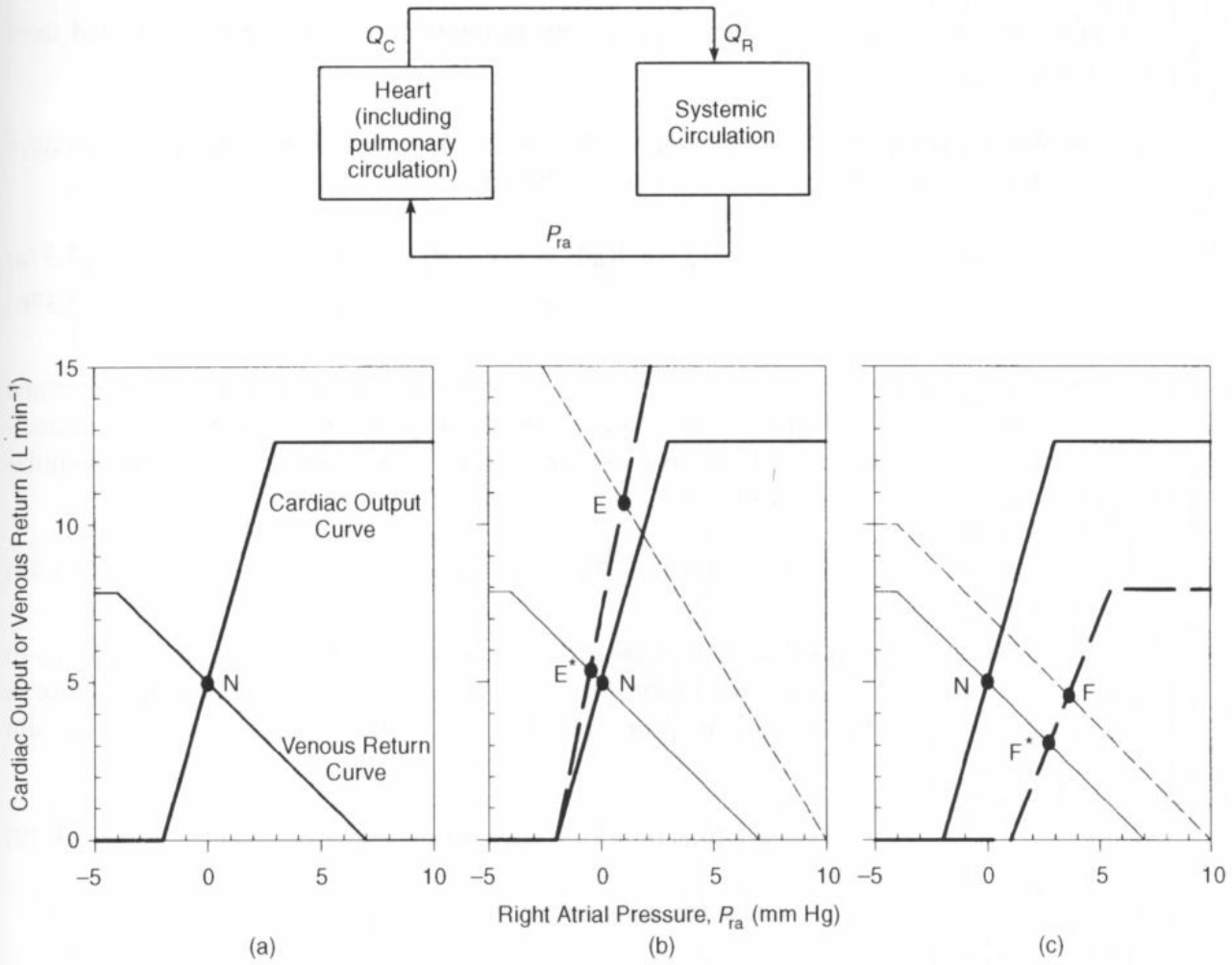

Figure 3.11 Steady-state closed-loop analysis of cardiac output regulation during (a) normal resting conditions; (b) moderate exercise; and (c) compensated heart failure.

3.6 REGULATION OF GLUCOSE

We turn to another example of a physiological control system with negative feedback: the system that regulates blood glucose levels. When plasma glucose levels are elevated, insulin secretion is stimulated. This raises the level of insulin in the blood, which increases the uptake of blood glucose by the tissues. The increased outflow of glucose from the blood and interstitial fluid leads to a decrease in glucose concentration, which subsequently produces a reduction in insulin secretion.

The model we will introduce in this section was first proposed by Stolwijk and Hardy in 1974. We assume the total volume of blood and interstitial fluids to be represented by a single large compartment ($\sim$15 L in a normal adult), and that the steady-state concentration of glucose in this compartment is x (in units of mg ml^{-1}). For this level of x to remain constant, the total inflow of glucose into the compartment must equal the total outflow from the compartment. Figure 3.12 shows a schematic representation of the main processes that affect this balance. Under normal circumstances, glucose enters the blood through absorption from the gastrointestinal tract or through production from the liver. We assume this input flow rate

to be Q_L (in mg h^{-1}). There are three major ways through which glucose is eliminated from the blood:

- When x is elevated beyond a certain threshold (θ), glucose is excreted by the kidneys at a rate proportional to the gradient between x and θ:

$$\text{Renal Loss Rate} = \mu(x - \theta), \qquad x > \theta \tag{3.37a}$$

$$= 0, \qquad x \leq \theta \tag{3.37b}$$

- Glucose leaves the blood to enter most cells through facilitated diffusion. In some tissues, the rate of glucose utilization depends only on the extracellular-to-intracellular concentration gradient. In most circumstances, we can ignore the intracellular concentration. Thus, we have

$$\text{Tissue Utilization Rate (Insulin-independent)} = \lambda x \tag{3.38}$$

- In certain types of cells, such as those in muscle and adipose tissue, insulin helps to stimulate this facilitated diffusion process. Therefore, the rate at which glucose is taken up by these cells is proportional to x as well as to the blood insulin concentration, y:

$$\text{Tissue Utilization Rate (Insulin-dependent)} = vxy \tag{3.39}$$

In the above equations, μ, λ, and v are constant proportionality factors.

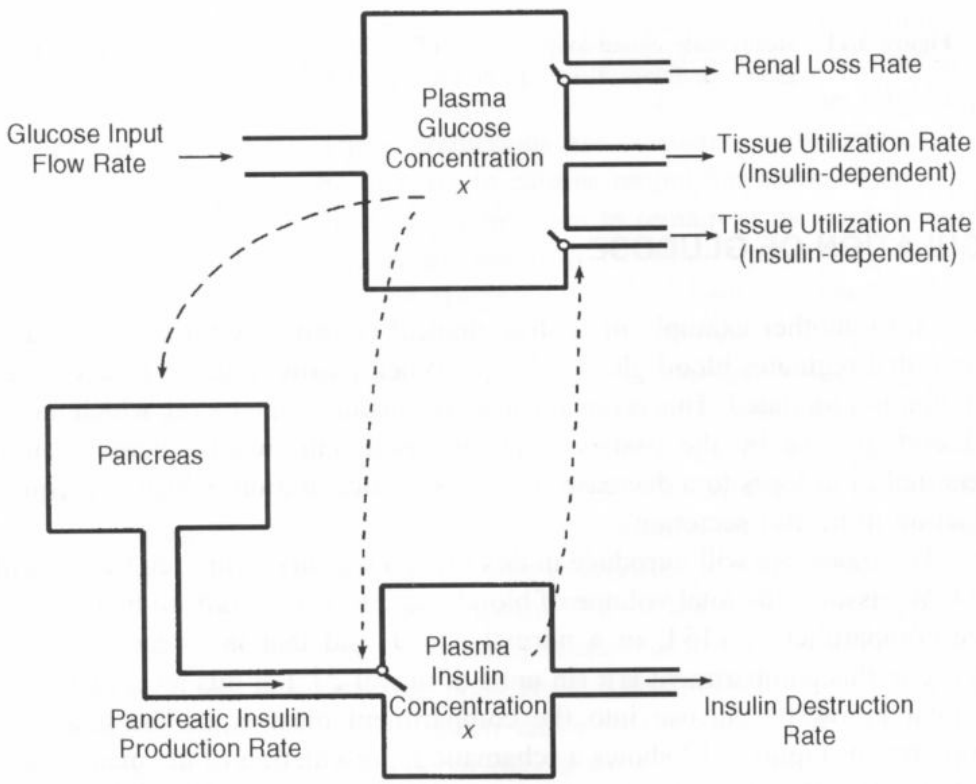

Figure 3.12 Schematic representation of the processes involved in the regulation of glucose and insulin.

Equating the inflow to the sum of the three outflows, we obtain the following mass balance equations for blood glucose:

$$Q_L = \lambda x + vxy, \qquad x \leq \theta \tag{3.40a}$$

$$= \lambda x + vxy + \mu(x - \theta), \qquad x > \theta \tag{3.40b}$$

Note that in the above equation, a strong *nonlinearity* in the form of the product of x and y is introduced, along with the *thresholding nonlinearity*, which defines one regime above θ and one below it. Also, the negative feedback in this control system is clearly embedded in the characteristics described by Equations (3.40a) and (3.40b): since Q_L is a constant, an increase in x must lead to a corresponding decrease in y, and vice versa.

A similar mass balance can be established for blood insulin. Insulin is produced by the pancreas at a rate dependent on the plasma glucose level. However, if x falls below a certain threshold (ϕ), insulin production ceases. Thus, we have

$$\text{Insulin Production Rate} = 0, \qquad x \leq \phi \tag{3.41a}$$

$$= \beta(x - \phi), \qquad x > \phi \tag{3.41b}$$

Insulin is destroyed through a reaction involving the insulinase enzyme, at a rate proportional to its concentration in blood:

$$\text{Insulin Destruction Rate} = \alpha y \tag{3.42}$$

Combining Equation (3.41) and Equation (3.42), we obtain the following equation relating the steady-state level of y to that of x:

$$y = 0, \qquad x \leq \phi \tag{3.43a}$$

$$= \frac{\beta}{\alpha}(x - \phi), \qquad x > \phi \tag{3.43b}$$

Therefore, aside from the threshold nonlinearity, the insulin response to glucose is basically linear.

The steady-state level of glucose and insulin in the blood under a given set of conditions can be predicted from this model by solving Equations (3.40) and (3.43) simultaneously. As we have shown in the regulation of cardiac output example, graphical analysis is useful in providing not only the steady-state solution but also substantial insight into the overall problem. In Figure 3.13a, steady-state insulin concentration (in milliUnits per ml blood) is plotted against the steady-state blood glucose concentration (in mg per ml). The insulin response to glucose is shown as the bold curve, while the lighter curve reflects the glucose mass balance equation. The parameter values employed in this calculation correspond to the normal adult: $\theta = 2.5\,\text{mg ml}^{-1}$, $\mu = 7200\,\text{ml h}^{-1}$, $\lambda = 2470\,\text{ml h}^{-1}$, $v = 139000\,\text{mU}^{-1}\,\text{h}^{-1}$, $\phi = 0.51\,\text{mg ml}^{-1}$, $\beta =$ mU ml mg^{-1} h^{-1}, $\alpha = 7600\,\text{ml h}^{-1}$, and $Q_L = 8400\,\text{mg h}^{-1}$. The intersection of the glucose and insulin curves yields the steady-state operating point labeled N, where the glucose concentration is $0.81\,\text{mg ml}^{-1}$ and the insulin concentration is $0.055\,\text{mU ml}^{-1}$.

The model is used next to predict the steady-state operating levels of glucose and insulin that would arise from diabetes. In *Type-1* or *insulin-dependent diabetes*, the main defect is in the inability of the islet cells in the pancreas to produce sufficient insulin. The most common form of this disorder begins in childhood and, for this reason, is frequently called *juvenile-onset* diabetes. The other form begins in adulthood and is known as *ketone-prone* diabetes. We can model this condition by lowering the sensitivity of the insulin

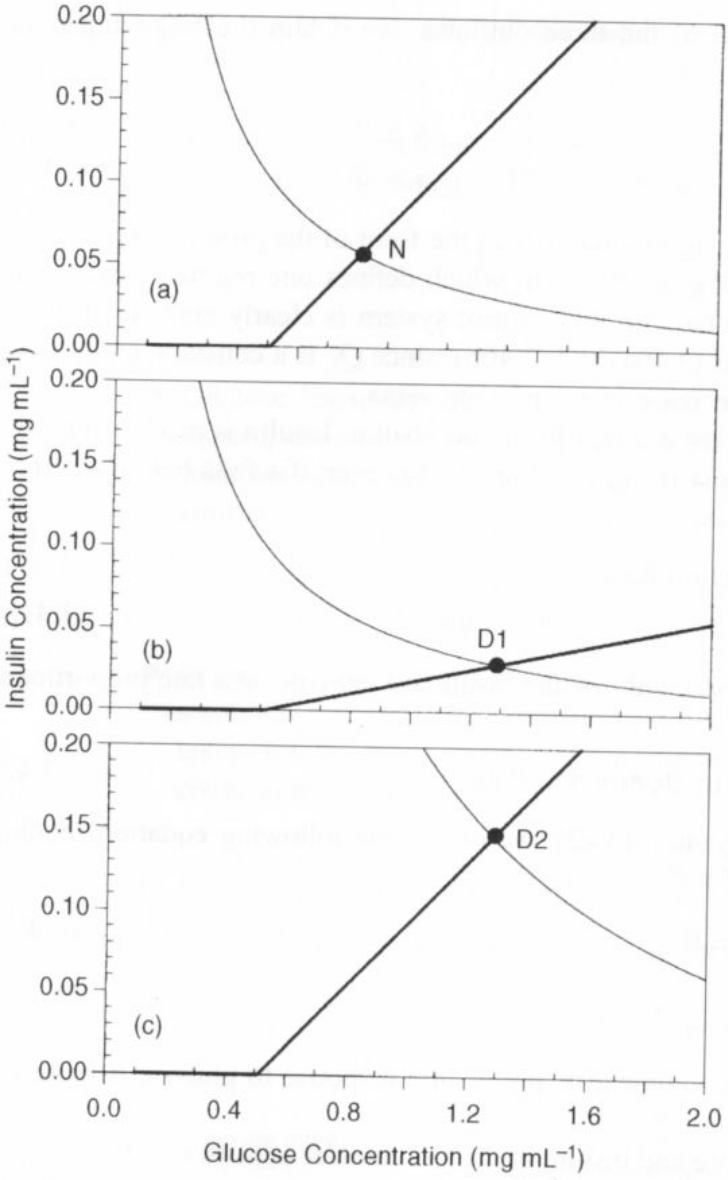

Figure 3.13 Steady-state analysis of glucose regulation under (a) normal conditions; (b) Type-1 diabetes; and (c) Type-2 diabetes.

response to glucose, β. Figure 3.13b demonstrates the effect of reducing β to 20% of its normal value. The new steady-state operating point is now established at D1, resulting in a highly elevated blood glucose concentration of 1.28 mg ml^{-1} and a depressed plasma insulin concentration of 0.029 mU ml^{-1}.

Type-2 diabetes is also referred to as *non-insulin-dependent* diabetes since, here, the pancreas may be making normal amounts of insulin. However, for reasons that remain unclear, there is a drastic reduction in the ability of insulin to stimulate glucose uptake by the body tissues. We model this condition by changing the value of the parameter v, which is the constant that multiplies the product of x and y in the glucose mass balance equation. The insulin response to glucose may remain normal or may decrease. In Figure 3.13c, however, we have reduced v to 20% of its original value while leaving the insulin curve unchanged. This change produces a shift of the glucose curve away from the origin as well as a steepening in local slopes. The new equilibrium point is established at D2, where the glucose concentration is elevated to 1.29 mg ml^{-1}. A somewhat counterintuitive result is that the steady-state insulin concentration now is actually almost three times higher than normal, at a level of 0.146 mU ml^{-1}. Thus, in this case, treatment with insulin clearly would not be useful.