

**Cox J L, McLaughlin V W, Flowers N C & Horan L G.** The ischemic zone surrounding acute myocardial infarction. Its morphology as detected by dehydrogenase staining. *Amer. Heart J.* 76:650-9, 1968.  
[Sect. Cardiology, Dept. Medicine, Univ. Tennessee, Memphis, TN]

This article offers the first pathologic description of the so-called 'twilight zone' of intermediate cellular injury located at the periphery of an acute myocardial infarction. The presence of this twilight zone served as the stimulus for the evaluation of much of the pharmacologic and mechanical therapy subsequently introduced for the treatment of acute myocardial ischemic injury and is believed to be the site of origin of reentrant ventricular tachyarrhythmias associated with coronary artery disease. [The SCJ® indicates that this paper has been cited in over 235 publications since 1968.]

James L. Cox

Division of Cardiothoracic Surgery  
Washington University School of Medicine  
St. Louis, MO 63110

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"Prior to the mid-1960s, the general concept of an acute myocardial infarction was that the tissue injury that followed acute coronary artery occlusion was most likely nonuniform. However, this nonuniformity of tissue injury had never been demonstrated, and thus, from a diagnostic and therapeutic standpoint, an acute myocardial infarction was perceived as being a single event that resulted in tissue death within a predetermined region of myocardium. The likelihood of altering the course of tissue death following acute coronary artery occlusion was, therefore, considered remote because therapeutic interventions could be applied only after the fact.

"In the spring of 1965, as a sophomore medical student at the University of Tennessee Medical School in Memphis, I was given the opportunity to work in the research laboratory of Leo G. Horan and Nancy C. Flowers, both cardiac electrophysiologists. We felt that it might be possible to demonstrate by histochemical techniques that tissue injury in acute myocardial infarction was nonuniform and that the progression of injury during the

first several hours following coronary occlusion was a dynamic process amenable to potentially beneficial therapeutic intervention. I was given a copy of A.G.E. Pearse's histochemistry textbook,<sup>1,2</sup> a small laboratory, a certain amount of research funds, and a great deal of encouragement to document our hypothesis pathologically. After an entire year of literally hundreds of failures, I adjusted the pH of the tissue incubating solution incorrectly in one experiment and, as a result, was able to document quite clearly for the first time the nonuniformity of injury in acute myocardial infarction. My euphretic at seeing this zone for the first time must be deleted.

"Within a few months, I was joined by Victor W. McLaughlin, a medical intern, and together we were able to reconstruct two-dimensional, then three-dimensional, 'histochemical maps' of acute myocardial infarctions that clearly documented the presence of an ischemic but viable zone of tissue separating the central zone of progressive necrosis from surrounding normal myocardium. I presented this work at the American Heart Association meeting in New York City in October 1966,<sup>3</sup> and subsequently published it in the *American Heart Journal* in November 1968. The ischemic zone that we identified has frequently been referred to as the 'twilight zone' of injury in acute myocardial infarction. Although subsequent, more sophisticated pathologic studies have questioned the existence of such an intermediate zone of ischemic injury,<sup>4</sup> much of the pharmacologic and mechanical (i.e., intra-aortic balloon pumping) therapy introduced for the treatment of myocardial ischemic injury in the past 15 years has been based on the presence of such a zone. In addition, most investigators feel that this twilight zone is the site of origin of reentrant ventricular tachyarrhythmias associated with coronary artery disease.

"I believe this work has been cited often for two reasons: 1) it formed the basis for rational efforts to decrease the size of an acute myocardial infarction by therapeutic intervention, and 2) it established the anatomic basis of ischemic ventricular tachyarrhythmias that led to the development of direct endocardial surgical techniques that are now being applied widely for the treatment of refractory ventricular tachycardia associated with coronary artery disease."<sup>4</sup>

1. Pearse A G E. *Histochemistry: theoretical and applied*. London: Churchill, 1960. 998 p.

2. .... Citation Classic. Commentary on *Histochemistry: theoretical and applied*.

*Current Contents/Life Sciences* 24(32):17, 10 August 1981.

3. Cox J L, McLaughlin V W, Flowers N C & Horan L G. Changes in cellular dehydrogenase enzymes in acute myocardial infarction. *Circulation* 34:III-80, 1966.

4. Cox J L. Anatomic-electrophysiologic basis for the surgical treatment of refractory ischemic ventricular tachycardia. *Ann. Surg.* 198:119-29, 1983.