

## Urinary System 3 Glomerular disease I

Professor John Simpson

## Diseases of the glomeruli

- some of the commonest causes of end-stage renal failure
- include some you already know about, e.g. HT, diabetes
- prevalence varies by country, region, ethnicity, gender and age
- many glomerular diseases involve inflammatory processes (usually immune processes) - collectively known as "glomerulonephritis" (GN)
- in general GN is more common and more severe in tropical regions and in countries where incomes are low – associations with infection probably explain this

## Glomerulonephritis (GN)

- unfortunately a confusing area – especially as regards terminology
- lots of different diseases or lesions with different aetiologies, pathologies and prognoses, but only limited range of clinical expressions/syndromes
- classification can be by aetiology OR pathogenesis OR histological pattern OR clinical syndrome OR mixtures of any/all of these!

## The possible clinical presentations

- acute nephritis (acute nephritic syndrome)
- rapidly progressive GN (acute nephritis with acute renal failure)
- nephrotic syndrome
- chronic renal failure
- proteinuria and/or haematuria
- but overlaps occur and the same patients can have different presentations at different stages of his/her disease
- and some of these presentations can also be due to non-glomerular disease

## The glomerulus is a filter

It can clog up, holding back material that it should be letting through -  
OR it can break down, letting through material that it should be holding back –  
OR both can happen at the same time

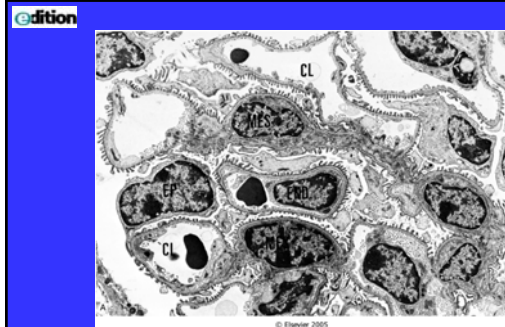
The clinical presentation depends on what's happening to the filter, how many glomeruli are involved, how quickly it happens and whether or not it resolves

## The glomerular filter

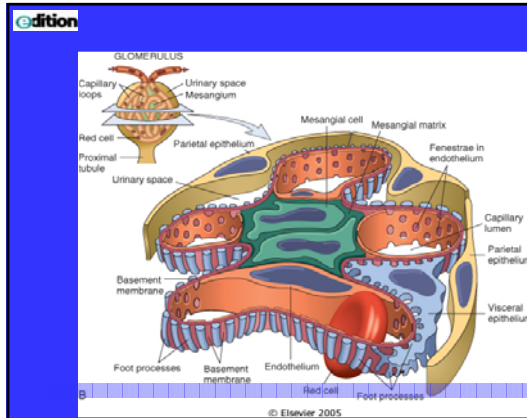
- all three glomerular cell types contribute
- endothelial and epithelial cells, with their glomerular basement membrane (GBM), provide combination of physical and electrical barriers
- mesangial cells help keep filter clean

## The glomerular filter

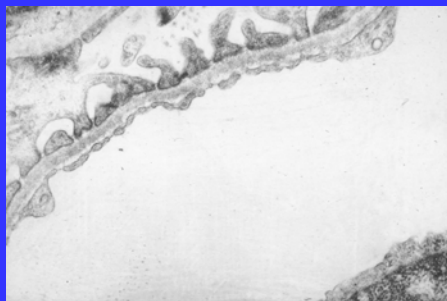
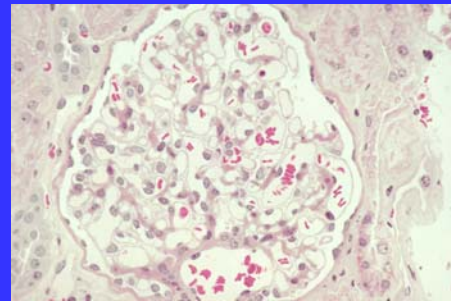
LAYER	STRUCTURE	FILTER SIZE/TYPE
inner	endoth cell fenestrae	course/physical
middle	<b>GBM</b>	fine/physical and <b>electrical</b>
outer	interepithelial cell junctions	fine/physical
-----	mesangial cell	keeps filter clean



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## Terminology of glomerular involvement

Number of glomeruli involved -

- "Diffuse" - all glomeruli
- "Focal" - some glomeruli

Amount of the glomerulus involved -

- "Global" - all of the glomerulus
- "Segmental" - part of the glomerulus

## Pathogenesis of GN

- immunological events centre on the filter, often on GBM itself
- many involve Ag/Ab interaction (B cell reactions)
- (animal experiments over the years have been very helpful in clarifying what happens in human disease)

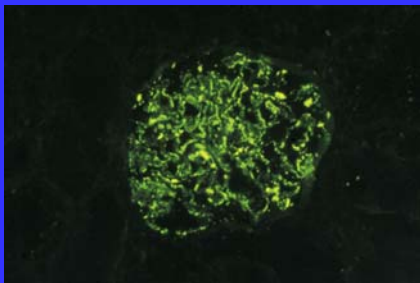
## Pathogenesis of GN

2 main types of Ag/Ab reactions –

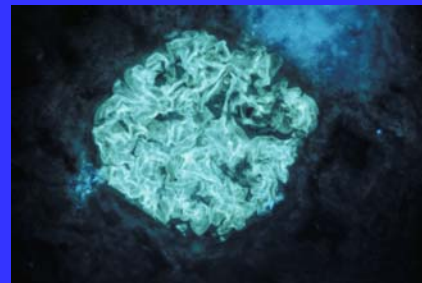
- most commonly, *immune complex nephritis* where circulating Ag<sup>\*</sup>/Ab complexes deposit in glomeruli
  - (? sometimes non-glomerular Ag circulates to glomeruli - later, circulating Ab attaches to it)
  - \*Ag can be foreign or native
- rarely, *anti GBM nephritis* where Ab reacts with native/self antigen present in GBM

Ab & complement demonstrable in glomeruli in both types

## Immune complex GN – “granular pattern” on immunofluorescence



## Anti-GBM GN – “linear pattern” on immunofluorescence



## GN due to Ag/Ab interactions (*immune complex and antiGBM*)

- basic problem is Ag/Ab interaction adjacent to GBM
- interactions activate complement, attract PMNs and often also activate local blood coagulation
- it's these secondary reactions that damage the glomerulus – causing the filter to clog up OR leak OR do both at the same time

## Effector reactions

- **complement** activation (“C5b-9 attack complex”)
  - mesangial cell release of proteases, O<sub>2</sub> free radicals and cytokines
  - GBM damage
  - neutrophil attraction
- **neutrophils** (proteases, O<sub>2</sub> free radicals and cytokines)
  - GBM damage
  - mesangial cell stimulation
- activation of platelets & blood coagulation
- glomerular cell reaction(s)

## Main pathological reactions

Glomerulus has few ways of reacting to injury

- cell proliferation (hypercellularity) – of one or more of its cells
- GBM thickening
- hyalinisation or sclerosis (i.e. scarring)
  
- but each can occur on their own OR in various combinations, so actually a lot of different histological patterns of disease

## What causes so many different disease patterns?

- the number of Ag/Ab reactions and the speed with which they occur seem to determine the pattern, severity and outcome of the GN
  
- so the particular kind of GN any one patient develops may depend on how much Ag is around for what period of time and the precise immune (Ab) response mounted to that Ag

Another example of pathology often being an exaggeration of normal physiological responses

## If large numbers of reactions occur simultaneously in all glomeruli

- diffusely, mesangial & endothelial cells proliferate & PMNs fill capillaries – and this hypercellularity makes filter clog up, causing oliguria, Na<sup>+</sup>/H<sub>2</sub>O retention, hypertension and oedema
- also GBM damage, so any non-blocked parts of filter leak blood & protein
- glomeruli look hypercellular (“diffuse proliferative GN” is histopathological term)
- essentially it's acute inflammation of all the glomeruli and it causes acute nephritis

## Acute nephritis

- the glomerular syndrome when clogging up of the filter is most acute and extreme
- usually immune complex origin (? circulating complexes or ? Ab attaching to local Ag)
- Ag usually exogenous and often related to infection (bacterial, viral, protozoal etc)

## Acute nephritis

- the classical example of this syndrome is associated with streptococcal infection –  
“**post-streptococcal GN**”

## Post-streptococcal GN

- common worldwide, though not now in developed countries
- typically follows throat, ear or skin infection in children
- usually,  $\beta$  haemolytic streptococcus of Lancefield group A (mainly types 12, 4, and 1)
- presents 7-14 days after infection with oliguria, "smoky" urine (rbcs, protein, wbc's and casts\*), mild oedema (especially periorbital) and mild HT
- raised ASO (antistreptolysin O) titre and reduced serum C3 levels & raised urea (azotaemia)
- \* casts = aggregates of cells and protein

## Periorbital oedema

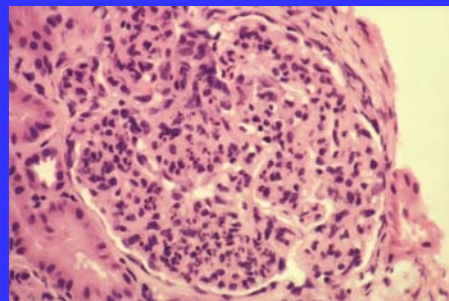
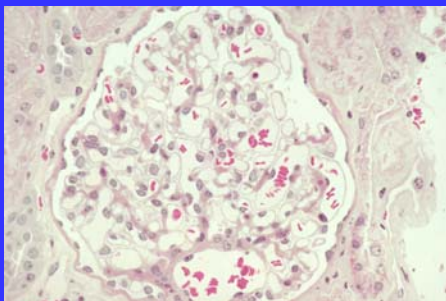


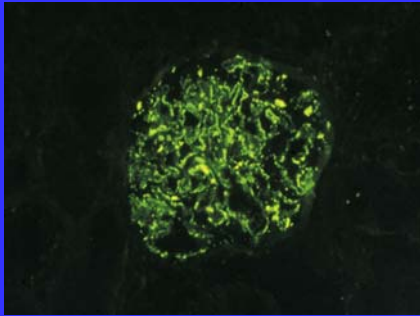
## Cause and effect

- 7- 10 days delay – to allow Ab production
- oliguria and azotaemia due to decreased GFR
- oedema and hypertension due to salt and water retention
- "smoky" urine (haematuria - rbcs with casts) due to GBM damage – (proteinuria usually also present)
- raised ASO titre and decreased C3 because of Ab formation to streptococci and complement consumption/activation by Ag/Ab reaction

## Post-streptococcal GN

- pathological pattern is diffuse proliferative GN
- swollen hypercellular bloodless glomeruli
- demonstrable evidence of local Ag/Ab reactions





## Outcome of post-strep GN

- usually (especially in children) resolves completely
- in some, gradual fibrosis of glomeruli (glomerulosclerosis) over years (?why), eventually causing end-stage renal failure ("chronic GN")
- in a few, more rapid progression (weeks) to renal failure ("rapidly progressive GN")

## Terminology/classification

- clinical – acute nephritis
- pathogenetic – immune complex GN
- pathology – diffuse proliferative GN
- aetiology – post streptococcal GN

## Other immune complex GNs

- exactly the same pathological appearance and clinical syndrome can follow other infections, but the prognosis is less good than post-streptococcal, e.g.
  - schistosomiasis, TB, malaria, HIV, filariasis, s. typhi, brucella, leptospirosis –
  - though often these produce different (path. reaction and clinical effects) forms of GN
- the same lesion & effect can also follow exposure to other foreign or self Ags, e.g. in drug reactions or autoimmune diseases, like SLE
- in fact, in most non-streptococcal cases, Ag in Ag/Ab reaction is unknown – not least because we don't always know what to look for

## "Primary and secondary GNs"

- *what those terms are supposed to mean*
- *confusing*
- *perhaps best not to use these terms*

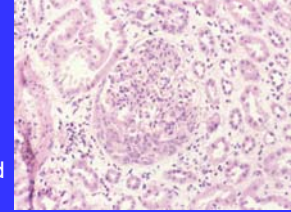
## Anti-GBM GN

- rare - mainly affects young men
- Ab produced against GBM component (collagen IV) – probably autoimmune
- effects on complement, PMNs, blood coagulation exactly as before
- if untreated, resolution does not take place
- in some cases, Abs not just to GBM, but also to pulmonary capillary BM, causing acute nephritis and lung haemorrhage = Goodpasture's syndrome

- all these GNs (immune complex and antiGBM) are examples of what happens when large numbers of immune reactions occur simultaneously in all glomeruli
- they are also examples of GNs which can enter a very quick downhill course, becoming “rapidly progressive GN” (often known as RPGN) – which is acute nephritis causing acute renal failure

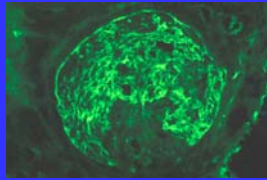
## Rapidly progressive GN (RPGN)

- severe destructive type of GN causing acute renal failure
- pathological term is “crescentic GN”
- cellular crescents fill Bowman’s space and eventually compress glomeruli



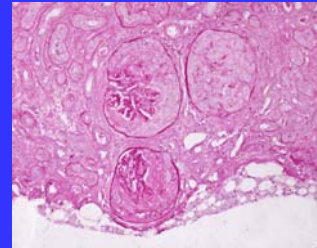
## RPGN

- cells in crescent are macrophages & T cells
- ? arise because of leakage of blood into Bowman’s space with fibrin formation



## RPGN

- affected glomeruli eventually scar completely



## RPGN

- can occur in any nephritis which does not resolve – if untreated, renal failure occurs in weeks
- rare in most post-infectious (e.g. streptococcal) GNs
- but common in anti-GBM GN
- also common in the GNs associated with systemic vasculitis (Wegener’s granulomatosis and microscopic polyarteritis) – (the “pauci-immune” GNs)
- but, in at least 50% of cases, RPGN is “idiopathic” – i.e. no known association

What happens when immune reactions are not enough to affect all glomeruli at the same time?

## When Ag/Ab reactions are fewer in number

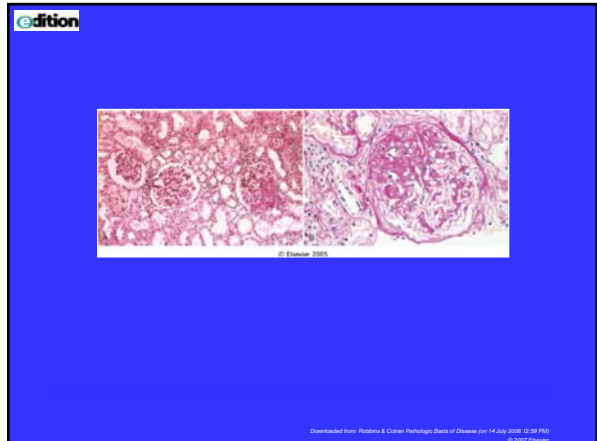
- because of renal reserve, the initial clinical effect more in terms of “leakage”
  - usual presentation is proteinuria and/or haematuria
- pathology shows “focal GN” – lesions also often segmental
- again, variety of aetiological agents and/or situations (post-infection, autoimmune disease etc), but again Ag usually unknown

## Focal GN

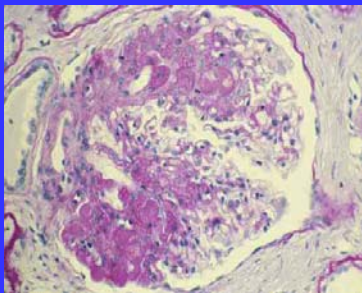
- only some glomeruli or parts of glomeruli are involved at first, but often with time more are involved with increasing glomerulosclerosis
- so, progression to end-stage renal failure (chronic GN) can take place
- (in fact, focal GN has worse prognosis than post-streptococcal disease, even though the latter is a diffuse lesion!)

## Focal GN in patients with HIV

- HIV-associated nephropathy (HIVAN) common
  - up to half or more renal biopsies show it, but overall prevalence in disease maybe ~10+%
- often seen before AIDS
- probably due to anti-HIV Abs
- typical lesion is *focal segmental glomerulosclerosis (FSGS)* – accompanied by characteristic collapse of GN capillaries



## FSGS in HIVAN

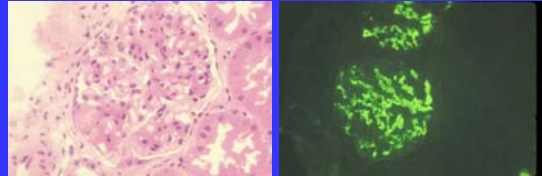


## Focal GN in patients with HIV

- presentation – usually proteinuria, maybe severe enough to cause nephrotic syndrome (next lecture)
- prognosis worse in adults
- (patients with HIV can have a variety of other renal problems)

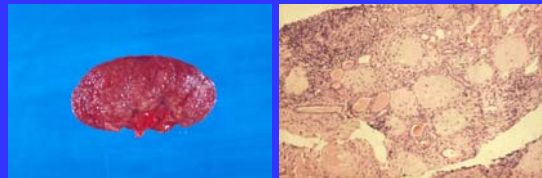
## The other common focal GN is IgA disease

- one of commonest GNs worldwide
  - ? not so in Africa
- predominantly children & young adults
- classically, recurrent macroscopic haematuria, sometimes associated with URT, urinary or GI infection
- IgA deposits in mesangium
- raised serum IgA levels - ? therefore related to abnormal mucosal immunity?
- (Henoch-Schonlein syndrome – IgA-like nephropathy associated with joint and/or GIT symptoms)



## “Chronic” GN

- may result from ANY GN failing to resolve – but also may appear “de novo”
- glomeruli become fibrosed (global glomerulosclerosis) with secondary tubular loss, so kidneys shrink
- rate of glomerular loss determines how quickly renal function deteriorates
- GNs thus one cause of “end-stage” kidney (or “granular contracted kidney”) and so chronic renal failure
- most patients hypertensive & require renal replacement therapy



## The possible clinical presentations

- acute nephritis (aka acute nephritic syndrome)
- rapidly progressive GN (acute nephritis with acute renal failure)
- nephrotic syndrome
- chronic renal failure
- proteinuria and/or haematuria
  
- but overlaps occur and the same patients can have different presentations at different stages of his/her disease
- and some of these presentations can also be due to non-glomerular disease