RJR Inter-office Memorandum

Subject: Research Proposal Submitted to R. J. Reynolds by Robert B. Jennings, Keith A. Reimer, Raymond Ideker, James E. Lowe, Charles Steenbergen, et. al.

Date: May 7, 1981

To: Dr. Frank G. Colby

From: Kenneth G. Orloff

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This proposal is concerned with biochemical, physiological and pathological changes in myocardial cells as a consequence of ischemia. The proposal is divided into 4 major sections which reflect the specific interests of the 4 co-investigators. Since, in my opinion, the proposals do not have equal merit, I'll discuss each separately.

K. Reimer is interested in developing techniques for producing myocardial tissue that has been uniformly injured by ischemia. Presently available techniques yield myocardial tissue containing cells with varying degrees of ischemic exposure. This variability complicates interpretation of subsequent studies. Therefore, the ability to produce a more uniform injury is desirable.

Reimer proposes to achieve this objective by complex techniques which involve pumping arterial blood for long periods of time through the vasculature of living animals. The technique, itself, has little theoretical importance. Its value lies in its use for subsequent studies. Therefore, the merits of this proposal depend on the merits of those studies which utilize this technique.

R. Ideker is interested in studying arrhythmias which result from ischemic injury to myocardial tissue. Since most deaths following a myocardial infarction result from ventricular arrhythmia, this is an obviously important area of study. This proposal study falls in the domain of fundamental research. As such, it is not possible to predict whether this study could lead to benefits in the treatment or prevention of cardiac arrhythmias.

J. Lowe proposes to monitor various biochemical parameters as indicators of ischemic death in myocardial cells. In particular he proposes to use antibody fragments to the contractile protein, myosin, to monitor ischemic injury. Presumably ischemic injury to the sarcolemma allows molecules of myosin to escape from the myocyte which can then be detected by the antibody fragments to myosin. In my opinion, the leakage of myosin from the cell represents a late stage of necrosis - and well past the reversible stage of cell death. Therefore, I do not think it is particularly useful to measure a phenomenon which occurs after cell death has already occurred. It would be more useful to measure a parameter which could indicate that cell death is about to occur - i.e., while the cell is at a still reversible stage. In this regard, J. Lowe's proposal to measure local pH and/or ionic concentrations might be a more useful parameter. As stated in the proposal, this information might be useful in monitoring ischemic injury during cardiac operations.

C. Steenbergen proposes to measure biochemical changes in the sarcolemma after ischemic injury. My comments on J. Lowe's study also apply to this study - i.e., he is studying a phenomenon that occurs after cell death has already occurred. On this basis, I would not recommend approval for this particular section of the proposal.