1. Complete the following statements for a low molecular weight drug which does not bind to plasma proteins.
   (10 points)

A. The maximum value which renal clearance can approach is that of ________
   \[ \text{Renal Blood Flow (RBF)} \]

B. If this drug is hydrophilic and not interacting with transporters the largest possible renal clearance is that of ________
   \[ GFR \]

C. If this drug is lipophilic, neutral drug and not interacting with transporters the smallest possible renal clearance is that of ________
   \[ \text{URINE FLOW} \]

D. Assuming that the lipophilic drug is a base, renal clearance can be reduced by...
   \[ \uparrow \text{pH} \quad \uparrow \text{Base pK}_a \quad \uparrow \text{pH} \quad \uparrow \text{no change} \]

2. Consider the two drugs A and B. Drug A shows perfusion limited distribution into the brain. Drug B is entering the brain characterized by permeability limited distribution. List the statements in agreement with this observation (10 points).

a) Drug A might be more lipophilic than drug B.
b) Drug A will enter the brain faster than drug B.
c) Drug A might be a stronger base than drug B.
d) Drug B might be a stronger base than drug A.
e) Drug B will enter the brain faster if blood flow through the brain is increased.
f) Drug A will enter the brain faster if blood flow through the brain is increased.

List correct statement(s):

\[ A = \text{Cross membrane easily} \]
\[ B = \text{not hindered by membrane} \]
\[ D = \text{Strong base } \uparrow \text{charge @ physiologic pH } \Rightarrow \text{superiority} \]
\[ F = \uparrow \text{blood flow } \uparrow \text{amount} \]
3. Choose whether the following statements for a high extraction drug are True or False (10 points)

   T or F The volume of distribution has to be small
   T or F A decrease in liver blood flow will increase oral bioavailability
   T or F An increase in intrinsic clearance, due to enzyme induction will increase hepatic clearance
   T or F An increase in plasma protein binding will decrease clearance
   T or F Oral bioavailability is increased with increased liver blood flow

\[ F = \frac{Q_H}{f_u \cdot CL_{int}} \]

4. For the following relationships, draw a line that best describes the relationship between the two parameters. If no relationship exists, write “N/R”. (15 points)

   a) \[ V_D = \frac{f_u \cdot V_T}{f_a} \]
   b) \[ \text{Clearance} \]
   c) \[ AUC \]
   d) \[ \text{Cl}_{int} \]

\[ (\text{When } E < 0.2) \]

\[ \text{Cl}_{int} = \frac{f_a \cdot CL_{int}}{\text{AUC}} \]
5. For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a lipophilic, unionizable (no acid or basic group in the molecule), protein bound drug that shows extensive liver metabolism \( E=1 \) and renal elimination. (some answers may be used more than once). (15 points)

<table>
<thead>
<tr>
<th>Physiological change</th>
<th>Effect on kinetics</th>
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<tbody>
<tr>
<td>1.) Decrease metabolic enzymes ( E )</td>
<td>a. ( \text{Cl}_{\text{REN}} \downarrow )</td>
</tr>
<tr>
<td>2.) Decrease in urine flow ( A )</td>
<td>b. ( \text{Cl}_{\text{REN}} \downarrow )</td>
</tr>
<tr>
<td>3.) Increase in liver blood flow ( E )</td>
<td>c. oral bioavailability ( \downarrow )</td>
</tr>
<tr>
<td>4.) Decrease in number of fat cells ( F )</td>
<td>d. ( V_D \uparrow )</td>
</tr>
<tr>
<td>5.) Increase in creatinine clearance ( G )</td>
<td>e. oral bioavailability ( \uparrow )</td>
</tr>
<tr>
<td></td>
<td>f. ( V_D \downarrow )</td>
</tr>
<tr>
<td></td>
<td>g. none of the above</td>
</tr>
</tbody>
</table>

\[
\text{for high } \ E = 1 \\
\text{CL}_H = Q_H \\
F = \frac{Q_H}{S_{\text{CL}_{\text{INT}}}}
\]
6. For the following situations, indicate whether the drug is filtered, reabsorbed or actively secreted (Assume GFR is 130 mL min\(^{-1}\), urine flow is 1.5 mL min\(^{-1}\)) (15 points)
   - A drug with \(f_u = 0.01\) and a \(C_{\text{REN}} = 20\) mL min\(^{-1}\) is secretion
   \[
   \frac{f_u \cdot GFR}{C_{\text{REN}}} = \frac{1.3}{C_{\text{REN}}}
   \]
   - A drug with \(f_u = 0.50\) and a \(C_{\text{REN}} = 65\) mL min\(^{-1}\) is filtration
   \[
   \frac{f_u \cdot GFR}{C_{\text{REN}}} = \frac{65}{C_{\text{REN}}}
   \]
   - A drug with \(f_u = 0.20\) and a \(C_{\text{REN}} = 0.3\) mL min\(^{-1}\) is Reabsorbed
   \[
   \frac{f_u \cdot GFR}{C_{\text{REN}}} = \frac{2.6}{C_{\text{REN}}}
   \]

7. A drug is eliminated through glomerular filtration and hepatic metabolism. It does not bind to plasma proteins. Glomerular filtration rate is normal. No active renal secretion and passive or active reabsorption after renal filtration is observed. The volume of distribution is 50 L. When given as an i.v. bolus, plasma concentrations one hour after administration were 5.2 mg/L. 3 hours after administration the concentration was 2.6 mg/L. (25 pts)

a. What is the plasma concentration 8 hours after administration of the drug?
   \[
   k_e = \frac{\ln 5.2 - \ln 2.6}{1 - 3} = \frac{0.347 \cdot h^{-1}}
   \]
   \[
   \text{after 8h}
   \]
   \[
   t = 3h \quad C_p = 2.6 \text{mg/L}
   \]
   \[
   C_t = C \cdot e^{-k_e \cdot t}
   \]
   \[
   = 2.6 \cdot e^{-0.347 \cdot \frac{5}{36}}
   \]
   \[
   = 0.486 \text{mg/L}
   \]
   or
   \[
   C_t = C \cdot e^{-k_e \cdot t}
   \]
   \[
   = 5.2e^{-0.347 \cdot \frac{7}{36}}
   \]
   or
   \[
   5.2 = C_0 \cdot e^{-k_e \cdot 0.347 \cdot 1}
   \]
   \[
   C_0 = 7.36 \text{mg/L}
   \]
   \[
   = C_0 \cdot e^{-k_e \cdot t} = 7.36e^{-0.346 \cdot \frac{8}{36}}
   \]
7b. What is the hepatic clearance?

\[ \text{CL}_{\text{TOTAL}} = \text{CL}_{\text{HEP}} + \text{CL}_{\text{REN}} \]

\[ \text{CL}_{\text{TOTAL}} = k_e \cdot V_d \]

\[ = 0.346 \text{ hr}^{-1} \cdot 50 \text{L} \]

\[ = 17.3 \text{ L/hr} \]

\[ \text{CL}_{\text{REN}} = \text{GFR} \cdot f_u \]

\[ = 130 \text{mL min}^{-1} \cdot 1 \]

\[ = 130 \text{ mL min}^{-1} \text{ or } 7.8 \text{ L/hr} \]

\[ \text{CL}_{\text{TOTAL}} - \text{CL}_{\text{REN}} = \text{CL}_{\text{HEP}} \]

\[ 17.3 - 7.8 = \frac{9.5 \text{ L/hr} = \text{CL}_{\text{HEP}}}{2} \]