Excretion Routes: Polar drugs that don't undergo metabolism as well as polar metabolites of lipophilic drugs are eliminated through a variety of routes. Minor routes of elimination include biliary excretion, sweat, saliva, tears, and exhaled air, but the major route of elimination is by far renal excretion.

Renal excretion: Renal excretion involves three stages: (1) Glomerular filtration, (2) tubular secretion, (3) and tubular reabsorption.

Glomerular Filtration: The first stage of renal elimination is Glomerular Filtration or GF. As you recall, the kidneys are made up of small functional units called nephrons. Here's a schematic showing a single nephron. Blood from afferent arteriole enters a structure made up mesh of densely branched capillaries, known as glomerulus. The glomerulus allows only plasma and small molecules of less than 20,000 dalton in size to filter through. Since most drugs are smaller than this size limit, they will be filtered through. Glomerular filtration makes up about 20% of the renal drug elimination. The remaining 80% will continue to pass on to a network of peritubular capillaries that surround the proximal tubule. Only a free drug is removed during this stage. Albumin-bound drugs would not be filtered. For example, warfarin is about 98% albumin bound, so not much will be removed.
• **Glomerular filtration rate (GFR):** When it comes to drug elimination through the kidneys, we often use the Glomerular Filtration Rate or GFR as a benchmark for choosing a dose or predicting toxicity. GFR is a calculation that serves as an indicator of how well the kidneys are functioning. Some drugs are eliminated mostly through renal elimination, so if the kidneys aren’t working properly, the plasma concentrations could rise and lead to toxic side effects. For these drugs, GFR is an important factor to consider because it has a predictive value in terms of how well such drugs will be eliminated.

• **Tubular reabsorption:** The second stage in renal elimination is tubular reabsorption. Since only 20% of the plasma is filtered through the glomerulus, the remaining 80% goes through the peritubular capillaries. These capillaries are in close proximity to the proximal tubule, and this allows passive diffusion of drugs and other solutes that are already in the proximal tubule back into the peritubular capillaries. Since this is passive diffusion, only lipophilic drugs will be reabsorbed to any significant degree. Reabsorption does not really affect most of the drugs because most drugs that are renally eliminated are either polar to begin with or are polar metabolites of drugs that underwent biotransformation in the liver. An important parameter that influences urinary excretion of drugs is urine pH. Typically, the filtrate within the tubules has a lower pH than the blood. The blood is around pH 7.4 but the urine pH is in the range of 5-7. Drugs that are weak bases tend to be ionized at lower pH, so once they are in the tubules they are more likely to be in the ionized form and will be unable to cross the membrane again for reabsorption. This causes ion trapping of drugs that are weak bases. So generally low urine pH favor elimination of weak bases. On the other hand, drugs that are weak acids are not excreted that easily when the urine is acidic, so sometimes it is necessary to alkalinize the urine to enhance excretion of weak acids. For example,
in cases of aspirin overdose, alkalization of urine is carried out to increase its elimination because aspirin is a weak acid

- **Tubular Secretion**: The third stage in renal elimination is tubular secretion. This also happens between the proximal tubule and the peritubular capillaries. The proximal tubule contains several transporter proteins of the OAT and OCT subfamilies, which selectively secrete solutes including drugs into the proximal tubule. So the drugs that were not filtered through the glomerulus are effectively removed at this stage. This is a highly efficient process, and unlike glomerular filtration, plasma protein binding does not affect drug secretion at this stage. Drugs that are organic anions in particular are efficiently secreted by the transporters. For example, over 90% of penicillin is secreted intact.

- **Renal Excretion—Quantitative aspects**:  
  - Total renal excretion = GFR – Reabsorption + Secretion

- **Creatinine Clearance**: Creatinine is a byproduct of muscle breakdown and is produced at a fairly constant rate of course depending on your muscle mass, so there is an expected range of plasma concentration of creatinine. Creatinine is excreted unchanged by the kidneys, so the kidney function will directly affect the plasma concentrations of creatinine. Furthermore, in terms of renal elimination, creatinine is mostly removed during glomerular filtration and little is removed by secretion and it is not reabsorbed. So for practical purpose it is assumed that creatinine is removed by glomerular filtration, and the rate at which creatinine is removed is used as an indicator of glomerular filtration rate. Inulin is also another reference that is used. Inulin is a polymer of fructose that is entirely removed by glomerular filtration with no contribution from secretion or reabsorption, so inulin is in fact more accurate indicator of glomerular filtration rate.

- **Biliary Excretion**: Biliary excretion essentially involves excretion of drugs that are dissolved in bile salts. The process begins in the liver where bile salts are produced
from cholesterol. These bile salts then travelled to the gall bladder where they are stored until needed, so the second stage is storage. Finally, when we eat something fatty, the gall bladder releases the bile salts into the small intestine. Many drugs travel along with bile salts are released into the small intestine and are then excreted in feces.

- **Enterohepatic Recycling**: Once the bile salts enter the intestine, there is no guarantee that they will be all excreted out, because of enterohepatic recycling. Through this process, 95% of the bile salts and associated content is reabsorbed from the duodenum and back into the liver. That means that only 5% of the content is removed in feces. Some drugs keep undergoing enterohepatic recycling so that only a small fraction is removed at a time. If a drug is toxic to the hepatocytes, this raises the possibility of liver damage in case of overdose.

- **Hepatocytes & Biliary Excretion**: Below is a schematic showing a hepatocyte within the liver. In the cell, cholesterol is being converted to bile acid. Bile acid will
be converted to bile salts and exported out of the cells. Bile salts will be mixed with lipids and free cholesterol on its way to the gall bladder where it will be stored. Drug metabolism in hepatocytes will result in metabolites that will also be exported out of the hepatocytes through solute carriers such as OAT and OCT transporters. These drugs will also mix in with bile salts and store in the gall bladder until they are released into the small intestine. One important feature of this mode of drug excretion is that glucuronic acid conjugation actually increases the excretion of drugs. However, some glucuronic acid conjugates are hydrolyzed in the duodenum, releasing the free (unconjugated) drug. This free drug will then be reabsorbed into circulation. This would give such a drug a very long half-life. For example, the anti-inflammatory drug Leflunomide has a very long half-life because it undergoes glucuronidation followed by enterohepatic recycling.