Chronic Renal Failure

History of Presenting Illness

- **Most patients present with:**
- **heavy proteinuria,**
- **most commonly in the nephrotic range**
- **insidious in onset.**

Earliest : → **LETHARGY, FATIGUE** — ANAEMIA
→ **OEDEMA** — HYPOALBUMINAEMIA
→ **NOCTURIA** — Failure of **CONCENTRATION**
→ **ANOREXIA, NAUSEA, VOMITING** — Early URAEMIA
→ **INFECTIONS, THROMBI** — Early URAEMIA
→ **PRURITIS, BONE PAIN or FRACTURE** — Renal OSTEOMALACIA

Latest: → **CONFUSION, DEMENTIA, COMA** — Late URAEMIA

Differential Diagnoses

- Acute renal failure
- Liver failure
- Congestive heart failure
- Hyperparathyroidism
- Inherited Clotting disorder
- Gastrointestinal malignancy
- Acute glomerulonephritis
- Central Nervous System Lesion

Past History

DIABETES Hypertension systemic infections, exposure to drugs and toxins

Want to know about:

- **LUPUS, and autoimmune disease in general**
- **Hypertension**
- **History of renal disease in family**
- **CHEST PAIN**
- **EASY BRUISING**
- **Recent Fractures**
- **Shortness of Breath**
- **Ankle Swelling**
- **Frequency of Nocturia**
- **? hematuria**
- **frothy urine**
- **Itching/scratching**
- **Cognitive decline**
- **RECENT ILNNESSES (screen for post-strep GN)**

Drugs of particular importance
- analgesics
- NSAIDs,
- gold,
- penicillamine,
- vancomycin,
- lithium,
- ACE inhibitors

Questions about uremia:
- Appetite
- Nausea/vomiting
- SOB
- Oedema
- Weight change
- Muscle cramps
- Bone pain
- Easy bruising
- Mental acuity
- Decreased libido
- Erectile dysfunction
- ADLs

Examination

Want to look for:

- **Uremic complexion**
- **Oedema + ascites**
- **Bruising / ecchymoses**
- **Infected dialysis fistula**
- **Anaemia**
- **Pericarditis**
- **Bony tenderness**
- **Neuropathy**
- **Subcutaneous Ca++ nodules**
- **Scratch marks**
- **Kussmaul breathing**
- **Hydration status**

Tests and Investigations: ITS ALL ABOUT THE URINE

URINALYSIS is FIRST!!

→ **DIPSTICK** (for suspicion)
→ **URINE MICROSCOPY** for confirmation
→ **URINE BIOCHEMISTRY** to supplement serum biochemistry:
try to work out what is gettinbg filtered and what is not.

24 hr collection→
TESTING FOR PROTEIN:
over 3 grams = NEPHROTIC

PROTEINURIA = PARENCHYMAL DISEASE

NORMALLY:
Low molecular weight proteins are reabsorbed at the proximal tubule
Some escapes: <150 mg./day
Normal urine contains up to 30 mg of albumin

PROTEINURIA on DIPSTICK ANALYSIS:
= concentration of about 300 mg/L.

SELECTIVE Proteinuria
= you must be >this tall< to enter
Eg. only a certain size of protein is being lost
= this means damage to the glomerulus is mild

HEMATURIA ALONE = TRACT PROBLEM

NORMALLY:
No more than 5 million RBCs per litre
VISUALLY:
Naked eye can see 5 billion RBCs per L
DIPSTICK TEST:
Sensitive up to 5 million RBCs
MICROSCOPY:
Sensitive up to 0.5 million RBCs
Dysmorphic tattered RBCs = origin of bleed is in the renal parenchyma
Must differentiate:
IS IT RED BECAUSE OF BLOOD?
IS THERE AN ALTERATIVE SOURCE eg. menses?...

~SPECTRUM OF URINARY SEDIMENT~

NEPHROTIC
- proteinuia,
- hypoalbumiaemia,
- oedema

NEPHRITIC
- proteinuia,
- hematuria
- hypoalbumiaemia,
- oedema

UROLOGICAL
= stones, cystitis, UTI, cancer, trauma.
Morphology of RBCs determines level of disease

Non-proliferative glomerular disease
Eg membranous
Minimal change disease

Proliferative glomerular disease
Eg. mesangial IgA
post-strep GN

Contraindications to renal biopsy include
- bilateral small kidneys,
- polycystic kidney disease,
- uncontrolled hypertension
- urinary tract or perinephric infection, bleeding diathesis,
- respiratory distress,
- and morbid obesity.

FBC: looking for

- increased WCC(inflamm. process)
- normocytic normochromic anaemia

Kidney Ultrasonography + BIOPSY

looking for

- small diseased fibrotic kidneys (to prove its chronic failure, not acute)
- is it worthwhile to do a biopsy? **In late stage renal failure all aetiologies look the same**

Pathguy's renal biopsy interpretation: http://www.pathguy.com/lectures/kidney.htm#intro

Diffuse (all glomeruli) vs. focal (only some glomeruli, maybe under 80%)

Global (entire glomerulus) vs. segmental (a part of a glomerulus)

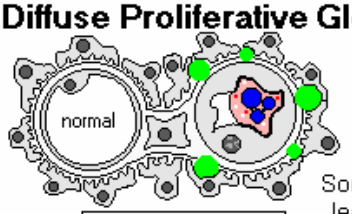
(Global diseases are usually diffuse, and segmental diseases are usually focal. Unless otherwise specified, the diseases we will describe today are usually diffuse.)

* **Hyalinosis** ("fibrinoid"): deposits of plasma proteins. (This stuff doesn't stain blue with "trichrome" or black with "silver", distinguishing it from fibrosis and sclerosis respectively.)

Sclerosis: enough increase in basement membrane - mesangial matrix material to compromise the lumens of capillaries. (The distinguishing feature is that this stains positive with silver).

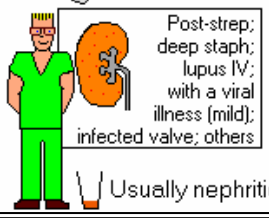
Fibrosis: type I collagen, i.e., an organized scar. (Blue on "trichrome". Unlike hyalinosis and sclerosis, this is essentially PAS-negative.)

Diffuse Proliferative Glomerulonephritis

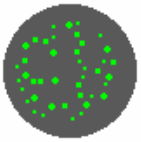


Large, irregularly-spaced subepithelial deposits
Endothelial cell edema
Neutrophils

Some cellular proliferation leading to the appearance of hypercellularity on H&E



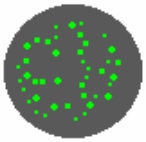
Coarse granularity ("lumpy bumpy")



Usually nephritic syndrome

Rapidly-Progressive Glomerulonephritis... Etiologies

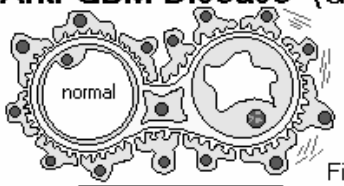
RPGN I: Anti-GBM disease
Goodpasture's, etc.



RPGN II: Immune complex disease
Post-strep, very bad lupus, etc., etc.

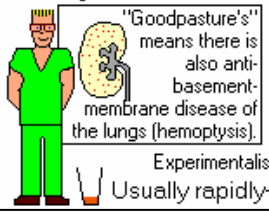
RPGN III: Vasculitis
Wegener's, polyarteritis nodosa
Look for segmental necrosis

Anti-GBM Disease (Goodpasture's, etc.)



Do not expect to see any immune deposits, or any specific changes, on electron microscopy.

Fibrin forms the basis for the crescents of RPGN.

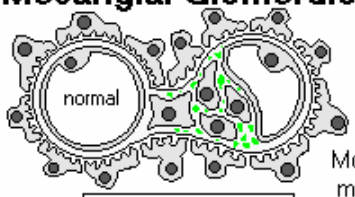


linear immuno-fluorescence

Experimentalists: Masugi nephritis!

Usually rapidly-progressive glomerulonephritis

Mesangial Glomerulonephritis



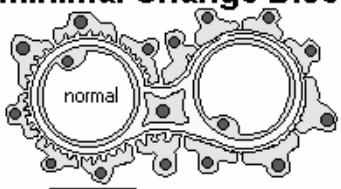
Deposits primarily in the mesangium, with some proliferation of the mesangial cells.

Most often IgA is the major immunoglobulin.

Mesangial pattern ("tree in winter")

Usually asymptomatic hematuria

Minimal Change Disease



"nil disease"
"lipoid nephrosis"

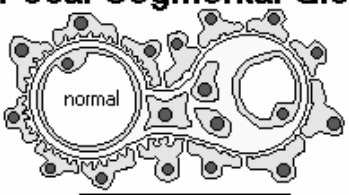
Usually an idiopathic, Rx-able kid's disease.

Foot processes are fused / obliterated.

No immune deposits.

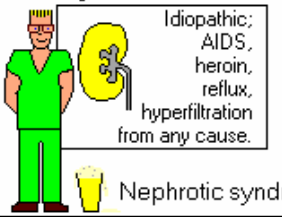
Nephrotic syndrome
Expect selective proteinuria

Focal-Segmental Glomerulosclerosis



"Sclerosis" means extra mesangial matrix and thickened GBM's obliterate the loops.

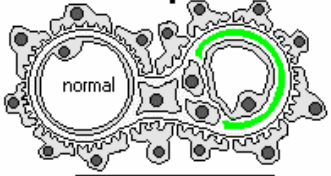
Foot processes are always obliterated / fused.



No interesting immune deposits.

Nephrotic syndrome

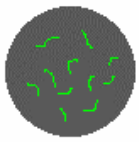
Membranoproliferative GN Type II



The split GBM presents "tram tracks."

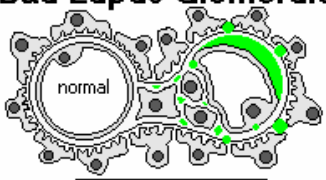
The "dense deposit" is a broad band with C3 but usually no Ig.

Worms.
C3 stain only.



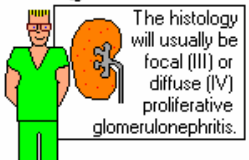
Usually nephritic-nephrotic

Bad Lupus Glomerulopathy

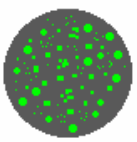


Anything but anti-GBM.

The subendothelial mega-deposits are the famous "wire loops."



Coarse granularity, often mixed chunks



Hematuria or nephritic syndrome or RPGN

Disease Definition

Membranous glomerulonephritis is an antibody mediated disease in which the immune complexes localize to the subepithelial aspect of the capillary loop. That is, between the outer aspect of the basement membrane and the podocyte (epithelial cell)

How is this diagnosis made? → by BIOPSY (no other way)

Management :

Maintenance:

- fluid restriction
- dietary restriction (more protein!)
- diuretics (loop first, then thiazides)
- STEROIDS + cyclosporins
  (to reduce inflammatory damage)

Palliative: DIALYSIS

Hemodialysis

- every 3 days for 4-5 hrs
- home, hospital or satellite centre
- blood infections are a worry
- ruined veins, etc.

Peritoneal (CAPD)

- 3-4 times per day for 45 mins
- Continuous Ambulatory Dialysis
- Peritonitis and tube site infections *(Pseudomonas and Candida are the commonest)*
- Do-It-Yourself, thus relies on 100% sterile accuracy tri-daily …!

Curative:

TRANSPLANTATION: living or cadaver donor

- great if you survive dialysis for several years while you wait
- 8% of people per year get theirs (500, of which 300 from cadavers)

PREVENTABLE CAUSES

- Diabetic renal disease
- Hypertensive diseases
- Rapidly progressive glomerulonephritis caused by focal necrotizing or cresentic glomerulonephritis (Vasculitis, Goodpastures, Wegeners Granulomatosis, and polyarteritis nodosa)
- Drug-related interstitial nephritis
- Drug toxicity (cyclopsorin, penicillamine)
- Obstructive uropathy
- Possibly membranous GN

NEED TO CATCH IT EARLY:

Once renal function drops below **35%** → **POINT OF NO RETURN**; **progression to end-stage is inevitable**

Prognosis

Clinical Course

The course of untreated idiopathic membranous glomerulonephritis is variable.
Of patients presenting with the nephrotic syndrome and a normal serum creatinine:

- **30% will have a spontaneous complete remission and a stable GFR for up to 20 years.**
- **25% will have a spontaneous partial remission with a stable GFR.**
- **20-25% experience persistent nephtrotic syndrome with stable or very slowly progressive loss of GFR.**

Twenty to 25% of patients progress to end-stage renal failure over a 20 to 30 year follow-up.

Patients in whom a causitive agent is identified usually respond to treatment of the underlying disorder, or withdrawal of the offending agent.

Australia and Iceland: worst rates of renal failure!!

Epidemiology

Membranous glomerulonephritis is more common in adults and most patients are older than 30 years at diagnosis.
Membranous glomerulonephritis accounts for 35-50% of cases of adult nephrotic syndrome.

CHRONIC RENAL FAILURE IS RAMPANTLY PREVALENT AMONG THE ABORIGINAL COMMUNITY

→ Related to maternal malnutrition (thus, underweight infants born with far fewer nephrons are more predisposed to CRF earlier in life; 1 more Kg of birth weight = 250, 000 more nephrons!
PLUS for whatever reason DIABETES IS ALSO RAMPANT; + ON THE RISE!!!

PATHOGENESIS: full score for the biochem psycho 8.03

IgG subclass 4
→ is the culprit

- **the rarest of the circulating IgG** subclasses
- **accounts for only 3-6% of total IgG**.
- **unique in its inability to activate classical complement pathway.**

THIS IS IMPORTANT!!
Classical pathway is responsible for preventing immune complex deposition
→ C3 binds to the antigen/antibody complexes, then links the complex to the CR1 Receptor on erythrocytes, which then circulate to the liver where the immune complexes are destroyed

IgG is also a LOW AFFINITY antibody
Hence it is able to dissociate pre-GBM, then penetrate the GBM and allegedly re-aggregate afterwards (inside the membrane)

Exposure to endogenous or exogenous antigen(s)
In the Heymann mouse model this is a glomerular epithelial glycoprotein called megalin, but it has no equivalent in humans
→ induction of low affinity IgG immune response

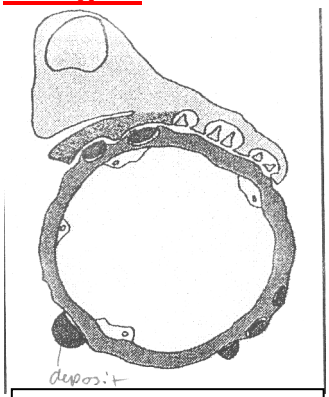
Genetic component:
HLA DR3 = risk factor
Also Cancer, SLE, lead, mercury, gold, penicillamine, hep B/C, and syphilis

Antibody + antigen complexes CIRCULATE FREELY

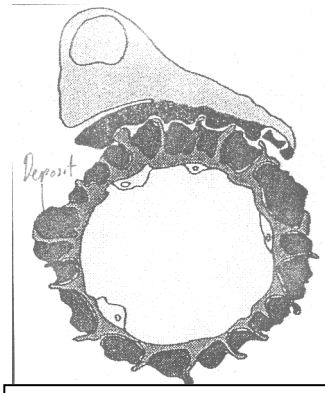
DEPOSITION OF IMMUNE COMPLEXES IN THE GLOMERULAR BASEMENT MEMBRANE

@ KIDNEY:
low affinity of the IgG4 allows **dissociation of the complexes**
→ thus their **FILTRATION** through the GBM and fixation in it
(then, re-aggregation?…PLUS hemodynamic stress eg. tortuous capillaries also increase the likelihood of immune complex deposition) **either way…**

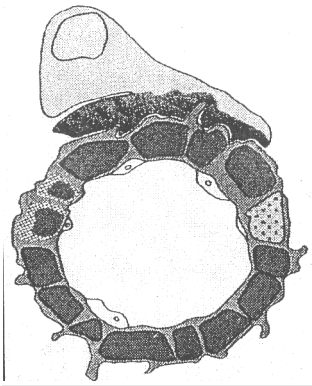
4 stages:



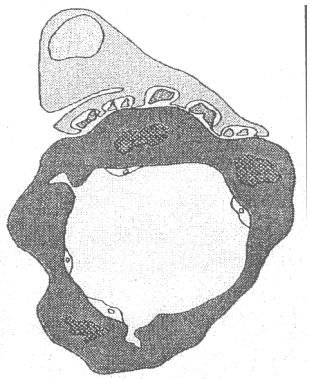
Stage 1:
Scattered subendothelial deposits (subendothelial meaning behind the GBM, on the urine side of things)



Stage 2:
Large uniform deposits;
Spikes of epithelium between them
Foot processes are being destroyed by the membrane attack complex (invoked by complement cascade, the alternative pathway)



Stage 3:
DEPOSITS ENCIRCLED and incorporated into the glomerular basement membrane; this is the famed "membranous transformation"



Stage 4:
Complete absorption of antibody complexes into the now-homogenous, irregular basement membrane .

TUBULAR DAMAGE:

NORMALLY:
Some proteins slip through the GBM
Eg. low mol. weight proteins with neutral charge
The low molecular weight proteins are usually reabsorbed by the proximal tubule

In Membranous Glomerulonephritis:
The poor tubule tries to reabsorb (pinocytose) the extra protein out of the urine and is thus overloaded with it
(vis. histological finding: *vacuolisation"* of the tubule)
THIS MUCH PROTEIN IS TOXIC:

- **Toxic on its own eg. heme**
- **The act of pumping it depletes ATP**
- **THUS the tubules atrophy and die**

→ then release cytokines
thus attract FIBROBLASTS
→ FIBROSIS

Antibody-associated Glomerular Injury

Trapping of soluble circulating Ag-Ab complexes in the glomerulus	Injury by Ab reacting *in situ* within the glomerulus	
Strep Post-infectious, Serum-sickness, Hep C	Anti–GBM or mesangial Ag	Ag planted within the glomerulus (drugs, bugs, DNA)

Site of immune complexes largely determine glomerular response:

- ***Subendothelial*** → activate complement, acute inflammatory response
- ***Mesangial*** → mesangioproliferative response
- ***Subepithelial*** → induce production of basement membrane material

NORMALLY:
The filtering in the GBM is done by

- **a size-barrier** (i.e the type IV collagen mesh)
- **a charge barrier** (i.e the polyanionic inclusions in the mesh and the nephrin on the podocyte foot processes)

In Membranous Glomerulonephritis:
the defect in membranous glomerulonephritis results **mainly from a loss of size selectivity.** *–NEJM 1998*

CHRONIC RENAL FAILURE and its many COMPLICATIONS 8.03

Glomerular Basement Membrane Damage → PROTEINURIA

DECLINE IN GLOMERULAR FILTRATION RATE
As measure of the time elapsed since the beginning of the end

100mls

Tubular Endothelium Damage:
Tubule attempts to reabsorb the excess protein by means of ATP-dependent pinocytosis; thus depletes ATP quickly, becomes starved and **ATROPHIES**
PLUS: protein toxicity induces cytokine production and thus **FIBROSIS**

THINGS LOST IN URINE:
- **PROTEIN-BOUND SUBSTANCES**: particularly **HORMONES**, eg androgens → Loss of libido, Infertility, Loss of appetite
- **COMPLEMENT PROTEINS:** Thus dysfunction of opsonisation + phagocytosis → INFECTIONS
- **Rarely, CLOTTING FACTORS** → DEEP BLEEDS
- **Rarely, ANTI-CLOTTING FACTORS** Particularly proteins C, S; Antithrombin3 → Thromboembolism
- **LIPID HOMEOSTASIS PROTEINS** Thus, overproduction and impaired catabolism of Apolipoprotein B (compensation by the liver) → HYPERLIPIDAEMIA
- **And most importantly, LOSS OF ALBUMIN** → OEDEMA

Retention of Phosphate → Inhibited Vitamin D activation → Increased levels of **PARATHYROID HORMONE** → hyperparathyroidism

70

Resorption of bone calcium + Reduced Ca++ uptake @ gut → **Osteomalacia + hypocalcaemia**

LOSS OF ERYTHROPOIETIN
Thus, Normocytic Normochromic Anaemia → Lethargy, Fatigue

Failure to excrete **ACID**
→ titratable eg. phosphate, ammonium
→ inversely, by failing to produce bicarbonate buffer
→ directly, by not excreting H+

Bone used as BUFFER
…up to a certain point → Mild metabolic acidosis

Calcified ATHEROMA
= 50% of deaths in chronic renal failure are the result of ***CARDIOVASCULAR complications***

Point of no return: failure is progressive from 35ml

30

Damage to thick ascending limb of Henle
THUS reduced concentrating function → **NOCTURIA:** Early presenting symptom

25

HYPERPHOSPHATAEMIA

Phosphate binds Ca++ and **PRECIPITATES @ TISSUES** → **METASTATIC CALCIFICATION** → **Vascular deposits** *Looks like angiography* **PRURITIS PERICARDITIS**

20

Failure to excrete **nitrogenous wastes** → **URAEMIA**
- UREA → Nausea, Vomiting, Anorexia
- Guanidosuccinic acid → IMPAIRED CLOTTING Failure to crosslink platelets with **vWF**
- AMMONIA → Confusion, dementia, COMA

10

Na+ disregulation:
Narrowed homeostatic range:
Dying tubules versus uncontrollable RAAS → HYPERTENSION

5

Although the healthy nephrons will attempt to upregulate K+ channels to keep up with the excretory demand, and the gut continues to normally excrete K+…
→ **HYPERKALEMIA, thus neuromuscular and cardiological complications** → **Risk of ASYSTOLE**

COMPLICATIONS OF HEMODIALYSIS: beta-2-microglobulin, a normal component of the MHC HLA molecule, is prone to collecting @ the kidney thus causing AMYLOIDOSIS
…plus infections of the vulnerable fistula, hemolysis in the machine, and heparinisation
COMPLICATIONS OF AMBULATORY PERITONEAL DIALYSIS is continued peritonitis, thus adhesions…

~ALL DIALYSIS IS UNDER-DIALYSIS~

Immunology of Glomerulonephritis

Table 270-2: Uremic ``Toxins"
By-products of protein and amino acid metabolism

Urea-80% of total (excreted nitrogen)
Guanidino compounds
Guanidine
Methylguanidine
Dimethylguanidine
Creatinine
Creatine
Guanidinosuccinic acid
Urates and hippurates
End products of nucleic acid metabolism
End products of aliphatic amine metabolism
End products of aromatic amino acid metabolism
Tryptophan
Tyrosine
Phenylalanine
Other nitrogenous substances
Polyamines
Myoinositol
Phenols
Benzoates
Indoles
Advanced glycation end products
Inhibitors of ligand-protein binding
Glucuronoconjugates and aglycones
Inhibitors of somatomedin and insulin action

antigenic targets in glomerulonephritis

- ***fixed native glomerular antigens*** (type II reaction): formed by complexing of antibodies to normal cell-associated antigens already in the glomerulus
  - **type IV collagen** in Goodpasture ' s disease
  - **glomerular epithelial cell membrane antigens** in Heymann nephritis (antiepithelial cell nephritis, an experimental model of membranous GN)
  - **?mesangial cell antigens** in IgA nephropathy, Henoch-Schönlein purpura
- **" planted " foreign antigens (type II reaction):** non-glomerular material bound to glomerular structures eg. via charge-dependent interaction with glomerular capillary wall anionic proteoglycans
  - **DNA, histones and nucleosomes** (DNA-histone complexes) in lupus nephritis
  - **trapped bacterial, viral and parasitic antigens**
  - **certain drugs**
- ***circulating immune complex deposition*** (type III reactions): deposition of circulating pre-formed immune complexes within glomeruli
  - **serum sickness reactions**, postinfectious GN, mesangiocapillary GN type I, cryoglobulinaemic GN (eh. hepatitis C antigen-antibody complexes).

cationic immune complexes are able to cross capillary walls from the capillary lumen THUS bind to subepithelial sites (eg. membranous GN),

anionic and neutral complexes are trapped in

- mesangium (eg. IgA nephropathy)
- subendothelial sites (eg. mesangiocapillary GN);

immune complexes that persist for long periods in the circulation are most likely to deposit in glomeruli; thus IgG subclass 4 is best for this (its not cleared by the [erythrocyte→liver] transport system

high hydrostatic pressures generated within the glomerular capillary make it a common site of immune complex deposition.

mediators of glomerular damage

- complement activation
- leucocyte infiltration
- platelet activation
- activation of coagulation cascade
- release of reactive oxygen species
- cytokine and chemokine secretion

the glomerulus has a limited range of responses to inciting stimuli. These include:

1. coagulation, fibrin deposition and crescent formation
2. cellular proliferation: mesangial, epithelial and/or endothelial
3. deposition of mesangial matrix or basement membrane material
4. vasoactive mediator release and altered glomerular filtration

Chronic Glomerulonephritis

PROGRESSIVE loss of renal function associated with inflammation.
CREEPS UP ON YOU: most commonly an incidental finding, for example:

- Routine Urinalysis:
  - **Proteinuria and hematuria**
- Routine FBC:
  - **Normocytic normochromic anaemia**
- Abdominal Imaging:
  - **Bilateral small kidneys**

Usually a chronic GN results from the resolution of an acute GN.
Initial injury = reduction in the number of working nephrons. Therefore your GFR aint what it used to be, and the remaining nephron units detect this and hypertrophy to compensate.
So now you are working your few remaining nephrons much harder: the same amount of blood needs to get filtered, but the filter is much smaller and thus the blood is forced through it at a greater pressure. This is fine for a while, but we all know what happens to arterioles under constant hemodynamic stress: SCLEROSIS. Thats right, the glomeruli literally work themselves into an early grave. Hence the progression to end-stage renal failure (ESRF)

DISEASE DEFINITIONS: "STAGING"

- **Stage 1:** kidney damage with a normal GFR (≥90 mL/min). The action plan is diagnosis and treatment, treatment of comorbid conditions, slowing of the progressing of kidney disease, and reduction of cardiovascular disease risks.
- **Stage 2:** kidney damage with a mild decrease in the GFR (60-90 mL/min). The action plan is estimation of the progression of kidney disease.
- **Stage 3:** moderately decreased GFR (30-59 mL/min). The action plan is evaluation and treatment of complications.
- **Stage 4:** severe decrease in the GFR (15-29 mL/min). The action plan is preparation for renal replacement therapy.
- **Stage 5:** kidney failure. The action plan is kidney replacement if the patient is uremic.

Usually secondary to
Another glomerulopathy, gone chronic;
Rare hereditary stuff, eg.

- **Alport syndrome:** Mutation in type IV collagen, = GBM is 5 times thicker
- **Sickle cell anaemia:** Due to sustained glomerular hypertension
- **Fabry Disease:** Lysosomal storage disease, X-linked mutation in the a-galactosidase gene, causing small vessel dysfunction at the kidney and elsewhere
- **Plus Lypodystrophy, "Nail-Patella" syndrome, etc etc**

Connective tissue diseases

- **Amyloidosis** with Rheumatoid Arthritis
- **Lupus Nephritis**

Infection

- **Hepatitis B and C**
- **HIV**
- **Secondary to infective endocarditis**
- **P. falciparum malaria**

Neoplasia

- **Hodgkins' Lymphoma**

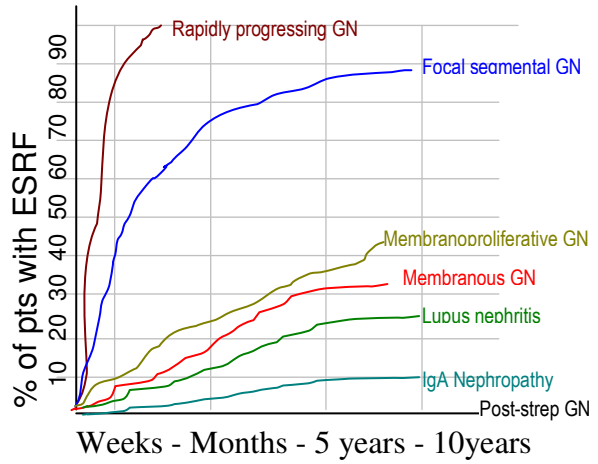
Drugs

- **NSAIDs**
- **Gold therapy**
- **Penicillamine**
- **IV heroin**

General approach:

Find and treat the systemic cause.
No apparent cause?
→ TREAT UREMIA
→ DELAY END-STAGE RENAL FAILURE
→ DIALYSIS
→ TRANSPLANTATION

Rates of Progression to ESRF



MONITORING PROGRESSION:

URINALYSIS: to calculate protein loss using protein / creatinine ratio
Eg. 300 protein and 150 creat. = 300 / 150 = 2 (g protein/day)
EUC: to calculate GFR using online creatinine clearance calculator in CIAP
Use this to monitor response to therapy; GFR = all important
ALSO look at calcium (low?), phosphate (high?)
FBC looking for normochromic normocytic anaemia
Albumin: to monitor effect of protein loss
COAGS: watch out for thrombophilia
..may also want to do a kidney ultrasound:

GOALS OF MANAGEMENT:

- **Reduce blood pressure (ACE-I, lasix, etc)**
- **Replace EPO and activated Vitamin D**
- **Manage hyperlipidaemia (reduce CVS risk factors)**

The NEPHROTIC SYNDROME

Leakage of 3 grams of protein per day.

Pathophysiology

You have a charge barrier and a size barrier. Normally nothing larger than 70kD and nothing polyanionic can get through. With GBM damage, both of these barriers can be disrupted.

SEQUELAE and STRATEGIES FOR THE MANAGEMENT THEREOF

Oedema: *due to protein loss uncompensated by liver synthesis and tissue mobilsation of albumin*

Sodium Retention: *due to increased distal resorption; ? due to activated RAAS?*

Loop Diuretics

Must get rid of the extra sodium. Loop diuretics and salt restriction are the go. Might even want to combine frusemide with a thiazide or a K-sparing diuretic. NOTE: frusemide has a short half life. Use it 2-3 times a day in large doses. BEWARE: abrupt natriuresis can cause a sudden hypovolemia and even ARF! Plus by excreting so much water you will hyperconcentrate the blood, so give these diuretics in tandem with heparin and TED stockings.

Thromboembolic Complications: *especially renal vein thrombosis! This is due to a number of factors, only one of which is the increased excretion of anticoagulation proteins (eg. antithrombin III) into the urine. There is aso unexplainable thrombocytosis (? Due to hyperconcentration of blood cells? Remember, all that water moving out into the interstitial spaces leaves behind the cells in the blood.);*

Heparin

Aspirin

Must prevent thromboembolism. Just give them heparin, evidence shows that the number of fatal emboli prevented is greater than the number of fatal bleeding events induced. Also consider aspirin (because much of the antithrombin III has been excreted and heparin has fewer targets to bind with).

Infectious Complications: *you are peeing out all of your immunoglobulins and complement cascade components. Especially dangerous in children.*

Sadly, still no justification for prophylactic antibiotics, as you may end up simply selecting for resistant organisms. Use ad-hoc intravenous antibiotics.

Hyperlipidaemia: *due to overproduction and under-catabolism of LDLs. Undercatabolism seems to result from urinary excretion of ..something. Something vital to lipid catabolism. Exactly what it is has not been determined yet. Nor do we know what causes the increased synthesis of blood lipids.*

Low-fat Diet
Statins
ACE-inhibitors

Manage this with a soy-based low fat diet and statins. ACE-inhibitors also help indirectly, by reducting protein excretion.

ACE Inhibition: ***indicated even in normotensive patients. The BP-lowering effects take place within 24hrs, but the antinephrotic protein-saving effects take a month. The anti-nephrotic effect is totally unrelated to the blood-pressure effects, its a completely different poorly understood mechanism. It can be enhanced with a low-sodium diet and diuretics.***

Common Causes

- **Diabetic Nephropathy**
- **Minimal Change Glomerulopathy (idiopathic)**
  - Loss of charge selectivity
- **Membranous glomerulonephritis (often linked to neoplasia)**
  - Carcinomas, lymphoma, leukaemia, myeloma, sarcoma...
  - Loss of size selectivity
- **Primary Renal Amyloidosis**
- **HIV**
- **Preeclampsia**