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Limitations of Routine Long-Term Electrocardiographic Monitoring to Assess Ventricular Ectopic Frequency

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SUMMARY **Variations in the frequency of ventricular premature depolarizations (VPDs) were evaluated with three consecutive 24-hour long-term electrocardiograph monitor recordings from 15 clinically stable patients with various cardiac disorders. Mean hourly VPD frequencies ranged from 37–1,801 per hour. Data were subjected to 4 and 5 factor nested analyses of variance. The extent of spontaneous variation in arrhythmia frequency that occurred in individual patients from day to day was 23%, between 8-hour periods within days was 29%, and from hour to hour was 48%. In addition, the variability between repeated three-day monitoring periods over time was quantified in five patients and found to be 37%. This analysis determined that to distinguish a reduction in VPD frequency attributable to therapeutic intervention rather than biologic or spontaneous variation alone required a greater than 83% reduction in VPD frequency if only two 24-hour monitoring periods were compared, and greater than 65% reduction if two 72-hour periods were compared. The limitations of routine 24-hour electrocardiographic monitoring must be considered in diagnostic and therapeutic decision-making.**

THE EFFECTIVE MANAGEMENT of ventricular arrhythmias is a difficult therapeutic challenge. Sudden death is usually due to ventricular fibrillation, and ventricular ectopy has been considered as a major risk factor.[1-7] Identification of ventricular ectopy in the ambulatory patient is not easy, however, since arrhythmias often occur sporadically, and patients are not always aware of their presence.[6, 8-10] The availability of recorders that can monitor the electrocardiogram continuously in ambulatory patients has greatly enhanced our ability to detect and understand the nature of ventricular arrhythmias beyond that possible with standard resting electrocardiography (45 seconds) or electrocardiographic rhythm strips (several minutes to 1 hour).[8-10] Twenty-four-hour long-term electrocardiographic monitoring has further documented cardiac arrhythmias as a cause of disability and death and has found widespread application as a means of quantitating ventricular ectopy and guiding antiarrhythmic therapy.[6, 11]

The evaluation of antiarrhythmic agents has led to increased awareness of the limitations of present methods of arrhythmia detection.[12, 13] Previous studies have noted the inconstant relation of ventricular ectopy to patient physical activity, diurnal, neural and psychological factors, and current monitoring recommendations have increased from 8–24 hours to better account for these physiologic variables.[5, 6, 9, 10, 14-17]

The use of exercise testing has been considered complementary to 24-hour ambulatory electrocardiographic monitoring.[18, 19] Recently, however, the reproducibility of arrhythmia detection by this technique has been questioned by Sheps et al.[20] They demonstrated that, in two successive exercise tests performed only 45 minutes apart, there was a marked variability of arrhythmia frequency, thus limiting the usefulness of paired exercise tests in evaluating antiarrhythmic therapy.

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Supported by a grant from E.I. du Pont de Nemours & Company and grant #NIH 5 MO 1 PR00040.

Dr. Michelson is recipient of a Research Fellowship Award of the Southeastern Pennsylvania Chapter of the American Heart Association.

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Received March 15, 1978; revision accepted May 16, 1978.

However, sufficient attention has not been given to the possible variability in arrhythmia frequency that may occur spontaneously in individual patients during repeated periods of long term ambulatory electrocardiographic monitoring.[12, 21] Our study has applied statistical analysis to three successive 24-hour ambulatory electrocardiographic monitorings in individual patients to determine the degree of arrhythmia variability and the extent of reduction in arrhythmia frequency necessary to define drug efficacy. This analysis may bear upon the accurate evaluation of arrhythmias and antiarrhythmic therapy and will, therefore, have an impact on the use of ambulatory monitoring in clinical, epidemiologic and research trials. Also, this study provides further insight into the extent that one must account for biologic (i.e., spontaneous) variability in a series of quantitative clinical measurements.

Methods

Twenty-four hour long-term ambulatory electrocardiographic recordings using a two channel (precordial leads V1 and V5) Avionics 445 recorder were obtained from 15 patients with premature ventricular depolarizations ($\geq$ 30/hr over 24 hours in their first recording) on three successive days before their entry into a study of a new antiarrhythmic drug. Patients' ages ranged from 38–68 years, with a mean of 56 $\pm$ 10 (SD) years. Fourteen patients were male; three had hypertensive cardiovascular disease, eight coronary artery disease, one congestive cardiomyopathy, one valvular heart disease, and two had no cardiac diagnosis. None received any antiarrhythmic therapy for at least one week before entry into the study. All were clinically stable before and during the 72-hour monitoring period. Activity routines and medical regimens were kept constant while each patient resided in the Clinical Research Center. Five patients of this group underwent repeated three-day recordings approximately three months apart. They were selected only on the basis of availability for restudy. Changes in frequency of ventricular premature depolarizations (VPDs) over the 72 hours were subjected to an analysis of variance.[22] Analysis of variance is a statistical method that allows for isolation of the contribution of each of many components of the observed variation in a complex model. This method is well suited to define the sources of inter- and intra-subject variation and to determine the extent of biologic variation in a series of quantitative clinical measurements. The standard deviation is the statistical measure of variation. The square of the standard deviation (the variance) is the means to distinguish among the multiple sources of variation.

A 4-factored nested analysis of variance (pure Model II) was applied to determine the amount of variation in the frequency of ventricular premature depolarizations attributable to each of the following four sources: variation "between patients," "between days" within patients, "between 8-hour periods" within days and "between hours" within 8-hour periods. Since variance components are additive, the total variation in hourly ventricular premature depolarization frequency for all patients is given by the formula: S^2(total) = S^2("between patients") + S^2("between days") + S^2("between periods") + S^2("between hours") (where S = standard deviation for each of the respective variances). The total variation observed for a given patient during the three-day monitoring period is: S^2(total) = S^2("between days") + S^2("between periods") + S^2("between hours"). The first equation (which underlies the four factor nested analysis of variance) was utilized to obtain estimates of the day-to-day, period-to-period and hour-to-hour variance components pooled for all patients. Since five of the patients were studied more than once, it was also possible to estimate the degree of variance that might be expected with repeated 72-hour monitoring of the same patient. This information was obtained from a five factor nested analysis of variance involving the following five sources of variation: "between patients," "between days," "between 8-hour periods," "between hours" and, in addition, "between three-day periods in the same patient." In all the analyses of variance, the frequency of VPDs was transformed to natural logarithms using the formula ln (VPD + 1) to insure that the statistical assumptions of normal distribution and homogeneous variance would be more closely satisfied. Zero arrhythmia frequencies were present in occasional hours and, therefore, "1" was added to each hourly arrhythmia frequency before the logarithm was computed. The variance of daily average arrhythmia frequency was computed using the formula: V(average variance) = S^2("between days") +

$$\frac{S^2(\text{"between periods"})}{P} + \frac{S^2(\text{"between hours"})}{PH}.$$

(P = the number of 8-hour periods sampled and H = the number of hours per period). The 95% confidence limit for the difference between any control monitoring period when compared to a test period in which an intervention was being evaluated was calculated by the formula

$$D = 2\sqrt{\text{average variance}\left(\frac{1}{C}+\frac{1}{T}\right)}$$

(C = the number of days in the control period and T = the number of days in the test period). The percentage reduction from control during the test period was calculated by the formula D = ln (test) – ln (control) which equals $\ln\left(\frac{\text{test}}{\text{control}}\right)$. Therefore, e^D = test. The percent change = $100\left(\frac{\text{test}}{\text{control}}-1\right)$ which, therefore, = $100(e^D-1)$. If during the test period there is a reduction in VPD frequency, then D will be negative and, therefore, the percent reduction = $100(e^{-D}-1)$.

TABLE 1. *Mean Hourly Ventricular Premature Depolarization Frequency for Each of Three 24-Hour Control Monitoring Periods*

Patient*	Age	Sex	Diagnosis	Day 1	Day 2	Day 3	3 Day Mean ± SD
1	53	M	CAD	27	44	39	37 ± 9
2	52	M	CCM	209	62	159	143 ± 74
3a	60	M	HCVD	352	527	180	360 ± 173
3b				9	5	3	5 ± 3
3c				5	22	28	17 ± 12
4	65	M	CAD	122	18	18	48 ± 60
5	57	M	VHD	498	525	595	539 ± 49
6a	44	M	HCVD	1696	1296	1462	1433 ± 201
6b				1498	1217	1477	1379 ± 152
6c				1093	1268	1588	1306 ± 248
7a	68	F	CAD	259	189	215	218 ± 35
7b				434	496	306	414 ± 95
8	34	M	CAD	1942	1752	1698	1801 ± 126
9a	61	M	CAD	79	156	332	187 ± 131
9b				289	495	1266	685 ± 514
10	64	M	no disease	212	103	38	115 ± 89
11a	38	M	no disease	16	121	60	65 ± 33
11b				59	25	61	47 ± 20
12	59	M	CAD	175	295	217	231 ± 60
13	65	M	HCVD	806	384	342	516 ± 258
14	64	M	CAD	51	42	86	88 ± 47
15	60	M	CAD	†	49	68	59 ± 13

*Some patients were studied more than once (e.g., patients 3, 6, 7, 9, 11).
†No data available, recorder malfunction.
Abbreviations: M = male; F = female; CAD = coronary artery disease; VHD = valvular heart disease; CCM = congestive cardiomyopathy; HCVD = hypertensive heart disease.

In addition, the data from individual patients were used to compute a "between days" coefficient of variation using the formula:

$$\frac{\text{(standard deviation of the mean 72 hr VPD frequency)} \times 100}{\text{mean hourly VPD frequency}}$$

In order to validate the methodology of interpreting the Avionics tapes utilized in this study, a sample of at least 2 hours from five individual patients was analyzed in real time and compared to the data derived by analyst interaction with the Avionics 660A computerized scanner. A sample of each different designated ventricular premature depolarization was printed out and further verified by a cardiologist. The relative error ratio between the real time and analyst-computer analysis varied inversely with the degree of ventricular premature depolarization frequency per hour but was, on the average, 7.2%. In addition, the system was subjected to five 24-hour tapes from patients with ventricular premature depolarizations varying from 10–1,000 per hour over 24 hours in which the analyst-computer arrhythmia frequency was compared to an independent real time analysis. The average error rate using these five 24-hour tapes was 7.0%. In addition, real time analyzed tapes were used at intermittent intervals to insure quality control.

TABLE 2. *Analysis of the Sources of Variance in Mean Hourly Ventricular Premature Depolarization Frequency*

Source	Percent of variance from each source	
Pooled Data from 15 Patients		
"Between patients"	66	
"Between days"	8	
"Between 8-hour periods"	10	
"Between hours"	16	
		100%
Data from 15 Individual Patients		
"Between days"	23	
"Between 8-hour periods"	29	
"Between hours"	48	
		100%
Data from All 22 Monitoring Periods in 15 Patients		
"Between three-day monitoring periods"	37	
"Between patients"	35	
"Between days"	7	
"Between 8-hour periods"	8	
"Between hours"	13	
		100%

Results

The mean hourly ventricular premature depolarization frequency during each of the 24-hour monitoring periods as well as demographic data for all 15 patients is detailed in table 1. The variance components by source are listed in table 2. Using pooled data, the major variation in ventricular premature depolarization frequency occurred "between patients." When repeat three-day studies in the same patient were taken into account, there was as much variance between repeat monitoring periods as there was between patients. An illustrative example of monitoring for 72 hours several months apart is presented in

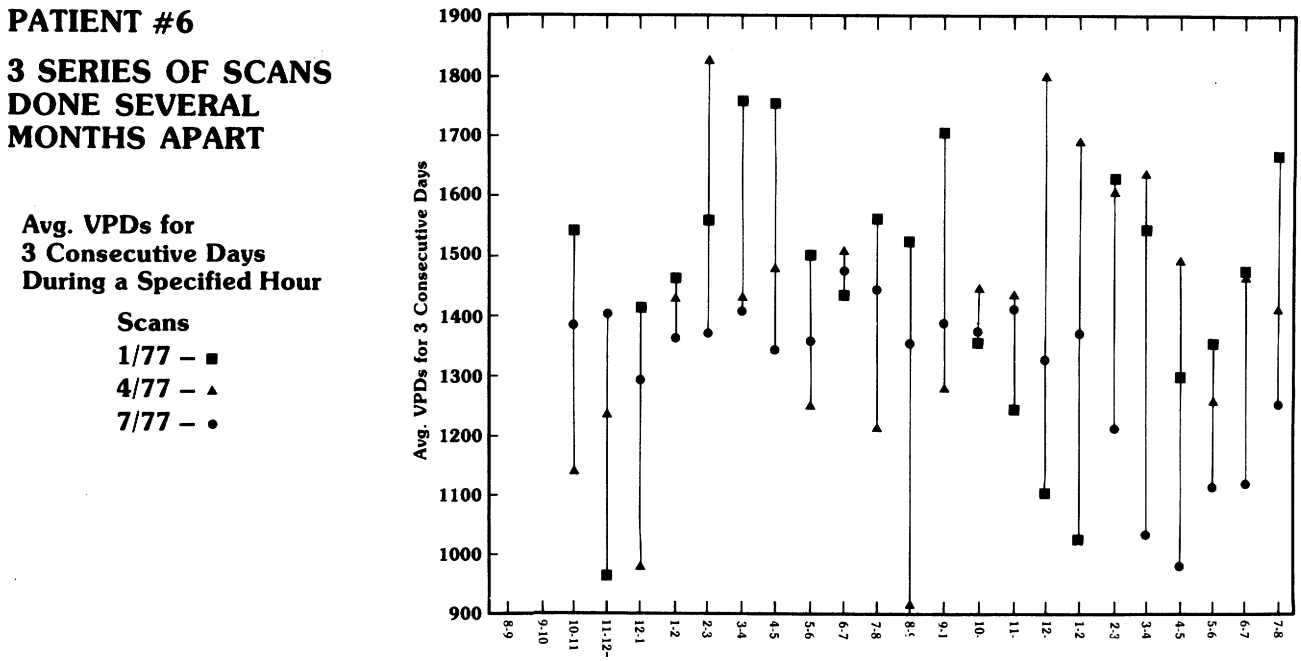

FIGURE 1. *The extent of variability in mean hourly ventricular premature depolarization (VDP) frequency for repeated three-day monitoring periods repeated months apart in an illustrative patient.*

figure 1. In addition, a further analysis of sources of variation in individual patients revealed that the "between days" variance contributed 23% to the total variation, the "between 8-hour periods" 29% and the "between hours" variance 48%. Thus, within an individual patient, the hour-to-hour variation in VPD frequency accounted for approximately one-half the variance (fig. 2).

Utilizing the formulae developed in the Methods section, one can utilize variances to determine the percent reduction in VPD frequency required during a test period to demonstrate statistically significant ($P \leq 0.05$) reduction compared to a control period. Table 3 illustrates a variety of possible protocols using 8-, 12- and 24-hour electrocardiographic scan with various numbers of control and test period scans

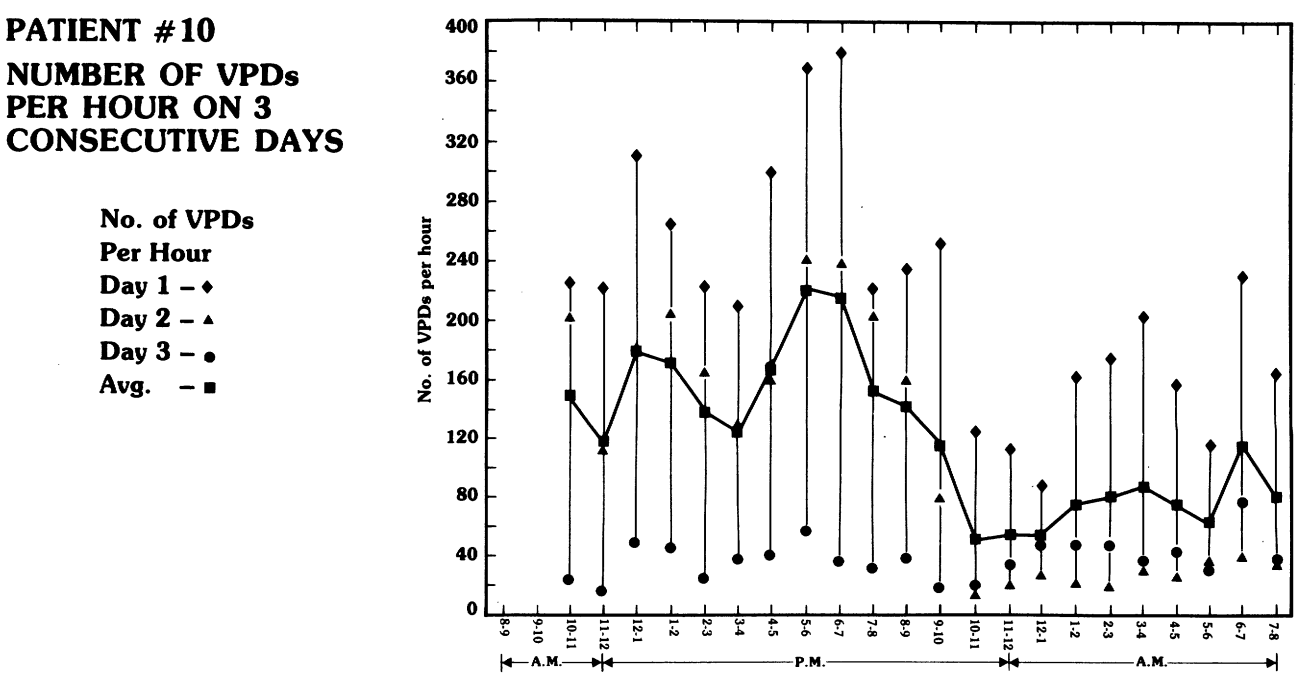

FIGURE 2. *The extent of variability in the mean hourly ventricular premature depolarization (VDP) frequency on three consecutive days in an illustrative patient.*

TABLE 3. *Minimal Percentage Reduction in Mean Hourly Ventricular Premature Depolarization (VPD) Frequency Required to Demonstrate an Effect Attributable to the Intervention Rather Than Spontaneous Variation at the 95% Level of Confidence*

Length of monitoring	Number of days		Minimal percent VPD reduction
	Control	Test	
8 hours	1	1	−90.3
12 hours	1	1	−89.0
24 hours	1	1	−83.4
8 hours	3	3	−74.0
12 hours	3	3	−73.4
24 hours	3	3	−64.6
24 hours	3	7	−58.4
24 hours	3	14	−55.5
24 hours	3	21	−54.4
24 hours	7	7	−49.3
24 hours	14	14	−38.2

The coefficients of variation in various groups of patients ordered by frequency of VPDs is detailed in table 4. As the frequency of VPDs increased, the coefficient of variation decreased. Thus, in patients with a mean hourly VPD frequency > 1,000/hr, the coefficient of variation "between days" was only 13%.

Differences "between 8-hour periods" were analyzed to determine whether they were systematic or random. In comparing the third 8-hour period (midnight to 8 a.m.) of each monitoring period with the other two 8-hour periods per day, a tendency for arrhythmia frequency to decrease during sleep was suggested for individual patients, though this trend was not strong enough to be considered a systematic effect.

Discussion

This study documents that marked variability occurs in the frequency of ventricular premature depolarizations in otherwise stable individuals even under controlled conditions. This variability is marked not only "between hours" and "between successive 8-hour periods" but also "between days" in a single subject during a continuous electrocardiographic monitoring period of 72 hours. In addition, marked variability was also demonstrated in individual patients comparing successive three-day monitoring periods repeated months apart. These results suggest that the number of ambulatory monitoring periods to detect whether changes in arrhythmia frequency after interventions exceed those accounted for by spontaneous variation alone can be determined statistically. The percent reduction in VPD frequency necessary to document that a decrease is likely to be due to therapeutic effect (at the 95% confidence level) rather than spontaneous variation is illustrated in table 3. For example, if only two 8-hour periods are compared, a greater than 90% reduction in mean hourly VPD frequency is necessary to demonstrate a statistically significant change due to an intervention rather than to spontaneous variation alone. If two 24-hour monitoring periods are compared, 84% reduction is necessary to show a statistically significant difference. Thus, a single 24-hour monitoring period may be statistically sufficient for clinical or research studies if an 84% reduction is obtained.

Previous studies[11-23] have not quantitated the degree of spontaneous variability in VPD frequency and have used less rigorous criteria for defining efficacy of antiarrhythmic interventions. Efficacy is used in the sense of reducing the frequency or severity of ventricular arrhythmias and does not imply that such a reduction prevents sudden death. Their specific conclusions, therefore, based on more limited monitoring, may need reconsideration. Previously, a 50%–75% reduction in arrhythmia frequency has been used as an index of efficacy of a prescribed intervention.[11, 23] In addition, some have even suggested that monitoring for periods even less than a full 24 hours might be sufficient not only for the identification of arrhythmias associated with an increased risk of sudden death but also adequate for the evaluation of antiarrhythmic therapy.[1-3, 6, 7] such evaluations failed to consider the extent of variability in ventricular arrhythmia frequency that can be expected to occur spontaneously. The cost effectiveness of such extensive monitoring to determine efficacy seems justified in clinical trials, particularly since the need remains for effective, safe and practical antiarrhythmic agents. Thus, our protocol for studying new antiarrhythmic agents in ambulatory patients includes three 24-hour control monitoring periods and seven 24-hour periods of test monitoring. Even with this study design, a ≥ 60% reduction (table 3) in mean hourly ventricular ectopic frequency during the test period compared to control is necessary to be 95% confident of efficacy.

The data also indicate that the day-to-day variation in VPD frequency was less marked when subjects had higher frequencies of ventricular arrhythmias (e.g., > 1,000/hr) (table 4) and, therefore, in selected individuals, less extensive monitoring periods may be sufficient for statistical significance. However, since the risk of sudden death is not necessarily directly related to the absolute magnitude of ventricular arrhythmias before therapy, new antiarrhythmic drugs will have to be tested in representative patients with the more commonly observed frequencies (e.g., 30–300 VPDs/hr).[24] The frequency of VPDs does not always relate to the risk of sudden death, since a single complex form may produce ventricular fibrillation. Our study was not primarily concerned with the statistical analysis of observed changes in the grading of severity of ventricular premature depolarizations which, of course, also bears on this subject.[11] In addition, as demonstrated by this analysis, the marked "between patient" variability in arrhythmia frequency is so great that the potential for pooling patient data to detect trends in changes in frequency may be inadvisable if one is comparing control and intervention data in separate patients. Statistically, this becomes even more hazardous, since patients with the same cardiac disorder may have marked variability in ectopic frequency and response to therapy. Further-

TABLE 4. *Summary of mean hourly ventricular premature depolarizations (VPDs) listed by relative frequency. Data from patients 3B, 3C (each had less than 30 VDPs per hour on the average) and 15 (only two recording sessions were available) were omitted from this analysis.*

Mean Frequency VPD's/hour	Patient Number	Mean No. of VPD's/Hour over 24 Hours: Lowest Day	Median Day	Highest Day	Mean No. of VPD's/Hour over 3 Days	Coefficient of Variation $\frac{S.D.}{Mean} \times 100$	
	1	27	39	44	37	24	
	11 B	25	59	61	47	43	Avg.
<100	4	18	18	122	48	125	59%
	11 A	16	60	121	65	51	
	14	42	86	51	88	53	
	10	38	103	212	115	77	
100-200	2	62	159	209	143	52	66%
	9 A	79	156	332	187	70	
	7 A	189	215	259	218	16	
	12	175	217	295	231	26	
	3 A	180	352	527	360	48	
200-1000	7 B	306	434	496	414	23	35%
	13	342	384	806	516	50	
	5	498	525	595	539	9	
	9 B	289	495	1266	685	75	
	6 C	1093	1268	1588	1306	19	
	6 B	1217	1477	1498	1379	11	
>1000	6 A	1296	1462	1696	1433	14	13%
	8	1698	1752	1942	1801	7	

more, although it may be possible epidemiologically to identify populations at high risk for sudden death using only a short duration of monitoring time (e.g., 1 hour),[1-3, 6, 7] the marked variability in hour-to-hour frequency demonstrated in this study cautions against generalizations in terms of arrhythmia frequency for individual patients from such limited monitoring.

This analysis provides documentation of the extent that biologic variability may occur even under controlled conditions in a series of quantitative clinical measurements, which bears upon other diagnostic and therapeutic decision-making.

Acknowledgments

The authors thank Ronald Snee, Ph.D., for the statistical analysis, John A. Kastor, M. D., Paul D. Stolley, M. D. and Sara A. Mahler, M. D. for their constructive review, Ms. Ellen McCrea for graphic artwork, Mrs. Marilyn Stiles, R.N., for technical assistance and Mrs. Frances E. Laird for secretarial assistance.

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