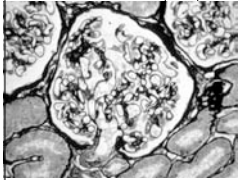


The Nephrotic Syndrome



Gerald B Appel, MD
Vivette D'Agati, MD

Objectives –Nephrotic Syndrome

- Define the nephrotic syndrome.
- Review the mechanism of proteinuria.
- Discuss the mechanisms of the major manifestations of the NS – edema, hyperlipidemia, thrombotic tendency
- Discuss the clinical features and pathology of major clinical forms of the NS .

The Nephrotic Syndrome

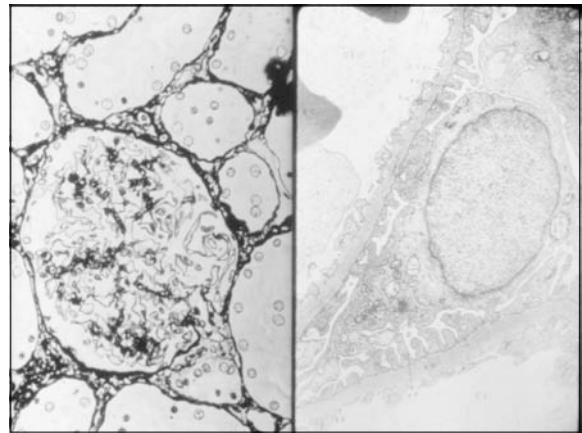
Glomerular Disease associated with heavy albuminuria (> 3-3.5 g/day)

Hypoalbuminemia

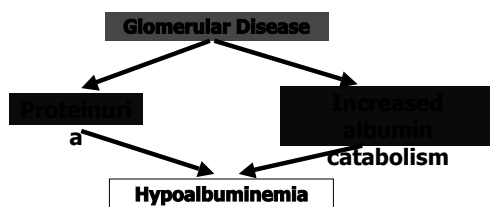
Edema

Hyperlipidemia

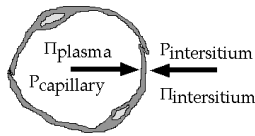
Thrombotic tendency



Genesis of Hypoalbuminemia



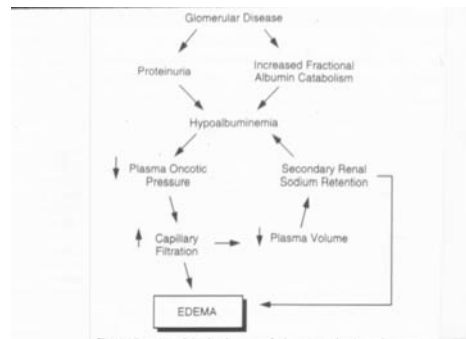
Pathogenesis of Nephrotic Edema



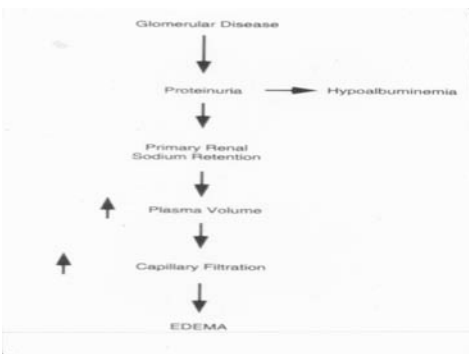
(Starling forces)

- Hypoalbuminemia:
 - Low oncotic pressure
- Na and Water retention:
 - High hydrostatic pressure

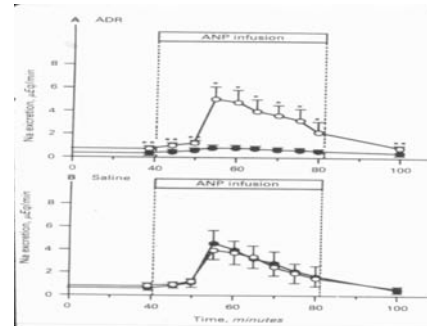
Pathogenesis of Edema



Pathogenesis of Edema



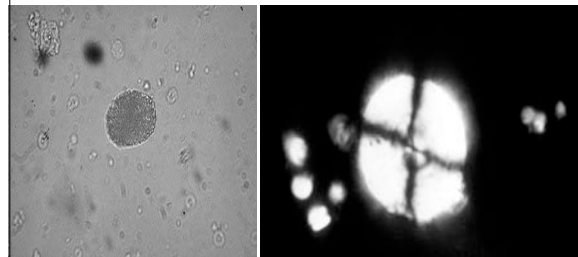
Pathogenesis of Edema



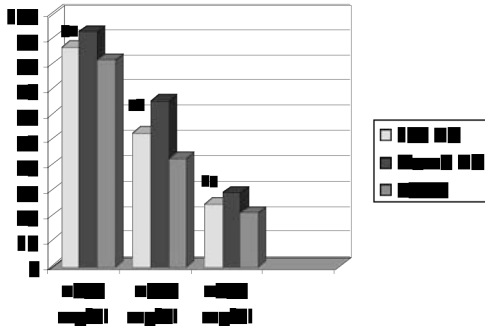
Therapy of Edema in NS

- Put pt on low Na+ diet
- Use oral loop diuretics
- Start w low dose - double doses
 - add zaroxylyn
 - +/- high BID doses
- IV diuretics and colloid rarely needed
- Goal is 1-2 # edema loss/ day

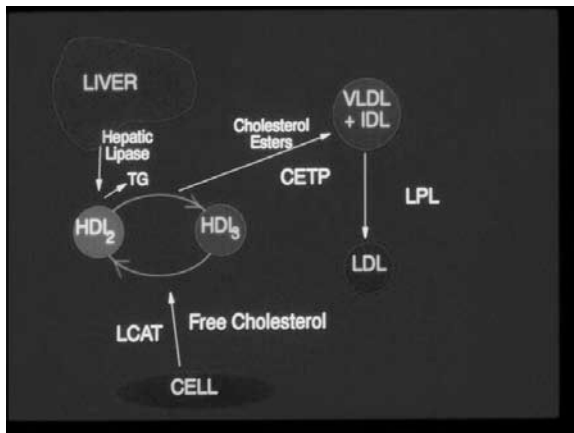
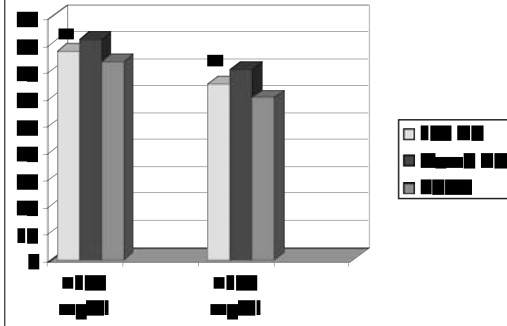
Lipiduria and Oval Fat Bodies



Total Cholesterol Levels in 100 Consecutive Nephrotic Synd. Pts



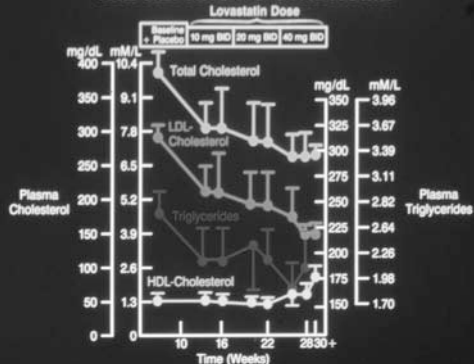
LDL Cholesterol Levels in 100 Consecutive Nephrotic Synd. Pts



Treatment of Hyperlipidemia of the Nephrotic Syndrome

- Select high risk pt (high LDL, low HDL, unlikely to rapidly remit)
- Attempt to induce a remission of the proteinuria (ACEi/ARBs , specific immunosuppressives, etc.)
- Dietary Therapy
- Medical Therapy (statins +)

LOVASTATIN EFFECTS ON LIPIDS IN THE NEPHROTIC SYNDROME



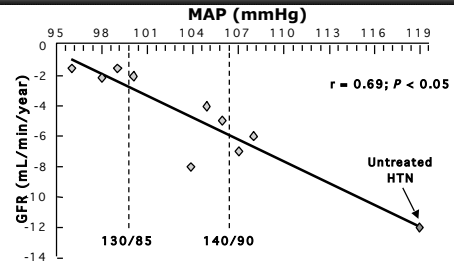
Treatment Principles

- Treatment of Primary Disease- Often immune modulating medications
- Symptomatic Treatment - Diuretics, statins, diet, in some anticoagulation
- Reduction of Proteinuria/Slowing Progression

Reduction of Proteinuria and Slowing Progression

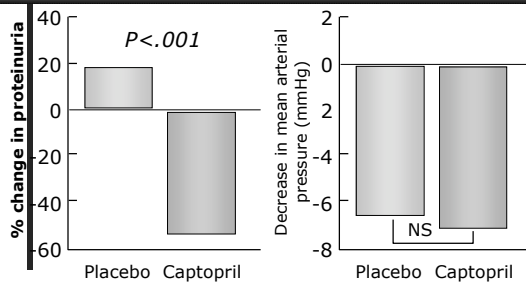
- Blood pressure reduction
- Inhibition of the renin-angiotensin-aldosterone axis

Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics



Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

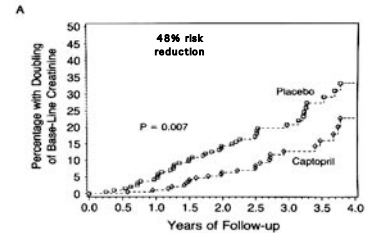
ACE-I Is More Renoprotective than Conventional Therapy in Type 1 Diabetes



Lewis EJ, et al. N Engl J Med. 1993;329(20):1456-1462.

The Effect of ACE-I on Diabetic Nephropathy: The Collaborative Study Group

- Type 1 DM with Urine Alb > 500mg /d



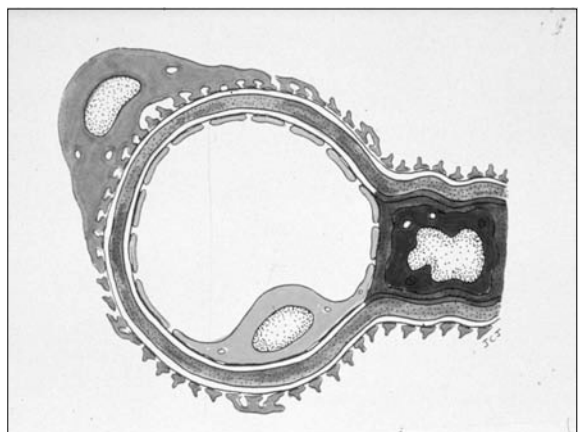
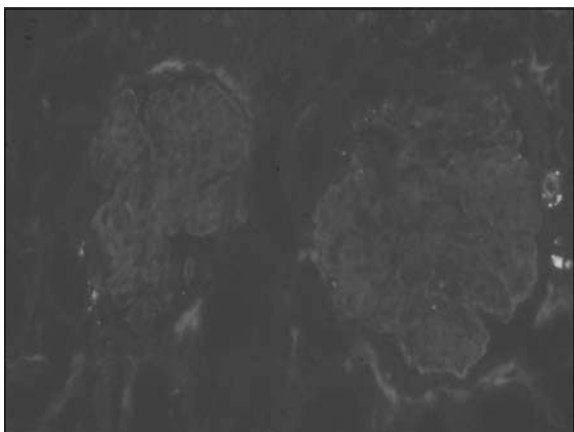
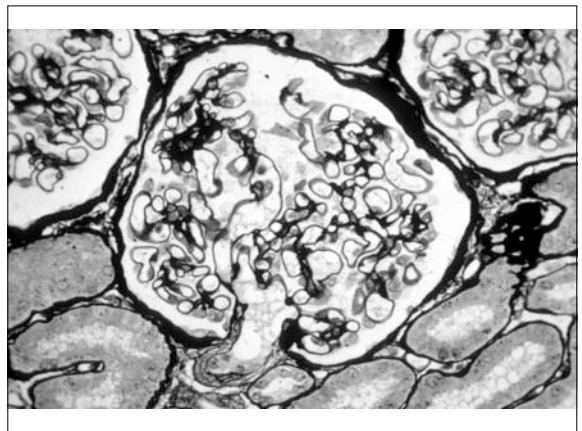
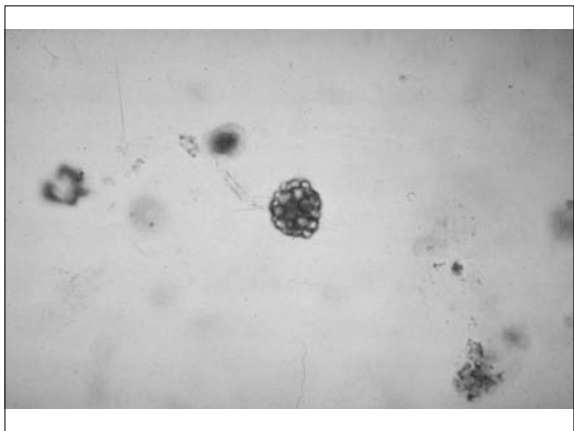
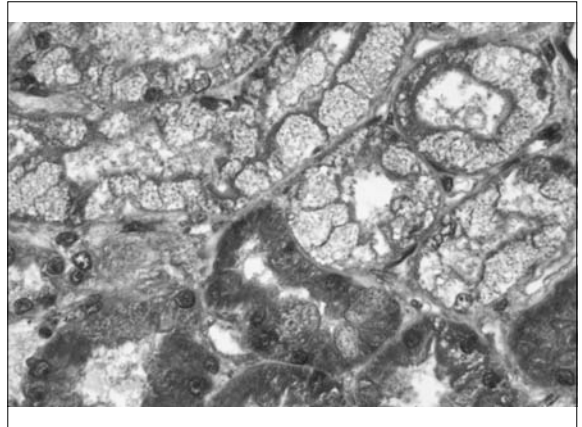
Lewis EJ, et al. N Engl J Med. 1993 Nov 11;329(20):1456-62.

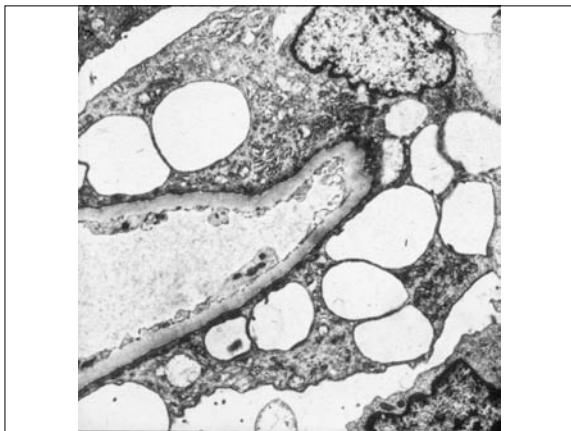
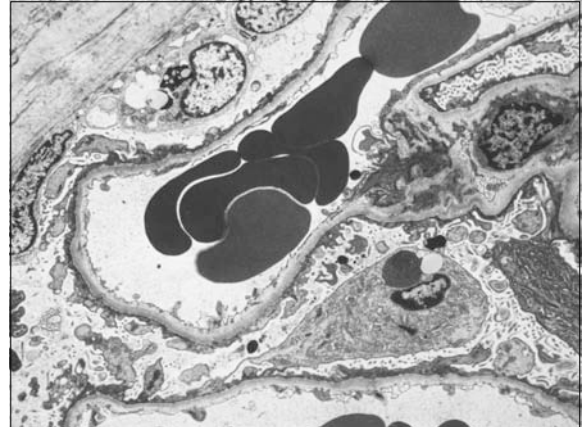
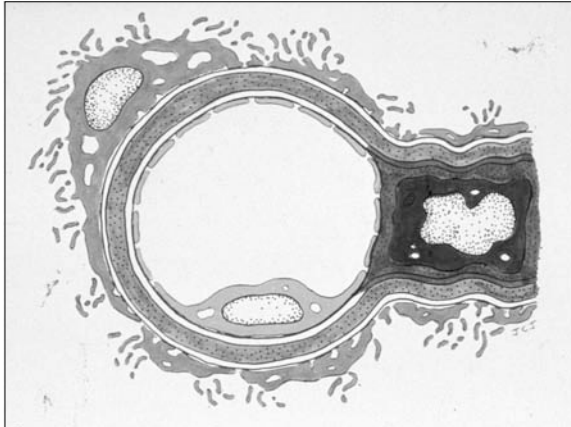
Case 1 – 8 year old child



Case 1

- An 8 year old child presents with swelling of his eyes and ankles. He has 4+ proteinuria on urine dipstick
- Other labs:
 - BUN 8 mg/dl
 - Creatinine 0.5 mg/dl
 - Albumin 2.2 g/dl, serum cholesterol 400mg/dL
 - 24 hour urine protein 6.0 g/day (normal <150mg)
- Serologic tests are negative or normal





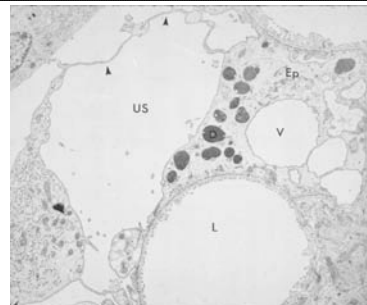
Synonyms

- Minimal Change Disease
- Nil Disease
- Lipoid Nephrosis
- Childhood Nephrosis

Evidence for Immunologic Derangements in Nil Disease

- Viral infections may precede onset or recrudescences.
- May follow recent immunizations.
- Altered in vitro response to mitogens.
- Circulating lymphocytotoxins.
- Altered lymphocyte subpopulations.
- ↑ HLA B-12
- Association with Hodgkin's Disease and other lymphoproliferative disease

Puromycin Aminonucleoside Nephrosis



Minimal Change Disease

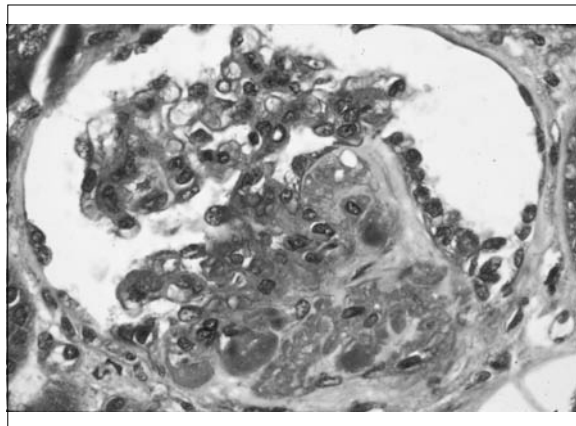
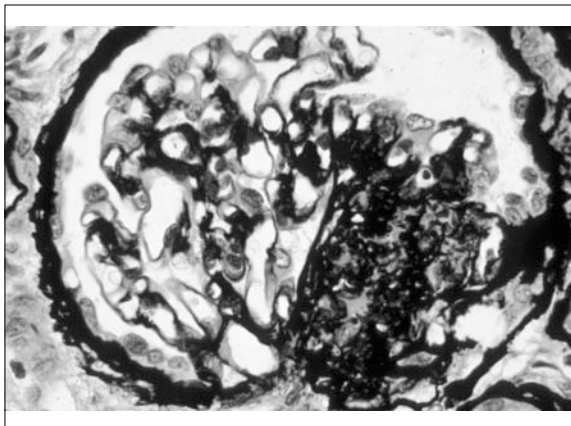
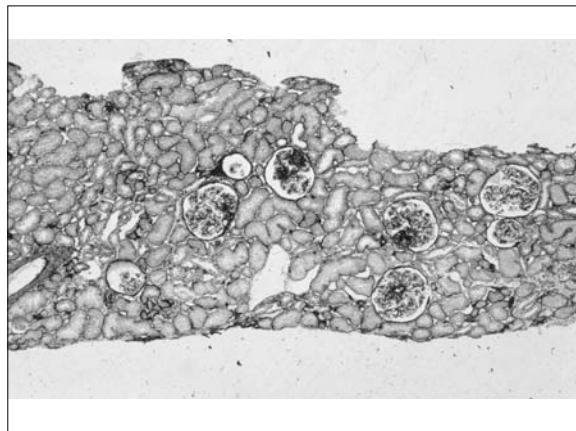
- 5-10% Adults with NS, >85% children
- Usually sudden onset, hvy proteinuria, and edema
- HBP 30%, Microhem 30 %, +/- Low GFR (volume depletion)
- Pathology: LM-NI, IF-Neg, EM-FFP
- Course : Respond to Strds, Relapse, No RF

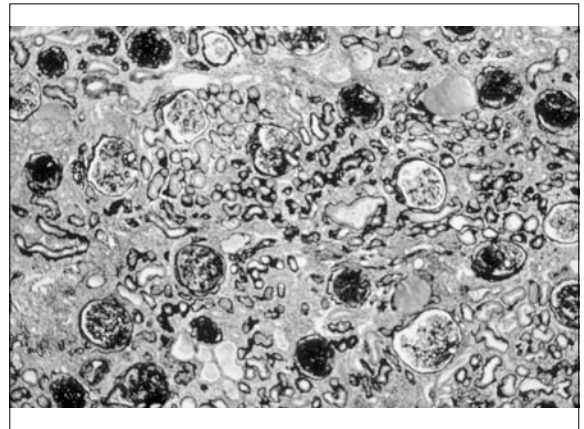
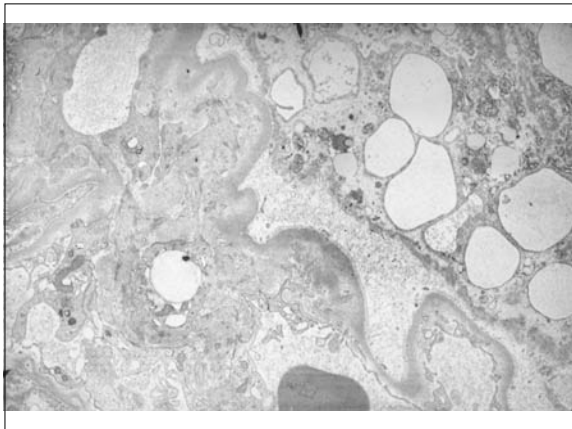
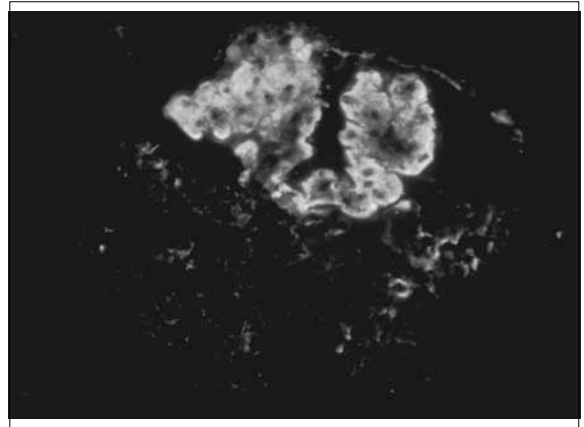
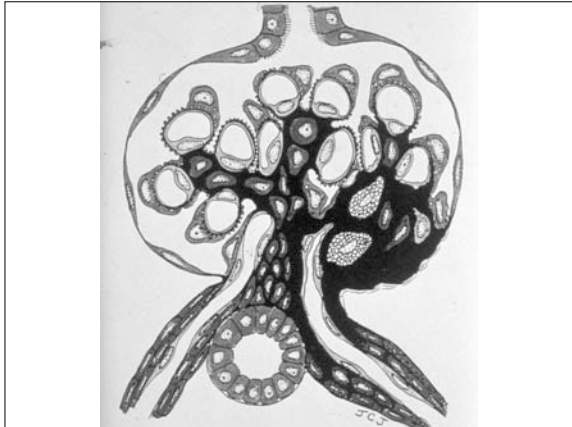
Case 1: Treatment and Course

- Prednisone 1mg/kg was started
- Furosemide was prescribed for edema
- 3 weeks later the patient was edema-free.
- Urine dipstick tests for protein were negative.
- Prednisone was tapered and stopped by the third month

Case 2

- A 19 year old female college student gains 12 pounds and has lower extremity edema. Her physician finds 4+ albuminuria.
- Labs:
 - Creatinine 1.0 mg/dl
 - Albumin is 2.0 g/dl
 - Cholesterol 425 mg/dl
 - 18g proteinuria/day
 - Serologic tests are negative
- Corticosteroid treatment is without improvement.



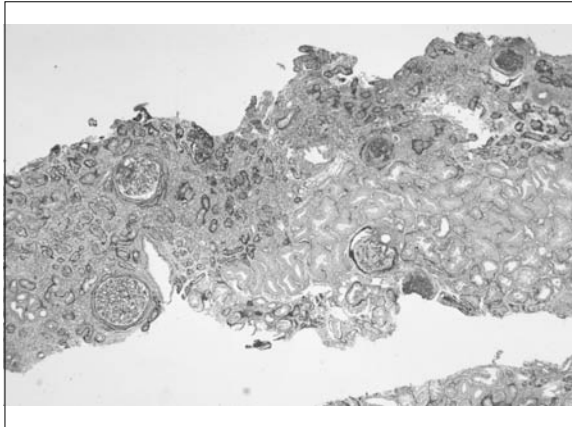


MCD and FSGS

- Separate or related entities?

Circulating Factors in MCD and FSGS:

| Ref | Source | Biologic Activity | Biochemical Characteristics |
|-------------|------------------------------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------|
| Bakker 1986 | Serum or mononuclear cells of MCD | Increases vasc. permeability Binds anionic sites | ~ 120 Kd Kallikrein-like |
| Koyama 1991 | T cell hybridoma from MCD | Causes proteinuria and foot process fusion in rats | 60-160 Kd Not an Ig |
| Savin 1996 | Serum or plasma of FSGS (initial, collapsing, recurrent) and steroid-resistant MCD | Increases glom permeability in vitro | 50 Kd Binds protein A Not Ig Not Cationic |
| Dantal 1994 | Plasma of recurrent FSGS in txp | Causes proteinuria and foot process fusion in rats | < 100,000 Kd Binds protein A Not Ig |



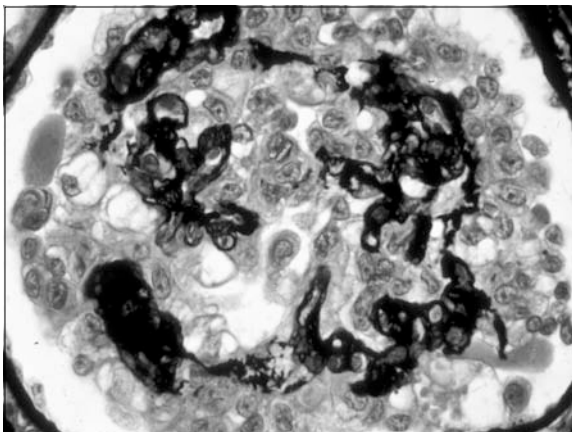
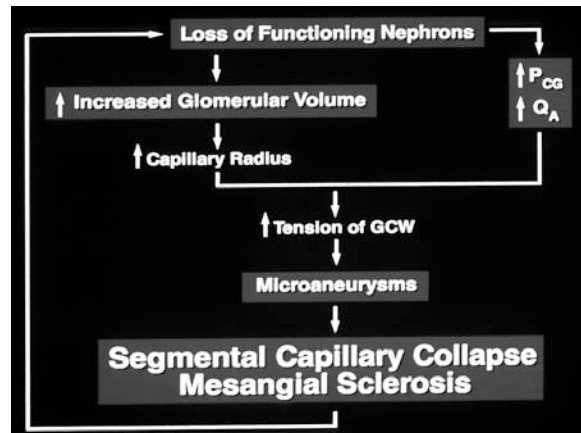
Secondary FSGS due to Adaptive Responses

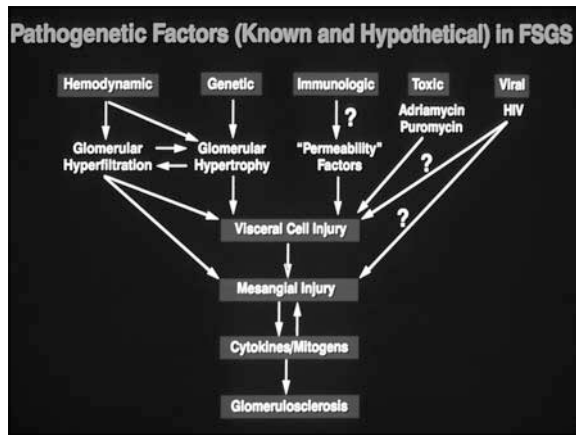
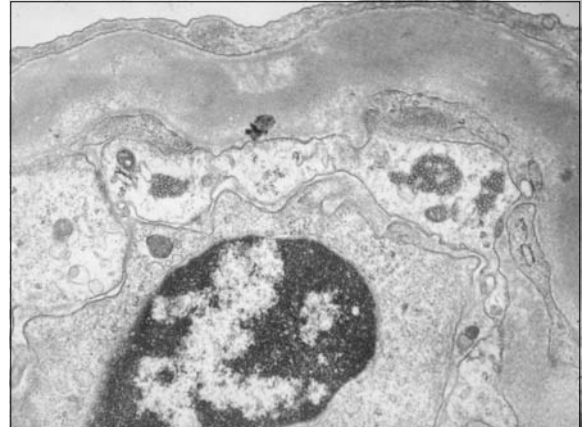
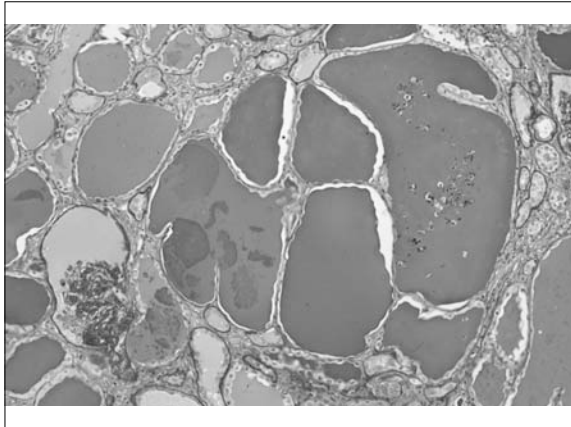
- Reflux nephropathy
- Renal agenesis (solitary functioning kidney)
- Any Chronic Renal Disease
- Obesity

Obesity-Glomerular "Stress"



...AND YOU THINK YOU HAVE STRESS.



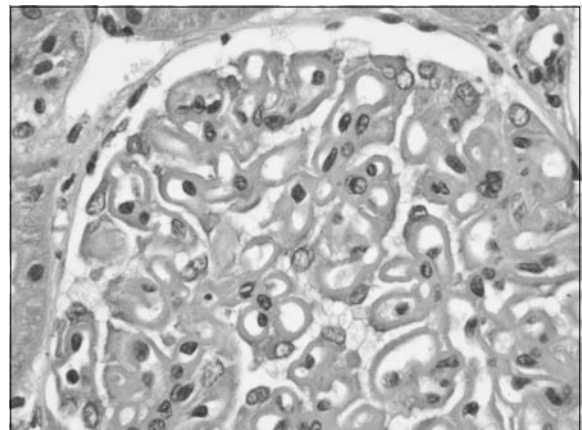


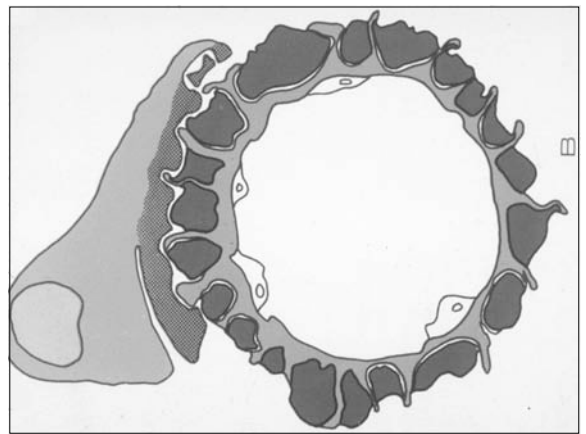
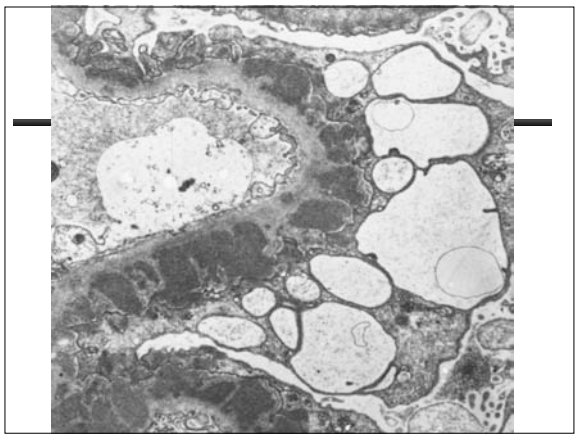
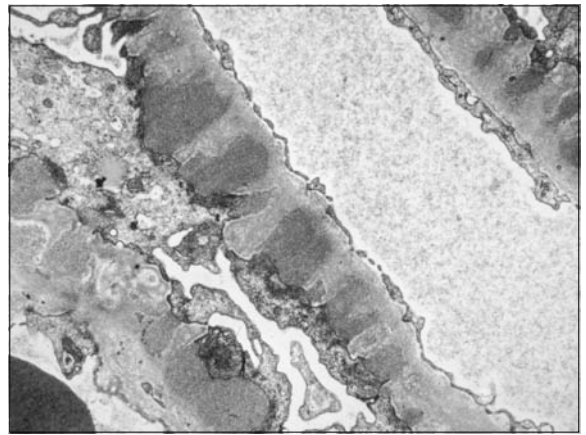
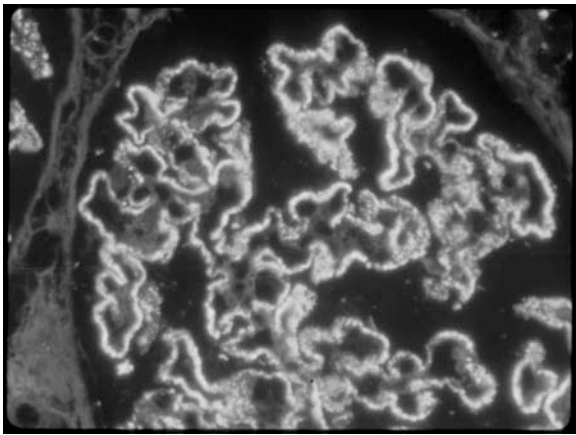
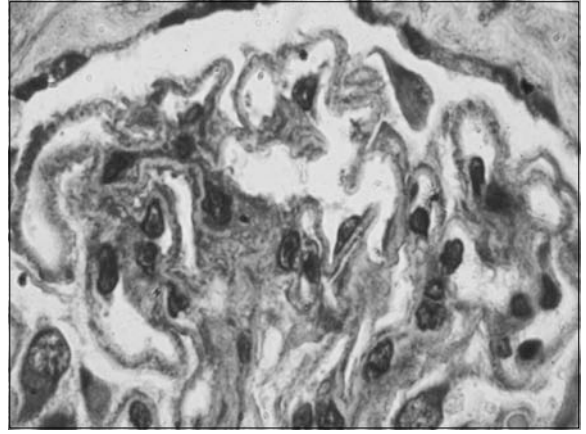
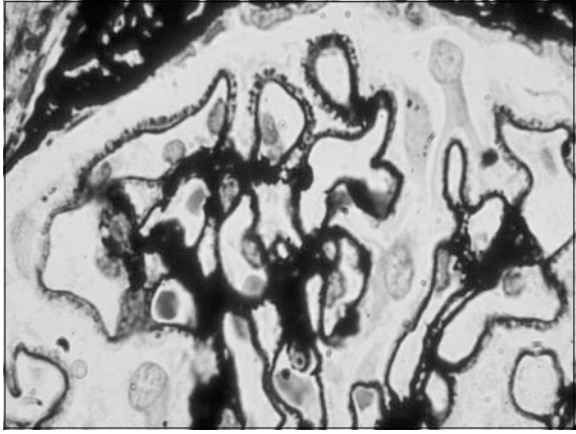
Focal Segmental Glomerulosclerosis

- Increased frequency > 20% NS - Blacks!
- In adults onset 2/3 NS, 1/3 proteinuria
- HBP > 30 %, Microhematuria >30 %, renal dysfunction 50 %
- Predictors of ESRD: hvy prot.,Blks, high creatinine, on BX - int fibrosis & Collapse
- Strds >50% respnd, cytoxa, cyA, MMF
- Recurs 1/3 Txps-

Case 3

- A 67 year old Caucasian Male develops ankle edema and weight gain.
- Labs:
 - 12 g proteinuria/day
 - GFR normal (creatinine 1.1 mg/dl)
 - Albumin of 1.4 g/dl
 - Cholesterol 635 mg/dl





Conditions Associated with Membranous Glomerulopathy

- Infections
Hepatitis B, Hepatitis C, secondary and congenital syphilis, malaria, schistosomiasis
- Drugs
Gold, penicillamine, captopril
- Collagen vascular disease
SLE, Hashimoto's thyroiditis, Rheumatoid Arthritis
- Neoplasia
Carcinoma (lung, breast, colon, stomach)

GENERATION OF HEYMANN NEPHRITIS

FX1A (fractionated material from renal cortex)



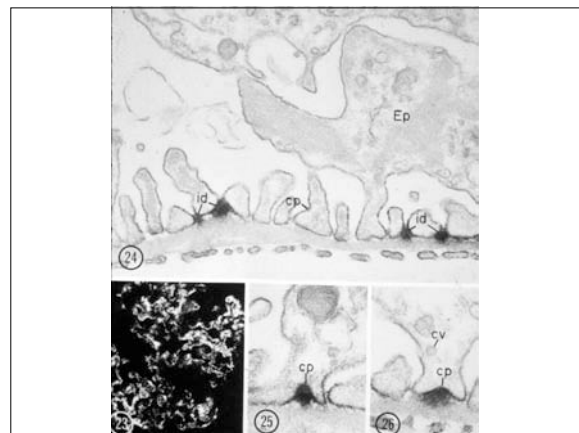
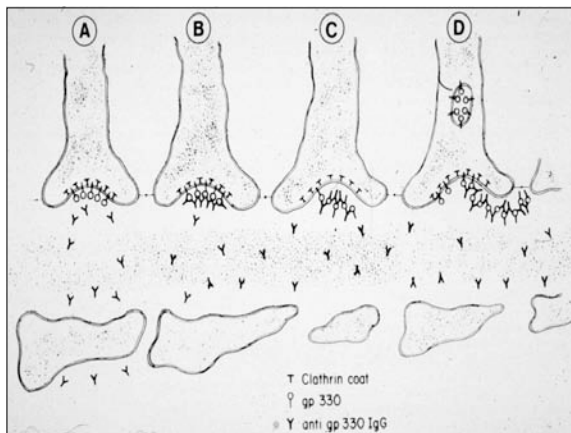
RAT

ACTIVE HEYMANN NEPHRITIS

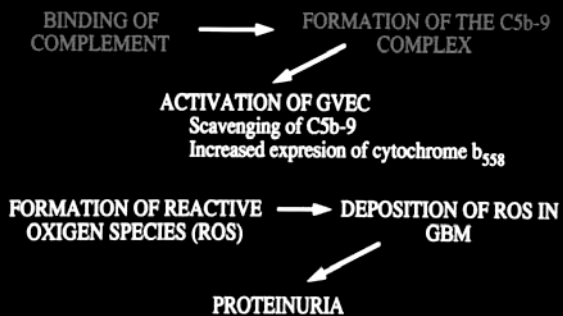
SERUM

RAT

PASSIVE HEYMANN NEPHRITIS



CONSEQUENCES OF IMMUNE DEPOSIT FORMATION



Membranous Nephropathy

- The most common etiology of idiopathic nephrotic syndrome in white adults
- Course variable
- Renal survival at 10 y: 65%-85%
- Renal survival at 15 y: 60%
- Spontaneous remission rate: 20%-30%

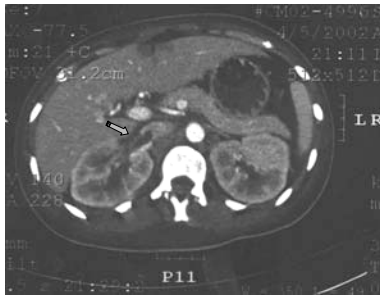
Treatment of Membranous Nephropathy

- Conservative Therapy
- Corticosteroids
- Alternating Steroids -Cytotoxics
- Cyclosporine
- Mycophenolate
- Anti C5 Ab, Rituximab

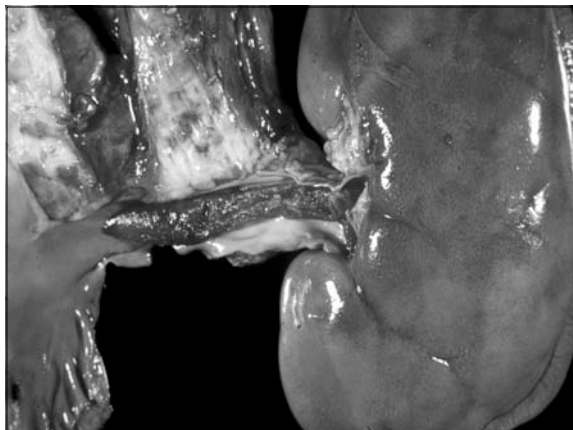
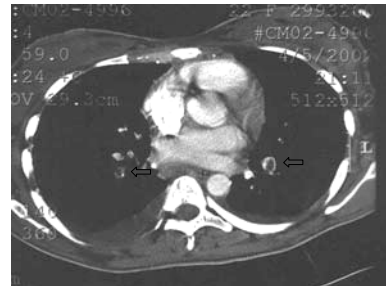
Case 3: Post Biopsy Course

- All serologic tests are normal
- Normal Colonoscopy and CT abdomen/chest
- 3 days after admission, he develops a dull back ache and then becomes acutely short of breath.
- Chest X-ray is normal
- ABG: pH=7.45 pCO2=30, pO2 =60 on room air
- CT angiogram is requested

CT angiogram: Abdomen



CT angiogram: Chest



Thrombotic Abnormalities in the Nephrotic Syndrome

Increased coagulation tendency
(plat. hyperaggregability, high fibrinogen and fibrinogen-fibrin transfer, decreased fibrinolysis, low anti-thrombin III)

DVT, RVT, pulmonary emboli

Membranous NS greatest risk (up to 35%)

Most RVT asymptomatic , but flank pain, microhematuria, low GFR



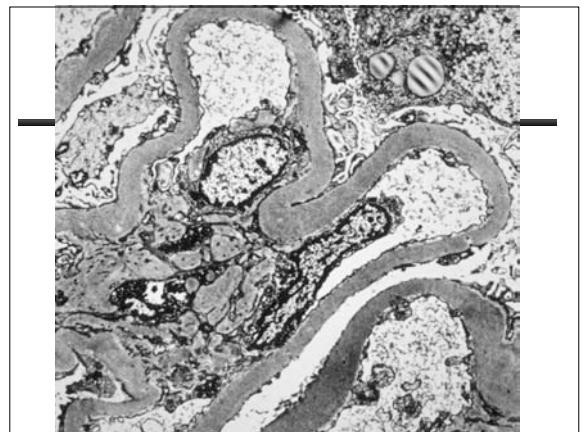
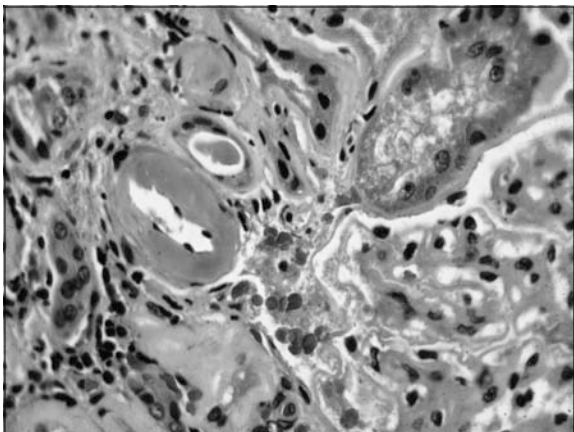
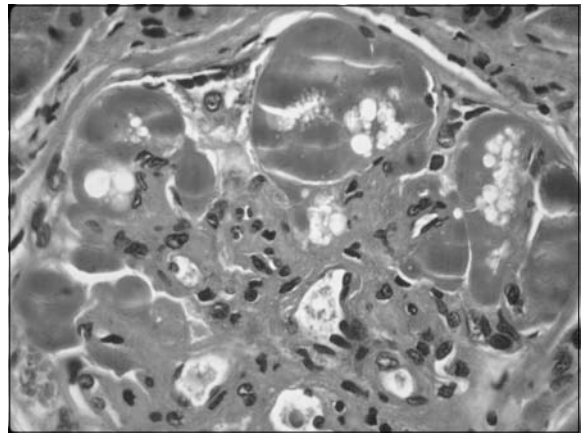
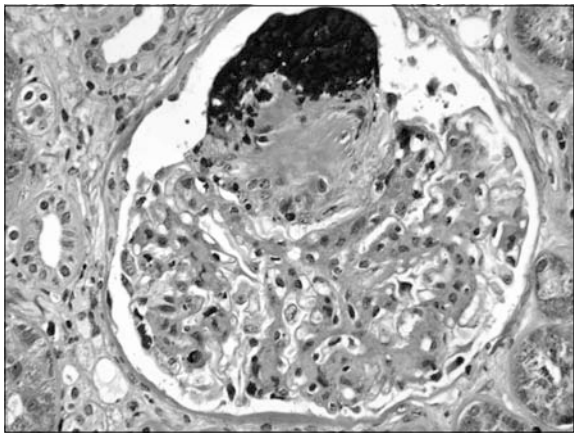
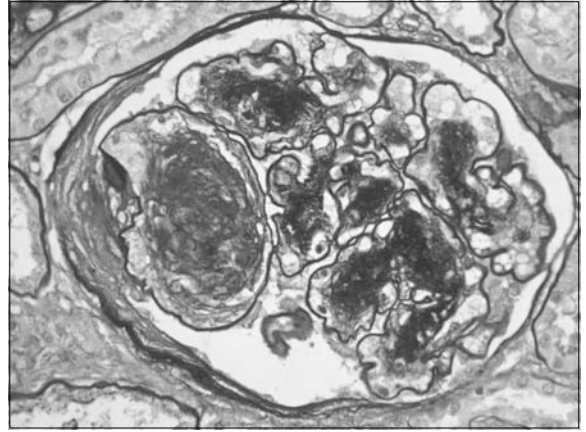
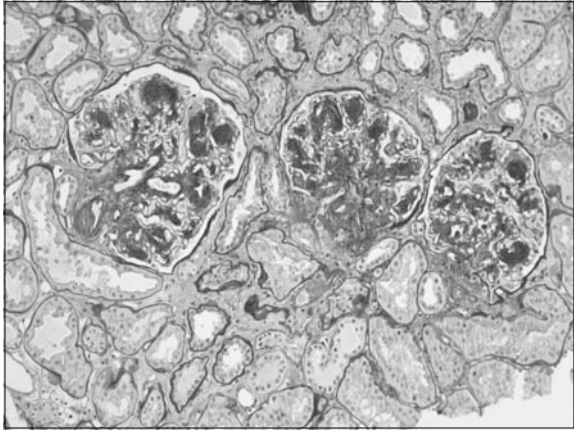
Case 4

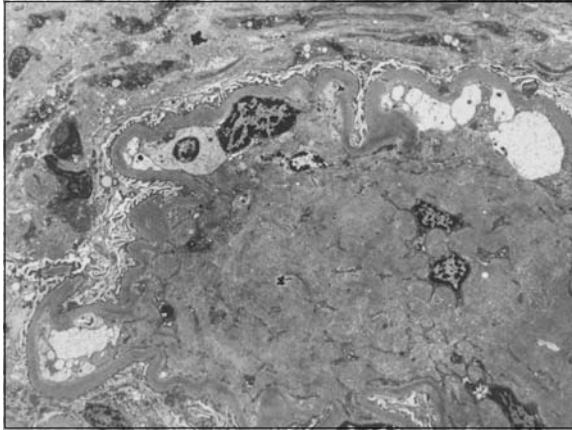
- A 38 year AA female has had Type 1 diabetes since the age of 19.
- She has severe retinopathy and multiple admissions for labile blood sugars.
- Her internist refers her for proteinuria which has gone up from 200mg/day to 3.2 grams. Her serum creatinine is 1.5mg/dL
- She has experienced a 22 pound weight gain and pitting edema to her thighs.
- She is on twice/daily insulin and Diltiazem

Case 4: Physical Exam

BP :160/102

Case 4: Ophthalmologic Exam





Types of Diabetes Mellitus

- Type I - Insulin Dependent (hypoinsulinemic, ketotic, juvenile onset)
- Type II - Non-Insulin Dependent (Normoinsulinemic, non-ketotic, maturity onset)

Basement Membrane Thickening in Diabetes Mellitus

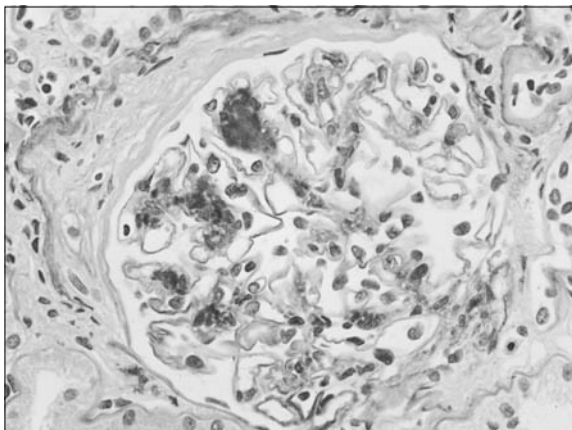
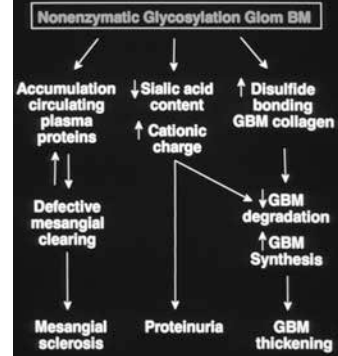
Vascular BM

- Glomerular Capillaries
- Muscle Capillaries
- Retinal Capillaries
- Arterioles

Other BM

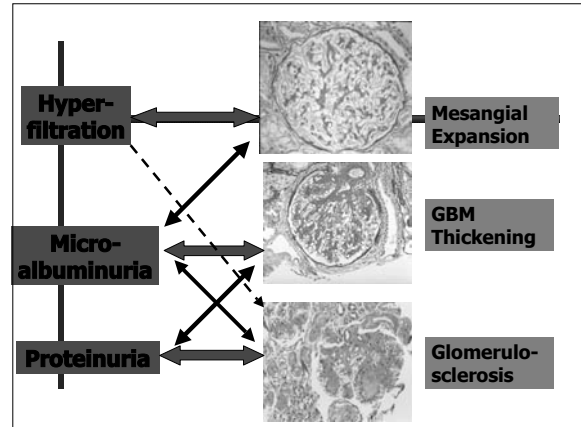
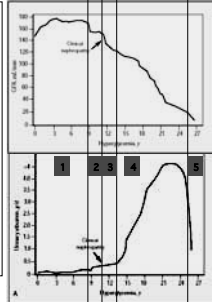
- Renal Tubules
- Mammary Ducts
- Schwann Cells

Diabetic Nephropathy

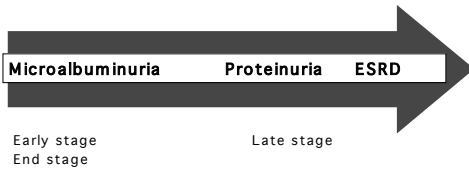


Stages of Diabetic Renal Disease Type 1 Diabetes

- Stage 1
Hyperfiltration
- Stage 2
Clinically silent
- Stage 3 (AER: 20-200ug/min)
Incipient Nephropathy
- Stage 4
Overt Nephropathy
- Stage 5
ESRD



Progression of Diabetic Nephropathy



Current Strategies to Limit Renal Injury in Diabetic Nephropathy

- Blood pressure reduction
- Inhibition of the renin-angiotensin-aldosterone axis
- Blood sugar control
- Metabolic manipulation

Blood Pressure Targets

| Clinical Status | BP Goal |
|-----------------------------------------------------------------------------|---------------------------------------|
| Hypertension (no diabetes or renal disease) | <140/90 mmHg (JNC 7) |
| Diabetes Mellitus | <130/80 mmHg (ADA, JNC 7) |
| Renal Disease with proteinuria >1 gram/day or diabetic kidney disease | <130/80 mmHg <125/75 mmHg (NKF) |

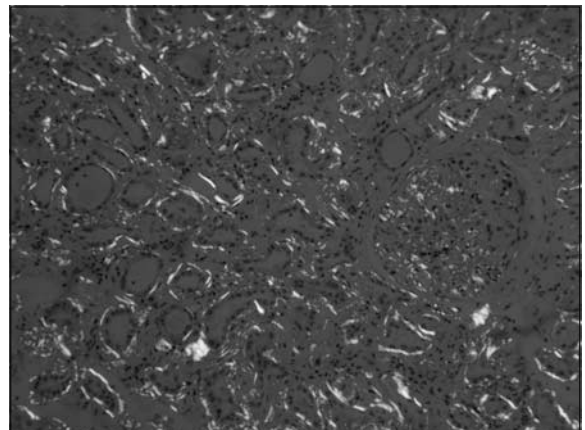
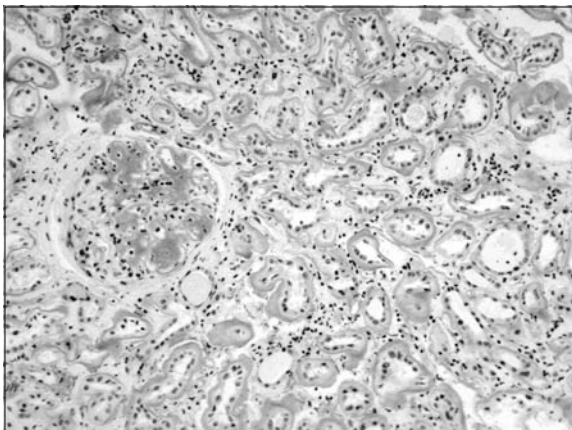
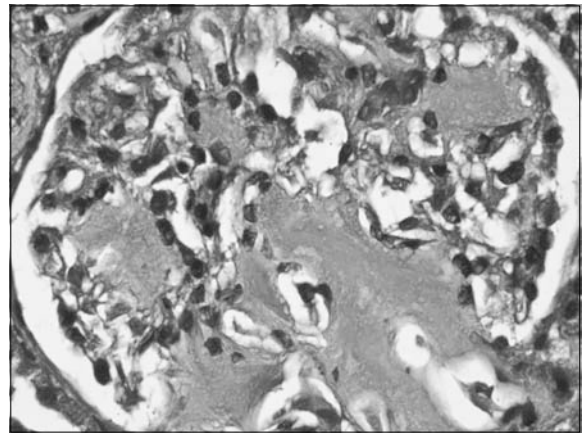
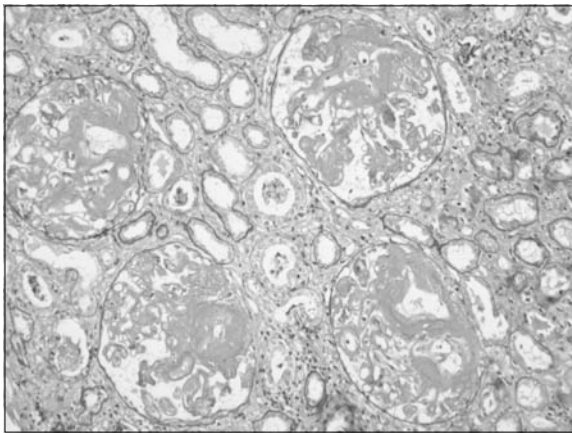
Case 4: Follow up

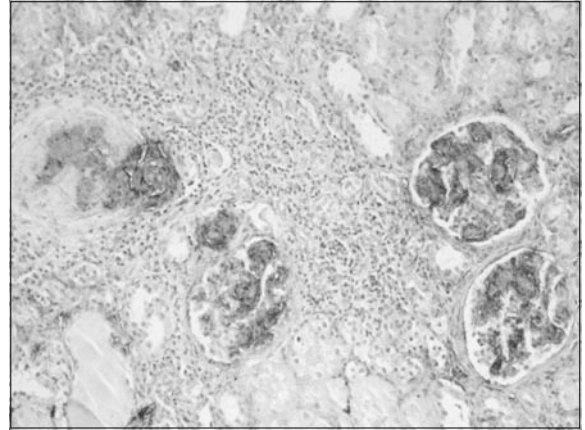
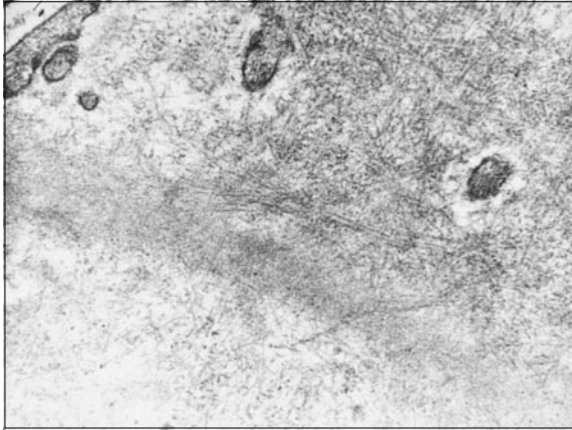
- Symptomatic
 - Furosemide 80mg + Metolazone 5mg
 - Pravastatin 40mg
- Reduction of Proteinuria
 - Ramipril 10mg+ Candesartan 16mg/day
- Edema improved and proteinuria decreased to 200mg/day
- Her GFR however gradually deteriorated over 6 years and she is on hemodialysis awaiting a kidney transplant.

Case 5

- A 66 y o housewife with severe rheumatoid arthritis for 22 years develops edema. She is currently taking no medications.
- Labs:
 - 9 g proteinuria/day
 - Serum creatinine 1.2mg/day
 - Serologic tests are negative
 - Creatinine clearance of 100 cc/min

Rheumatoid Hands





Amyloid

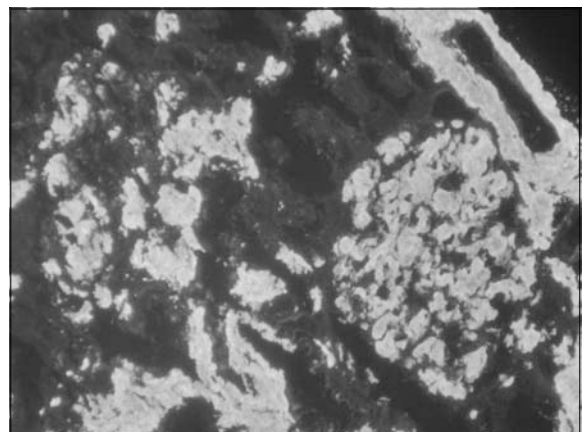
- **LM:** A homogenous, hyaline eosinophilic proteinaceous substance.
 - **Special Stains:**
 - Congo Red
 - Methyl Violet
 - Thioflavin t
- **EM:**
 - **Fibrillar Constituent**
 - Random arrays of non-branching fibrils, 80-100Å in width, beading with 55Å periodicity
 - **Non-Fibrillar Constituents**
 - Pentameric discs (AP protein)
- **X-ray Diffraction:** beta pleated sheet conformation

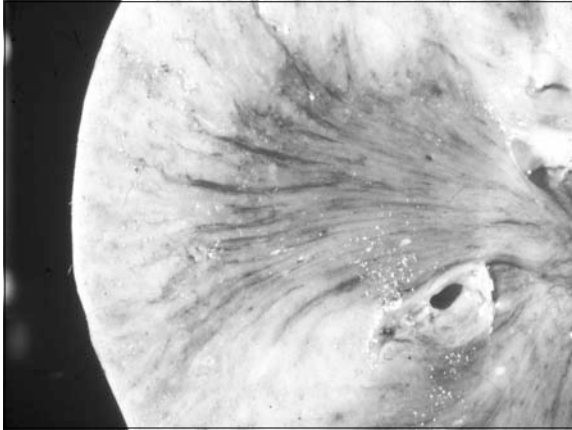
Amyloidosis

| Cause | Type | Precursor Protein |
|------------------------------------------------|----------------|------------------------------------|
| Dysproteinemias | Primary "AL" | Light chains |
| Longstanding inflammatory or infectious states | Secondary "AA" | SAA-protein (acute phase reactant) |

Chronic Diseases Associated with "AA" Amyloidosis

| | |
|--------------------------|--------------------------------|
| ■ Tuberculosis | ■ Chronic Heroin Addiction |
| ■ Leprosy | ■ Rheumatoid Arthritis |
| ■ Chronic Osteomyelitis | ■ Psoriasis |
| ■ Paraplegia | ■ Familial Mediterranean Fever |
| ■ Chronic bronchiectasis | |
| ■ Cystic Fibrosis | |



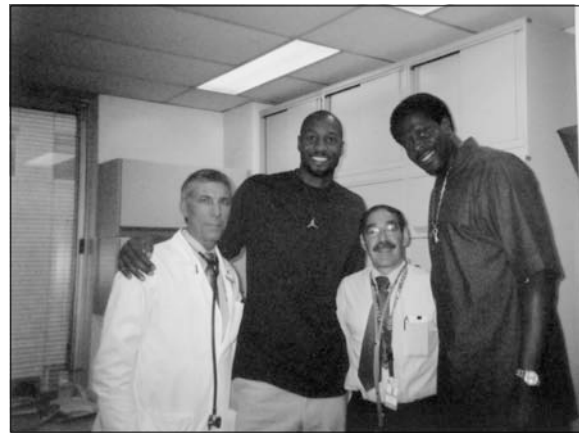


Case 5: follow up

- Symptomatic treatment
 - HCTZ 25mg qd
- Reduction of proteinuria
 - Lisinopril 10mg/day
- Rheumatoid Arthritis
 - Anti TNF therapy

Conclusions

- Glomerular disease due to the Nephrotic Syndrome (nephrosis) is a common cause of renal disease.
- A renal biopsy and good nephropathologist are essential in diagnosis
- Treatment includes BP control, use of ACE-inhibitors in addition to specific and symptomatic therapy.



The End
(Et Cetera!)