Although it has long been recognized that adenosine is a potent vasodilator, only during the past 20 years has serious consideration been given to its possible role in the local regulation of blood flow. Prior to that time other potential mediators of regional blood flow regulation, such as reduced $PO_2$, increased $PCO_2$, or decreased pH were often suggested, but definitive experimental proof for a physiological role for these agents was lacking. In more recent years, more evidence has appeared in support of a reduced pH, and additional substances such as potassium ions, inorganic phosphate, and increased osmolarity have been suggested with varying degrees of acceptance. In all likelihood, several factors, including a myogenic response, are involved in local blood flow regulation, but adenosine appears to be the primary factor. Since most of the studies on adenosine have been focused on its mediation of the control of coronary, cerebral, and skeletal muscle blood flow, in that order, discussion will be limited to these three tissues. This in no way means that adenosine does not act similarly in several other tissues. In the kidney, however, adenosine induces vasoconstriction, a subject considered in detail by Dr. Osswald in Chapter 25.
HEART

Reduced oxygen supply

The earliest attempts to demonstrate adenosine release from hypoxic or ischemic hearts met with failure, because only the degradative products of adenosine, namely, inosine and hypoxanthine, were recovered in the effluents of isolated perfused hearts or in blood-perfused hearts of the open-chest dog [1]. Nevertheless, it was demonstrated by Gerlach et al. [2] and by Imai et al. [3] that adenosine was formed in extirpated unperfused cardiac tissue incubated in moist chambers at 37°C. Adenosine was first found in the perfusate of isolated perfused hearts in 1964 [4], with the use of an uncoupler of oxidative phosphorylation, and in 1966 [5], with the aid of an adenosine deaminase inhibitor. Since that time, several studies have appeared showing that adenosine is released following brief periods of ischemia or hypoxia in anesthetized animals, or in isolated perfused hearts, and is also present in the normal heart [6]. Furthermore, the magnitude of the increase in adenosine release and the increment in the coronary conductance showed a striking parallelism [7, 8]. Finally, it was demonstrated that, within a single cardiac cycle, a significant increase in adenosine occurred during systole when compared to diastole [9]. This observation emphasizes the rapidity of the adenosine response as well as its close association with the contractile state of the myocardium.

With respect to the regulation of coronary blood flow by adenosine, the key problem is whether adenosine release is coupled to myocardial metabolism, since the cardiac oxygen demand is the parameter that is altered under physiological conditions, not the oxygen supply. Nevertheless, there is obviously a balance between oxygen supply and oxygen demand of the heart and, as depicted in Figure 19.1, adenosine may play a key role in adjusting blood flow (oxygen supply) to myocardial needs. How this balance can be disturbed is illustrated in Figure 19.2. The line to the right, which originates near the abscissa, represents the increase in coronary flow obtained with reduction in the oxygen content of the perfusion fluid in the isolated perfused guinea pig heart. The line to the left, which also originates at the same point near the abscissa, represents the increase in coronary flow when the coronary vasodilator nitroglycerin is added to the perfusion fluid. In the latter instance, flow, and hence oxygen supply, exceeds the needs of the myocardium and there is a progressive decrease in the adenosine content of the heart as flow increases at a high oxygen content in the perfusion fluid. However, in physiological states, we do not have excess perfusion; blood flow usually closely parallels changes in oxygen demand.

Increased oxygen demand

When myocardial metabolic activity is increased, even in the presence of a large oxygen supply, there is an associated increment in adenosine formation