



# Diagnosis of Amyloidosis

## Why fat pad is not always the way

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Outline

Congo red dye

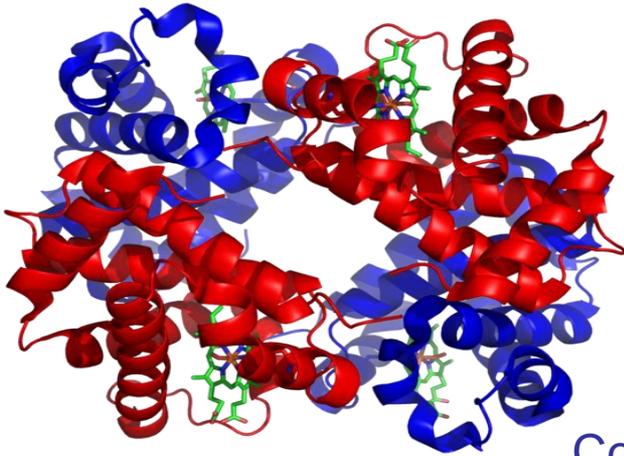
Generic diagnosis of amyloidosis

Fat pad

Other options

# Amyloidoses

$\alpha$  helix



$\beta$  pleated sheet



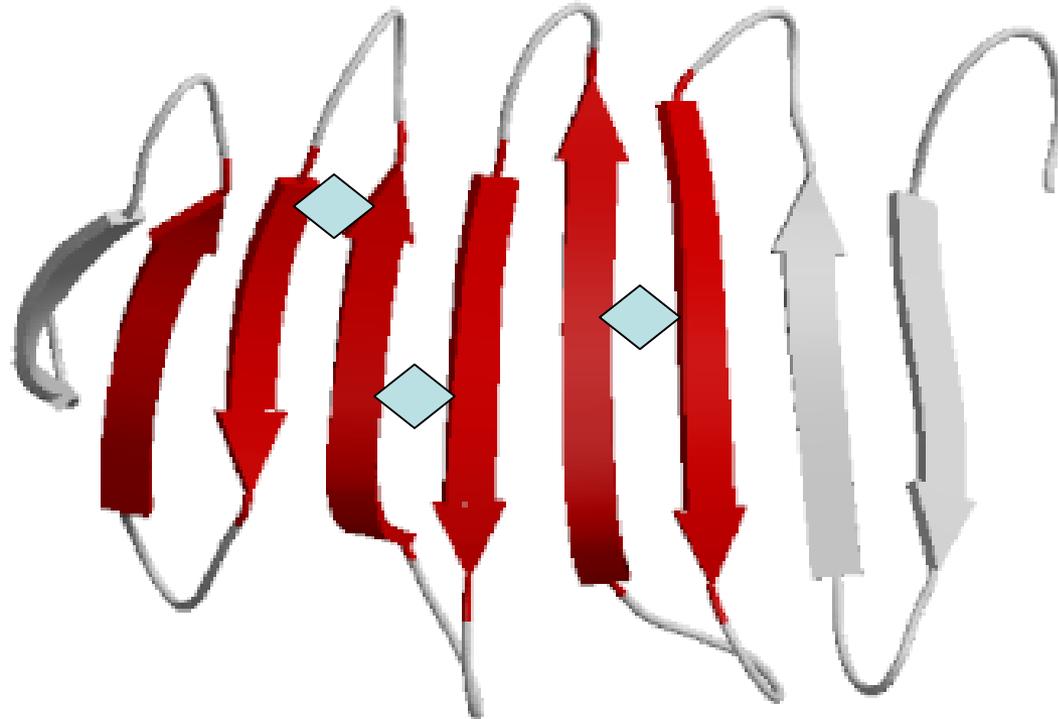
Amyloid formation

Conformational shift to  
 $\beta$ -pleated sheet 2<sup>o</sup> structure

$\beta$ -pleated sheet conformation confers  
affinity to Congo red

**common to ALL types of amyloid**

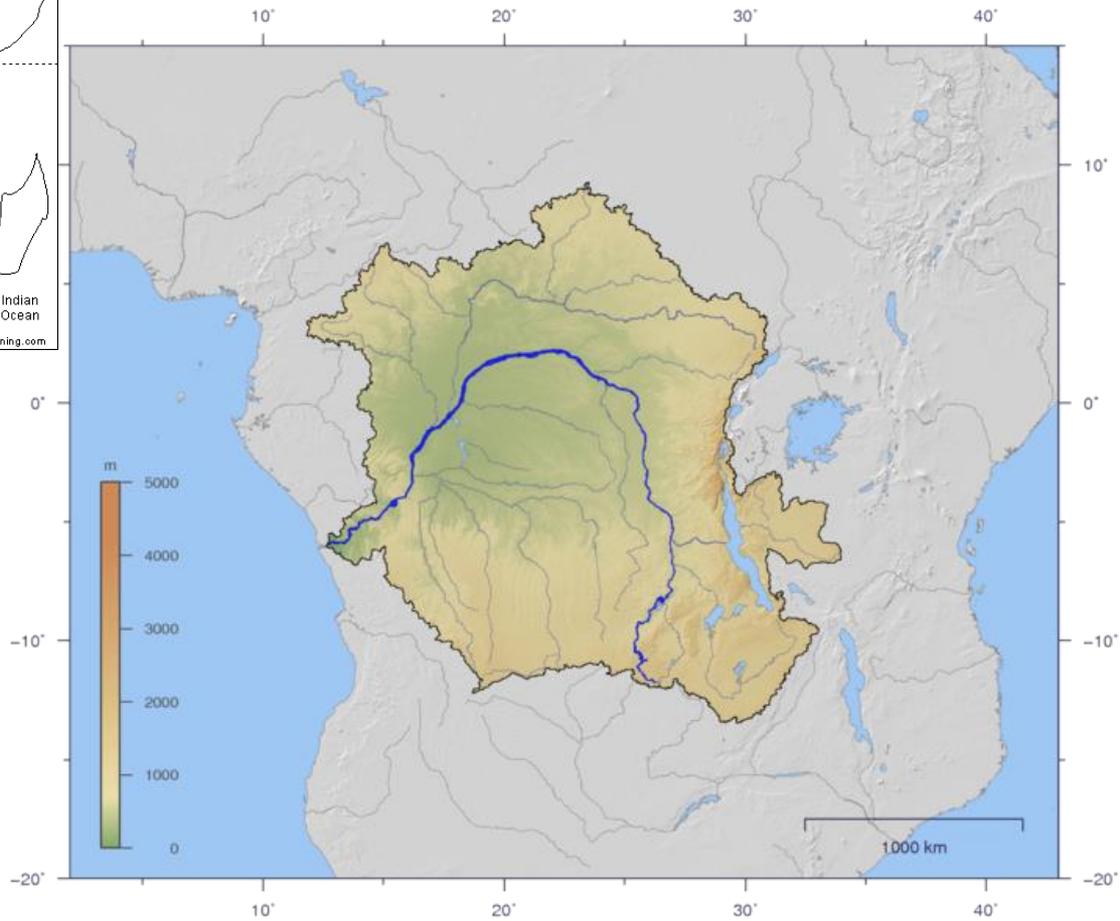
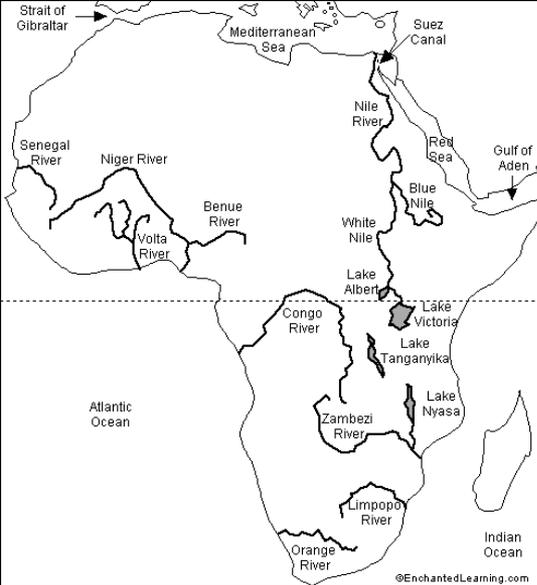
**Diagnosis of amyloid requires biopsy**



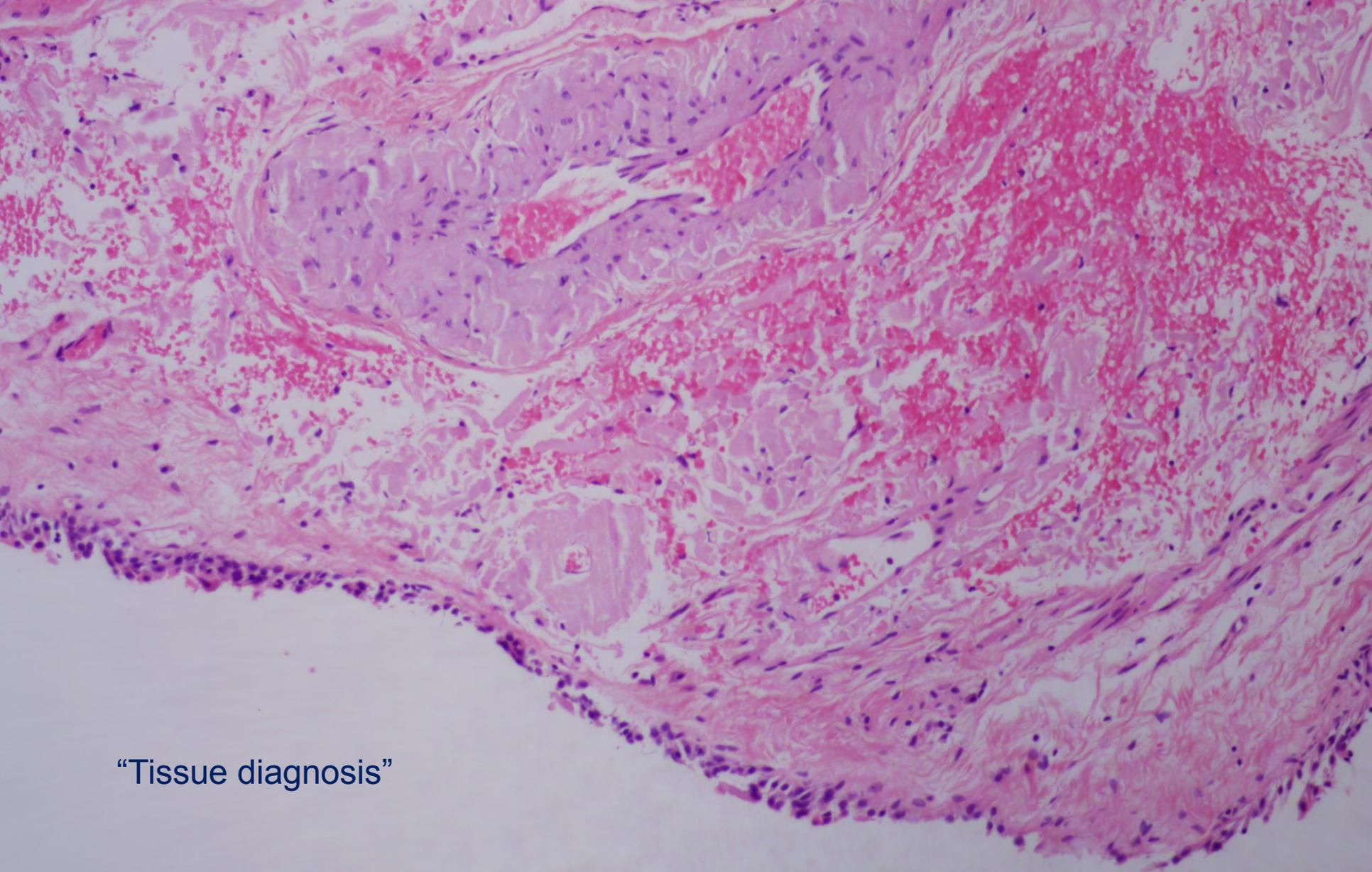
◆ Congo red binding sites

## Congo red = bright red color:

- first synthesized in 1883 by Paul Bottiger (Friedrich Bayer Company, Germany)
  - textile dye
  - the company was not interested, filed the patent under his name and sold it to the AGFA company of Berlin
  - AGFA marketed the dye under the name "Congo red"
- 1884 Berlin West Africa Conference, colonization of Africa



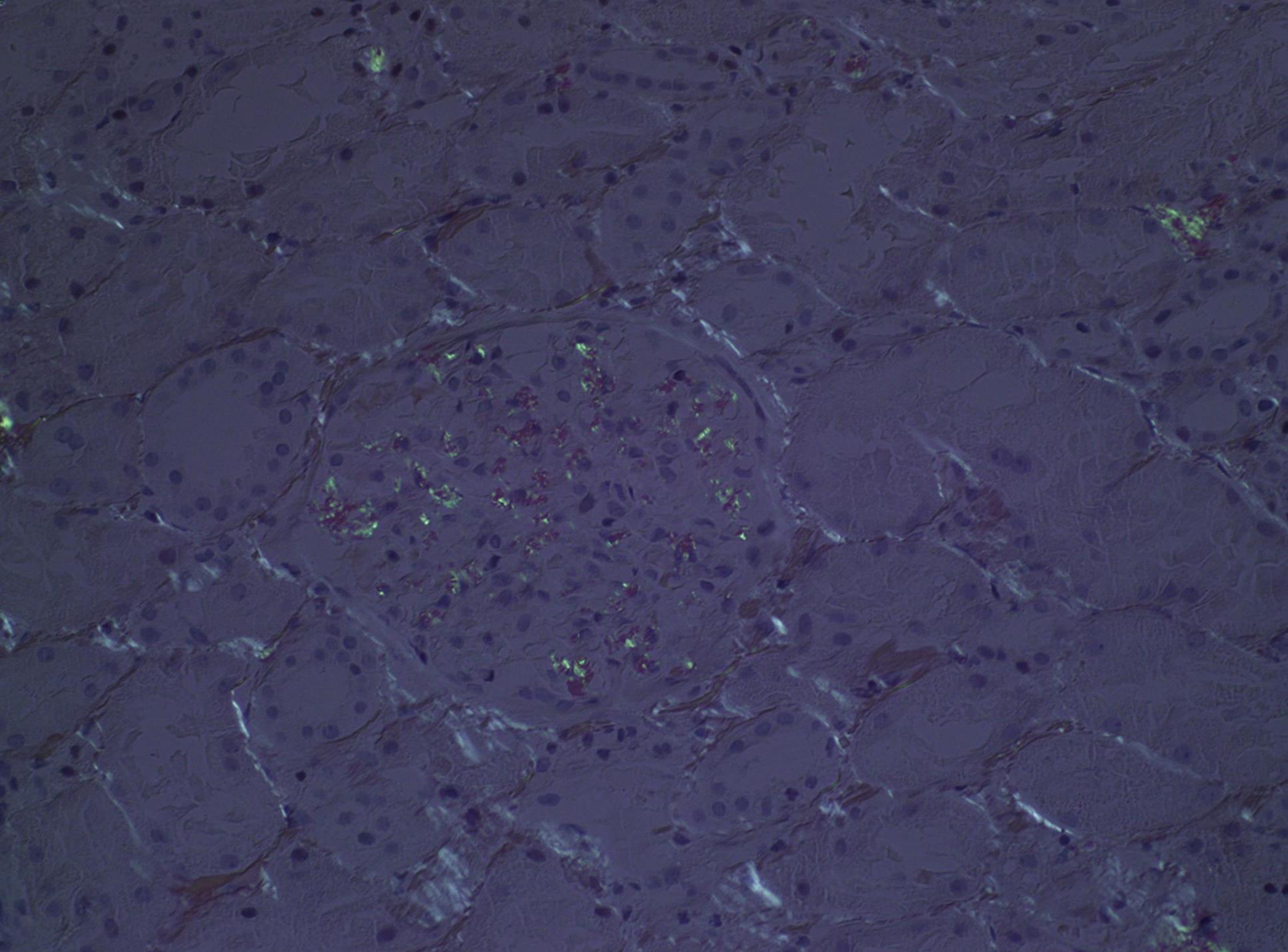
- The **Congo River** (aka the **Zaire River**) = a river in Africa
- deepest river in the world, with measured depths >230 m (750 ft)
  - 2nd largest river in the world by volume of water discharged (after Amazon)

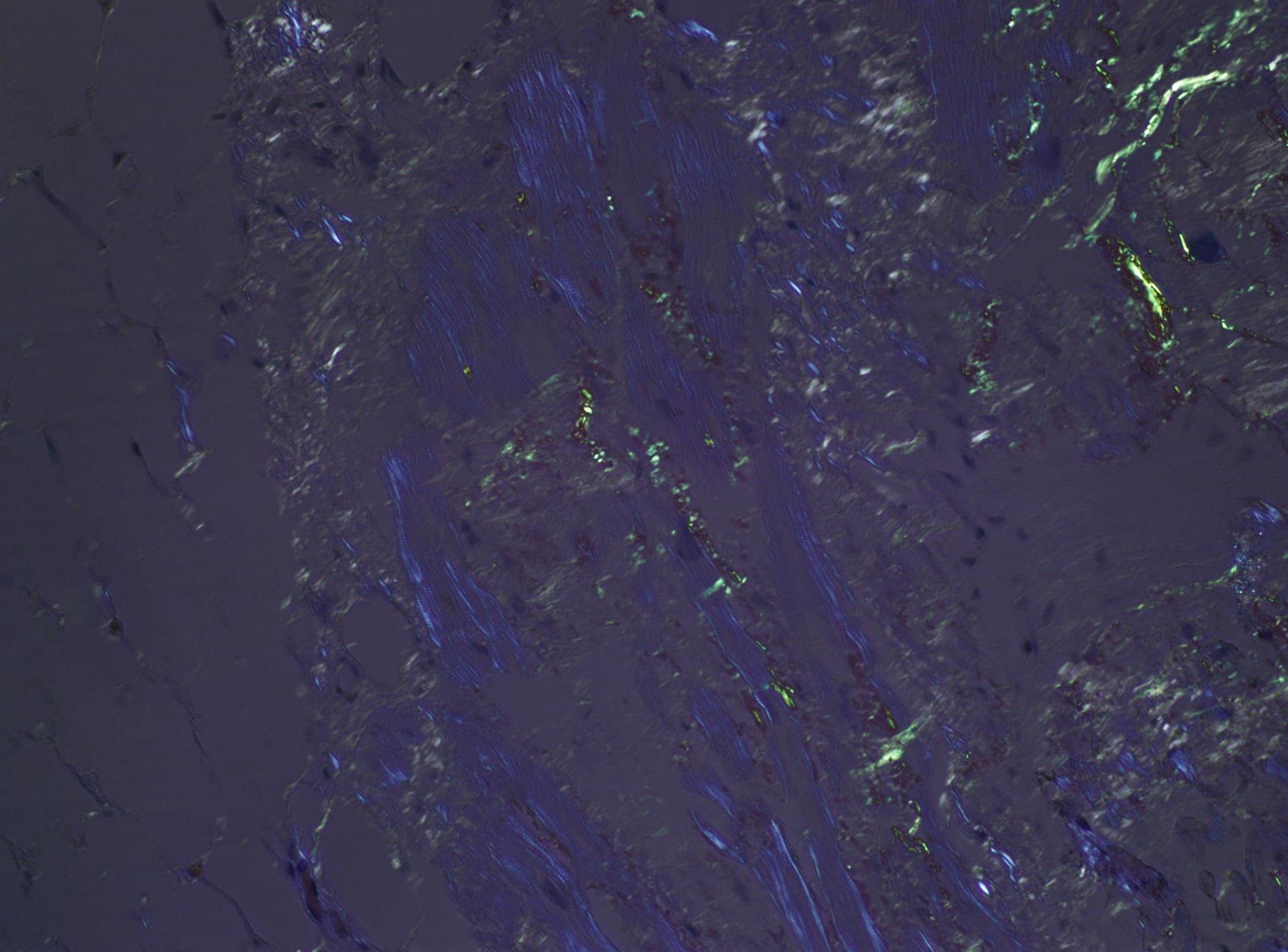


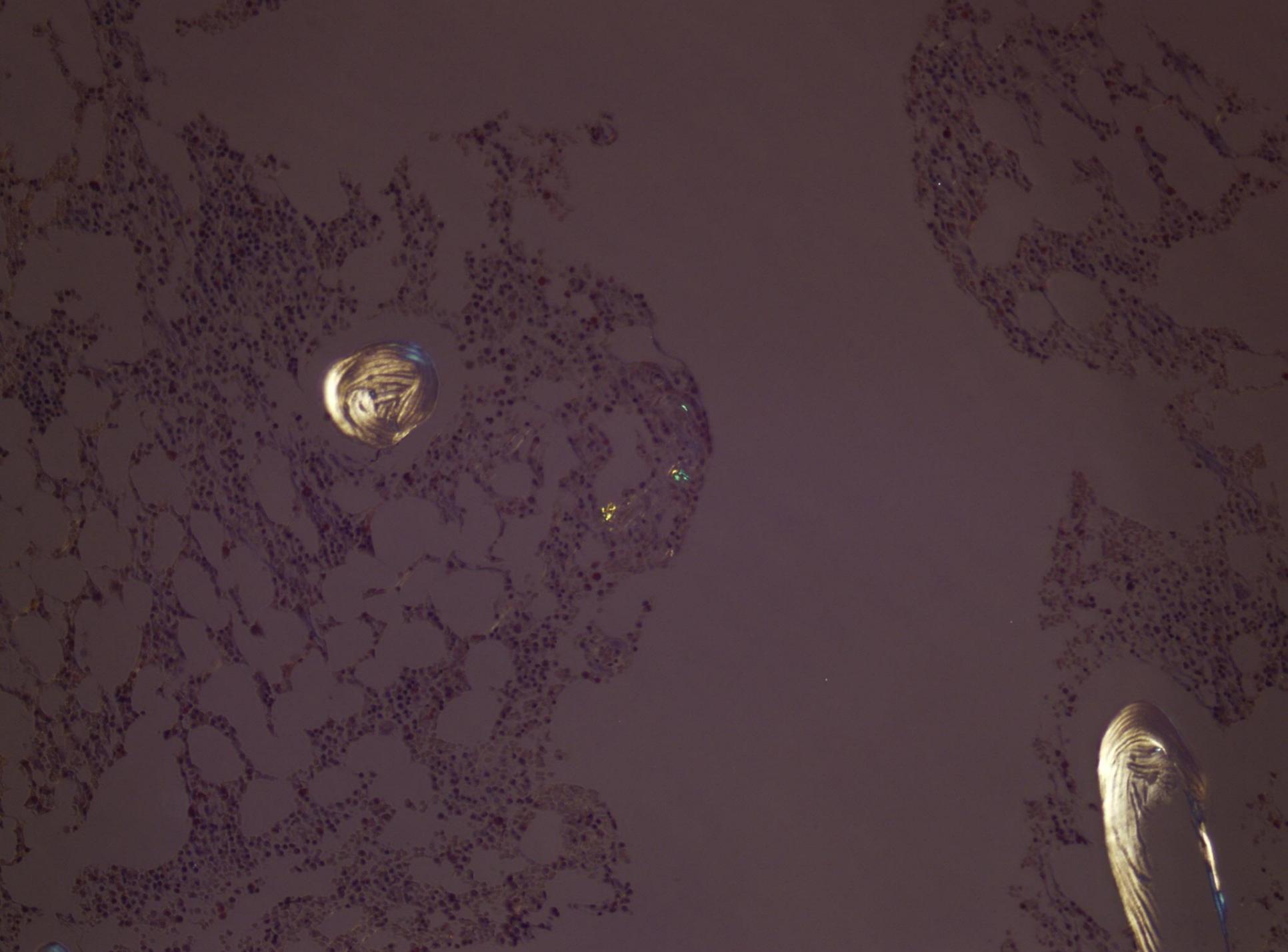
“Tissue diagnosis”

**Current gold standard**







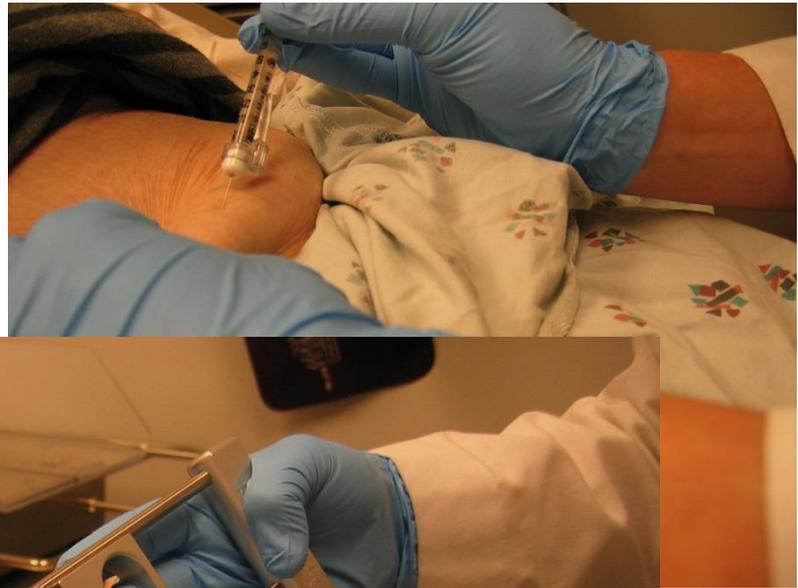


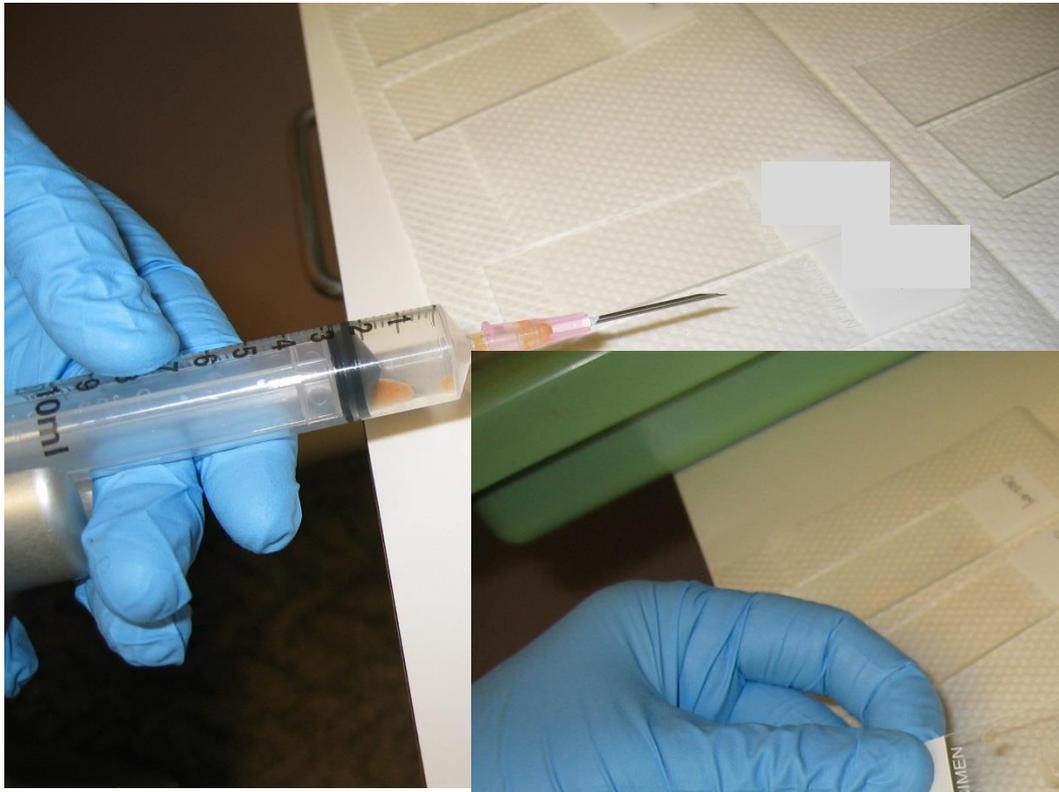
## FAT STORY

Schilder (1909): amyloid frequently present in subcutaneous fat tissue in patients with amyloid A (AA) amyloidosis

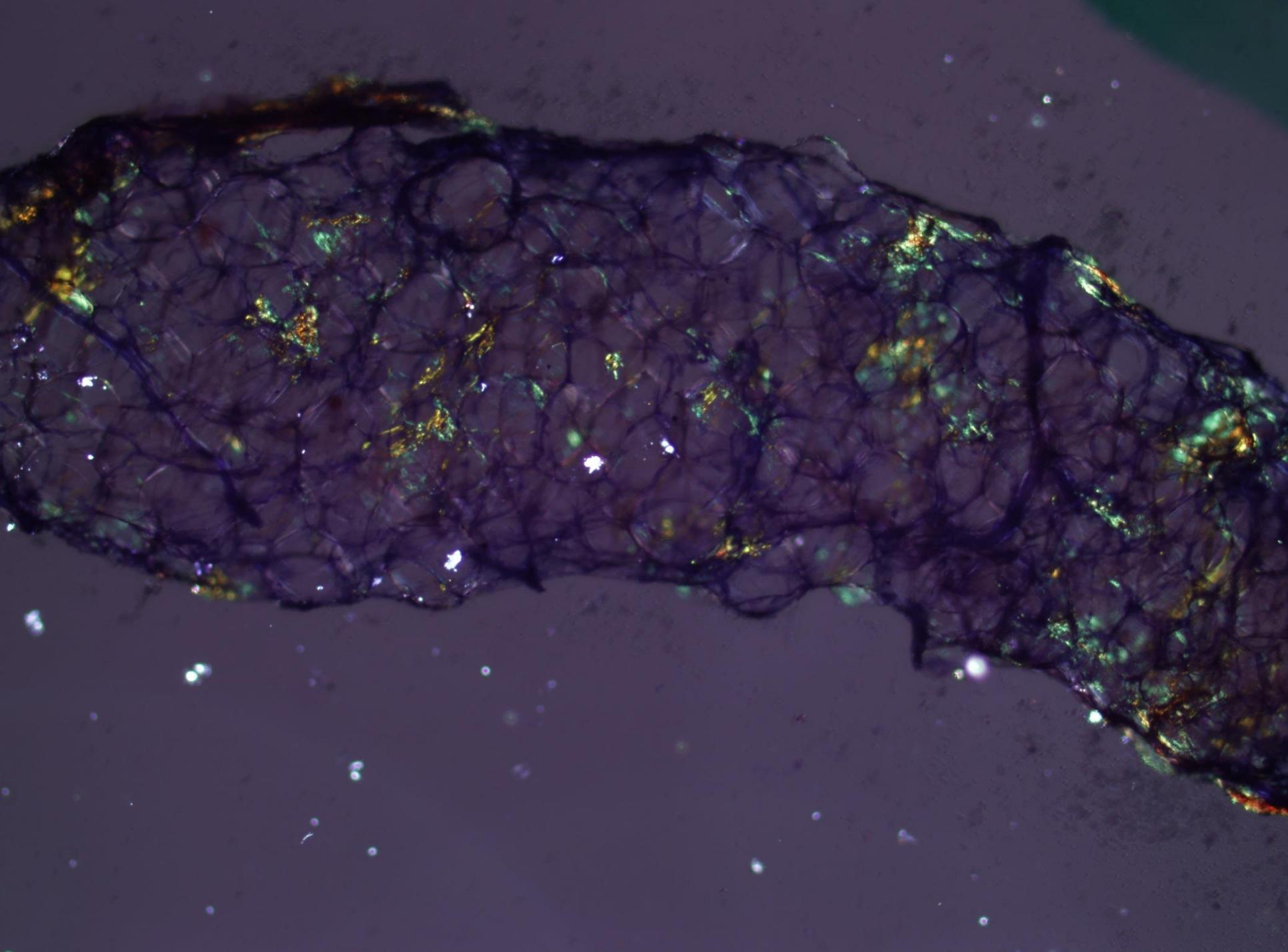
P. Westermark and Stenkvist B (1971):  
diagnosis of secondary (AA) generalized amyloidosis by  
fine needle biopsy of the skin

Libbey, Skinner, Cohen, 1983, high yield of detection (88%) in AL, ATTR



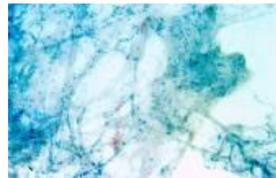




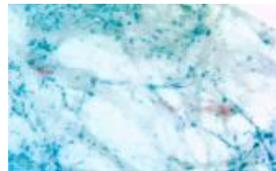




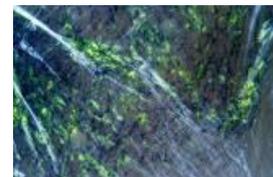
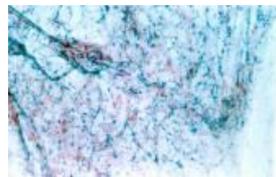
# Congo red stained fat smears: semi-quantitative assessment



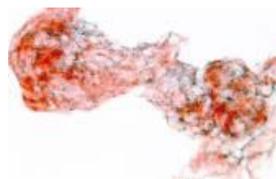
1+ (< 1%)



2+ (1-10%)



3+ (10-60%)



4+ (> 60%)

Bright field

Polarised light

CR Score

*Hazenberg et al, AMYLOID 2007*

Congo red - a great stain in experienced hands but too many pitfalls for general pathologists! scoring, quantification....Hazenberg et al;

Amyloid detection in fat – AA, AL, ATTR:

Sensitivity highly variable 54-93%

Specificity: 93-100%

Affected organ – best yield

Other options?

Fine et al, 2014:

ATTR, cardiac versus non-cardiac tissue sampling:

biopsy	all	Familial ATTR	Wild type Senile ATTR
Fat aspirate	225/106+ 47%	141/94+ 67%	84/12+ 14%
Bone marrow	164/60+ 37%	100/41+ 41%	64/19+ 30%
heart	131/131+ 100%	42/42+ 100%	89/89+ 100%
Sural nerve	54/45+ 83%	54/45+ 83%	0

Fat aspiration was the most commonly performed  
followed by bone marrow biopsy

Other: rectum, kidney, carpal ligament, liver, small intestine, sural nerve

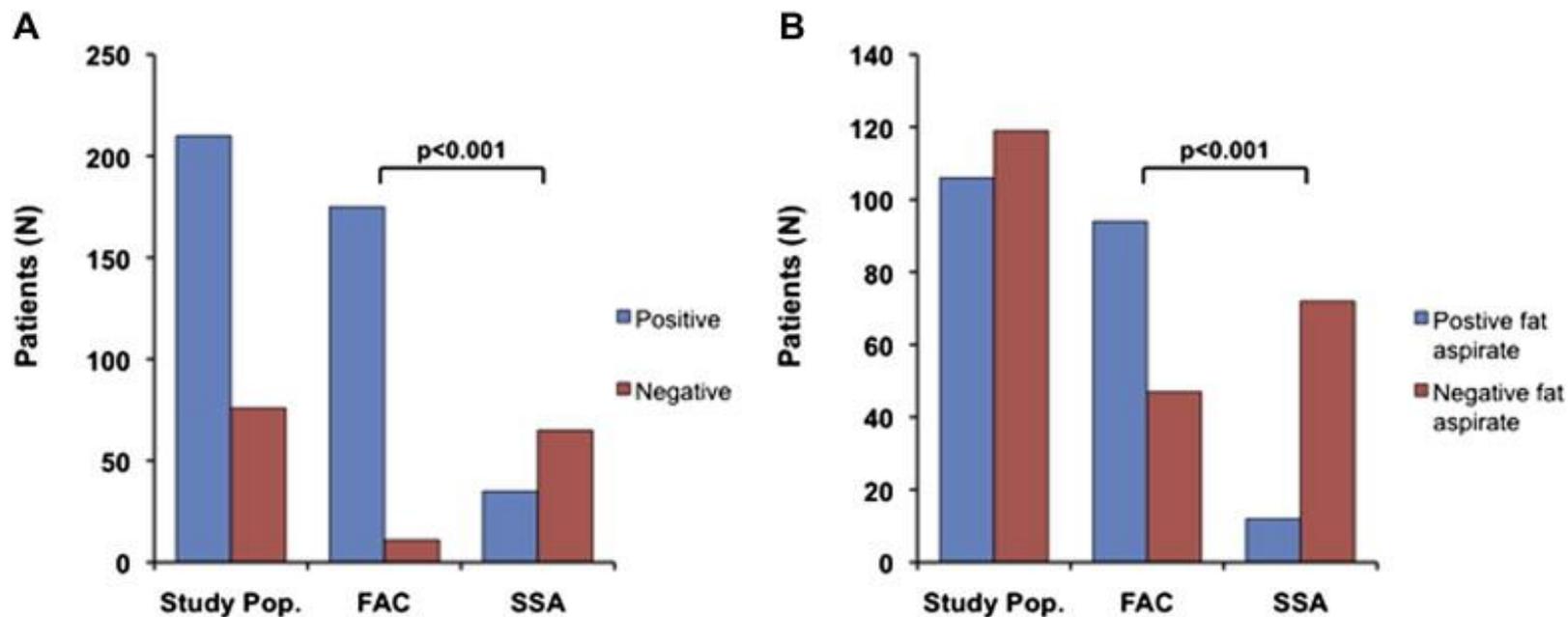


Figure 1. Prevalence of amyloid protein deposition among patients with ATTR cardiac amyloidosis for the study population and for patients with FAC and SSA for (A) any type of noncardiac tissue sampling including noncardiac biopsy or abdominal subcutaneous fat aspiration and (B) only abdominal subcutaneous fat aspiration. Positive = positive for amyloid protein deposition, Negative = negative or equivocal for amyloid protein deposition.

Nowell M. Fine, Adelaide M. Arruda-Olson, Angela Dispenzieri, Steven R. Zeldenrust, Morie A. Gertz, Robert A. Kyle, Paul L. Swiecicki, Christopher G. Scott, Martha Grogan

#### **Yield of Noncardiac Biopsy for the Diagnosis of Transthyretin Cardiac Amyloidosis**

The American Journal of Cardiology, Volume 113, Issue 10, 2014, 1723–1727

<http://dx.doi.org/10.1016/j.amjcard.2014.02.030>

Coelho et al in FAP:

Labial salivary gland: 89%

Abdominal fat: sensitivity 50-70%

Nerve biopsy: 75-90%

## Fat aspirate in wild-type (senile) ATTR amyloid cardiomyopathy

Fine et al 2014, 84 patients, sensitivity of 14%

Ikeda et al 2011, sensitivity increased to 73% (8 of 11 patients),  
deep layer of **surgical fat biopsy**, patchy distribution

Takashio et al 2012: amyloid in blood vessels of fat  
AL > ATTR cardiomyopathy (14 patients)

# Amyloid in fat in non-AA, non-AL, non-ATTR

systemic amyloidosis:

AApoAI (apolipoprotein AI), A $\beta_2$ M ( $\beta_2$ -microglobulin) - frequently absent  
AFib (fibrinogen  $\alpha$ -chain)

ALys (lysozyme) amyloidosis

AGel: amyloid was easily detected in fat tissue in 3/3 patients  
(Hazenberget al, unpublished observation)

No published data for:

AApoAII (apolipoprotein AII),

AH (immunoglobulin heavy chain),

ALect2 (leukocyte chemotactic factor 2) amyloidosis

# ALns (insulin) amyloidosis:

- rare localized type of nodular amyloidosis,
- site of repeated insulin injections

## Potential pitfall

long-term diabetics can have hypertrophic cardiomyopathy, proteinuria, peripheral polyneuropathy, and autonomic neuropathy, symptoms and signs can be mistaken for systemic amyloidosis.

Presence of monoclonal gammopathy may even confound the situation

# Pathology of Familial amyloidoses:

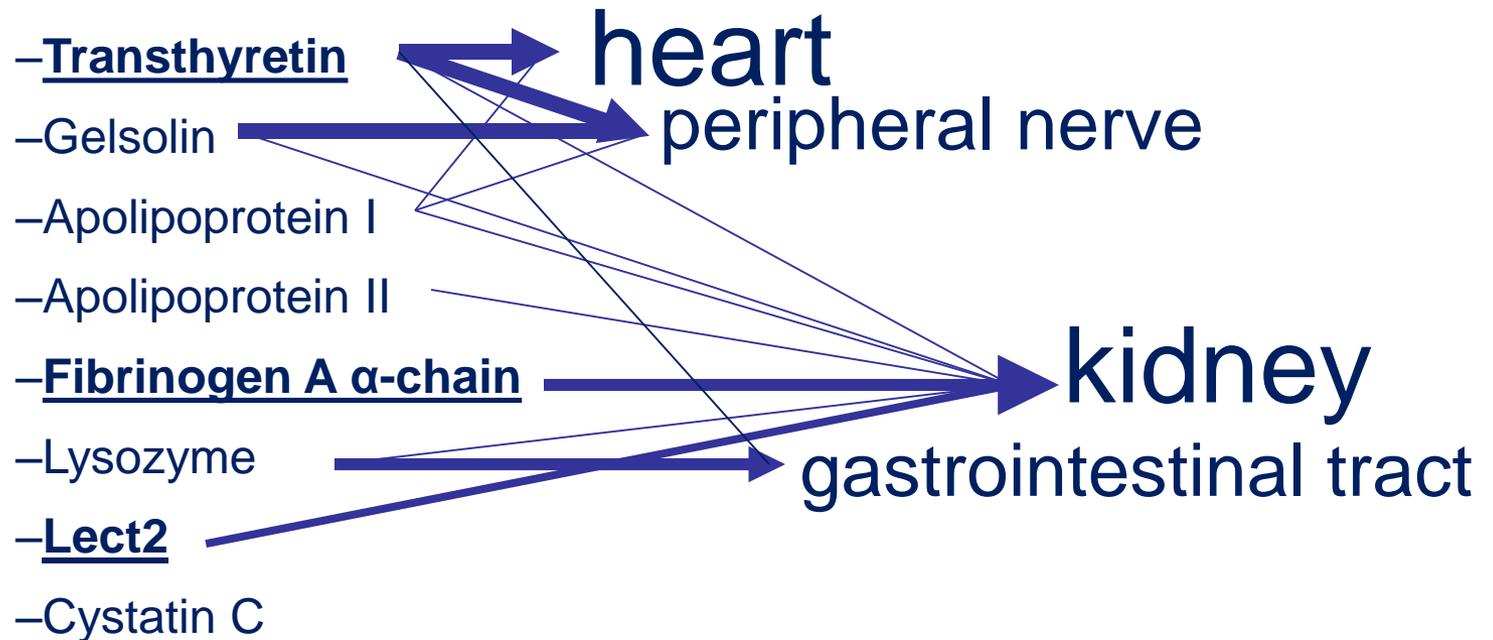
1. Detection of amyloid in the index patient
  - lack of a family history
  - new mutation
2. Examination of family members/known carriers
  - experience from domino transplants
3. Staging, definition of organ involvement

# Familial Amyloidoses

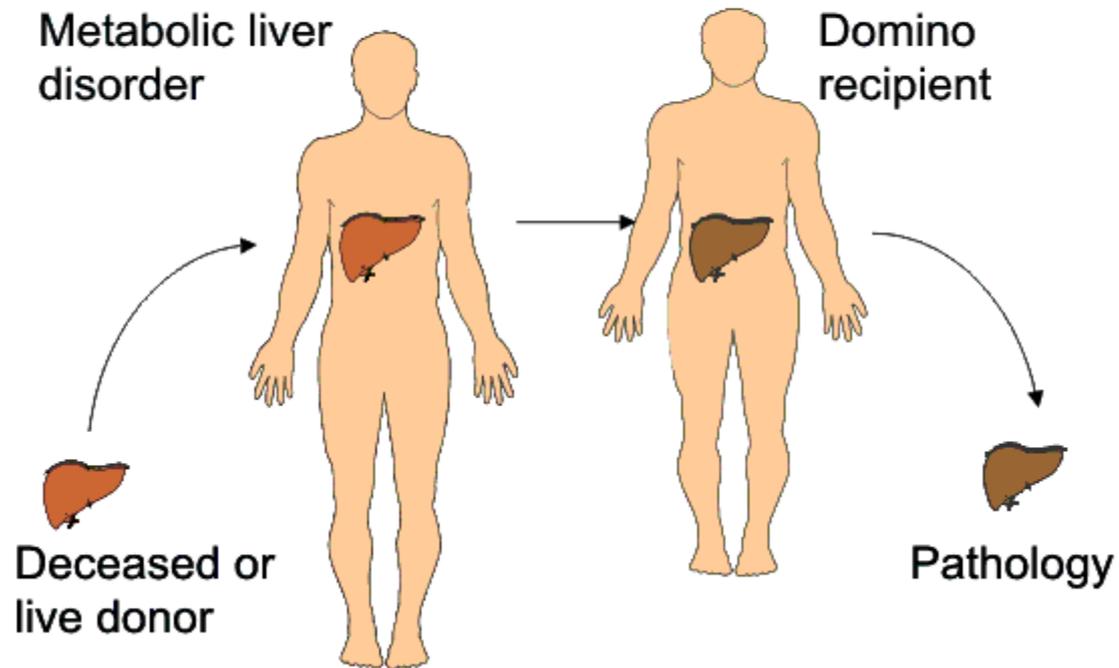
Mutation in the amyloid fibril protein

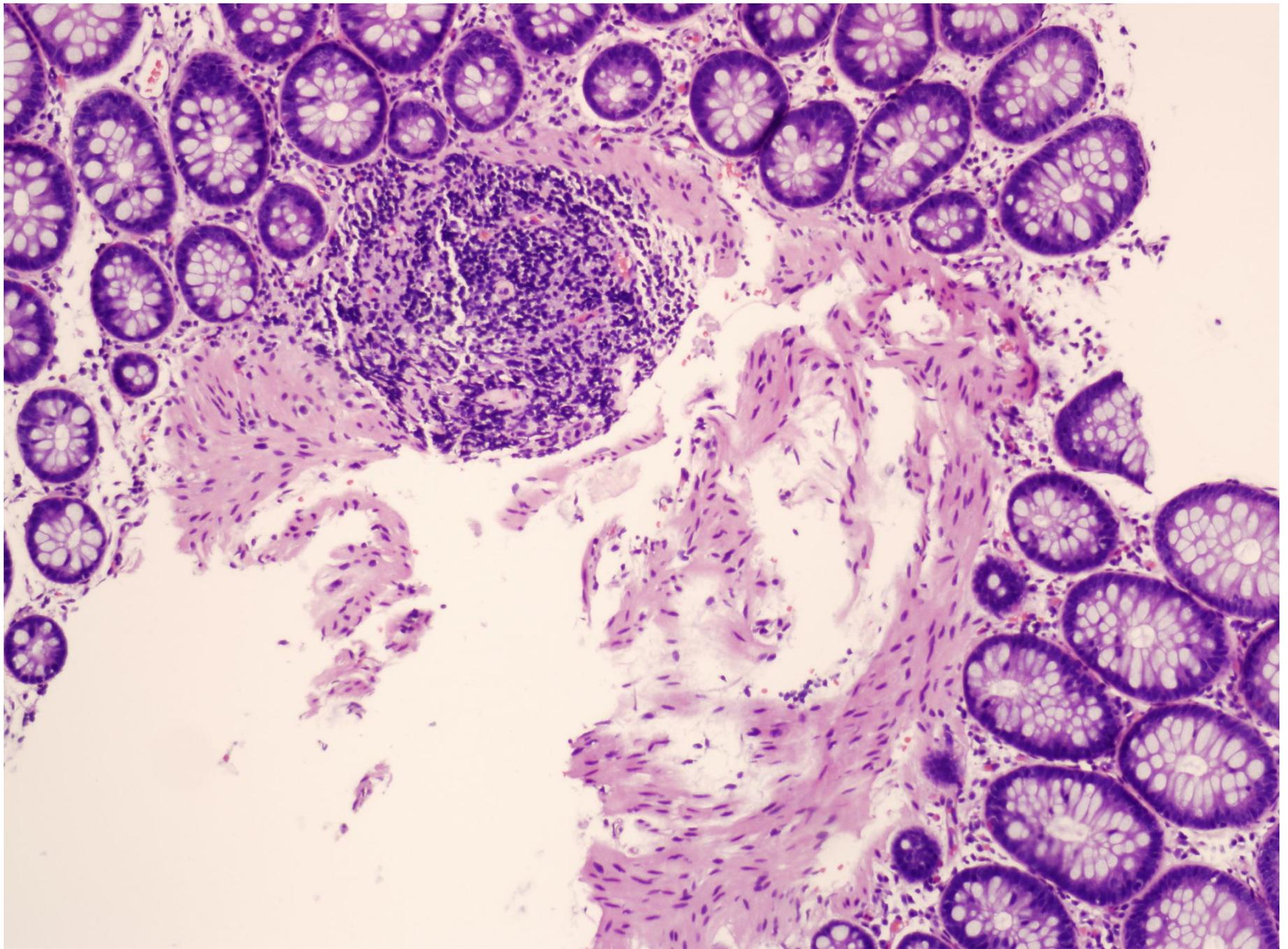
Variants of serum proteins

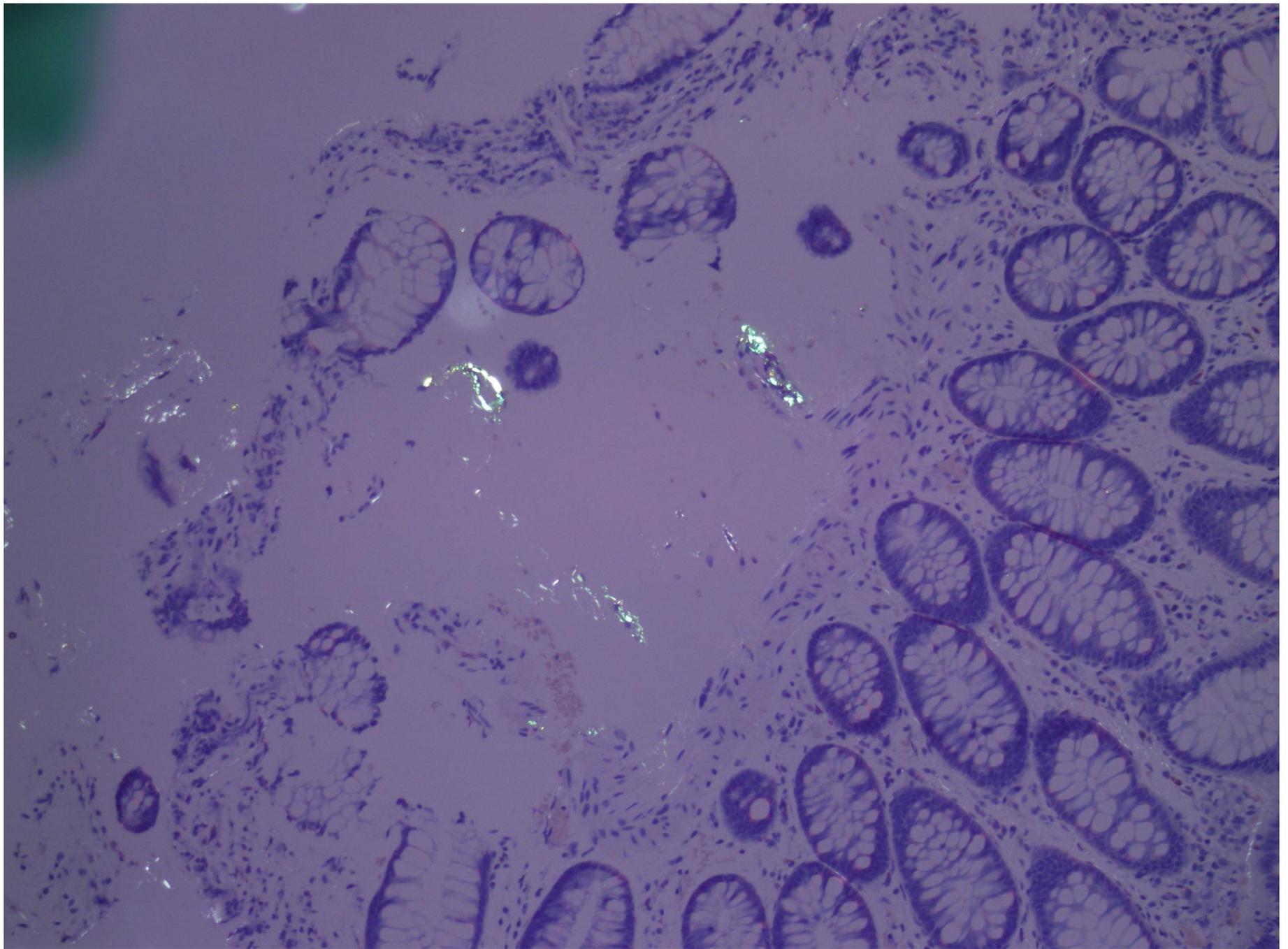
Phenotypes

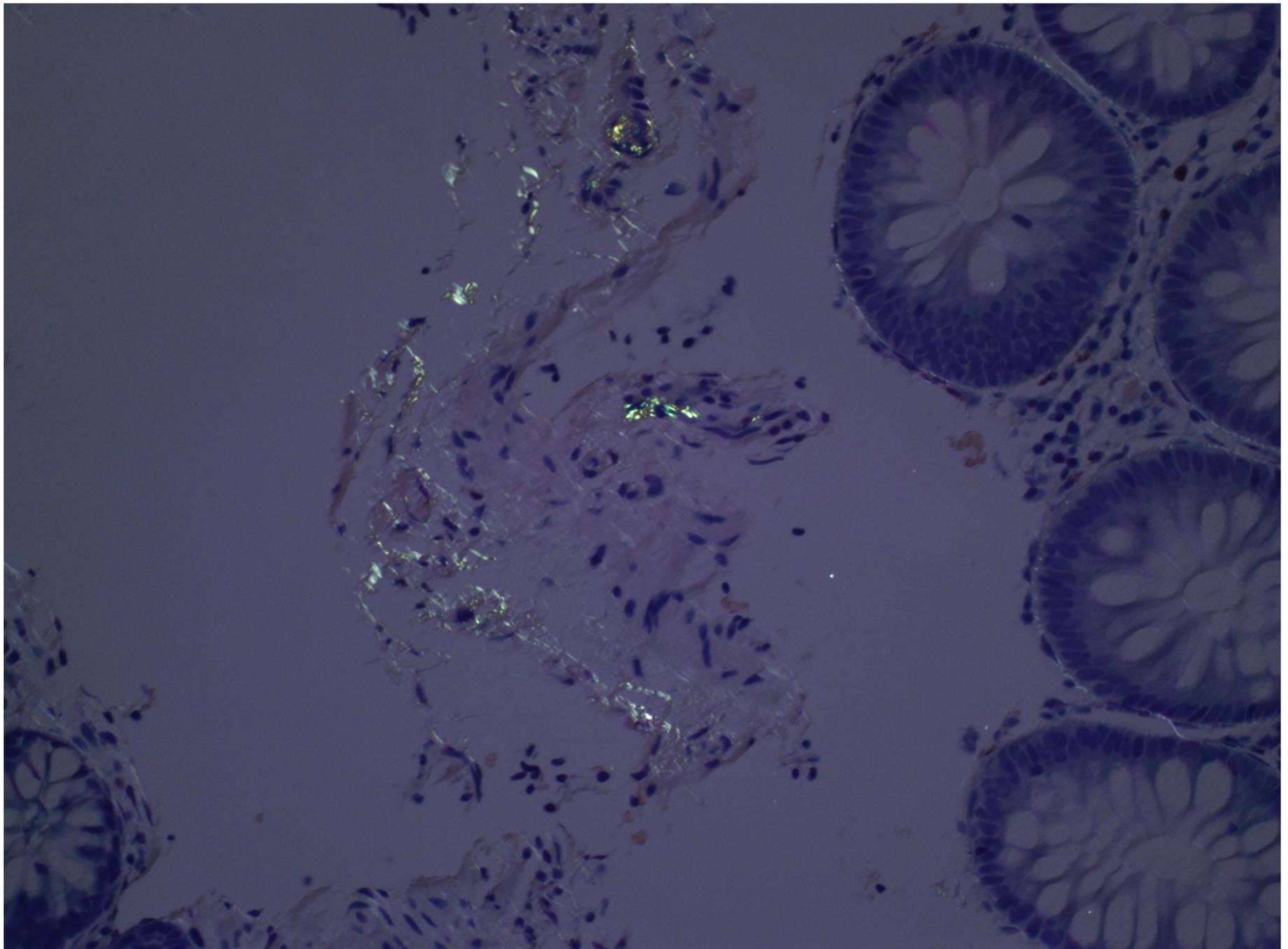


## Domino liver transplantation – the Concept







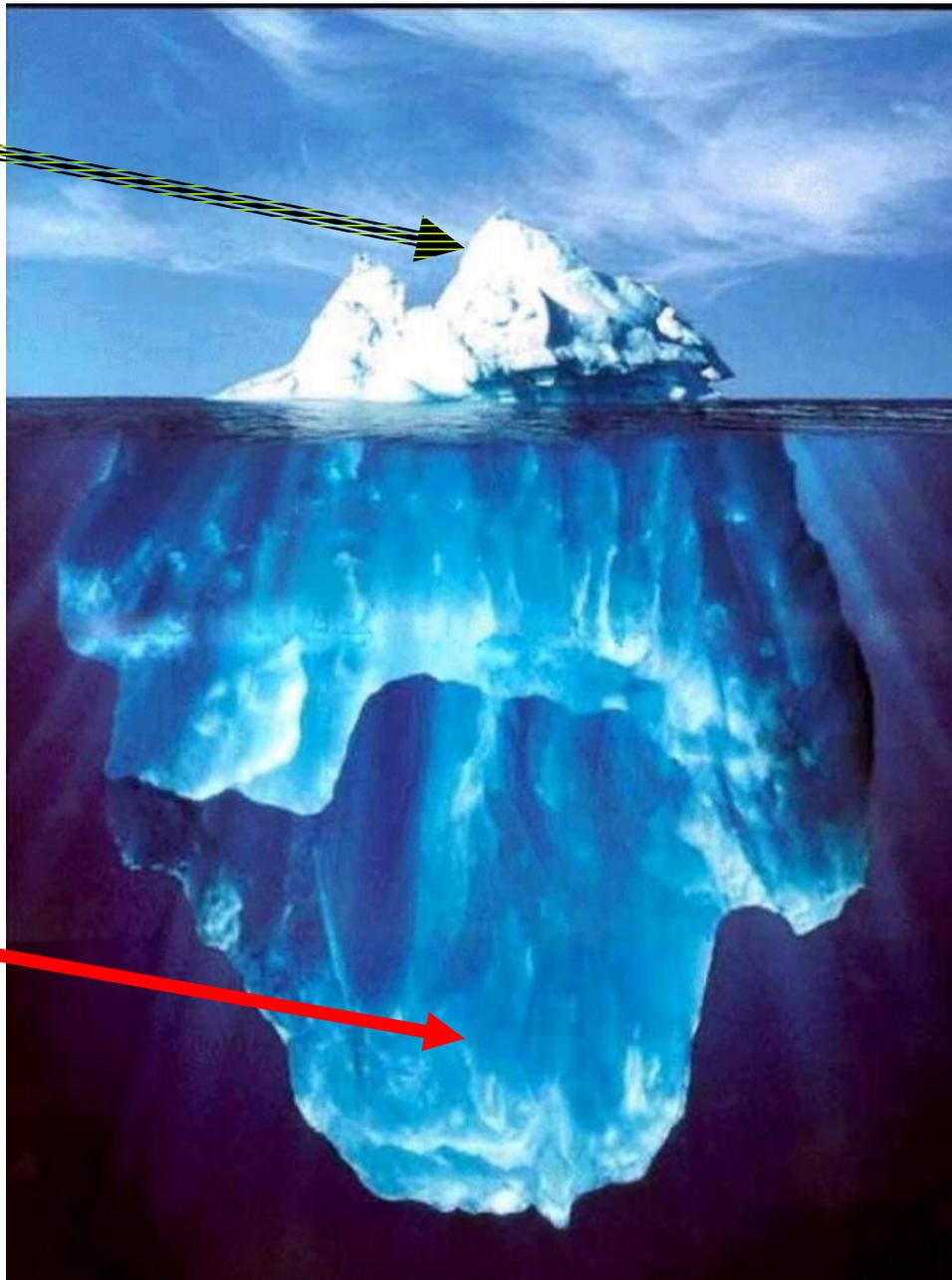


Screening?

↑ awareness

Suspicion → 2<sup>nd</sup> opinion

**amyloid**



**pre-amyloid phase  
toxicity**

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Maria M. Picken  
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# Amyloid and Related Disorders

Surgical Pathology and  
Clinical Correlations

 Humana Press