

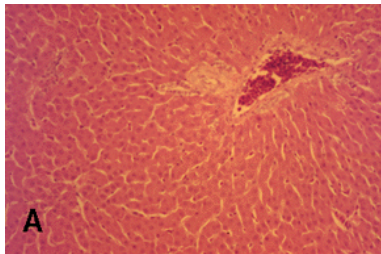
# HEPATOTOXICITY

- Liver –target organ of many chemicals, due to central role in biotransformation and elimination.
- Most chemicals cause centri-zonal damage.
- Pharmaceuticals cause of 5% of liver damage

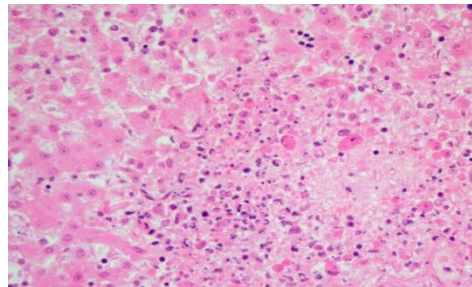
# 1. Chemicals causing dose-dependent injury (primary, obligatory toxicity)

- - high incidence
- - in all exposed persons
- - short latency
- - dose-dependent injury
- - similar lesions in experimental animals

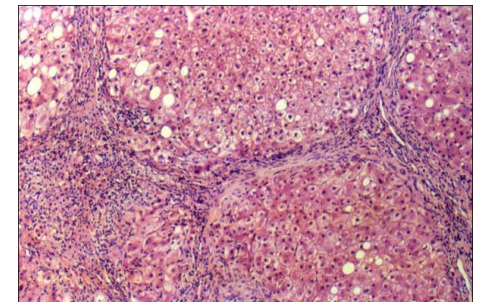
normal liver structure



necrosis

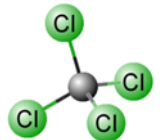
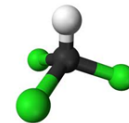


cirrhosis



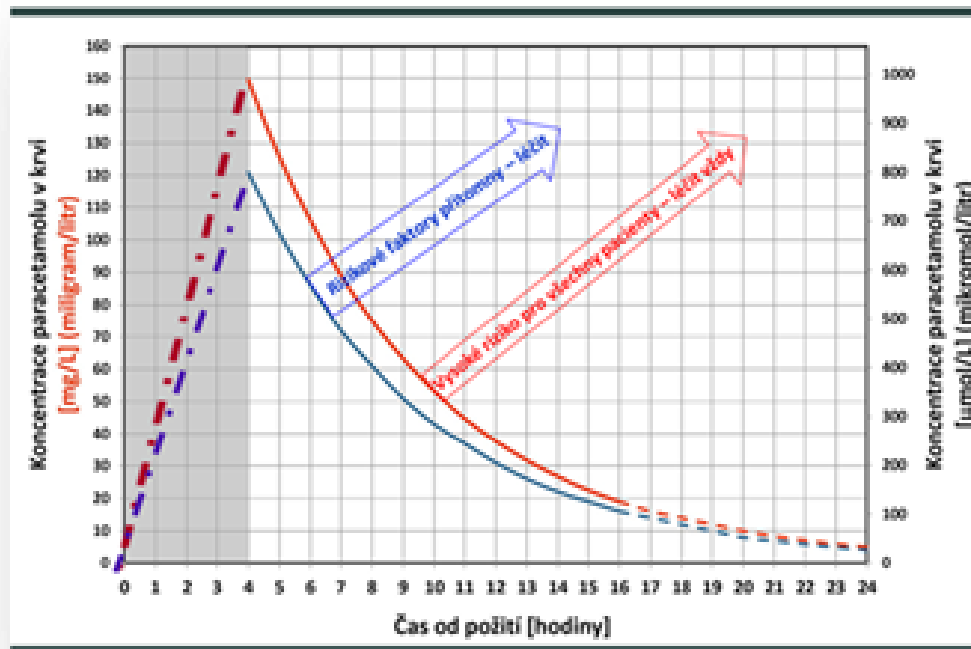
## a. direct hepatotoxins

- – injury the hepatocyte by a direct physicochemical effect- denaturation of proteins, peroxidation of membrane lipids
- most of industrial hepatotoxins:
- Carbon tetrachloride  $\text{CCl}_4$ – organic solvent
- Chloroform  $\text{CHCl}_3$ – organic solvent
- Phosphorus – periportal damage
- Paracetamol (acetaminophen)



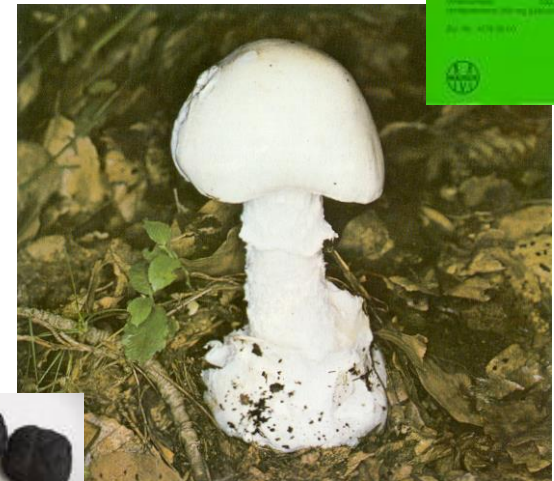
# Nomogramme for hepatotoxic damage due to paracetamol (acetaminophen) in blood – dose-response

The lower line 120 mg/l used in vulnerable patients  
150 mg/l in all other patients



## b. indirect hepatotoxins

- - interference with metabolic pathways-  
antimetabolites, intrahepatic cholestasis
- - mostly pharmaceuticals and botanicals
- Methotrexate
- Mercaptopurin
- Mushroom alkaloids
- **Amanitin** – *A. phalloides*  
(inhibition of RNA-polymerase)
- also dose-dependent toxicity



## 2. Chemicals due to special vulnerability of the individual (secondary, facultative toxicity)

- unpredictable
- in **small number** of exposed persons
- seldom dose-dependent
- individual latency period
- low experimental toxicity

# Mechanism

**Defects in biotransformation** – production of hepatotoxic metabolites

## **a. viral-like hepatitis**

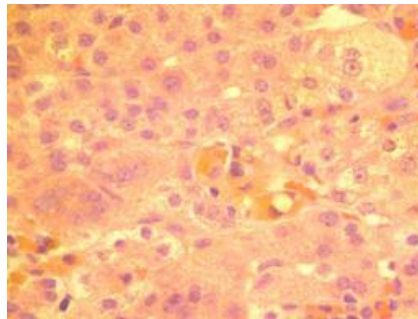
- isoniazid reactive metabolite
- due to rapid acetylation (1:100)
- halothan – due to induction of cytochrome P 450
- indomethacin
- rifampicin

## **b. cholestasis**

- contraceptives
- chlorpromazin
- chlorpropamid
- furantoin

## **a. + b.:**

- amoxicilin + clavulanic acid



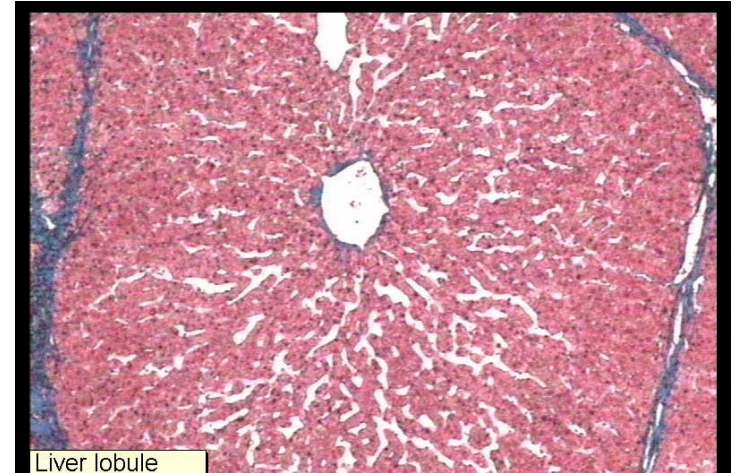
# CONSEQUENCES OF THE TOXIC LIVER DAMAGE

- Liver has a great regeneration potency
- Prognosis depends on the **extent** and **localisation**
- of the damage.



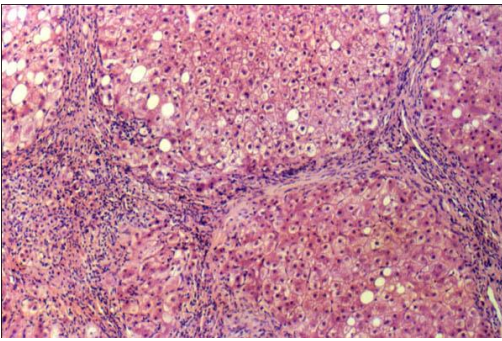
- **MONOCELLULAR OR FOCAL DAMAGE -  
complete recovery**
- **MASSIVE DAMAGE**
- **diffuse necrosis, per acute damage,**
- **often death in few hours or days**

# CENTRIOLOBULAR DAMAGE



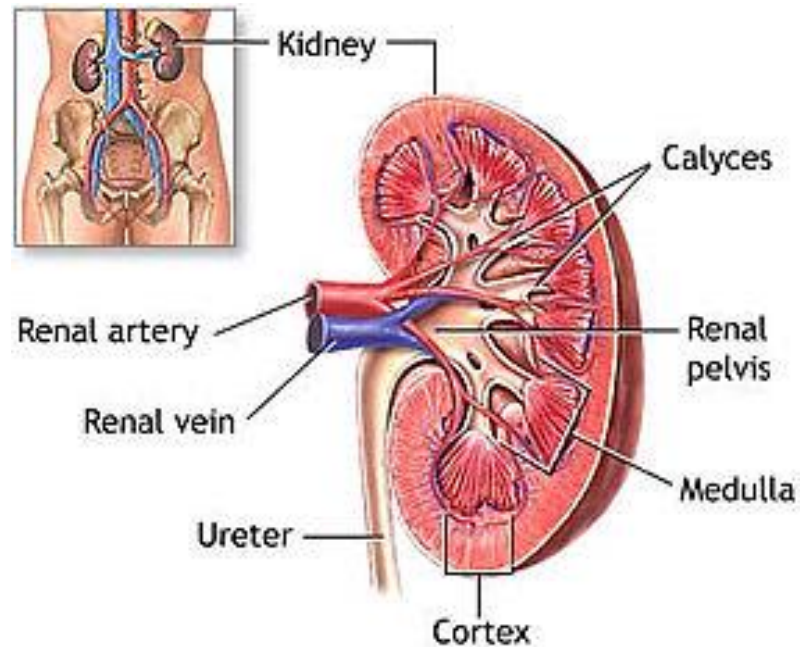
- **centrilobular** – most frequent, most of chemicals
- good prognosis, centrilobular hepatocytes are the most sensitive, but are easily replaced from the periphery
- **complete recovery**

# PERIPORTAL DAMAGE



- **periportal** – peripheral, damage of cells, that are essential for the regeneration of the hepatic lobules
- Few chemicals (**phosphorus, iron, aflatoxins**)
- **post necrotic cirrhosis** –hyperplasia of few intact hepatocytes
- **diffuse** – damage of the reticular structure of the lobule
- **fibrosis or post necrotic scar**

# NEPHROTOXICITY



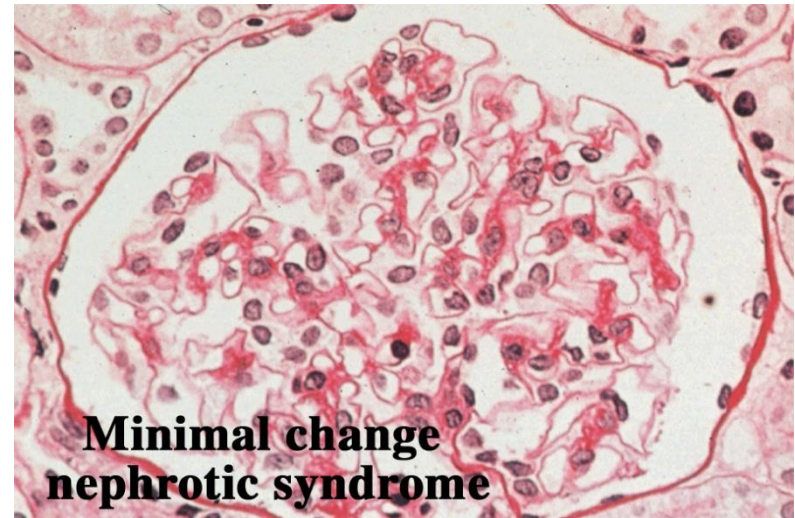
KIDNEY FAILURE— consequence of kidney damage

# KIDNEY FAILURE

- PRERENAL – shock, cardiovascul. colaps
- RENAL
- Compensatory mechanisms
- after nephrectomy, solitary kidney increases GF by 40-60 %

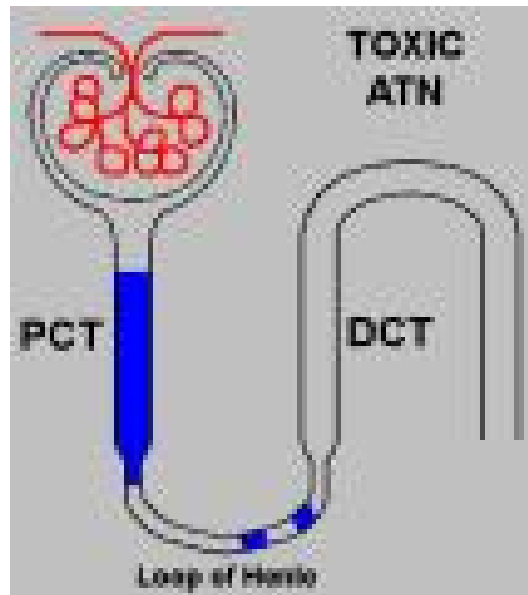
# ACUTE KIDNEY FAILURE

- **GLOMERULAR DAMAGE** – more rare
- - nephrotic syndrome
- mercury <sup>2+</sup>
- non-steroidal  
antirheumatics



**Minimal change  
nephrotic syndrome**

# TUBULAR DAMAGE – ACUTE TUBULAR NECROSIS

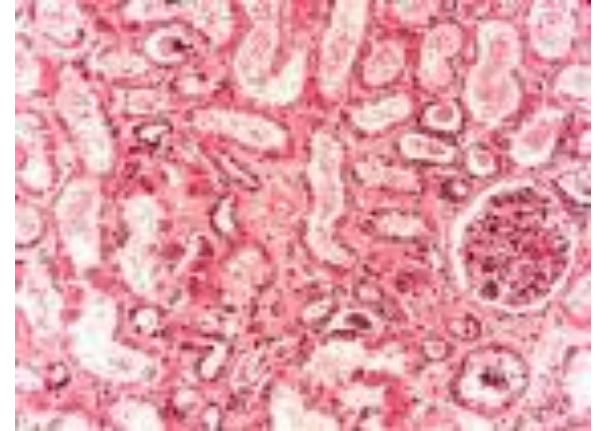


Pale swollen kidney with a sharp line of demarcation between the **pale cortex** and the **dusky congested medulla**.



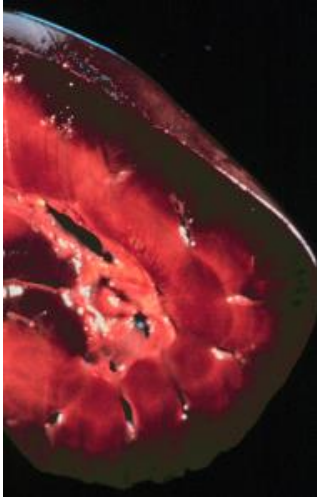
# TUBULAR DAMAGE – ACUTE TUBULAR NECROSIS

- ETHYLENE GLYCOL
- – obstructive uropathy
- AMATOXINS
- $\text{Hg}^{2+}$  proxim. tubulus
- toxic solvents:  $\text{CCl}_4$ ,  $\text{CCl}_3$
- **ORELANIN** (*Cortinarius orellanus*,  
*Pavučinec plyšový*) - bad prognosis, irreversible
- damage of stem cells in the Bowman capsule





# PIGMENT NEPHROPATHY

- Acute tubular necrosis
  - obstruction of tubules
- 
- methemoglobin – aniline, nitrobenzene
  - hemoglobin – arsine
  - myoglobin – in rhabdomyolysis due to
    - a) seizures and hypertermia, heroine, amphetamine
    - b) immobilisation – position trauma (longterm coma)

# CHRONIC RENAL FAILURE

- METALS:
- Hg<sup>2+</sup>
- Pb
- Cd – Fanconi syndrome

# CHRON. REN. FAILURE

- DRUGS

Analgesic nephropathy  
with papillary necrosis.

- NSA – ANALGETIC NEPHROPATHY in analgetics abuse - diclofenac, ibuprofene, lithium
- paracetamol – NAPQI hepato-nephrotoxic metabolite
- cefalosporines
- aminoglycosides