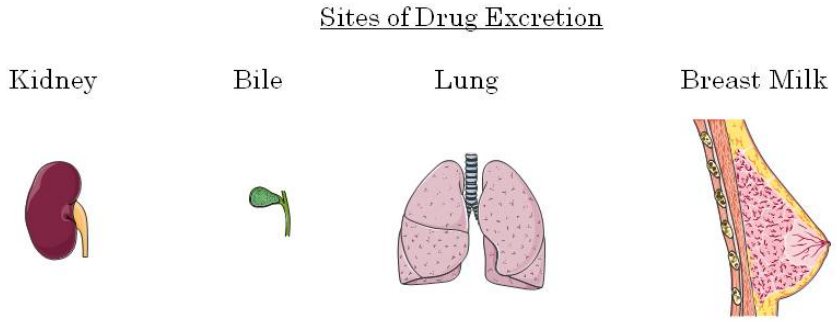
# PHARMACOKINETICS – EXCRETION

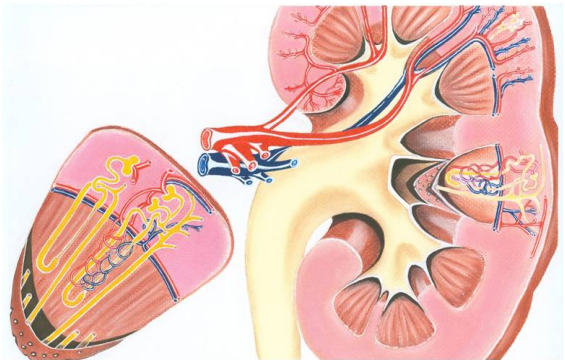
## 5.1 ROUTES OF DRUG EXCRETION

Drug Excretion

- Is the removal of parent drug and drug metabolites from the body.

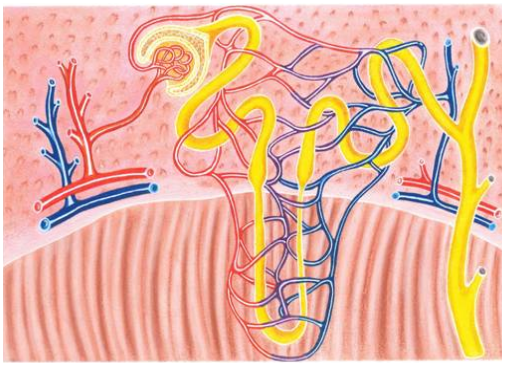



Renal Drug Excretion



- The kidneys account for the majority of drug excretion.
- Healthy kidneys serve to limit the duration and intensity of drug effects.
- Decreased kidney function prolongs the duration of action and intensity of drug effects.

The Nephron



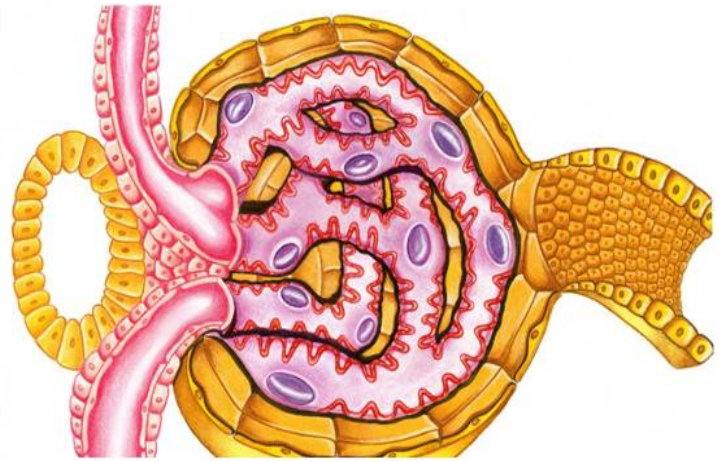
- The basic structural and functional unit of the kidney.
- Regulates water, electrolyte and drug excretion.
- Controls blood volume, blood pressure, blood pH and solute (including drug) excretion.

## 5.2 FACTORS AFFECTING RENAL DRUG EXCRETION

1) Glomerular Filtration
2) Tubular Secretion
3) Tubular Reabsorption

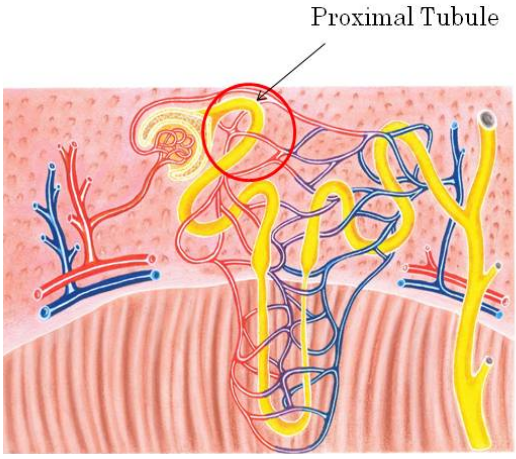
**Note: gaining a thorough understanding of the kidney here will make **Module 13** MUCH easier.

1) Glomerular Filtration



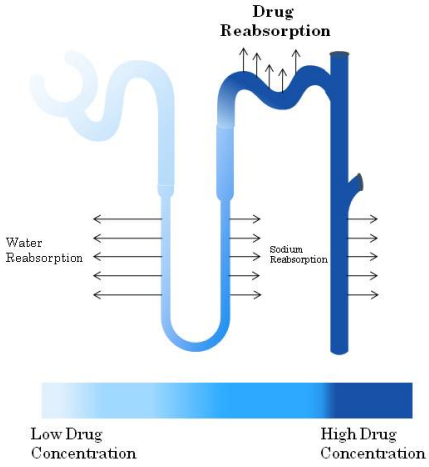
- Drugs enter the kidney from the renal artery.
- Hydrostatic pressure within glomerular capillaries forces low molecular weight drugs into the renal tubules.
- Glomerular filtration rate is ~ 120 ml/min/1.73 $m^2$ or about 20% of total renal plasma flow.
- Lipid solubility and pH do not affect glomerular filtration of drugs.
- Only non-protein bound (i.e. free) drugs are filtered at the glomerulus.

2) Tubular Secretion




- Drugs not filtered by the glomerulus leave the glomerulus by the efferent arteriole.
- The efferent arterioles divide to form capillaries that surround the proximal tubule.
- Drugs can be secreted from the blood surrounding the tubules into the lumen of the proximal tubule.
- Drug secretion in the kidney primarily occurs by two transport systems, one for weak acids and one for weak bases.

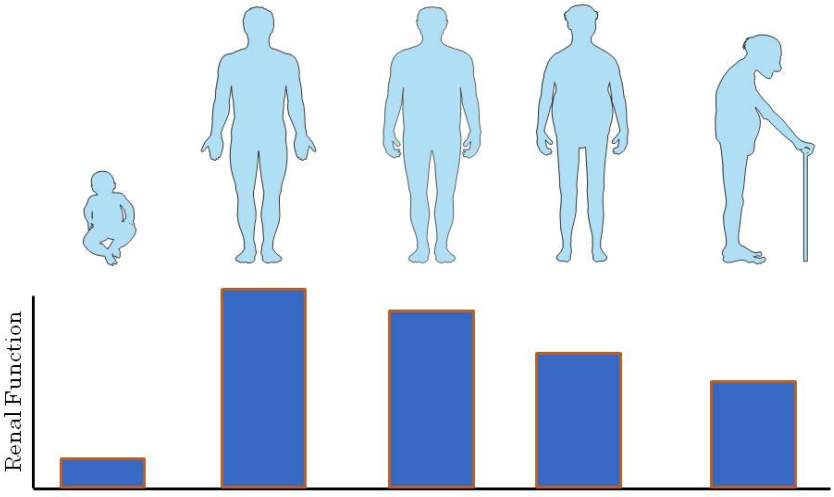
3) Tubular Reabsorption



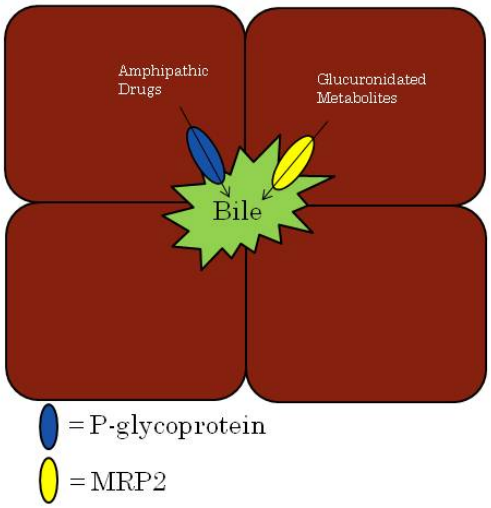

- As drugs move toward the distal tubule, their concentration increases.
- This is primarily due to the actions of the loop of henle which functions to concentrate tubular solutes.
- Once in the distal tubule the drug concentration often exceeds the concentration in the blood that immediately surrounds the distal tubule.
- If the drug is uncharged or lipid soluble, it's able to leave the tubule and be reabsorbed back into the blood.

The Effect of Age on Renal Function

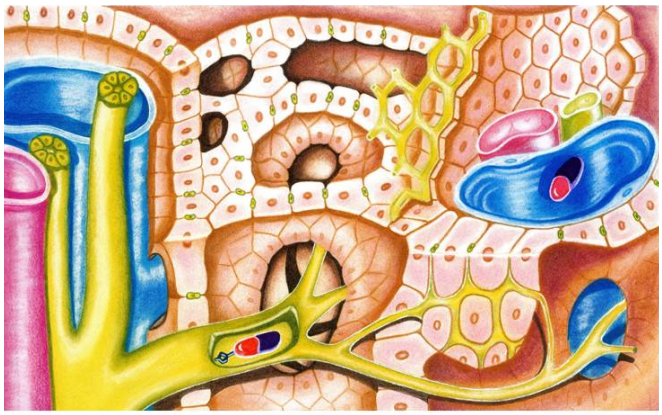
- Kidney function is low in newborn infants. Typical glomerular filtration rate (GFR) of newborns 40 mL/min/1.73 $m^2$. By two years old the GFR reaches that of a healthy adult (120 mL/min/1.73$m^2$).
- As we age renal function decreases.
- If renal function is decreased, renal drug excretion is decreased.




**5.3 BILIARY DRUG EXCRETION**

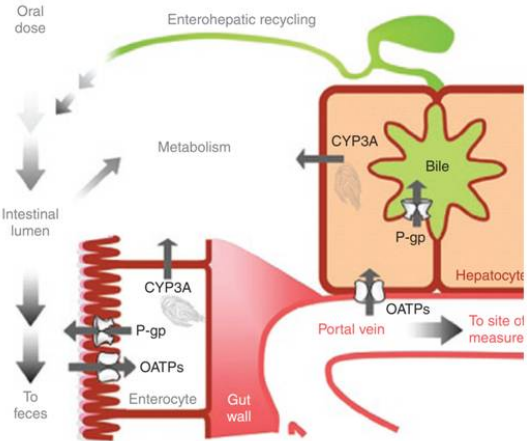



- Some drugs are eliminated into the bile and ultimately excreted in the feces.
- Characteristics of drugs eliminated in the bile include:
  1) molecular weight > 300 Da
  2) have both polar and lipophilic groups (amphipathic molecules)
  3) are glucuronidated.
- Transporters on the canalicular membrane of hepatocytes transport drugs and metabolites from the liver into the bile.
- P-glycoprotein transports a variety of amphipathic drugs into bile and MRP2 transports glucuronidated metabolites into bile.
- Drugs released into the bile are ultimately released into the intestine during digestive processes.
- Drugs released into the intestine may be excreted into the feces or undergo enterohepatic recycling.



Enterohepatic Recycling

- Drugs and drug conjugates excreted in the bile enter the intestinal lumen.
- Intestinal bacteria can cleave conjugate metabolites leaving the original drug.
- The original drug may be reabsorbed in the intestine to re-enter the body.
- This process is known as enterohepatic recycling.
- Drugs that undergo enterohepatic recycling persist in the body for substantially longer periods.



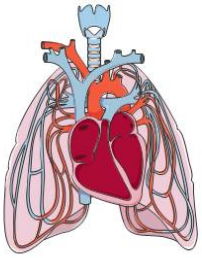

**5.4 PULMONARY DRUG EXCRETION**

- Drugs eliminated by pulmonary excretion are usually gaseous and/or highly volatile.
- The best examples are general anesthetics.
- Pulmonary drug excretion is not heavily reliant on drug metabolism.
- Factors affecting pulmonary drug excretion include:

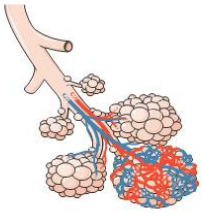
    1) Rate of Respiration
    2) Cardiac Output
    3) Solubility of Drug in blood:

-High drug blood solubility → low pulmonary excretion
-Low blood drug solubility → high pulmonary excretion

Pulmonary Circulation



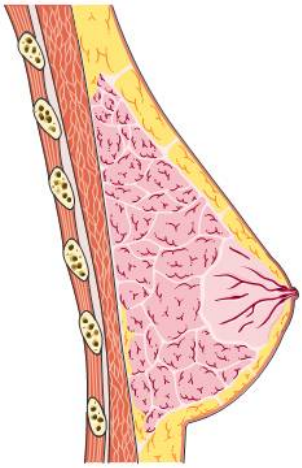
Intra-Pulmonary Airway



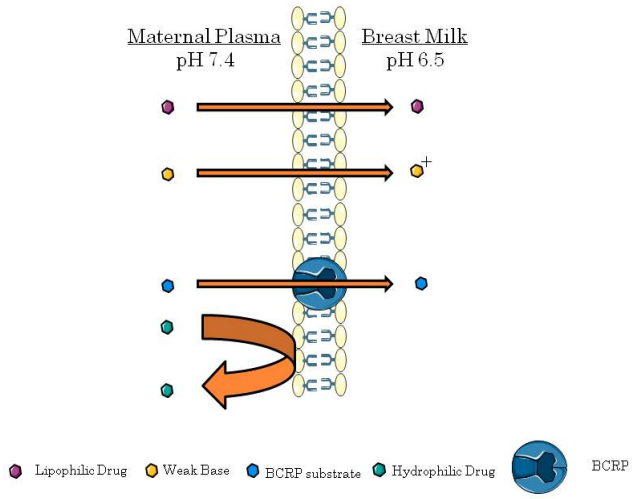
**5.5 DRUG EXCRETION IN BREAST MILK**

- > 90% of women take at least one drug in the first week post-partum.
- Drug excretion in breast milk is important because breast-fed infants may be inadvertently exposed to drugs.
- Drugs excreted in breast milk usually have:

    1) Low protein binding
    2) Low molecular weight
    3) High lipophilicity



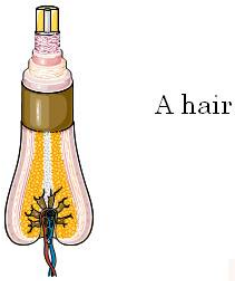
- The drug transporter breast cancer resistance protein (BCRP) transports drugs into breast milk.
- Breast milk has a lower pH and higher lipid content than plasma.
- It is important to note that while drug exposure via breast milk is an important concern, only relatively few drugs pose a clinically relevant risk to infants. Consultation with a pediatrician is suggested to help guide dosing.
- More information can be found at: www.motherisk.org

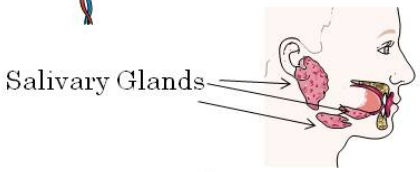


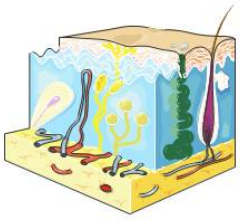

## 5.6 OTHER ROUTES OF DRUG EXCRETION

- Hair – Drugs may be excreted into hair follicles. Drugs can be measured in hair to determine how long a person has been exposed. This is especially useful in forensics. Hair grows ~ 1 cm/month.
- Saliva – drug excreted in saliva is usually swallowed and then subject to either intestinal absorption or fecal excretion.
- Sweat – Drugs excreted in sweat are mostly washed away although a minor amount of dermal reabsorption may occur.

*** These routes of excretion are considered minor in comparison with excretion by renal, biliary, pulmonary and breast mechanisms.*


A hair follicle





Layers of the skin