Diagnosis of Amyloidosis

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Amyloid: what is it and why it forms

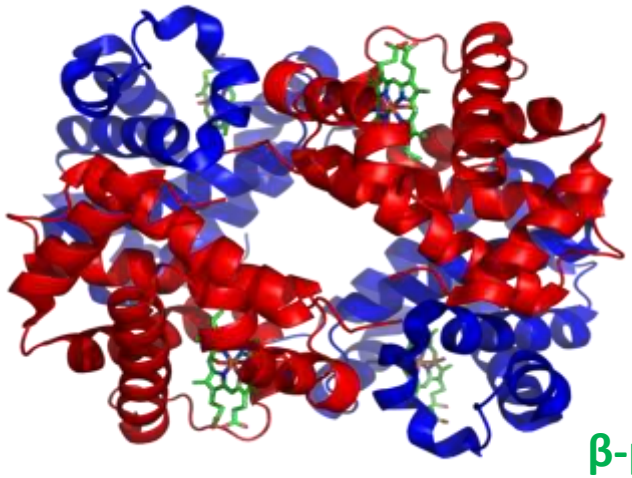
Name = misnomer: “amyloid” means starch*
but deposits of amyloid contain predominantly protein which became mis-folded

Amyloidoses = amyloid diseases

amylum = starch in Latin, ἄμυλον *amylon* = starch in Greek
* the name *amyloid* comes from the early mistaken identification by Rudolf Virchow (XIX century) of the substance as starch based on crude iodine-staining techniques

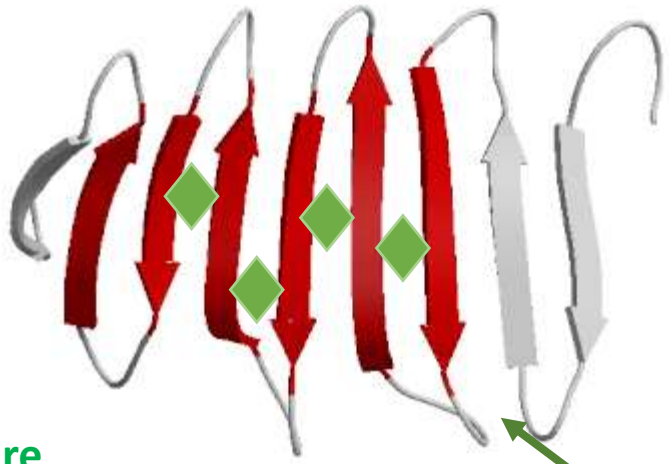
Amyloidoses – protein folding disorders

α helix

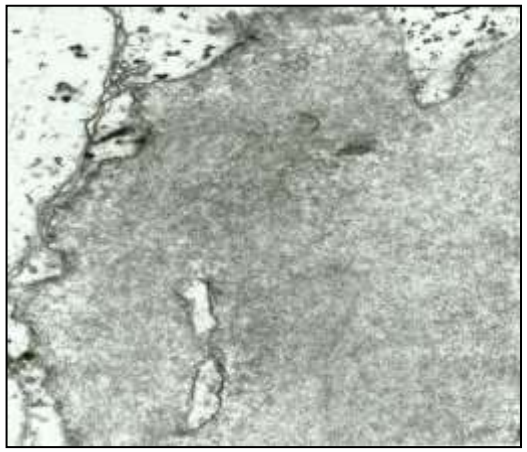


Fibrillogenesis
Conformational shift to
β-pleated sheet 2^0 structure

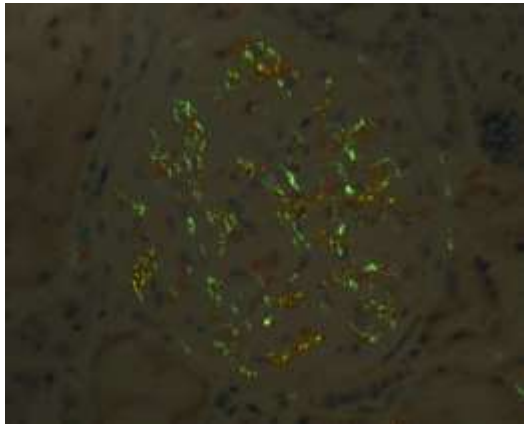
β pleated sheet



non-branching fibrils by electron microscopy



hydrophobic, insoluble
non-functional
resistant to degradation
sticky (prone to aggregation)
extracellular
affinity to Congo red stain
fibrillar (by electron microscopy)



Congo red positivity
with green birefringence
under polarized light

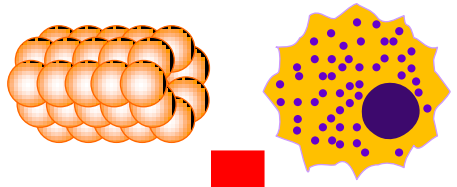
amyloid binding sites

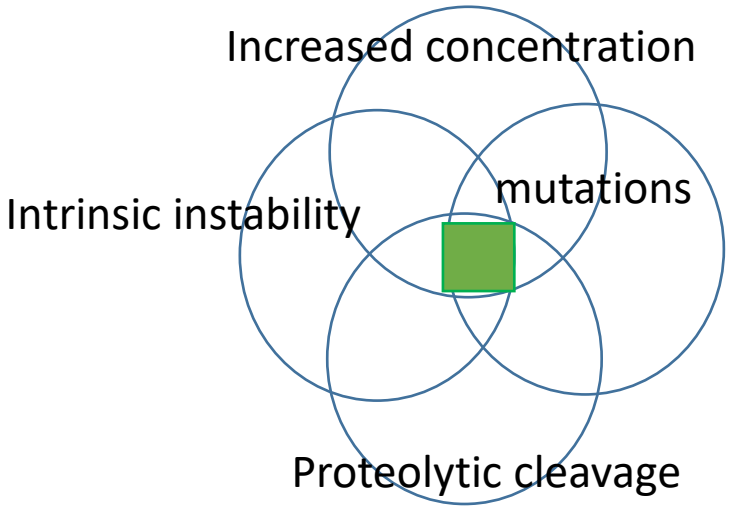
Amyloidoses – protein folding disorders

protein quality control systems:

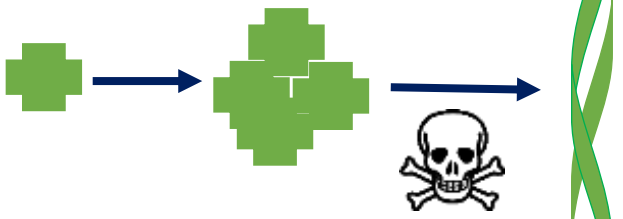
intracellular (**proteasomes***)

extracellular (macrophages)

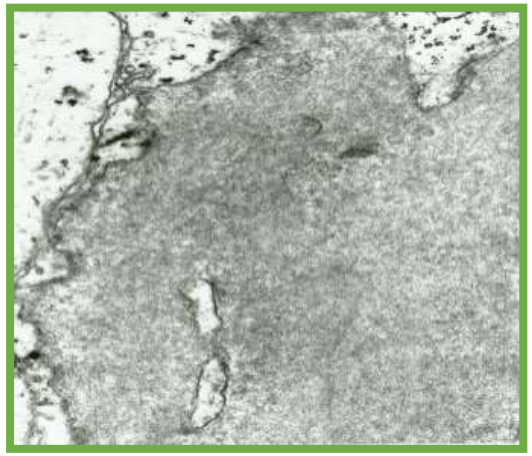




Older age



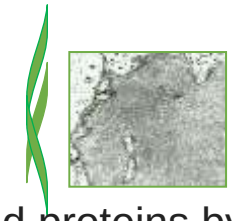
proteotoxicity



precursor protein

misfolded protein

protofibril



mature fibrils

Proteasomes = protein complexes which degrade unneeded or damaged proteins by proteolysis

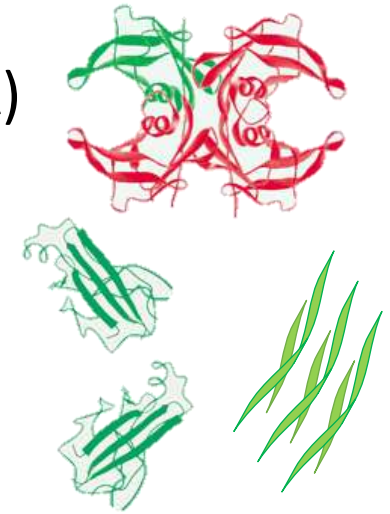
Proteasomes are part of a major mechanism by which cells degrade misfolded proteins

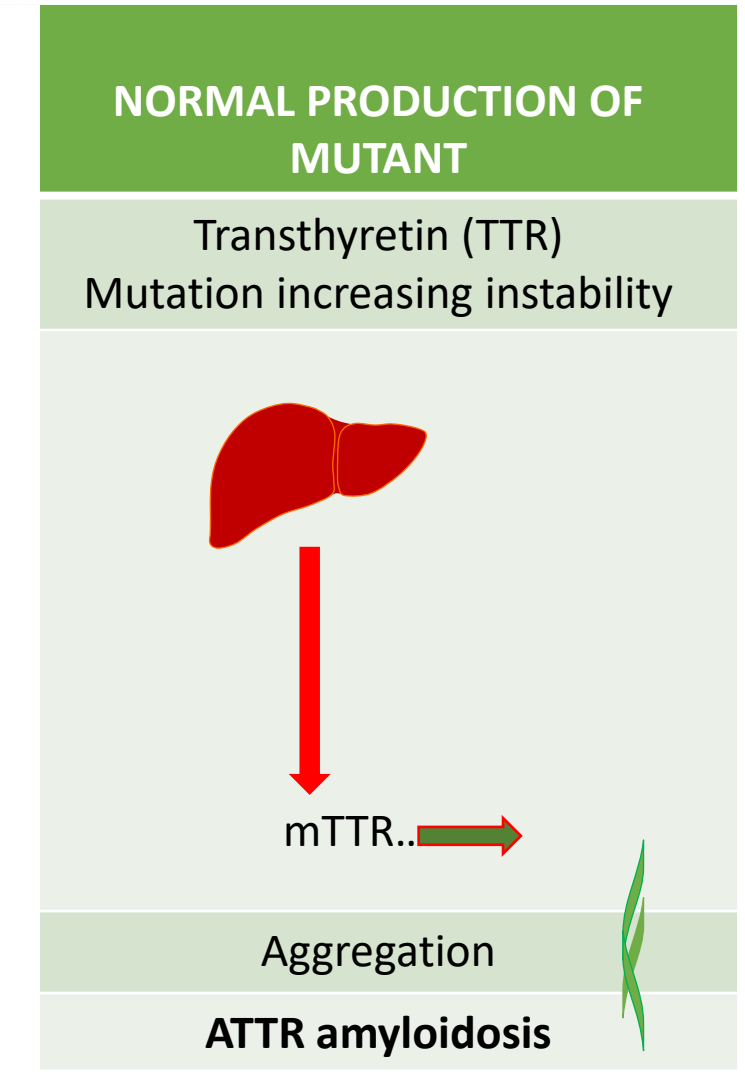
Pathogenesis of hereditary amyloidosis

Hereditary: ATTR, AFib, AApoAI, AII, C-III…

Amyloidosis derived from **t**rans**t**hy**r**etin: ATTR

- The most common hereditary amyloidosis in the US
- TTR circulates as tetramer,
- transport of thyroxin & retinol (vitamin A)
- inherited mutation destabilizes tetramer
- >95% liver; choroid plexus, eye
- >100 mutations





Hereditary: ATTR

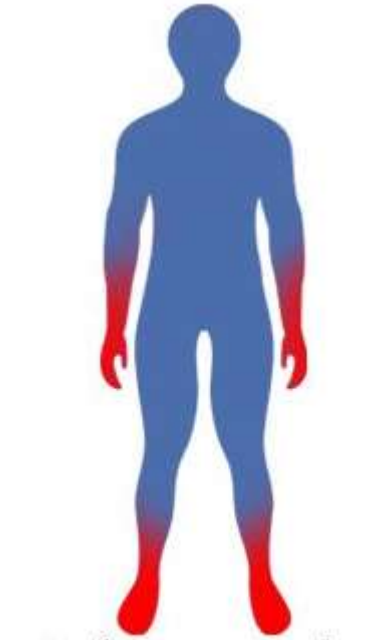
Amyloidosis derived from transthyretin: ATTR

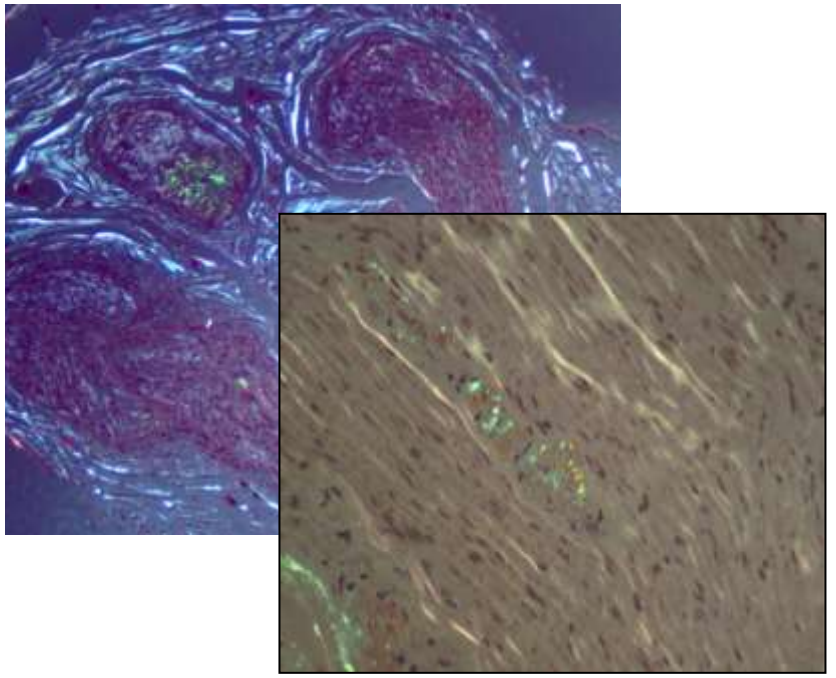
- polyneuropathies (sensory, autonomic), cardiac gastrointestinal, some kidneys

The most common hereditary amyloidosis in the US

~4% of African Americans (TTR V122I)

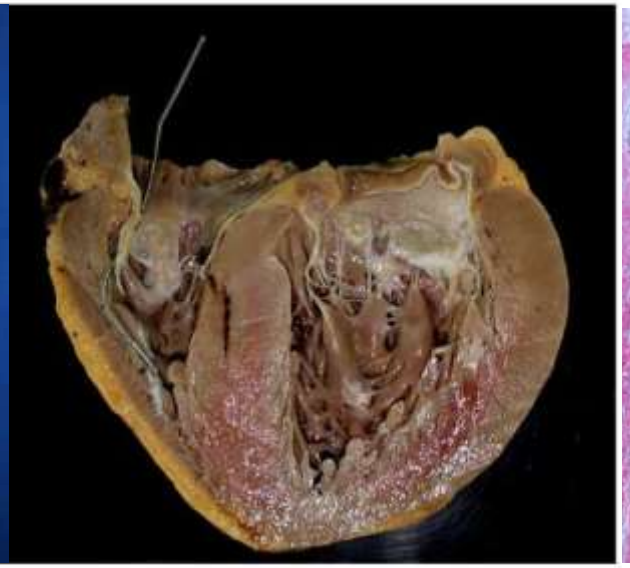
Variable penetrance
Late onset in some
Family history often missing
Can MIMICK AL – danger of misdiagnosis



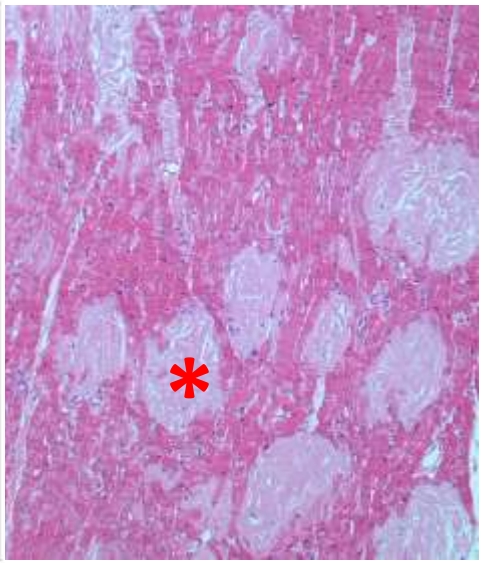


Peripheral nerve with amyloid

Carpal tunnel bilateral

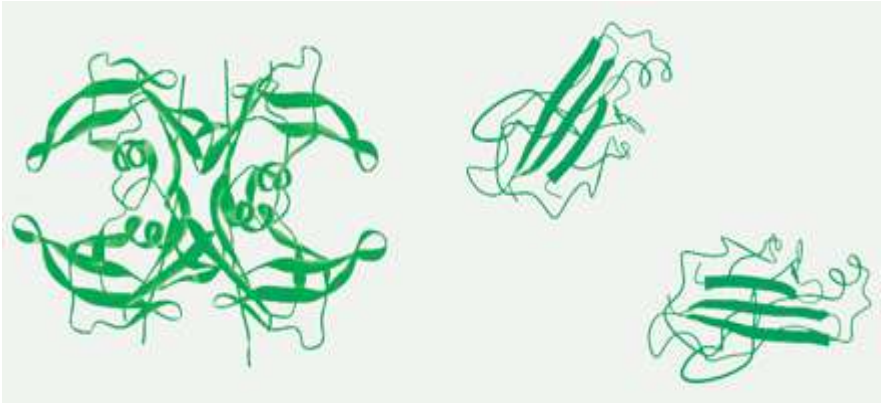


enlarged heart



* deposits of amyloid

ATTRwt (wild type):



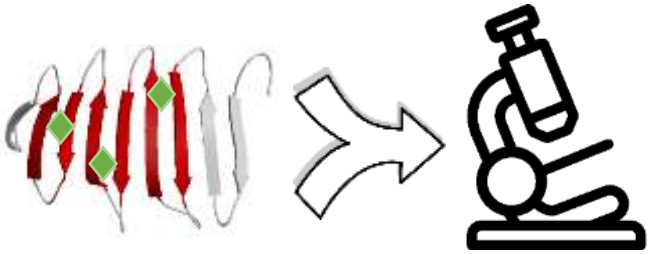
normal (wild type) transthyretin
is prone to fibrillogenesis at older age
protein quality control systems are less effective at older age…

- cardiac amyloid at old age
“cardiac Alzheimer”
Formerly SSA: senile systemic amyloidosis
males,
under-diagnosed – 25% of octogenarians
risk factors?
prevention?

How to diagnose amyloidosis?

1. Detection:

- ALL amyloids are Congo red positive



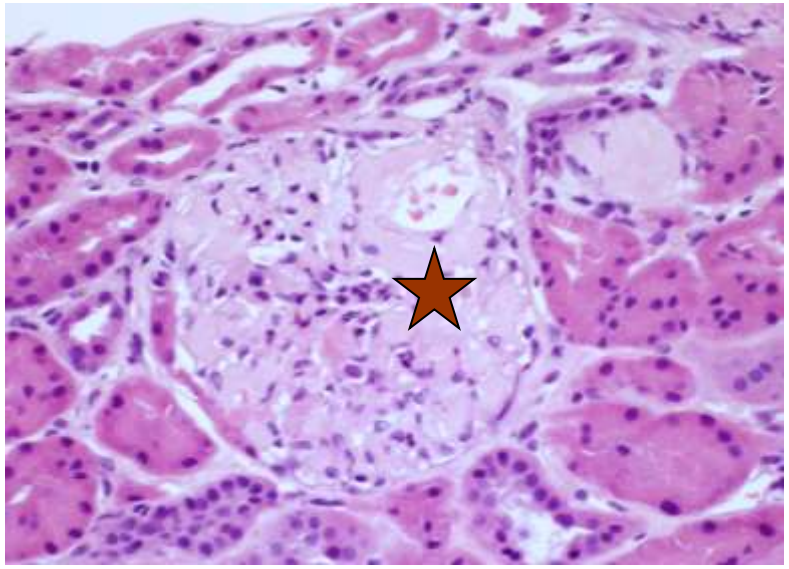
2. Typing of amyloid protein

DIAGNOSIS:

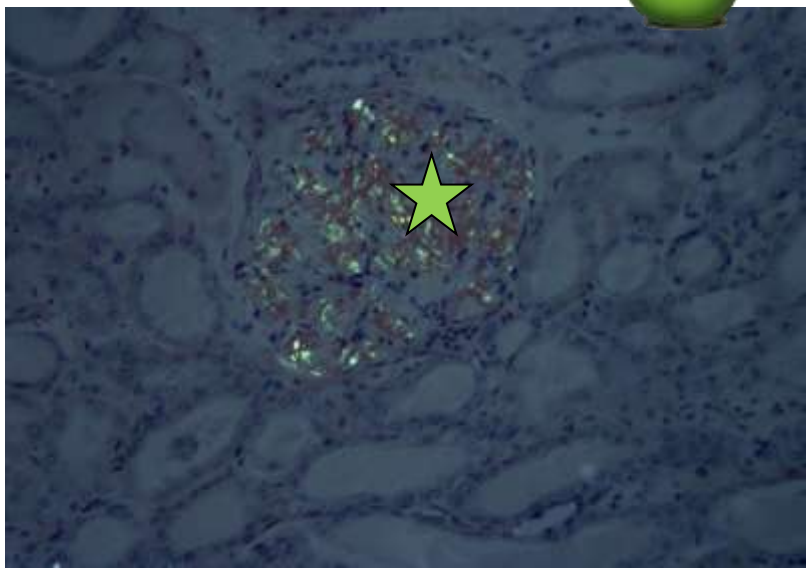
kidney, cardiac, peripheral nerves, other sites

laboratory tests to support the diagnosis but not to make it

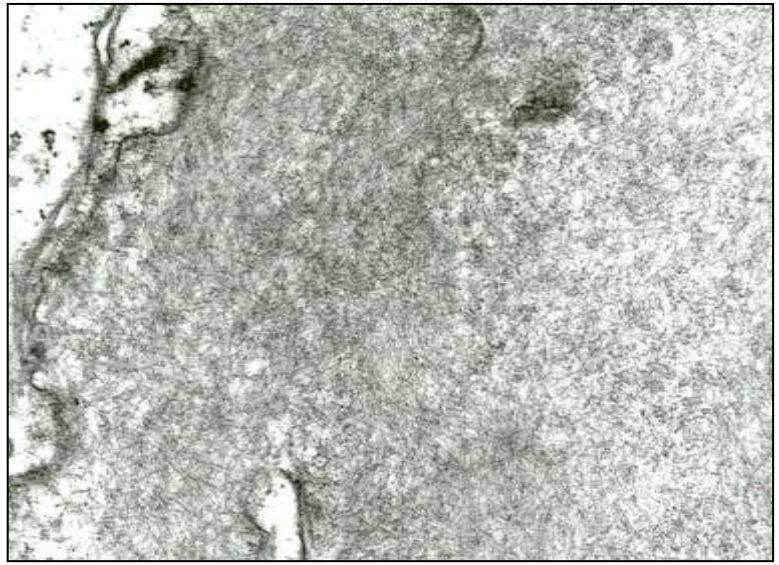
think – amyloid
order Congo red stain



Routine stain: extracellular "amorphous" deposits, not-specific for amyloid



Diagnosis = Congo* red stain with green birefringence under polarized light ["apple green" birefringence]



Amyloid is fibrillary only by electron microscopy

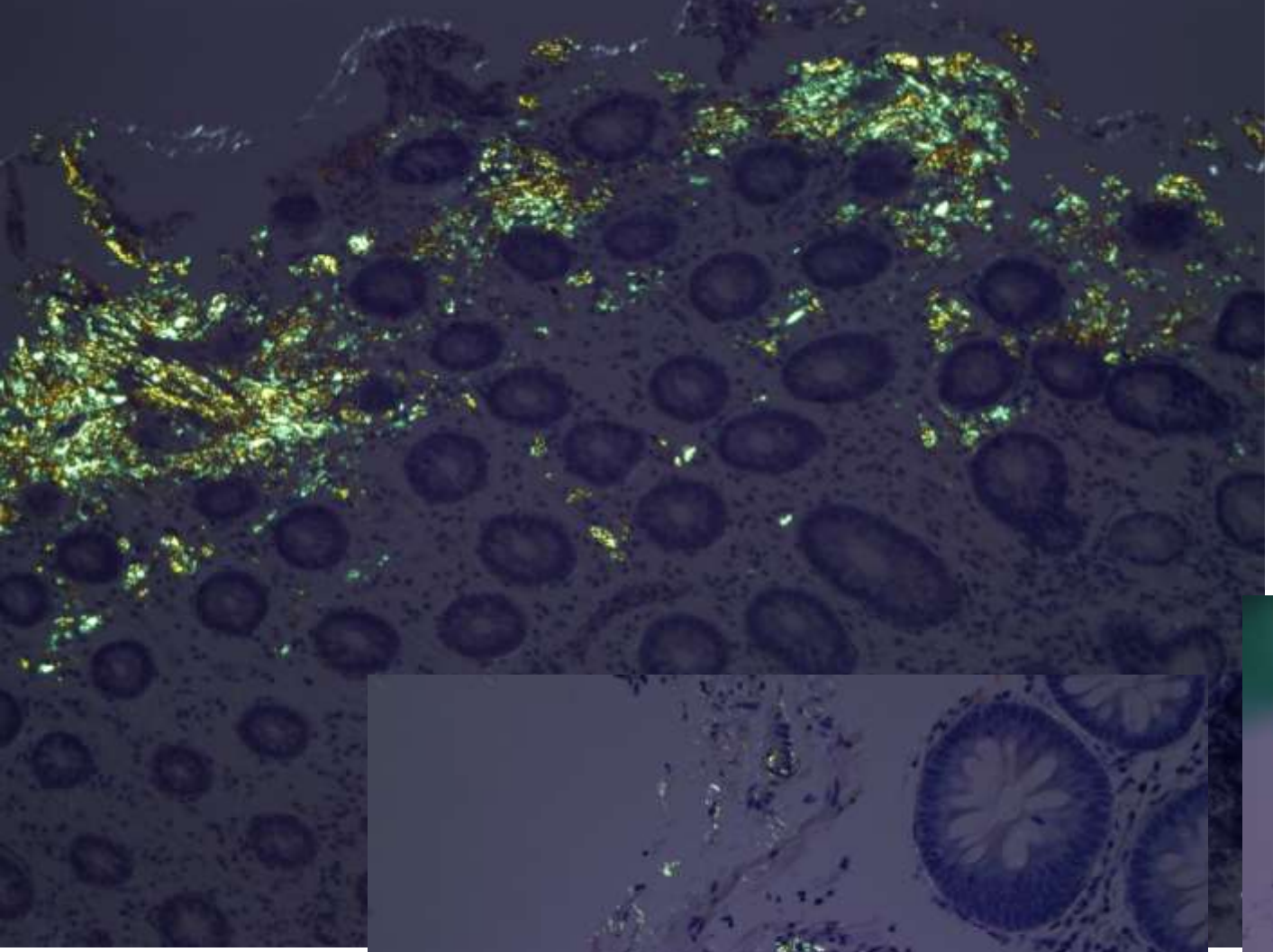
** the name "Congo" was given for marketing purposes but the stain has NO origins in African river*

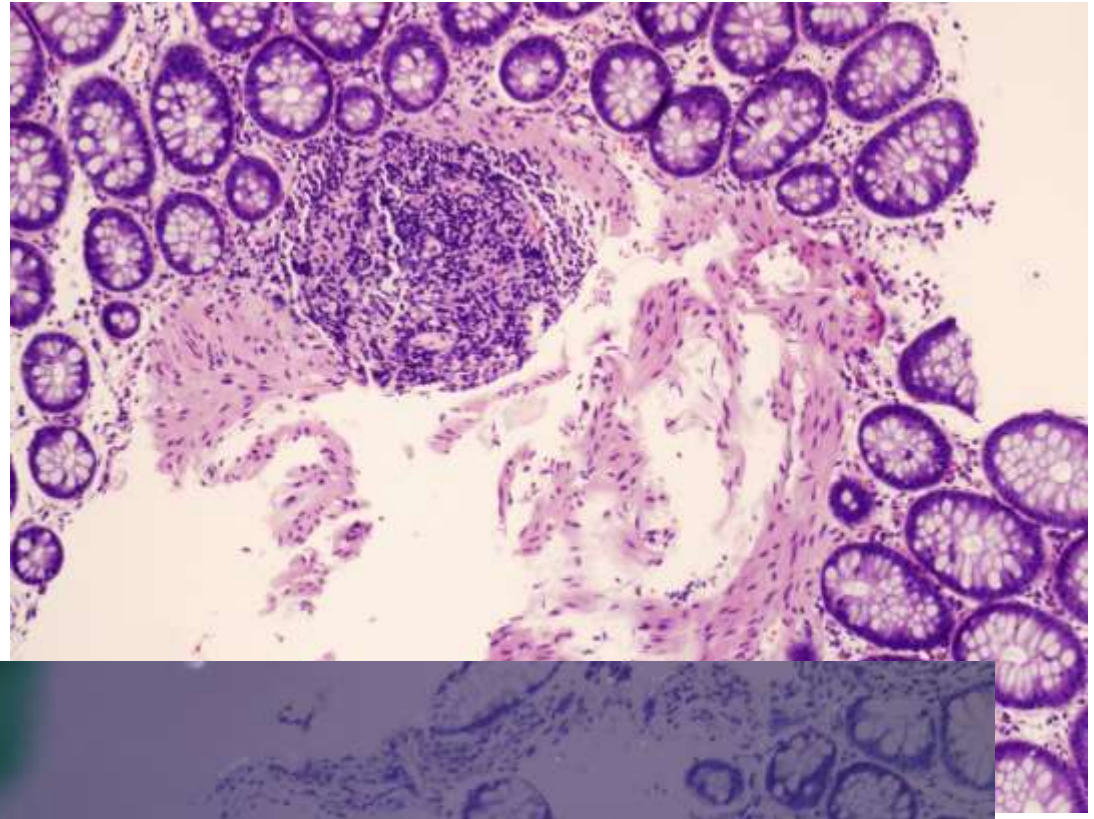
Differential diagnosis

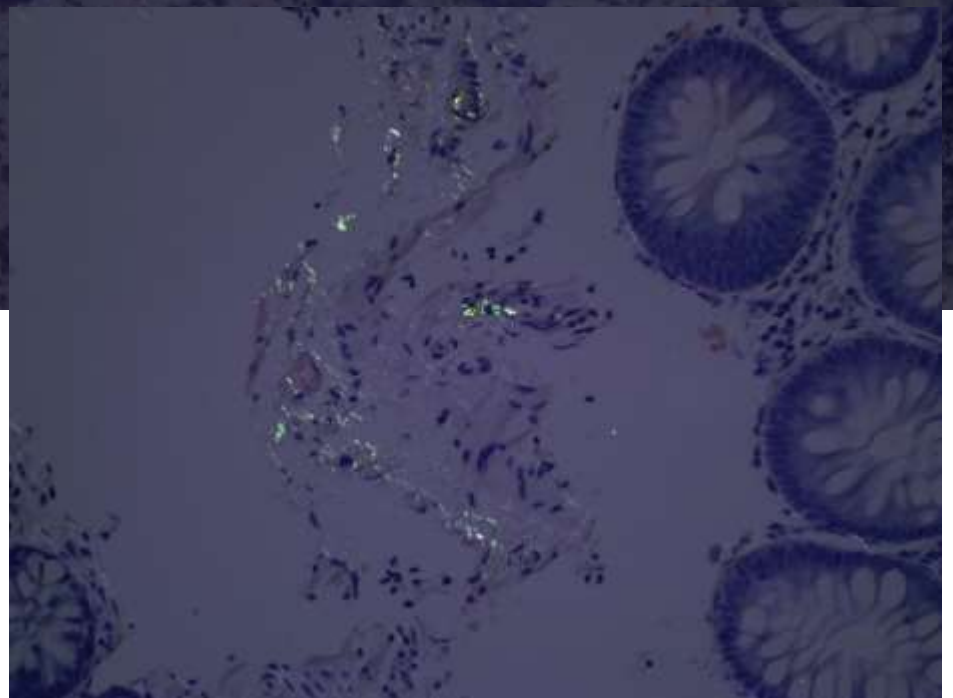
of proteinuria/nephrotic syndrome in adults:

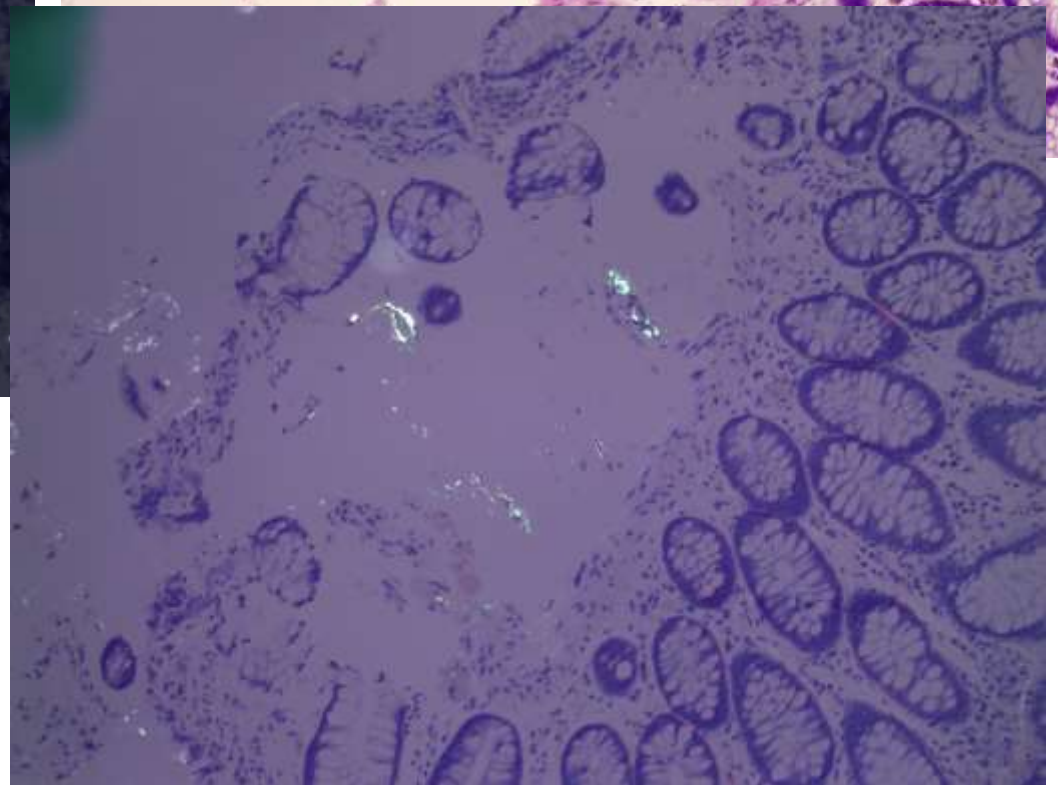
1.Focal and Segmental Glomerular Sclerosis/Minimal change disease
2.Membranous nephropathy
3.Diabetes
4.Amyloidosis!!!

Cardiac amyloidosis – heart failure, arrhythmia, long list of differential
Polyneuropathy – sensory and autonomic disturbances, long list of differential
Amyloid deposits are unevenly distributed in tissues

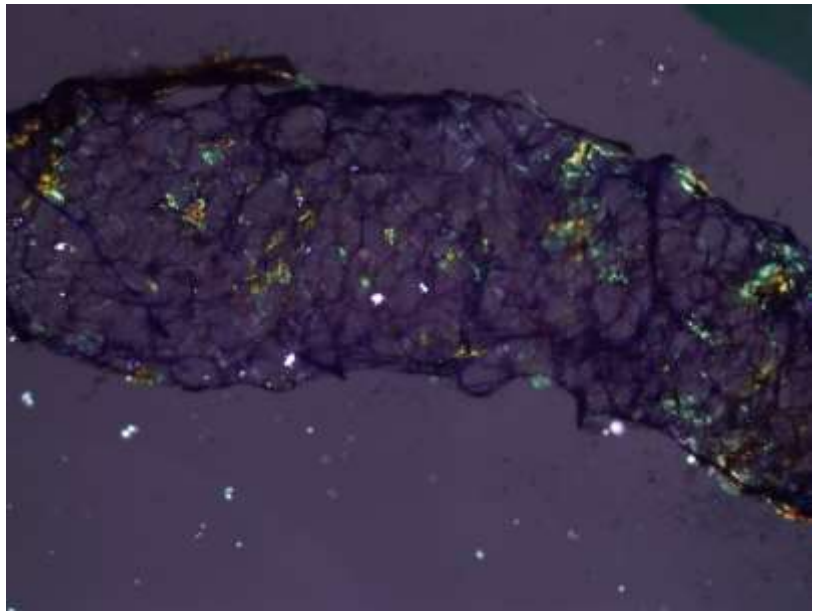








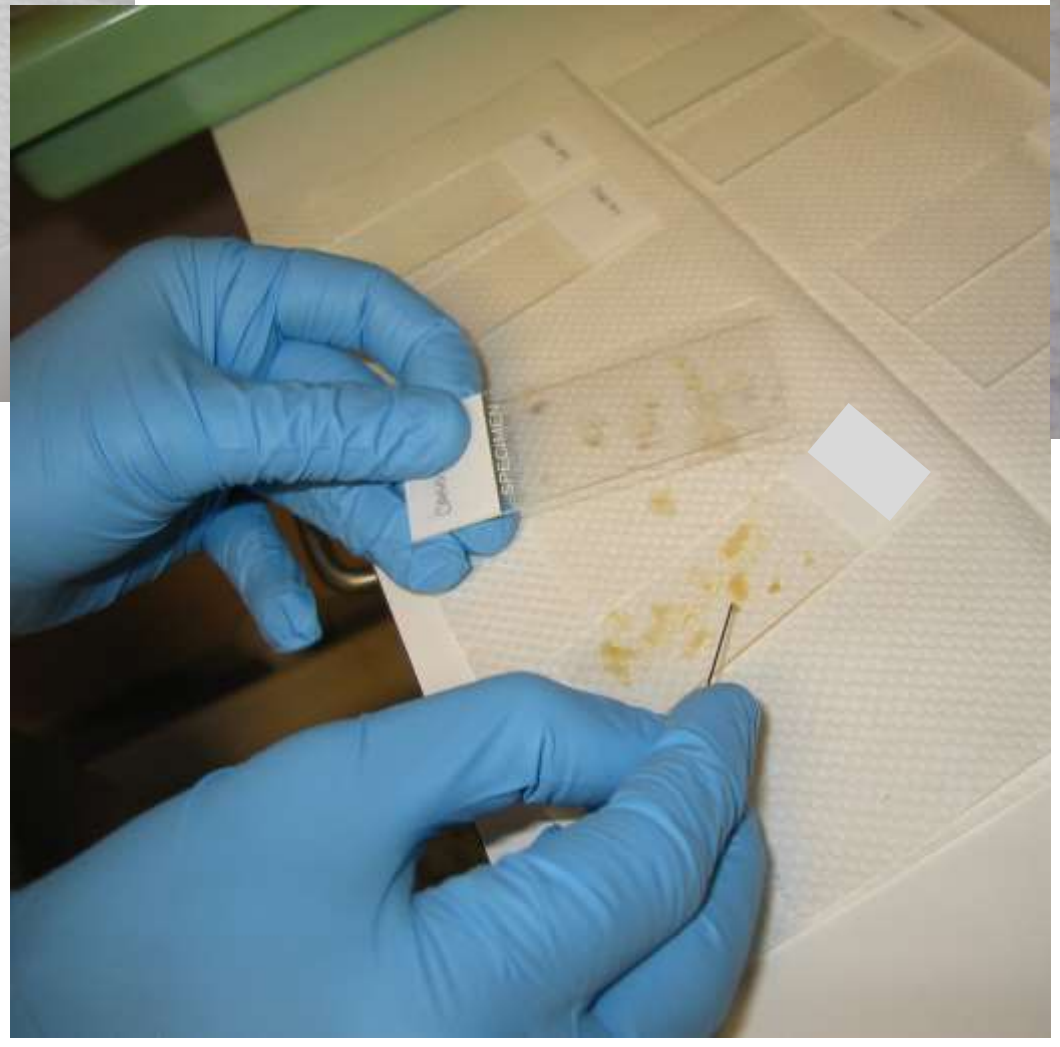
“Surrogate” site biopsy



Amyloid can be detected in subcutaneous fat

Fat biopsy typically from periumbilical abdomen (“surrogate site”)
for diagnosis and screening of patients at risk


10ml


SPECIMEN


CM
1
2

Amyloid detection in fat:

Sensitivity highly variable 54-93%
Specificity: 93-100%

Affected organ – best yield

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

Pathology of Familial amyloidoses:

1. Detection of amyloid in the index patient
   - lack of a family history
   - new mutation
2. Screening of family members/known carriers

3. Staging, organ involvement

Thank you
Questions?
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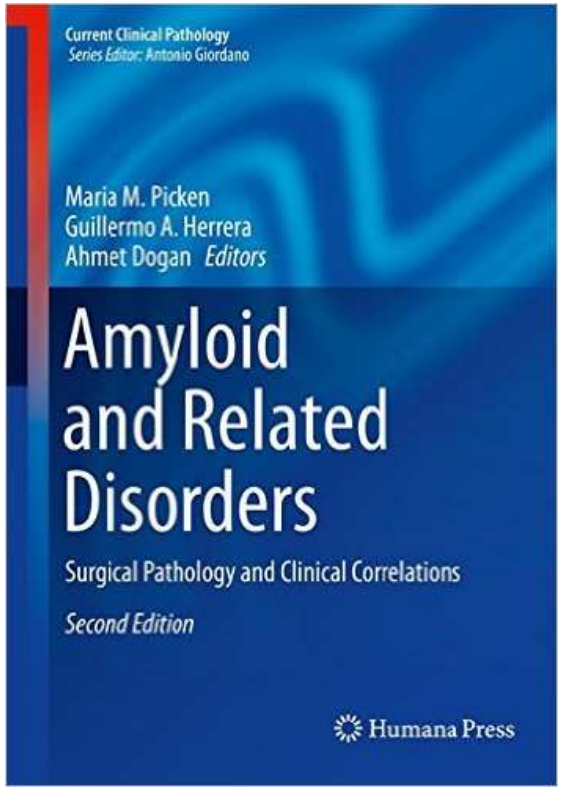

Early diagnosis of amyloidosis = biggest challenge

Increased awareness and education

Clinical suspicion…
Pathologic suspicion… second opinion

Patients' perspective…