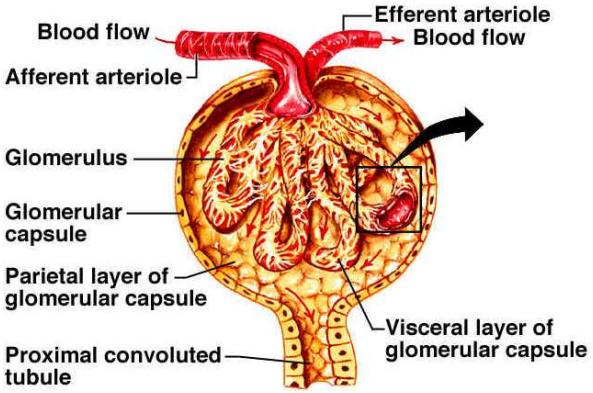
GLOMERULAR FILTRATION

Anatomy: Filtration barrier is formed by fenestrated (375A pore radius) vascular endothelium, glomerular basement membrane (GBM), and visceral epithelial **podocytes** separated by **slits** with **diaphragms**.



Chemistry: GBM formed by collagen, laminin, other extracellular matrix proteins such as negatively **charged heparan sulfate proteoglycans**. GBM provides **support** and has a **sieving** function.

Sieving Function: GBM allows free passage of neutral molecules up to 6Kd MW (18 A radius). Negatively charged pores progressively restrict passage of large (> 18A radius) and almost completely sieve out neutral molecules larger than 40A or smaller negatively charged molecules (albumin). In disease, **proteinuria** may be due to loss of **negative charge selectivity** or to increasing **numbers of large size pores**.

Filtrate composition: Small MW neutral solutes (<6 Kd) have concentrations in the filtrate equal to those in plasma (freely filtered). Larger size, particularly negatively charged solutes are sieved partially or completely. Hb, with 68 kD appears in urine when there is intravascular hemolysis but negatively charged albumin also with 68 kD is absent. Donnan equilibrium affects distribution of freely filtered ions across GBM (slightly more diffusible anions and slightly less diffusible **cations** in filtrate than in plasma), but this effect is not large, so glomerular fluid can be described as an **ultrafiltrate** of plasma. Red cell casts appear in urine in glomerular inflammatory diseases.

Glomerular Filtration Rate (GFR) is the amount of filtrate formed per unit time. Normal value: 110 ml/min, 160 L/day, 20% of RPF. Each nephron filters about 55 nl/min.

Determinants of rate: GFR= Kf (ultrafiltration coefficient) x Pu (net ultrafiltration pressure).

Pu is 10 mm Hg at afferent arteriole end and 2-0 mmHg at efferent arteriole end of glomerular capillaries (gc). Pu= P(hydrostatic)gc- P(osmotic)gc –P(hydrostatic)bs. When Pu = 0 by the time the capillary blood reaches the efferent arteriole, there is filtration equilibrium and GFR becomes proportional to RPF (constant filtration fraction).

P(hydrostatic)gc = 45-60 mm Hg all along the capillary (higher than in other capillaries in the body), is under both autoregulation (intrinsic) and extrinsic control, decreases with increasing afferent arteriole resistance (induced by AVP or AII, opposed by PG or ANP) and increases with efferent arteriole resistance (AII).

P(osmotic)gc = 20 at start and increases to 30 mm Hg at end of gc as filtration occurs and plasma proteins become concentrated. It opposes filtration , increases in dehydration, and decreases with plasma protein concentration in starvation, liver and kidney diseases.

Kf is 50x greater than in other capillaries. Kf depends on surface area for filtration (SA) and on Lp, the fluid conductivity per unit area (how easily the fluid goes through). Contraction of **mesangial cells** (AVP, AII) reduce SA; **prostaglandins** relax mesangial cells and increase SA. Excess mesangial cell proliferation (induced by PDGF and EGF) after inflammation and excess matrix production (induced by TGF) during scarring reduce SA. Lp has not been measured. It is though not to be limiting for filtration.

GFR Measurement: Needed as index of functioning kidney mass, to evaluate progression of renal disease and to adjust dose of drugs excreted by filtration.

Principle: If a solute is freely filtered (same concentration in glomerular filtrate as in plasma), is neither reabsorbed nor secreted and is not metabolized by the kidneys, then, in the steady state, the amount filtered equals the amount excreted, VU= GFRxP, so VU/P = C = GFR. I**nulin**, DPTA, EGTA, and iothalamate all have these properties and have been used to measure GFR, but these **must be injected** as they do not occur naturally in the body.

Creatinine (Cr) is produced in the body from muscle phosphocreatine and its properties approach those of **inulin**. However, at normal GFR, 10% of excreted creatinine is secreted. Because of measurement limitations, measured Pcr is 10% higher than true Pcr, so these two errors cancel each other and Ccr = Cinulin in normal subjects. In theory, if GFR decreases Pcr must increase so GFRx Pcr (and VUcr) remain constant when a steady state is achieved. But when GFR is reduced to 1/20, Pcr does not increase 20 times but only 10 times because of Cr secretion. So changes in Pcr are an index but not an exact measure of GFR and of its changes.

BUN also varies inversely with GFR (uremia, azotemia). However BUN can also increase due to increased urea reabsorption (as in dehydration and volume depletion resulting in a high BUN/Pcr, typical of prerenal azotemia) or because of excess protein in the diet. In patients starved or with liver disease BUN may remain low or normal in spite of reduced GFR.