Since the introduction of glucagon into clinical medicine as a potentially useful positive inotropic cardiac agent in 1968, hundreds of papers dealing with its cardiovascular properties have been published. This surge of interest reflects the fact that even the best present-day therapy is frequently inadequate for many grave cardiac problems, such as cardiogenic shock, intractable congestive heart failure, and low cardiac output states. The initial animal studies suggested strongly that glucagon would assume a prominent place in the treatment of the extremely ill cardiac patient. These studies demonstrated that: (1) glucagon was a potent inotropic agent; (2) its effects were additive to those of digitalis; (3) although it stimulated the adenyl cyclase system to produce cyclic AMP, which resembles the mechanism of action of the catecholamines, its effects were not blocked by beta-receptor blocking agents; and (4) it did not produce premature beats or cardiac arrhythmias, and actually reverted arrhythmias to sinus rhythm in some instances.

With these findings as justification, clinical studies were undertaken to determine whether glucagon was useful therapeutically. The results of the early investigations were conflicting, with some workers reporting excellent responses and others observing no benefits. These disparate findings, in retrospect, were predictable since drug dosage varied widely and the patient population studied was markedly heterogeneous. Thus, glucagon was given sometimes as a bolus and sometimes as an infusion; patients ranged from those with chronic congestive heart failure of many years’ duration to those with acute episodes of failure secondary to myocardial infarction or operation. The possible importance of patient selection was emphasized by the animal studies of Gold et al. in which it was shown that papillary muscles, taken from cats in heart failure produced by pulmonary arterial banding, did not respond to glucagon either by an increase in inotropism or by an increase in adenyl cyclase activity; yet, these same papillary muscles could still respond normally to catecholamines. On the other hand, Strauer reported that human papillary muscles obtained at the time of operation from patients who had been in chronic congestive failure continued to react to glucagon. Contradictory findings are perhaps to be expected since it seems reasonable to suppose...
that many routes lead to the final common pathway of congestive heart failure, and that one or another drug may be more or less efficacious, depending on the initial insult to the heart and the homeostatic mechanisms utilized by the body. For example, the amount of endogenous glucagon secreted by the alpha-cells of the pancreas has not been determined in various cardiac conditions. If it is found that glucagon levels in some of these patients are elevated (it is known that insulin levels may be reduced) and, therefore, virtually all the glucagon receptors in the heart are occupied, it would seem reasonable to assume that additional glucagon administered by injection would have little or no beneficial effect. Such an explanation would account for the finding of Levey et al. that, in cats subjected to right heart failure, impairment in responsiveness to glucagon was present in both the adenyl cyclase system isolated from the stressed right ventricle and from the unstressed left ventricle. In some respects, an inquiry into the explanation as to why glucagon does not exert its usual effects in some abnormal hearts may be even more fascinating than why it does work in the normal heart. The answer to this question may provide a clue to the biochemical aberrations that produce cardiac decompensation.

Besides the lack of a detectable beneficial effect in some patients, certain untoward reactions have been reported. The most distressing has been the frequent development of nausea and vomiting which has, on occasion, necessitated discontinuation of therapy. In addition, the serum potassium level is generally lowered and hypoglycemia or hyperglycemia has been reported, although these changes have not usually been of clinical importance. It is also conceivable that patients with ischemic heart disease could be placed at a further disadvantage if the increase in myocardial oxygen consumption resulting from the augmented inotropic state produced by glucagon is not counterbalanced by an increase in coronary blood flow and/or in myocardial efficiency. This potential difficulty, of course, accompanies the use of any positive inotropic agent. Finally, it must be pointed out that the manufacturer has recently observed that, in dogs, small gel-like particles are occasionally seen in the 200–400 μ pulmonary arterioles when infusions of glucagon are given in high dosages for prolonged periods of time. These particles may represent the gel form of glucagon (Eli Lilly and Co.: Personal communication). The significance of this finding awaits further investigation and clarification.

What, then, is the present status of glucagon in cardiac therapy? The paper by Lvoff and Wilcken in this issue of Circulation helps to clarify the answer. First, they show that concomitant administration of an antiemetic agent allows glucagon to be administered in doses that are therapeutically effective. Second, they emphasize that glucagon should be used as adjunctive therapy and that standard treatment should be continued. Third, they demonstrate that many patients who are gravely ill are improved by addition of glucagon. Fourth, they subdivide their patients into groups in an attempt to define those patients in whom glucagon will be most useful, although we are still not in a position to predict which patients will be benefited. Further studies in which important hemodynamic variables such as cardiac output, intravascular pressures, myocardial metabolism, and myocardial wall motion are measured may provide the answer to this question. Fifth, they report data to indicate that for the patient who has received an excessive amount of a beta-receptor blocking agent, glucagon is an effective means of treatment. Sixth, they show that, in certain patients who have developed functional blocks in the bundle-branch system of the heart after an acute myocardial infarction, administration of glucagon may produce reversion to normal conduction. Most important, the paper gives testimony that glucagon is neither miraculous nor worthless; we must, however, learn the indications and contraindications for its use.

To that end, more empiric clinical studies must be carried out to try to define further the patient population that will benefit most from
glucagon administration. More biochemical studies are needed to elucidate the metabolic and possible stearic effects glucagon exerts on the normal and diseased myocardium. In short, answers that have already been obtained serve merely as a prelude to further intensive investigation.

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References
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