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Contract Title: ESTABLISHING TIME-QUALIFIED REFERENCE VALUES FOR SPACELAB 1, HEMATOLOGY EXPERIMENT INS 103

Final Report: Final Report for:

Contract No. NAS9-16911

Submitted by: Chronobiology Associates

14610 Cedar Point Road

Houston, Texas 77070

Date: September 4, 1984

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PREFACE

This report provides the findings of the evaluation of the space environment and factors associated with space flight on selected hematologic variables. Since many of the investigated variables had been shown to exhibit circadian changes, these were taken into account by first obtaining time-qualified reference ranges for each astronaut using data acquired from three separate 28-hour transverse studies. During these, blood and urine were sampled and oral temperature was measured at 4-hour intervals. These data have been analyzed for circadian variation separately for each astronaut as well as for the three participating astronauts considered together as a homogeneous group.

This final report is divided into four parts. Part I relates the results of the transverse studies conducted to evaluate the variables for circadian changes and to obtain data for creating the time-qualified reference ranges. Part II discusses based on urinary and also oral temperature data obtained prior to and immediately after flight the evidence for the achievement of successful biological-rhythm adjustment following the scheduled alteration of the sleep-wakefulness routine of astronauts 1 and 3 by 12 hours from diurnal activity and nocturnal sleep (Houston time reference) to diurnal rest and nocturnal work. Part III presents the evaluation of the space environment and associated factors on the studied hematologic variables using the individualized time-qualified reference ranges. Part IV discusses the findings with recommendations for follow-up investigations based on the experiences and results of this research.

Included also in this final report are several appendices. Appendix A gives the results of the cosinor analyses applied to each astronaut's tranverse data sets. Appendix B provides time-qualified data either as the parameters of the cosinor analysis (mesor, amplitude and acrophase), chronograms and/or clock-hour references ranges for the variables being investigated through this contract. The data of the figures in this appendix are not differentiated according to age. The figures of Appendix C, on the other hand, do provide age-specific, 20-49 years of age, time-qualified references for the variables under study.

ESTABLISHING TIME-QUALIFIED REFERENCE VALUES FOR SPACELAB 1, HEMATOLOGY EXPERIMENT INS 103

Final Report

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PART I: TRANSVERSE STUDIES

Table 1 summarizes for each astronaut the degree of participation as well as the dates and features of each transverse 28-hour study during which blood samples were withdrawn at 4-hour intervals. The information pertains to the scheduling of the 28-hour investigations such as before or after transatlantic travel between the United States and Germany, as well as the number of blood and urine samples obtained and the number of oral temperature measurements made.

Discussion of the findings from the first three transverse studies, which were carried out well before the mission, is separated into two sections. The first relates the means, standard deviations and coefficients of variation of each blood variable by astronaut. For the majority of the variables, the means and standard deviations were derived from the six to seven samplings of every transverse investigation. Two of the astronauts (Nos. 1 and 2) participated in all three transverse studies; one astronaut participated in only two such investigations. The second section gives the results of the Single Cosinor analyses (1) on data from the transverse studies.

TABLE 1

Summary of the Degree of Participation in the Three Transverse Studies

Astronaut Name	Study No.	Wake/Sleep Schedule	Medications What/When	Calendar* Date	No. of Blood Samples	No. of Urine Samples (dates)	No. of Oral Temperatures (dates)
Merbold	1**			3-02-83	6	5 (3/02-3/03)	(3/02-3/03)
	2 (DFVLR)	No data	No data	3-14-83	7	9 (3/15-3/17)	Did not measure
	3**			5-11-83	7	No data yet	8 (5/11-5/13)
Ockels	1 (MSFC)	~0700-0100/ ~0100-0700	None	3-02-83	7	16 (3/02-3/04)	16 (3/02-3/05)
	2 (DFVLR)	~0630-0045/ ~0045-0630	None	3-16-83	7	26 (3/07-3/15)	28 (3/07-3/15)
	3 (MSFC)	~0700-2245/ ~2245-0700	None	5-13-83	7	No data yet	16 (5/10-5/13)
Parker	1 (Did not participate in first transverse study)						
	2 (DFVLR)	~0700-2300/ ~2300-0700	Aspirin and sleeping pills	3-17-83	7	12 (3/17-3/19)	11 (3/17-3/19)
	3 (MSFC)	~0630-2230/ ~2230-0630	Aspirin and sleeping pills	5-11-83	7	No data yet	19 (5/10-5/13)

*Date of blood sampling on first day of each transverse (24- to 28-hour) study.

**Data sheets not as yet received from laboratory or astronaut providing the needed information.

SECTION ONE: MEANS AND DISPERSION INDICES

Tables 2 through 9 present the means and standard deviations by variable and astronaut for each transverse study. The contents of these tables reveal, in general, rather excellent consistency in the means of each variable between astronauts from one transverse study to another (Tables 2-6). For some of the variables, the coefficient of variation ($S.D./\bar{x} \cdot 100$) is remarkably small, less than 5% (Tables 7-10). As Table 10 shows, serum sodium and osmolarity as well as MCV, MCHC, MCH and RBC are very well regulated, both within and between the 24-hour transverse studies. In two of the three astronauts, total protein and HCT also are finely regulated (the coefficient of variation, CV, is less than 5%). On the other hand, certain blood values are less precisely regulated, exhibiting at least a 20% CV (see Table 10). These include serum erythropoietin, monocytes, eosinophils, reticulocytes and alpha-1 protein. In two of the three astronauts, these include as well alpha-2 protein and haptoglobulin.

In general, findings similar to these were detected by Sargent (2) who conducted a series of single-time-point (unqualified for circadian rhythms) studies on large numbers of United States Army recruits more than three decades ago. Those hematological variables most critical for optimal biological efficiency were found to exhibit the lowest coefficients of variation; less critical ones exhibited greater variability. Coefficients of variation were greatest for certain enzymes and for metabolites of nutrients. Sargent hypothesized that the efficiency of homeostatic regulation is hierarchical with those functions and variables most critical for life processes having the most precise regulatory mechanisms. Moderate to large coefficients of variation may represent several factors.

TABLE 2

Means and Standard Deviations for Each Study by Variables and Astronaut

ROWS: ASTRO / TEST

		MCV COUNT	MCV MEAN	MCV STD DEV	MCH COUNT	MCH MEAN	MCH STD DEV	MCHC COUNT	MCHC MEAN	MCHC STD DEV
1										
	1	6	90.000	0.632	6	31.167	0.408	6	34.333	0.516
	2	7	86.857	1.069	7	28.714	0.756	7	33.143	0.690
	3	7	90.714	0.488	7	31.000	0.000	7	34.286	0.488
2										
	1	7	91.143	1.215	7	31.286	0.488	7	34.000	0.577
	2	7	85.429	1.988	7	29.286	1.113	7	34.429	0.535
	3	7	90.714	0.756	7	31.143	0.378	7	34.143	0.378
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	81.571	3.823	7	27.714	1.254	7	33.714	0.951
	3	7	88.286	0.756	7	30.857	0.378	7	35.000	0.000
ALL										
	ALL	55	88.055	3.546	55	30.127	1.466	55	34.127	0.747

		RBC COUNT	RBC MEAN	RBC STD DEV	HGB COUNT	HGB MEAN	HGB STD DEV	HCT COUNT	HCT MEAN	HCT STD DEV
1										
	1	6	4.8967	0.0946	6	15.183	0.232	6	44.333	1.211
	2	7	4.9757	0.1942	7	14.329	0.675	7	43.286	1.890
	3	7	4.7657	0.1624	7	14.770	0.640	7	43.000	1.528
2										
	1	7	4.3943	0.1427	7	13.700	0.300	7	40.429	1.397
	2	7	4.7271	0.1973	7	13.929	0.832	7	40.429	2.149
	3	7	4.5100	0.1874	7	14.029	0.616	7	40.857	1.574
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	4.9900	0.2459	7	13.729	0.787	7	40.714	1.604
	3	7	5.1043	0.1130	7	15.586	0.441	7	45.000	1.155
ALL										
	ALL	55	4.7936	0.2852	55	14.575	1.722	55	42.218	2.307

TABLE 3

Means and Standard Deviations for Each Study by Variables and Astronaut

ROWS: ASTRO / TEST

		RETIC COUNT	RETIC MEAN	RETIC STD DEV	WBC COUNT	WBC MEAN	WBC STD DEV	POLY COUNT	POLY MEAN	POLY STD DEV
1										
	1	6	0.56667	0.12111	6	6.0667	0.6377	6	47.167	9.065
	2	7	0.30000	0.08165	7	5.8286	1.6059	7	41.714	4.889
	3	3	1.03333	0.23094	7	5.5857	0.4880	7	41.000	6.055
2										
	1	7	0.81429	0.10690	7	6.0857	0.7515	7	44.000	4.655
	2	7	0.44286	0.05345	7	6.1714	1.0950	7	44.714	4.680
	3	4	0.50000	0.11547	7	5.0571	0.6754	6	45.333	3.266
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	0.44286	0.09759	7	7.9286	1.4115	7	52.857	7.198
	3	6	0.98333	0.21370	7	6.0429	0.7871	7	53.286	3.302
ALL										
	ALL	47	0.60426	0.27263	55	6.0964	1.2276	54	46.259	6.890

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		BAND COUNT	BAND MEAN	BAND STD DEV	LYMPH COUNT	LYMPH MEAN	LYMPH STD DEV	MONO COUNT	MONO MEAN	MONO STD DEV
1										
	1	1	1.0000	--	6	44.333	9.331	6	3.6667	1.8619
	2	7	6.4286	2.4398	7	46.286	6.075	7	4.1429	1.3452
	3	0	--	--	7	53.429	6.321	5	1.2000	0.4472
2										
	1	1	2.0000	--	7	43.286	3.251	7	2.4286	0.5345
	2	7	3.0000	1.5275	7	42.571	3.780	7	3.0000	1.7321
	3	0	--	--	6	48.167	4.491	6	1.8333	1.1690
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	6.1429	1.5736	7	36.429	6.503	7	3.5714	0.9759
	3	0	--	--	7	43.571	2.149	1	2.0000	--
ALL										
	ALL	23	4.8696	2.5281	54	44.704	6.984	46	2.8913	1.5089

TABLE 4

Means and Standard Deviations for Each Study by Variables and Astronaut

ROWS: ASTRO / TEST

		EOS COUNT	EOS MEAN	EOS STD DEV	BASO COUNT	BASO MEAN	BASO STD DEV	TOTPRO COUNT	TOTPRO MEAN	TOTPRO STD DEV
1										
	1	6	4.5000	2.2583	1	1.0000	--	5	7.4400	0.1342
	2	6	1.6667	0.8165	0	--	--	7	7.1571	0.2699
	3	7	4.7143	2.6277	0	--	--	6	7.1333	0.2944
2										
	1	7	10.0000	3.7859	0	--	--	7	7.3000	0.3162
	2	7	8.0000	2.7689	1	1.0000	--	7	7.4857	0.3805
	3	6	4.6667	1.2111	0	--	--	7	7.1429	0.2936
3										
	1	0	--	--	0	--	--	0	--	--
	2	4	1.7500	0.9574	0	--	--	7	7.1714	0.3684
	3	4	2.2500	0.5000	0	--	--	7	7.3286	0.3638
ALL										
	ALL	47	5.1064	3.5888	2	1.0000	0.0000	39	7.2718	0.3128

		ALBUM COUNT	ALBUM MEAN	ALBUM STD DEV	ALPHA1 COUNT	ALPHA1 MEAN	ALPHA1 STD DEV	ALPHA2 COUNT	ALPHA2 MEAN	ALPHA2 STD DEV
1										
	1	5	4.8600	0.2074	5	0.30000	0.00000	5	0.50000	0.00000
	2	7	4.0286	0.3352	7	0.32857	0.14960	7	0.80000	0.12910
	3	6	4.3333	0.3266	6	0.26667	0.05164	6	0.53333	0.08165
2										
	1	7	4.2143	0.3805	7	0.28571	0.08997	7	0.61429	0.10690
	2	7	4.4286	0.9105	7	0.38571	0.17728	7	0.70000	0.14142
	3	7	4.8429	0.6024	7	0.18571	0.03780	7	0.44286	0.07868
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	4.2000	0.5538	7	0.34286	0.07868	7	0.57143	0.09512
	3	7	4.5714	0.5851	7	0.27143	0.07559	7	0.48571	0.08997
ALL										
	ALL	53	4.4208	0.5789	53	0.29623	0.11087	53	0.58491	0.14858

TABLE 5

Means and Standard Deviations for Each Study by Variables and Astronaut

ROWS: ASTRO / TEST

		BETA COUNT	BETA MEAN	BETA STD DEV	GAMMA COUNT	GAMMA MEAN	GAMMA STD DEV	HAPTO COUNT	HAPTO MEAN	HAPTO STD DEV
1										
	1	5	0.72000	0.04472	5	1.0800	0.1304	5	59.20	14.43
	2	7	0.67143	0.04880	7	1.3143	0.1345	7	99.71	8.71
	3	6	0.75000	0.08367	6	1.2667	0.1862	7	51.29	6.55
2										
	1	7	0.81429	0.10690	7	1.4000	0.2517	7	110.86	6.34
	2	7	0.75714	0.16183	7	1.1857	0.6362	7	113.14	15.38
	3	7	0.70000	0.10000	7	0.9857	0.2268	7	131.57	10.52
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	0.70000	0.08165	7	1.3857	0.2035	7	60.71	8.77
	3	7	0.70000	0.16330	7	1.4000	0.2160	7	51.71	13.55
ALL										
	ALL	53	0.72642	0.11120	53	1.2585	0.3141	54	85.72	32.36

		TRANSF COUNT	TRANSF MEAN	TRANSF STD DEV	FERRIT COUNT	FERRIT MEAN	FERRIT STD DEV	NA COUNT	NA MEAN	NA STD DEV
1										
	1	5	261.40	19.88	5	130.80	10.89	6	139.50	1.05
	2	7	234.29	13.87	7	118.57	7.21	7	137.57	0.53
	3	7	281.71	29.84	7	100.57	6.70	7	138.14	0.90
2										
	1	7	286.43	23.76	7	43.57	4.47	7	139.71	0.49
	2	7	313.86	38.71	7	35.57	2.99	7	139.71	0.95
	3	7	287.86	17.42	7	33.57	2.07	7	139.43	0.98
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	255.86	27.82	7	42.86	3.89	7	140.57	0.79
	3	7	283.29	27.80	7	54.14	2.79	7	141.00	1.00
	ALL	54	276.11	33.99	54	67.70	36.87	55	139.45	1.34

TABLE 6

Means and Standard Deviations for Each Study by Variables and Astronaut

ROWS: ASTRO / TEST

		K COUNT	K MEAN	K STD DEV	OSMO COUNT	OSMO MEAN	OSMO STD DEV	SER EP COUNT	SER EP MEAN	SER EP STD DEV
1										
	1	6	4.5000	0.7239	6	291.83	2.93	6	0.37500	0.23347
	2	7	4.9429	1.5873	7	288.14	6.84	7	0.79857	0.85981
	3	7	5.2714	1.2379	7	289.00	2.24	0	--	--
2										
	1	7	4.6143	0.2911	7	291.43	1.13	7	0.29429	0.09537
	2	7	4.8857	0.9045	7	293.86	3.80	7	0.39143	0.14088
	3	7	4.6429	0.4315	7	290.00	3.42	0	--	--
3										
	1	0	--	--	0	--	--	0	--	--
	2	7	4.6143	0.7625	7	303.00	11.14	7	0.42286	0.10828
	3	7	4.8857	1.0495	7	294.86	7.52	0	--	--
ALL										
	ALL	55	4.8000	0.9286	55	292.78	7.06	34	0.45882	0.42756

These may include among others, laboratory technique, specificity and reliability of chemical analyses, astronaut activity (the effects of training or travel), nutrition, alcohol and circadian rhythmicity.

There do appear to be differences between the means of some of the variables of Transverse Study No. 2 (conducted 3 to 11 days depending on the astronaut after arrival in Germany from the United States), Transverse Study No. 1 (conducted several days before transatlantic travel to Germany) and Transverse Study No. 3 (conducted several weeks after return to the United States from Germany). In particular, the mean MCV and MCH values determined in Germany for astronauts 1 and 2 (Tables 2-6) were lower in Germany than were they in the United States. With respect to astronaut 3, who did not participate in Transverse Study No. 1, certainly one can conclude that the means of MCV and MCH of Transverse Study No. 2 conducted in Germany are markedly lower than those of Transverse Study No. 3 done in the United States. Except for astronaut 2, the findings for MCHC are generally similar. This is the case also for reticulocytes. Although there appear to be some location-dependent differences in other variables, such as in haptoglobin, eosinophils, ferritin, erythropoietin (EP) and monocytes, they are not large and/or the standard deviations are great. Except for reticulocytes, bands, eosinophils and ferritin, there is surprisingly little deviation in the means of the variables between astronauts.

The finding of apparently statistically significant differences between the $\bar{x}$s of certain variables as found from comparisons of the means and standard deviations of studies done in the United States (Transverse Studies No. 1 and No. 3) and the one done in Germany (Transverse

TABLE 7

Overall Means, Standard Deviations and Coefficients of Variation for Astronaut 1 (Data for the Three Transverse Studies Combined)

Hematological Variables

Studied Variable	No. of Data	Overall $\bar{x} \pm$ S.D.	Coefficient Variation (S.D./$\bar{x}$·100)	Rank of Coefficient Variation
MCV	20	89.15 ± 1.90	2.13	3
MCH	20	30.25 ± 1.25	4.14	8
MCHC	20	33.90 ± 0.79	2.32	4
RBC	20	4.88 ± 0.18	3.60	5
HGB	20	15.24 ± 2.48	16.27	15
HCT	20	43.50 ± 1.61	3.69	6
RETICULOCYTES	16	0.54 ± 0.30	55.79	22
WBC	20	5.82 ± 1.02	17.50	17
POLYMORPHS	20	43.10 ± 6.95	16.12	14
LYMPHOCYTES	20	48.20 ± 7.96	16.51	16
MONOCYTES	18	3.17 ± 1.82	57.57	23
EOSINOPHILS	19	3.68 ± 2.43	65.90	24
TOTAL PROTEIN	18	7.23 ± 0.27	3.76	7
ALBUMIN	18	4.36 ± 0.45	10.26	10
ALPHA 1	18	0.30 ± 0.10	32.34	20
ALPHA 2	18	0.63 ± 0.17	26.66	19
BETA	18	0.71 ± 0.07	9.51	9
GAMMA	18	1.23 ± 0.17	14.18	13
HAPTO	19	71.21 ± 24.42	34.29	21
TRANSF	19	258.89 ± 30.92	11.94	11
FERRITIN	12	115.16 ± 14.63	12.70	12
SODIUM	20	138.35 ± 1.14	0.82	1
POTASSIUM	20	4.93 ± 1.23	25.02	18
OSMOLARITY	20	289.55 ± 4.59	1.59	2
SERUM EP	13	0.60 ± 0.66	110.07	25

TABLE 8

Overall Means, Standard Deviations and Coefficients of Variation for Astronaut 2 (Data for the Three Transverse Studies Combined)

Hematological Variables

Studied Variable	No. of Data	Overall $\bar{x} \pm$ S.D.	Coefficient Variation (S.D./$\bar{x}$·100)	Rank of Coefficient Variation
MCV	21	89.10 ± 2.98	2.35	4
MCH	21	30.57 ± 1.17	3.81	5
MCHC	21	34.19 ± 0.51	1.50	3
RBC	21	4.54 ± 0.22	4.84	9
HGB	21	13.89 ± 0.61	4.37	7
HCT	21	40.57 ± 1.66	4.09	6
RETICULOCYTES	18	0.60 ± 0.20	32.84	20
WBC	21	5.77 ± 0.97	16.76	17
POLYMORPHS	20	44.65 ± 4.11	9.20	10
LYMPHOCYTES	20	44.50 ± 4.40	9.88	11
MONOCYTES	20	2.45 ± 1.28	52.09	25
EOSINOPHILS	20	7.70 ± 3.50	45.40	23
TOTAL PROTEIN	21	7.31 ± 0.35	4.74	8
ALBUMIN	21	4.50 ± 0.69	15.29	16
ALPHA 1	21	0.29 ± 0.14	48.61	24
ALPHA 2	21	0.59 ± 0.15	25.93	19
BETA	21	0.76 ± 0.13	17.00	18
GAMMA	21	1.19 ± 0.43	36.22	21
HAPTO	21	118.52 ± 14.37	12.12	13
TRANSF	21	296.05 ± 29.61	10.00	12
FERRITIN	21	37.57 ± 5.44	14.47	15
SODIUM	21	139.62 ± 0.80	0.57	1
POTASSIUM	21	4.71 ± 0.59	12.42	14
OSMOLARITY	21	291.76 ± 3.30	1.13	2
SERUM EP	14	0.34 ± 0.13	36.78	22

TABLE 9

Overall Means, Standard Deviations and Coefficients of Variation for Astronaut 3 (Data for the Three Transverse Studies Combined)

Hematological Variables

Studied Variable	No. of Data	Overall $\bar{x} \pm$ S.D.	Coefficient Variation (S.D./$\bar{x}$·100)	Rank of Coefficient Variation
MCV	14	84.93 ± 3.55	5.15	6
MCH	14	29.29 ± 1.86	6.34	8
MCHC	14	34.36 ± 0.93	2.70	2
RBC	14	5.05 ± 0.19	3.82	4
HGB	14	14.66 ± 1.14	7.79	9
HCT	14	42.86 ± 2.60	6.06	7
RETICULOCYTES	13	0.69 ± 0.32	46.23	25
WBC	14	6.99 ± 1.47	21.05	19
POLYMORPHS	14	53.07 ± 5.39	10.15	10
LYMPHOCYTES	14	40.00 ± 5.95	14.87	15
MONOCYTES	7	3.38 ± 1.06	31.42	23
EOSINOPHILS	8	2.00 ± 0.76	45.40	24
TOTAL PROTEIN	14	7.25 ± 0.36	4.98	5
ALBUMIN	14	4.39 ± 0.58	13.23	12
ALPHA 1	14	0.31 ± 0.08	26.98	21
ALPHA 2	14	0.53 ± 0.10	18.81	18
BETA	14	0.70 ± 0.12	17.72	16
GAMMA	14	1.39 ± 0.20	14.49	14
HAPTO	14	56.21 ± 11.92	21.21	20
TRANSF	14	269.57 ± 30.27	11.23	11
FERRITIN	14	48.50 ± 6.70	13.81	13
SODIUM	14	140.79 ± 0.89	0.63	1
POTASSIUM	14	4.75 ± 0.89	18.79	17
OSMOLARITY	14	298.93 ± 10.06	3.37	3
SERUM EP	7	0.42 ± 0.11	25.62	22

Table 10

Precision of Regulation Assessed By Coefficient of Variation (CV)

Hematological Variables Across Astronauts Exhibiting:	
CV Less than 5%	CV More than 20%
SERUM SODIUM	SERUM EP
MCV	EOSINOPHILS
MCHC	RETICULOCYTES
MCH*	MONOCYTES
OSMOLARITY	ALPHA 1
RBC	ALPHA 2*
HCT*	HAPTO*
TOTAL PROTEIN*	

*For two of the astronauts studied.

Study No. 2) is intriguing. On the one hand, the differences might indicate changes arising from the adjustments in the circadian system following alteration in the rest-activity schedule of the astronauts subsequent to rapid geographic displacement by jet aircraft from Houston to Germany. On the other hand, these findings might result from differences in life style followed by the individual astronauts while studied in the United States in comparison to Germany. The latter might include the effects of variations in the quantity or quality of food and/or alcohol consumed. Another factor to consider is the possibility of laboratory-related analytical biases since blood samples were analyzed in more than one laboratory. The effect of the laboratory influence should be reviewed in order to assess the contribution of such, if any, to the apparent location-dependent differences for the variables specificed above.

SECTION TWO: CIRCADIAN RHYTHMS

The data which were collected at approximately equal intervals over the 28-hour continuous spans of the three separate transverse studies on each astronaut were analyzed by the Single Cosinor method (1). Initially, cosinor analyses were conducted on the data of each astronaut by variable and transverse study. The results of these analyses, which are reported in the tables of Appendix A of this report, indicate no consistent phase differences among the variables between the studies done in the United States and Germany. Thus, it appears that the transverse study done in Germany was conducted at a time apparently when complete physiological adjustment to the activity-sleep routine of Germany had been achieved.

To further analyze the data of each astronaut, every one of the time series of the transverse studies was combined as if the data were obtained at approximately 4-hour intervals during two (astronaut 3) or three (astronauts 2 and 3) successive 24-hour spans. The results of the analyses are presented in Table 11. In this as well as the other tables summarizing the results of the cosinor analyses, the statistical significance of rhythm detection is indicated as are the rhythmometric endpoints: mesor (24-hour rhythm-adjusted mean), amplitude (a measure of the predictable variation due to circadian rhythmicity) and acrophase (the clock hour of the peak value in the time series referenced to 0000), all determined by the fitting of the approximating model--a single cosine curve.

Using the data of each astronaut separately (for all but astronaut 3, three transverse studies with between 8 and 21 data points per variable), statistically significant circadian rhythmicity is detected for total protein, osmolarity, WBC and potassium for all the astronauts and albumin for two of the three astronauts. The amplitudes, considered as the peak-to-trough difference (equal to twice the amplitude value, i.e., 2A), expressed relative to the mesor differ between astronauts and variables. For example, for WBC the total (peak-to-trough) variation expressed relative to the respective mesor amounts to between 29.5% (astronaut 1) and 37.2% (astronaut 3), with peak numbers occurring between 2004 and 2156. For potassium, a circadian rhythmicity of similar timing (2100-2200) with peak-to-trough variation ranging from 17.1% (astronaut 2) to 51.8% (astronaut 1) relative to the respective mesor is detected. For albumin, for which statistically significant rhythms were detected for two of the astronauts, the peak-to-trough

TABLE 11

Circadian Change in Hematological Variables (data of all transverse studies combined per astronaut)

Hematological Variables	Astronaut Studies	No. of Samples	Mesor M ± S.D.	Circadian[a] 2A	Circadian[a] Acro-phase	2A as % M
Erythropoietin	Merbold	13	0.58 ± 0.20	0.42	1031	73.7%
	Ockels	14	0.34 ± 0.04	0.06	0748	16.5%
	Parker	7	0.42 ± 0.05	0.11	0154	26.1%
RBC	Merbold*	20	4.87 ± 0.04	0.26	1419	5.3%
	Ockels	21	4.53 ± 0.05	0.26	1332	5.7%
	Parker	14	5.04 ± 0.04	0.40	1409	7.9%
HGB	Merbold	20	15.16 ± 0.54	2.88	1504	19.0%
	Ockels**	21	13.84 ± 0.12	0.94	1409	6.8%
	Parker	14	14.65 ± 0.33	0.61	1424	4.2%
HCT	Merbold*	20	43.38 ± 0.33	2.45	1354	5.6%
	Ockels*	21	40.46 ± 0.34	2.13	1255	5.3%
	Parker	14	42.84 ± 0.74	1.58	1500	3.7%
MCV	Merbold	20	89.14 ± 0.45	0.19	1548	0.2%
	Ockels	21	89.13 ± 0.69	1.16	0429	1.3%
	Parker	14	84.97 ± 1.23	3.26	0154	3.8%
MCH	Merbold	20	30.24 ± 0.30	0.49	1605	1.7%
	Ockels	21	30.57 ± 0.27	0.64	1910	2.1%
	Parker	14	29.30 ± 0.53	1.02	0130	3.5%
MCHC	Merbold	20	33.89 ± 0.19	0.26	1046	0.8%
	Ockels**	21	34.18 ± 0.10	0.72	1745	2.1%
	Parker	14	34.35 ± 0.27	0.49	1013	1.4%
Reticulocytes	Merbold	16	0.50 ± 0.08	0.30	1230	60.0%
	Ockels	18	0.59 ± 0.05	0.19	1734	32.2%
	Parker	13	0.69 ± 0.10	0.18	1146	26.1%
WBC	Merbold*	20	5.89 ± 0.20	1.74	2004	29.5%
	Ockels**	21	5.84 ± 0.16	1.94	2156	33.2%
	Parker**	14	7.01 ± 0.32	2.61	2132	37.2%
Polymorphs	Merbold	20	43.14 ± 1.65	2.80	0505	6.5%
	Ockels**	20	44.49 ± 0.80	6.87	1910	15.4%
	Parker	14	53.01 ± 1.46	5.61	1412	10.6%
Bands	Merbold	8	5.43 ± 1.22	2.84	0554	46.8%
	Ockels**	8	3.22 ± 0.33	3.25	0536	100.9%
	Parker	8	6.24 ± 0.33	3.80	0244	60.9%

TABLE 11 (continued)

Hematological Variables	Astronaut Studies	No. of Samples	Mesor M ± S.D.	Circadian[a] 2A	Circadian[a] Acro-phase	2A as % M
Lymphocytes	Merbold	20	48.29 ± 1.84	5.44	1907	11.3%
	Ockels	20	44.63 ± 1.01	3.16	0520	7.1%
	Parker	14	40.04 ± 1.65	4.87	0316	12.2%
Monocytes	Merbold	18	3.13 ± 0.44	1.64	1257	52.4%
	Ockels	20	2.44 ± 0.28	1.34	0936	54.9%
	Parker	8	3.48 ± 0.32	2.16	1236	62.1%
Eosinophils	Merbold	19	3.56 ± 0.60	1.54	1108	43.3%
	Ockels	20	7.69 ± 0.83	0.42	1006	5.5%
	Parker	8	1.82 ± 0.28	1.25	1015	68.7%
Sodium	Merbold	20	138.31 ± 0.27	0.74	1325	0.5%
	Ockels	21	139.61 ± 0.26	0.42	0836	0.3%
	Parker**	14	140.78 ± 0.20	1.46	0719	1.0%
Potassium	Merbold**	20	5.06 ± 0.18	2.62	2224	51.8%
	Ockels*	21	4.74 ± 0.12	0.81	2141	17.1%
	Parker**	14	4.76 ± 0.19	1.60	2053	33.6%
Osmolarity	Merbold*	20	289.86 ± 0.97	2.97	2230	1.0%
	Ockels**	21	292.00 ± 0.64	5.10	2324	1.7%
	Parker**	14	299.18 ± 2.04	21.38	0105	7.1%
Total Protein	Merbold**	18	7.18 ± 0.06	0.49	1526	7.0%
	Ockels**	21	7.29 ± 0.07	0.53	1625	7.3%
	Parker**	14	7.25 ± 0.07	0.71	1632	9.8%
Albumin	Merbold	18	4.34 ± 0.11	0.32	1534	7.4%
	Ockels*	21	4.46 ± 0.14	0.93	1012	20.7%
	Parker*	14	4.38 ± 0.14	0.89	1616	20.3%
Alpha 1	Merbold	18	0.29 ± 0.02	0.08	1124	27.6%
	Ockels	21	0.28 ± 0.03	0.17	1828	60.0%
	Parker*	14	0.31 ± 0.02	0.10	0001	32.3%
Alpha 2	Merbold	18	0.63 ± 0.04	0.07	2001	11.1%
	Ockels	21	0.59 ± 0.03	0.15	2031	25.0%
	Parker	14	0.53 ± 0.03	0.09	2304	17.0%
Beta	Merbold	18	0.71 ± 0.02	0.08	1657	11.4%
	Ockels	21	0.76 ± 0.03	0.16	2000	21.1%
	Parker	14	0.70 ± 0.03	0.09	1006	12.9%
Gamma	Merbold	18	1.22 ± 0.05	0.11	1300	9.0%
	Ockels**	21	1.20 ± 0.09	0.64	2040	53.3%
	Parker					

TABLE 11 (continued)

Hematological Variables	Astronaut Studies	No. of Samples	Mesor M ± S.D.	Circadian[a] 2A	Circadian[a] Acro-phase	2A as % M
Transf	Merbold*	19	259.21 ± 6.74	40.8	1901	15.7%
	Ockels	21	295.24 ± 6.42	29.2	1702	9.9%
	Parker	14	269.24 ± 7.92	39.2	1504	14.6%
Ferrit	Merbold	19	114.34 ± 3.54	11.8	1403	10.3%
	Ockels	21	37.45 ± 1.19	5.0	1724	13.4%
	Parker	14	48.46 ± 1.93	3.0	1200	6.2%
Hapto	Merbold	19	70.39 ± 6.0	13.2	0848	18.8%
	Ockels	21	118.22 ± 3.28	7.8	1032	6.6%
	Parker	14	56.11 ± 14.73	14.73	1548	26.3%

[a]Amplitude given as total peak-to-trough difference (2A) and acrophase given as clock hour and referenced to 0000; both determined by Single Cosinor.

Statistical significance: *$0.10 > p > 0.05$; **$p \leq 0.05$

(2A) difference expressed relative to the mesor is slightly lower. For albumin it is between 7.0% (astronaut 1) and 20.7% (astronaut 2) with an acrophase between 1000 and 1600.

For the other hematological variables circadian rhythmicity was not detected. Although the peak-to-trough differences are rather large for certain variables--polymorphonucleocytes, monocytes, lymphocytes and eosinophils, the variance accounted for by the approximation of the data using a single cosine is not statistically significant. For some variables, the amount of peak-to-trough variation over the 24 hours is rather low, equal to about 5% of the mesor. These variables include RBC, HCT, MCV, MCH, MCHC and sodium. It is of interest to note that these variables which exhibit the least peak-to-trough difference over the 24 hours are precisely those which have the lowest coefficients of variation (Table 10). Conversely, those variables which exhibit the greatest peak-to-trough difference, even if circadian rhythmicity is not statistically validated, are those which have the highest coefficients of variation (Table 10).

Table 12 presents the findings of the cosinor analyses of the variables when the data of each are considered as being derived from a homogeneous sample of the three astronauts. The table shows for which variables circadian rhythms are documented among the 27 or so studied. Except for bands, WBC, albumin, beta protein, potassium and transferritin, the peak-to-trough (2A) difference is moderate. As expected, RBC, HGB and HCT exhibit similar acrophases; all occur in the afternoon around 1400. WBC, osmolarity, potassium and beta protein have nocturnal acrophases.

TABLE 12

Circadian Rhythms in Hematological Variables of the Three Astronauts Using All the Data of the Three Transverse Studies[†]

Studied Variable	Mesor, M M ± S.D.	Circadian		2A as % M
		Amplitude	Acrophase	
RBC**	4.78 ± 0.04	0.13	1402	5.6%
HGB**	14.36 ± 0.11	0.43	1410	6.0%
HCT*	42.14 ± 0.30	1.00	1340	4.7%
WBC**	6.16 ± 0.15	0.89	2301	32.1%
Bands**	4.94 ± 0.47	1.78	0440	51.8%
Total Protein**	7.25 ± 0.04	0.28	1603	7.7%
Albumin*	4.39 ± 0.08	0.25	1326	11.48%
Beta*	0.73 ± 0.01	0.05	1855	14.0%
Potassium**	4.85 ± 0.10	0.84	2147	34.6%
Osmolarity**	293.18 ± 0.87	4.66	0011	3.2%
Transf**	275.59 ± 4.44	17.19	1708	12.44%

[a]Amplitude expressed as one-half the peak-to-trough difference and acrophase in clockhours from 0000; both estimated by the least squares fit of a single cosine to the data of all subjects placed end-to-end.

Statistical significance of rhythm detection: *$0.05 < p < 0.10$; **$p < 0.05$.

[†]The variance accounted for by the fit of a single cosine curve to the time series is approximately 5 to 10% for HCT, HGB, RBC, Albumin, Beta and Transf; approximately 20% for WBC, Bands and Osmolarity and approximately 30% for total protein and 40% for serum potassium. Thus, although circadian rhythmicity was detected for several variables, the single cosine model for fitting the data appears to be best representative only of the temporal patterns in WBC, Bands, osmolarity, total protein and potassium.

At the onset it was anticipated that circadian differences would be detected in a greater number of variables than found. An explanation for the failure to substantiate circadian rhythmicity in more variables can be hypothesized only. In the case of those variables which have been previously reported to exhibit small-amplitude 24-hour changes (see Appendices B and C), the so-called "noise" resulting from factors and conditions related to the rigors of the astronauts' training cannot be ignored. Too, the required travel between training bases within the United States and also between continents with the possibility of a consequent desynchronization of circadian bioperiodicities makes rhythm detection difficult and/or description less accurate. In future chronobiologic investigations, it is receommended that the transverse studies be conducted at a time when synchronization of circadian function can be ensured and in facilities where important exogenous factors, such as activity level and meal timings and content, can be carefully controlled.

SUMMARY

The data acquired from the three transverse studies indicate that several hematological variables are rather finely regulated at one atmosphere. This is exemplified by the fact that several exhibit relatively little variation in their individual values over the 24 hours. Furthermore, for many variables there is relatively little difference between the means of the astronauts. In general, only a few variables exhibit large-amplitude circadian rhythms. Circadian rhythms in those functions/variables which are precisely regulated are either not detect-

able or of quite low amplitude (generally the peak-to-trough differences over the 24 hours are less than 5% M).

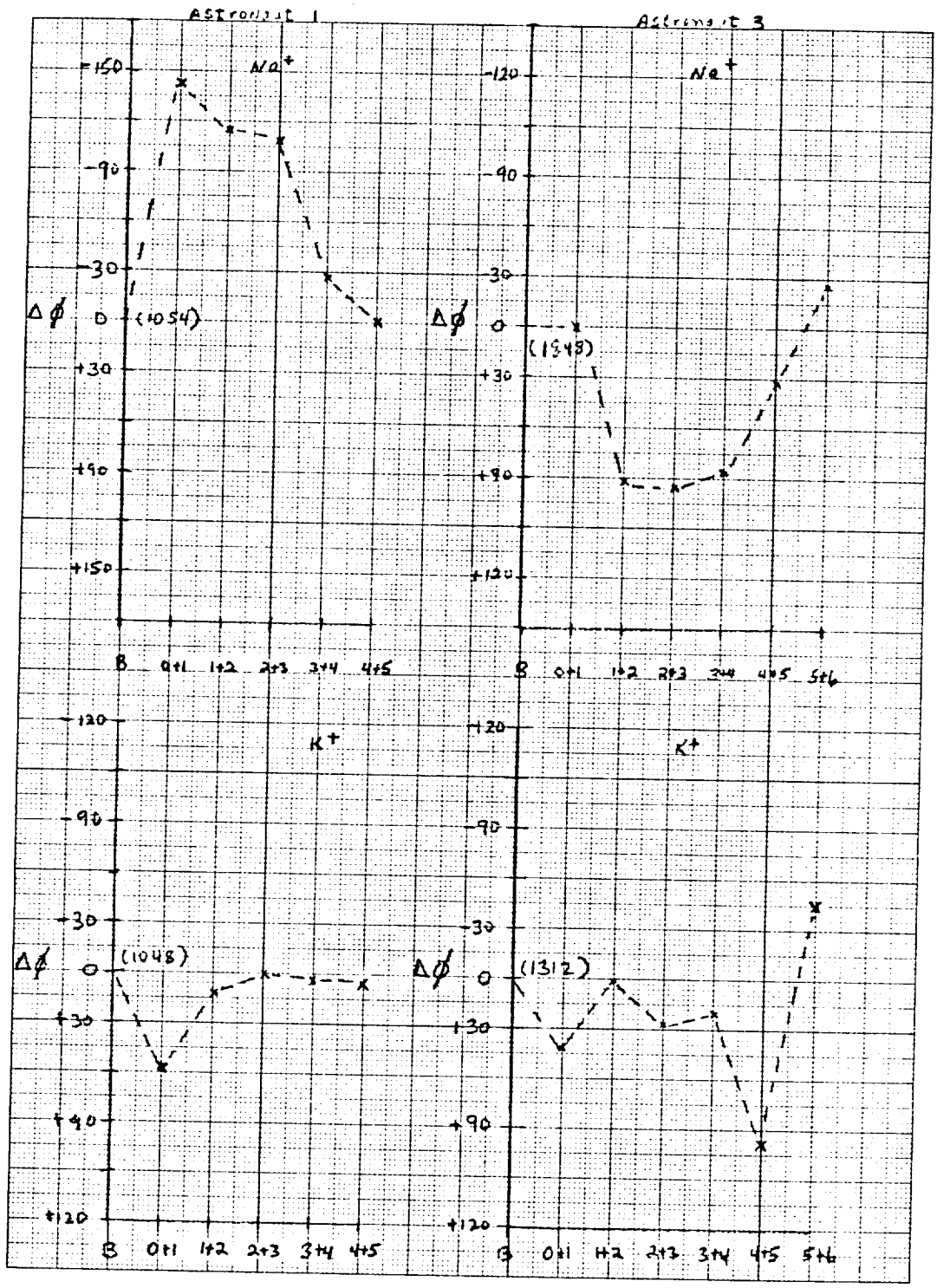
PART II: PHASE SHIFTING OF TEMPORAL STRUCTURE DUE TO THE IMPOSED NOCTURNAL WORK, DIURNAL REST SCHEDULE

The activities of this space flight necessitated that work be performed continuously throughout each 24 hours. In order to meet this need, different crew members were assigned (relative to Houston time) to either diurnal work and nocturnal rest or to nocturnal work and diurnal rest. Astronauts 1 and 3 who are reported upon here were assigned to the latter shiftwork schedule.

Although it was hoped that a sufficient number of urine samplings as well as oral temperature determinations could be gathered during the period of isolation before flight in order to assess the degree to which adjustment of circadian functions was achieved following the preflight alteration in the schedule of sleep and activity, this was not possible. Since the mission was delayed from its scheduled date the proposed protocol for gathering the needed data could not be followed. However, a similar protocol was used during the postflight span to obtain time series data on oral temperature as well urinary Na+, k+ and cortisol among others. These latter were analyzed by Cosinor analysis to indirectly assess to what extent if any phase shifting ($\Delta\phi$) of these circadian functions did occur.

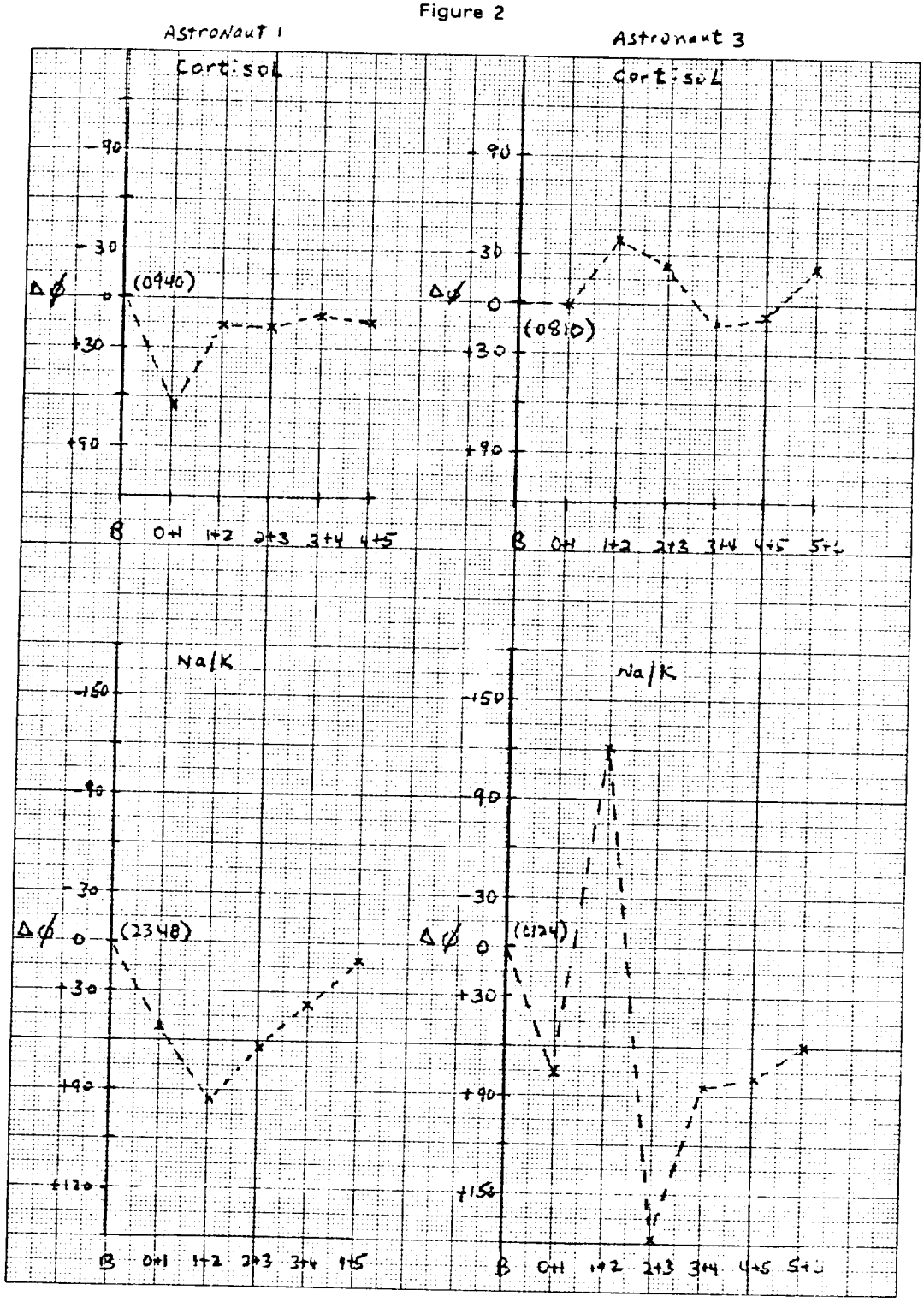
Figures 1-3 depict the results of the cosinor analyses applied to the time series of urinary Na^+, K^+, Na/K and cortisol obtained by collecting sequential urine voidings and by recording oral temperature at specified times throughout the waking span of each 24 hours for the 4 to 6 days postflight. In these figures, the ordinate scale indicates by a positive or negative sign an advance or delay in the circadian acrophase (peak time = ϕ) for a given 48-hour postflight span relative to the baseline

Figure 1



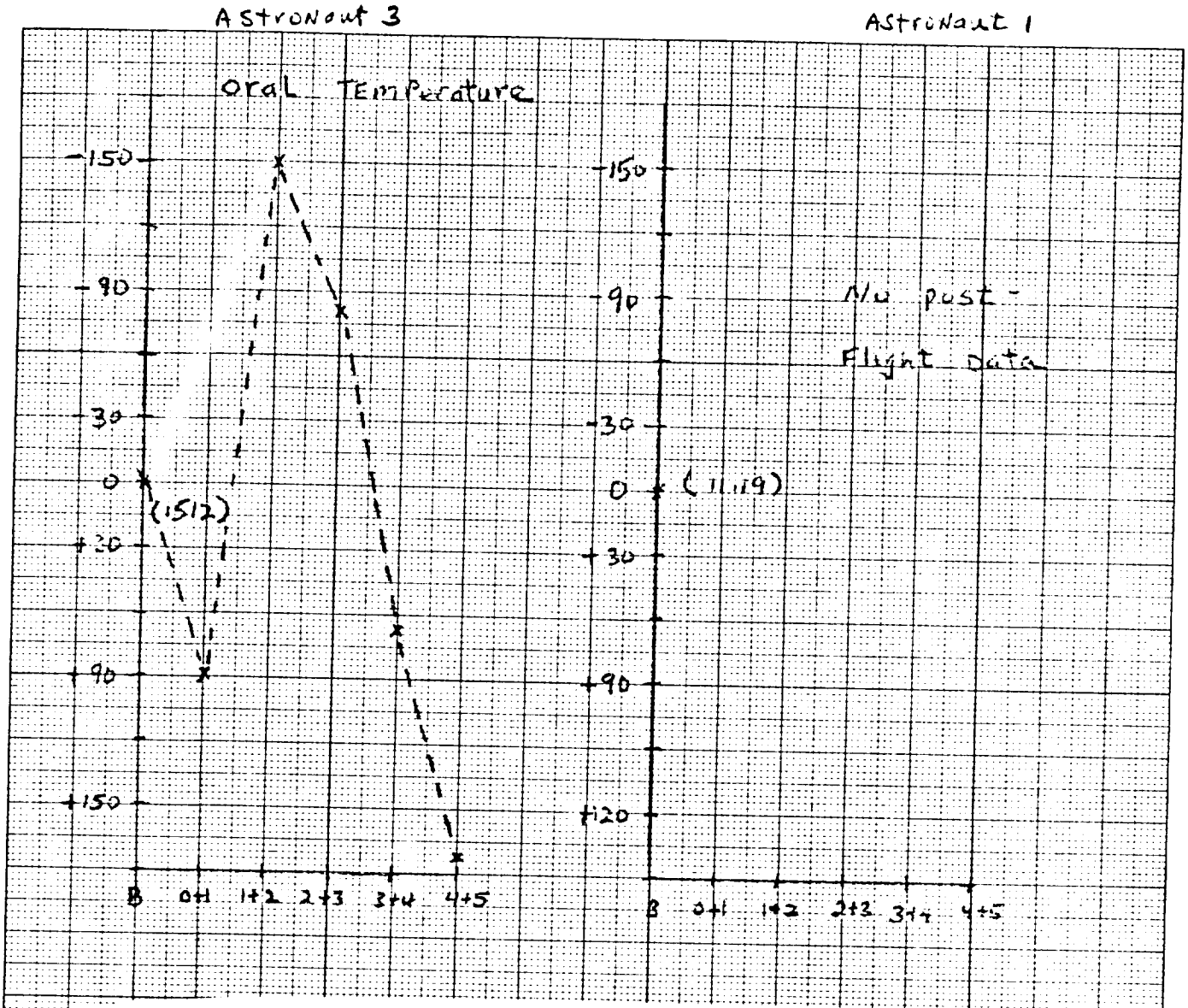
Acrophase adjustments (Δφ) of circadian rhythms using data collected over indicated 48-hour post-flight sampling spans (see text). Note a + Δφ represents an acrophase advance while a - Δφ represents an acrophase delay relative to the before-space-flight baseline φ shown in parentheses. Note also the ordinate is given in degrees; each 15° equals one hour clock time.

Figure 2



Acrophase adjustments (Δφ) of circadian rhythms using data collected over indicated 48-hour post-flight sampling spans (see text). Note a + Δφ represents an acrophase advance while a - Δφ represents an acrophase delay relative to the before-space-flight baseline φ shown in parentheses. Note also the ordinate is given in degrees; each 15° equals one hour clock time.

Figure 3



Acrophase adjustments of the circadian rhythm of oral temperature using data collected over indicated 48-hour post-flight spans (see text). Note a + $\Delta\phi$ represents an acrophase advance while a - $\Delta\phi$ represents an acrophase delay relative to the before-space-flight baseline ϕ shown in parentheses. Note also the ordinate is given in degrees; each 15° equals one hour clock time.

circadian ϕ (as determined utilizing all the urine or oral temperature time series data obtained during the three transverse studies). To ensure a sufficient data base to obtain the best possible estimates of the circadian acrophase on a day-by-day basis following space flight, Cosinor analyses were conducted on data sets of 48-hour durations. Analyses proceeded in a stepwise progression; data for each sequential 24-hour span were added as data for the earliest 24 hours were deleted. For example, the acrophase shown for the 48-hour span labeled 0+1 on the abscissa was derived from a Cosinor analysis of the data of the 48-hour duration defined by the day of landing (0) from 0000 until 2359 Houston time of the next day (+ 1); the acrophase for the span labeled on the abscissa 1+2 was derived from a Cosinor analysis of data obtained during the 48 hours extending from 0000 of day 1 until 2359 of day 2 after landing and so on.

Overall, the plots shown in the three figures reveal relative little evidence that the circadian acrophase of each studied variable underwent significant alteration due to night work with daytime rest in these two astronauts. Since the baseline acrophase of each variable was determined from data obtained from each astronaut while adhering to diurnal activity and nocturnal sleep, it was expected that a 12-hour shift in the activity-sleep schedule would induce a corresponding shift in the circadian time structure, measureable by $\Delta\phi$s in the variables plotted, assuming complete adjustment of the circadian system to the new routine. Thus, the acrophase values for each of the variables were expected to exhibit a significant displacement ($\Delta\phi$), by around 12 hours, from the baseline especially for the first few days after landing, a time when the astronauts were once again adhering to their diurnal activity/nocturnal rest

routine such as before flight. Except for the acrophase plots of urinary sodium of both astronauts 1 and 3 and perhaps to a limited extent for that of Na/k of astronaut 3, there is no convincing evidence of complete, or perhaps even partial, circadian adjustment as denoted by acrophase shifts ($\Delta\phi$) to the altered work-rest schedule. With respect to Na^+, it is difficult to determine what these $\Delta\phi$s represent, i.e., a true alteration in the staging of the circadian rhythm or a "masking" effect due to a different meal scheduling from that occurring in flight, for example. In fact, the plot for urinary cortisol, usually a rhythm exhibiting relatively slow adjustment of its acrophase with changes in the work-rest routine, reveals at most only slight difference from the (diurnal activity) baseline acrophase. Only for the 0+1 data of astronaut 1 and for 1+2 data of astronaut 3 are there deviations from the baseline ϕ and these are rather insignificant, constituting no more than a $\Delta\phi$ of two hours. Sufficient data on oral temperature are available only from astronaut 3 during the postflight duration. There were not enough data from astronaut 1 to conduct analyses. The acrophase plot for astronaut 1 is inconclusive. In most persons the oral temperature circadian rhythm exhibits rather rapid adjustment to alterations in synchronizer schedule. Although the ϕ values are at first displaced by many hours relative to the baseline reference, the trend in the timing of the circadian ϕ with the passage of time postflight is not toward the reference ϕ. Thus, the monitoring of this variable alone in a retrospective manner as done here does not provide insight into the question of whether the circadian system of this astronaut shifted due to the imposed change in his sleep-activity routine.

Based on the urinary cortisol acrophase plots of astronauts 1 and 3 which appear to be the best index of circadian system staging, it is suggested, lacking the availability of other time series data immediately before and throughout flight, that complete and perhaps even partial chronobiologic adjustment to the altered rest-activity schedule did not result. If indeed this is the case and with the flight log documenting work during the night and rest during the daytime relative to Houston time, one wonders in the space environment if other more dominant synchronizers of circadian rhythms are in operation than the one currently believed to be the most important for human beings on earth, the rest-activity schedule. Such speculation most be tempered in view of the small number of astronauts thus far studied in this manner and the relatively small number of samples available during each 24-hour span after flight and also without time series data on indicator variables <u>before</u> <u>and</u> <u>during</u> flight.

PART III: EFFECT OF THE SPACE ENVIRONMENT AND ASSOCIATED FACTORS ON HEMATOLOGIC VARIABLES

The contents of Table 12 on page 20 reveal 8 hematologic parameters (RBC, HGB, WBC, bands, total protein, potassium, osmolarity and transferritin) to be circadian rhythmic and 3 others (HCT, albumin and beta protein) to exhibit near statistical significance. It is especially relevant that time-qualified reference values (TQRV) be used for these variables. It seems worthwhile as well that TQRV be used for variables (reticulocytes, monocytes, alpha-1, and alpha-2 protein) exhibiting large coefficients or variations in the absence of demonstrable circadian rhythmicity.

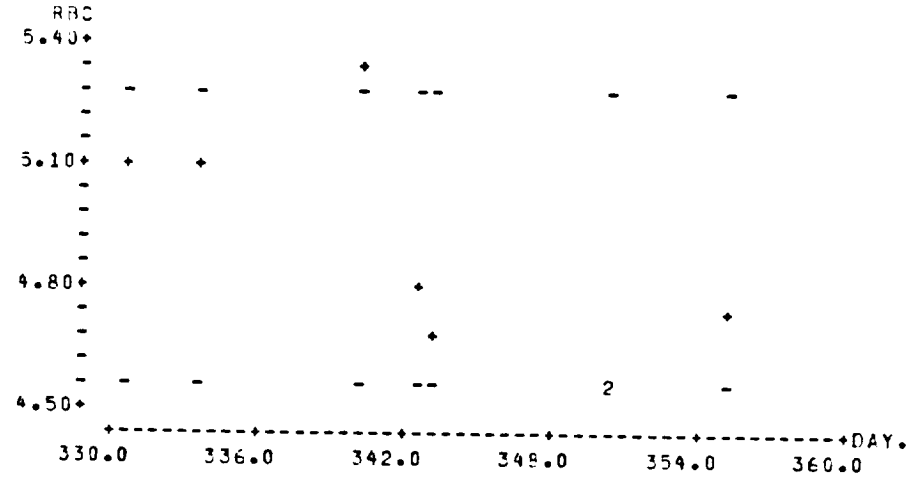
In the series of Figures (4-39) included in this part, TQRV are shown for the variables mentioned in the paragraph above as well as for related ones. Each figure shows for a given astronaut from top to bottom a series of three plots. The one at the top provides the 5 to 95 percentile limits created by using the entire set of data obtained from the designated astronaut during the scheduled pre-flight transverse 28-hour investigations. The plots shown in the middle and at the bottom of each of these figures provides the 5 and 95 percentile limits calculated by using a portion of the aforementioned data base--for data collected during a 6-hour span of time from 0600 to 1200 (Houston time), as shown in the middle plot, or from 1800 to 0000 (Houston time), as shown in the bottom plot. A 6-hour span was chosen to ensure that a sufficient number of data would be used to calculate representative percentile limits. The clock times of 0600 to 1200 were selected since the majority of blood samplings during the mission and postflight were reported to

have been done within this interval. Two separate TQRV plots were created for each variable and astronaut to evaluate whether a given hematologic value was typical or atypical, considering on the one hand complete adjustment of the circadian system to night work did not occur and therefore the limits shown in the middle plot of each page are the most appropriate or, on the other hand, complete adjustment did occur and therefore the limits shown in the plot at the bottom of each page are the most appropriate. The 5 and 95 percentile limits of each plot are shown by horizontal darkened lines; the raw data are shown as "plus" signs relative to the day of the year numerically indicated. Data are shown for the following sampling dates in the top plots of each figure: F-1, MD2, MD6, L+0, L+1, L+8 and L+13. In the middle and lower plots of each figure data for day F-7 precede these aforementioned ones. Below each plot is the calculated average, standard deviation and high (95 and 5) percentile limits.

The effect of the space environment and associate factors on each variable is considered separately. The variables, however, have been grouped with respect to category.

RBC: Figures 5 and 6 present the plots of RBC. The one at the top reveal the RBC on MD6 are beyond the 95th percentile limit in both the astronauts. The TQRV indicate as well that the RBC is either at the 95th percentile limit assuming no $\Delta\phi$ or well beyond it assuming a $\Delta\phi$ of 12 hours for astronaut 1 (Figure 5). The same feature is apparent in the data of astronaut 3 (Figure 6). Thereafter, there a is trend of gradual decline in the RBC of both astronauts with the L+13 counts being below or at the 5th percentile limit. Relative to the overall (non-time-qualified) average using the entire data set the highest RBC

Figure 5



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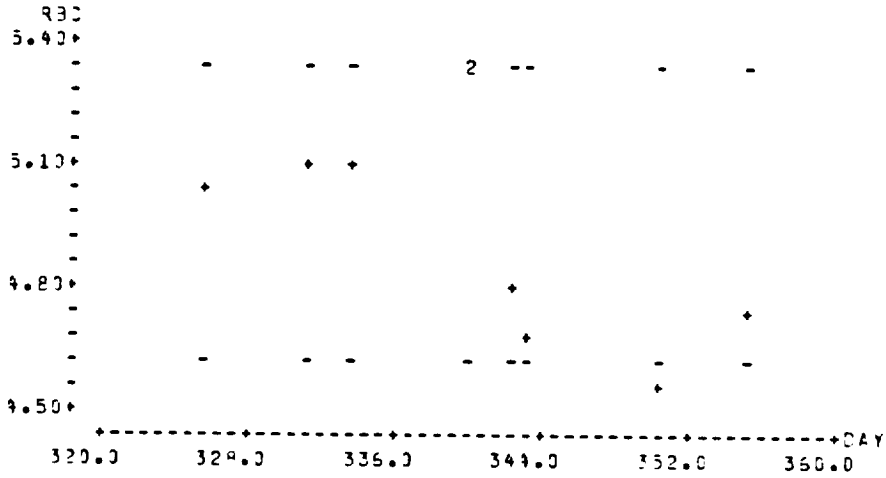

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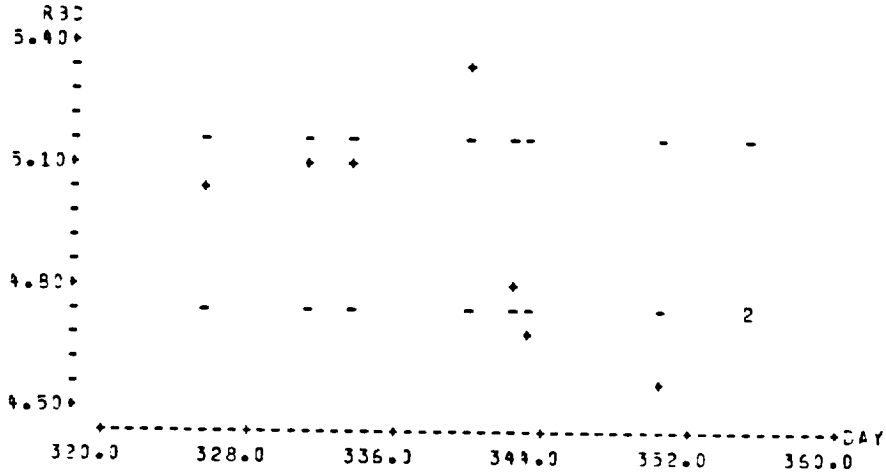

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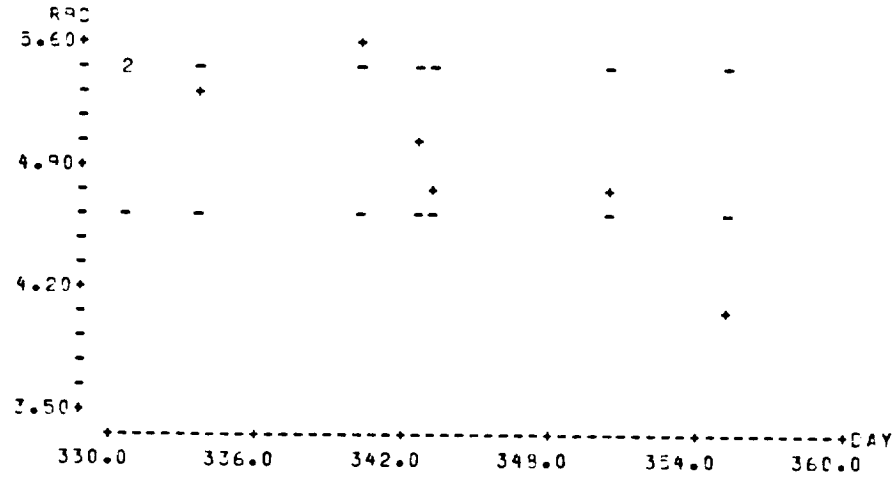
Figure 6



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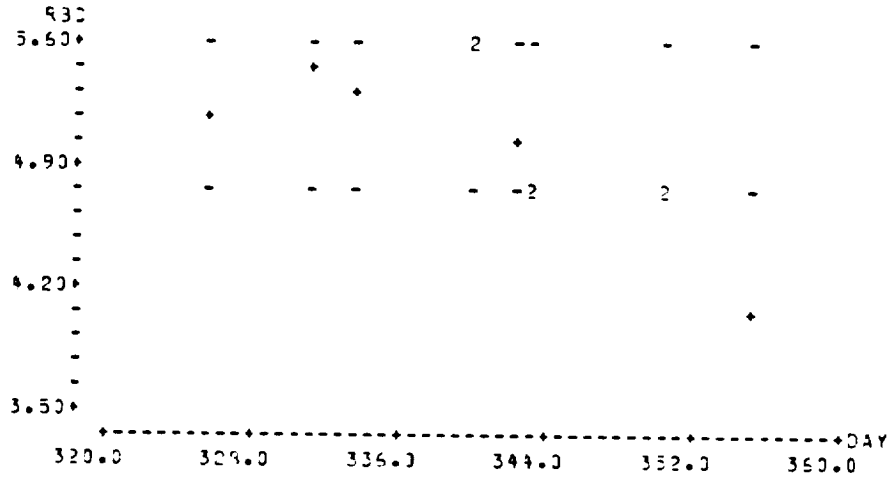
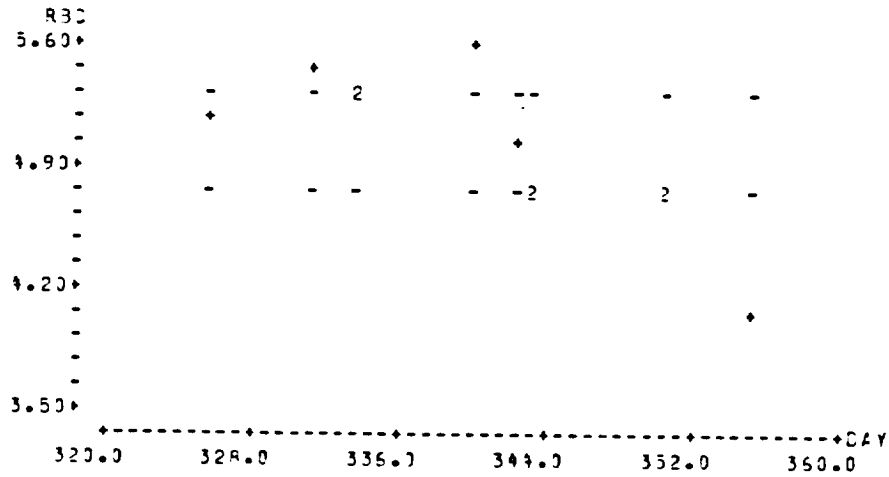
HI 5.46722
LO 4.68026



5.13337
.213235
5.56980
4.69686



5.03300
.152053
5.34211
4.73389

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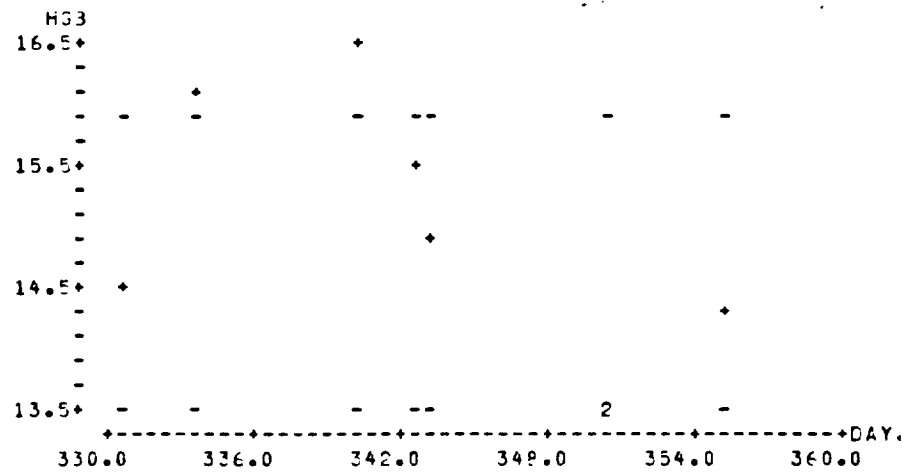
on MC6 is approximately 8.5% greater while that on L+8 and L+13 is from 6.5% (astronaut 1) to 20% (astronaut 3) lower.

HGB: Figures 7 (astronaut 1) and 8 (astronaut 3) show the plots for HGB. The pattern in this variable over time is similar, as might be expected, as the one for RBC. Initially, in each astronaut there is a rise in HGB peaking by MD6 (both MD2 and MD6 values extend beyond the 95th percentile limit of astronaut 1). Thereafter, there is a decline in HGB with the L+8 value of astronaut 1 being below the 5th percentile. The MD6 value is 11.3% greater than the (non-time-qualified) average for astronaut 1 and 15.3% greater than that for astronaut 3.

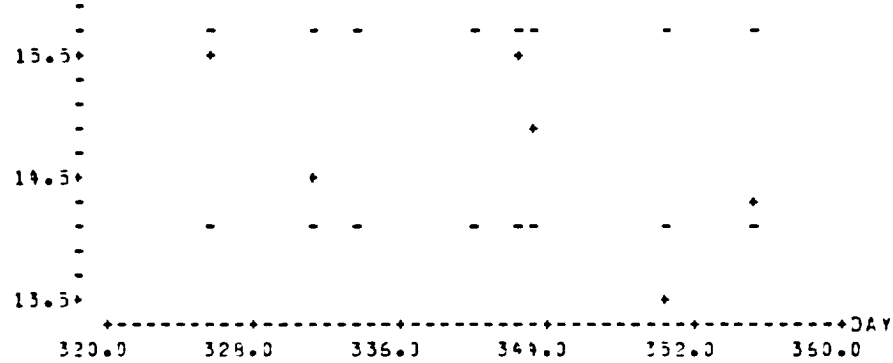
HCT: Figures 9 (astronaut 1) and 10 (astronaut 3) reveal similar patterns in HCT as RBC and HGB. There is an increase in HCT during flight with a peak on MD6. Thereafter, there is decline. For both astronauts the HCT are extraordinary only if a complete $\Delta\phi$ of the circadian rhythm can be assumed (bottom plot). Similarly, the low values found for astronaut 3 on L+1, L+8 and L+13 are atypical only if this assumption is valid (bottom plot). The peak value for HCT found on MD6 is between 5.3% and 10% greater than the respective overall (non-time-qualified) mean of each astronaut.

MCHC: Figures 11 (astronaut 1) and 12 (astronaut 3) for MCHC show in both astronauts atypical values beyond the 95th percentile at least on MD2, if not on MD6 as well (astronaut 3). Thereafter, the values decline although remaining within the percentile limits. The greater value for MCHC during flight relative to the respective overall (non-time-qualified) mean of each astronaut varies from 6.4% to 4.7% (astronaut 3).

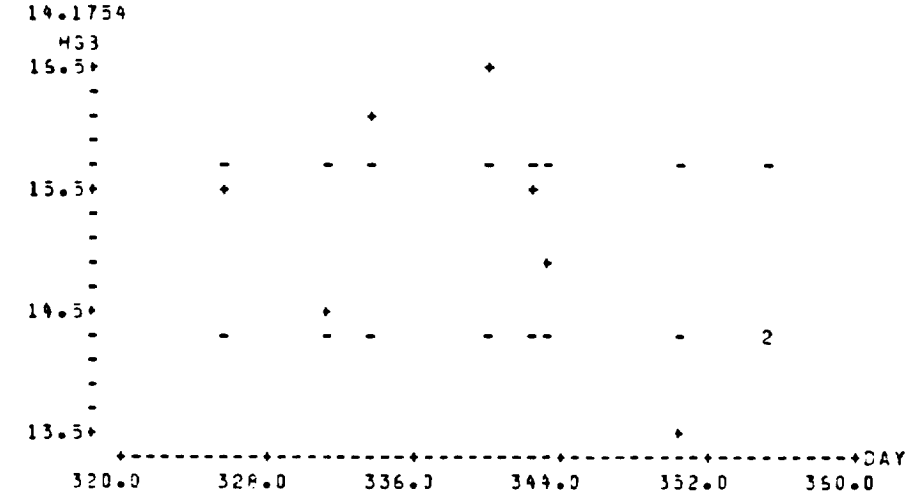
Figure 7



AV 14.7435
SD .575899
HI 15.8953
LO 13.5917



14.9222
.373423
15.6691
14.1754



15.0000
.355903
15.7119
14.2882

HG3 DAY

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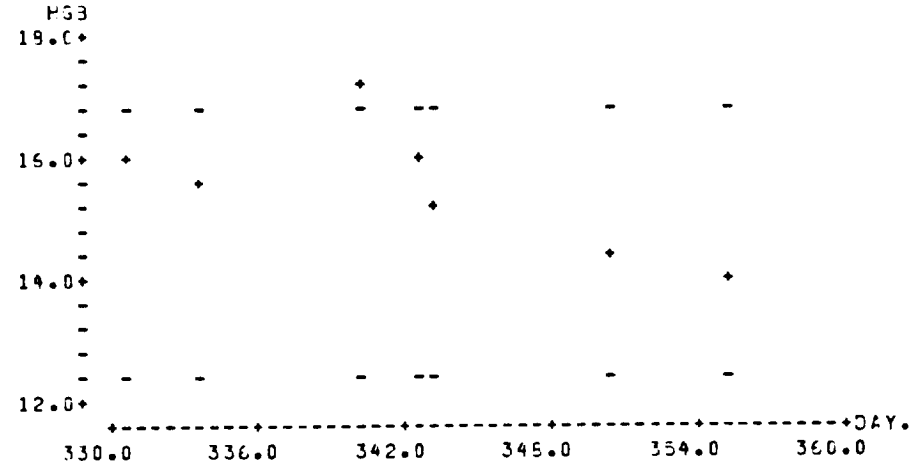
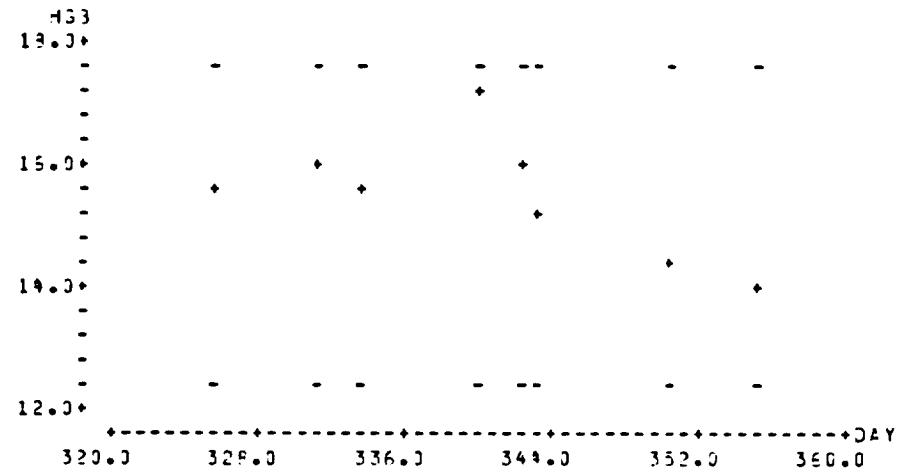
Figure 8



AV 14.7563
SD 1.10089
HI 16.9580
LO 12.5545



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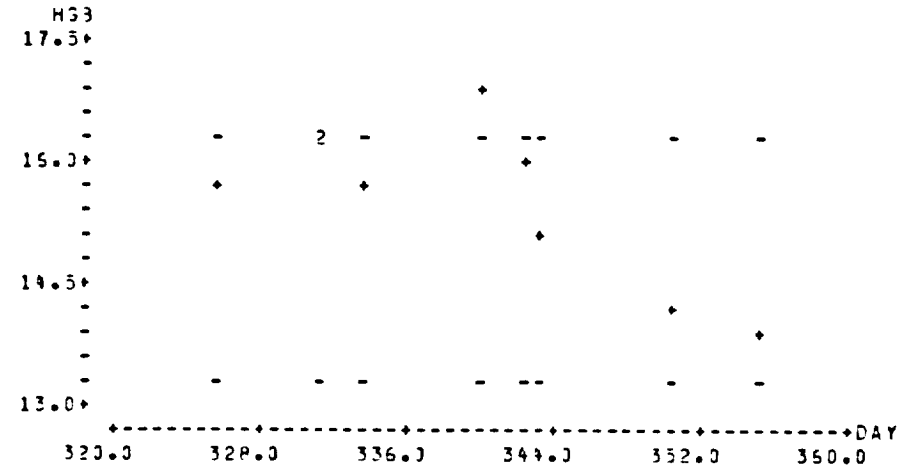
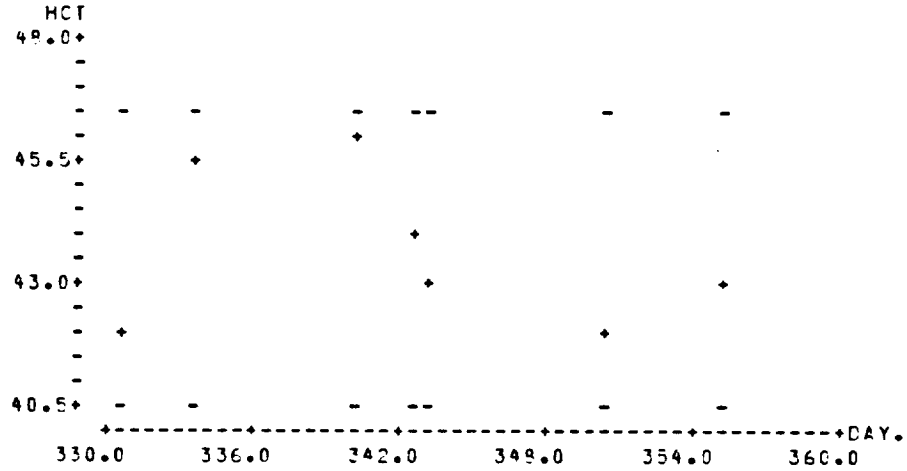
17.5199
12.2801



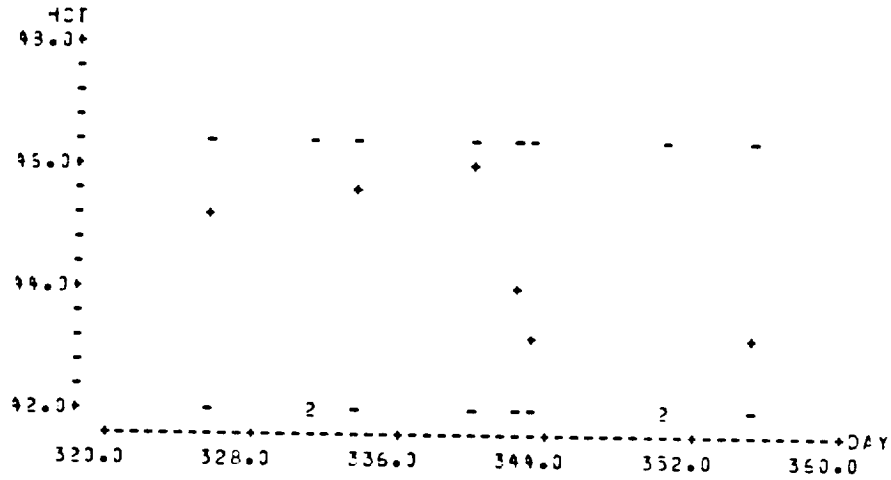
14.7500
.733303
16.3386
13.1614

36N

Figure 9



AV 43.5652
SD 1.53226
HI 46.5297
LO 40.5007



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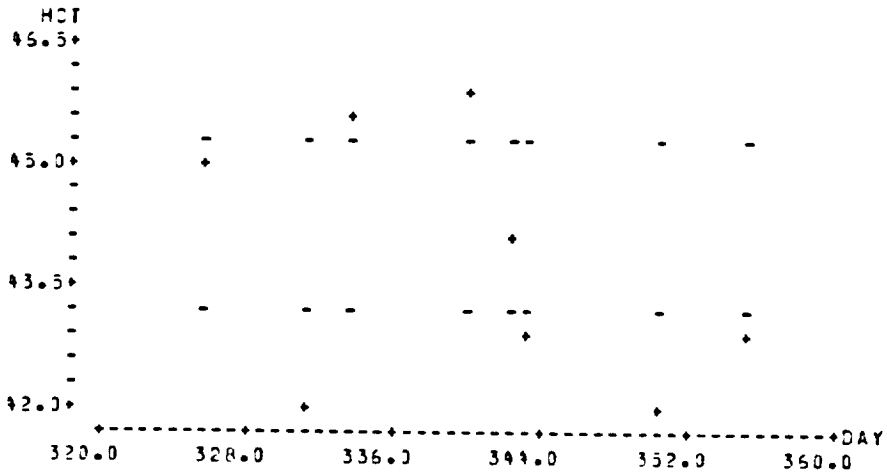
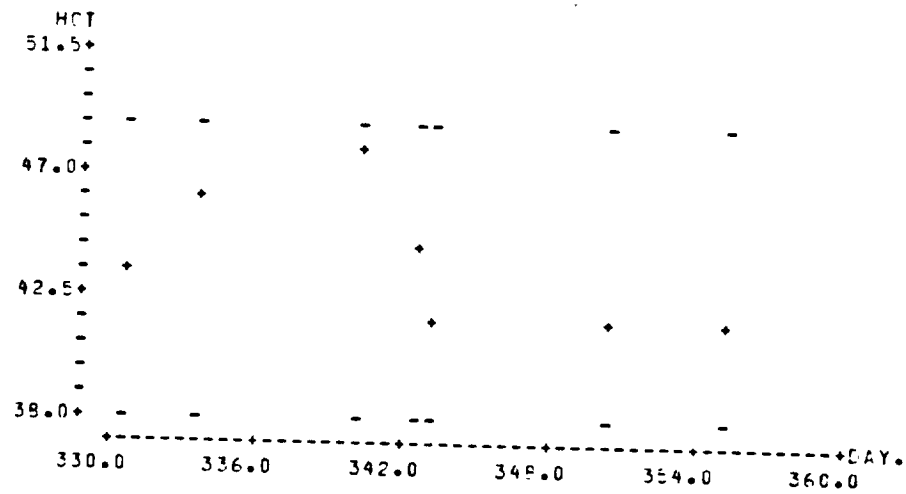
46.5594
42.0973

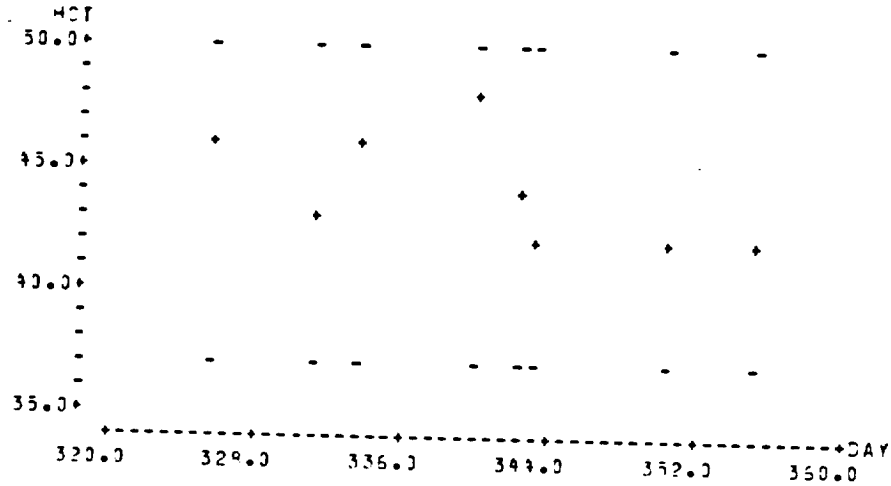


44.2500
.500000
45.2500
43.2500

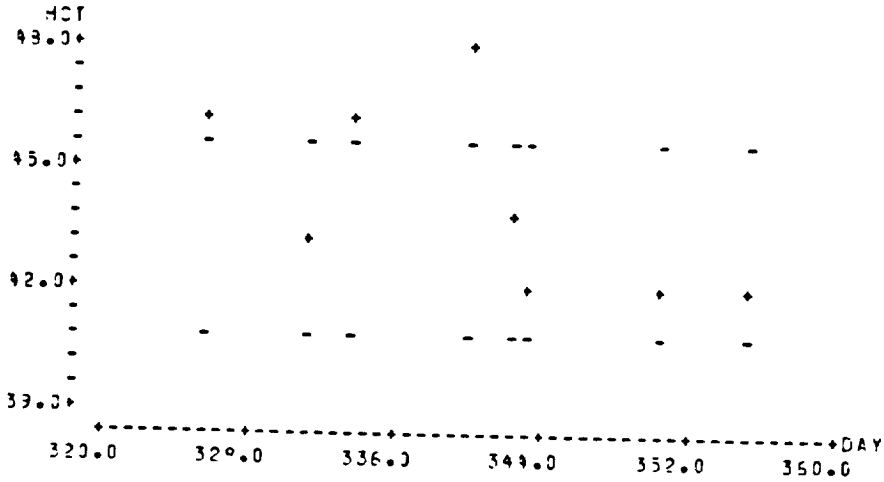
Figure 10



AV 43.1875
SD 2.59763
HI 48.3628
LO 38.0122

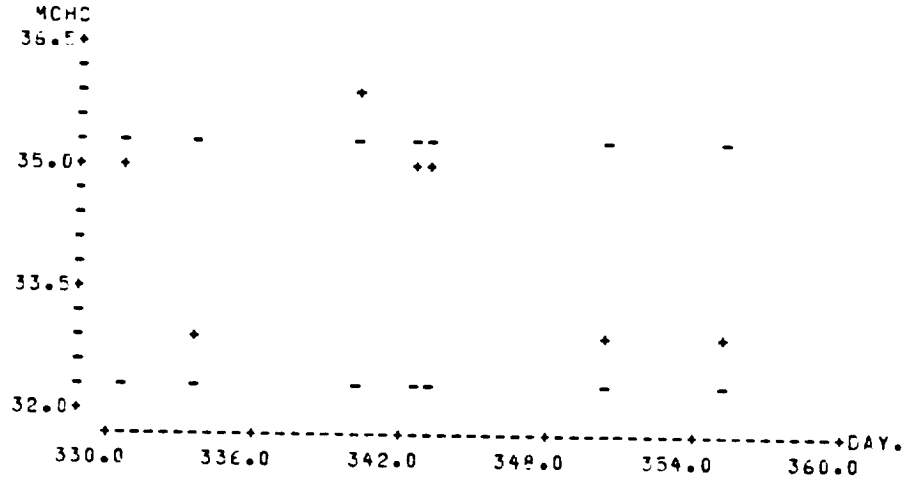


43.5000
3.13543
49.7929
37.2071

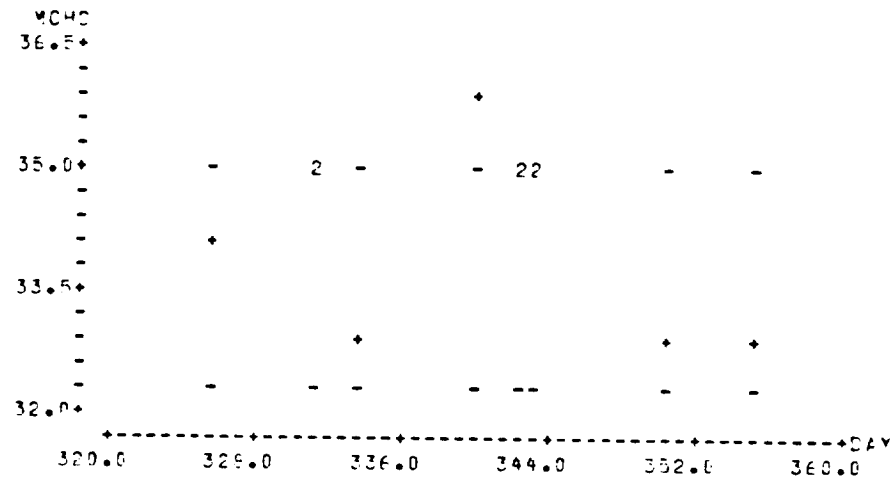


43.2000
1.33384
45.3077
40.5923

Figure 11



AV 33.8261
SD .777652
HI 35.3814
LO 32.2708



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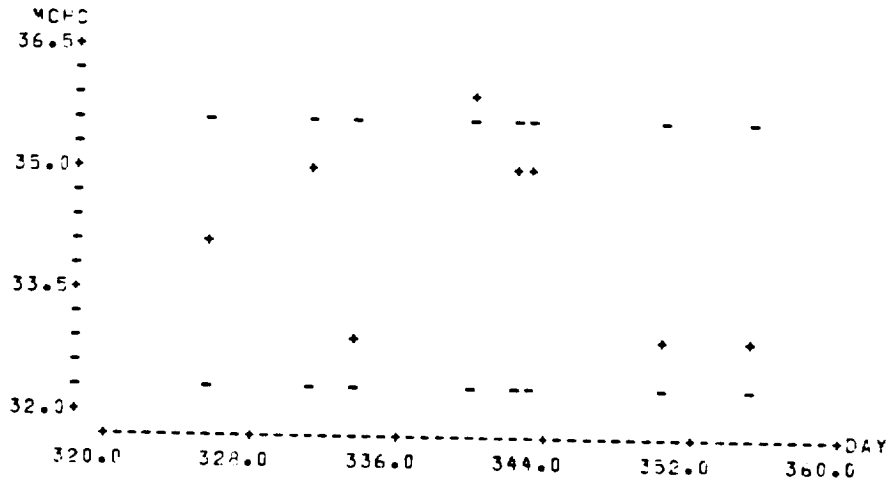
35.1111
32.4444



34.0000
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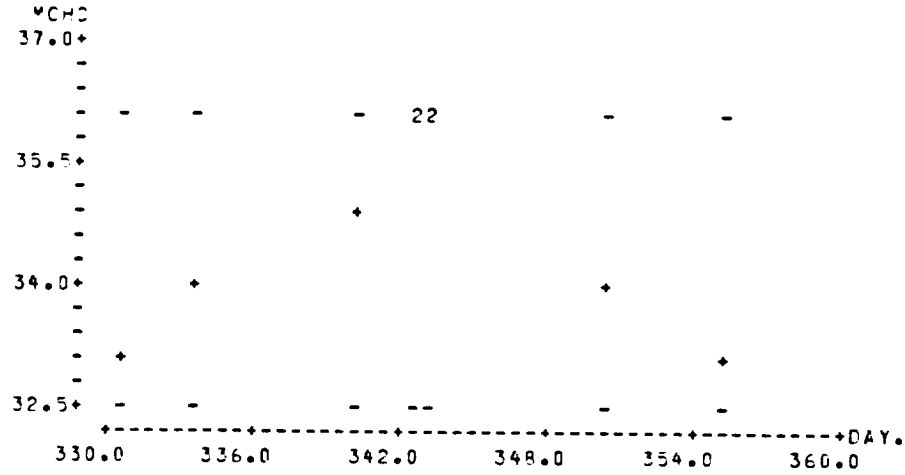
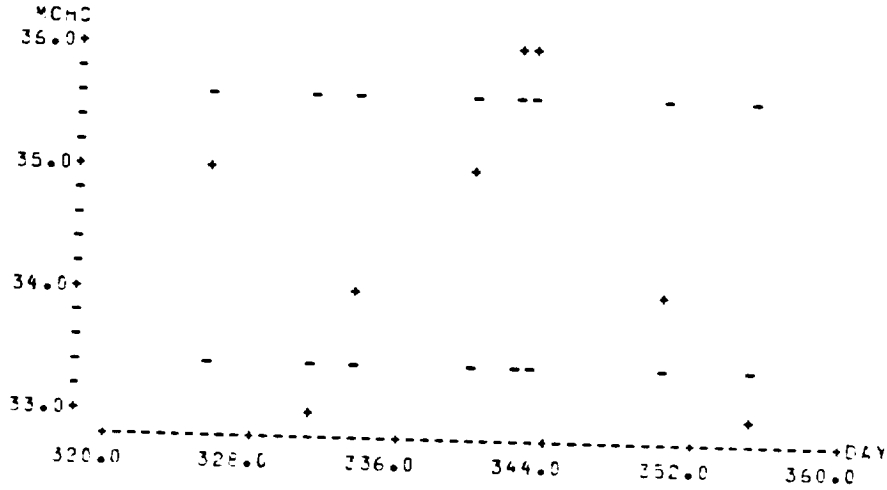
35.6330
32.3670

Figure 12



AV	34.3750
SD	.885061
HI	36.1451
LO	32.6049



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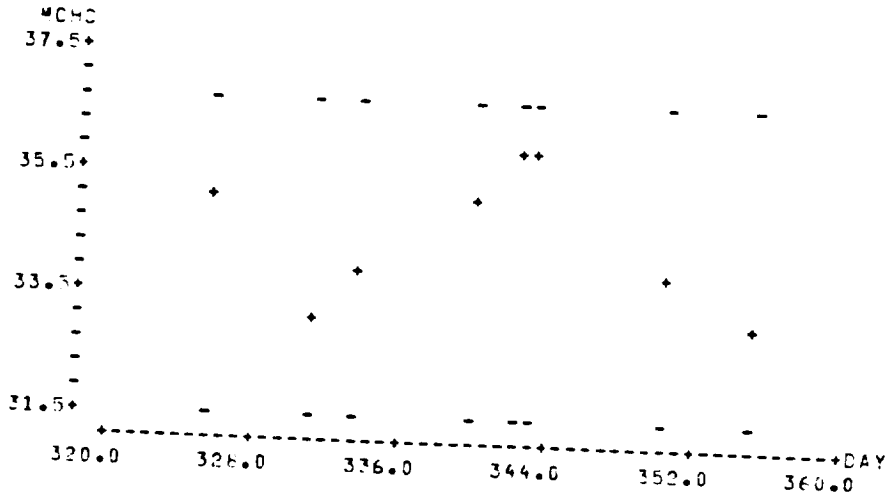
	35.5954
	33.4046



	34.2000
	1.30384
	36.5077
	31.5923

MCH: Figures 13 (astronaut 1) and 14 (astronaut 3) for MCH reveal similar trends as those depicted for the variables of RBC, HGB, MCHC and HCT; however, like the latter none of the values are atypical.

MCV: Figures 15 (astronaut 1) and 16 (astronaut 3) for MCV reveal only the F-1 value is low, unusually so in the case of astronaut 1 in particular unless one assumes a completed circadian system $\Delta\phi$ by this time (bottom plot). All other values are within each astronaut's considered normal range.

WBC: Figures 17 (astronaut 1) and 18 (astronaut 3) show the plots for WBC. For astronaut 1, all the variables are unremarkable. For astronaut 2 assuming no $\Delta\phi$, all the preflight and inflight counts appear to be elevated beyond the 95th percentile.

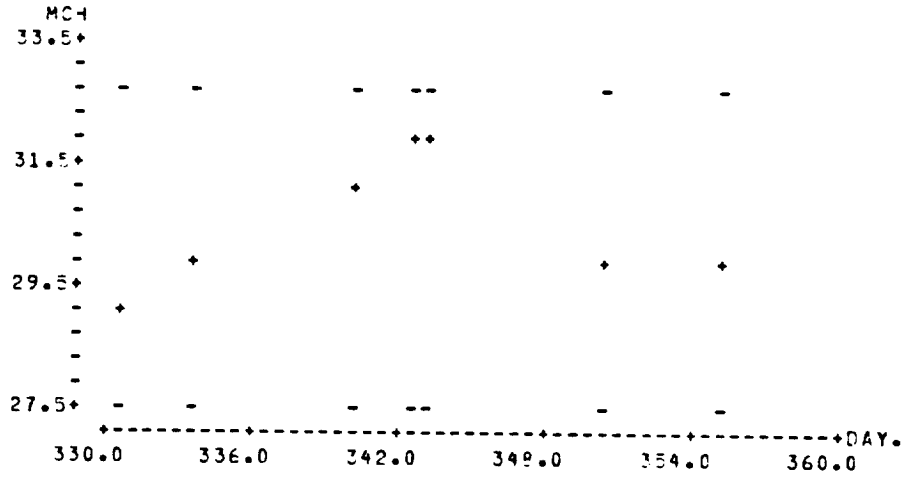
EOSINOPHILS: The plots for eosinophils are shown in Figures 19 (astronaut 1) and 20 (astronaut 3); for neither one of the two astronauts were the values unusual.

MONOCYTES: The trends shown in Figures 21 (astronaut 1) and 22 (astronaut 3) for the two astronauts are similar; both the F-1 and L+13 values are beyond the 95th percentile.

LYMPHOCYTES: Figure 23 (astronaut 1) and 24 (astronaut 3) present the plots for lymphocytes. The data of astronaut 1 are not unusual unless it can be assumed that a complete $\Delta\phi$ was successfully achieved. Accordingly, all the lymphocytes values fall below the 5th percentile limit. The data of astronaut 3 reveal below usual values for MD2, MD6 and L+0 (in all the plots).

BANDS AND BASOPHILS: The plots of Bands are shown in Figures 25 (astronaut 1) and 26 (astronaut 3) and basophils for astronaut 1 only,

Figure 13



AV 30.1739
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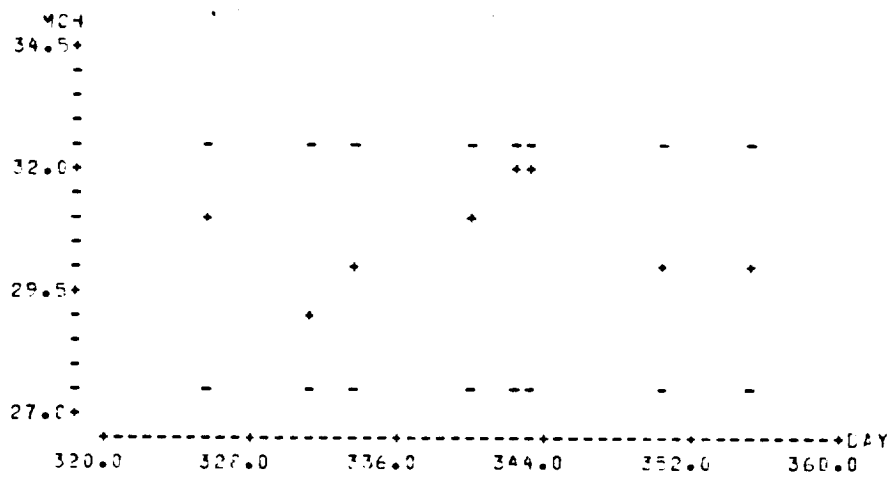
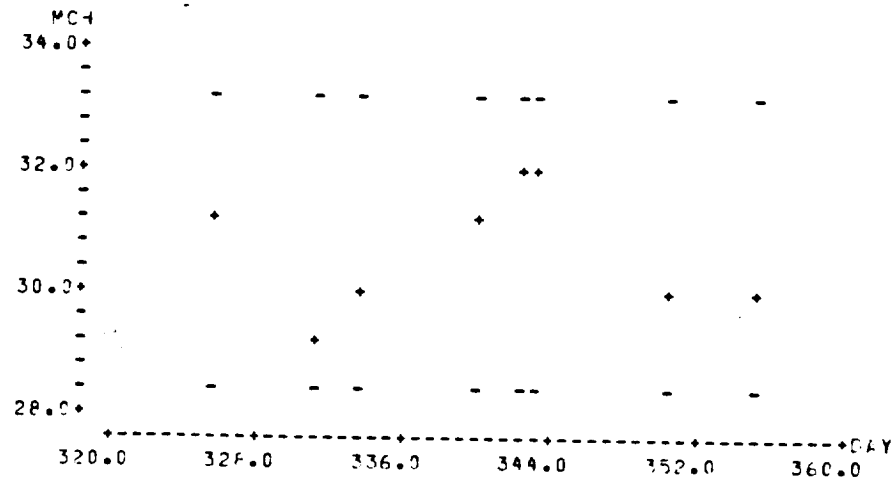
HI 32.7075
LO 27.6403

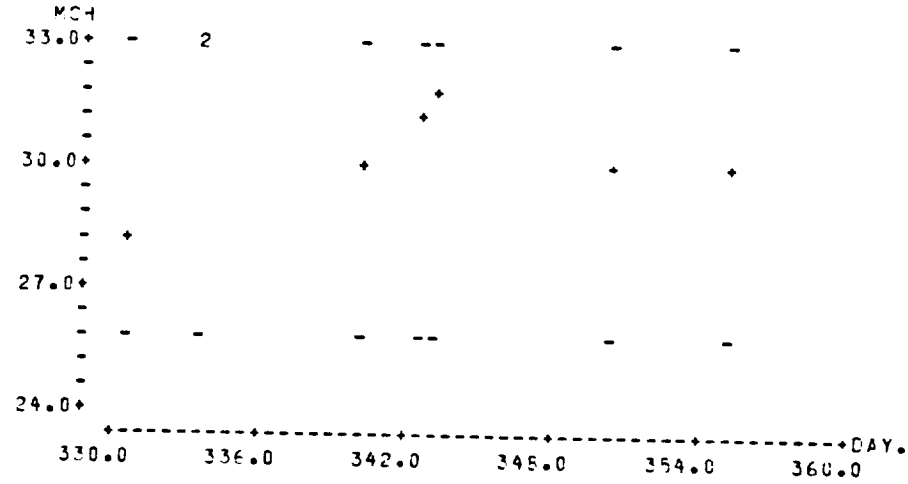


30.0000
1.32286
32.6458
27.3542

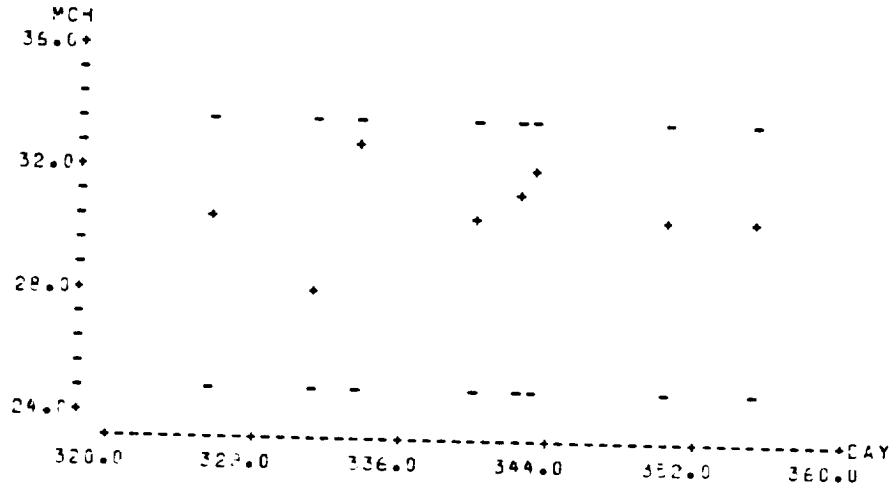


30.7500
1.25831
33.2666
28.2334

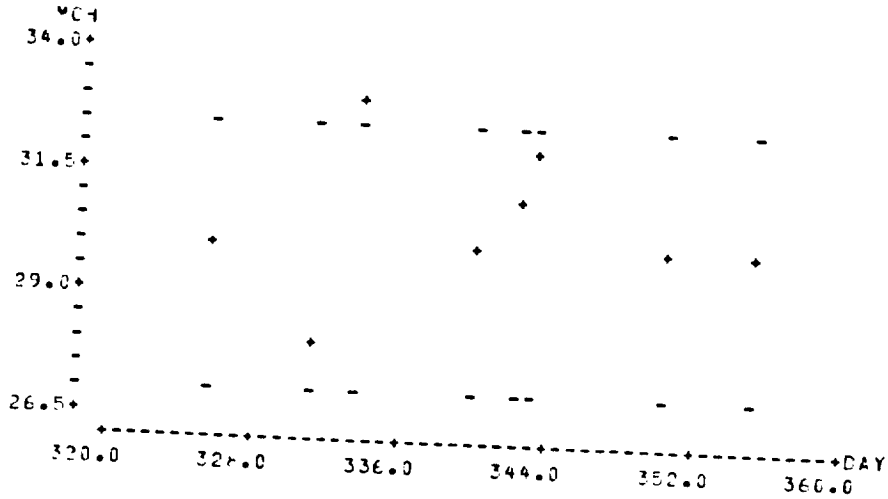
Figure 14



AV 29.2500
SD 1.77012
HI 32.7902
LO 25.7098



29.1667
2.13696
33.4406
24.8927



29.6000
1.34164
32.2533
26.9167

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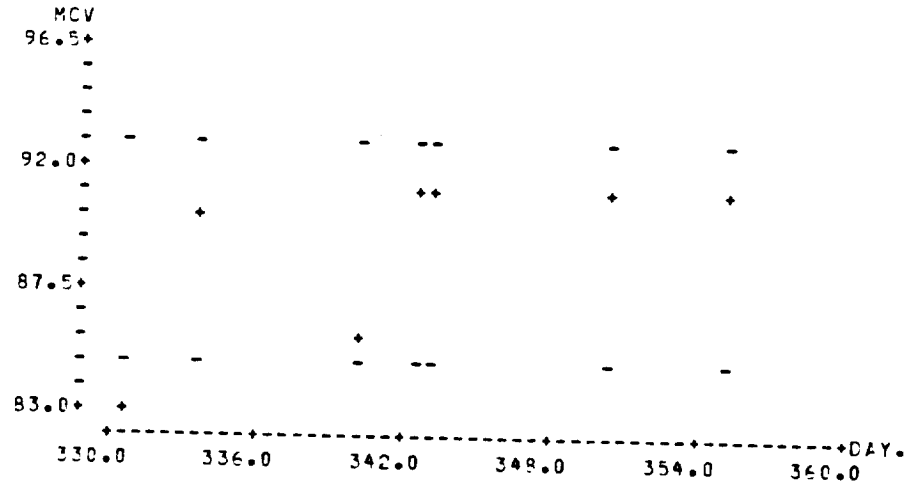
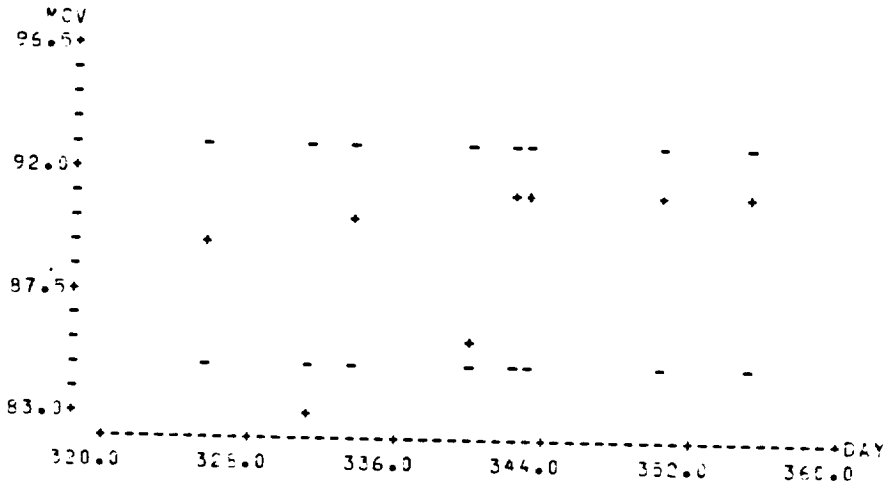
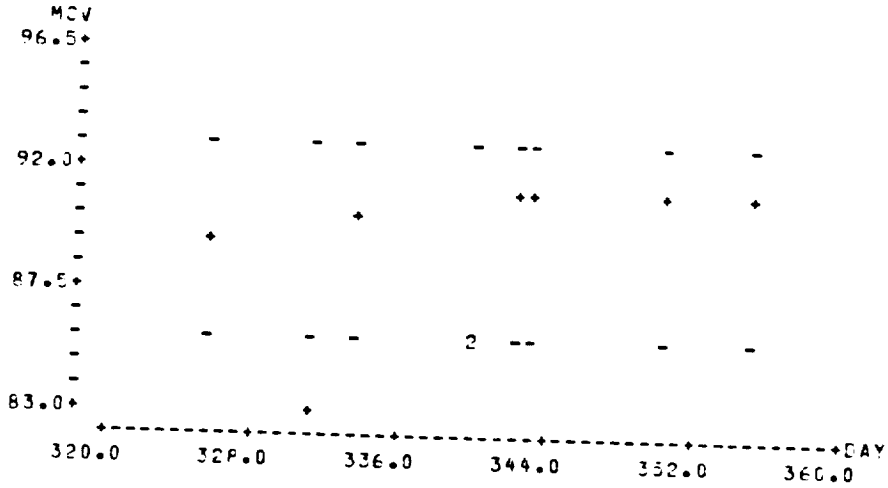
Figure 15



AV 89.3000
SD 1.97714
HI 92.9543
LO 85.0457



86.5859
2.20479
93.2985
84.4793



89.5000
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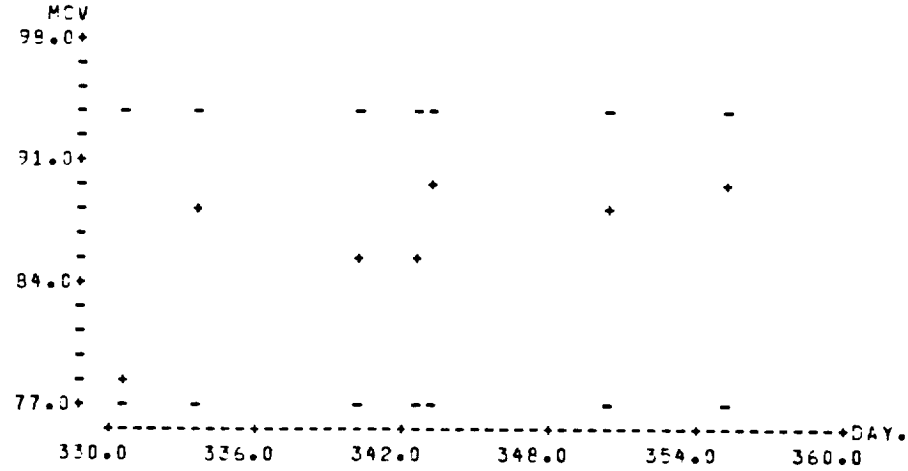
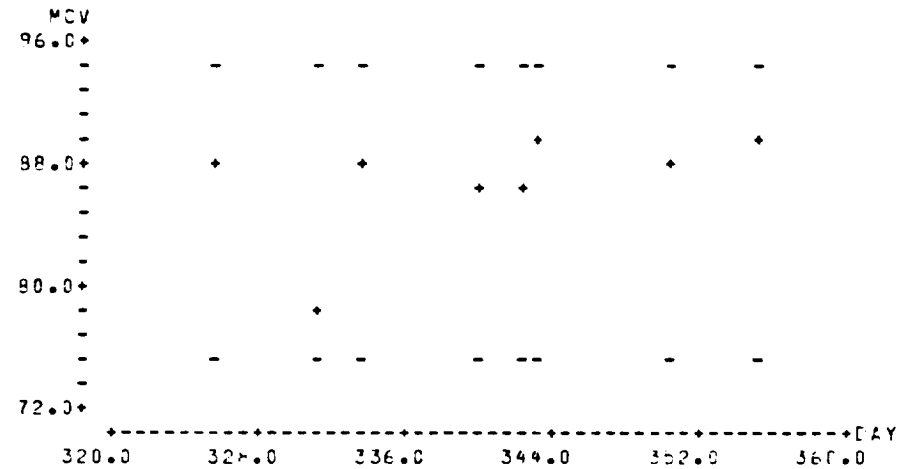
92.9641
86.0359

Figure 16



AV 85.0625
SD 4.15482
HI 93.3721
LO 76.7529



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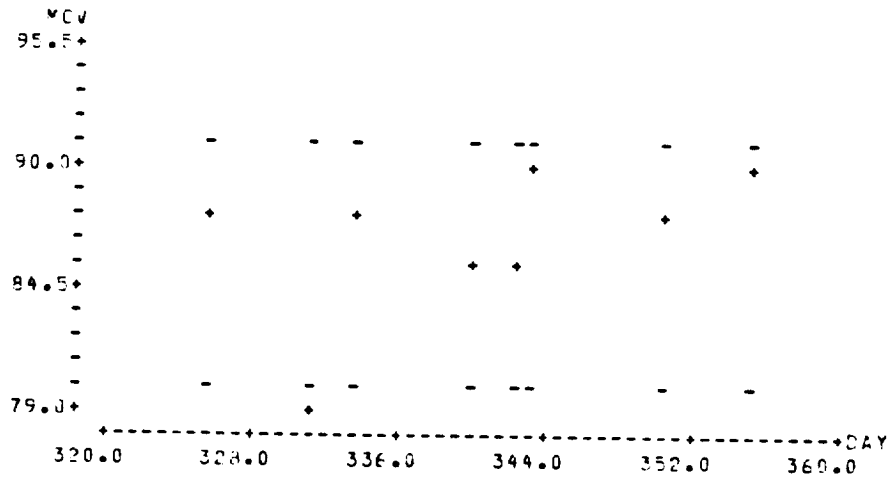
94.3808
75.6192



85.6000
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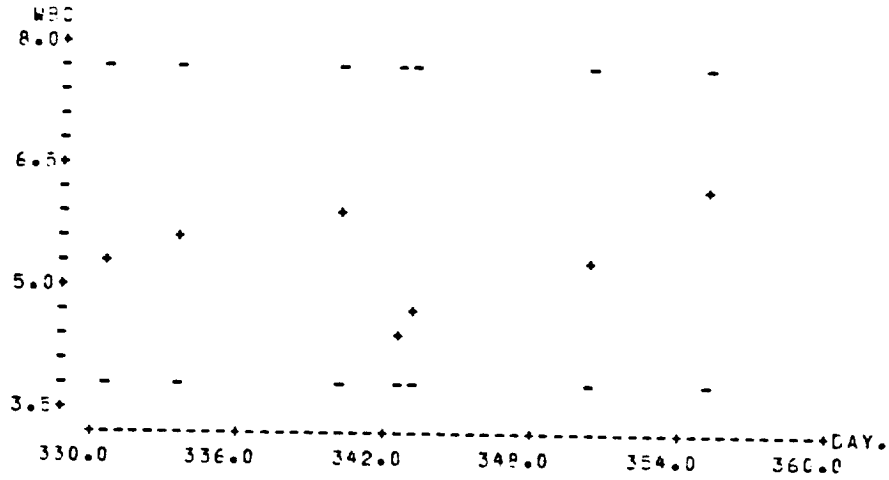
91.3519
79.8381

Figure 17



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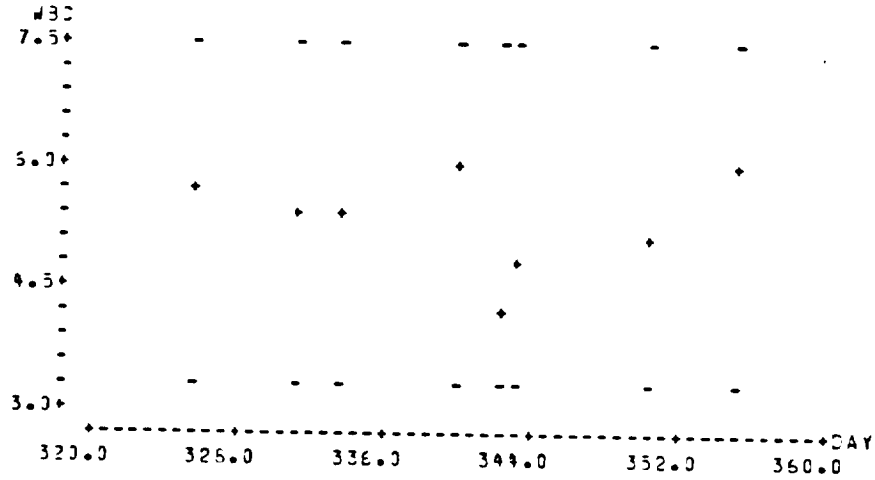
LO 3.80326



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3.35729

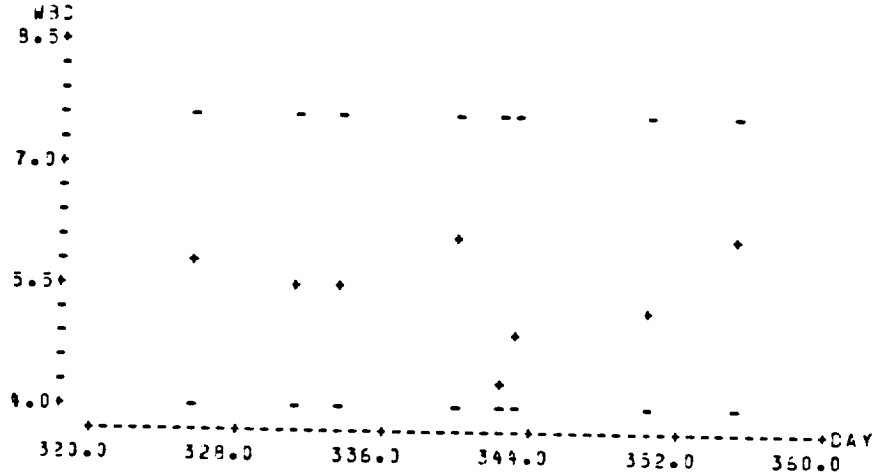

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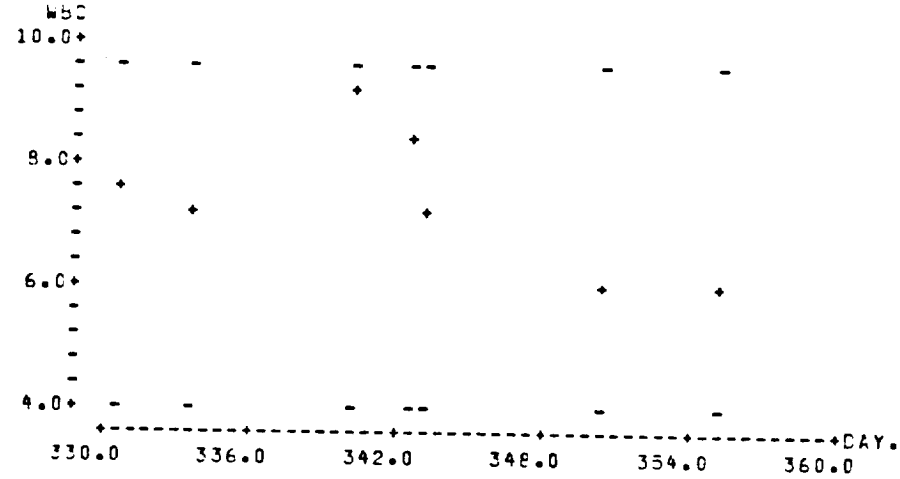
Figure 18



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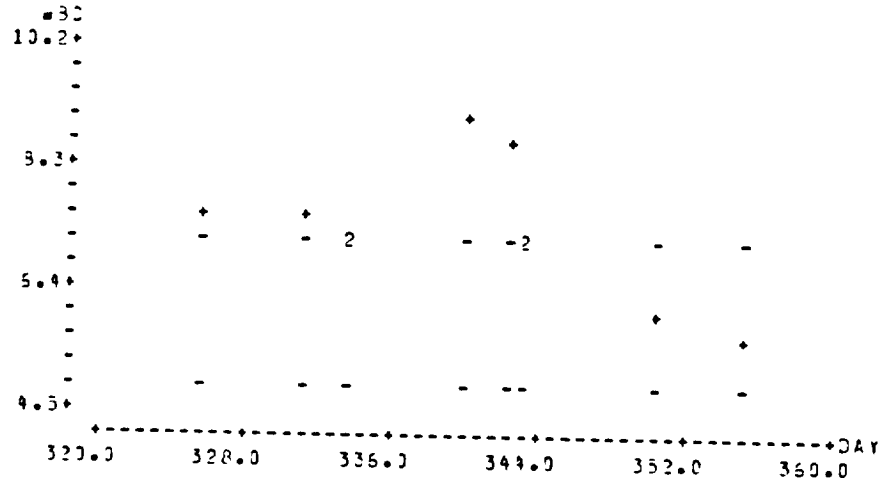
SD 1.39629
HI 9.77383
LO 4.18867



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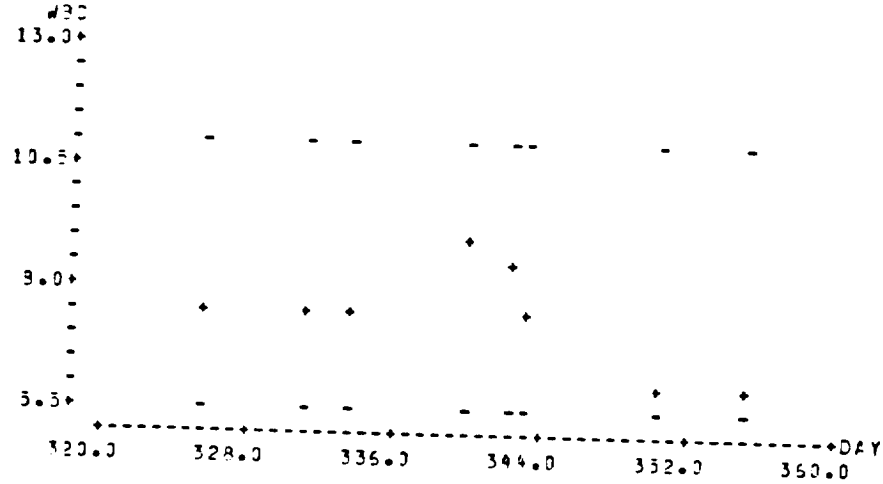
4.96509



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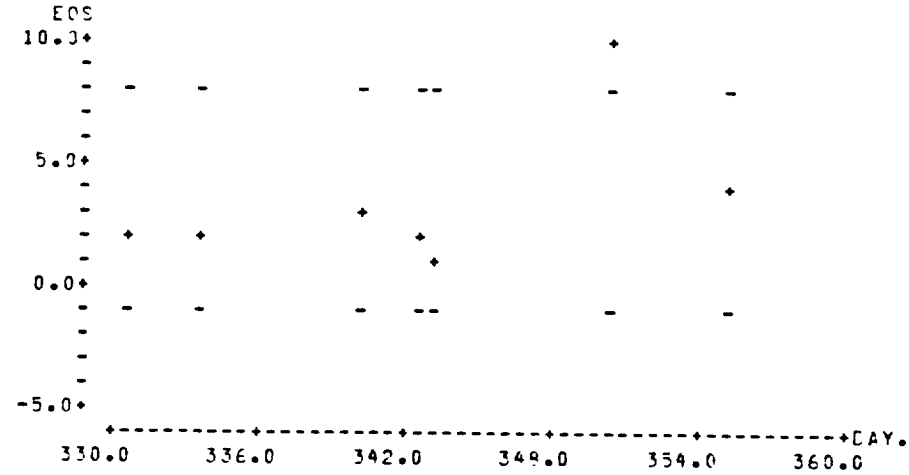
1.43996
11.1799
5.54007

Figure 19



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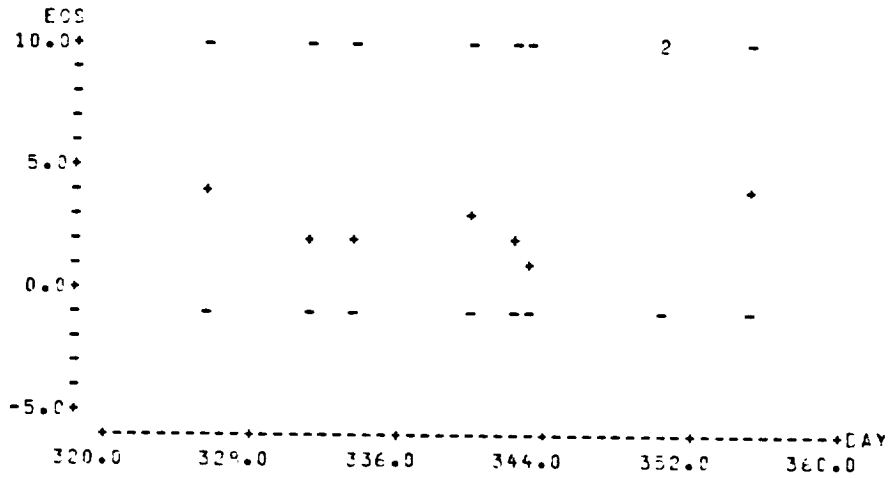

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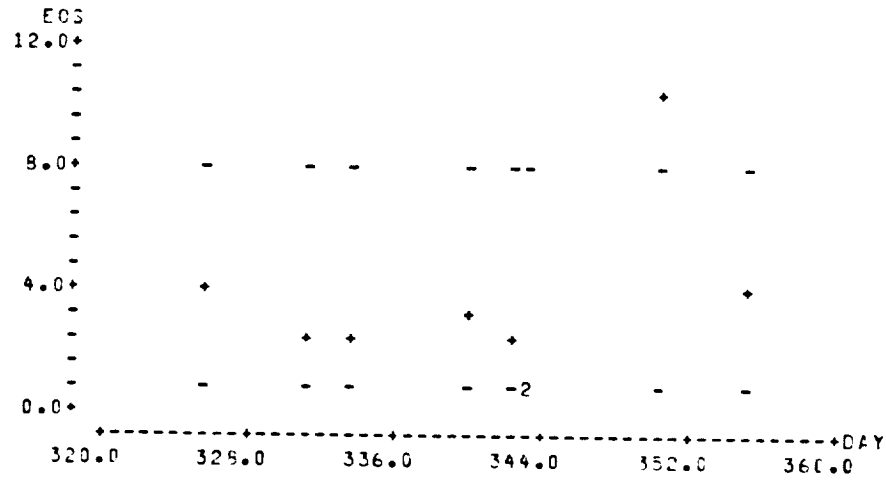

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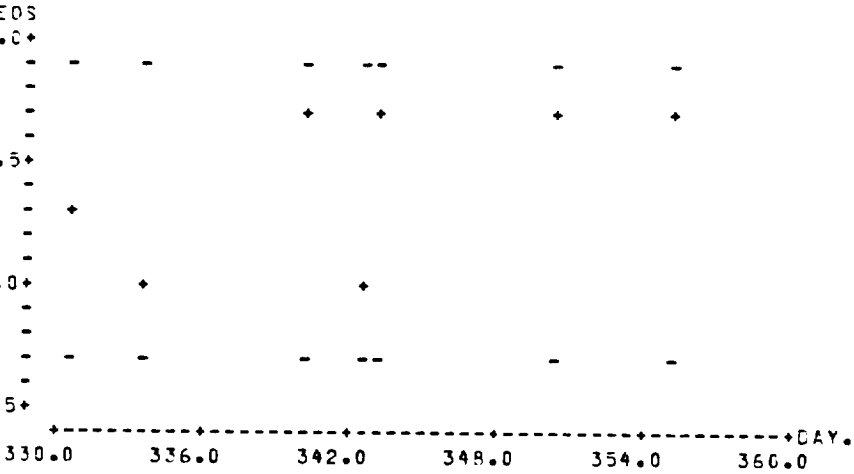
Figure 20



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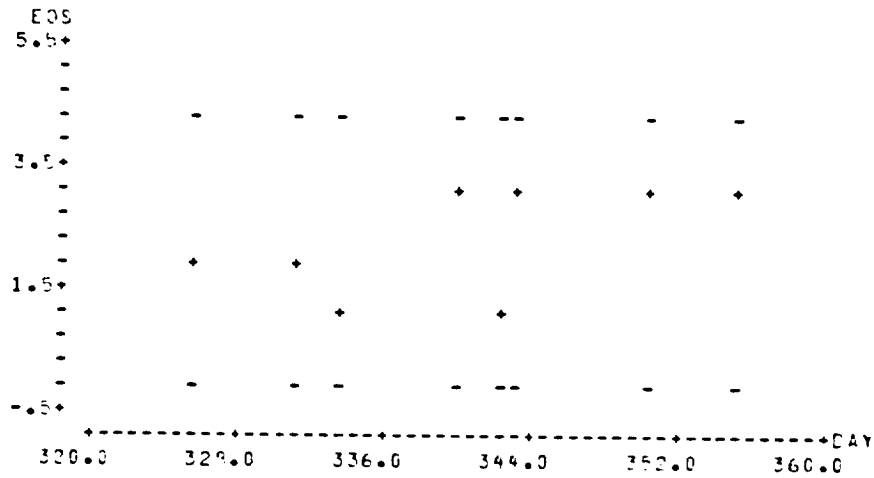

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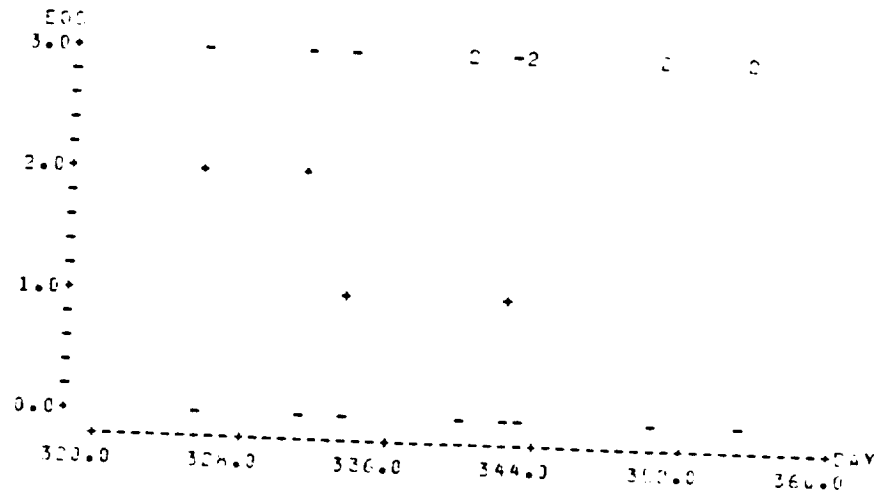

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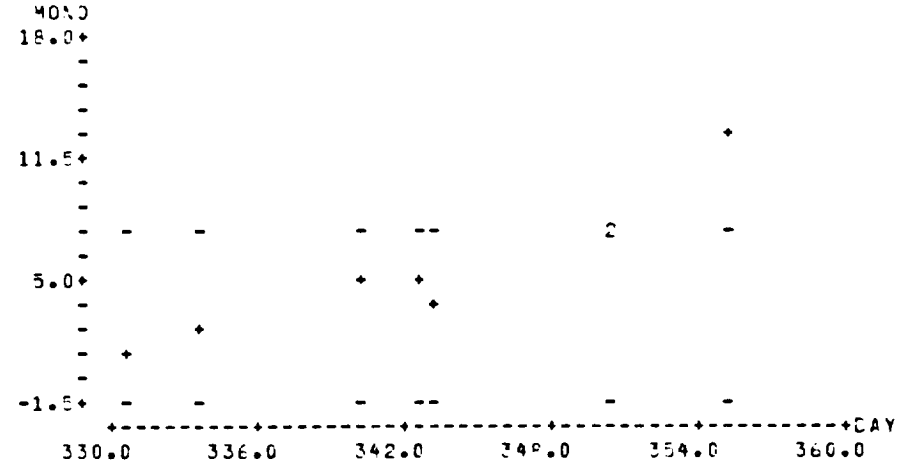
Figure 21



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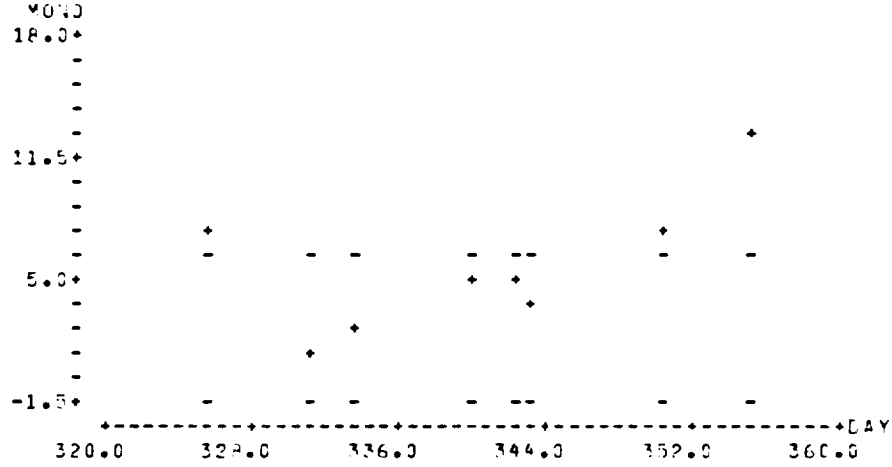
HI 7.46220
LO -1.08125



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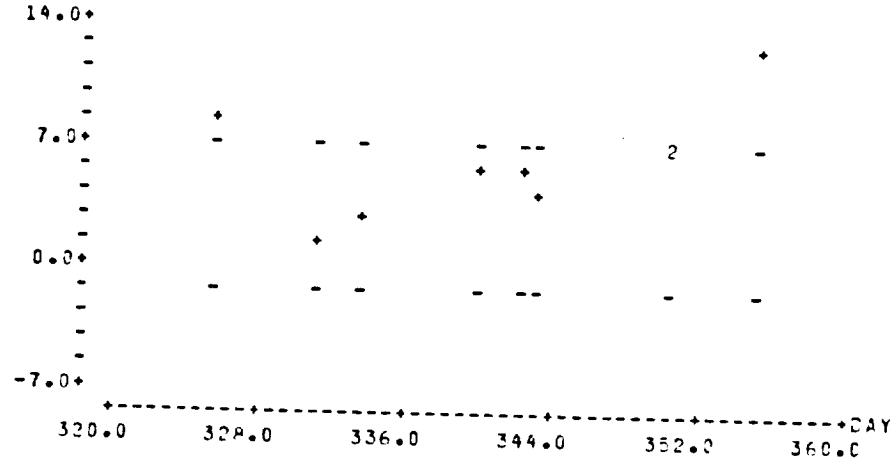
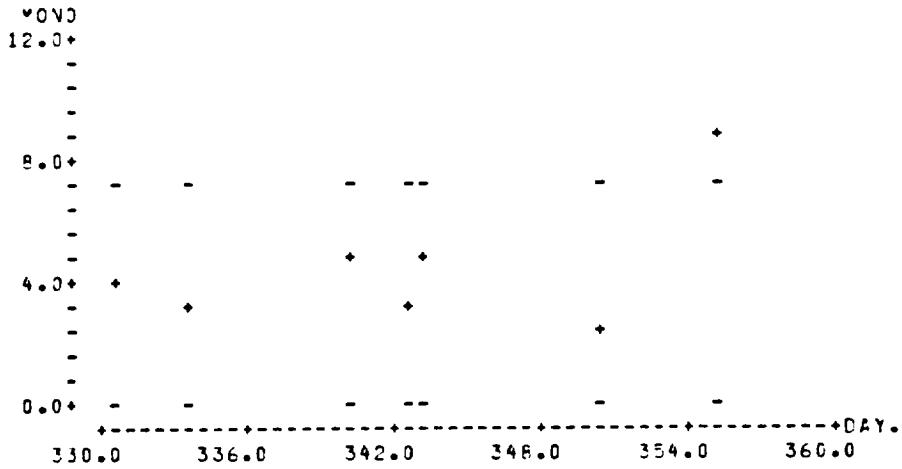
6.92794
-1.21366



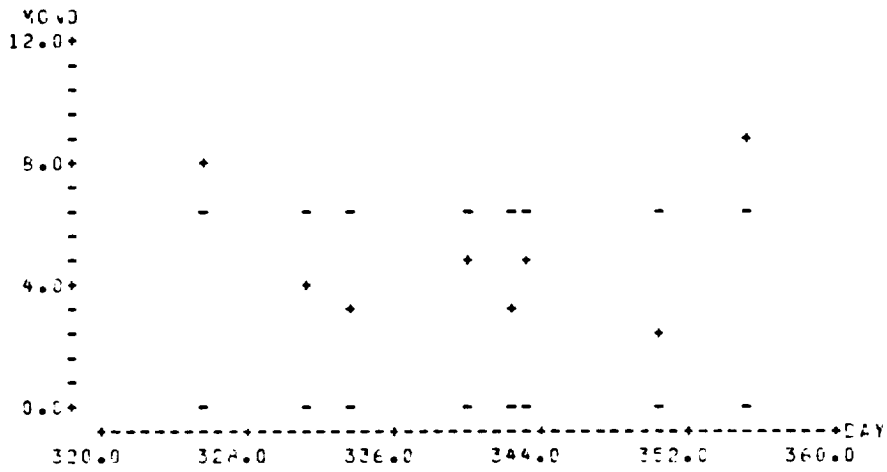
2.75000
2.35291
7.47582
-1.97582

50N

Figure 22



AV 3.70000
SD 1.82878
HI 7.35756
LO .0424355



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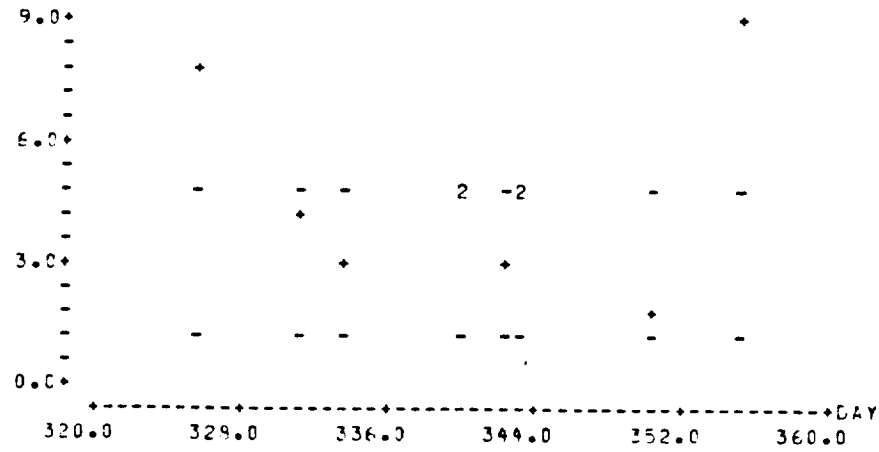
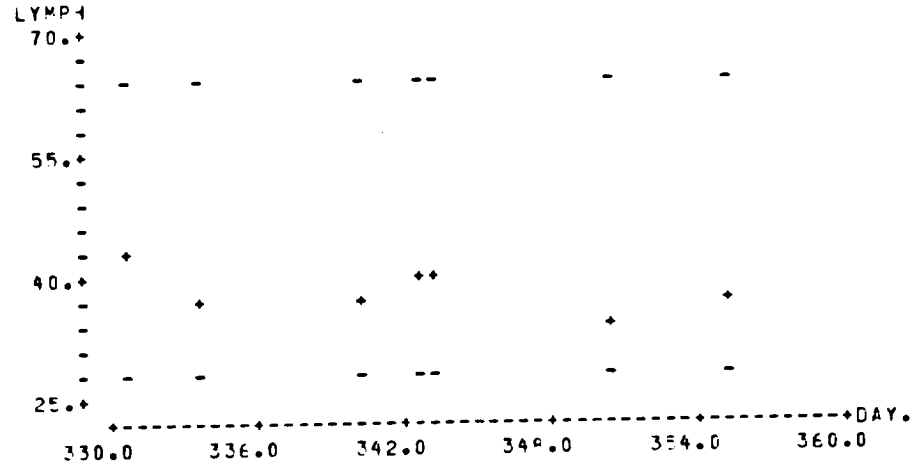
3.33333
1.52753
6.35839
.278283

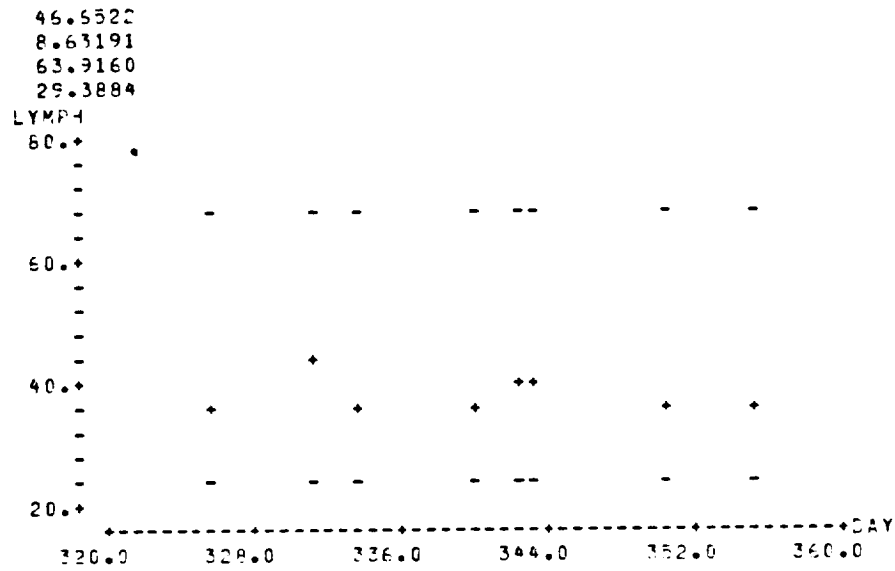


3.00000
1.00000
5.00000
1.00000

Figure 23



AV 46.5522
SD 8.63191
HI 63.9160
LO 29.3884



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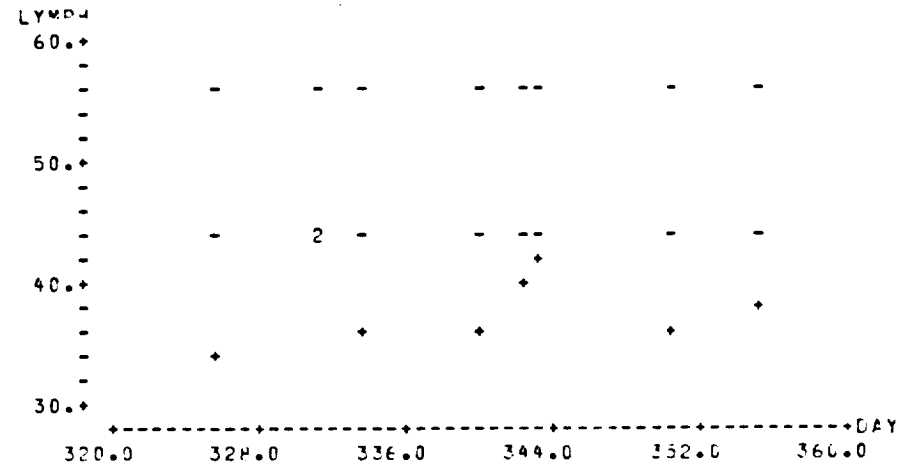
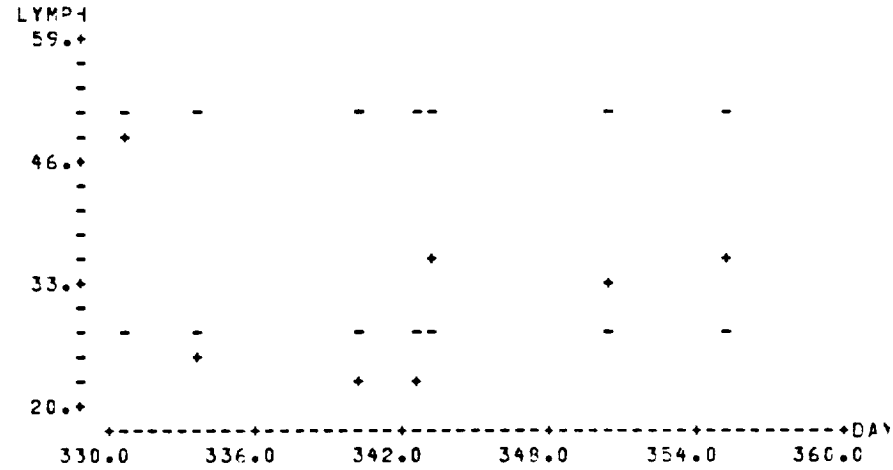
45.3333
10.7819
66.8972
23.7695

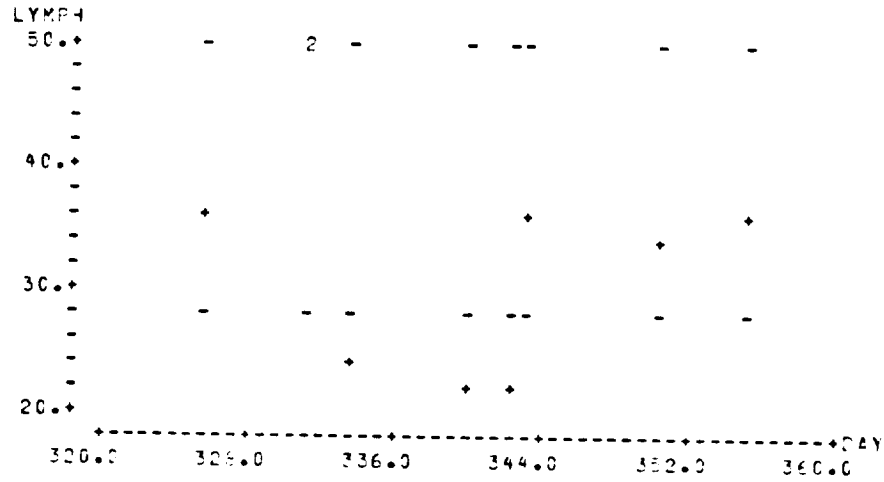


50.0000
2.70801
55.4160
44.5840

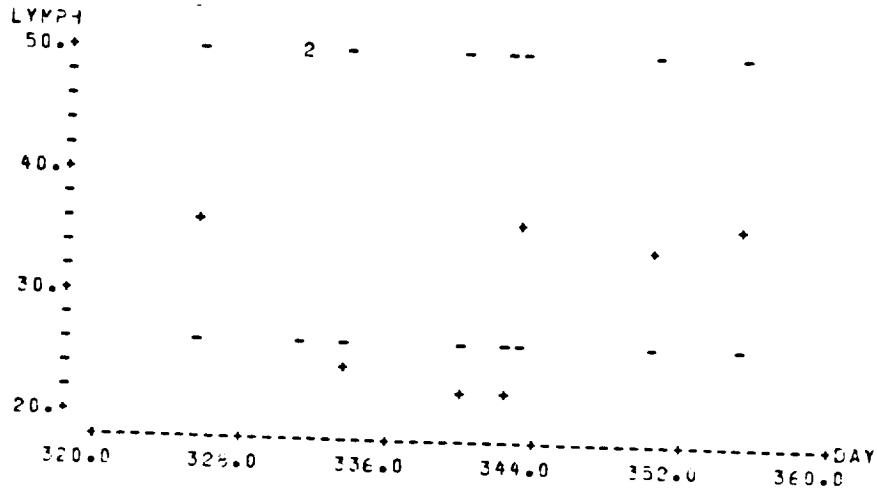
Figure 24



AV 39.5000
SD 5.70380
HI 50.9076
LO 28.0924

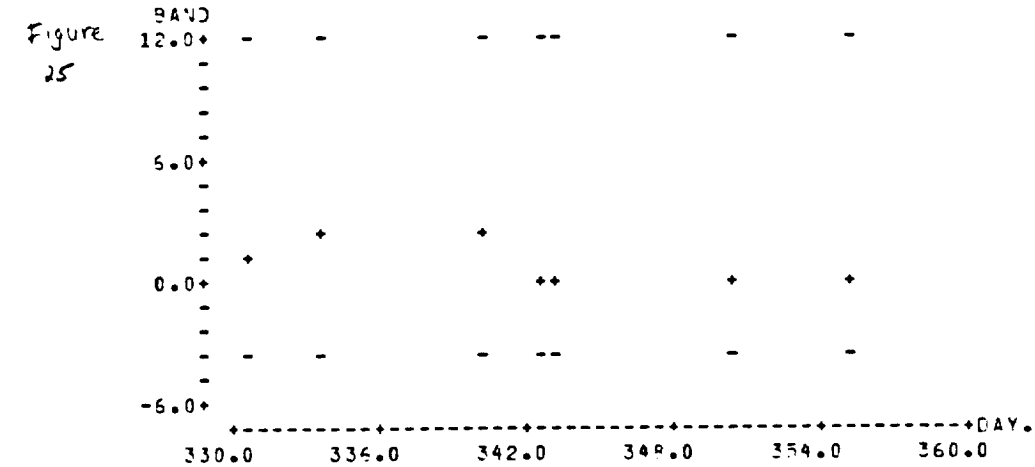


38.3333
5.52871
49.8908
27.7759

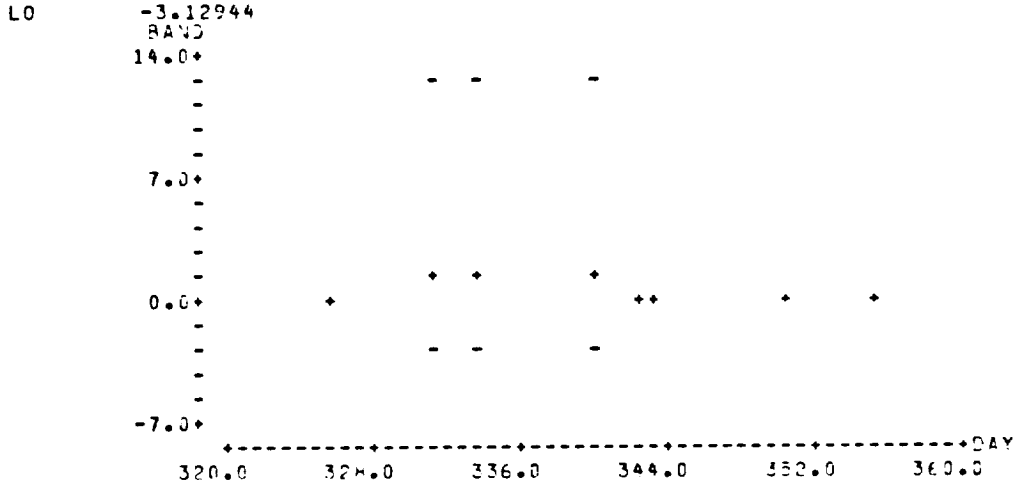


38.4000
5.94138
50.2828
26.5172

Figure 25



AV 4.19182
SD 3.65563
HI 11.4931
LO -3.12944



G OBSERVATIONS

4.00000
4.02492
12.3499
-3.24984

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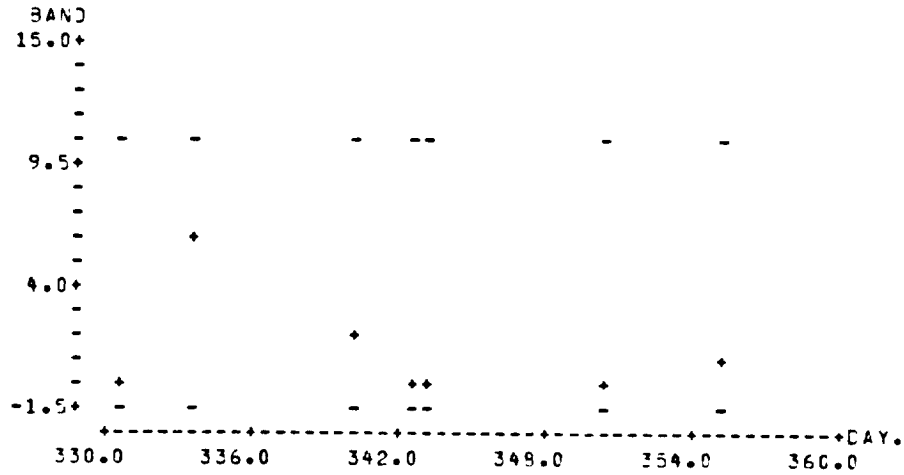
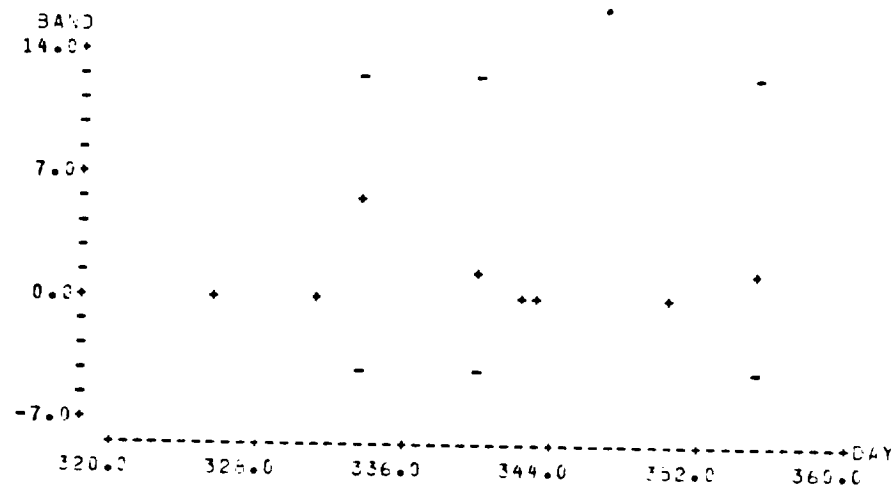
Figure 26



AV 4.77776
SD 3.03223
HI 10.8422
LO -1.28669



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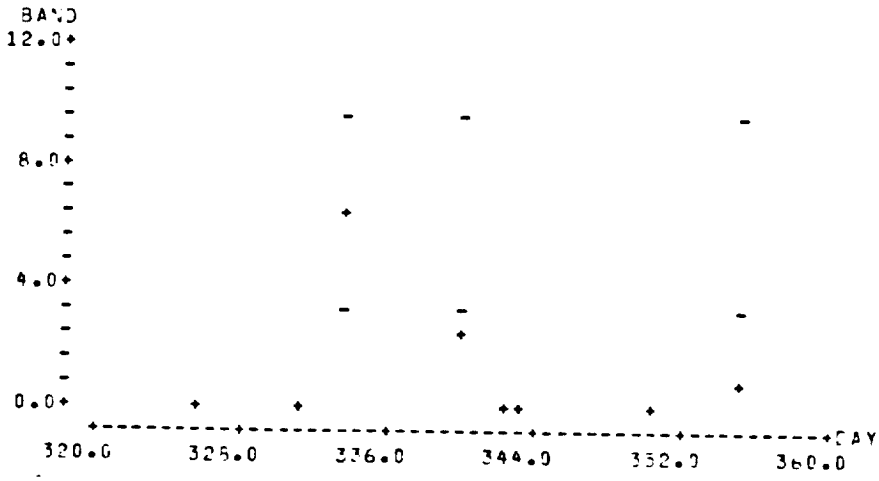
NG OBSERVATIONS

4.33333
4.04145
12.4162
-3.74957



6.33333
1.52753
9.38438
3.27828

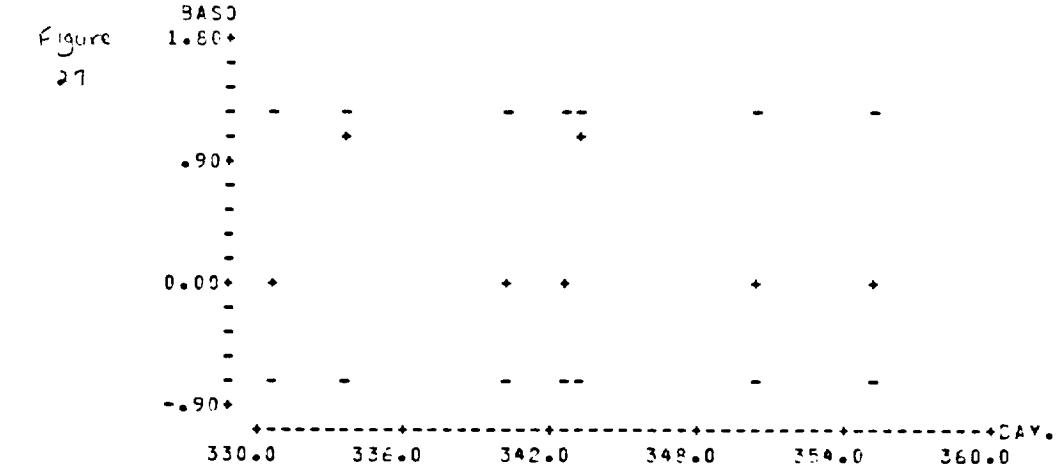
Figure 27, reveals that only very minor changes were detectable in these variables.

TOTAL PROTEIN: Figures 28 (astronaut 1) and 29 (astronaut 3) give the plots for total protein. For astronaut 3, the data are mostly within the expected range with the L+8 and L+13 values being lowest and below the 5th percentile assuming a complete $\Delta\phi$. This is the case for astronaut 3 also, although nearly all the values are at or below the 5th percentile assuming a complete $\Delta\phi$. For astronaut 3 the lowest total protein represents a 7.5% reduction relative to his overall (non-time-qualified) mean, while for astronaut 1 the lowest value represents a 8.5% reduction.

ALBUMIN: Figures 30 (astronaut 1) and 31 (astronaut 3) provide the plots for albumin. In comparison to total protein above, the data during and after flight for astronaut 3 are all within the usual range even if TQRV are taken into consideration. Similar to total protein, for astronaut 1, the flight and L+0 and L+1 data appear to be unusual, assuming a complete $\Delta\phi$. The greatest value for albumin for astronaut 1 on MD2 is 16.1% higher than his overall (non-time-qualified) mean. For astronaut 3 the greatest value is 12.9% higher than his overall mean. In general, both astronauts exhibit a trend of declining values by L+8 and L+13 relative to the inflight levels.

ALPHA-1 PROTEIN: Figures 32 (astronaut 1) and 33 (astronaut 3) reveal no unusual deviations in alpha-1 protein levels unless the percentile limits of the lower plot are used. In this case the L+8 and L+13 values are atypical. However since by this time it can be expected that had a complete $\Delta\phi$ been achieved in the first place, by L+8 and L+13, the circadian system should have shifted back to its original timing. Thus,

Figure 27



AV	.250000
SD	.500000
HI	1.25000
LO	-.750000

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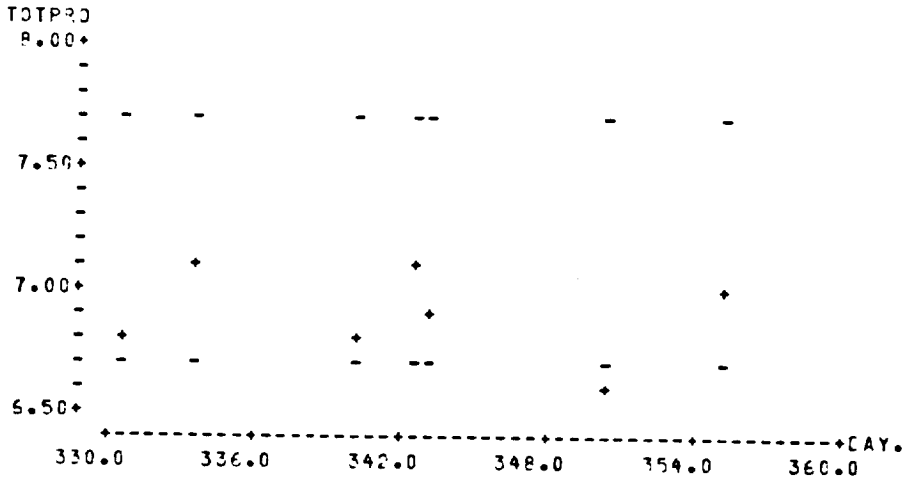
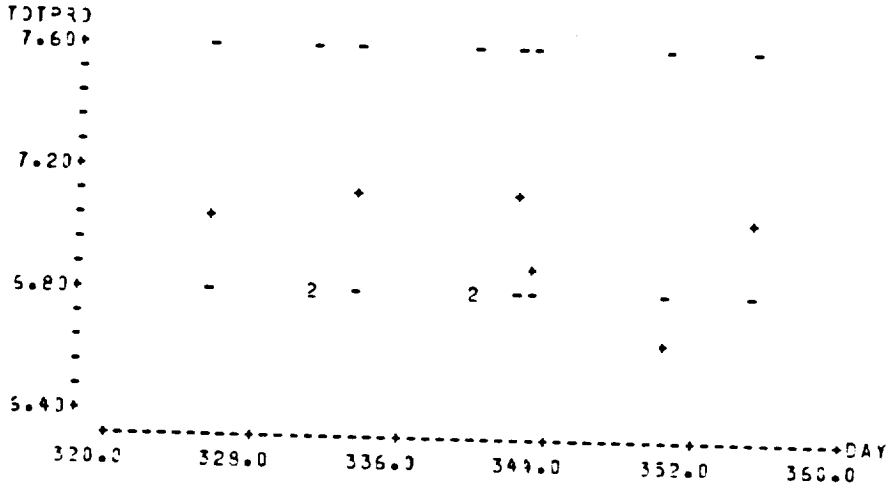
Figure 28



AV 7.21000
SD .263379
HI 7.73676
LO 6.68324



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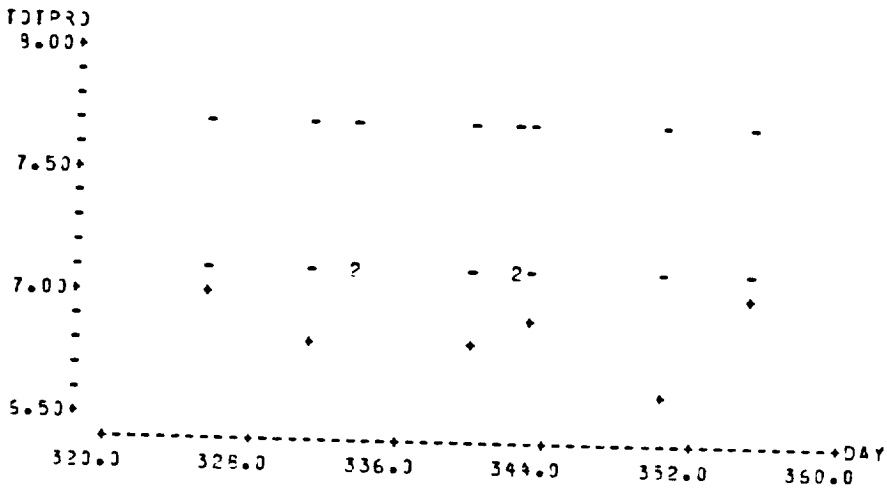
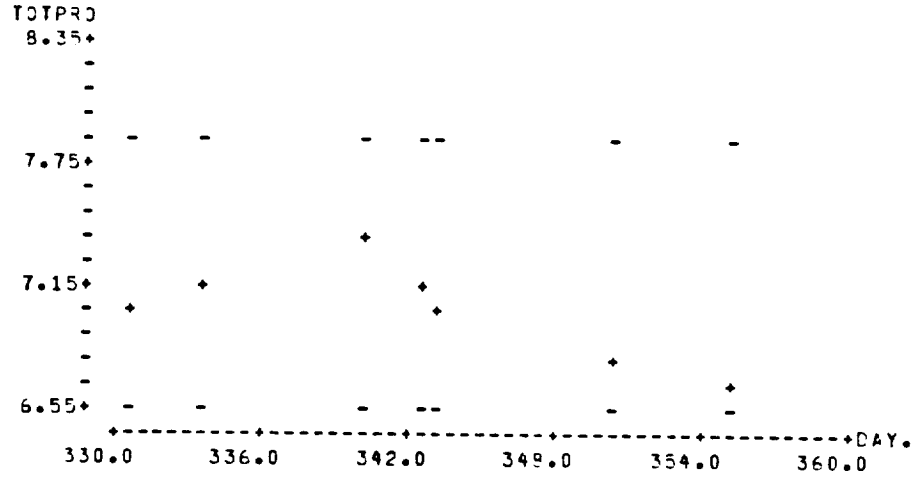
7.20000
.200000
7.60000
6.80000

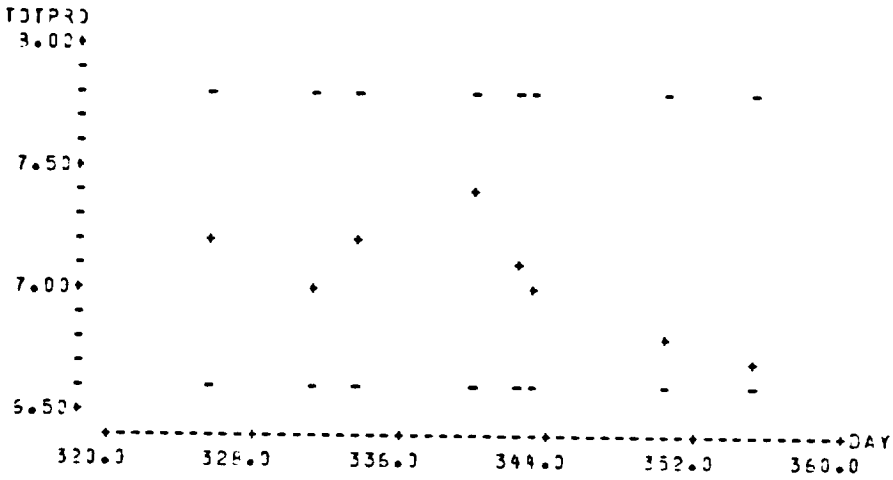


7.40000
.173205
7.74641
7.05359

Figure 29



AV 7.24375
SD .336588
HI 7.91693
LO 6.57057



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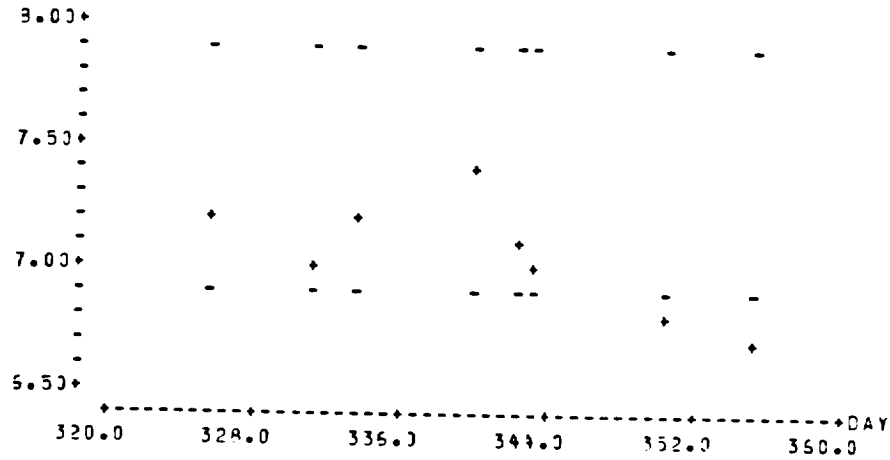
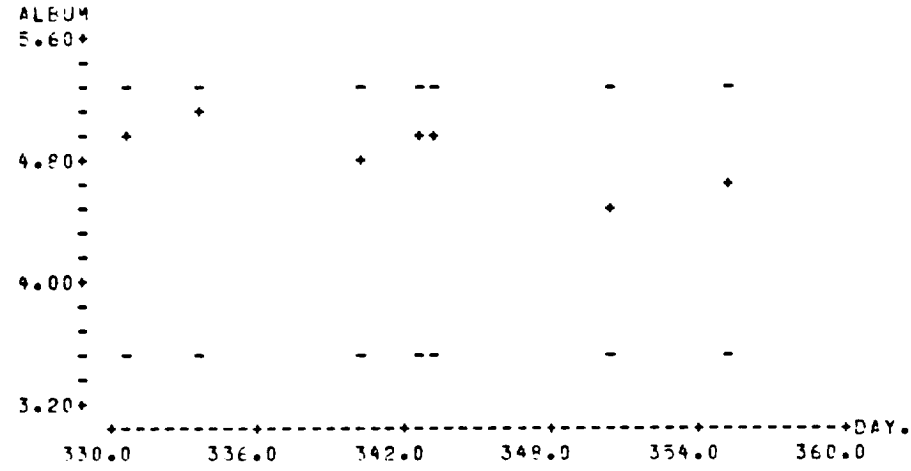
7.15557
.307579
7.73203
6.55131

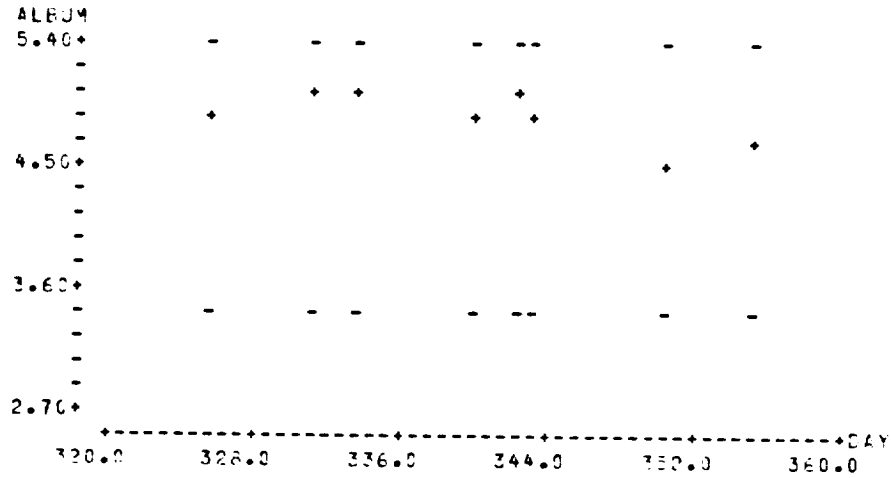


7.42000
.233747
7.93749
6.94251

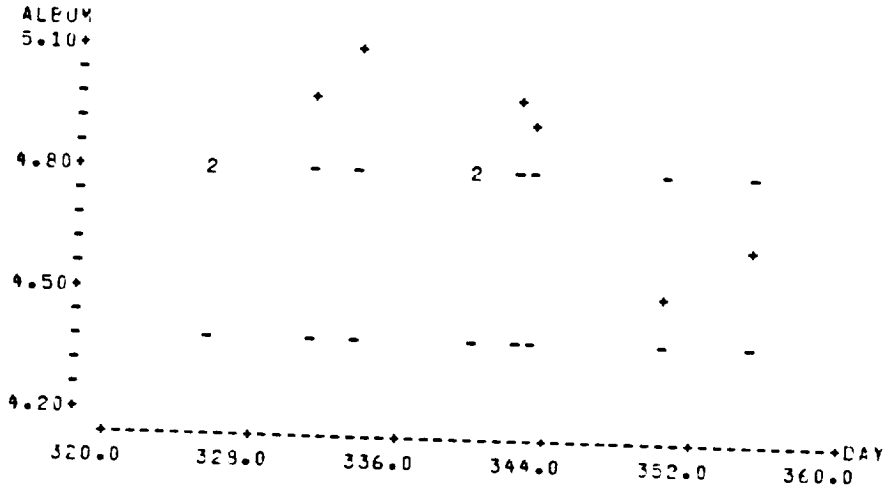
Figure 30



AV 4.38000
SD .435165
HI 5.26033
LO 3.51967



4.35667
.512348
5.39136
3.34197



4.60000
.100000
4.50000
4.40000

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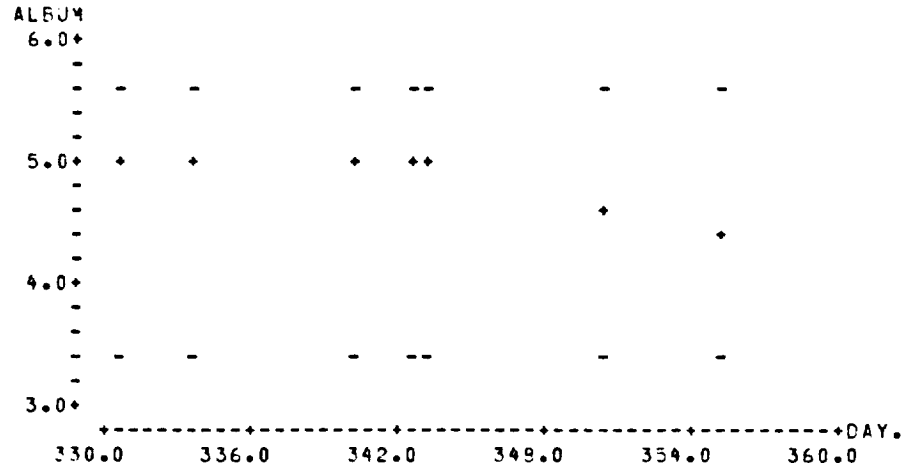
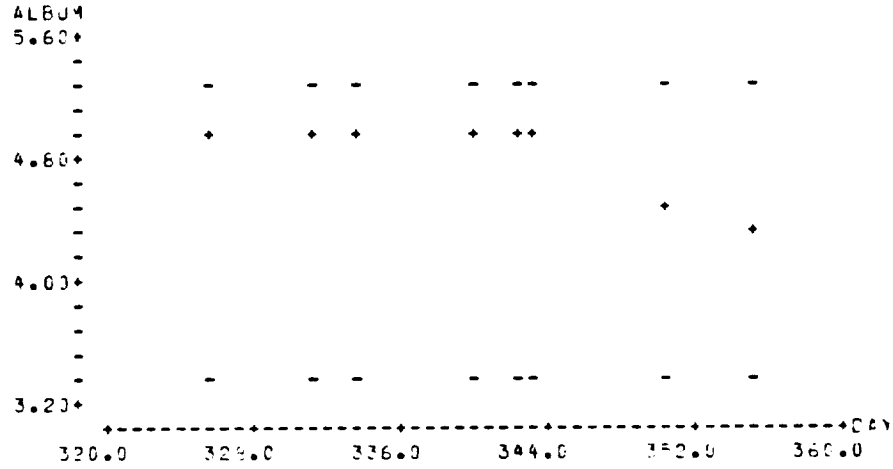
Figure 31



AV 4.43125
SD .561805
HI 5.55486
LO 3.30764



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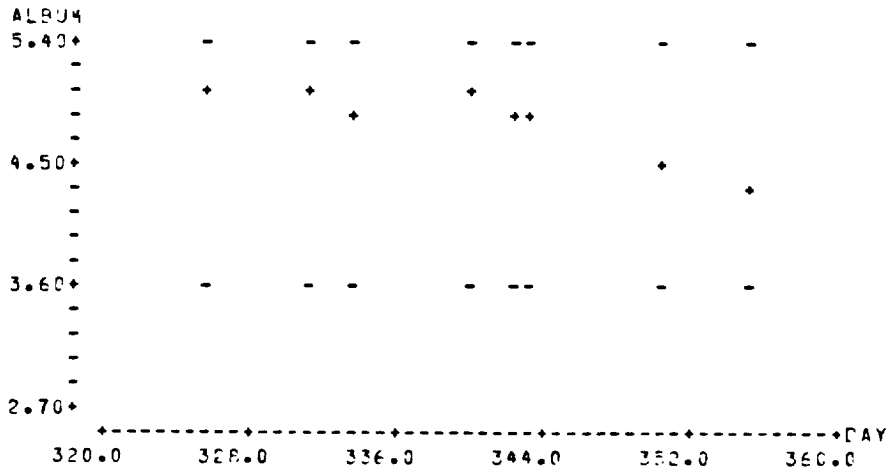
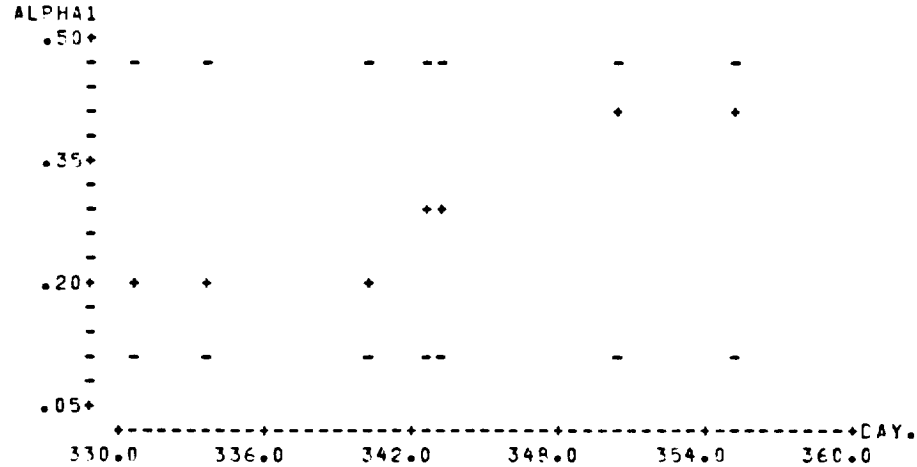
4.25667
.487618
5.20190
3.33143

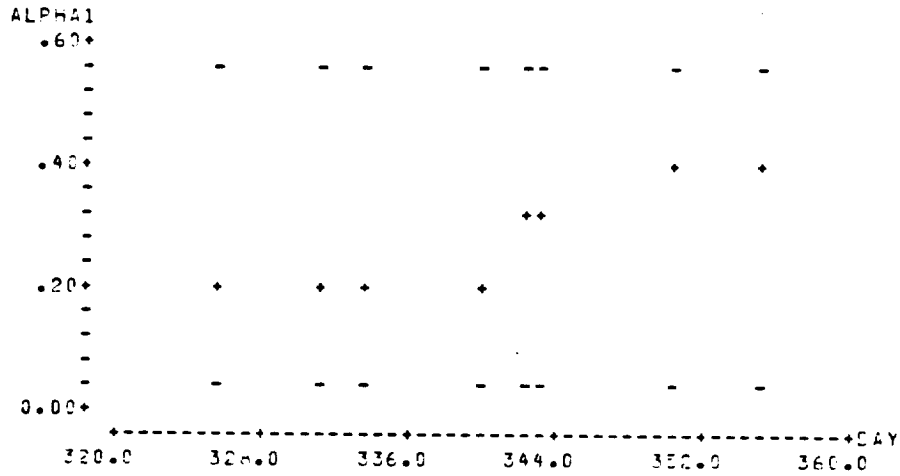


4.43000
.481664
5.44333
3.51667

Figure 32



AV .290000
SD .0967906
HI .483581
LO .0964188



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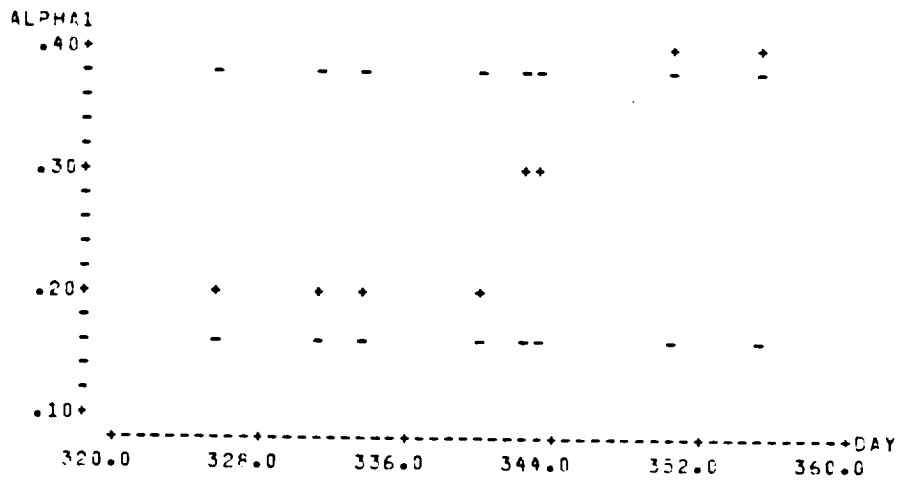
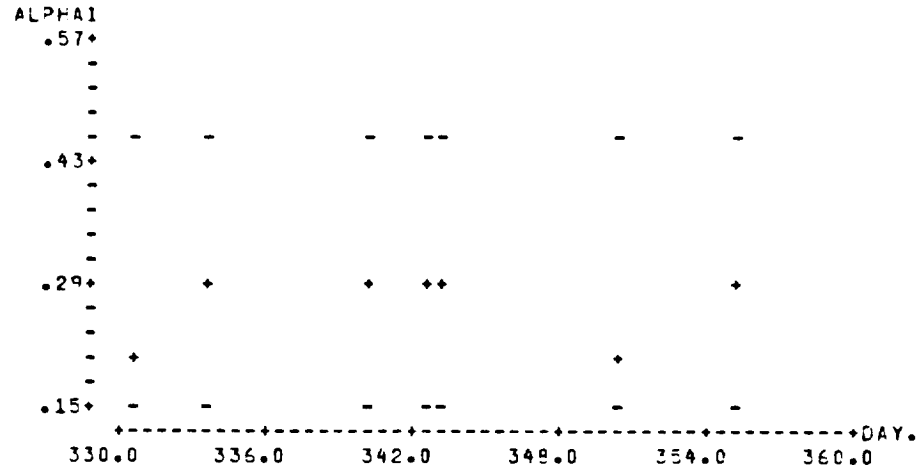
.311111
.126930
.564970
.0572520

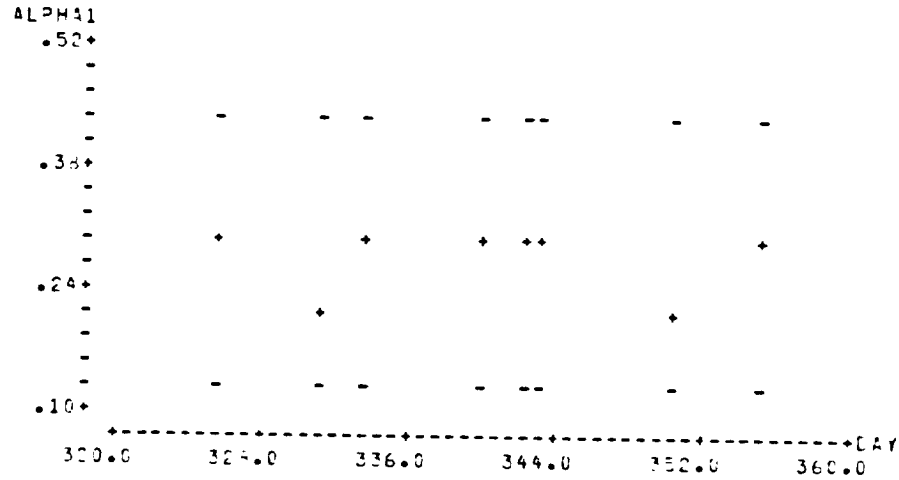


.266667
.0577350
.382137
.151197

Figure 33



AV .305250
SD .0771902
HI .460530
LO .151370



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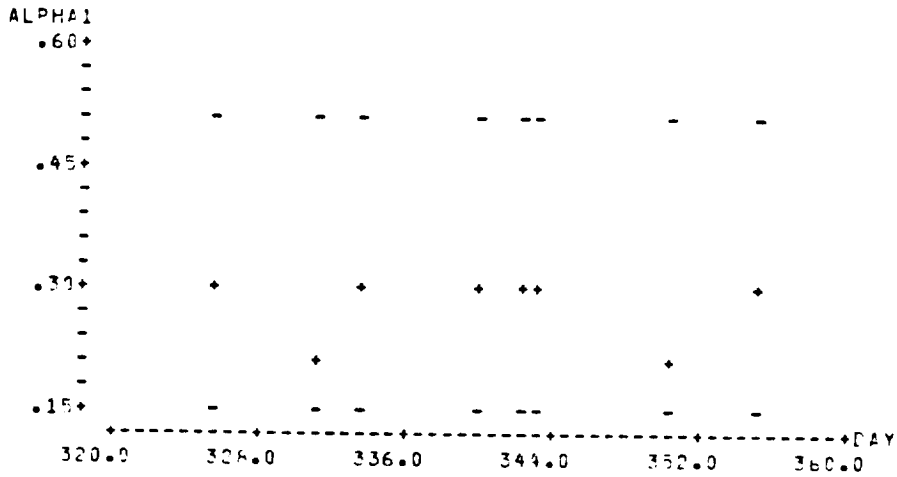
.283333
.0752773
.433983
.132779



.340000
.0954427
.519885
.161115

it would be inappropriate to consider these data as atypical since the limits of the middle plot would then be the correct ones to use.

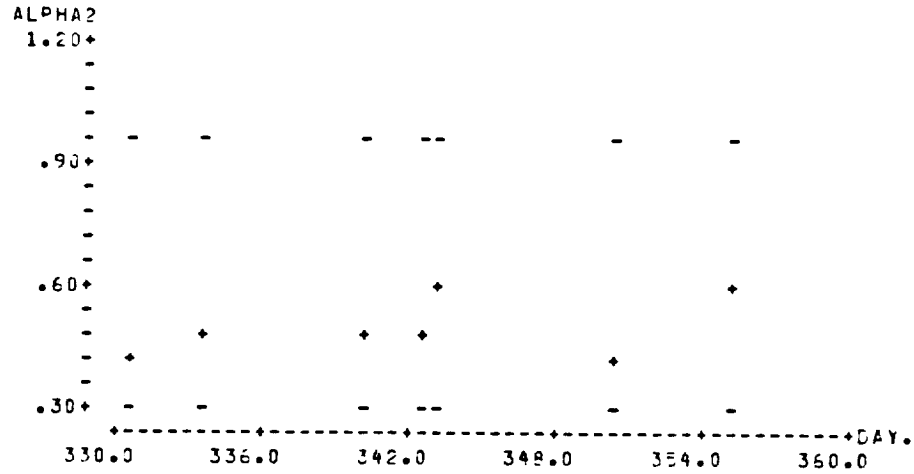
ALPHA-2-PROTEIN: Figure 34 (astronaut 1) and 35 (astronaut 3) present the alpha-2 protein plots. None of the data are beyond the calculated percentile limits.

BETA PROTEIN: Figures 36 (astronaut 1) and 37 (astronaut 3) give the plots for beta protein. The values, in general, for astronaut 1 are reduced being near the 5th percentile in the upper and middle plots and below it assuming a complete phase shift (lower plot). For astronaut 3, the values on L+0 and L+13 are reduced below the 5th percentile limit as is the value on F-1 considering the TQRV shown in the bottom plot.

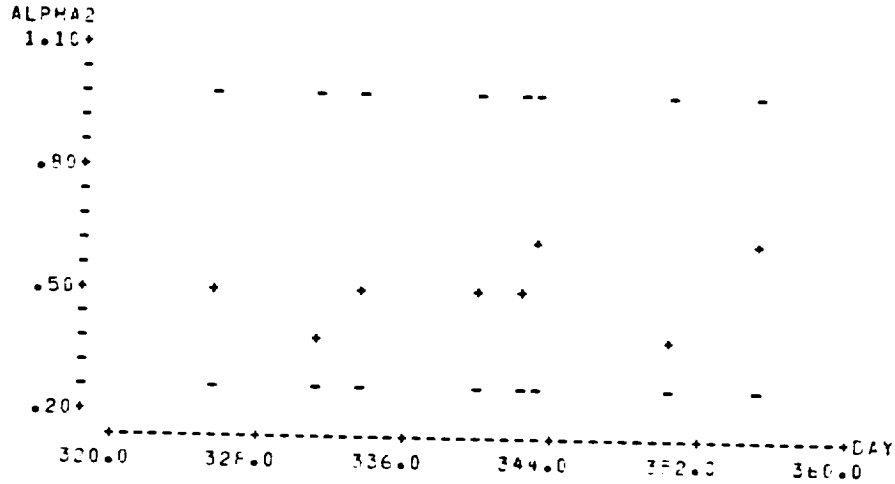
GAMMA PROTEIN: Figures 38 (astronaut 1) and 39 (astronaut 3) reveal that the levels of gamma protein both during and after the space flight were reduced to around or below the 5th percentile limit. This is especially evident for astronaut 1. The lowest value around L+0 or L+1 represents an approximately 50% difference from the overall (non-time-qualified) mean of the respective astronauts.

POTASSIUM, OSMOLARITY AND TRANSFERRITIN: Although all but osmolarity exhibited marked circadian differences when studied during the preflight transverse 24-hour studies, these variables apparently were not investigated during or following the mission. Nonetheless, graphic representation of these limits (without consideration of TQRV) can be found in Appendix D as can those for other hematologic variables for which studies were not conducted in or postflight.

Figure 34



AV	.615000
SD	.163111
HI	.941222
LO	.288778



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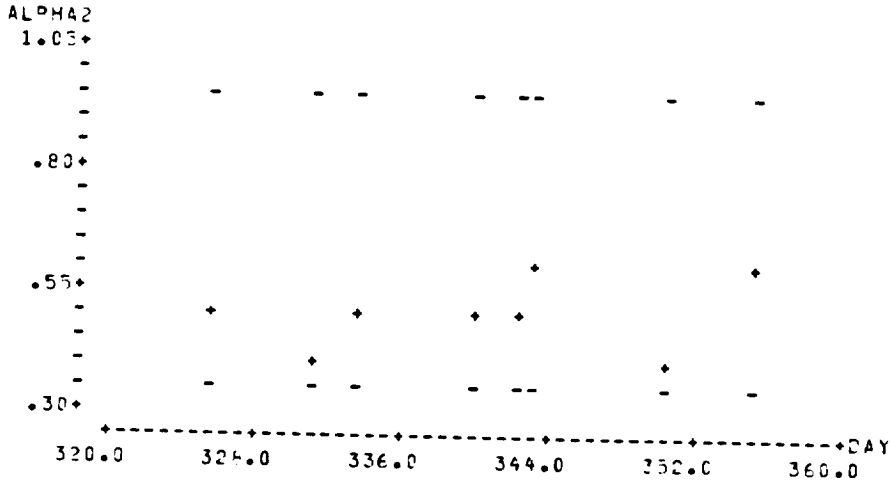
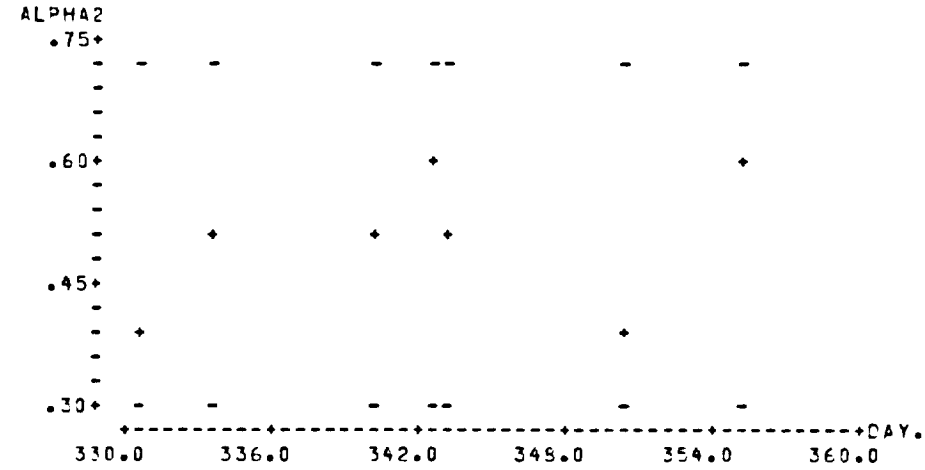
	.600000
	.180278
	.940555
	.239445

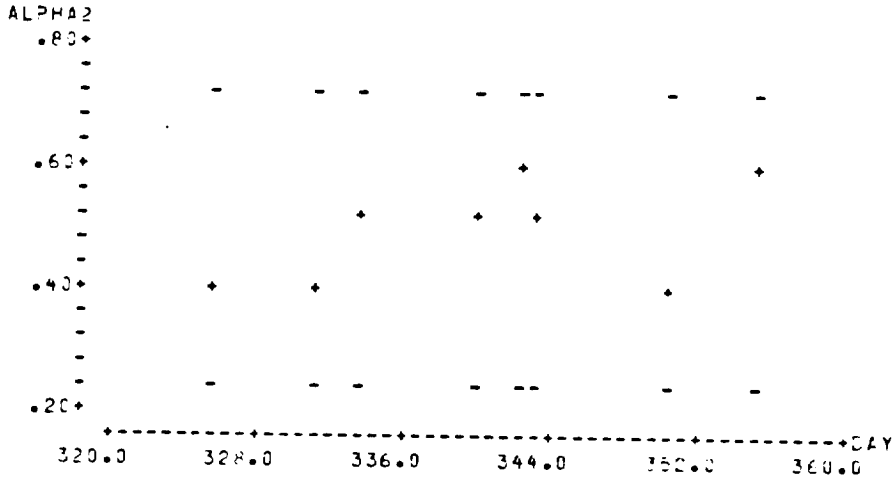


	.633333
	.152753
	.938838
	.327828

Figure 35



AV	.512500
SD	.102470
HI	.717439
LO	.307561



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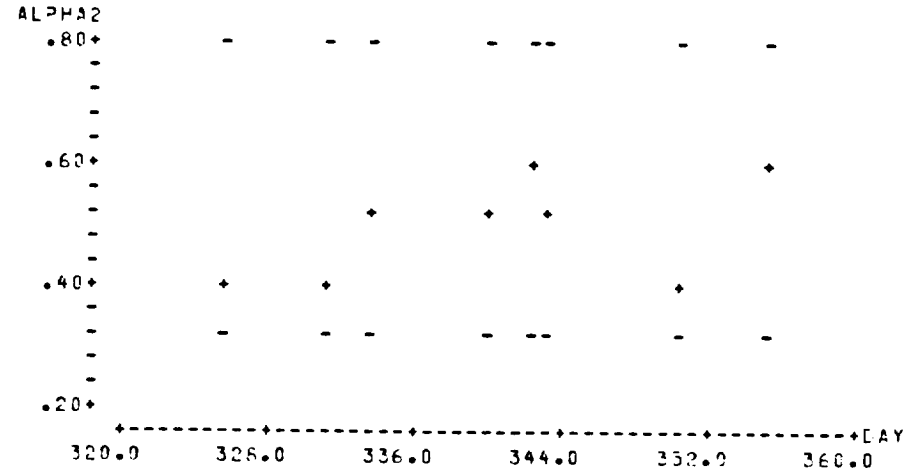
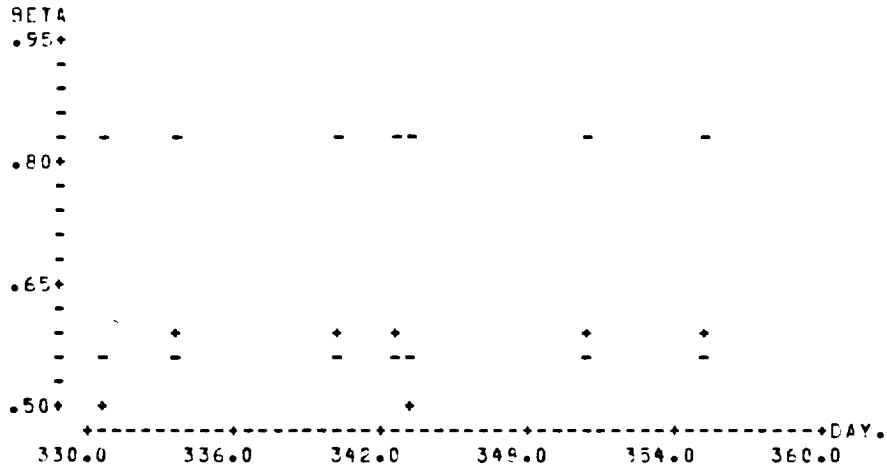
	.493333
	.115905
	.717142
	.249524

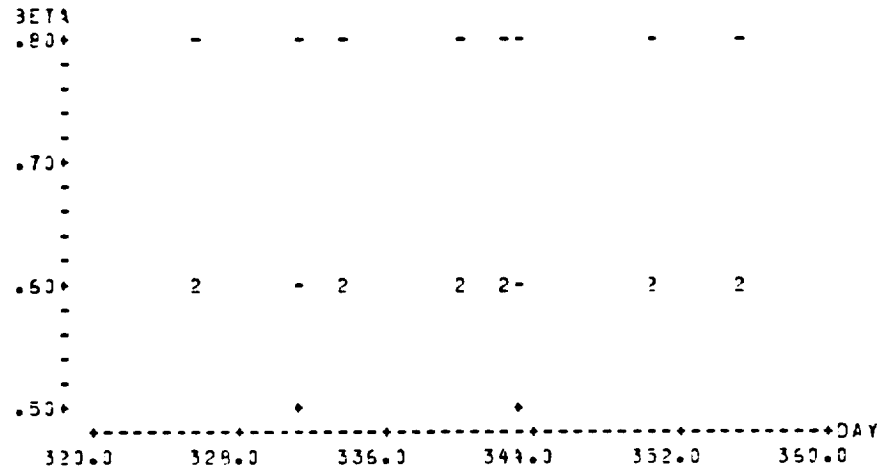


	.560000
	.114018
	.783035
	.331965

Figure 36



AV .705000
SD .0685333
HI .842267
LO .567733



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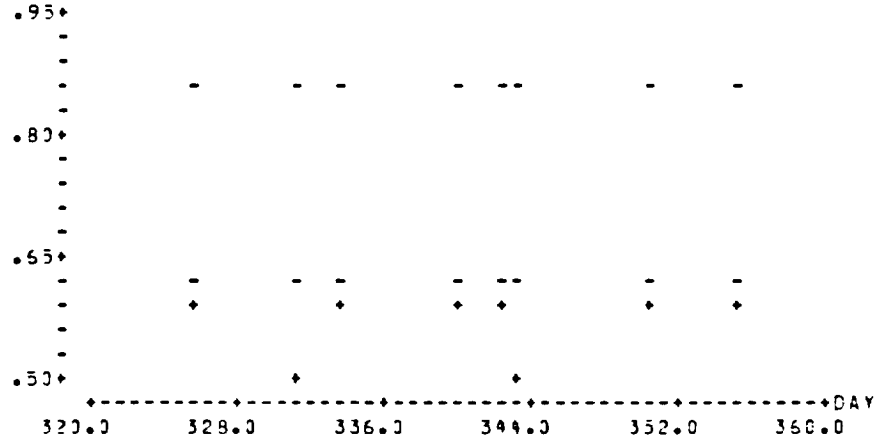
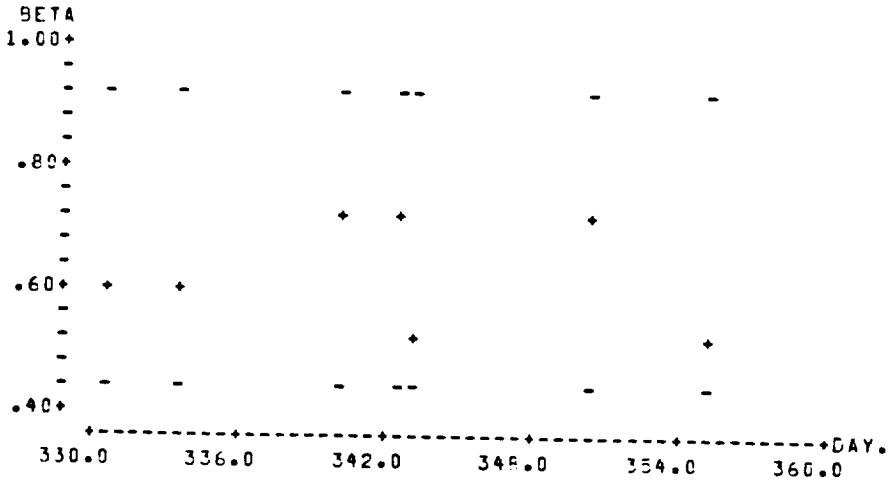
.700000
.0500000
.800000
.600000

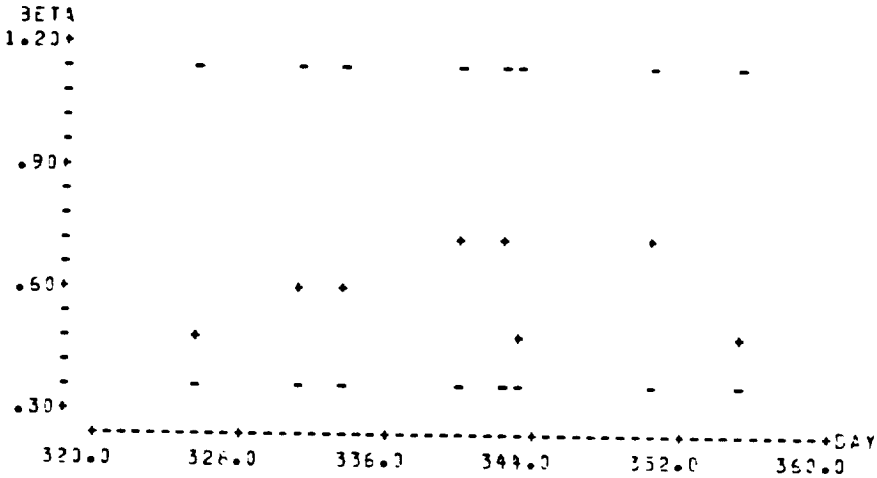


.733333
.0577350
.843303
.617363

Figure 37



AV	.687500
SD	.125831
HI	.939161
LO	.435839



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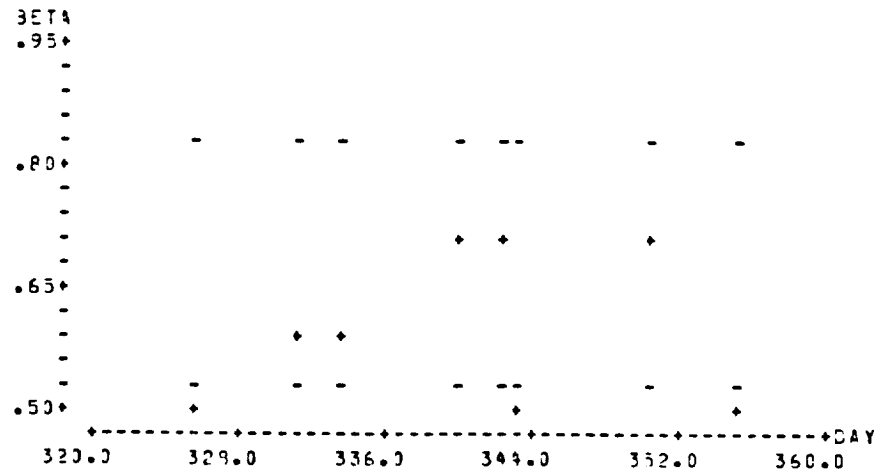
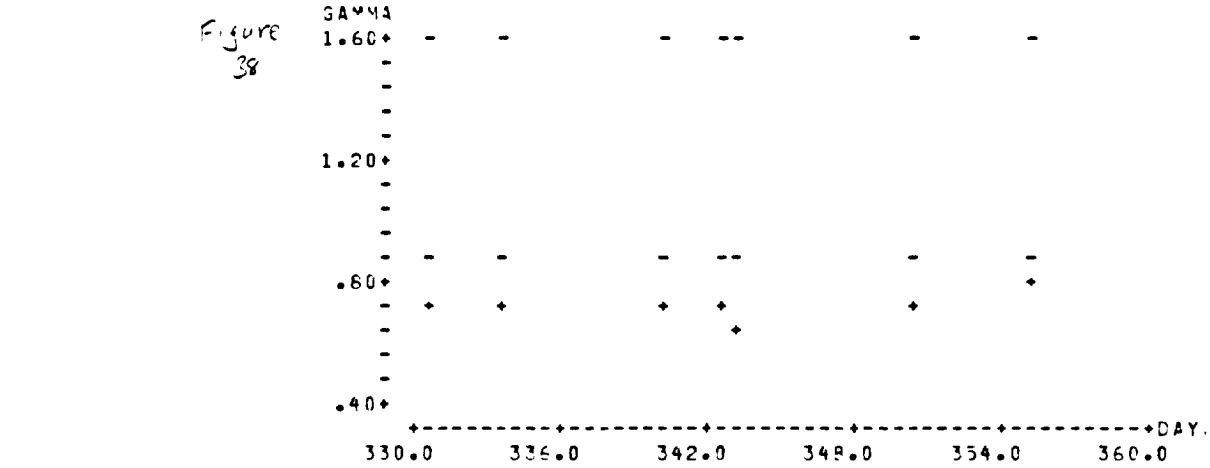
	.740000
	.133935
	1.12987
	.350128



	.683333
	.3752773
	.833888
	.532779

Figure 38



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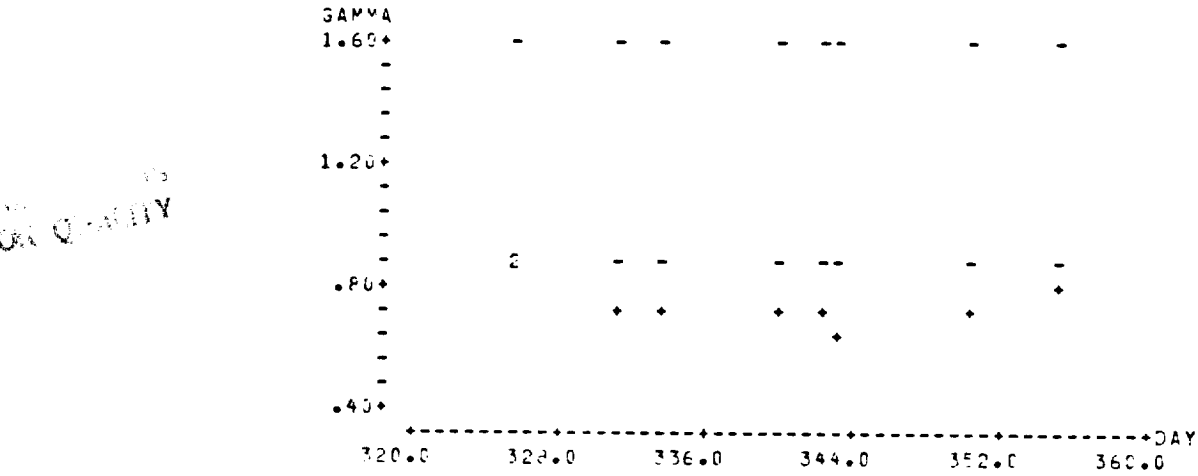

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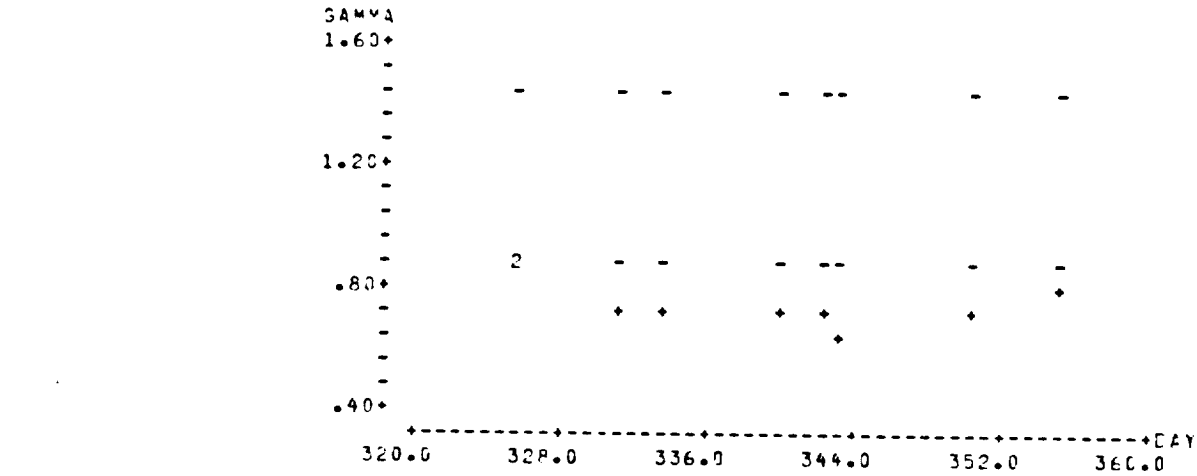

1.15667
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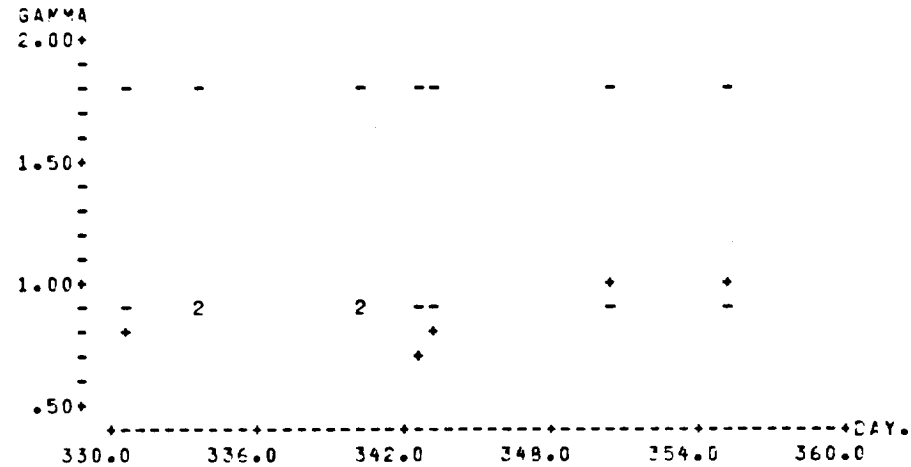
1.47217
.861162

Figure 39



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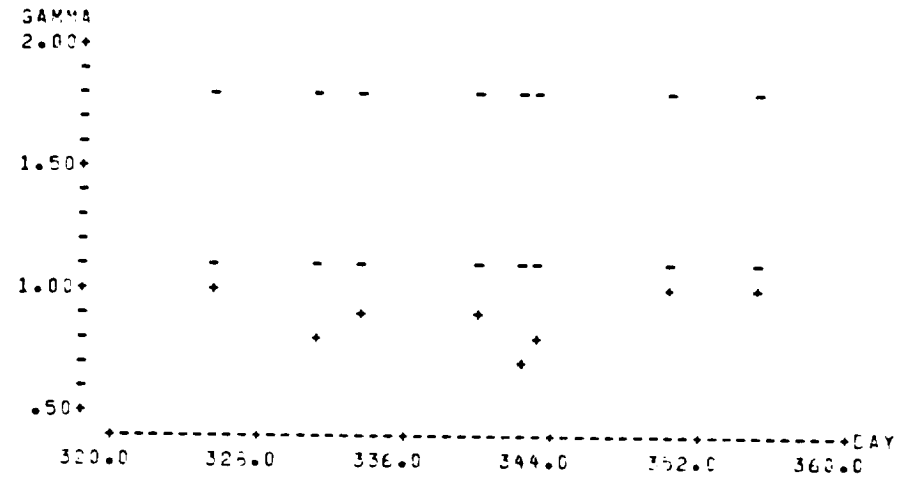
LO	.937451



OF POOR QUALITY

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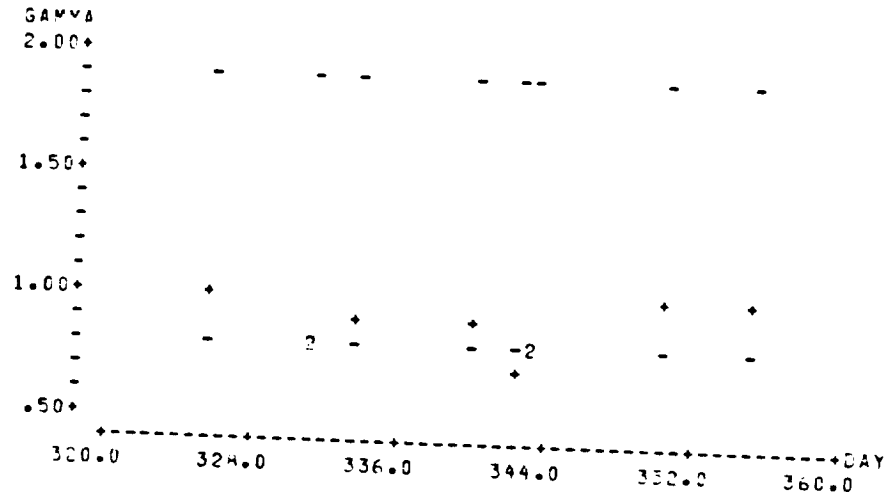

	1.35000
	.298097
	1.93814
	.763806

PART IV: DISCUSSION OF FINDINGS AND RECOMMENDATIONS FOR FUTURE INVESTIGATIONS

The findings for both the astronauts although exhibiting individual differences were similar with respect to RBC, HGB, HCT and MCHC. Greatest values were observed by MD6 or L+0 and lowest ones were seen on L+8 or L+13. This is the case in particular for RBC and HGB.

Although WBC and eosinophils did not exhibit atypical levels, monocytes tended be above the 95th percentile by L+13 while lymphocytes were reduced below the 5th percentile at least during the mission in both astronauts. The bands and basophils being in such low number did not enable useful analysis and interpretation.

In spite of the fact there were no consistent trends in both the astronauts for the variables of total protein, albumin, aphla-1 and alpha-2 and beta proteins, there was a suggestion that the level of gamma protein was reduced in both astronauts at least during the mission.

In reviewing the findings of the effect of space flight and its associated effects, one is left with the impression that very few statistically significant changes (these being defined as values below or above the 5th and 95th percentiles, respectively) resulted. Although trends were noted in the RBC, HGB, HCT and MCHC for example, these do not appear significant from a performance and health perspective. Similarly, changes in monocytes during the post-flight phase and also in lymphocytes during the mission, itself, have not been related to decrements in immunosurveillance.

In this project, time-qualified reference values (TQRV) were used to ascertain whether hematologic parameters during and after flight were within the usual range. Although the original intent was to use appropriate TQRV adjusted for the degree of the $\Delta\phi$ when the two astronauts were switched from day to nighttime activity, it was impossible to discern with certainty whether the circadian system of the astronauts actually did undergo a significant alteration. Most of the variables graphed in Figure 1-3 of Part III reveal minor or no $\Delta\phi$. This is the case for example for cortisol immediately postflight. This is definitely unexpected, especially in individuals regularly adhering to night work or rotating shift work schedules (3,4), although it is known there exist individual differences in the rate of the $\Delta\phi$ for a given variable as well as differences between variables in the rate of $\Delta\phi$ within the same individual (5).

Focusing upon the urinary cortisol data of Part III and in the absence of other data to the contrary, it appears that no meaningful alteration of the circadian system resulted. This indicates the most appropriate reference limits were those shown in the middle plots of the figures of Part III. It must be pointed out that even if one wished to assume that a complete $\Delta\phi$ of the circadian system was accomplished by each astronaut, without supporting data before and during flight it is not possible to confirm this; nor is it possible to determine the date when the hypothesized $\Delta\phi$ was complete. Thus, even if there were evidence that a $\Delta\phi$ had occurred, it would not be known with certainty if the data taken on MD2, MD6 or L+0 should be compared to the percentile limits given in the bottom plots of each figure. Furthermore, without "marker rhythm" data during the postflight period, it is not known if

the L+8 and L+13 data are representative of a re-entrained (to diurnal activity and nocturnal rest) circadian system.

For these reasons further projects incorporating TQRV, especially when shift, night or altered work schedules of some nature are used, must incorporate monitoring equipment to obtain time series data on body temperature, heart rate and activity over continuous 24-hour periods to know when the different TQRV are most appropriately applied. With the availability of new generation, light-weight, telemetry monitoring systems, this requirement for the additional needed data can be rather easily satisfied. These data also could be used to supplement those obtained from scheduled 28-hour blood, urinary and/or salivary samplings to provide the necessary data to better assess the effects of space flight on human being on an individual basis as discussed herein (Part III).

Finally, this project has evaluated the effects of a unique environment using a substantial data base--up to 13 to 21 determination per variable per astronaut. This data base has enabled using 5 and 95 percentile limits to ascertain whether mission or postflight data are typical or atypical. From a traditional point of view, the non-TQRV shown at the top of each of the figures, with few exceptions, reveal that mission and postflight conditions generally are not associated with atypical hematologic parameters. Our large data base provides a greater level of confidence in evaluating data from astronauts studied in and after flight. It is the understanding of this investigator and also the consultants to this project that a rather large data base for every astronaut exists from scheduled preflight biological samplings and also from several once-yearly physical examinations at the JSC. We recommend all these

data be assembled on an individual basis in order to generate percentile limits to evaluate retrospectively more comprehensively the inflight and postflight data already on hand, assuming this has not yet been done. Also, we recommend the creation and use of normal ranges for astronauts participating in future missions to continue the study of biological adjustments of human beings to space conditions with greater precision.

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1. Halberg, F., Johnson, E.A., Nelson, W., Runge, W. and Sothern, R.: Autorhythmometry. Procedures for physiologic self-measurements and their analysis. Physiol. Teacher 1:1, 1972.
2. Sargent, F.S. II: Human biometeorology. In Seminar on Human Biometeorology, Environmntal Health Series (Air Pollution), U.S.H.E.W. New York, 1971, Chapter 1.
3. Reinberg, A. (Ed.): Chronobiological field studies of oil refinery shift workers. Chronobiologia 6(Suppl 1), 1979.
4. Klein, K.E. and Wegmann, H.M.: Circadian rhythms of human performance and resistance: operational aspects. In Sleep, Wakefulness and Circadian Rhythm. AGARD Lecture Series No. 105, 1979, pp. 2-1 to 2-9.
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APPENDIX A

Results of Single Cosinor Analyses by Astronaut, Variable and Transverse Study

TABLE A

Results of Single-Cosinor Analyses for Hematology Variables

Astronaut One

Studied Variable	Transverse Study No.	Mesor M	Circadian Amplitude	Circadian Acrophase*
EP	1	0.30	0.22	1535
	2	0.76	0.36	1042
RBC	1	4.92	0.06	0403
	2	4.97	0.21	1344
	3	4.77	0.23	1519†
HGB	1	15.26	0.22	0330
	2	14.33	0.72	1346
	3	14.77	0.64	1424†
HCT	1	44.57	0.91	0536
	2	43.25	1.51	1308
	3	43.04	2.09	1504†
MCV	1	90.07	0.36	0636
	2	86.80	0.68	0430
	3	90.75	0.43	1726
MCH	1	31.29	0.46	0024
	2	28.69	0.35	1206
	3	31.00	--	--
MCHC	1	34.36	0.30	2154
	2	33.10	0.44	1111
	3	34.25	0.45	0514
Reticulocytes	1	0.56	0.06	1046
	2	0.29	0.09	0412†
	3		No data	
WBC	1	6.29	0.66	0300
	2	5.75	1.89	0259
	3	5.62	0.55	2307†
Polymorphs	1	45.64	6.92	1145
	2	41.33	3.75	0502
	3	41.17	8.07	0124†
Lymphocytes	1	46.36	9.00	2349
	2	47.06	6.32	1803
	3	53.33	7.95	1345†

TABLE A (continued)

Studied Variable	Transverse Study No.	Mesor M	Circadian Amplitude	Circadian Acrophase*
Bands	2	6.07	2.83	0605†
Monocytes	1	3.21	1.39	1540
	2	4.07	0.67	1024
	3	1.10	0.45	0024
Eosin	1	4.35	1.78	0955
	2	1.77	0.43	2032
	3	4.60	1.32	1002
Total Protein	1	7.35	0.23	1100
	2	7.17	0.27	1547
	3	7.10	0.34	1654
Albumin	1	4.80	0.21	0955
	2	4.07	0.31	2145
	3	4.32	0.10	1129
Alpha 1	1	0.30	-	-
	2	0.31	0.13	1000
	3	0.27	0.06	1900
Alpha 2	1	0.50	-	-
	2	0.80	0.18	1500†
	3	0.54	0.08	2100
Beta	1	0.70	0.04	1418
	2	0.67	0.06	1409
	3	0.76	0.06	2131
Gamma	1	1.05	0.06	1300
	2	1.30	0.15	1155
	3	1.24	0.20	1529
Hapto	1	53.00	20.35	1004
	2	99.66	9.48	1341
	3	50.97	5.20	1140
Transf	1	249.50	22.61	1320
	2	237.10	21.75	1829†
	3	284.16	29.23	1807
Ferrit	1	132.00	13.23	2022†
	2	117.73	6.41	0904
	3	100.37	3.23	0449

TABLE A (continued)

Studied Variable	Transverse Study No.	Mesor M	Circadian	
			Ampli-tude	Acro-phase*
Sodium	1	139.8	0.86	0300
	2	137.5	0.37	0842
	3	138.1	0.91	1352
Potassium	1	4.60	0.81	2227
	2	5.11	1.73	2251
	3	5.40	1.32	2051†
Osmolarity	1	292.4	1.98	0116
	2	288.9	7.23	2224
	3	289.0	0.78	0352

*Amplitudes listed as one-half the peak-to-trough difference; acrophase given in clock hours from 0000.

†Statistical significance: $p < 0.05$

TABLE B

Results of Single Cosinors Analyses for Hematological Variables

Astronaut Two

Studied Variable	Transverse Study No.	Mesor M	Circadian Amplitude	Circadian Acrophase*
EP	1	0.30	0.04	0832
	2	0.39	0.02	0618
RBC	1	4.38	0.15	1108
	2	4.71	0.15	1559
	3	4.50	0.15	1321
HGB	1	13.68	0.37	1022†
	2	13.82	0.82	1608
	3	14.02	0.53	1402
HCT	1	40.43	1.22	1018
	2	40.43	1.46	1548
	3	40.86	1.21	1248
MCV	1	91.28	0.99	0152
	2	85.41	0.16	1654
	3	90.64	0.60	0637
MCH	1	31.31	0.35	2320
	2	29.17	0.90	1656
	3	31.19	0.31	2043
MCHC	1	33.96	0.26	1500
	2	34.36	0.61	1726†
	3	34.19	0.31	2043
Reticulocytes	1	0.80	0.09	1613
	2	0.44	0.06	1728†
	3	0.51	0.12	1712†
WBC	1	6.10	0.73	2142
	2	6.25	1.35	2236†
	3	5.15	0.74	2218†
Polymorphs	1	43.61	3.08	1652
	2	44.42	5.54	1930†
	3	45.32	2.37	2129

TABLE B (continued)

Studied Variable	Transverse Study No.	Mesor M	Circadian Amplitude	Circadian Acrophase*
Lymphocytes	1	43.39	1.61	0713
	2	43.09	4.03	0106
	3	48.19	3.52	1040
Bands	2	3.18	1.71	0542†
Monocytes	1	2.43	0.29	0912†
	2	2.86	2.11	1028†
	3	1.83	0.87	0210
Eosin	1	10.31	2.22	0330
	2	7.70	2.28	1330
	3	4.66	0.75	2310
Total Protein	1	7.26	0.31	1715
	2	7.46	0.31	1808
	3	7.13	0.24	1313
Albumin	1	4.20	0.25	1033
	2	4.41	0.87	0922
	3	4.82	0.42	1322
Alpha 1	1	0.27	0.10	1238
	2	0.38	0.21	2015
	3	0.19	0.02	2024
Alpha 2	1	0.61	0.62	1936
	2	0.70	0.12	2039
	3	0.44	0.06	0154
Beta	1	0.81	0.10	1839
	2	0.76	0.15	2052
	3	0.70	0.03	0405
Gamma	1	1.39	0.32	2031†
	2	1.18	0.62	2051
	3	0.99	0.06	0104
Hapto	1	111.33	4.81	2354
	2	111.56	10.97	1455
	3	130.36	8.87	0903
Transf	1	285.41	17.68	1936
	2	311.65	20.66	1742
	3	287.17	13.97	1315

TABLE B (continued)

Studied Variable	Transverse Study No.	Mesor M	Circadian	
			Ampli-tude	Acro-phase*
Ferrit	1	43.15	4.56	1818
	2	35.41	2.24	1854
	3	33.37	1.65	1030
Sodium	1	139.7	0.07	1500
	2	139.8	1.05	0718
	3	139.5	0.38	1654
Potassium	1	4.62	0.12	2242
	2	4.88	0.67	2038
	3	4.69	0.47	2318
Osmolarity	1	291.4	1.16	2031
	2	294.3	3.32	0054
	3	290.3	3.56	2354

*Amplitudes listed as one-half the peak-to-trough difference; acrophase given in clock hours from 0000.

†Statistical significance: $p < 0.05$

TABLE C

Results of Single Cosinor Analyses for Hematological Variables

Astronaut Three

Studied Variable	Transverse Study No.	Mesor M	Circadian Amplitude	Circadian Acrophase*
EP	2	0.42	0.05	0154
RBC	2	4.97	0.27	1526†
	3	5.09	0.15	1236†
HGB	2	13.64	0.72	1933
	3	15.55	0.56	1236†
HCT	2	40.51	1.80	1950†
	3	44.93	1.49	1312†
MCV	2	81.47	4.41	0020
	3	88.25	0.87	1317
MCH	2	27.65	1.53	2349†
	3	30.86	0.31	1442
MCHC	2	33.72	0.28	1209
	3	35.00	--	--
Reticulocytes	2	0.43	0.06	2054
	3	0.98	0.21	1136
WBC	2	7.79	1.83	2224†
	3	6.12	0.59	1924
Polymorphs	2	52.32	7.06	1545
	3	52.95	2.79	0632
Lymphocytes	2	36.71	5.71	0246
	3	43.70	1.62	1647
Bands	2	6.24	1.90	0243†
Monocytes	2	3.61	0.94	1155
	3		No data	
Eosin	2	1.59	1.32	1121†
	3	2.01	0.60	0522

TABLE C (continued)

Studied Variable	Transverse Study No.	Mesor M	Circadian Amplitude	Circadian Acrophase*
Total Protein	2	7.12	0.43	1900†
	3	7.33	0.47	1442†
Albumin	2	4.14	0.54	1743
	3	4.59	0.46	1521
Alpha 1	2	0.34	0.01	0625
	3	0.28	0.09	0011†
Alpha 2	2	0.58	0.04	0411
	3	0.50	0.07	2131
Beta	2	0.70	0.06	2330
	3	0.70	0.11	1533
Gamma	2	1.39	0.09	0134
	3	1.38	0.22	1133
Hapto	2	61.09	5.39	1042
	3	52.73	13.17	1642
Transf	2	252.84	25.80	1942
	3	281.63	35.58	1308†
Ferrit	2	42.44	4.04	1712
	3	53.90	1.86	0718
Sodium	2	140.6	0.61	0515
	3	140.9	0.92	0856
Potassium	2	4.51	0.92	1836†
	3	5.01	1.10	2251
Osmolarity	2	303.1	12.27	0127
	3	295.2	8.55	0117

*Amplitudes listed as one-half the peak-to-trough difference; acrophase given in clock hours from 0000.

†Statistical significance: $p < 0.05$

APPENDIX B

TIME-QUALIFIED REFERENCES: IRRESPECTIVE OF AGE

For greater detail see related bibliography:

(1) Haus, J.E., Lakatua, D.J., Sackett-Lundeen, L.L. and Swoyer, J.: Chronobiology in laboratory medicine. In Reitveld, W. (Ed.), Clinical Aspects of Chronobiology. Madition in Buaen, Holland, in press.

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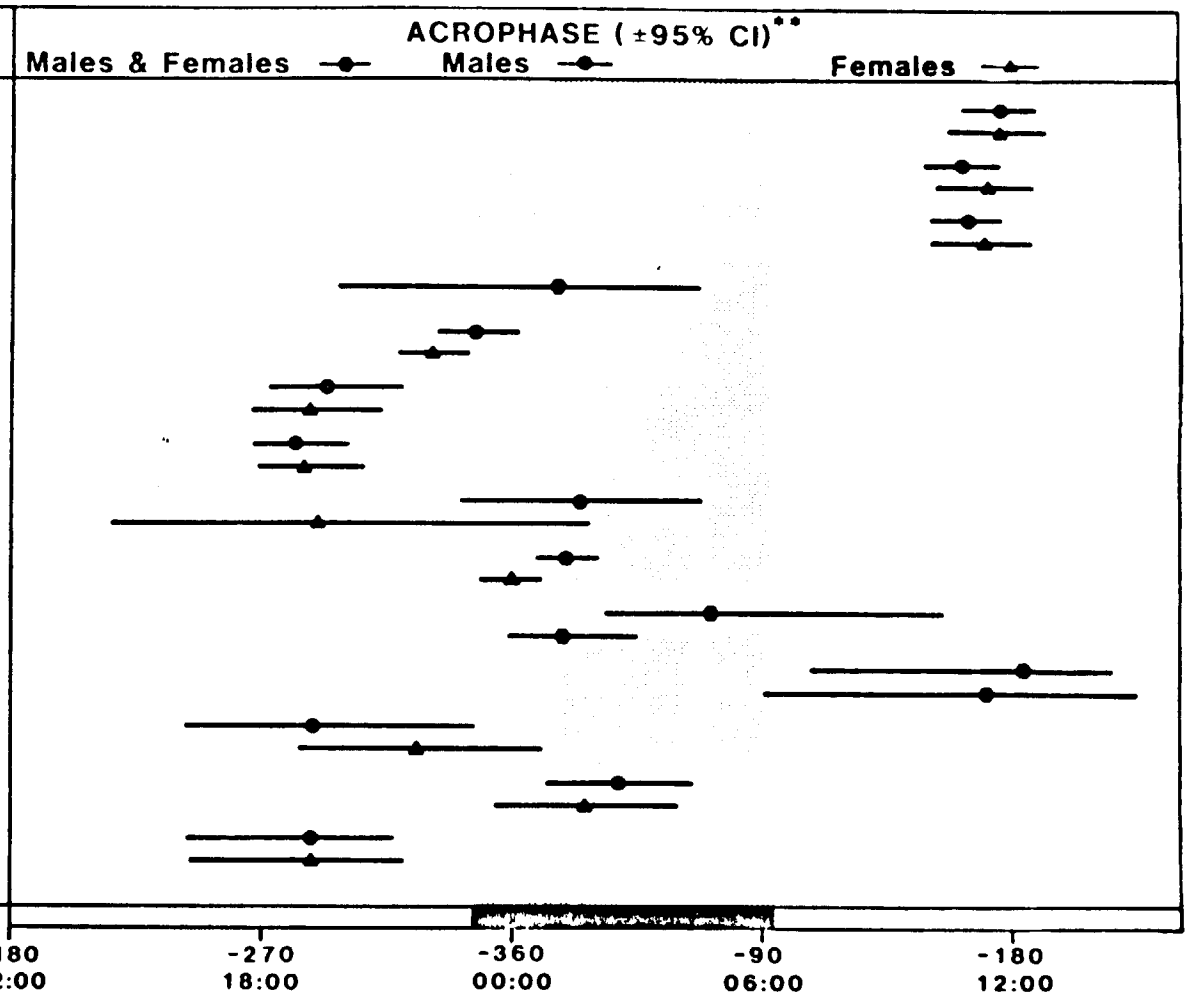
Phase Relation of Human Circadian Rhythms*

I. Hematology

FUNCTIONS	SUBJECTS Sex	SUBJECTS No.
Hemoglobin	M	79
	F	71
Hematocrit	M	79
	F	71
Red Blood Cells	M	79
	F	71
Reticulocytes	M & F	37
Total WBC	M	79
	F	71
Total Neutrophil	M	79
	F	71
Adult Neutrophil	M	79
	F	71
Bands	M	79
	F	71
Lymphocytes	M	79
	F	71
B Cells	M & F	15
T Cells	M & F	15
PHA Response	M & F	17
PWM Response	M & F	12
Monocytes	M	79
	F	71
Eosinophils	M	79
	F	71
Platelets	M	30
	F	25



* In Clinically Healthy Diurnally Active Subjects of both sexes (mean age 24 ± 10, range 11 to 57), studied by serially dependent sampling (6 or 7 timepoints/24 hours) at St. Paul Ramsey Medical Center, St . Paul, MN.

** by mean cosinor

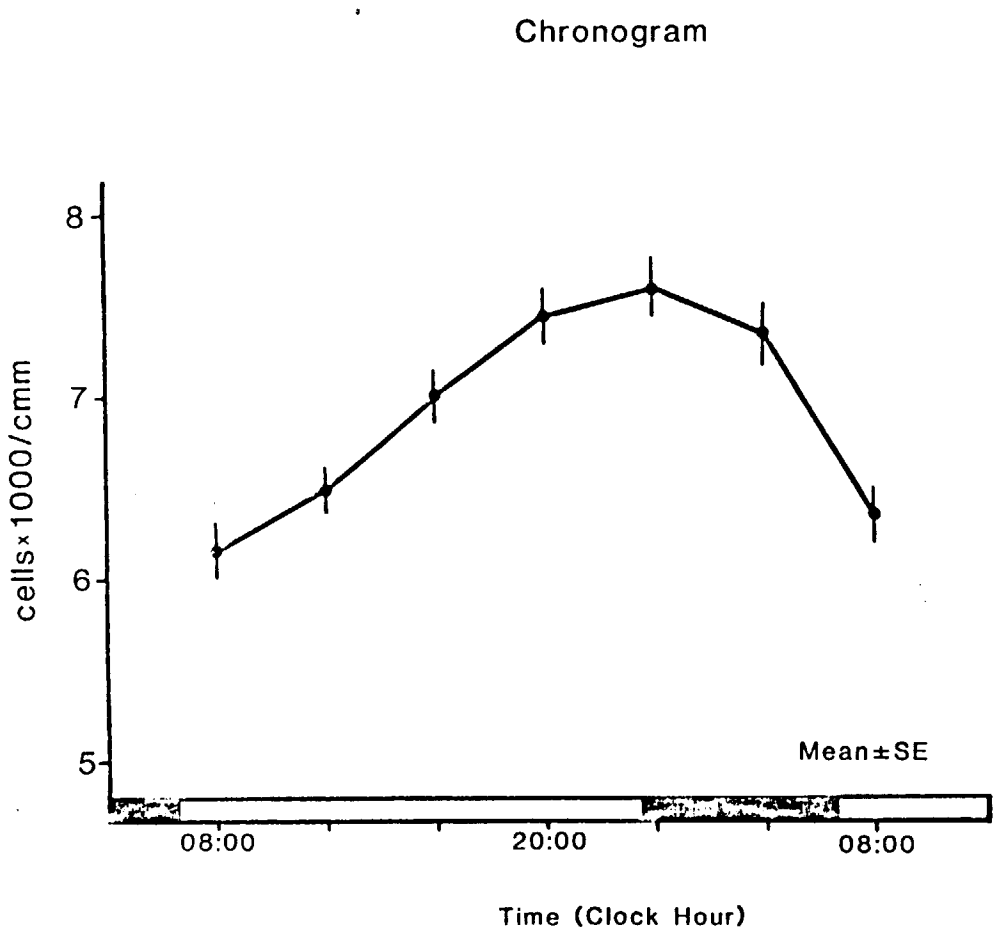
FUNCTIONS	UNITS	SUBJECTS Sex	No.	RHYTHM DETECTION(p)	PR*	RHYTHM ADJUSTED MEAN MESOR	± 95% C.I.		AMPLITUDE ½PEAK-TROUGH DIFF. A	±95% C.I.		PEAK-TROUGH (2 x A) as % of MESOR A x 200/M ± 95% C.I.			ACROPHASE** in CLOCK HOUR Ø	± 95% C.I.	
ENDOCRINOLOGY																	
A. PLASMA																	
ACTH	pg/ml	M&F	14	.045	52	70	17	122	9	0.1	28	25.71	0.29	80.00	09^{08}	05^{28}	16^{56}
Cortisol	mcg/dl	M	87	<.001	64	10.7	3.1	18.4	4.9	4.4	5.4	91.59	82.24	100.93	08^{48}	08^{16}	09^{24}
		F	71	<.001	62	11.4	3.0	19.7	4.7	4.2	5.3	82.46	73.68	92.98	08^{08}	07^{28}	08^{48}
B. SERUM																	
Aldosterone	ng/dl	M	27	<.001	52	7.1	3.1	11.2	3.4	2.4	4.4	95.77	67.60	123.94	08^{00}	06^{44}	09^{16}
		F	19	<.001	49	9.0	1.3	16.7	3.2	1.8	4.9	71.10	40.00	108.89	07^{48}	06^{12}	10^{32}
DHEA	ng/dl	M&F	16	.017	56	284	0	653	25	4	46	17.60	2.82	32.39	16^{32}	14^{08}	19^{48}
Follicle Stimulating Hormone	mIU/ml	M&F	38	.002	44	7.8	0.4	15.1	0.3	0.1	0.6	7.69	2.56	15.38	04^{40}	02^{28}	07^{44}
Growth Hormone	ng/ml	M&F	97	.010	39	3.6	0	12.6	1.5	0.3	2.8	83.33	16.67	155.56	00^{48}	21^{36}	05^{08}
Insulin	mcU/ml	M	33	<.001	46	27	3	51	10	6	15	74.07	44.44	111.11	18^{04}	16^{20}	19^{36}
		F	25	<.001	46	27	3	52	8	4	13	59.26	29.63	96.30	16^{24}	13^{44}	18^{40}
Luteinizing Hormone	ng/ml	M&F	38	<.001	43	11.2	2.9	19.4	1.5	0.6	2.4	26.78	10.71	42.86	02^{36}	01^{08}	04^{40}
Prolactin	ng/ml	M	27	<.001	43	15.0	9.0	21.1	5.4	4.0	6.7	72.00	53.33	89.33	04^{20}	03^{24}	05^{24}
		F	19	<.001	42	24.2	8.4	39.9	0.6	5.9	15.4	87.60	48.76	127.27	04^{00}	02^{56}	05^{00}
Thyroid Stimulating Hormone	mcIU/ml	M	27	<.001	42	2.2	0	4.4	10.5	0.2	0.8	45.45	18.18	72.73	02^{48}	00^{28}	04^{24}
		F	16	.015	56	1.9	0.1	3.6	0.4	0.1	0.7	42.10	10.53	73.68	01^{04}	21^{08}	05^{32}
Compound S	mcg/dl	M&F	21	<.001	50	2.0	0.1	4.1	0.6	0.2	0.9	60.00	20.00	90.00	07^{36}	06^{00}	08^{56}
Renin	ng/ml/hr	M&F	20	.027	38	0.72	0	1.61	0.27	0.02	0.52	75.00	5.55	144.44	12^{52}	09^{24}	16^{56}
C. URINE																	
Cortisol	mcg/hr	M&F	34	<.001	42	2.66	1.04	4.28	1.70	1.27	2.14	127.82	95.49	160.90	08^{40}	07^{48}	09^{32}
Free Adrenalin	mcg/hr	M&F	18	.004	25	1.09	0	3.63	0.85	0.25	1.45	155.96	45.87	266.06	14^{08}	11^{56}	15^{32}
Free Noradrenalin	mcg/hr	M&F	18	.001	25	14.2	0	31.4	4.13	1.47	7.24	58.17	20.70	101.97	15^{20}	11^{36}	17^{04}
CLINICAL DATA																	
Systolic Blood Pressure	mmHg	M&F	47	<.001	66	119	100	138	2.9	1.3	4.5	4.87	2.18	7.56	17^{48}	16^{04}	20^{04}
Heart Rate	beats/min	M&F	47	<.001	66	75	56	95	2.9	1.5	4.3	7.73	4.00	11.47	18^{04}	16^{32}	20^{12}
Oral Temperature	°F.	M&F	63	<.001	65	98.2	97.5	98.8	0.4	0.3	0.5	0.81	0.61	1.02	17^{24}	16^{48}	18^{08}
Urinary Volume	ml/hr	M&F	34	.021	25	58.8	20.0	97.7	7.3	1.0	13.7	24.83	3.40	46.60	17^{44}	13^{12}	22^{08}

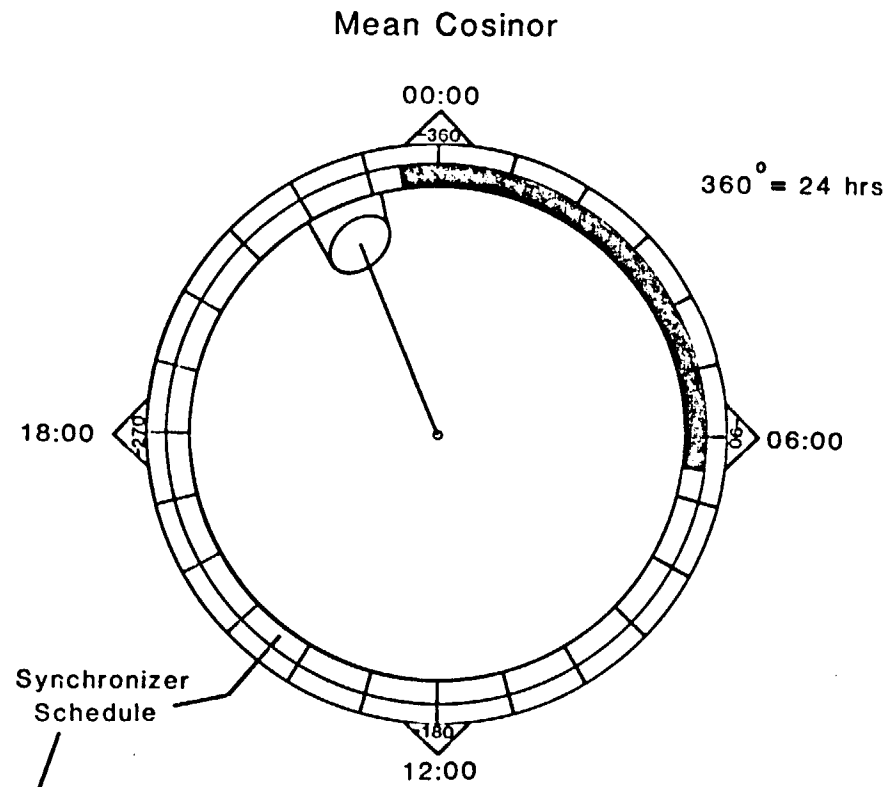
FUNCTIONS	UNITS	SUBJECTS Sex	No.	RHYTHM DETECTION (p)	PR*	RHYTHM MESOR	ADJUSTED MEAN ± 95% C.I.		AMPLITUDE ½PEAK-TROUGH DIFF. A	±95% C.I.		PEAK-TROUGH (2 x A) as % of MESOR A x 200/M ± 95% C.I.			ACROPHASE** in CLOCK HOUR Ø	± 95% C.I.	
CHEMISTRY																	
A. SERUM																	
Serum Iron	mcg/dl	M	81	<.001	63	90	30	151	14	9	19	31.11	20.00	42.22	12^{16}	11^{00}	13^{12}
		F	61	<.001	57	81	35	127	13	8	19	2.47	19.75	46.91	11^{04}	09^{08}	12^{44}
Ferritin	ng/ml	M	38	.026	37	26	2	50	1.0	0.1	1.9	7.69	7.70	14.61	14^{20}	12^{08}	19^{28}
		F	23	.003	46	23	0	48	0.9	0.3	1.6	7.83	2.61	13.91	10^{48}	07^{48}	14^{36}
TIBC	mcg/dl	M	21	<.001	63	337	262	411	11	4	18	6.53	2.37	10.68	14^{48}	13^{04}	18^{08}
		F	13	.027	66	323	255	390	14	2	28	8.67	1.24	17.34	14^{04}	10^{52}	19^{08}
Acid Phosphatase	ng/ml	M&F	34	<.001	40	1.6	0.1	3.1	0.1	0	0.2	12.50	0.00	25.00	20^{44}	18^{32}	23^{44}
Calcium	mg/dl	M&F	16	.031	49	9.2	8.8	9.6	0.1	0	0.3	2.17	0.00	6.52	18^{28}	14^{08}	22^{00}
Ionized Calcium	mg/dl	M&F	18	<.001	48	5.3	5.1	5.5	0.1	0	0.2	3.77	0.00	7.55	20^{00}	18^{20}	22^{00}
Cholesterol	mg/dl	M&F	47	.019	27	187	131	243	3.1	0.4	5.8	3.31	0.42	6.20	17^{04}	13^{24}	21^{36}
Phosphorus	mg/dl	M&F	47	<.001	50	4.5	3.5	5.4	0.33	0.26	0.41	14.66	11.55	18.22	01^{00}	00^{16}	01^{44}
Total Bilirubin	mg/dl	M&F	13	.030	47	0.58	0.34	0.83	0.05	0	0.11	17.24	0.00	37.93	11^{20}	06^{08}	15^{00}
Albumin	gm/dl	M&F	47	<.001	34	4.54	3.71	5.38	0.08	0.03	0.12	3.52	1.32	5.28	18^{44}	16^{40}	21^{00}
Total Protein	gm/dl	M&F	47	<.001	36	7.61	6.90	8.31	0.14	0.08	0.21	3.67	2.10	5.51	15^{52}	13^{52}	17^{52}
Uric Acid	mg/dl	M&F	47	.040	35	5.22	3.21	7.24	0.04	0	0.09	1.53	0.00	3.44	19^{20}	14^{16}	01^{00}
Blood Urea Nitrogen	mg/dl	M&F	47	<.001	42	18	11	24	0.90	0.50	1.20	10.00	5.55	13.33	23^{00}	21^{36}	00^{16}
Glucose	mg/dl	M&F	47	<.001	29	97	85	109	4	3	6	8.24	6.18	12.37	06^{32}	04^{52}	08^{24}
LDH	W.U.	M&F	47	<.001	26	112	77	147	6	3	9	10.71	5.35	16.07	23^{52}	22^{04}	01^{20}
Alkaline Phosphatase	K.-A.U.	M&F	46	.033	37	18	0	37	0.47	0.03	0.91	5.22	0.33	10.11	20^{28}	15^{52}	00^{16}
SGOT	K.U.	M&F	13	<.001	60	25	13	38	5	3	7	40.00	24.00	56.00	13^{28}	12^{44}	14^{08}
Folate	ng/ml	M&F	12	.044	53	3.3	0.7	5.9	0.5	0.01	1.0	30.30	0.61	60.61	14^{36}	09^{36}	18^{16}
B. URINE																	
N-acetyl-β-glucosaminidase (NAG)	U/mgCr	M	15	.019	30	21.4	3.7	39.1	3.8	0.6	7.0	35.51	5.61	65.42	10^{28}	07^{20}	13^{40}
		F	19	.008	43	32.2	5.0	59.4	10.6	1.8	20.2	65.84	11.18	125.47	09^{28}	08^{16}	13^{52}
Sodium	mEq/hr	M	15	.003	39	9.2	5.6	12.7	2.5	0.8	4.2	54.35	17.39	91.30	20^{12}	16^{56}	22^{36}
		F	19	.009	33	6.3	3.1	9.6	1.4	0.3	2.5	44.44	9.52	79.36	19^{00}	16^{00}	23^{16}
Potassium	mEq/hr	M	15	<.001	33	3.3	1.5	5.1	1.0	0.7	1.5	60.61	42.42	90.91	16^{16}	13^{28}	18^{20}
		F	19	.049	33	2.2	0.7	3.7	0.5	0	1.0	45.45	0.00	90.91	14^{40}	10^{00}	21^{20}
Creatinine	gm/hr	M	15	<.001	38	84.2	58.3	110.0	13.0	8.7	18.2	30.88	20.66	43.23	21^{08}	19^{44}	23^{16}
		F	19	<.001	23	49.2	28.9	69.6	4.7	2.1	7.4	19.11	8.54	30.08	20^{20}	17^{36}	23^{36}

*PR - Percent of total variance due to circadian rhythm.
** Calculated Peak Time.
Rhythm evaluation by LSQ and cosinor analysis, rhythm detection $p < 0.05$.

B-5

Circadian Rhythm of Total White Blood Cell Count*



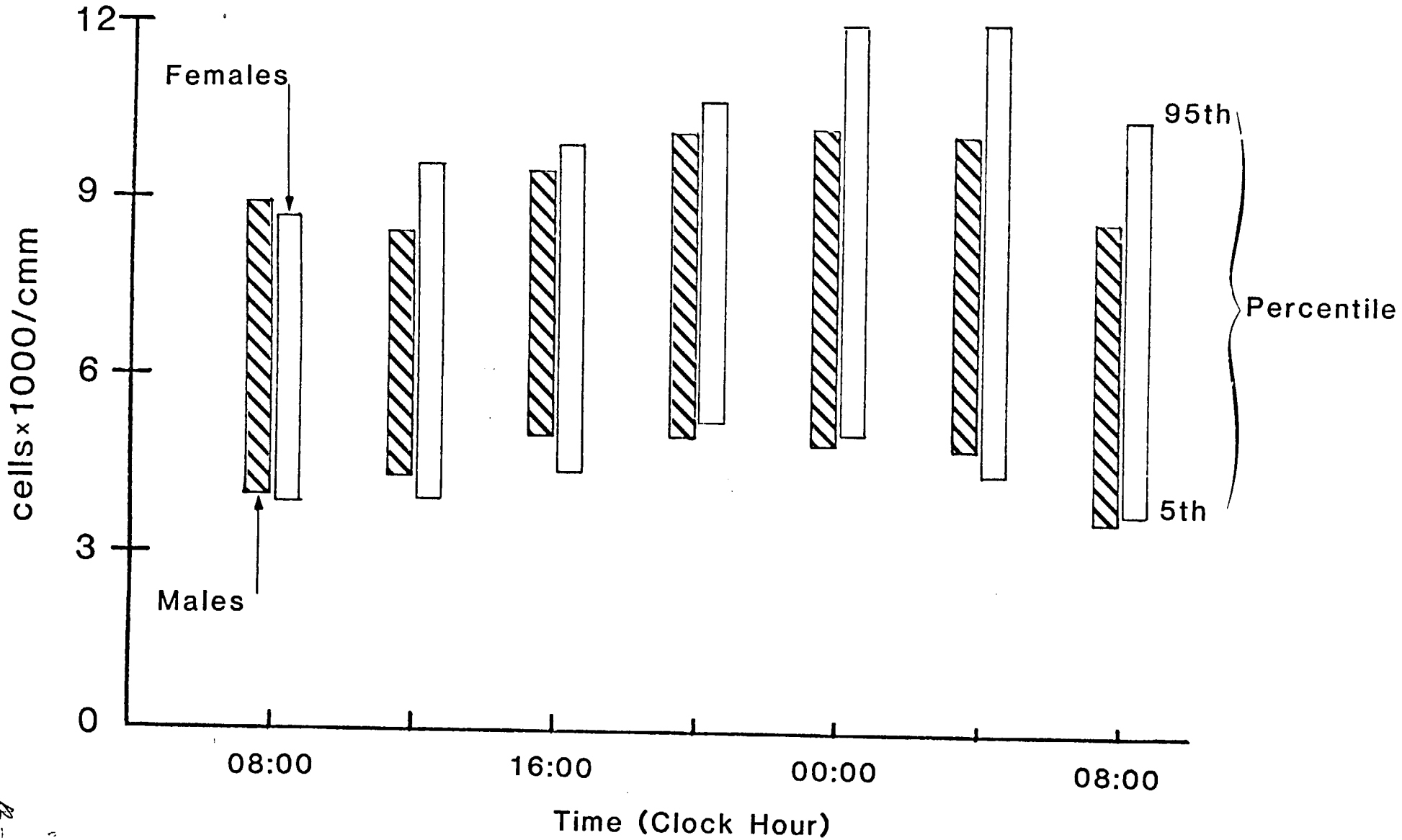


Units	No.	PR	P	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
cells×1000/cmm	150	64	<.001	7.1 4.2 10.0	0.69 0.59 0.78	-338 -329 -347

*150 Clinically Healthy Subjects: 71 Females, 79 Males

B-6

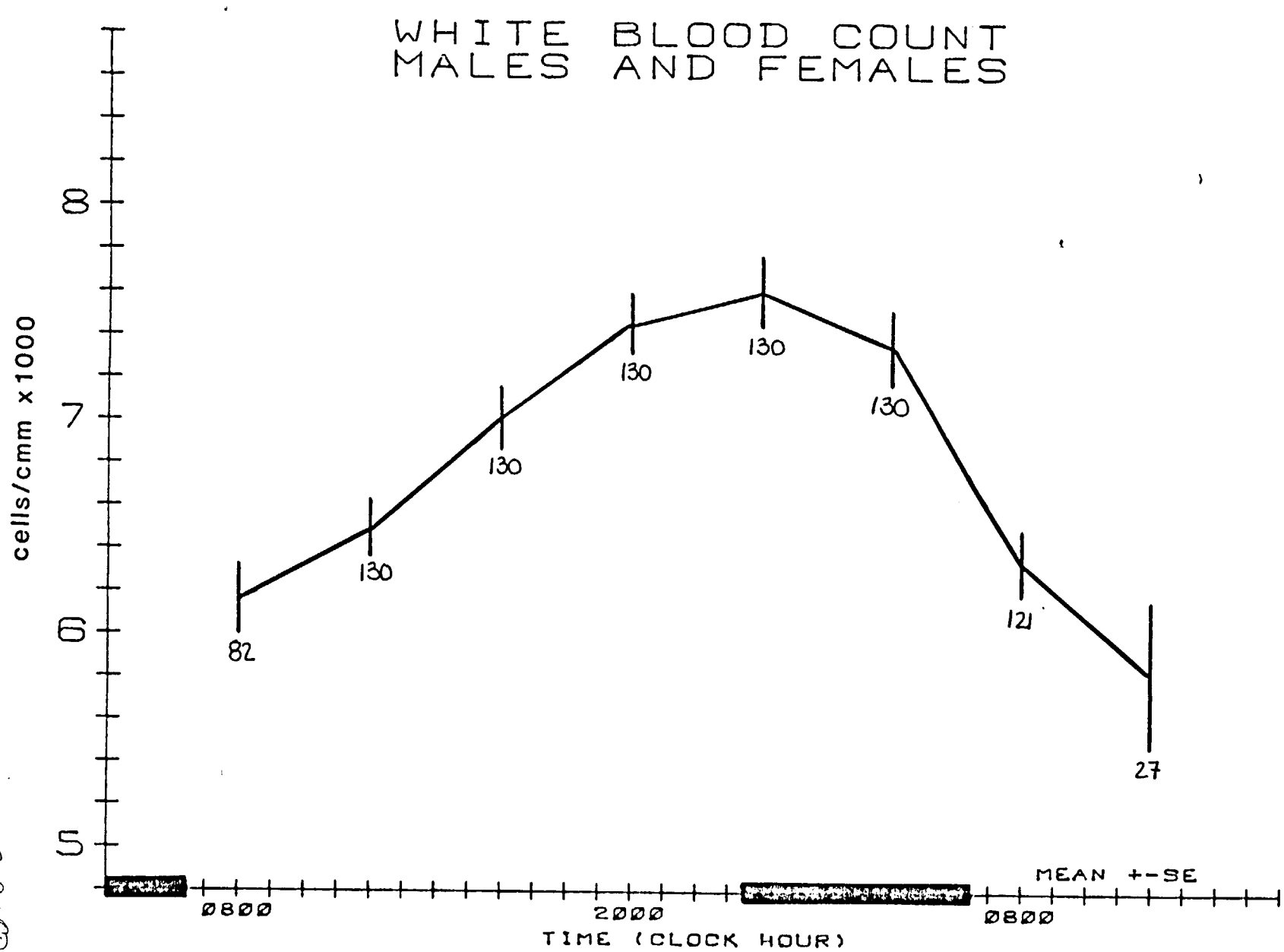
Total Number of Circulating White Blood Cells



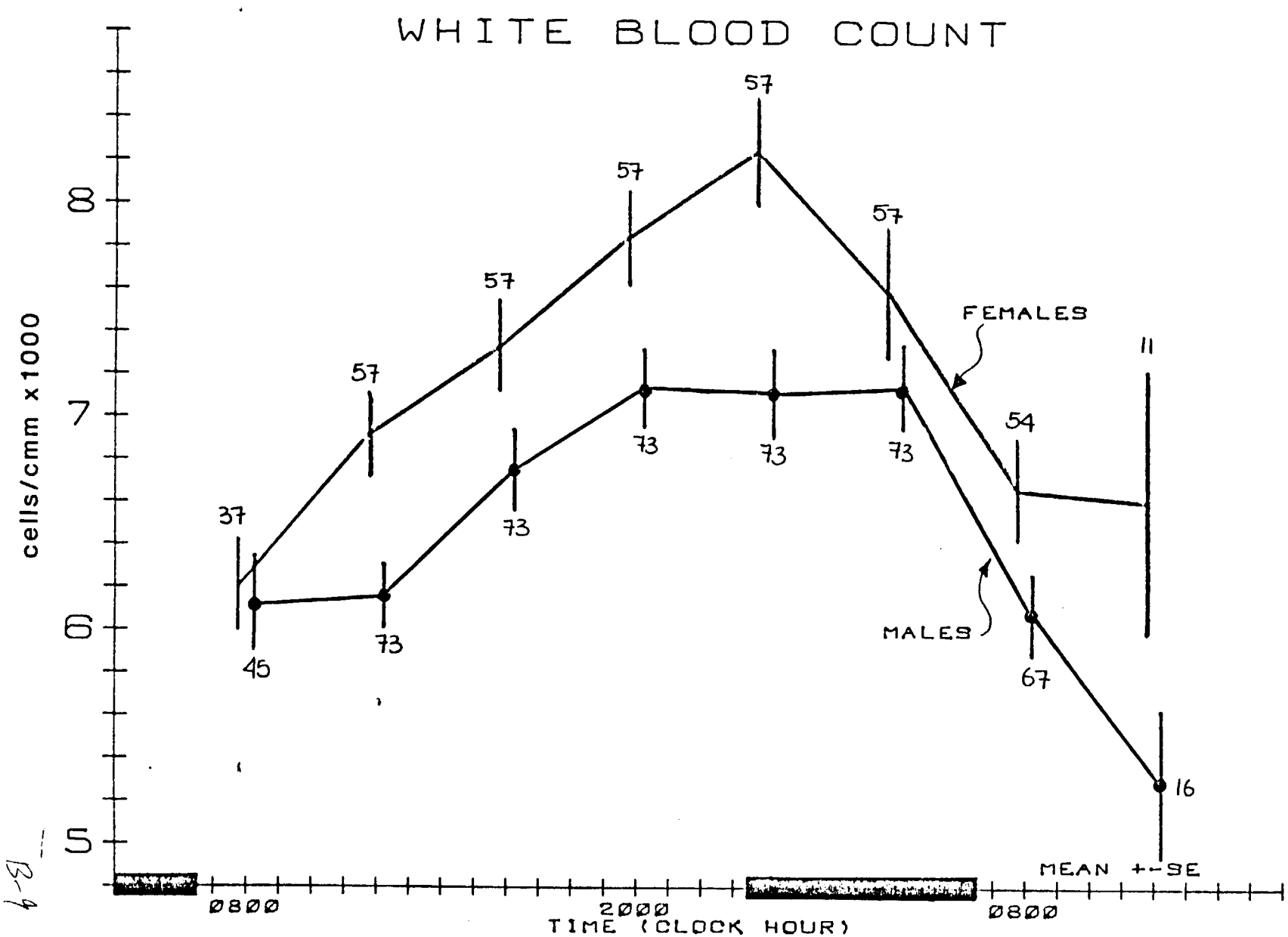
*expressed as 5th to 95th percentile

**150 Clinically Healthy Subjects (71 Females, 79 Males)

B-7

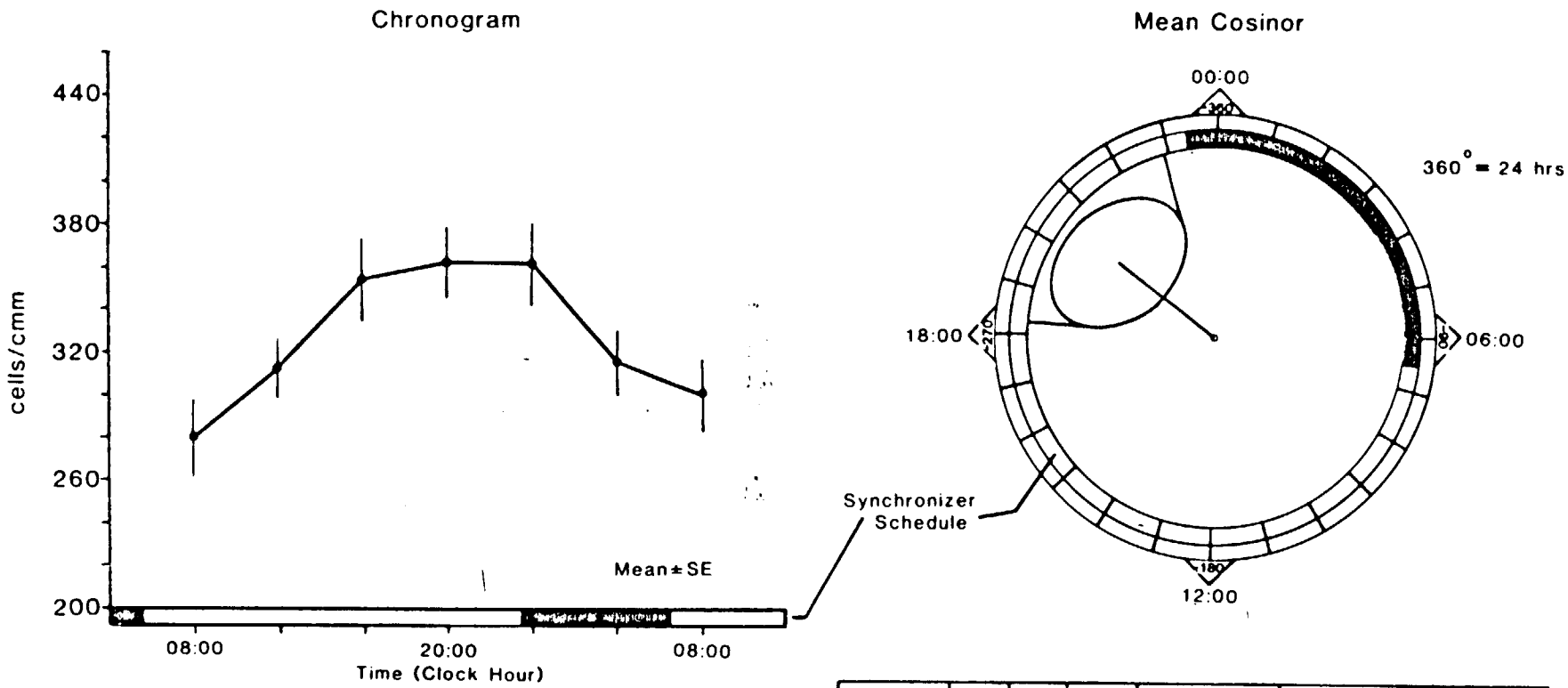

WHITE BLOOD COUNT
MALES AND FEMALES
cells/cmm x1000
8
7
6
5
82
130
130
130
130
130
121
27
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-8-02


WHITE BLOOD COUNT
cells/cmm x1000
8
7
6
5
57
57
57
57
57
37
73
73
73
73
73
45
73
FEMALES
MALES
54
11
67
16
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-4

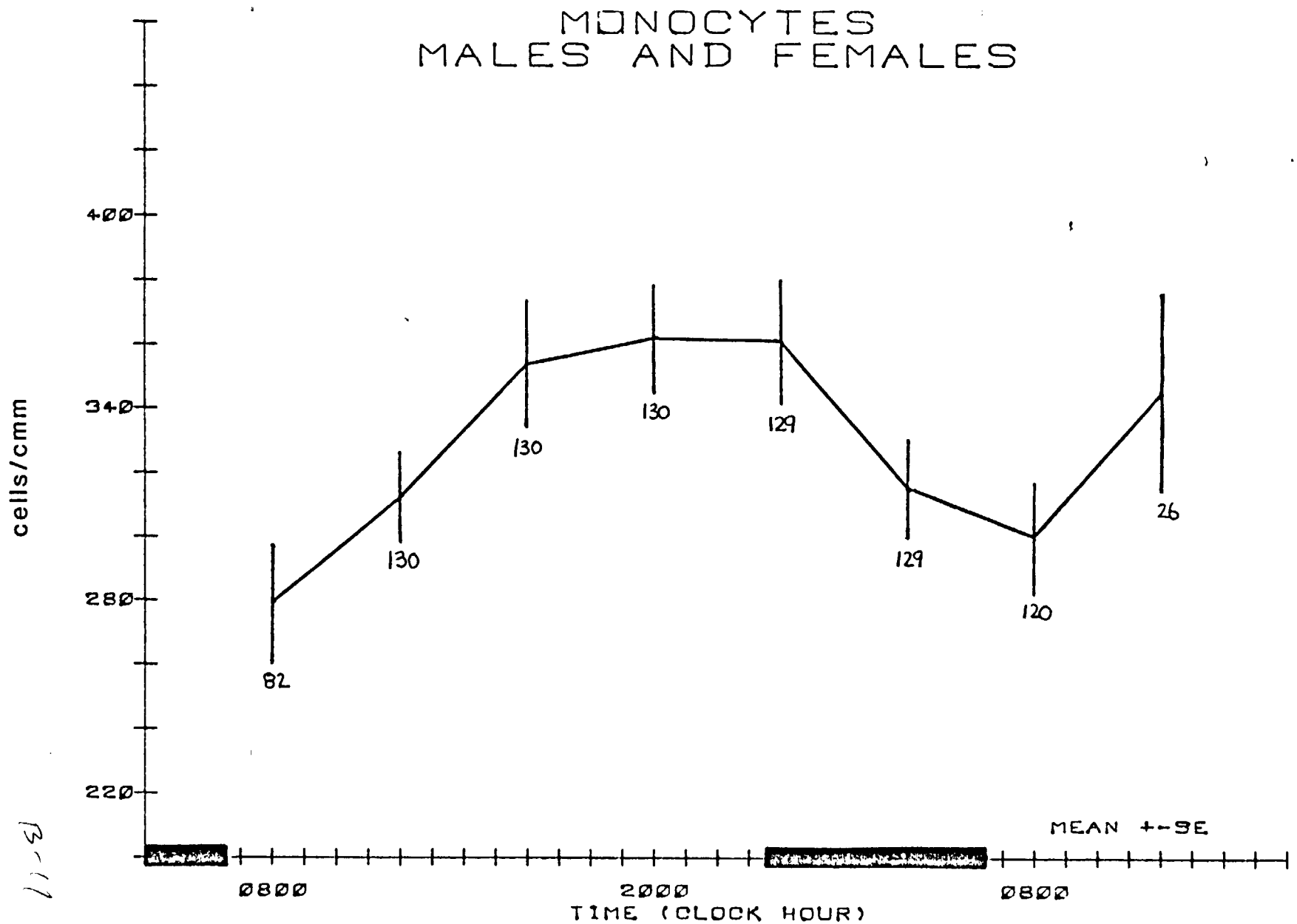
Circadian Rhythm in Number of Circulating Monocytes*



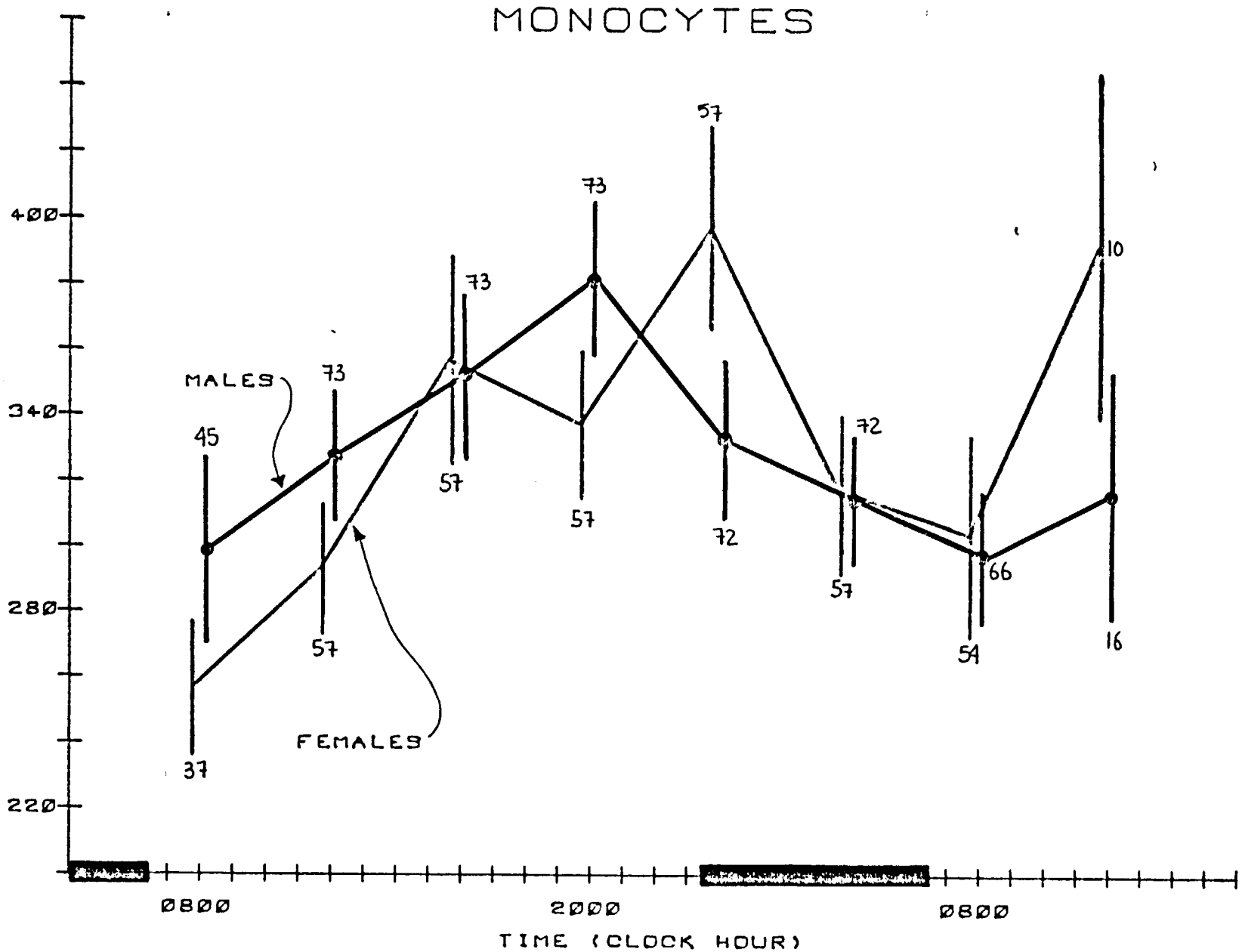
Units	No.	PR	P	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
cells/cmm	150	43	<.001	331 82 581	34 17 50	-308 -274 -344

*150 Clinically Healthy Subjects: 71 Females, 79 Males

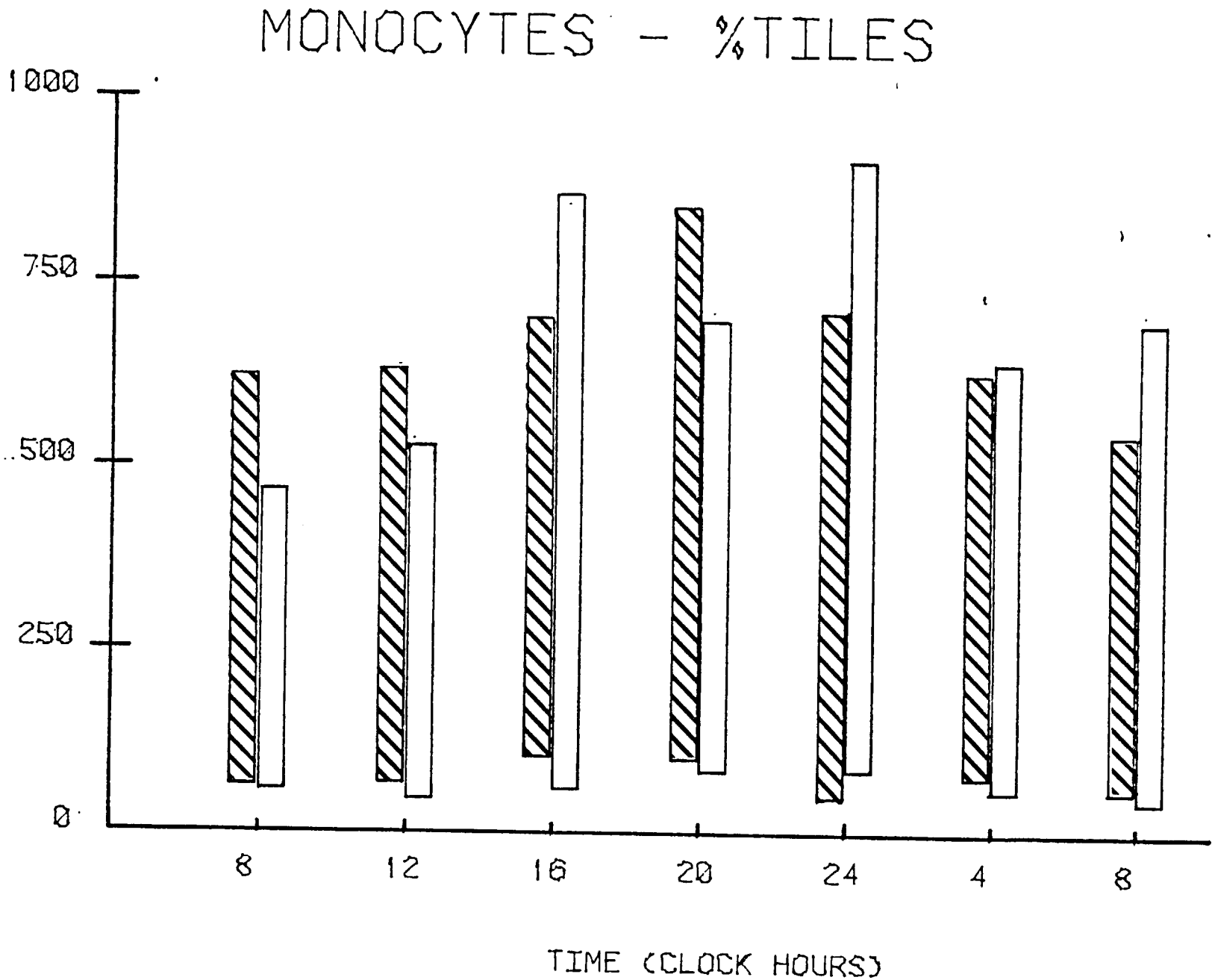
B-10

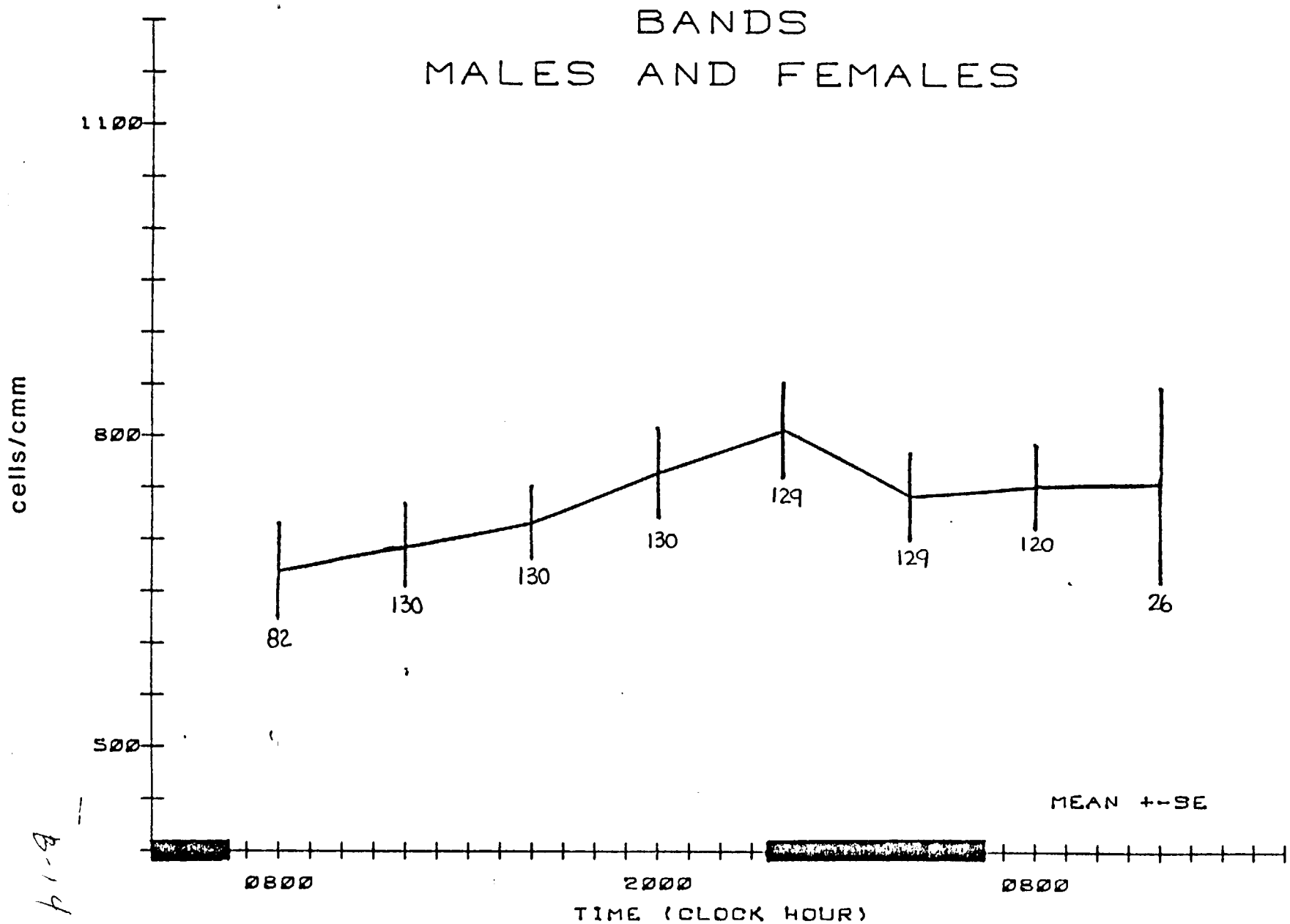

MONOCYTES
MALES AND FEMALES
cells/cmm
400
340
280
220
82
130
130
130
129
129
120
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-11

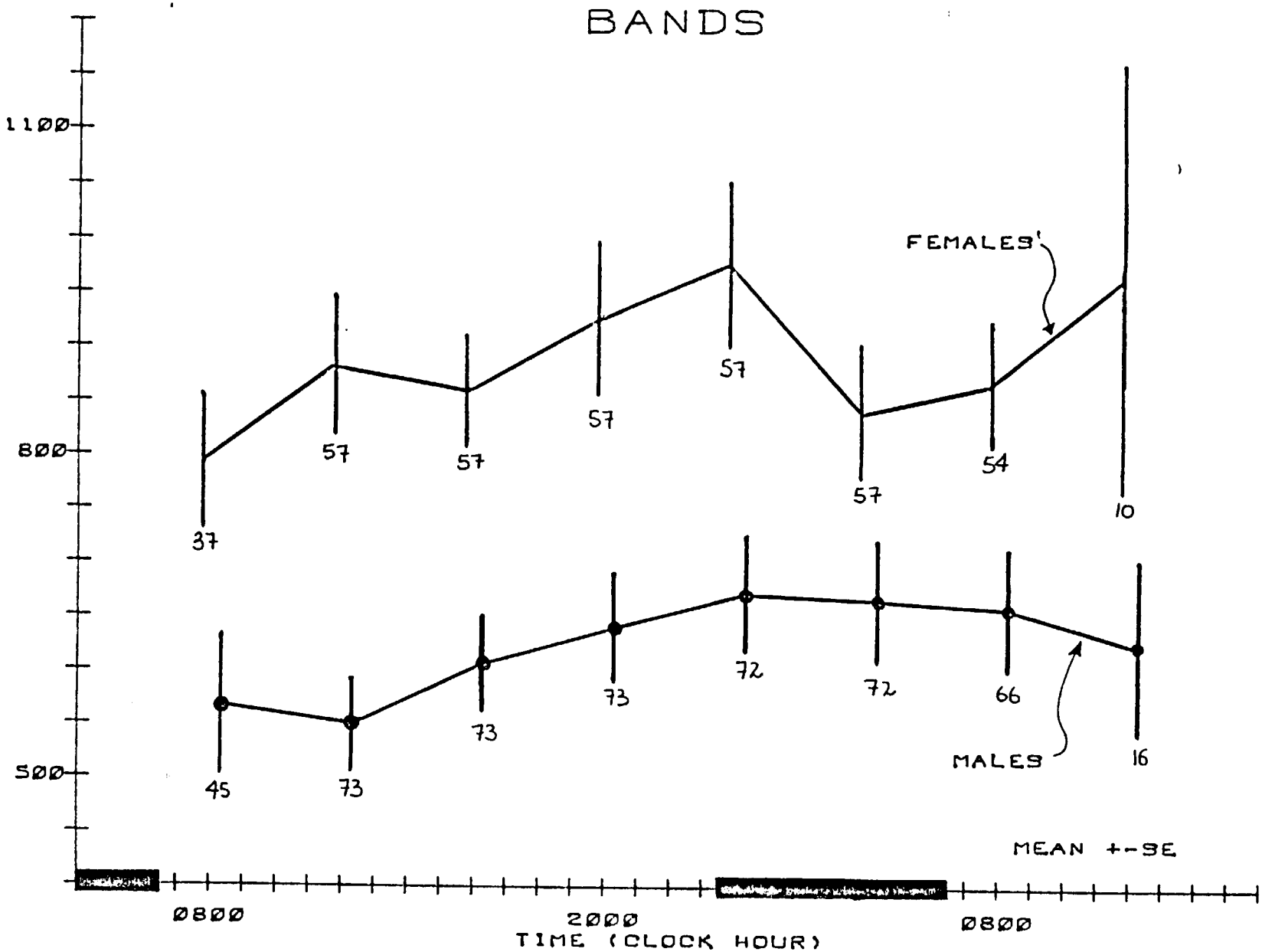

MONOCYTES
cells/cmm
400
340
280
220
MALES
FEMALES
45
37
73
57
73
57
73
57
57
72
72
57
66
54
10
16
0800
2000
0800
TIME (CLOCK HOUR)

B-12

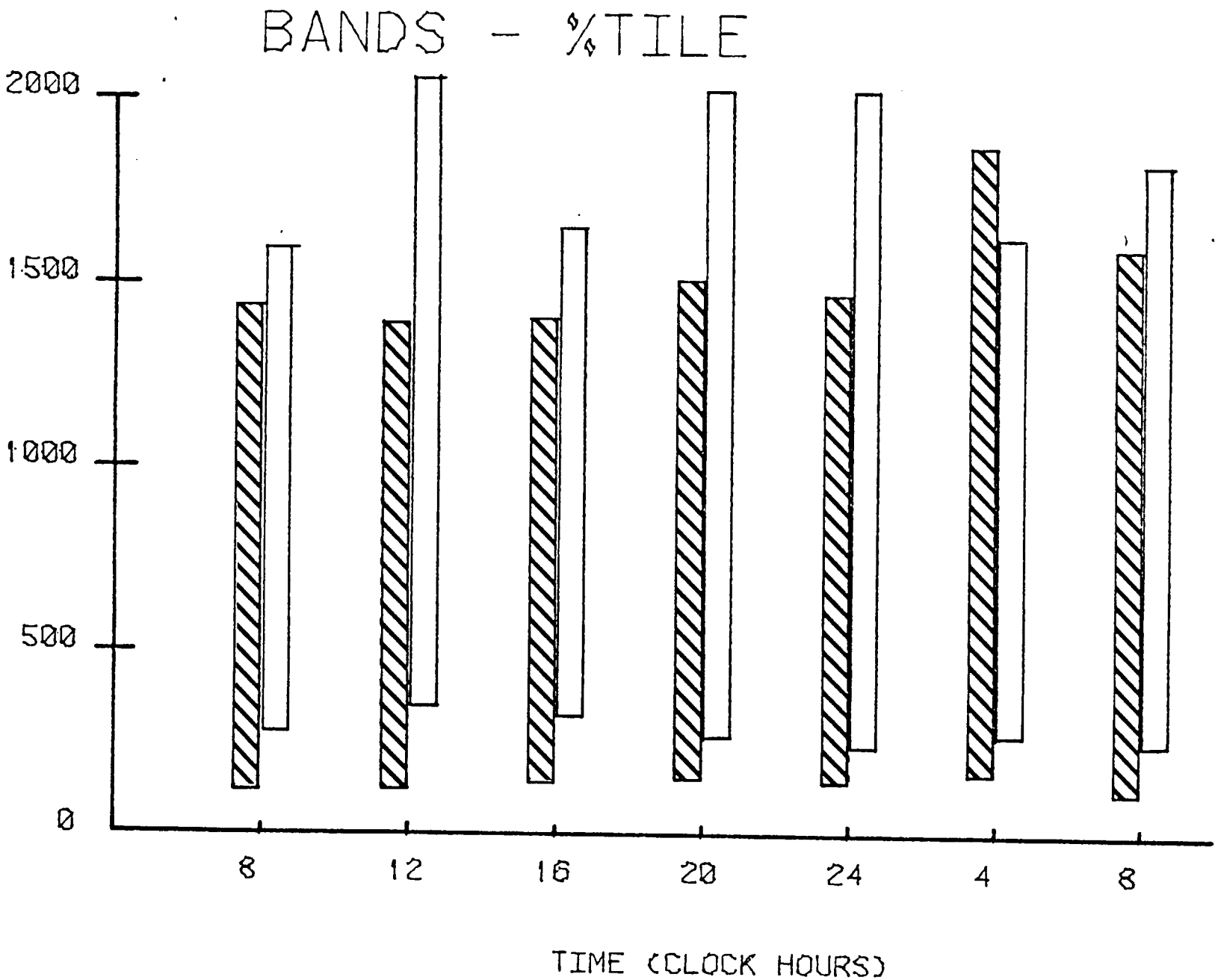

MONOCYTES - %TILES
1000
750
500
250
0
8
12
16
20
24
4
8
TIME (CLOCK HOURS)


BANDS
MALES AND FEMALES
cells/cmm
1100
800
500
82
130
130
130
129
129
120
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-14

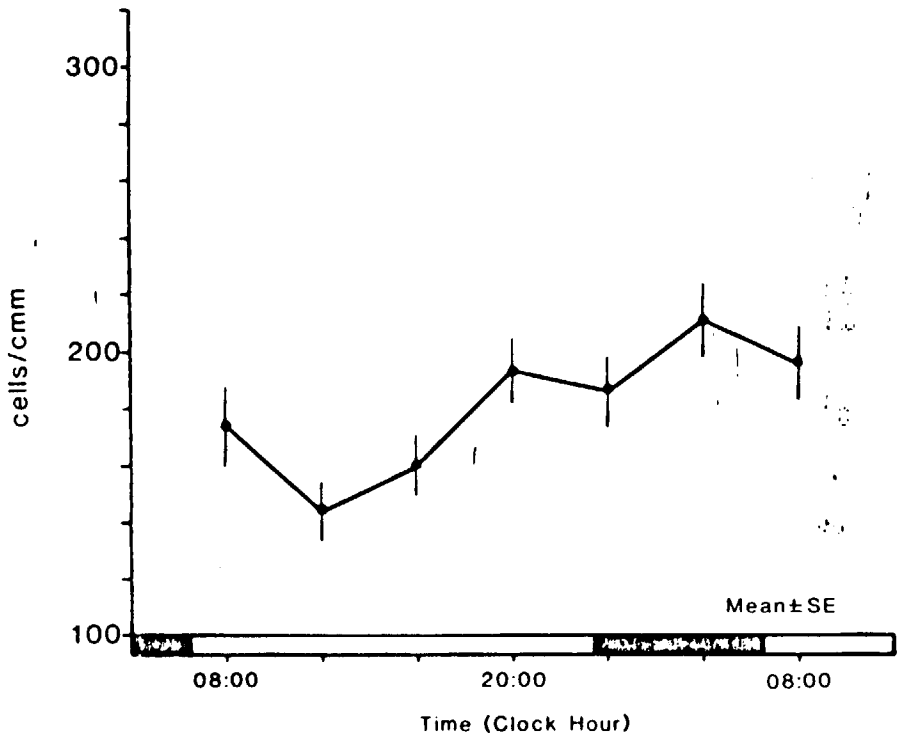

BANDS
cells/cmm
1100
800
500
FEMALES
MALES
37
57
57
57
57
57
54
10
45
73
73
73
72
72
66
16
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

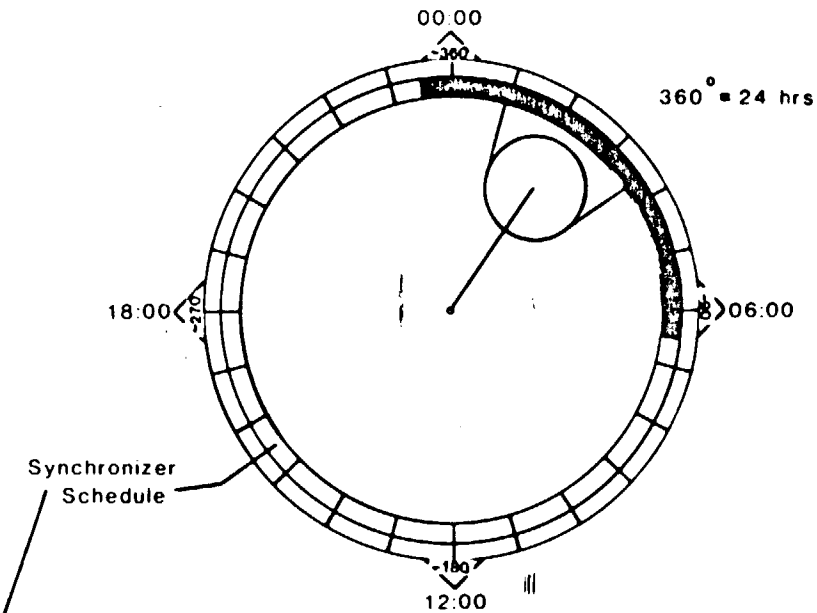
B-15


BANDS - %TILE
2000
1500
1000
500
0
8
12
16
20
24
4
8
TIME (CLOCK HOURS)

B-16

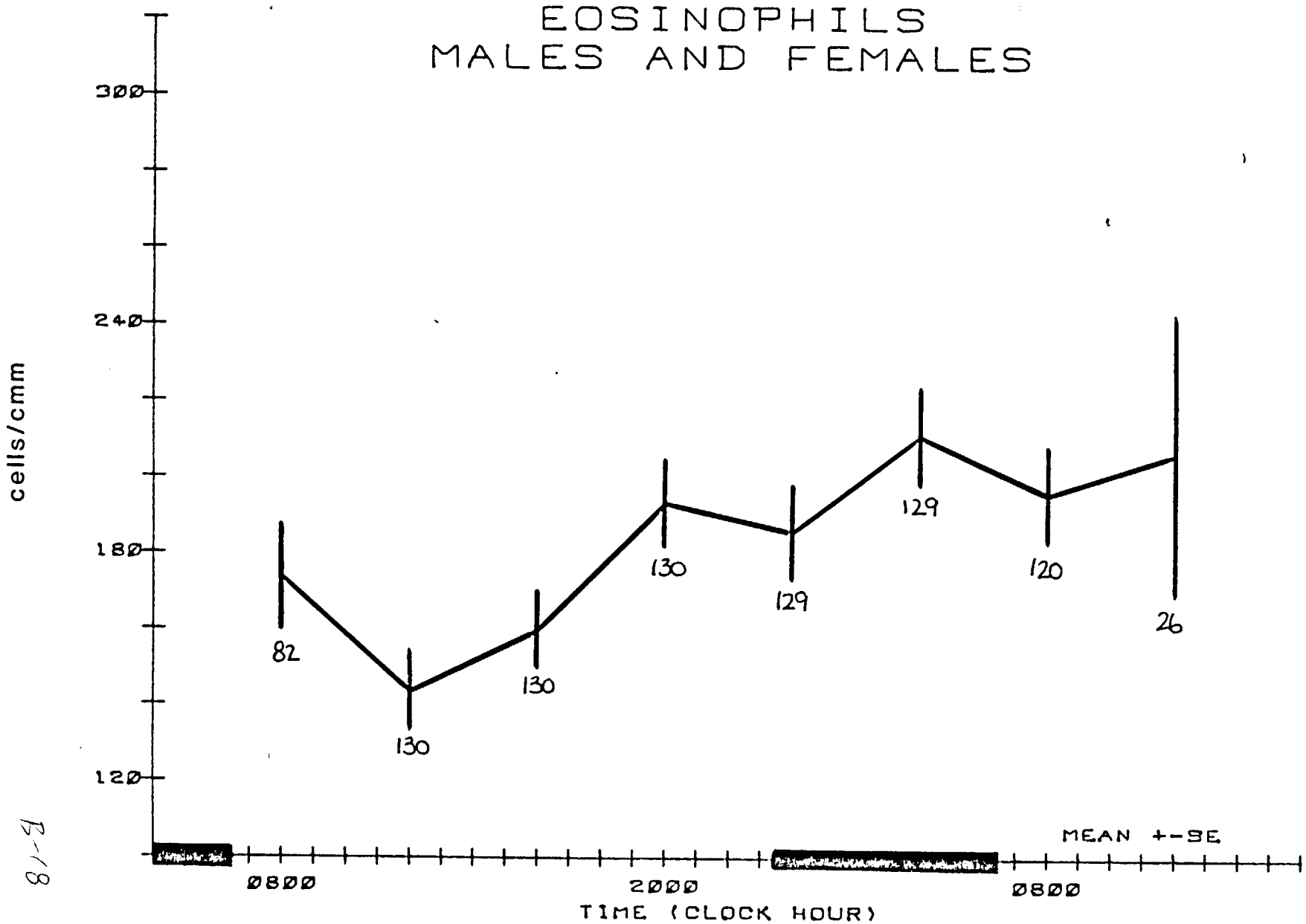
Circadian Rhythm in Number of Circulating Eosinophils*



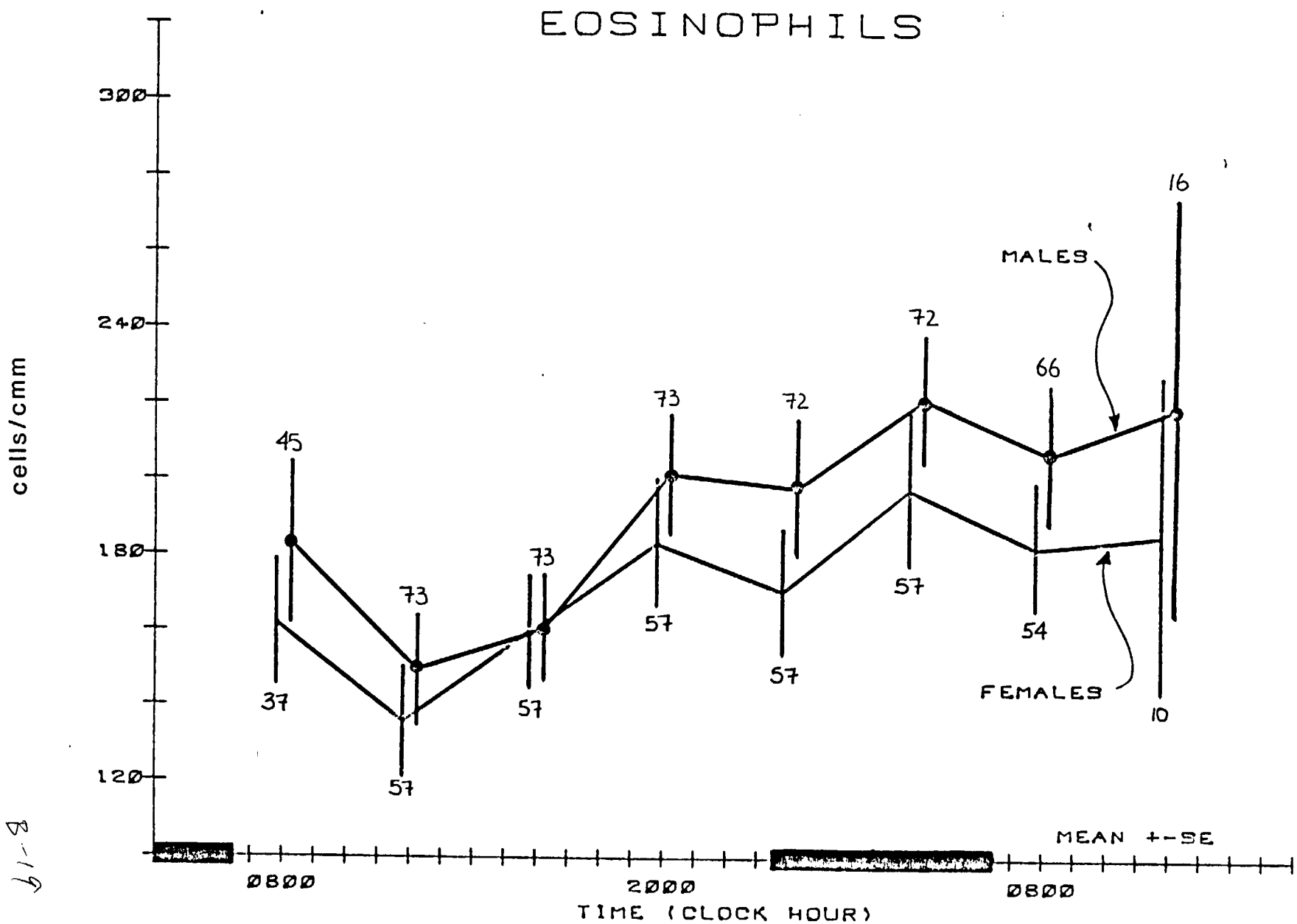


Units	No.	PR	P	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
cells/cmm	150	38	<001	189 0 404	29 18 40	-33 -14 -53

*150 Clinically Healthy Subjects: 71 Females, 79 Males

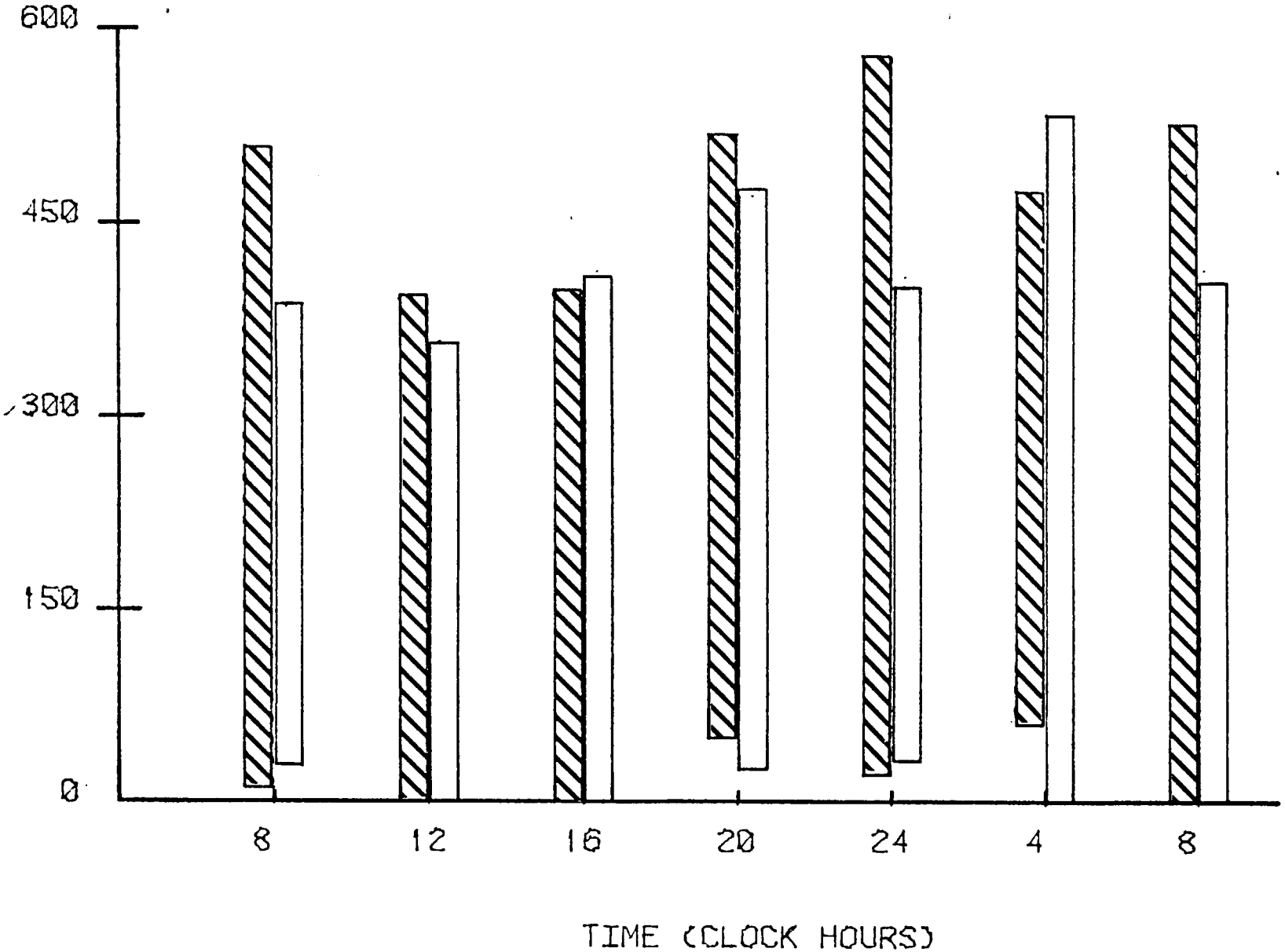

EOSINOPHILS
MALES AND FEMALES
cells/cmm
300
240
180
120
82
130
130
130
129
129
120
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-18


EOSINOPHILS
cells/cmm
300
240
180
120
45
37
73
57
73
57
73
57
72
57
72
57
66
54
16
10
MALES
FEMALES
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

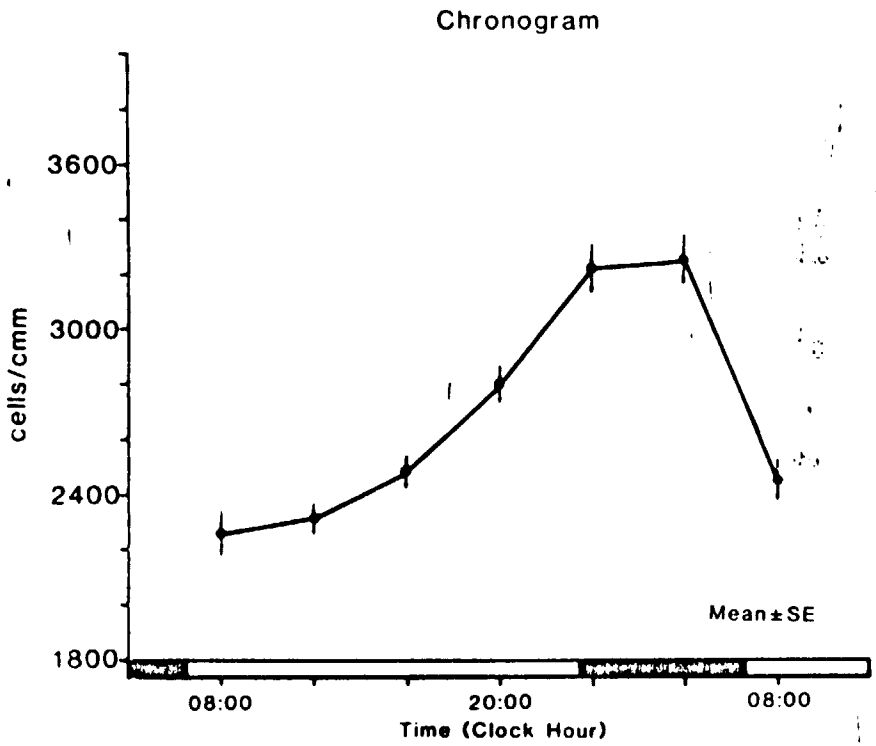
B-19

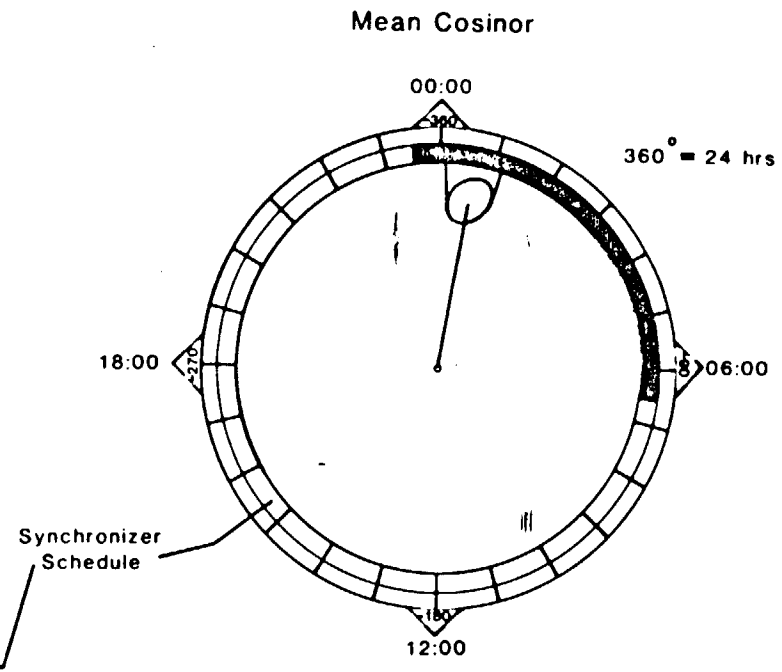
EOSINOPHILS - %TILES



B-20

Circadian Rhythm in Number of Circulating Lymphocytes*



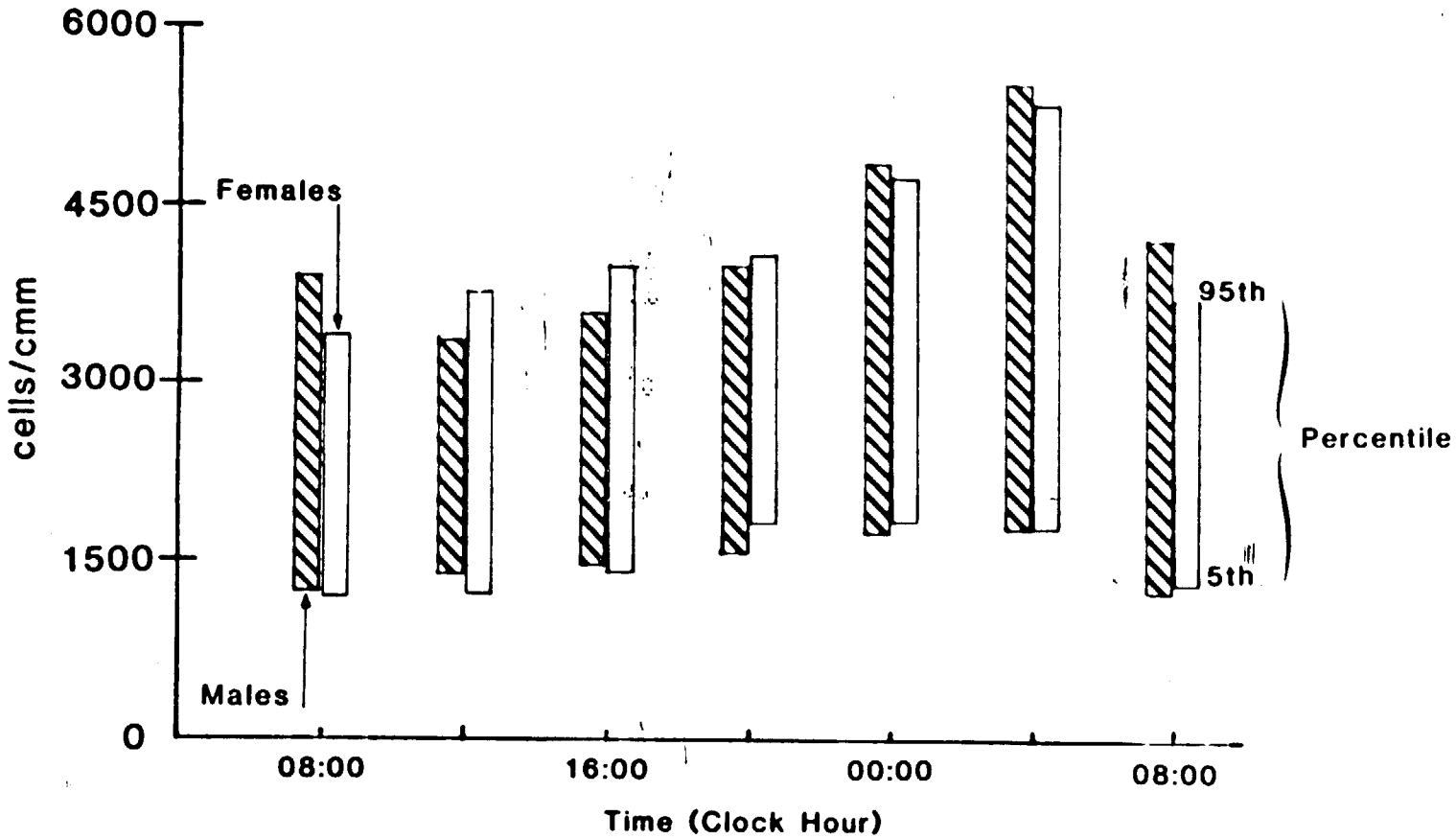


Units	No.	PR	p	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
cells/cmm	150	59	<.001	2784 1519 4049	483 416 551	-9 -1 -17

*150 Clinically Healthy Subjects: 71 Females, 79 Males

B-21 N

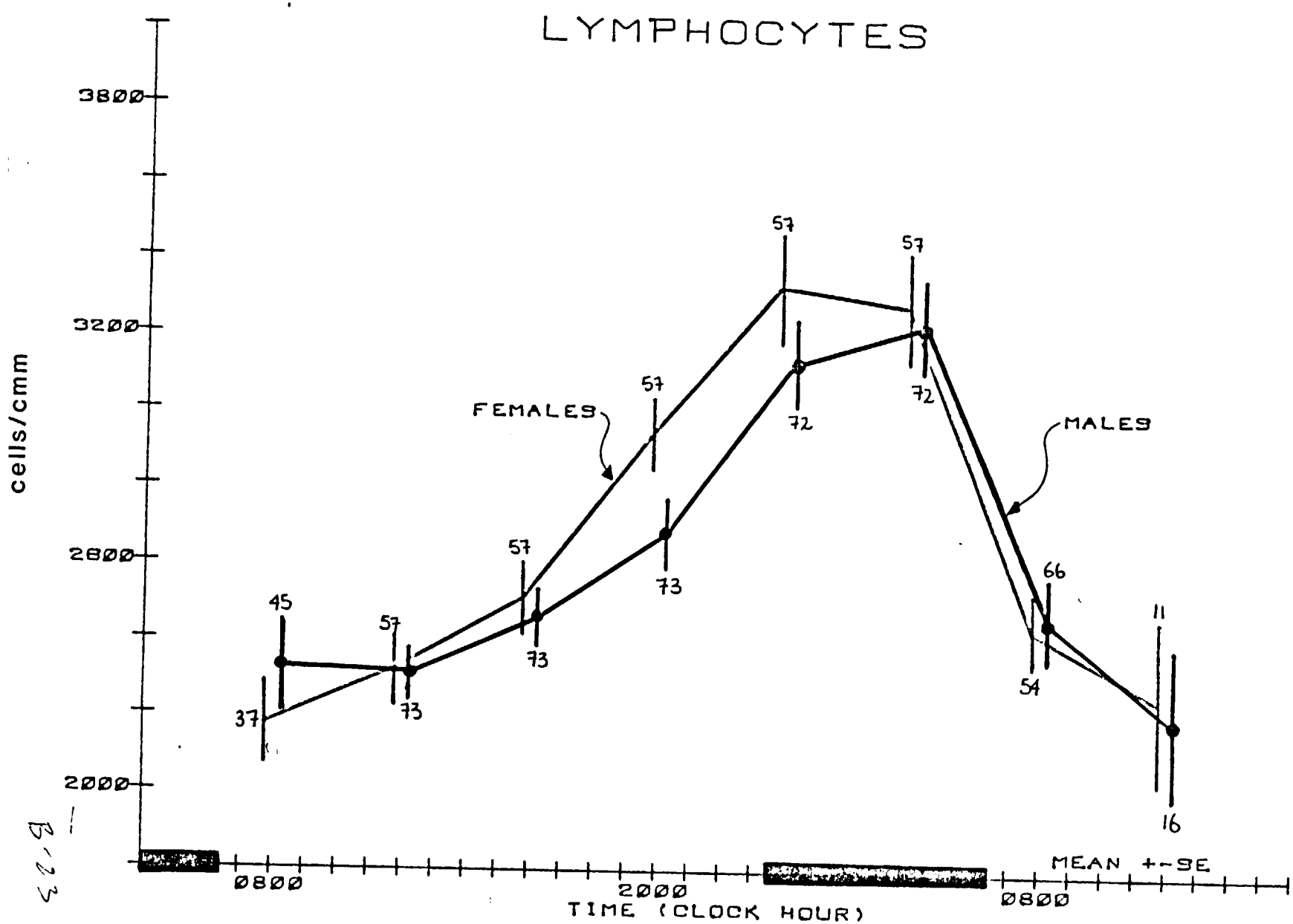
Circadian Variation of Usual Range*
in Number of Circulating Lymphocytes**



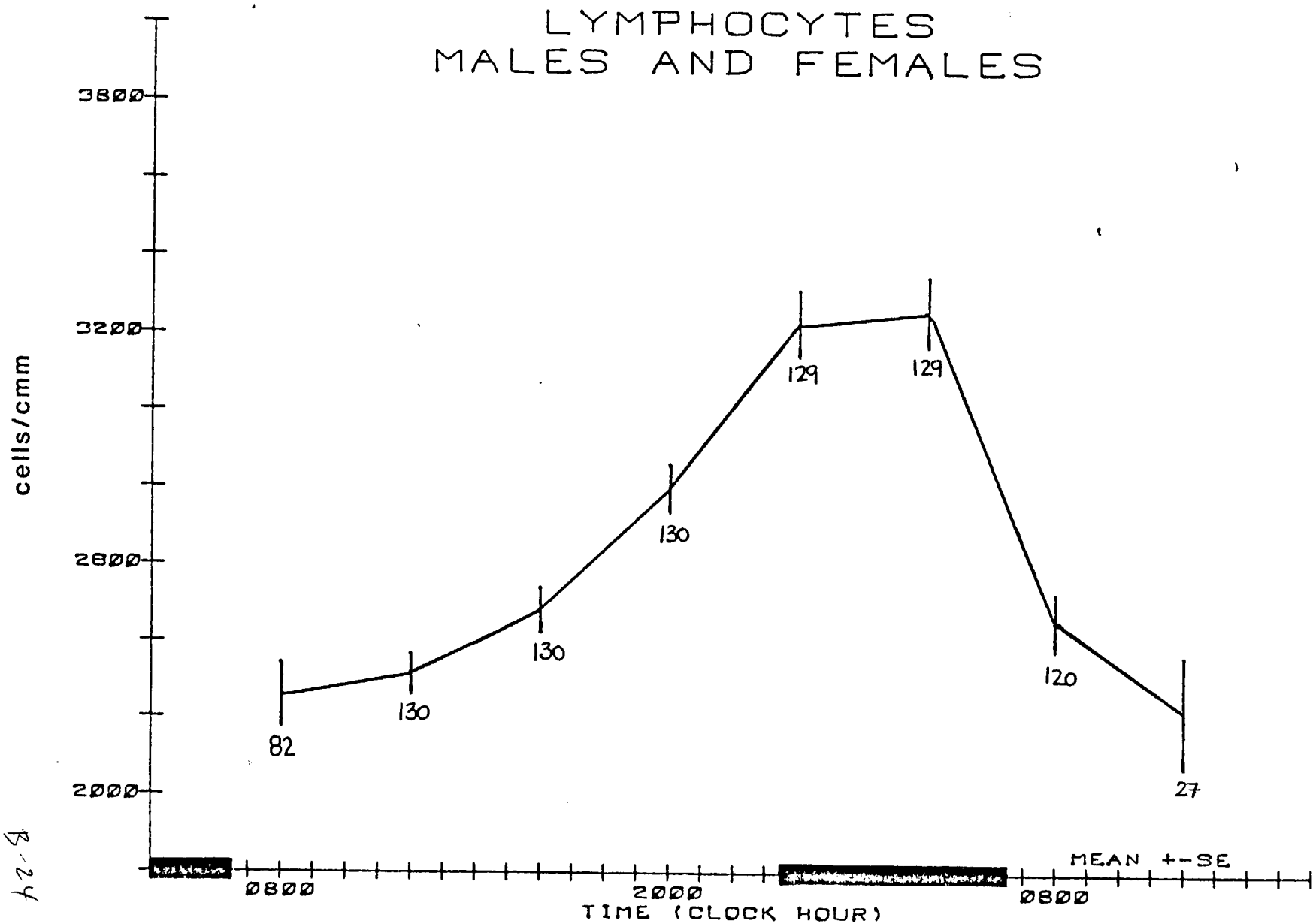
*expressed as 5th to 95th percentile

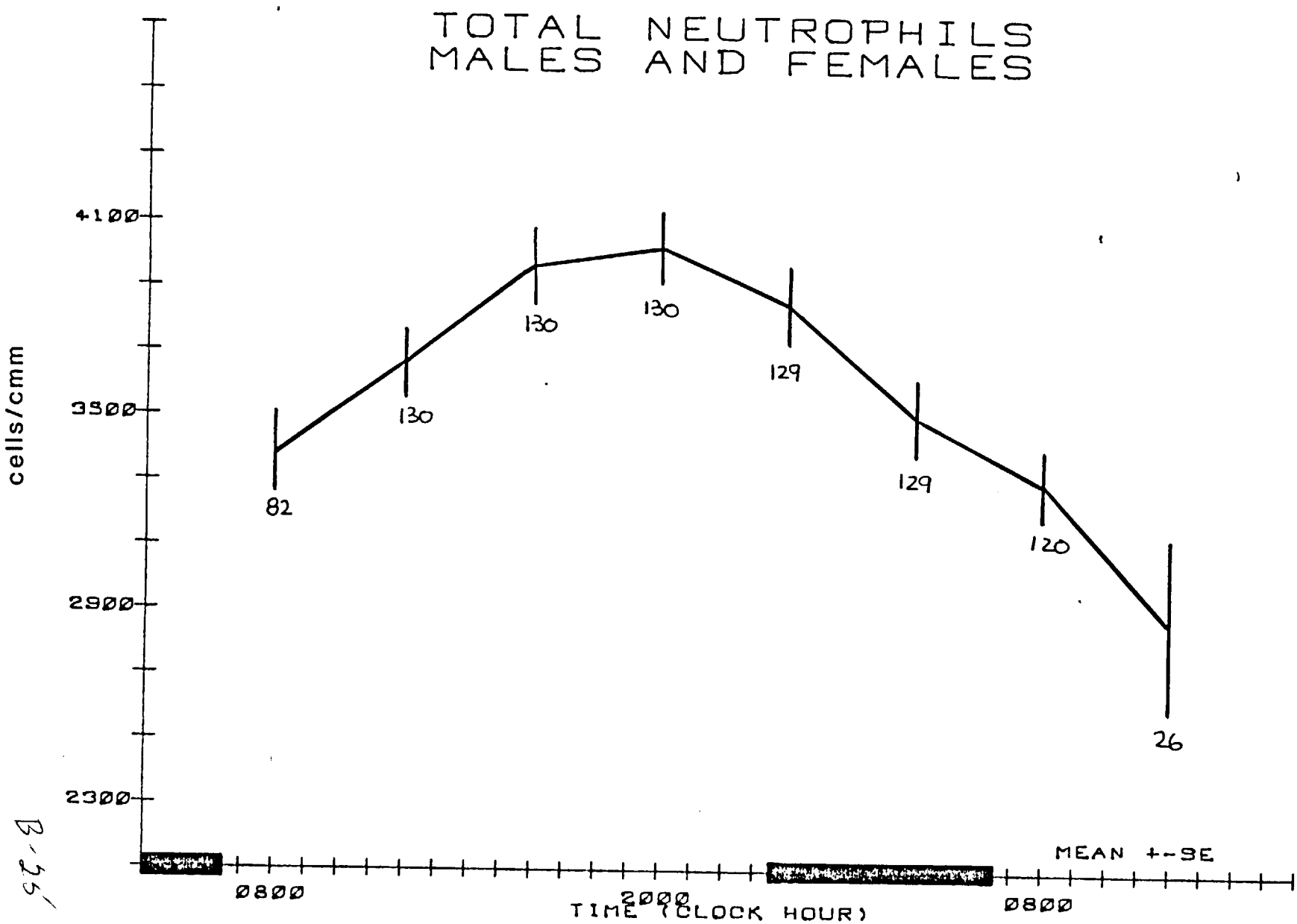
**150 Clinically Healthy Subjects (71 Females, 79 Males)

B-22

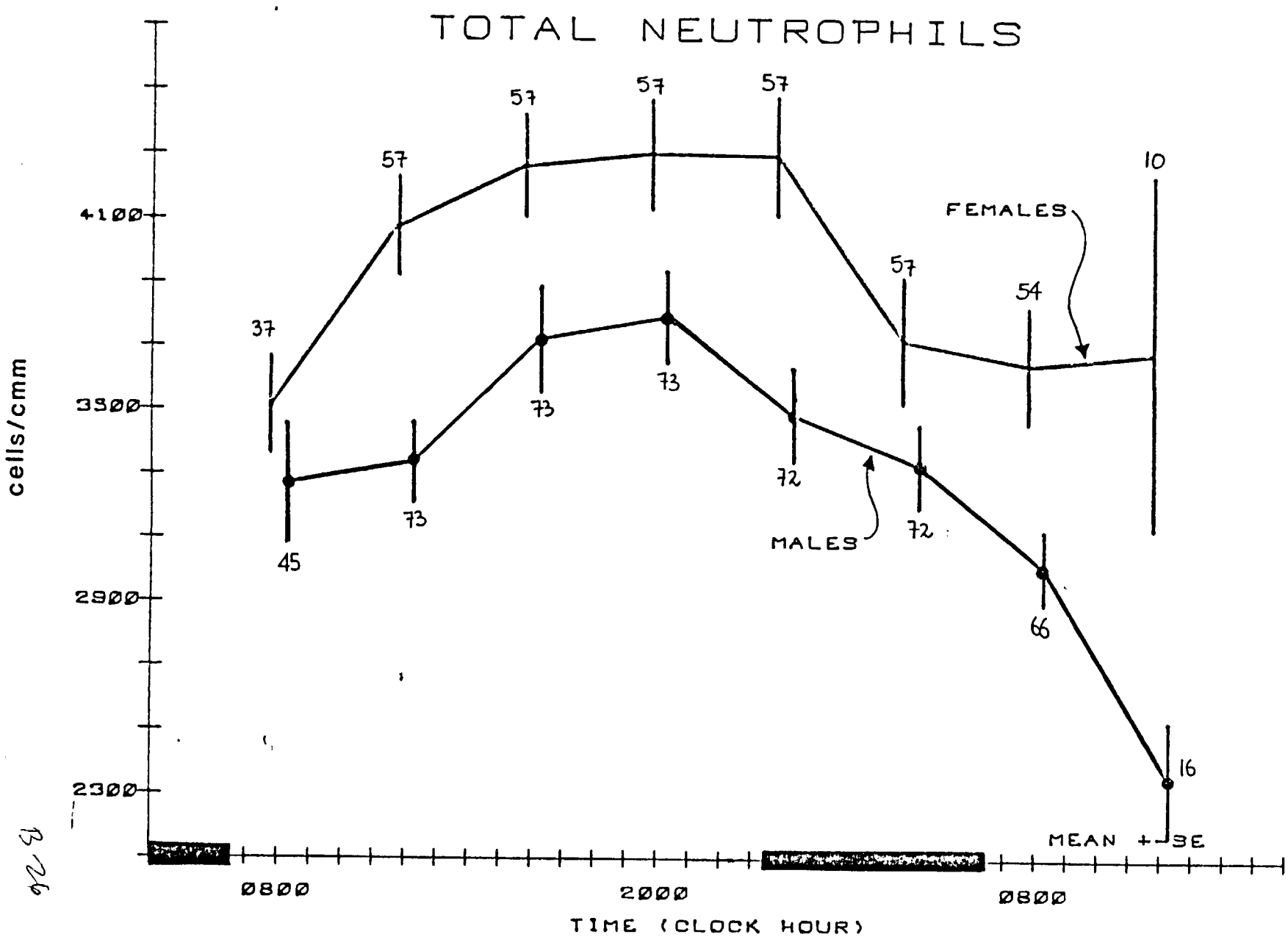

LYMPHOCYTES
cells/cmm
3800
3200
2800
2000
FEMALES
MALES
45
37
57
73
57
73
57
73
57
72
57
72
66
54
11
16
0800
2000
0800
TIME (CLOCK HOUR)
MEAN +-SE

B-23


LYMPHOCYTES
MALES AND FEMALES
cells/cmm
3800
3200
2800
2000
82
130
130
130
129
129
120
27
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

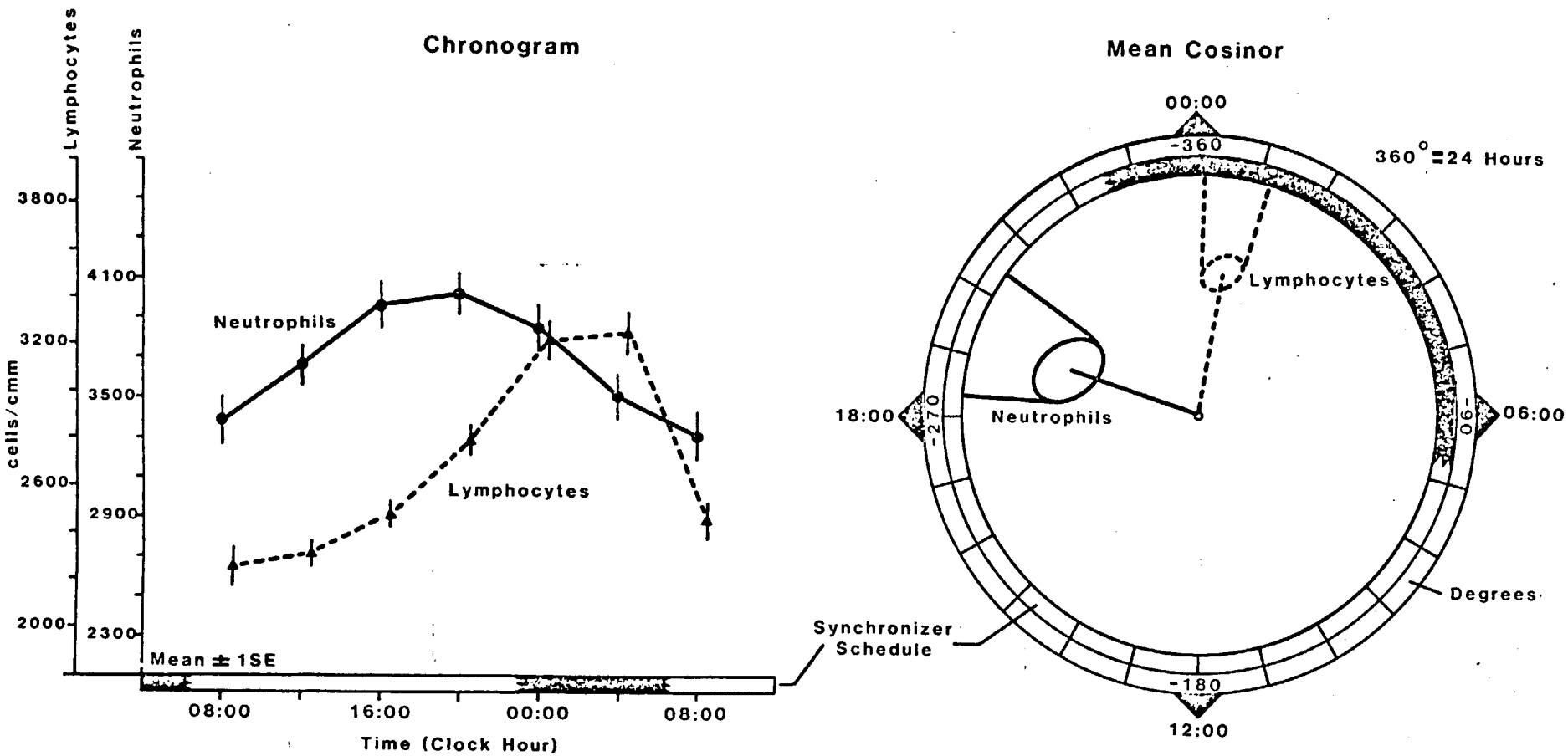

TOTAL NEUTROPHILS
MALES AND FEMALES
cells/cmm
4100
3500
2900
2300
82
130
130
130
129
129
120
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-35

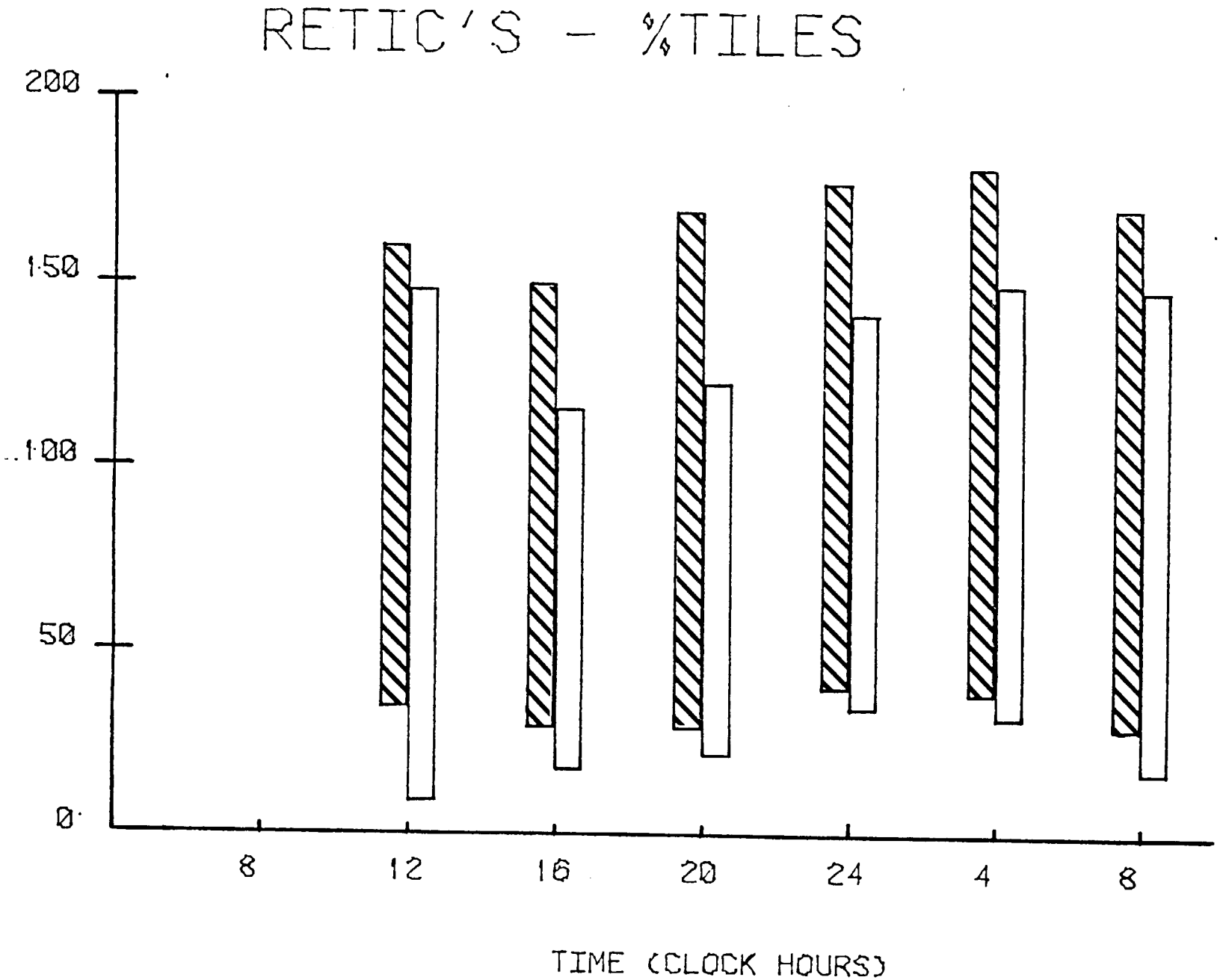

TOTAL NEUTROPHILS
cells/cmm
4100
3500
2900
2300
FEMALES
MALES
MEAN +- SE
0800
2000
0800
TIME (CLOCK HOUR)
37
57
57
57
57
57
54
10
45
73
73
73
72
72
66
16

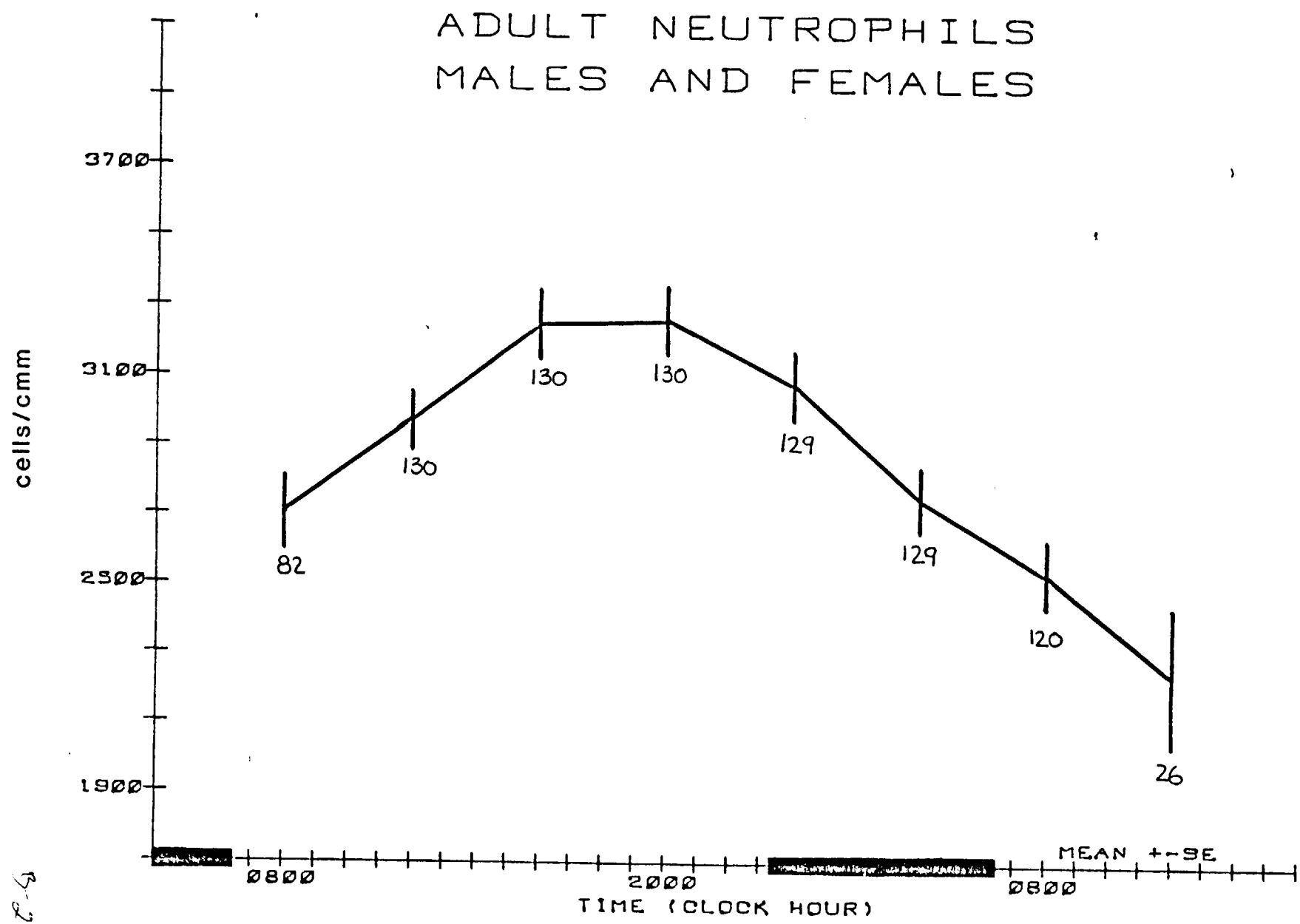
B 26

Circadian Rhythm of Circulating Neutrophils and Lymphocytes in Clinically Healthy Subjects

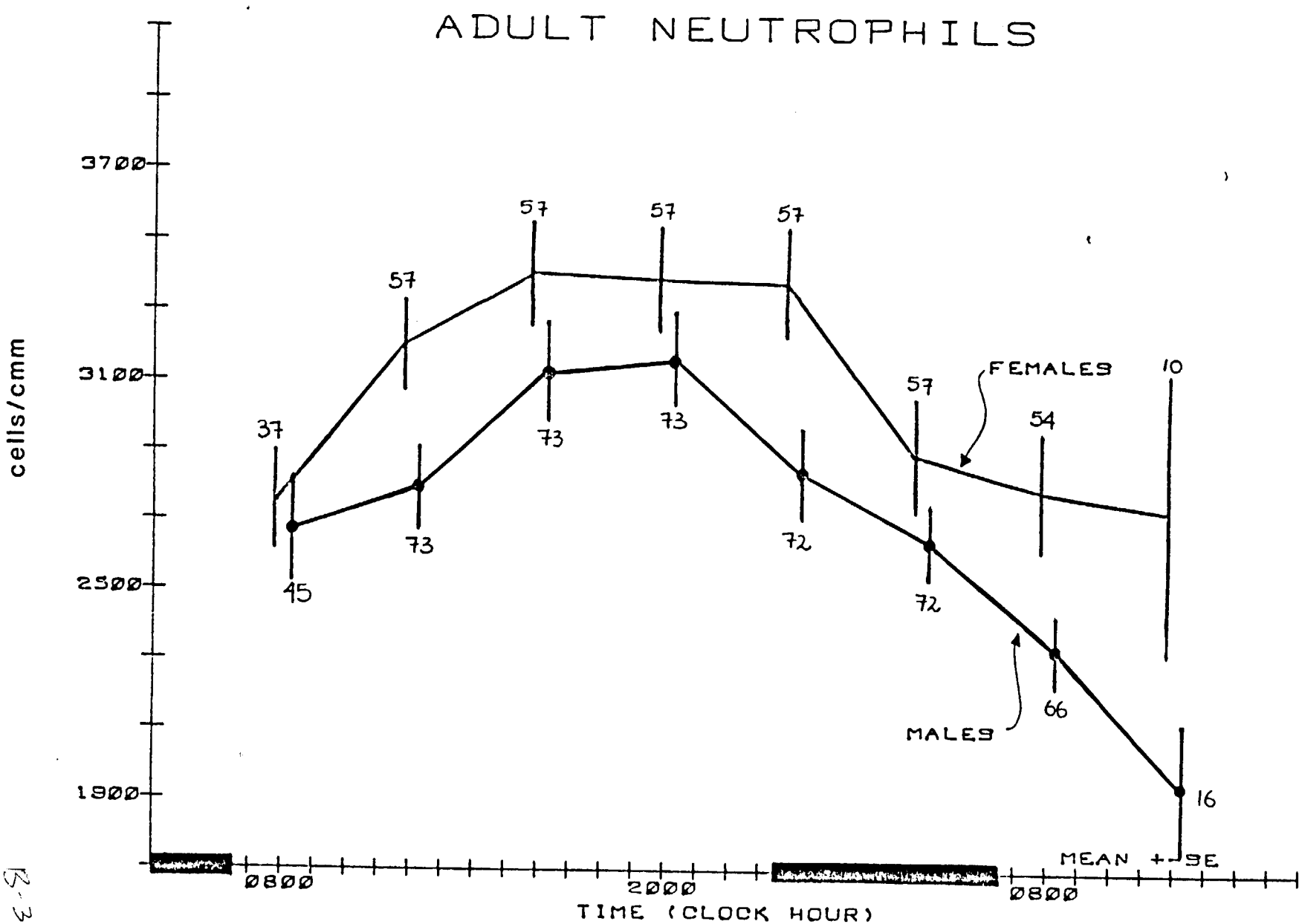


B-27

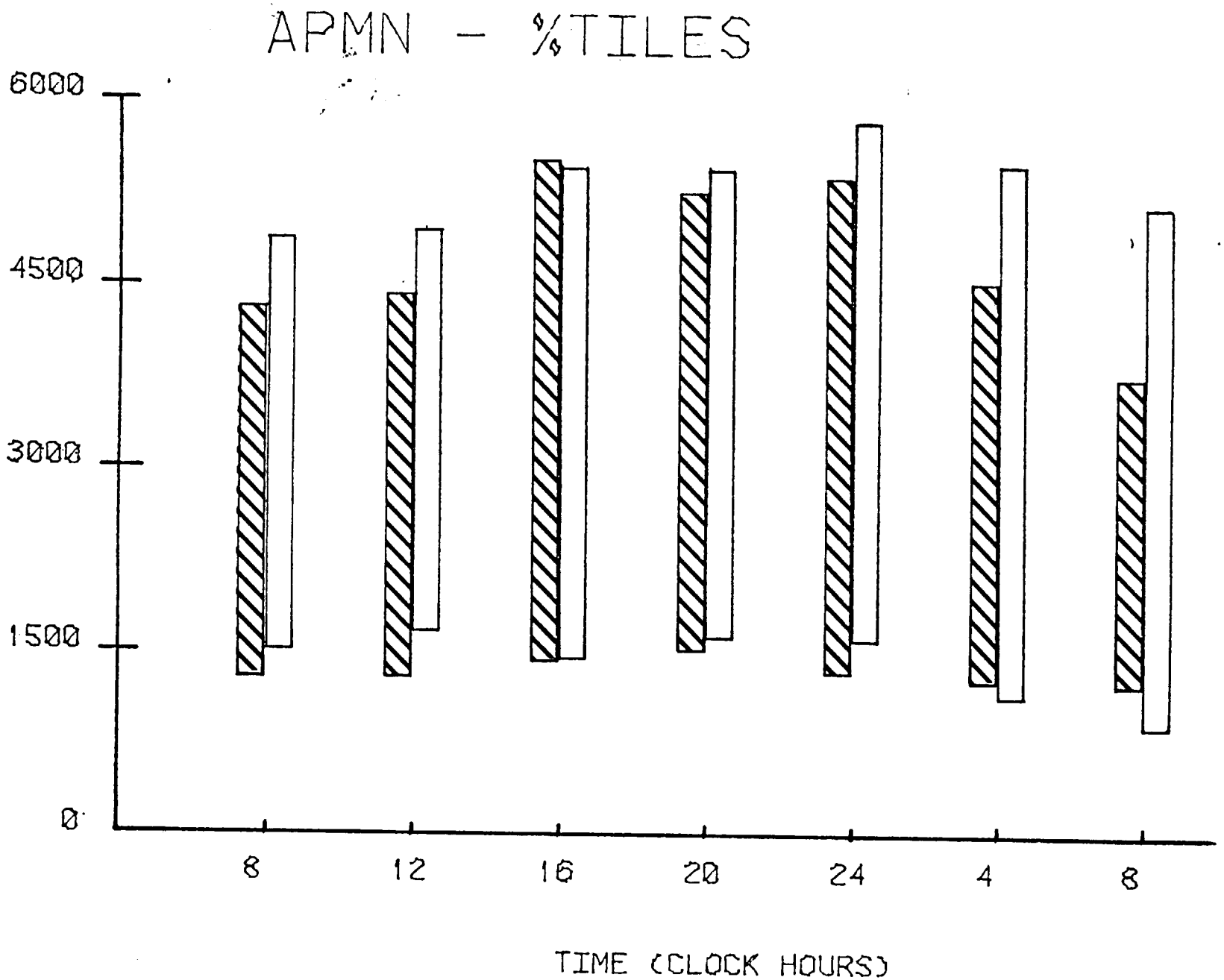

RETIC'S - %TILES
200
150
100
50
0
8
12
16
20
24
4
8
TIME (CLOCK HOURS)


ADULT NEUTROPHILS
MALES AND FEMALES
cells/cmm
3700
3100
2500
1900
82
130
130
130
129
129
120
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

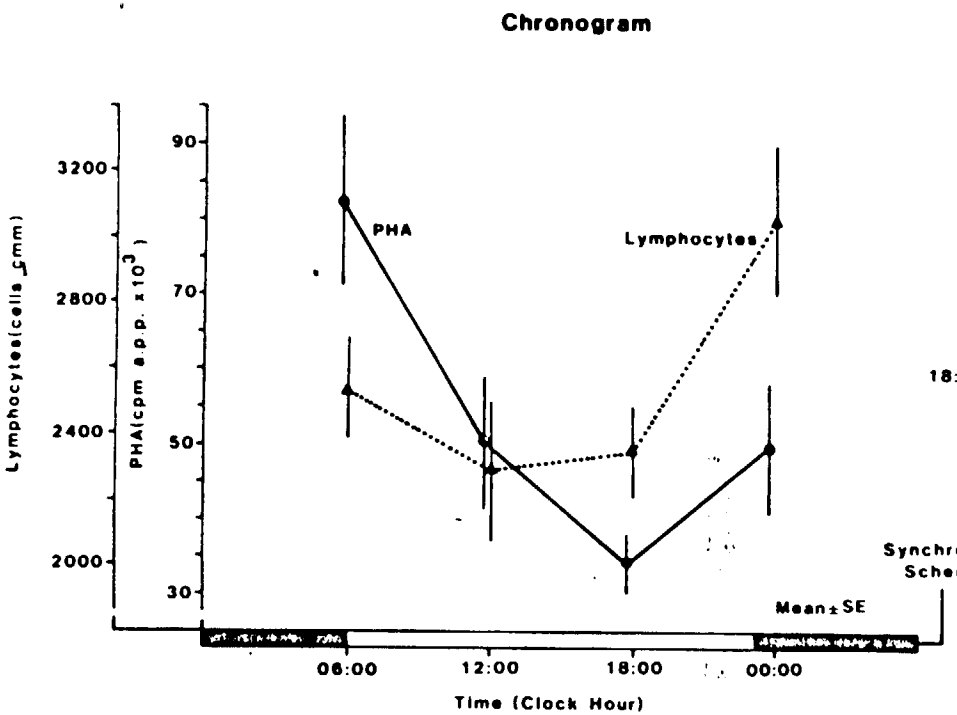
B-24

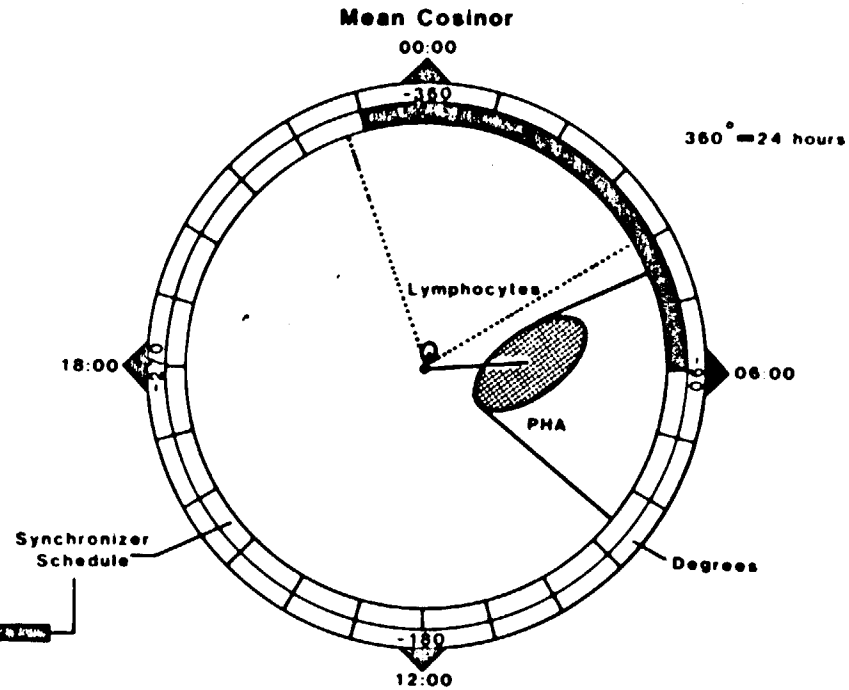

ADULT NEUTROPHILS
cells/cmm
3700
3100
2500
1900
57
57
57
57
57
54
10
37
45
73
73
73
72
72
66
16
FEMALES
MALES
MEAN +- SE
0800
2000
0800
TIME (CLOCK HOUR)

B-30


APMN - %TILES
6000
4500
3000
1500
0
8
12
16
20
24
4
8
TIME (CLOCK HOURS)

Circadian Rhythm in Number and *in vitro* Responsiveness of Human Lymphocytes* to Phytohemagglutinin (PHA)**





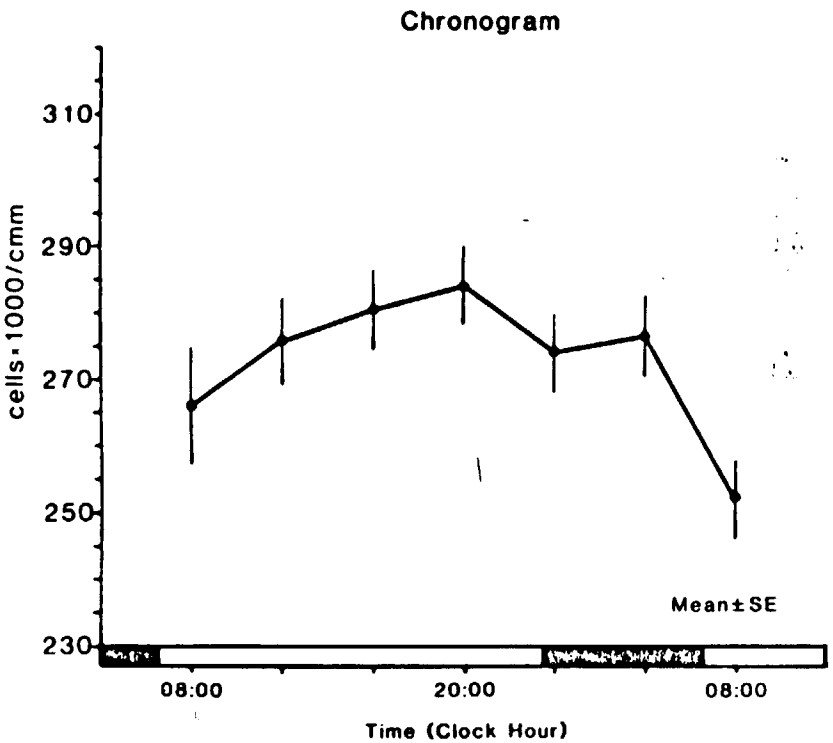
* 9 clinically healthy subjects (5 males and 4 females) sampled once a week

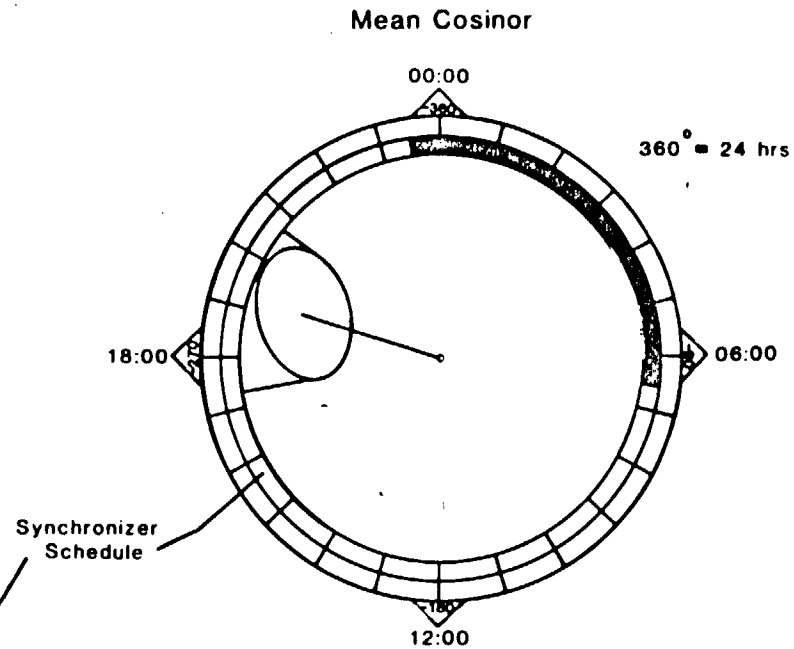
** ^{3}H-Thymidine incorporation in 48-hour cultures of 1×10^{6} lymphocytes obtained at different circadian systems stages (cpm/cultures)

Key to Ellipses	No.	PR	p	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
PHA	9	88	< .001	55.32 15.18 95.46	24.26 11.59 39.44	-85 -65 -128
Lymphocytes	9	82	.010	2546 1679 3412	366 102 633	-14 -341 -59

B-32

Circadian Rhythm in Number of Circulating Platelets*

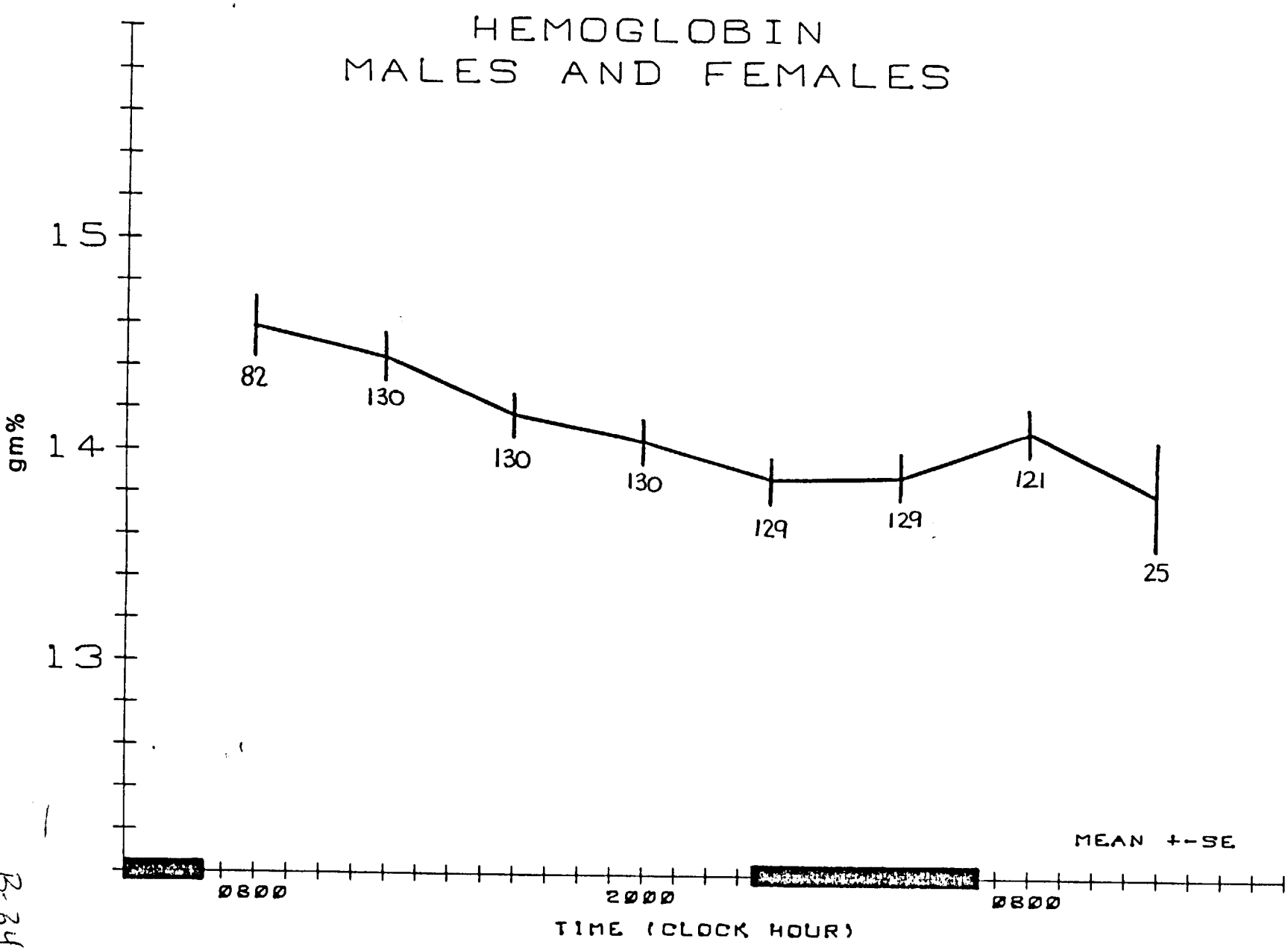




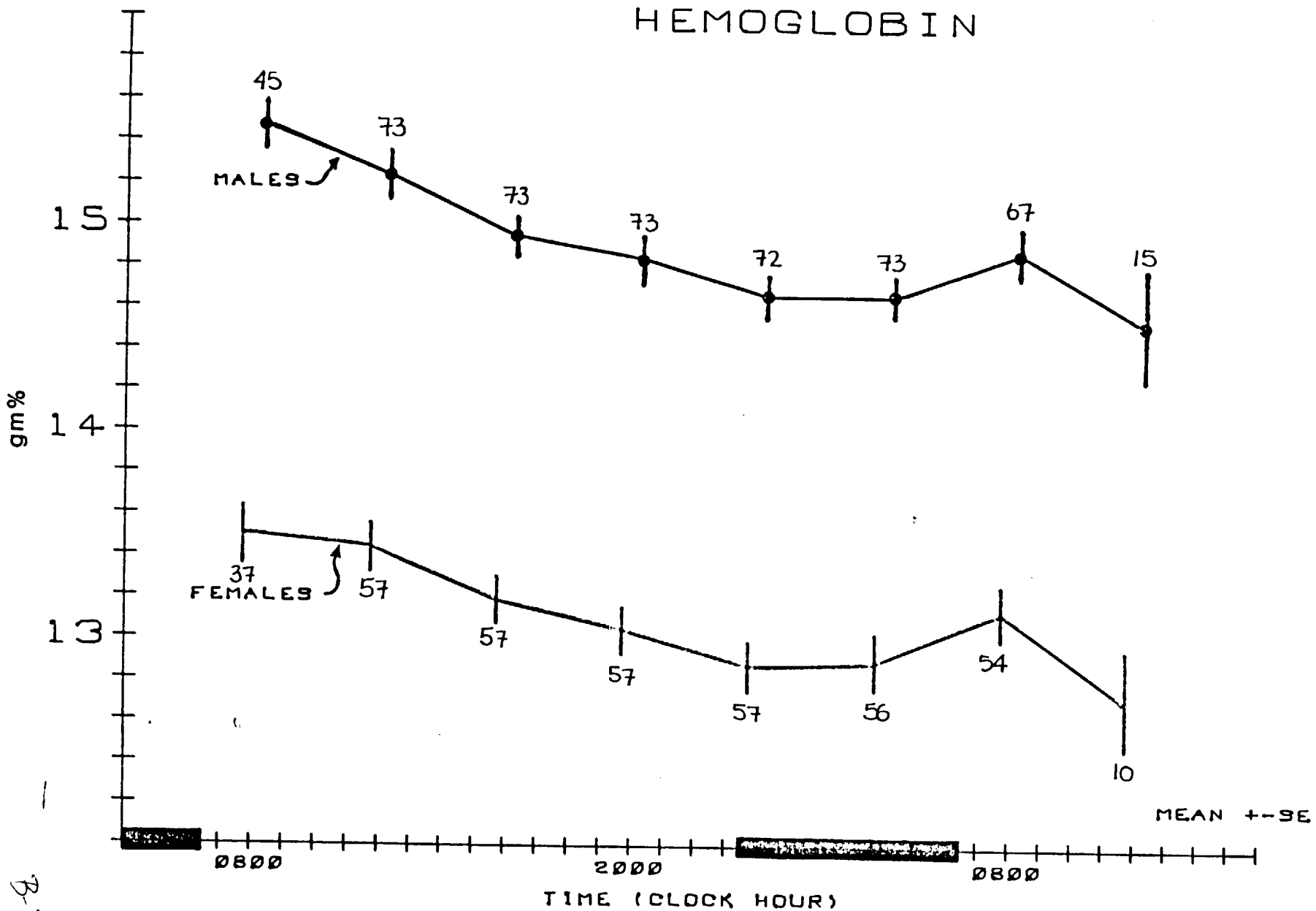
Units	No.	PR	P	Mesor (95% CI)	Amplitude (95% CI)	Acrophase (95% CI)
cells×1000/ ccm	55	40	<.001	272 184 361	10.5 6.8 14.5	-288 -259 -310

*55 Clinically Healthy Subjects: 25 Females, 30 Males

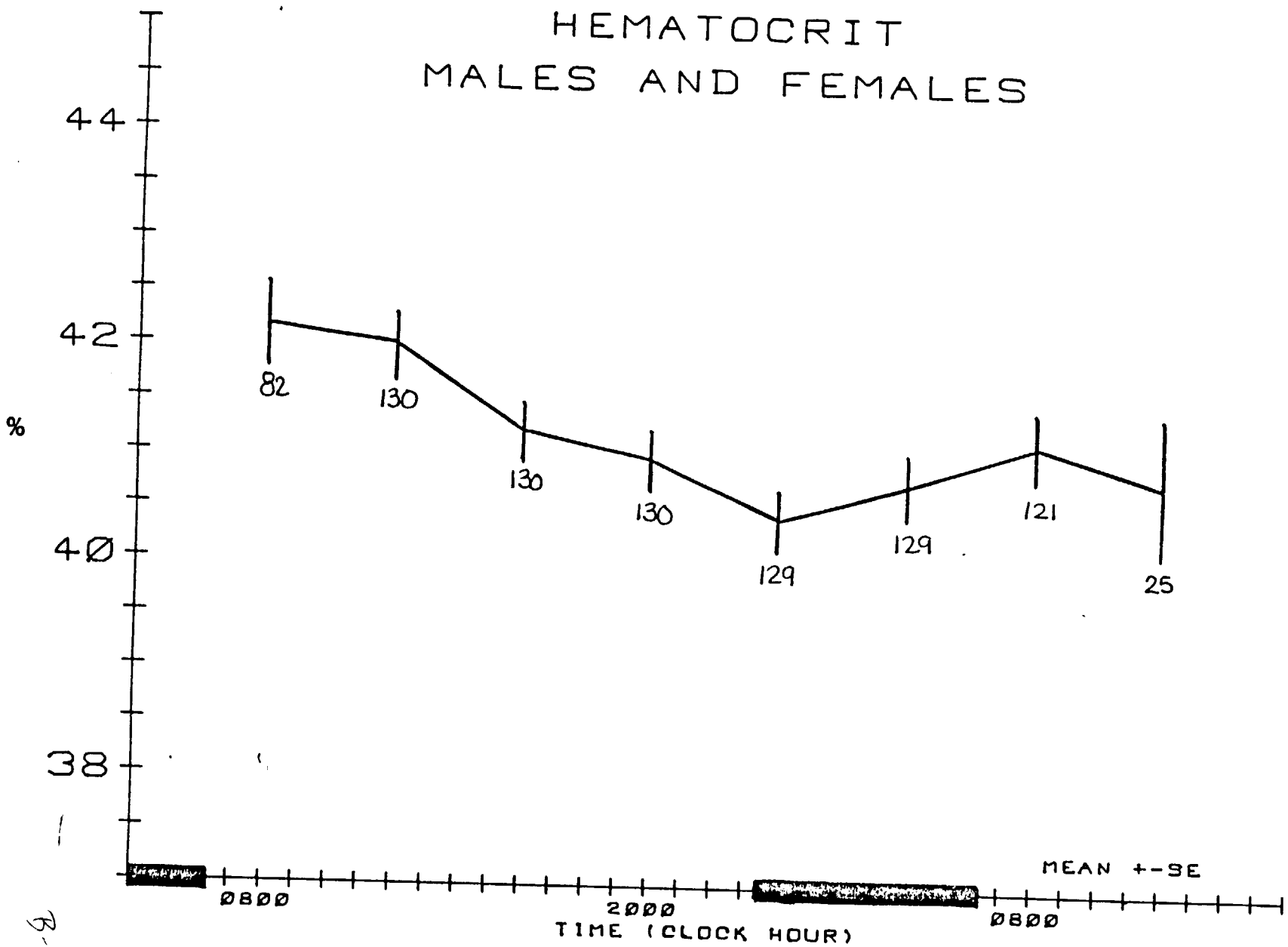
B-33


HEMOGLOBIN
MALES AND FEMALES
gm%
15
14
13
82
130
130
130
129
129
121
25
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

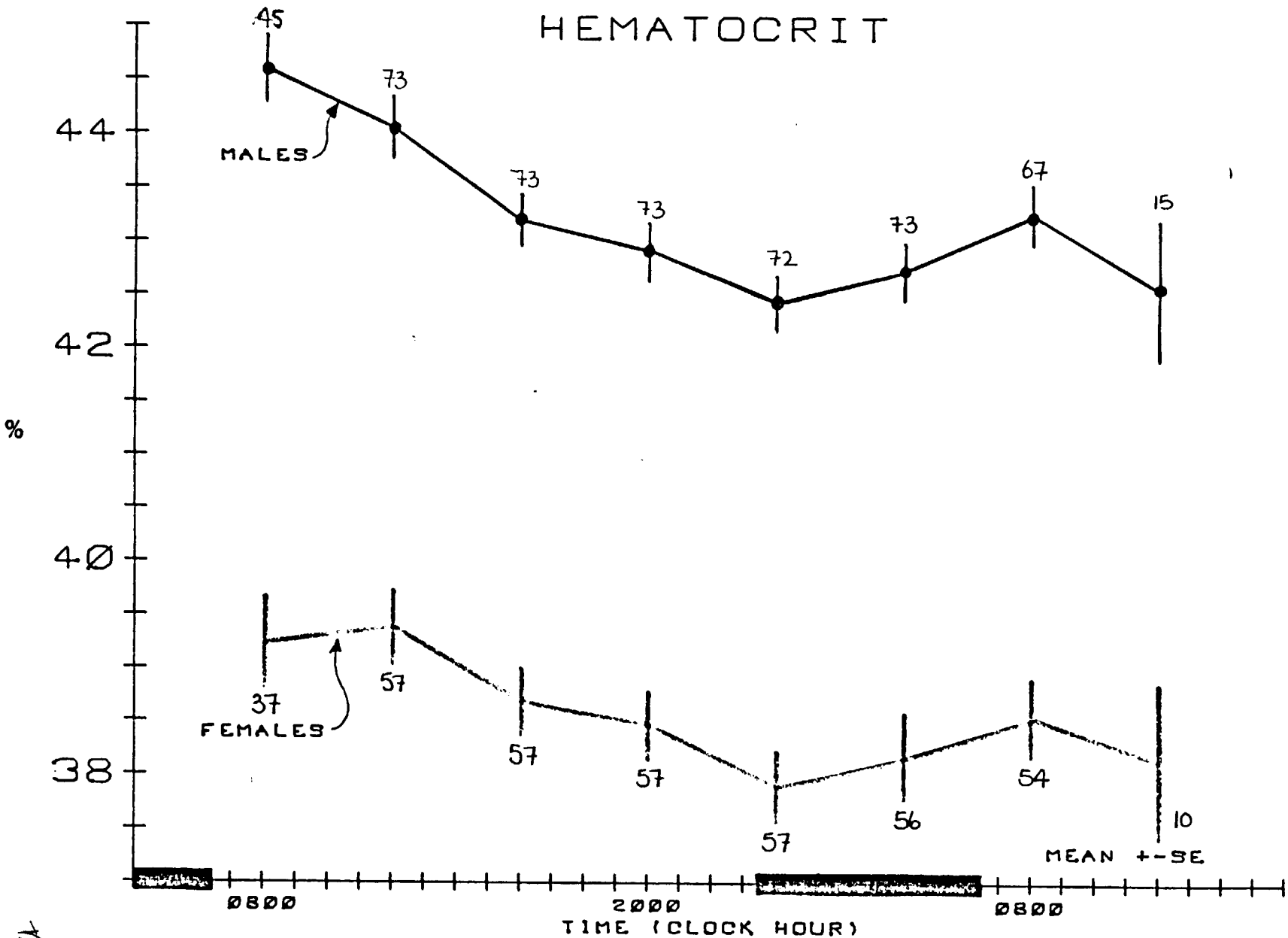
B-34


HEMOGLOBIN
gm%
15
14
13
MALES
45
73
73
73
72
73
67
15
FEMALES
37
57
57
57
57
56
54
10
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

Nsc-8

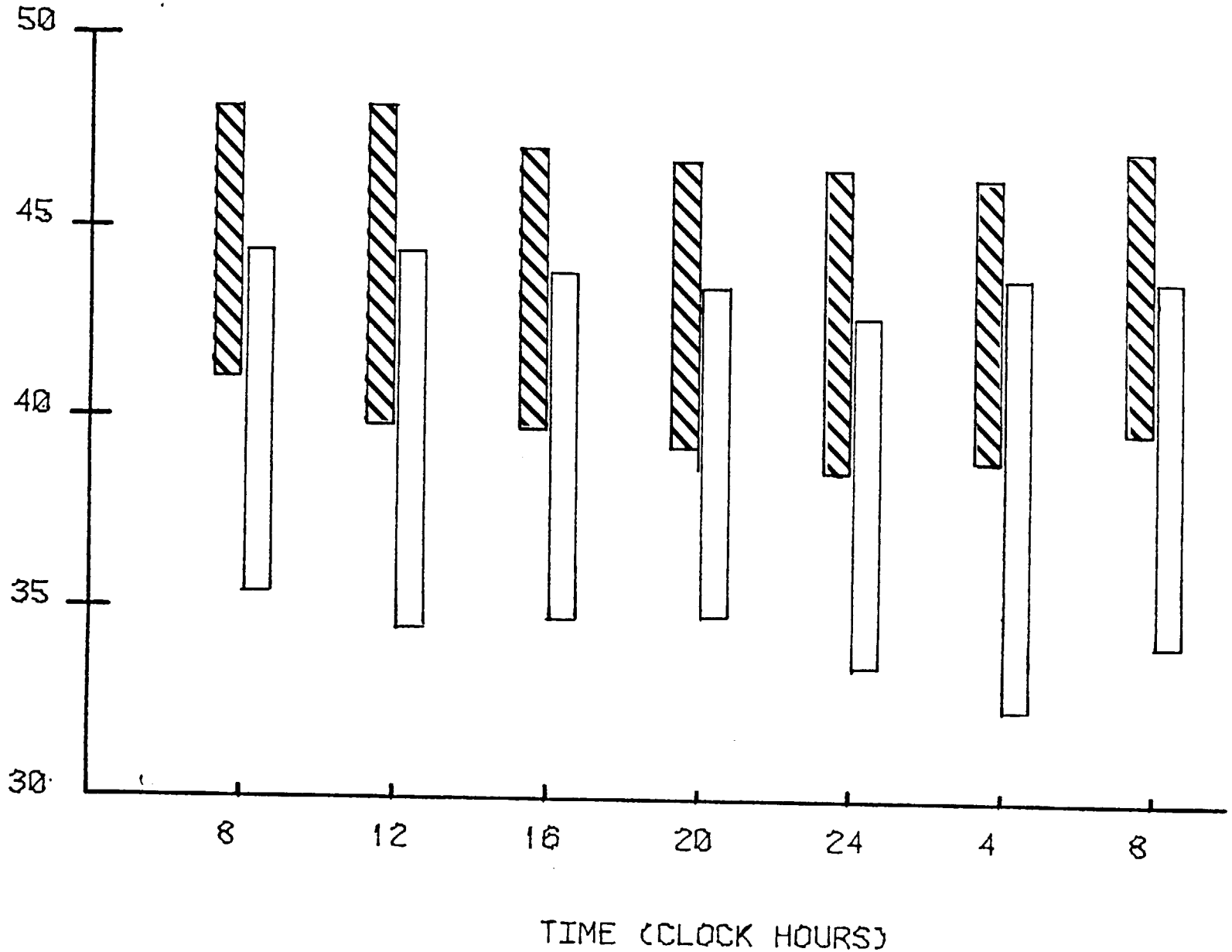

HEMATOCRIT
MALES AND FEMALES
44
42
40
38
%
82
130
130
130
129
129
121
25
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-36

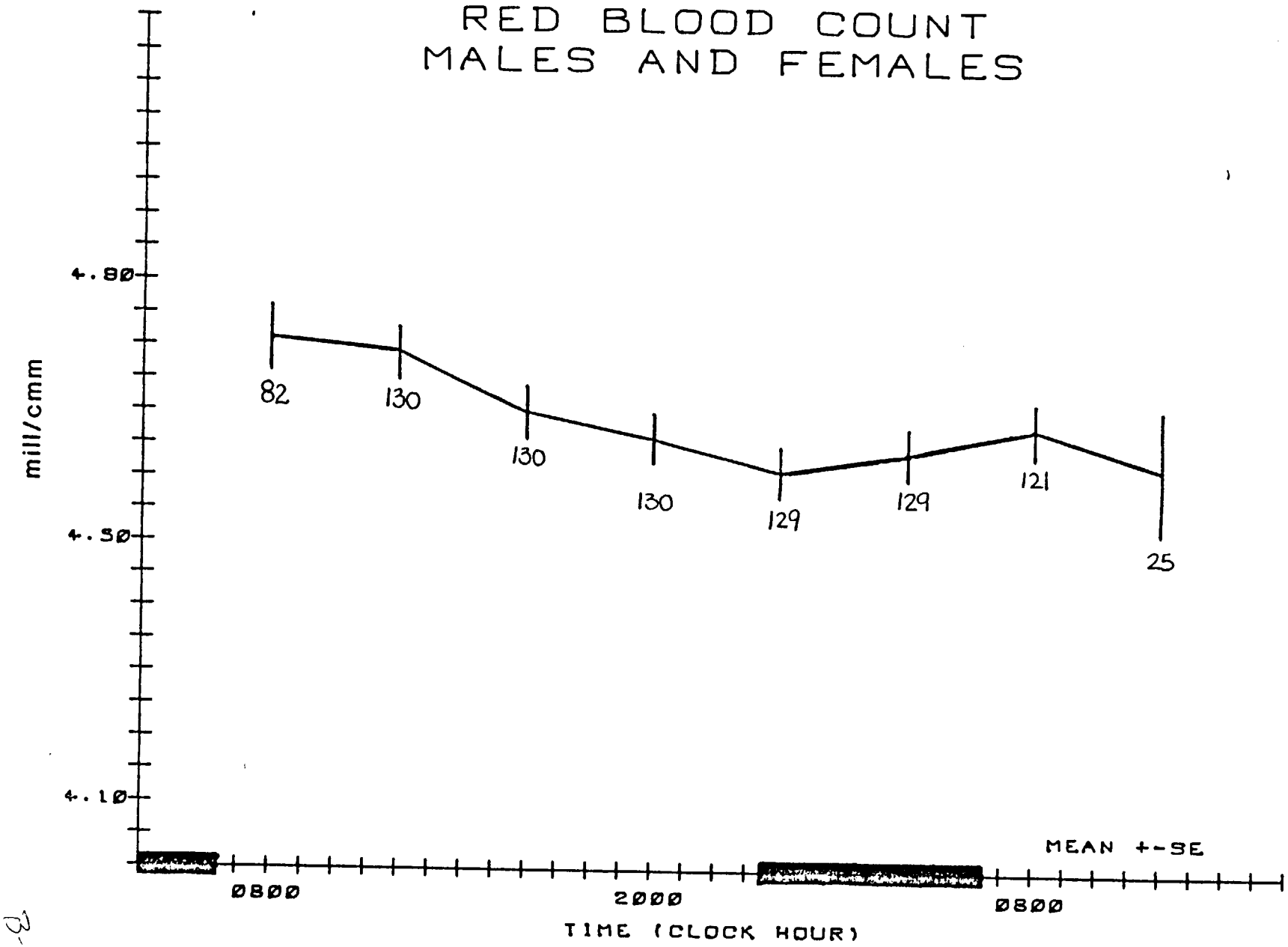

HEMATOCRIT
%
44
42
40
38
45
73
73
73
72
73
67
15
MALES
37
57
57
57
57
56
54
10
FEMALES
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

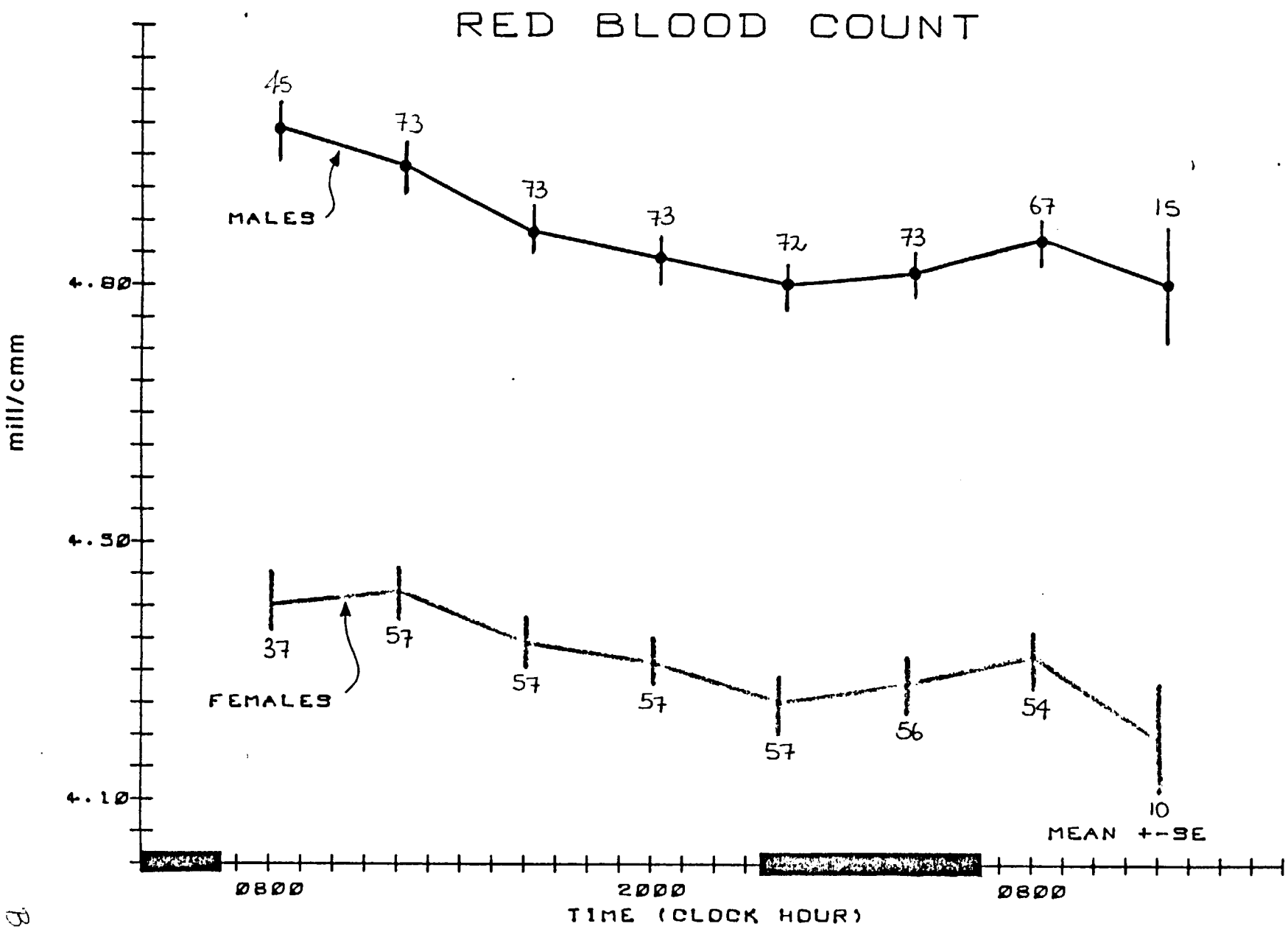
B-37

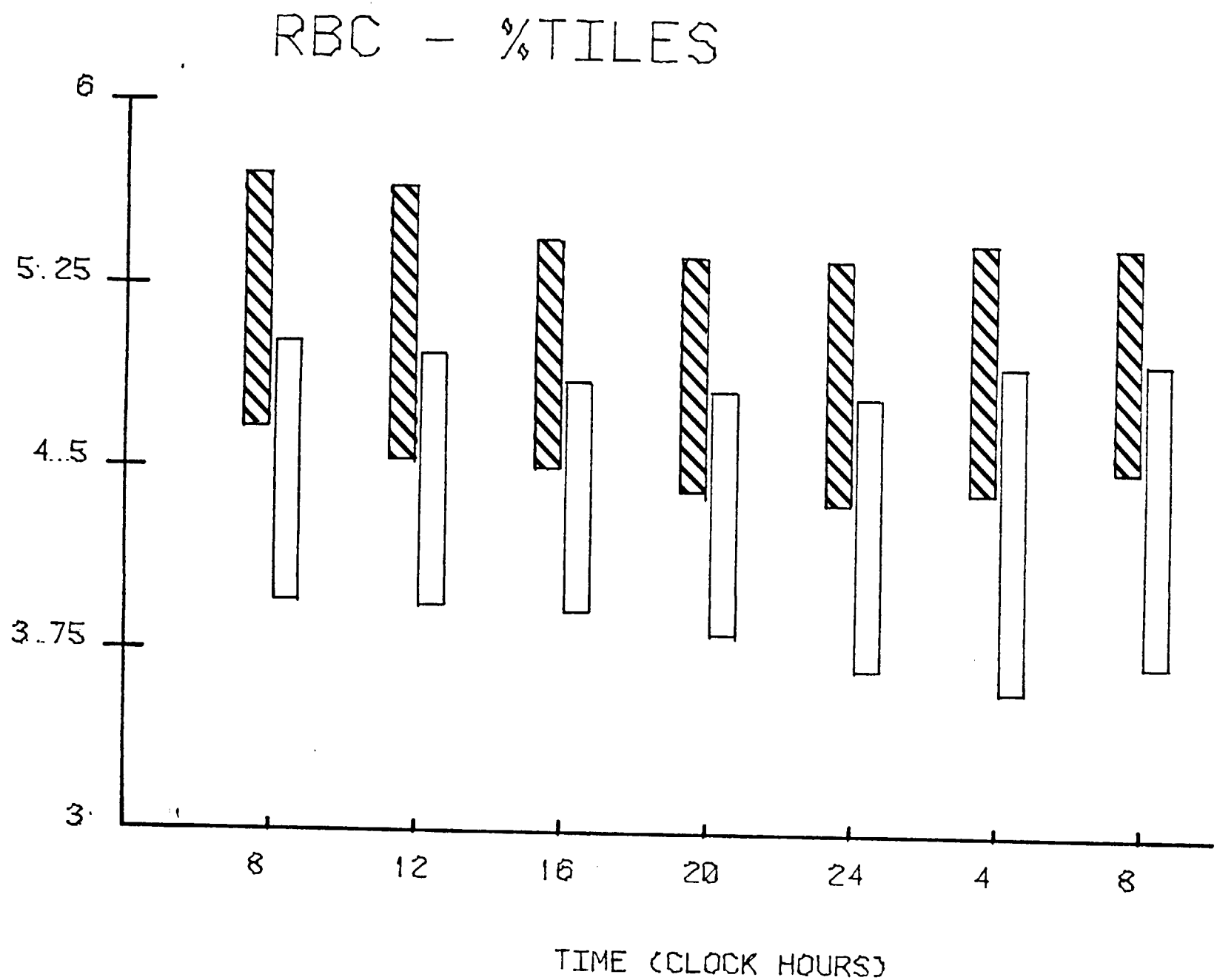
HEMATOCRIT - %TILES

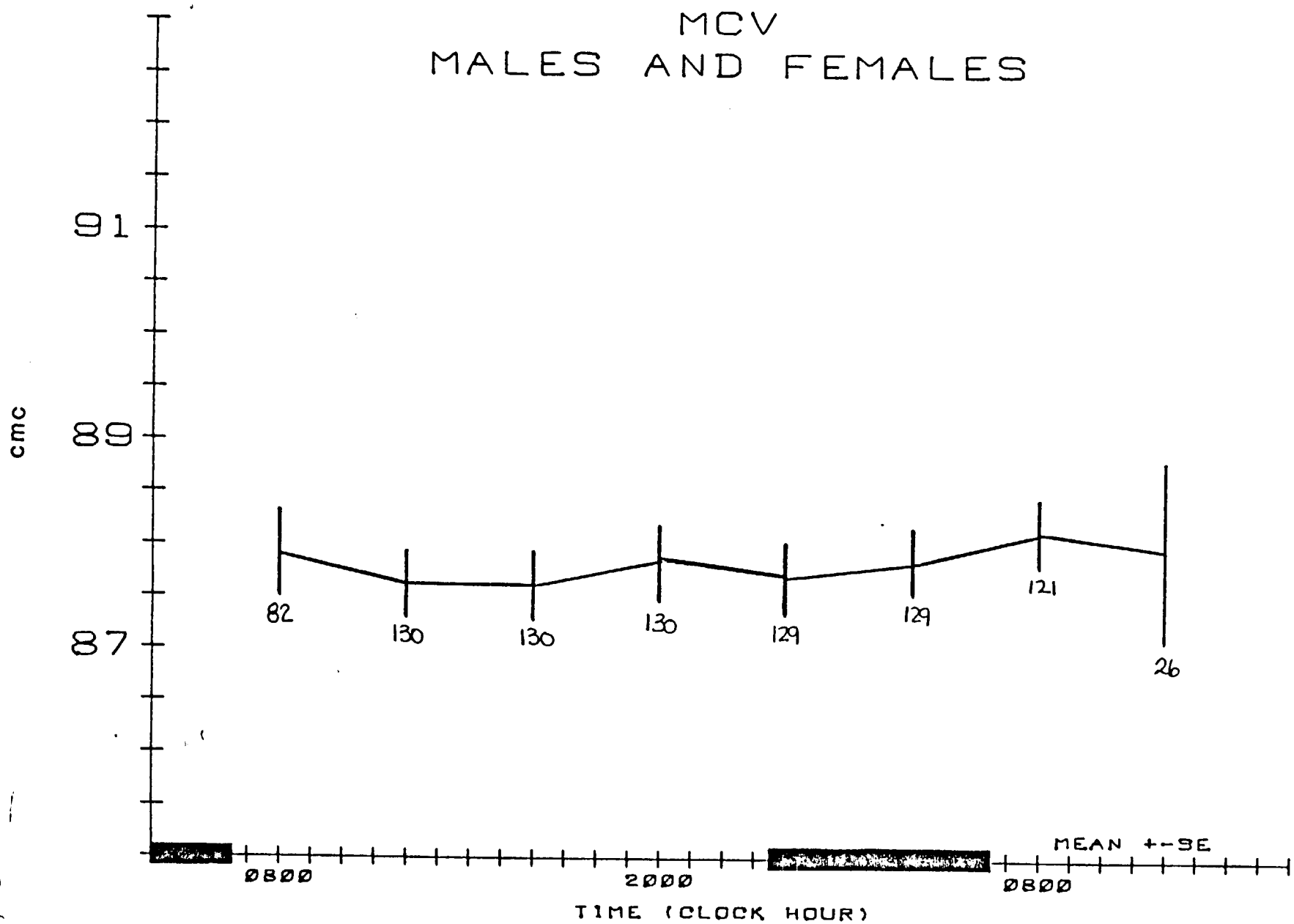


RED BLOOD COUNT
MALES AND FEMALES

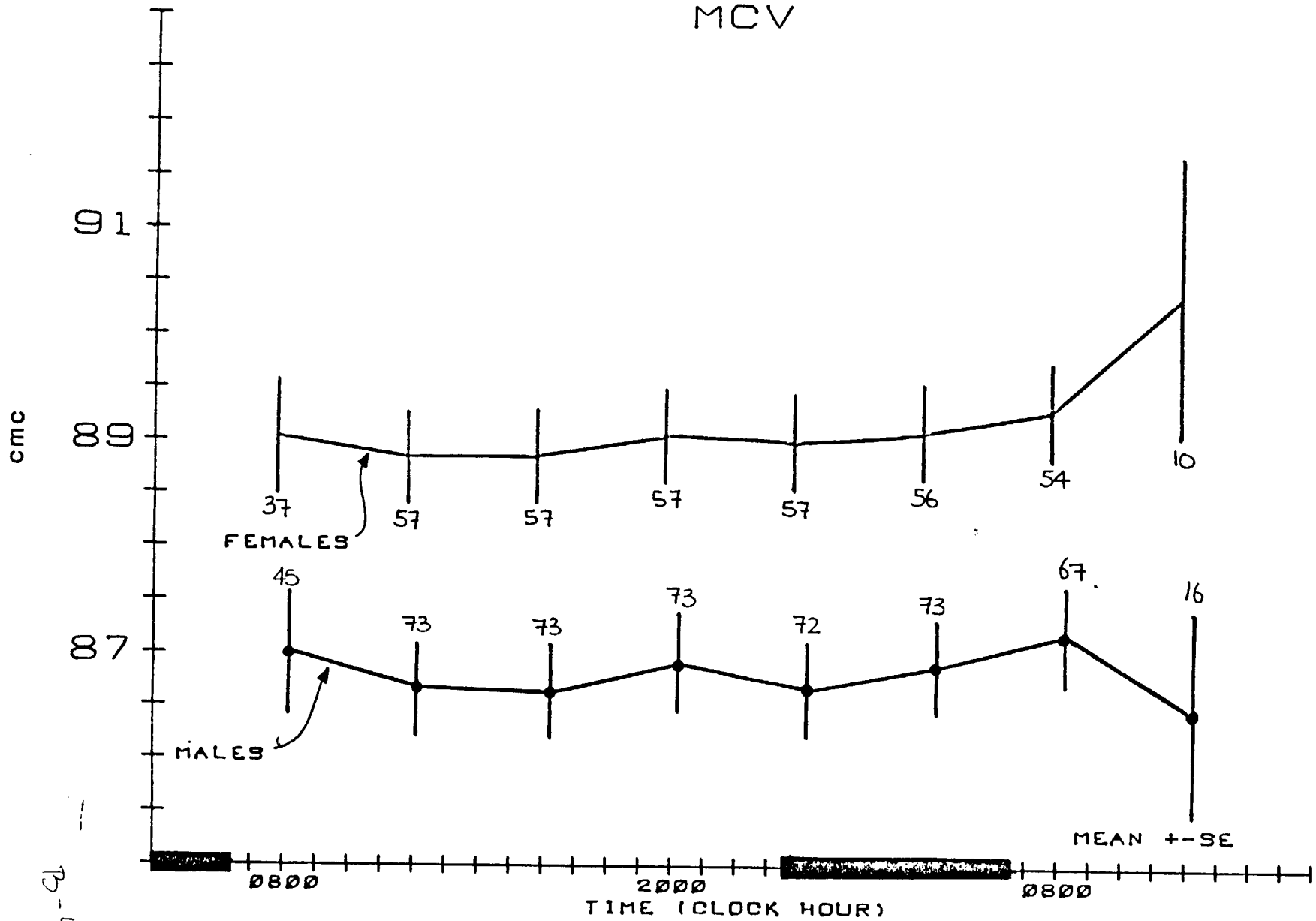



RED BLOOD COUNT
mill/cmm
4.80
4.50
4.10
MALES
45
73
73
73
72
73
67
15
FEMALES
37
57
57
57
57
56
54
10
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)


RBC - %TILES
6
5.25
4.5
3.75
3
8
12
16
20
24
4
8
TIME (CLOCK HOURS)

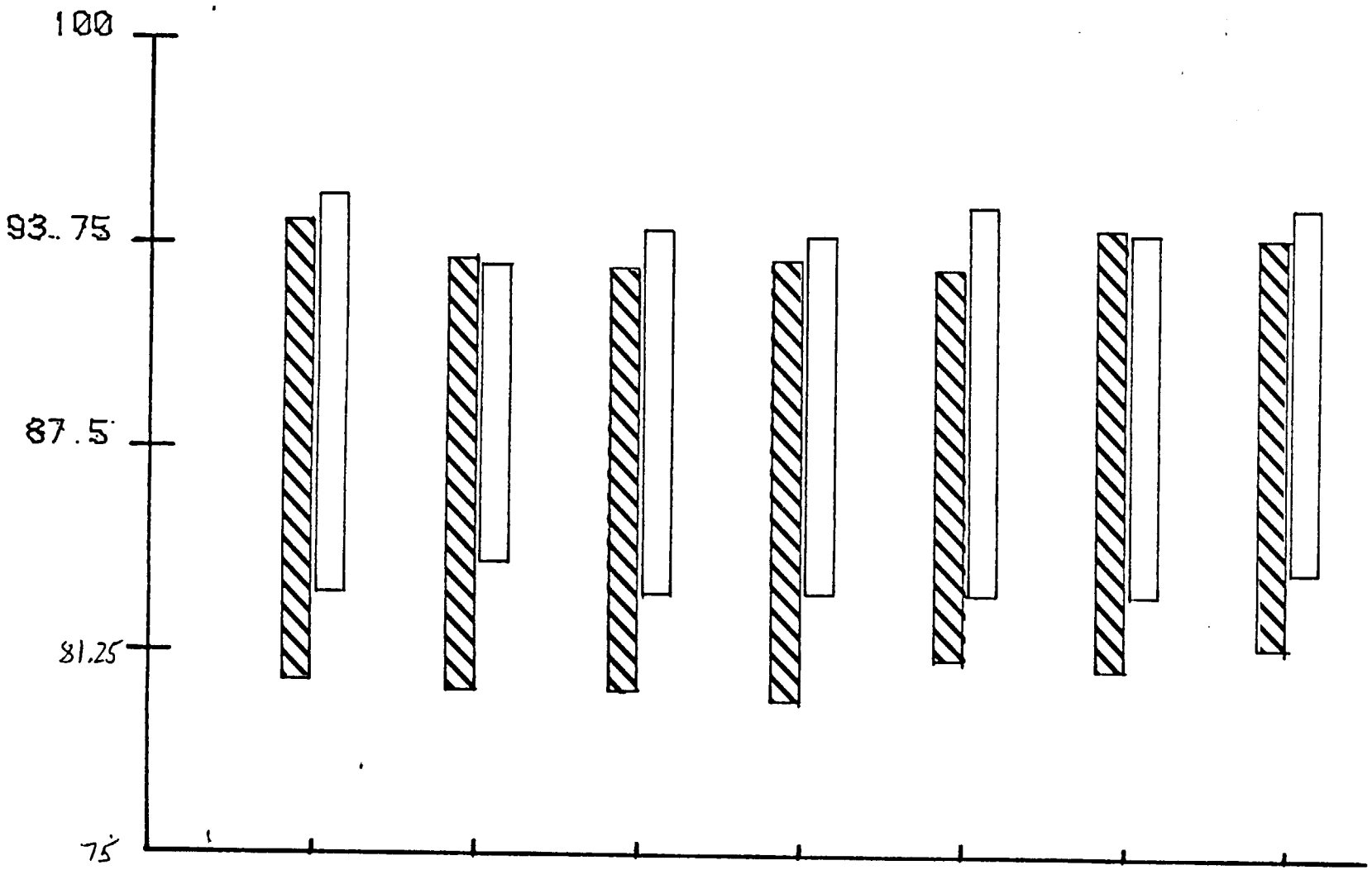

MCV
MALES AND FEMALES
91
89
87
cmc
82
130
130
130
129
129
121
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

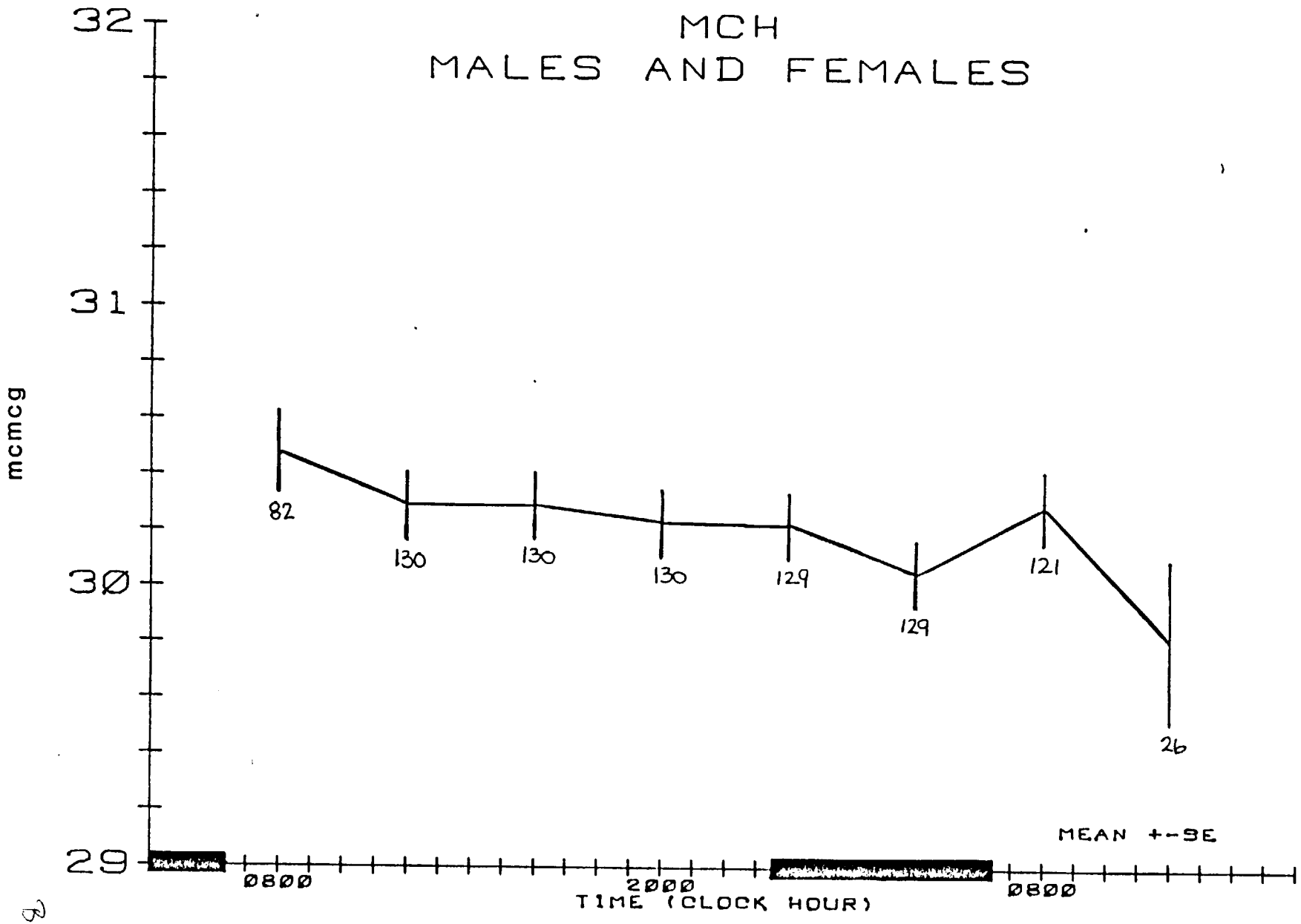
B-42


MCV
cmc
91
89
87
37
57
57
57
57
56
54
10
FEMALES
45
73
73
73
72
73
67
16
MALES
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

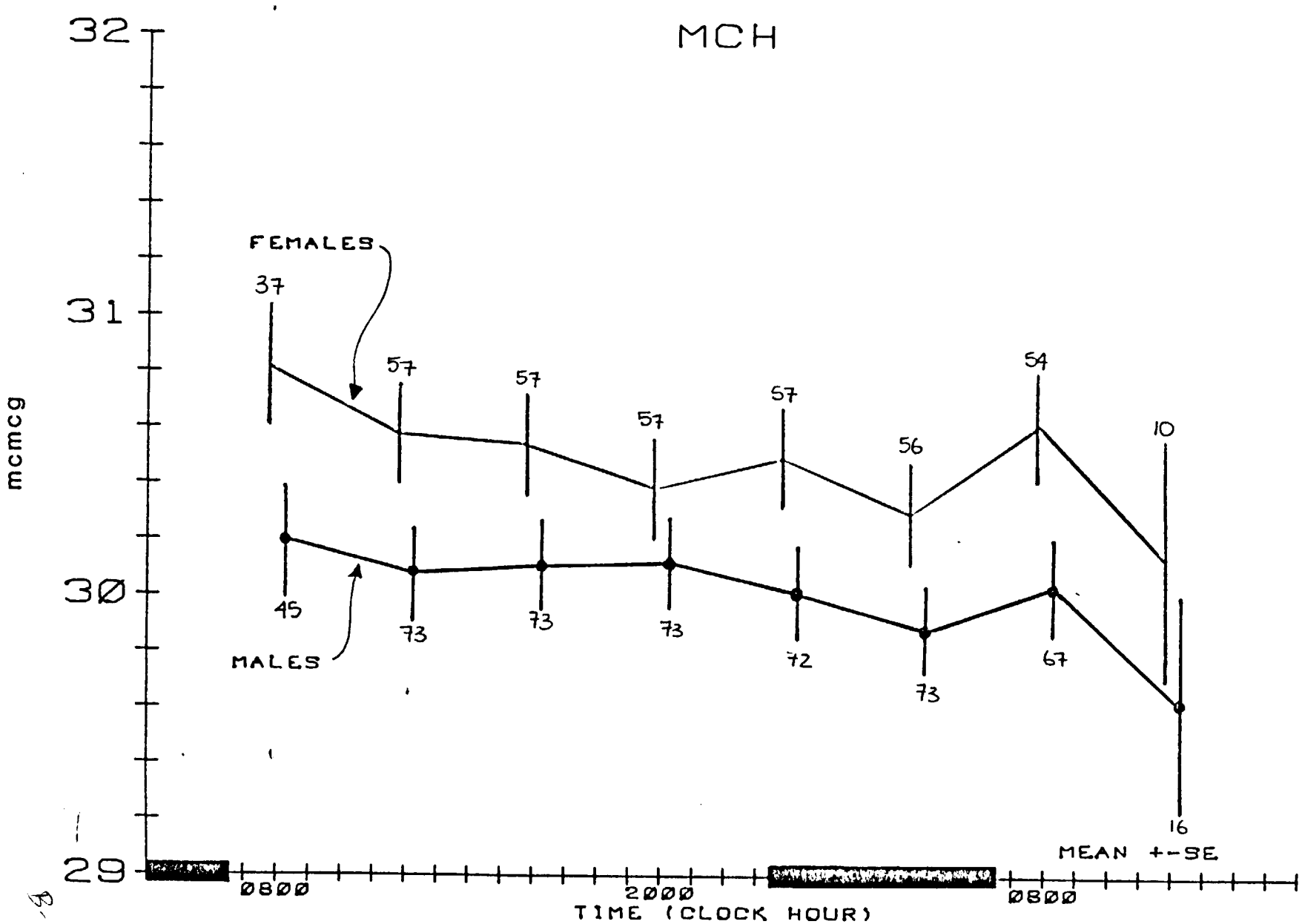
B-43

MCV - %TILES

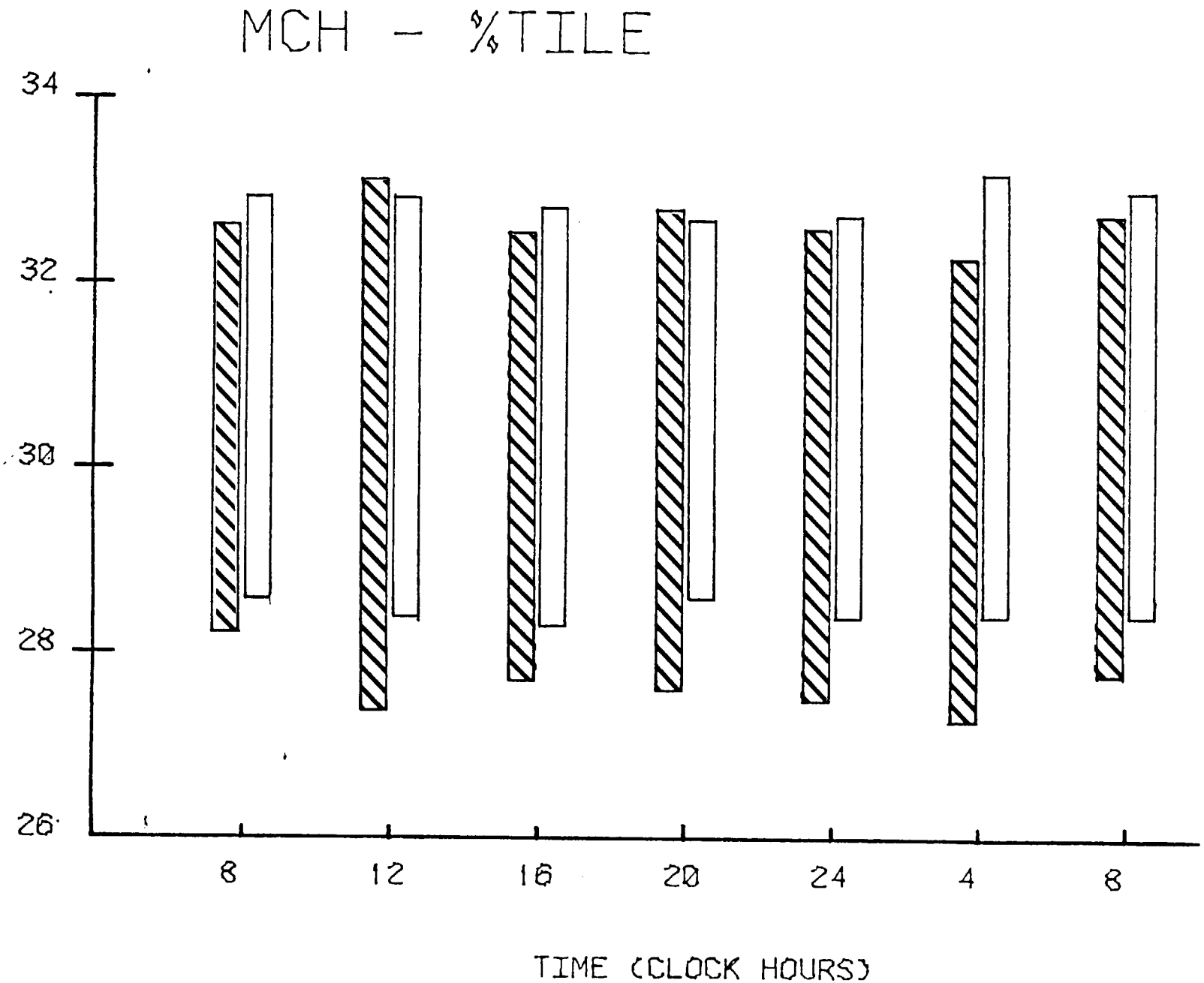


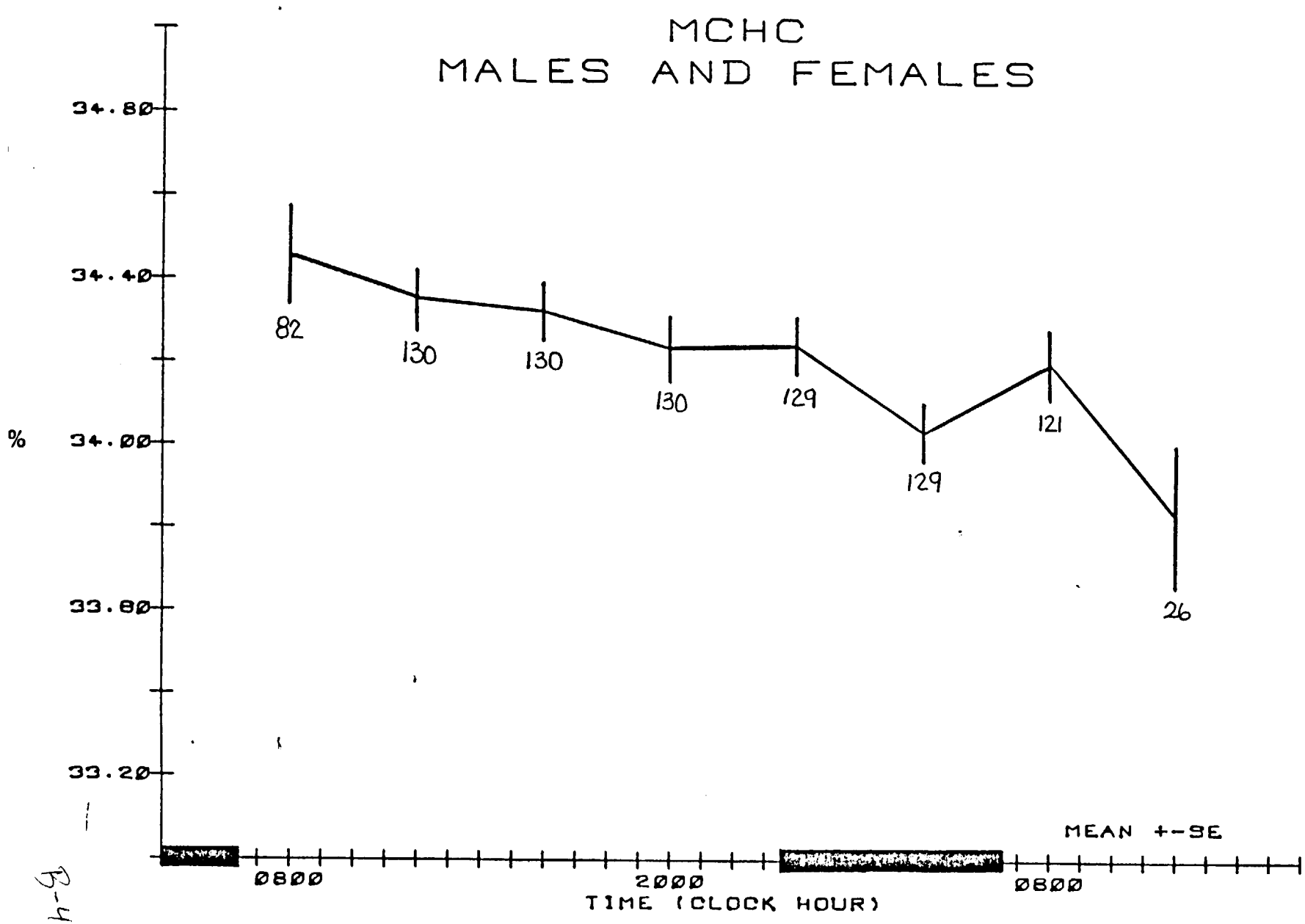

MCH
MALES AND FEMALES
32
31
30
29
mcmcg
82
130
130
130
129
129
121
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-45

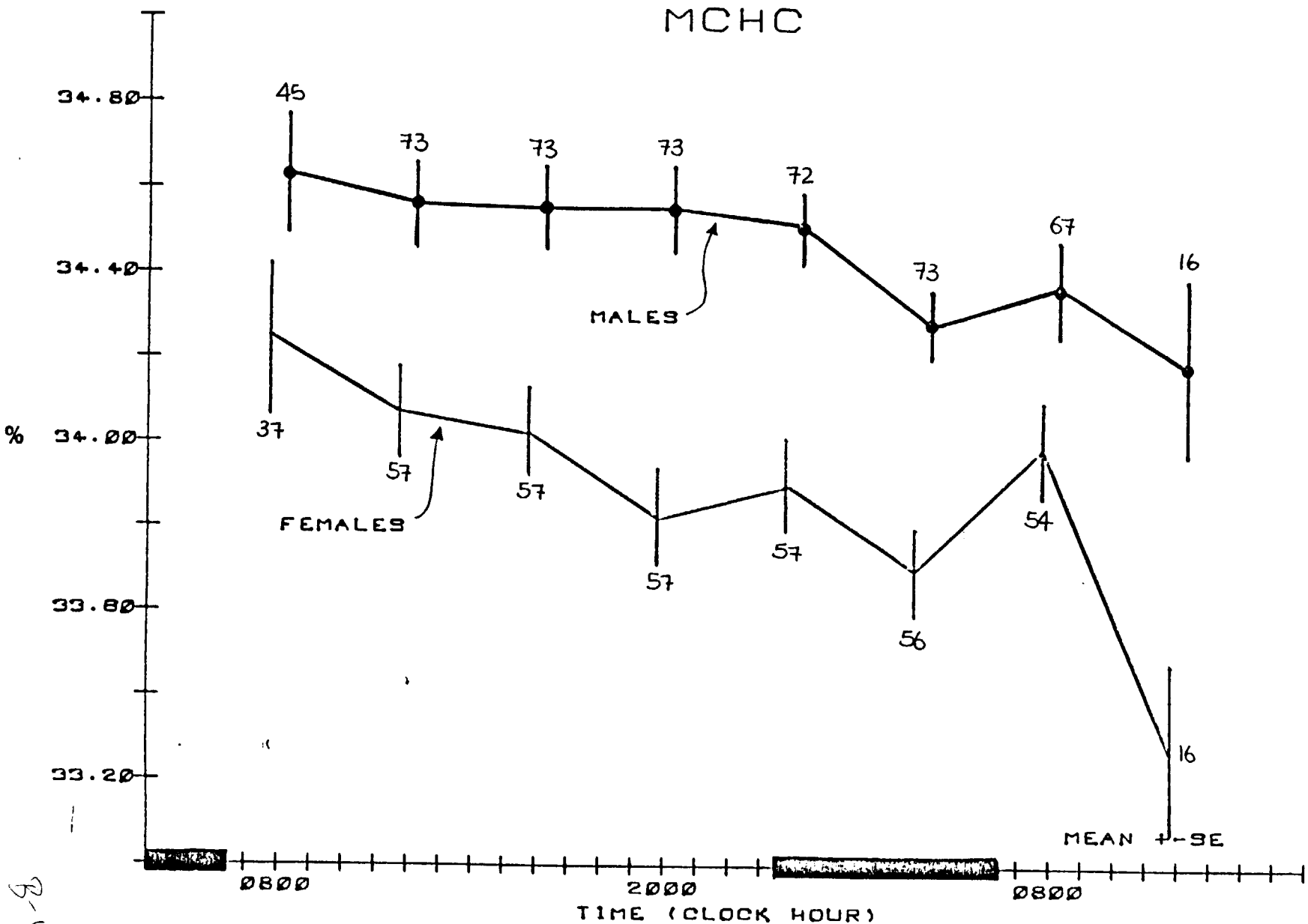

MCH
32
31
30
29
mcmcg
FEMALES
MALES
37
57
57
57
57
56
54
10
45
73
73
73
72
73
67
16
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-46

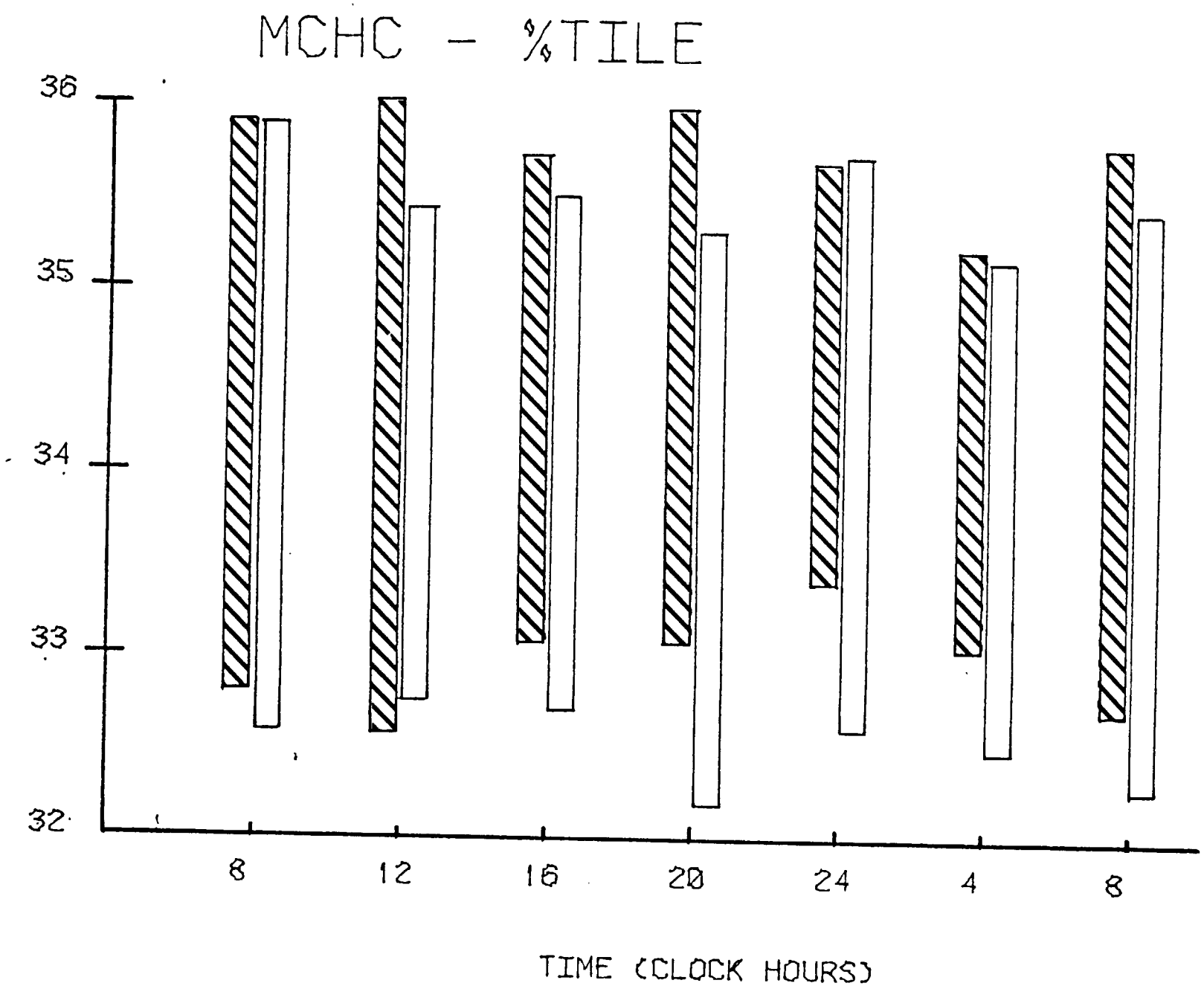

MCH - %TILE
34
32
30
28
26
8
12
16
20
24
4
8
TIME (CLOCK HOURS)

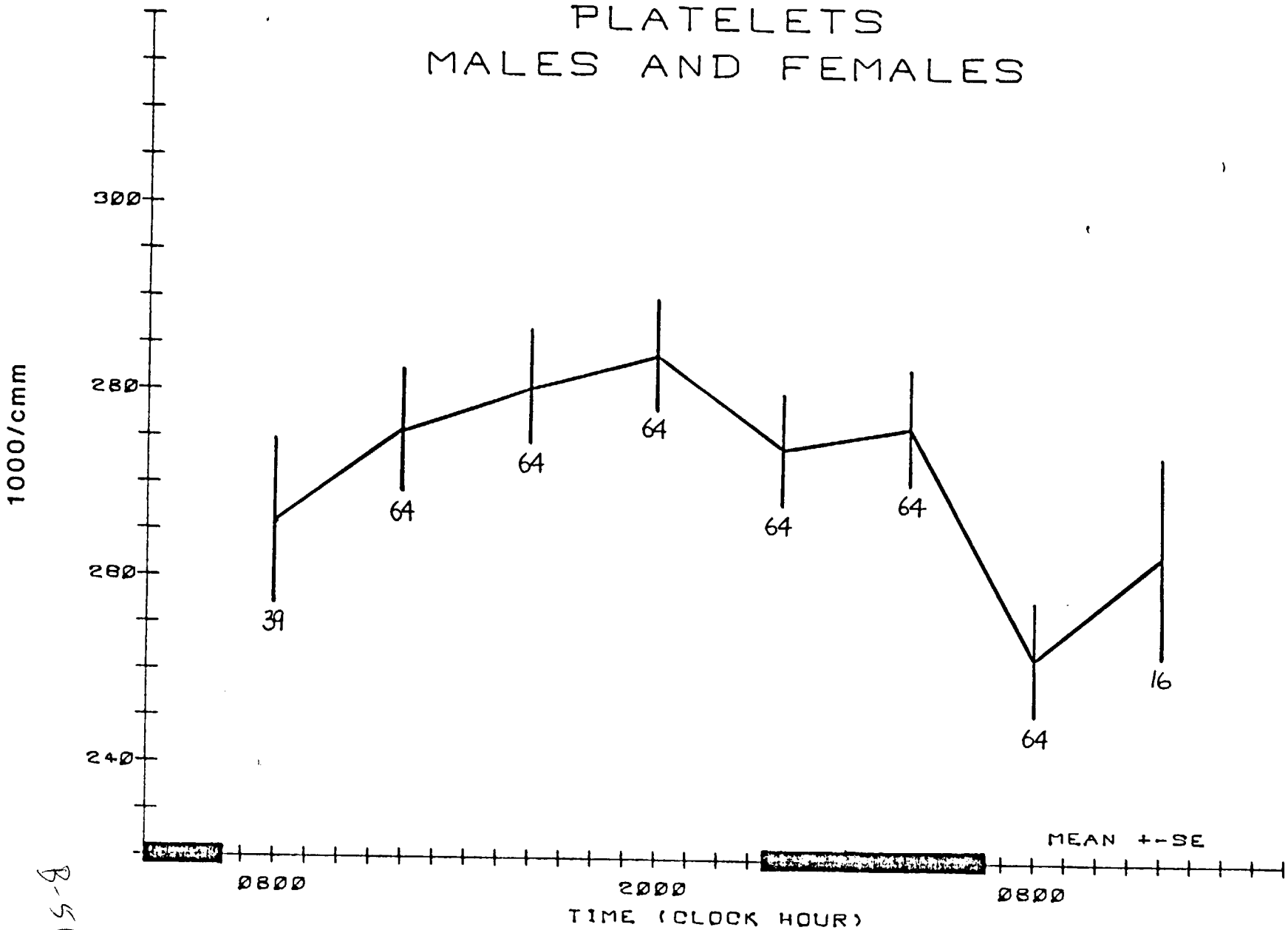

MCHC
MALES AND FEMALES
34.80
34.40
34.00
33.80
33.20
%
82
130
130
130
129
129
121
26
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-48

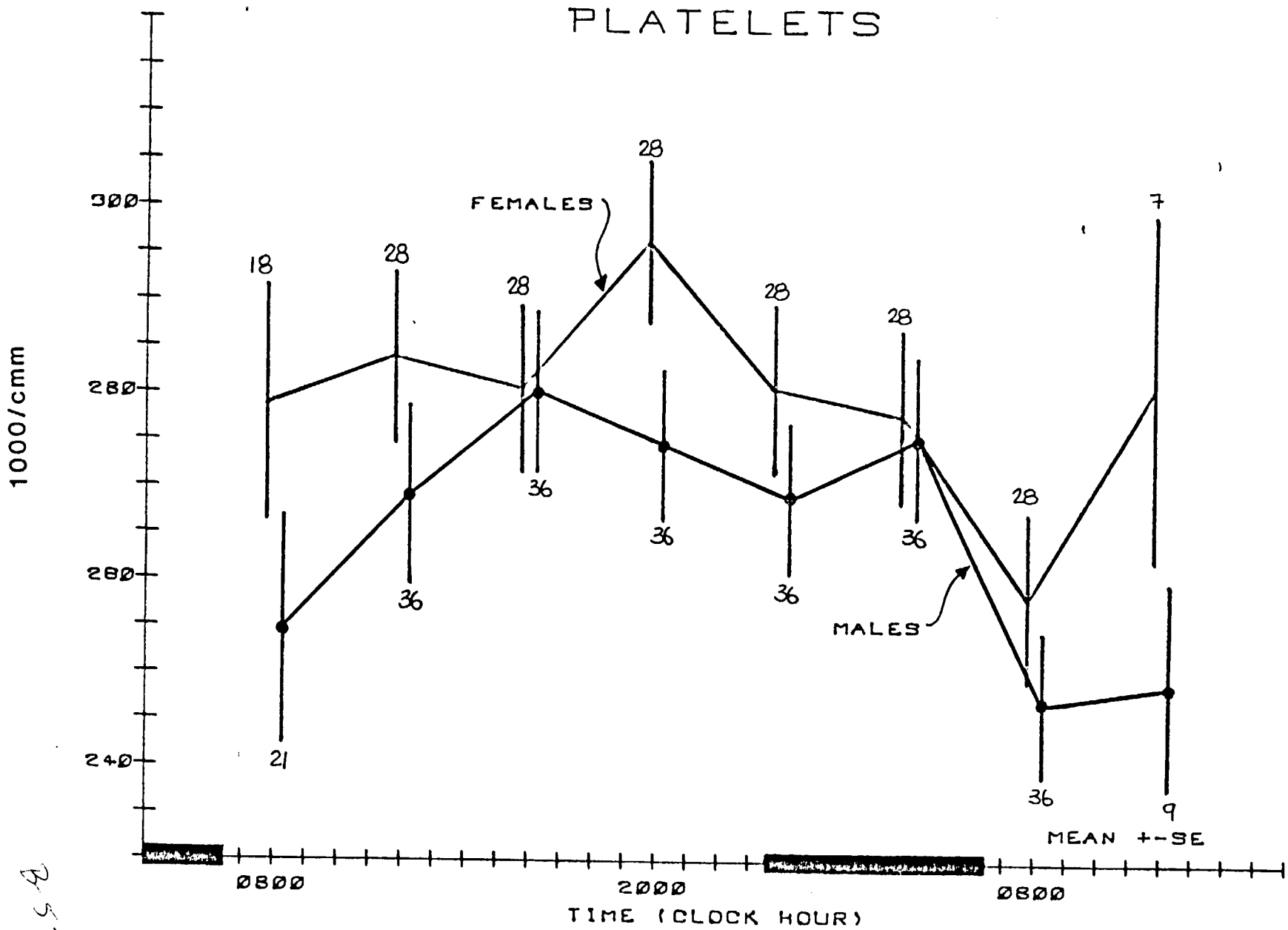

MCHC
34.80
34.40
34.00
33.80
33.20
%
45
73
73
73
72
73
67
16
MALES
37
57
57
57
57
56
54
16
FEMALES
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-49N


MCHC - %TILE
36
35
34
33
32
8
12
16
20
24
4
8
TIME (CLOCK HOURS)

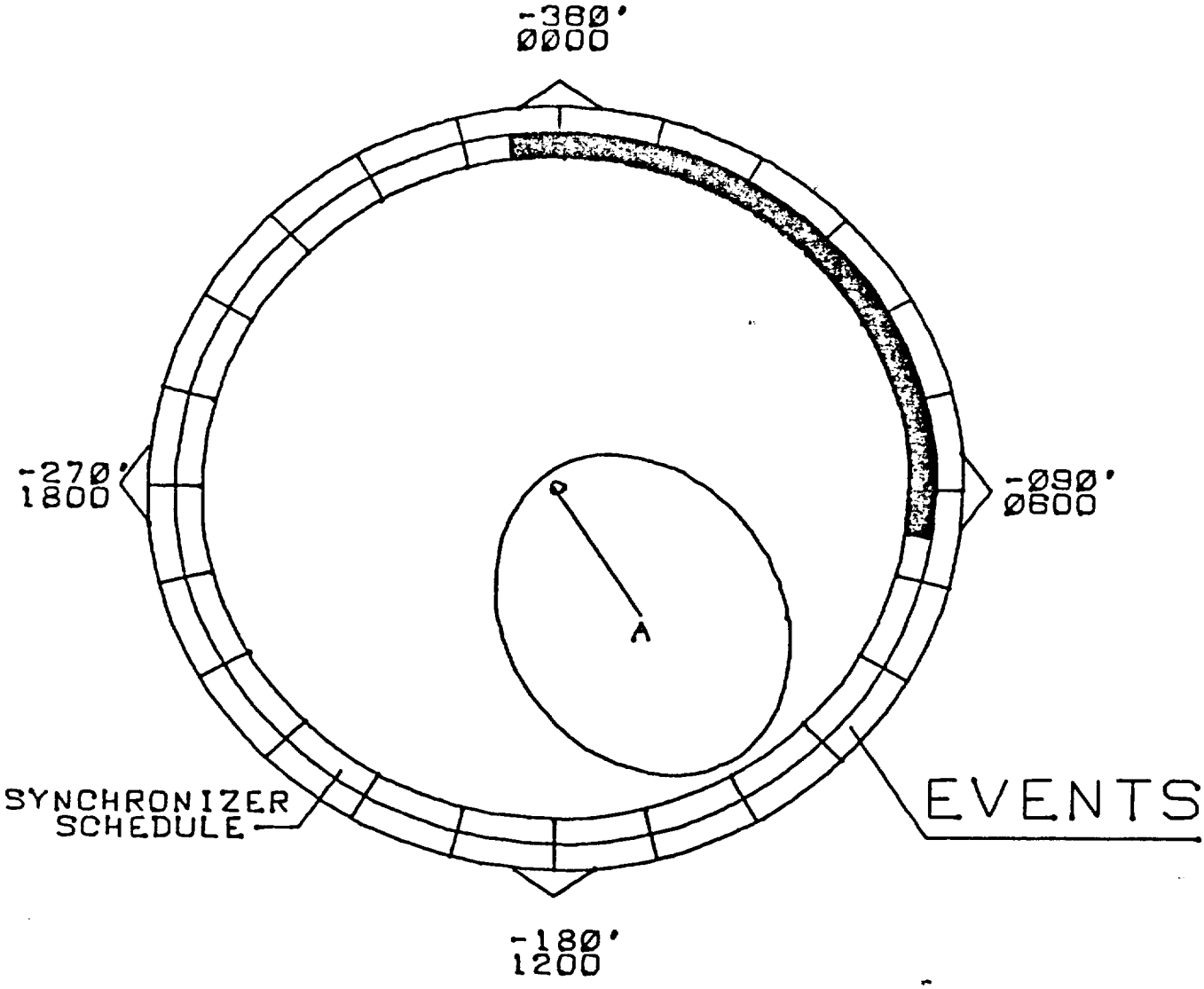

PLATELETS
MALES AND FEMALES
1000/cmm
300
280
280
240
39
64
64
64
64
64
64
16
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-51


PLATELETS
1000/cmm
300
280
280
240
FEMALES
MALES
18
28
28
28
28
28
28
7
21
36
36
36
36
36
36
9
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

258

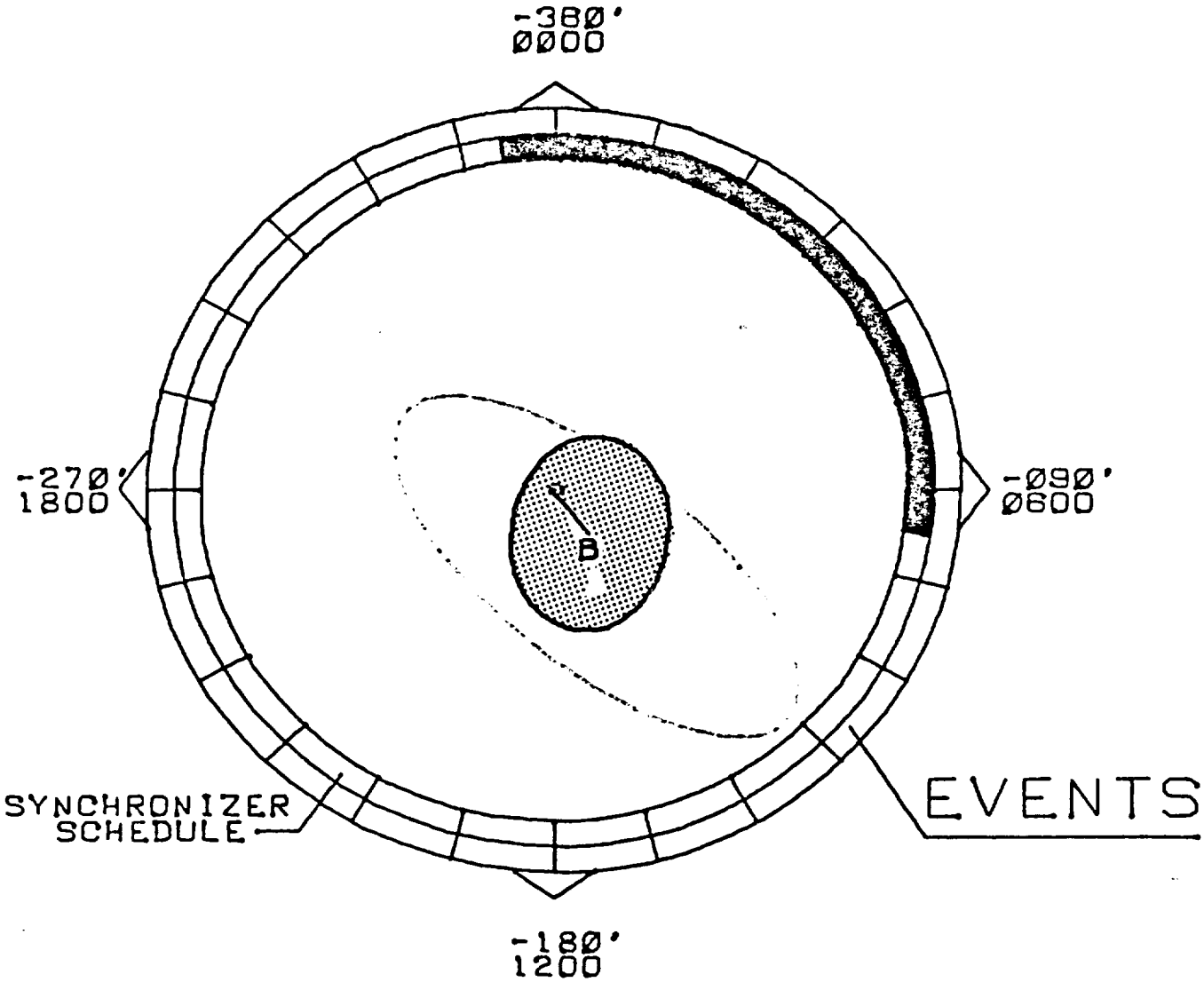
ERYTHROPOIETIN
FEMALES AND MALES



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.078	44	18	96.68 45.43 147.94	21.57	-148

ERYTHROPOIETIN
A=FEMALES B=MALES

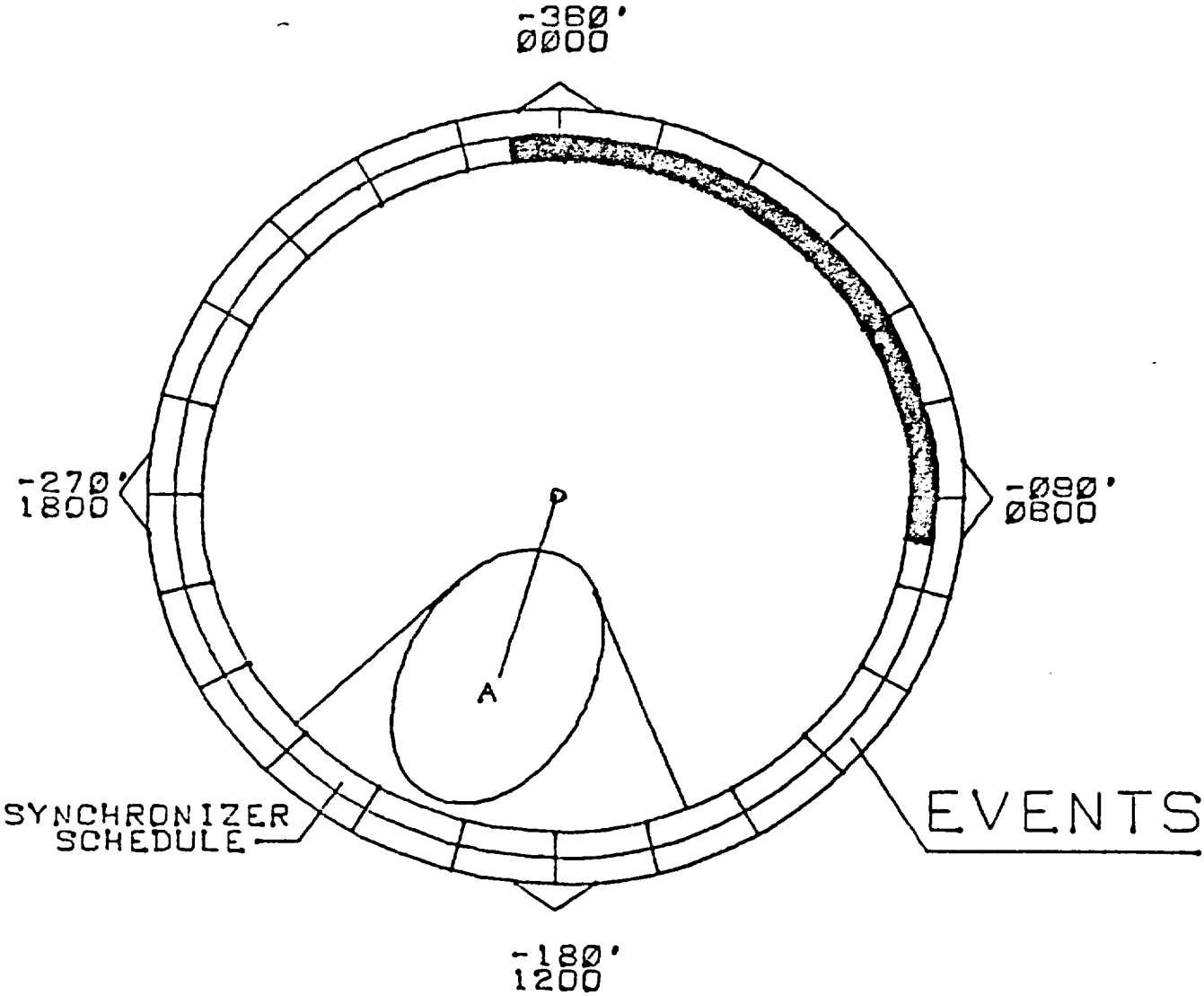


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
B	.213	45	12	98.38 52.28 140.48	18.28	-142

B54

FERRITIN
FEMALES AND MALES

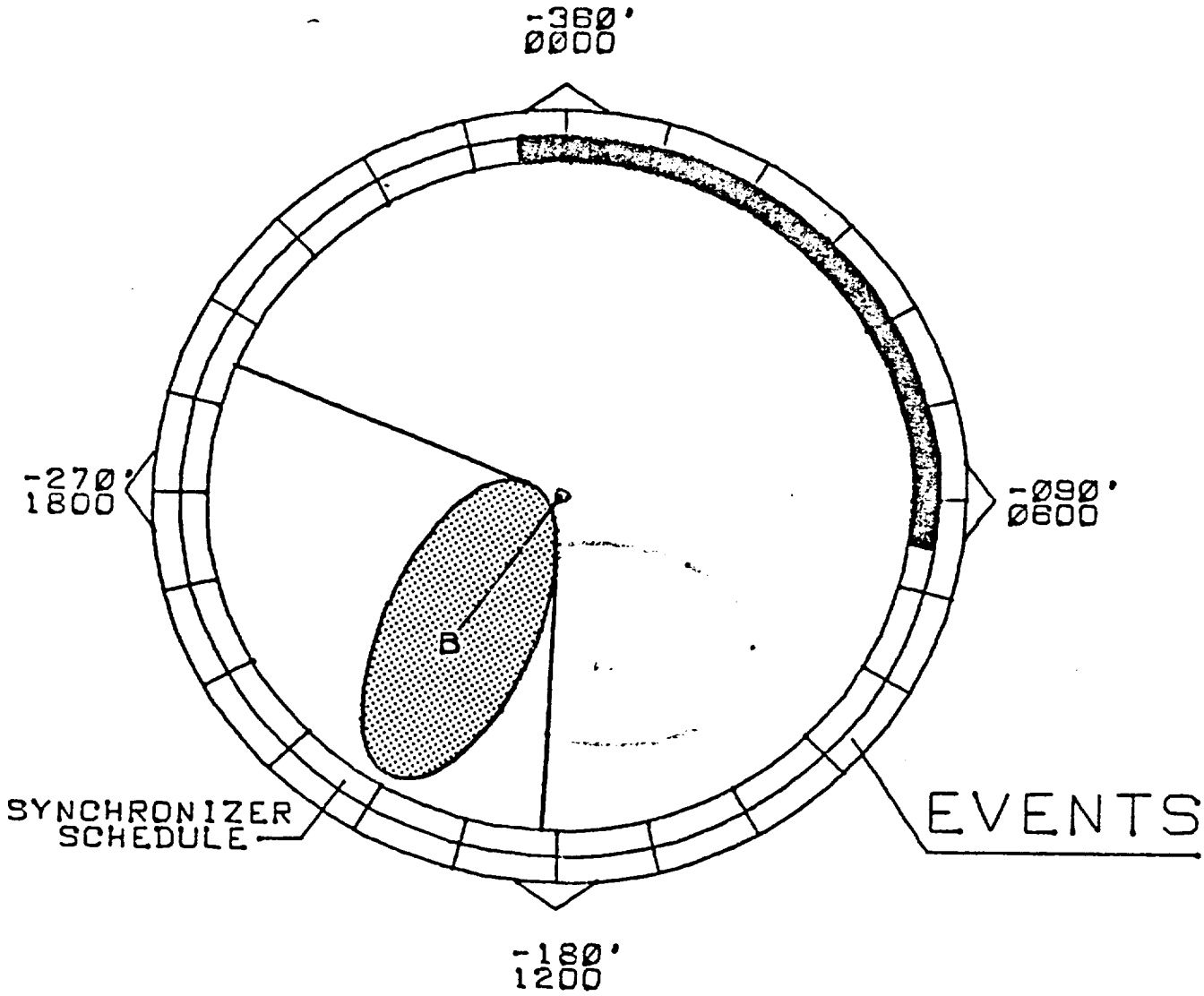


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.003	40	61	24.74 0.30 49.18	0.86 0.25 1.48	-196 -157 -228

B-55

FERRITIN
A=FEMALES B=MALES

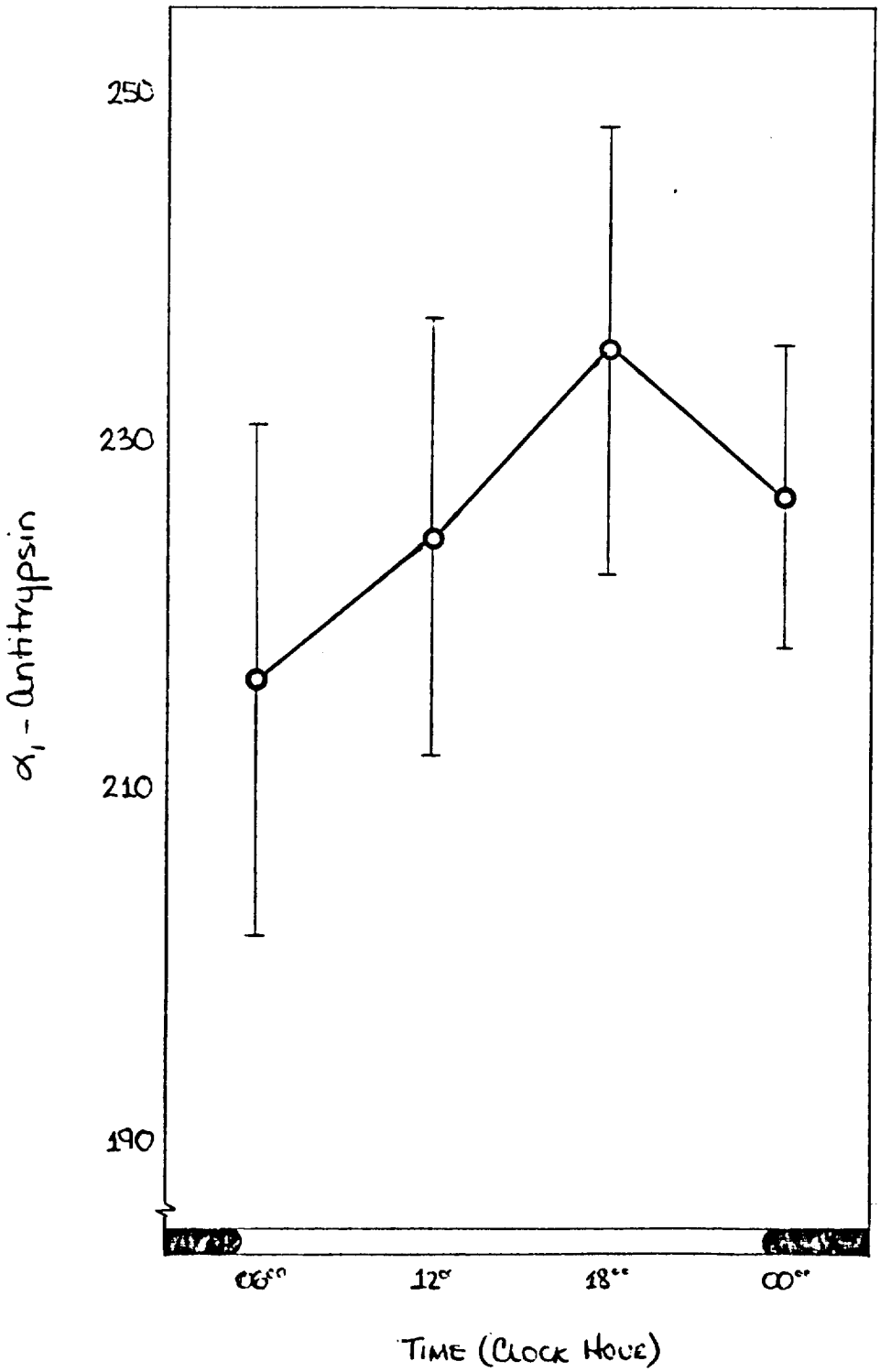


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
B	.028	37	38	28.07 2.17 48.97	0.98 0.08 1.93	-215 -182 -292

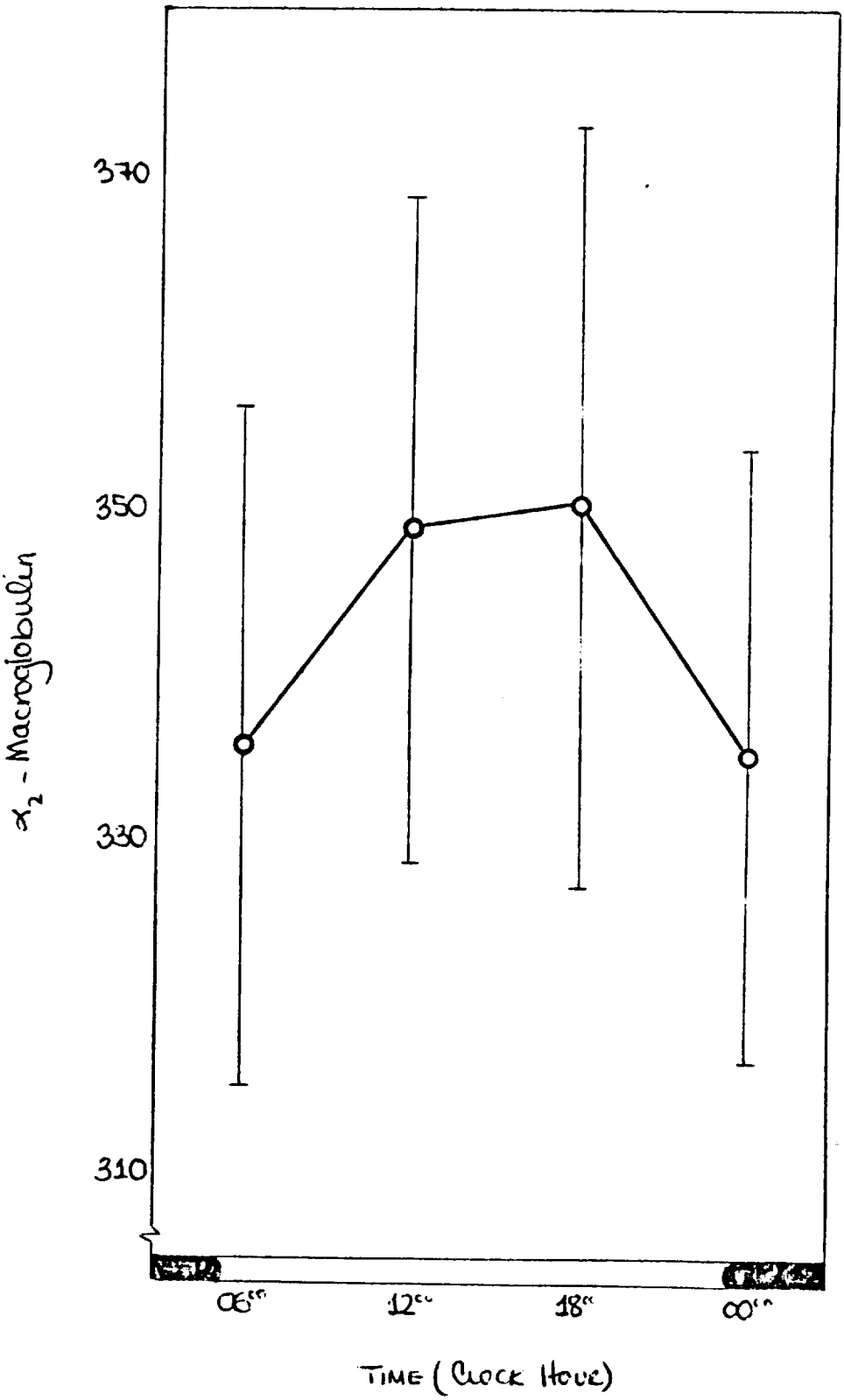
B-56

α_1 – ANTITRYPSIN



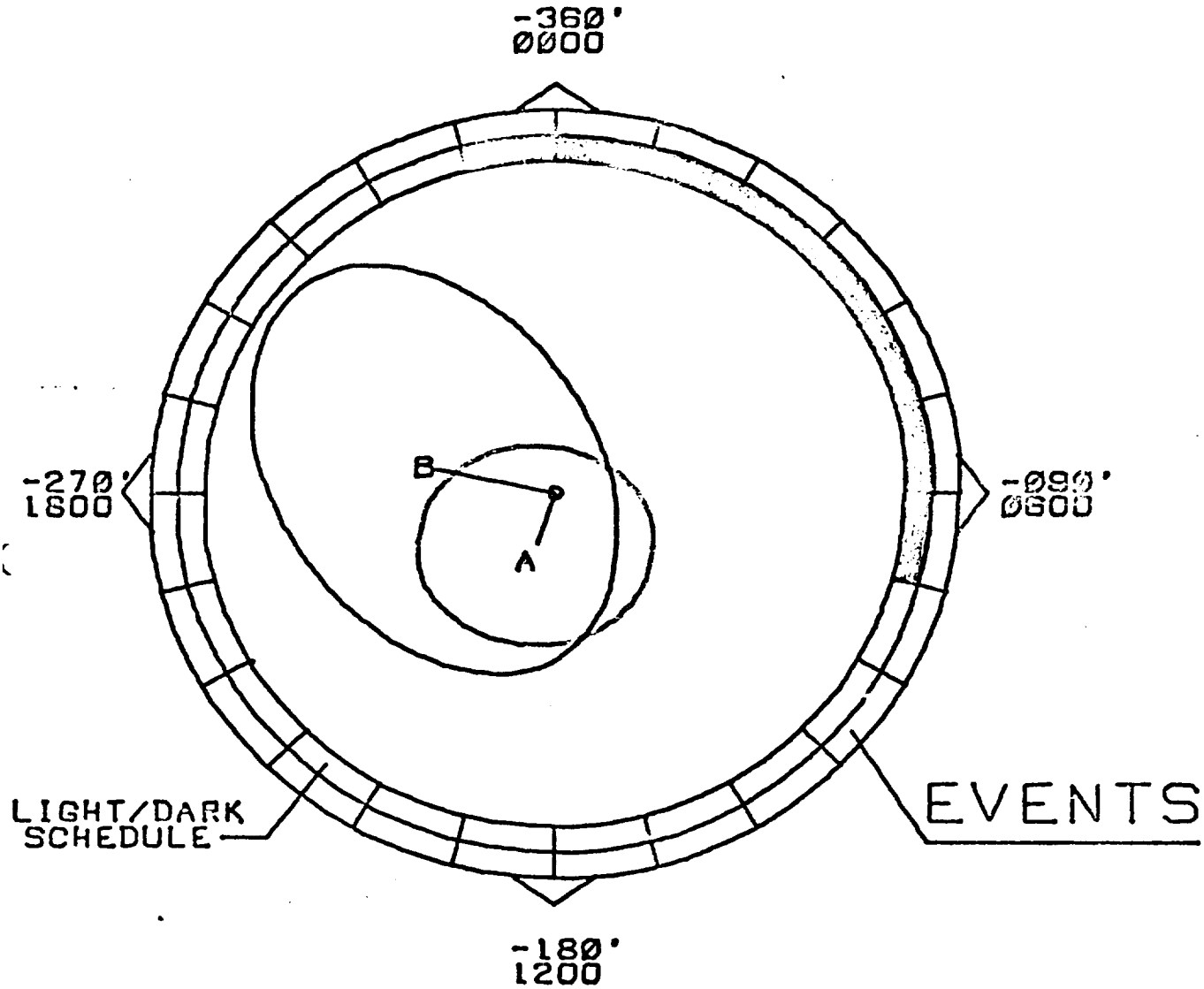
B-57

α_2 - MACROGLOBULIN



B-50

MELOY STUDY-IN RELATIVES
A=MACROGLOB B=ANTITRYP

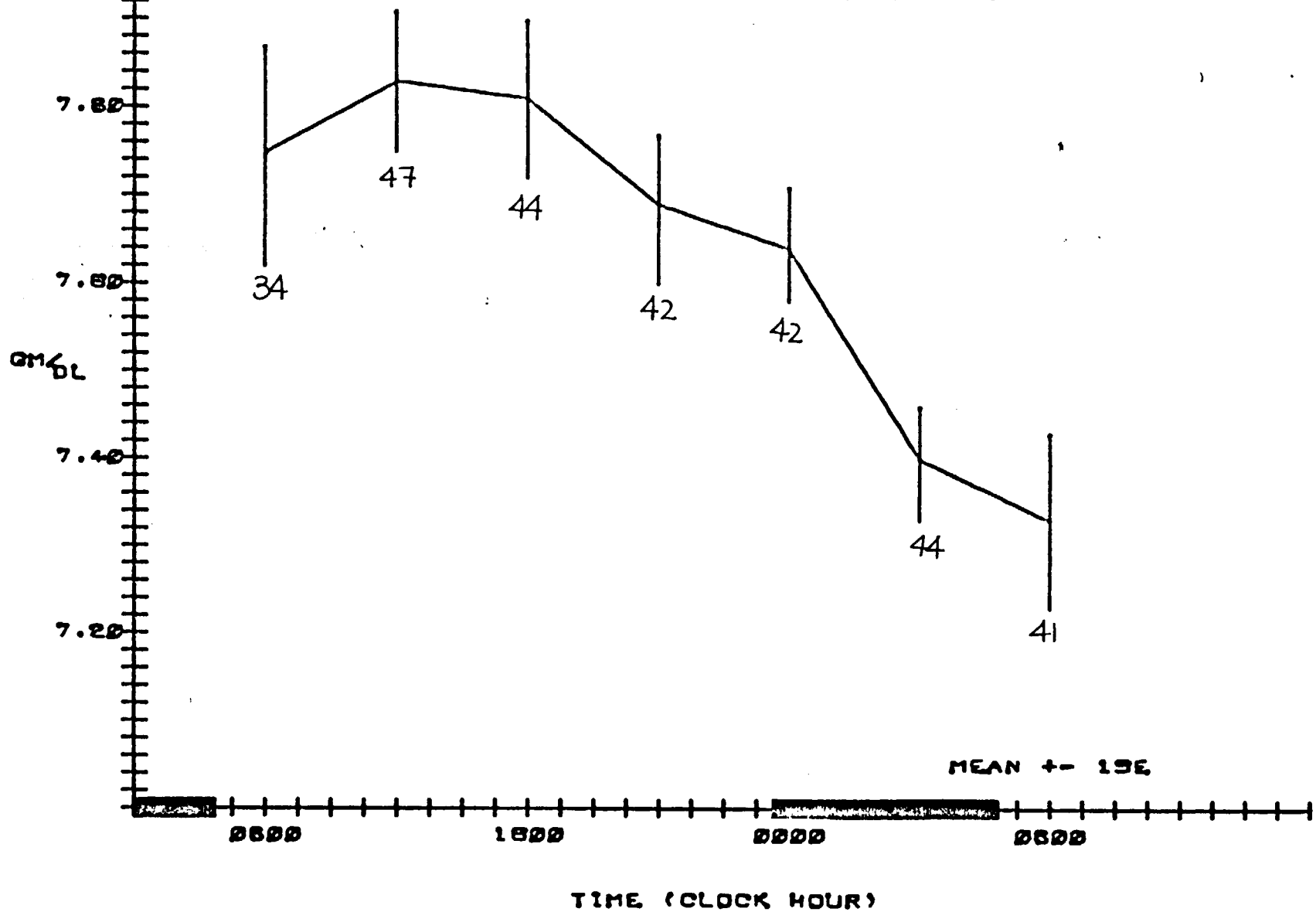


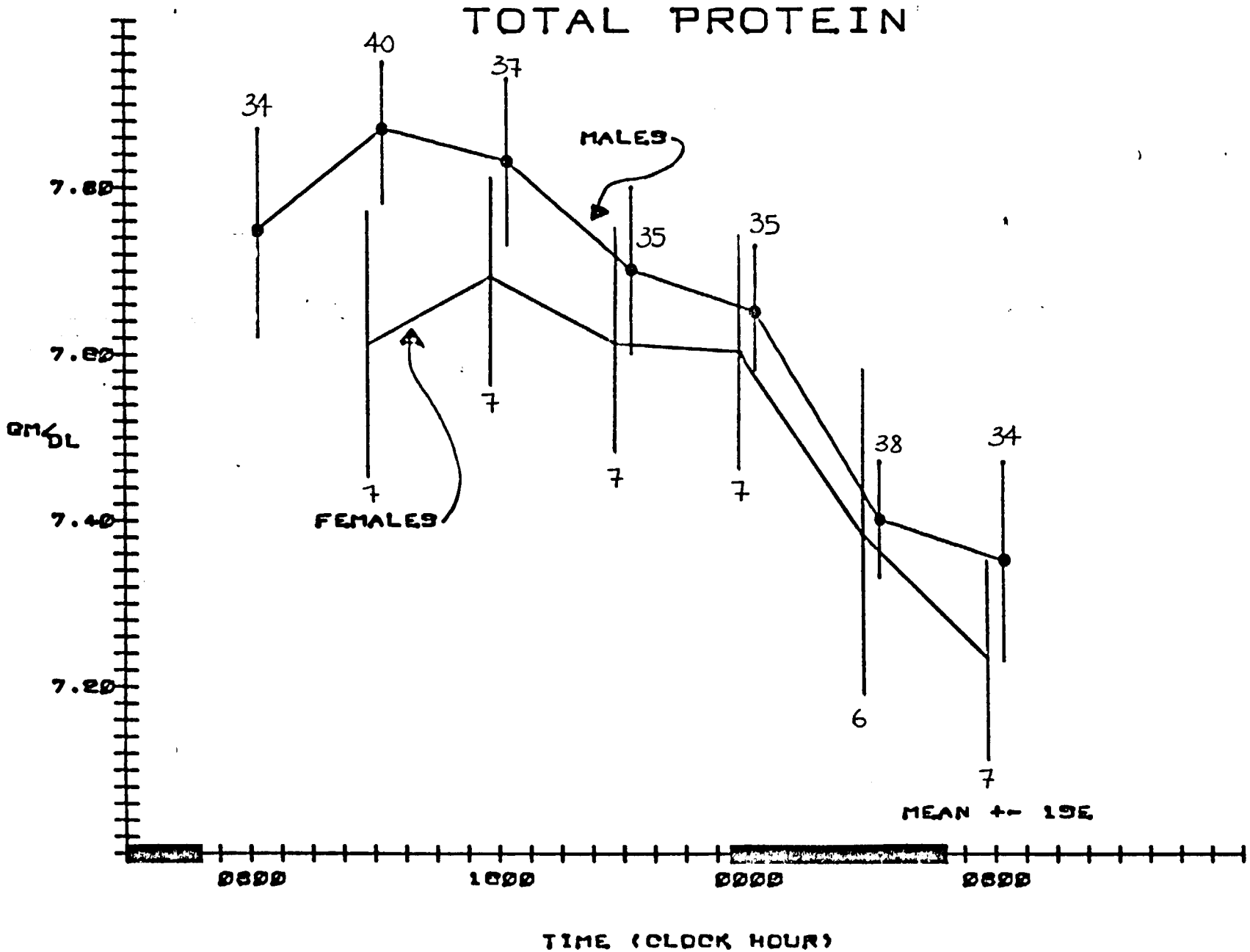
MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.00[illegible]	[illegible]	1[illegible]	[illegible] [illegible]	1.31	-1.[illegible]
B	.231	64	16	228.92 145.33 312.00	3.88	-281

B-59

TOTAL PROTEIN
MALES AND FEMALES

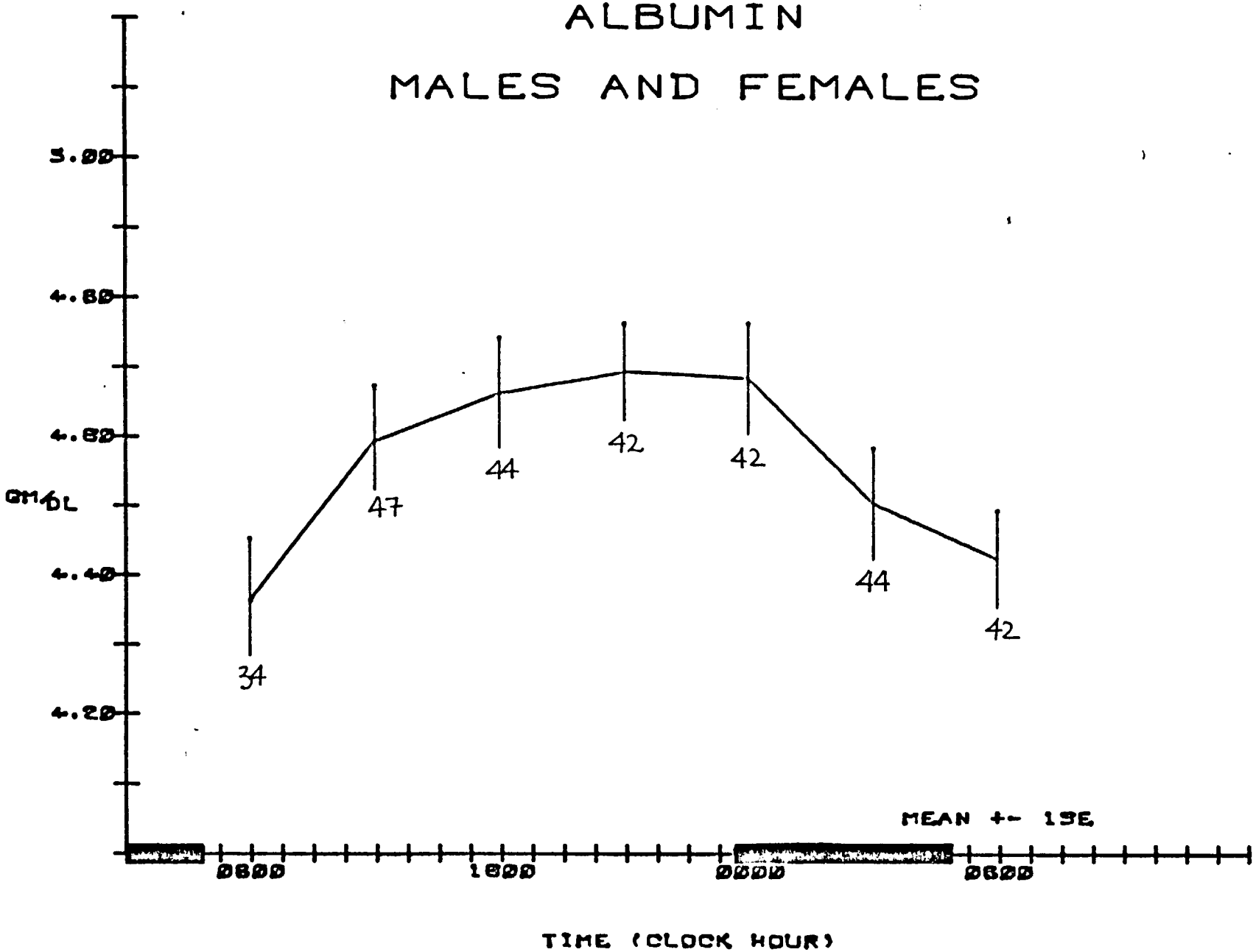



TOTAL PROTEIN
MALES
FEMALES
34
40
37
35
35
38
34
7
7
7
7
7
6
7
7.60
7.80
8.00
8.20
GM/DL
0600
1000
0000
0600
TIME (CLOCK HOUR)
MEAN +- 1SE

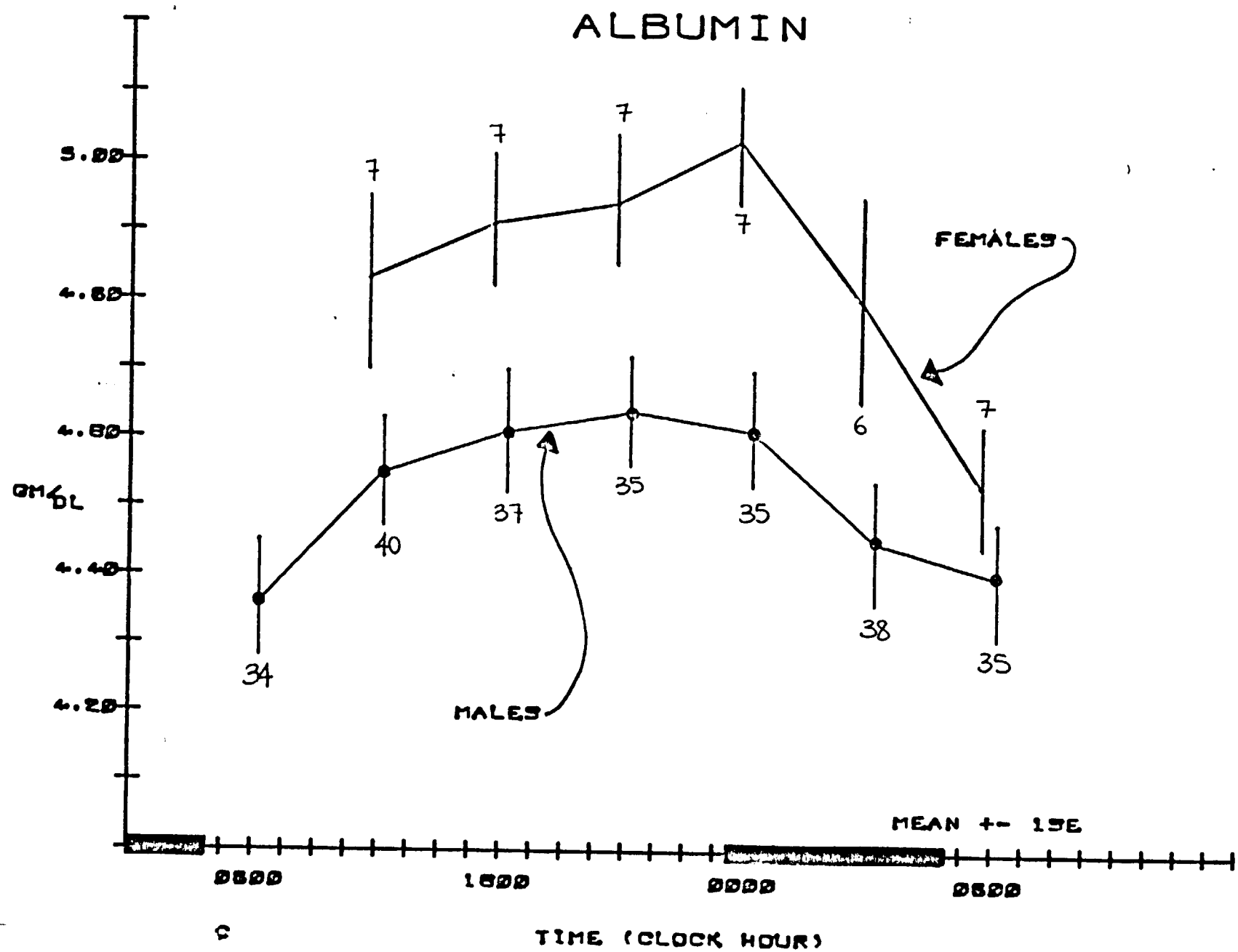
B-11

ALBUMIN

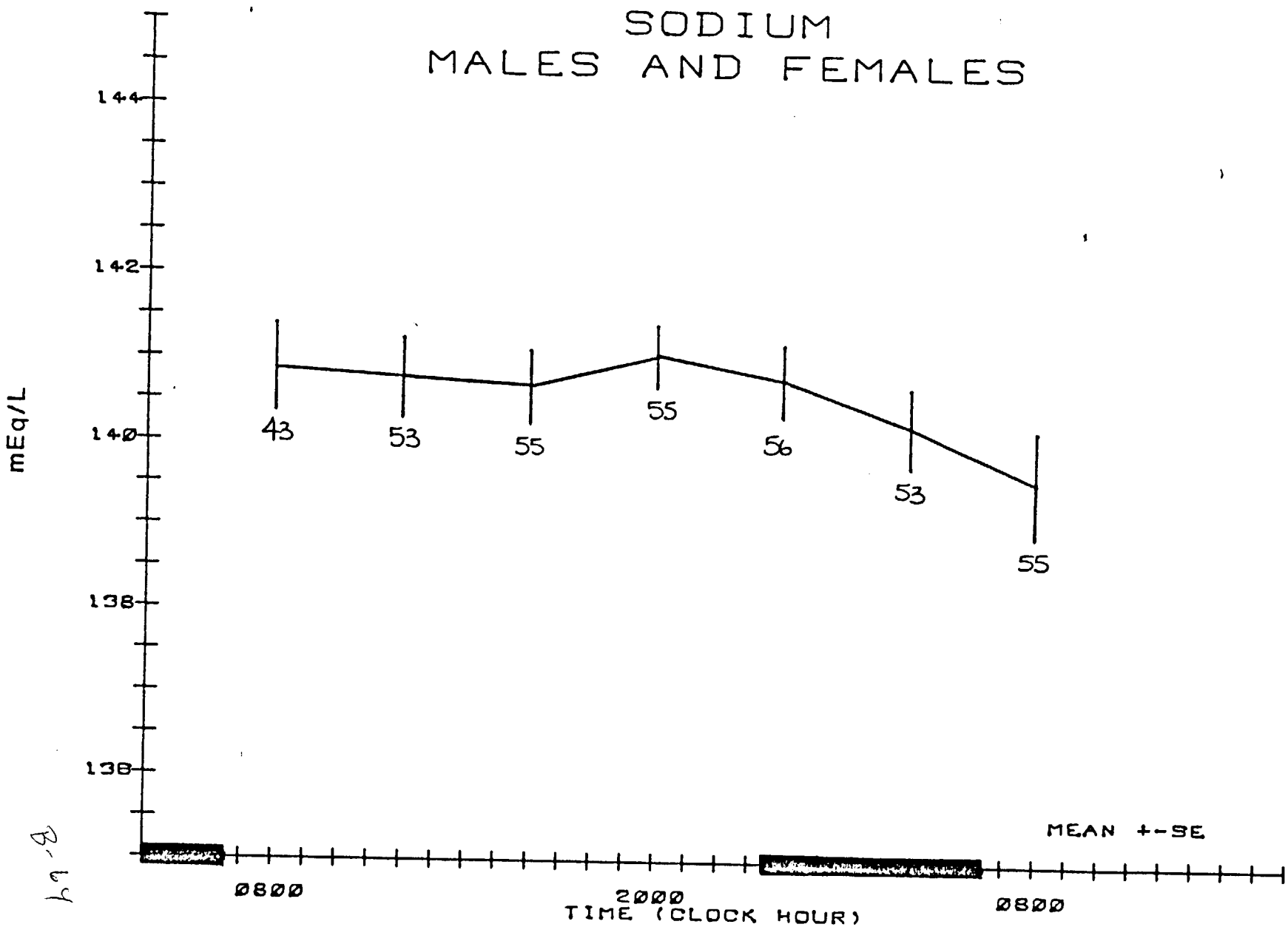
MALES AND FEMALES



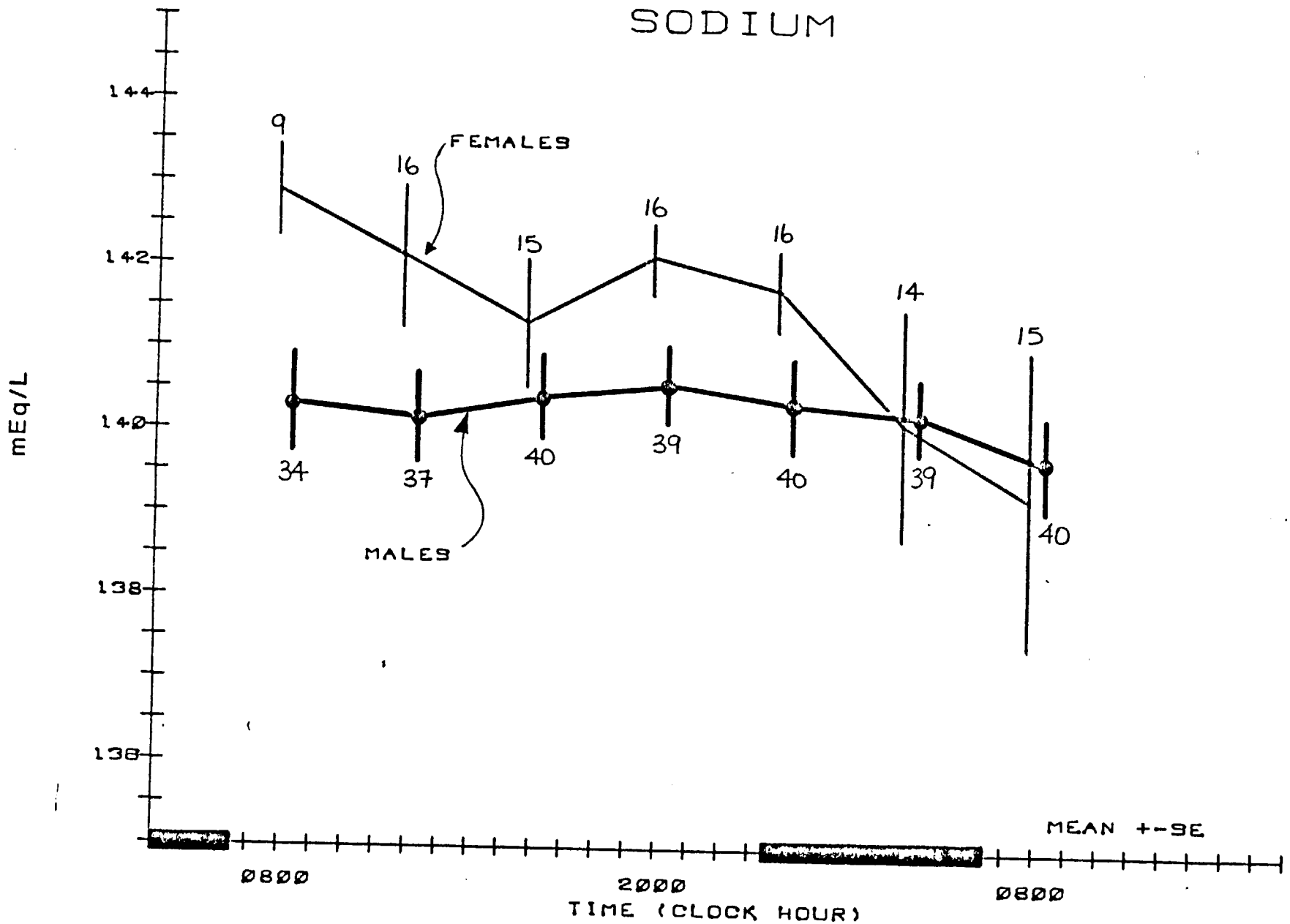
3-62


ALBUMIN
5.00
4.80
4.60
4.40
4.20
GM/DL
7
7
7
7
6
7
FEMALES
34
40
37
35
35
38
35
MALES
MEAN +- 1SE
0800
1600
0000
0800
TIME (CLOCK HOUR)

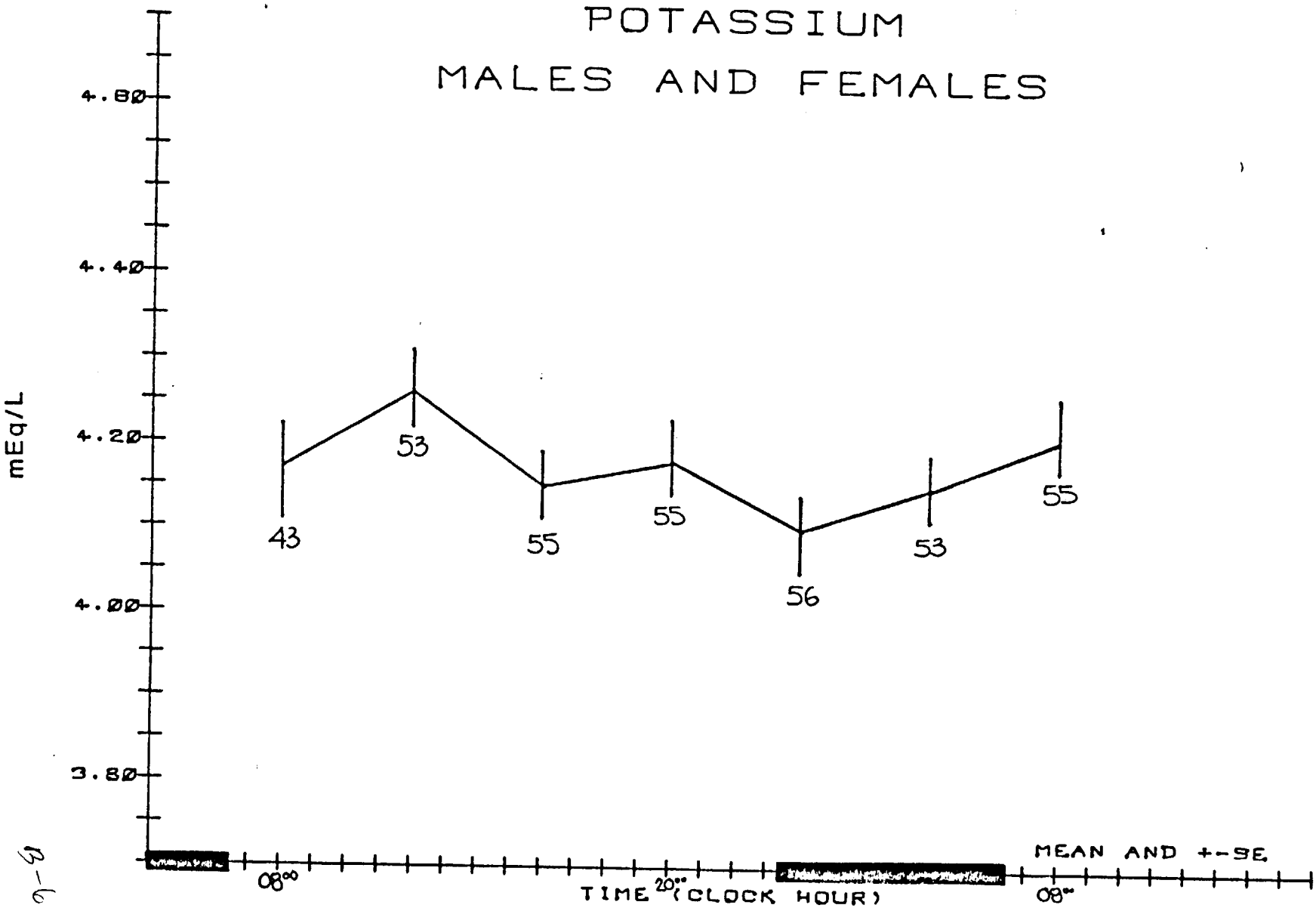
B-63N


SODIUM
MALES AND FEMALES
mEq/L
144
142
140
138
138
43
53
55
55
56
53
55
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

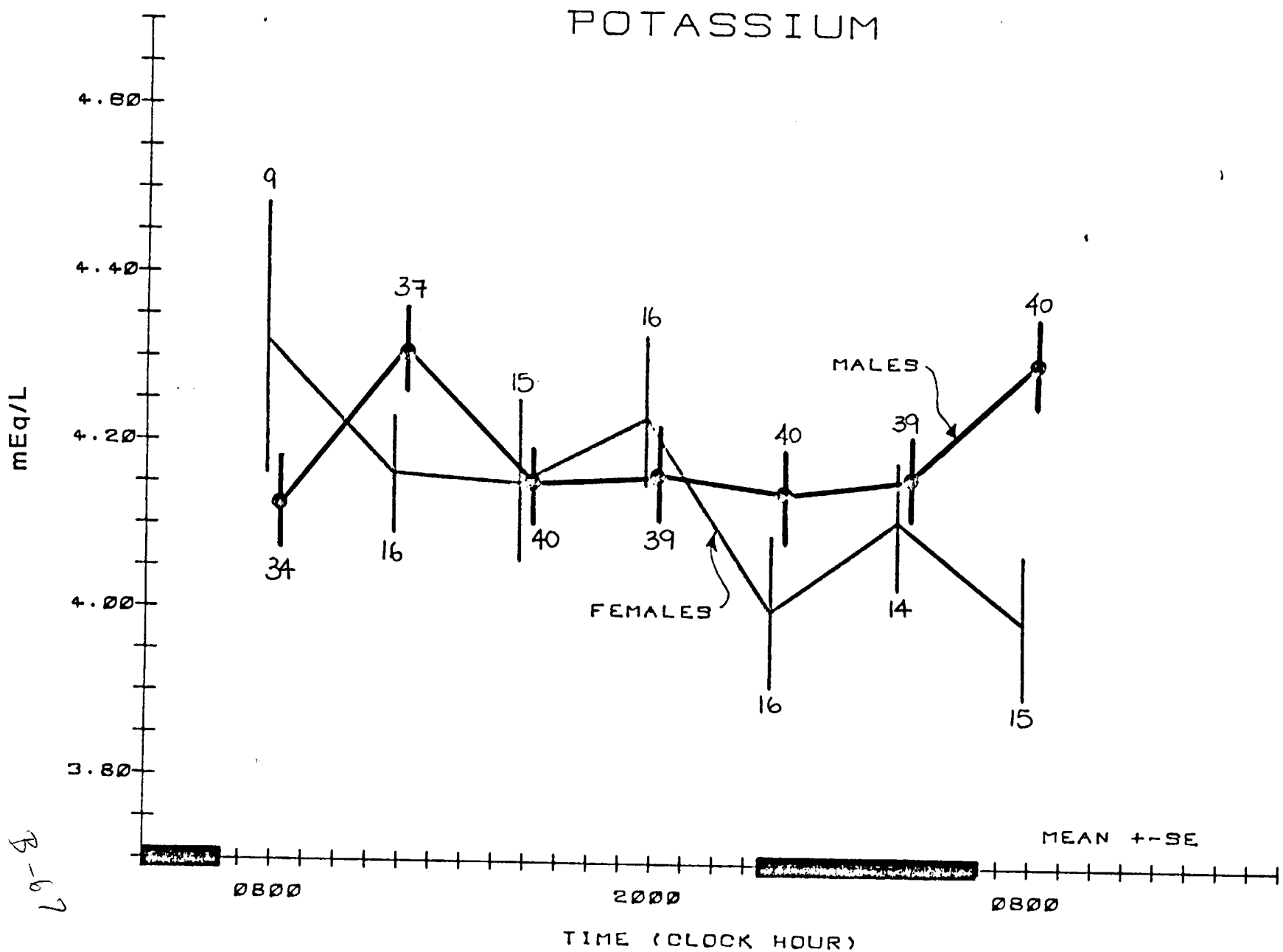
B-64


SODIUM
mEq/L
144
142
140
138
138
9
16
15
16
16
14
15
FEMALES
MALES
34
37
40
39
40
39
40
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

B-65


POTASSIUM
MALES AND FEMALES
mEq/L
4.80
4.40
4.20
4.00
3.80
43
53
55
55
56
53
55
MEAN AND +-SE
08⁰⁰
20⁰⁰
08⁰⁰
TIME (CLOCK HOUR)

B-66

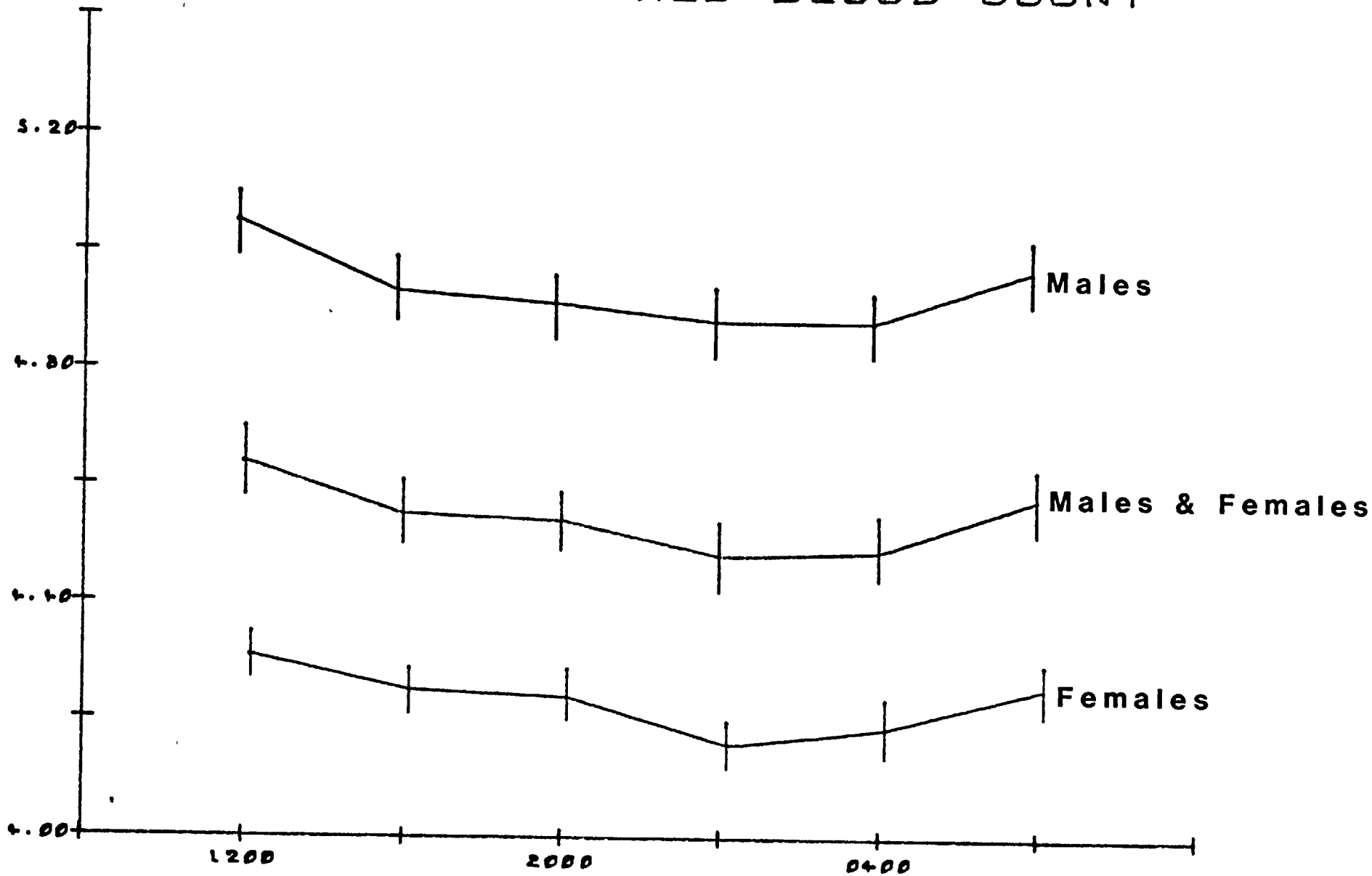

POTASSIUM
mEq/L
4.80
4.40
4.20
4.00
3.80
9
37
15
16
40
34
16
40
39
40
39
16
14
15
MALES
FEMALES
MEAN +-SE
0800
2000
0800
TIME (CLOCK HOUR)

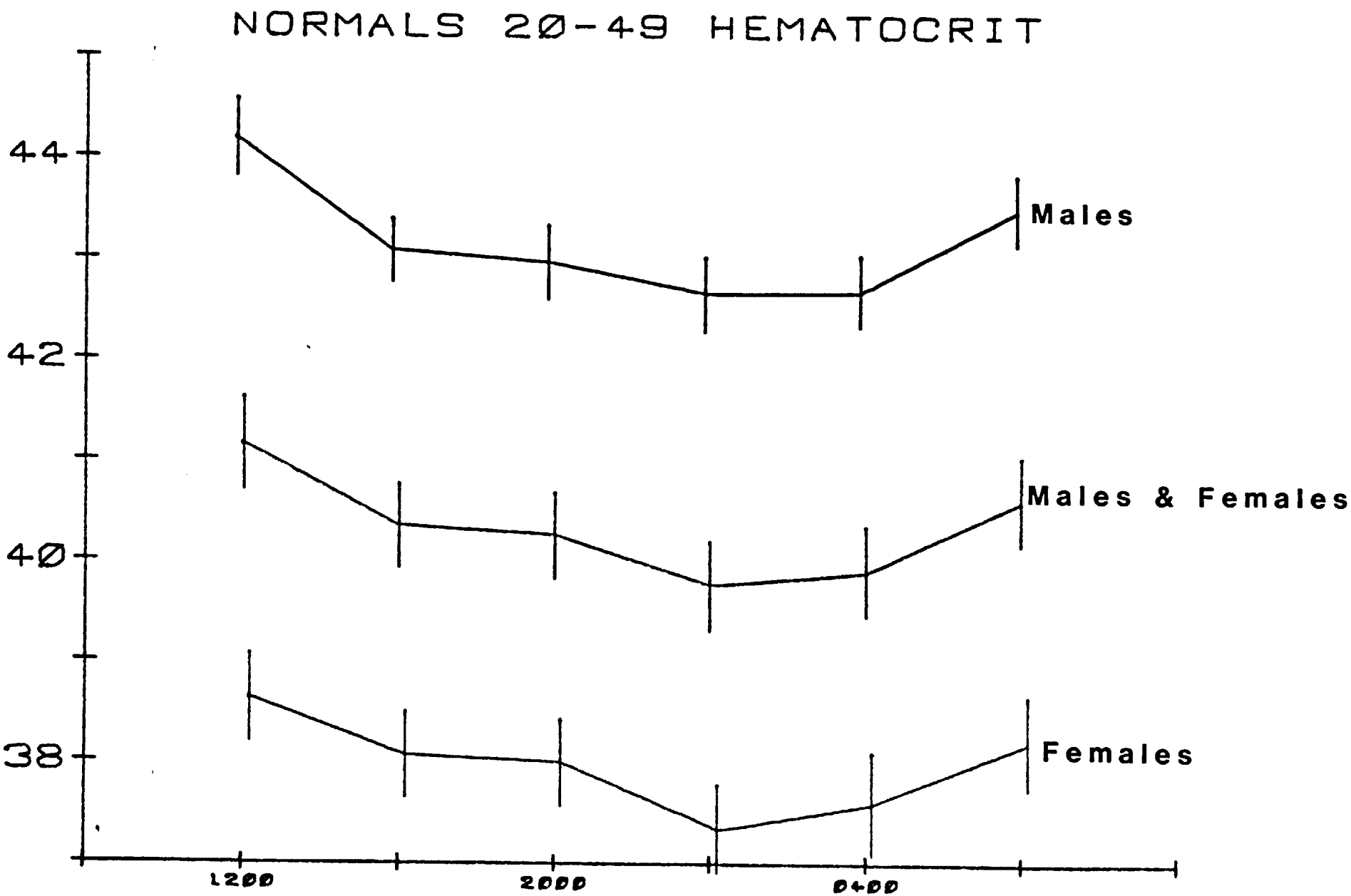
B-67

APPENDIX C

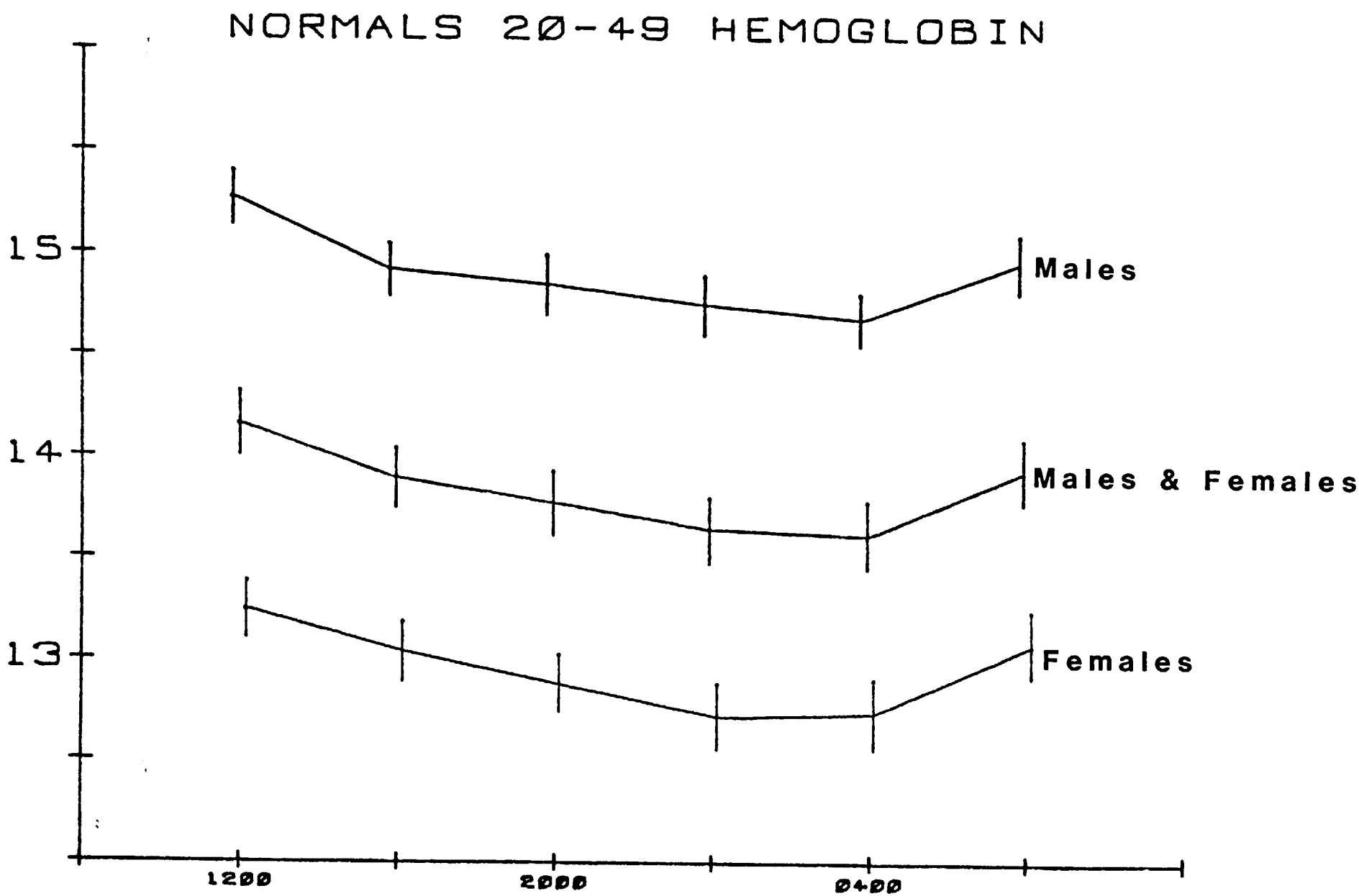
MEANS AND STANDARD DEVIATIONS OF HEMATOLOGIC VARIABLES FOR HEALTHY PERSONS 20-49 YEARS OF AGE AS A FUNCTION OF CLOCK HOUR (4-HOUR INTERVAL DATA)

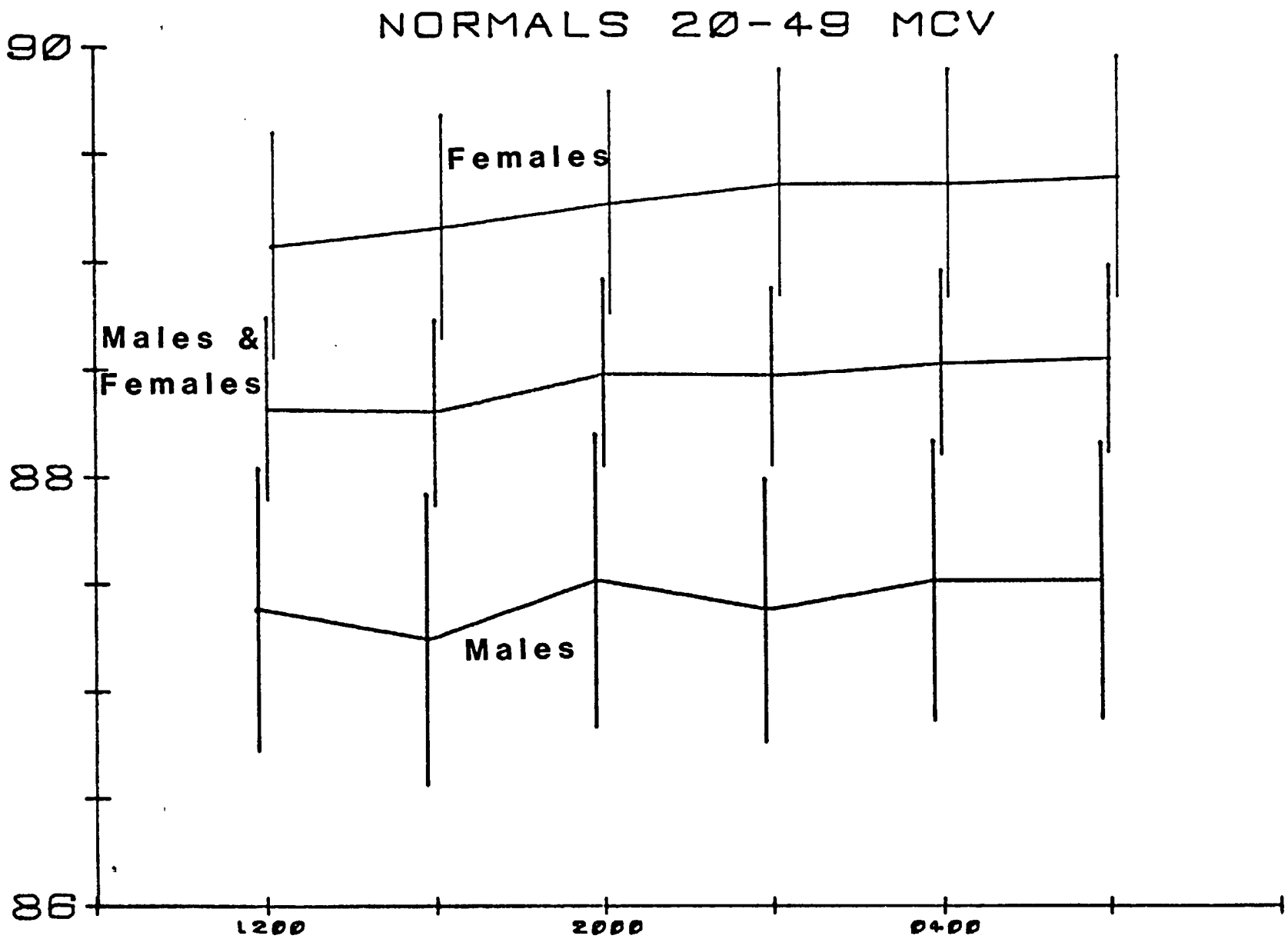
NORMALS 20-49 RED BLOOD COUNT

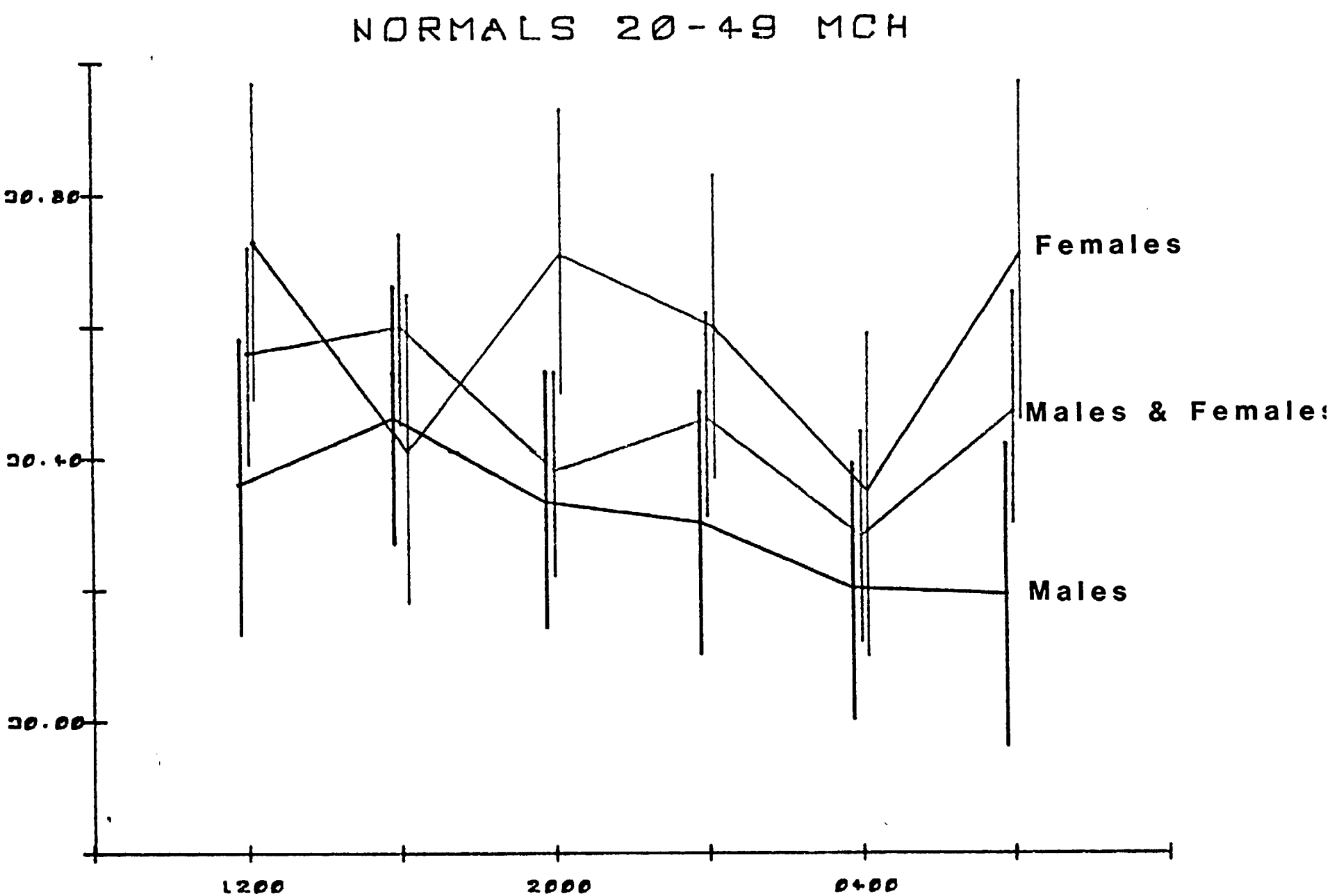


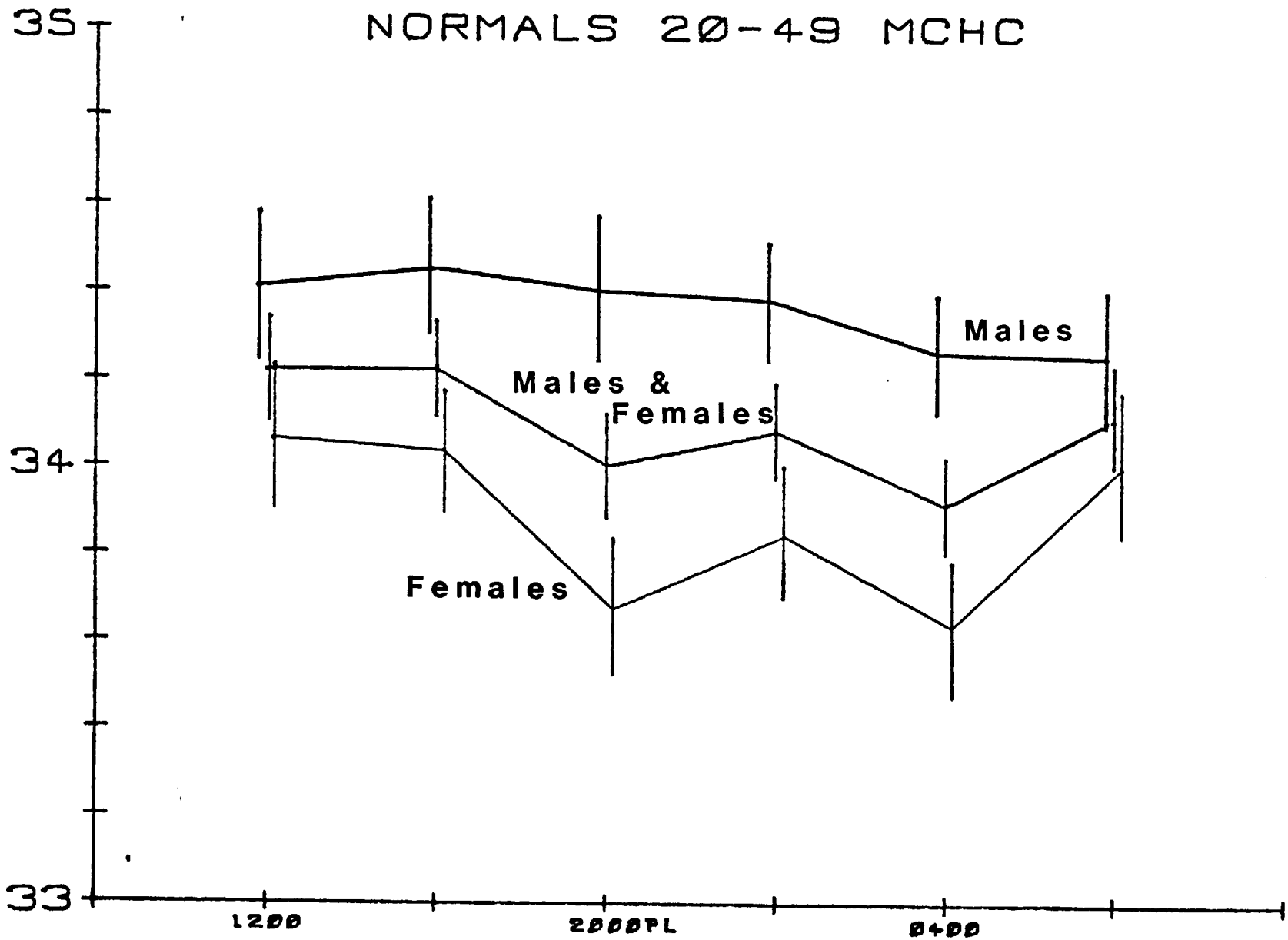

NORMALS 20-49 HEMATOCRIT
44
42
40
38
Males
Males & Females
Females
1200
2000
0400

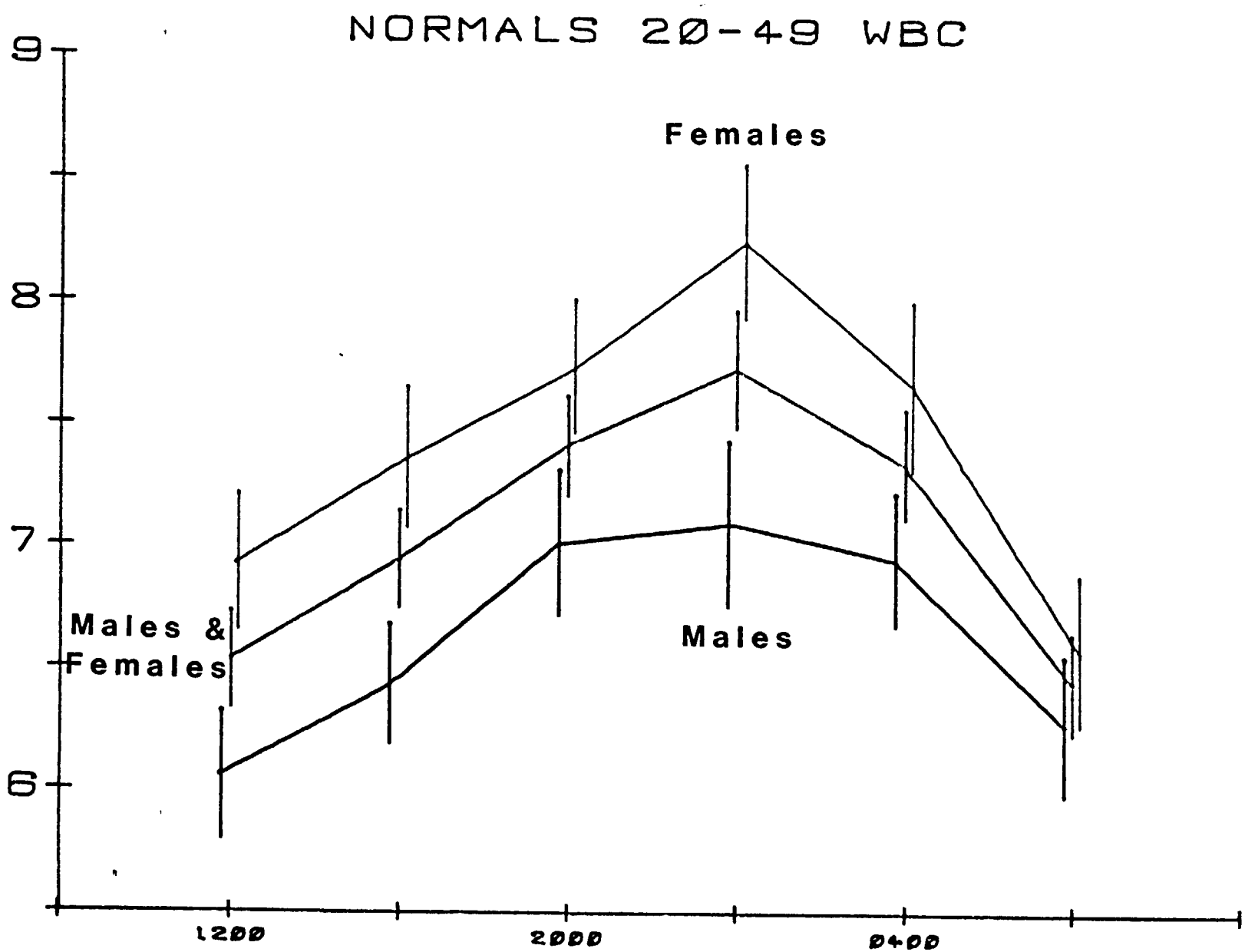
C3


NORMALS 20-49 HEMOGLOBIN
15
14
13
Males
Males & Females
Females
1200
2000
0400

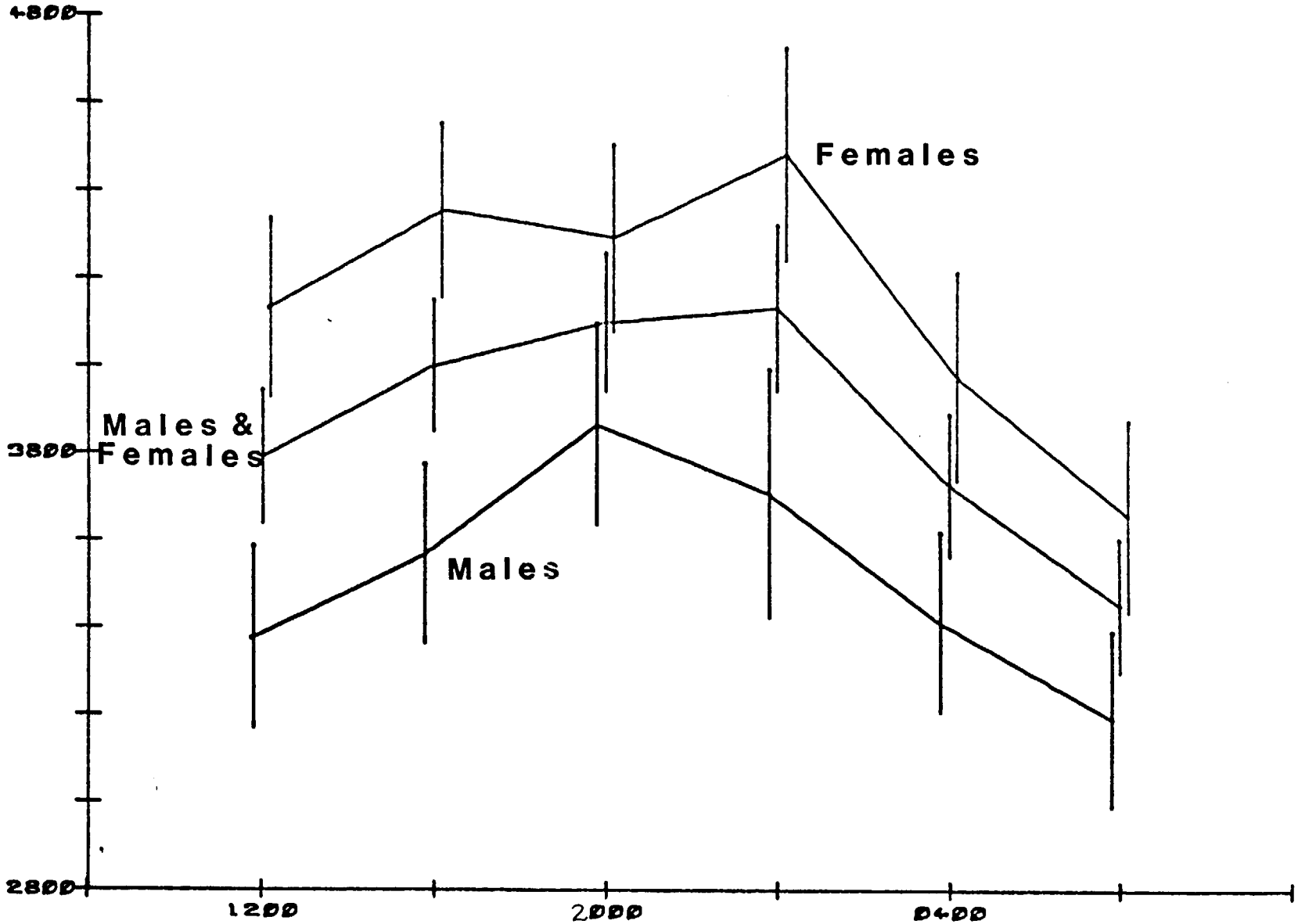

NORMALS 20-49 MCV
90
88
86
Females
Males &
Females
Males
1200
2000
0400

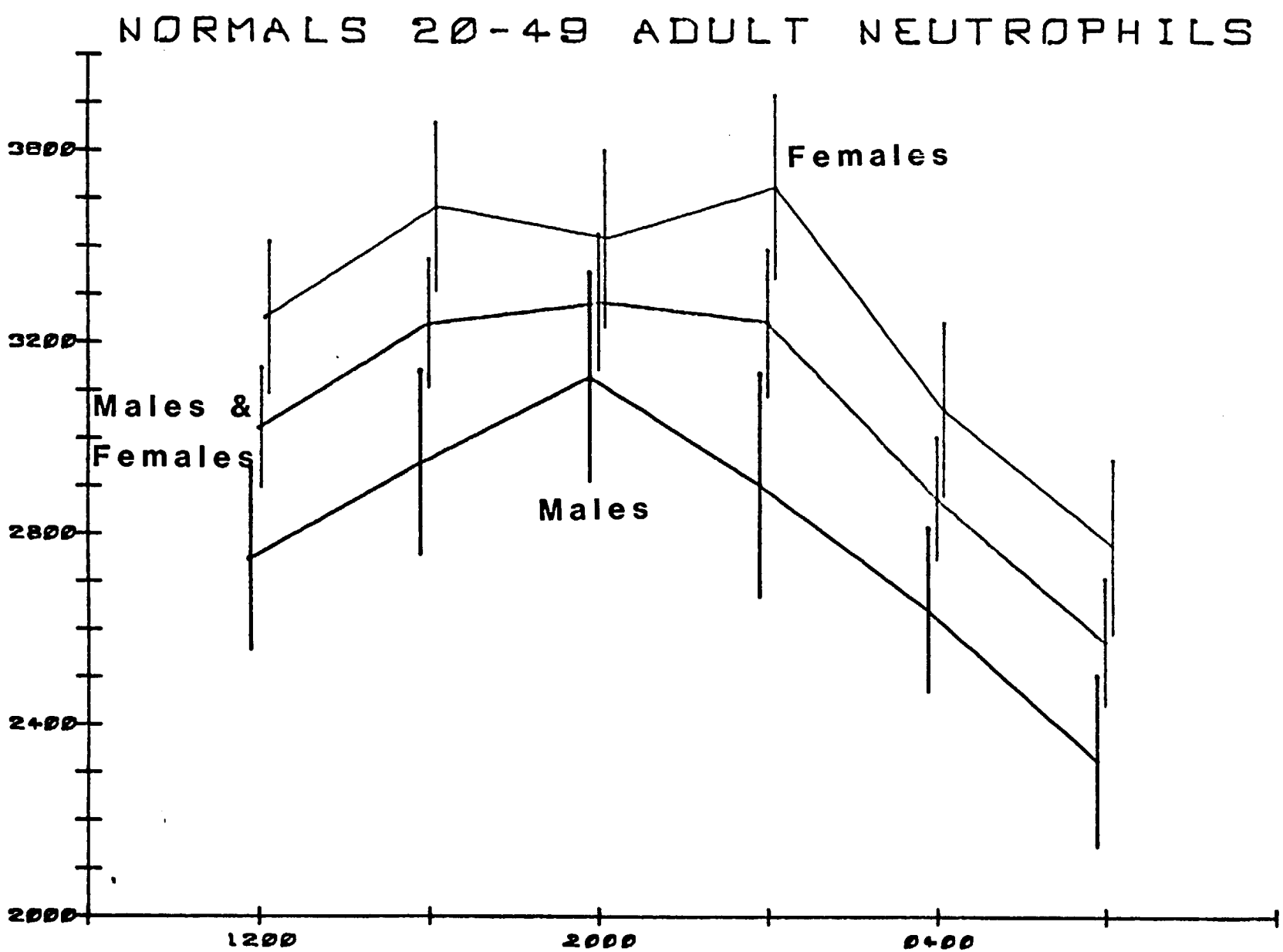

NORMALS 20-49 MCH
30.80
30.40
30.00
1200
2000
0400
Females
Males & Females
Males


NORMALS 20-49 MCHC
35
34
33
Males
Males &
Females
Females
1200
2000PL
0400

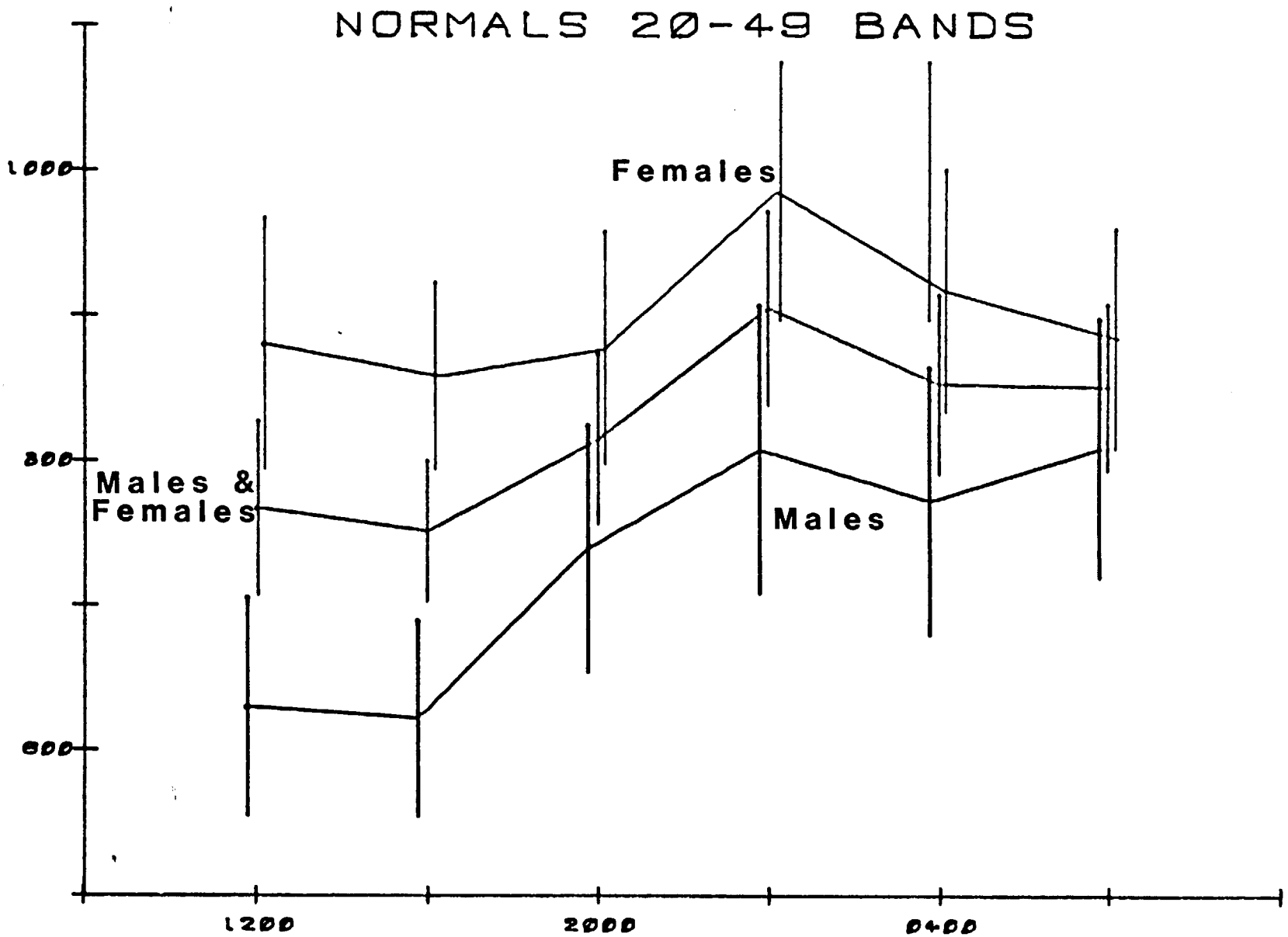

NORMALS 20-49 WBC
9
8
7
6
Females
Males & Females
Males
1200
2000
0400

NORMALS 20-49 TOTAL NEUTROPHILS

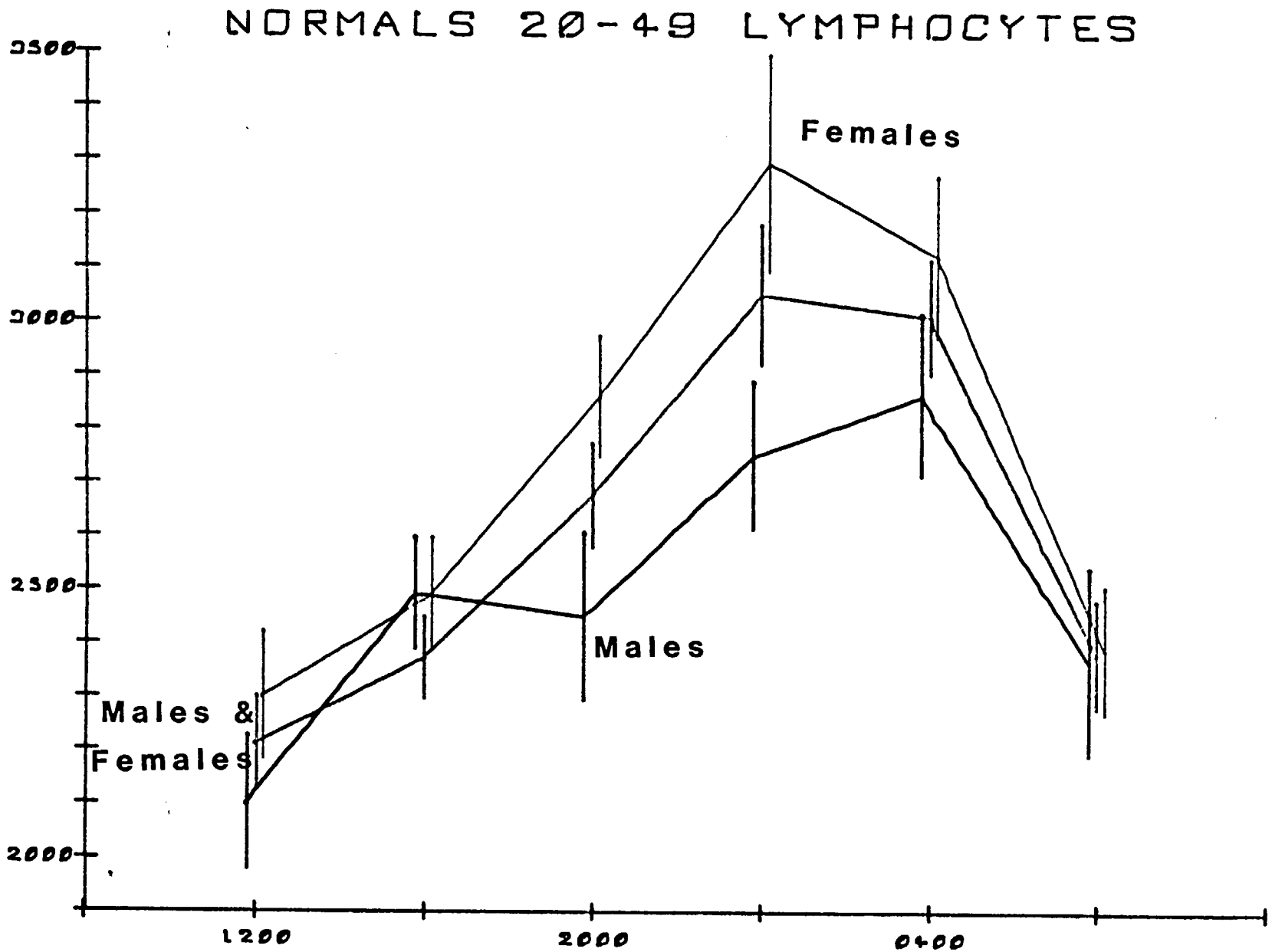



NORMALS 20-49 ADULT NEUTROPHILS
3800
3200
2800
2400
2000
1200
2000
0400
Females
Males & Females
Males

C 10N

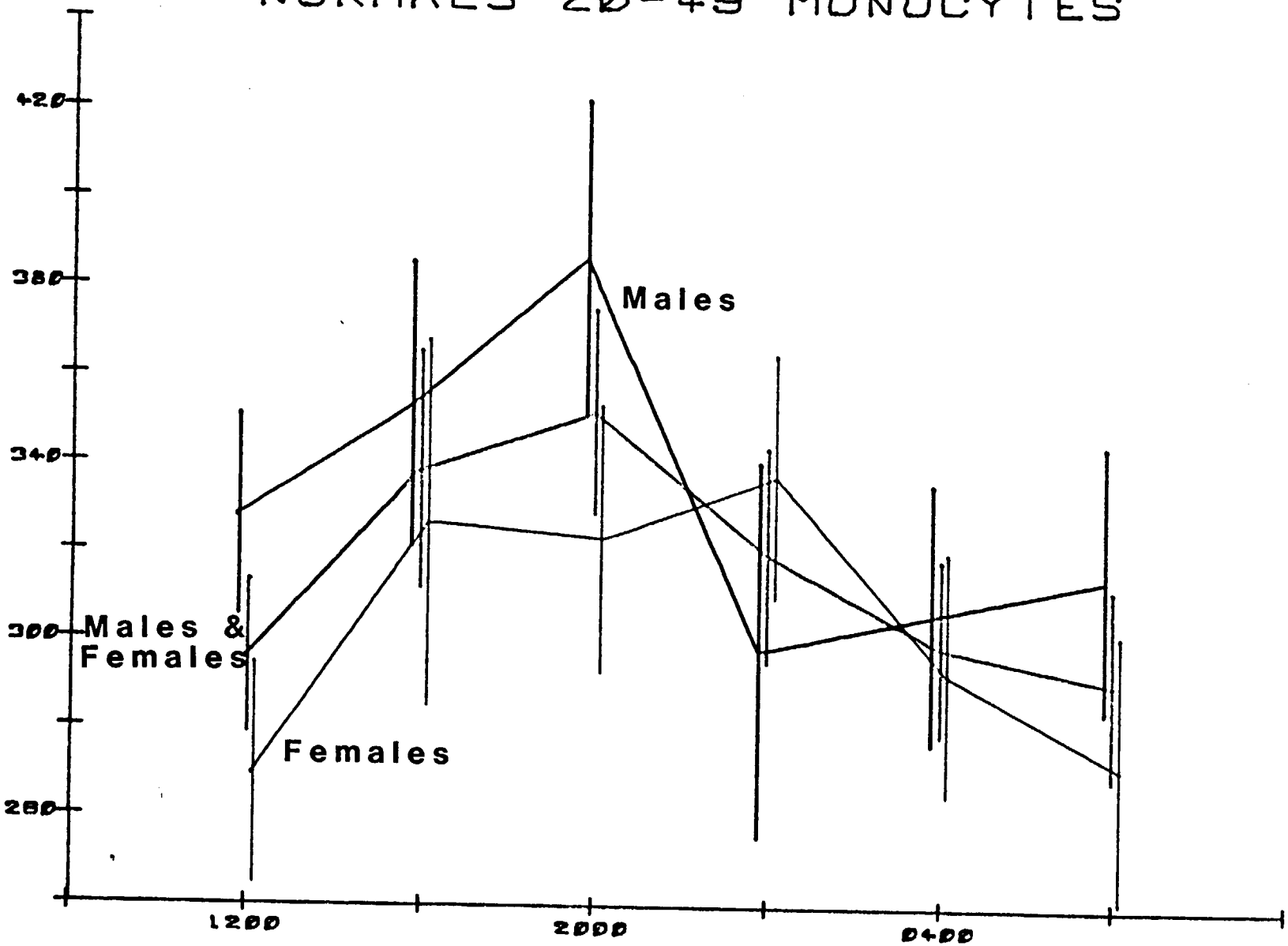

NORMALS 20-49 BANDS
1000
800
600
Females
Males & Females
Males
1200
2000
0400

C11

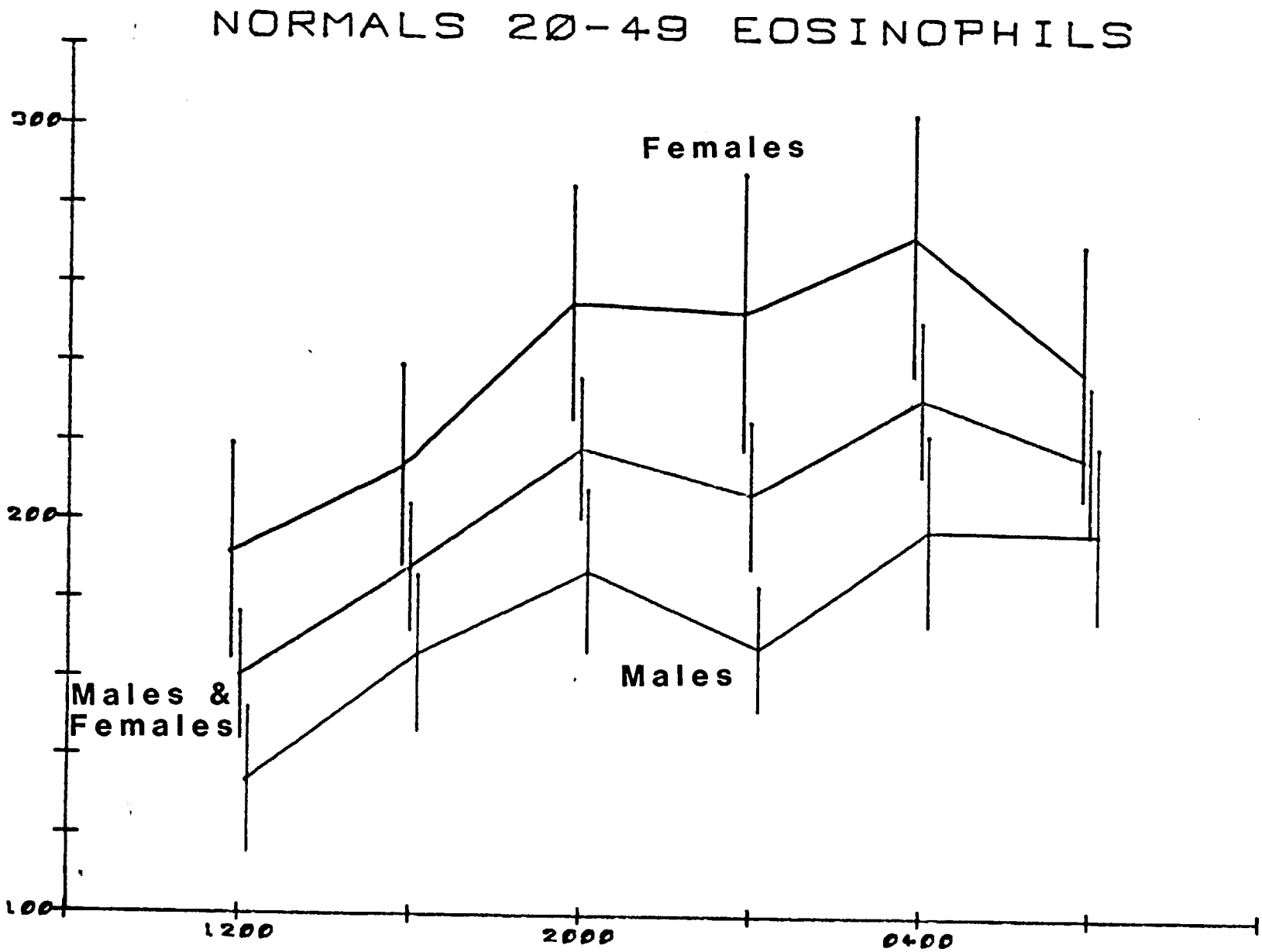

NORMALS 20-49 LYMPHOCYTES
3500
3000
2500
2000
Females
Males
Males &
Females
1200
2000
0400

C12

NORMALS 20-49 MONOCYTES

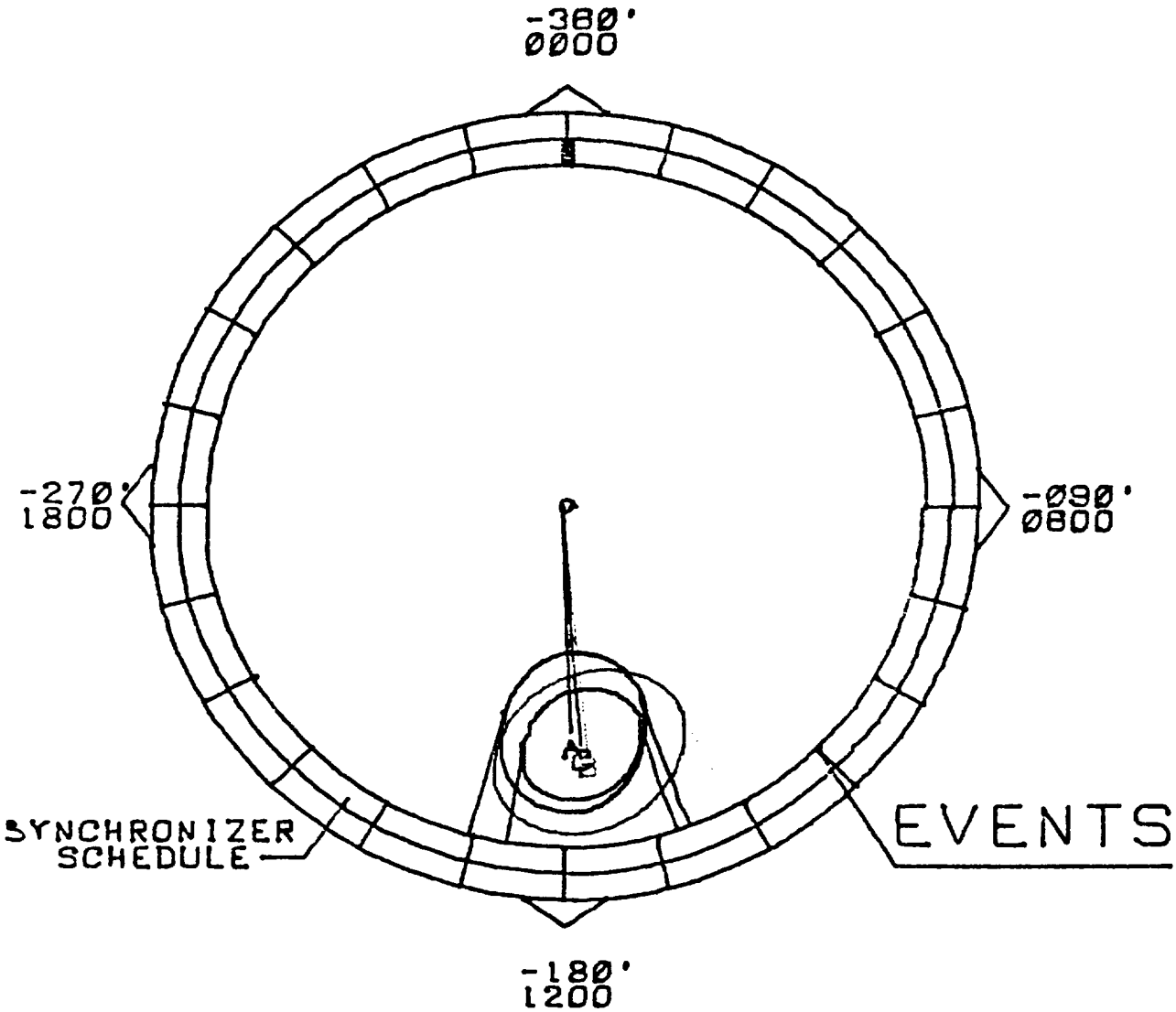


C13


NORMALS 20-49 EOSINOPHILS
300
200
100
Females
Males
Males &
Females
1200
2000
0400

C14

NORMALS 20-49 HGB
A = M B = F C = M+F

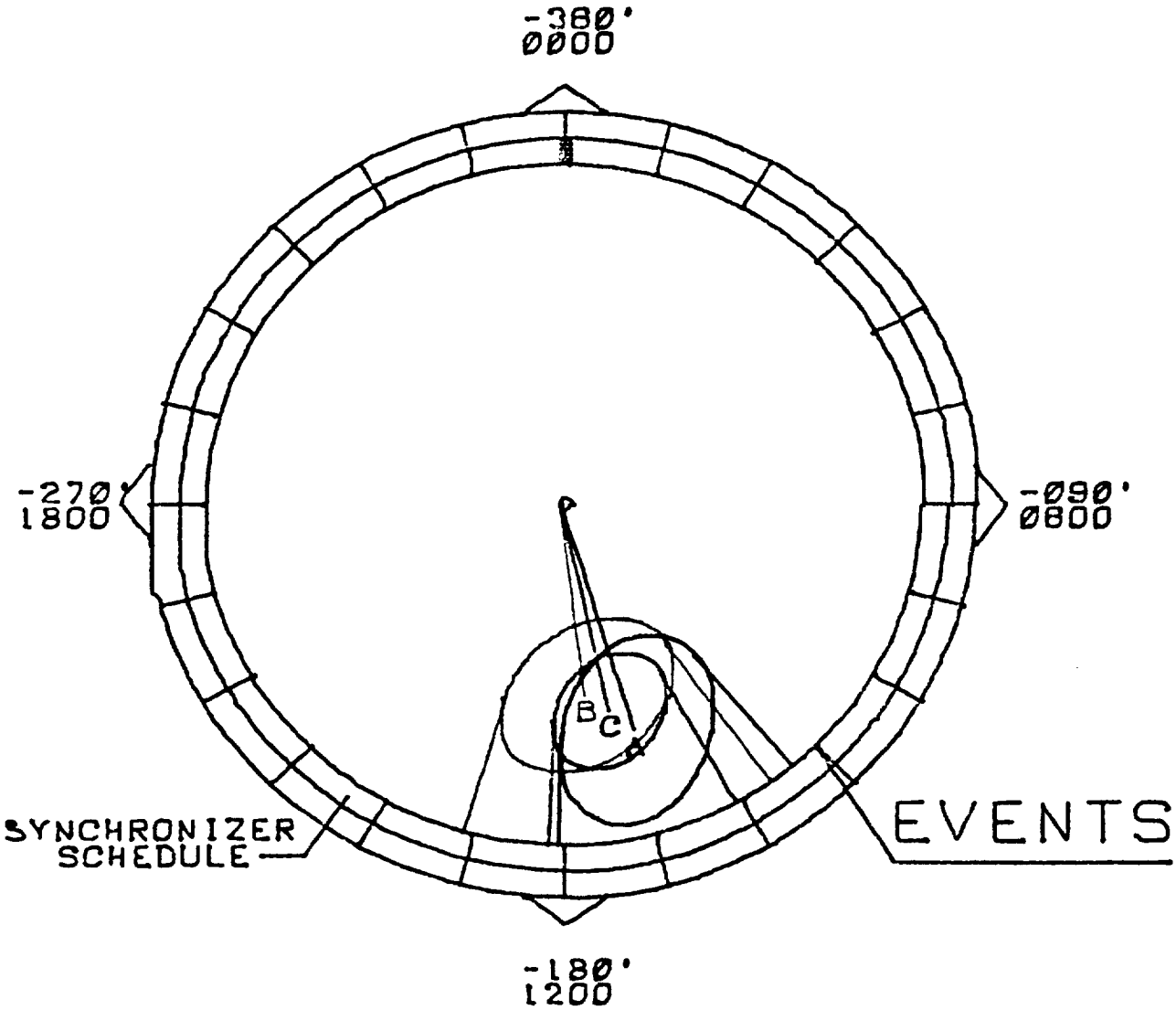


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	44	29	14.99 13.55 16.43	0.25 0.18 0.33	-177 -158 -195
B	.000	56	37	13.02 11.32 14.73	0.27 0.18 0.36	-174 -151 -194
C	.000	51	68	13.88 11.39 16.38	0.28 0.20 0.32	-175 -161 -189

C15

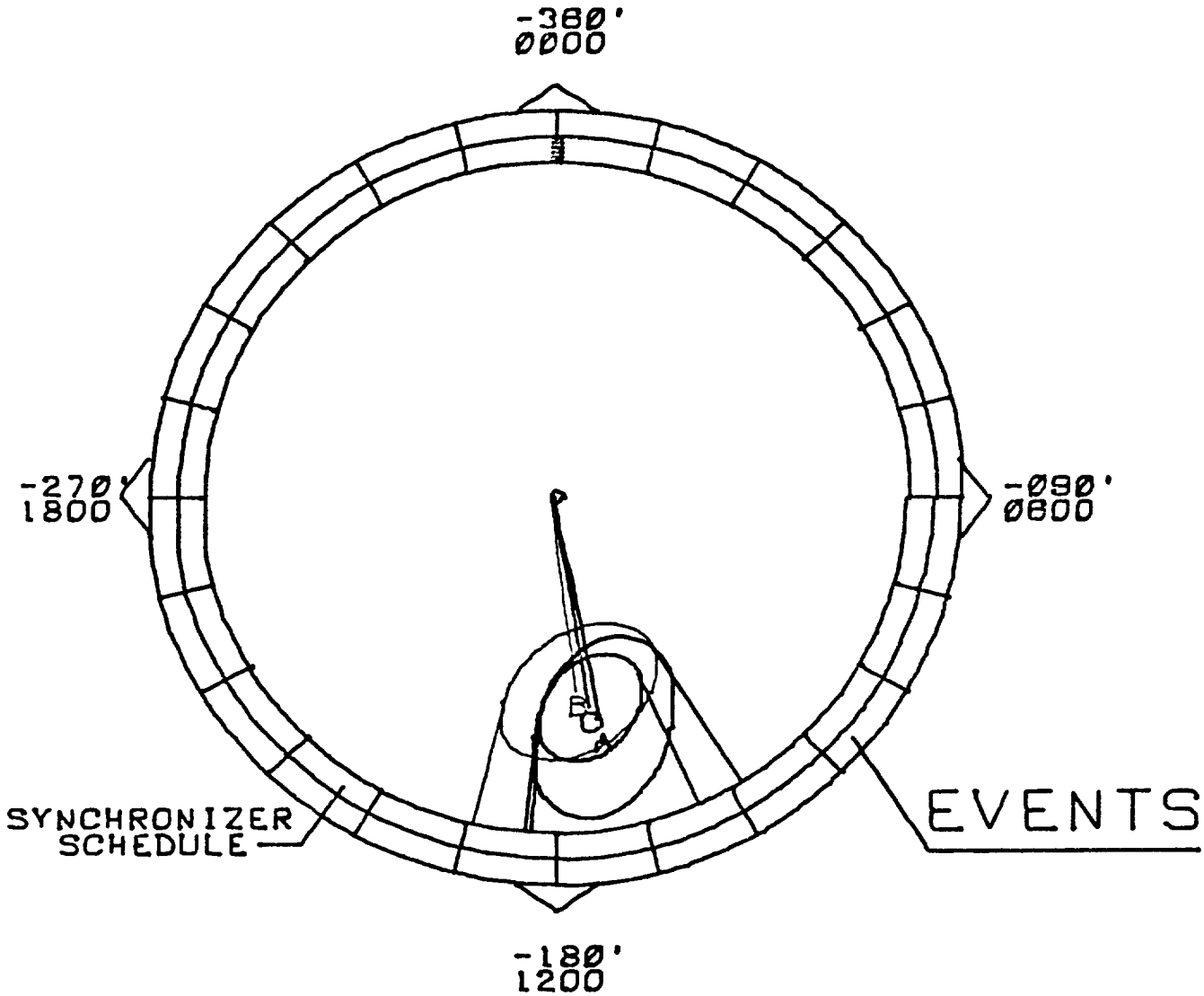
NORMALS 20-49 HCT
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	49	28	43.27 39.80 46.75	0.71 0.44 0.98	-182 -140 -180
B	.000	50	37	38.97 28.25 49.69	0.57 0.38 0.80	-172 -144 -198
C	.000	50	68	40.88 31.55 50.17	0.83 0.47 0.80	-187 -150 -182

NORMALS 20-49 RBC
A=M B=F C=M AND F

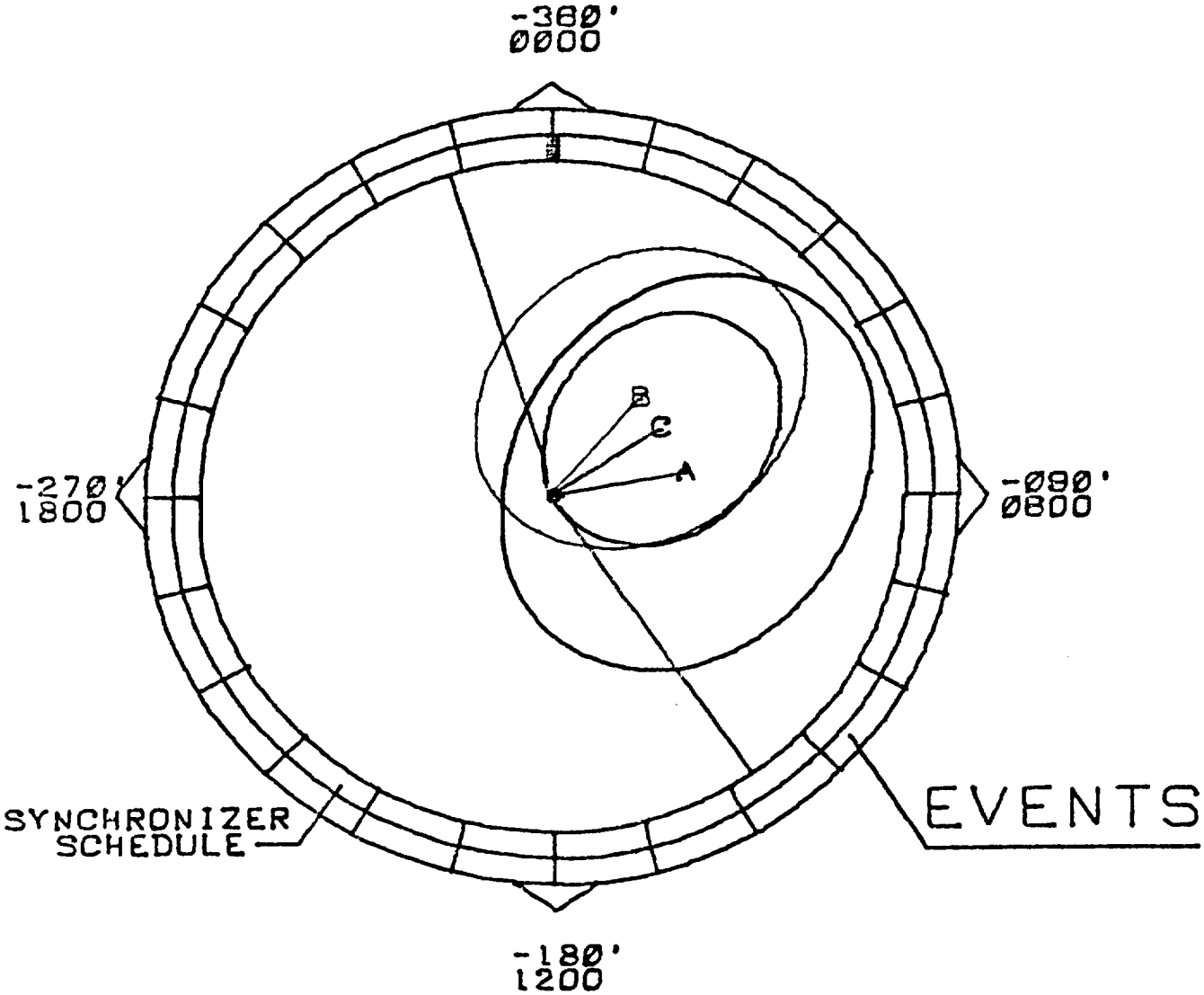


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	51	29	4.95 4.39 5.51	0.08 0.05 0.11	-168 -147 -185
B	.000	49	37	4.25 3.77 4.72	0.08 0.04 0.09	-172 -147 -193
C	.000	50	66	4.58 3.70 5.42	0.07 0.05 0.09	-170 -155 -184

C17

NORMALS 20-49 MCV
A=M B=F C=M AND F

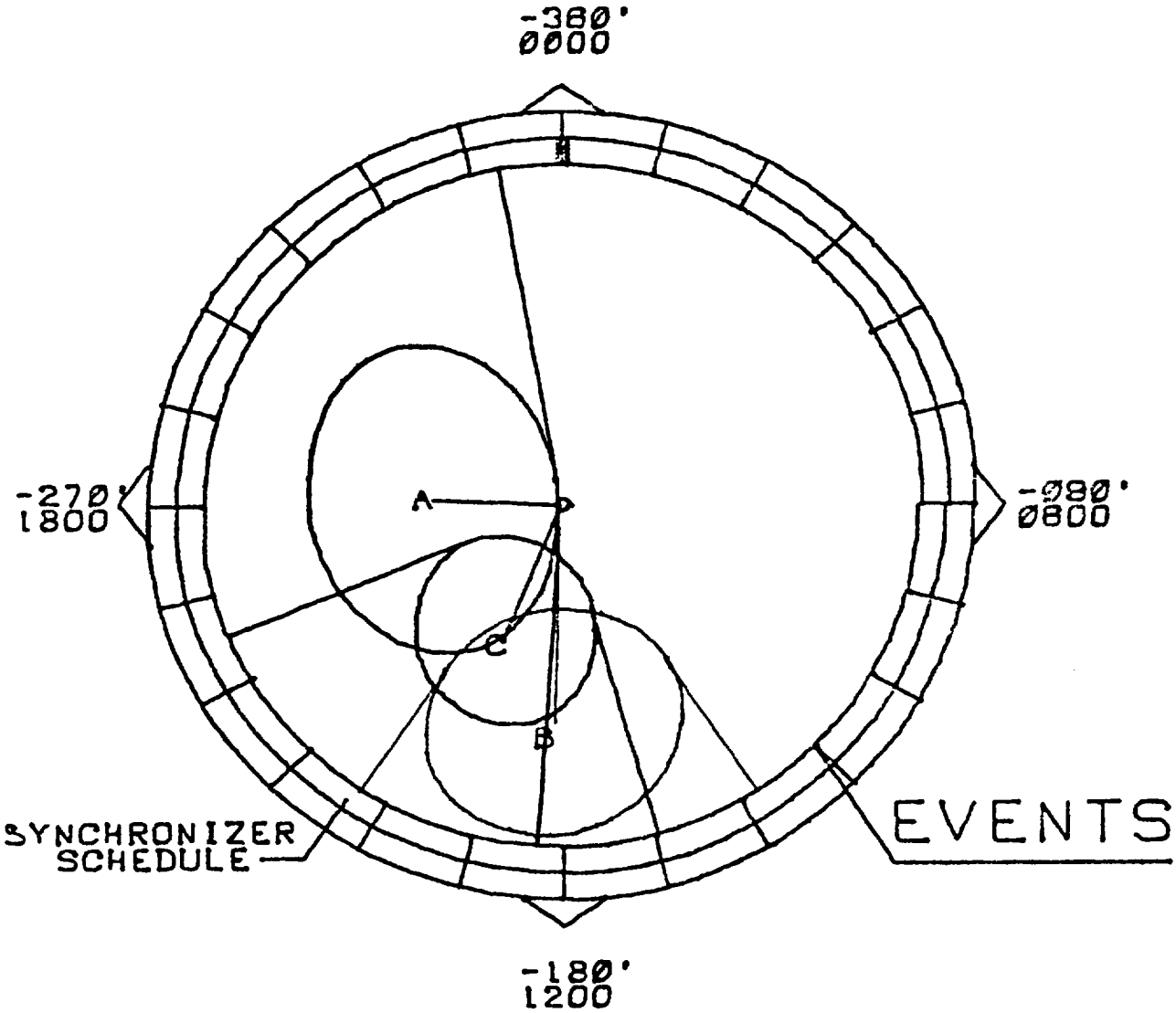


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.189	32	28	87.20 80.44 93.96	0.12	-80
B	.146	35	37	89.42 83.44 95.40	0.12	-41
C	.047	34	65	88.48 81.82 95.10	0.11 0.00 0.23	-57 -342 -145

C18

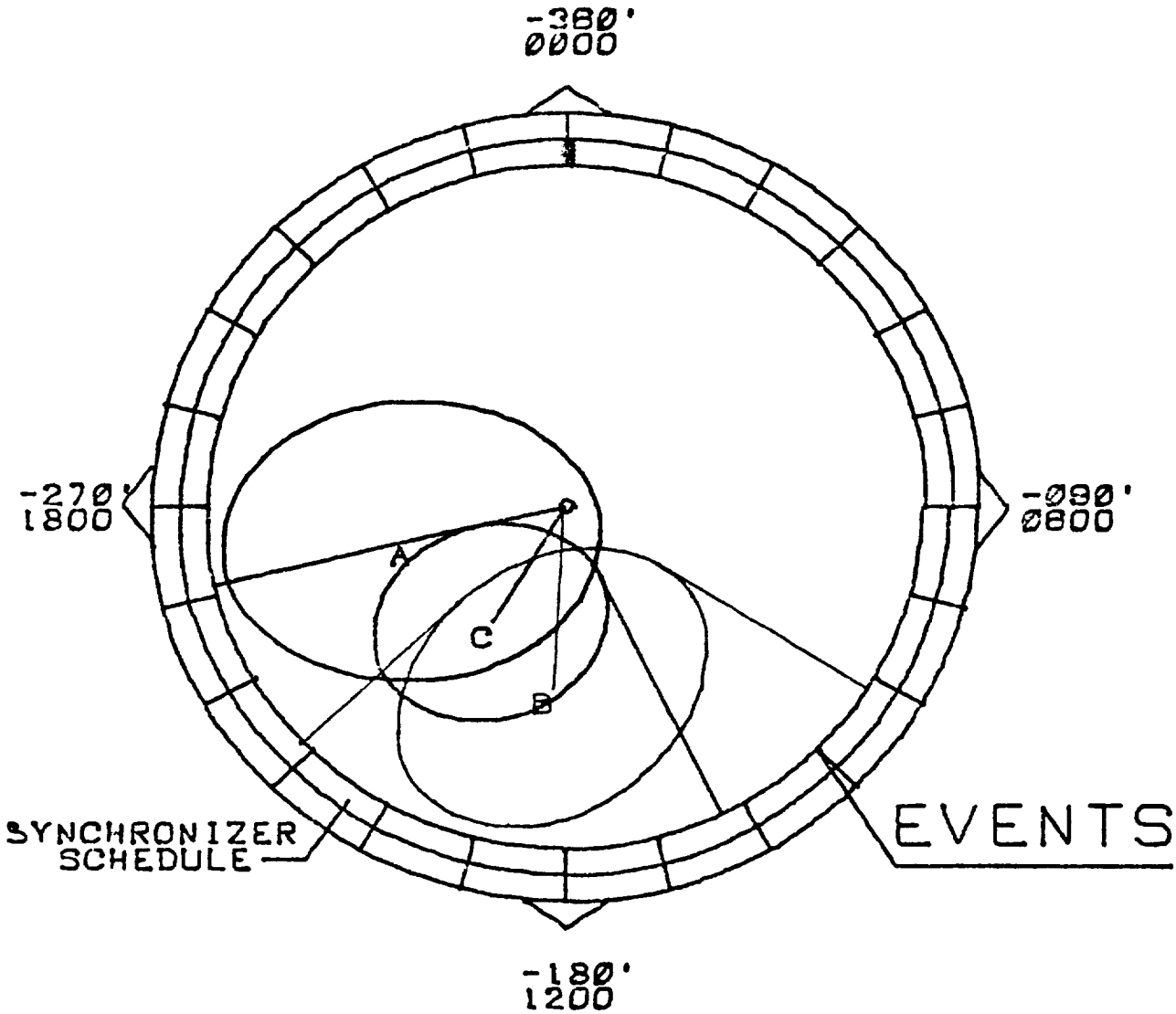
NORMALS 20-49 MCHC
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.048	38	27	34.43 33.18 35.68	0.12 0.00 0.24	-272 -184 -349
B	.000	37	39	33.98 32.35 35.61	0.21 0.10 0.33	-181 -148 -214
C	.001	36	66	34.17 32.82 35.71	0.13 0.04 0.23	-202 -163 -247

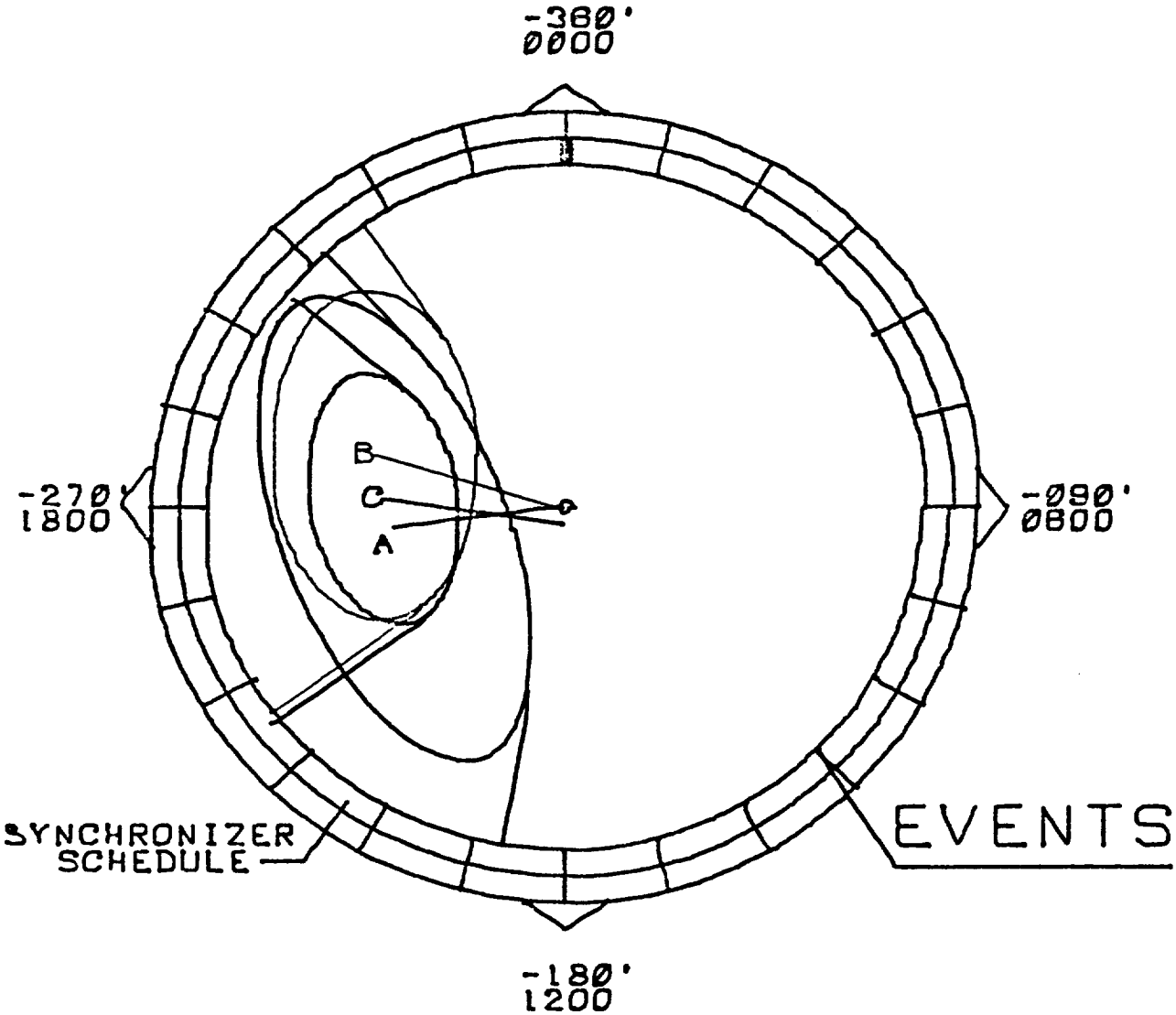
NORMALS 20-49 MCH
A = M B = F C = M+F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.113	36	29	30.36 28.16 32.56	0.12	-257
B	.007	37	37	30.70 28.14 33.27	0.14 0.03 0.26	-183 -121 -226
C	.008	37	68	30.55 28.14 32.97	0.11 0.02 0.20	-211 -153 -258

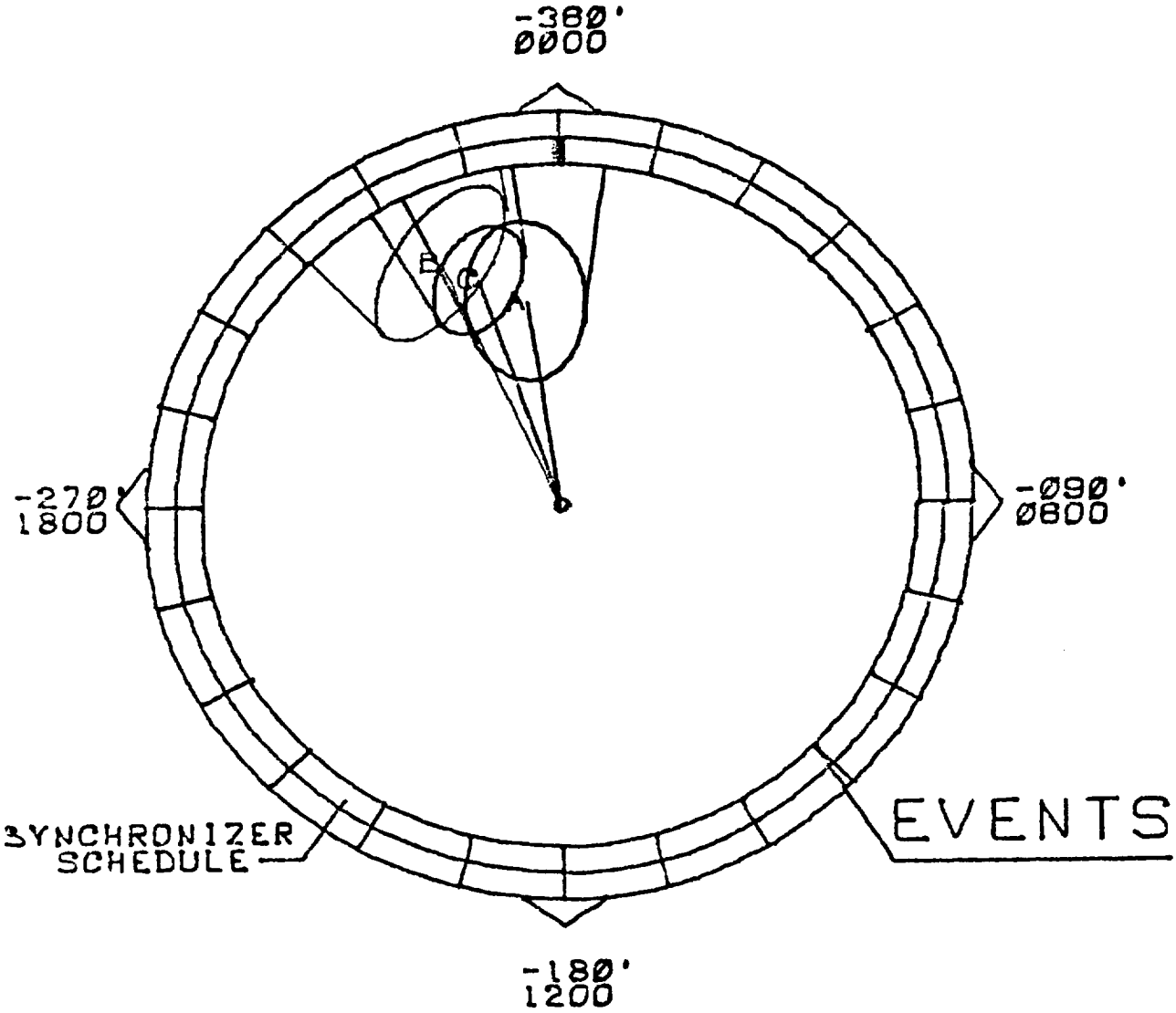
NORMALS 20-49 PLATELETS
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.004	41	14	260.89 191.44 330.34	9.81 3.15 18.48	-282 -190 -317
B	.000	41	22	284.64 196.82 372.46	11.05 4.92 18.11	-286 -233 -325
C	.000	41	38	275.41 192.05 358.77	10.27 5.89 15.40	-278 -234 -310

NORMALS 20-49 WBC
A = M B = F C = M + F

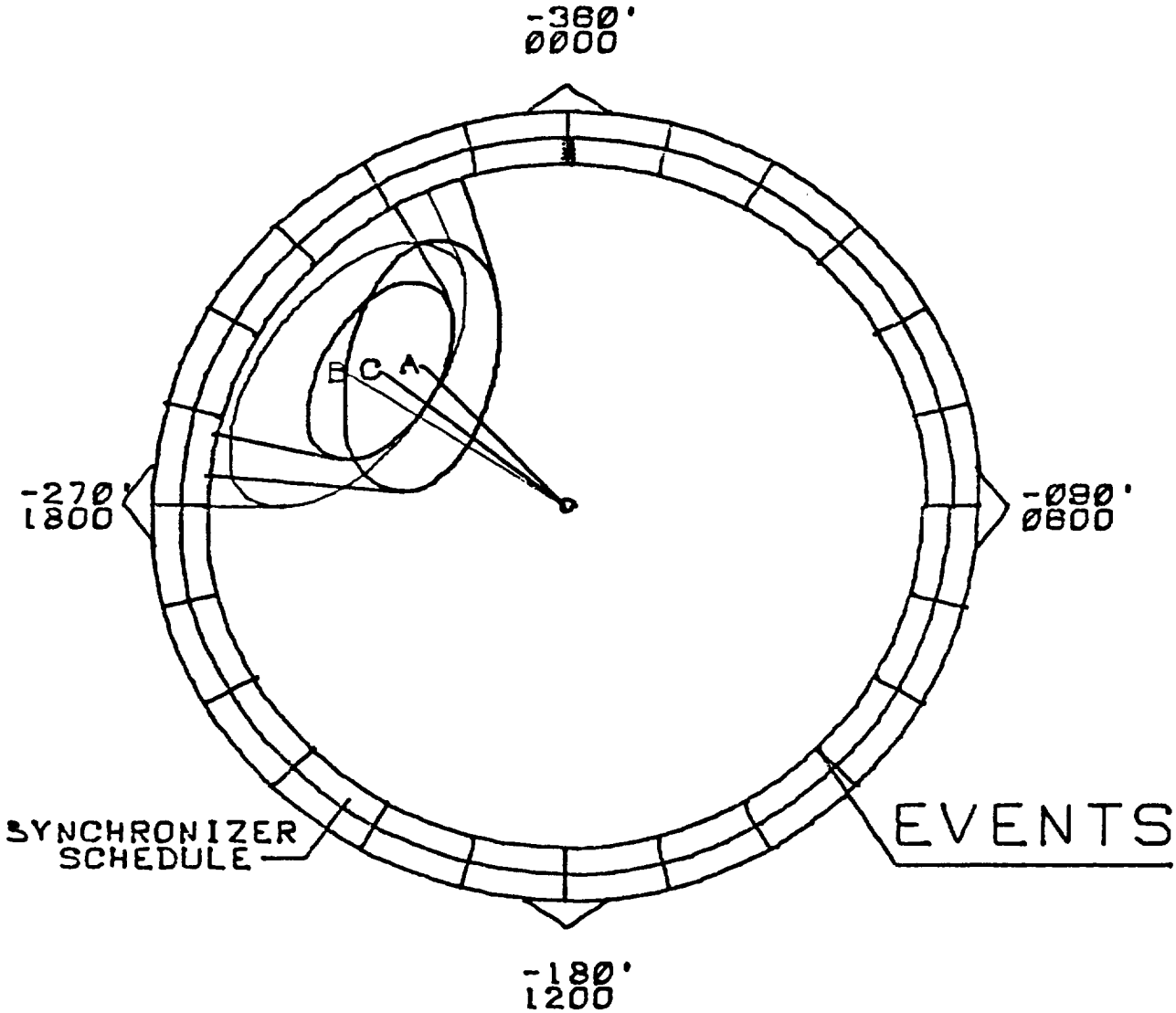


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	67	29	6.49 3.78 9.19	0.67 0.41 0.94	-351 -334 -7
B	.000	66	37	7.44 4.21 10.67	0.87 0.69 1.08	-335 -315 -350
C	.000	68	68	7.02 3.89 10.15	0.78 0.62 0.94	-341 -328 -352

C22

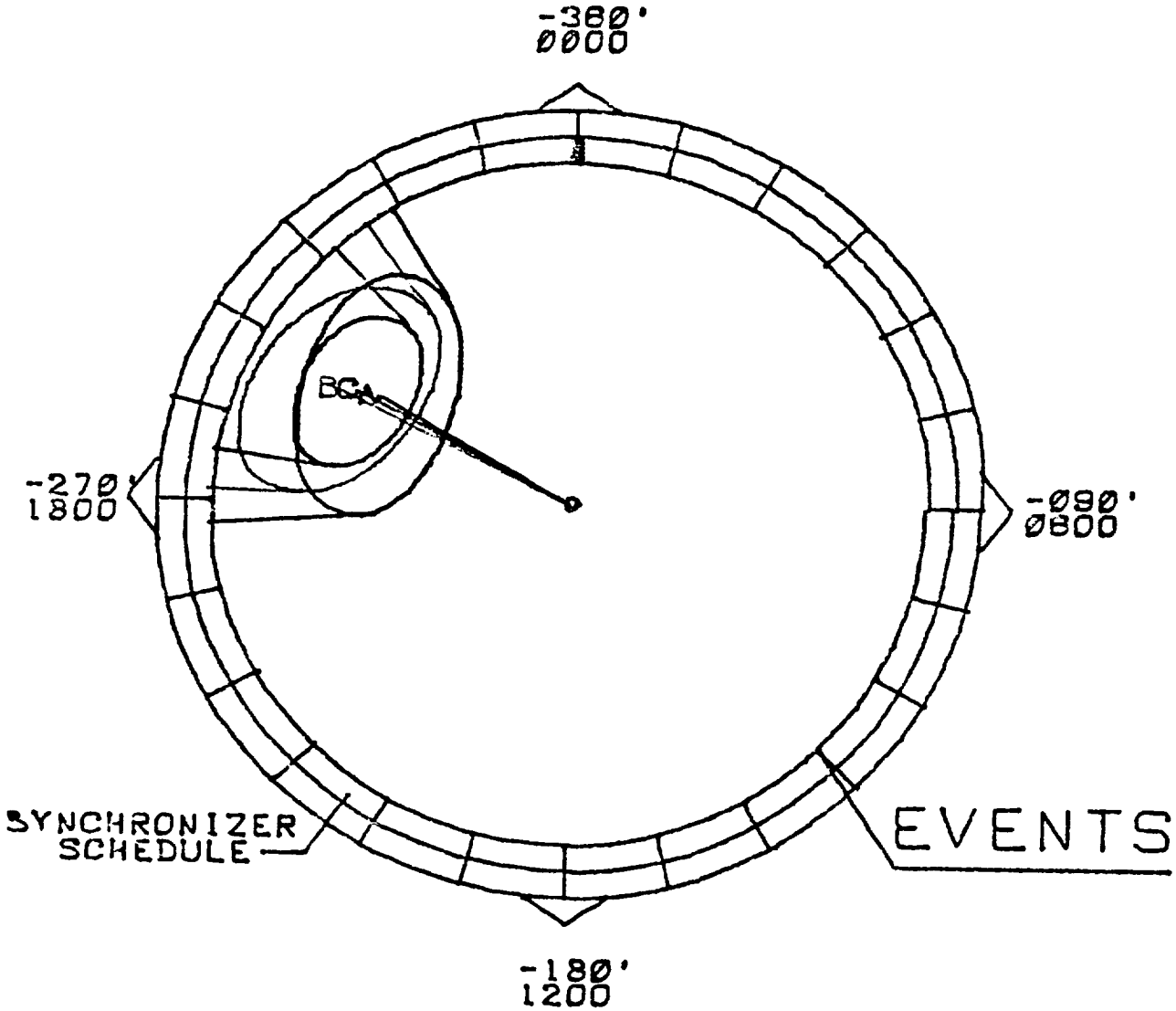
NORMALS 20-49 T.PMNS X 100
A= M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	47	29	33.99 14.00 53.97	3.33 1.86 5.05	-315 -275 -342
B	.000	52	37	41.89 17.93 65.86	4.14 2.76 5.57	-302 -269 -337
C	.000	50	66	38.42 14.96 61.88	3.76 2.79 4.75	-307 -282 -331

NORMALS 20-49 ADULT PMNS
A = M B = F C = M + F

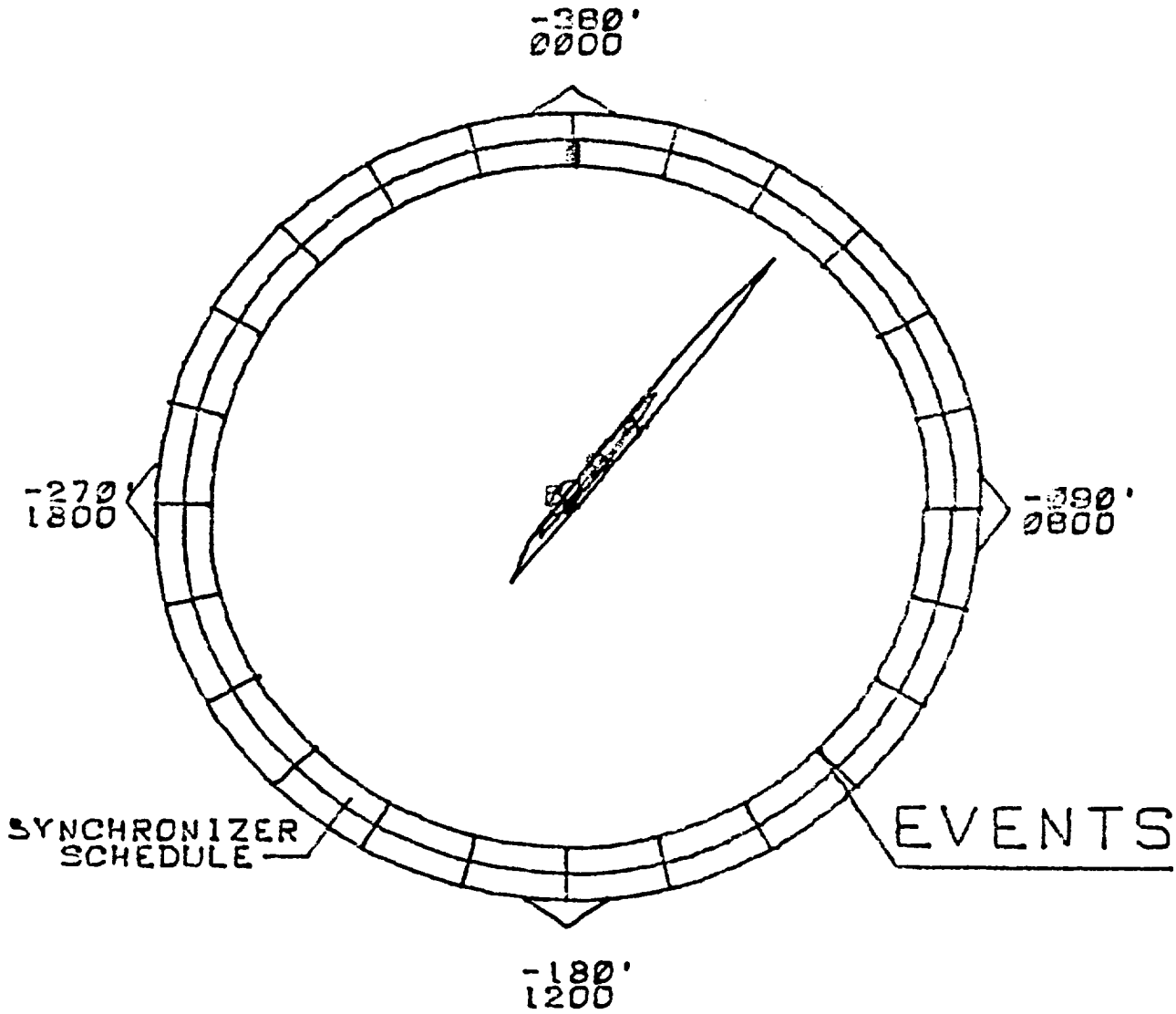


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	58	29	28.90 10.06 43.74	3.34 2.11 4.84	-300 -288 -328
B	.000	52	37	32.98 11.82 54.10	3.85 2.59 5.14	-298 -271 -324
C	.000	53	68	30.30 10.17 50.42	3.62 2.78 4.48	-298 -278 -317

C24N

NORMALS 20-49 BANDS X 10
A = M B = F C = M F

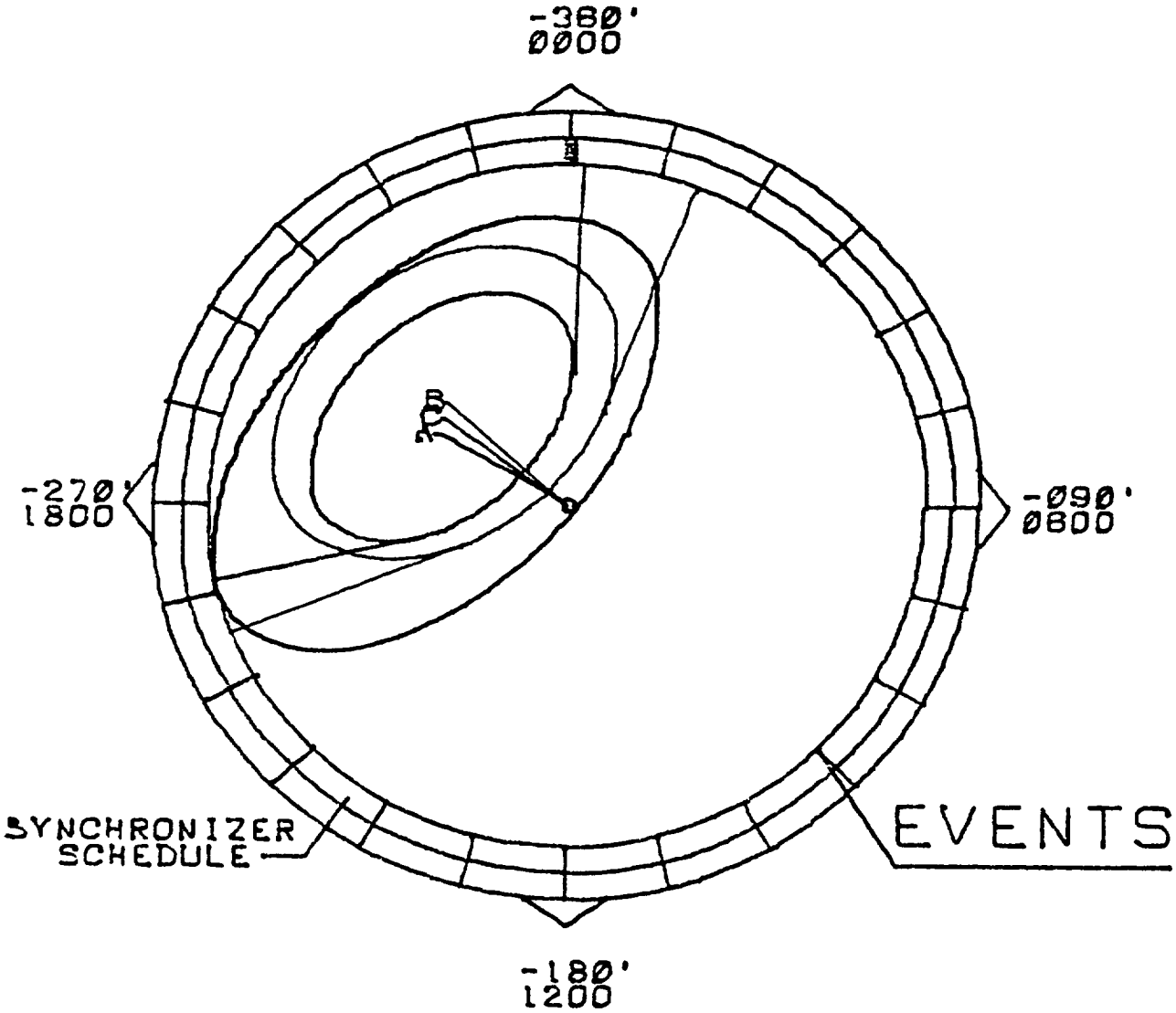


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.500	38	29	22.01 -137.06 181.09	5.07	-37
B	.227	42	37	8.92 1.24 16.61	0.48	-352
C	.185	40	88	14.87 -90.67 120.02	2.42	-33

C25

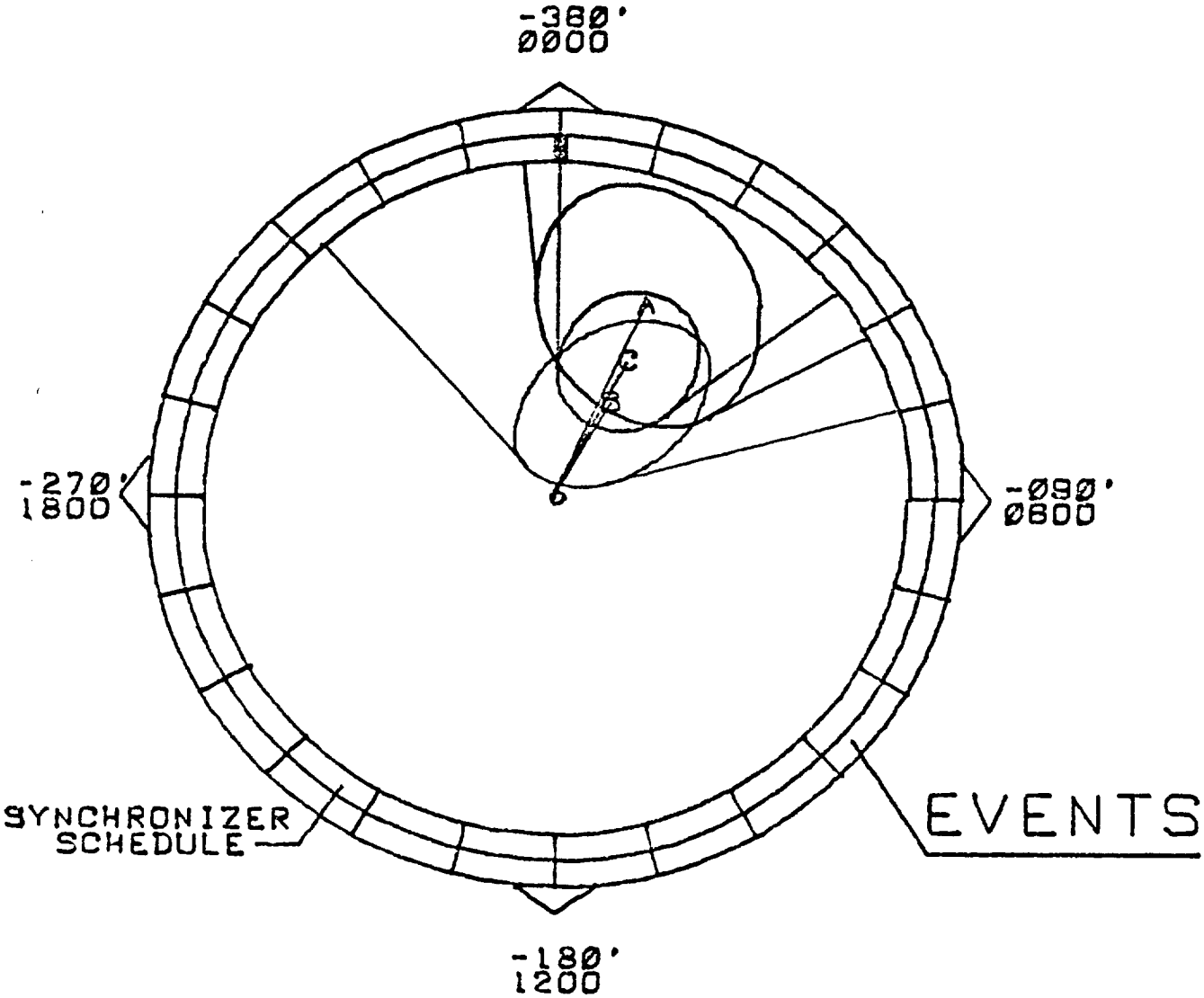
NORMALS 20-49 MONOCYTES
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.073	48	28	330.73 76.23 585.23	30.84	-298
B	.019	41	37	303.98 60.49 547.43	32.88 4.61 61.71	-311 -247 -21
C	.001	44	66	315.72 67.89 563.55	31.70 11.09 53.34	-308 -257 -2

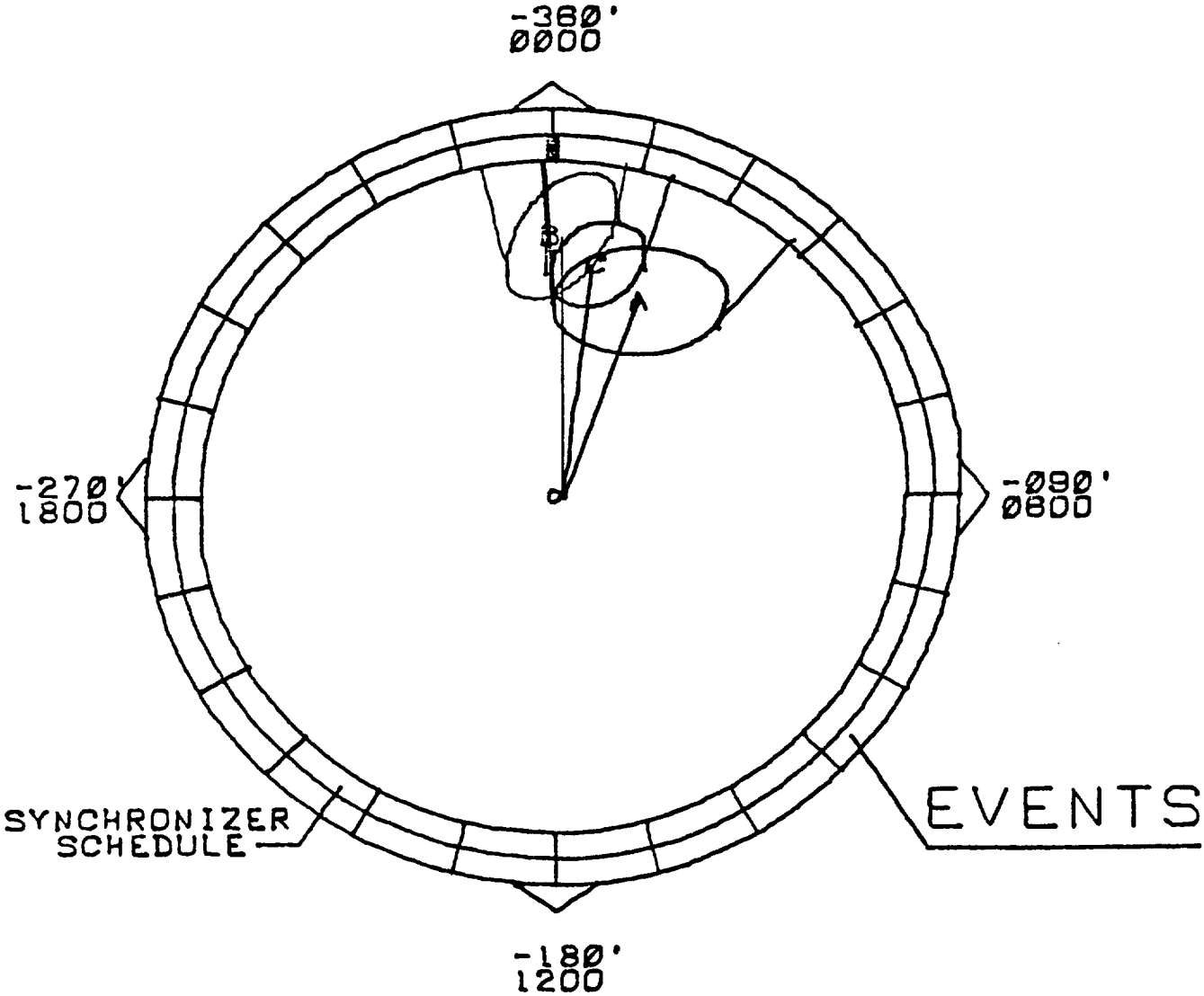
NORMALS 20-49 EOSINOPHIL
A = M B = F C = M+F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	38	29	227.73 -65.21 520.87	41.37 19.50 63.74	-24 -354 -81
B	.022	34	37	178.25 -22.28 378.79	21.42 2.50 41.26	-30 -318 -74
C	.000	38	66	199.99 -48.18 448.17	30.15 15.92 44.38	-27 -0 -52

NORMALS 20-49 LYMPHS X 100
A = M B = F C = M + F

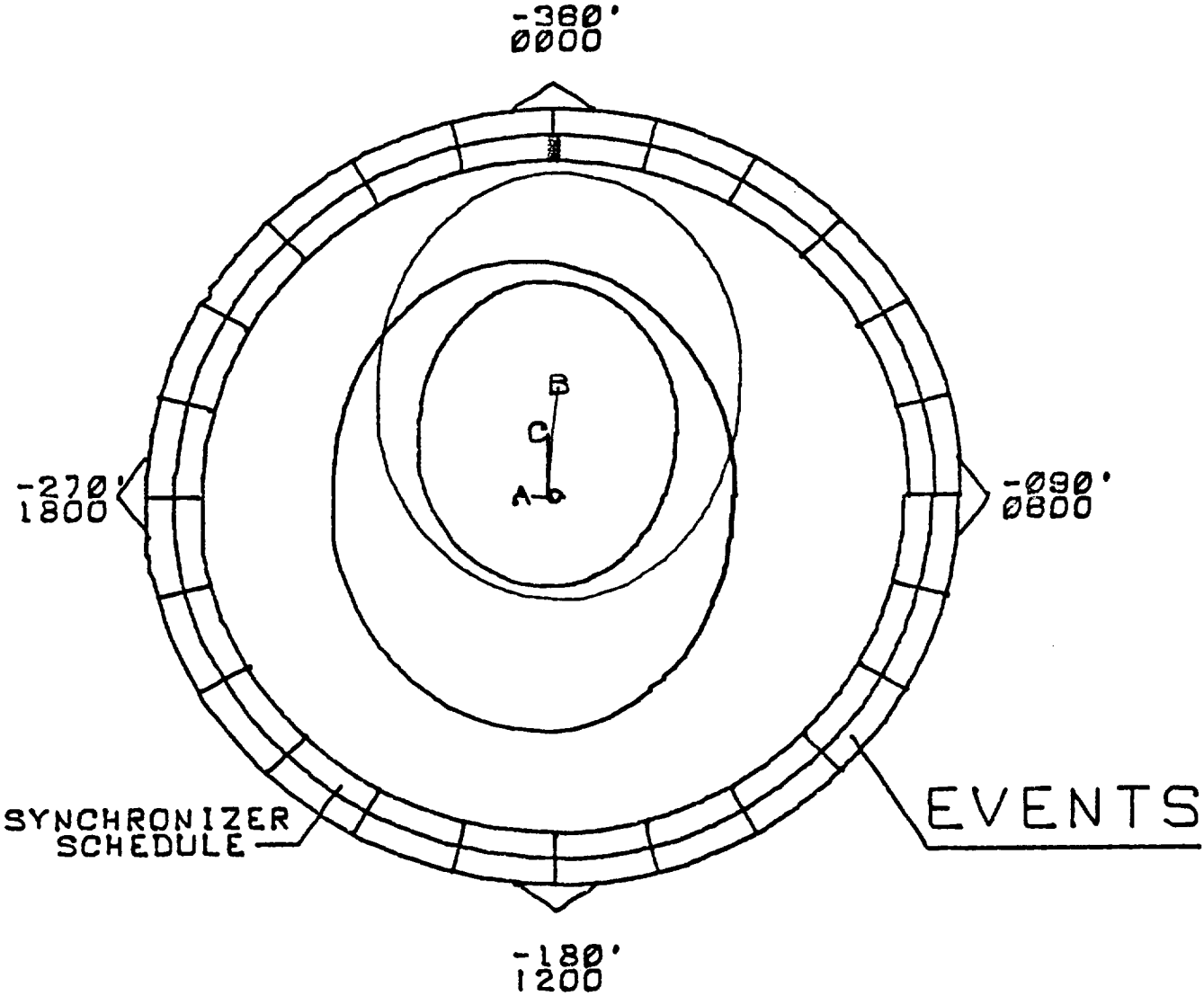


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.000	81	28	24.81 10.88 38.34	4.22 3.05 5.45	-20 -358 -40
B	.000	57	37	27.18 15.41 38.90	5.30 4.04 8.80	-359 -345 -10
C	.000	59	85	26.06 13.28 38.84	4.78 3.88 5.85	-7 -355 -18

C28

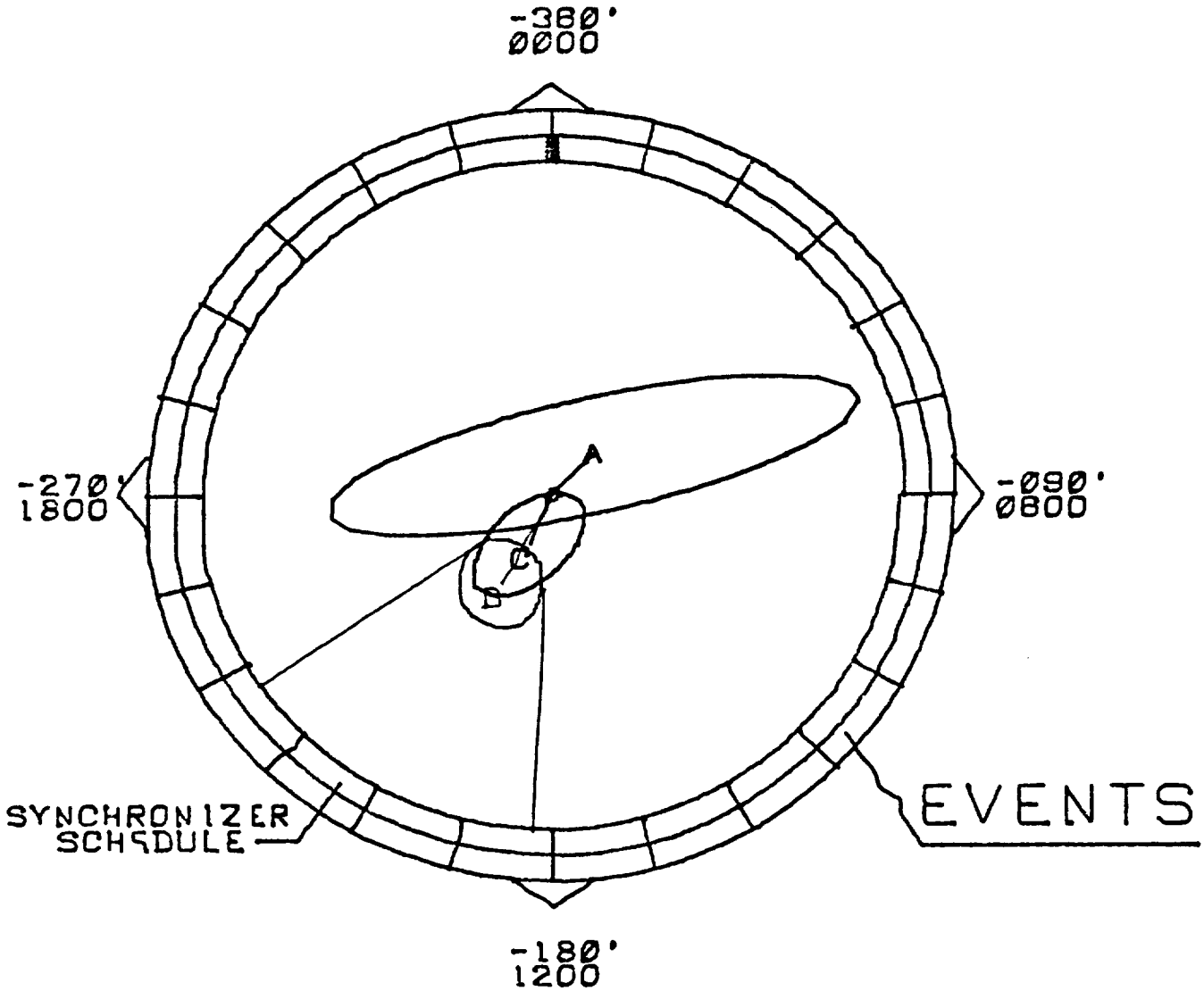
NORMALS 20-49 BASOPHILS
A = M B = F C = M+F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.968	39	28	53.24 -26.70 133.18	1.17	-274
B	.425	39	37	54.67 -13.99 123.33	8.93	-5
C	.587	39	85	54.05 -19.08 127.20	3.98	-358

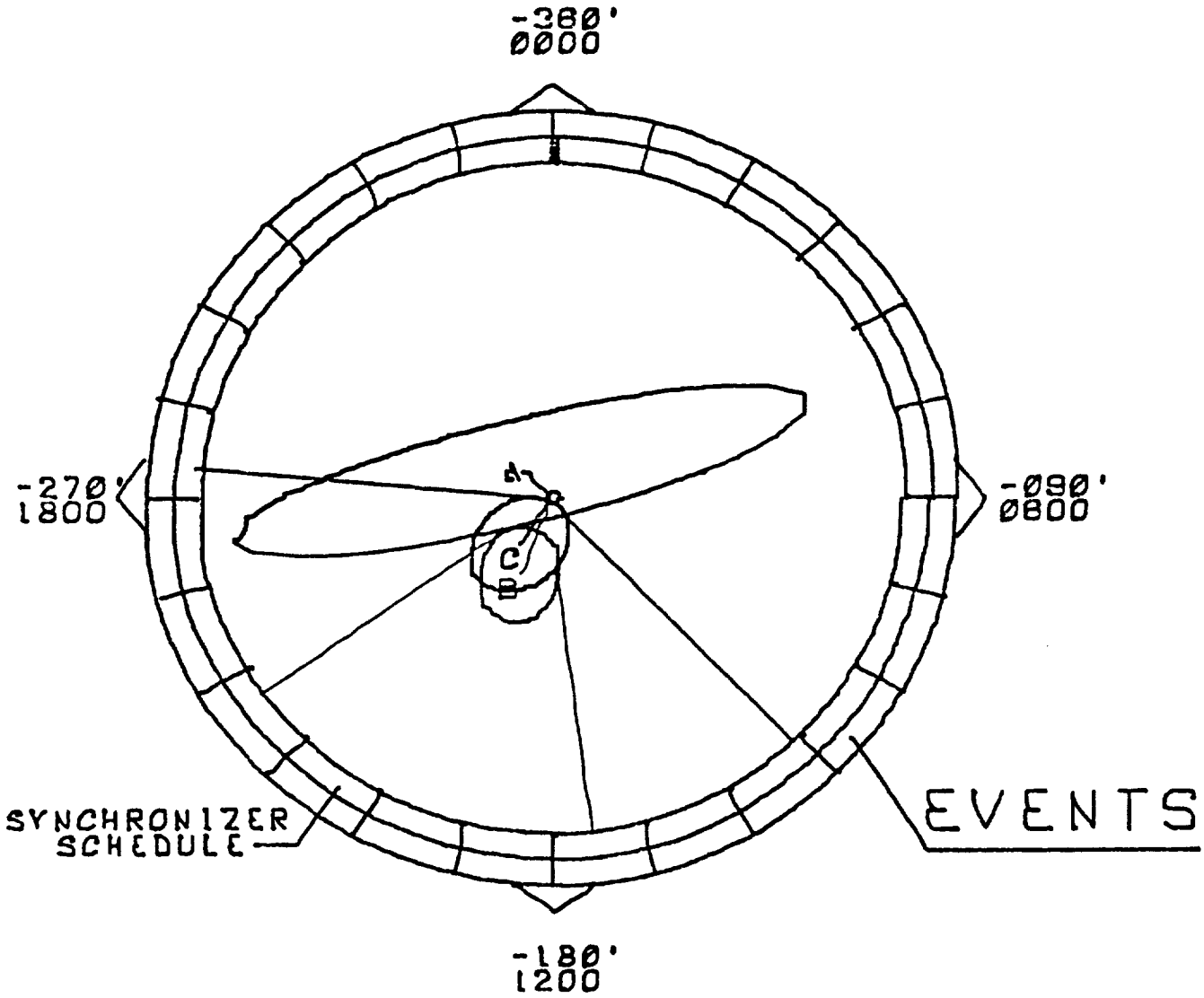
NORMALS 20-49 ALB-SMAC
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.181	43	5	4.32 4.07 4.57	0.07	-45
B	.000	50	12	4.20 3.86 4.53	0.13 0.07 0.18	-208 -182 -235
C	.062	48	17	4.23 3.91 4.58	0.07	-202

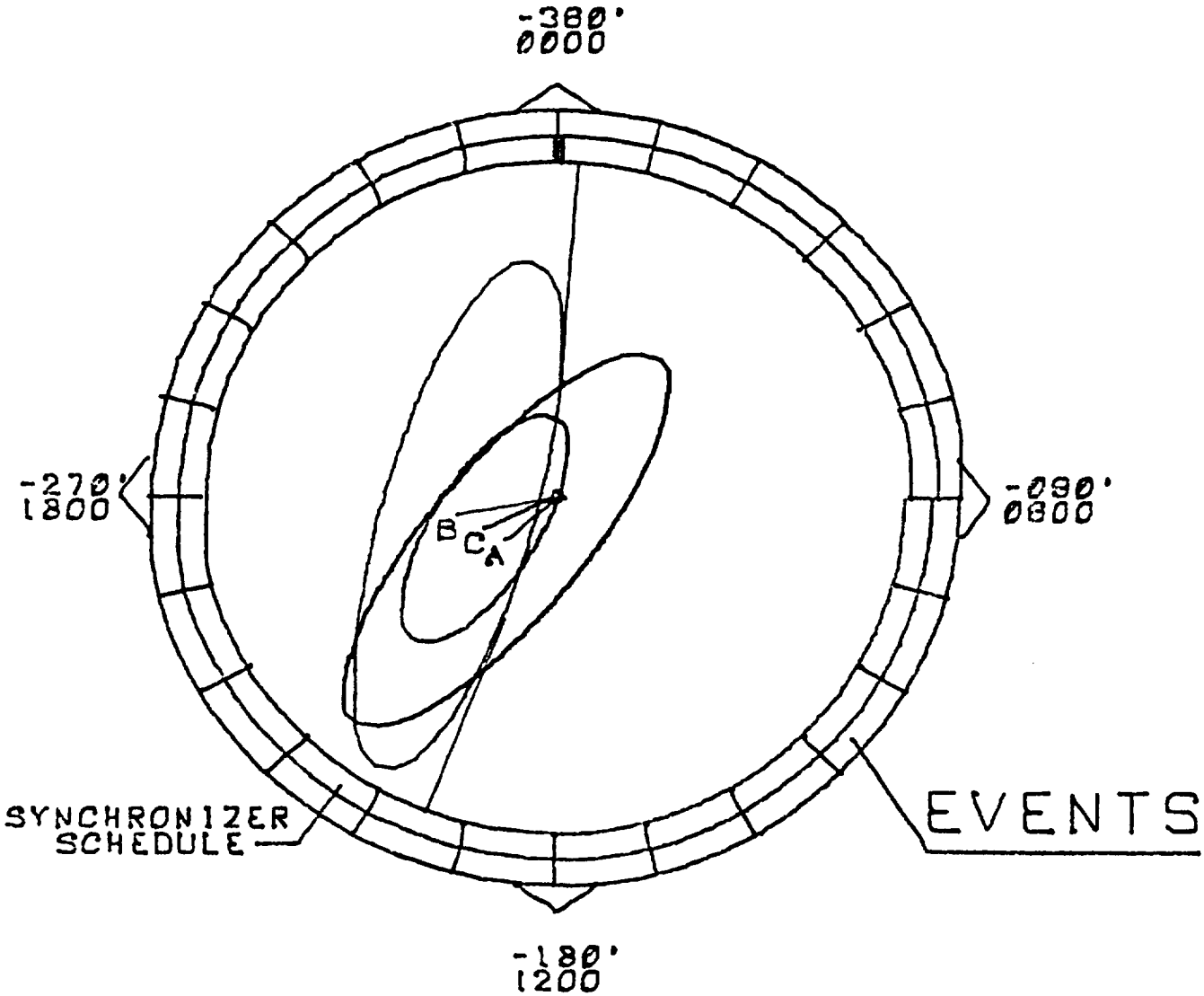
NORMALS 20-49 T. PRO-SMAC
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.154	45	5	6.88 6.24 7.11	0.09	-313
B	.001	47	12	6.68 6.03 7.34	0.19 0.08 0.31	-201 -172 -235
C	.038	48	17	6.88 6.09 7.27	0.13 0.00 0.25	-212 -135 -275

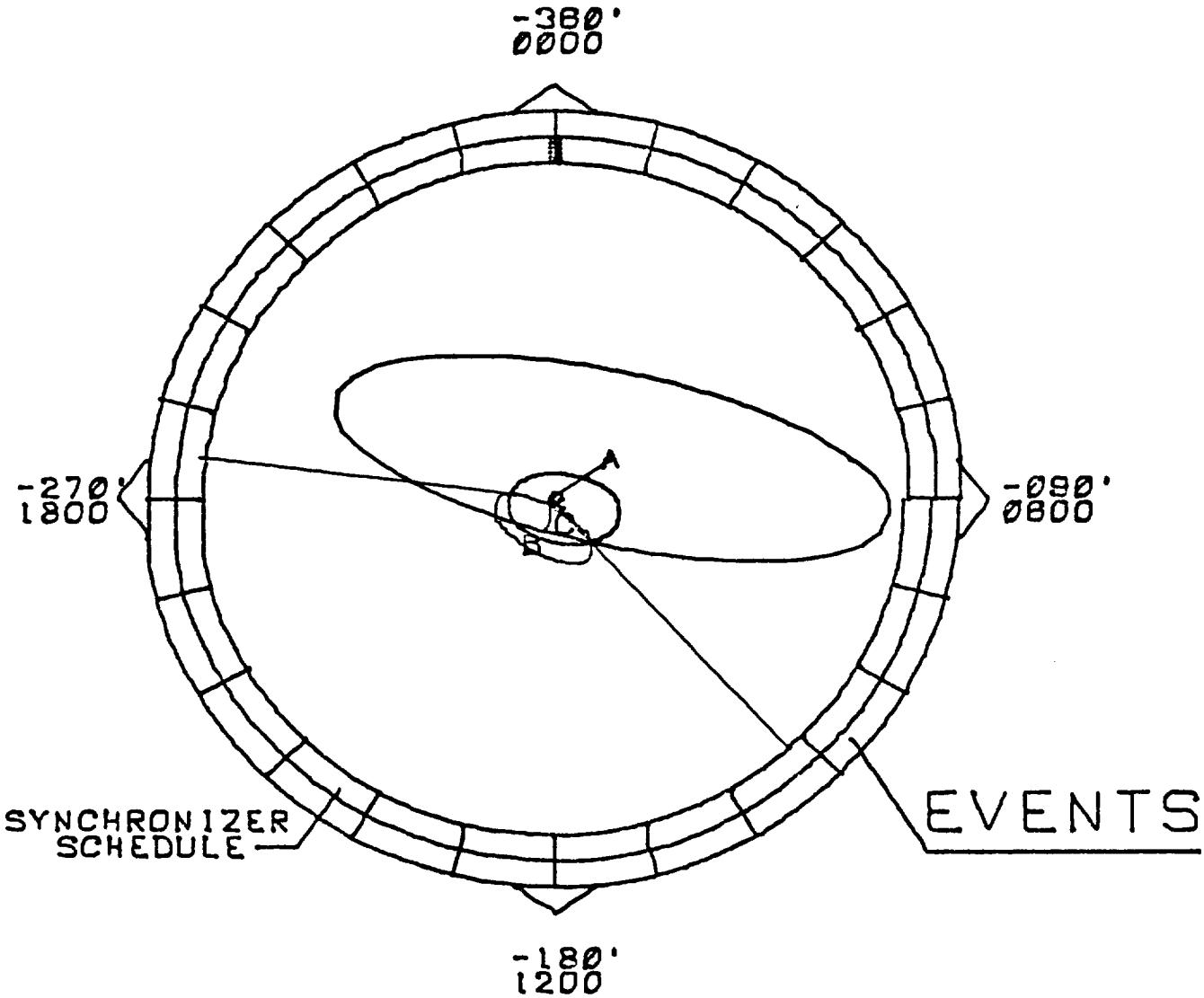
NORMALS 20-49 NA
A = M B = F C = M + F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.667	33	8	143.28 139.87 146.89	0.44	-227
B	.034	45	6	142.19 139.30 145.08	0.65 0.06 2.30	-259 -201 -4
C	.083	38	14	142.81 139.55 146.08	0.51	-244

NORMALS 20-49 NA-SMAC
A = M B = F C = M & F

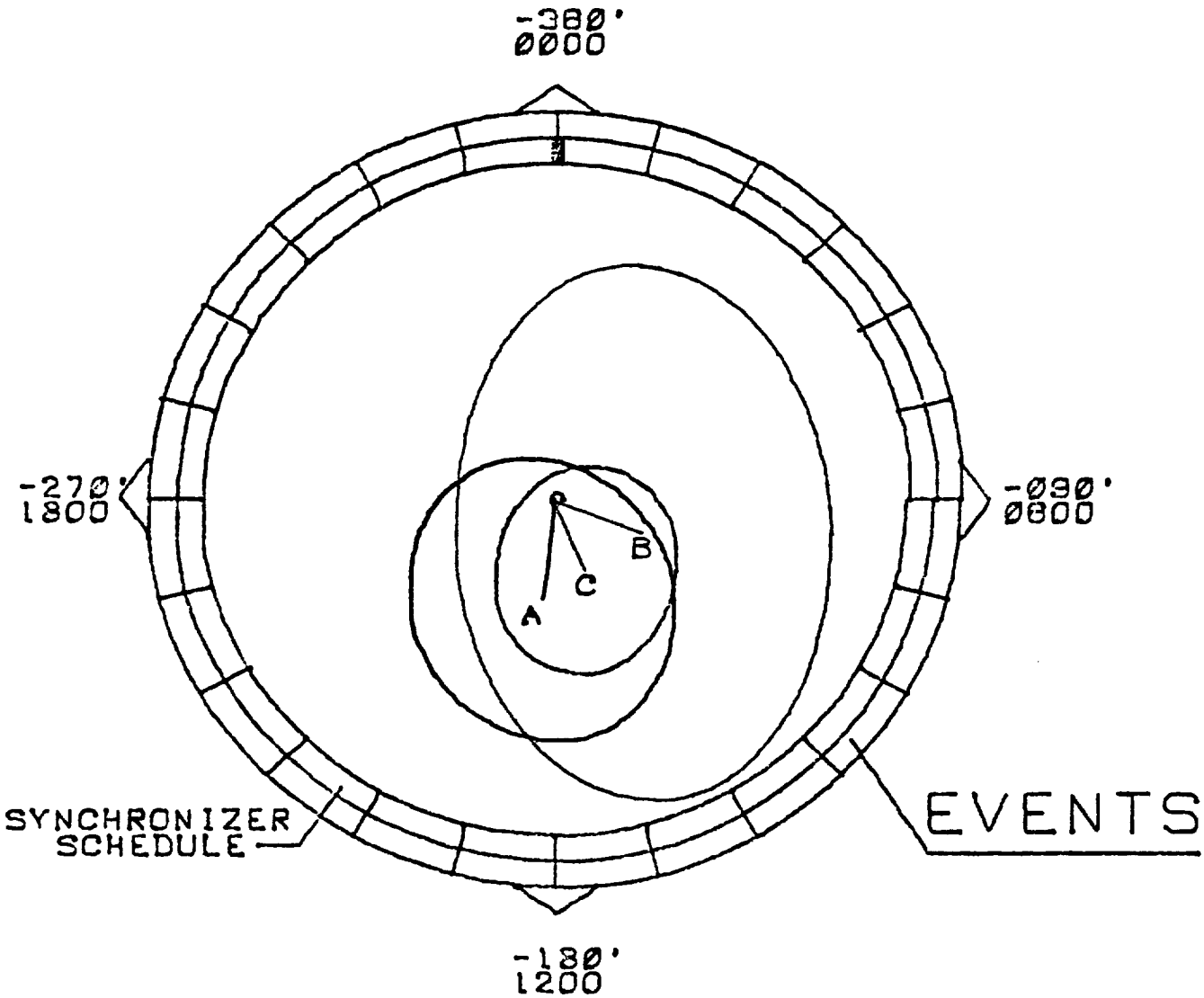


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.159	41	5	142.35 140.37 144.33	2.08	-55
B	.011	48	12	142.56 138.39 146.74	0.93 0.22 2.15	-194 -137 -277
C	.699	48	17	142.50 138.90 146.11	0.44	-130

NORMALS 20-49 K

A =M B = F C = M + F

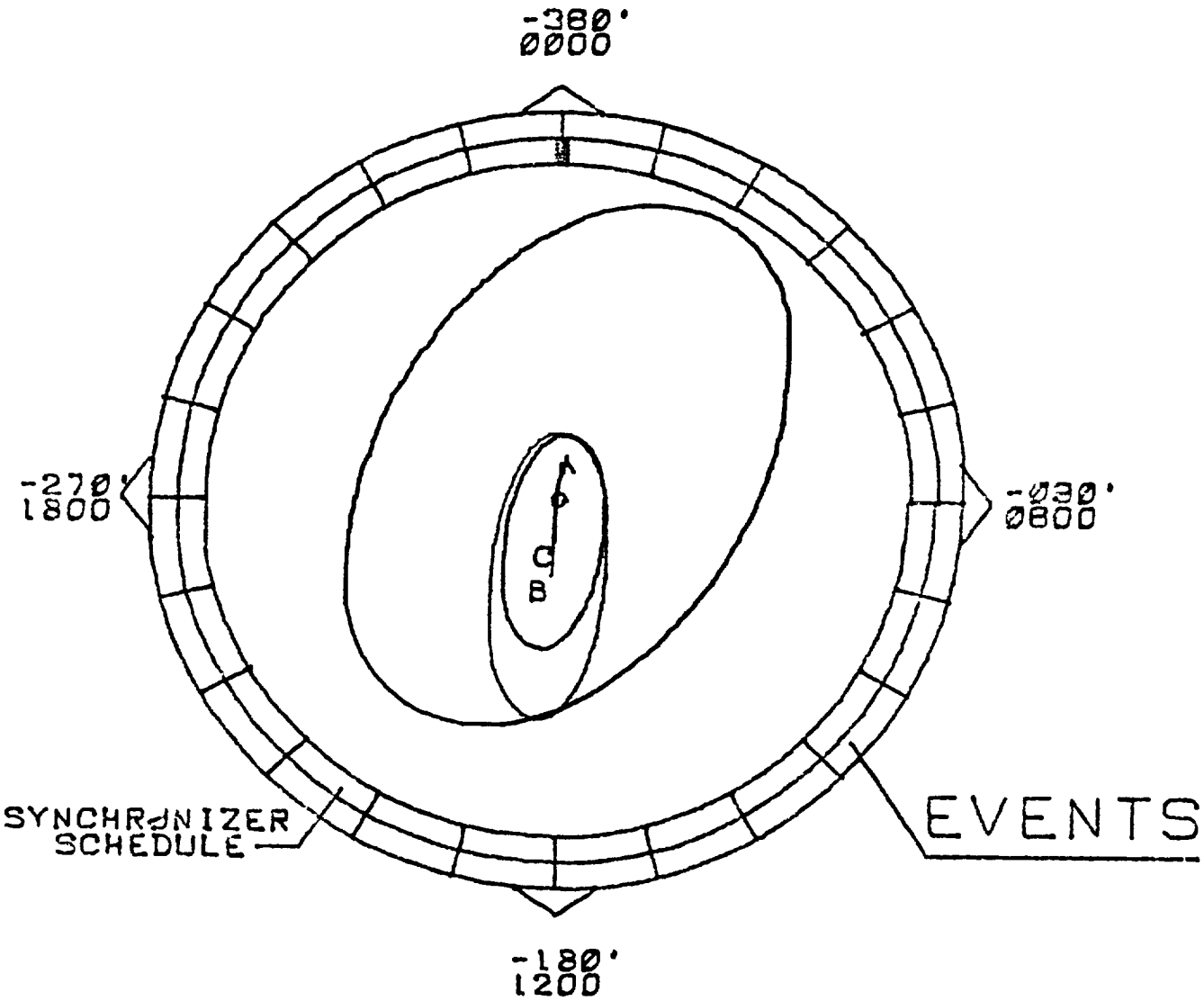


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.141	46	8	4.00 3.68 4.35	0.08	-188
B	.300	35	8	4.08 3.68 4.49	0.08	-110
C	.136	41	14	4.04 3.87 4.40	0.07	-158

C34

NORMALS 20-49 K - SMAC
A = M B = F C = M+F



MEAN COSINOR

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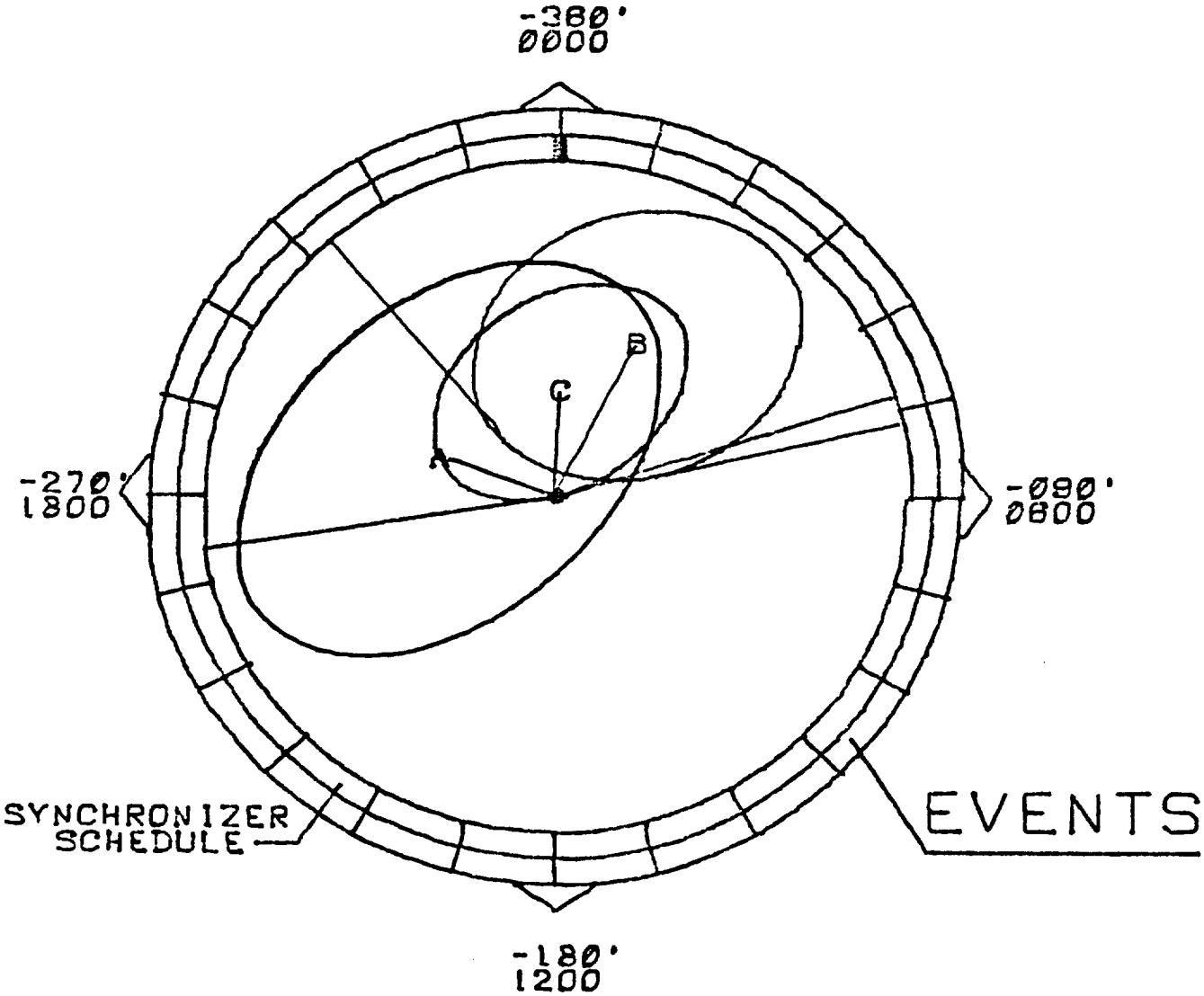
A	.840	40	5	4.38 4.22 4.55	0.05	-18
B	.362	45	12	4.38 3.97 4.80	0.11	-185
C	.575	44	17	4.38 4.03 4.74	0.08	-182

C35

NORMALS 20-49 RETICS
A = M B = F C = M + F

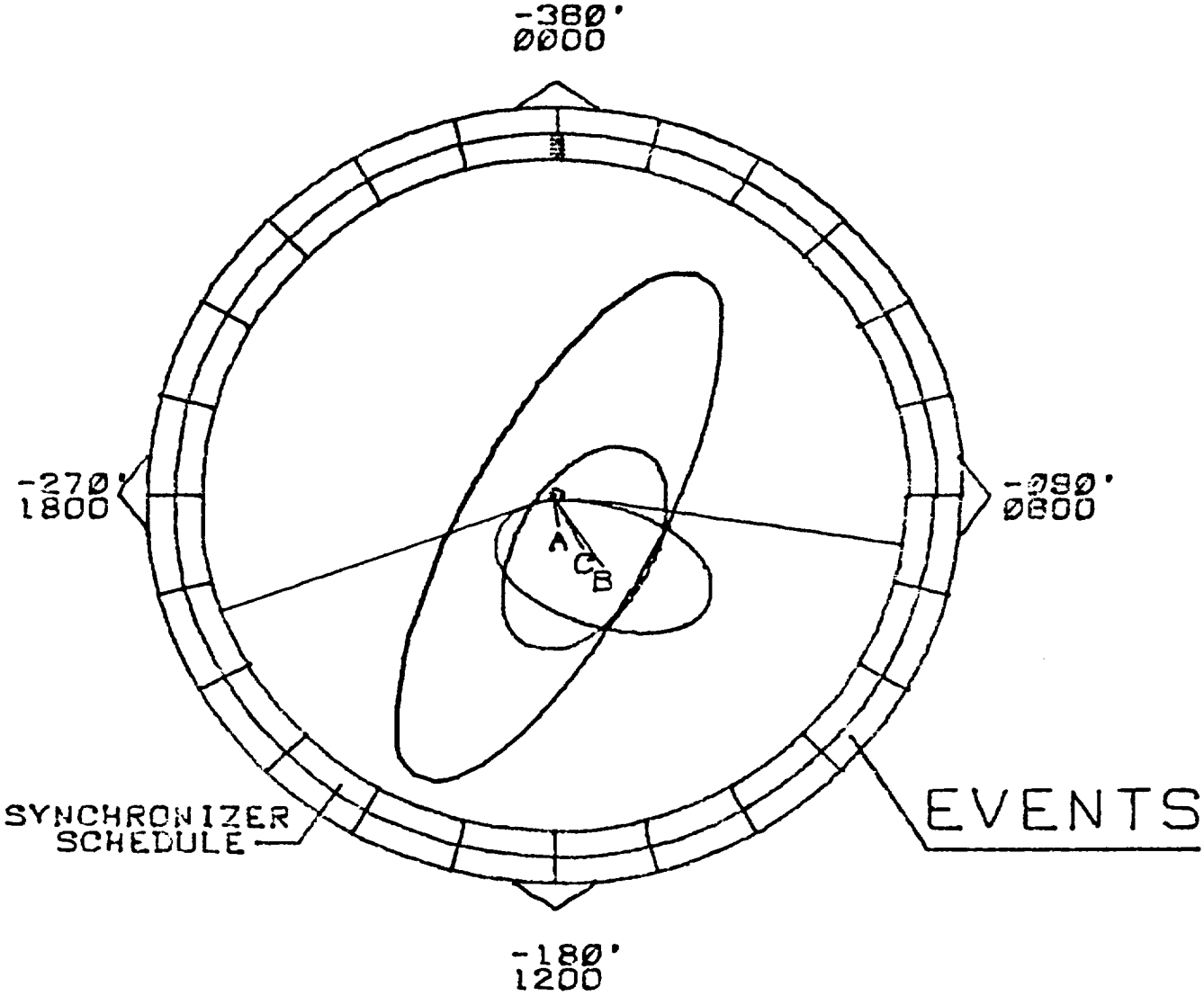


MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.239	34	19	85.12 27.89 142.34	5.11	-290
B	.018	46	27	71.71 16.90 126.53	8.20 1.23 15.41	-27 -320 -77
C	.048	41	46	77.25 20.54 133.97	5.01 0.01 10.57	-2 -280 -72

C36

NORMALS 20-49 FERRITIN
A = M B = F C = M & F



MEAN COSINOR

	P	PR	NO. SER	MESOR 95 PCT CL	AMPLITUDE 95 PCT CL	ACROPHASE 95 PCT CL
A	.816	35	11	38.97 -3.86 81.81	0.37	-170
B	.038	43	14	24.91 -6.06 55.89	1.01 0.04 2.20	-145 -98 -249
C	.117	39	25	31.10 -7.38 69.58	0.72	-151

C37

APPENDIX D

TIME-QUALIFIED REFERENCE VALUES FOR SELECTED VARIABLES

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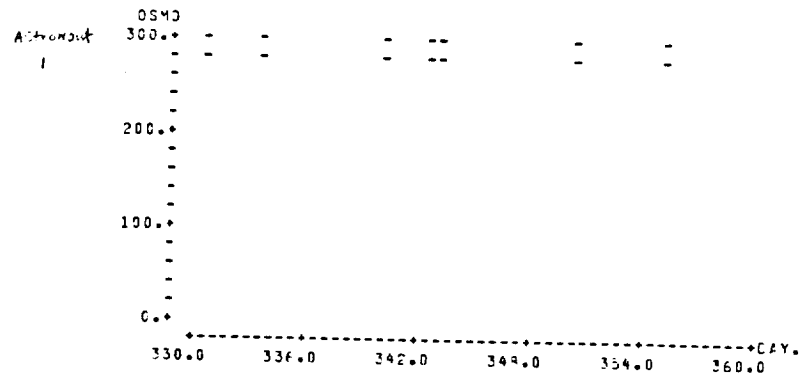

7 MISSING OBSERV+TIONS

AV	284.550
SD	4.59376
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LO	280.362

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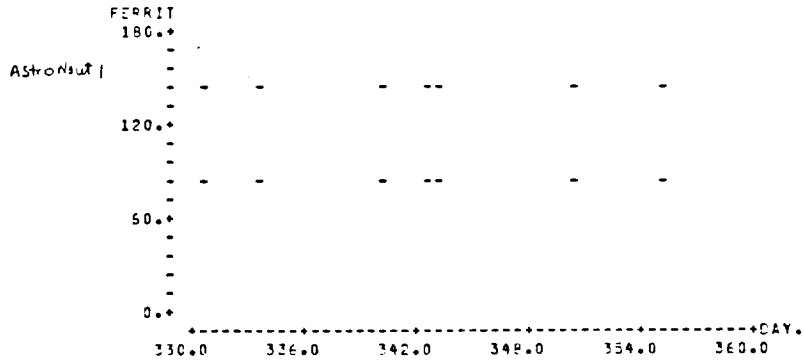

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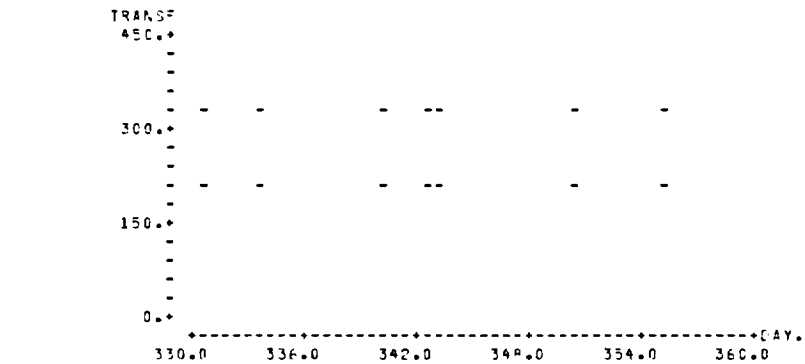

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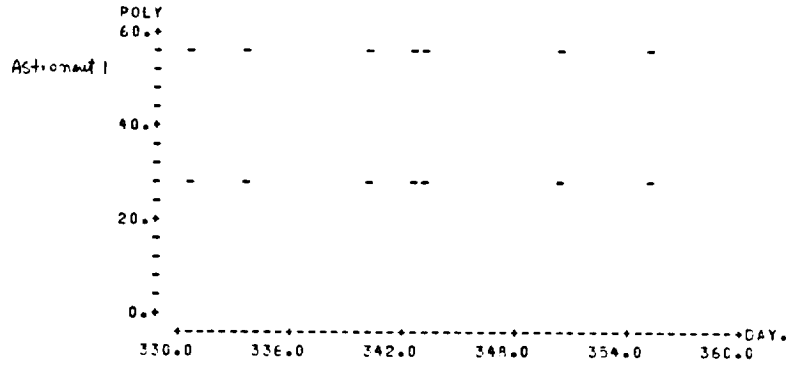

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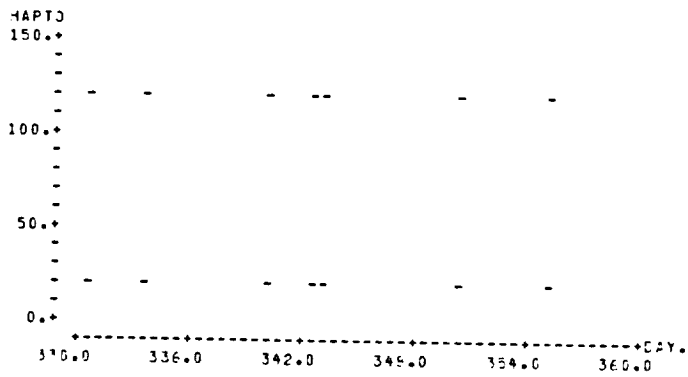

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LO	22.3726

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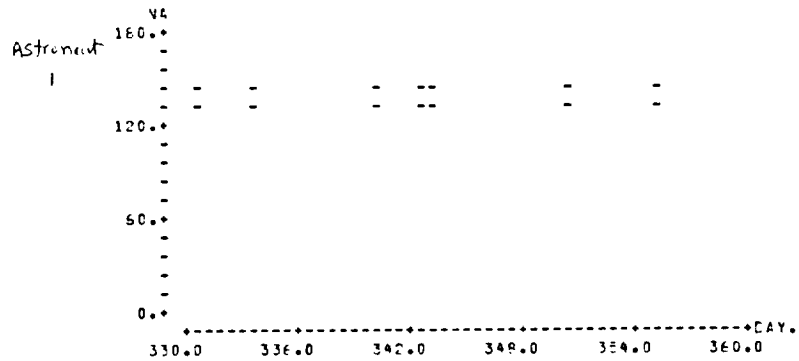

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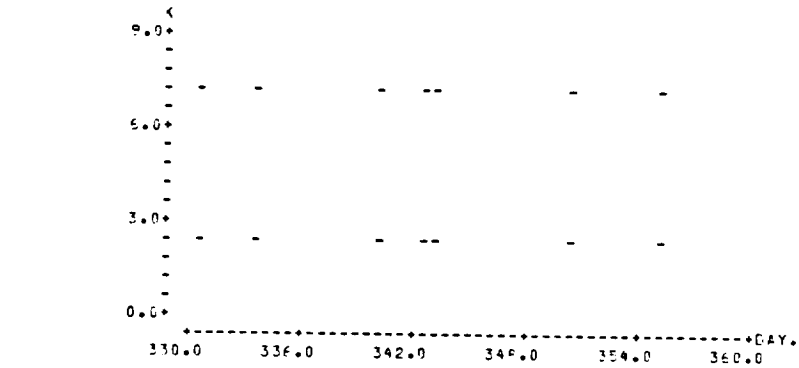
LO	136.077



7 MISSING OBSERV+TIONS

AV	4.92500
SD	1.23240
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LO	2.45020

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               -
               -
               -
               -
         0.0+
               -
               -
               -
               -  -    -          -   --          -       -
        -1.0+
             +---------+---------+---------+---------+---------+DAY.
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7 MISSING OBSERV+TIONS

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SD        .663820
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         1.55+
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               -
               -
               -  -    -          -   --          -       -
         1.00+
               -
               -
               -
               -
          .45+
               -
               -
               -
               -
        -.10+  -    -          -   --          -       -
             +---------+---------+---------+---------+---------+DAY.
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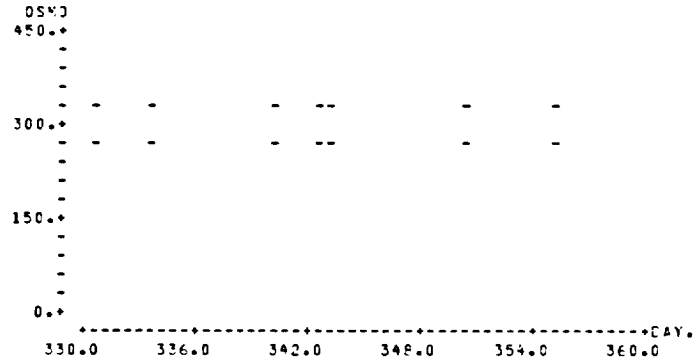

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AV	298.929
SD	10.3573
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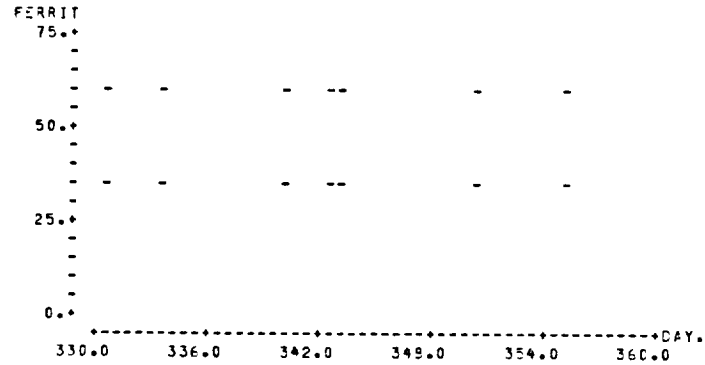

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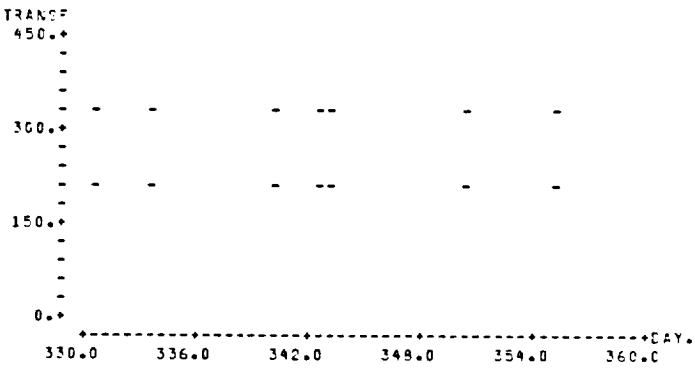

7 MISSING OBSERV+TIONS

AV	269.571
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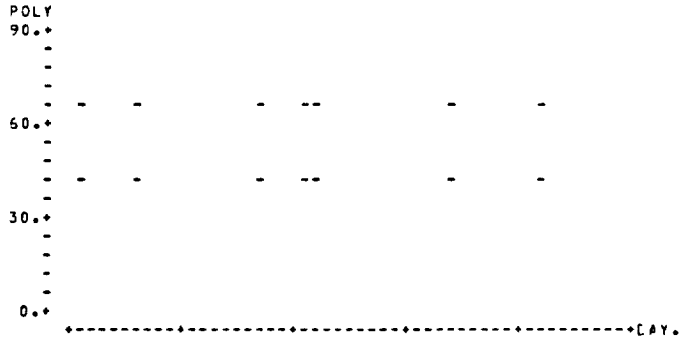

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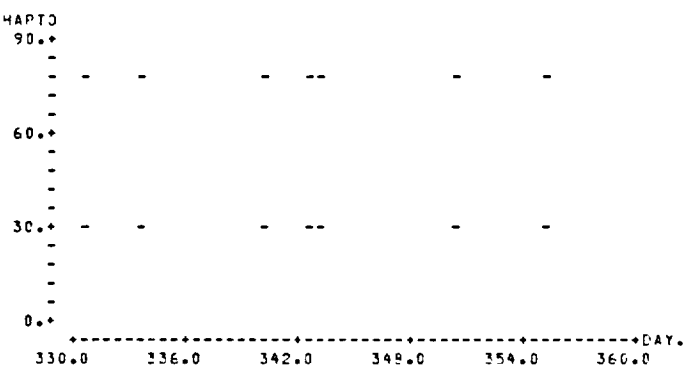

7 MISSING OBSERV+TIONS

AV	56.2143
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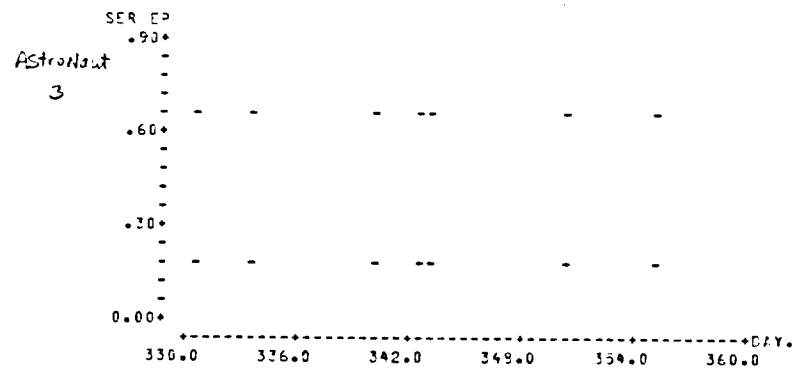

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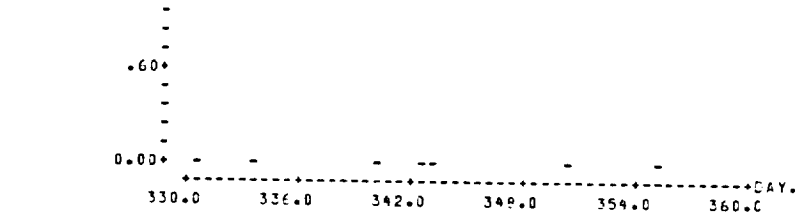

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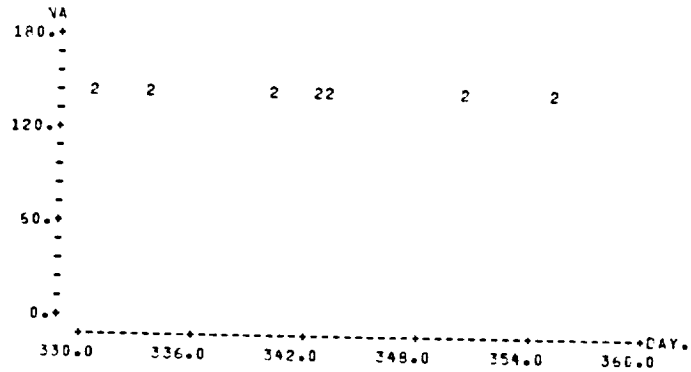

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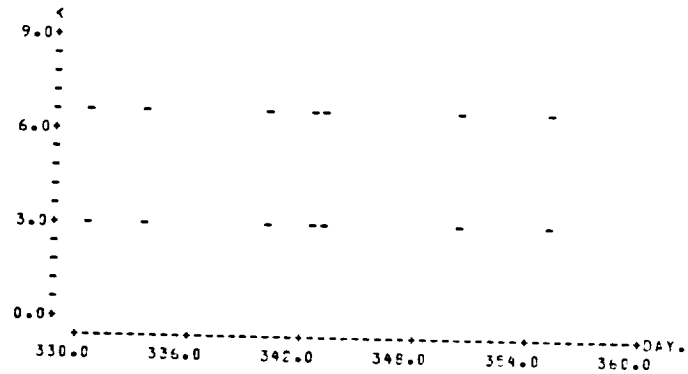

7 MISSING OBSERV+TIONS

AV	4.75000
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D11