of Ca^{++} reported by Makinose and Hasselbach (14) is uncertain. In our experiments, addition of external Ca^{++} inhibited formation of the phosphoryl enzyme, but it could form from P_i in presence of internal Ca^{++} when ATP synthesis accompanies Ca^{++} efflux. Indeed Hasselbach et al. (37) have quite recently reported that $^{32}P_i$ was incorporated into the protein of sarcoplasmic reticulum vesicles preloaded with Ca^{++}. The amount of ^{32}P incorporated (2 moles/10^6 gm protein) was much larger than that obtained by us (0.125 moles/10^6 gm protein) using Ca^{++}-unloaded sarcoplasmic reticulum vesicles. Such apparent contrast in behavior can be explained by shifts of steps 4 and 5 toward the right due to binding of preloaded Ca^{++} with free E-P at step 4.

The cooperativity observed in the Ca^{++} inhibition of the $P_i \rightleftarrows HOH$ exchange suggests that an allosteric transition could be induced by Ca^{++} in the Ca^{++}-transport system of sarcoplasmic reticulum. A possibility previously suggested (13), based on the dependence of the breakdown of the phosphorylated intermediate on internal Mg^{++}, is that Mg^{++} is transported by sarcoplasmic reticulum as counter ion to Ca^{++}. The cooperative inhibition of the $P_i \rightleftarrows HOH$ exchange may reflect a Ca^{++}-induced transition of the transport system from one form (Mg^{++}-carrier), which has a binding site with high affinity for Mg^{++} and catalyzes translocation of Mg^{++} across membranes coupled with Mg^{++}-dependent $P_i \rightleftarrows HOH$ exchange, to the other form (Ca^{++}-carrier) which has two binding sites with high affinity for Ca^{++} and catalyzes translocation of Ca^{++}. This explanation is consistent with the fact that the breakdown of the phosphorylated intermediate was unaffected by external Ca^{++} as shown in Fig. 6 in spite of almost complete inhibition of the $P_i \rightleftarrows HOH$ exchange by external Ca^{++}.

The inhibition of the $P_i \rightleftarrows HOH$ exchange by nucleotides such as ATP and ADP could be explained by assuming that Mg^{++}-carrier form of the enzyme is