In the first section of this chapter, we set a goal of understanding \( k_{el} \), which determines a drug's half-life and is a function of two variables – clearance and volume of distribution. We have thoroughly discussed clearance, and now we need to focus upon volume of distribution.

Volume of distribution is the *hypothetical* volume of blood – or, more precisely, a volume of plasma – that contains a drug in the body. How we describe this volume of distribution depends on the which *compartment model* we choose. To keep things simple, we will start with the *one-compartment model*, and we will stick with an IV bolus.

In the one-compartment model with an IV bolus, we assume that the drug is instantaneously administered into the blood, which defines the *central compartment*, the only compartment in the one-compartment model. From the central compartment, the drug is slowly cleared by the kidneys and/or the liver. The effect of drug clearance is captured by the elimination rate constant, \( k_{el} \). The central compartment defines the volume of distribution for our model, but we cannot directly measure the volume. We need to determine the volume indirectly.

At time=0, we know quite a bit about our system. Since no time has elapsed, no drug has been cleared. That means the entire mass of the drug dose \((D_0)\) resides in the central compartment at time=0. Furthermore, we can determine \( C_p \) at time=0, \( C_p^0 \), by plotting \( \ln C_p \) vs. time and extrapolating the line back to the \( y \)-intercept, which is \( \ln C_p^0 \).

If we know the mass \((D_0)\) and the concentration \((C_p^0)\) in the compartment, then we can
calculate the volume of the compartment ($V_d$).

\[
\text{concentration} = \frac{\text{mass}}{\text{volume}}
\]

\[
\text{volume} = \frac{\text{mass}}{\text{concentration}}
\]

\[
V_d = \frac{D_0}{C_p^0}
\]

It is important to note that because we are using the plasma concentration of the drug ($C_p$), then the calculated volume of distribution is a volume of plasma, not a volume of blood.

It is very important to remember (and yet easy to forget), that $V_d$ is not a real number. The amount of plasma in a 70-kg human is about 2.7 L (54% of the blood volume of 5 L). It would seem that the $V_d$ for all drugs in a 70-kg patient must be 2.7 L. The drug is after all injected into the bloodstream, which contains 2.7 L of plasma. In fact, 2.7 L is the minimum value for $V_d$. If $V_d$ is greater than 2.7 L, then the drug must have left the central compartment.

The simple assumptions of the one-compartment model, which only accommodates the central compartment, are showing their limitations. Despite its shortcomings, the one-compartment model is by far the most widely used method for describing a drug's volume of distribution.

To come full circle, we engaged this discussion to finish the puzzle of understanding $CL$, $V_d$, and $k_{el}$. A consequence of a large $V_d$ is that $k_{el}$ will be smaller, and the half-life of the drug will be longer.