Image Atlas of Aging

Age-Related Structural and Functional Changes in the Liver

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Summer Intern 2013

Roadmap

Concepts of Aging

- Implications for Your Practice
- Key Points of Aging
- The Aging Phenotype
- Homeostenosis

The Aging Liver

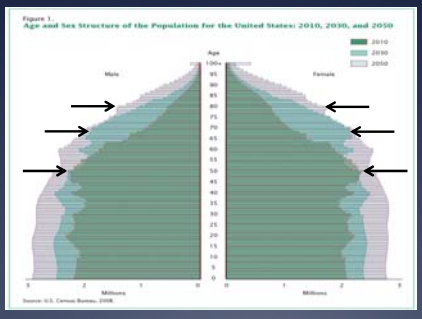
- Overview of the Liver
- Gross Structural Changes
- Histological/Cellular Changes
- Functional Changes
  - Pseudocapillarisation
  - Regeneration
  - Drug Metabolism
  - Liver Function Tests

Advancing Geriatrics Education (AGE): *A UMMS initiative funded by the Donald W. Reynolds Foundation*

Age: Implications for Your Practice

- The increase in life expectancy, influx of aging baby boomers, and shortage of geriatricians means more of your future patients will be over 65.
- The ability to explain to patients how the body changes with age builds rapport and enhances patient care.
- Knowing when age-related changes are clinically significant is good practice.

Follow the Wings…



Key Points of Aging

- Aging is not a disease
- Aging is a significant risk factor for disease
- Aging occurs at different rates between:
  - individuals
  - organ systems
  - physiological functions within an organ

The Phenotype of the Aging Process

- Increased susceptibility to diseases
- High risk of multiple coexisting diseases
- Impaired response to stress
- Emergence of "geriatric syndromes"
- Altered response to treatment
- High risk of disability
- Loss of personal autonomy

Homeostasis *x* Aging ➡ Homeostenosis

HOMEOSTASIS

The dynamic physiological processes employed to maintain a stable and constant internal environment in the face of internal and external challenges ("stress").

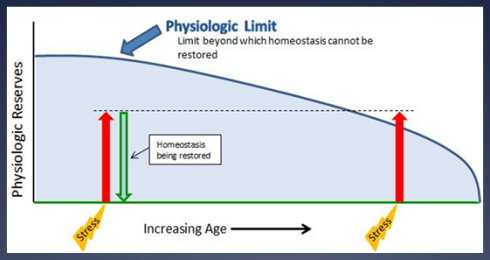
AGING

1. Cellular alterations occur leading to micro and macro structural and functional changes;
2. the amount of metabolic energy required to maintain some homeostatic processes may increase;
3. physiological functional reserves decline.

HOMEOSTENOSIS

Due to aging, less physiological functional reserve is available to respond to stress, thereby leading to increased vulnerability and greater consequences.

Homeostenosis + Sufficient Stress = Trouble



Physiological Functional Reserve

AMOUNT OF FUNCTIONAL RESERVE
DETERMINES
ABILITY TO HANDLE STRESS

As we age, we have less physiological functional reserve and our ability to handle challenges from external and internal stimuli decreases.

Result is *greater susceptibility to disease*

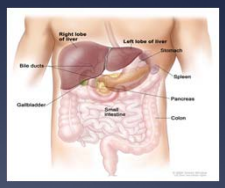
The Aging Liver

Major Themes

1. Enormous functional reserve and regenerative capacity
2. Liver physiologic functions age at different rates
   - acinus zonation and gradation of changes
   - degeneration and compensatory mechanisms
3. From a clinical standpoint, liver function remains stable despite age-related cellular and physiologic changes.

Liver Basics

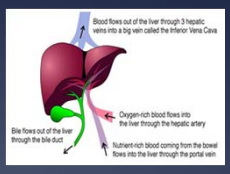
- Largest single organ and gland in the body: 1.4 -1.5kg in adult
- 4 lobes – right, left, caudate, quadrate
- Covered by rib cage and resides in the Upper Right Quadrant and in some of the Upper Left



Hepatic Blood Supply

Dual Afferent blood supply

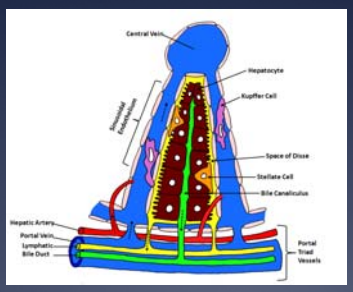
- ***Hepatic artery:*** from heart oxygen-rich, nutrient-poor blood - 25% of blood supply to liver
- ***Hepatic portal vein:*** from GI oxygen-poor, nutrient-rich blood - 75% of blood supply to liver



Single Efferent blood supply

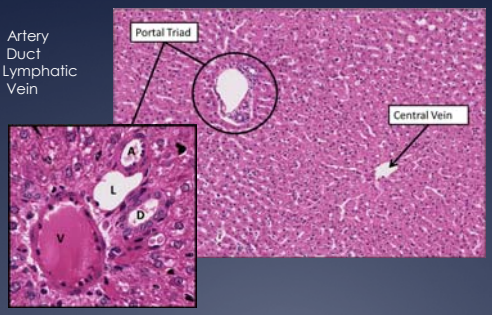
Central veins in acini → Hepatic vein → IVC → Heart

Hepatic Blood Flow, Major Cells, and Internal Structure

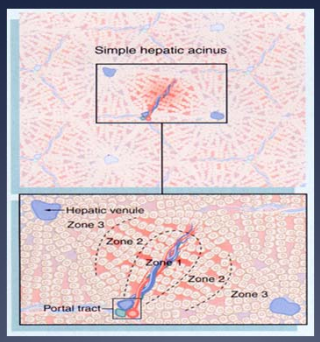


The Hepatic Acinus

A Artery
D Duct
L Lymphatic
V Vein

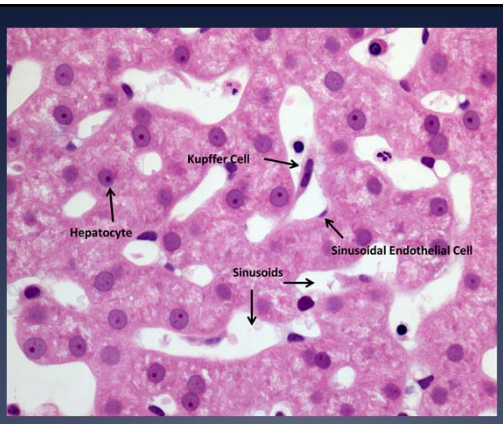


Hepatic Zonation

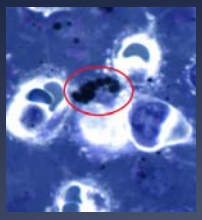


The Cellular Cast of Characters*

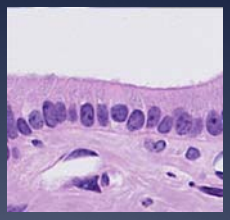
- Hepatocytes (epithelial cells)
- Kupffer Cells (resident macrophages)
- Sinusoidal Endothelial Cells (aka liver sieve)
- Stellate Cells (aka Ito Cells)
- Cholangiocytes (bile duct epithelial cells)



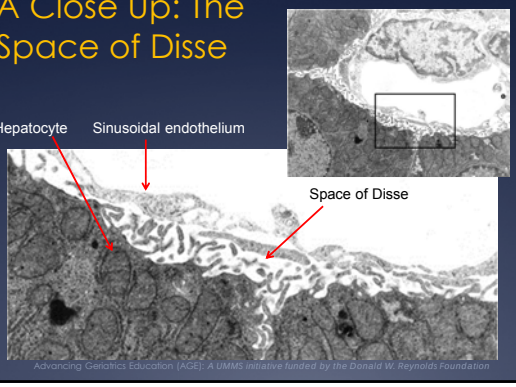
Stellate Cell



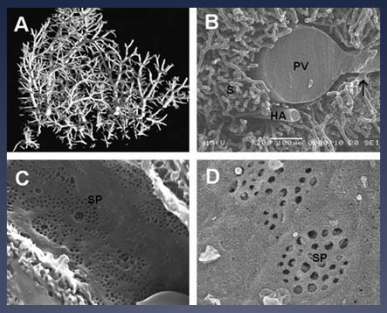
Cholangiocytes



A Close Up: The Space of Disse



The Liver Sieve



Major Liver Functions

1. **Vascular** storage & formation
2. **Immune** dirty portal -> clean systemic
3. **Metabolic** carbohydrates, protein, lipids
4. **Storage** vitamins & iron
5. **Synthesis** proteins & clotting factors
6. **Detoxification/Metabolism** drugs, hormones
7. **Bile Production/Excretion**

The Aging Liver: Anatomical Changes

- Decreased mass of functional hepatocytes
  - 30-40% reduction
- Decrease in hepatic volume
  - 20-40% reduction
- Decreased hepatic blood flow
  - 30-50% reduction
- "Brown Atrophy:" lipofuscin accumulation

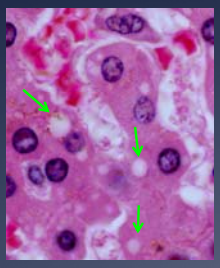
The Aging Liver: Histological/Cellular Changes

Hepatocytes

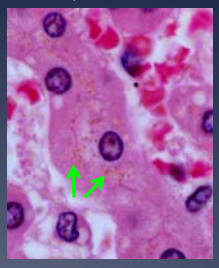
1. Compensatory enlargement
2. Increased incidence of polyploidy
3. Decrease # of mitochondria (enzymatic activity within them remains stable)
4. Decrease in the surface area of smooth and rough endoplasmic reticulum
5. Steatosis: the accumulation of lipid
6. Lipofuscin: the accumulation of residual degradation products

Age-Related Changes to Hepatocytes

Steatosis



Lipofuscin



The Aging Liver: Histological/Cellular Changes

Kupffer cells

1. Decrease in number
2. Decrease in phagocytic capacity
3. No discernible change in morphology

Cholangiocytes

Appear to be the least impacted by age-related processes and, to date, there are limited data on the subject.

The Aging Liver: Histological/Cellular Changes

Sinusoidal Endothelia

1. Endothelium increases 50% in thickness
2. Defenestration – 80% reduction in # of pores as well as a decrease in pore diameter
3. Increase in basement membrane

Stellate Cells

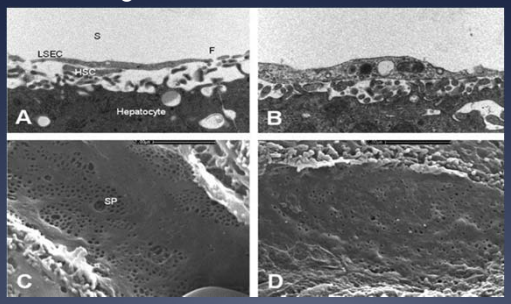
1. Quiescent Vitamin A storage state and activated myofibroblast-like state
2. Possible implication in the extravascular deposition of collagen in the space of Disse

Pseudocapillarisation

Young Liver	Aged Liver
– Thin sinusoidal endothelium	– Thick sinusoidal endothelium
– Numerous fenestrations	– Decreased # of fenestrations
– Scant discontinuous basal lamina	– Formation of a basal lamina and increased amounts of collagen in space of Disse
– Minimal collagen in space of Disse	– Markedly increased expression of von Willebrand Factor

Pseudocapillarisation

Young Liver Old Liver



Hepatic Regeneration

- Only organ in the adult to regenerate
  - *Two Phases Post-Resection*

    Note: critical residual liver volume 20-30%

    1. via hypertrophy
    2. via global hyperplasia, if hypertrophy not sufficient to replace lost mass
- Rate of regeneration diminishes with age
  - fewer hepatocytes enter S-phase and are slower to make the entry
  - hyperplasia impacted more than hypertrophy

Medication in the Older Adult

- **Common**
- Co-administration of multiple medications
- Co-morbidities
- Hospitalization and death due to adverse drug reactions

Clinical Drug Trials: A Dirty Secret

The "elderly" are often under-represented.

Spheres of Impact

- Accurate dosing (Pharmacokinetic & Pharmacodynamic age-related changes) – currently extrapolated
- Potential side-effects attributable to drug interactions (polypharmacy is the norm among people over 65)

Drug Metabolism

- Inter-individual differences
- Phase 1 Metabolism: microsomal mixed-function oxidative system – Diminished (Zone 1)
- Phase 2 Metabolism: Synthetic reactions - Conjugation, acetylation, methylation - Little Impact (Zone 2 +3)

Factors that Impact Drug Metabolism

1. Reduced liver volume, size, and hepatic blood flow
2. Reduced smooth endoplasmic reticulum
3. Changes in body composition with age affect various aspects of drug metabolism, especially volume of distribution
4. Receptor concentration and responsiveness
5. Inter-individual variability in amount and availability of CYP450 make generalizations with respect to the impact of aging difficult.

Age-Related Changes: Pharmacokinetics

Absorption	Unchanged (Net Impact)
Gastric pH	Increased
Secretory capacity	Decreased
Gastrointestinal blood flow	Diminished
Distribution	
Plasma albumin	Diminished
Protein affinity	Diminished
Metabolism	
Size of liver	Decreased
Hepatic blood flow	Decreased
Renal Function	
Glomerular filtration rate	Decreased
Renal plasma flow	Decreased
Filtration fraction	Increased

Liver Function Tests

- Panel of Tests - No one test available to capture all liver functions
- Panel only provides an overall snapshot
- Despite age-related liver changes, functional tests remain within normal range
- Abnormal results – ***must*** consider presence of liver disease and work up accordingly

Liver Function Tests in the Aging Liver

- ALT – no change
- AST – no change
- GGT – no change
- Alk Phos – no change
- Albumin – slight decrease
- Total Protein – no change
- Total Bilirubin – no change
- PT – no change

Summary of Age-Related Changes in the Liver

Anatomical decrease in mass, volume, and blood flow plus brown atrophy

Cellular there are changes to all cells types with the most significant being to the hepatocytes and sinusoidal endothelia

Pseudocapillarisation flow-limited to barrier-limited distribution

Regeneration continues throughout lifespan but at a reduced capacity

Drug Metabolism predominantly impacts Phase I first pass metabolism

Liver Function Test no clinically significant changes

Advancing Geriatrics Education (AGE): *A UMMS initiative funded by the Donald W. Reynolds Foundation*

Acknowledgements

Krista Johansen, MD*
Mark Dershwitz, MD*
Gyongyi Szabo, MD, PhD
Catherine DuBeau, MD
Sarah McGee, MD, MPH*
Erika Oleson, DO, MS*
Jerry Gurwitz, MD
Colleen Burnham, MBA*

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