The Histologic Border Zone of Acute Myocardial Infarction—Islands or Peninsulas?

Stephen M. Factor, MD, Edmund H. Sonnenblick, MD, and Edward S. Kirk, PhD

Observation of isolated islands of apparently surviving myocardium within areas of necrotic tissue at the edge of myocardial infarctions has been interpreted by some as histologic evidence of a unique "border zone" region. Serial section reconstruction of transmural canine myocardial infarctions was performed in this study to establish whether these islands were truly isolated or were continuous peninsulas of tissue separated by the plane of section. Three-dimensional analysis of the infarcts revealed no true islands but instead demonstrated a region composed of highly complex interdigitating peninsulas. We conclude that there is an extremely irregular but sharp boundary demarcating normal and infarcted myocardium with no intermediate zone. This observation is discussed in relation to recent data, based on coronary blood flow and creatine phosphokinase analysis, which also demonstrates a sharp boundary between the normal and infarct zones. (Am J Pathol 92:111–124, 1978)

IN ACUTE MYOCARDIAL INFARCTION, the region of the ventricle between an area of grossly normal tissue and infarcted tissue has been termed a "border zone." The existence of this zone has been inferred from biochemical,[1-3] electrocardiographic,[4-6] and histochemical [7] studies, which have demonstrated intermediate values in the region between the clearly necrotic and normal myocardium. Histologically, the observation of islands of apparently surviving myocardium within areas of necrotic tissue at the border of infarcts has been considered a manifestation of myocardium which is jeopardized or at risk but which receives sufficient oxygen to survive in a precarious "twilight zone."[8]

Although several authors [9-11] have disputed the existence of a distinct zone or region of moderately ischemic myocardium which separates necrotic and normally perfused tissue, histologic delineation of such a region has not been forthcoming. In particular, no study has attempted to answer the question whether the islands of viable tissue commonly observed in the so-called border zone are discrete or are peninsulas of homogeneous tissue irregularly separated by the plane of section. In the following report, serial reconstruction of myocardial infarcts are described in 5 dogs.

From the Departments of Pathology, Medicine, and Physiology, Albert Einstein College of Medicine, Bronx, New York.

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Address reprint requests to Dr. Stephen M. Factor, Department of Pathology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.

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In these studies, a discrete interface between necrotic and normal myocardium is delineated and its irregular features are defined.

Materials and Methods

Five mongrel dogs weighing 25.0 ± 0.7 kg (mean ± 1 SE) were anesthetized with sodium pentobarbital (27.5 mg/kg) intravenously. Additional pentobarbital was administered as required to maintain anesthesia. After intubation with a cuffed endotracheal tube, the dogs were ventilated with an intermittent positive-pressure respirator with 100% oxygen. Under sterile conditions, a thoracotomy was performed in the fifth left intercostal space. The heart was exposed by incising the pericardium parallel to the phrenic nerve, and the left anterior descending coronary artery (LAD) was isolated below its first diagonal branch. The LAD was ligated acutely, and the pericardium and chest cavity were closed. Blood pressure, heart rate, and the electrocardiogram were monitored continuously throughout the procedure.

Following closure of the chest, the chest cavity was evacuated by a suction tube for 4 hours. Premature ventricular beats and tachycardias occurring after coronary occlusion were suppressed with bolus injections of 50 to 100 mg of a 2% solution of lidocaine hydrochloride. Additionally, 300 to 400 ml of physiologic saline were administered during the first hours of recovery along with a single dose of sodium ampicillin (500 mg) intramuscularly and morphine sulfate (10 to 15 mg) subcutaneously as needed for comfort.

On the following day, the dogs received 10 mg of morphine sulfate intramuscularly followed by less than one half the initial dose of pentobarbital. A 24-hour period was chosen to allow for unequivocal delineation of infarcted and normal tissue by gross and microscopic examination. After induction of anesthesia, the chest was opened and ventricular fibrillation was induced. A 5- to 8-ml bolus of 2% Evans blue dye was injected into the ligated vessel as previously described.[12] The dye stained the area originally supplied by the LAD distal to the site of ligature. The heart was removed and sectioned horizontally (Text-figure 1). Three zones were grossly identified: a central pale unstained infarct zone, a peripheral zone stained blue by the dye, and normal-appearing unstained myocardium. In all 5 dogs, transmural infarction was observed. A transmural section of left ventricle measuring approximately 5.0 × 1.2 × 0.5 cm, including normal tissue, blue stained border zone, and central infarct, was removed and fixed in phosphate-buffered 4% formaldehyde. The remainder of the heart was frozen quickly in a bath of dry ice and alcohol. Frozen tissue from the center of the infarcted zone and the normal myocardium were analyzed for tissue creatine phosphokinase (CPK) activity by the method of Kjekshus and Sobel.[1]

The formaldehyde-fixed tissue was carefully oriented and embedded on end, with the vertical axis extending from epicardium to endocardium and the horizontal axis representing the original thickness of the myocardial ring. Thus, when the tissue was entirely sectioned, sequential changes in the normal, border, and central necrotic zones could be traced histologically. The tissue was sectioned at 6 μ, with two or three serial sections on each slide. In an initial pilot study in which all sections were examined, it was determined that geographic features of the infarcted and normal tissue could be recognized and traced adequately at 200-μ intervals. This interval was, therefore, maintained throughout the study. In all, between 200 and 290 slides (average 247) were examined in each case.

The serial sections were stained with hematoxylin and eosin; every tenth slide was stained with von Kossa stain for calcium salts. Histologic criteria used for the evaluation of infarcted myocardium included cytoplasmic hypereosinophilia and hyalinization, nuclear pyknosis, myocytolysis, contraction bands, intracytoplasmic calcification, and interstitial polymorphonuclear cells. Hypereosinophilia and cytoplasmic hyalinization were generally the most helpful characteristics for differentiating normal and infarcted tissue. Each section was examined at scanning and medium (10×) power, and the entire section was

sketched on paper, identifying normal and necrotic tissue. By maintaining the proper geographic orientation, it was possible to sequentially track the border of the infarct including islands of isolated tissue from section to section.

Results

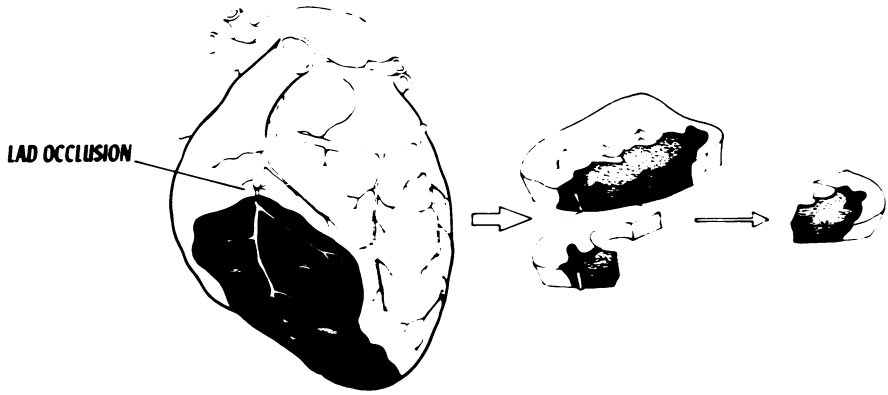
Creatine Phosphokinase Depletion

The CPK activity from the transmural central necrotic zone averaged 45.2 ± 6.8% (mean ± SE) of the activity of CPK analyzed from distal normal tissue. These data confirmed the gross and histologic observations of infarcted myocardium.

Histologic Border Zone

The serial sections from the 5 animals revealed similar changes and will be described together except where noted. Twenty-four hours after acute coronary occlusion, infarcts were histologically distinct, allowing sharp delineation of the borders between necrotic and normal tissue (Figures 1 and 2). The infarcted myocardium was intensely hypereosinophilic with hyalinization and loss of cytoplasmic detail. Nuclei were pyknotic and hyperchromatic. Both infarcted and normal tissue could be identified in each section. In the endocardial region of the sample, a zone of relatively homogeneous necrosis was found with areas of focal prominent contraction bands and myocytolysis in the immediate subendocardial muscle. In the epicardial region, normal myocardium was predominant except in sections where transmural necrosis was present. In general, the extent of infarcted tissue was greater in the subendocardial portions of the sections. A narrow zone of preserved muscle, usually no more than one to two cells thick was focally observed in the subendocardium, and similar preservation was present beneath the epicardium in those sections with transmural necrosis. The epicardial adipose tissue was infiltrated by polymorphonuclear leukocytes, presumably a result of surgical manipulation.

A highly irregular zone of infarcted or normal muscle cells ("islands") was found between the necrotic and normal zones and extended for a variable distance in either direction away from the sharp line dividing the two areas (Text-figure 2 and Figure 1). This "border zone" was variable in size but never exceeded more than one half the vertical dimension of the section (approximately 0.5 cm). Section-to-section tracing of these seeming islands of tissue demonstrated that all could be followed back to either homogeneous normal or homogeneous necrotic myocardium (Figures 3 through 10). The only exception encountered was infarcted or normal masses of tissue at the lateral borders of the section. Presumably, these continued into homogeneous tissue either above or below the plane of

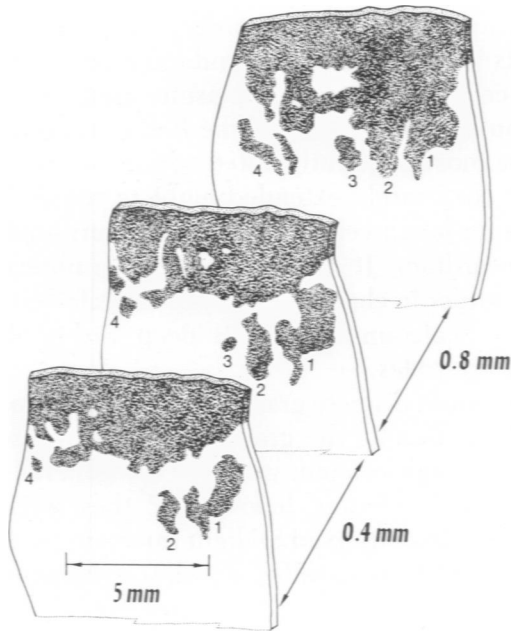


TEXT-FIGURE 1 — Twenty-four hours after ligation of the left anterior descending (LAD) coronary artery, Evans blue dye (*black* in this illustration) was injected below the ligature to delineate the area supplied by the vessel. The heart was sectioned horizontally from apex to base and a representative tissue slice (at *right*) was removed. Three zones can be identified: a) a central, focally transmural region (finely strippled) of unstained necrotic myocardium, b) a peripheral zone stained by the dye and corresponding to the border zone, and c) completely unstained normal myocardium. A segment of the formaldehyde-fixed myocardial ring including all three zones (at *far right*) was rotated 90° and embedded on end in paraffin. The entire tissue segment was sectioned at 200-μ intervals to allow for sequential tracing of the histologic changes from the normal zone through the border and infarct regions.

section, ie, confluent with similar myocardium either above or below the horizontal ring of myocardium removed for histologic analysis. Serial reconstruction of the border zone revealed that it was a highly irregular but histologically sharp boundary, with numerous *peninsulas* of interdigitating necrotic and normal myocardium (Text-figure 2). These peninsulas were observed throughout the infarct, as the serial sections followed the progressive increase in the necrotic tissue from the normal zone toward the transmural (central) necrotic zone. Only where the tissue was infarcted transmurally were these peninsulas absent. Thus, random two-dimensional sectioning of an infarct at any level in the wall would create the impression of three zones of tissue: a central necrotic area, a peripheral normal area, and an intermediate area interposed between these two, containing varying amounts of isolated infarcted and normal tissue. It is only with serial sections that the appearance of histologically discrete islands can be seen to be a function of two-dimensional sectioning of a complex three-dimensional border.

Inflammation

Polymorphonuclear leukocytes (PMNs) extended from the subendocardium to a depth of approximately one half the thickness of the infarct where they appeared as a bandlike infiltrate. In general, only small



TEXT-FIGURE 2 — This composite illustration is based on original drawings of three myocardial sections. Intervening sections have been omitted for clarity. Preserved subepicardial normal myocardium (*shaded area*) can be seen at the top of each section. In the foreground, two islands of normal tissue (*1* and *2*) are completely separated from the subepicardial normal zone. Two sections deeper within the block, island Number 1 is attached to the subepicardial normal muscle and forms a peninsula; island Number 2 is still isolated. At the same level, a new island (*3*) becomes apparent. The last drawing, four sections away, shows complete continuity between islands Number 1 and 2 and the overlying subepicardial myocardium. Island Number 3 is larger at this level and becomes attached in subsequent sections. Several islands on the left (*4*) progressively enlarge and eventually become peninsulas. Additionally, the islands of necrotic tissue (*unshaded*) within the subepicardial zone demonstrate continuity with the infarct region at various levels, and, therefore, are also peninsulas. The reconstruction illustrates that the border region consists of numerous interdigitated peninsulas which may appear like islands of normal or necrotic tissue when any one section is viewed.

numbers of PMNs were in the histologic border zone. Surprisingly, rather than continuing as a sharply demarcated infiltrate throughout all sections, the inflammation was discontinuous, waxing and waning irregularly. No observed differences were noted between necrotic tissue containing large numbers of PMNs and necrotic tissue devoid of a significant infiltrate to account for the variability.

Calcification

All infarcts demonstrated small groups of cells or individual cells containing intracytoplasmic depositions of granular calcium. The calcification which was confirmed with von Kossa stain was readily observed in the hematoxylin and eosin sections as basophilic granules. The calcium was

localized entirely to the histologic border, except for rarely observed deposition in cells just beneath the endocardium. Small numbers of widely separated cells containing cytoplasmic granules of calcium were always observed on the infarct side of the border (Figures 1 through 6). Involved cells were most frequently noted within two to three cells of the normal tissue, but they rarely extended eight to ten cells deep into the infarct zone. Calcium-laden cells were observed surrounding the normal peninsulas of myocardium. It was not unusual to observe small patent vessels within the border in close proximity to the calcified cells. In several instances, groups of calcium-laden cells deep within the infarct zone surrounded patent arterioles.

Calcium was present in discrete granules measuring 1 to 3 μ in diameter within the cytoplasm. Rarely, the granules were so dense as to obscure cellular outlines. Although calcium granules are generally considered to represent mitochondrial calcium deposition,[13] they were clearly larger than normal mitochondria observed by light microscopy. This may be due to marked swelling of these organelles, which is a characteristic feature of early cell necrosis.[14]

Discussion

In this study, serial sections have been used to reconstruct the anatomy of the interface between normal and infarcted myocardium 24 hours after acute coronary occlusion. This border was shown to be irregular but remarkably discrete. The complex interdigitations of irregular projections along the interface with the normal tissue precludes the separation of either normal or necrotic muscle in this region by gross methods. Islands of viable myocardium at the border of infarcts, which others have noted [15-18] and have considered to be the histologic hallmark of a zone of intermediately ischemic myocardium,[4,8] result from the sectioning of peninsulas or fingers of necrotic and viable myocardium in a two-dimensional plane.

This three-dimensional model of a myocardial infarction supersedes the usual two-dimensional mental image of infarcts and may provide new insights for recent studies [4,6,19-21] designed to define and modify a moderately ischemic border zone in the hope of salvaging significant myocardium following a clinical or experimental infarct. Studies in which electrophysiologic markers have been used to assess the status of underlying ischemic tissue [4,6,19-21] have inferred that intermediate degrees of ischemia are present in the zone between the necrotic and normal myocardium. This has been identified as a border zone at risk for complete infarction. Although the electrocardiographic approach has been criti-

cized on theoretic electrophysiologic grounds,[22] it may also be questioned on the basis of the histology of this zone, which suggests that the zone may consist of an intimate admixture of confluent normal and ischemic or infarcted muscle. Caution must be used, however, in extrapolating our histologic observations made at 24 hours after occlusion to electrical activity measured at various times while the infarct evolved. A detailed comparison may not be useful since the histologic approach provides spacial detail and resolution that cannot be approached by extracellular electrophysiologic techniques.

It is conceivable that the myocardium in the border zone, which we interpreted as normal when studied histologically with hematoxylin and eosin, could demonstrate severe but potentially reversible damage if studied with other stains or with electron microscopy. Our observation of a discrete interface between normal and necrotic myocardium is somewhat at variance with the findings of Buja et al,[23] who described viable but damaged cells at the edge of 24- to 48-hour-old infarcts. That the border we observed was sharp was fortunate because it allowed precise tracing of the infarct geometry. In general, we found the necrotic tissue to be remarkably homogeneous with the exception of focal areas of contraction bands and myocytolysis in the immediate subendocardial zone. Although it is possible that we overlooked small foci of damaged but viable myocardium in the border, it is difficult to be certain that the cells described by Buja et al[23] with nuclear pyknosis, cytoplasmic eosinophilia, and vacuolization were viable.

In regard to the present findings based on an analysis of myocardial infarction after 24 hours of vascular occlusion, studies by Jennings and coworkers [16,24,25] have led to the view that the ultimate fate of the myocardium is determined in a relatively short period following coronary ligation. In their model, posterior papillary muscle demonstrated irreversible damage after 60 minutes of ischemia, while mid-wall and subepicardial myocardium survived for as long as 3 to 6 hours after coronary occlusion.[25] Since the histologic criteria and temporal progression of myocardial infarction are so well established,[26,27] it seems unlikely that significant amounts of viable myocardium judged histologically after 24 hours of ischemia are at risk due to the initial vascular occlusion.

The concept that the borders of infarcts are distinct but highly complex boundaries also raises questions regarding interpretation of intermediate levels of tissue CPK depletion as an indicator of jeopardized ischemic myocardium.[1,2] Any portion of myocardium removed from this zone must include both normal and infarcted tissue and may, therefore, result in levels of CPK proportional to the ratio of normal and necrotic muscle in

the sample. This was confirmed by recent data from our laboratory [11] which demonstrated that CPK is uniformly depleted from the lateral edge to the center of the myocardium supplied by the occluded LAD, without an intermediate zone of depletion, when tissue normally supplied by vessels other than the LAD is excluded from the analysis.

In addition to this latter study, several other recent reports support the histologic concept of a sharply defined boundary. Marcus et al [9] analyzed small segments of myocardium with injected radioactive microspheres following occlusion of the circumflex coronary artery and were unable to demonstrate a "buffer zone" of moderately ischemic myocardium surrounding the severely ischemic central zone. Their description of the geometry of the ischemic area, as defined by microspheres, as "a central ischemic core with multiple segments attached to the core," could be taken as the equivalent of the histologic geometry with peninsulas of necrotic tissue extending from a mass of homogeneously infarcted myocardium. Barlow and Chance [10] used NADH fluorescence as a marker of myocardial ischemia in perfused rat hearts in which a coronary artery was ligated. A sharp line of transition between the ischemic and normal areas was demonstrated, which suggested that any hypoxic border zone would be extremely small, if present at all. It should be noted that microsphere studies [9,11] cannot rule out the possibility of a border zone approximately 1 mm in width. Histologically, even this small a zone, representing five sections, could not be identified in the present study.

The present findings based on observations at 24 hours after occlusion neither support nor refute the observations of Cox et al.[7] These authors utilized histochemical staining for dehydrogenase enzymes to demonstrate an intermediate zone between depleted central infarct and peripheral normal muscle. This intermediate zone was characterized by myocardial cells with swollen mitochondria and an increased affinity for the histochemical stain. These findings were felt to be indicative of a zone of intermediate ischemia. As the time course of ischemia lengthened, this intermediate zone shrank in size. It may be that the intermediate zone described by Cox corresponds to the necrotic interface in which we observed focally calcified granules. The size and location of the granules reported by Cox suggest that they could be the swollen mitochondria containing calcium salts that we observed; their size is consistent with the "large dot" staining observed in the histochemical study. It is significant that the calcium-laden cells were only observed on the necrotic side of the tissue interface, as noted recently by Buja et al[28] and previously by Jennings.[29]

Two ancillary observations in this study are of interest. The previously noted localization of focal calcification in a narrow zone parallel to the

necrotic interface confirms the description of Buja,[28] Jennings,[29] and other investigators. Identification of these calcium-laden cells around seemingly patent vessels and, in several instances, around arterioles deep within the infarct zone supports Jenning's hypothesis [13,29] that calcification occurs following perfusion by vessels in the normal area or by reflow in the occluded vascular tree. Why only small numbers of cells in a sharply delimited zone should be so affected is unknown. A second observation pertains to the localization of polymorphonuclear leukocytes within the infarct zone. The inflammatory cells extend from the subendocardium to an area of dense infiltration approximately one half the way into the zone of necrosis 24 hours after a vascular occlusion. Only rarely were they noted in the interdigitated border and then only in small numbers. Unexpectedly, however, the infiltrate was not continuous deep within the infarct, and in some sections it was virtually absent. Although probably a function of vascular patency, no specific explanation for this phenomenon is forthcoming.

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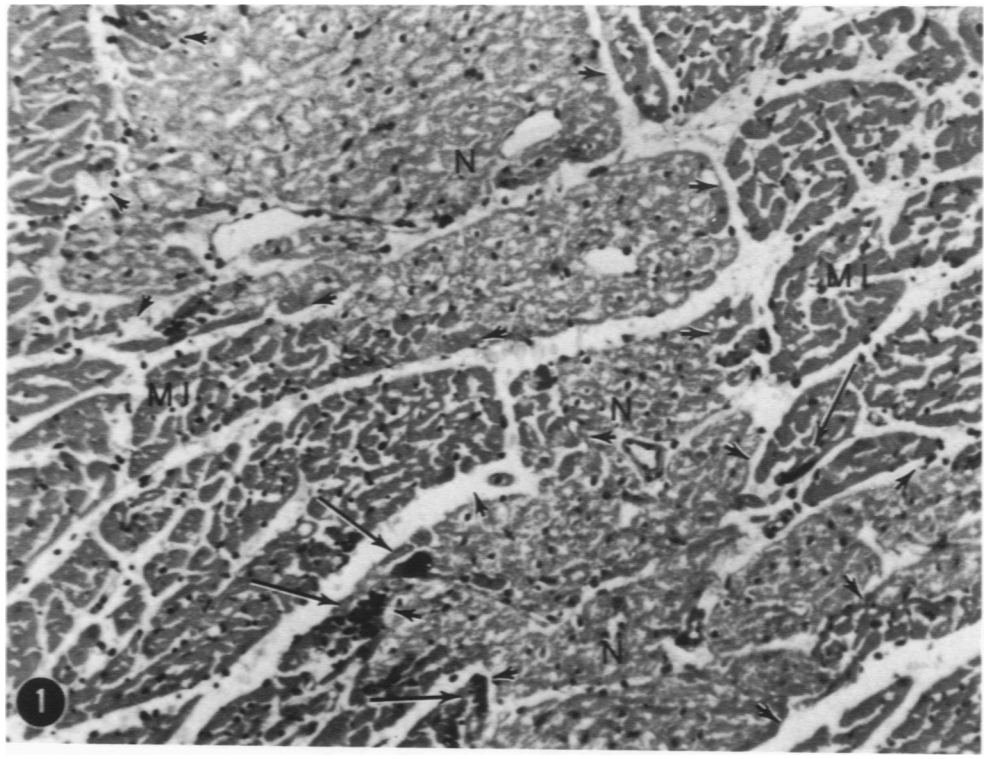


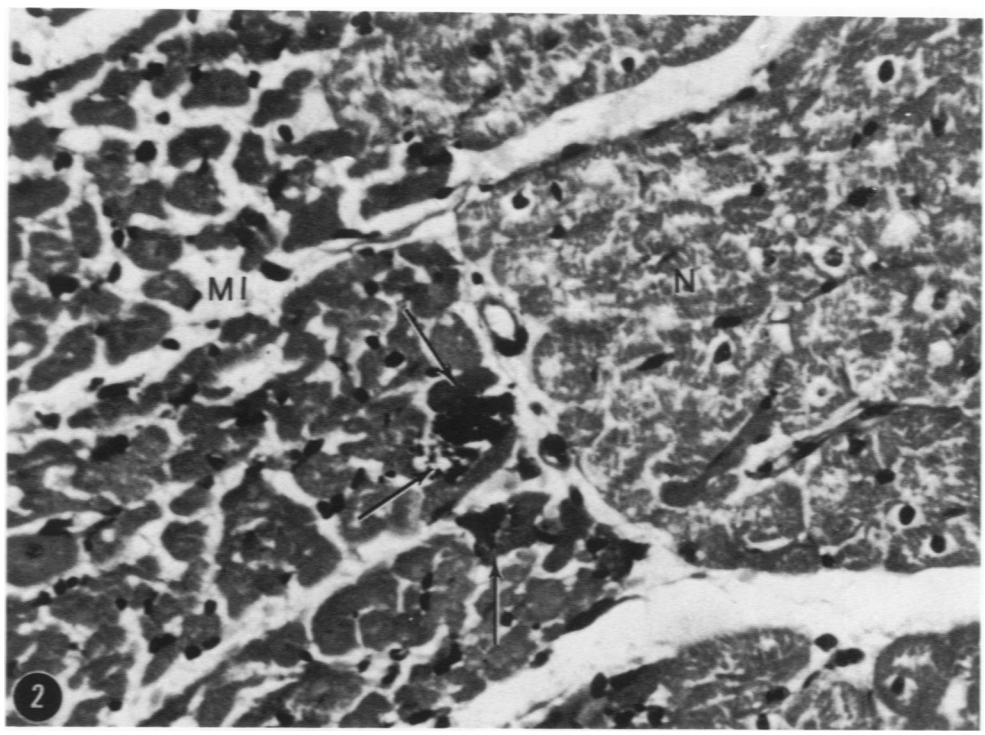


Figure 1—An island of normal tissue (*N*) is completely surrounded by necrotic myocardium (*MI*) in this low-power photomicrograph of the border region. The sharp boundary between the necrotic and normal muscle (*short arrows*) is obvious. The necrotic myocardium stains more intensely with eosin (*darker in black and white*). Scattered but relatively few polymorphonuclear leukocytes are apparent in the interstitium of the necrotic zone. Several darkly staining cells containing calcium granules (*long arrows*) closely parallel the boundary between the two zones but are located on the infarct side of the border. (H&E, × 96) **Figure 2**—The sharp boundary between normal tissue (*N*) and hyper-eosinophilic, hyalinized necrotic tissue (*MI*) is apparent. Several cells with multiple calcium granules (*arrows*) are present in the infarct zone parallel to the normal myocardium. (H&E, × 384)

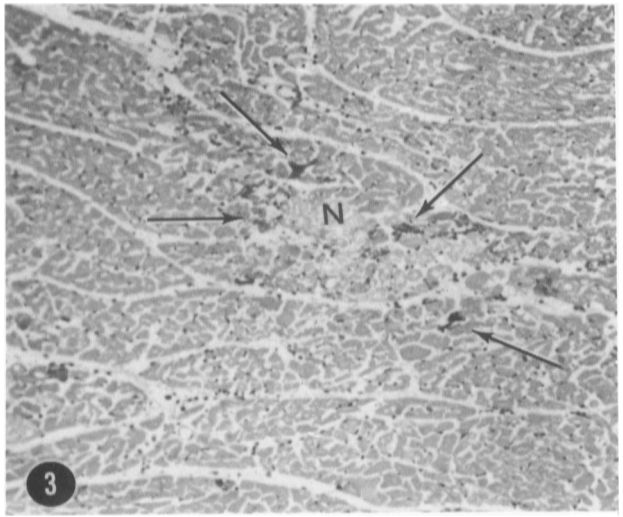
Figures 3 through 10—The following eight photomicrographs represent sequential sections, each separated by 200 μ. They demonstrate that when an island of normal tissue is progressively traced, it becomes confluent with the main mass of normal myocardium and is, therefore, a peninsula. The eight sections were stained with hematoxylin and eosin and are depicted at a magnification of 96×.

Figure 3—A small group of normal myocardial cells (*N*) is completely surrounded by necrotic tissue. Darkly staining calcium containing cells (*arrows*) are close to the border.

Figure 4—The isolated group of cells in Figure 3 is now a well-defined island of normal tissue (*N*). Many necrotic cells surrounding the island contain calcium granules (*arrows*).

Figure 5—The normal tissue (*N*) is enlarging and is becoming confluent with normal myocardium at *upper left.* Calcium-containing cells are prominent in the necrotic zone (*arrows*).

Figure 6—Continued enlargement of the normal zone (*N*) is apparent; other areas of noninfarcted myocardium are visible at this level. A group of heavily calcified cells (*arrows*) surrounds a thin-walled patent vessel (*V*).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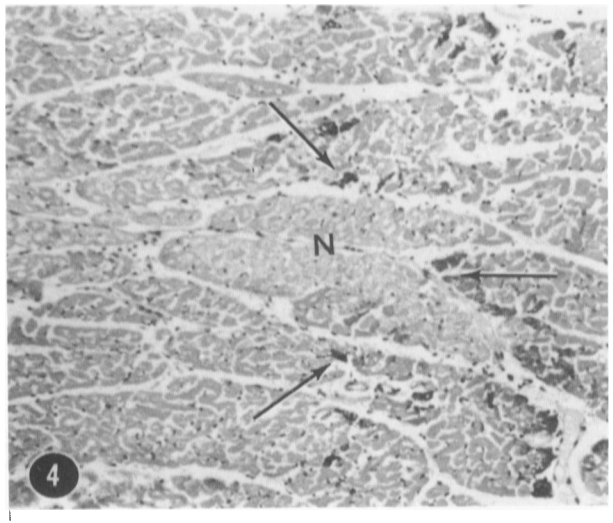
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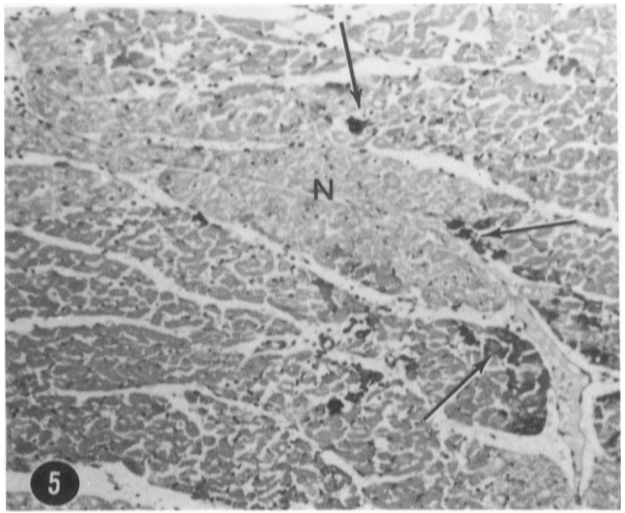
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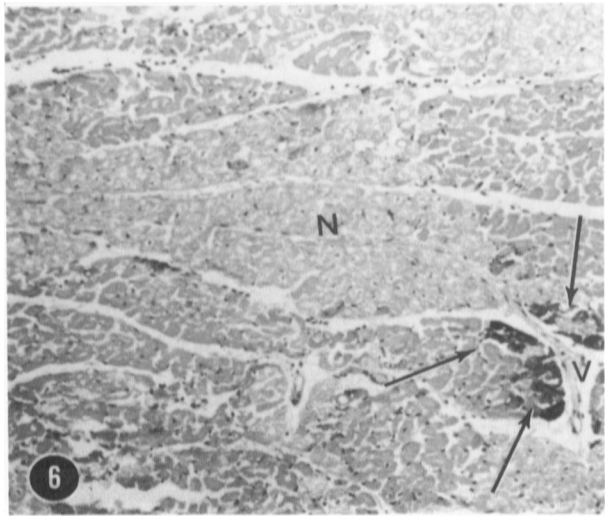
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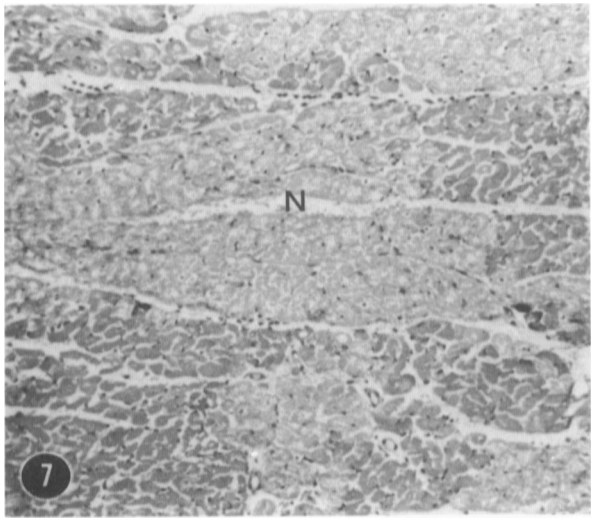

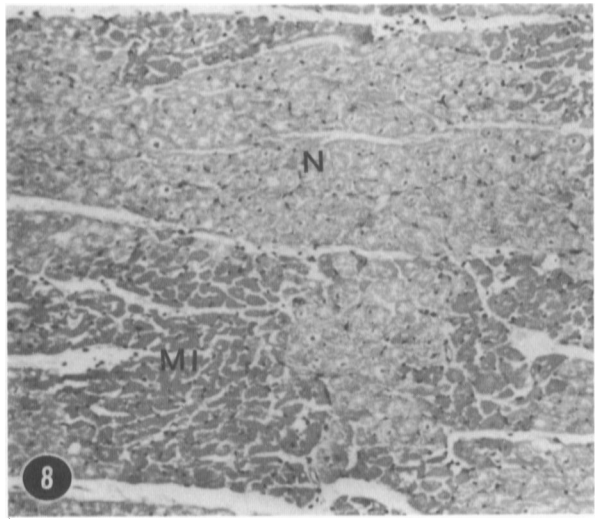

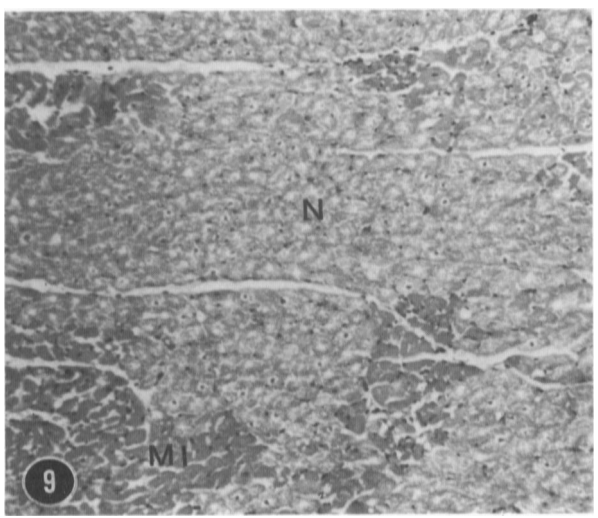

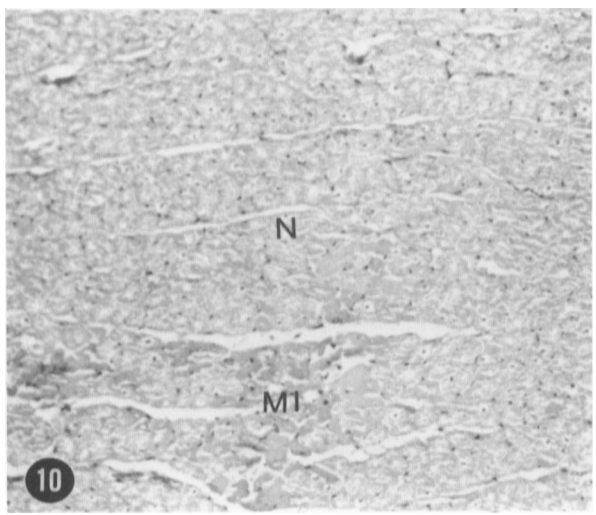

Figure 7—Further progression of the normal island (*N*) is noted with beginning separation and isolation of the necrotic tissue into islands. Calcified cells are rare at this level. **Figure 8**—At this level, the original normal island (*N*) is extensively attached to other areas of normal tissue. A completely separated island of necrotic tissue (*MI*) is surrounded by normal myocardium. **Figure 9**—Progressive increase in normal myocardium (*N*) and diminution of necrotic myocardium (*MI*) are observed at this level. **Figure 10**—The final section of this sequence shows the original island to be entirely confluent with normal myocardium (*N*). An island of necrotic myocardium (*MI*) is present; however, it too is a peninsula confluent with the necrotic tissue observed in the preceding sections.