Time-dependent change in electrophysiologic milieu after myocardial infarction in conscious dogs

HENRY J. DUFF, M.D., JUSTIN M. E. MARTIN, M.D., AND M. RAHMBERG

ABSTRACT This study was designed to assess the time-dependent change in propensity to induction of malignant ventricular tachyarrhythmia after myocardial infarction. Instrumented conscious dogs were assessed during serial drug-free electrophysiologic studies over 26 ± 9 days (range 17 to 35 days) after 2 hr occlusion-reperfusion of the left anterior descending coronary artery. Of the 19 animals studied, 11 continued to have sustained ventricular tachyarrhythmias inducible (group I) over this time period. In the eight remaining animals, spontaneous loss in the ability to induce sustained ventricular tachycardia occurred (group II). Myocardial infarct size in group I animals (18 ± 8%) was significantly greater than that in group II dogs (12.5 ± 5%; p<.05). Even in group I animals, time-dependent changes occurred in the number of extrastimuli required to induce ventricular tachycardia and the frequency with which left ventricular stimulation was necessary. A differential pattern of time-dependent changes in electrophysiologic variables was observed when comparing group I and II animals. The conduction time to the infarct zone was prolonged during follow-up in group I animals, while in group II animals this variable was unchanged. Repolarization time recorded in the border zone remained unchanged in group I animals, but it was significantly shortened in group II animals. In addition, ventricular effective refractory period in the infarct zone shortened over time in group I animals but did not change in group II animals. In conclusion, time-dependent changes occur in electrophysiologic variables that are associated with a progressive decrease in propensity to induction of ventricular tachycardia after myocardial infarction. A critical determinant of whether propensity to ventricular tachycardia resolves over time is size of myocardial infarction.


VENTRICULAR TACHYARRHYTHMIAS are responsible for the majority of sudden cardiac deaths in the posthospital phase after myocardial infarction.1 The relative risk of sudden cardiac death (per unit of time) is greatest in the first few months after discharge from the hospital.2 Almost 60% of the 6 month mortality after infarction occurs within 2 months after hospital discharge.3 Recent studies have reported that during the chronic healing phase, time-dependent electrophysiologic changes occur and mediate a decreased propensity to ventricular tachycardia.3–5 While the electrophysiologic characteristics have been extensively examined during and early after infarction,6–17 the time course of changes in electrophysiologic characteristics of the infarct and border zones late after infarction have not been systematically assessed in vivo. Accordingly, electrophysiologic studies were performed in 19 conscious instrumented dogs beginning 4 days after occlusion-reperfusion injury and serial electrophysiologic studies were repeated at 4 to 5 day intervals.

Methods

Preparation. Mongrel dogs weighing between 17 and 25 kg were anesthetized with pentobarbital followed by a mixture of nitrous oxide and halothane and ventilated with a Harvard respirator. A thoracotomy was performed in the fifth interspace of each, a pericardial cradle was produced, and the left anterior descending coronary artery was dissected free at the tip of the left atrial appendage. A noose occluder was placed around the left anterior descending coronary artery. A transient occlusion (30 sec) was made so that the area of myocardium that was likely to be infarcted could be visualized. Silver–silver chloride electrodes were sutured to the epicardial surface with an interelectrode distance of 5 mm: one pair in the right ventricular pulmonary outflow tract, two pairs in the center of the infarct zone, and one pair in the border zone. In addition a quadripolar endocardial catheter was introduced through the apex of the right ventricle and manually adjusted to be in contact with the septum

Vol. 77, No. 1, January 1988
Repolarization time was similarly measured during constant-rate ventricular pacing and measured as the QT interval of the electrogram. This was measured from the onset of the surface QRS to the termination of the QT interval of the electrogram. In some animals the QT intervals recorded in the infarct zone were of a lower amplitude than those recorded in the normal zones. Because of this lower amplitude it is possible that significant changes within this zone may occur that would not be measurable. However, in the majority of animals electrograms were sharply demarcated and the termination of the T waves could be well defined (figure 1). An additional issue is whether the electrogram QT interval measures local phenomena or far-field activity. This issue is not addressed in this study. However, the extent far-field view depends on interelectrode distance. To minimize the probability of visualizing far-field activity the interelectrode distance in this study was 5 mm. Haus et al. 18 assessed the relationship between electrogram QT interval duration and ventricular refractoriness measured at that site and found a close correlation. It is therefore likely that the recorded electrograms measure relatively local events. Levine et al. 19 assessed the field of view when recording from a monophasic action potential catheter. By use of this technique it was estimated that the field of view was 3 to 6 mm away from this recording electrode.

Ventricular refractoriness in the present study was assessed by the extrastimulus technique and measured at all five bipolar electrode sites. Induction of sustained ventricular tachyarrhythmias was attempted with use of single, double, and triple extrastimuli from the right ventricular endocardial site. If sustained ventricular tachycardia was not induced from this site then programmed electrical stimulation was repeated while pacing from all electrode sites in the infarct zone and the border zone. The sequence of stimulation was constant and proceeded from the two endocardial right ventricular sites to the epicardial infarct sites and finally to the border zone in the left ventricle. This same stimulation protocol was used during all studies. The end point of each study was the induction of sustained ventricular tachyarrhythmias. Rapid ventricular burst pacing was not used to induce tachyarrhythmias in this study.

Definitions. In this study inducible monomorphic sustained ventricular tachycardia was defined as consecutive ventricular depolarizations at a cycle length of less than 400 msec, elicited by programmed electrical stimulation, that lasted more than 30 sec or produced hemodynamic compromise requiring immediate tracheoscopy coronary or ventricular burst pacing (figures 2 and 3). An induced tachyrhythmia was referred to as polymorphic ventricular tachycardia if organized electrical activity was seen at local electrogram sites, even if the surface QRS morphology was indistinguishable from ventricular fibrillation. Such organized activity was manifest as organized and sequential activity over widely distributed areas of the right and left ventricles. In this study pleomorphic ventricular tachycardia always began with greater than 5 beats of an organized ventricular rhythm but frequently degenerated to ventricular fibrillation. However, the time to degeneration varied widely (figures 2 and 3). Although ventricular fibrillation was frequently observed in this study, in all cases it was preceded by at least 5 beats of organized ventricular tachycardia.

Pathologic studies. Autopsies were performed on all animals. Animals were euthanized with pentobarbital and a 300 ml bolus of 10% nitroblue tetrazolium dye was given intravenously and the heart was rapidly removed. 20 The left ventricle was transversely sectioned in slices of 0.5 cm thickness from apex to base. Infarct zone and viable myocardium were then grossly distinguished by visual color analysis. Because of the mottled histology of most of the infarcts, our measurements of infarct size are only estimates. To our knowledge no preferable way of measuring infarct size in

![Figure 1](http://circ.ahajournals.org/content/82/3/210/F1.large.jpg)
mottled infarcts has been reported. The wet weight of the infarct zone and total heart (excluding atria) were measured and infarct size was calculated. Myocardial biopsy samples were made in the normal zone and in the infarct zone. Biopsy samples were fixed in formalin dehydrated in graded alcohols, cleaned in xylene, and embedded in paraffin wax (surgiplast, Grayslake, IL). Sections were stained with hematoxylin and eosin.

**Statistics.** Analysis of variance was used to compare the electrophysiologic effects over time. Continuous data are presented as millisecond change from baseline, mean ± SD. Chi-square analysis was used for unpaired discrete data. The null hypothesis was rejected at p<.05.

**Results**

A total of 31 animals was studied. Only the 28 animals with inducible sustained ventricular tachyarrhythmias during the first electrophysiologic study were candidates for further investigations. The number of extrastimuli required for induction of sustained ventricular tachyarrhythmias during the first study and the site of stimulation were related to infarct size. To allow a linear regression analysis the stimulation intensity required to induce ventricular tachyarrhythmias was graded. Sustained ventricular tachyarrhythmias induced with a single extrastimulus were assigned grade 1, two extrastimuli in the right ventricle were assigned grade 2, three extrastimuli in the right ventricle were assigned grade 3, two extrastimuli in the left ventricle were assigned grade 4, and three extrastimuli in the left ventricle were assigned grade 5.
FIGURE 3, A to E. The spectrum of rates and morphologies of pleomorphic ventricular tachycardia.

FIGURE 3, A to C. Panel A, Pleomorphic ventricular tachycardia is induced, but the intracardiac electrograms are highly organized with sequential electrical activation. B, A similar pleomorphic ventricular tachycardia in another animal. C, A very stable pleomorphic ventricular tachycardia is induced that eventually degenerates (after 22 sec) to ventricular fibrillation.

ventricle were assigned grade 5. The grade of extrastimuli required to induce sustained ventricular tachyarrhythmias was correlated with infarct size with an r value of .48, p<.02.

Of the 28 animals with inducible sustained ventricular tachyarrhythmias, nine animals were excluded from the temporal analysis because of premature death before at least four electrophysiologic studies could be performed. None of these deaths was sudden. Data from these dogs were excluded because their incorporation would have biased data analysis since any electrophysiologic changes seen could be due to either a true time-dependent change or due to drop out of dogs with specific electrophysiologic characteristics. Of the 19 animals included in this analysis, 11 dogs had sustained ventricular tachyarrhythmias that continued to
be inducible throughout the serial studies. These animals are termed group I animals. In eight animals, there was spontaneous loss of the ability to induce sustained ventricular tachycardia during the serial studies. These animals are termed group II. Myocardial infarction size was significantly greater in group I than in group II animals (group I, 18 ± 8%; group II, 12.5 ± 5%; p<.004). Animals in group I and group II were studied over nearly identical time periods of 24 ± 10 and 27 ± 9 days, respectively.

**Time-dependent changes in results of programmed electrical stimulation.** Figure 4 and table 1 review the time-dependent changes in results of programmed ventricular stimulation in the two groups. As can be seen, 100% of the group I animals continued to be inducible over the serial studies. However, even in these animals
time-dependent changes occurred in the number of extrastimuli necessary to induce the ventricular tachycardia and the frequency with which left ventricular stimulation was necessary. In the initial study 33% of group I animals had ventricular tachycardia induced by a single extrastimuli in the right ventricle. An additional 45% had sustained ventricular tachyarrhythmias induced by multiple extrastimuli in the right ventricle, while only 22% required multiple extrastimuli in the left ventricle to induce their tachycardia. In contrast, by the fifth serial study all group I animals required application of multiple extrastimuli in the right ventricle or in the left ventricle to induce sustained ventricular tachycardia. In figure 4 results seen in group II are contrasted with those seen in group I. In group II animals a progressive decrease was observed in the proportion of dogs in which sustained ventricular tachyarrhythmias could be induced. By the fifth serial study none of the group II animals had inducible ventricular tachyarrhythmia.

**Time-dependent changes in electrophysiologic measurements.** Table 2 shows the time-dependent changes in electrophysiologic measurements in the two groups. A differential pattern in the change in conduction time in the infarct zone was seen after comparison of group I and II animals. In group I animals this conduction time was prolonged over time, while in group II animals it was unchanged. No significant changes in conduction to other areas of the myocardium were observed over time in either group. A differential pattern was also observed in time-dependent changes in repolarization time recorded in the border zone and in the right ventricle. In group I animals the border zone electrogram QT interval did not change with time, while in group II animals it shortened significantly. No significant changes in electrogram QT intervals in other areas of the myocardium were seen over time in either group. In addition, time-dependent changes in ventricular refractoriness were seen in the infarct zone. In group I animals ventricular refractoriness in the infarct zone shortened over time but it did not change in group II animals.

**Time-dependent changes in histopathology.** Adequate pathologic specimens for histologic analysis were available from 12 animals. Marked interindivdual variability in the histopathology was seen in these ani-


**TABLE 1**

<table>
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<th>Study 3</th>
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<td>RV-S4</td>
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</table>

### Group II (NI)

| 12 | VT | 85 | IFZ-S4 | NI | NA |
| 13 | PVT-VF | 109 | RV-S4 | PVT-VF | NA | IFZ-S4 | NI | NA |
| 14 | VT | 130 | IFZ-S3 | VT | 125 | IFZ-S3 | VT | 125 | IFZ-S4 | NA |
| 15 | VT | 130 | BZ-S4 | VT | 110 | LVE | VT | 115 | IFZ-S4 | PVT-VF | NA | LVE | NI |
| 16 | PVT-VF | 90 | RV-S4 | NI | NI | NI |
| 17 | VT | 160 | BZ-S3 | PVT-VF | NA | BZ-S3 | NI | NI | NI |
| 18 | PVT-VF | 110 | IFZ-S4 | NA | PVT-VF | 110 | RV-S4 | PVT-VF | 95 | RV-S4 | NI |
| 19 | PVT-VF | NA | RV-S4 | VT | 100 | LVE | VT | 100 | LVE | PVT-VF | NA | LVE | NI |

Group I (inducible; I) animals are compared with group II animals, which became noninducible (NI) over time. Time-dependent changes are shown for each dog in the morphology of the rhythm induced, the cycle length (CL) of that rhythm, and the site of stimulation (Site-ST) that induced that rhythm. VT designates a monomorphic sustained ventricular tachycardia, PVT-VF designates a pleomorphic ventricular tachycardia that degenerates to ventricular fibrillation, and NA designates not available. Extrastimuli were introduced in the right ventricle (RV), in the infarct zone of the left ventricle (IFZ) or in the left ventricular (LV) border zone (BZ), or in the endocardium of the left ventricle (LVE).

Despite the relatively small number of animals studied it was possible to divide the animals into three pathologic groups based on histology. Group A animals had extensive near-transmural necrosis but sparing of the subendocardial regions (figure 5, A), group B animals had islands of viable and ischemic myocardium surrounded by granulation tissue (figure 5, B), and group C animals had advanced collagen formation rather than necrosis or granulation tissue (figure 5, C). Group A animals all had sustained ventricular tachyarrhythmias inducible with a single extrastimulus in the first study. Three of the four group A animals continued to have ventricular tachycardia inducible throughout follow-up. Of the five group B animals (patchy necrosis), three had sustained ventricular tachyarrhythmias inducible throughout follow-up and two did not. As expected from the histologic findings, animals in group C generally died later after infarction than did group A animals (28 ± 8 and 20 ± 5 days, respectively; p < .05).

### Discussion

This study was designed to assess the time-dependent change in propensity to malignant ventricular tachyarrhythmia after myocardial infarction. A conscious dog preparation was used in this study to avoid the need for general anesthetics, which have been shown to bind to cardiac sodium channels and also to enhance propensity to malignant ventricular arrhythmias. 21, 22 In this study, time-dependent changes in inducibility were assessed in two ways. First, complete loss of inducibility was defined as the inability to induce sustained ventricular tachyarrhythmia when programmed electrical stimulation had been performed from all right and left ventricular sites. Second, time-dependent changes in the necessity of using left ventricular stimulation and an increased number of extrastimuli required to induce the tachyarrhythmias were also observed. These changes frequently preceded complete loss of inducibility. In a similar study, Cobbe et al. 23 evaluated the changes in ventricular electrophysiology from day 3 to day 7 after infarction. Marked variability in responses to programmed electrical stimulation occurred over time in that study. Of 15 dogs in the study of Cobbe et al., nine were not inducible on the first study (day 3), but ventricular tachycardia became inducible in five of these
nine dogs by day 7. Of the six dogs with inducible sustained ventricular tachycardia/fibrillation on the first study, two became noninducible by day 7. Similarities and differences exist between the present study and that of Cobbe et al. 23 The number of days of follow-up on Cobbe’s study was 6 ± 2 days (range 3 to 8 days) compared with 26 ± 9 days (range 17 to 35 days) in the current study. In the current study all animals had inducible sustained ventricular tachyarrhythmias on the first study. Another difference between the study of Cobbe et al. and the present study is that programmed electrical stimulation in the former study involved introduction of only two extrastimuli from a single ventricular site in the normal myocardium, while our study involved introduction of up to three extrastimuli from all five ventricular sites, including the left ventricular infarct zone. Both studies, however, confirm time-dependent changes in the responses to programmed electrical stimulation after infarction. In the study of Cobbe et al. an increase in inducibility was seen in five dogs over the time period of 3 to 8 days, while in the current study loss of inducibility occurred in eight animals at 17 ± 12 days.

Discrepancies in time-dependent changes in inducibility are also noted in other studies. 13, 17 These discrepancies appear to be related to variability in the number of extrastimuli and/or the number of sites at which stimulation is introduced. Karagueuzian et al. 13
observed that beyond 5 days arrhythmias are no longer inducible with single extrastimuli. Michelson et al.,\textsuperscript{14} using up to three extrastimuli at multiple sites, maintained inducibility for up to 30 days after infarction. In the study of Garan et al.,\textsuperscript{16} reproducibility was highest in animals with sustained monomorphic ventricular tachycardia and was least reproducible in animals with nonsustained ventricular arrhythmias. A number of methodologic differences emerge when comparing the study of Garan et al. and the present study. In the study

FIGURE 5. The heterogeneity of the ischemic injury. Sections stained with hematoxylin and eosin. A, Group A animals had near transmural infarctions with sparing of the subendocardial zone. The subendocardium (arrowed) was viable, but the majority of the myocardium was necrotic (original magnification $\times 100$; inset $\times 400$). B, This group B animal had an island of potentially viable myocardium surrounded by granulation tissue (original magnification $\times 200$). C, Group C animals had advanced collagen formation. Note viable myocardium on the right (original magnification $\times 40$).
of Garan et al., rapid ventricular burst pacing frequently induced ventricular fibrillation; burst ventricular pacing was not used in the present study. Also, in the study of Garan et al. the animals were under general anesthesia with methohexital and general anesthetics are well known to enhance inducibility, particularly ventricular fibrillation. In the present study animals were given diazepam only to mimic techniques used in man and to avoid the superimposition of the electrophysiologic effects of general anesthetics.

Data from this study and from recent studies in man support the concept that during the long-term healing phase after myocardial infarction there are progressive changes in the electrophysiologic milieu that parallel a progressive decrease in propensity for induction of malignant ventricular arrhythmia. Differential patterns of time-dependent electrophysiologic changes in the infarct zone conduction and refractoriness and border zone repolarization time were observed when comparing group I and group II animals. In the present study, prolongation of conduction within the infarct zone was seen in animals with continued inducibility, but no significant time-dependent change was seen in animals who lost inducibility. Spear et al. studied the time-dependent electrophysiologic changes occurring late after myocardial infarction in a similar dog preparation. They used techniques in vitro to assess electrophysiologic measures of conduction velocity, resting membrane potential, and repolarization time. In that study time-dependent improvement in resting membrane potential, rate of depolarization, and conduction velocity was noted from 5 to 15 days after infarction, but localized areas of slow conduction persisted. However, in Spear's study time-dependent electrophysiologic changes were not related to changes in inducibility that occur over time.

We also noted a differential pattern of change in ventricular refractoriness in the infarct zone when comparing group I and group II animals. Ventricular refractoriness shortened over time in group I animals, while in group II animals there was no significant change. In addition, a differential pattern of time-dependent change in the repolarization time in the border zone was seen on comparison of group I and group II animals. In animals that continued to be inducible there was no significant change in repolarization time in the border zone. In contrast, in animals in whom ventricular tachycardia could no longer be induced there was a progressive shortening of repolarization time in this region. While we recognize that a border zone may not exist when assessing histology, functional abnormalities appear to exist in zones bordering an infarction. Studies in vitro by Myerberg et al. have reported time-dependent changes in transmembrane action potential duration recorded from surviving cells bordering the infarct zone. In their studies these cells initially had a shortened action potential duration relative to normal zone cells. They showed that time-dependent changes in action potential in the border zone consisted of three types: (1) prolongation of action potential duration, (2) shortening of action potential duration, and (3) low-amplitude action potentials. Prolongation of action potential duration most frequently occurred beginning 1 week after myocardial infarction and was rarely recorded after 1 month. Shortening of action potential duration began later, at approximately 6 weeks after myocardial infarction. Moreover, even late after myocardial infarction there was marked dispersion of action potential duration in zones adjacent to and within the infarction. In keeping with shortening of repolarization time late after infarction, Spear et al. reported a mean action potential duration of 221 msec at 3 to 5 days after infarction and a shortening of this duration to 185 msec by 8 to 15 days after infarction. The present study provides new information because we assessed the time-dependent changes in electrophysiologic variables in vivo and related these to time-dependent changes in the results of programmed electrical stimulation.

The mechanism(s) underlying the time-dependent changes in electrophysiologic characteristics in surviving cells adjacent to areas of myocardial infarction are uncertain. We noted marked interindividual variability in both the histopathology of myocardial infarction and in the rate of its healing. Similar interindividual variability in healing rates have also been shown in man. The healing process could have altered the cellular constituents underlying the bipolar electrodes in this study. Alteration of the cellular constituents (inflammatory cell) or metabolism could alter the repolarization process. There are a number of potential explanations for differences in the time-dependent changes in ventricular electrophysiologic characteristics of group I and group II animals. First, the larger infarct size seen in group I animals would be expected to increase the extent of wall motion abnormalities. Lab has previously reported that wall motion abnormalities can alter action potential characteristics, and diastolic stretch has been shown to shorten action potential duration and cause depolarization. Abnormalities of systolic shortening (dyskinesia) can also alter action potential duration and may be associated with the development of afterdepolarizations. These wall motion abnormalities may perpetuate electro-
physiologic conditions predisposing to reentry. Second, wall motion abnormalities could activate ventricular-mechanical neural receptors, resulting in change in autonomic nervous system tone.32–34 Alternative mechanisms for time-dependent changes also relate to the healing process. In animals with large myocardial infarctions the healing process may cause a wide separation in individual myocardial fibers and produce inexcitable gaps.17 This anatomic change could enhance or maintain inducibility.17 This study does not specifically address which of these mechanisms is operative in these animals. Moreover, time-dependent electrophysiologic changes were manifest in both group I and group II animals. It is plausible that progressive changes seen in group I animals result in loss of inducibility during longer term follow-up studies.

There are a number of clinical implications of this study. Results of programmed electrical stimulation have been reported to change progressively over the first few months after the infarction,3 and there is marked interindividual variability in the rate of progression of these electrophysiologic changes.34–37 Therefore, the response to programmed electrical stimulation in patients after infarction may vary widely depending on the exact timing of study after infarction. The second implication of this study is that an individual’s propensity to sustained ventricular tachyarrhythmias after acute infarction may only be manifest when programmed ventricular stimulation is done from the left ventricle. These data are in keeping with similar observations reported in canine preparations of infarction38 and in some patients with ventricular tachycardia.39, 40 However, the extent to which left ventricular stimulation enhances the induction of ventricular tachyarrhythmia after myocardial infarction appears to be less important41 in man than is seen in animal preparations. Overall, site specificity may be more important in experimental myocardial infarction. Finally, a critical determinant of whether the propensity to ventricular tachycardia resolves over time is size of myocardial infarction and extent of left ventricular dysfunction. These data are in keeping with clinical observations that the presence of left ventricular dysfunction is a major determinant of risk for sudden death after infarction.42

The time-dependent changes in electrophysiologic variables and propensity to ventricular tachycardia seen in this preparation should be taken into consideration when serial drug studies are done to evaluate efficacy and electrophysiologic activity of antiarrhythmic drugs in this or similar dog preparations. Unless these time-dependent features are taken into consideration, one could falsely interpret a loss of inducibility as reflecting antiarrhythmic activity when this change may really only relate to a time-dependent healing phenomena. An experimental design that minimizes the contribution of these time-dependent changes in electrophysiologic responses after infarction should allow serial antiarrhythmic drugs to be administered in a randomized sequence and a drug-free electrophysiologic study should immediately precede each drug trial to document the ongoing ability to induce sustained ventricular tachycardia.

In conclusion, after acute myocardial infarction in conscious dogs, time-dependent electrophysiologic changes occur that are associated with a progressive decrease in ability to induce ventricular tachyarrhythmias. A critical determinant of whether propensity to ventricular tachycardia induction resolves over time is size of myocardial infarction.

We thank Gregory Douglas for help in preparation of this manuscript.

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Time-dependent change in electrophysiologic milieu after myocardial infarction in conscious dogs.
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Circulation. 1988;77:209-220
doi: 10.1161/01.CIR.77.1.209

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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