DRUG ELIMINATION

RENAL EXCRETION
BILIARY EXCRETION
MAMMARY, SALIVARY AND PULMONARY EXCRETION
DRUG ELIMINATION

- Irreversible removal of drug from the body by all routes of elimination
- Two major components: excretion and biotransformation
- Drug excretion: removal of the intact drug
- Non volatile drugs are excreted by: renal, sweat, saliva, milk excretion
- Volatile drugs are excreted by pulmonary excretion via the lungs into expired air
RENAL DRUG EXCRETION

THE KIDNEY

• is the main excretory organ for the removal of metabolic waste products and plays a major role in maintaining the normal fluid volume and electrolyte composition in the body

• To maintain the salts and water balance: excretes excess electrolytes, water, waste products and conserving solutes necessary for proper body function

• Two endocrine functions: (1) secretion of renin – regulates blood pressure; (2) secretion of erythropoietin – stimulates red blood cell production
Kidney – Urinary System

- Renal artery
- Cortex
- Medulla
- Renal vein
- Renal pelvis

RIGHT KIDNEY

LEFT KIDNEY (cut surface)

Ureters

Direction of urine flow

Urinary bladder
Anatomy of the kidney 2
Anatomic Consideration

- The outer zone of the kidney: **cortex**
- The inner region: **medulla**
- The basic functional unit - **nephron**:  
  - responsible for the removal of metabolic waste  
  - maintenance of water and electrolyte balance
- **Glomerulus**, start in the cortex
- **Cortical nephrons** have **short loops of Henle**, remain in the cortex
- **Juxta medullary nephrons** have **long loops of Henle** that extend into the medulla
- The longer the loops of Henle the greater the ability of nephron to reabsorb water, results in more concentrated urine
Figure 6-2. Longitudinal section of the kidney, illustrating major anatomical features and blood vessels. (From West, 1985, with permission.)

Figure 6-3. Cortical and juxtamedullary nephrons and their vasculature.
Anatomic of Kidney 3

- **Bowman’s Capsule (Glomerular)**
  - Filtration of smaller molecules

- **Proximal Tubule**
  - Active secretion of weak electrolytes (especially acids) and reabsorption of water

- **Distal Tubule**
  - Passive transfer of lipid soluble drugs and reabsorption of water

- **Loop of Henle**
  - Reabsorption of water

- **Urine**

**One Nephron of the Kidney**
Blood Supply

• 0.5% of the total body weight and receive ± 20-25% cardiac output, blood supply via renal artery, subdivides into interlobar arteries penetrating within the kidney and and branching further into afferent arterioles

• Each afferent arteriole carries blood toward a single nephron into the glomerular portion of the nephron (Bowman’s capsule)

• From the capillaries (glomerulus) within Bowman’s capsule, the blood flows out via the efferent arterioles – second capillary network that surround the tubules (peritubule capillaries and vasa recti), including the loop of Henle, where some water is reabsorbed
Renal Blood Flow - RBF

• Is the volume of blood flowing through the renal vasculature per unit time ≈ 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 – important factor in the rate of drug filtration at the glomerulus

• RPF = RBF − (RBF x Hct)  
RPF = RBF (1-Hct)  

• Hct = hematocrit = the fraction of blood cells in the blood ≈ 45% of the total blood volume or 0.45

• RPF = 1.2 -(1.2x0.45) = 0.66 L/min or 660 ml/min ≈ 950 L/day

• GFR - Glomerular Filtration Rate ≈ 125 ml/min in adults or about 20% of the RPF

• GFR/RPF = Filtration Fraction
Regulation of Renal Blood Flow

- Blood flow to organ $\propto$ arteriovenous pressure difference (perfusion pressure) across the vascular bed and indirectly proportional to the vascular resistance.
- The normal renal arterial pressure $\approx 100$ mm Hg and falls to $\approx 45-60$ mm Hg in the glomerulus (glomerular capillary hydrostatic pressure). This pressure difference is probably due to increasing vasculature resistance provided by the small diameters of the capillary network. Thus GFR is controlled by the changes in the glomerular capillary hydrostatic pressure.
- In the normal kidney, RBF and GFR remain constant even with large differences in mean systemic blood pressure. **Autoregulation** – the maintenance of constant blood flow in the presence of large fluctuations in arterial blood pressure.
- Because autoregulation maintains a relatively constant blood flow, the filtration fraction (GFR/RPF) also remains fairly constant in this pressure range.
Regulation of Blood Flow

[Diagram showing blood flow with pressure measurements: 100 mm Hg, 18 mm Hg, 13 mm Hg, 10 mm Hg, 60 mm Hg, 8 mm Hg, 0 mm Hg, and intersstitial fluid pressure 6 mm Hg.]
Drugs which are non volatile, water soluble, low MW (<500), are eliminated by renal excretion. The processes to which the drug excreted via kidney include:

- **Glomerular Filtration**
- **Active Tubular Secretion**
- **Tubular Reabsorption**

**Glomerular Filtration**
- GFR ± 125 ml/min, about 180 L/day fluid are filtered through the kidney, average urine volume 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 exception of protein and protein-bound drug, 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 in various sites, including the proximal tubule, loops of Henle, and distal tubule. Both active reabsorption and secretion mechanism are involved.
- The urine volume is reduced and urine generally contains a high concentration of metabolic wastes and eliminated drug products.
- The major driving force for GF is the hydrostatic pressure within the glomerular capillaries. The kidney receive a large blood supply – 25% of the cardiac output via renal artery, with very little decrease in the hydrostatic pressure.
- Undissociated and dissociated drugs, protein bound not
- Unidirectional process
Glomerular Filtration Rate

- Is measured by using a drug that is eliminated by filtration only: **inulin** and **creatinin**. Clearance of inulin = GFR = 125-130 mL/min. GFR ~ body surface area

- GFR ~ free/non protein-bound concentration in the plasma. Cf increases – GFR increases proportionally – increasing renal drug clearance for some drugs
# Quantitative Aspects of Urine Formation

<table>
<thead>
<tr>
<th>Substance</th>
<th>Filtered</th>
<th>Reabsorbed</th>
<th>Secreted</th>
<th>Excreted</th>
<th>Percent Reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ion</td>
<td>26,000</td>
<td>25,850</td>
<td>150</td>
<td></td>
<td>99.4</td>
</tr>
<tr>
<td>Chloride ion</td>
<td>18,000</td>
<td>17,850</td>
<td>150</td>
<td></td>
<td>99.2</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>4,900</td>
<td>4,900</td>
<td>0</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>870</td>
<td>460</td>
<td>410</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>Glucose mM</td>
<td>800</td>
<td>800</td>
<td>0</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Water mL</td>
<td>180,000</td>
<td>179,000</td>
<td>1000</td>
<td></td>
<td>99.4</td>
</tr>
<tr>
<td>Hydrogen ion</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium ion</td>
<td>900</td>
<td>900</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Active Tubular Secretion

- Is an active transport process – carrier mediated system that requires energy input – drug is transported against concentration gradient, capacity limited and may be saturated – competitively
- Two active renal secretion: weak acid and weak bases. Competition between probenecid and penicillin in the same carrier system (weak acid)
- Dependent on renal plasma flow
- p-amino-hippuric acid (PAH) and iodopyraset (Diodrast) – filtered by glomeruli and secreted by the tubular cells. 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 reflects the effective renal plasma flow (ERPF), varies from 425-650 mL/min
- For drugs excreted only by GF, t1/2 elimination may change markedly in accordance with the binding affinity of the drug to plasma protein
- In contrast, drug protein binding has very little effect on the t1/2 elimination of the drug excreted mostly by active secretion.
- Drug protein binding is reversible – drug bound rapidly dissociates as free drug and secreted by the kidney. **Penicillin is extensively bound but t1/2 elimination 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 passive process
- If the drug is completely reabsorbed, Clearance = 0; drugs partially reabsorbed – Clearance < GFR of 125-130 mL/min
- Reabsorption of acids or weak bases is influenced by pH of the fluid in the renal tubule (urine pH) and pKa of the drug – both determine the dissociated and undissociated drug (more lipid soluble and greater membrane permeability) – this undiss drug is easily reabsorbed back into the body
- Reabsorption can significantly reduce the amount of drug excreted depending on the urine pH and pKa of the drug (=constant). The urine pH vary from 4.5-8 depending on diet, pathophysiology, and drug intake
- Vegetables, fruits, high carbohydrate diet – urine pH higher; high protein diets result in lower urine pH
- Ascorbic acid – acidify the urinary pH; antacid – alkalinize the urinary pH
- IV fluids contains bicarbonate or ammonium chloride – acid-base therapy: changes the urinary pH drastically and alter drug reabsorption and drug excretion by the kidney
For weak acids Henderson-Hesselbalch equation:

\[ \text{pH} = \text{pKa} + \log \frac{[\text{ionized}]}{[\text{nonionized}]} \quad (3) \]

\[ \frac{[\text{ionized}]}{[\text{nonionized}]} = 10^{\text{pH}-\text{pKa}} \quad (4) \]

Fraction of drug ionized =

\[ \frac{[\text{ionized}]}{[\text{ionized}]+ [\text{nonionized}]} \quad (5) \]

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

\[ = 10^{\text{pH}-\text{pKa}} / 1 + 10^{\text{pH}-\text{pKa}} \]

For weak acidic drugs with pKa values from 3-8, a change in urinary pH affects the extent of dissociation

For a weak base drug:

\[ \text{pH} = \text{pKa} + \log \frac{[\text{nonionized}]}{[\text{ionized}]} \quad (6) \]

Fraction of drug ionized =

\[ 1 + \frac{10^{\text{pH}-\text{pKa}}}{10^{\text{pH}-\text{pKa}}} \quad (7) \]

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

Distribution of drug between urine and plasma:

Weak acids: \[ \text{U/P} = 1 + 10^{\text{pH urine}-\text{pKa}} / 1 + 10^{\text{pH plasma}-\text{pKa}} \quad (8) \]

Weak bases: \[ \text{U/P} = 1 + 10^{\text{pKa}-\text{pH urine}} / 1 + 10^{\text{pKa}-\text{pH plasma}} \quad (9) \]
Effect of Urinary pH on the Ionization of Drugs

<table>
<thead>
<tr>
<th>pH of urine</th>
<th>% of drug ionized at pKa=3</th>
<th>% of drug ionized at pKa=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>100</td>
<td>99.6</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>50.0</td>
</tr>
<tr>
<td>4</td>
<td>91</td>
<td>9.1</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Drug elimination is the process of drug clearance from a well-stirred compartment containing uniform drug distribution.

Clearance is the process of drug elimination from the body or from a single organ without identifying the individual processes involved.

Clearance is the volume of fluid cleared of drug from the body per unit of time.

Units for clearance are mL/minute or L/hr.

All drugs are dissolved and distributed in the fluids of the body (volume of distribution).

Clearance applies to all elimination rate processes, regardless of the mechanism for elimination.

For 1st-order elimination process, clearance is constant, whereas drug elimination rate is not constant.
Alternatively, $Cl_T$ may be defined as the rate of drug elimination divided by the plasma drug concentration. Drug elimination in this case is the volume of plasma eliminated of drug per unit time. This is to calculate clearance based on plasma drug concentration data.

- $Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration}} (C_P)$  \hspace{1cm} (10)
- $Cl_T = \frac{dD_E}{dt} = \frac{\mu g}{\text{min}} = \text{mL/min}$ \hspace{1cm} (11)
- $D_E = \text{amount of drug eliminated and } \frac{dD_E}{dt} \text{ is the rate of elimination}$
- Rearrangement gives:
  Elimination Rate $= \frac{dD_E}{dt} = C_P \cdot Cl_T$ \hspace{1cm} (12)
- 1st-order elimination rate, $\frac{dD_E}{dt}$, is equal to $kD_B$ or $k C_P V_D$
- $Cl_T = k C_P V_D = k V_D$ \hspace{1cm} (13)
- Clearance is constant as long as the rate of drug elimination is 1st-order process
- Renal Cle $= k_e V_D$; Lung Clea $= k_1 V_D$; Hepatic Clea $= k_m V_D$
- Body Clearance $= k_e V_D + k_1 V_D + k_m V_D = (k_e + k_1 + k_m) V_D$
Clearance Models

- Compartment model \( (\text{Cl}_T = k \text{ VD}) \), Physiologic model \( (\text{CL}_T = \text{Q ER}) \) and Model Independent \( (\text{Cl}_T = \text{Dose}/[\text{AUC}]) \)
- Many organ in the body have the capacity for drug elimination including excretion, metabolism; particularly organ: kidney and liver
- Physiologic pharmacokinetic models are based on drug clearance through individual organ/tissue group
- 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: Clearance = blood flow (Q) times Extraction Ratio = Q x ER
  \[ \text{ER} = \frac{(\text{Ca-Cv})}{\text{Ca}} \text{ ranging from 0-1} \]  \[ \text{Clearance} = \text{Q} \left[ \frac{(\text{Ca-Cv})}{\text{Ca}} \right] \text{, depends on blood flow and the ability of the organ to eliminate drug} \]
- From physiologic approach: needs invasive techniques to obtain measurements of blood flow and 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.

- *Renal Clearance*, may be defined as a constant fraction of the $V_d$ in which the drug is contained that is excreted by kidney per unit of time.

- *Renal Clearance*, is defined as the urinary drug excretion rate ($dD_U/dt$) divided by the plasma drug concentration ($C_P$).

$$Cl_R = \frac{\text{excretion rate}}{\text{plasma concentration}} = \frac{dD_U/dt}{C_P} \quad (18)$$
• 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

\[ \frac{C_I R \times C_P}{Q_U \times C_U} = \frac{Q_U}{C_U} = \text{excretion rate} \]

(19)

\[ mL/min \times mg/mL = mL/min \times mg/mL \]

\[ C_I R = Q_U \times C_U = \text{excretion rate} \]  

(20)

\[ C_P \quad C_P \]

Excretion rate = \( Q_U \times C_U = dD_U/dt \)
Comparison of Drug Excretion Method

- From a physiologic viewpoint:

\[
\frac{Cl}{R} = \frac{\text{filtration rate + secretion rate - reabsorption rate}}{C_P} \quad (21)
\]

- 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.

- A method to quantify renal drug excretion is to consider the kinetic nature of the elimination process.

- Some of the detailed steps may be omitted or simplified, for example, assume that \( V_D \) and \( C_P \) is changing after an IV bolus injection.
Comparison of Clearance of a Sample Drug to Clearance of a Reference

<table>
<thead>
<tr>
<th>Clearance Ratio</th>
<th>Probable Mechanism of Renal Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{C_l_{drug}}{C_l_{\text{inulin}}} &lt; 1 )</td>
<td>Drug is partially reabsorbed</td>
</tr>
<tr>
<td>( \frac{C_l_{drug}}{C_l_{\text{inulin}}} = 1 )</td>
<td>Drug is filtered only</td>
</tr>
<tr>
<td>( \frac{C_l_{drug}}{C_l_{\text{inulin}}} &gt; 1 )</td>
<td>Drug is actively secreted</td>
</tr>
</tbody>
</table>
# Urinary Drug Excretion Rate

<table>
<thead>
<tr>
<th>Time(min)</th>
<th>$C_P$ (µg/mL)</th>
<th>Excretion Rate (µg/min) (Drug filtered by GFR/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$(C_P)_0$</td>
<td>$(C_P)_0 \times 125$</td>
</tr>
<tr>
<td>1</td>
<td>$(C_P)_1$</td>
<td>$(C_P)_1 \times 125$</td>
</tr>
<tr>
<td>2</td>
<td>$(C_P)_2$</td>
<td>$(C_P)_2 \times 125$</td>
</tr>
<tr>
<td>$t$</td>
<td>$(C_P)_t$</td>
<td>$(C_P)_t \times 125$</td>
</tr>
</tbody>
</table>

*Assumes that the drug is excreted by filtration only and that the GFR is 125mL/min*
Filtration Only

• Amount of drug filtered at any time (t) will always be $C_P \times \text{GFR}$. Like inulin, if the $C/\text{R}$ is by GF only, $C/\text{R} = \text{GFR}$. Otherwise $C/\text{R}$ is the process by which the drug is cleared through the kidney, including any combination of filtration, reabsorption, and active secretion.

• The quantity of drug excreted per minute (≈the renal clearance of the drug) is always $C_P \times$ constants (e.g. 125 mL/min)
• The GFR may be treated as a first-order process relating to $C_P$

$$dD_U/dT = k_e V_D C_P \text{ (compartment)} \quad (22)$$

$$dD_u/dt = C_l R C_P \text{ (physiologic)} \quad (23)$$

• Eq.(22) = Eq.(23):

$$k_e V_D C_P = C_l R C_P$$

$$k_e = \frac{C_l R}{V_D} \quad (24)$$

• The Eq.(24) shows that in the absence of other drug elimination process, the excretion rate constant is a fractional constant reflecting the volume pumped out per unit time due to GFR relative to the volume of the body compartment ($V_D$)
Filtration and Reabsorption

- For a drug with a reabsorption fraction of $fr$, the drug excretion rate is reduced and Eq.(23) is restated into Eq.(25)

\[
\frac{dD_U}{dt} = Cl_R (1-fr)C_P \quad (25)
\]

\[
\frac{dD_U}{dT} = k_e V_D C_P \quad (22)
\]

\[
Cl_R (1-fr)C_P = k_e V_D C_P
\]

\[
k_e = Cl_R (1-fr) / V_D
\]

- In this case, the excretion rate constant is affected by the reabsorption fraction ($fr$) and the GFR.
- Because these two parameters remain constant, the general adoption of a first-order elimination process to describe renal drug excretion is a reasonable approach
Filtration and Active Secretion

- For drug that primarily filtered and secreted, with negligible reabsorption, the overall excretion rate will exceed GFR
- At low drug plasma concentration, active secretion is not saturated, and the drug is excreted by filtration and active secretion
- At high concentration, the percentage of drug excreted by active secretion decreases due to saturation. Clearance decrease because excretion rate decrease and because the total excretion rate of the drug increases to the point where it is approximately equal to the filtration rate
Determination of Renal Clearance

Graphical Methods

• The clearance is given by the slope of the curve obtained by plotting the rate of drug excretion in urine \((dD_U/dt)\) against \(C_P\) (Eq.26)

• For a drug that is excreted rapidly, \(dD_U/dt\) is large, the slope is steeper, and clearance is greater (line A in Figure)

• For a drug that is excreted slowly through the kidney, the slope is smaller (line B in Figure)
Rate of Drug Excretion vs Concentration of Drug in Plasma
Drug A (line A) has a higher clearance than B (line B)
• $Cl_R = \text{excretion rate} = \frac{dD_U}{dt}$ \hfill (18)
  
  plasma concentration $C_p$

• Multiplying both sides by $C_p$ gives:

• $Cl_R \cdot C_p = \frac{dD_U}{dt}$ \hfill (26)

• Rearranging and integrating,

\[ \int_0^{D_U} dD_U = \int_0^t C_p dt \] \hfill (27)

\[ [D_U]_0^t = Cl_R[AUC]_0^t \] \hfill (28)

• Plot cumulative drug excreted in the urine vs AUC. Renal clearance is obtained from the
Cumulative Drug Excretion vs AUC
The slope = $\frac{C}{R}$

Slope = Renal Clearance ($C/R$)

$D_u$

$(AUC)_{o-t}$
• By plotting cumulative drug excreted in the urine from \( t_1 \) to \( t_2 \), \([\text{DU}]_{t_1-t_2}\) vs \((\text{AUC})_{t_1-t_2}\), the similar equation can be obtained

\[
\int_{D_U}^{D_U^2} dD_U = Cl_R \int_{t_1}^{t_2} C_p dt \quad (29)
\]

\[
[D_U]_{t_1}^{t_2} = Cl_R [AUC]_{t_1}^{t_2} \quad (30)
\]

The slope = Renal Clearance
Determination of Renal Clearance
Model-Independent Methods

• Clearance may also be estimated by a single calculation from \([AUC]_0^\infty\), the total amount of drug absorbed, \(D_0\), and the total amount of drug excreted in the urine, \(D_U^\infty\).

• If a single drug injection is given to a patient and the \([AUC]_0^\infty\) is obtained from the plasma drug level-time curve, then the total body clearance is estimated by

\[
Cl_T = \frac{D_0}{[AUC]_0^\infty} \quad (31)
\]
• If the total amount of drug excreted in the urine, $D_U^\infty$, has been obtained, then renal clearance is calculated by

$$Cl_T = \frac{D_U^\infty}{[AUC]^\infty_0}$$  \hspace{1cm} (32)

• Clearance can also be calculated from fitted parameters. If $V_D$ and elimination constants are known, $Cl_T$, $Cl_R$ and $Cl_h$ can be calculated according to following expressions:

- $Cl_T = k \cdot V_D$  \hspace{1cm} (33)
- $Cl_R = k_e \cdot V_D$  \hspace{1cm} (34)
- $Cl_h = k_m \cdot V_D$  \hspace{1cm} (35)
• Total body clearance ($C_{\text{T}}$) is equal to the sum of renal clearance ($C_{\text{R}}$) and hepatic clearance ($C_{\text{h}}$) and is based on the concept that the entire body acts as a drug-eliminating system

- $C_{\text{T}} = C_{\text{R}} + C_{\text{h}}$ \hspace{1cm} (36)
- $k \ V_{\text{D}} = k_{\text{e}} \ V_{\text{D}} + k_{\text{m}} \ V_{\text{D}}$ \hspace{1cm} (37)
- $k = k_{\text{e}} + k_{\text{m}}$ \hspace{1cm} (38)
Calculation of Clearance in Multicompartmental Models

- The overall elimination rate constant, $k$, elimination from the central compartment
- Total body clearance = $k \times$ volume of the central compartment, $V_P$

\[
C_{LT} = k \ V_P \tag{40}
\]

\[
C_{LT} = b \ V_{D\beta} \tag{41}
\]

\[
C_{LR} = k_e \ V_P \tag{42}
\]
Fraction of Drug Excreted

• For many drugs, the total amount of unchanged drug excreted in the urine $D_{U}^{\infty}$ may be obtained by direct assay.

• The ratio of $D_{U}^{\infty}$ to the fraction of dose absorbed, FDo is equal to the fraction of drug excreted unchanged in the urine, $f_e$ and is also equal to $k_e/k$

  $$ke/k = D_{U}^{\infty}/FDo = \frac{D_{U}^{\infty}}{\text{Mu} + D_{U}^{\infty}}$$  

  (39)

  $$D_{U}^{\infty}/FDo = f_e = \frac{k_e}{k}$$  

  (43)

  $$Cl_R = D_{U}^{\infty}/FDo \times Cl_T = f_e \times Cl_T$$  

  (44)

  $$Cl_R = \frac{k_e}{k} \times Cl_T$$  

  (45)
Protein Bound Drug

- Protein bound are not eliminated by glomerular filtration, only free drug is excreted by a linear process.
- The bound drug are usually excreted by active secretion, following capacity limited kinetics.
- Clearance values for a protein-bound drug is calculated as follow:
  
  \[ C_{R} = \frac{\text{rate of unbound drug excretion}}{\text{concentration of unbound drug in the plasma}} \]  
  \[ (46) \]

- For protein-bound drug but not actively secreted
  
  \[ (1-\alpha) C_{P,\text{total}} = C_{P,\text{free}} \]  
  \[ (47) \]
• Plasma protein binding has very little effect on the renal clearance of actively secreted drugs such as penicillin.

• For these drugs, the free drug fraction is filtered at the glomerular, whereas the protein-bound drug appears to be stripped from the binding sites and actively secreted into the renal tubules.
Relationship of Clearance to Elimination Half-Life and Volume of Distribution

- \( C_{\text{T}} = k \ V_D \)
- \( k = \frac{0.693}{t_{1/2}} \), then
- \( C_{\text{T}} = \frac{(0.693 \ V_D)}{t_{1/2}} \) \hspace{1cm} (48)
- As \( C_{\text{T}} \) decrease (renal insufficiency), \( t_{1/2} \) increases
- The total body clearance may be calculated, considered a model-independent method and assumes no particular pharmacokinetic model for drug elimination:
  \[
  \frac{\text{FD}_0}{[\text{AUC}]_{0-\infty}}
  \] \hspace{1cm} (49)
- The total body clearance after infusion:
  \( C_{\text{T}} = \frac{R}{C_{\text{ss}}} \) \hspace{1cm} (50)
- \( R \) = the rate of infusion and \( C_{\text{ss}} \) is steady state plasma drug concentration
- Valid for 1 or 2 compartment open model
- For patients with renal impairment, \( t_{1/2} \) changes more drastically than the VD.
### Relationship of Clearance, Rate Constant of Elimination, and Elimination Half-Life

<table>
<thead>
<tr>
<th>CLEARANCE</th>
<th>Plasma water (3,000 mL)</th>
<th>Extracell fluid (12,000 mL)</th>
<th>Body water (41,000 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial reabsorption (30 mL/min)</td>
<td>1.00 x 10^{-2} (69 min)</td>
<td>2.50 x 10^{-3} (277 min)</td>
<td>7.32 x 10^{-4} (947 min)</td>
</tr>
<tr>
<td>Glomerular filtration (130 mL/min)</td>
<td>4.33 x 10^{-2} (16 min)</td>
<td>1.08 x 10^{-2} (64 min)</td>
<td>3.17 x 10^{-3} (219 min)</td>
</tr>
<tr>
<td>Tubular secretion (650 mL/min)</td>
<td>2.17 x 10^{-1} (3 min)</td>
<td>5.42 x 10^{-2} (13 min)</td>
<td>1.59 x 10^{-2} (44 min)</td>
</tr>
</tbody>
</table>

Entries are values for $ke$ (min$^{-1}$), parenthetic entries are values of $t_{1/2}$ (min).
Any clearance between 0 (complete reabsorption) and 650 mL/min is possible.