1. Discuss the histogram shown below that represents the metabolic clearance of sulfametazine. Number of subjects (y-axis) is plotted vs. metabolic clearance (x-axis).

This histogram indicates 3 distinct populations (trimodal). Population 1 have metabolic clearances <0.25 (slow metabolizers), Population 2 have metabolic clearances between 0.5-1.0 (normal metabolizers) and Population 3 have metabolic clearances of >1.125 (fast metabolizers). This suggests patients vary in the genetic for the metabolizing enzyme. If we indicate ‘A’ as the dominant allele (gene) and ‘a’ as the recessive allele, then the 3 populations would correspond to homozygote dominant (AA), heterozygote (Aa) and homozygote recessive (aa). (remember one allele is from mom and one allele is from dad)
2. Based on the Cockcroft-Gault-Equation, calculate the amount of creatinine that is produced every hour from muscle in a normal 20 year old and 90 year old male subject (body weight 70 kg) with a serum creatinine of 0.9 mg/dl.

- The Cockroft-Gault equation allows us to predict the creatinine clearance (and therefore renal function/GFR) for patients differing in age and weight. For male patients,

\[
\text{Cl}_{\text{creat}}(\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot \text{Cp}_{\text{creat}}}
\]

where age is in years, weight is in kg, and \( \text{Cp}_{\text{creat}} \) is in mg/dL. The Cl\(_{\text{creat}} \) is then in ml/min. This is an empirical equation which works only if the age, weight, and \( \text{Cp}_{\text{creat}} \) (or Scr) are entered in the units specified.

- For the 20 y.o.

\[
\text{Cl}_{\text{creat}} = \frac{(140 - 20)(70)}{(72)(0.9)} = 129.6\text{ml/min}
\]

Although clearance is expressed in volume-per-time, the amount of creatinine eliminated-per-time may be found using the creatinine concentration given:

Creatinine cleared per hour =
\[
(129.6\text{ml/min})(0.9\text{mg/dL}) \cdot \frac{60\text{min}}{1\text{hr}} \cdot \frac{10\text{dL}}{1\text{L}} \cdot \frac{1\text{L}}{1000\text{ml}}
\]

\[
= 69.98 \approx 70\text{mg/hr}
\]

(so in 1 day, almost 2 g of creatinine is lost which is balanced by eating and producing 2 g of creatine per day))

- For the 90 y.o.

\[
\text{Cl}_{\text{creat}} = \frac{(140 - 90)(70)}{(72)(0.9)} = 54.0\text{ml/min}
\]

Creatinine cleared per hour =
\[
(54.0\text{ml/min})(0.9\text{mg/dL}) \cdot \frac{60\text{min}}{1\text{hr}} \cdot \frac{10\text{dL}}{1\text{L}} \cdot \frac{1\text{L}}{1000\text{ml}}
\]

\[
= 29.2\text{mg/hr}
\]

(Remember, elderly have less muscle mass which means less creatinine production)
3. Compare the pharmacokinetic properties of amoxicillin and cloxacillin:

<table>
<thead>
<tr>
<th></th>
<th>amoxicillin</th>
<th>cloxacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL [L/h]</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Vd [L]</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>F&lt;sub&gt;oral&lt;/sub&gt;</td>
<td>0.93</td>
<td>0.43</td>
</tr>
<tr>
<td>f&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.18</td>
<td>0.95</td>
</tr>
<tr>
<td>F&lt;sub&gt;ren&lt;/sub&gt;</td>
<td>0.86</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Calculate and compare for both drugs the total daily oral dose necessary to maintain an average unbound concentration of 20 mg/L in plasma and urine. Assume a urine flow of 1 ml/min.

**Plasma**

\[
C = \frac{F \cdot D}{CL \cdot 24} = \frac{Cu}{fu}
\]

\[
D = \frac{Cu \cdot CL \cdot 24}{F \cdot fu} = \frac{20 \cdot 18 \cdot 24}{0.93 \cdot 0.82} = 11.3g \quad \text{(amoxicillin)}
\]

\[
\frac{20 \cdot 15 \cdot 24}{0.43 \cdot 0.05} = 335g \quad \text{(cloxacillin) (!)}
\]

**Urine** → to obtain 20 mg/L or 20 µg/mL → \( \frac{dE}{dt} = 20 \mu g / \text{min} = 1.2 mg / h \) (Excretion Rate) (Flow 1 mL/min)

\[
CL_{ren} = 15.5 \text{ L/h (amoxicillin)}
\]

\[
= 11.3 \text{ L/h (cloxacillin)}
\]

\[
CL_{ren} = \frac{dE}{C} \rightarrow C = \frac{1.2}{15.5} = 0.077 mg / L \quad \text{(amoxicillin)}
\]

\[
\frac{1.2}{11.3} = 0.106 mg / L \quad \text{(cloxacillin)}
\]

\[
D = \frac{C \cdot CL \cdot 24}{F} = \frac{0.077 \cdot 18 \cdot 24}{0.93} = 35.8 mg \quad \text{(amoxicillin)}
\]

\[
\frac{0.106 \cdot 15.24}{0.43} = 88.7 mg \quad \text{(cloxacillin)}
\]
4. An 80 kg patient receives 500 mg theophylline i.v. by bolus injection every 6 hr. Assume that Vd = 0.5 L/kg and t_{1/2} = 6.4 h. Predict steady state peak and trough concentration.

\[ V_d = 40L, \quad k = \frac{0.693}{6.4} = 0.108h^{-1} \]

\[ C_0 = \frac{500}{40} = 12.5 \mu g / mL \]

\[ C_{\text{max}} = \frac{12.5}{1 - e^{-0.108 \cdot 6}} = \frac{12.5}{0.477} = 26.2 \mu g / mL \]

\[ C_{\text{min}} = 26.2 \cdot e^{-0.108 \cdot 6} = 13.7 \mu g / mL \]
5. R.J., is a 50-year-old, 70kg patient with a serum creatinine of 1.0mg/dL. For several weeks he received tablets of 375 µg of digoxin per day to treat his CHF. Assume that this patient cannot take anything by mouth anymore and he must be converted to daily intravenous doses of digoxin. Calculate an intravenous dose equivalent to the 375 µg tablets he ingests daily.

Amount of drug absorbed = \( F \cdot Dose \)

\[
= 0.7 \cdot 375 \mu g = 262.5 \mu g
\]

The intravenous dose should be 262.5 \( \approx 250 \mu g \)