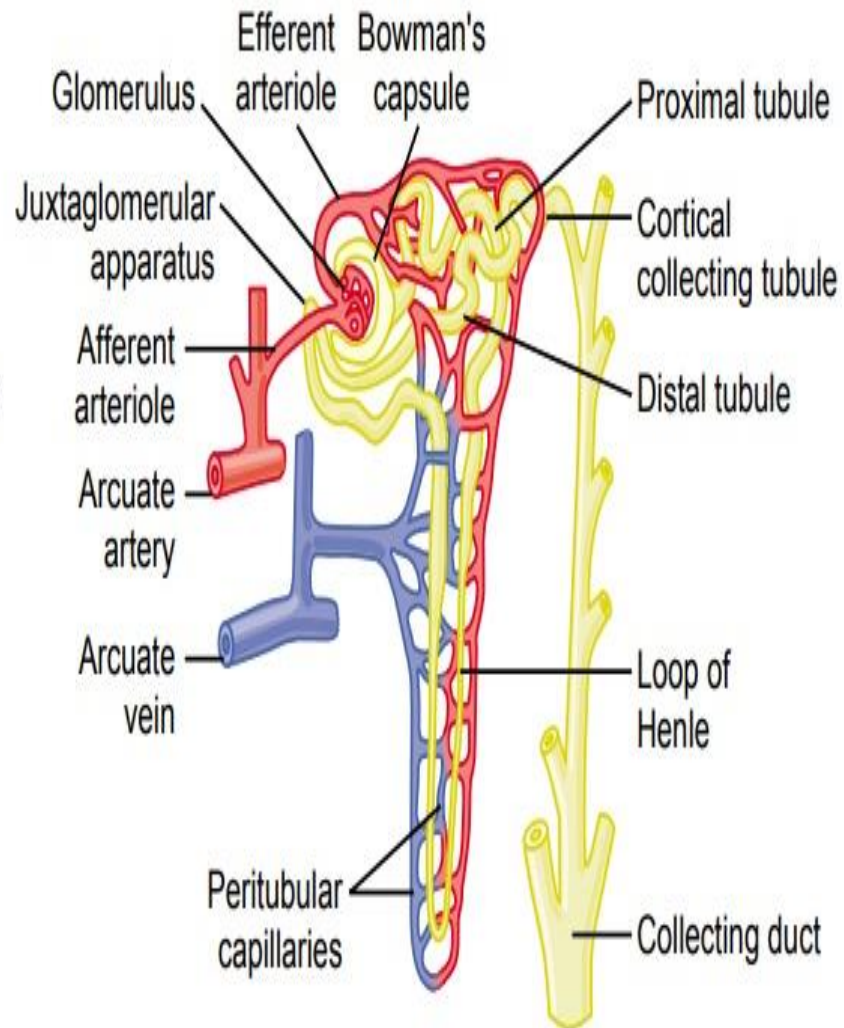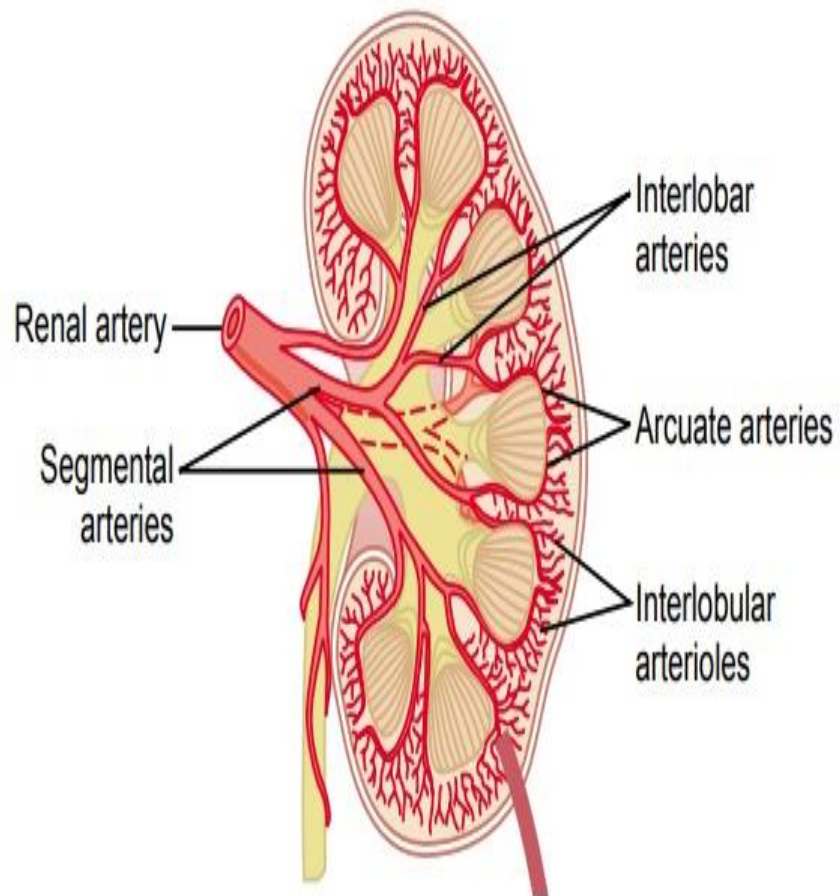# Drug elimination and Hepatic clearance
Chapter 6

Blood Supply

The kidneys represent about **0.5% of the total body weight** and receive approximately **20 -25% of the cardiac output**. The kidney is supplied by blood via the renal artery, which subdivides into the interlobar arteries penetrating within the kidney and branching farther into the afferent arterioles. Each afferent arteriole carries blood toward a single nephron into the glomerular portion of the nephron (*Bowman's capsule*). **The filtration of blood occurs in the glomeruli in Bowman's capsule.** From the capillaries (*glomerulus*) within Bowman's capsule, the blood flows out via the efferent arterioles and then into a second capillary network that surrounds the tubules (*peritubule capillaries* and *vasa recti*), **including the loop of Henle, where some water is reabsorbed.**

Interlobar arteries
Renal artery
Segmental arteries
Arcuate arteries
Interlobular arterioles

Efferent arteriole
Glomerulus
Bowman's capsule
Proximal tubule
Juxtaglomerular apparatus
Cortical collecting tubule
Afferent arteriole
Distal tubule
Arcuate artery
Arcuate vein
Loop of Henle
Peritubular capillaries
Collecting duct

http://www.brainkart.com/article/Renal-Blood-Supply_19390/

The *renal blood flow* (RBF) is the volume of blood flowing through the renal vasculature per unit time. Renal blood flow exceeds 1.2 L/min or 1700 L/day. ***Renal plasma flow* (RPF) is the renal blood flow minus the volume of red blood cells present. Renal plasma flow is an important factor in the rate of drug filtration at the glomerulus.**

$$RPF = RBF - (RBF \times Hct) \qquad (6.1)$$

where Hct is hematocrit.
Hct is the fraction of blood cells in the blood, about 45% of the total blood volume, or 0.45. The relationship of renal blood flow to renal plasma flow is given by a rearrangement of Equation 6.1:

$$RPF = RBF(1 - Hct)$$

Assuming a hematocrit of 0.45 and a RBF of 1.2 L/min, using the above equation, RPF = 1.2 - (1.2 x 0.45) =0.66 L/min or 660 mL/min, approximately 950 L/day. The *glomerular filtration rate* (GFR) is about 125 mL/min in an average adult, or about 20% of the RPF. The ratio GFR/RPF is the *filtration fraction* .

Glomerular Filtration and Urine Formation

A normal adult male subject has a GFR of **approximately 125 mL/min**. About 180 L of fluid per day are filtered through the kidneys. In spite of this large filtration volume, the average **urine volume is 1- 1.5 L.**

Up to 99% of the fluid volume filtered at the glomerulus is reabsorbed. **Besides fluid regulation, the kidney also regulates the retention or excretion of various solutes and electrolytes.**

With the exception of proteins and protein-bound substances, most small molecules are filtered through the glomerulus from the plasma.

The filtrate contains some ions, glucose, and essential nutrients as well as waste products, such as urea, phosphate, sulfate, and other substances. The essential nutrients and water are reabsorbed at various sites, including the proximal tubule, loops of Henle, and distal tubules.

RENAL DRUG EXCRETION

Renal excretion is a major route of elimination for many drugs. Drugs that are 1-nonvolatile, 2-water soluble, 3-have a low molecular weight (MW), or are 4-slowly biotransformed by the liver are eliminated by renal excretion. The processes by which a drug is excreted via the kidneys may include any combination of the following:

Glomerular filtration

Active tubular secretion

Tubular reabsorption

Glomerular filtration is a <u>unidirectional process</u> that occurs for most small molecules **(<u>MW < 500</u>)**, including <u>undissociated (nonionized) and dissociated (ionized) drugs</u>. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus. <u>The major driving force</u> for glomerular filtration is the <u>hydrostatic pressure</u> within the glomerular capillaries. The kidneys receive a large blood supply (approximately 25% of the cardiac output) via the renal artery, with very little decrease in the hydrostatic pressure.

Glomerular filtration rate **(GFR) is measured by using a drug that is eliminated by filtration only (ie, the drug is neither reabsorbed nor secreted). Examples of such drugs are inulin and creatinine.** <u>Therefore, the clearance of inulin is equal to the GFR, which is equal to 125-130 mL/min.</u> **The value for the GFR correlates fairly well with body surface area. Glomerular filtration of drugs is directly related to the free or nonprotein-bound drug concentration in the plasma.** <u>As the free drug concentration in the plasma increases, the glomerular filtration for the drug increases proportionately, thus increasing renal drug clearance for some drugs.</u>

Active tubular secretion is an active transport process. As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient. The carrier system is capacity limited and may be saturated. Drugs with similar structures may compete for the same carrier system.

1-**Two active renal secretion systems have been identified, systems for (1) weak acids and (2) weak bases**.

For example, **probenecid competes with penicillin for the same carrier system (*weak acids*).** 2-Active tubular secretion rate is dependent on **renal plasma flow**. 3-Drugs commonly used to measure active tubular secretion include *p* -amino-hippuric acid (PAH) and iodopyracet (Diodrast).

4-These substances are both filtered by the glomeruli and secreted by the tubular cells. 5-Active secretion is extremely rapid for these drugs, and practically all the drug carried to the kidney is eliminated in a single pass. The clearance for these drugs therefore reflects the *effective renal plasma flow* (ERPF), which varies from 425 to 650 mL/min.

6-For a drug that is excreted solely by glomerular filtration, the elimination half-life may change markedly in accordance with the binding affinity of the drug for plasma proteins. In contrast, drug protein binding has very little effect on the elimination half-life of the drug excreted mostly by active secretion. Because drug protein binding is reversible, drug bound to plasma protein rapidly dissociates as free drug is secreted by the kidneys. For example, some of the penicillins are extensively protein bound, but their elimination half-lives are short due to rapid elimination by active secretion.

Tubular reabsorption occurs after the drug is filtered through the glomerulus and can be an **active or a passive process**. If a drug is **completely reabsorbed** (eg, glucose), then the value for the clearance of the drug is approximately zero. For drugs that are **partially reabsorbed**, clearance values are less than the GFR of 125-130 mL/min.

The reabsorption of drugs that are acids or weak bases is influenced by the pH of the fluid in the renal tubule (ie, urine pH) and the pKa of the drug. Both of these factors together determine the **percentage of dissociated (ionized) and undissociated (nonionized) drug**. Generally, the undissociated species is more lipid soluble (less water soluble) and has greater membrane permeability.

1-The undissociated drug is easily reabsorbed from the renal tubule back into the body. 2-This process of drug reabsorption can significantly reduce the amount of drug excreted, depending on the pH of the urinary fluid and the pKa of the drug. The pKa of the drug is a constant, 3-but the normal urinary pH may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake. 4-Vegetable and fruit diets or diets rich in carbohydrates result in higher urinary pH, 5-whereas diets rich in protein result in lower urinary pH.

Drugs such as ascorbic acid and antacids such as sodium carbonate may decrease (acidify) or increase (alkalinize) the urinary pH, respectively, when administered in large quantities. **6-By far the most important changes in urinary pH are caused by fluids administered intravenously.** Intravenous fluids, such as solutions of bicarbonate or ammonium chloride, are used in acid-base therapy. Excretion of these solutions may drastically change urinary pH and alter drug reabsorption and drug excretion by the kidney.

The percentage of ionized weak acid drug corresponding to a given pH can be obtained from the *Henderson-Hasselbalch equation*

$$pH = pK_a + \log \frac{[\text{ionized}]}{[\text{nonionized}]} \qquad (6.3)$$

Rearrangement of this equation yields

$$\frac{[\text{ionized}]}{[\text{nonionized}]} = 10^{pH - pK_a} \qquad (6.4)$$

$$\text{Fraction of drug ionized} = \frac{[\text{ionized}]}{[\text{ionized}] + [\text{nonionized}]} \qquad (6.5)$$

$$= \frac{10^{pH - pK_a}[\text{nonionized}]}{[\text{ionized}] + [\text{nonionized}]}$$

$$= \frac{10^{pH - pK_a}}{1 + 10^{pH - pK_a}}$$

The fraction or percent of weak acid drug ionized in any pH environment may be calculated with Equation 6.5. For acidic drugs with pKa values from 3 to 8, a change in urinary pH affects the extent of dissociation. The extent of dissociation is more greatly affected by changes in urinary pH for drugs with a pKa of 5 than with a pKa of 3. Weak acids with pKa values of less than 2 are highly ionized at all urinary pH values and are only slightly affected by pH variations.

TABLE 6.2 Effect of Urinary pH and pK_a on the Ionization of Drugs

pH OF URINE	PERCENT OF DRUG IONIZED: $pK_a=3$	PERCENT OF DRUG IONIZED: $pK_a=5$
7.4	100	99.6
5	99	50.0
4	91	9.1
3	50	0.99

For a weak base drug, the Henderson-Hasselbalch equation is given as

$$pH = pK_a + \log + \frac{[\text{nonionized}]}{[\text{ionized}]} \qquad (6.6)$$

and

$$\text{Percent of drug ionized} = \frac{1 + 10^{pH - pK_a}}{10^{pH - pK_a}} \qquad (6.7)$$

The greatest effect of urinary pH on reabsorption occurs with weak base drugs with pKa values of 7.5-10.5.

From the Henderson-Hesselbalch relationship, a concentration ratio for the distribution of a weak acid or basic drug between urine and plasma may be derived. **The urine-plasma (U/P) ratios for these drugs are as follows.**

For weak acids,

$$\frac{U}{P} = \frac{1 + 10^{pH_{urine} - pK_a}}{1 + 10^{pH_{plasma} - pK_a}} \qquad (6.8)$$

For weak bases,

$$\frac{U}{P} = \frac{1 + 10^{pK_a - pH_{urine}}}{1 + 10^{pK_a - pH_{plasma}}} \qquad (6.9)$$

For example, amphetamine, a weak base, will be reabsorbed if the urine pH is made alkaline and more lipid soluble nonionized species are formed. In contrast, acidification of the urine will cause the amphetamine to become more ionized (form a salt). The salt form is more water soluble and less likely to be reabsorbed and has a tendency to be excreted into the urine more quickly. In the case of weak acids (such as salicylic acid), acidification of the urine causes greater reabsorption of the drug and alkalinization of the urine causes more rapid excretion of the drug.

DRUG CLEARANCE

Drug clearance **is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process**. Drug clearance (*body clearance, total body clearance ,* or *Cl* T) considers the entire body as a single drug-eliminating system from which many unidentified elimination processes may occur. **Instead of describing the drug elimination rate in terms of amount of drug removed per time unit (eg, mg/min), drug clearance is described in terms of volume of fluid clear of drug per time unit (eg, mL/min).**

There are several definitions of clearance, which are similarly based on volume of drug removed per unit time.

The simplest concept of clearance regards the body as a space that contains a definite volume of body fluid (apparent volume of distribution, VD) in which the drug is dissolved.

1-Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time. The units for clearance are volume/time (eg, mL/min, L/hr). For example, if the ClT of penicillin is 15 mL/min in a patient and penicillin has a VD of 12 L, then from the clearance definition, 15 mL of the 12 L will be cleared of drug per minute.

2-Alternatively, ClT may be defined as the rate of drug elimination divided by the plasma drug concentration. This definition expresses drug elimination in terms of the volume of plasma eliminated of drug per unit time. This definition is a practical way to calculate clearance based on plasma drug concentration data.

$$Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration}(C_p)} \qquad (6.10)$$

$$Cl_T = \frac{dD_E/dt}{C_p} = \frac{\mu g/\min}{\mu g/mL} = mL/\min \qquad (6.11)$$

where $D E$ is the amount of drug eliminated and $dD E /dt$ is the rate of elimination. Rearrangement of Equation 6.11 gives Equation 6.12.

$$\text{Elimination rate} = \frac{dD_E}{dt} = C_p Cl_T \qquad (6.12)$$

The two definitions for clearance are similar because dividing the elimination rate by the C p yields the volume of plasma cleared of drug per minute, as shown in Equation 6.10.

As discussed in previous chapters, a first-order elimination rate, dD E /dt , is equal to k DB or k Cp VD . Based on Equation 6.10, substituting elimination rate for kC p V p ,

$$Cl_\mathrm{T} = \frac{kC_\mathrm{P}V_\mathrm{D}}{C_\mathrm{P}} = kV_\mathrm{D} \qquad (6.13)$$

Equation 6.13 shows that clearance is the product of VD and k , both of which are constant. As the plasma drug concentration decreases during elimination, the rate of drug elimination, dD E /dt , decreases accordingly, but clearance remains constant. Clearance is constant as long as the rate of drug elimination is a first-order process.

Just as the elimination rate constant (k) represents the sum total of all the rate constants for drug elimination, including excretion and biotransformation, Cl T is the sum total of all the clearance processes in the body, including clearance through the kidney (renal clearance), lung, and liver (hepatic clearance).

$$\text{Renal clearance} = k_e V_D$$
$$\text{Lung clearance} = k_1 V_D$$
$$\text{Hepatic clearance} = k_m V_D$$
$$\text{Body clearance} = k_e V_D + k_1 V_D + k_m V_D$$
$$= (k_e + k_1 + k_n) V_D = k V_D$$

From Equation 6.14, body clearance *Cl* T of a drug is the product of two constants, *k* and *V*D , which reflect all the distribution and elimination processes of the drug in the body. The volume of distribution and elimination rate constant are affected by blood flow, which will be considered below using a physiologic model.

CLEARANCE MODELS

The calculation of clearance from k and VD assumes (sometimes incorrectly) a defined model, whereas clearance estimated directly from the plasma drug concentration time curve does not assume any model. Although clearance may be regarded as the product of k and VD, Equation 6.10 is far more general because the reaction order for the rate of drug elimination, dD_E/dt, is not specified, and the elimination rate may or may not follow
first-order kinetics.

Physiologic/Organ Clearance

Clearance may be calculated for any organ involved in the irreversible removal of drug from the body. **Many organs in the body have the capacity for drug elimination, including drug excretion and biotransformation. The kidneys and liver are the most common organs involved in excretion and metabolism, respectively.** <u>**Physiologic pharmacokinetic models are based on drug clearance through individual organs or tissue groups.**</u>
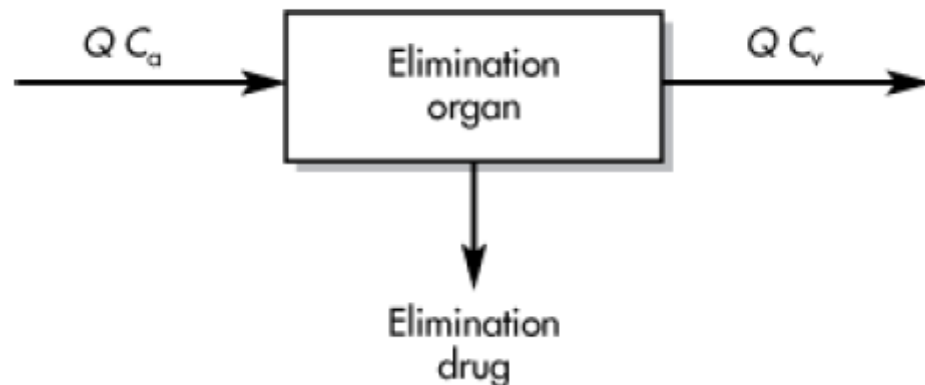
For any organ, **clearance may be defined as the fraction of blood volume containing drug that flows through the organ and is eliminated of drug per unit time. From this definition, clearance is the product of the blood flow (Q) to the organ, and the extraction ratio (ER). The ER is the fraction of drug extracted by the organ as drug passes through**.

$$\text{Clearance} = Q(ER) \qquad (6.15)$$

If the drug concentration in the blood (Ca) entering the organ is greater than the drug concentration of blood (Cv) leaving the organ, then some of the drug has been extracted by the organ. The ER is Ca - Cv divided by the entering drug concentration (Ca), as shown in Equation 6.16.

$$ER = \frac{C_a - C_v}{C_a} \qquad (6.16)$$

ER is a ratio with no units. The value of ER may range from 0 (no drug removed by the organ) to 1 (100% of the drug is removed by the organ). An ER of 0.25 indicates that 25% of the incoming drug concentration is removed by the organ as the drug passes through. Substituting for ER into Equation 6.15 yields

$$Cl = Q\left(\frac{C_a - C_v}{C_a}\right) \qquad (6.17)$$

The physiologic approach to clearance shows that clearance depends on the blood flow rate and the ability of the organ to eliminate drug, whereas the classical definitions of clearance is that a constant or static fraction of the volume in which the drug is contained is removed per unit time by the organ. However, clearance measurements using the physiologic approach require **invasive techniques to obtain measurements of blood flow and extraction ratio.** **The physiologic approach has been** used to describe hepatic clearance, which is discussed **under hepatic elimination.** More classical definitions of clearance have been applied to renal clearance because direct measurements of plasma drug concentration and urinary drug excretion may be obtained.

Compartment model

Static volume and first-order elimination is assumed.
Plasma flow is not considered. $Cl_T = k\, V_D$.

Physiologic model

Elimination
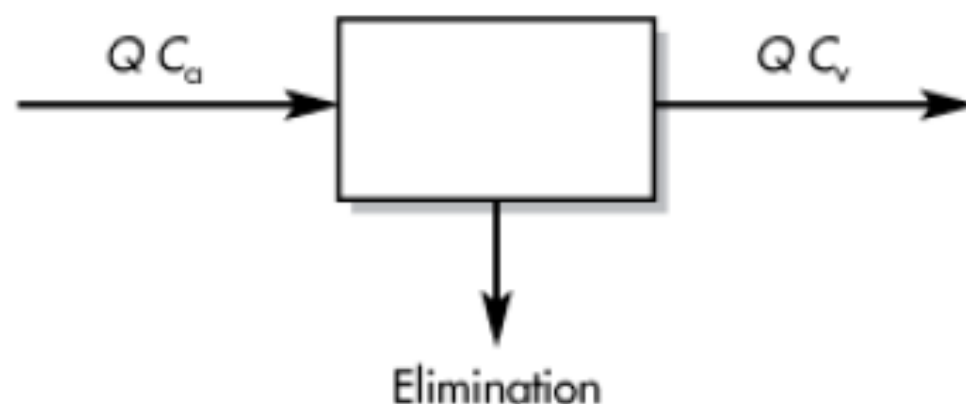
Clearance is the product of the plasma flow (Q) and the extraction ratio (ER).
Thus $Cl_T = Q\, ER$

RENAL CLEARANCE

Renal clearance, *Cl* R, is defined **as the volume of plasma that is cleared of drug per unit of time through the kidney.** Similarly, renal clearance may be defined as a **constant fraction of the *V*D in which the drug is contained that is excreted by the kidney per unit of time.** More simply, renal clearance is **defined as the urinary drug excretion rate (*dD*u /*dt*) divided by the plasma drug concentration (*C* p).**

$$Cl_{\mathrm{R}} = \frac{\text{excretion rate}}{\text{plasma concentration}} = \frac{dD_{\mathrm{u}}/dt}{C_{\mathrm{P}}} \qquad (6.20)$$

An alternative approach to obtaining Equation 6.20 is to consider the mass balance of drug cleared by the kidney and ultimately excreted in the urine.
For any drug cleared through the kidney, the rate of the drug passing through kidney (**via filtration, reabsorption, and/or active secretion**) must equal the rate of drug excreted in the urine.

Rate of drug passing through kidney = rate of drug excreted

$$Cl_{\mathrm{R}} \times C_{\mathrm{P}} = Q_{\mathrm{u}} \times C_{\mathrm{u}} \qquad (6.21)$$
$$\mathrm{mL/min} \times \mathrm{mg/mL} = \mathrm{mL/min} \times \mathrm{mg/mL}$$

where *Cl* R is renal clearance, *Cp* is plasma drug concentration, *Qu* is the rate of urine flow, and *Cu* is the urine drug concentration. Rearrangement of Equation 6.21 gives

$$Cl_R = \frac{Q_u C_u}{C_P} = \frac{\text{excretion rate}}{C_P} \tag{6.22}$$

because the excretion rate = $Qu\ Cu = dD_u/dt$, Equation 6.22 is the equivalent of Equation 6.20.

Comparison of Drug Excretion Methods
Renal clearance may be measured without regard to the physiologic mechanisms involved in this process. From a physiologic viewpoint, however, **renal clearance may be considered as the ratio of the sum of the glomerular filtration and active secretion rates less the reabsorption rate divided by the plasma drug concentration:**

$$Cl_R = \frac{\text{filtration rate + secretion rate} - \text{reabsorption rate}}{C_P}$$

$$\tag{6.23}$$

The actual renal clearance of a drug is not generally obtained by direct measurement. The clearance value for the drug is often **compared to that of a standard reference, such as inulin**, which is cleared completely through the kidney by glomerular filtration only. **The *clearance ratio,* which is the ratio of drug clearance to inulin clearance, may give an indication for the mechanism of renal excretion of the drug**. However, further renal drug excretion studies are necessary to confirm unambiguously the mechanism of excretion.

TABLE 6.3 Comparison of Clearance of a Sample Drug to Clearance of a Reference Drug, Inulin

CLEARANCE RATIO	PROBABLE MECHANISM OF RENAL EXCRETION
$\dfrac{Cl_{drug}}{Cl_{inulin}} < 1$	Drug is partially reabsorbed
$\dfrac{Cl_{drug}}{Cl_{inulin}} = 1$	Drug is filtered only
$\dfrac{Cl_{drug}}{Cl_{inulin}} > 1$	Drug is actively secreted

Hepatic elimination of drugs
Chapter 11

First-Order Elimination

The rate constant of elimination (k) is the sum of the first-order rate constant for **metabolism (k m) and the first-order rate constant for excretion (k e):**

$$k = k_e + k_m \qquad (11.1)$$

In practice, the excretion rate constant (k_e) is easily evaluated for drugs that are primarily renally excreted.

Nonrenal drug elimination is usually assumed to be due for the most part to hepatic metabolism, though metabolism or degradation can occur in any organ or tissue that contains metabolic enzymes or is in a degradative condition. Therefore, the rate constant for metabolism (k_m) is difficult to measure directly and is usually found from the difference between k and ke.

$$k_m = k - k_e$$

A drug may be biotransformed to several metabolites (metabolite A, metabolite B, metabolite C, etc); thus, the metabolism rate constant (k m) is the sum of the rate constants for the formation of each metabolite:

$$k_m = k_{mA} + k_{mB} + k_{mC} + \cdots + k_{mI} \qquad (11.2)$$

The relationship in this equation assumes that the process of **metabolism is first order and that the substrate (drug) concentration is very low**. Drug concentrations at therapeutic plasma levels for most drugs are much lower than the Michaelis-Menten constant, K M, and do not saturate the enzymes involved in metabolism.

Nonlinear Michaelis-Menten kinetics must be used when drug concentrations saturate metabolic enzymes.

Because these rates of elimination at low drug concentration are considered first-order processes, the percentage of total drug metabolized may be found by the following expression:

$$\% \text{ drug metabolized} = \frac{k_m}{k} \times 100 \qquad (11.3)$$
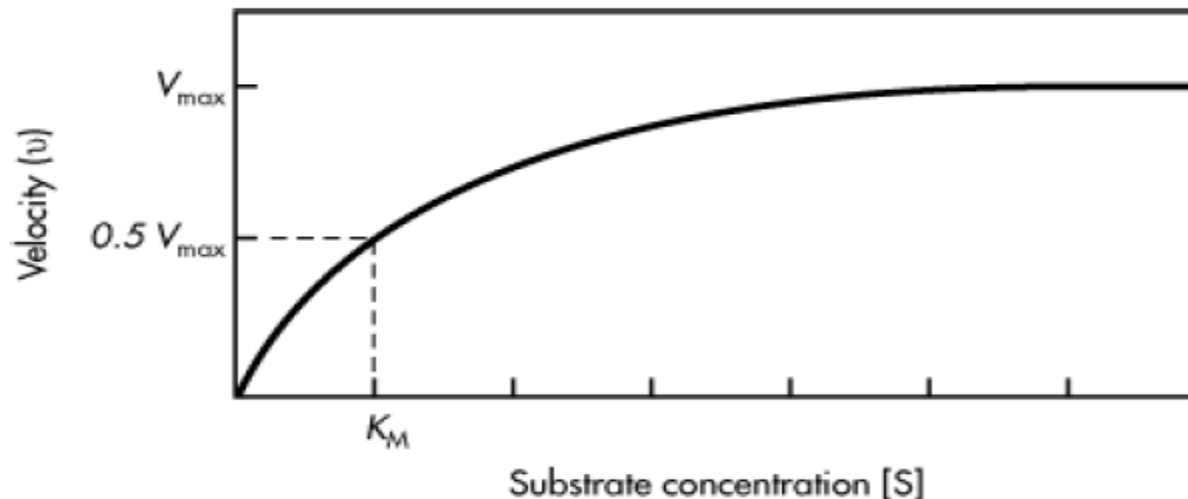
Fraction of Drug Excreted Unchanged (f e) and Fraction of Drug Metabolized (1-f e)

For most drugs, **the *fraction of dose eliminated unchanged (fe)* and the fraction of dose eliminated as metabolites can be determined**. For example, consider a drug that has two major metabolites and is also eliminated by renal excretion. Assume that 100 M of the drug were given to a patient and the drug was completely absorbed (bioavailability factor F = 1). A complete (cumulative) urine collection was obtained, and the quantities in parentheses in indicate the amounts of each metabolite and unchanged drug that were recovered. The overall elimination half-life (t 1/2) for this drug was 2.0 hours (k = 0.347 hr- 1).
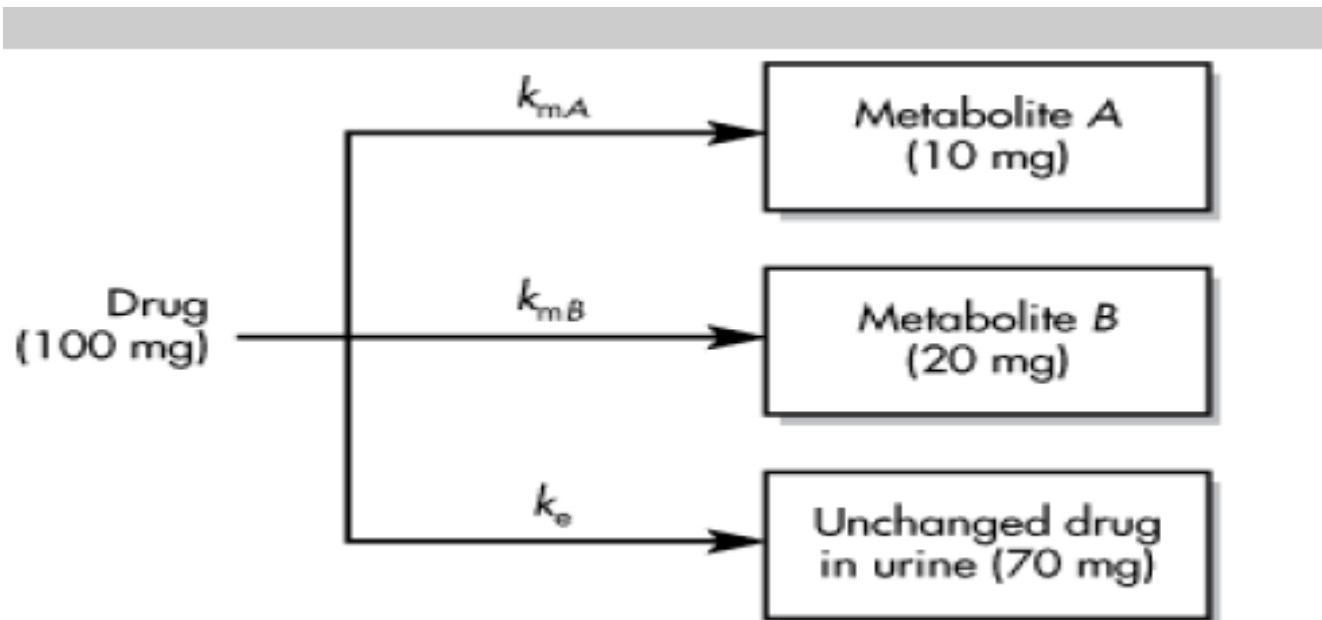
To determine the renal excretion rate constant, the following relationship is used:

$$\frac{k_e}{k} = \frac{\text{total dose excreted in urine}}{\text{total dose absorbed}} = \frac{D_u^\infty}{FD_0} \qquad (11.4)$$

where $D^\infty u$ is the total amount of unchanged drug recovered in the urine. In this example, k_e is found by proper substitution into Equation 11.4:

$$k_e = (0.347) \, \frac{70}{100} = 0.243 \, \text{hr}^{-1}$$

To find the percent of drug eliminated by renal excretion, the following approach may be used:

$$\% \text{ drug excretion} = \frac{k_e}{k} \times 100 = \frac{0.243}{0.347} \times 100 = 70\%$$

For many drugs, the literature has approximate values for the fraction of drug (f_e) excreted unchanged in the urine. In this example, the value of k_e may be estimated from the literature values for the elimination half-life of the drug and f_e. Assuming that the elimination half-life of the drug is 2 hours and f_e is 0.7, then k_e is estimated by Equation 11.5.

$$k_e = f_e k \qquad (11.5)$$

Because $t_{1/2}$ is 2 hours, k is 0.693/2 hr = 0.347 hr⁻¹, and k_e is

$$k_e = (0.7)(0.347) = 0.243 \, \text{hr}^{-1}$$

HEPATIC CLEARANCE

The clearance concept may be applied to any organ and is used as a measure of drug elimination drug by the organ. *Hepatic clearance* **may be defined as the volume of blood that perfuses the liver and is cleared of drug per unit of time**. As discussed in , total body clearance is composed of all the clearances in the body:

$$Cl_T = Cl_{nr} + Cl_r \qquad (11.6)$$

where Cl T is total body clearance, Cl nr is nonrenal clearance (often equated with hepatic clearance, Clh), and Clr is renal clearance. Hepatic clearance (Cl h) is also equal to total body clearance (Cl T) minus renal clearance (Cl R) assuming no other organ metabolism, as shown by rearranging Equation 11.6 to

ENZYME KINETICS

The process of ***biotransformation* or *metabolism* is the enzymatic conversion of a drug** to a metabolite. In the body, **the metabolic enzyme concentration is constant at a given site**, and the drug (substrate) **concentration may vary**. When the drug concentration is **low** relative to the enzyme concentration, there are **abundant** enzymes to **catalyze the reaction**, and the rate of metabolism is a **first-order process**. **Saturation** of the enzyme occurs when the drug concentration is **high**, all the enzyme molecules become complexed with drug, and the reaction rate is at a maximum rate; the rate process then becomes **a zero-order process**. The ***maximum reaction rate* is known as *V* max**, and the **substrate or drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter KM.** These two parameters determine the profile of a simple enzyme reaction rate at various drug concentrations. The relationship of these parameters is described by the *Michaelis-Menten* equation.
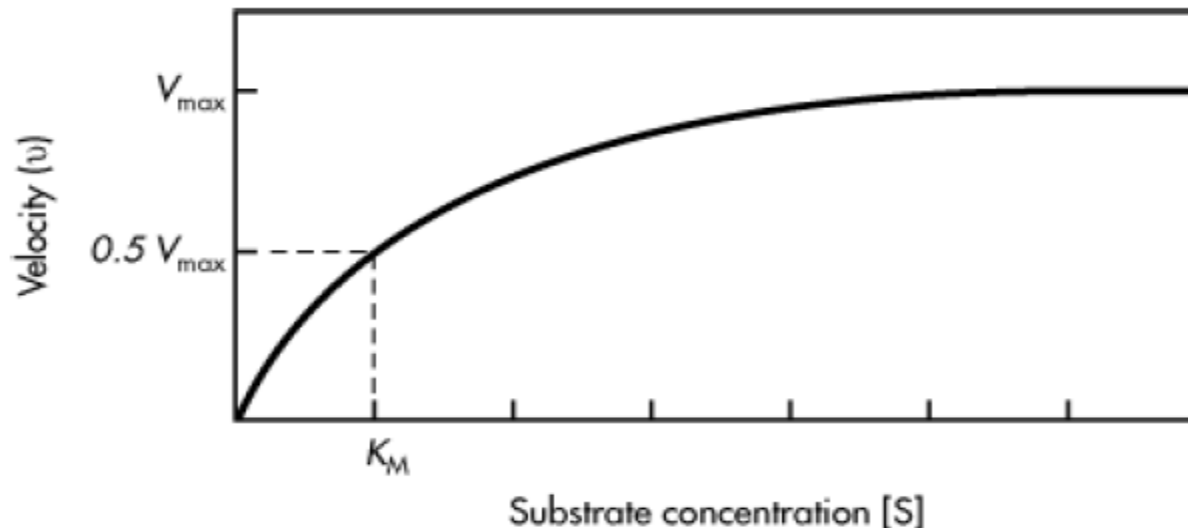
Enzyme kinetics generally considers that **1 mole of drug interacts with 1 mole of enzyme** to form an **enzyme-drug (ie, enzyme-substrate) intermediate**. The enzyme-drug intermediate further reacts to yield a reaction product or a drug metabolite. The rate process for drug metabolism is described by the Michaelis-Menten equation , which assumes that the rate of an enzymatic reaction is dependent on the concentrations of both the enzyme and the drug and that an energetically favored drug-enzyme intermediate is initially formed, followed by the formation of the product and regeneration of the enzyme.

Therefore, the velocity of metabolism is given by the equation

$$v = \frac{V_{max}[D]}{[D] + K_M} \qquad (11.20)$$

Equation 11.20 describes the **rate of metabolite formation**, or the Michaelis-Menten equation. The maximum velocity (**V max**) **corresponds to the rate when all of the available enzyme is in the form of the drug-enzyme (ED) intermediate**. At Vmax, the drug (substrate) concentration is in excess, and the forward reaction, k 3[ED], is dependent on the availability of more free enzyme molecules. The *Michaelis constant,K* M, is defined as the substrate concentration when the velocity (v) of the reaction is equal to one-half the maximum velocity, or 0.5V max. The KM is a useful parameter that reveals the concentration of the substrate at which the reaction occurs at half V max. **In general, for a drug with a large KM, a higher concentration will be necessary before saturation is reached**.

Relationship between Blood Flow, Intrinsic Clearance, and Hepatic Clearance

For example, factors that affect the hepatic clearance of a drug include (1**) blood flow to the liver, (2) intrinsic clearance, and (3) the fraction of drug bound to protein.**

A change in liver blood flow may alter hepatic clearance and _F'_. A large blood flow may deliver enough drug to the liver to alter the rate of metabolism. In contrast, a small blood flow may decrease the delivery of drug to the liver and become the rate-limiting step for metabolism.

In experimental animals, **the blood flow (_Q_) to the liver**, the drug concentration in the artery (_Ca_), and the drug concentration in the vein (_Cv_) may be measured. As the arterial blood containing drug perfuses the liver, a certain portion of the drug is removed by metabolism and/or biliary excretion. Therefore, the drug concentration in the vein is less than the drug concentration in the artery. An extraction ratio may be expressed as 100% of the drug entering the liver less the relative concentration (_C_ v/_C_ a) of drug that is removed by the liver.

$$ER = \frac{C_a - C_v}{C_a} \qquad\qquad (11.40)$$

The ER may vary from 0 to 1.0. An ER of 0.25 means that 25% of the drug was removed by the liver. If both the ER for the liver and the blood flow to the liver are known, then hepatic clearance may be calculated by the following expression:

$$Cl_h = \frac{Q(C_a - C_v)}{C_a} = Q \times ER \qquad (11.41)$$

For some drugs (such as isoproterenol, lidocaine, and nitroglycerin), the extraction ratio is high (greater than 0.7), and the drug is removed by the liver almost as rapidly as the organ is perfused by blood in which the drug is contained. **For drugs with very high extraction ratios, the rate of drug metabolism is sensitive to changes in hepatic blood flow**. Thus, an increase in blood flow to the liver will increase the rate of drug removal by the organ. Propranolol, a -adrenergic blocking agent, **decreases hepatic blood flow by decreasing cardiac output**. In such a case, the drug decreases its own clearance through the liver when given orally. Many drugs that demonstrate first-pass effects are drugs that have high extraction ratios with respect to the liver.

Intrinsic clearance (*Cl* int) is used **to describe the total ability of the liver to metabolize a drug in the absence of flow limitations, reflecting the inherent activities of the mixed-function oxidases and all other enzymes.**
Intrinsic clearance is a distinct characteristic of a particular drug, and as such, it reflects the inherent ability of the liver to metabolize the drug. Intrinsic clearance may be shown to be analogous to the ratio Vmax/K M for a drug that follows Michaelis-Menten kinetics.
Hepatic clearance is a concept for characterizing drug elimination based on both blood flow and the intrinsic clearance of the liver, as shown in Equation 11.42.

$$Cl_h = Q\frac{Cl_{int}}{Q + Cl_{int}} \qquad (11.42)$$

When the blood flow to the liver is constant, hepatic clearance is equal to the product of blood flow (Q) and the extraction ratio (ER) Equation 11.41. However, the hepatic clearance of a drug is not constant. **Hepatic clearance changes with blood flow and the intrinsic clearance of the drug, as described in Equation** 11.42.

For drugs with low extraction ratios (eg, theophylline, phenylbutazone, and procainamide), the hepatic clearance is less affected by hepatic blood flow. Instead, these drugs are more affected by the intrinsic activity of the mixed-function oxidases. Describing clearance in terms of all the **factors in a physiologic model allow drug clearance to be estimated when physiologic or disease condition causes changes in blood flow or intrinsic enzyme activity. Smoking, for example, can increase the intrinsic clearance for the metabolism of many drugs.**
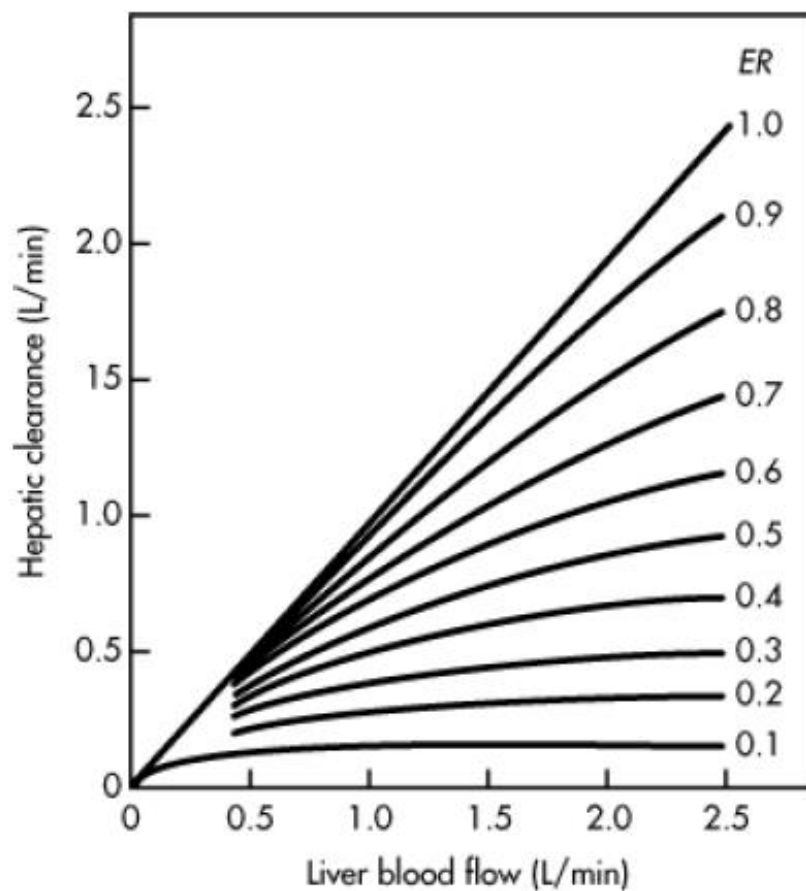
The relationship between liver blood flow and total hepatic clearance for drugs with varying extraction rates (*ER*).

For example, the elimination half-life of theophylline varies from 3 to 9 hours. This variation in t 1/2 is thought to be due to genetic differences in intrinsic hepatic enzyme activity. Moreover, the elimination half-lives of these same drugs are also affected by enzyme induction, enzyme inhibition, age of the individual, nutritional, and pathologic factors.

Clearance may also be expressed as the rate of drug removal divided by plasma drug concentration:

$$Cl_h = \frac{\text{rate of drug removed by the liver}}{C_a} \qquad (11.43)$$

Because the rate of drug removal by the liver is usually the rate of drug metabolism, Equation 11.43 may be expressed in terms of hepatic clearance and drug concentration entering the liver (C a):

$$\text{Rate of liver drug metabolism} = Cl_h C_a \qquad (11.44)$$

HEPATIC CLEARANCE OF A PROTEIN-BOUND DRUG: RESTRICTIVE AND NONRESTRICTIVE CLEARANCE FROM BINDING

It is generally assumed that **protein-bound** drugs are not easily **metabolized** (*restrictive clearance*), while **free (unbound)** drugs are subject to metabolism. **Protein-bound** drugs do **not easily diffuse through cell membranes, while free drugs can reach the site of the mixed-function oxidase enzymes easily**. Therefore, an increase in the free drug concentration in the blood will make more drug available for hepatic extraction. The concept is discussed under restrictive and nonrestrictive clearance of protein-bound drugs.

Most drugs are *restrictively* cleared-for example, diazepam, quinidine, tolbutamide, and warfarin. The clearance of these drugs is proportional to the fraction of unbound drug (fu). **However, some drugs, such as propranolol, morphine, and verapamil, are *nonrestrictively* extracted by the liver regardless of drug bound to protein or free.** Kinetically, a drug is **nonrestrictively cleared if its hepatic extraction ratio (ER) is greater than the fraction of free drug (fu), and the rate of drug clearance is unchanged when the drug is displaced from binding.** Mechanistically, the protein binding of a drug is a reversible process and for a nonrestrictively bound drug, the free drug gets "stripped" from the protein during the process of drug metabolism. The elimination half-life of a nonrestrictively cleared drug is not significantly affected by a change in the degree of protein binding. This is an analogous situation to a protein-bound drug that is actively secreted by the kidney.

For a drug with restrictive clearance, the relationship of blood flow, intrinsic clearance, and protein binding is

$$Cl_h = Q\left(\frac{f_u Cl'_{int}}{Q + f_u Cl'_{int}}\right) \qquad (11.45)$$

where f_u is the fraction of drug unbound in the blood and Cl'_{int} is the intrinsic clearance of free drug. Equation 11.45 is derived by substituting $f_u Cl'_{int}$ for Cl_{int} in Equation 11.42. From Equation 11.45, **when Cl'_{int} is very small in comparison to hepatic blood flow (ie, Q > Cl'_{int}), then Equation 11.46 reduces to Equation 11.47.**

$$Cl_h = \frac{Q f_u Cl'_{int}}{Q} \qquad (11.46)$$

$$Cl_h = f_u Cl'_{int} \qquad (11.47)$$

As shown in Equation 11.47, a change in Cl'_{int} or f_u will cause a proportional change in Cl_h for drugs with protein binding.
In the case where Cl'_{int} for a drug is very large in comparison to flow (Cl'_{int} >> Q), Equation 11.48 reduces to Equation 11.49.

$$Cl_h = \frac{Q f_u Cl'_{int}}{f_u Cl'_{int}} \qquad (11.48)$$

$$Cl_h \approx Q \qquad (11.49)$$

Thus, for drugs with a very high Cl'_{int}, Cl_h is dependent on hepatic blood flow, and independent of protein binding.