Agents that increase cellular cyclic adenosine monophosphate (cyclic AMP) levels exert several effects on cardiac function. These include increases in heart rate and both the force of contraction and rate of relaxation. The latter effects, which might appear to be contradictory, actually represent essential components of the response needed to allow the heart to increase its stroke volume when heart rate is accelerated. This article reviews the mechanisms by which cyclic AMP exerts both contraction-promoting and relaxation-promoting effects in the integrated response of the heart to sympathetic stimulation.

The Man and the Satyr

It is said that a man once offered friendship to a satyr. And when winter arrived and it became cold, the man blew on his hands with his mouth. When the satyr asked the reason that he did this, the man said that he was warming his hands because of the cold. But later, when the table was placed before them and the food was too hot, the man took it up little by little, and brought it to his mouth and blew on it. Again the satyr asked why he did this; the man answered that he was cooling the food since it was too hot. And the satyr replied to him, "I am done with friendship with you, oh man, because you blow hot and cold from the same mouth."

MORAL: We should avoid friendship with those who, in one breath, express opposing views.

Aesop's Fables (translated by Phyllis B. Katz, PhD)

As Aesop noted over 2,000 years ago, a man who speaks simultaneously to opposing viewpoints should be viewed with suspicion. Yet Nature, in her wisdom, has provided our hearts with at least one system that brings about two entirely opposite effects on myocardial contractile performance, and does so at the same time in response to a single intracellular messenger! This is the response of the heart to the sympathetic nervous system and its neurotransmitters, the beta-adrenergic agonists, which includes effects that promote both contraction and relaxation (Fig. 1).

These effects, which at first glance might appear paradoxical, are essential for the physiologic response to the beta-adrenergic agonists. This is because activation of the sympathetic nervous system, which plays a central role in the response of the heart to stress, leads to a marked increase in cardiac output that is brought about by increases in both stroke volume (an inotropic effect) and heart rate (a chronotropic effect). Were this important response not accom-
Singer modulates the processes involved in excitation and cyclic monophosphate (cyclic AMP). This intracellular messenger, cyclic AMP, and the role of protein phosphorylation are the subject of this review.

Figure 1. Schematic representation of the effects of catecholamines on the mechanical response of cardiac muscle. Catecholamines increase maximal tension, the rate of tension increase and the rate of tension decrease. As a result, the duration of mechanical systole is shortened. (Reprinted with permission from Katz AM [6] and Raven Press, New York.)

It is now clear that at least some of the steps in the complex mechanisms responsible for both contraction and relaxation are active processes in that they require the expenditure of chemical energy (2). In the case of myocardial contraction, chemical energy derived from the hydrolysis of the terminal, high energy phosphate bond of ATP provides the mechanical energy that propels blood under pressure into the aorta and pulmonary artery. ATP is also needed to restore the contractile proteins to their relaxed state; this relaxing effect does not require hydrolysis of the high energy phosphate bond of ATP, instead, it is accomplished by the binding of this nucleotide to an active site on myosin.

Mechanisms activating contraction. The active interactions between the contractile proteins during systole require an input of chemical energy, but the mechanisms that activate contraction are, for the most part, passive. This reflects the fact that the complex signal generated by the action potential depends largely on energy stored as ionic gradients across the sarcolemma. Thus, the electrogenic sodium (Na⁺) and calcium (Ca²⁺) fluxes across the cardiac sarcolemma, which generate the depolarizing currents responsible for the action potential, occur when these ions move down their electrochemical gradients from regions of high activity outside the cell into the cytosol, where their activities are much lower. Similarly, the flux of activator Ca²⁺ into the cytosol from stores within the sarcoplasmic reticulum, an intracellular membrane system that in the adult mammalian heart provides most of the Ca²⁺ that activates the cardiac contractile proteins during systole, is downhill. Systole, therefore, is an active process, and the mechanisms of “excitation-contraction coupling” that initiate systole are passive.

Mechanisms activating relaxation. Chemical energy derived from ATP is also expended during relaxation, although the active nature of relaxation is less obvious than is the shortening and development of tension in the walls of the heart during systole. The active processes in relaxation, however, are readily appreciated when it is recognized...
Beta Adrenergic Agonist Binding to Its Sarcolemmal Receptor

Activation of Adenylate Cyclase

Increased Cytosolic Cyclic AMP

Activation of Cyclic AMP-Dependent Protein Kinase

Protein Phosphorylation

Altered Function

Figure 2. Cascade of reactions by which the binding of a beta-adrenergic agonist to its sarcolemmal receptor alters cellular function.

that the activator Ca^{2+} that is passively released from the sarcoplasmic reticulum into the cytosol to provide for the activation of the contractile process at the onset of systole must, during diastole, be pumped out of the cytosol against an electrochemical gradient. In other words, the potential energy stored in the Ca^{2+} gradient across the sarcoplasmic reticulum that is used to activate the contractile proteins must be regenerated during diastole through the expenditure of chemical energy. This is accomplished by a Ca^{2+} pump ATPase protein in the membrane of the sarcoplasmic reticulum. Chemical energy must also be expended to restore the Na^{+} and Ca^{2+} gradients across the sarcolemma that provided for the depolarizing ionic currents that generated the action potential. This is accomplished largely by the sarcolemmal sodium pump (Na,K-ATPase) which utilizes ATP to pump Na^{+} out of the cell. The resulting Na^{+} gradient is largely responsible for the active transport of Ca^{2+} out of the cell by a Na:Ca exchange mechanism. A smaller amount of active Ca^{2+} efflux may be mediated by a sarcolemmal Ca^{2+} pump ATPase.

Cyclic AMP Effects on Energy Production in the Heart

As chemical energy must be expended during both contraction and relaxation, it is not surprising that the response of the heart to agents that increase cyclic AMP production includes an increased rate of ATP synthesis. Although cyclic AMP accelerates both glycolysis and lipolysis (3–5), these metabolic effects are not directly responsible for the mechanical response of the heart to agents that increase cellular cyclic AMP levels (6). Instead, by accelerating ATP production, these metabolic responses aid the heart in meeting the increased rate of energy expenditure caused by the response of other systems to cyclic AMP.

Cyclic AMP Effects on the Cardiac Contractile Proteins

Considerable controversy remains regarding the actions of cyclic AMP, mediated through its ability to promote the phosphorylation of the myofibrillar proteins, that alter the functions of the contractile proteins of the heart (6). One effect for which there is general agreement is brought about by the phosphorylation of troponin I, one of a complex of regulatory proteins that regulates the response of the heart to an increase in cytosolic Ca^{2+} concentration.

Phosphorylation of troponin I. Although troponin I does not contain the actual Ca^{2+} binding site that initiates systole, this protein participates in an allosteric response by which Ca^{2+} binding to troponin C, another of these regulatory proteins, is recognized as a signal that initiates the contractile process in the myocardium (7). There is now convincing evidence (6) that cyclic AMP leads to the phosphorylation of troponin I, and that this reaction has an important effect on the response of the contractile apparatus to Ca^{2+}.

Many investigators predicted that cyclic AMP-dependent protein kinase-catalyzed phosphorylation of the contractile proteins might, in some way, alter their interactions in a manner that would explain the positive inotropic effects of the interventions that lead to cyclic AMP production in the heart. It now appears, however, that the opposite is true; phosphorylation of troponin I inhibits the response to the increase in cytosolic Ca^{2+} during excitation-contraction coupling (6). This inhibitory effect is due to desensitization of the response of the contractile proteins to Ca^{2+}; that is,
a greater increase in cytosolic Ca\textsuperscript{2+} concentration is needed to activate the contractile proteins after troponin I is phosphorylated, an effect that inhibits the contractile response to Ca\textsuperscript{2+}. At the same time, however, this effect favors relaxation by causing Ca\textsuperscript{2+} to dissociate more readily from the contractile proteins during diastole when cytosolic Ca\textsuperscript{2+} concentration is reduced by the Ca\textsuperscript{2+} pump of the sarcoplasmic reticulum. In this manner, phosphorylation of troponin I contributes to the lusitropic (relaxation-promoting), rather than the inotropic (contraction-promoting) effect of cyclic AMP.

**Cyclic AMP Effects on the Sarcoplasmic Reticulum**

**Sarcoplasmic reticulum calcium channel.** As has already been mentioned, the sarcoplasmic reticulum is an intracellular membrane system whose primary function is to accumulate, store and release the Ca\textsuperscript{2+} involved in the activation of the contractile process. Accumulation of Ca\textsuperscript{2+} by the sarcoplasmic reticulum, an active process in which this ion is transported from a region of relatively low activity in the cytosol to one of high activity within this membrane system, is brought about by a Ca\textsuperscript{2+}-pump ATPase protein that couples the hydrolysis of one molecule of ATP to the active transport of two Ca\textsuperscript{2+} ions (8). Conversely, the release of activator Ca\textsuperscript{2+} from the sarcoplasmic reticulum is a passive, downhill process in which the cation moves down its concentration gradient, presumably through a "channel" that opens within these membranes. Although the nature of this sarcoplasmic reticulum channel remains poorly understood, there is evidence that the Ca\textsuperscript{2+} pump ATPase protein itself might, at the appropriate phase of the contraction-relaxation cycle, become a channel through which activator Ca\textsuperscript{2+} is released to initiate systole (9).

**Phospholamban phosphorylation.** Almost a decade ago it was recognized that Ca\textsuperscript{2+} transport is stimulated when cardiac sarcoplasmic reticulum vesicles are incubated with cyclic AMP and a cyclic AMP-dependent protein kinase (6, 10), and that this stimulatory effect is brought about by the phosphorylation of phospholamban, a protein within these membranes that is a substrate for this protein kinase. The mechanism of this stimulatory response is quite complex, involving both an increase in the turnover rate of the Ca\textsuperscript{2+} pump enzyme and an increase in its Ca\textsuperscript{2+} sensitivity (10). Phosphorylation of phospholamban may also hasten the transitions between Ca\textsuperscript{2+} uptake and Ca\textsuperscript{2+} release in the cardiac sarcoplasmic reticulum (6). By promoting the removal of activator Ca\textsuperscript{2+} from the cytosol during diastole, these effects contribute to the lusitropic response of the heart to beta-adrenergic agonists. The increased turnover rate of the Ca\textsuperscript{2+} pump would accelerate the removal of activator Ca\textsuperscript{2+} from binding sites on the troponin complex, while the increased Ca\textsuperscript{2+} sensitivity of this ion pump would sustain rapid Ca\textsuperscript{2+} pumping activity well into diastole when Ca\textsuperscript{2+} levels in the cytosol become low. The latter response may also contribute to a decrease in diastolic stiffness by allowing the sarcoplasmic reticulum to achieve lower cytosolic Ca\textsuperscript{2+} concentrations.

Phospholamban phosphorylation stimulates not only the active uptake of Ca\textsuperscript{2+} into the sarcoplasmic reticulum, but also appears to be associated with an increased rate of Ca\textsuperscript{2+} release from this internal membrane system (6). This effect, which would lead to an increased rate of tension development, probably contributes to the inotropic response to cyclic AMP. Thus, like the satyr's friend, phospholamban appears to blow hot (inotropy) and cold (lusitropy) through one reaction: phosphorylation.

**Cyclic AMP Effects on the Sarcolemma**

Agents that increase cytosolic cyclic AMP concentration lead to complex, incompletely understood changes in the functional properties of the sarcolemma. The heterogeneity and large number of functional activities associated with this membrane have, so far, made it difficult to define the biochemical basis for these important functional effects.

**Na\textsuperscript{+} pump stimulation.** There is strong, but not yet conclusive, evidence that cyclic AMP activates the Na\textsuperscript{+} pump (11). The resulting stimulation of Na\textsuperscript{+} extrusion from the cell would increase the Na\textsuperscript{+} gradient across the sarcolemma. This, in turn, would accelerate Ca\textsuperscript{2+} influx across the sarcolemma during the cardiac action potential (12,13). Initial analyses of the ionic current generated by this inward Ca\textsuperscript{2+} movement across the sarcolemma indicated that this inotropic mechanism is produced by the recruitment of additional voltage-sensitive Ca\textsuperscript{2+} channels (14). More recent evidence suggests that this effect may be due to a change in the mechanism that controls the opening of Ca\textsuperscript{2+} channels in response to membrane depolarization, which prolongs the transient openings of the individual Ca\textsuperscript{2+} channels when the membrane is depolarized (15). In either case, the increase in this important inward Ca\textsuperscript{2+} current, which plays a major role in the inotropic response to beta-adrenergic stimulation, appears to be mediated by cyclic AMP-dependent protein kinase (12,13). At
Table 1. Effects of Beta-Adrenergic Stimulation of the Heart on Biochemical and Electrophysiologic Properties of the Myocardium

<table>
<thead>
<tr>
<th>Process</th>
<th>Substrate(s)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Energy production</td>
<td>Many</td>
<td>Increases ATP availability</td>
</tr>
<tr>
<td>II. Electrophysiologic properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Sinoatrial node</td>
<td>Unknown</td>
<td>Increases heart rate</td>
</tr>
<tr>
<td>B. Atrioventricular node</td>
<td>Unknown</td>
<td>Accelerates AV conduction</td>
</tr>
<tr>
<td>C. &quot;Working&quot; myocardium and His-Purkinje system</td>
<td>Unknown</td>
<td>Increases slow inward current (I, same as III.C.1)</td>
</tr>
<tr>
<td>III. Mechanical properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Contractile proteins</td>
<td>Troponin I</td>
<td>Facilitates dissociation of Ca$^{2+}$ in diastole (L) Reduces Ca$^{2+}$-binding in systole (negative I)</td>
</tr>
<tr>
<td>1. Ca$^{2+}$ sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Sarcoplasmic reticulum</td>
<td>Phospholamban</td>
<td>Accelerates Ca$^{2+}$ uptake (L) Facilitates Ca$^{2+}$ uptake (L) Abbreviates systole (L) Accelerates Ca$^{2+}$ release (I)</td>
</tr>
<tr>
<td>1. Ca$^{2+}$-uptake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Ca$^{2+}$ pump turnover rate</td>
<td></td>
<td>Accelerates Ca$^{2+}$ uptake (L)</td>
</tr>
<tr>
<td>b. Ca$^{2+}$ sensitivity</td>
<td></td>
<td>Facilitates Ca$^{2+}$ uptake (L)</td>
</tr>
<tr>
<td>c. Transitions between Ca$^{2+}$ uptake and release</td>
<td></td>
<td>Abbreviates systole (L)</td>
</tr>
<tr>
<td>2. Ca$^{2+}$ release</td>
<td>Phospholamban</td>
<td>Accelerates Ca$^{2+}$ release (I)</td>
</tr>
<tr>
<td>C. Sarcolemma</td>
<td>Unknown</td>
<td>Increases cellular Ca$^{2+}$ content (I) (same as II.C) Promotes Na$^+$ efflux, thereby facilitating Ca$^{2+}$ efflux by Na$^+$/Ca$^{2+}$ exchange (L)</td>
</tr>
<tr>
<td>1. Ca$^{2+}$ influx</td>
<td>Unknown</td>
<td>Promotes Ca$^{2+}$ influx (L)</td>
</tr>
<tr>
<td>2. Na$^+$ pump rate</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>3. Ca$^{2+}$ pump rate</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; AV = atrioventricular; I = inotropic (contraction-promoting) effect, L = lusitropic (relaxation-promoting) effect.

during this time, the substrate for this important phosphorylation reaction has not been identified.

**Sarcolemmal Ca$^{2+}$-activated ATPase.** A number of reports indicate that cyclic AMP-dependent protein kinases stimulate a sarcolemmal Ca$^{2+}$-activated ATPase (10). Because of several technical problems, however, these studies do not provide conclusive evidence for an effect of cyclic AMP that accelerates Ca$^{2+}$ efflux from the myocardial cell by way of a sarcolemmal Ca$^{2+}$ pump. Should such a response be confirmed with more highly purified sarcolemmal membranes, it would represent a lusitropic effect in that it promotes the removal of Ca$^{2+}$ from the myocardium.

**Interrelations Between the Inotropic and Lusitropic Effects of Cyclic AMP**

The many effects of beta-adrenergic stimulation of the heart on the biochemical and electrophysiologic properties of the myocardium are listed in Table 1. Table 2, which tentatively relates some of these responses to the major features of the contractile response to agents that increase cytosolic cyclic AMP levels, summarizes these effects in a different manner. It is possible, if not probable, that future research will add to the effects of beta-adrenergic stimulation listed in these tables.

Table 2. Possible Mechanisms for the Mechanical Response of the Heart to Agents That Increase Cyclic AMP

*Increased tension (inotropic)*
- Increased Ca$^{2+}$ influx via the slow inward current (III.C.1)
- Increased Ca$^{2+}$ release from the sarcoplasmic reticulum (III.B.2)

*Increased rate of tension rise (inotropic)*
- Increased Ca$^{2+}$ release from sarcoplasmic reticulum (III.B.2)

*Abbreviation of systole (lusitropic)*
- Accelerated transition between Ca$^{2+}$ pumping and Ca$^{2+}$ release states of the sarcoplasmic reticulum (III.B.1.C)

*Increased rate of tension decay (lusitropic)*
- Decreased Ca$^{2+}$ sensitivity of the contractile proteins (III.A.)
- Increased rate of Ca$^{2+}$ uptake into the sarcoplasmic reticulum (III.B.1.a and b)
- Increased Ca$^{2+}$ efflux via a sarcolemmal Ca$^{2+}$ pump (III.C.3)
- Increased Ca$^{2+}$ efflux via Na$^+$/Ca$^{2+}$ exchange (III.C.2)

Codes in parentheses refer to Table 1.
It should be pointed out that Tables 1 and 2 list only those effects believed to be due to direct actions of the beta-adrenergic agonists, and do not include a number of indirect responses that arise from other effects of these agents, notably the increased cytosolic Ca\(^{2+}\) during systole that is responsible for the important inotropic response. There is now growing evidence that an increase in cytosolic Ca\(^{2+}\) can amplify many of the primary effects of the catecholamines on both the sarcolemma (13) and sarcoplasmic reticulum (16).

Patterns of cyclic AMP modulation of excitation, excitation-contraction coupling, contraction and relaxation. An interesting pattern emerges from an examination of the many points at which cyclic AMP modulates the processes of excitation, excitation-contraction coupling and contraction and relaxation. This is especially clear in the case of troponin I phosphorylation, which, as discussed previously, has a lusitropic rather than an inotropic effect. Faced with the requirement for an elevated cytosolic Ca\(^{2+}\) concentration during systole to accomplish the essential positive inotropic response to agents that increase cytosolic cyclic AMP, the cell actually reduces the Ca\(^{2+}\) sensitivity of the contractile proteins, which has a negative inotropic effect.

One explanation for this pattern stems from a consideration of the general nature of the processes involved in excitation-contraction coupling and relaxation. As has already been pointed out, the delivery of Ca\(^{2+}\) to the contractile proteins during systole is a passive process that utilizes preexisting Ca\(^{2+}\) gradients to promote the flux of this cation across channels that open in the sarcoplasmic reticulum and sarcolemma. Thus, the rate at which Ca\(^{2+}\) appears in the cytosol during excitation-contraction coupling is limited by diffusion, which is a very rapid process. The maximal flux of Ca\(^{2+}\) across a single sarcolemmal ion channel, for example, has been estimated to be as high as 3 million Ca\(^{2+}\) ions per second (13). In contrast, the processes responsible for relaxation, which depend on ATP-utilizing ion pumps, are much slower. Measurements of the turnover rate of the Ca\(^{2+}\) pump of cardiac sarcoplasmic reticulum, for example, give values in the range of 10 Ca\(^{2+}\) ions per second for each pump monomer (17) (at 25° C, so that at 37° one might predict a rate of approximately 30 Ca\(^{2+}\) ions per second). Comparison of these rates shows clearly that relaxation is intrinsically much (approximately 100,000-fold) slower than activation.

It is not surprising, therefore, that in the response to an increase in cellular cyclic AMP, which promotes relaxation and contraction, Nature has chosen to make it easier to dissociate Ca\(^{2+}\) from the contractile proteins. Looked at another way, phosphorylation of troponin I and the cardiac sarcoplasmic reticulum, by producing opposite shifts in Ca\(^{2+}\) sensitivity (Fig. 3), promote the intrinsically slow processes of relaxation at the expense of the much more rapid processes of excitation. Figure 3 shows that under the influence of cyclic AMP, Ca\(^{2+}\) will dissociate more readily from the contractile proteins, whereas during diastole when cytosolic Ca\(^{2+}\) concentration becomes lowered, the Ca\(^{2+}\)-dependent rate of Ca\(^{2+}\) transport by the sarcoplasmic reticulum will remain high. In this way, the sympathetically stimulated heart is able to meet the requirement that an increased amount of activator Ca\(^{2+}\) be removed in a shorter time.

In summary, this brief report describes the manner by which each cardiac cycle after beta-adrenergic stimulation manifests both inotropic and lusitropic effects. The ability of the myocardium to effect these apparently opposite responses "from one mouth" can be explained by the com-
plex, yet beautiful integration among the many systems that participate in cardiac contraction and its control.

References
8. Tada M, Yamamoto T, Tonomura Y. Molecular mechanisms of active calcium transport by sarcoplasmic reticulum. Physiol Rev 1978,58,1-79