Mechanism of Membranous Glomerulonephritis

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

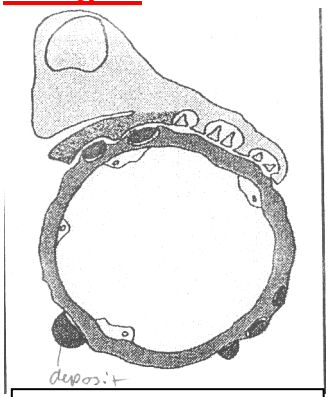
Genetic component:
HLA DR3 = risk factor
Also Cancer, SLE, lead, mercury, gold, penicillamine, hep B/C, and syphilis

Antibody + antigen complexes CIRCULATE FREELY

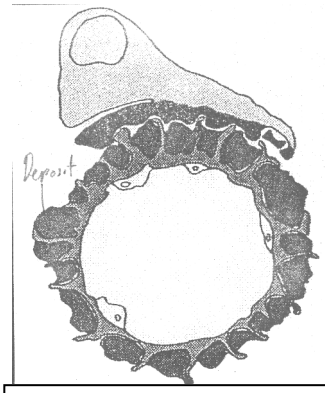
DEPOSITION OF IMMUNE COMPLEXES IN THE GLOMERULAR BASEMENT MEMBRANE

@ 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…**

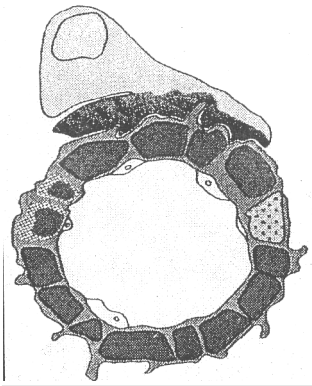
4 stages:



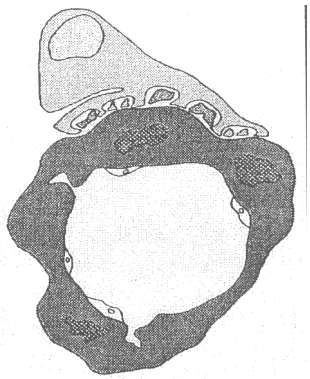
Stage 1:
Scattered subendothelial deposits (subendothelial meaning behind the GBM, on the urine side of things)



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 .

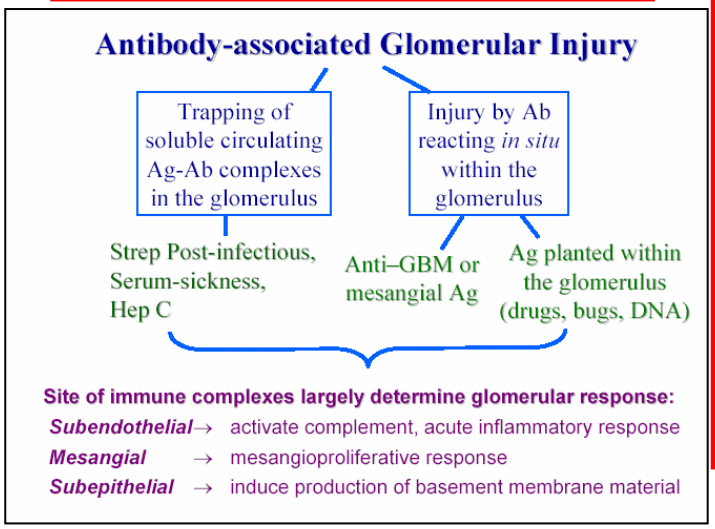
TUBULAR DAMAGE:

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



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*