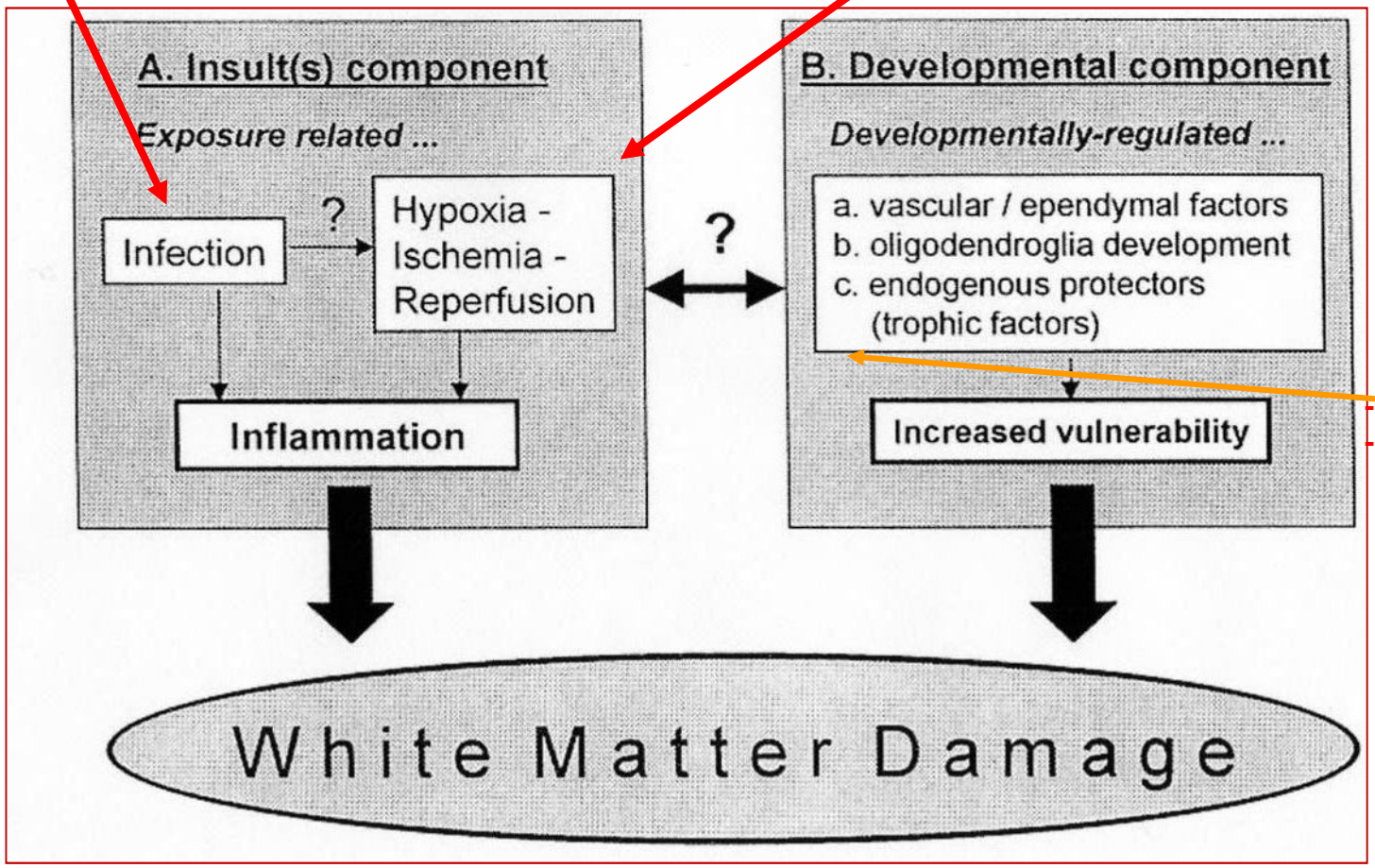
FIGURE 1.20 Activation of microglial cells in a tissue section from human brain. Resting microglia in normal brain (A). Activated microglia in diseased cerebral cortex (B) have thicker processes and larger cell bodies. In regions of frank pathology (C) microglia transform into phagocytic macrophages, which can also develop from circulating monocytes that enter the brain. Arrow in B indicates rod cell. Sections stained with antibody to ferritin. Bar = 40 µm.

(courtoisie du Prof Sarnat)

L'activation macrophagique par l'hypoxie cérébrale

This is in about 15- 25 % of cases

This is about in 70- 80 % of cases



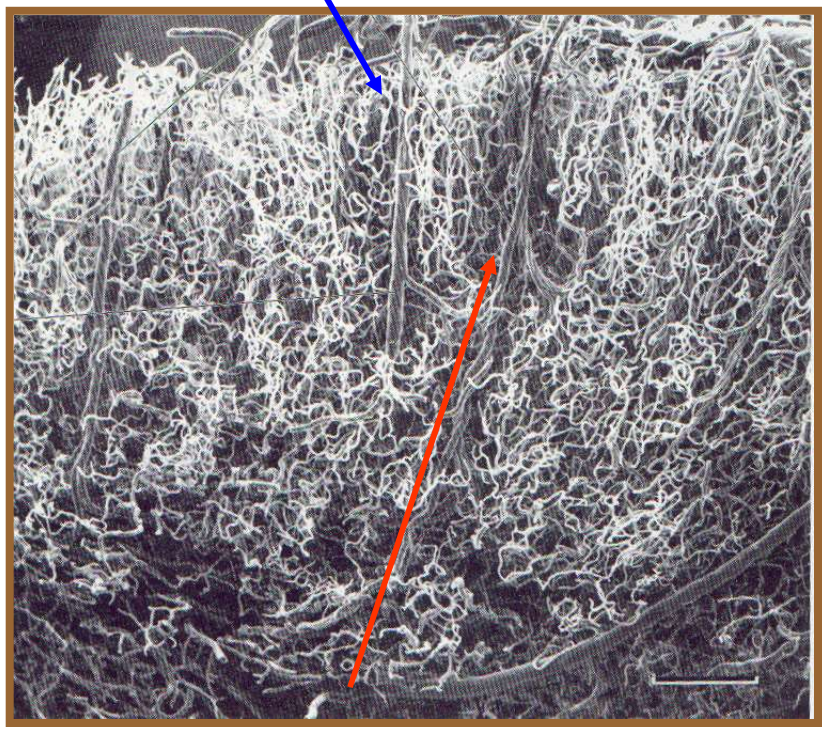
- Late migration
- CBF autoreg

Fetal and neonatal Brain development: histology and biochemistry

- Early neuronal migration (Rakic)
- Late neuronal migration (Sarnat)
- Cerebral blood flow (Lou)
- Autoregulation of CBF (Lou, Greisen)
- Cerebral metabolism (Volpe)
- Autoregulation of CM
- Focus on neurons
- Focus on glial cells
- Clinical aspects

L'atteinte inflammatoire du SNC
Avant 34 semaines → Atteinte de la région PV
- par production locale dans 80 %
-Par production hors SNC dans 20 % des cas

Kernicterus is …



40 % glial cells , 4 % neurons, 4 % blood,
10 % CSF, 35 % ECF, 10 % variance

Metabolic aspects
Intracerebral Consequences of iCDO2 and/or iCDG

- **At BBB level**: entry of small molecules (15 ‘) and big molecules (120 ‘); of neutrophils and monocytes (120 ‘)
- **At neurons level**: axones then dendrites edema (30-55 ‘), followed by retraction and hypersensitivity to EAA; body edema (50-75 ‘), action on peptides and nucleus;
- **At vessels’level** :capillaries surrounded, , thrombosis;
- At OL level:
- At astrocytes level:→ glutamate, NO, FR, proteolytic enzymes
- At microglia level:

- **Energy failure and oxydative stress:**

→ **Free radicals** (OFR, NO, Fe+++)

→ **EAA**

→ **Release of NA from locus ceorulus**

→ **Activation of microglia and LycT4**

→ **Genes activation (CREB, JUN**

→ **Relesa of toxins: AOAA, MPP, 3NPA**

→ **Inflammatory products:**

- Proteolytic enzymes on matrix: from neurons, astrocytes, microglia;

- Il 1,6,8,9, TNFa, complement, antithrombin III, factor V, protein C, antipohospolipid antibody

damage

repair

- Similarity of reactions by neurons;
- **more dependency of environment**
- **damage from inside CNS**:

--> ***astrocytes***,

loss of nutrition, of cytoskeletal compound, activation of GAP3 and release of toxins

--> ***microglia***,

release of toxins and activation of MHCII and CR3

--> ***neurons***:

loss of targed-derived factors;

dendritic and axons atrophy and loss of molecules transport

--> low synthesis of growth factors and low leullar guidance

- **impairement of BBB** and arrival of cytokines (lungs, digestive tract, blood cells, bone marrow)
-

- **Neurotrophic factors have specific targets;**
- **their main roles are to prevent neuronal loss and maintenance of axons regrowth;**

1. ***Neurotrophins family*** (NGF, BDNF)
2. **Cytokins growth factors** (LIF, CNTF, CT-1)
3. **Fibroblats growth factors (FGF1 and 2);**
   mainly for layers II and III, hippocampus.
4. **The insulin growth factors**
5. **The transforming factor beta family of growth factors;**
6. **Epidermal growth factor**
7. **Hepatocyte GF and Immunophilins**

Reversible & irreversible injury

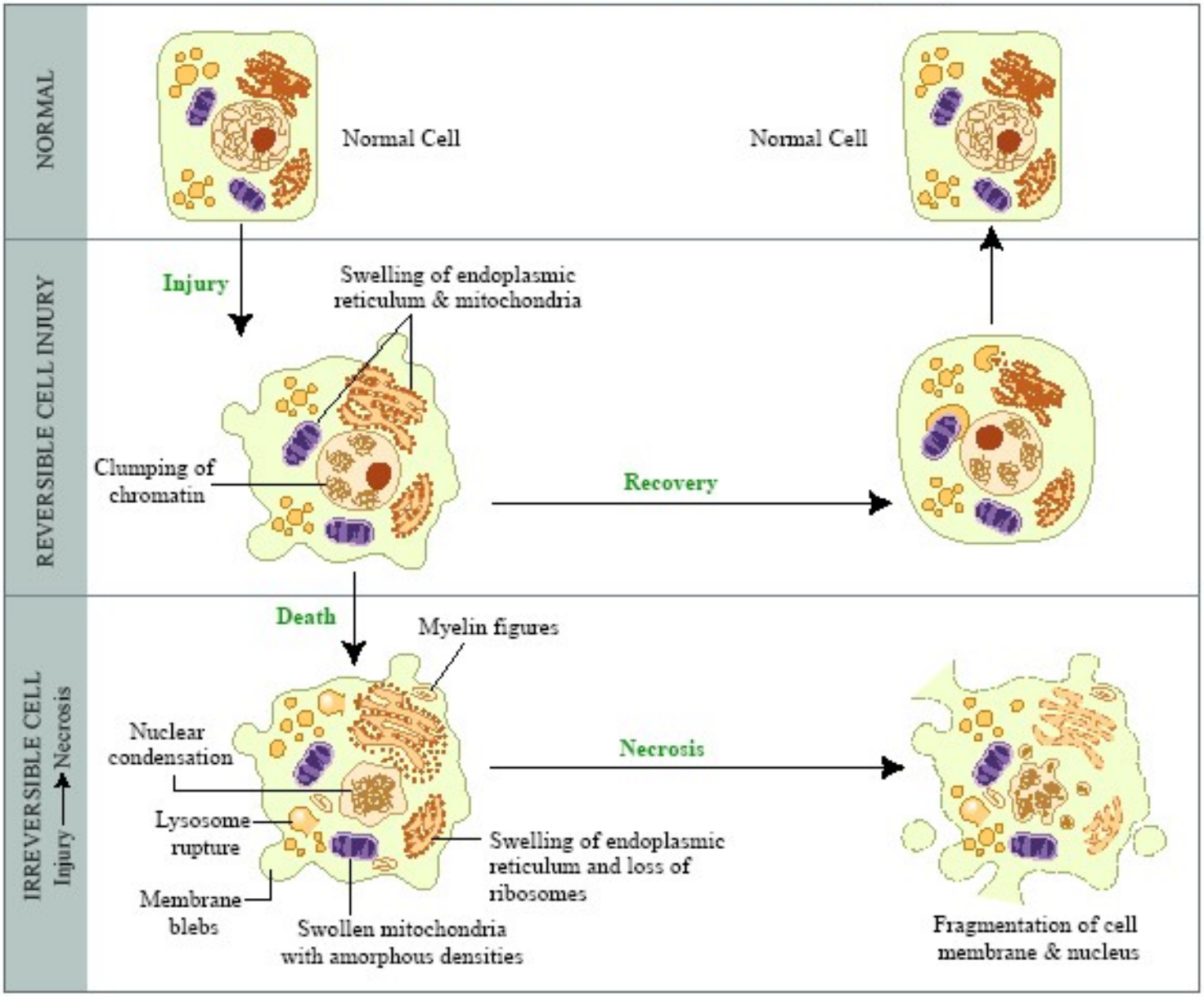


Figure by MIT OCW.

Reversible Injury

1. **Cellular swelling**
2. **Fatty change**

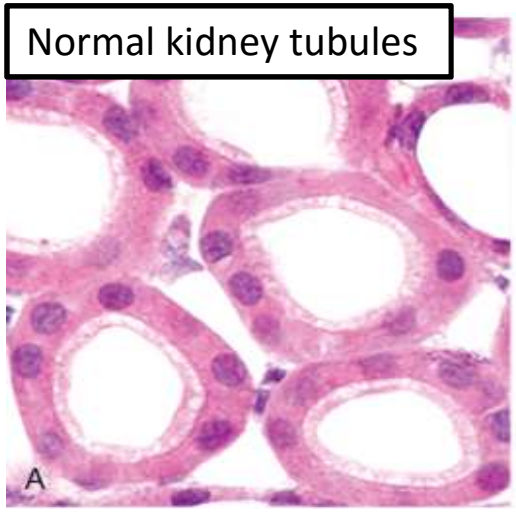
Reversible Injury

1. Cellular swelling

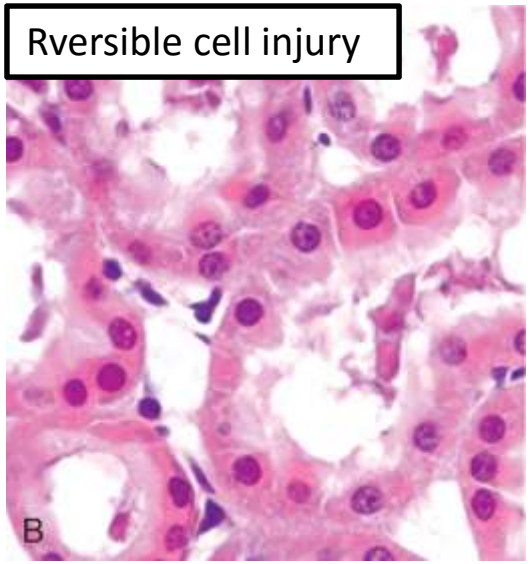
- Also called hydropic change or vacuolar degeneration
- Earliest change
- Grossly: organ pallor, increased weight
- Microscopy: small, clear cytoplasmic vacuoles

- Adenosine triphosphate (ATP) depletion
- water influx ---Cellular swelling

Normal kidney tubules



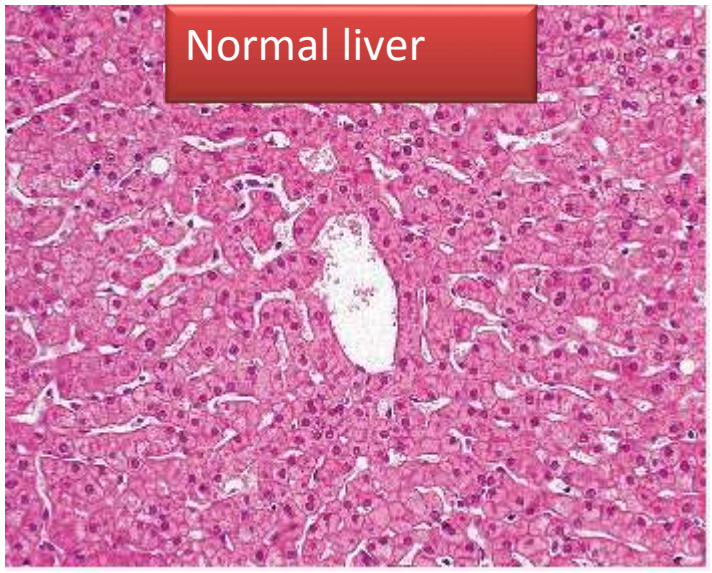
Rversible cell injury

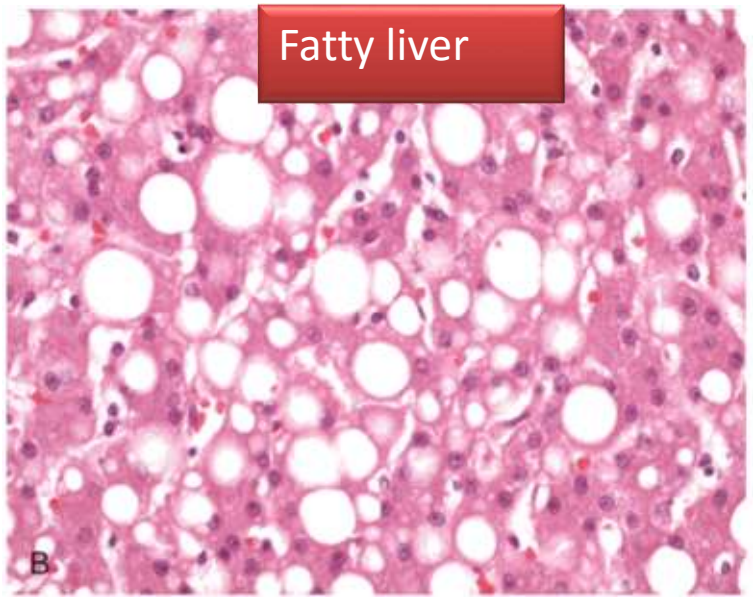


Reversible Injury

2. Fatty change

- Lipid vacuoles in the cytoplasm.
- In cells participating in fat metabolism (e.g., hepatocytes and myocardial cells).





Fatty change

- Liver, heart, kidney
- Accumulation of intracellular parenchymal triglycerides

  -increased transport

  -decrease mobilization

  -decreased use

  -overproduction

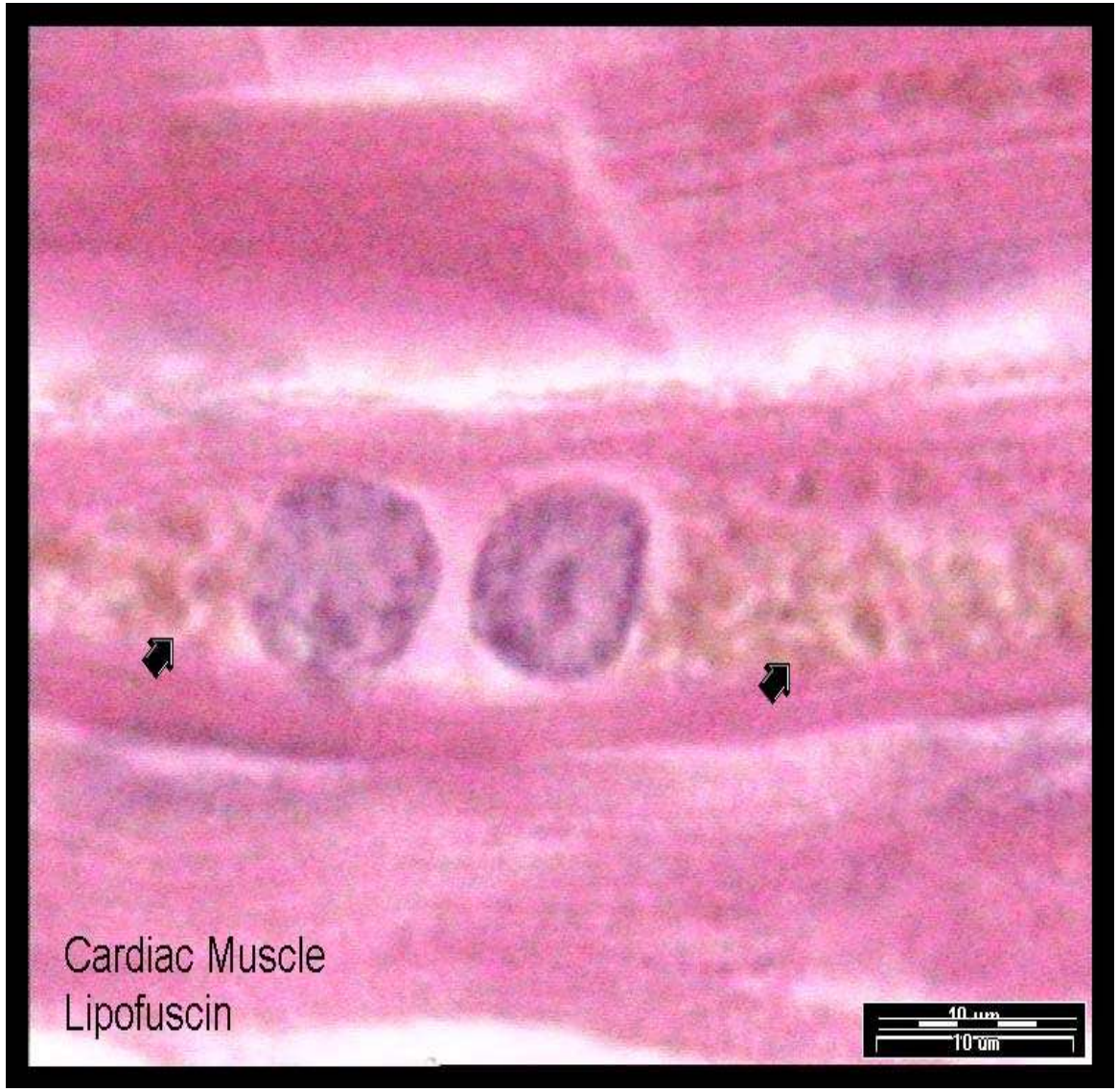
Lipofuscin

- S'accumule parfois avec l'âge dans le foie, le coeur, le cerveau. N'est pas toxique mais est le résidu d'un stress oxydatif.

- Complexes lipido-protidique formé par la peroxydation des acides gras polysaturés provenant des membranes cellulaires.

- Lipofuscin
- “wear and tear” pigment
- Elderly patients
- Liver, heart

- Brown atrophy

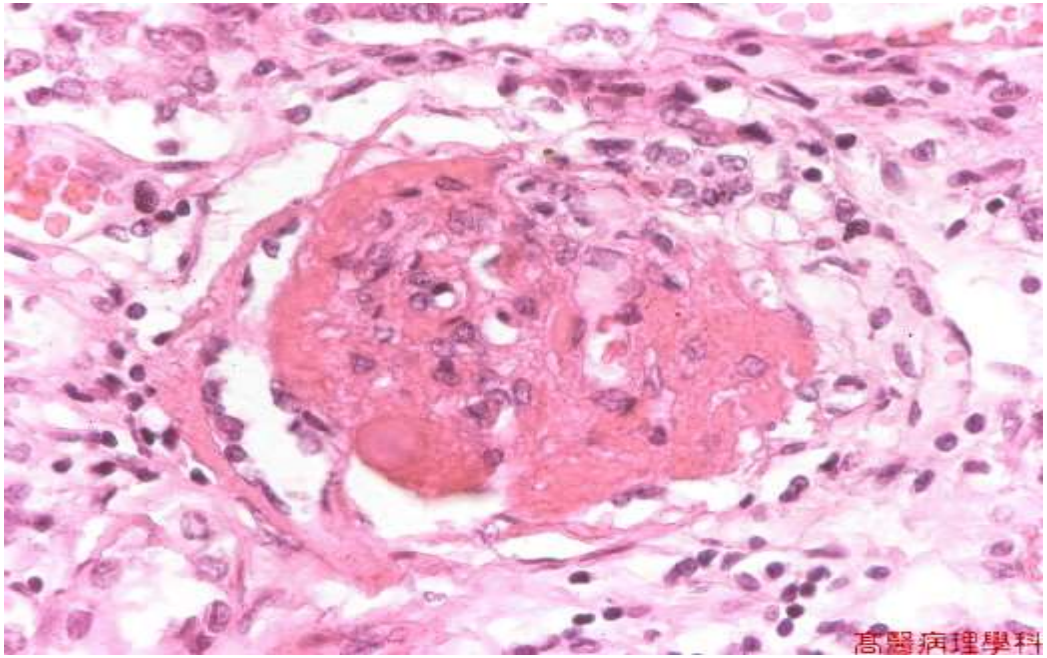


Melanine

- Produite par les melanocytes
- Et accumulé dans les keratinocytes voisins dans la peau (dermal macrophages)

Hyaline change

- Accumulation of hyaline
- HYPERTENSION; DIABETES MELLITUS
- “glassy” appearance



CALCIFICATION “bizarre”

- *dystrophic calcification*
- deposition occurs in dead or dying tissues,
- normal serum levels of calcium.

Forme la plus fréquente chez l’enfant

SNC: après infection (CMV, toxoplasmose)

Ganglions

Tube digestif: appendice !

Muscles

- *metastatic calcification*
- deposition in normal tissues
- *almost always reflects some derangement in calcium metabolism (hypercalcemia).*

Forme rare chez l’enfant

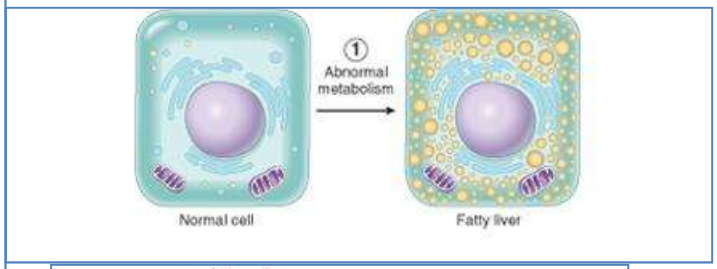
Les accumulations intracellulaires

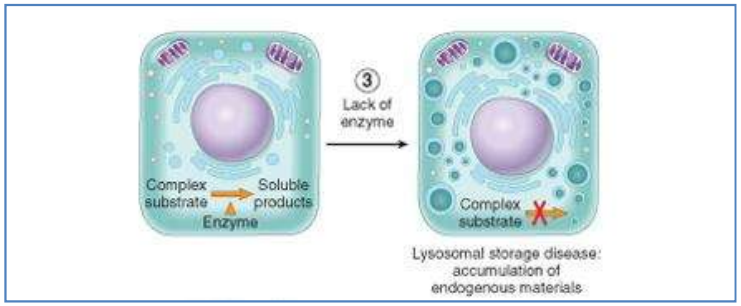
→ <u>Provocation de la cascade inflammatoire</u>:

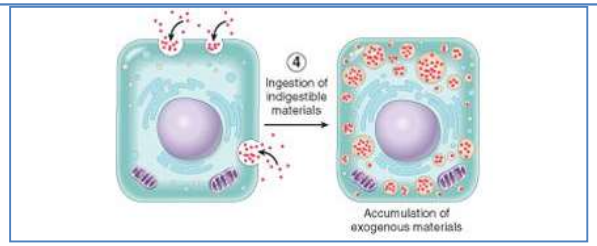
- Hyper réactivité immunitaire
- “folie cellulaire”: dans la malignité cellulaire

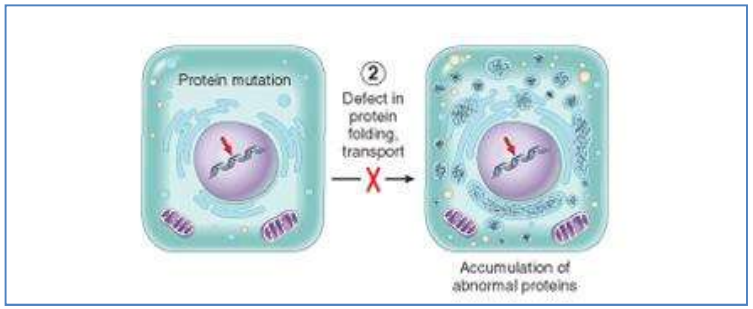
→ <u>Anomalie du métabolisme</u> par provocation ou par accumulation

→ <u>Anomalie de la cinétique métabolique</u> d’une substance









Two types of cell death

Necrosis

- Large No. of cells
- Invariably (*always)* pathologic
- Disrupted Plasma membrane
- Inflammation

Apoptosis

- Single cells or small clusters
- Often physiologic; may be pathologic
- Intact Plasma membrane
- No inflammation ,
- phagocytes to eleminate it

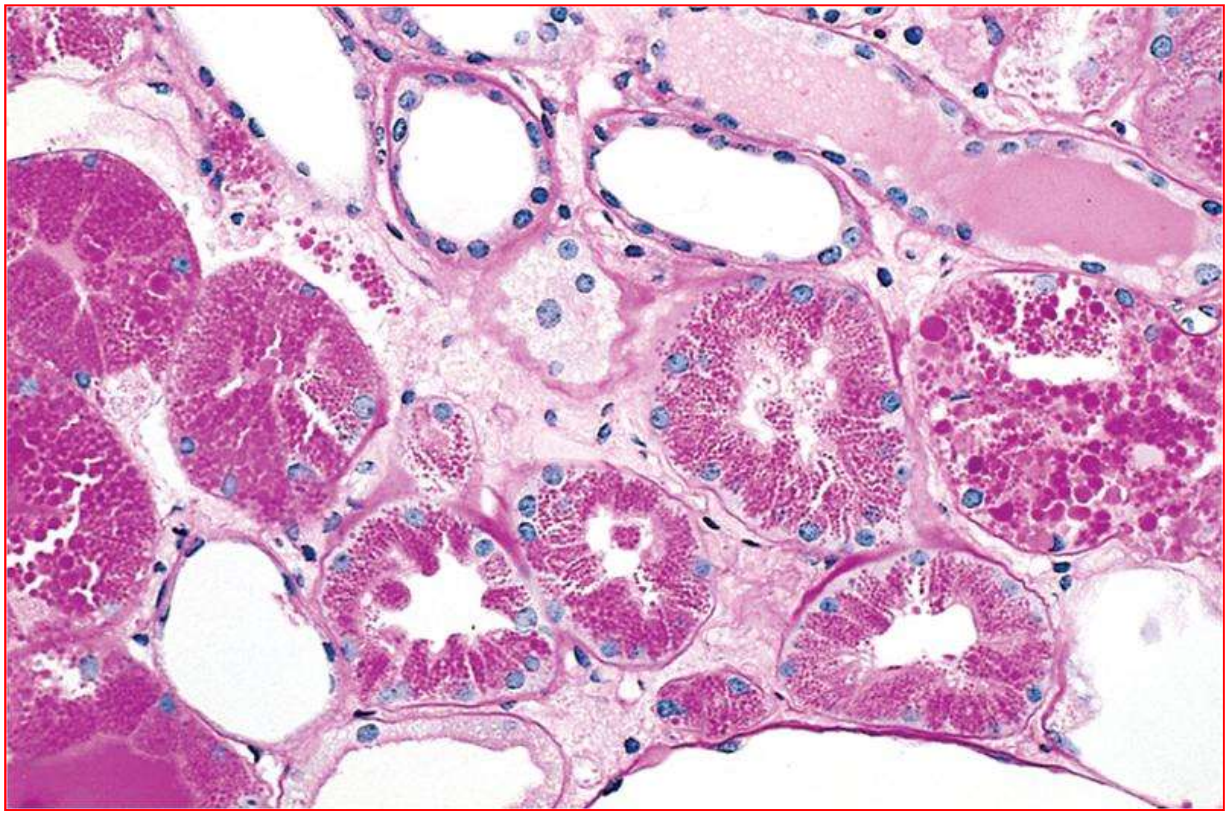
Cytostéatonécrose du nouveau-né

Irreversible injury Cell Death

- Irreversible damage to the cell membranes
- Calcium influx
- Mitochondria calcifies
- Release of cellular enzymes (CKMB, LDH)
- Most vulnerable cells: neurons, glial cells, renal tubules, hepatocytes, enterocytes.

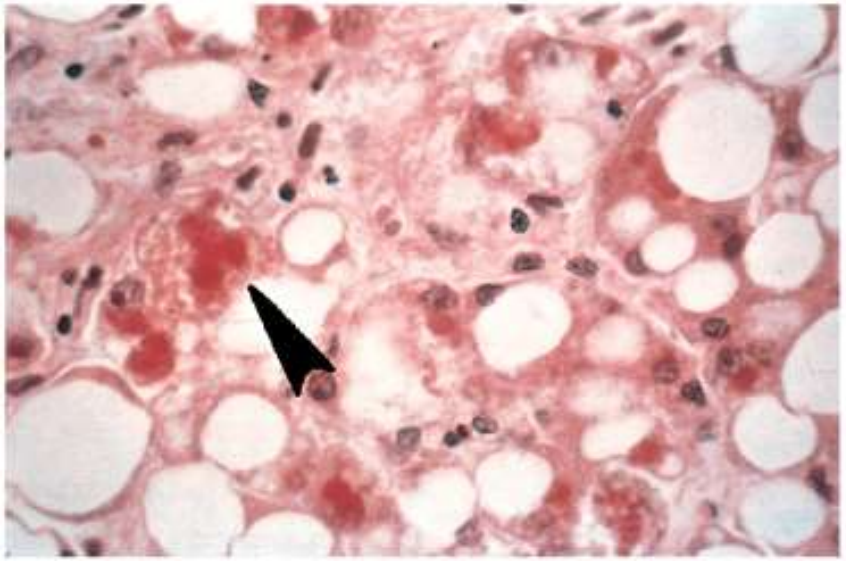
Accumulation de Proteines

Le syndrome néphrotique



Foie: corps de Mallory
(A and NAFLD)

Cerveau et Alzheimer

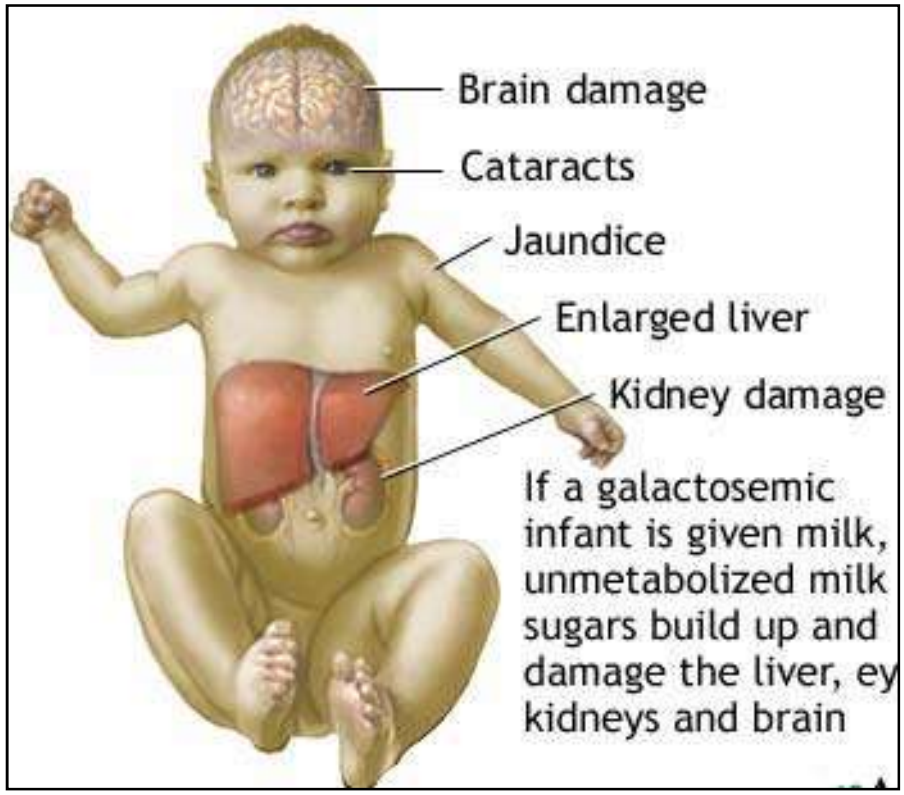


Ce sont le plus souvent :
-des filaments peptidiques « abandonnés »: foie, cerveau
-Des immunoglobulines inutiles ou corps de Russel dans le système RE

Accumulation of Glycogen

“Hypoglycémies précoces”:

-fructosémie, galactosémie
-Hyperinsulinisme
-Déficit en hGH



Traitement: éviction définitive du glucide: éviter le lactose ou le fructose

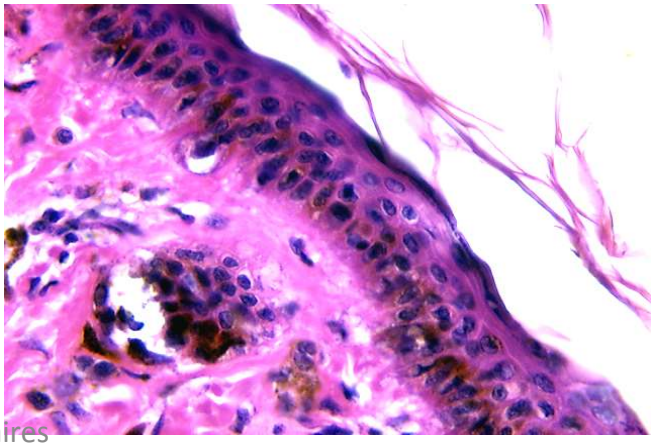
L’accumulation de Pigments

Pigments endogènes

- Bilirubine non conjuguée
- Bilirubine conjuguée
- lipofuscin,
- melanin,
- Dérivatés de l'hémoglobine.

Intracellular Accumulations

- Endogenous Pigments
  - Melanin
    - brown-black pigment produced in melanocytes
    - It is synthesized exclusively by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation



Hémosiderosis

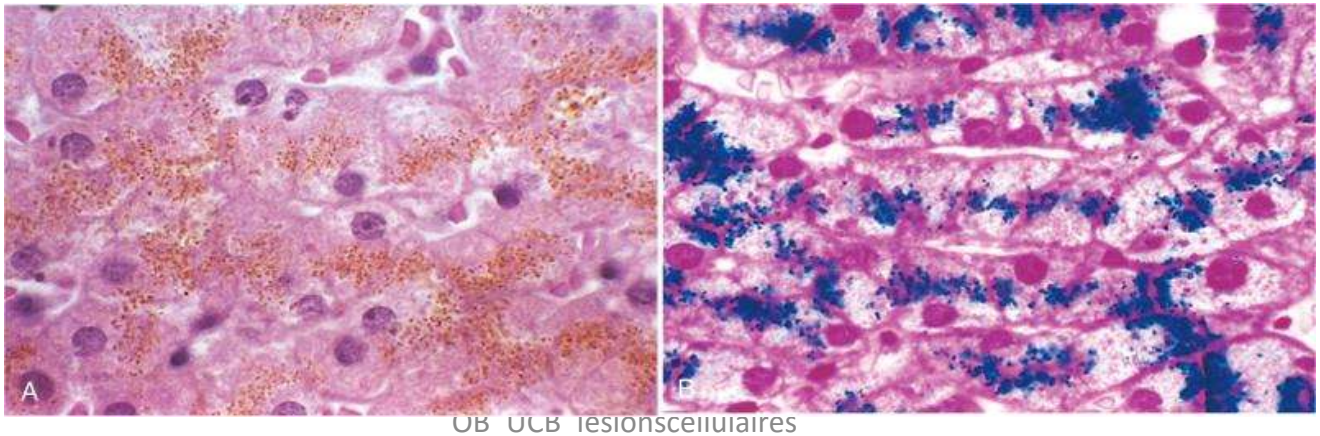
Augmentation du pool en fer

→Absorption

→Mauvaise utilisation

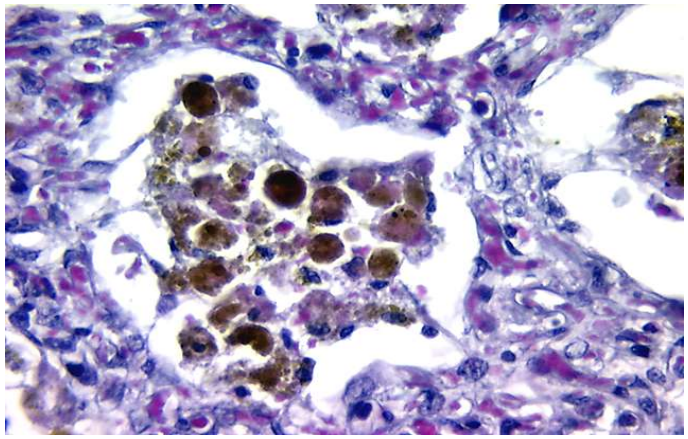
→Hemolyses chroniques

→transfusions



Intracellular Accumulations

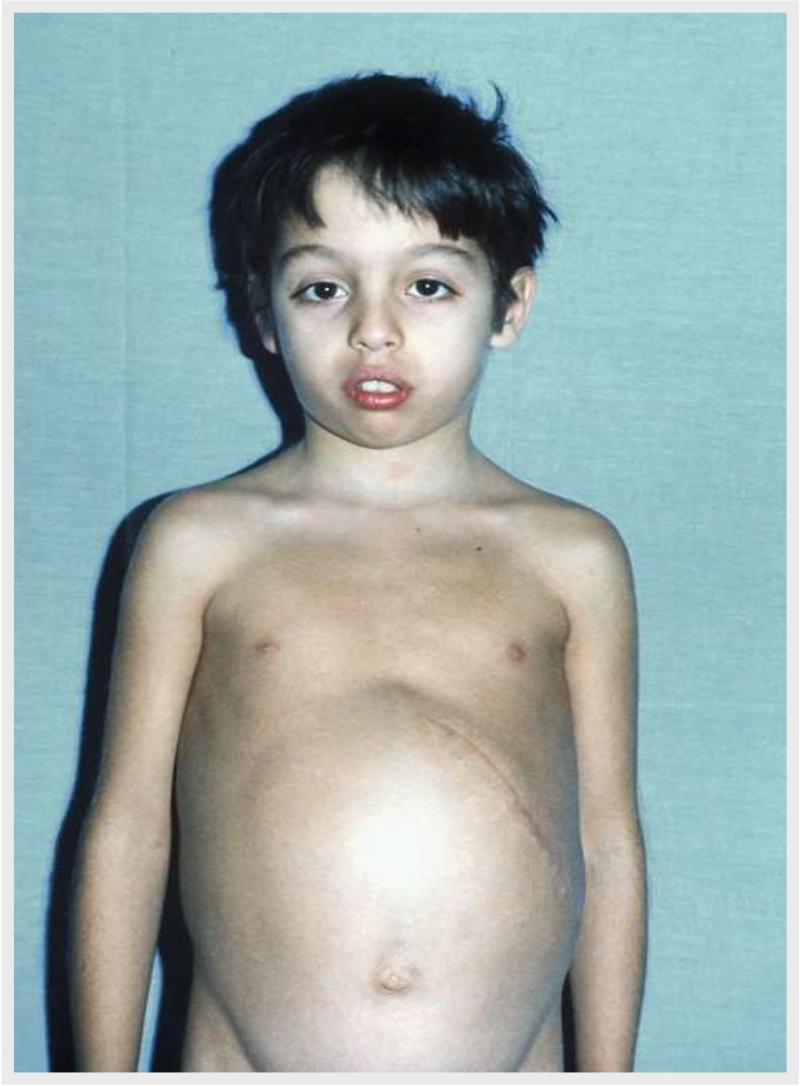
- Endogenous Pigments
  - Hemosiderin
    - iron containing golden-yellow pigmen
    - Local or systemic
    - *Local excesses* of iron and hemosiderin result from hemorrhages or vascular congestion, eg hemosiderosis is the common bruise. With lysis of the erythrocytes, the hemoglobin eventually undergoes transformation to hemosiderin.

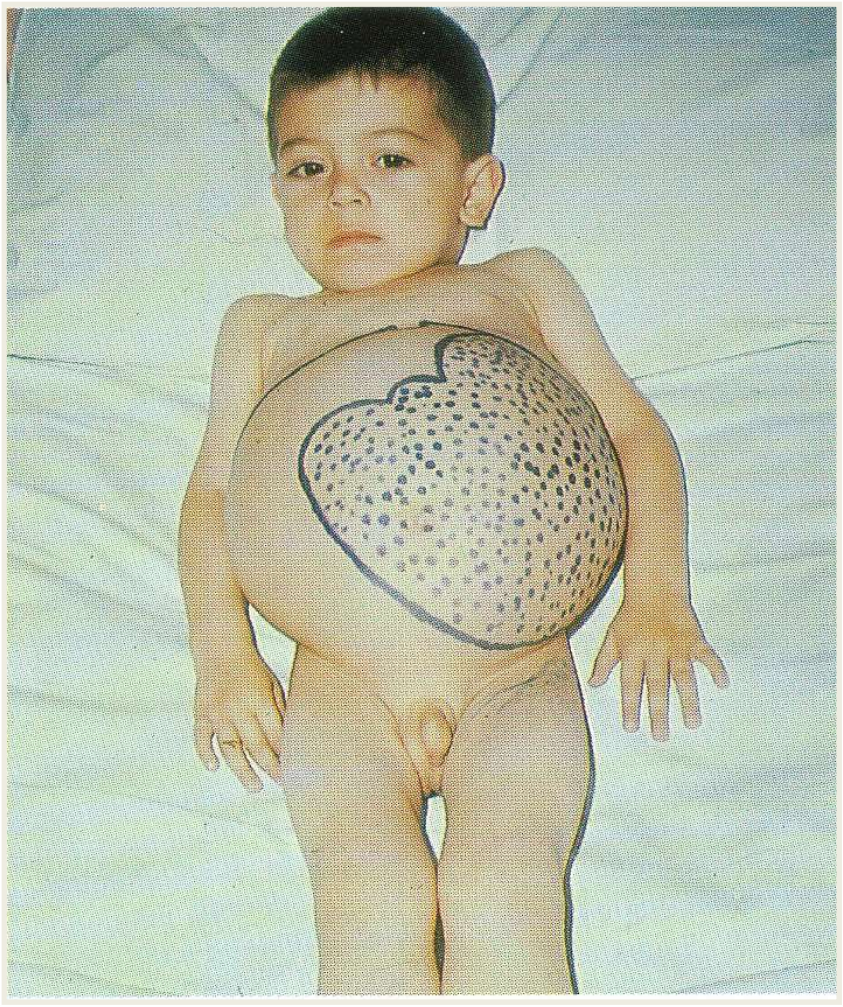


Hemosiderine

- En cas d'excès de fer et ou d'hémorragie:
- L'hémosidérine combinée à la ferritine forme des micelles
- Se trouvent souvent en petite quantité dans les foyers d'hémopoièse
- Mais en cas de processus plus intense et soutenu, l'ensemble des macrophages sont concernés (foie, pancréas et glandes endocrines)

β thalassémie majeure (Anémie de Cooley)





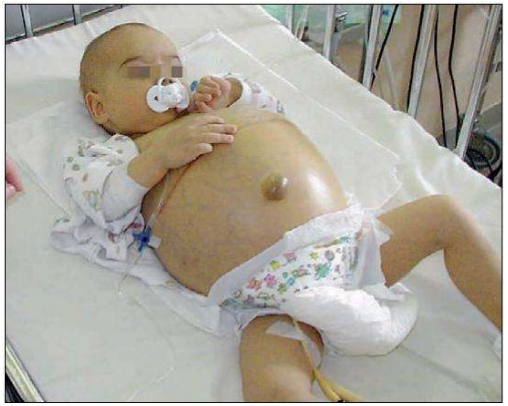
Incidence of Kernicterus Related to Total Serum Bilirubin Levels

TSB level			%
30 to 40 mg/dl			73
25 to 29 mg/dl			35
19 to 24 mg/dl			8
10 to 18 mg/dl			0

En cas de cholestase

La cholestase semble activer
-les lymphocytes NK
-Les lymphocytes CD
qui vont dégénerer l'épithelium des caux biliaires

Atrésie des voies biliaires et ascite



L’accumulation de triglycérides

- À cause de toxines
- **Diabète sucré**
- Malnutrition déficitaire
- Malnutrition excessive
- Anoxie cellulaire
- Troubles ioniques (hyper- hypo natrémie)

Ce sont surtout le foie et les muscles striés qui sont concernés

Rappel biochimique

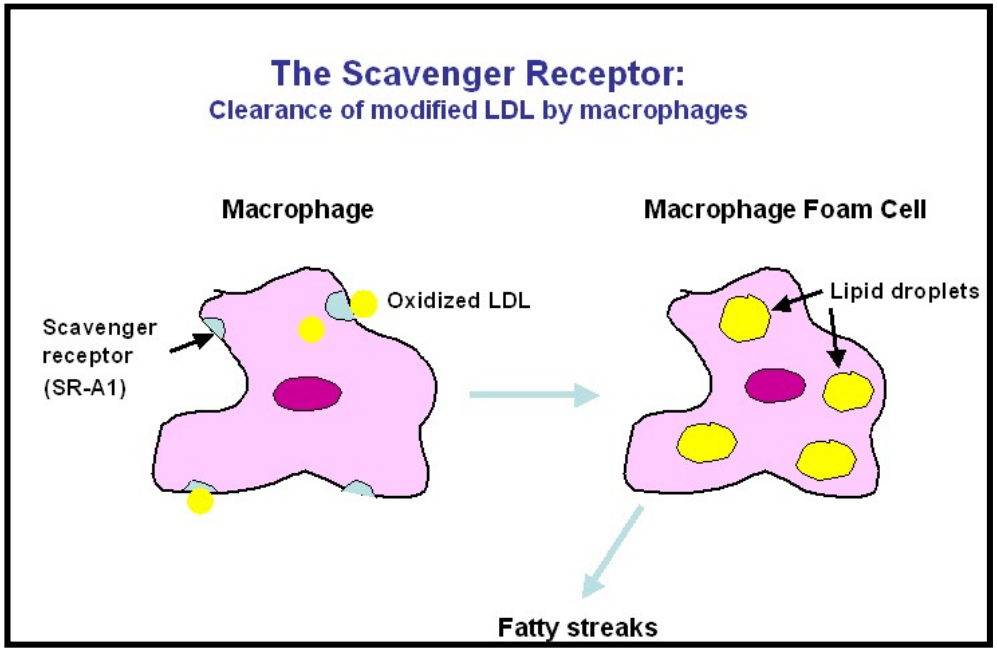
- Le cholestérol a un métabolisme étroitement corrélé au renouvellement de la membrane cellulaire accumulation

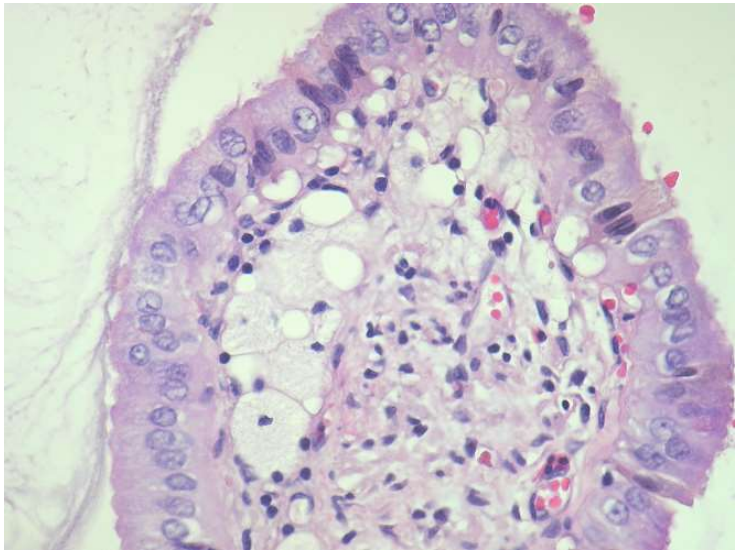
Élévation du Cholesterol et son Ester
→ accumulation

In hereditary and acquired hyperlipidemic syndromes, macrophages accumulate intracellular cholesterol

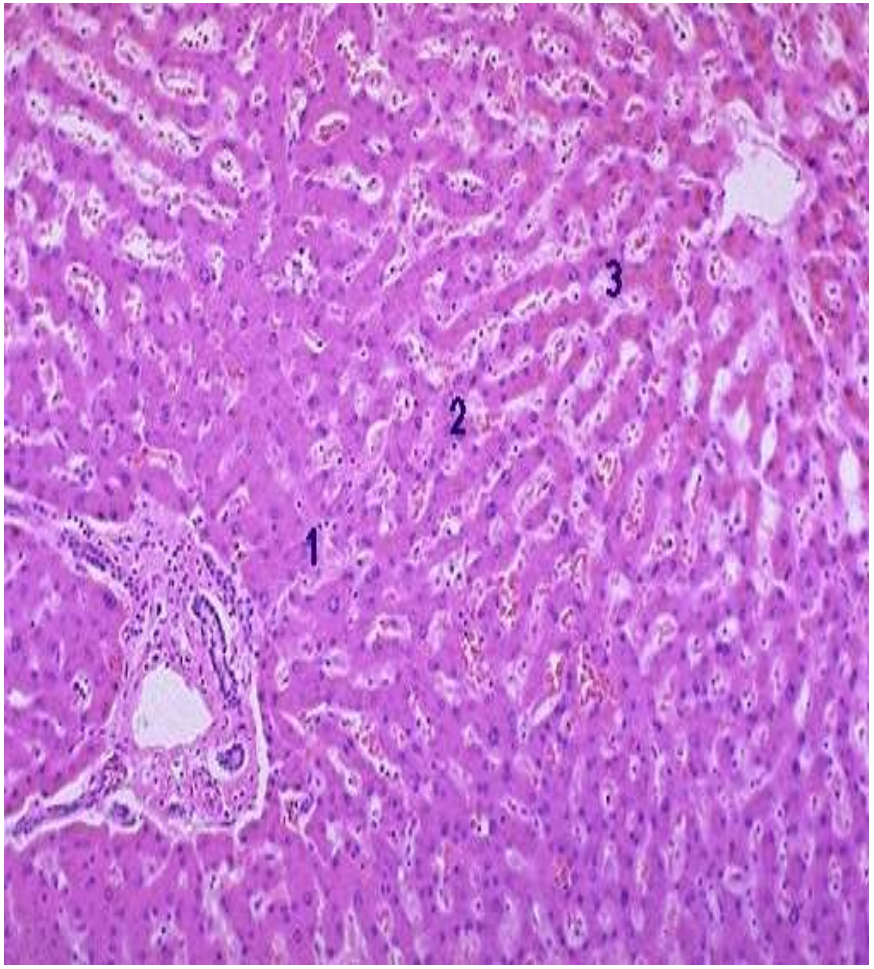
Xanthomas: clusters of foamy macrophages present in the subepithelial connective tissue of skin or in tendons

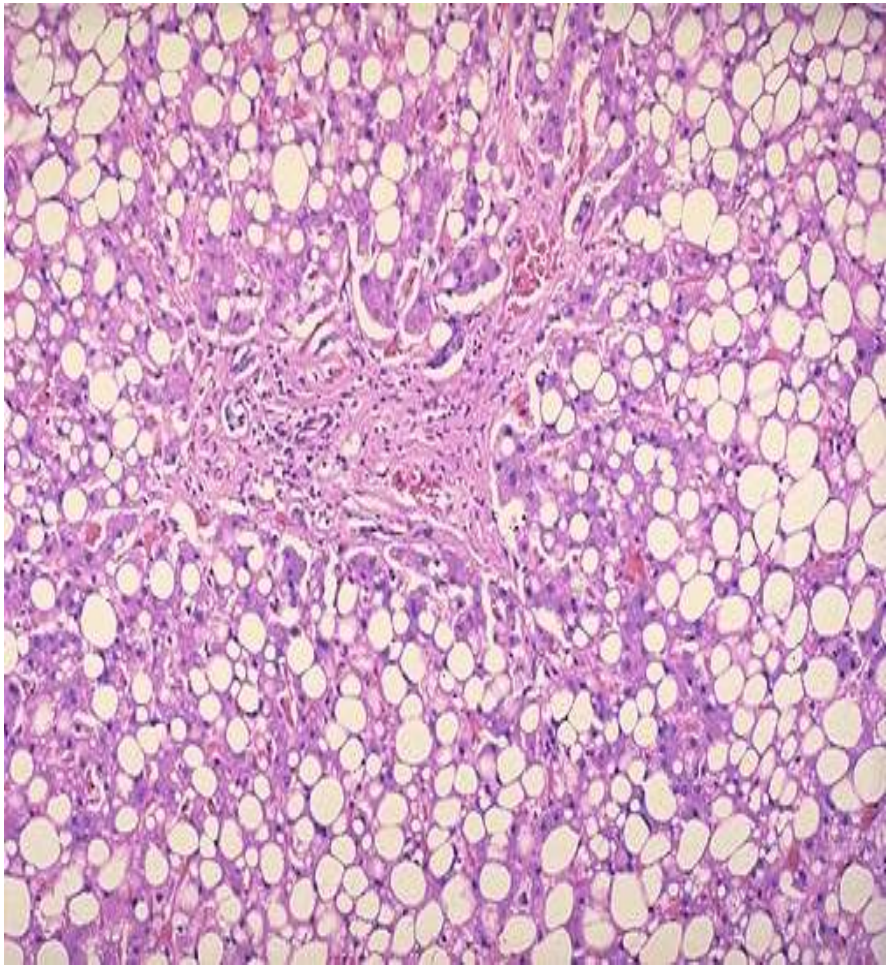
Macrophages en contact avec des débris lipidiques: ils deviennent spumeux





Fatty change: LIVER





La stéatose hépatique non alccolique

- **Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children**.
- NAFLD has emerged to be extremely prevalent, and predicted by obesity and male gender.
- It is defined by hepatic fat infiltration >5% hepatocytes, in the absence of other causes of liver pathology. It includes a spectrum of disease ranging from intrahepatic fat accumulation (steatosis) to various degrees of necrotic inflammation and fibrosis (nonalcoholic steatohepatatis [NASH]).
- NAFLD is associated, in children as in adults, with severe metabolic impairments, determining an increased risk of developing the metabolic syndrome. It can evolve to cirrhosis and hepatocellular carcinoma, with the consequent need for liver transplantation. Both genetic and environmental factors seem to be involved in the development and progression of the disease, but its physiopathology is not yet entirely clear. In view of this mounting epidemic phenomenon involving the youth, the study of NAFLD should be a priority for all health care systems
- Magnetic resonance imaging (MRI) and 1H-MRS have the greatest accuracy to determine hepatic fat content.
- The first step consists of the intrahepatic accumulation of fatty acids, which is closely associated with insulin resistance, and which increases the susceptibility of hepatocytes to secondary injuries or insults (oxidative stress, mitochondrial dysfunction, overproduction and the release of pro-inflammatory cytokines, and the endotoxin-mediated activation of the innate immune response).
- Increased susceptibility to these factors might also explain the progression of NAFLD to NASH

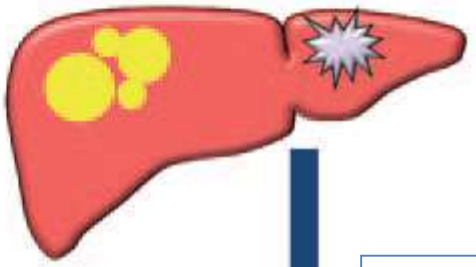
Proposed pathways by which nonalcoholic fatty liver disease is programmed in offspring of mothers with prepregnancy obesity and insulin resistance. The gestational environment drives increased metabolic fuel delivery to the fetus, leading to fetal hepatic fat accumulation. Via epigenetic changes acquired prenatally, the liver is now "primed" for postnatal fat storage and inflammation mediated by Kupffer cells. A childhood high-fat diet then triggers further steatosis, hepatocyte injury, inflammation, and fibrosis via activation of hepatic stellate cells. DAG, diacylglycerol; TG, triglyceride.

Pre-gravid obesity
Excess weight gain
Inflammation
Excess lipids/glucose

Insulin resistance
Increased fuel to fetus

Other factors
Maternal microbiome transfer to neonate
Placental inflammation

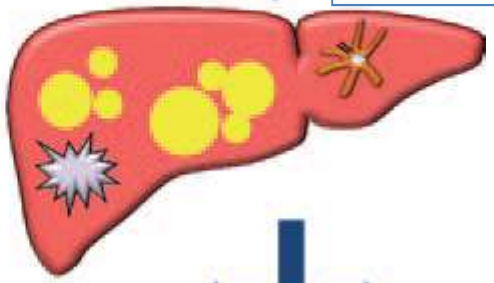
Fetal liver—a "first hit?"



Hepatic fat accumulation
Oxidative damage
Mitochondrial dysfuction (sirtuins)
Kupffer cell priming
Epigenetic changes

Postnatal Western, high-fat diet
Genetic polymorphisms?
Environmental or dietary factors?

Childhood "second hit"



Ongoing fat accumulation
Increased *de novo lipogenesis (SREBP1C*
Reduced FA oxidation (PPAR)

Hepatocellular injury
Kupffer cell activation
Stellate cell activation
Hepatocyte apoptosis
Oxidative damage
Endoplasmic reticulum stress

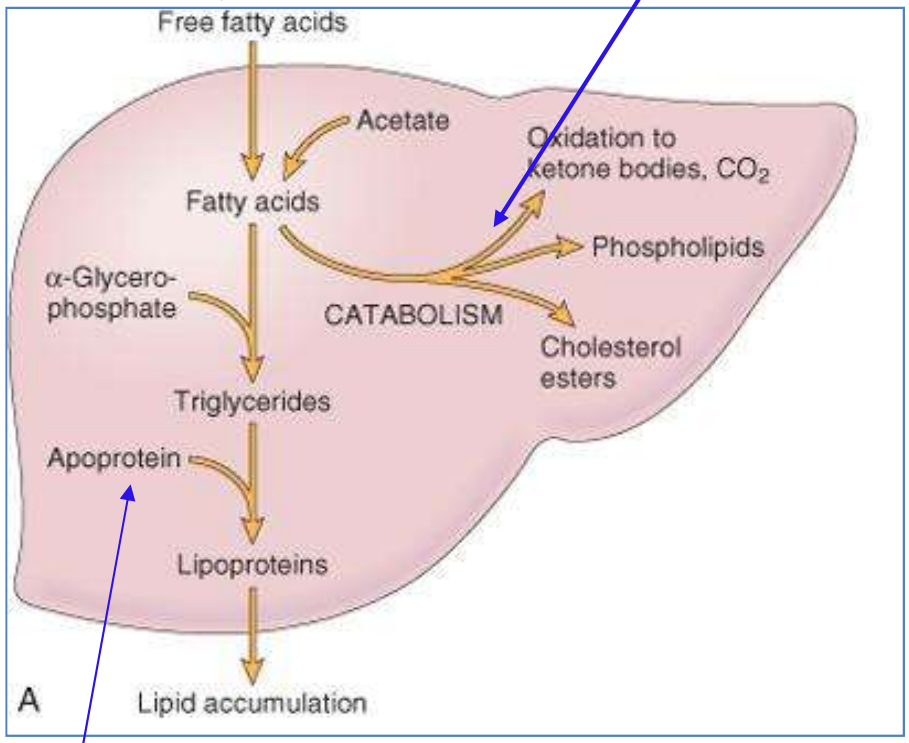
Hepatocyte injury

Fibrosis

Inflammation

Starvation will increase this

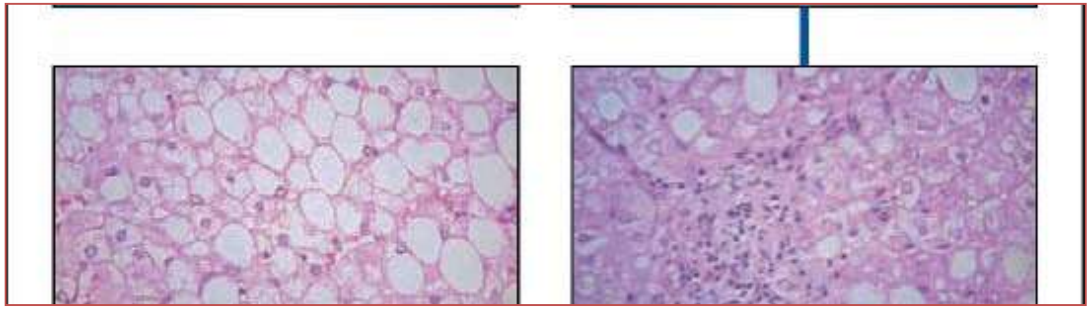
Hepatotoxins (e.g. alcohol) by disrupting mitochondria and SER ; anoxia



Mécanismes des potentiels provocateurs

CCl4 and protein malnutrition

La stéatose hépatique non alcoolique



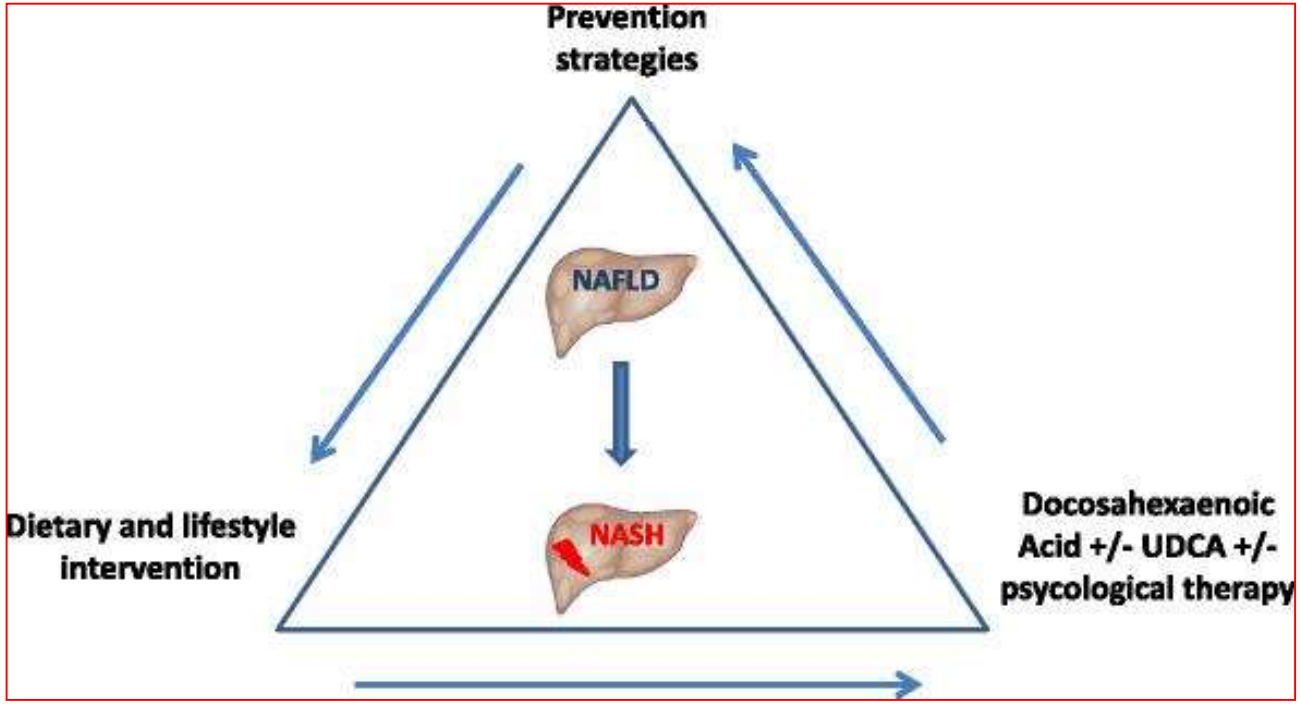
Chez l'enfant:
-Prise de médicaments
-Syndrome métabolique

traitement.

-Changer le comportement alimentaire et le « style ou mode » de vie. (approche égale psychologique)

-Attention aux toxiques et intoxications (y compris les médicaments)

-N acétyl cystéine ?



Prognostic de la stéatose hépatique

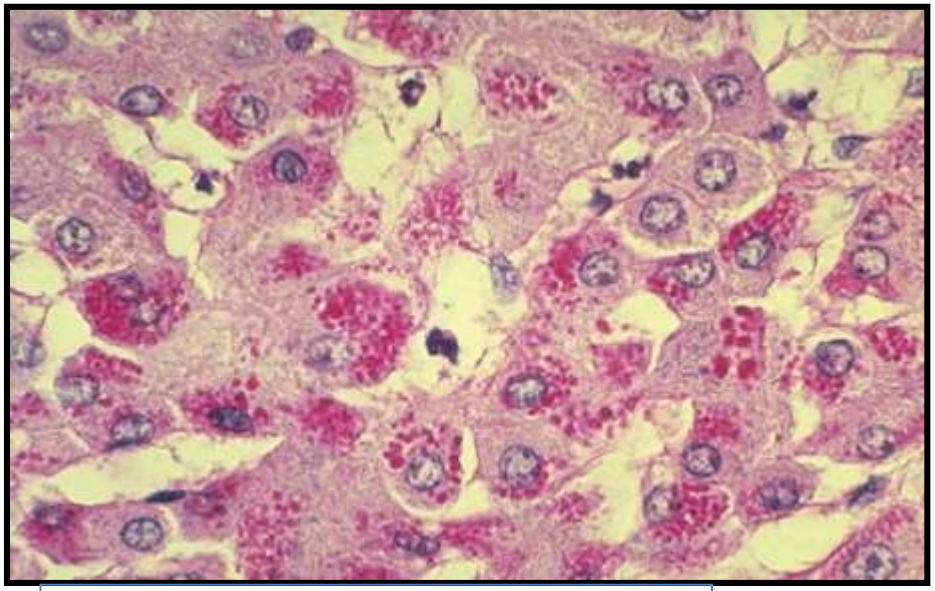
- Forme débutante: environ 3% vers la cirrhose
- Forme moyenne à sévère: inflammation, degeneration hépatocytaire, fibrosis: 30% vers la cirrhose

Le déficit en alpha-1 antitrypsine

- Cause importante de transplantation hépatique chez l'enfant
- Suivant l'atteinte génétique:

- MS ou MZ: porteur « sain »
- SS ou SZ: Démarrage des symptomes respiratoires (bronchites à répétition)
- ZZ: démarrage des symptomes hépatiques et pulmonaires

Dans le déficit en α-1antitrypsine:



Foie évoluant vers la cirrhose