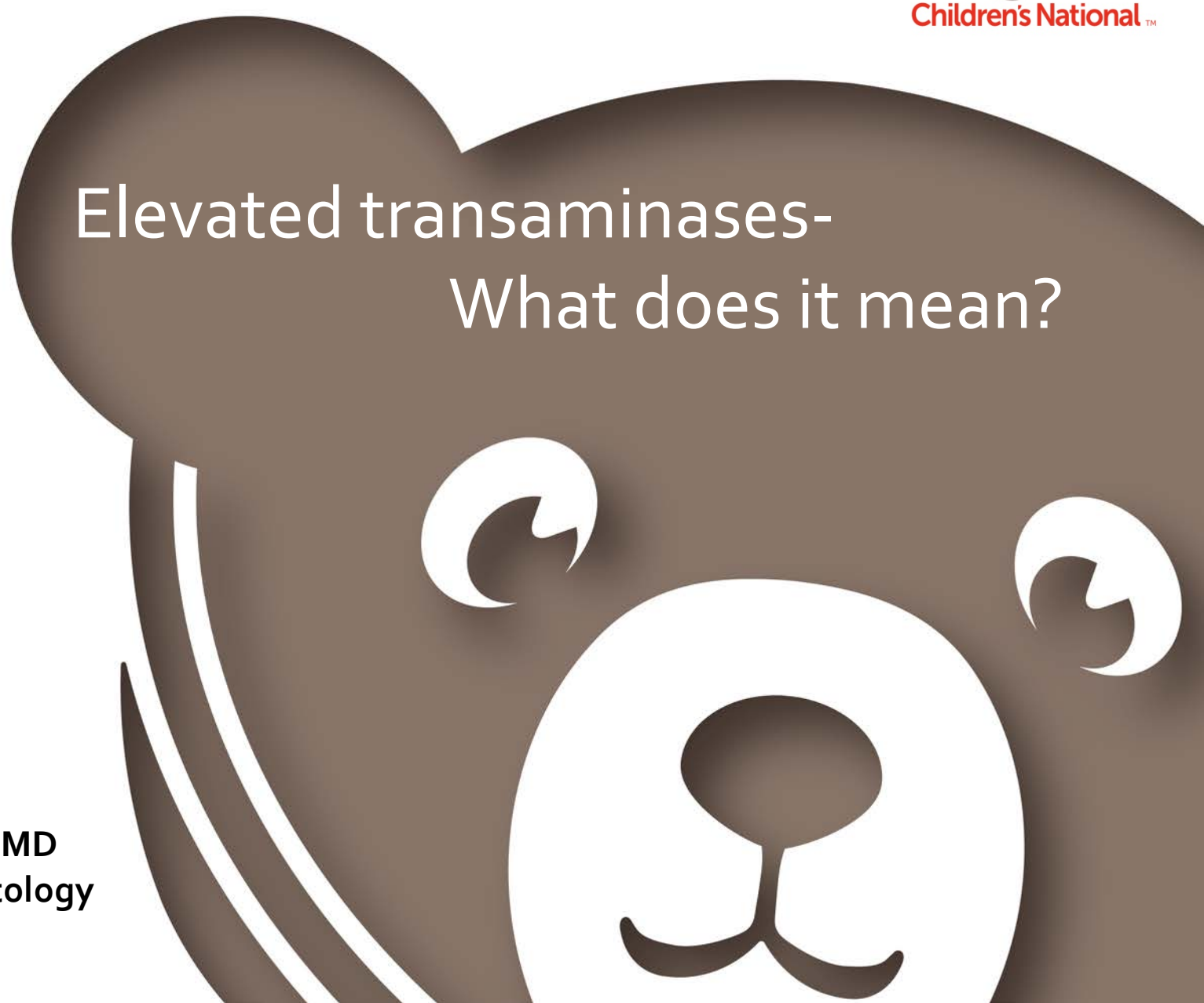
Elevated transaminases- What does it mean?



Parvathi Mohan, MD
Director of Hepatology

June 2, 2014

Case -1

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- Reason: routine check up
- History: diarrhea, mild fever two weeks ago
- Examination: weight 95% , height 25%, edge of liver palpable
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Transaminase elevation-Possible Etiology

- An acute illness
- Recovery from an acute hepatitis
- An existing chronic liver dysfunction
- Unrelated to a primary liver disorder

Case – 2

- An eight year old boy presents to your office
- Reason: Yellow eyes, abdominal pain
- History: Diarrhea, mild fever 2 weeks ago

  A trip to Mexico
- Exam: Weight 40% , height 35%, jaundice, hepatosplenomegaly
- Labs: ALT 385, AST 265, TB 7, INR 1.6, A/G 0.7

Transaminase Elevation - Possible Etiology

- An acute liver disease
- An exacerbation of a chronic liver dysfunction
- Secondary to an acute infection

Liver Function Tests

- Metabolic diseases : Acidosis, hypoglycemia
- Tumors : Alpha fetoprotein, LDH
- Chronic dysfunction : Fasting bile acids, platelets

Liver Function tests

- Hepatocellular: *Liver injury*
  - AST, ALT, LDH
- Excretory: *Impaired bile flow, cholestasis*
  - Bilirubin, GGT, Alk. Phosphatase, Bile salt
- Synthetic: *Defective production*
  - PT/PTT, Albumin, Ammonia, cholesterol

Transaminases

- AST - in liver, muscle, kidney, red cell, pancreas, macro AST
- Elevated in any injury- trauma, ischemia, drugs, infection, hemolysis
- ALT- mostly in liver, less in muscle

Transaminases –high and low

- **Very high ALT (> 1000 IU)**

  Drugs, anoxia, acute viral infections
- **Moderate elevations (200-300 IU)**

  Chronic hepatitis, autoimmune, NASH
- **AST > ALT:** Hemolysis, muscle pathology, macro AST

  Fibrosis/cirrhosis, Wilson's
- **ALT elevation alone:** Celiac Disease and NASH
- **ALT low:** Cell death, B6 deficiency, uremia

Hepatitis B in Children

- 90 % children-- asymptomatic
- Risk of chronic HBV decreases with age
- Chronic HBV in:
  - 90 % of infants infected at birth
  - 20-50% if infected at 1-5 yrs.
  - 2-6 % if infected later

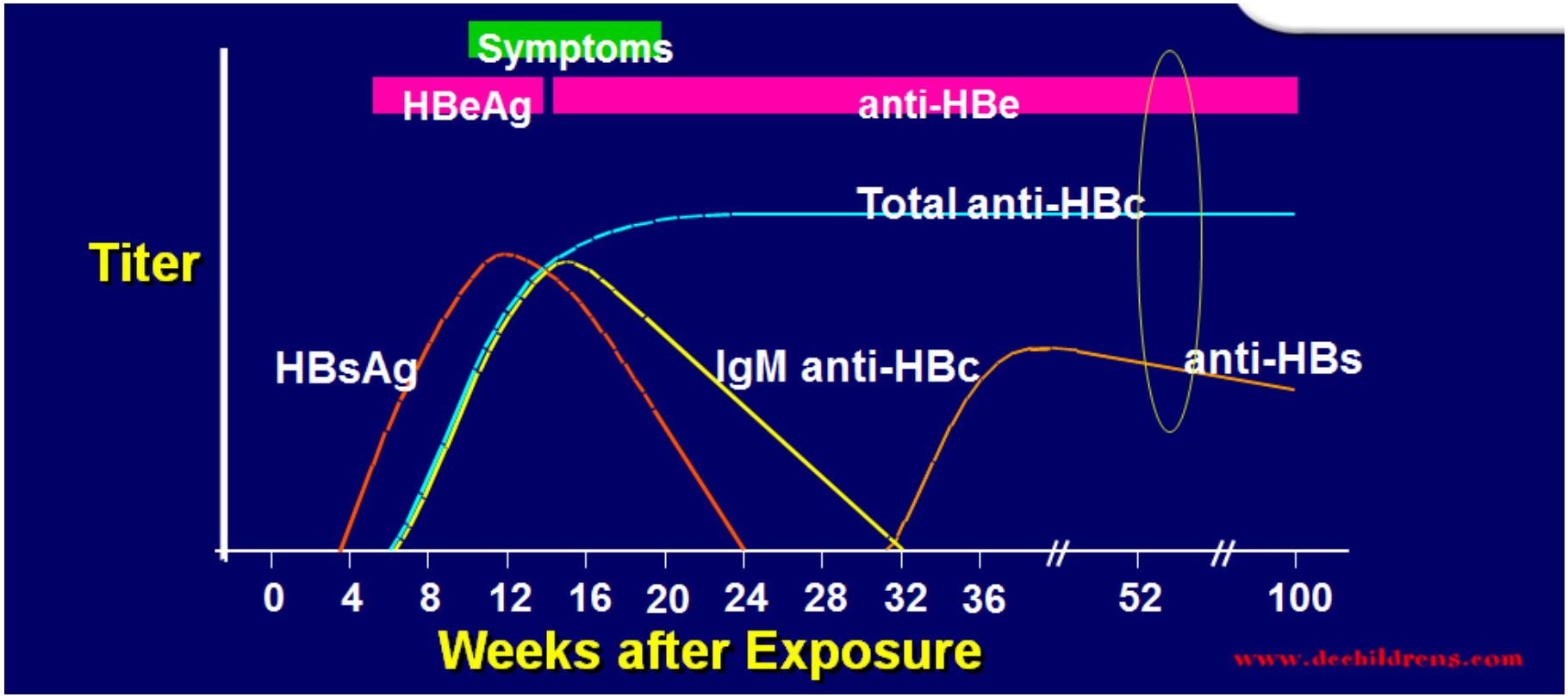
HBV Modes of Transmission

- Parenteral
- Perinatal
- Sexual

HBV- Serologic Markers

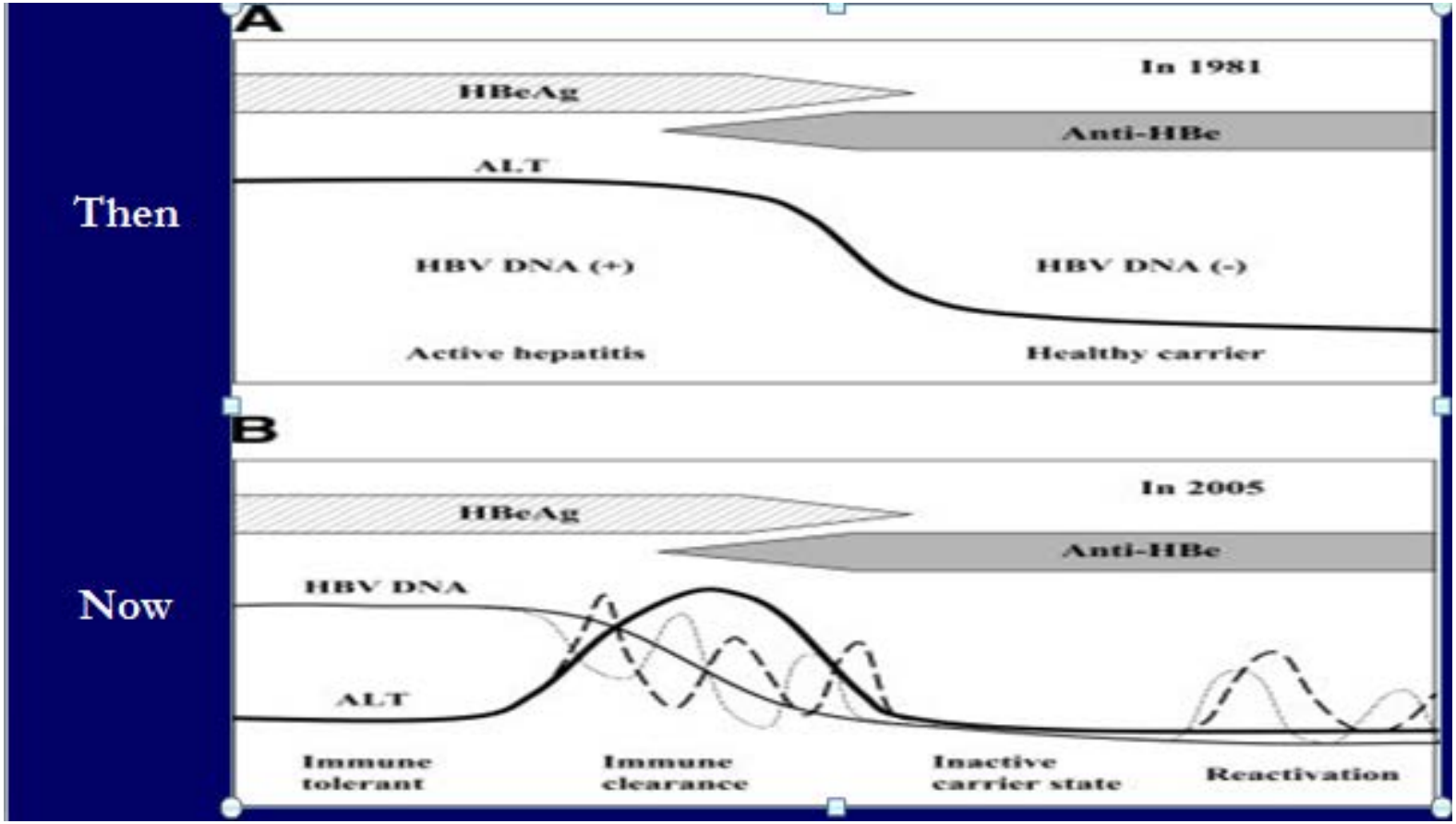
- HBsAg: Infection-acute or chronic
- HBsAb: Clinical recovery, immunity
- HBcAb: Presence of infection- acute, chronic
- HBeAg: Active viral replication, infectivity
- HBeAb : Resolution of active infection
- HBV DNA: Measure of viral replication
- ALT: Normal or mild elevation

Acute Hepatitis B Virus Infection with Recovery



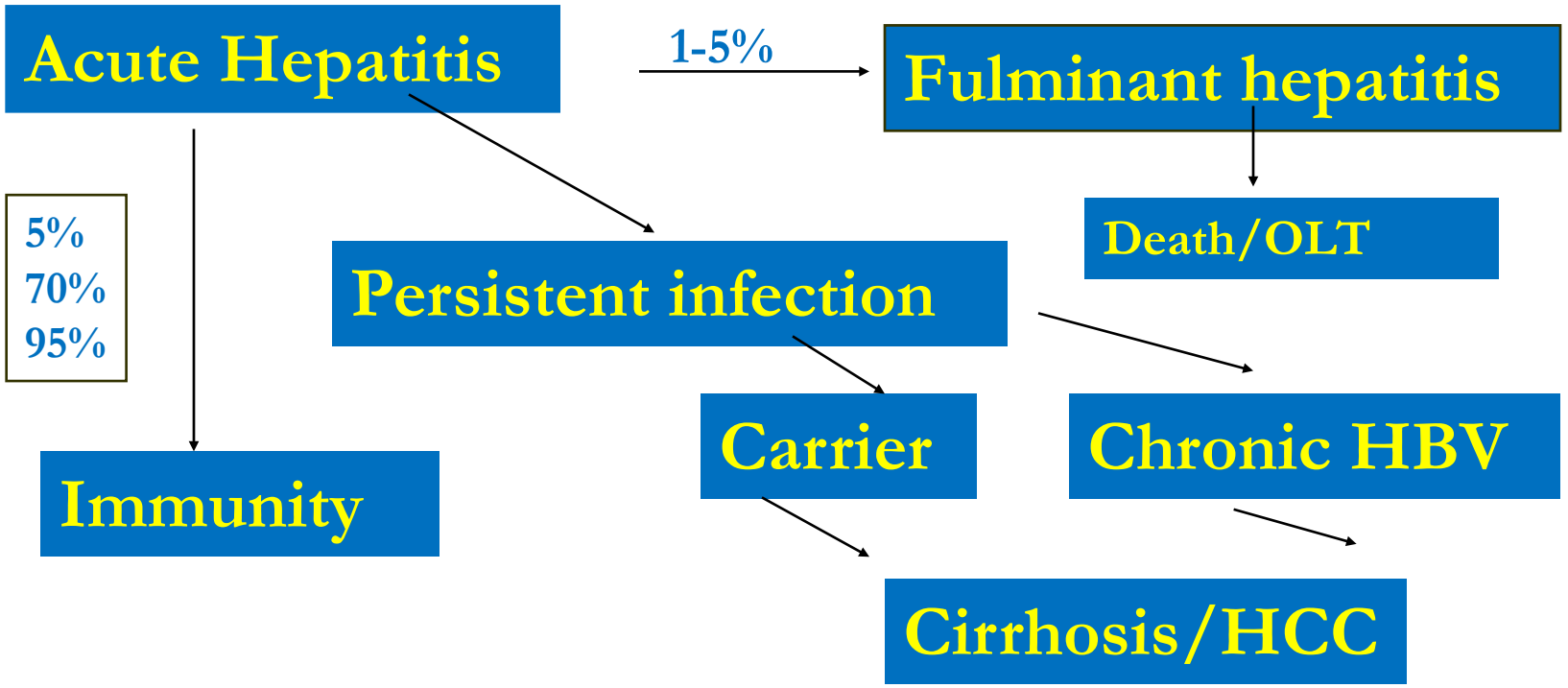
Children's National

What we know about course of HBV- then & now



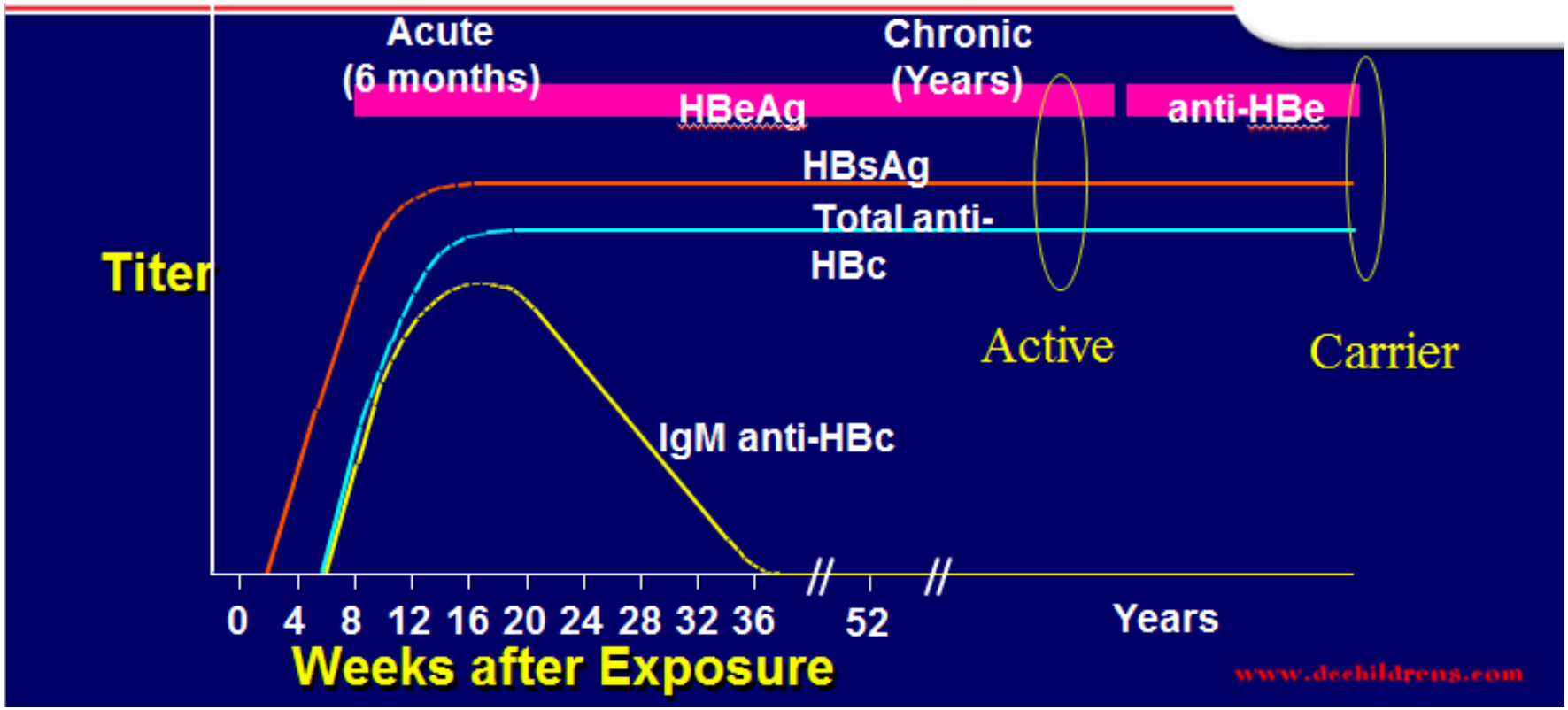
Children's National

Course of HBV infection



Children's National

Progression to Chronic Hepatitis B Virus Infection



Children's National

HBV- Prevention

- HBIG- for temporary, post exposure
  - ***Perinatal, Needle stick, sexual***
- Vaccinate all children 0-18 yrs
- Dose (0, 1-2, 6 mo.)
- Engerix-B, Recombivax HB
- ? Re-vaccination: test if high risk

Post Vaccine testing

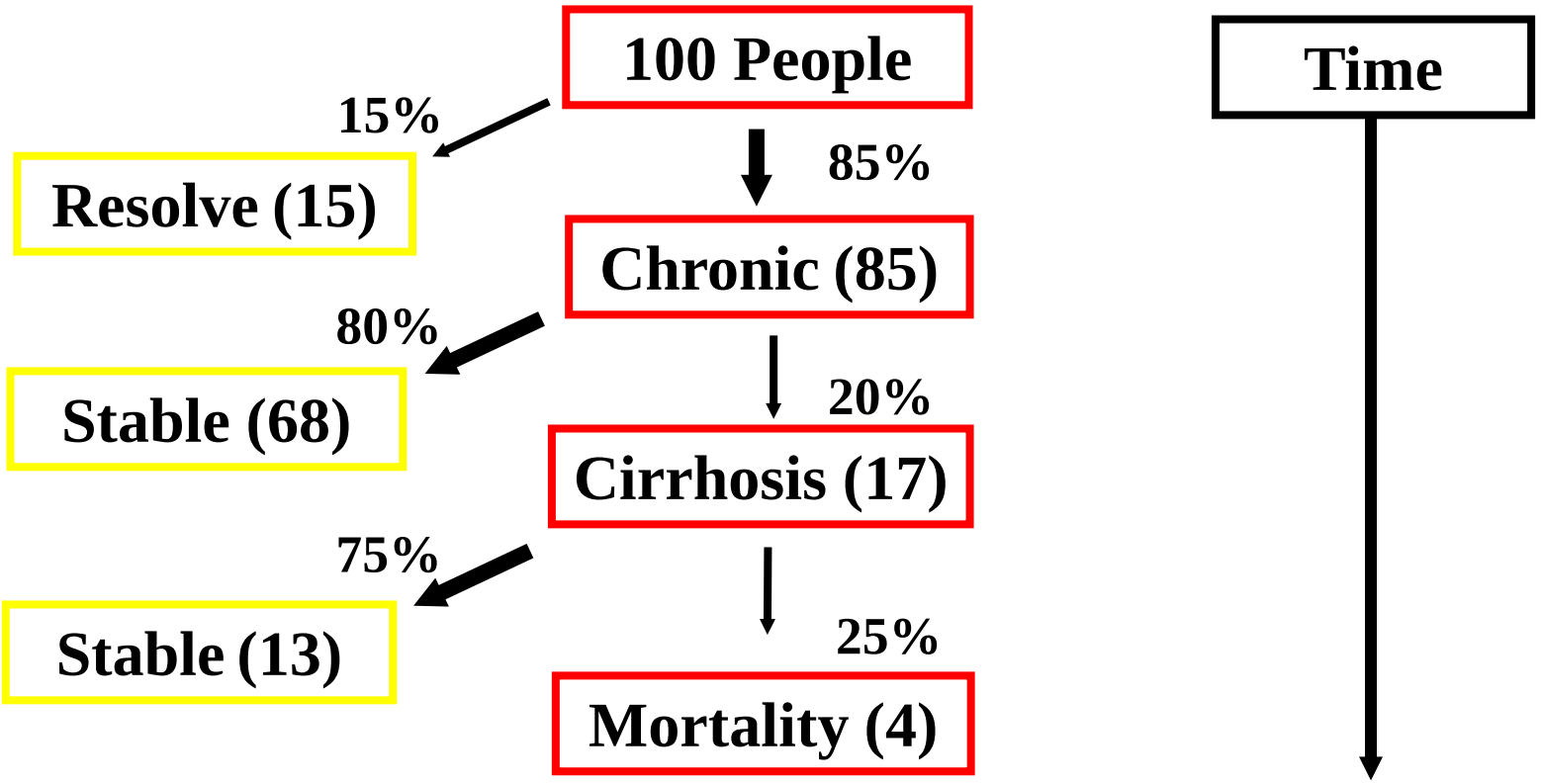
- Immuno compromised patients
- Vaccine in the buttocks
- Infants born to HBsAg + mothers
- Health care workers in contact with infected blood
- Sex partners of HBV infected persons

HCV - Background

Hepatitis C antibody in the US population, 1988-1994, NHANES III data :

		%	Estimated no
All subjects	:	1.8	3.9 million
6-11 years	:	0.2	0.4 million
12-19 years	:	0.4	0.8 million

Natural History of HCV Infection

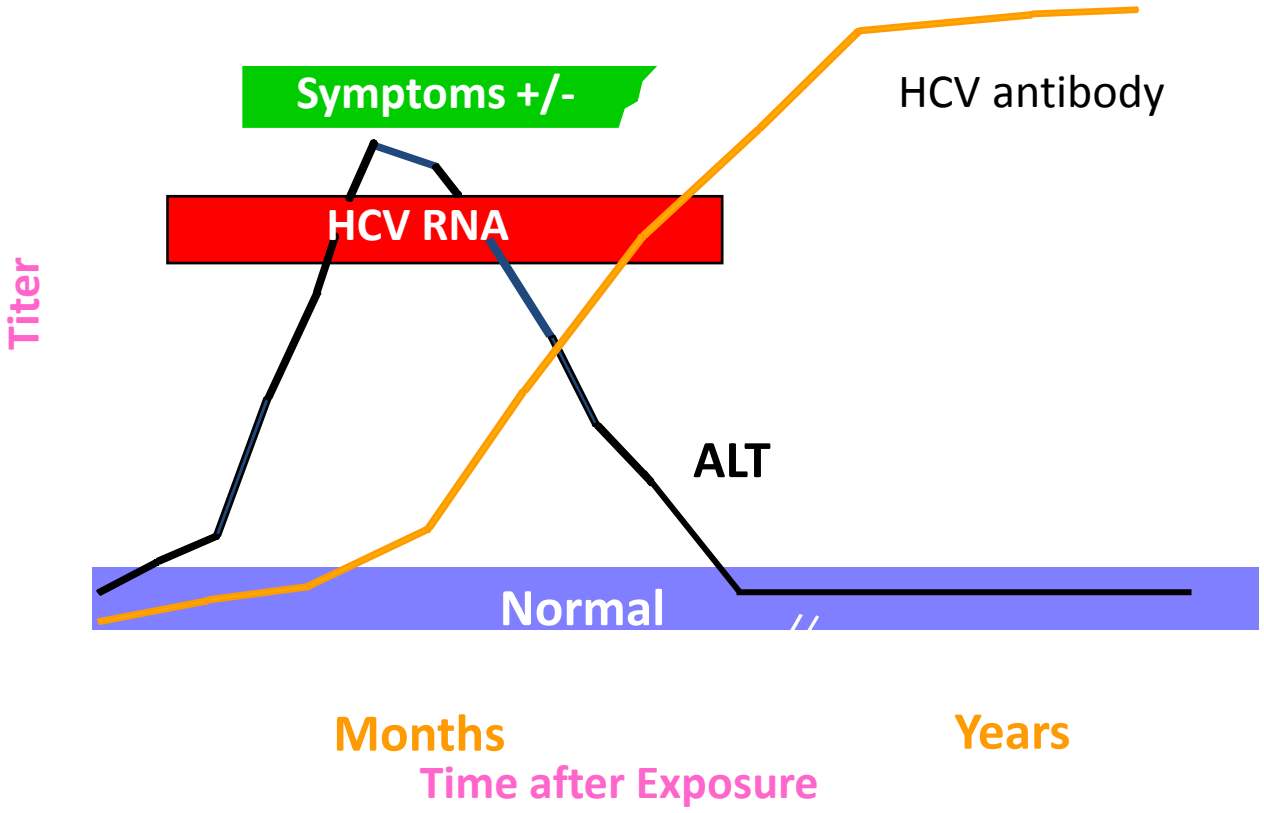


Children's National

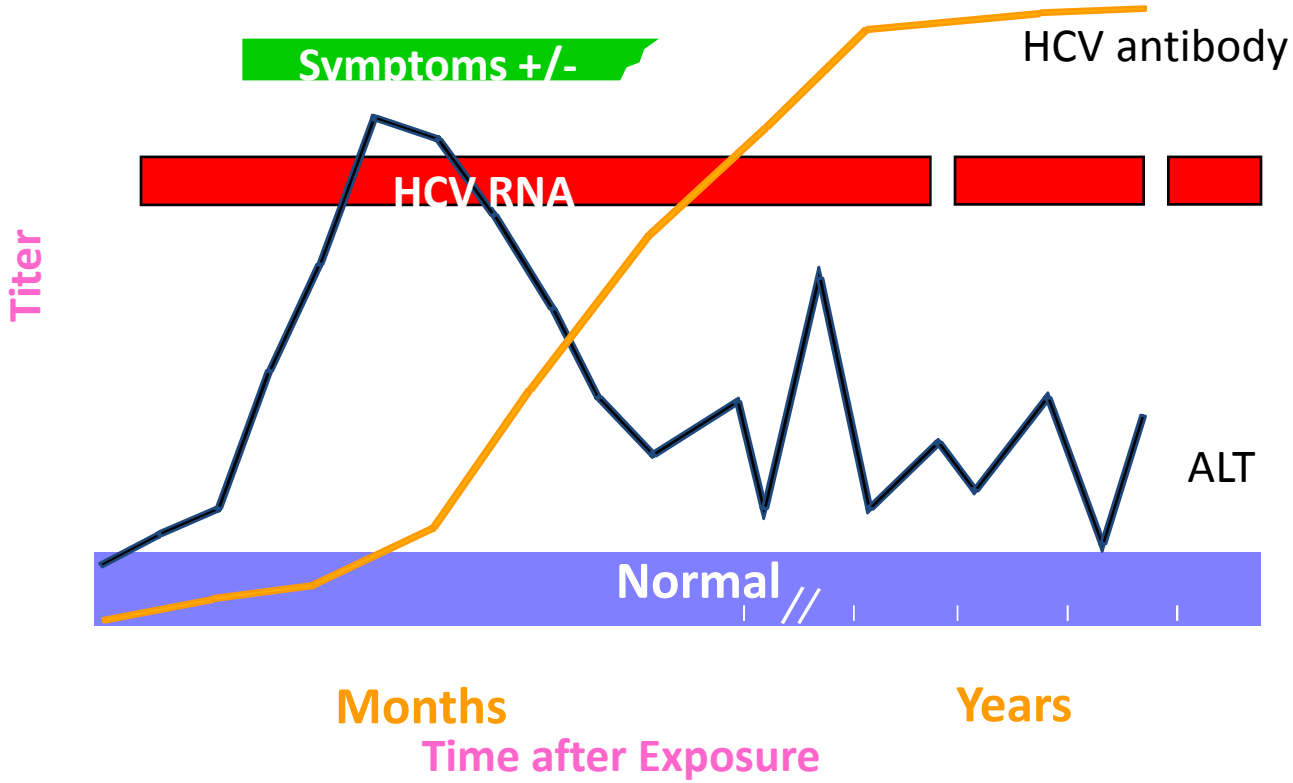
HCV- screening

- History of drug use
- Children born to HCV positive mother
- Transfusion/ solid organ Tx before 1992
- Recipient of clotting factors before 1992
- Chronic hemodialysis
- After known parenteral exposure
- Persistently high ALT

Serologic Pattern of Acute HCV Infection with Recovery



Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Children's HCV Study (1996-2001)

- Transfusion look-back and referrals
- Perinatal (13 %), transfusion (68 %), both (7 %) in 60 children, 7 adoptees
- Duration of infection about 13 years
- Mostly asymptomatic, mild liver disease
- Bridging fibrosis in 12 %
- Severe liver disease in 3 children - perinatal

Mohan, Luban, Alter et al: J Pediatr, 2007

The most common nutritional disorder in the US…

Obesity

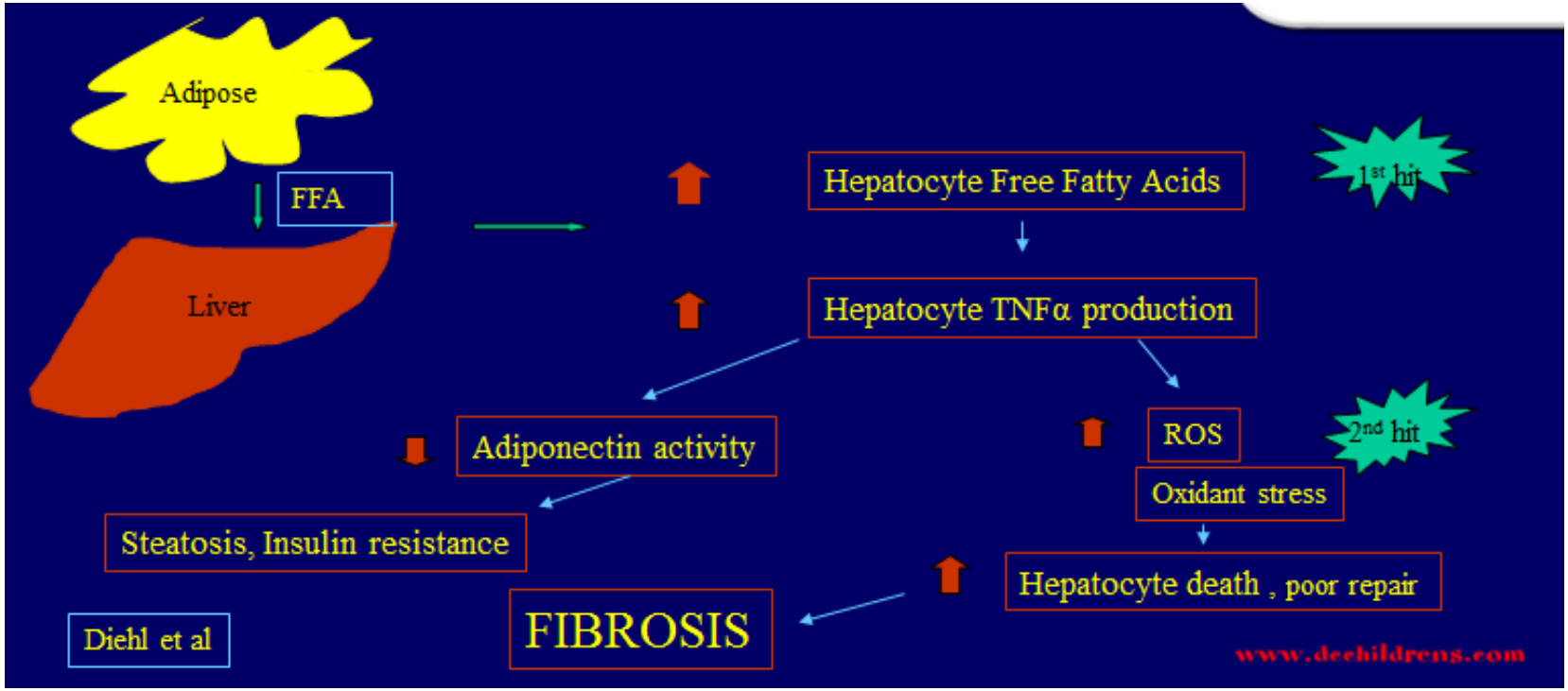
NAFLD

- Prevalence of obesity 22 % over 20 years
- Prevalence of NAFLD in children 7-10%
- Steatosis in 60 %; steatohepatitis in 20 % of obese people
- Association with Type 2 diabetes and hyperlipidemia, insulin resistance
- Higher prevalence in Hispanic children and African American-22 %
- Other genetic/metabolic liver diseases excluded

NAFLD- pathogenesis

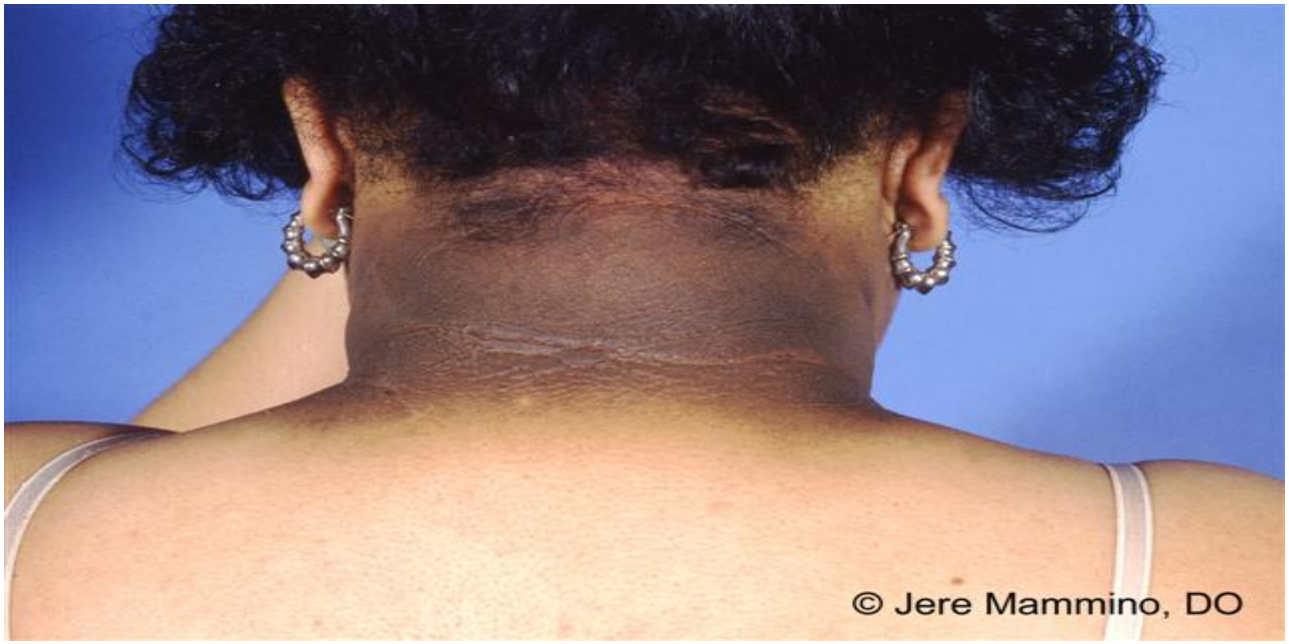
- Hyperinsulinemia, insulin resistance- most essential component
- Increased free fatty acids in plasma and liver
- Inhibition of free fatty acid oxidation by insulin
- Hepatocellular oxidant stress, changes in mitochondria and peroxisomes

Progression of NAFLD



Children's National

Acanthosis nigricans- metabolic syndrome



Acanthosis nigricans-hyperplasia of cells with insulin receptors- indicates insulin resistance

Diagnosis of NAFLD

- Serum ALT: (> AST)
  - Screening Tool
  - Poor sensitivity, no cut off value
- Ultrasonography:
  - Low cost, no radiation
  - Increased ECHO texture and vascular blurring
- MRI/MR Spectroscopy
  - Ideal- direct measurement/distribution of fat
- Liver biopsy: *controversial*

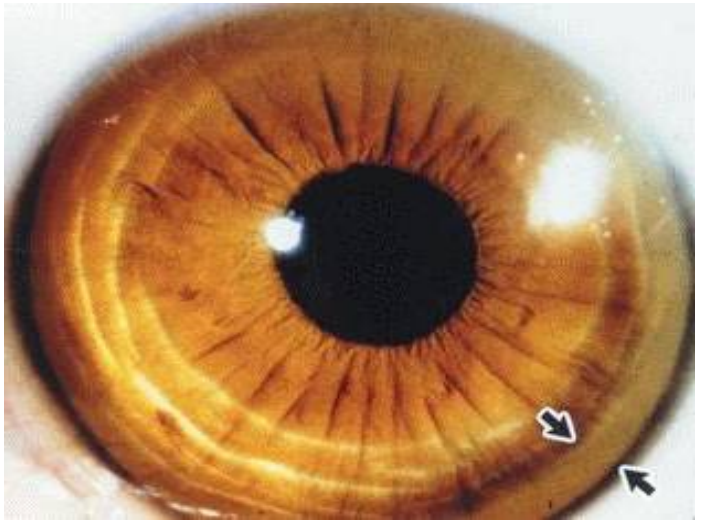
Wilson's Disease

- Think "Wilson's" in anyone over 3 years with unexplained, elevated transaminases

Wilson's Disease

- Genetic disorder- systemic copper accumulation
- Chromosome 13
- Mutation of ATP7B gene
- Hepatitis, liver failure, cirrhosis
- Extra-pyramidal lesions
- Psychiatric disorders
- Hemolysis, renal disease

K-F Ring



Wilson's Disease- Diagnosis

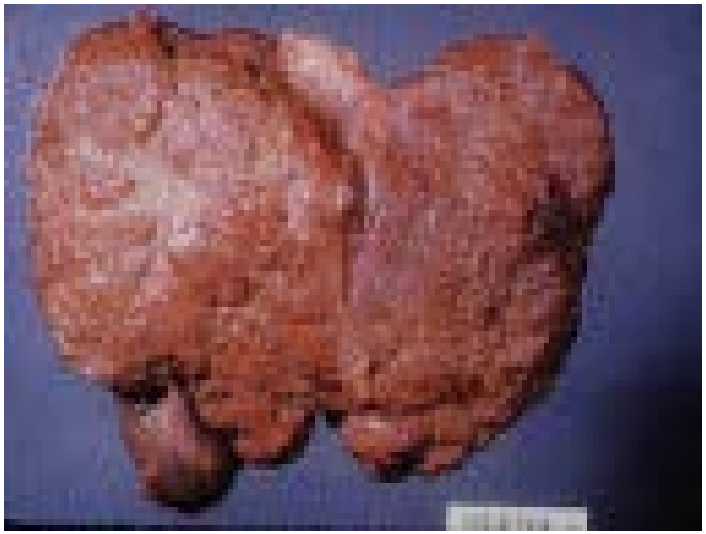
- Ceruloplasmin < 20 mg/dl
- Liver copper > 250 mcg/dl
- 24 hour urine copper > 100 mcg
- Liver biopsy and measurement of copper
- Mitochrondrial changes on EM
- Genetic studies

Alpha-1-antitrypsin deficiency

- Autosomal recessive
- Presentation
  - Asymptomatic : elevated AST, ALT
  - Liver disease, portal HTN
  - Emphysema
- Diagnosis
  - Low serum levels
  - Pi phenotyping : PiZZ
  - Histology

Autoimmune hepatitis-Overview

- Interface hepatitis
- Autoantibodies, high IgG
- Propensity for cirrhosis
- 5.9 % of Liver Tx
- Female preponderance



Autoimmune Hepatitis

- Type I :
  - Predominantly in women
  - Acne, amenorrhea
  - ANA, ASMA, High IgG
- Type II :
  - Mainly in children- Europe
  - More aggressive course
  - Anti LKM antibody

Type III : Similar to Type I
- Soluble Liver Antigen

Drugs and Hepatitis

- Hepatitis-Cholestasis: Erythromycin
- Zonal necrosis: Acetaminophen
- Bland Cholestasis: Cyclosporin
- Steatosis: Valproate
- Adenoma: Estrogens
- Allergic: Phenytoin
- Malignancy: Anabolic steroids

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Asymptomatic patient-High liver enzymes

- Sub clinical HBV or HCV
- Sub clinical Auto-immune Hepatitis
- A-1 AT deficiency
- Wilson's Disease
- NAFLD/NASH
- Myopathy, celiac

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  A trip to Mexico
- Exam: Weight 40% , height 35%, jaundice, hepatosplenomegaly
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"Yellow and sick" – high transaminases

- Acute hepatitis: Hepatitis A
- An exacerbation of chronic hepatitis:
  - Hepatitis B/C
  - Autoimmune
  - Metabolic: Wilson's
- Drugs
  - INH, bactrim

Management

- Medical
- Liver transplantation

Treatment of chronic hepatitis

- Hepatitis B & C- Interferons, oral antiviral agents
- Drug toxicity- stop offending drug
- Wilson's Disease- chelation
- A1 AT deficiency- liver transplant
- Autoimmune- steroids, immunosuppressant, ursodiol
- Steatohepatitis- weight loss, bariatric surgery